Prevention of Mother to Child Transmission: From Clinical Trials to Implementation

Charles van der Horst, MD, FACP
Professor of Medicine
University of North Carolina
UNC: 20 years in Lilongwe, Malawi

- 13 million people
- GNI $181, the lowest in Africa
- Health Care Expenditure $58 per person
- Life expectancy: 39 years
- 2 physicians/100,000 people
UNC Project

25,000 Sq Ft
High speed satellite internet
Cell storage facility
300 employees
BAN Research Site at Bwaila Hospital in Lilongwe, Malawi
Train
The Trainers
Malawi College of Medicine
Wits South Africa
Dan Namarika
Agnes Moses
Timeline for BAN

- RFP Issued April 2001
- Proposal submitted June 1, 2001
- Funded October 1, 2001
- Final IRB approval March 18, 2004
- First patient April 22, 2004
- Last randomization January 2009
- Last 28 week visit August 2009
- Last 48 week visit January 2010
PMTC: In the beginning 2001
HIV prevalence trend estimates from ANC clinics, Lilongwe and Blantyre, 1982-2004


Blantyre Prevalence
Lilongwe Prevalence
Estimated number of children (<15 years) newly infected with HIV, 2007

Total: 420 000 (350 000 – 540 000)
200,000 Infected by Breastmilk
Timing of MTCT

- Antepartum Prophylaxis
- Intrapartum Prophylaxis
- ?Efficacy Postpartum ARV Infant and/or Mother?

- Early Antenatal (<36 wks)
- Late Antenatal (36 wks to labor)
- Labor and Delivery
- Early Postpartum (0-1 mo)
- Late Postpartum

Proportion of infections:

0% 20% 40% 60% 80% 100%
Perinatal HIV Transmission and Maternal Antiretroviral Therapy, Women and Infants Transmission Study: 1990-2004 (USA)
Limitations of PMTCT with sdNVP

• Orphans
• HIV resistance to NNRTIs
• No impact on in utero transmission
• No impact on transmission through Breast Milk
The Six Questions for PMTCT

1. At what CD4 count do we start HAART?
   All? < 500? < 350?

2. Above that, do what antenatally?
   AZT monotherapy? Resistance?
   sdNVP with or without tail peripartum?

3. Above that, do what postnatally?
   Infant daily NVP post partum vs HAART

4. To wean or not to wean?

5. What HAART regimen?
   TB (NVP/PI and Rifampin)
   Lactic acidosis (D4T)
   Teratogen (EFV)
   Anemia (AZT)

6. How implement?
HIV Infected Women with CD4 <350 Need HAART for Own Health

CD4 < 200: 55% of maternal deaths, 47% of postnatal infections

ZEBS Study – Thea D et al. 2008
TB incidence rates & Cases saved per 100 pys of HAART

Lawn, Bekker, Wood AIDS 2005

Cases saved

<table>
<thead>
<tr>
<th>CD4 &gt;350</th>
<th>CD4 200-350</th>
<th>CD4&lt;200</th>
<th>WHO3&amp;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td>9.4</td>
<td>11.3</td>
<td>18.8</td>
</tr>
</tbody>
</table>

95% CI

<table>
<thead>
<tr>
<th>CD4 &gt;350</th>
<th>CD4 200-350</th>
<th>CD4&lt;200</th>
<th>WHO3&amp;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.3-2.9)</td>
<td>(3.8-14.3)</td>
<td>(6.2-19.1)</td>
<td>(13.2-26.1)</td>
</tr>
</tbody>
</table>
For Women with CD4 >350

Antepartum/Intrapartum PMTCT

AZT/sdNVP + “tail”
vs
Maternal HAART

May Have Comparative Efficacy
AZT at 28 wks gestation + sdNVP results in MTCT Rates of 1% in Women with CD4 >200, Thailand


Comparing Difference in Transmission Rates Between AZT/Placebo-Placebo and AZT/NVP-NVP by CD4
Single dose Nevirapine: What are the risks?

• Long half-life
• Low genetic barrier to resistance
• NVP resistance mutations in up to 69% of mothers\(^1\) and 87% of infected infants\(^2\)
• Mutations in plasma and breast milk
• Poor response to future NNRTI-based therapy (24% failure vs 7%)\(^3,4,5\)
• Poor response to sdNVP in future pregnancies\(^6\)

\(^1\)Eshleman; \(^2\)Eshleman; \(^3\)Chi; \(^4\)Lockman; \(^5\)Octane; \(^6\)NIH Bulletin, 10/2008
NVP Levels in Breast Milk Are Detectable Up to 2 Weeks Following SD NVP

Kunz A. 2006 Internat AIDS Conf, Toronto, Canada, Abs. TuPe0353

Days after maternal SD NVP

Median NVP level ng/ml

- <2 (N=37)
- 6 (N=5)
- 7 (N=16)
- 8 (N=16)
- 9 (N=7)
- 13 (N=4)
- 14 (N=11)
- 15 (N=13)
- 16 (N=5)
- 17-20 (N=10)
- 21-48 (N=25)
OCTANE Trial 1: ARV response post sd NVP  October 28, 2008 N=243

• Definition of Virologic Failure: did not have 10 fold decrease after 12 weeks or > 400 after 24 wks of HAART
• 24% receiving NVP+Truvada died or failed vs 7% receiving Kaletra+Truvada
• If sdNVP 6-11 months before 37% vs 3%. If 2 yrs before 8% vs 10%
BAN Cohort Study

• Assess to what extent 7 days ZDV+3TC reduces HIV resistance to NVP in mothers at 2 and 6 weeks postpartum
• Determine what additional factors predict NVP resistance postpartum
• Determine resistance to ZDV and 3TC
Study Groups

• Intervention group
  – Women in the BAN study (control arm)
  – sdNVP + 7 days ZDV+3TC, no further therapy

• Comparison group
  – PMTCT women
  – sdNVP alone
Study Design

Intervention: 132 women from BAN study
sdNVP/ZDV+3TC

Comparison: 66 women from PMTCT program
sdNVP alone

1st antenatal visit  2nd antenatal visit  Labor and delivery  2 weeks pp  6 weeks pp

Study drugs taken
Laboratory Methods

• Resistance mutations (NVP, ZDV, 3TC)
  – Population sequencing
    • Detect 20%-30% levels of mutant virus amidst wild type
  – Sensitive real-time PCR
    • K103N, Y181C, V106M, T215F/Y, M184V
    • Detect 0.5%-1.0% mutant virus amidst wild type

• Drug concentrations (NVP, ZDV, 3TC)
  – by HPLC/UV or MS to 10ng/mL LLQ
## Demographic and health characteristics

<table>
<thead>
<tr>
<th></th>
<th>sdNVP + ZDV/3TC</th>
<th>sdNVP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26 (17-44)</td>
<td>25 (19-37)</td>
<td>0.45</td>
</tr>
<tr>
<td>Viral load†</td>
<td>19,575 (400-479,286)</td>
<td>22,519 (313-390,421)</td>
<td>0.94</td>
</tr>
<tr>
<td>CD4† (cells/ul)</td>
<td>437 (210-2,000)</td>
<td>419 (202-1,329)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hb† (g/dL)</td>
<td>10.9 (7.9-13.3)</td>
<td>10.6 (8.2-13.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hours NVP ingestion to delivery</td>
<td>6.9 (0.7-732)</td>
<td>6.4 (0.6-1095)</td>
<td>0.57</td>
</tr>
<tr>
<td>Obstetric complication</td>
<td>6.9%</td>
<td>4.5%</td>
<td>0.75</td>
</tr>
<tr>
<td>Electricity in home</td>
<td>23.8%</td>
<td>3.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Antenatal value
Median Viral Load

Antenatal
- sdNVP/ZDV+3TC: Log VL 4.2
- sdNVP alone: Log VL 4.1

2 weeks pp
- sdNVP/ZDV+3TC: Log VL 2.5
- sdNVP alone: Log VL 2.5

6 weeks pp
- sdNVP/ZDV+3TC: Log VL 3.5
- sdNVP alone: Log VL 3.5

p-values:
- Antenatal: p=0.91
- 2 weeks pp: p<0.0001
- 6 weeks pp: p=0.72
Women with detectable NVP concentrations

- Delivery: p=0.39
- 2 weeks pp: p<0.0001
- 6 weeks pp: p=0.80
Prevalence of NVP resistance mutations, by drug regimen

- Mutations detected through real-time PCR testing only
- Mutations detected through population sequencing

**2 weeks**
- sdNVP + ZDV+3TC: 10%
- sdNVP: 74%

**6 weeks**
- sdNVP + ZDV+3TC: 10%
- sdNVP: 64%

*p < 0.0001*
### Associations with NVP Resistance at 6 weeks postpartum

<table>
<thead>
<tr>
<th></th>
<th>unadj RR</th>
<th>aRR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>sdNVP + ZDV+3TC</td>
<td>0.15 (0.08 – 0.27)</td>
<td>0.20 (0.10-0.40)</td>
</tr>
<tr>
<td>Age</td>
<td>0.98 (0.93 – 1.02)</td>
<td>*</td>
</tr>
<tr>
<td>Antenatal VL</td>
<td>0.80 (0.56 – 1.15)</td>
<td>*</td>
</tr>
<tr>
<td>Antenatal CD4 count</td>
<td>1.00 (1.00 – 1.00)</td>
<td>*</td>
</tr>
<tr>
<td>Antenatal Hb</td>
<td>0.89 (0.72 – 1.09)</td>
<td>*</td>
</tr>
<tr>
<td>[NVP], delivery</td>
<td>1.00 (1.00 – 1.00)</td>
<td>*</td>
</tr>
<tr>
<td>[NVP], 2 wks pp</td>
<td>1.01 (1.00 – 1.01)</td>
<td>1.00 (1.00-1.06)</td>
</tr>
</tbody>
</table>

*Adjusted for drug regimen, [NVP] at 2 wks pp
### HIV Vertical Transmission and Infant Drug Resistance*  

<table>
<thead>
<tr>
<th></th>
<th>Infant HIV transmission rate, 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>sdNVP/ZDV+3TC (BAN control arm)</td>
<td>7.1% (5.1% - 9.1%)</td>
</tr>
<tr>
<td>sdNVP</td>
<td>13.8% (7.3% - 22.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Infant NVP resistance, 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>sdNVP/ZDV+3TC</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>sdNVP</td>
<td>38% (3/8)</td>
</tr>
</tbody>
</table>

*No ZDV or 3TC resistance mutations*
For Women with CD4 >350

What to do about Postnatal PMTCT via Breastfeeding?

Infant ARV Prophylaxis
 Vs
 Maternal HAART
Infant feeding patterns in Malawi (DHS, 2004)
WHO PMTCT Guidelines are Silent on Breastfeeding June 2006
sdNVP alone MUST GO!

<table>
<thead>
<tr>
<th></th>
<th>Maternal HAART Indicated</th>
<th>Maternal HAART not yet indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum</td>
<td>AZT/3TC/NVP</td>
<td>AZT at 28 wks</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>Ditto</td>
<td>AZT + 3TC + sdNVP</td>
</tr>
<tr>
<td>Postpartum</td>
<td>Ditto</td>
<td>AZT+3TC x 7d</td>
</tr>
<tr>
<td>Infant</td>
<td>AZT x 7d</td>
<td>sdNVP + AZT 7d</td>
</tr>
</tbody>
</table>

What about AZT monotherapy and resistance?
2.7% (0.3-14.0%) K70R PACTG 076 Eastman JID 1998-small sample
24% (14.9% K70R) WITS Welles AIDS 2000-prior AZT
Breastfeeding provides optimal nutrition for first 6-12 months and is associated with decreased infant morbidity and mortality over the 1st year of life.

However, prolonged breastfeeding is associated with ~10-15% increased risk of HIV transmission.


BAN: All Clients Receive

- Antenatal vitamins, iron, Tetanus toxoid
- Cotrimoxizole prophylaxis (June 2006)
  - Mothers with CD4 < 500
  - Infants from 6 weeks to 36 weeks if DNA negative.
- Pediatric Vaccines
  - BCG at birth
  - Polio at birth, 6 weeks
  - DPT-HepB + Hib at 6, 10, 14 weeks
  - Measles vaccine at 9 months
- Family Maize supplement 2 kg/week
- Mosquito nets from 2007 to 2008 when MoH took over.
- Care for all intercurrent illnesses including antibiotics
- Full microbiology laboratory available
- Weaning food at from 24 wks to 48 wks
  - powdered milk, peanut butter, sugar, oil, and fortified with micronutrients.
  - 400 kcal and 9.5 g of protein per day
They understand the constraints of poverty and lack of access to resources to protect their health status, particularly in light of their infection. They are acutely aware of the dilemma they face as they balance the risks of continuing to breastfeed (increasing the risk of HIV transmission through breastmilk and adverse consequences on their own health) versus the risk of not breastfeeding for their infants (the potential for growth faltering and malnutrition). Their knowledge and ability to articulate these issues, with a mean educational level of just six years, is both remarkable and poignant in light of the extreme conditions of poverty and chronic food insecurity that they experience.

BAN Study Description

2x3 factorial, randomized, controlled, open-label design to evaluate 2 interventions given to HIV-infected mothers or their infants during 24-weeks of exclusive breastfeeding and 4 weeks weaning:

1. Antiretroviral medications given either to infants or to their mothers to prevent infant HIV transmission compared to an enhanced standard of care arm

2. Nutritional supplementation given to women to prevent maternal depletion compared to enhance standard of care

van der Horst CM, et al. Contemporary Clinical Trials. 2009;30:24-33

www.thebanstudy.org
BAN Study

Primary Eligibility Criteria

- Age ≥ 14 years
- Able to give informed consent
- HIV positive with no other active serious infections
- Pregnant and ≤ 30 weeks gestation with no serious complications
- Intend to breastfeed
- Intend to deliver at study site
- No previous ARV use
- Mother’s CD4 ≥ 250 cell/µL
- Mother’s Hb ≥ 7g/dL
- Mother’s ALT < 2.5xULN

Secondary Eligibility Criteria

- Deliver at study site or must present with infant within 36 hours of delivery
- Mother accepts enhanced standard of care regimen for herself and baby
- Infant birthweight ≥ 2000 g
- No severe congenital malformations or conditions not compatible with life
ARV intervention*

Mother and Infant

Enhanced Control
- ZDV/3TC
- sdNVP x1
- ZDV/3TC x 1 wk

Maternal HAART
- ZDV/3TC
- sdNVP x1
- ZDV/3TC x1 wk
- ZDV/3TC/NVP** x 28 wks to mother

Infant NVP
- ZDV/3TC
- sdNVP x1
- ZDV/3TC x1 wk
- NVP x 28 wks to infant

*Exclusive Breastfeeding for 24 weeks with weaning over 4 weeks.
  Weaning food “plumpy nut” provided until week 48
**NVP changed to NFV February 2005 – NFV Changed to LPV/r January 2006
BAN Study Primary Endpoints

• The primary end point was infant HIV status at 28 weeks in those uninfected at birth
• Standard survival analysis methods were used to estimate time to first positive HIV-1 test and time to first positive HIV-1 test or death by treatment arm
• Infant testing real time at birth, 2, 12, 28 and 48 weeks by DNA PCR
  – Dried Blood Spots (DBS) obtained at each visit and tested to narrow the window of transmission to less than 4 weeks
  – All positives were confirmed with a second specimen
3572 HIV-infected pregnant women consented to screening at antenatal visit.

2790 women delivered.

2370 mother-infant pairs randomized.

850 Maternal HAART

852 Infant NVP

668 Enhanced Control

- 377 Failed primary eligibility
  - 289 CD4<250
  - 22 Prev ARV
  - 66 Other
  - 405 Did not report at delivery

- 404 Failed secondary eligibility
  - 185 late presentation
  - 91 < 2kg infants
  - 47 still birth
  - 81 Other
  - 19 Chose not to participate
<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Maternal HAART N=850</th>
<th>Infant NVP N=852</th>
<th>Enhanced Control* N=668</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Med (IQR)</td>
<td>26 (22-29)</td>
<td>25 (22-30)</td>
<td>26 (22-29)</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI &lt; 17kg/cm² (%)</td>
<td>0.51</td>
<td>0.26</td>
<td>0.17</td>
<td>0.57</td>
</tr>
<tr>
<td>CD4 Med (IQR)</td>
<td>429 (323-566)</td>
<td>441 (331-591)</td>
<td>442 (334-587)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hgb* g/dl Med (IQR)</td>
<td>11.0 (10.0-12.0)</td>
<td>11.0 (10.0-12.0)</td>
<td>11.0 (10.0-12.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Infant Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight Mean (STD)</td>
<td>3.0 (2.7-3.2)</td>
<td>3.0 (2.7-3.3)</td>
<td>3.0 (2.7-3.3)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*Arms uneven due to DSMB recommended change in study design March 2008
## BAN: Grade 3 and 4 Toxicities (Birth to 28 weeks)

<table>
<thead>
<tr>
<th>Maternal toxicities</th>
<th>Maternal (N = 850)</th>
<th>Infant NVP (N = 852)</th>
<th>Enhanced Control (N = 668)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Hgb (%)</td>
<td>2.1</td>
<td>0.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Low Neutrophil Count (%)</td>
<td>6.7*</td>
<td>2.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Low Platelets (%)</td>
<td>1.5</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>High ALT (%)</td>
<td>1.6</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>NVP Hypersensitivity (n)</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death (n)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infant toxicities</th>
<th>Maternal (N = 850)</th>
<th>Infant NVP (N = 852)</th>
<th>Enhanced Control (N = 668)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Hgb (%)</td>
<td>19.4</td>
<td>21.3</td>
<td>22.8</td>
</tr>
<tr>
<td>Low ANC (%)</td>
<td>0.4</td>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Low Platelets (%)</td>
<td>1.0</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>High ALT (%)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>NVP Hypersensitivity (n)</td>
<td>1</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

*Neutrophil Count for Maternal HAART vs Control: p<0.0001
BAN: Probability HIV positive by week 28 visit in infants uninfected at birth April 1

Control vs Maternal HAART: p = 0.0032
Control vs Infant NVP: p < 0.0001
Maternal HAART vs Infant NVP: p = 0.1203
BAN: Probability HIV positive or death by week 28 visit in infants uninfected at birth

Control vs Maternal HAART: p = 0.0310
Control vs Infant NVP: p < 0.0001
Maternal HAART vs Infant NVP: p = 0.0698
28 Week HIV Infection in infants negative 2 weeks

- Maternal HAART vs Control: p = 0.0096
- Infant NVP vs Control: p < 0.0001
- Maternal HAART vs Infant NVP: p = 0.0611

Number at risk:
- Infant NVP: 778 742 728 693 686 684 641
- Maternal HAART: 759 717 699 663 652 648 620
- Control: 589 518 502 480 463 461 452

28 Week HIV Infection/Death in infants Negative 2 weeks

- Maternal HAART vs Control: p = 0.0371
- Infant NVP vs Control: p < 0.0001
- Maternal HAART vs Infant NVP: p = 0.0318

Number at risk:
- Infant NVP: 778 743 728 695 688 686 642
- Maternal HAART: 761 719 702 665 654 650 623
- Control: 591 519 503 482 464 462 452
Mma Bana: Compares 2 Maternal HAART Regimens: AP/IP/PP Intervention
Shapiro R et al. IAS, Capetown S Africa, July 2009, Abs. WE LB B101

All infants breastfed

26-34 weeks
Delivery
Breastfeeding 6 months
f/u to 2 yrs

ARM 1
Mom
AZT/3TC/ABC
AZT/3TC/ABC
AZT/3TC/ABC
f/u to 2 yrs
sdNVP
AZT x 1 mo

BABY

CD4 ≥200: 560 HIV+ pregnant women

ARM 2
Mom
AZT/3TC/LPV-r
AZT/3TC/LPV-r
AZT/3TC/LPV-r
f/u to 2 yrs
sdNVP
AZT x 1 mo
Infections among live-born infants, by maternal arm

<table>
<thead>
<tr>
<th></th>
<th>Arm A (TZV) N=283</th>
<th>Arm B (KAL/CBV) N=270</th>
<th>Obs Arm (NVP/CBV) N=156</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero</td>
<td>3 (1.1%)*</td>
<td>1 (0.4%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>2 (0.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total at 6 months</td>
<td>5 (1.8%)*</td>
<td>1 (0.4%)</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

Overall Transmission 1% (95% CI, 0.5-2.0%) Through Age 6 Months
Kesho Bora: AP/IP + - PP Intervention
de Vincenzi I et al. IAS, Capetown, South Africa, July 2009, Abs. LB PE C01

77% breastfed, median 21 wks <50% exclusive to 3 mos

28-36 weeks

Delivery (1 wk)

6.5 months

ARM 1: Short Course (N=411)

Mom

AZT

AZT/3TC

AZT/3TC X 1 wk

Baby

sdNVP

ARM 2: Triple (N=413)

Mom

AZT/3TC/LPV-r

AZT/3TC/LPV-r

AZT/3TC/LPV-r

Baby

77% breastfed, median 21 wks <50% exclusive to 3 mos

CD4 200-500: 824 HIV+ pregnant women

HIV+ pregnant women
Kesho Bora: HIV Infection Over Time in HAART through Breastfeeding Vs Short AZT/sdNVP Arms

De Vincenzi I et al. IAS, Capetown, South Africa, July 2009 Ab LBPEC01

No significant difference in AP MTCT rates in short vs triple at birth-1 week (2.2 vs 1.8%)

Significant difference in MTCT rates starting after age 1 month with postnatal maternal HAART vs no postnatal prophylaxis

log rank p = 0.039
### Kesho Bora: HIV Infection Over Time in HAART through Breastfeeding Vs Short AZT/sdNVP Arms

*De Vincenzi I et al. IAS, Capetown, South Africa, July 2009 Ab LBPEC01*

<table>
<thead>
<tr>
<th>Age</th>
<th>HIV Infection</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Triple</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>No. infected</td>
<td>Rate (95% CI)</td>
<td>No. infected</td>
</tr>
<tr>
<td>Birth</td>
<td>7</td>
<td>1.8 (0.8, 3.7)</td>
<td>9</td>
</tr>
<tr>
<td>6 wks</td>
<td>13</td>
<td>3.3 (1.9, 5.6)</td>
<td>19</td>
</tr>
<tr>
<td>6 mths</td>
<td>19</td>
<td>4.9 (3.1, 7.5)</td>
<td>33</td>
</tr>
<tr>
<td>12 mths</td>
<td>21</td>
<td>5.5 (3.6, 8.4)</td>
<td>36</td>
</tr>
</tbody>
</table>

**Risk reduction at age 12 months:** 42% (p=0.04)
Randomized Clinical Trials Assessing Maternal HAART or Infant ARV Prophylaxis of MTCT During Breastfeeding

Sinead Delany-Moretlwe, Rapporteur Track C IAS Capetown S Africa July 2009

HIV TRANSMISSION DURING BREASTFEEDING (6 Wks-6 Mos)

<table>
<thead>
<tr>
<th>BAN CD4≥250</th>
<th>NO ARV</th>
<th>MOTHER</th>
<th>Reduction: 56%</th>
<th>CHILD (6 Mo)</th>
<th>Reduction: 63%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kesho Bora 200≤CD4≤500</td>
<td>NO ARV</td>
<td>MOTHER</td>
<td>Reduction: 54%</td>
<td>CHILD (3 Mo)</td>
<td>Reduction: 40%</td>
</tr>
<tr>
<td>PEPI ALL CD4</td>
<td>NO ARV</td>
<td>CHILD (3 Mo)</td>
<td>Reduction: 40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kesho Bora 200≤CD4&lt;350</td>
<td>NO ARV</td>
<td>MOTHER</td>
<td>Reduction: 60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEPI 200≤CD4&lt;350</td>
<td>NO ARV</td>
<td>CHILD (3 Mo)</td>
<td>Reduction: 45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kesho Bora 350≤CD4&lt;500</td>
<td>NO ARV</td>
<td>MOTHER</td>
<td>Reduction: 52%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEPI 350≤CD4</td>
<td>NO ARV</td>
<td>CHILD (3 Mo)</td>
<td>Reduction: 48%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kesho Bora: LBPEC01   BAN: WELBC103   PEPI: TUPEC053   Mma Bana: WELBB101
### SWEN, PEPI, MASHI, and BAN comparison:
Mother baseline CD4 > 250/200, infant not HIV+ by day 7 April 1

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>Death</th>
<th>HIV or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SWEN</td>
<td>PEPI</td>
<td>MASHI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BAN</td>
</tr>
<tr>
<td>6wNVP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14wNVP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14wNVP+AZT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6mAZT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MART INVP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV or Death</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Est cumulative incidence by 6 months*
SWEN, PEPI, MASHI, and BAN comparison:
Mother baseline CD4 > 250/200, infant not HIV+ by day 7 April 1

Est cumulative incidence by 6 months

Control

HIV

Increasing duration of infant NVP increases benefit in the face of continued BF
SWEN, PEPI, MASHI, and BAN comparison:
Mother baseline CD4 > 250/200, infant not HIV+ by day 7 April 1

<table>
<thead>
<tr>
<th></th>
<th>SWEN</th>
<th>PEPI</th>
<th>MASHI</th>
<th>BAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV or Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Est cumulative incidence by 6 months

Kesha Bora 3.1% vs 6.3%, Mma Bana 0 to 0.7%
What about weaning?
Proportion of infants hospitalized due to diarrhea

Age in months

Proportion of infants with diarrhea (%)

K-M curve probability of first diarrhea among HIV-uninfected infants.

Rainy season = November - March

Weaning: The BAN Study
Rates of Gastroenteritis Hospitalizations by Infant Age, Comparing CDC HAART Study (KiBS) with Early Weaning to Natural History Study (VT) in Kisumu, Kenya

Age in months

GE rate per 100 infants in age group observed

GE rate VT
GE rate KiBS

Age of Weaning in KiBS

(Mary Glenn Fowler MD)
Growth Faltering Post Weaning at 6 Months in KiBS Study (N=63) Compared to VT Study Without Early Weaning (N=440), Kisumu, Kenya

(Mary Glenn Fowler MD)
Increased mortality with abstinence from breastfeeding in a program in rural Rakai, Uganda

Unadjusted RH=6.1 (95% CI=1.7-21.4, P-value<0.01)

Increased mortality with abstinence from breastfeeding in a clinical trial in urban Botswana

Thior I, Lockman S, Smeaton LM et al. *JAMA* 2006; 296: 794-805
Increased mortality with abstinence from breastfeeding in a \textbf{clinical trial} in urban Botswana

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Does “no benefit” = “no harm”?}
\end{figure}

Thior I, Lockman S, Smeaton LM et al. \textit{JAMA} 2006; 296: 794-805
“No benefit” means
# deaths caused = # HIV prevented

0-6 months
Thior et al. Botswana

6-24 months
ZEBS Zambia

% with outcome

Breastfeed
Formula feed
Breastfeed 18m
Stop BF at 4 m

Uninfected child death
HIV infection
In women with higher CD4 counts, early weaning had worse outcomes

Diarrheal Morbidity Increases with Weaning Prior to Age 6 Months in Uninfected Infants: ZEBS

Fawzy A et al. IAS, Capetown, South Africa, July 2009, Abs. TuAC104

![Graph showing the percentage of children with diarrhea-related clinic visits by age and breastfeeding status.](chart.png)
Charlie says: Stop weaning
PMTCT Cascade: Most Critical Thing for PMTCT is Number of Women Completing Cascade

P. Barker, WHO Mtg Nov 2008

100 HIV+ mothers

Enter into program

- Attend ANC clinic 92%
- Counseled and tested for HIV, CD4 95%
- Get ARVs (pre- and perinatal) 95%

Missed - no PMTCT

- Overall Program Effectiveness (early MTCT)
  - sdNVP: 11% tx
  - AZT/sdNVP: 7% tx
  - HAART: 6.1% tx

No ARV (25% MTCT): 4.5 infected
sdNVP (8% MTCT): 6.5 infected
AZT/sdNVP (3% MTCT): 2.5 infected
HAART (2% MTCT): 1.6 infected
**Traditional Birth Attendants’ (TBAs) involvement in prevention of mother to child transmission (PMTCT) of HIV-1 service delivery in Lilongwe District, a semi-urban area**

C, Kabonda et al. IAS Cape Town 2009 Abstract MOAD104.

44% deliver at home. We identified 14 TBAs with at least 5 deliveries/month.

<table>
<thead>
<tr>
<th>NAME OF TBA</th>
<th>MONTH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DATE</th>
<th>NAME OF CLIENT</th>
<th>PMTCT#</th>
<th>Has started pushing at her home</th>
<th>The mother’s condition is good</th>
<th>The mother has taken NVP</th>
<th>The mother is on ARVs</th>
<th>The mother has died</th>
<th>The baby’s condition is good</th>
<th>The baby has taken NVP</th>
<th>The baby has died</th>
<th>Has been referred to hospital</th>
<th>Delivery during the day</th>
<th>Delivery at night</th>
</tr>
</thead>
</table>
Male Partner HIV Testing and Antenatal Clinic Attendance Associated with Reduced HIV Transmission to Infants

Aluisio A et al. IAS, Capetown, South Africa, July 2009, Abs. TuAC105

Multivariate model adjusted for maternal viral load & infant feeding modality
ART Initiation and Increased Survival of HIV Infected Infants Traced from Prevention of Maternal to Child Transmission Facilities to Pediatric HIV Care: Need for Program Coordination in Lilongwe, Malawi
M. Braun et al WEPDD103 IAS Cape Town 2009

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women tested 2004-2008</td>
<td>106,259</td>
</tr>
<tr>
<td>HIV Positive Women</td>
<td>15,814</td>
</tr>
<tr>
<td>Infants tested</td>
<td>7875</td>
</tr>
<tr>
<td>Positive Infants</td>
<td>1084</td>
</tr>
<tr>
<td>Infants traced to an ART clinic</td>
<td>221</td>
</tr>
</tbody>
</table>

Mean Ages and Time Durations in Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at HIV diagnosis</td>
<td>5.9</td>
</tr>
<tr>
<td>Age at ART clinic enrollment</td>
<td>7.4</td>
</tr>
<tr>
<td>ART Initiators (N=110)</td>
<td></td>
</tr>
<tr>
<td>Age at ART initiation</td>
<td>10.5</td>
</tr>
</tbody>
</table>
**Design:** Retrospective review of collected data. We compiled a list of HIV positive infants, which were then linked to maternal data and to ART clinic data from Baylor.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women tested</td>
<td>106,259</td>
<td>From Bwaila, Kawale, A18, A25 ANC</td>
</tr>
<tr>
<td>Positive Women</td>
<td>15,814</td>
<td>15% of women tested were positive</td>
</tr>
<tr>
<td>Infants tested</td>
<td>7875</td>
<td>50% of exposed infants tested</td>
</tr>
<tr>
<td>Positive Infants</td>
<td>1084</td>
<td>13.8% of infants tested were positive</td>
</tr>
<tr>
<td>Infants traced to an ART clinic</td>
<td>221</td>
<td>20% of positive infants linked to care</td>
</tr>
<tr>
<td>Infants traced to Baylor^4</td>
<td>202</td>
<td>19% of known positive infants found at Baylor</td>
</tr>
<tr>
<td>Infants initiated on ART at Baylor</td>
<td>110</td>
<td>54.5% of infants were initiated on ART during study period</td>
</tr>
<tr>
<td>Infant deaths</td>
<td>69</td>
<td>34% died during study period</td>
</tr>
<tr>
<td>Infant deaths on ART</td>
<td>17</td>
<td>15.5% of infants initiated on ART died during study period</td>
</tr>
<tr>
<td>Infant deaths not on ART</td>
<td>52</td>
<td>56.5% of infants NOT initiated on ART died during study</td>
</tr>
<tr>
<td>Infant deaths in first 3 months of care</td>
<td>25</td>
<td>12.5% early mortality, death within 3 months of enrollment</td>
</tr>
</tbody>
</table>

Braun et al IAS 2009 Abstract WEPDD103
### Mean Ages and Time Durations in Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N=202)</th>
<th>Outpatient (N=145)</th>
<th>Inpatient (N=57)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at HIV diagnosis</td>
<td>5.9</td>
<td>3.8</td>
<td>11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at ART clinic enrollment</td>
<td>7.4</td>
<td>6.1</td>
<td>11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from diagnosis to ART clinic enrollment</td>
<td>1.5</td>
<td>2.2</td>
<td>-0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up time for infants</td>
<td>10.3</td>
<td>11.6</td>
<td>7.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ART Initiators</th>
<th>(N=110)</th>
<th>(N=83)</th>
<th>(N=27)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at ART initiation</td>
<td>10.5</td>
<td>9.6</td>
<td>13.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Time from enrollment to ART initiation</td>
<td>4.1</td>
<td>4.3</td>
<td>3.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Time on ART</td>
<td>9.5</td>
<td>10.5</td>
<td>6.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### ART Initiation and Increased Survival

- A medical emergency
- All children must be tested within 6 weeks
  - Rapid test
  - If positive, PCR

![Bar chart showing number of infants on and not on ART](chart.png)
Charlie’s 12 Steps to Solve all the Problems

1. Universal ID with bar code to track, link families
2. Universal HIV testing
3. Rapid semi quantitative CD4 same day
4. Below 350 HAART within 4 weeks
5. Above 350 antenatal AZT, sdNVP with tail, post natal infant NVP
6. Insecticide treated nets, ? In home spraying
7. Rapid viral load to monitor Rx, not CD4
8. Empiric deworming of children
9. Pneumococcal conjugated vaccine
10. Rotavirus vaccine
11. Early infant dx at vaccination with rapid ELISA then rapid VL
12. Circumcise male infants
13. Active TB case finding (fever, cough, night sweats, weight loss)
14. Safe deliveries (TBAs)
15. Clean water, food
BAN Study Workload

Employees 111
Volunteers Screened 66,318
Volunteers enrolled 3,572
Mothers/Baby Pairs Randomized 2,370
Clinical Visits 160,000
Blood draws 130,300
Pages of Case Report Forms 1,000,000
Number of CRFs Expected by the End of Study

1,000,000 CRFs
330 feet

Statue of Liberty
305 feet
The BAN Study Team

BAN Study Team at University of North Carolina Chapel Hill, Centers for Disease Control and Prevention, Atlanta, and UNC Project team in Lilongwe including: Linda Adair, Yusuf Ahmed, Sandra Albrecht, Shrikant Bangdiwala, Ronald Bayer, Margaret Bentley, Brian Bramson, Emily Bobrow, Nicola Boyle, Sal Butera, Charles Chasela, Charity Chavula, Joseph Chimerang’ambe, Maggie Chigwenembe, Maria Chikasema, Norah Chikhungu, David Chilongozi, Grace Chiudzu, Nelecy Chome, Anne Cole, Amanda Corbett, Amy Corneli, Ann Duerr, Henry Eliya, Sascha Ellington, Joseph Eron, Sherry Farr, Yvonne Owens Ferguson, Susan Fiscus, Shannon Galvin, Laura Guay, Chad Heilig, Irving Hoffman, Elizabeth Hooten, Mina Hosseinipour, Michael Hudgens, Stacy Hurst, Lisa Hyde, Denise Jamieson, George Joaki (deceased), David Jones, Zebrone Kacheche, Esmie Kamanga, Gift Kamanga, Coxcilly Kampani, Portia Kamthunzi, Deborah Kamwendo, Cecilia Kanyama, Angela Kashuba, Damson Kathyola, Dumbani Kayira, Peter Kazembe, Rodney Knight, Athena Kourtis, Robert Krysiak, Jacob Kumwenda, Misheck Luhanga, Victor Madhlopa, Maganizo Majawa, Alice Maida, Cheryl Marcus, Francis Martinson, Chrissie Matiki (deceased), Isabel Mayuni, Joyce Meme, Ceppie Merry, Khama Mita, Chimwemwe Mkomawanhu, Gertrude Mndala, Ibrahim Mndala, Agnes Moses, Albans Msika, Wezi Msungama, Beatrice Mtimuni, Jane Muita, Noel Mumba, Bonface Musis, Charles Mwansambo, Gerald Mwapasa, Jacqueline Nkhoma, Richard Pendame, Ellen Piwoz, Byron Raines, Zane Ramdas, Mairin Ryan, Ian Sanne, Christopher Sellers, Diane Shugars, Dorothy Sichali, Alice Soko, Allison Spensley, Gerald Tegha, Martin Tembo, Roshan Thomas, Hsiao-Chuan Tien, Beth Tohill, Charles van der Horst, Jeffrey Wiener, Cathy Wilfert, Patricia Wiyo, Innocent Zgambo, Chifundo Zimba. Finally and most especially, all the women and infants that have agreed to participate in the study.
Thanks

UNC-Chapel Hill
- Myron Cohen MD
- Irving Hoffman PA, MPH
- Susan Fiscus PhD
- Kristina Abel PhD
- Julie Nelson PhD
- Linda Adair, PhD
- Margaret Bentley, PhD
- Angela Kashuba, PharmD
- Amanda Corbett PharmD
- Rod Knight PhD
- Joseph Eron MD
- Ann Cole
- Byron Raines
- Rob Krysiak
- Dustin Long
- Sarah Beth Smith
- Michael Hudgens PhD

Current and former doctoral students
- Emily Bobrow MPH, PhD
- Roshan Thomas MPH
- Megan Parker MPH
- Anna Dow MPH
- Amy Corneli, MPH, PhD
- Daniel Westreich MPH, PhD
- Yvonne Ferguson PhD
- Brian Bramson MD, MPH
Thanks 2

UNC Project Malawi
- Francis Martinson MBBS, PhD
- David Chilongozi, CO, MPH
- Charles Chasela, CO, MPH
- Mina Hosseinipour, MD, MPH
- Cecilia Kanyama MBBS
- Lisa Hyde MD
- Esmie Kamanga RN
- George Joaki MD (deceased)
- Deborah Kamwendo
- Gerald Tegha
- Martin Tembo
- Wezi Msungama MPH
- Charity Chavula CO
- Dumbani Kayira MBBC
- Zebrone Kacheche BSc
- Innocent Mofolo
- Chimwemwe Mkhomawanhu BSc
- Dorothy Sichali
- Agnes Moses MBBC
- Jacqueline Nkhoma RN, MPH
- Chifundo Zimba RN, BSc
- Robert Jafali
- The Community Advisory Board
- Beatrice Mtimuni PhD
- Our patients

BAN Clinic staff:
- Joseph Chimerang’ambe
- Maggie Chigwenembe
- Maria Chikasema
- Norah Chikhungu
- Phindile Chitsulo
- Neley Chome
- Henry Eliya
- Gift Kamanga
- Coxcilly Kampani
- Jacob Kumwenda
- Misheck Luhanga
- Victor Madhlopa MBBC
- Maganizo Majawa
- Chrissie Matiki (deceased)
- Isabel Mayuni
- Khama Mita
- Gertrude Mndala
- Ibrahim Mdala
- Albans Msika
- Noel Mumba
- Bonface Musisi
- Gerald Mwapasa
- Alice Soko
- Tapiwa Tembo
- Patricia Wiyo
- Innocent Zgambo
- Tiwonge Kumwenda
Thanks

CDC
- Denise Jamieson MD
- Yusuf Ahmed BM
- Beth Tohill, PhD
- Athena Kourtis, MD, PhD
- Sal Butera, PhD
- Sherry Farr PhD
- Sandra Albrecht MPH
- Sascha Ellington MSPH
- Jeffrey Wiener, PhD

UNICEF
- Juan Ortiz MD
- Jane Muita MD
- Joyce Meme PhD
- Miriam Chipimo MD

USAID
- Alisa Cameron

Pharmaceutical Companies
- GSK
  - Edde Loeliger MD
  - Jean Marc Steens MD
  - Mounir Ait-Khaled MD
- Boehringer Ingelheim
  - Marita McDonough
  - Pat Robinson MD
- Abbott
  - John Rublein Pharm D
  - Rob Dintroff
- BMS
  - Steve Schnittman MD
- Roche
  - David Reddy
  - Esther Waalberg

Elizabeth Glaser Pediatric AIDS Foundation
- Cathy Wilfert MD
- Allison Spensley
- Nina Pagadala

Ellen Piwoz (Previously AED, now Gates Foundation)
Thanks 4

**Kamuzu Central Hospital**
- Peter Kazembe MBChB
- Grace Chiudzu, MBBS
- Portia Kamthunzi MBBS
- Charles Mwansambo MBChB
- Tarek Maguid MBBS
- Damson Kathyola
- Hadge Juma MD (deceased)

**South Africa**
- Ian Sanne, MBChB
Acknowledgements

**Funding/Support:** This research was funded by the Prevention Research Centers Special Interest Project SIP 13-01 U48-CCU409660-09 and SIP 26-04 U48-DP000059-01, Centers for Disease Control and Prevention; supported by the NIAID P30-AI50410 UNC Center for AIDS Research; DHHS/NIH/FIC 2-D43 Tw01039-06 AIDS International Training and Research Program and Abbott Laboratories, GlaxoSmithKline, Boehringer-Ingelheim, Roche Pharmaceuticals and Bristol-Myers Squibb. The Call to Action PMTCT program has been supported by the Elizabeth Glaser Pediatric AIDS Foundation Call to Action Award and International Leadership Awards, UNICEF, World Food Programme, Malawi Ministry of Health and Population, Johnson and Johnson and USAID.
The BAN Team
UNC Project, Lilongwe, Malawi
September 2005