HIV-1 mother-to-child transmission and prevention: success and controversies

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Transmission occurs any time!!

Early Antenatal (<28 wks) 20%

Pregnancy

Labor and Delivery

Late Antenatal (>28 wks to labor) 45-50%

Early Late Postpartum

0-1 mo 1-6 mos 6-24 mos

Breastfeeding ~30-40%
The first decade of Perinatal HIV Clinical Trial Results:
HIV-1 MTCT can be prevented

- **1994 ACTG076 ZDV long**
  - 67% reduction in transmission

- **1998 Thai PHPT-1**
  - AP/IP ZDV trial short
  - 50% reduction in transmission

- **1998 Cote d’Ivoire DITRAME049**
  - short AP/IP ZDV trial
  - 37% reduction in transmission (breastfeeding)

- **1999 PETRA ZDV/3TC trial (6 wk)**
  - 50% reduction with longest arm.
  - 38% reduction with the IP/PP arm

- **1999 HIVNET 012, Uganda sdNVP**
  - 47% reduction in transmission (breastfeeding)

- **2000 Thai Long vs short ZDV**
  - 4% TR in LL (non BF)

- **2002 Cote d’Ivoire DITRAME +1**
  - 6.2% TR< with ZDV & IP/PP NVP

- **2003 Cote d’Ivoire DITRAME +1.1**
  - 4.7% TR: ZDV/3TC+ IP/PP NVP

- **2004: Thai PHPT-2**
  - <2% TR ZDV + NVP IP/PP

- **2004 ++**
  - **2004: Thai PHPT-2**
  - <2% TR ZDV + NVP IP/PP

Presented at the 6th Int. Workshop on HIV Transmission, 14 – 15 July 2011, Rome, Italy
Estimates of new HIV infections in children

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Data source WHO/UNAIDS
Estimated number of children (<15 years) newly infected with HIV | 2009

Total: 370 000 [230 000 – 510 000]

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Is HIV transmission from Mother To Child a selective or stochastic process?

Pregnancy  | Labour Delivery  | Breast feeding
--- | --- | ---
Placenta | Blood Secretions | Milk Blood
Amniotic fluid  |  |  

Only FEW virus variants detected in the newborn!

!! a SELECTIVE barrier ??

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One or few viral variants are transmitted to the child

The transmitted variant is either a minor or a major maternal viral variant.
IntraPartum transmitted variants have shorter variable loops and fewer PNG sites than viruses transmitted InUtero
HIV-1 phenotype: which virus is transmitted?

**R5**
(NSI, Slow/Low)

**X4**
(SI, Rapid/High)

**CD4+ T Lymphocytes**

**Mononuclear Phagocytes**

**CD4+ T-Cell Lines**

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### R5 virus is predominant

<table>
<thead>
<tr>
<th>Mother</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>R5 X6</td>
<td>R5 X6</td>
</tr>
<tr>
<td>R5 X4</td>
<td>R5 X4</td>
</tr>
<tr>
<td>R5 X4 R3</td>
<td>R5 X4 R3</td>
</tr>
</tbody>
</table>

Mother: R5 21 → R5 21
Mother: R5 X6 2 → R5 X6 2
Mother: R5 X4 5 → R5 X4 1
Mother: R5 X4 R3 2 → R5 X4 R3 1

Compiled from Tscherning AIDS Res 2000; Salvatori AIDS Res 2001; Casper JID 2002

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The magnitude of R5 biological variation is vast

From Karlsson, AIDS 2006
The R5broad phenotype is not predictive of mother-to-child transmission...

...but R5broad phenotype is frequently found in children close to birth

Cavarelli et al., PlosOne 2008
Chimeric receptor use correlates with RANTES resistance

$p = 0.043$

RANTES IC50 (ng/ml)

R5 Broad          R5 Narrow

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Cavarelli et al., AIDS 2009
The R5broad phenotype is predictive of early immunological failure in children

**FAST PROGRESSORS**
- Severe immunological failure or early death <12mos
  - R5broad (n=4)
  - R5narrow (n=2)

**SLOW PROGRESSORS**
- Severe immunological failure between 13 to 36 mos
  - R5narrow (n=4)
  - R5broad (n=10)

**Viral phenotype at birth**
- R5narrow (n=5)
- R5broad (n=4)
Pathways of HIV transmission from Mother To Child

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# Risk of Postnatal HIV Infection is Associated with Cumulative HIV RNA Exposure in Breast Milk

(Between 6 Weeks of Age and Estimated Age of HIV Infection)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>P-value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUMULATIVE HIV-RNA exposure in MILK</td>
<td>.04</td>
<td>2.06</td>
<td>1.02-4.16</td>
</tr>
<tr>
<td>Maternal antepartum CD4 cell counts</td>
<td>.37</td>
<td>1.2</td>
<td>0.80-1.81</td>
</tr>
<tr>
<td>Maternal antepartum plasma HIV load</td>
<td>.92</td>
<td>1.05</td>
<td>0.45-2.46</td>
</tr>
<tr>
<td>Duration of MIXED breast feeding</td>
<td>.43</td>
<td>1.04</td>
<td>0.94-1.15</td>
</tr>
<tr>
<td>Male compared to female infants</td>
<td>.23</td>
<td>3.40</td>
<td>0.44-26.40</td>
</tr>
</tbody>
</table>

From Neveu D, Clin Infect Dis 2011
HIV-1 infection at mucosal sites

Mucosal lesion

Alternative Receptor (Gal Cer)

Fc receptor

Transcytosis

M cells

Lumen

Epithelial cells

Sub mucosa

Monocytes/macrophages

T Lymphocytes

Dendritic Cells

Infected Cells

Free virus

Adapted from van de Perre
Acknowledgments

DIBIT – VET
Mariangela Cavarelli
Stefania Dispineri
Chiara Foglieni
Lara Mainetti
Monica Tolazzi

IFOM, Milan
Maria Rescigno

Lund University, Lund
Eva Maria Fenyo
Ingrid Karlsson

Clinica Pediatrica DeMarchi, Milan
Anna Plebani

Presented at the 6th Int. Workshop on HIV Transmission, 14 – 15 July 2011, Rome, Italy