How Do We Manage Elite Controllers?

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2-20-2020
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Virtual HIV Provider Rounds
February 20, 2020
CFP 310 & Via Skype
#21299

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Case Scenario

- 61 yo male with no significant PMH presenting to establish care for HIV
- No acute complaints
- Four months ago he presented to his PCP for penile pain
- HIV 4th generation was positive
- Risk factors included MSM, anal receptive intercourse with multiple partners
  - Unknown HIV statuses
Physical Examination

- General: Obese, pleasant
- HEENT: no oral thrush or lymphadenopathy
- Cardio: No murmurs, rubs or gallops
- Respiratory: Clear breath sounds bilaterally
- Abdomen: Soft, non distended
- Extremities: Peripheral pulses present
- Skin: No rashes
HIV Diagnosis at Time of Initial Encounter

- HIV 1: reactive
- HIV 1 VL: <20 copies
- No CD4 available at this time
Any Questions So far?

What Do We Do In These Situations?
In the last decade, the strategy for timing of initiation of ART for the treatment of HIV has shifted from a cutoff CD4 T cell count to immediate initiation. This change is a result of better tolerated ART options and multiple clinical trials. The shift leads to diminished HIV transmission in sero-discordant couples.

Beneficial course for “Elite Controllers” is less clear.
Elite Controllers

- Maintain undetectable viral load and CD4 T cell counts above 200 in routine assays in the absence of ART
  - Undetectable VLs for at least 6-12 months or undetectable VLs on at least 90% of measurements over 10 years
  - Estimated prevalence ranges from 0.15 to 1.5% of all PLWH
- “Viremic controllers” – maintain RNA cutoff of 2000 copies/mL
- “Long-term non-progressors” – refers to immunological control with a CD4 T cell count of at least 500 cells over more than 8 years
- Somehow managed to naturally control HIV in the absence of medications
Characteristics of Elite Controllers

- Deleterious viruses
- Genetic variability
- Pathogenicity
- Fitness

- Cellular immunity
- Humoral immunity
- Innate immunity
- NK activity

- LTNP EC
- Functional Cure?

- HLA Alleles
- Genetic polymorphisms
- Restriction factors
Table 1

<table>
<thead>
<tr>
<th>Viral protein</th>
<th>Host factor</th>
<th>Mechanism of action</th>
<th>Reference</th>
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<tbody>
<tr>
<td>nef</td>
<td></td>
<td>Decreases MHC-I and MHC-II</td>
<td>[12, 13]</td>
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<td>vpu</td>
<td></td>
<td>Modulates TCR signaling, promotes cleavage of Nef, and inhibits viral replication</td>
<td>[14-16]</td>
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<tr>
<td>vif</td>
<td></td>
<td>Prevents insertion of SERINC-5 into HIV-1 virions, enhancing infectivity</td>
<td>[17]</td>
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<tr>
<td>TRIM5α</td>
<td></td>
<td>Decreases CD4, and inhibits Tetherin</td>
<td>[18, 19]</td>
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<tr>
<td>Mx2/MxB</td>
<td></td>
<td>Delays HIV-1 DNA nuclear import and integration by targeting viral capsid, exact mechanism of action uncertain</td>
<td>[20, 21]</td>
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<tr>
<td>APOBEC3</td>
<td></td>
<td>Inhibits viral reverse transcription and integration</td>
<td>[22]</td>
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<tr>
<td>Tetherin</td>
<td></td>
<td>Inhibits HIV-1 release by binding virus particles that bud through the cell membrane</td>
<td>[23]</td>
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<tr>
<td>Serinc-3/5</td>
<td></td>
<td>Inhibits HIV-1 particle infectivity</td>
<td>[24]</td>
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MHC: major histocompatibility complex; TCR: T Cell Receptor; NFAT: nuclear factor of activated T-cells; BST-2: bone marrow stromal antigen 2; APOBEC: apolipoprotein B mRNA editing enzyme 3 catalytic polypeptide; Mx2/MxB: myxovirus resistance protein 2; BST-2: bone marrow stromal antigen 2.
Cellular Immune Responses

- Strong correlation with viral control and cellular and immune responses in humans
- Tight association between Gag-specific cytotoxic T lymphocyte responses and viral control
- HIV-1 specific CD8 T cell responses against viral structural proteins are inversely correlated to set point levels of viral RNA
- If CD4 T cells from elite controllers are intrinsically more resistant to HIV investigation remains controversial
<table>
<thead>
<tr>
<th>Genes</th>
<th>Author</th>
<th>Journal, year [ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DRB1*13</td>
<td>Malhotra, U. et al</td>
<td>J Clin Invest, 2001 [146]</td>
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<td></td>
<td>Chen, Y. et al</td>
<td>Hum Immunol, 1997 [147]</td>
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<td>MICB, TNF, RDBP, BAT1-5, PSORS1C1, HLA-C</td>
<td>Limou, S. et al</td>
<td>J Infect Dis., 2009 [148]</td>
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<td>HLA-B57, HLA-C</td>
<td>Fellay, J. et al</td>
<td>Science, 2007 [105]</td>
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<td></td>
<td>Trachtenberg, E. et al</td>
<td>Genes Immun, 2009 [107]</td>
</tr>
<tr>
<td>HLA-B57, HLA-B27</td>
<td>Pereyra, F. et al</td>
<td>Science, 2010 [51]</td>
</tr>
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<td>HLA-DRB1<em>13 and/or HLA-DRB1</em>06</td>
<td>Ferre, AL. et al</td>
<td>J Virol, 2010 [149]</td>
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<td>Han, Y. et al</td>
<td>AIDS, 2008 [108]</td>
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<td>HLA-B57</td>
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<td></td>
<td>Migueles, SA. et al</td>
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<td>Gao, X. et al</td>
<td>Nat Med, 2005 [150]</td>
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<td>HLA-A, HLA-B, CCR3</td>
<td>McLaren, P.J. et al</td>
<td>PNAS, 2015 [151]</td>
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</tbody>
</table>
But What Does This Mean Clinically?

Let’s Take a Look at a few clinical scenarios...
In a retrospective study, Okulicz et al. found that individuals achieving elite controller status for ten years had more favorable time to AIDS and death.

Some viremia controllers did progress to AIDS and death.

- Loss of virological control and immune function can occur in some individuals.

A study of more than four hundred elite controllers revealed that 30% of them lost viral control, resulting in reduced CD4 counts.
Clinical Outcomes - CVD

- CVD in PLWH – increased rates of myocardial infarctions and traditional CVD risk factors
- HIV: independent risk factor for the development of atherosclerosis
- SCOPE cohort: strong association between HIV sero-status and carotid intima-media thickness irrespective of VL, CD4 T cell count, ART and other confounders of arterial inflammation
- Despite viral suppression, elite controllers appears to have similar levels of coronary atherosclerosis to medical controllers
  - Unknown if ART in elite controllers impacts CVD risk

Co-Infection with Hepatitis C

- Impacts elite controllers more significantly than medical controllers
- PLWH: 2.4% prevalence of co-infection with hepatitis C
  - Rate increases to 82.4% with associated IVDU
- Elite controllers have less associated fibrosis
- Compared to medical controllers, demonstrate differences in immune reactivation
  - Associated with lower CD4 and CD8 T cells and increased CD8 T cell apoptosis
  - Does not translate to loss in elite controller status
- Still no definite evidence that ART would benefit these patients

Need for Immunosuppression?

- Limited information
- Case reports have revealed recovery of elite control after intense periods of immunosuppression without the use of ART
- Further studies are needed

Future Direction

• Need more clinical trials to help determine optimal timing of therapy

• DHHS guidelines note the insufficient number of elite controllers in clinical trials prevents an adequate comparison of the risks and benefits of ART
  • ART should not be delayed in an effort to see if a patient is an elite controller

• These patients need to be regularly monitored for signs of loss of control, which would definitely justify initiation of ART

Conclusion

• Little is known regarding the precise mechanisms that allow robust control of HIV infection, especially in elite controllers

• Further investigation into how controllers achieve such a high degree of virologic control may help facilitate efforts directed towards a “functional cure” for HIV, in which the virus is still present in latent reservoirs but never reaches high levels of replication, all in the absence of ART
Questions?

Thank You!