Quantifying HIV transmission by age from cross-sectional viral phylogenetic deep sequence data: a population-based study in Rakai, Uganda

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PANGEA webinar, April 2 2020
The cycle of infection in South Africa

- Young women between 16 and 23 acquire HIV from older men. Mean: 18
- Women in their mid-20s infect and are infected by similarly aged men. Mean: 26
- Men between 23 and 35 have a high incidence of HIV. Mean: 27

Figure from: Cohen et al. Science News 2016
Based on de Oliveira et al. Lancet HIV 2017
Figure 2: Maximum likelihood tree for 90 heterosexual transmission clusters

Clusters with a bootstrap support higher than 90% and whose sequences had an intraclade genetic distance of 4.5% or less. 123 women were linked to 103 men in the 90 heterosexual clusters. For better visualisation of the clusters, the tree is represented with proportional branch length transformation. The age (years) of the individuals in each transmission cluster is presented inside the boxes. Grey boxes represent men and red boxes represent women.
HIV phylogenetic analysis, KZN, 2014-2015

<table>
<thead>
<tr>
<th></th>
<th>Men (n=103)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25 years (7.6%)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>25–40 years (40.3%)</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>41–49 years (47.2%)</td>
<td>36</td>
</tr>
<tr>
<td>F&lt;25 linked with M25+:</td>
<td>42/60 = 70% (95% CI 57%-80%)</td>
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</tr>
<tr>
<td>F&lt;25 linked with any M:</td>
<td>average age difference 8.7 yrs</td>
<td></td>
</tr>
<tr>
<td>Suggesting that such age-discordant pairings may be important driver of epidemic</td>
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</tbody>
</table>

Figure 3: All possible pairings from 90 clusters of men and women stratified by age group
The community-based HIV prevalence in each age group is shown in parentheses.
Association HIV incidence with partner age, primarily Durban area, 2009-2012

Figure from: Baltus et al. JAIDS 2015

**TABLE 2. Association Between Age-Disparate Relationship and HIV-1 Infection Within 1 Year**

<table>
<thead>
<tr>
<th></th>
<th>HIV Infections/ Person-Years</th>
<th>HIV Incidence* (95% CI)</th>
<th>Univariate Model† HR (95% CI)</th>
<th>Multivariable Model‡ HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary analysis</strong></td>
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</tr>
<tr>
<td>All participants</td>
<td>243/3343.57</td>
<td>7.27 (6.41 to 8.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary partner &gt;5 yrs older</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67/871.84</td>
<td>7.68 (6.05 to 9.76)</td>
<td>1.10 (0.82 to 1.45)</td>
<td>1.17 (0.88 to 1.56)</td>
</tr>
<tr>
<td>Do not know partner age</td>
<td>5/70.36</td>
<td>7.11 (2.96 to 17.07)</td>
<td>0.97 (0.40 to 2.37)</td>
<td>0.98 (0.40 to 2.39)</td>
</tr>
<tr>
<td>No</td>
<td>171/2401.37</td>
<td>7.12 (6.13 to 8.27)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Primary partner &gt;10 yrs older</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>10/160.43</td>
<td>6.23 (3.35 to 11.58)</td>
<td>0.87 (0.46 to 1.64)</td>
<td>1.01 (0.53 to 1.92)</td>
</tr>
<tr>
<td>Do not know partner age</td>
<td>5/70.36</td>
<td>7.11 (2.96 to 17.07)</td>
<td>0.94 (0.39 to 2.29)</td>
<td>0.94 (0.38 to 2.28)</td>
</tr>
<tr>
<td>No</td>
<td>228/3112.78</td>
<td>7.32 (6.43 to 8.34)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Participants &lt;25 yrs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary partner &gt;5 yrs older</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47/480.43</td>
<td>9.78 (7.35 to 13.02)</td>
<td><strong>1.09 (0.78 to 1.53)</strong></td>
<td><strong>1.13 (0.80 to 1.59)</strong></td>
</tr>
<tr>
<td>Do not know partner age</td>
<td>4/35.30</td>
<td>11.33 (4.25 to 30.19)</td>
<td><strong>1.17 (0.43 to 3.18)</strong></td>
<td><strong>1.13 (0.41 to 3.09)</strong></td>
</tr>
<tr>
<td>No</td>
<td>121/1361.81</td>
<td>8.89 (7.43 to 10.62)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

- VOICE trial, South African sites
- 3789 women, 2143 aged <25
- Suggesting age-discordant relationships may not be driver of epidemic among young women
Incidence estimates may vary by reporting behavior

- Africa Centre DSS, 2004-2015
- 10,260 women, 7,251 reporting age of most recent partner
Association HIV incidence with partner age, KZN, predicted at 2009

- Africa Centre DSS, 2004-2015
- Considering 7251 women reporting age of most recent partner

Figures from: Akullian et al. AIDS 2017
Study objective

• Estimate proportion of infections among women that are attributable to older men using deep-sequence data

• South-eastern Uganda, MRC/UVRI and Rakai
Convenience sample, MRC/UVRI, 2014-2017

Figure from: Dwyer Lindgren et al. Nature 2019

Figure from: Bbosa et al. Viruses 2020
- 72 source-recipient pairs between men and women
- 22 pairs involving female recipient <25 at enrollment

<table>
<thead>
<tr>
<th></th>
<th>Men 18–24 years</th>
<th>Men 25–59 years</th>
<th>Women 18–24 years</th>
<th>Women 25–59 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women 18–24 years</td>
<td>34.7% (17.1%–55.9%)</td>
<td>65.3% (44.1%–82.9%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Women 25–59 years</td>
<td>27.7% (14.1%–45.7%)</td>
<td>72.3% (54.3%–85.9%)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Table from: Bbosa et al. Viruses 2020
Population-based deep-sequence data, Rakai, 2011/08/10-2015/01/30

Figure from: Dwyer Lindgren et al. Nature 2019

Figure from: Ratmann et al. Lancet HIV 2020
Population-based deep-sequence data, Rakai, 2011/08/10-2015/01/30

37,645 age-eligible individuals in 40 communities of the Rakai Community Cohort Study

- 29,116 age-eligible individuals in 36 inland communities
- 8,529 age-eligible individuals in 4 fishing communities
- 19,799 participants
- 6,083 participants
- 2,703 found HIV-positive
- 2,439 found HIV-positive
- 1,803 reported not to be on antiretroviral therapy on first visit
- 2,059 reported not to be on antiretroviral therapy on first visit
- 1,138 with virus deep-sequenced
- 1,514 with virus deep-sequenced
- 293 phylogenetically strongly supported source-recipient pairs

Figure from: Ratmann et al. Lancet HIV 2020
Source-recipient pairs by age

- 96 source-recipient pairs involving women <25
- 57 source-recipient pairs with female recipient <25

From female to male:
- n=120

From male to female:
- n=173

Xi et al. in preparation
Adjusting for sampling cascade

Xi et al. in preparation
Fit of statistical flow model

from female to male

\[ n = 120 \]

from male to female

\[ n = 173 \]

Xi et al. in preparation
50% of infections in women attributed to men aged 26-37
50% of infections in men attributed to women aged 23-34

Xi et al. in preparation
Age of sources by age of recipient

Xi et al. in preparation
Age difference between source and recipient

\[ \text{age of male source} \]

\[ \text{age of female source} \]

\[ \text{ages of female recipients} \]

\[ \text{ages of male recipients} \]
Contribution of age-discordant relationships, male -> female

Male -> female transmission

- Probability vs. age of male source
- Male source is older by at least 5 years or 10 years

Xi et al. in preparation
• Overall, half of all infections among women were attributed to men aged 26-37, whereas half of all infection among men were attributed to women aged 23-34.

• However the mean age of the source case depended on the age of the recipient, and on gender. Women aged >35 were typically infected by younger men. Men aged >25 were typically infected by younger women.

• Most young women (aged 15-24) were infected by men who are >5 years older. An estimated 91% of women aged 15 were infected by men >5 years older, which declined to 73% at age 20, and 51% at age 25.
Youth bulge + rapid increases in prevalence among men and women
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MRC/UVRI Program Staff and Study participants

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Melodie Monod
High performance computing center
Thank you
Contribution of age-discordant relationships, female -> male

Female -> male transmission

- Male recipients are older by at least 5 years or 10 years.

Xi et al. in preparation
An intuitive example (1)

actual transmissions

<table>
<thead>
<tr>
<th>from 1</th>
<th>to 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>50 10</td>
<td></td>
</tr>
<tr>
<td>20 20</td>
<td></td>
</tr>
</tbody>
</table>

observed transmissions

<table>
<thead>
<tr>
<th>from 1</th>
<th>to 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>18 6</td>
<td></td>
</tr>
<tr>
<td>12 20</td>
<td></td>
</tr>
</tbody>
</table>
An intuitive example (2)

Actual transmissions:

<table>
<thead>
<tr>
<th>from 1</th>
<th>to 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Observed transmissions:

<table>
<thead>
<tr>
<th>from 1</th>
<th>to 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
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Sampling:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>60%</td>
<td>100%</td>
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Estimated flows:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>32.1%</td>
<td>10.7%</td>
</tr>
<tr>
<td>[21.4%-45.1%]</td>
<td>[5.0%-21.4%]</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>21.4%</td>
<td>35.7%</td>
</tr>
<tr>
<td>[12.7%-33.8%]</td>
<td>[24.5%-48.8%]</td>
</tr>
</tbody>
</table>