TRANSMISSION OF HIV IN BREASTMILK

Ameena Goga
Health Systems Research Unit, SA Medical Research Council
Department of Paediatrics, University of Pretoria, SA

SAHIV Clinicians Society Conference
24-27 October 2018
ELIMINATING MTCT AS A PUBLIC HEALTH PROBLEM: IMPACT CRITERIA

- <50 new paediatric infections per 100,000 live births
- MTCT <5% in breastfeeding populations

Both achieved for 1 year at a lowest sub-national level

OUTLINE OF PRESENTATION

Road travelled

Dilemmas

Infant PEP options

Future possibilities
Never before in the history of science has so much been known about the complex importance of breastfeeding for both mothers and children. Scaling up breastfeeding to a near universal level would prevent 823,000 annual deaths in children <5 and 20,000 annual deaths from breast cancer.

- Children who are breastfed for longer periods have lower infectious morbidity and mortality, fewer dental malocclusions, and higher intelligence than do those who are breastfed for shorter periods, or not breastfed. This inequality persists until later in life. Growing evidence also suggests that breastfeeding might protect against overweight and diabetes later in life.
BREASTFEEDING
It Rocks!
In the absence of PMTCT 55-80% of HIV exposed infants remain uninfected.
<table>
<thead>
<tr>
<th>Breastmilk characteristic</th>
<th>Protection conferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>slgA</td>
<td>Local immunity against entry of HIV</td>
</tr>
<tr>
<td>T and B lymphocytes</td>
<td>Antiviral activity</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>Form viral ligands to prevent mucosal entry of free HIV</td>
</tr>
<tr>
<td>Glycoconjugates</td>
<td></td>
</tr>
<tr>
<td>α Defensins</td>
<td>reduces risk of intrapartum and postnatal MTCT.</td>
</tr>
<tr>
<td>IFN-γ cellular immune responses</td>
<td>associated with ≈70% reduction in early MTCT.</td>
</tr>
</tbody>
</table>

Lohman-Payne B et.al. Clin Perinatol 2010
Kuhn L et.al. J Pediatr 2004

Kuhn L et.al. AIDS 2001
Bode L et.al. Am J Clin Nutr 2012
In settings where lifelong ART is provided and supported (incl. adherence counselling) and breastfeeding is promoted and supported, an HIV+ mother

- **should breastfeed for at least 12** months and
- **may continue breastfeeding for up to 24 months** or longer (similar to the general population)
- **while being fully supported for ART adherence**

*(Strong recommendation; Quality of evidence: up to 12 m – Low; to 24 m – Very low)*
Before 2011

Individual approach:
Individual counselling of mothers living with HIV for individual decision making

From 2011

Public health approach:
National or local authorities recommend infant feeding method for children of mothers living with HIV with extended NVP/ART
### Main Feeding Recommendation

<table>
<thead>
<tr>
<th>HIV-negative women</th>
<th>Continue breastfeeding for 2 years or longer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive mothers (and whose infants are HIV uninfected or of unknown HIV status)</td>
<td>Exclusively breastfeed their infants during the first 6 months of life.</td>
</tr>
<tr>
<td>On lifelong ART</td>
<td>Introduce adequate, safe and appropriate complementary foods after 6 months.</td>
</tr>
<tr>
<td>HIV-negative mothers (and whose infants are HIV uninfected or of unknown HIV status)</td>
<td>Continue breastfeeding for 12-24 months or life (recommended) while being fully supported for ART adherence. The mother and/or infant should receive ARVs as prescribed in accordance with current PMTCT guidelines. This section no longer relevant as all HIV-infected women should receive ART.</td>
</tr>
<tr>
<td>Not on lifelong ART</td>
<td>Continue breastfeeding for 2 years or longer while being fully supported for ART adherence for mother and infant.</td>
</tr>
<tr>
<td>HIV-positive mothers and whose infants are HIV infected</td>
<td></td>
</tr>
</tbody>
</table>

Breastfeeding cessation needs to occur gradually over one month.

Abstinence is discouraged.

7 June 2017
PROMOTING HIV-FREE SURVIVAL, THRIVING AND TRANSFORMING FOR CHILDREN
DILEMMAS: CAN WE ELIMINATE BREASTMILK TRANSMISSION OF HIV?
BY 2015: OVERALL MTCT HAS REDUCED, BUT BREASTMILK CONTRIBUTES TO >50% MTCT IN SOME COUNTRIES

Does U=U for breastfeeding mothers and infants? Breastfeeding by mothers on effective treatment for HIV infection in high-income settings

Catriona Waitt, Nicola Low, Philippe Van de Perre, Fiona Lyons, Mona Loutfy, Karoline Aebi-Popp

Can the campaign Undetectable=Untransmittable (U=U), established for the sexual transmission of HIV, be... Lancet HIV 2018; 5: e531-36

NO
BLOOD AND BREAST MILK OF TREATED AND UNTREATED HIV INFECTED PATIENTS

**Untreated Patient**

- Virions
- Unactivated T-cell
- Latent T-cell

**Treated Patient**

- Activated T-cell

Van de Perre et al. Science Translational Medicine 2012
CELL-CELL TRANSFER - CENTRAL ROLE IN CELL-ASSOCIATED MTCT THROUGH GUT

Entry of free virions and cell-associated virus

Before 9 months postpartum, most MTCT is associated with cell-associated virus.

Breast tissue might be seeded with a lineage of latently infected resting cells.

ART typically reduces breastmilk HIV RNA but not DNA.
CONCERNS

A safe threshold of plasma and breastmilk viral load has not been established AND

We do not routinely measure breastmilk viral load
RISKS OF BREASTMILK TRANSMISSION

UNAIDS mathematical modelling:

- Among mothers who initiated ART pre-delivery: 1 in 625 probability (0.16%) of MTCT
MTCT WITH ART

ART initiated between 26 and 34 weeks
Plasma VL at baseline, delivery, 1, 3, 6, months
One BM VL measurement post-hoc
MTCT HAS BEEN REPORTED IN WOMEN WITH UNDETECTABLE BASELINE PLASMA VL

Maternal and Breastmilk Viral Load: Impacts of Adherence on Peripartum HIV Infections Averted—The Breastfeeding, Antiretrovirals, and Nutrition Study

Nicole L. Davis, MPH, PhD,*‡‡ William C. Miller, MD, PhD, MPH,† Michael G. Hudgens, PhD,§ Charles S. Chasela, PhD,∥ Dorothy Sichali, BSc,¶ Dumbani Kayira, MBBS,‖ Julie A. E. Nelson, PhD,# Susan A. Fiscus, PhDr Gerald Tegha, BSc,¶ Deborah D. Kamwendo, MSc,‖ Joseph Rigdon, PhDr,‡ Jeffrey S. A. Stringer, MD,** Jonathan J. Juliano, MD, MSPH,† Sascha R. Ellington, MSPH,†† Athena P. Kourtis, MD, PhD, MPH,†† Denise J. Jamieson, MD,†† and Charles van der Horst, MD,† for the BAN study team

J Acquir Immune Defic Syndr • Volume 73, Number 5, December 15, 2016
BAN STUDY

✓ Better adherence  lower breastmilk HIV RNA  lower MTCT

✓ 90% vs 100% ART adherence: same MTCT

✓ No MTCT if plasma VL consistently <100
TIME TO SUPPRESSION AFTER ART INITIATION

If pre-ART VL > 100,000

Myer L et al. HIV Med 2017;18:80-8 n=620
FREQUENCY OF VIREMIC EPISODES IN HIV-INFECTED WOMEN ACHIEVING VIRAL SUPPRESSION

523 HIV+ women initiating antenatal ART with initial suppression. 85% breastfeeding

POSTNATAL MTCT IN BREASTFED INFANTS OF WOMEN ON ART

11 studies - all clinical trial settings – mothers on ART for 6 months. Rapid weaning advised

If maternal HIV prev is 20% translates into 220 new infections per 100 000 live births

Pooled estimate: 1.1% (0.3-1.9)

Bispo S et al. JIAS 2017;20:21251
POSTNATAL MTCT IN BREASTFED INFANTS OF WOMEN ON ART

11 studies - all clinical trial settings – mothers on ART for 6 months. Rapid weaning advised

Postnatal MTCT
4-6 weeks and 12 months: 2 studies

If maternal HIV prev is 20% translates into 580 new infections per 100 000 live births

Pooled estimate 2.9% (0.7-5.5%)

Bispo S et al. JIAS 2017;20:21251
<table>
<thead>
<tr>
<th></th>
<th>Pair 1</th>
<th>Pair 2</th>
<th>Pair 3</th>
<th>Pair 4</th>
<th>Pair 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mum</strong></td>
<td>Misses doses No transport VL 2 million cpml Non-adherent: resistance unlikely</td>
<td>Newly diagnosed when baby admitted to ICU Resistance unlikely VL very high</td>
<td>VL never done Reports adherence Poor VL monitoring: resistance unlikely</td>
<td>Stopped ART after delivery Non-adherent: Resistance unlikely</td>
<td>VL never done. Reports adherence Poor VL monitoring: resistance unlikely</td>
</tr>
<tr>
<td><strong>BF Baby</strong></td>
<td>3 months HIV neg EBF</td>
<td>3 months PCP pneumonia EBF</td>
<td>4 months Mixed feeding</td>
<td>7 months HIV neg</td>
<td>13 months Mixed feeding</td>
</tr>
</tbody>
</table>
Resource-constrained settings: 5 issues

Late ANC booking

Incident HIV infections during pregnancy / BF

Drug stock-outs

Poor VL Monitoring/ delayed return of results

High maternal HIV prevalence

**Start ANC (mo of preg)**

**Late ANC booking**

- Sub-Saharan Africa
  - 28%
  - 1st trimester

- United States, 2010
  - 73%

**Incident HIV infections during pregnancy / BF**

- 4.7 (3.3, 6.1)

**Drug stock-outs**

**Poor VL Monitoring/ delayed return of results**

**High maternal HIV prevalence**

**4.7 (3.3, 6.1)**

**2.9 (1.8, 4.0)**

**3.8 (2.0, 4.6)**

*CDC, Drake AL et al. PLoS Med 2014;11:e1001608*
INFANT PEP OPTIONS
1. Full viral suppression in breast milk takes several weeks to months

2. Thus, hypothetically, maternal ART may be less effective than infant prophylaxis if initiated postpartum or late in pregnancy

NICHD-HPTN 040/P1043: NO MATERNAL ANC ARVS

Randomisation 48 hrs post-delivery

- **Standard** 6 weeks AZT (8mg if ≤ 2kg or 12mg >2kg bd)
  - 3/12 MTCT 4.8%

- **DUAL**
  - **Standard** + 3 doses NVP in week 1 (1st dose 0-48 hrs, 2nd dose 48 hours after 1st dose, 3rd dose 96 hours after 2nd dose)
  - MTCT 2.2%

- **TRIPLE**
  - **Standard** + 2 weeks 3TC (4mg or 6mg bd) + nelfinavir (100/150/300mg bd)
  - MTCT 2.4%

- 17 sites – Brazil (70%), SA (27%), Argentina (2%), USA (1%) Apr 2004 – Jul 2010
- 9% BF at birth. <1% BF at 2 weeks
- **96% ARV adherence (diaries)**
- **Dual** - and triple-combination regimens reduced risk of intrapartum MTCT by ≈ 50% at 3 months compared with **Standard (n=1684)**
- Triple - more hematologic toxicity (neutropaenia) + difficult to administer
- Resulted in USA moving to **DUAL INFANT ARV prophylaxis**
WHO 2016 guidance for extended postnatal prophylaxis (ePNP)

All HIGH RISK newborns: daily AZT + NVP for 6 weeks

HIGH RISK breastfeeding infants continue either AZT and NVP or NVP alone for an additional 6 weeks

High risk assessed at delivery or later

**Known HIV+ mother:**
1. not on ART OR
2. on ART with VL>1000 OR
3. ART duration<5 weeks

**Newly identified HIV+ mother within 72 hours of delivery**
2016 guidance for extended postnatal prophylaxis (ePNP)

All HIGH RISK newborns: daily AZT + NVP for 6 weeks

HIGH RISK breastfeeding infants continue either AZT and NVP or NVP alone for an additional 6 weeks

Dilemmas:

1. Diagnosed during BF
2. Not virally suppressed & BF
3. Mother refuses ART or
4. Poor adherence

1. not on ART OR
2. on ART with VL>1000 OR
3. ART duration<5 weeks
AZT dosing is tricky since AZT clearance increases between birth and 6 weeks so the dose goes up 4-fold.

<table>
<thead>
<tr>
<th>Infant age (and birthweight)</th>
<th>Dosing of NVP</th>
<th>Dosing of AZT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW 2000–2499g</td>
<td>10 mg once daily</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td>BW ≥ 2500g</td>
<td>15 mg once daily</td>
<td>15 mg twice daily</td>
</tr>
<tr>
<td>6 to 12 weeks</td>
<td>20 mg once daily</td>
<td>60 mg twice daily</td>
</tr>
</tbody>
</table>

Doses are for term infants >35 weeks gestation.
Are we making life complicated?

Who is high risk? Assessing risk is difficult and time-consuming in busy clinics

1

Do you use two drugs or one drug from week 6 to 12? It seems easier to use 2 drugs but the jump in AZT dose is challenging

2

Formulations… Syrups are difficult to use and there is no FDC tablet for infant prophylaxis

3
<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>ePNP DURATION</th>
<th>REGIMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cote D’Ivoire</td>
<td>4 wks</td>
<td>NVP for HIV-1, AZT for HIV -2 or mixed</td>
</tr>
<tr>
<td>Angola, Cameroon, Malawi, Mozambique</td>
<td>6 wks</td>
<td>NVP</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>6 or 12 wks</td>
<td>NVP, duration based on timing of diagnosis and feeding</td>
</tr>
<tr>
<td>Uganda</td>
<td>12 wks</td>
<td>NVP</td>
</tr>
<tr>
<td>Tanzania</td>
<td>6 wks</td>
<td>AZT + NVP</td>
</tr>
<tr>
<td>Nigeria</td>
<td>6 wks</td>
<td>NVP if VL&lt;1,000; AZT+ NVP for HIGH RISK infants</td>
</tr>
<tr>
<td>Kenya</td>
<td>12 weeks</td>
<td>6 wks AZT + NVP then 6 weeks NVP</td>
</tr>
<tr>
<td>Ghana</td>
<td>12 weeks</td>
<td>AZT + NVP</td>
</tr>
<tr>
<td>South Africa, Zimbabwe</td>
<td>6 weeks</td>
<td>NVP</td>
</tr>
<tr>
<td></td>
<td>12 wks</td>
<td>AZT+ NVP for HIGH RISK</td>
</tr>
<tr>
<td>Zambia</td>
<td>6 wks</td>
<td>AZT+ NVP for LOW RISK: Mother&gt;12 wks on ART / complicated mother on ART&gt;12 wks, home delivery with arrival at HF &lt;72h</td>
</tr>
<tr>
<td></td>
<td>12 wks</td>
<td>AZT+ NVP for HIGH RISK : &lt;12 wks on ART /VL&gt;1,000/ Identified at delivery or during BF until infant’s final outcome: AZT+ NVP if mother refuses ART</td>
</tr>
<tr>
<td>COUNTRY</td>
<td>ePNP DURATION</td>
<td>REGIMEN</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cote D'Ivoire</td>
<td>4 wks</td>
<td>NVP for HIV-1, AZT for HIV -2 or mixed</td>
</tr>
<tr>
<td>Angola, Cameroon</td>
<td>6 wks</td>
<td>NVP</td>
</tr>
<tr>
<td>Malawi, Mozambique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td></td>
<td>HIV-1, AZT for HIV-2 or mixed</td>
</tr>
<tr>
<td>Ethiopia</td>
<td></td>
<td>HIV-1, AZT for HIV-2 or mixed</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>6 or 12 wks</td>
<td>NVP</td>
</tr>
<tr>
<td>Malawi</td>
<td></td>
<td>HIV-1, AZT for HIV-2 or mixed</td>
</tr>
<tr>
<td>Malawi</td>
<td></td>
<td>HIV-1, AZT for HIV-2 or mixed</td>
</tr>
<tr>
<td>Mozambique</td>
<td>12 wks</td>
<td>NVP</td>
</tr>
<tr>
<td>Tanzania</td>
<td>6 wks</td>
<td>AZT + NVP</td>
</tr>
<tr>
<td>Nigeria</td>
<td>6 wks</td>
<td>NVP, duration based on timing of diagnosis and feeding</td>
</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>6 wks</td>
<td>NVP if VL&lt;1,000; AZT+ NVP for HIGH RISK infants</td>
</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>12 weeks</td>
<td>NVP</td>
</tr>
<tr>
<td>Ghana</td>
<td>12 weeks</td>
<td>AZT + NVP</td>
</tr>
<tr>
<td>South Africa, Zimbabwe</td>
<td>6 weeks</td>
<td>AZT + NVP if mother&gt;12 wks on ART / complicated mother on ART &gt;12 wks on ART / delivery with arrival at HF &lt;72h</td>
</tr>
<tr>
<td>South Africa, Zimbabwe</td>
<td>12 weeks</td>
<td>AZT + NVP if mother&lt;12 wks on ART /VL&gt;1,000/ Identified at delivery or during BF until infant’s final outcome: AZT+ NVP if mother refuses ART</td>
</tr>
<tr>
<td>Zambia</td>
<td>6 wks</td>
<td>AZT + NVP</td>
</tr>
<tr>
<td>Zambia</td>
<td>12 wks</td>
<td>AZT + NVP</td>
</tr>
</tbody>
</table>

No programme/pragmatic trial data on ePNP effectiveness
FUTURE POSSIBILITIES
POSSIBLE SA OPTIONS

- NVP for baby for 6 weeks or until mother virally suppressed or breastfeeding has stopped
2 PLANNED TRIALS OF RESCUE THERAPY

Randomisation to infant ePNP (3TC) at 6-8 weeks immunization if maternal VL>1000
**Improved Neutralization Potency**

**VRC01 → VRC07-523-LS**

- 10 fold more potent
- Coverage improves to 96%
- Particularly good vs clade C (Seaman, Williamson et al, PlosPath 2016)
- Improved in vivo protection (SHIV) (Rudicell et al, J Virol 2014)
SUMMARY

Road travelled

Dilemmas

Infant PEP options

Future possibilities
We know:

- Cell-associated MTCT
- Viral suppression: 1-3 mo to < 1000, 5-6 mo to <50
- Postpartum rebound viraemia
- Increased mastitis/breast inflammation with ART
- In high HIV prev settings, case rates are >50 despite low MTCT %
Gaps

• Do newer dugs influence cell-associated HIV?
• Registry to track MTCT
• Clinical monitoring and pharmacokinetics
• Mastitis during ART?
• Optimal prophylaxis for infants – what combinations? Neutralising antibodies?
• Health systems issues and differential models of care
DO WE KNOW HOW TO SUPPORT BREASTFEEDING?

• Back to basics: attachment, positioning, breast health
• But also important to monitor viral load!!!!
Can we eliminate breastmilk MTCT?

Perhaps with:

- maternal ART + infant ePNP OR
  maternal ART + infant ePNP + infant bNAb OR
  maternal ART + maternal bNAb + infant ePNP + infant bNAb AND
- Viral load monitoring AND
- Breastfeeding monitoring AND
- Reducing maternal HIV incidence and prevalence
THANK YOU!

- Lynne Mofenson
- Hoosen Coovadia
- Landon Myer
- Hermione Lyall
- Shaffiq Essajee
- Philippe van der Perre
- SAMRC:
  - Vundli Ramokolo
  - Nobubelo Ngandu
  - Witness Chirinda
  - Duduzile Nsibandé

Breastfeeding rocks!
Let’s make it risk free!

Health Systems Research Unit, South African Medical Research Council
Ameena Goga: Ameena.Goga@mrc.ac.za