Do we need immune based therapies for HIV infection?

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Do we need immune-based therapies to manage the HIV pandemic?

• Newer antiretroviral drugs, are safe, well tolerated, can be given conveniently
• Survival in treated HIV infection can be normal (or close to it) particularly if treatment is started in early infection
• Treatment of HIV infection and Pre-exposure prophylaxis can prevent HIV transmission
• So, why bother?
Could we apply immune-based therapies to manage the HIV pandemic?

- Can we provide durable protection against HIV transmission by passive or active immunization?
- Can we prevent the morbidities of treated HIV infection by enhancing immune restoration?
- Can we prevent the accelerated morbidities of aging in treated HIV infection by blocking inflammation?
- Can we cure or control HIV infection by application of immune based therapies?
- Can we learn anything interesting by exploring these questions?
~10yr Decreased Life Expectancy in Older HIV+ Adults in Modern ART Era

Legarth/Obel, JAIDS, 2016
Life Expectancy Further Reduced By Low CD4 Nadir

By pre-ART CD4 count

- Life expectancy of patients on or starting ART in North America
- ~23,000 person-years FU
- 1,622 deaths
- Majority of HIV+ around the world still starting ART <350.
- May overestimate life expectancy
  - Excludes those out of care
  - “Survivorship bias” for older patients who survived 80s and 90s.

*For 20-year old initiating ART

Even after > 5 yrs of HAART and controlled VL, ~20% of adult pts have CD4 T cell counts below a defined normal range.

Rodriguez, Myerson
Who is at greater risk for immune failure

• Late starters
• Older persons
• Men
• Years of viremia?
All CD4 cell maturation subsets are decreased in Immune Failure (immune non responders) ** P<0.001 compared to immune success and to controls

Lederman *J Inf Dis* ‘11
CD4 T cell cycling is increased in Immune Failure

*Increased cycling seen in memory CD4 T cells*
Yet cycling cells of immune non-responders fail to divide ex vivo.
Can we improve outcomes in immune failure by driving CD4 T cell expansion?
Increasing CD4 T cells by IL-2 injections did not decrease Opportunistic Disease/Deaths

SILCAAT and ESPRIT

** Hazard Ratio (IL-2 versus témoin)

<table>
<thead>
<tr>
<th></th>
<th>HR** (IC 95 %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SILCAAT</td>
<td>0.91 (0.70-1.18)</td>
<td>0.47</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>0.93 (0.75-1.16)</td>
<td>0.52</td>
</tr>
<tr>
<td>BOTH</td>
<td>0.93 (0.78-1.09)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Systemic administration of recombinant human interleukin 7 (rhIL-7) increases CD4 T cell counts

Does a CD4 T cell increase after IL-7 administration confer clinical benefit?

A difficult clinical trial design in the HAART era

Could an agent like IL-7 be useful in the setting of drug resistant TB?

Systemic indices of inflammation and coagulation are increased in immune failure

Fig. 8
Increased IL-1β in lymph nodes in treated HIV infection

Shive, Mudd, Estes J Inf Dis ‘14
Role of inflammation in CD4 T cell restoration failure?

- **Fibrosis** blocks normal cell trafficking, communication e.g. access to IL-7: needed for T cell homeostasis.

- **Cytokines** - IL-1β drives memory CD4 T cell cycling.

- **Cytokines** IL-1β, IL-6 and Interferon α block CD4 cell responses to IL-7 that include:
  - Bcl2 (prosurvival)
  - α4β7 (gut repopulation)

Zeng, Haase, Schacker 2012

Shive et al J Inf Dis ‘14
Nguyen et al J Leuk Biol ‘15
Soluble markers of inflammation/coagulation predict morbid events in treated HIV infection with controlled viremia

<table>
<thead>
<tr>
<th>Pre-event Marker</th>
<th>Odds Ratio per 1 IQR increase</th>
<th>P Value</th>
<th>OR for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td>IL6</td>
<td>Unadjusted</td>
<td>2.58 (1.91-3.48)</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>2.48 (1.83-3.35)</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>IP-10</td>
<td>Unadjusted</td>
<td>1.49 (1.16-1.91)</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.42 (1.10-1.84)</td>
<td>0.007*</td>
</tr>
<tr>
<td>sTNFr-I</td>
<td>Unadjusted</td>
<td>1.99 (1.49-2.66)</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.94 (1.45-2.60)</td>
<td>&lt;.001**</td>
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<tr>
<td>sTNFr-II</td>
<td>Unadjusted</td>
<td>1.88 (1.44-2.46)</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.81 (1.38-2.38)</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>Soluble CD14</td>
<td>Unadjusted</td>
<td>1.74 (1.29-2.35)</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.67 (1.23-2.27)</td>
<td>&lt;.001**</td>
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<tr>
<td>D-Dimer</td>
<td>Unadjusted</td>
<td>2.41 (1.78-3.27)</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>2.38 (1.75-3.25)</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>CD8+ %DR+38+</td>
<td>Unadjusted</td>
<td>1.06 (0.88-1.28)</td>
<td>0.516</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>0.98 (0.80-1.20)</td>
<td>0.863</td>
</tr>
</tbody>
</table>

*Similar findings by Hunt et al JID ‘14

**Adjusted by CD4 count
There is an inflammatory “soup” that is linked to morbid events in treated HIV infection so:

1. What is driving inflammation and coagulation in treated HIV infection?
2. How do these things cause disease? (or do they?)
3. Which (if any) of these elements is on the causal pathway of sickness; which are “bystanders”?  
4. What are the actual mechanisms responsible for these morbid events?
5. Are the drivers of different morbid outcomes events (e.g. cardiovascular events and malignancies) the same?
6. How do we untangle the relationships among these elements to determine who is doing what?
Things worth remembering

• Cytokines are “messengers” made to facilitate/mediate communications between cells
• They are generated locally and work locally
• Their concentrations typically fall with the cube of the distance from their source
• Their presence in serum/plasma largely reflects their “leakage” from local sites of production
• We don’t have a good sense as to the tissue source of cytokines that we measure in plasma
• We only measure what we measure
Residual HIV production

HIV-associated fat Metabolic syndrome

Copathogens e.g. CMV, HCV

Inflammation

- ↑ Endothelium adhesion
- ↑ Monocyte activation
- Dyslipidemia
- Hypercoagulation/thrombotic events
- Endothelial dysfunction

Homeostatic Response

Treg loss, dysfunction

(Modified from S. Deeks)
How to block inflammation and decrease morbidity in treated HIV infection?

The Challenges:

• Ordinarily we prefer to block the drivers of a pathogenic process at its upstream source, but.....
• If there are multiple drivers of inflammation in treated HIV infection, targeting a single process may be futile!
• We may need to study thousands to have measurable impact on occurrence of morbid events
• If there are common “downstream” mediators of pathogenesis, perhaps we can interfere at that level?
Targeting putative upstream drivers of inflammation/activation has had only modest effect (or no effect) in treated HIV infection

- Sevalemer or Rifaxamin to block translocation of gut microbial products (Sandler JID’14; Tenorio, JID ‘15)
- Chloroquine to block endosomal toll like receptor signaling (Jacobson AIDS Res Hum Retroviruses ‘16)
- Aspirin to block platelet aggregation (O’Brien Open Forum ID ‘17)
- Gancyclovir to decrease CMV replication? (Hunt JID ‘11)
- Treatment of Hepatitis C?
Not clear if blocking any single putative upstream driver of “activation/inflammation” will have impact on morbid outcomes
Might we do better if we target and block downstream mediators of morbidity?

- Methotrexate? (ACTG 5314 results at CROI 2018?)
- IL-6 inhibition? (CWRU trial just completed)
- Statins? (e.g. REPRIEVE - ACTG 5332)
- IL-1 inhibition? (as per Cantos?)
- Blocking JAK/STAT signals (e.g. with Ruxolitinib – ACTG 5366 – ongoing)
In the meantime how, do we “test a concept”?

- CD4 monitoring may not suffice
  - But it’s a start
- Consider a combined readouts of:
  - Increasing CD4 T cell numbers
  - A decreased systemic inflammatory signal?
  - An improved vaccine response?
  - A functional monitoring of intervention target?
  - And remember, it is plausible that different “useful” interventions may selectively affect one readout and not another
Stability of an HIV reservoir in Resting Memory CD4 T Cells

$T_{1/2} = 44$ months
Eradication time $= 73$ years

Key Barriers to HIV Cure

• Latency
  – Little death/turnover of latently infected cells
  – Poor targets for ART, for antiviral defenses

• Sites of persistence may be protected from ART, from host defenses

• Stupid virologists who can’t measure replication competent virus without exsanguinating my patients!!
Treatment strategies should be considered in the context of:

- Plausibility
- Precedent
- Scalability
- Durability
- Tolerability
- Limitations

- “should it work?”
- “does it work?”
- “for how many could it work?”
- “for how long does it work?”
- “can we stand it?”
- “what’s the downside?”
Strategies for cure

1. Promote viral expression from latency and knock off virus expressing cells ("shock and kill")
2. Render viruses inexpressible - "locked in place"
3. Find a marker that selectively identifies latently infected cells and target those cells for destruction (e.g., using monoclonal antibodies).
4. Kill immune cells non-selectively, eliminating reservoir(s) allowing (or promoting) immune restoration under ART
5. Mobilize antiviral host immune defenses
6. Target host elements used for persistence  
   e.g. blocking or disabling checkpoint elements (PD-1, CTLA-4)
7. Render cells "resistant" to HIV
8. Try something that you don’t know how it works!
Strategies for cure

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Trying something that you don’t know how it works!

• Treating SIV infected macaques with antibody to α4β7 (Vedolizumab) allowed sustained control of SIV replication after ART withdrawn (Byareddy, Science ‘16)

• Mechanism not clear
  – Interference with viral infection of CD4 T cells?
  – Effect on gut homing?
  – Was the viral isolate “less pathogenic”?

• Human trials warranted and ongoing
Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.
The Hutter Case Report

- HIV+ patient (CCR5 wt/Δ32) suppressed on HAART developed AML and failed chemotherapy.
- During first induction, HAART held and viremia rebounded.
- After recurrence, conditioned with: TBI; amsacrine, fludarabine, cytarabine, cyclophosphamide, ATG.
- Allo stem cell transplant (CCR5 Δ32/Δ32 donor); HAART held.
- Mild GVHD (treated with immune suppressants).
- Plasma levels of virus remained undetectable off HAART. No viral RNA or DNA in blood, BM, rectal biopsy, meningeal biopsy.
- CD4 T cell counts rose, serum Abs to gag/pol proteins decreased and T cell responses to HIV fell to background levels.
- He remains well without evidence of virus recurrence more than 9 years after transplant and off antiretrovirals.

Hutter et al NEJM ‘09
Can this outcome be replicated?

Table 1. Men with Human Immunodeficiency Virus Type 1 (HIV-1) Infection Who Received an Allogeneic Transplant from a Stem-Cell Donor Who Was Homozygous for the CCR5 delta32/delta32 Mutation.*

<table>
<thead>
<tr>
<th>Location of Transplantation</th>
<th>Age of Patient yr</th>
<th>Type of Cancer</th>
<th>Type of Graft</th>
<th>Outcome after Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin</td>
<td>40</td>
<td>Acute myeloid leukemia</td>
<td>HLA-matched unrelated</td>
<td>Alive after 7 yr, no viral rebound, no ART</td>
</tr>
<tr>
<td>Utrecht, the Netherlands‡</td>
<td>53</td>
<td>Myelodysplastic syndrome</td>
<td>Combined haploidentical bridge with umbilical-cord blood</td>
<td>Died from relapse of the myelodysplastic syndrome and pneumonia after 2 mo</td>
</tr>
<tr>
<td>Münster, Germany§</td>
<td>51</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-mismatched unrelated</td>
<td>Died from infection after 4 mo</td>
</tr>
<tr>
<td>Essen, Germany¶</td>
<td>30</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-matched unrelated</td>
<td>CXCR4-tropic HIV-1 rebound, died from relapse of non-Hodgkin’s lymphoma after 12 mo</td>
</tr>
<tr>
<td>Minneapolis§</td>
<td>12</td>
<td>Acute lymphoblastic leukemia</td>
<td>Umbilical-cord blood</td>
<td>Died from GVHD after 3 mo</td>
</tr>
<tr>
<td>Santiago, Chile§</td>
<td>46</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>HLA-matched related</td>
<td>Died from pneumonia shortly afterward</td>
</tr>
<tr>
<td>Barcelona§</td>
<td>37</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Combined haploidentical bridge with umbilical-cord blood</td>
<td>Died from relapse of non-Hodgkin’s lymphoma after 3 mo</td>
</tr>
</tbody>
</table>

* ART denotes antiretroviral therapy, and GVHD graft-versus-host disease.
† Data are from Hütter et al.¹
‡ Data are from Kwon et al.³
§ Data are from a personal communication with the transplantation center.
¶ Data are from Kordelas et al.²
So why was Tim Brown (the Berlin Patient) cured?

- A combination of non-selective myeloablation and replacement of the immune repertoire with HIV resistant cells resulted in a “Cure”
- Can’t find virus or viral sequences
- Are all HIV-infected cells gone?
- Maybe, Maybe not: His CD4 T cells are all HIV resistant, any HIV reactivation cannot amplify to produce detectable rebound
Can a similar effect be achieved genetically?

• Without risking morbidity of allo transplantation?
Zinc Finger Nucleases can target host elements and delete them

- Comprised of two domains:
  - Nuclease domain of FokI restriction enzyme
  - Engineered zinc finger protein (ZFP) provides DNA binding specificity
  - Targets 12 nucleotides each for a total of 24-bps of DNA

- ZFN cleaves genomic DNA as a heterodimer within a 5-6 bp gap between the two binding domains

- Repair typically renders a deletion in the target gene

- Introduction of this vector into host target cells or host stem cells can render the target or stem cell progeny resistant to HIV infection (if both gene copies are knocked out)
Adoptive Transfer of CCR5 Gene Modified Autologous CD4+ T-cells

• This immunotherapy is minimally invasive, with no severe adverse events

• It is more accessible than HSCT; it removes the need of searching for compatible donors and the risks associated with GVHD
Infusion of autologous CD4 cells with modified CCR5

Dramatic CD4 rises – mechanism? Modified cells persisted durably (were they protected?)

Tebas et al NEJM ‘14
What if we can render all HSC and their progeny resistant to HIV

• Will knocking out CCR5 work for everyone?
  – There are other ways to help cells become HIV resistant

• Will brain microglia be protected by resistant HSC?

• Are there other sites of viral persistence?

• Will HIV eradication “fix” the residual fibrosis, inflammation and coagulation characterize treated HIV infection?
Engaging participants in Cure Studies?

- Eradication – a high priority for many persons with HIV infection
- Be careful not to promise too much
- Journalistic and Institutional Sensationalism hurt the field
- Remember that ART regimens are now safe, effective, well tolerated and life expectancy can be normal or near normal
- The bar is high!!
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http://www.sciencemag.org/news/2016/01/5-minute-journal-submission

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