Primary HIV Infection in Antenatal and Postnatal Women, Northern KwaZulu-Natal, South Africa

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South African Supervisor
Professor Marie-Louise Newell (UCL; UKZN)

Aberdeen Supervisors
Professor Cairns Smith
Dr Julia Hussein
Dr Etheline Enoch
Background

• MB ChB Aberdeen 1993
• UK Specialist Register 2007
  – Infectious Diseases and Microbiology

• Trial Coordinator and Physician, Africa Centre, SA
  – WHO Coordinated Multicentre “Kesho Bora” Study
  – Impact of HAART during Pregnancy and Breastfeeding on Mother-To-Child-Transmission of HIV and Mother’s Health

• MD:- “Primary HIV Infection in Antenatal and Postpartum Women”
The Africa Centre

Mtubatuba

Durban
Africa Centre Demographic Surveillance Area

90,000 Zulu Speaking people
Rural/ peri-urban
Complex, fluid households
Scattered homesteads
77% piped water/toilet facilities
70% Unemployment
Mother-to-Child-Transmission of HIV

BACKGROUND
Mother to Child Transmission of HIV

- 35% transmission risk in mixed feeding populations
  - 5% In Utero
  - 15% Intrapartum
  - 15% Postpartum through breast feeding

- Factors Increasing vertical transmission
  - Low maternal CD4,
  - High Viral load,
  - STIs,
  - Vaginal delivery,
  - Duration of breastfeeding,
  - Mastitis,
  - Mixed feeding
Prevention of Mother to Child Transmission (PMTCT)

• Western Approach
  – Triple therapy
  – Caesarian Section if viral load not suppressed
  – Avoidance of breastfeeding

• Developing Country approach
  - Zidovudine 28/40; Nevirapine stat; 1/52 Combivir
  - Infant Prophylaxis: Nevirapine stat; 1/52 ZDV
  - Promotion of Exclusive Breastfeeding (EBF)
  - Rapid cessation of EBF at 6 months
Future prospects for PMTCT

• Kesho Bora/ BAN studies
  – Triple therapy during breastfeeding
• Infant Prophylaxis
  – Lamivudine
  – Nevirapine
INTRODUCTION

Primary HIV Infection (PHI) in Antenatal and Postpartum Women
Primary HIV Infection (PHI) in Antenatal and Postpartum Women

• Epidemiology
  – Incidence
  – Socio-economic Associations
• Detection of PHI in Pregnancy
• Molecular Aspects of Vertical Transmission
Assessment of Incidence of PHI

- Prospective, longitudinal studies
- Cross-sectional; Changes in prevalence over time
- Laboratory tests to detect recent infections
  - Eg Capture BED Assay
Epidemiology of PHI

• Incidence
  – Longitudinal- 2.3-3.8/100 woman years

• Risk factors
  – Marital Status;
  – Number of sexual partners;
  – Report of an STD;
  – HSV2 serology;
  – Irregular condom use
  – ??Pregnancy

• Socio-economic
  – Education
    • Higher education ↓ risk of HIV acquisition by 7% /year (S.Africa)
    • Higher education ↑ RR3.14 in pregnant women (Uganda)
  – Income
    • Middle 40% income bracket associated with 72% ↑ risk (S.Africa)

• Geographic
  – Decreasing distance from a primary road
  – Increasing distance from a government health clinic
Primary HIV Infection in Antenatal and Postnatal Women

AIMS
Aims

1. Epidemiology
   1. What is the Incidence of PHI in antenatal and postnatal women Northern KwaZulu-Natal?
   2. Who are these women?
      1. Socio-economically
      2. Geographically
   3. How accurate is the Capture BED assay in determining incidence in this population?

2. Detection of Primary Infection

3. Vertical Transmission
Epidemiology of PHI in Antenatal and Postnatal Women

METHODS (1)
 Archived Dataset

• Vertical Transmission Study (2001-05)
  – Recruited HIV infected and uninfected antenatal women
  – Observational cohort study which demonstrated the benefits of exclusive breastfeeding over mixed feeding

Coovadia *et al.* Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study
*Lancet* 2007;369:1107-1116

### Vertical Transmission during the VTS Study

<table>
<thead>
<tr>
<th>HIV-Infected Mothers (n=1708):</th>
<th>127</th>
<th>70</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Perinatal period</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Postnatal period</em></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Unknown timing of infection</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV “Negative” mothers (n=1623):</th>
<th>1</th>
<th>18</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Perinatal period</em></td>
<td></td>
<td></td>
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<tr>
<td><em>Postnatal period</em></td>
<td></td>
<td></td>
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<tr>
<td><em>Unknown timing of infection</em></td>
<td></td>
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</tbody>
</table>
## Archived Sample and Data Availability

<table>
<thead>
<tr>
<th>Sample</th>
<th>ANTEnatal</th>
<th>POSTnatal</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>INFANT (DBS)</td>
<td>A/N visit</td>
<td>&lt;72 hrs</td>
<td>6 wk</td>
<td>10 wk</td>
<td>14 wk</td>
<td>18 wk</td>
<td>22 wk</td>
<td>26 wk</td>
<td>9 mt</td>
<td>12 mt</td>
<td>15 mt</td>
<td>18 mt</td>
<td>21 mt</td>
<td>24 mt</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MOTHER Breastmilk</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>MOTHER Blood</td>
<td>X Serum/DBS</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>X Serum</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- Socio-economic data on participating women
  - Income source
  - Education
  - Water Source
  - Toileting facilities
Incidence of PHI and socio-economic associations
(Ruth Bland, James Ndirangu, Marie-Louise Newell)

• Antenatal HIV antibody negative women
• Maternal 6 month postnatal sample.
  – HIV 3rd generation Elisa
• Socioeconomic Associations
  – Water source; toileting; education; source of income;
Epidemiology of PHI in Antenatal and Postnatal Women

RESULTS (1)
Incidence

- 36/875 who provided a 6 month postpartum sample
  - Crude incidence 5.2/100 (95% CI 2.3-11.6) women years
# Socio-economic Associations

Comparing antenatal women who recently acquired HIV with those who remained HIV negative

<table>
<thead>
<tr>
<th>Variables</th>
<th>HIV-positive (n=36)</th>
<th>HIV-Negative (n=839)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Maternal age</strong></td>
<td>36 21 (16-38)</td>
<td>839 21 (15-52)</td>
<td>0.689</td>
</tr>
<tr>
<td><strong>Maternal Education</strong></td>
<td>34</td>
<td>830</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (3.0%)</td>
<td>45 (5.4%)</td>
<td>0.543</td>
</tr>
<tr>
<td>Primary</td>
<td>15 (45.5%)</td>
<td>292 (35.2%)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>17 (51.5%)</td>
<td>493 (59.4%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3 ()</td>
<td>9 ()</td>
<td></td>
</tr>
<tr>
<td><strong>Water supply</strong></td>
<td>36</td>
<td>836</td>
<td></td>
</tr>
<tr>
<td>Piped water</td>
<td>24 (66.7%)</td>
<td>571 (68.3%)</td>
<td>0.856</td>
</tr>
<tr>
<td>Other</td>
<td>12 (33.3%)</td>
<td>265 (31.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Toilet Type</strong></td>
<td>36</td>
<td>836</td>
<td></td>
</tr>
<tr>
<td>Flush</td>
<td>27 (75.0%)</td>
<td>724 (86.6%)</td>
<td>0.079</td>
</tr>
<tr>
<td>Other</td>
<td>9 (25.0%)</td>
<td>112 (13.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Main Income Provider</strong></td>
<td>36</td>
<td>836</td>
<td></td>
</tr>
<tr>
<td>Household Member Away</td>
<td>30 (83.3%)</td>
<td>709 (84.8%)</td>
<td>0.221</td>
</tr>
<tr>
<td>Household Member at home</td>
<td>1 (2.8%)</td>
<td>27 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>Self</td>
<td>5 (13.9%)</td>
<td>52 (6.2%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>46 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Refuses to disclose/Don't know</td>
<td>0</td>
<td>2 (0.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• PHI in this population is common.

• Need to do a Logistic Regression

• However, results will probably not contradict previous literature showing effect of increased education.
FUTURE WORK
Assessment of C-BED assay and mapping of incident cases
(Till Barnighausen, Frank Tanser, Marie-Louise Newell)

- c-BED Assay Assessment
- Mapping of Incident Cases
Primary Infection in Antenatal and Postnatal Women

DETECTION OF PHI
Primary HIV Infection

![Graph showing the stages of HIV infection and the detection of various markers over time.](image)
Detection of PHI in Antenatal women

- Single Antenatal HIV antibody
- Repeat Rapid test (different kit)
- 2\textsuperscript{nd} Antenatal test in 3\textsuperscript{rd} trimester
- Intrapartum testing
- Nucleic Acid Amplification
  - Pooling

DISCARD
Dried Blood Spots (DBS)

- Useful in resource-poor settings
  - preparation
  - storage
  - transport
- 50-100μl
- DBS DNA exceptionally stable
- DBS RNA stable up to 1 year at room temperature
Aims

1. Epidemiology

2. Detection of Primary Infection
   1. How many PHIs can be detected by Intrapartum testing?
   2. How many Antenatal PHIs can be detected using Nucleic Acid Amplification Techniques (NAAT)?
   3. Can Dried Blood Spots (DBS) be pooled together to screen for PHI?
   4. Modelling Exercise:- How cost-effective at a programmatic level is
      1. Pooled antenatal NAAT testing
      2. Intrapartum testing

3. Molecular Virological aspects of Vertical Transmission
Assessment of Intrapartum Testing in the Detection of PHI

(Johannes Viljoen, Siva Danaviah, Marie-Louise Newell)

- Assessment of Intrapartum testing (Breastmilk delivery HIV antibody)
Assessment of Antenatal NAAT Testing in the Detection of PHI

(Johannes Viljoen, Siva Danaviah, Marie-Louise Newell)

(1) NAAT testing of antenatal booking samples

(2) DBS pooling project
  Serial “dilutions” of spiked blood samples using known standards

(3) Cost-effectiveness Analysis
  - (a) NAAT testing
  - (b) Intrapartum testing
Primary Infection in Antenatal and Postnatal Women

MOLECULAR ASPECTS OF PHI
Virological Aspects of Mother-to-Child Transmission

(Tulio de Oliveria, Siva Danaviah, Johannes Viljoen, Marie-Louise Newell)

- Vertical Infection caused by small number of HIV variants
- Transmitted virus have an advantage
  - Crossing mucosal barriers
  - Infecting/replicating in cells
  - CCR5 tropic
- Cell free virus or Cell associated virus
- Chronic Infection versus Primary Infection
Aims

1. Epidemiology
2. Detection of Primary Infection
3. Vertical Transmission
   1. How many infants are infected as a result of Primary Infection?
   2. Does vertical infection occur as a result of single or multiple HIV viral variants?
   3. Which compartment does the infection come from?
   4. What is the timing of Vertical Transmission in Primary Infection?
      1. Primary infection versus established HIV infection
      2. Evolutionary Sequence analysis
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<th>POSTNATAL</th>
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<tbody>
<tr>
<td></td>
<td>A/N visit</td>
<td>&lt;72 hrs</td>
</tr>
<tr>
<td>INFANT (DBS)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>MOTHER Breastmilk</td>
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<td>MOTHER Blood</td>
<td>X Serum/DBS</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Methods
(Tulio de Oliveria, Siva Danaviah, Johannes Viljoen, Marie-Louise Newell)

- 8 Infected Mother-Infant pairs
- Nucleic acid extraction
  - Mother (antenatal, post partum)
    • Blood
    • Breastmilk
  - Infant (4 time points)
    • Blood
- Single Gene Amplification of highly variable regions
  - Pol, env from different HIV RNA variants
- Creation of a phylogenetic tree
- Evolutionary Sequence Analysis
CONCLUSION
ACKNOWLEDGEMENTS

AC LAB: GREG, GEORGE, SHARON, SURESHMI
DATA SETS: COLIN NEWELL, RUTH BLAND
(1) Epidemiology of PHI - Methodology of incidence assessment

- Cross-sectional; Changes in prevalence over time
  - Relies on mortality assumptions of HIV-infected individuals
  - Difficult to measure; may change quickly
- Laboratory tests to detect recent infections (May not produce valid results especially in high prevalence settings)
  - Eg Capture BED Assay

- Prospective, longitudinal studies
  - Gold standard
(2) Epidemiology of PHI

- Incidence
  - Longitudinal- Crude rates 2.3-3.8/100 woman years (FP clinic)
  - Horizontal cBED- 1.8/100 person years (Uganda)

- Risk factors
  - Marital Status (significance varies with society examined); Female; Number of sexual partners; Report of an STD; HSV2 serology; condom use
  - ??Pregnancy

- Socio-economic
  - Longitudinal study better than cross-sectional
  - Education
    - 1 year additional education reduced the risk of HIV acquisition by 7% (S.Africa)
    - Higher education ↑RR3.14 in pregnant women (Uganda)
  - Income
    - Middle 40% income bracket associated with 72%↑ risk (S.Africa)

- Geographic
  - Decreasing distance from a primary road
  - Increasing distance from a government health clinic
## Socio-economic Associations

Comparing antenatally negative mothers who provided a post natal sample with those who did not

<table>
<thead>
<tr>
<th>Variables</th>
<th>Provided a sample (n=897)</th>
<th>Did not provide a sample (n=765)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Maternal age</strong></td>
<td>897 21 (18-28)</td>
<td>765 21 (18-26)</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal Education</strong></td>
<td>884</td>
<td>755</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>46 (5.2%)</td>
<td>33 (4.4%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Primary</td>
<td>314 (35.5%)</td>
<td>227 (30.0%)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>524 (59.3%)</td>
<td>495 (65.6%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>13 ()</td>
<td>11 ()</td>
<td></td>
</tr>
<tr>
<td><strong>Water supply</strong></td>
<td>894</td>
<td>556</td>
<td></td>
</tr>
<tr>
<td>Piped water</td>
<td>611 (68.3%)</td>
<td>413 (74.3%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Other</td>
<td>283 (31.4%)</td>
<td>143 (25.7%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3 ()</td>
<td>209 ()</td>
<td></td>
</tr>
<tr>
<td><strong>Toilet Type</strong></td>
<td>894</td>
<td>556</td>
<td></td>
</tr>
<tr>
<td>Flush</td>
<td>124 (13.9%)</td>
<td>422 (75.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>770 (86.1%)</td>
<td>134 (24.1%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3 ()</td>
<td>209 ()</td>
<td></td>
</tr>
<tr>
<td><strong>Main Income Provider</strong></td>
<td>894</td>
<td>556</td>
<td></td>
</tr>
<tr>
<td>Household Member Away</td>
<td>759 (84.9%)</td>
<td>478 (85.9%)</td>
<td>0.654</td>
</tr>
<tr>
<td>Household Member at home</td>
<td>28 (3.1%)</td>
<td>21 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Self</td>
<td>57 (6.4%)</td>
<td>32 (5.7%)</td>
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<tr>
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<td>3 ()</td>
<td>209 ()</td>
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