I. Transmission Biology: How Does Transmission Occur and How Can it be Prevented?
- Breastfeeding RCT
- Viral Correlates
- Antiretrovirals
- Host Defense

II. Infants and Mothers: Do Infants and Mothers Face Unique Challenges with HIV?
- Infant Pathogenesis
- Maternal Pathogenesis

III. Translation: How Can we Translate Research to Practice?
- Program Evaluation
- Facilitators
I. Transmission Biology

- *How does transmission occur and how can it be prevented?*
Breastfeeding RCT

- What is the risk of breastmilk HIV transmission?
- What is the best way to prevent breastmilk HIV transmission?
Breastfeeding vs. Formula Feeding RCT
Nduati, Kreiss JAMA 2000

To compare risk of HIV or death in infants of HIV-infected mothers randomized to breast or formula

Context

Rationale
- Only way to estimate breastmilk transmission risk
- Competing risks: breastmilk HIV transmission vs. formula mortality
Ethical Issues

Breastfeeding vs. Formula Feeding Randomized Clinical Trial

- Consent
- Confidentiality
- Standard of care
- Equipoise
- Randomization

Hannah Kippax “Absolute Indecision06”
Architecture of the Study
Breastfeeding vs. Formula Feeding Randomized Clinical Trial

Accepted HIV VCT
16,529

HIV positive
2,315 (14%)

Returned for results
1,708 (74%)

Enrolled
425

Pregnancy
Delivery
Birth
2 year follow-up
2 year follow-up

MCH1
MCH2
MCH3
MCH4

KNH
## Characteristics of Study Population

**Breastfeeding vs. Formula Feeding Randomized Clinical Trial**

|                      | BF  
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>N=212</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FF</td>
</tr>
<tr>
<td></td>
<td>N=213</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Age yrs</td>
<td>23 (16-39)</td>
</tr>
<tr>
<td></td>
<td>23 (15-40)</td>
</tr>
<tr>
<td>Married</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>78%</td>
</tr>
<tr>
<td>CD4 count</td>
<td>399 (10-1165)</td>
</tr>
<tr>
<td></td>
<td>415 (15-1209)</td>
</tr>
<tr>
<td>Log HIV RNA</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td>Cesarean</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>Birthweight</td>
<td>3.2 (1.1-4.4)</td>
</tr>
<tr>
<td></td>
<td>3.2 (1.0-4.2)</td>
</tr>
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</table>
Transmission and Mortality Risk
Nduati JAMA 2000

- Risk of breastmilk HIV transmission 16%
- Formula fed infants lower risk of HIV or death 30% vs. 42%
Breastfeeding Studies and Policy After 2000

- Antiretrovirals make breastfeeding safe
  - With ART no FF benefit in Botswana RCT *Thior JAMA 2006*

- FF implementation
  - Program may not assure safety net for FF
Viral Correlates

- How does maternal virus influence transmission?
Viral Correlates

- Plasma, cervical, vaginal and breastmilk HIV
- Correlates of compartmental HIV
  - Low CD4, high plasma VL
Viral Correlates of Transmission


- Adjusted for plasma VL
  - Cervical HIV aOR 2.4 p = 0.004
  - Vaginal HIV aOR 2.7 p = 0.03

- Breastmilk HIV
- Mastitis, GUD

Plasma VL

- Breach
- Genital or BM VL

TRANSMISSION

Age months

Log BM VL

No Transmission
Transmission
Short-Course Antiretroviral Mechanism

- How do short-course ARVs prevent transmission?
Short-course Antiretroviral Mechanism

Three Phase II RCTs

- Compartmental HIV shedding
  - ZDV: genital HIV
  - NVP vs. ZDV: breastmilk HIV
  - NVP/ZDV vs. HAART: breastmilk HIV

- Frequent sampling
  - every 2-3 days
Plasma, cervical, and vaginal HIV after zidovudine

*Mbori-Ngacha, J Virol 2003*
Breast milk HIV-1 suppression and decreased transmission: a randomized trial comparing HIVNET 012 nevirapine versus short-course zidovudine

Michael H. Chung\textsuperscript{a}, James N. Kiarie\textsuperscript{b}, Barbra A. Richardson\textsuperscript{c,d}, Dara A. Lehman\textsuperscript{e,f}, Julie Overbaugh\textsuperscript{d,f} and Grace C. John-Stewart\textsuperscript{a,g}
Highly active antiretroviral therapy versus zidovudine/nevirapine effects on early breast milk HIV type-1 RNA: a Phase II randomized clinical trial

Michael H Chung1*, James N Kiaria2, Barbra A Richardson3,4, Dara A Lehman5,6, Julie Overbaugh4,6, John Kinuthia2, Francis Njiri2 and Grace C John-Stewart1,7

Plasma HIV-1 RNA

Breast milk HIV-1 RNA

HAART

ZDV/NVP

Antiviral Ther 2008
Short-course ARV Mechanism

- Compartmental
- ~1 log decrease
- Regimen differences
- Exposure prophylaxis

### HIV-1 transmission risk

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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<tr>
<td>&lt;3.5, NVP</td>
<td>2.5</td>
<td>1.3, 5.0</td>
<td>0.01</td>
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<tr>
<td>&gt;3.5, NVP</td>
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</tr>
<tr>
<td>&lt;3.5, no NVP</td>
<td>0.12</td>
<td>0.02, 0.97</td>
<td>0.05</td>
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<tr>
<td>&gt;3.5, no NVP</td>
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</tr>
</tbody>
</table>

Chung, JAIDS 2006
Host Defenses

- Why do some infants escape HIV infection?
Host Determinants of Non-Transmission
CTL Study 1999-2005

- HIV-1 specific cellular immune responses

- 36,844 offered
- 32,424 HIV VCT
- 4,578 HIV positive (14%)
- 3,286 results
- 1,432 KNH
- 510
Infant HIV Specific Responses
John-Stewart Mbori-Ngacha, Lohman-Payne JID 2009

- Infant HIV specific immune responses
  - 12% of HIV uninfected infants at 1 month
  - No transmission in those with responses (7% in those without)
- Some sustained, broad and high magnitude
HLA Discordance
Mackelprang, Farquhar JID 2008

![Chart showing the proportion of infants infected at different times of infection.](chart.png)
Host Determinants Evaluated in the Cohort


Co-infections
*HSV co-infection
*Bacterial vaginosis
*CMV

Genetic
*HLA type
*HLA concordance/discordance
Chemokine polymorphisms
HIV co-receptor polymorphisms

Adaptive
Humoral: Neutralizing antibodies
Mucosal IgA
Cellular:
*CD8+ cytotoxic T cells
CD4+ T cells

Innate
*Infant SLPI
CC and CXC chemokines
## I. Transmission Biology Summary

- What is the risk of breastmilk transmission? ✓
- What is the best way to prevent breastmilk transmission? ✓
- How does maternal virus influence transmission? ✓
- How do short-course ARVs prevent infection? ✓
- How do infants escape infection? ✓?
- Vertical transmission model and new directions
II. Infants and Mothers

- Does infancy influence HIV?
- How do changes during and after pregnancy affect maternal HIV?
Infancy

- Do infants differ from adults in their HIV disease course?
- Does age at acquiring HIV influence their course?
- Why do infants fail to control of HIV?
Infants Progress More Rapidly Than Adults


**FIGURE 1.** Kaplan-Meier survival curves of 62 HIV-1-infected infants during the first 2 years of life, according to maternal CD4 count during pregnancy. Log rank statistic, 8.20; $P = 0.005$. 

- 95% CI for Peak
- Mean Peak
- 95% CI for Set Point
- Mean Set Point
Infants Infected Early Fare Worse Than Infants Infected Later


**Mortality**

![Bar chart showing mortality rates for early and late infections.](image)

- Early: P<0.001
- Late: p=0.003

**Log HIV RNA Plasma Viral Load Set Point**

![Graph showing viral load set points for adults and infants.](image)

- Early Infants
- Late Infants
- Adults

Mbori-Ngacha JAMA 2001

Richardson J Virol 2003
Older Infants Make HIV-specific Immune Responses Faster than Younger Infants

Age in months

P=0.03
Infants born to HIV infected women frequently acquire and contain CMV

- ~90% of infants had CMV by 3 months
- HIV-infected infants controlled CMV more slowly
- HIV-infected infants contain CMV but not HIV
Infant Summary

- Do infants differ from adults in their HIV disease course? ✓
- Does age at acquiring HIV influence their course? ✓
- Why do infants fail to control of HIV-1? ✓?
- New directions
Mothers and HIV

- Do changes in pregnancy, breastfeeding and contraception influence HIV?
Breastfeeding and Maternal HIV Progression

Nduati Lancet 2001

- BF women have higher mortality
- Hormonal, metabolic or immunologic costs of BF

Figure 2: Mortality of mothers in breastfeeding and formula feeding groups
Breastfeeding was associated with a higher risk of death in mothers than formula feeding, p=0.009.

Lactation and Contraceptive Effect on HIV Progression

- **Breastfeeding**
  - Minimal impact with expanded HIV care

- **Contraception**
  - No impact on VL and CD4

Fig. 1. Longer-term effect of hormonal contraceptive use on HIV-1 disease status. D, ——— Depo medroxyprogesterone acetate; N, ——— non-hormonal; O, ——— oral contraceptive pill.
HIV Acquisition During Pregnancy
Kinuthia CROI 2010

- 2,135 previously HIV-1 uninfected
- 2,035 (95%) accepted re-test
- HIV-1 incidence: 6.8/100 women-yrs (95% CI: 5.1-8.8)
- Cofactors for HIV incidence
  - Marriage 3.8 (0.9-16.0)
  - Western Kenya 3.5 (2.0-6.1)
  - Polygamous 9.2 (2.0-43.6)
Mothers Summary

- Do changes in pregnancy, lactation and contraception influence HIV? ✓
- New directions
III. Translation: How Can we Move Research to Practice?

- How much PMTCT is being currently implemented?
- How can we improve PMTCT implementation?
Percentage of pregnant women in low- and middle-income countries receiving an HIV test, 2004-2007

- Sub-Saharan Africa: 8%, 10%, 13%, 18%
- East, South and South-East Asia: 4%, 3%, 7%, 8%
- Latin America and the Caribbean: 40%, 40%, 52%
- Europe and Central Asia: >95%, >95%

No data are available for the Middle East and North Africa.
Social Constraints in PMTCT


- Domestic violence
  - 28% at baseline
  - <1% post-HIV test

- Partner involvement
  - increased intervention uptake
  - better infant outcomes
PMTCT Report Card

Kinuthia CROI 2010

- 6 MCH clinics
- Hypothesis: stigma a barrier

6 wks vaccine visit

Pregnancy  →  HIV test  →  ARV  →  Delivery
PMTCT Uptake and Transmission Impact

- 2,700 mothers
- 12-55% stigma
- 92% HIV test, >80% ARV
- 8% transmission
- Systems rather than stigma barrier

✓ Opt-out
✓ Rapid test
✓ Decentralized services
Percentage of pregnant women living with HIV receiving antiretrovirals for preventing mother-to-child transmission of HIV in the 10 countries with the highest estimated number of pregnant living with HIV, 2007.


The bar indicates the uncertainty range around the estimate.
Translating Research to Practice
Person, Place, Time

- UW-IARTP Scholars
  - Ruth Nduati – NARESA >100,000 mothers/year
  - Dorothy Mbori-Ngacha – CDC-PMTCT Head
  - James Kiarie – PMTCT at largest PMTCT sites
  - Elizabeth Obimbo – Director KNH Ped HIV Clinic
Translation Summary

- How much PMTCT is being currently implemented? ✓
- How can we improve PMTCT implementation? ✓
Summary

- Transmission Biology
- Infants and Mothers
- Translation
- New Frontiers
Acknowledgements

- **Participants (parents, children)**
- **Institutions**
  - University of Washington, University of Nairobi, Kenyatta National Hospital, Kenya Medical Research Institute, Fred Hutchinson Cancer Research Center, Oxford University, Karolinska Institutet
- **Funders**
  - NICHD, NIAID, Fogarty, Elizabeth Glaser Pediatric AIDS Foundation, Royalty Research Fund
Children have a right to be born free from HIV. No cost is too high for saving mothers and babies. We can achieve this if we leverage the AIDS response to also strengthen maternal child health services.

Michel Sidibé, UNAIDS Executive Director.