Sexual transmission of HIV: a heterogeneous event

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Pietro L. Vernazza, Infectious Diseases, KSSG
St. Gallen, Switzerland
Heterosexual Transmission

Sexual network and HIV

*MMWR, 2000;49:861-864*
Transmission risk per sex contact

**Partner studies**

♀ → ♂ 1-9% partner pos.  
<0.3% per contact

♂ → ♀ 9-18% partner pos  
0.3% per contact

**Anonymous contact**

3.1% - 8.2%

Padian, JAMA 1987  
De Vincenzi, NEJM 1994  
Nicolosi, Epidemiology 1994  
Mastro, AIDS 1994  
Cameron, Lancet 1989
Risk after single sexual exposure

- 422 customers of Kenyan prostitutes
- 293 HIV-neg, prospectively followed
- 12% s/c rate in 12 wk period
  - Non circumcision: OR 8.2 (3-23)
  - GUD OR 4.7 (1.3-17)
- 73 men: only one single contact
  - 8.2% s/c rate (6/73), 43% of uncircumcised

Cameron et al, 1989, Lancet ii:403-7
Mastro study, Thailand

- 1115 military conscripts (21y)
  - 6.9% HIV-pos (n=77)
- Sex with female prostitutes
- mathematical modelling:
  - risk after single contact: 3.1% (2.5-4.0)
  - adjusted for random error in self reported frequency of contact: 5.6% (4.1-7.5%)
- Risk signif. higher in men reporting Hx of STD

Mastro et al, 1994, Lancet 343:204-7
Calculating Transmission Risk in HIV Discordant Couples

Frequently cited: De Vincenzi et al, NEJM, 1994;331:341-6
Selection of Non-Transmittors

HIV-pos.

HIV-neg.

„Friality selection“
Results from Math Modelling

- Transmission risk within partnership highest during early period of sexual relationship

- Transmission best prescribed per partnership, not per contact

- Downs et al, Probability of heterosexual transmission of HIV: Relationship to the number of unprotected sexual contacts. JAIDS, 1996, 11:388
Reasons for Frailty Selection

• Genetic predisposition
  – CCR5 Δ32-deletion variant
  – other chemokine polymorphisms
  – HLA phenotype

• Acquired immunity
  – cell mediated immune response
  – humoral immune response
Immune response in highly exposed seronegative partners

- 12 HIV- partners of HIV-positive
- Frequent unprotected sexual exposure
- Last exposure < 6 months
- No CCR5-deletion mutant
- In vitro p24 stimulation of PBMC
  - Cytokine expression
  - Compared with non-exposed controls

Eyson et al, AIDS 2003, 17:2299–2311
p24 response in SN-exposed

SN-exposed (n=5)  SN-controls (n=11)

Eyson et al, AIDS 2003, 17:2299–2311
IgA in Exposed Seronegative

Mazzoli et al, 1999, JID
Acquired protective Immunity?
Phylogenetic Relationship of HIV-1 C2-V5 Consensus Sequences of LSC, their Long-term Sexual Partners and Control Sequences (n=82) of Subtype B HIV-1 from the Los Alamos Database Published from 1997-2002

Zhu et al, CROI 2004
Pairwise Distance Distributions of HIV-1 C2-V5 Sequences

US (n=82, published 1997-2002)

P<0.001

Genetic distance (%)

LSC63 vs. PX63
LSC48 vs. PX48
LSC28 vs. PX28
LSC59 vs. PX59
Conclusion

• HIV transmission risk highly heterogenous
• Immune response may reduce risk
Sexual Transmission of HIV

Infectiousness

Susceptibility

Sexual contact
Sexual Transmission of HIV

- Risk of transmission enhanced with:
  - Low CD4 counts
  - Symptomatic disease
  - High blood viral load
  - Genital inflammation
  - PHI

$r = 0.5-0.6$
VL and HIV-Transmission

- Rakai (Uganda)
- 453 HIV-disk. couples
- 11.6 % TR / year

Quinn et al, NEJM, 2000,342:921
HIV- Primary Infection

![Graph showing the correlation between HIV-RNA in blood and semen.](image)

Vernazza et al., CROI, 2000; Abst 564

$r = 0.80$

$P < 0.001$
Cervical viral load and HAART

Cu-Uvin et al., AIDS, 2000; 14:415
HIV in Semen and Risk of Tx

Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model

Hrishikesh Chakraborty, Pranab K. Sen\textsuperscript{a}, Ronald W. Helms\textsuperscript{a}, Pietro L. Vernazza\textsuperscript{b}, Susan A. Fiscus\textsuperscript{c}, Joseph J. Eron\textsuperscript{d}, Bruce K. Patterson\textsuperscript{e}, Robert W. Coombs\textsuperscript{f}, John N. Krieger\textsuperscript{g} and Myron S. Cohen\textsuperscript{d}
HIV in semen & risk per coital act

Probability

Log_{10} Seminal viral load in one ejaculate

- NSI 70%
- NSI 100%
- NSI 50%

Chakraborty et al. AIDS 2001,15: 621-7
Risk per coital act in couples

- 235 monogamous, discordant couples, Uganda
HIV in Semen during HAART

Vernazza et al., AIDS, 2000; 14:117-21

No Therapy (control)  n=55
HAART, RNA<400  n=114

p<0.0001
HIV in Semen during HAART

Vernazza et al., AIDS, 2000; 14:117-21
Decline in infectivity* w. HAART

- HIV incidence in SF-MSM during 1994-1999

<table>
<thead>
<tr>
<th>Time period at risk for infection</th>
<th>No. of Subjects</th>
<th>Infectivity</th>
<th>Mean no. of unprotected RAI partners</th>
<th>Crude incidence rate/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/94 – 9/95</td>
<td>534</td>
<td>0.12</td>
<td>0.6</td>
<td>1.36%</td>
</tr>
<tr>
<td>9/95 – 11/96</td>
<td>481</td>
<td></td>
<td>0.75</td>
<td>1.29%</td>
</tr>
<tr>
<td>11/96 – 9/97</td>
<td>445</td>
<td>0.048</td>
<td>0.8</td>
<td>0.78%</td>
</tr>
<tr>
<td>9/97 – 3/99</td>
<td>320</td>
<td></td>
<td>1.3</td>
<td>1.02%</td>
</tr>
</tbody>
</table>

* per-partnership probability of trx from HIV+ partner

- 60%

Conclusion 2

• HIV transmission risk highly heterogenous
• Immune response may reduce risk
• Viral load (genital / blood) most potent predictor of trx risk
Malawi urethritis project: HIV-RNA in semen

Tx of Cervicitis and Shedding of HIV

McClelland et al, AIDS 2001; 15:105-110
Urethritis during HAART (n=24)

Plasma HIV-RNA

- 20
+ 4

Semen HIV-RNA

2 / 20 positive (low level)
4 / 4 positive (high level)

Heterosexual Transmission

Conclusion 3

- HIV transmission risk highly heterogenous
- Immune response may reduce risk
- Viral load (genital / blood) most potent predictor of trx risk
- STDs enhance trx risk
Infectiousness & Susceptibility

Infectiousness Index

Resistance Partner

Weeks

Months
Cave: Treatment interruption

Bernasconi et al, JAIDS, 2001; 27:209–211
Consequences for clinical practice

- STD’s should be carefully monitored
- STD prevention remains a key issue
- Transmission risk likely to be highly variable over time
- Effect of HAART on txm risk