INFANT FEEDING STRATEGIES FOR MOTHERS WITH HIV

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OBJECTIVES

- Review historical perspectives of perinatal HIV infection related to infant feeding
- Review contemporary evidence for infant feeding and perinatal HIV risk reduction
- Discuss new recommendations related to infant feeding strategies for U.S. mothers with HIV

EVIDENCE FOR INFANT FEEDING AND PERINATAL HIV INFECTION

OBSERVATIONAL STUDIES

EARLY CASE SERIES DATA FOR PHIV THROUGH BREAST FEEDING

TABLE I—ESTIMATES OF THE RISK OF HIV-1 TRANSMISSION FROM A BREASTFEEDING MOTHER INFECTED POSTNATALLY

Location	Description of study or report	Risk of transmission	Notes
Kigali,[12,13] Rwanda	212 mothers seronegative at delivery. Mothers and children bled 3 monthly. PCR on stored samples from children of seroconverting mothers. 6 mothers seroconverted before 3 months, 10 between 3 months and 18 months; presumably infected through heterosexual contact. Follow-up of children 36 months after maternal seroconversion.	5/9	Excluding 6 mothers who seroconverted before 3 months (5 of their children are infected); 1 child who was weaned before mother seroconverted. The 5 infected children had last negative PCR at delivery (2 children), 3 months, 12 months, and 18 months
Lusaka,[14] Zambia	1720 mothers seronegative at delivery. 634 returned for serological testing 1 year post partum. 19 had seroconverted; all seem to have been antigen-negative at delivery. Presumably infected through heterosexual contact. Children's serostatus tested between 12 and 24 months.	3/19	No details given of 3 infected children or their mothers other than children antibody positive at 18, 20 and 22 months. All children breastfed for 15–18 months.
Australia[10]	11 mothers received infected blood transfusion post partum; no other risk factors; 10 breastfed for 2 weeks to 3 months. 1 IVDU mother seroconverted 6–10 months post partum; breastfed until 14 months.	3/11	Child of IVDU mother infected. All children's serostatus tested at least 3 months after cessation of breastfeeding.
Kinshasa,[11] Zaire	3 mothers seronegative at delivery. Infected via blood transfusion, 2 during caesarean section, 1 when child 11 months old.	1/3	2 children born to mothers transfused at delivery seronegative when last tested at 6 months, 9 months and still being breastfed.
Total		12/42 (29%, 95% CI 16–42%)	

Cumulative risk of PHIV diagnosed in infants born to women who were HIV negative at birth

Dunn et al. Lancet. 1992

"*In 1996, the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended that HIV-1 seropositive women in resource-poor areas be encouraged to make informed choice about infant feeding.*"

Most-at-risk infants in the developing world breast fed to reduce the risk of infectious morbidity and mortality (ex. diarrhea, pneumonia, and otitis media)

Nduati et al. JAMA. 2000.

INFANT FEEDING AND RISK OF PHIV IN BRAZIL

TABLE 1. *Risk of vertical transmission of HIV-1 by breast-feeding*

Risk factors	No. of children	No. of infected children (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	*p* Value[d]
Breast feeding ($N = 432$)					
Never	264	33 (13)	1.0	1.0	
Ever	168	36 (21)	1.9 (1.1–3.2)	2.2 (1.3–3.8)	.004
Duration of breast-feeding (days) ($N = 151$)[b]					
1–3	38	5 (13)	1.0	1.0	
4–30	42	8 (19)	1.6 (0.5–5.2)	1.2 (0.3–4.5)	
31–90	34	5 (15)	1.1 (0.3–4.3)	1.4 (0.4–5.7)	.06[c]
≥91	37	11 (30)	2.8 (0.9–9.0)	3.1 (0.9–10.6)	

- Observational study of Brazilian women-infant pairs, many women initiated breast feeding before HIV status was known; n, 432
- Median duration of breast feeding 30 days
- Outcome= PHIV (HIV-1 Ab+ at 18 months)
- 69/432 (16%) infants were diagnosed with HIV; advanced maternal HIV, longer duration of breast feeding, and mixed feeding were associated with increased risk (but not statistically significant)

Tess et al. JAIDS. 1998

"When children born to women with HIV can be ensured uninterrupted access to nutritionally adequate breast-milk substitutes that are safely prepared and fed to them, they are at less risk of illness and death if they are not breastfed. However, when these conditions are not fulfilled, in particular in an environment where infectious diseases and malnutrition are the primary cause of death during infancy, artificial feeding substantially increases children's risk of illness and death."

UNAIDS, UNICEF, and WHO. HIV and infant feeding: guidelines for decision-makers.

1998

INFLUENCE OF INFANT-FEEDING PATTERNS ON EARLY PHIV

- Observational study in Durban, South Africa
- N, 549 women with HIV-1 + singleton infants
- Infant-feeding strategies: formula, exclusive BF, and mixed feeding
- Infants tested at birth, 1 weeks, 6 weeks, 12 weeks, and every 3 months until 15 months
- Median duration of exclusive breast feeding 6 months (IQR 1-10)
- Infants who exclusively breast fed were at the lowest risk of HIV-1 infection by 3 months age
- *No comments on maternal ARV use

	Estimated proportion (%) HIV-1 infected (95% CI)		
	Never breastfed (n=156)	Exclusively breastfed ⩾3 months (n=103)	Introduced other food <3 months (n=288)
Total sample			
By day 1	6·4 (2·5–10·3)	6·8 (1·9–11·7)	5·2 (2·6–7·8)
By 1 month	14·8 (9·2–20·4)	8·7 (3·3–14·2)	14·2 (10·1–18·3)
By 3 months	18·8 (12·6–24·9)	14·6 (7·7–21·4)	24·1 (19·0–29·2)
Infants HIV-1 negative on day 1			
By 1 month	8·3 (3·8–12·8)	2·1 (0–4·9)	9·5 (6·0–13·0)
By 3 months	13·2 (7·7–18·7)	8·3 (2·8–13·9)	19·9 (15·0–24·9)

Coutsoudis et al. Lancet. 1999.

RCT OF BREAST AND FORMULA FEEDING IN WOMEN WITH HIV-1

Randomized controlled trial of 425 HIV-1 seropositive women in Nairobi, Kenya 1992-1998

212 to breastfeed and 213 to formula feed

401 mother-infant pairs followed for 24 months; 17% lost to follow up

Estimated risk of HIV-1 transmission through breast feeding 16% in 24 months

Most transmissions occurred in the first 6 months (75%)

Infant mortality rates were similar between groups

Table 3. Cumulative Human Immunodeficiency Virus Type 1 (HIV-1) Infection for Infants in the Breastfeeding and Formula Feeding Arms*

	No. of Infants With HIV-1 Infection†		No. of Infants Whose HIV-1 Status Is Known‡		Cumulative HIV-1 Infection Rate (95% CI)§		Difference in Cumulative HIV-1 Infection Rates (95% CI)	*P* Value
Infant Age	Breastfeeders	Formula Feeders	Breastfeeders	Formula Feeders	Breastfeeders	Formula Feeders		
Birth	15	7	191	193	7.0 (2.3 to 11.7)	3.1 (–2.4 to 8.6)	3.9 (–3.3 to 11.1)	.35
6 Weeks	43	20	186	180	19.9 (14.2 to 25.6)	9.7 (5.4 to 14.0)	10.2 (3.1 to 17.3)	.005
14 Weeks	47	28	182	173	24.5 (18.4 to 30.6)	13.2 (7.9 to 18.5)	11.3 (3.2 to 19.4)	.007
6 Months	53	32	175	169	28.0 (21.7 to 34.3)	15.9 (9.6 to 22.2)	12.1 (3.2 to 21.0)	.009
12 Months	63	36	165	161	32.3 (25.6 to 39.0)	18.2 (11.9 to 24.5)	14.1 (4.9 to 23.3)	.003
24 Months	71	41	142	128	36.7 (29.4 to 44.0)	20.5 (14.0 to 27.0)	16.2 (6.5 to 25.9)	.001

Nduati et al. JAMA. 2000.

ESTABLISHED RISK FACTORS & SUGGESTED INTERVENTION

TABLE 2. Proven or Potential Interventions to Prevent Human Milk Transmission of HIV-1

Risk Factor for Transmission	Associated Intervention
Longer exposure to human milk from an HIV-1-infected woman	Complete avoidance of breastfeeding Early weaning
Greater maternal infectivity (eg, higher maternal viral load in peripheral blood and in human milk)	Maternal antiretroviral therapy while breastfeeding
Factors facilitating viral transfer from mother to child (eg, mixed breastfeeding)	Avoidance of mixed breastfeeding (encouragement of exclusive breastfeeding)
Infant susceptibility to infection	Improvement of infant defenses against infection (eg, with passive immunization or with antiretroviral prophylaxis to breastfeeding infants)
Maternal breast abnormalities (infection)	

- Author/committee recommended
  - Exclusive breast feeding for short duration (4-6 mo)
  - Rapid weaning by 6 months
  - Treat mastitis and infant oral candidiasis quickly

Read and Committee on Pediatric AIDS. Pediatrics. 2003 .

POSTNATAL TRANSMISSION OF HIV-1 IN BREASTFED CHILDREN: META-ANALYSIS

9 studies, 4,085 African children breastfed

3,025 children were HIV negative at 4 weeks of age

All breastfed at least 28 days

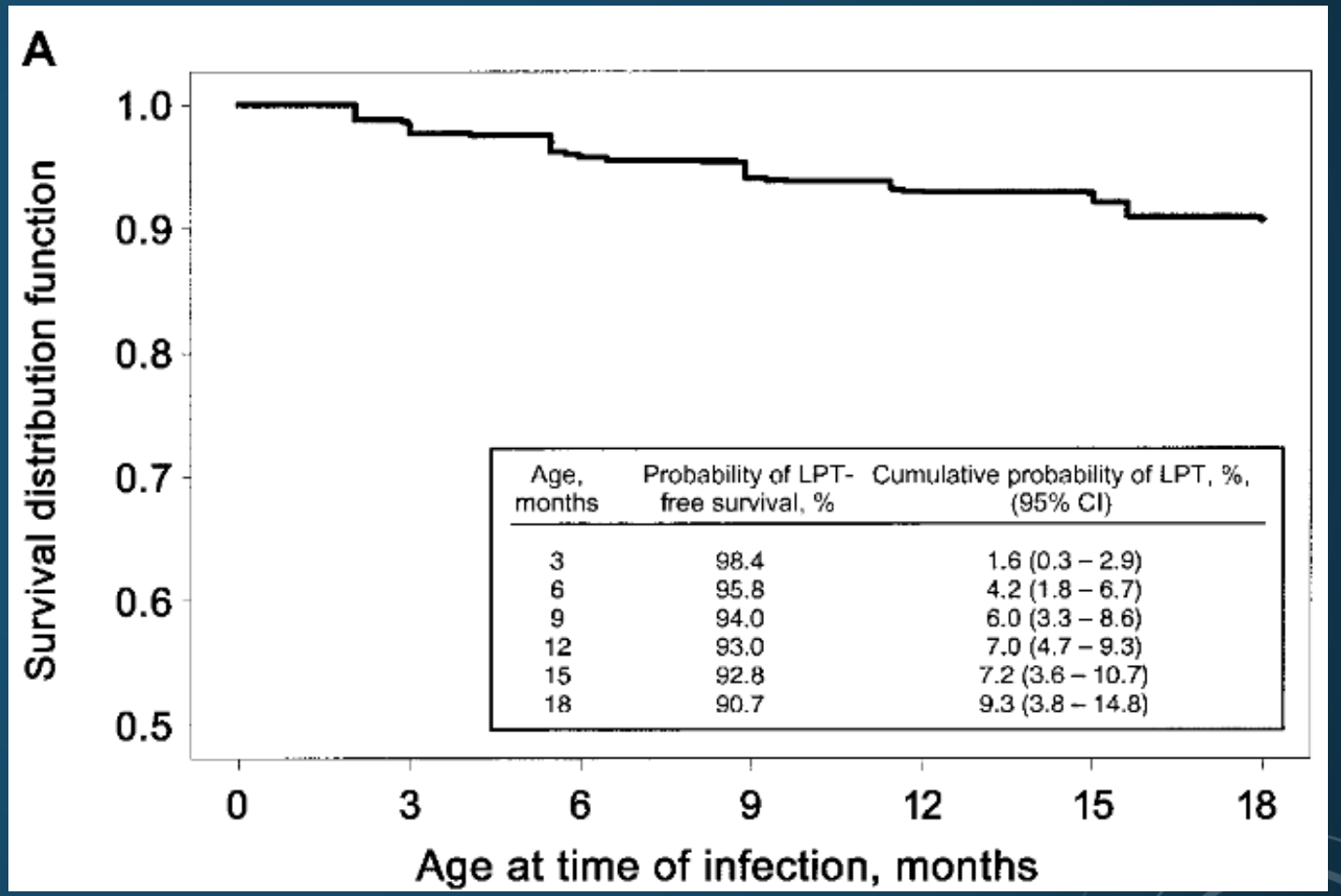
- Median 10 months (IQR 4.7-17 mo)

223 (7%) had late postnatal transmission

Independent risk factors for postnatal HIV

- Maternal CD4 cell count < 200, aHR 8.0 (4.8-13.3)
- Female infant, aHR 0.6 (0.4-0.9)

Infants were at risk of postnatal HIV infections while breastfeeding up to 18 months



Age, months	Probability of LPT-free survival, %	Cumulative probability of LPT, %, (95% CI)
3	98.4	1.6 (0.3 – 2.9)
6	95.8	4.2 (1.8 – 6.7)
9	94.0	6.0 (3.3 – 8.6)
12	93.0	7.0 (4.7 – 9.3)
15	92.8	7.2 (3.6 – 10.7)
18	90.7	9.3 (3.8 – 14.8)

Breastfeeding and HIV Int Trans Study Group. JID. 2004.

CLINICAL TRIALS

MASHI STUDY: SUPPRESSION OF HIV-1 RNA IN BREAST MILK

- Nested cohort study Botswana 2001-2003
- Women randomized to ART (n, 26) or no ART (n,25)
- ART: zidovudine, lamivudine, and nevirapine
- All women on ART had CD4 < 200 cells/mm3 and/or AIDS-defining illness. Controls were matched by CD4 cell count
- Breast milk collected 2 or 5 months postpartum
- No postnatal infections occurred

- **Women on ART had lower HIV-1 plasma and milk RNA. No difference in milk HIV-1 DNA.**

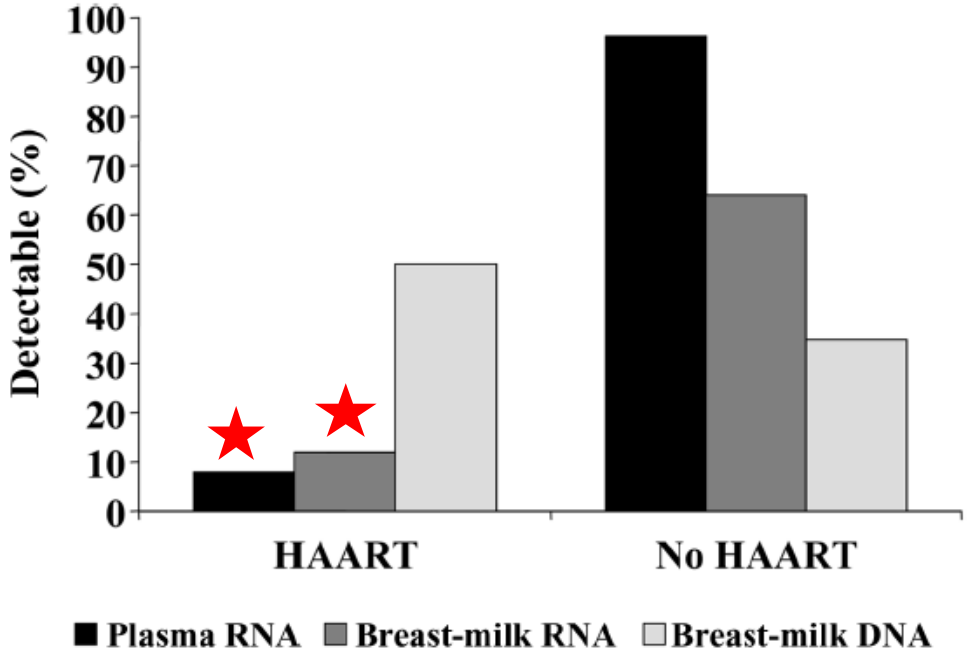
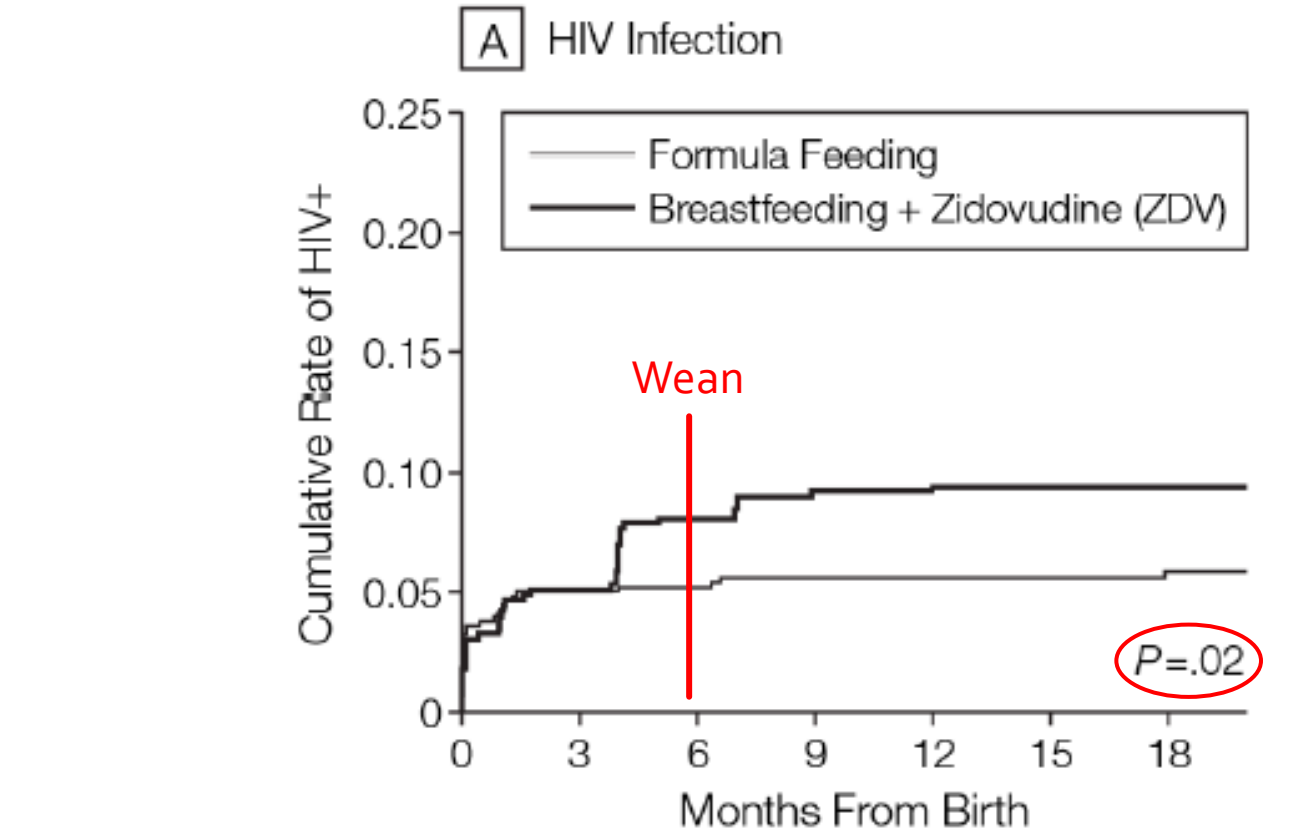


Figure 3. Comparison of plasma HIV-1 RNA load, breast-milk HIV-1 RNA load, and breast-milk HIV-1 DNA load, by highly active antiretroviral therapy (HAART) status. Limits of detection were 400 copies/mL for plasma HIV-1 RNA load, 50 copies/mL for breast-milk HIV-1 RNA load, and 10 copies/mL for HIV-1 DNA load.

Shapiro et al. JID. 2005.

MASHI STUDY: FORMULA AND BREAST FEEDING + INFANT ZIDOVUDINE PROPHYLAXIS



1,200 Botswanan women were randomized to formula feed or breast feed + infant zidovudine prophylaxis, 2001-2003

Infant dose: ZDV 4mg/kg BID 0-1 month, 4m/kg TID 1-2 months, and 6mg/kg TID 2-6 months

Wean between 5- 6 mos

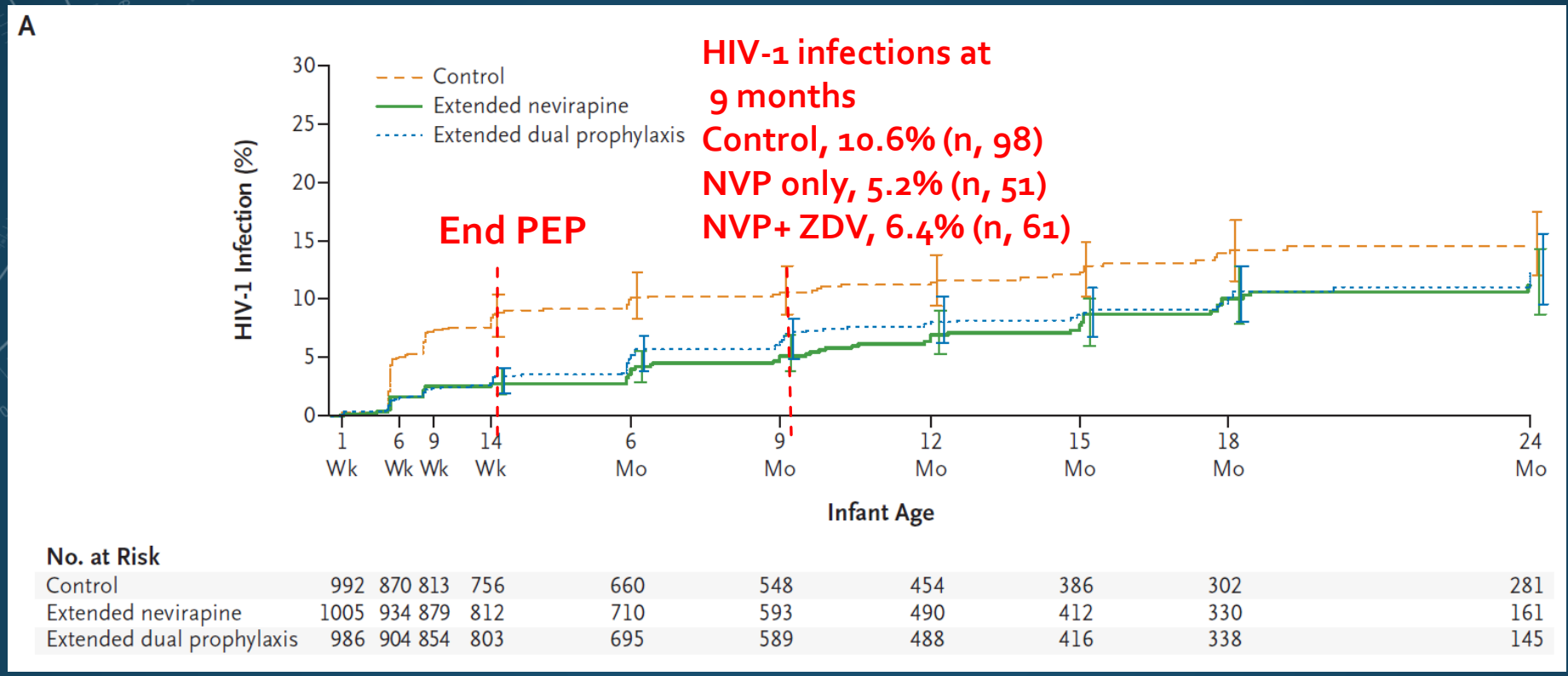
Infants were evaluated at birth, monthly for 7 months, and q3 months until 18 months old

Outcome= PHIV

PHIV occurred in 6.0% of formula-fed infants and 9.5% of breastfed/ZDV infants

Thior et al. JAMA. 2006.

EXTENDED PROPHYLAXIS TO REDUCE BREAST-MILK HIV-1 TRANSMISSION



No. at Risk										
Control	992	870	813	756	660	548	454	386	302	281
Extended nevirapine	1005	934	879	812	710	593	490	412	330	161
Extended dual prophylaxis	986	904	854	803	695	589	488	416	338	145

HIV-1 infections
At 24 months
Control, 15.6%
NVP only, 10.8%
NVP+ZDV, 11.2%

RCT of 3,216 women and infants in Malawi, 2004-2007. All infants received sdNVP 2mg/kg+ ZDV 4mg/kg BID x 7 days (control)

NVP only: 2mg/kg daily x2 wks, 4mg/kg daily week 3-14

NVP + ZDV 4mg/kg BID 2-5 weeks, 4mg/kg TID 6-8 weeks, 6mg/kg TID 9-14 weeks

< 3% of women in each arm were prescribed maternal ART

Outcome, PHIV at 9 months; most weaned by 6 mos but 20% continued to breast feed at 9 months

Conclusion, either extended infant prophylaxis strategy was more effective than control at prevention of PHIV

Kumwenda et al. NEJM. 2008.; Taha et al. JAIDS. 2011

MMA BANA STUDY

- Botswana, 2006-2008, 709 women 18-34 wks and followed 6 months postpartum until weaning
- Maternal treatment groups while breast feeding
- (obs) NVP+ZDV/3TC BID, n 156
- NRTI-based, ABC/ZDV/3TC BID n,283
- PI-based, ZDV/3TC+ LPV/RIT BID n, 270
- Outcomes: viral suppression and PHIV
- Viral suppression (<400 copies/mL) was similar between 3 groups
- PHIV occurred in **1.1% infants** (6 DOL4 and 2 HIV+ while breast feeding. Both infants in NRTI group)
- Maternal ART and viral suppression resulted in fewer infant infections

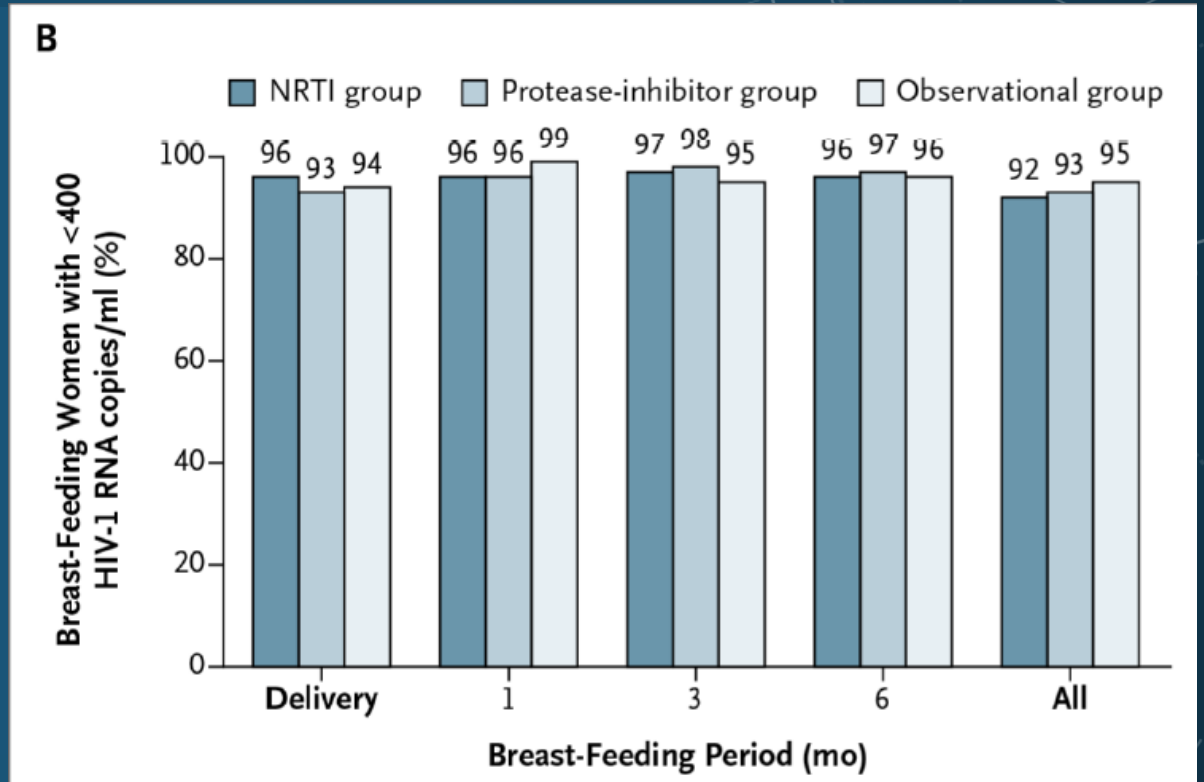


Figure 2. Analyses of Selected Outcomes, According to Study Group.

Shapiro et al. NEJM. 2010

BAN STUDY: BREASTFEEDING, ANTIRETROVIRALS, AND NUTRITION

- Malawi RCT, 3 groups: 2,469 participants
- maternal ART (849), infant ART (852), controls (668)
- All mothers at birth: ZDV/3TC BID x 7 d during labor to PPD 7
- All infants ZDV/3TC BID birth to DOL7
- Maternal ART while breastfeeding: ZDV/3TC+NVP (39), ZDV/3TC+NFV (146), & ZDV/3TC+LPV/RIT (664)
- Infants PEP while BF: NVP daily birth to 6 months
- Outcome: PHIV
- PHIV diagnoses after DOL14 were more common in controls and least likely among infants treated during breast feeding.

Table 2. Estimates of the Cumulative Risk of HIV-1 Infection and a Composite of HIV-1 Infection or Death among Infants Who Were HIV-1–Negative at 2 Weeks.*

No. of Days	Maternal Regimen		Infant Regimen		Control	
	No. of End Points	Probability of End Point % (95% CI)	No. of End Points	Probability of End Point % (95% CI)	No. of End Points	Probability of End Point % (95% CI)
HIV-1 infection						
42	7	0.9 (0.4–1.9)	1	0.1 (0.0–0.9)	12	2.0 (1.2–3.6)
84	13	1.7 (1.0–3.0)	4	0.5 (0.2–1.4)	21	3.6 (2.4–5.5)
126	14	1.9 (1.1–3.2)	4	0.5 (0.2–1.4)	25	4.4 (3.0–6.4)
203†	21	2.9 (1.9–4.4)	12	1.7 (1.0–2.9)	32	5.7 (4.1–8.0)

Chasela et al. NEJM. 2010.

"We now have the tools to make a considerable difference in controlling the pediatric HIV-1 epidemic. A generation of children awaits our actions."

Lynne M. Mofenson, Peds Inf Dis

Retired NIH

NEJM. 2010.

"WHO recommends that women who breastfeed and receive ARVs or whose infants are receiving ARVs should exclusively breast feed their infants for 6 months and continue breast feeding until 12 months of age and only then consider stopping."

World Health Organization guidelines on "HIV and Infant Feeding 2010"

Option A: maternal ZDV 14wks to delivery and infant NVP daily for 7 days

Option B: maternal cART during pregnancy and 7 days post-weaning

Option B+: lifelong cART for all pregnant women

https://www.who.int/publications/i/item/FWC-MCA-12.1

In well resourced settings, the complete avoidance of breastfeeding has been a major factor in reducing transmission, and breastfeeding is not recommended for HIV-infected women (including those receiving HAART) [18••,19••]. Although the use of replacement feeding has been documented to be safe and feasible in some less resourced settings, such as in Thailand, Brazil and some African urban areas, it is not a feasible option in many low-resource settings [37•,46,47•,48]. The use of exclusive breastfeeding rather than 'mixed' feeding has been shown to provide some protection against infection, but this does not prevent all infections, with transmission rates in exclusively breastfed infants of up to 14% at 6 weeks and 20% at 6 months even in the best managed research settings [49]. Exclusive

McIntrye. "Use of antiretrovirals during pregnancy and breast feeding in low-income and middle-income countries." Curr Opin HIV AIDS. 2010.

KESHO BORA STUDY

RCT in Burkina Faso, Kenya, & S. Africa 2003-2008

Aim: assess efficacy of ART vs ZDV/NVP for prevention of PHIV during pregnancy and breast feeding. Outcome: PHIV by 1yr

Pregnant women with HIV-1 at 34wks: cART (ZDV/3TC+LOP/RIT) (n,412) or ZDV+ sdNVP (n,412)

*12/2006, protocol amendments: all women start ART28 weeks, receive ZDV/3TC x 7d pp for women in ZDV/NVP group and all infants received ZDV BID x 1 week pp

	Triple antiretroviral (n=401)		Zidovudine and single-dose nevirapine (n=404)		Relative risk reduction	p value
	Cumulative number of events/number at risk	Rate (95% CI)*	Cumulative number of events/number at risk	Rate (95% CI)*		
Infection						
Birth	7/394	1·8% (0·9–3·7%)	10/402	2·5% (1·3–4·6%)	28%	..
6 weeks	13/375	3·3% (1·9–5·6%)	20/374	5·0% (3·3–7·7%)	34%	..
6 months	19/349	4·9% (3·1–7·6%)	33/339	8·4% (6·0–11·6%)	42%	..
12 months	21/333	5·4% (3·6–8·1%)	37/305	9·5% (7·0–12·9%)	43%	0·029†
Infection or death						
Birth	11/399	2·8% (1·5–4·9%)	12/404	3·0% (1·7–5·2%)	7%	..
6 weeks	19/376	4·8% (3·1–7·4%)	25/376	6·2% (4·2–9·1%)	23%	..
6 months	33/352	8·4% (6·0–11·6%)	50/339	12·6% (9·7–16·3%)	33%	..
12 months	40/334	10·2% (7·6–13·6%)	63/304	16·0% (12·7–20·0%)	36%	0·017†

PHIV 2x more likely among ZDV/NVP group

Maternal cART while BF reduces PHIV

Lancet Inf Dis. 2011

HIV PREVENTION TRIALS NETWORK (HPTN) 046

2008-2010 S. Africa, Tanzania, Uganda, and Zimbabwe

HIV DNA negative infants randomized to placebo (n, 765) OR NVP daily for 6 months or until weaned (n, 762)

All infants received 6 weeks of prophylaxis; Outcome: PHIV age 6 months

	Extended nevirapine (n=769)		Placebo group (n=753)		Relative-risk reduction	p value*
	Endpoints	Probability of endpoint† (95% CI)	Endpoints	Probability of endpoint† (95% CI)		
All randomly allocated infants						
HIV-1 infection						
6 months	8/700	1·1% (0·3–1·8)	18/699	2·4% (1·3–3·6)	54%	0·049
9 months	11/692	1·5% (0·6–2·4)	21/683	2·9% (1·7–4·1)	48%	0·078
12 months	15/557	2·1% (1·0–3·1)	22/545	3·0% (1·8–4·2)	30%	0·265
Death						
6 months	9/716	1·2% (0·4–2·0)	8/725	1·1% (0·3–1·8)	0%	0·81
9 months	16/703	2·2% (1·1–3·2)	19/705	2·6% (1·4–3·7)	15%	0·61
12 months	20/580	2·8% (1·6–4·0)	26/572	3·6% (2·2–4·9)	22%	0·39
HIV-1 infection or death						
6 months	17/706	2·3% (1·2–3·4)	24/707	3·2% (2·0–4·5)	28%	0·27
9 months	26/693	3·6% (2·2–4·9)	39/687	5·3% (3·7–6·9)	32%	0·10
12 months	32/562	4·5% (3·0–6·0)	46/547	6·3% (4·6–8·1)	29%	0·12

Infants receiving NVP daily while BF at a 50% risk reduction of PHIV at 6 months of age.

Coovadia et al. Lancet. 2012.

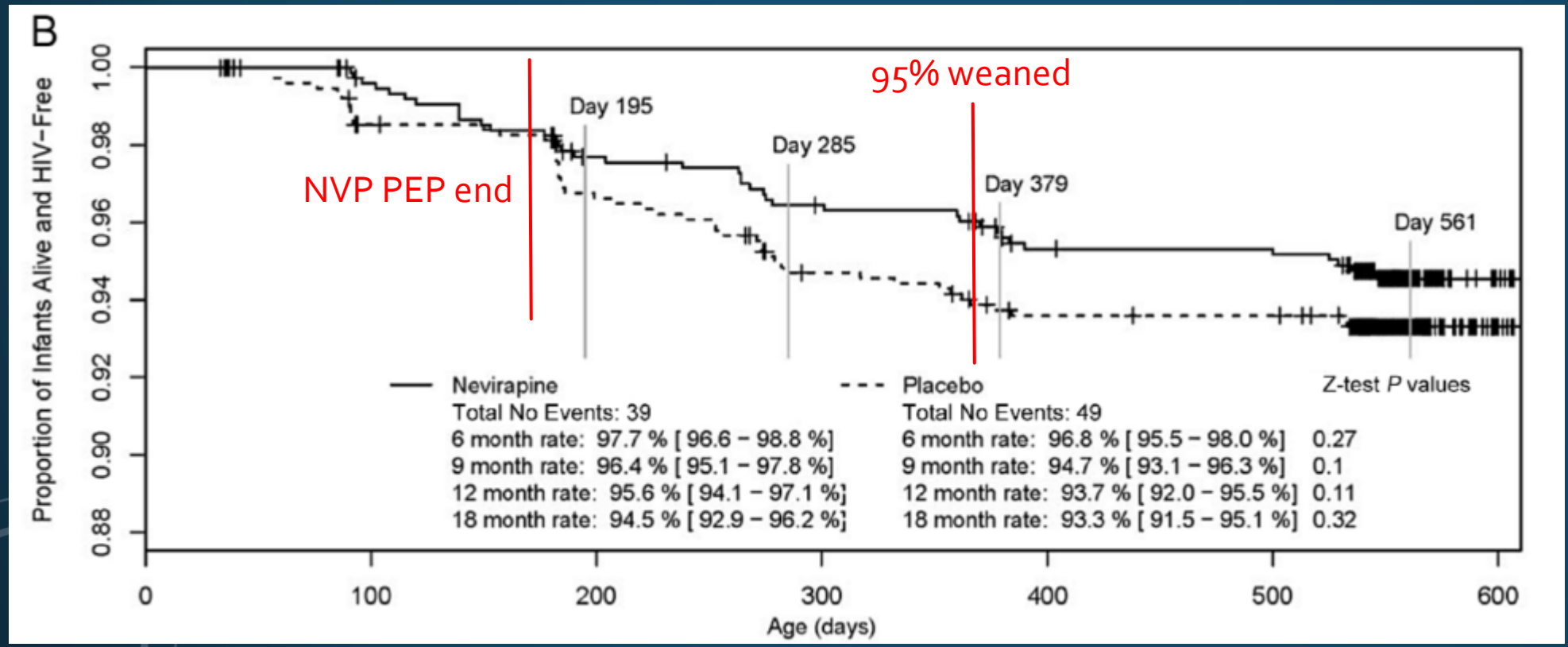
HPTN 046 SUBGROUP ANALYSES

Subgroup analyses	Extended nevirapine (n=769)		Placebo group (n=753)		Relative-risk reduction	p value*
	Endpoints	Probability of endpoint† (95% CI)	Endpoints	Probability of endpoint† (95% CI)		
Infection from mothers on HAART at randomisation, independent of CD4 cell count						
6 months	1/210	0·5% (0–1·4)	0/203	0%	0%	..
9 months	1/169	0·5% (0–1·4)	1/166	0·5% (0–1·4)	0%	0·976
12 months	1/90	0·5% (0–1·4)	1/81	0·5% (0–1·4)	0%	0·976
Infection from mothers not on HAART at randomisation, independent of CD4 cell count						
6 months	7/490	1·3% (0·4–2·3)	18/492	3·4% (1·9–5·0)	62%	0·027
9 months	10/483	2·0% (0·8–3·2)	20/480	3·8% (2·2–5·5)	47%	0·071
12 months	14/401	2·8% (1·3–4·2)	21/398	4·0% (2·3–5·7)	30%	0·263
Infection from mothers with high CD4 cell counts (≥350 cells per μL) and not on HAART at randomisation						
6 months	3/418	0·7% (0–1·5)	13/434	2·8% (1·3–4·4)	75%	0·014
9 months	4/414	0·9% (0–1·8)	15/422	3·3% (1·7–4·9)	73%	0·014
12 months	7/340	1·7% (0·4–2·9)	15/346	3·3% (1·7–4·9)	48%	0·116
Infection from mothers with low CD4 cell counts (<350 cells per μL) and not on HAART at randomisation						
6 months	4/71	4·8% (0·2–9·4)	5/54	8·1% (1·3–14·8)	41%	0·438
9 months	6/68	7·5% (1·7–13·3)	5/54	8·1% (1·3–14·8)	7%	0·901
12 months	7/59	8·9% (2·6–15·1)	6/48	9·8% (2·3–17·3)	9%	0·850

Women on ART while breastfeeding regardless of infant prophylaxis had VERY LOW rates of HIV-1 transmission

EXTENDED HPTN 046 TRIAL

- Outcome: PHIV at 18 months of age in infant who were HIV negative at 6 weeks of age and breast fed
- 1/3 of women were taking ART, 2/3 no ART
- Infant NVP stopped at 6 months in study group. 95% infants were weaned by 12 months of age.
- HIV-free survival was similar between groups at 18 months
- PHIV rates were similar: NVP 2.2% (95% CI 1.1-3.3%) and Placebo 3.1% (95% CI 1.-4.4%)



Fowler et al. JAIDS. 2014

"The longer duration of extended NVP dosing of infants, the longer the duration of protection against MTCT of HIV. Once prophylaxis is discontinued, the cumulative infant HIV infection rates continue to increase- suggesting that infant ARV prophylaxis…must continue as long as breast feeding continues."

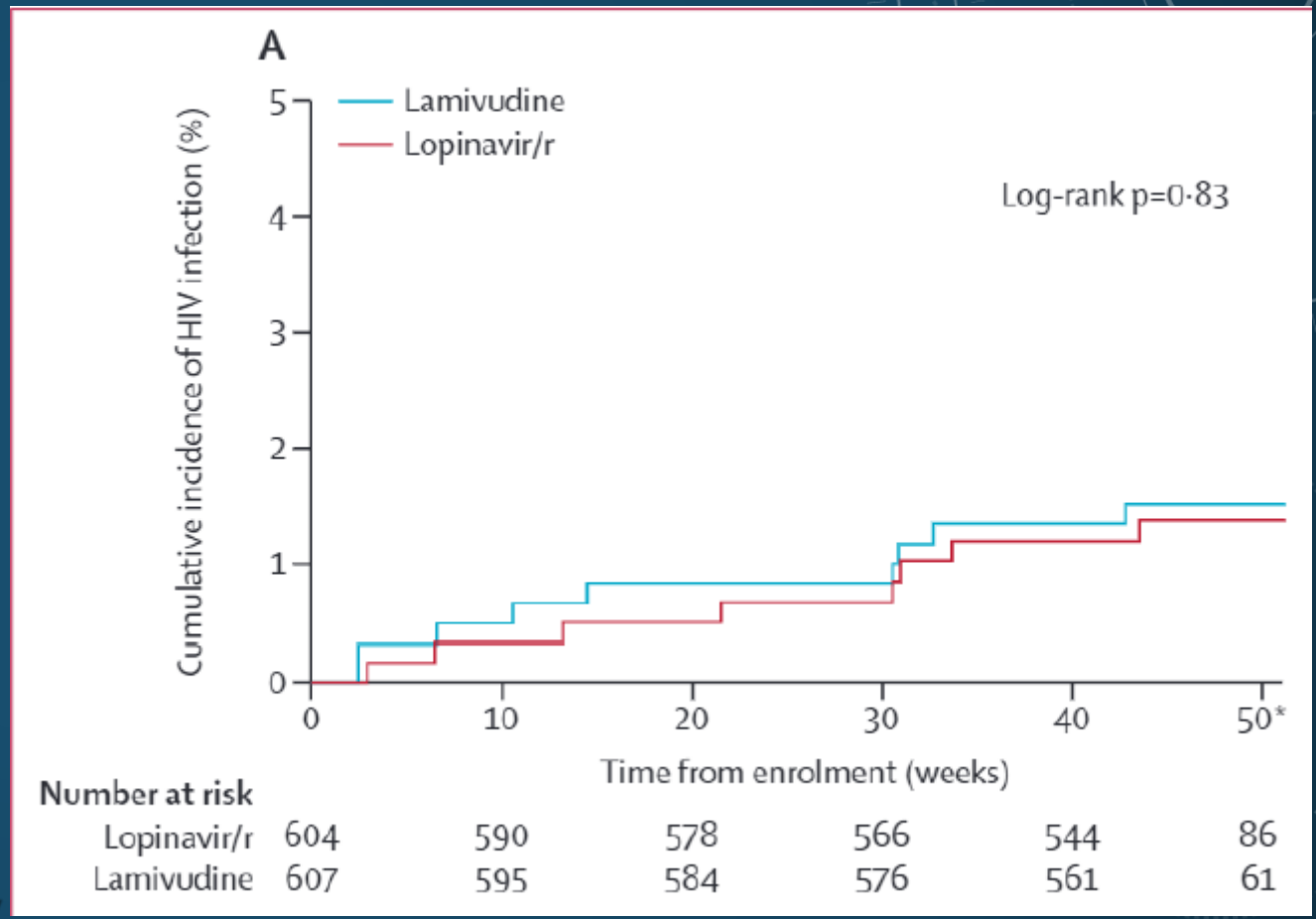
Cochrane Review, 2014

Studies included: Gray 2005, SWEN 2008, Kumwenda 2008, Shapiro 2010, Chasela 2010, Kesho Bora 2011, and Coouvadia 2012

ANRS (FRENCH HIV RESEARCH STUDY) 12174

- 2009-2012 Burkina Faso, S. Africa, Uganda, and Zambia
- PMTCT protocol: maternal ZDV at 28 weeks until delivery, single dose NVP in labor, and ZDV/3TC 7 days pp
- Outcome: PHIV in infants 7-50 weeks of life
- HIV-1 DNA negative infants DOL7 randomized to LPV/RIT (n, 636) or 3TC (n, 357) until 50 weeks or 7 days after weaning
- Chose 3TC instead of NVP due to lower rates of ASEs and drug resistance profile.
- PHIV weeks of life 1-50 occurred in LPV/RIT 1.4% (95% CI 0.4-2.5) and 3TC 1.5% (95% CI 0.7-2.5)

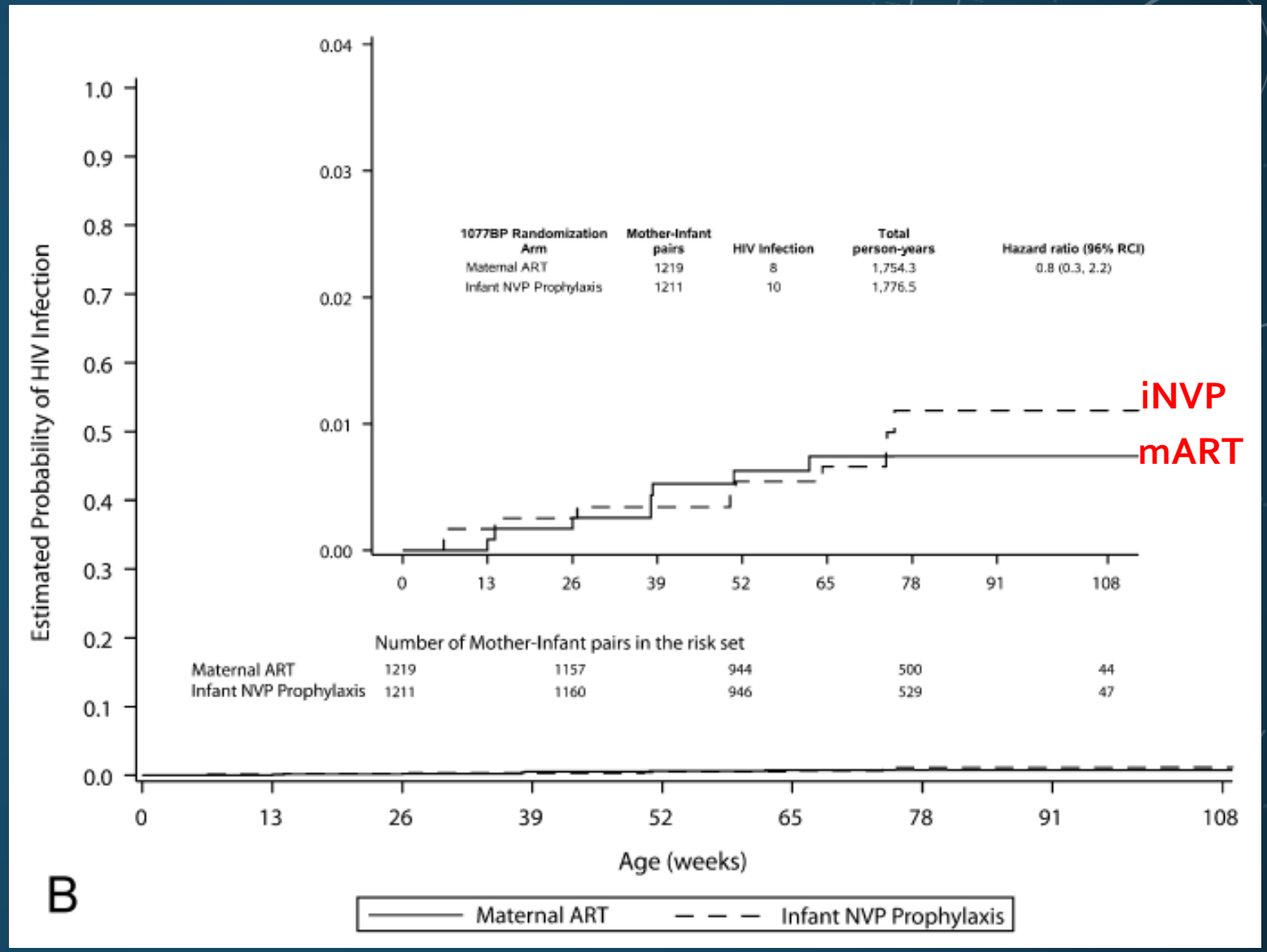
- **Infant prophylaxis should be extended until HIV exposure through breastfeeding ends.**



Nagot et al. Lancet. 2016.

IMPAACT PROMISE POSTPARTUM COMPONENT

- 2011-2014, Malawi, S. Africa, Zimbabwe, Uganda, Zambia, Tanzania, and India
- 2431 maternal-infant pairs RCT maternal ART (n, 1220) OR infant prophylaxis (n,1211) while breast feeding
- ART regimens: Zidovudine only, ZDV/3TC+ LOP/RIT, or TDF/FTC+ LOP/RIT
- Infant prophylaxis = NVP daily
- Outcome: PHIV at 24 months of age
- PHIV by 24 months mART 0.7% and iNVP 0.8%
- PHIV/infant death by 24 months mART 2.9% and iNVP 2.3%
- **HIV-free survival 97% in both groups**



Fowler et al. JAIDS. 2018

"Mothers living with HIV 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 (see the WHO consolidated guidelines on ARV drugs for interventions to optimize adherence).[b]"

World Health Organization guideline updates on "HIV and Infant Feeding" 2016

https://apps.who.int/iris/bitstream/handle/10665/246260/9789241549707-eng.pdf

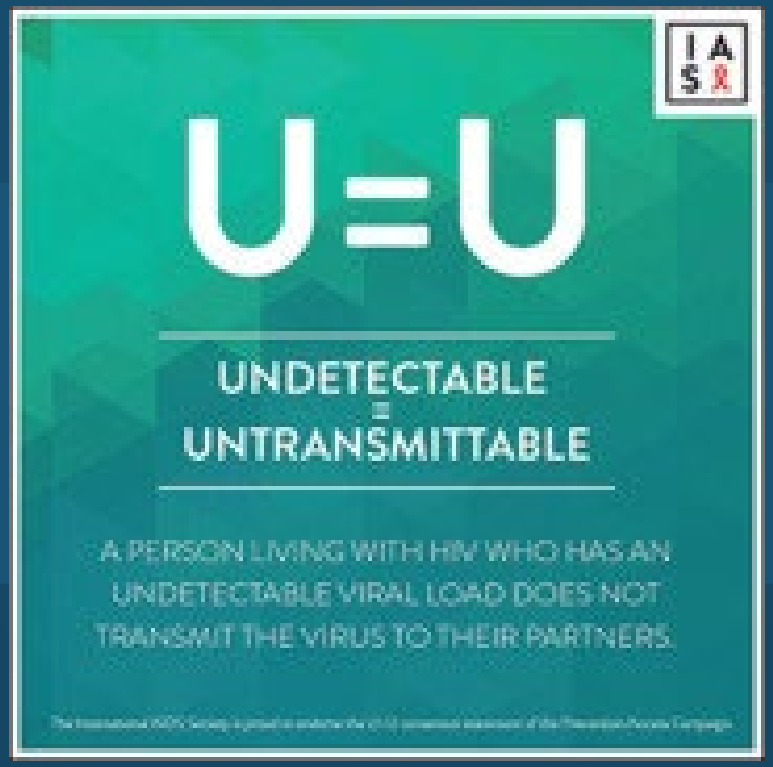
SUMMARY OF CURRENT DATA

IMPACT OF MATERNAL ART ON PREVENTION OF POSTNATAL PHIV

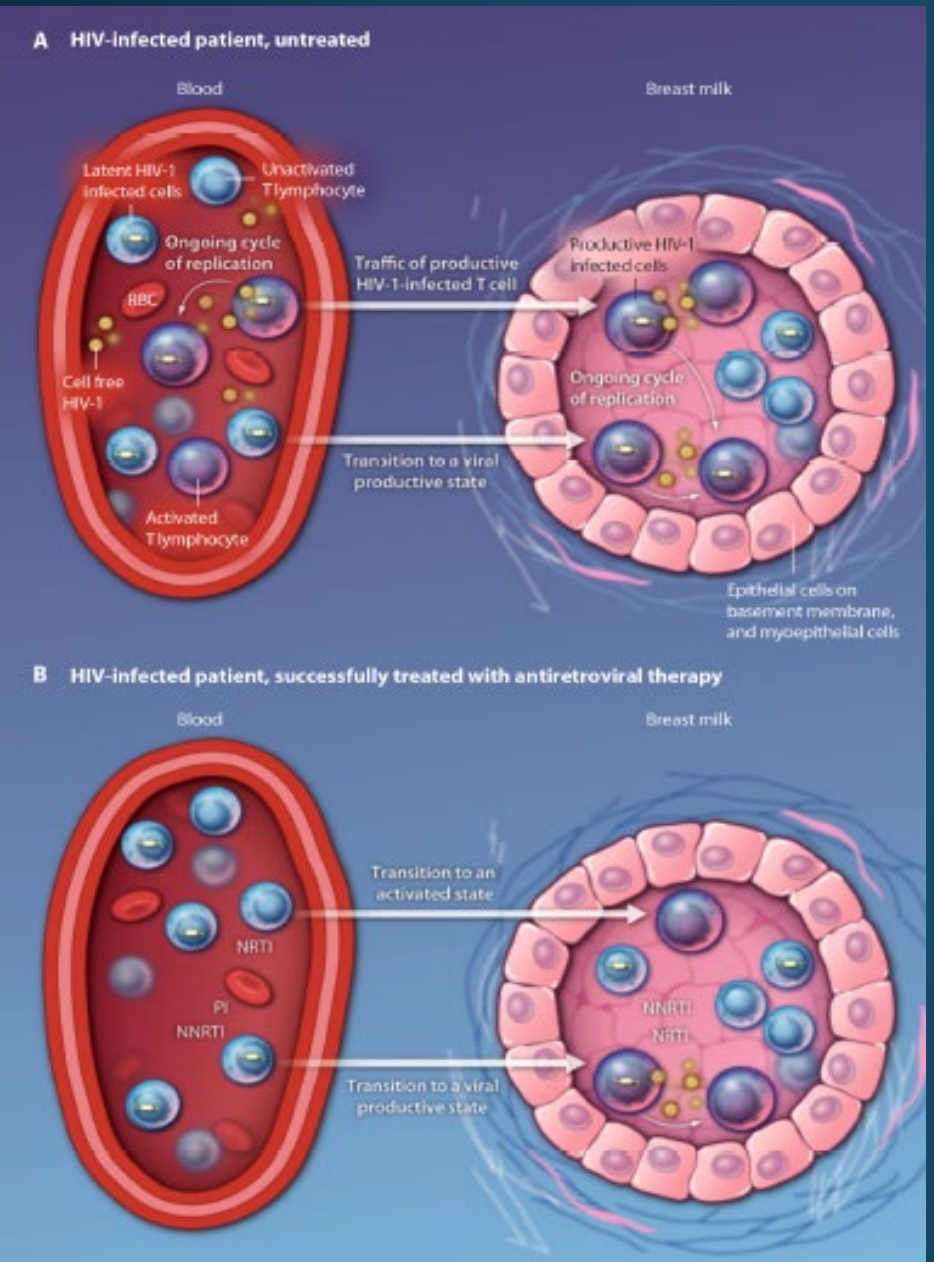
Study	Maternal ART	Infant PEP	PHIV
MMA BANA NEJM. 2010	NVP/ZDV/3TC n, 156 ABC/ZDV/3TC n, 283 ZDV/3TC/LPV/r n, 270	n/a	6 months NVP 1.1% n, 2
BAN study NEJM. 2010	ZDV/3TC BID x labor/7 d ZDV/3TC/NVP n, 39 ZDV/3TC/NFV n, 146 ZDV/3TC+ LPV/r n, 664	ZDV/3TC BID birth to DOL 7 NVP daily 6 months	7 months control, 5.7% n, 32 mART, 2.9% n, 21 iPEP, 1.7 n, 12
Kesho Bora Lancet Inf Dis. 2011	ZDV BID+ sdNVP n, 412 (added 7 days pp) ZDV/3TC/LOP/r n, 412	ZDV BID 7 d pp	12 months sdNVP, 9.5% n, 37 mART, 5.4% n, 21
PROMOTE AIDS. 2015	ZDV/3TC/EFV n, 195 ZDV/3TC/LPV/r n, 194	ZDV 7 d pp Or NVP 6 wks pp	12 months EFV, 0% LPV/r 1.1% n, 2
IMPACT PROMISE NEJM. 2018	ZDV only+ sdNVP n,506 ZDV/3TC/LOP/RIT n, 508 TDF/FTC/LOP/RIT n, 140	NVP daily n, 1211	24 months mART, 0.7% n,7 iPEP, 0.8% n,7

There is insufficient evidence to state with certainty that undetectable = untransmittable in the context of breast feeding.

Waitt et al. Lancet HIV. 2018.



Factors Associated with HIV-1 Transmission in Breast feeding Infants



1) High maternal HIV-1 RNA viral load, ex. advanced HIV/AIDS (low CD_4 cell count) or primary HIV infection (extreme viremia) while breast feeding

2) Mixed feeding before age 6 months

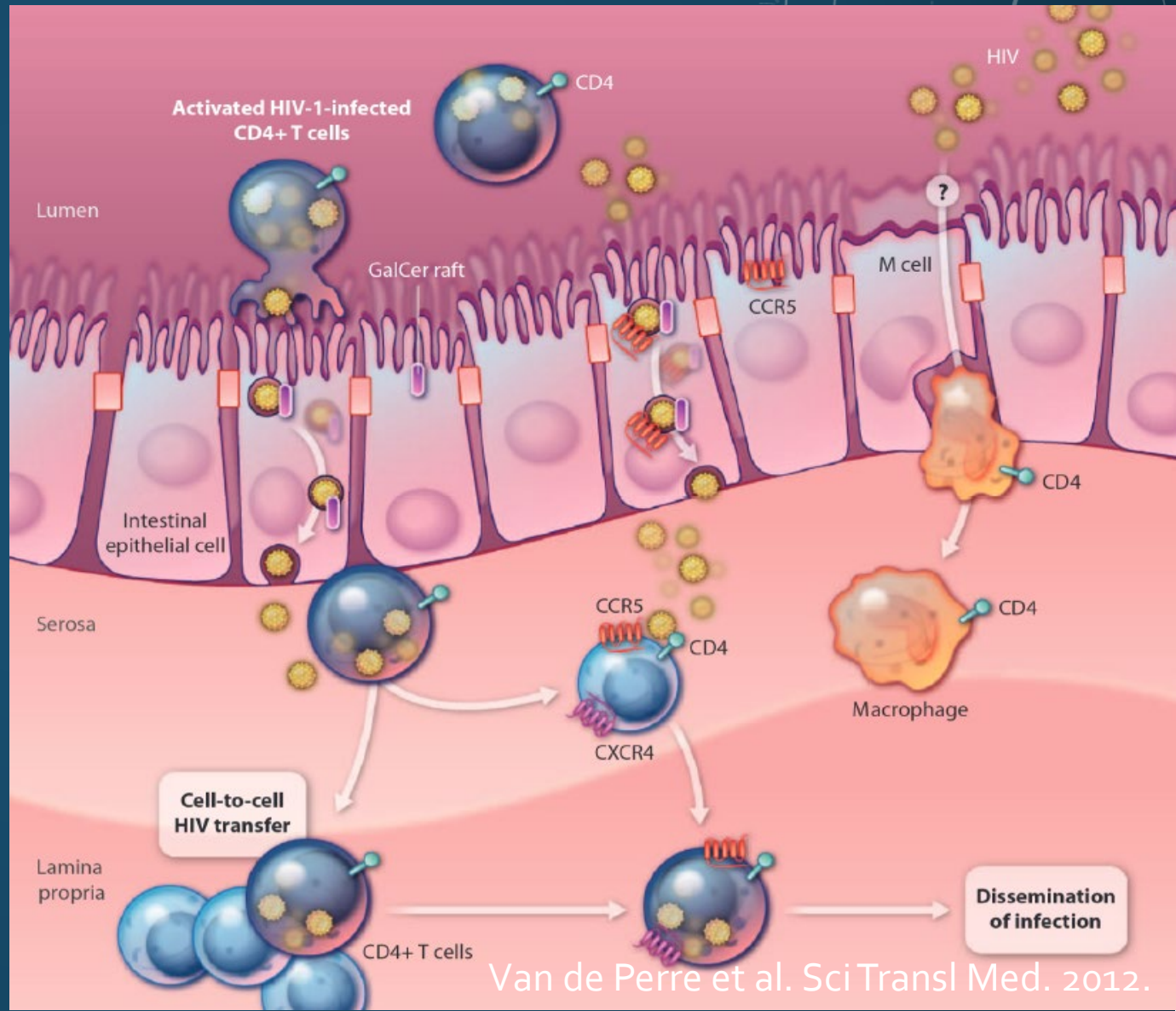
3) Breast inflammation i.e. mastitis, abscess, or engorgement

Van de Perre et al. Sci Transl Med. 2012.

Potential Mechanism for HIV-1 Transmission through Breast Milk Despite Maternal Viral Suppression on Antiretroviral Therapy

"HIV-1 secreting cells in breast milk have direct access to gut mucosa and active immune cells from breast milk can infiltrate the gut mucosa."

"An infant breast-fed by an HIV-1 infected woman ingests ~ 178 HIV-1 secreting cells/daily…(expected cumulative) exposure ~ 178,000 cell-associated viruses with a high capacity for cell-cell transfer"



Van de Perre et al. Sci Transl Med. 2012.

Before 2023, U.S. Perinatal HIV Treatment Guidelines Recommendations remained unchanged because…

- Although low, there is a potential for HIV-1 transmission through breast milk despite maternal viral suppression.
- The availability of safe formula feeding in high resource settings.
- Provider and parents' fears regarding HIV transmission.

SUMMARY OF INFANT FEEDING OPTIONS AND RISK OF PHIV

Table 1. Potential Risks and Benefits of Different Feeding Options for HIV-Exposed Infants in the United States

Feeding Option	Risk of HIV Transmission	Cultural Acceptability	Feasibility	Affordability	Sustainability	Safety
Formula feeding	None	+/–	++	++	++	+++
Milk bank	None[a]	+/–	+/–	+/–	+/–	+++
Exclusive breastfeeding while on maternal ARVs	1.1% (Mma Bana) 2.9% (BAN) 5.4% (Kesho Bora)	Unknown in the US; +++ outside of US	Unknown in the US; +++ outside of US	Unknown in the US; +++ outside of US	Unknown in the US; +++ outside of US	+
Exclusive breastfeeding and infant ARV prophylaxis	1.7% (BAN)	Unknown in the US; +++ outside of US	Unknown in the US; +++ outside of US	Unknown in the US; +++ outside of US	Unknown in the US; +++ outside of US	No US data
Flash-heat treatment	No efficacy data available	Unknown in the US, + outside of US	Unknown in the US, + outside of US	++	Unknown	++
Lactational surrogate ("wet nurse")	None/minimal[b]	+/–	+/–	+/–	+/–	++

Abbreviations: +/–, potential for both risks and benefits; ++, benefit; +++, great benefit; ARV, antiretroviral; BAN, Breastfeeding, Antiretrovirals, and Nutrition study; HIV, human immunodeficiency virus.

[a] Assuming adequate HIV testing of milk donor.

[b] Assuming adequate HIV testing of and no risk for incident HIV in wet nurse.

Levison, Weber, and Cohan. CID. 2014

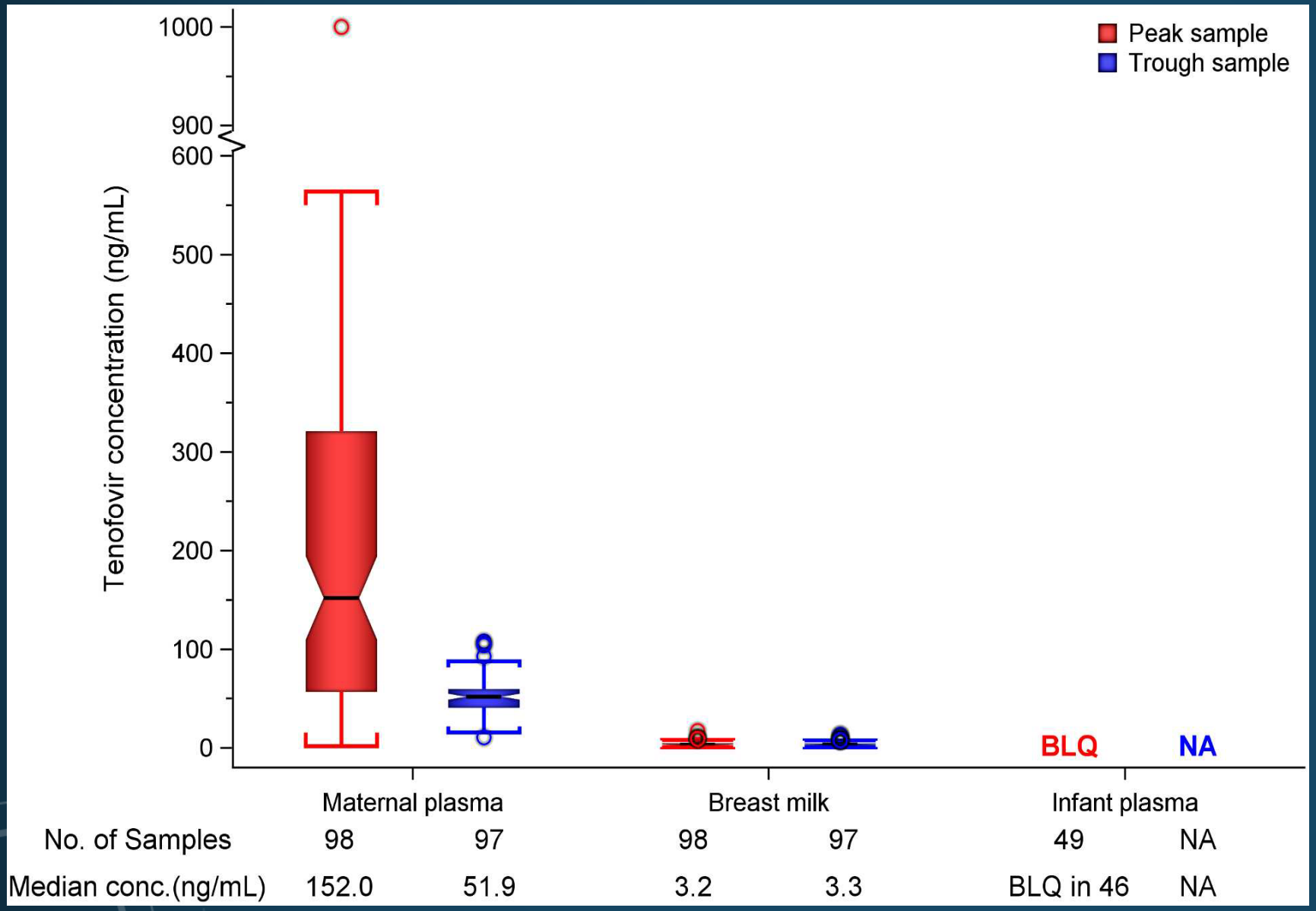
MATERNAL ANTIVIRAL THERAPY AND BREAST MILK

TRANSFER OF TDF/FTC INTO BREASTMILK

- 50 HIV-uninfected lactating women and infant pairs
- Primary outcome: infant plasma concentrations of TDF and FTC
- Secondary outcomes: maternal plasma and breast milk concentrations; maternal milk: plasma and infant plasma: milk ratios
- Methods: directly observed doses of daily oral FTC-TDF for 10 days. Maternal serum and breast samples days 7 and 10 obtained 1-2 hours after Infant serum sample on day 7

Mugwanya et al. PLOS Medicine. 2016

TDF CONCENTRATION IN BREAST MILK AND INFANT PLASMA



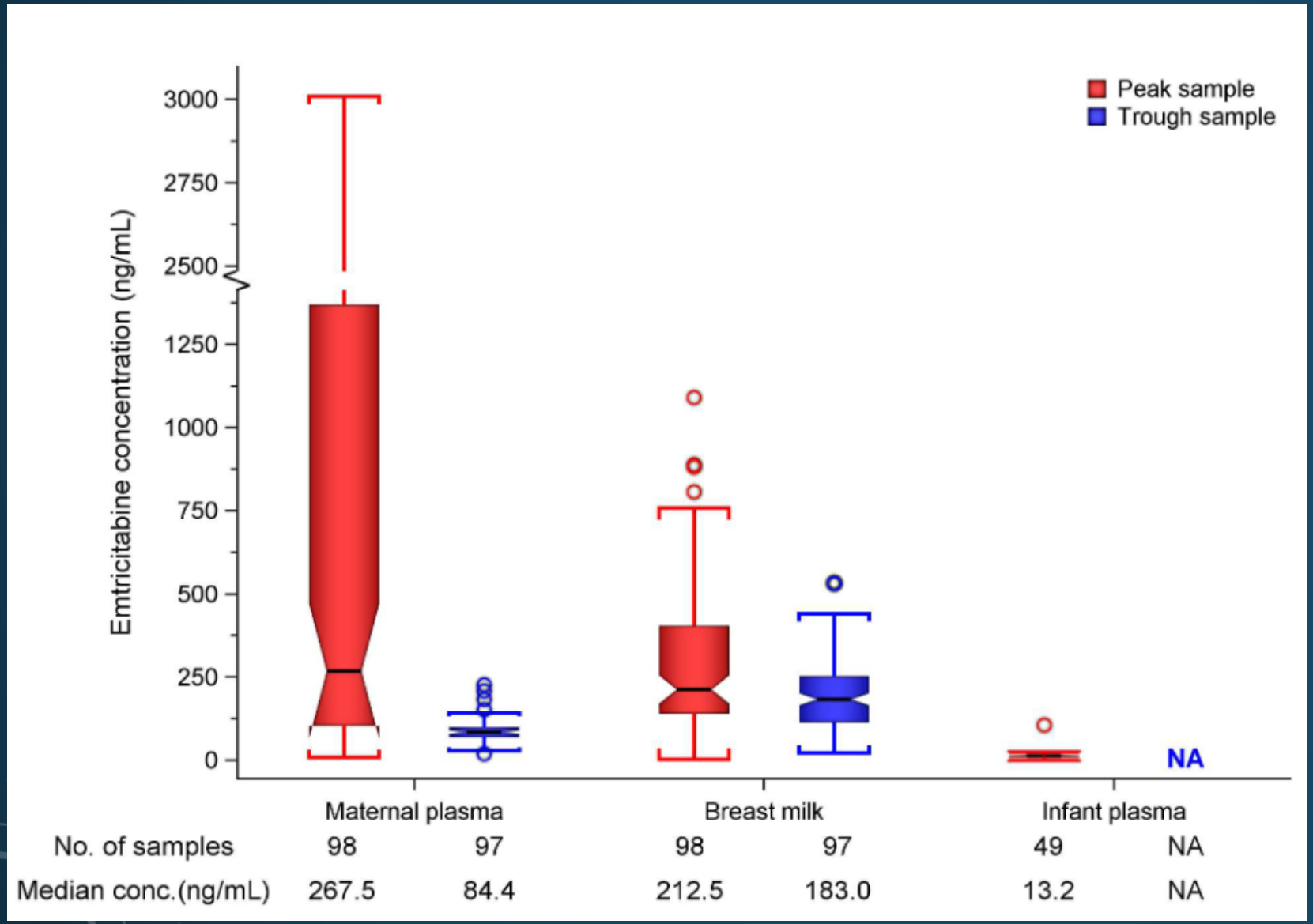
No. of Samples	98	97	98	97	49	NA
Median conc.(ng/mL)	152.0	51.9	3.2	3.3	BLQ in 46	NA

Median breastmilk doses of tenofovir have been shown to be 0.03% of infant oral doses.

Tenofovir was undetectable in 46 of 49 (94%) infant plasma samples

Mugwanya et al. PLOS Med. 2016

FTC CONCENTRATION IN BREAST MILK AND INFANT PLASMA



FTC detectable in 47 of 49 (96%) of infant samples

Infant plasma concentration was 5% of breast milk concentration

FTC infant plasma concentration was 0.05% of pediatric therapeutic dose.

Mugwanya et al. PLOS Med. 2016

TRANSFER OF ANTIRETROVIRALS INTO BREASTMILK

- Prospective Swiss Mother and Child HIV Cohort
- 21 WWH who elected to breast feed
- Measured maternal and infant plasma and milk concentrations of ARVs

Aebi-Popp et al. J Antimicro Chemother. 2022

TRANSFER OF ANTIRETROVIRALS INTO BREASTMILK

ARV, frequency	Maternal Milk/Plasma Ratio	Median Infant Dose (mg/kg)
Raltegravir, daily	0.96	0.02
Raltegravir, BID	0.39	0.25
Bictegravir, daily	0.01	0.01
Rilpivirine	1.08	0.02
Darunavir + ritonavir, daily	0.12	0.05
Tenofovir alafenamide, daily	4.09	0.007

ARVs are minimally secreted in breast milk and infants are exposed to subtherapeutic doses

EMERGING COMMENTARY ON INFANT FEEDING STRATEGIES FOR PERSONS WITH HIV

"Low HIV MTCT figures in low-resource settings, even if HIV-infected mothers do breastfeed, question whether a recommendation to abstain from breastfeeding in high-income countries is still justified."

Christian et al. Swiss Medical Weekly. 2018

PROVIDER PERSPECTIVES TOWARDS INFANT FEEDING IN PWH

Patients' concerns about not breastfeeding N, 93	
What concerns do your patients living with HIV raise about not being able to breastfeed? Patient concerns	
Not being able to reap the health benefits of breastfeeding for mother and/or infant	47 (50.5)
Cost of formula feeding	13 (14)
Stigma associated with not breastfeeding with family/community	54 (58.1)
Stigma associated with formula feeding in society	15 (16.1)
Physical discomfort of breast engorgement	9 (9.7)
Not being able to bond with their child through breastfeeding	35 (37.6)
None of these	4 (4.3)
Open-ended responses:	
"They always seem to already know it is not recommended"	
Providers' concerns about supporting breastfeeding	
What concerns do you have about supporting your HIV positive patients in breastfeeding? Provider concerns	
The ongoing risk of mother to child transmission	61 (65.6)
Concern for non-compliance with ARV and/or extended infant prophylaxis	65 (70)
Concern for side effects of extended infant prophylaxis	32 (34.4)
Legal risks associated with potential transmission	21 (22.6)

Providers recognize that persons affected by HIV and medical providers have different perspectives on the safety of BF.

Tuthill et al. J Int AIDS Soc. 2019.

"Given potential benefits of breastfeeding and very low perinatal transmission risk with undetectable VL, breast may be best for infants of cART-adherent WLHIV. As with decisions about having children, WLHIV have a right to make an informed choice about breastfeeding, especially given clinical equipoise regarding infant outcomes, maternal health considerations and personal significance."

Gross et al. J of Law, Medicine & Ethics. 2019.

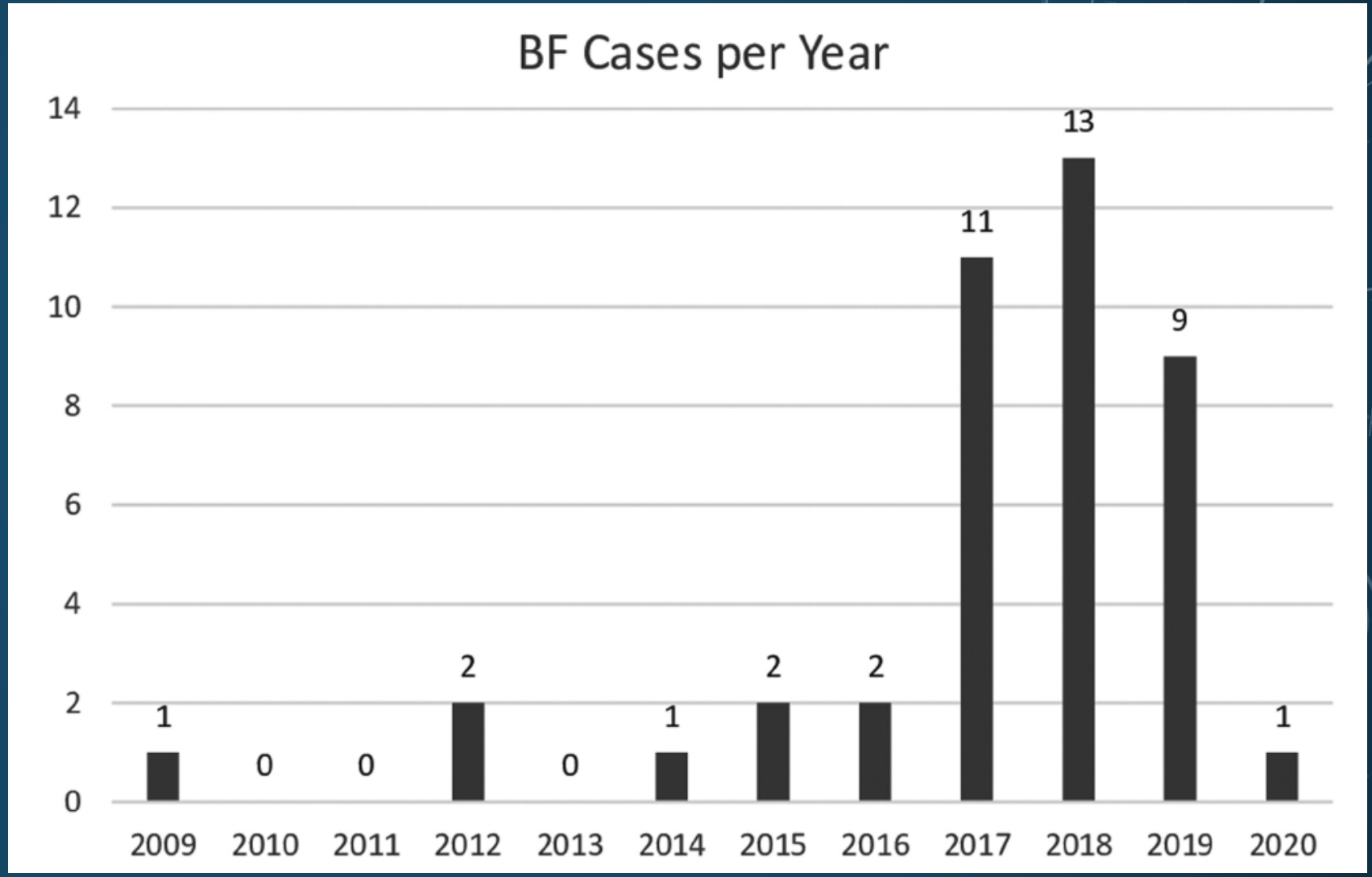
PROPOSED ADDITIONS TO CURRENT NIH PERINATAL HIV GUIDANCE

- Women who desire to breastfeed and who are adherent to ART, undergo regular monitoring, and have undetectable HIV viral load have a choice to breastfeed.
- Health professionals should be trained to identify WLHIV who can safely breastfeed based on their viral load status at birth and other clinical and social factors.
- A risk profile and clinical tools should be developed to identify WLWH who are good candidates for breastfeeding.
- WLHIV who choose to breastfeed should receive increased support and clinical monitoring, including consideration of more frequent viral load testing to insure HIV viral suppression.
- WLHIV should be provided with counseling, clinical and social support, and home services that could enable them to safely breastfed their children.

Gostin and Kavanagh. J Law, Medicine & Ethics. 2019

BREASTFEEDING AMONG WOMEN WITH HIV IN GERMANY

- 2009-2020, retrospective cohort of women with HIV electing to breast feed (HELENE)
- 20 centers
- 63% of women born outside of Germany.
- Increasing cases of maternal choice to BF against national recommendation to formula feed.
- **Clinicians should prepare to care for PWH who chose to breast feed.**



Haberl et al. AIDS Patient Care and STDS. 2021.

RECOMMENDATIONS FOR PWH WHO ELECT TO BREAST FEED

- Discuss the risks and benefits of breastfeeding as well as feeding alternatives such as formula, donor breast milk, or use of a lactational surrogate.
- Ensure the person receives an effective ART regimen. Specifically, address barriers to adherence and counsel on the importance of this regimen in reducing transmission.
- Counsel on the importance of exclusive breastfeeding rather than mixed feeding with formula and breast milk.
- Discuss the benefits of infant antiretroviral prophylaxis. Ensure the infant has a pediatrician who feels comfortable and supportive managing an infant breastfeeding from a parent with HIV.
- Monitor an individual's viral load every 1 to 2 mo during breastfeeding to ensure viral suppression. If the viral load becomes detectable, counsel regarding the increased risk of transmission and consider breastfeeding weaning.
- Educate the individual regarding the signs of mastitis or infant oral thrush, which may increase the risk of HIV transmission, to ensure prompt treatment.
- Test the infant for HIV acquisition during breastfeeding, typically every 3 mo during breastfeeding.

Givens, Levison, and Rahangdale.
Obstet Gynecol.
Clinical Expert Series.
2021.

UNANSWERED CLINICAL QUESTIONS

- Which ARVs should be recommended in breast feeding PWH?
- How should mothers be counselled to handle mastitis and ongoing breast feeding?
- Should HIV RNA be measured in breast milk in addition to plasma?
- Should extended infant prophylaxis be given in breast feeding infants when maternal HIV viral load is undetectable?

Waitt et al. Lancet HIV. 2018.

REVISIONS TO THE CURRENT NIH GUIDELINES FOR HIV-EXPOSED INFANT FEEDING ARE EXPECTED 2023

Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States

Counseling and Managing Individuals with HIV in the United States Who Desire to Breastfeed

https://clinicalinfo.hiv.gov/en/guidelines/perinatal/counseling-and-managing-individuals-with-hiv-united-states-who-desire-breastfeed?view=full

SUMMARY OF RECOMMENDATIONS FOR INFANT FEEDING

- People with HIV should receive evidence-based, patient-centered counseling to support shared decision-making about infant feeding. Counseling about infant feeding should begin prior to conception or as early as possible in pregnancy; information about and plans for infant feeding should be reviewed throughout pregnancy and again after delivery **(AIII).** During counseling, people should be informed that—
  - Replacement feeding with properly prepared formula or pasteurized donor human milk from a milk bank eliminates the risk of postnatal HIV transmission to the infant **(AI).**
  - Achieving and maintaining viral suppression through antiretroviral therapy (ART) during pregnancy and postpartum decreases breastfeeding transmission risk to less than 1%, but not zero **(AI).**
- Replacement feeding with formula or banked pasteurized donor human milk is recommended to eliminate the risk of HIV transmission through breastfeeding when people with HIV are not on ART and/or do not have a suppressed viral load during pregnancy (at a minimum throughout the third trimester), as well as at delivery **(AI).**
- Individuals with HIV who are on ART with a sustained undetectable viral load and who choose to breastfeed should be supported in this decision **(AIII).**
- Individuals with HIV who choose to formula feed should be supported in this decision. Providers should ask about potential barriers to formula feeding and explore ways to address them **(AIII).**

CONCLUSIONS

- Prior to universal ART use in pregnancy, 1/3 of infant HIV infections were attributed to breast feeding.
- When maternal ART or infant prophylaxis are used, the estimated risk of HIV transmission by breast feeding is 1-5%.
- Maternal ART adherence and viral suppression during breast feeding are recommended to reduce the risk of HIV transmission.
- Infant antiviral prophylaxis may provide some protection in addition to maternal ART.
- Interdisciplinary care should be considered to support people with HIV who chose to breast feed and prevent infant HIV infection.