The Effect of Age on Immune System Reconstitution Among HIV-infected Patients on Antiretroviral Therapy in Resource Limited Settings

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• No conflicts to declare

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Overview

• Background
• Methods
• Results
• Strengths and Limitations
• Discussion
BACKGROUND
HIV in Adults 50 and Older

• Sub-Saharan Africa
  – 2011: 3.1 million (13% of the HIV population)
  – 2040: 9.1 million (27% of the HIV population)
  – Change in age distribution is a result of
    • Increased life expectancy due to antiretroviral therapy
    • New infections among older adults

Hontelez, 2012 AIDS.
Importance

• Most studies of HIV in older adults are from the US and Europe

• Immunologic response to ART may differ in sub-Saharan Africa
  – Higher levels of immune activation due to nutritional deficiencies, endemic parasitic, helminth, and bacterial infections

• Studies of immune response in resource limited settings have mostly been limited to 12 months after ART start

• Need to assess whether the association between age and CD4 cell gain differs by level of baseline immunosuppression
Age and Immune Response

• Studies from the US and Europe
  – Moderately lower immune response in older compared to younger patients (25 cells)
  – No clear age threshold identified
• Studies from resource limited settings
  – Moderately lower immune response (22 cells)
• Two smaller studies
  – No effect of age

Grabar 2004, AIDS; Nogueras 2006 BMC ID; Moore 2007, CID
Balestre 2010, AIDS; Mutevedzi 2011, PLOS ONE; Eduardo 2014, PLOS ONE
Tumbarello 2004, BMC ID; Orlando 2006, HIV Med
METHODS
UMB-IHV was the medical lead in a five member consortium with Catholic Relief Services as the prime grantee

- Technical assistance and training
  - Medical
  - Nursing
  - Laboratory
  - Community Based Treatment Services
  - Program Evaluation and Quality Improvement

- Eight countries, 270 clinics, 700,000 people
Design

• Retrospective open cohort
• Adults who initiated ART
  – August 1, 2004 and September 1, 2012
  – 157 PEPFAR funded and AIDSRelief supported facilities
  – Kenya, Nigeria, Tanzania, and Uganda
Study Sample

• Eligibility criteria
  – HIV positive
  – 20 years of age or older
  – Initiated ART during the study period
  – No previous ART exposure including single-dose nevirapine
• 452,819 ever enrolled
• 158,160 eligible
Analyses for Statistical Inference

• Random effects linear models
• Heterogeneous Toeplitz covariance structure
• Created by adding one variable at a time and assessing changes in the beta estimate for the exposure outcome association, Akaike’s information criterion, and -2 log likelihood
• Mediation analysis for effect of medication adherence
Aim

Estimate the association between age at start of treatment and the mean CD4 cell count at six month intervals after initiation of cART
## Results

<table>
<thead>
<tr>
<th>Baseline CD4 strata, n (%)</th>
<th>≤ 200</th>
<th>201 – 350</th>
<th>&gt; 350</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 29 (n=38,854)</td>
<td>16,054 (41)</td>
<td>29,550 (47)</td>
<td>17,377 (47)</td>
<td>2,227 (44)</td>
</tr>
<tr>
<td>30 – 39 (n=63,220)</td>
<td>11,239 (29)</td>
<td>16,282 (26)</td>
<td>9,596 (26)</td>
<td>1,445 (29)</td>
</tr>
<tr>
<td>40 – 49 (n=36,959)</td>
<td>4,149 (11)</td>
<td>4,680 (7)</td>
<td>2,462 (7)</td>
<td>338 (7)</td>
</tr>
<tr>
<td>50 – 59 (n=14,102)</td>
<td>7,412 (19)</td>
<td>12,708 (20)</td>
<td>7,524 (20)</td>
<td>2,874 (20)</td>
</tr>
<tr>
<td>≥ 60 (n=5,025)</td>
<td>7,412 (19)</td>
<td>12,708 (20)</td>
<td>7,524 (20)</td>
<td>1,015 (20)</td>
</tr>
</tbody>
</table>

| Median CD4 (IQR)          | 197 (97 – 298) | 170 (80 – 270) | 169 (83 – 266) | 176 (91 – 273) | 182 (97 – 277) |
Adjusted* mean CD4 cell count among patients started on ART with a baseline CD4 cell count ≤ 200 by age group

*Adjusted for sex, WHO stage, functional status, ART regimen, TB, and other OIs
Adjusted* mean CD4 cell count among patients started on ART with a baseline CD4 cell count of 201 – 350 by age group

*Adjusted for sex, WHO stage, functional status, ART regimen, TB, and other OIs
Adjusted* mean CD4 cell count among patients started on ART with a baseline CD4 cell count of > 350 by age group

*Adjusted for sex, WHO stage, functional status, ART regimen, TB, and other OIs
Mean Difference Over Time Compared to Patients Age 20 – 29 at ART Start with a baseline CD4 cell count ≤ 200 cells/mm³

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 – 39</td>
<td>0</td>
<td>-21</td>
<td>-24</td>
<td>-28</td>
<td>-24</td>
<td>-24</td>
<td>-26</td>
<td>-24</td>
<td>-24</td>
<td>2</td>
</tr>
<tr>
<td>40 – 49</td>
<td>9</td>
<td>-29</td>
<td>-32</td>
<td>-37</td>
<td>-35</td>
<td>-31</td>
<td>-36</td>
<td>-31</td>
<td>-23</td>
<td></td>
</tr>
</tbody>
</table>
Mean Difference Over Time Compared to Patients Age 20 – 29 at ART Start with a baseline CD4 cell count between 201 – 350 cells/mm³

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 – 49</td>
<td>4</td>
<td>-44</td>
<td>-41</td>
<td>-52</td>
<td>-57</td>
<td>-45</td>
<td>-55</td>
<td>-36</td>
<td>-51</td>
<td></td>
</tr>
<tr>
<td>60+</td>
<td>10</td>
<td>-52</td>
<td>-77</td>
<td>-82</td>
<td>-92</td>
<td>-90</td>
<td>-97</td>
<td>-109</td>
<td>-76</td>
<td></td>
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</tbody>
</table>
Mean Difference Over Time Compared to Patients Age 20 – 29 at ART Start with a baseline CD4 cell count > 350 cells/mm$^3$

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Months</th>
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<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 – 49</td>
<td>-10</td>
<td>-89</td>
<td>-109</td>
<td>-82</td>
<td>-64</td>
<td>-85</td>
<td>-95</td>
<td>-31</td>
<td>-51</td>
<td></td>
</tr>
<tr>
<td>50 – 59</td>
<td>-1</td>
<td>-96</td>
<td>-87</td>
<td>-82</td>
<td>-53</td>
<td>-80</td>
<td>-108</td>
<td>-65</td>
<td>-48</td>
<td></td>
</tr>
<tr>
<td>60+</td>
<td>-7</td>
<td>-89</td>
<td>-85</td>
<td>-91</td>
<td>-154</td>
<td>-104</td>
<td>-73</td>
<td>-114</td>
<td>-74</td>
<td></td>
</tr>
</tbody>
</table>
STRENGTHS & LIMITATIONS
Up and Down Sides

• Down side
  – Data was collected for routine care, not research
  – Probably more missing and incorrect data than in a prospectively designed study
  – Missing information on some important confounders (duration of HIV infection, VL)
  – Selection bias due to death and loss to follow-up
    • Frequency of both was low in this study population (9% and 8%)

• Upside
  – Sensitivity analysis yielded similar and slightly larger differences by age and CD4 strata
  – Methods used may explain why other studies found only moderate differences
  – Follow-up was well beyond the first 12 months where differences tend to be smallest
DISCUSSION
Summary

• Mean CD4 cell count differs over time by age within CD4 strata

• The size of the differences at lower levels of baseline CD4 cell count may not be clinically relevant
  – Over time they translate to staying at risk for certain infections longer

• Among patients starting ART with a CD4 between 201 and 350 cells/mm$^3$, differences increase with age and are clinically meaningful
  – Delays in achieving same level of immune reconstitution are more pronounced

• While large differences were observed in the highest strata of baseline CD4, it is unclear if these differences reflect a clinical disadvantage among older adults
Conclusion

• The removal of CD4 thresholds for the initiation of ART in resource limited settings has the potential to mitigate clinically meaningful age related differences in CD4 cell reconstitution

• 50 may not be the appropriate cut off for “older” individuals living with HIV in resource limited settings
Thank You

• **AIDSRelief**
  Patients and staff of the AR clinics
  AR partners
  Catholic Relief Services
  Futures Group
  International
  Catholic Medical Mission Board
  IMA World Health

• **Co-authors**
  Dr. Mona Baumgarten
  Dr. Samer El-Kamary
  Dr. Jack Guralnik
  Dr. Laura Hungerford
  Dr. Laurence Magder
  Dr. Robert Redfield
Why Stratify by Baseline CD4

- Controlling for baseline CD4 cell count estimates a constant mean difference over time by CD4 category
- The effect of other covariates may differ at different levels of baseline CD4
  - Male sex
    - -43 at ≤ 200, -25 at 201 – 350, -51 at >350, -24 in a model controlling for CD4
  - TB
    - -28 at ≤ 200, -15 at 201 - 350, -4 at >350, -9 in a model controlling for CD4
Mean CD4 cell count controlling for baseline CD4 by age

CD4 cells/mm³

Months after ART start

- 20 - 29
- 30 - 39
- 40 - 49
- 50 - 59
- 60+