Risk of HIV Transmission with Low Levels of Viremia

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Last Updated: August 17, 2023
No conflicts of interest or relationships to disclose.
Funding for this presentation was made possible by U1OHA29296 from the Human Resources and Services Administration HIV/AIDS Bureau. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. *Any trade/brand names for products mentioned during this presentation are for training and identification purposes only.*
Undetectable = Untransmittable

Source: Prevention Access Campaign, www.preventionaccess.org
Risk of HIV Transmission with Undetectable Viral Load

Statements from CDC

A person with HIV who takes HIV medicine as prescribed and gets and stays virally suppressed or undetectable can stay healthy and will not transmit HIV to their sex partners.

Risk of HIV Transmission With Undetectable Viral Load by Transmission Category

<table>
<thead>
<tr>
<th>Transmission Category</th>
<th>Risk for People Who Keep an Undetectable Viral Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (oral, anal, or vaginal)</td>
<td>Studies have shown no risk of transmission</td>
</tr>
<tr>
<td>Pregnancy, labor, and delivery</td>
<td>1% or less†</td>
</tr>
<tr>
<td>Sharing syringes or other drug injection equipment</td>
<td>Unknown, but likely reduced risk</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>Substantially reduces, but does not eliminate risk.</td>
</tr>
</tbody>
</table>

https://www.cdc.gov/hiv/risk/art/index.html
## HIV Treatment is Prevention

### Summary of Principal Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Definition of Undetectable (HIV RNA level)</th>
<th>Approximate # CLS Acts</th>
<th># Transmissions When Undetectable*</th>
<th>Estimated HIV Transmission Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 052</td>
<td>ART early vs delayed for partner with HIV (1,763 serodifferent couples)</td>
<td>&lt;400 copies/mL</td>
<td>-</td>
<td>Zero</td>
<td>93-96% risk reduction</td>
</tr>
<tr>
<td>Partner 1</td>
<td>888 serodifferent couples (548 MF couples, 350 MM couples); 1,238 CYFU</td>
<td>&lt;200 copies/mL</td>
<td>58,000</td>
<td>Zero</td>
<td>95% CI 0.0-0.3/100 CYFU (0.0-0.84 for MM couples)</td>
</tr>
<tr>
<td>Partner 2</td>
<td>783 serodifferent couples (all MM); 1,596 CYFU</td>
<td>&lt;200 copies/mL</td>
<td>77,000</td>
<td>Zero</td>
<td>95% CI 0.0-0.23/100 CYFU</td>
</tr>
<tr>
<td>Opposites Attract</td>
<td>343 serodifferent couples (all MM); 591 CYFU</td>
<td>&lt;200 copies/mL</td>
<td>17,000</td>
<td>Zero</td>
<td>95% CI 0.0-0.62/100 CYFU</td>
</tr>
</tbody>
</table>

*Genetically linked transmissions in which person with HIV had undetectable viral load

Abbreviations: MM = male-male, MF = male-female, CLS = condomless sex acts, CYFU = couple years of follow up

Sources: Cohen 2011, Cohen 2016, Roger 2016, Bavinton 2017, Rodger 2018
Key Points About “U=U”

• Powerful message that can reduce stigma
• Important to continue STI prevention counseling
• Outstanding question: what is the risk of transmission with low levels of viremia?

Viral load does not equal Value $V \neq V$

The Third $U = \text{UNIVERSAL}$

Source: Prevention Access Campaign, www.preventionaccess.org
• Community-based study of 15,127 persons in rural district of Uganda

• 415 serodifferent, heterosexual couples; 90 seroconversions

“The viral load is the chief predictor of the risk of heterosexual transmission of HIV-1, and transmission is rare among persons with levels of less than 1500 copies of HIV-1 RNA per milliliter.”
HPTN 052: HIV Treatment as Prevention

- Sexually active couples, partner with HIV had baseline CD4 350-550 cell/mm$^3$

- Primary outcome: genetically-linked partner infections

HPTN 052: HIV Treatment as Prevention

78 partner infections

46 before ART

32 after ART start

8 linked:
4 within 90 days of ART
4 after virologic failure

21 unlinked

3 linkage unclear

- 0 linked infections when partner with HIV had stable viral load <1,000 copies/mL
- 1 linked infection with viral load 617 copies/mL (50 days prior to estimated transmission date)

New review: what is the documented risk of HIV transmission with low levels of viremia?
The risk of sexual transmission of HIV in individuals with low-level HIV viraemia: a systematic review

Laura N Broyles, Robert Luo, Debi Boeras, Lara Vojnov

Background The risk of sexual transmission of HIV from individuals with low-level HIV viraemia receiving antiretroviral therapy (ART) has important public health implications, especially in resource-limited settings that use alternatives to plasma-based viral load testing. This Article summarises the evidence related to sexual transmission of HIV at varying HIV viral load levels to inform messaging for people living with HIV, their partners, their health-care providers, and the wider public.

Methods We conducted a systematic review and searched PubMed, MEDLINE, Cochrane Central Register of Controlled Trials, Embase, Conference Proceedings Citation Index-Science, and WHO Global Index Medicus, for work published from Jan 1, 2010 to Nov 17, 2022. Studies were included if they pertained to sexual transmission between serodiscordant couples at various levels of viraemia, the science behind undetectable=untransmittable, or the public health impact of low-level viraemia. Studies were excluded if they did not specify viral load thresholds or a definition for low-level viraemia or did not provide quantitative viral load information for transmission outcomes. Reviews, non-research letters, commentaries, and editorials were excluded. Risk of bias was evaluated using the ROBINS-I framework. Data were extracted and summarised with a focus on HIV sexual transmission at varying HIV viral loads.

Findings 244 studies were identified and eight were included in the analysis, comprising 7762 serodiscordant couples across 25 countries. The certainty of evidence was moderate; the risk of bias was low. Three studies showed no HIV transmission when the partner living with HIV had a viral load less than 200 copies per mL. Across the remaining four prospective studies, there were 323 transmission events; none were in patients considered stably suppressed on ART. Among all studies there were two cases of transmission when the index patient’s (ie, patient with previously diagnosed HIV infection) most recent viral load was less than 1000 copies per mL. However, interpretation of both cases was complicated by long intervals (ie, 50 days and 53 days) between the transmission date and the most recent index viral load result.

Interpretation There is almost zero risk of sexual transmission of HIV with viral loads of less than 1000 copies per mL. These data provide a powerful opportunity to destigmatise HIV and promote adherence to ART through dissemination of this positive public health message. These findings can also promote access to viral load testing in resource-limited settings for all people living with HIV by facilitating uptake of alternative sample types and technologies.

Funding Bill & Melinda Gates Foundation.
• 8 studies of sexual transmission in serodifferent couples that included VL data

• Certainty of evidence: “moderate;” risk of bias: “low”

• 4 cohort studies, 3 RCTs, 1 cross-sectional analysis; total 7,762 couples

• Only 2 transmissions with most recent VL <1,000; however, long intervals (50 days and 53 days) between last VL check and estimated transmission date

• Overall, no definitive evidence of HIV transmission with VL <600, and “incredibly rare” occurrence of possible transmission with VL 600 to 1,000
<table>
<thead>
<tr>
<th>Study name</th>
<th>Countries</th>
<th>Study type</th>
<th>Years</th>
<th>Sex of Couples</th>
<th># of Couples</th>
<th># of Linked Transmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavinton (2018)</td>
<td>Australia, Brazil, Thailand</td>
<td>Cohort</td>
<td>2012-16</td>
<td>100% MM</td>
<td>358</td>
<td>0</td>
</tr>
<tr>
<td>Cohen (2016)</td>
<td>9 countries</td>
<td>RCT</td>
<td>2005-10</td>
<td>97% MF, 3% unspecified</td>
<td>1763</td>
<td>43 delayed ART 3 with early ART</td>
</tr>
<tr>
<td>Fideli (2001)</td>
<td>Zambia</td>
<td>Nested case-control within prospective cohort</td>
<td>1994-2000</td>
<td>100% MF</td>
<td>318</td>
<td>109 couples with transmission and 209 with no transmission*</td>
</tr>
<tr>
<td>Mujugira (2016)</td>
<td>Kenya, Uganda</td>
<td>Analysis of couples in placebo arm of RCT</td>
<td>2008-2012</td>
<td>100% MF</td>
<td>1573</td>
<td>55 no ART; 3 prescribed ART**</td>
</tr>
<tr>
<td>Rodger (2016)</td>
<td>14 European countries</td>
<td>Cohort</td>
<td>2010-14</td>
<td>62% MF, 38% MM</td>
<td>1166</td>
<td>0</td>
</tr>
<tr>
<td>Rodger (2019)</td>
<td>14 European countries</td>
<td>Cohort</td>
<td>2010-17</td>
<td>100% MM</td>
<td>972</td>
<td>0</td>
</tr>
<tr>
<td>Tovanabutra (2002)</td>
<td>Thailand</td>
<td>Cross-sectional</td>
<td>1992-98</td>
<td>100% MF</td>
<td>493</td>
<td>44% of partners seropositive at enrolment***</td>
</tr>
</tbody>
</table>

*N No transmissions when partner with HIV had VL <1,000; 92% of transmissions occurred with VL >10,000

**All 3 within 6 months of ART initiation; 1 could have occurred with VL <1,000, but substantial uncertainty exists (VL 600’s to 800’s, but 53 days between last VL and likely transmission event)

***No transmission occurred with VL <1,000 copies/mL
“There is almost zero risk of sexual transmission of HIV with viral loads of less than 1000 copies per mL. These data provide a powerful opportunity to destigmatise HIV and promote adherence to ART through dissemination of this positive public health message.”
Questions for Discussion

• How do you discuss U=U with patients/clients?

• How do you counsel individuals who take ART but have low-level viremia? How will the systematic review data inform this counseling?

• What data are we still missing?
  - Inclusion of transgender and non-binary individuals in studies
  - Injection drug use/needle sharing
  - Needle stick injury (PEP)
  - Risk with concomitant bacterial STI
  - Innate HIV controllers (low viral load without ART)
  - What else???
Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $3,333,289 with 0% financed with non-governmental sources.

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