All HIV+ Women on Antiretroviral Therapy Should Breastfeed in Both Low and High Resource Settings

VOTE NO!!

Lynne Mofenson MD
Elizabeth Glaser Pediatric AIDS Foundation
My Esteemed Opponent Will Likely Present You With a Number of Arguments To Support “ALL HIV+ Women Should Breastfeed”

- Breastfeeding is critical to protect against mortality and morbidity in infants.
- Breast milk enhances the immune system.
- Breast milk is best to support nutrition of neonate.
- If a mother is on ART and virally suppressed, she won’t transmit HIV to her infant.
- Problem: “All” – means no exceptions.

All generalizations are false, including this one. Mark Twain

Decision requires consider geography & individual circumstances.
Breastmilk and Infant Mortality/Morbidity

- You can’t generalize from Africa to U.S.
  - Studies clearly show excess mortality/morbidity with formula feeding or early weaning – in Africa.
  - However, in resource-rich countries, infectious disease mortality/morbidity is low, and safe affordable formula available.

NIH
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Health research throughout the lifespan

Top 5 causes infant death reduced by BF

**Low Resource Countries**
- Neonatal encephalopathy
- Infections (blood)
- Cx preterm birth
- Lower respiratory tract infections
- Diarrheal disease

**United States**
- Birth defects
- Preterm birth
- SIDS
- Pregnancy complications
- Accidents
As you heard from Dr. Serghides, differences observed in breast milk from HIV+ vs HIV- mothers, diverging in:

- Protein and mineral levels, even when on ART (Fouche C. Breastfeed Med 2016;11:455-60)

- Oligosaccharide milk levels, resulting in differences in microbiome of HIV-exposed uninfected and unexposed infants (Bender JM. Sci Transl Med 2016;8:349)


- BAN trial (Malawi) found HIV+ women on ART have lower B vitamin levels (Allen LH. Am J Clin Nutr 2015;102:1468-71)

The assumed benefits of BF (in high-resource settings where mortality issues not critical), may be less than thought due to differences in BM composition in HIV+ mothers even on ART.
ART Does NOT Eliminate Postnatal MTCT Risk

- Even in “best scenario” – RCT PROMISE - still nearly a 1% postnatal infection risk with mothers on ART.
- RCT do not necessarily reflect “real life” clinical experience.

Monthly Risk PP MTCT from Mothers Starting ART During Pregnancy

*Mahy M et al. AIDS 2017 (in press)*

- Overall Estimate Late (>4-6 weeks) Postpartum MTCT: 0.12%/mo [not accounting for CD4/time on ART]
- 6.1% PP MTCT at 12 mos
- 3.3% PP MTCT at 12 mos
- 1.2% PP MTCT at 12 mos

None Of These Values Are Zero
Why Doesn’t ART Eliminate Risk?
BM Cell-Associated HIV DNA Important in Early Postnatal MTCT

Ndirangu J et al. PLoSOne 2012;7:e51493

<table>
<thead>
<tr>
<th>Breast</th>
<th>MTCT risk and BM sample age 6 weeks</th>
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</thead>
<tbody>
<tr>
<td>Milk</td>
<td>Adjusted OR*</td>
</tr>
<tr>
<td></td>
<td>P value</td>
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<tr>
<td>Cell-associated HIV DNA (/log ↑)</td>
<td>2.47</td>
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<tr>
<td>(1.3-4.6)</td>
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</tr>
<tr>
<td>Cell-free HIV RNA (/log ↑)</td>
<td>1.52</td>
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<tr>
<td>(1.2-2.0)</td>
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* Adjusted for maternal CD4 count and viral load at delivery

Controlling for CD4/plasma VL, cell-associated virus level more strongly associated with early 6 week postnatal HIV MTCT than cell-free virus, but cell-free more important at 6 months.

Cellular composition BM highest 4-6 wks life

![Cellular composition BM](chart.png)
ART Reduces Breast Milk HIV Cell-Free (RNA) But Not HIV Cell-Associated (DNA) Viral Load


- Significant decrease BM HIV RNA on ART, p=0.0001
- No significant decrease BM HIV DNA on ART, p=0.39
ART Adherence is Particularly Challenging Postpartum in Both High- and Low-Resource Settings

Nachega J et al. AIDS 2012;26:2039-52

- Meta-analysis 51 studies in 20,153 pregnant women.
- Adequate adherence defined as >80% adherence to doses.
- Overall, only 73% reported >80% adherence.

- Adherence was significantly worse in the postpartum period.

<table>
<thead>
<tr>
<th>% Adherent (95% CI)</th>
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<tr>
<td>75.7 (71.5-79.7)</td>
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<td>53.0 (32.8-72.7)</td>
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523 HIV+ women starting ART during pregnancy who had initial suppression.

- Proportion elevated VL increases steadily with increasing time after initial viral suppression.
- Cumulatively, by 1 year PP, 31% of women had experienced at least 1 VL >1,000 c/mL.
Poor Adherence = Viremia = Increased MTCT Risk

Detectable VL HIV+ Pregnant Women on Preconception ART Starting ANC, South Africa


- 364 HIV+ women on ART (68% NNRTI, 12% PI) at 1st ANC visit (pre-conception ART), 4/2013 and 1/2014; median duration 2.7 yrs. Assessed viral load at 1st ANC visit.

How do these VL translate to MTCT at 4-6 wks? Myer L et al. HIV Med 2017;18:80-8
BM penetration greatest (but variable) with NRTI > NNRTI > PI. Accumulation of TDF & PI minimal (BM contains tenofovir, not in bioavailable form; PI > 90% protein bound).

Infant BM ingestion results varying infant plasma levels for individual ARVs (estimated ingestion ~5-15% of infant daily therapeutic dose for NVP and 3TC; ~2-5% for EFV).

Infected infant is exposed to low ARV levels or “mono-therapy”; results in high rate drug resistance should infant become infected.
Drug Resistance – Including Multi-Drug Resistance - in Breastfeeding HIV+ Infants of Mothers Receiving ART

- **KiBS study, Kenya** (Zeh C. *PLoS Med* 2011;8:e1000430):
  - 24 infants infected PP by 6 mo; 16 (67%) resistance at 6 mos, most between 6-14 wks; none in 8 infants infected >6 mo (ARV stop at 6 months with recommended weaning)
  - Multiclass: most common M184V and K103N

- **PEPI-Malawi** (Fogel J. *CID* 2011;52:1069-76):
  - Analysis 6 mos after maternal ART initiation in 1st PP year
  - Resistance: 30/37 (81%) had NNRTI resistance; multi-class resistance detected in 11/37 (29.7%) infants

  - Drug resistance in 15% (dual class in 3%) of HIV+ children age <3 years starting 1st line ART (39% if PMTCT exposure)
  - Resistance was associated with current maternal ART (aOR 6.4) and current breastfeeding (aOR 7.4)
Instead of (Over) Generalizing to “ALL” Mothers, BF Risks & Benefits by HIV+ Mom are Situation-Dependent

- In situations where:
  - Infectious mortality is low;
  - There may be reduced benefit (immune/nutrition) of HIV+ mother breast milk regardless of ART;
  - We know ART doesn’t affect cell-associated HIV levels;
  - While ART decreases PP MTCT, it doesn’t eliminate it;
  - In women on ART, “perfect adherence” with persistent suppression is not seen, even with preconception ART;
  - Multiple studies show adherence is worse in PP period;
  - If infant infected, ARV presence in breast milk may lead to multi-class resistance; AND
  - Safe and affordable replacement feeding is available:
And Given We Know You Can **Completely Prevent** Postnatal Transmission by Replacement Feeding – Why Would You Take the Risk?

Even in ART era, mortality HIV+ children is still >30 fold higher than similarly aged children (0.49/100 HIV+ vs 0.02/100 children 5-14 years in US)  

*(Brady M et al. JAIDS 2010;53:86-94)*
For These Reasons, BF is Generally **Not** Recommended for HIV+ Women in US

**However, Individual Circumstances Need to be Considered**

- Women may face social, familial, and personal pressures to consider breastfeeding in U.S. despite recommendation.

- Without effective education and support, HIV+ women may breastfeed or use mixed feeding to resolve infant feeding pressures/conflicts, and increase risk transmission to infant.

- In such circumstances, *harm-reduction counseling strategy* recommended (see excellent paper describing such by Levison J et al. *Clin Infect Dis* 2014;59:304-9).
I know it is hard to vote against my esteemed opponent, *Washington Post*-featured pediatrician Dr. Rakhmania.

Natella Rakhmanina opened the door to exam room No. 4 and pulled two chairs next to the medical table, facing them toward each other. *Washington Post* September 24, 2015

- But in this case, you should! Vote THUMBS DOWN for ALL HIV+ women should breastfeed.
Thanks For Your Attention!

GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE
2011-2015

It always seems impossible until it’s done
- Nelson Mandela