Is HIV Infection Associated With Accelerated Aging?

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“The trouble with words is that they have meaning”

Mike Saag
• Progeria
• Werner’s syndrome
• Down’s syndrome
• Progeria
• Werner’s syndrome
• Down’s syndrome
• HIV?
Lifespan 10 years less

Survival from Age 25 Years
N= 3,990

Population controls
Late HAART (2000–2005)
Early HAART (1997–1999)

Presented at the 2nd Int. workshop on HIV & Aging, 27 – 28 Oct 2011, Baltimore, USA

Nadir CD4 predicts life expectancy with ART

<table>
<thead>
<tr>
<th>CD4 Nadir</th>
<th>&lt; 100</th>
<th>100-200</th>
<th>&gt;200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy, years (at age 20)</td>
<td>32</td>
<td>42</td>
<td>50</td>
</tr>
</tbody>
</table>

AIDS Patients Face Downside of Living Longer

59-year-old man with long h/o HIV disease, now with long-term viral suppression on HAART, but suffers from osteoporosis, “frailty” and several chronic illnesses, and feels less robust than 84-year-old father.
Elevated Incidence of Lung Cancer Among HIV-Infected Individuals
Eric A. Engels, Malcolm V. Brock, Jinbo Chen, Craig M. Hooker, Maura Gillison, and Richard D. Moore

INFECTION DISEASES
Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS
Charlotte Lewden, Dominique Salmon, Philippe Morlat, Sylhille Bévilaquatre, Eric Jouglé, Fabrice Bonnet, Laurence Héritier, Dominique Costagliola, Thierry May, Geneviève Chène, and the Mortality 2000 study group

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Immune Response to cART by Age

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Adjusted Hazard OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-&lt;30</td>
<td>ref</td>
</tr>
<tr>
<td>30-&lt;40</td>
<td>0.92 (0.85, 1.00)</td>
</tr>
<tr>
<td>40-&lt;50</td>
<td>0.85 (0.78, 0.92)</td>
</tr>
<tr>
<td>50-&lt;60</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
</tbody>
</table>

Althoff KN et al. AIDS 2010 24:2469-2479

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Lymphoid CD4 populations do not reconstitute with ART
CD4+ T cell subsets in LT were counted as described, and the mean body totals ± 1 SD (indicated by I) from Tables 1 and 2 are shown for uninfected and infected individuals before and after 3 weeks, 6 months, and 12–14 months of triple antiretroviral therapy.

Zhang Z et al. PNAS 1998;95:1154-1159

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HIV is a disease of immune activation

HIV negative

HIV positive
ART-suppressed Patients Have Persistently Abnormal T Cell Activation

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Hunt et al, JID, 2003 and 2008
BB1791, HIV+ on ART and fully suppressed for 13 years
Mucosal Translocation of Bacterial Products
Decreasing Asymptomatic CMV Replication with Valganciclovir Decreases Immune Activation in HIV+ Patients with CD4<350 despite ART

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Hunt et al, CROI, 2010

*P for difference in the change from week 0 between valgan- and placebo-treated groups.
Viral Replication \rightarrow Other Infections \rightarrow Microbial Translocation
\downarrow
Inflammation
\downarrow
Immune Activation

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Viral Replication \rightarrow Other Infections \rightarrow Microbial Translocation
\rightarrow Inflammation
\rightarrow Immune Activation \rightarrow cytokine production
• CNS disease
• Coagulopathy
• bone loss
• lipid abnormalities
• endocrine diseases

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Lymph Node FRC Network

HIV -

HIV +
IL-7 expression in lymph node correlates to loss of FRCn

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Increase in Naive T Cell Apoptosis

$p < 0.0001$

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LT Fibrosis is Associated With Depletion of the Naive CD4+ T Cells

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Viral Replication ➔ Other Infections ➔ Microbial Translocation ➔

Inflammation ➔ Immune Activation ➔ cytokine production ➔

Tissue Damage ➔
• CNS disease
• coagulopathy
• skeletal abnormalities
• bone loss
• lipid abnormalities
• endocrine diseases

ongoing T cell loss
impaired immune reconstitution
Viral replication in Thymus

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Haynes, JCI, 1999
Thymus output decreases with age

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Thymic output in HIV+ vs HIV - individuals matched for age

Thymic epithelial vs perivascular space during normal aging

Morphologic changes of human thymus in early and late stage HIV infection

Supplemental Figure 1.

Viral Replication Other Infections Microbial Translocation

Inflammation

Immune Activation cytokine production

Thymic involution Lymphoid Tissue Damage

ongoing (naive) T cell loss impaired immune reconstitution

• CNS disease
• coagulopathy
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Immunosenescence

• diminished capacity to replenish lymphocytes
• shortened telomeres on lymphocytes
• fewer phagocytes with less function
• impaired NK function
• fewer DC’s with less function
• fewer B cells with less Ig diversity
• reduced T cell repertorie
• impaired proliferative capacity
• increase in inflammatory cytokines
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With a nod to Mike Saag