Epidemiology of HIV transmission through Breastfeeding

SAHIV Clinicians Society Conference
25-28 November 2012
CTICC

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Outline

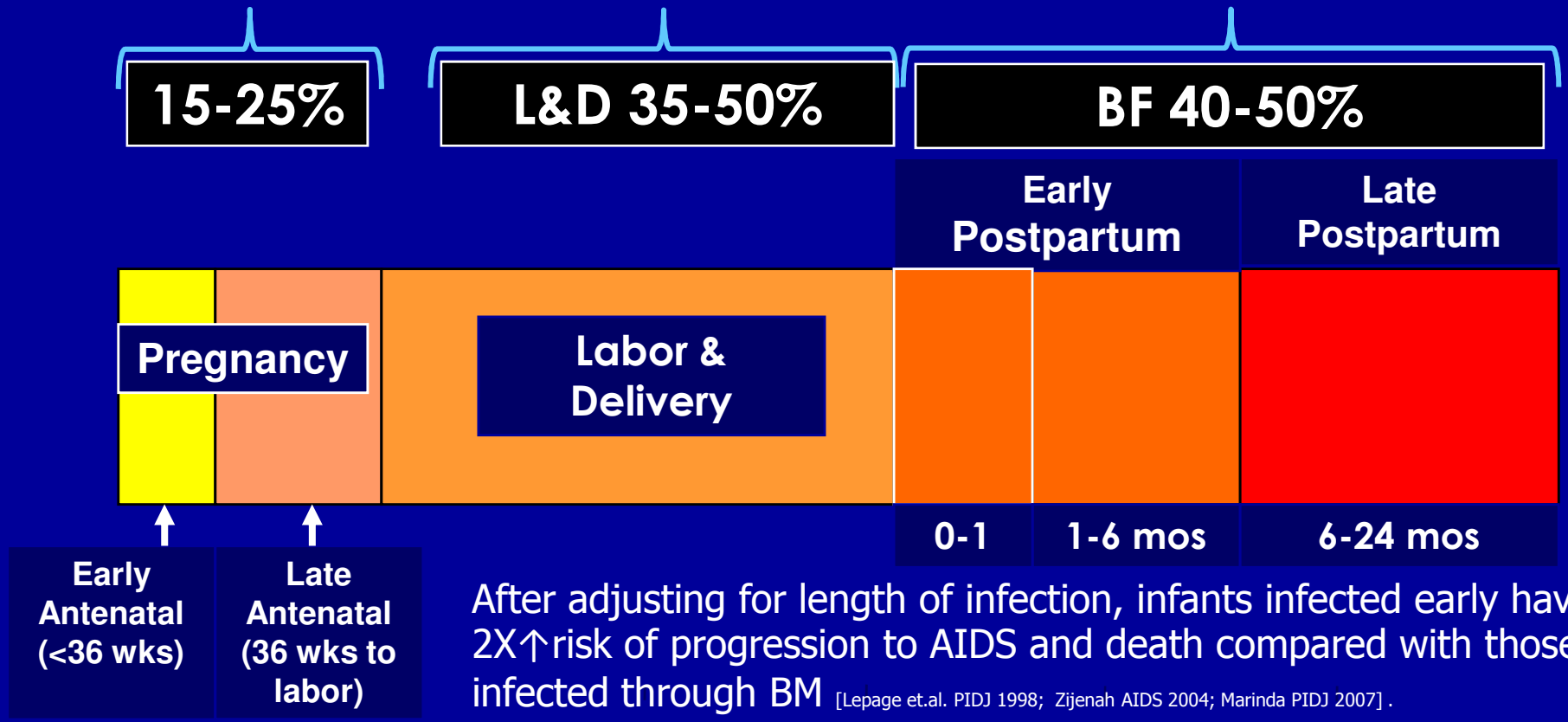
- HIV Transmission though breastfeeding pre-PN ARV prophlaxis:
  - What we know and have discussed before
- Revisiting pathophysiology of BF & breastmilk HIV transmission to determine:
  - drivers of BM HIV transmission
  - opportunities for intervention
- Summary

Estimated Timing and Risk of MTC HIV Transmission

Timing	No BF %		BF 6 months %		BF 18-24 months %	
	Rel. proportion	Absolute rate	Rel. proportion	Absolute rate	Rel. proportion	Absolute rate
I-U	25-35	5-10	20-25	5-10	20-25	5-10
I-P	65-75	10-20	40-55	10-20	35-50	10-20
PP early 0-2 months			20-25	5-10	20-25	5-10
PP late >2 months			5-10	1-5	20-25	5-10
Overall		15-30		25-35		30-45

MTCT is surprisingly inefficient: in the absence of any intervention 55-80% of HIV exposed infants remain uninfected **X** syphilis

With 18-24 months BF and no PMTCT interventions what proportion of HIV transmission is attributed to BF?

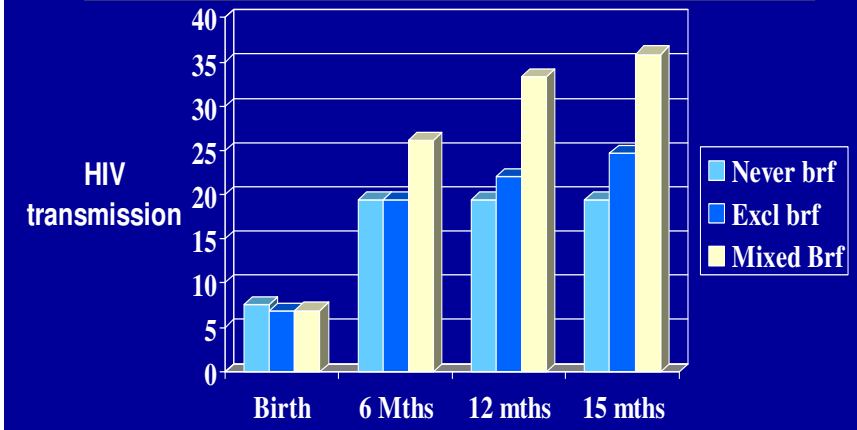


After adjusting for length of infection, infants infected early have a 2X↑risk of progression to AIDS and death compared with those infected through BM [Lepage et.al. PIDJ 1998; Zijenah AIDS 2004; Marinda PIDJ 2007] .

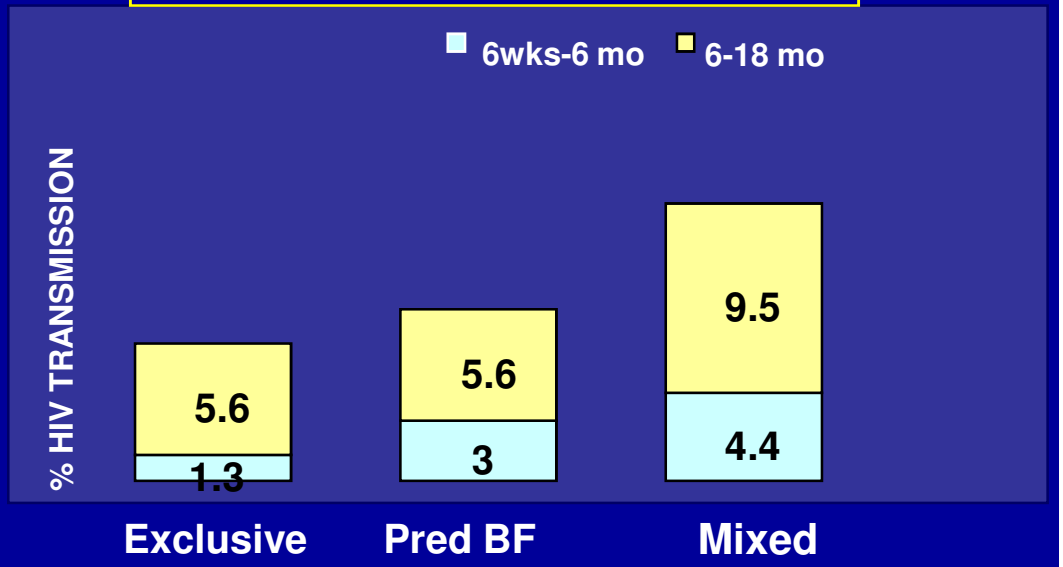
Why?

Studies on Transmission Risk Conducted before Postnatal ARVs

Coutsoudis et.al, *AIDS 2001 Feb 16,* 15(3):379-387



Illif et.al *AIDS 2005 April 29,* ***19 (7):699-708.***



Coovadia et.al *the Lancet 2007,* ***369:1107-1116***

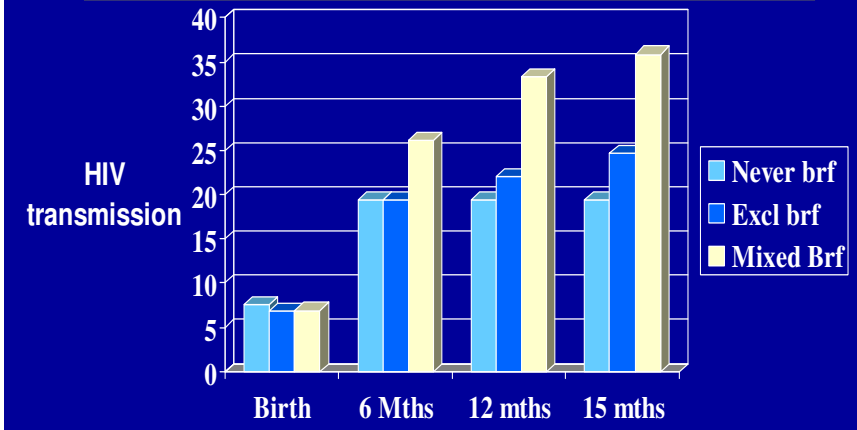
	Maternal antenatal CD4 count by feeding method (cells per µL)				HIV point prevalence rates
	<200	200–500	>500	Missing	
EBF (n=362)	30 (8%)	162 (45%)	155 (43%)	15 (4%)	55 (15%; 11·7–19·3)
RF (n=28)	10 (36%)	9 (32%)	8 (29%)	1 (4%)	2* (7%; 0·9–23·5)
MBF (starting <14 weeks; n=332)	40 (12%)	159 (48%)	113 (34%)	20 (6%)	89 (27%; 22·1–31·9)
MBF (starting >14 weeks; n=239)	30 (13%)	96 (40%)	101 (42%)	12 (5%)	61 (26%; 20·1–31·5)

Data are number (%) or number (%; 95% CI). EBF=exclusively breastfeeding. RF=replacement feeding. MBF=mixed breastfeeding. *Two children who switched from EBF to RF.

Table 2: **Maternal antenatal CD4-cell counts and HIV point prevalence rates at 26 weeks by method of feeding at 26 weeks**

Studies on Transmission Risk Conducted before Postnatal ARVs

Coutsoudis et.al, *AIDS 2001 Feb 16,* 15(3):379-387



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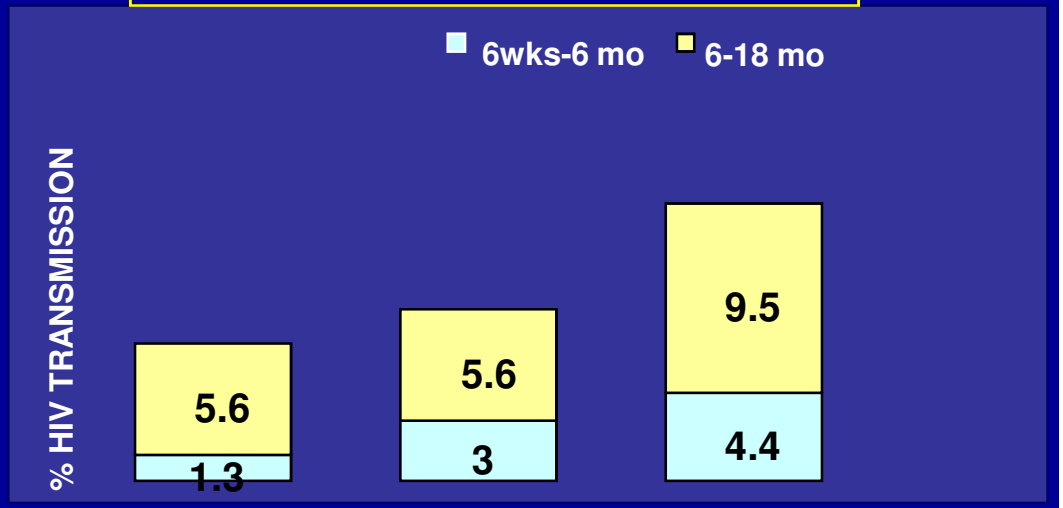
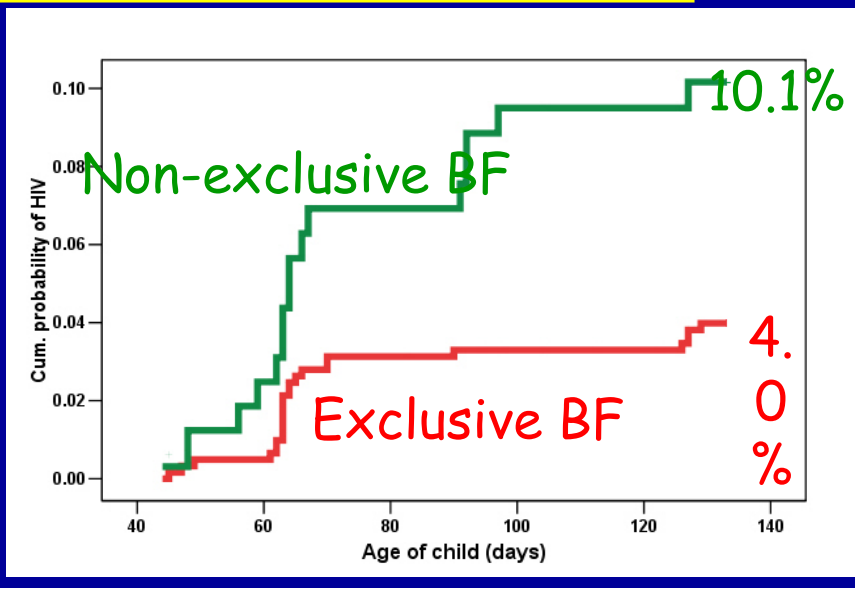


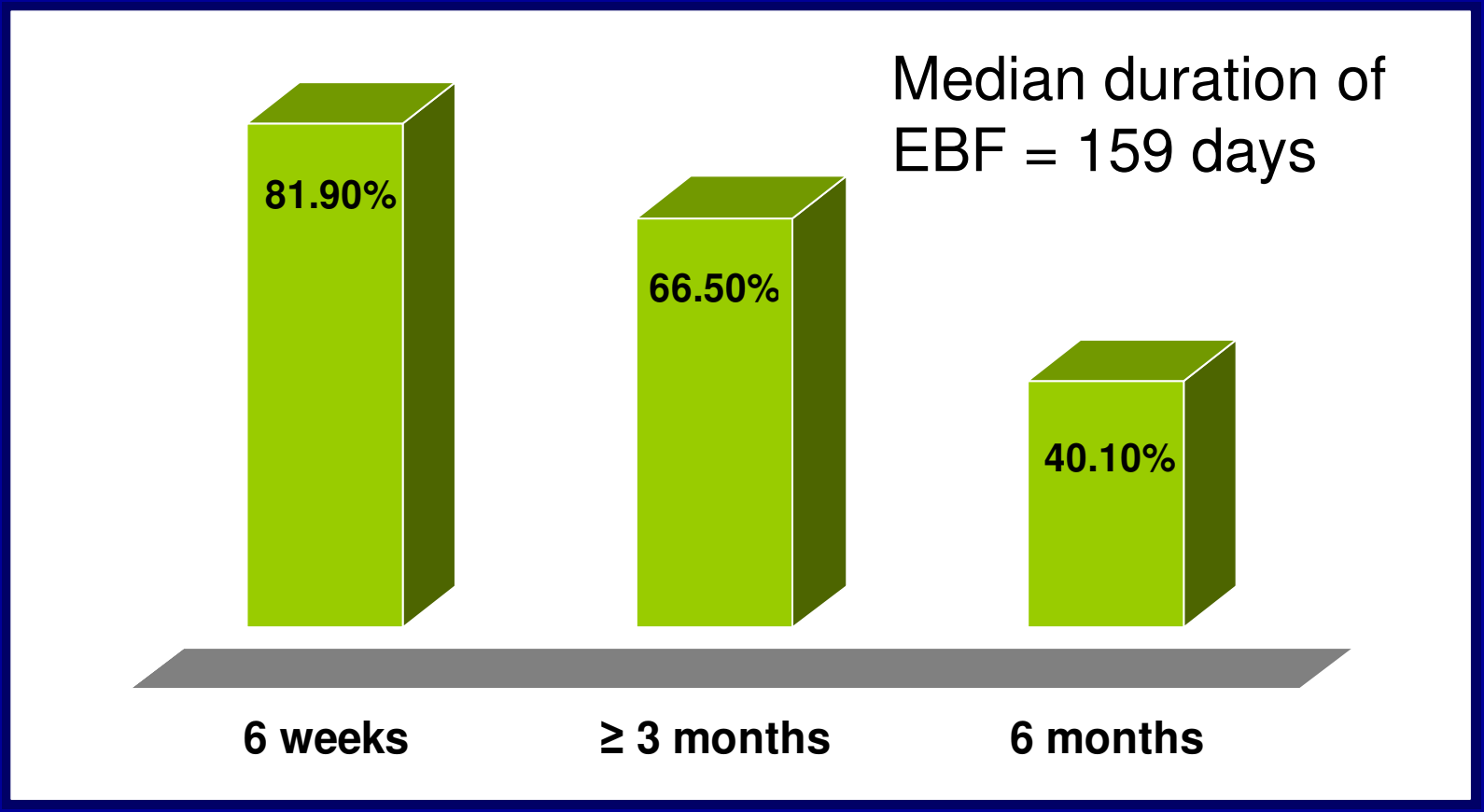
Coovadia et.al *the Lancet 2007,* ***369:1107-1116***

Sinkala et.al, CROI, 2007

In 723 exclusively breastfed infants who were HIV uninfected at or after 6 weeks, the estimated Kaplan-Meier cumulative risk of infection from 6 weeks of age was 1.1% (0.8–1.84) after 1 month, 2.2% (1.05–3.34) after 2 months, 2.7% (1.44–4.02) after 3 months, 3.3% (1.88–4 · 77) after 4 months, and 4.0% (2.29–5.76) after 5 months (ie, at about 6 months of age).



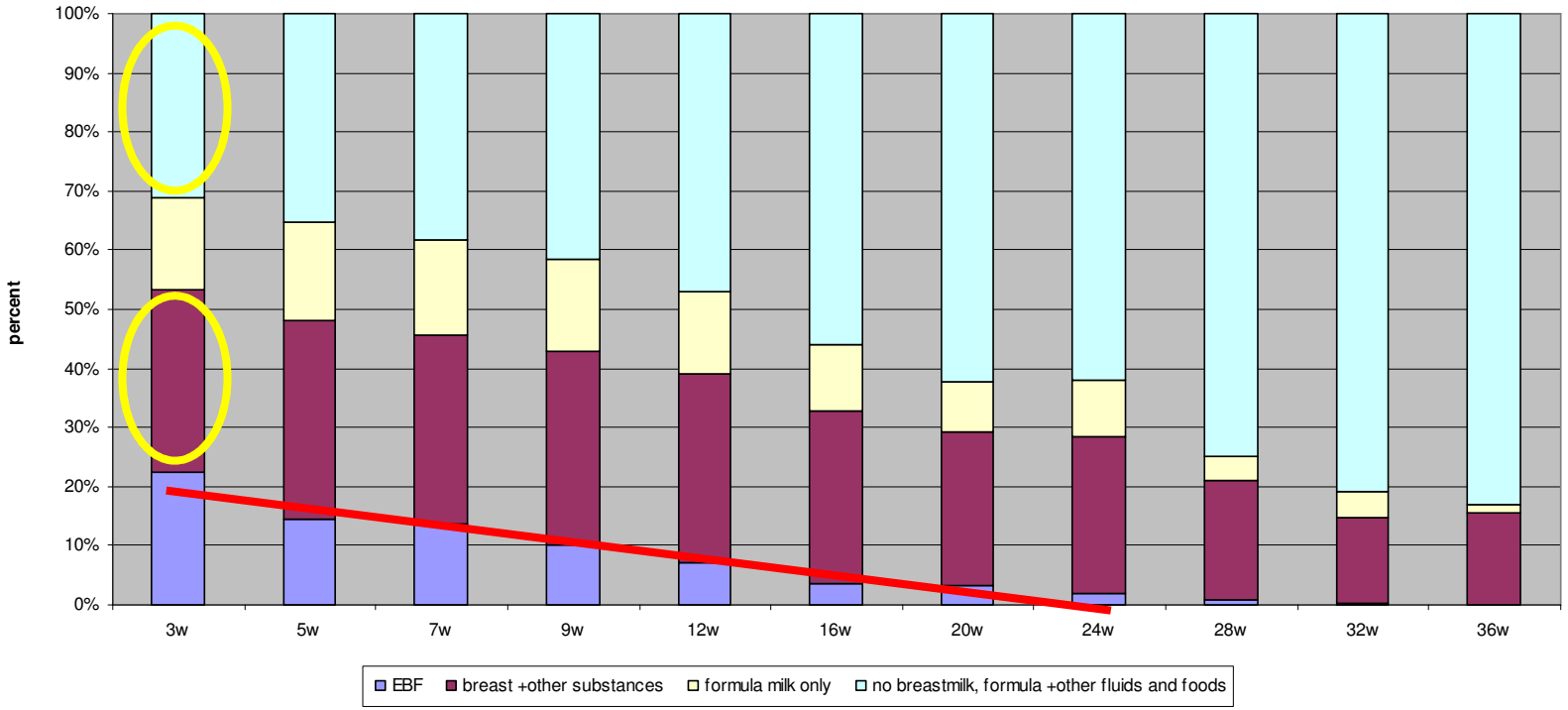
Is EBF possible? Duration of cumulative EBF



Coovadia et al., Lancet, 2007

IFP IN SA ARE ABYSMAL

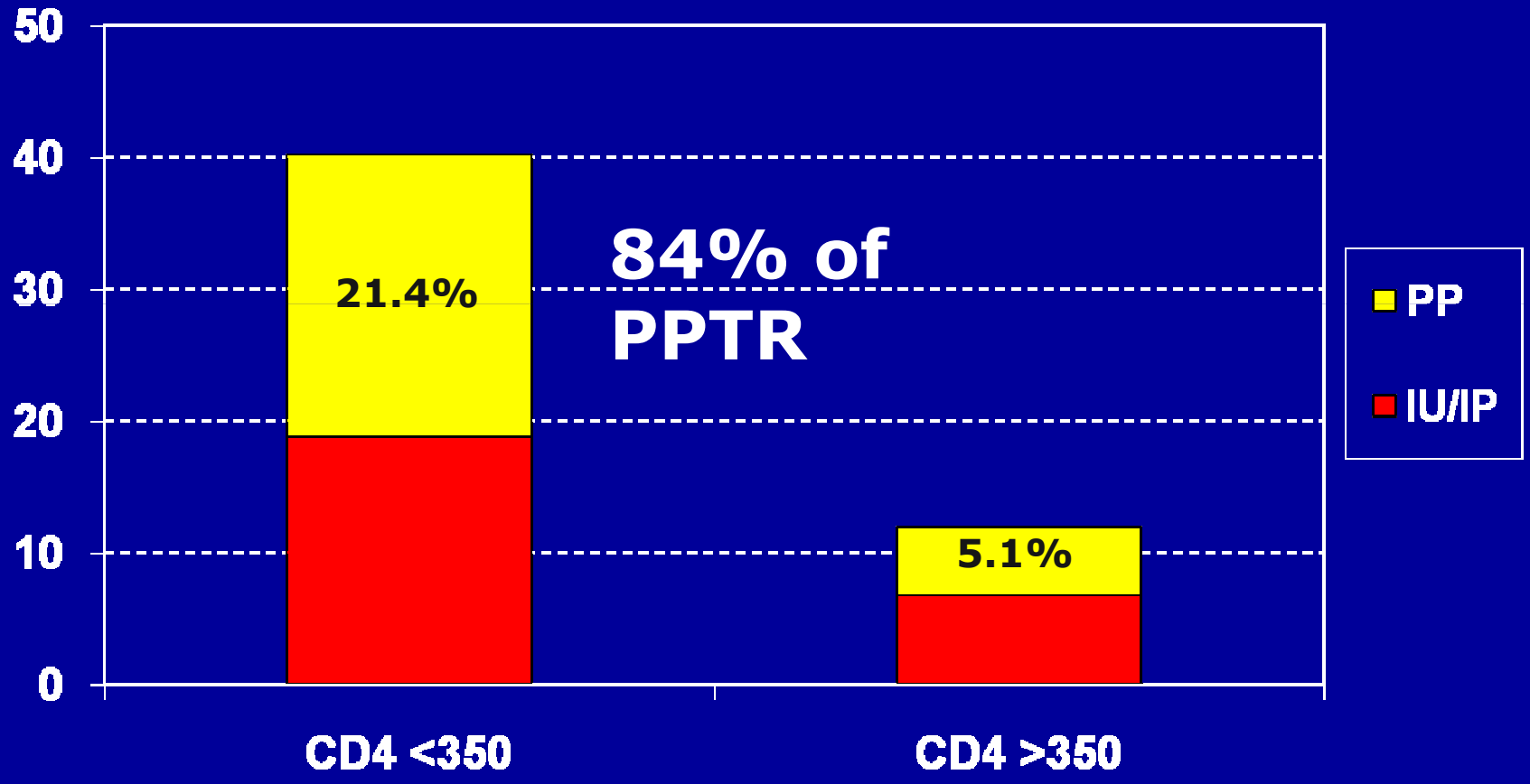
FEEDING PRACTICES HIV POSITIVE WOMEN - 4-DAY RECALL DATA



Goga et.al. Int BF Jnl 2012

	EBF (%)	MF (%)	FF (%)
Good Start HIV+ women	22.4	30.9	15.5 + *31.2
Among all infants 2010	27.2 (26.1-28.3)	44.8 (43.23-46.3)	28.0 (25.6-29.4)
HIV exposed infants 2010	20.4 (18.5-22.3)	18.1% (16.5-19.7)	*61.5 (59.2-63.8)
HIV exposed infants 2011		43.7 (41.3-46.0)	

Most postnatal HIV transmission occurs among mothers with low CD4 count (eligible for HAART)



Slide courtesy of Assoc. Prof Louise Kuhn, [5]Gertrude H. Sergievsky Center, Columbia University

Risk factors for breastmilk transmission

- Mat seroconversion /superinf. during BF Dunn et.al Lancet 1992, Semba et.al. 1999
- Longer duration of BF Miotti JAMA 1999, Nduati JAMA 2000, Coutsoudis JID 2004
- ↓Mat CD4 / ↑Mat illness Semba JID 1999, Embree et.al AIDS, 2000, Illif et.al, AIDS 2005
- Mastitis / BM stasis Ekpini Lancet 1997 Semba 1999
- DNA / RNA VL – BM + plasma John GC et.al JID 2001, Rousseau CM et.al, JID 2003, Richardson BA et.al, JID 2003 , Kulinska Virus res. 2006

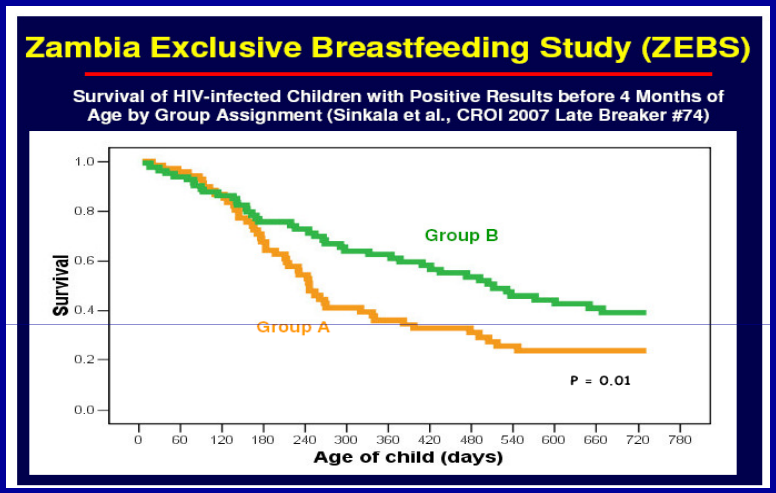
3x↑ Trans for 10x↑BM VL

- Type of feeding (EBF /MF) Coutsoudis et.al. AIDS 2001, Illif P et.al. AIDS 2005, Coovadia et.al Lancet 2007

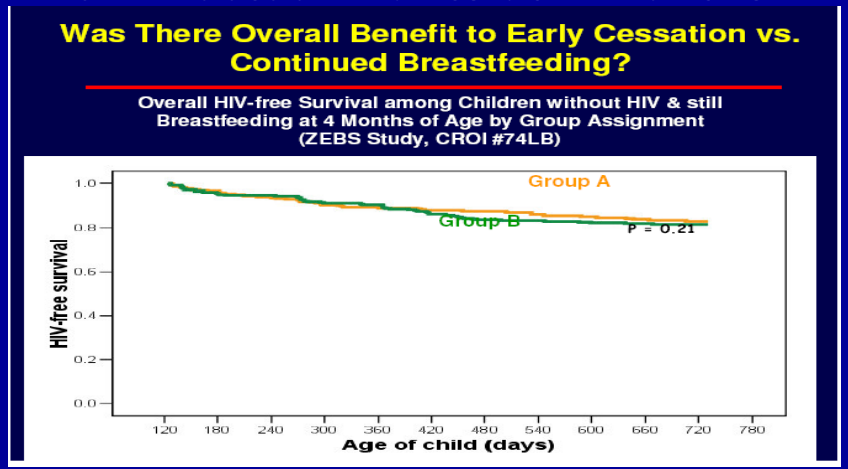
No HIV-free survival benefit seen with breastfeeding cessation at 4 month

- RCT – weaned at 4 mo vs not weaned
- Infants weaned at 4 months (group A) had high early mortality compared with cont BF infants (group B)
- Top graph: Survival worse among HIV-infected infants weaned at 4 months
- Bottom graph: Long-term "HIV-free" survival among uninfected infants (4mo) no different

HIV-infected infants at 4 months

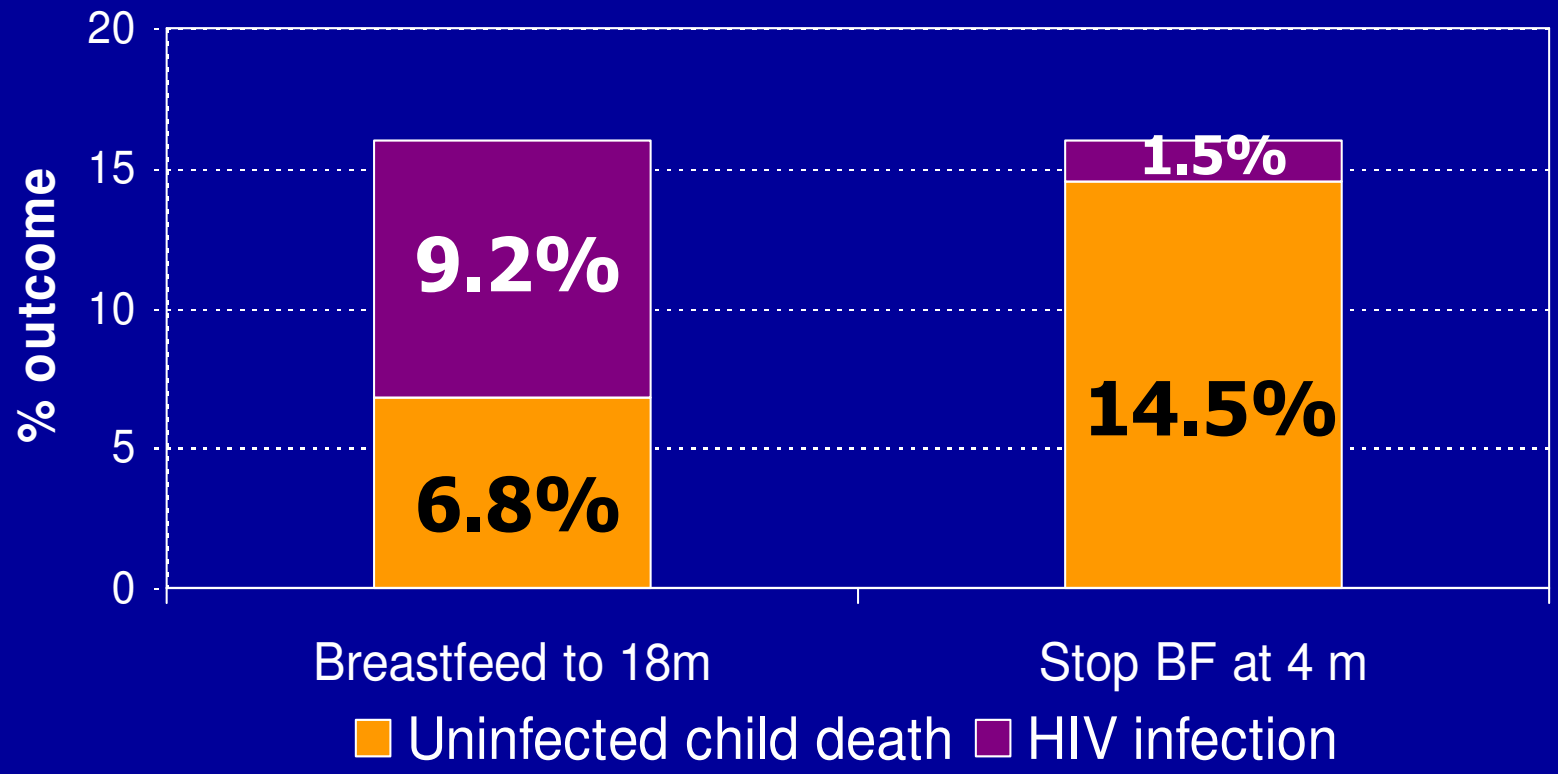


HIV-uninfected infants at 4 months



Graphs obtained from Marc Bulterys, CDC/Zambia.

Mortality caused canceled out HIV transmission prevented



Kuhn L, Aldrovandi G, Sinkala M et al. ***PLoS One*** 2009; June 4: e6059

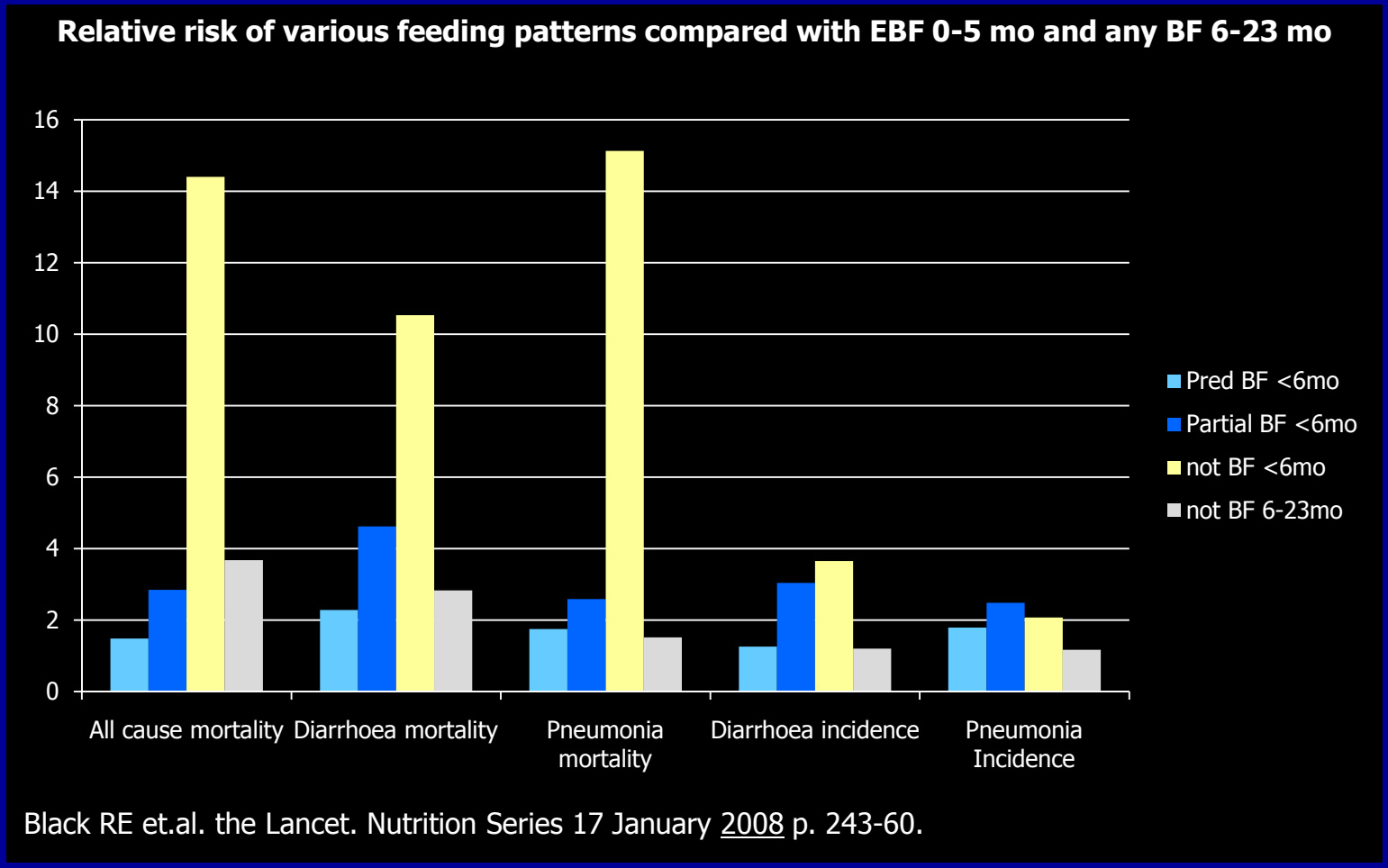
Slide courtesy of Assoc. Prof Louise Kuhn, [5]Gertrude H. Sergievsky Center, Columbia University

Inappropriate choice ↑HR for HIV transmission or death

Feeding choice according to defined criteria - presence or absence of piped water, fuel and HIV disclosure	Adjusted HR	95% CI
Met criteria – chose to FF (n=94)	1	
Did not meet criteria – chose to FF (n=195)	3.45	(1.89-6.32)
Met criteria – chose to BF (n=95)	2.72	(1.38-5.35)

Doherty et.al AIDS 2007

Why EBF?



Black RE et.al. the Lancet. Nutrition Series 17 January 2008 p. 243-60.

EBF = giving only breastmilk with the exception of minerals / vitamins / essential medication

PredBF = giving the infant breastmilk and non-nutritive liquids or partial breastfeeding

Partial BF = feeding breastmilk and non-nutritive and nutritive liquids

Breastmilk: A wonder liquid!

ADVANTAGES OF BREASTFEEDING

2/2

Breast milk
- Perfect nutrients
- Easily digested; efficiently used
- Protects against infection

Breastfeeding
- Helps bonding and development
- Helps delay a new pregnancy
- Protects mothers' health

- Costs less than artificial feeding

CONSTITUENTS OF BREASTMILK (3):

- Protein: casein:whey = 2:3
  - Casein
  - Whey - sIgA, Lactoferrin, alpha-lactalbumin, lysozyme, growth factors, cytokines, hormones, transporter proteins, digestive enzymes
- Fat:
  - mainly triglycerides. Long chain PUFA (arachidonic acid, decosahexanoic acid)- essential for mental and visual development
- Carbohydrates -

CONSTITUENTS OF BREASTMILK (5): Colostrum

2/7

Property	Importance
• Antibody rich	- protects against allergy & infection
• Many white cells	- protects against infection
• Purgative	- clears meconium - helps to prevent jaundice
• Growth factors	- helps intestine to mature - prevents allergy, intolerance
• Rich in Vitamin A	- reduces severity of infection

Constituents (9): Enzymes in breastmilk

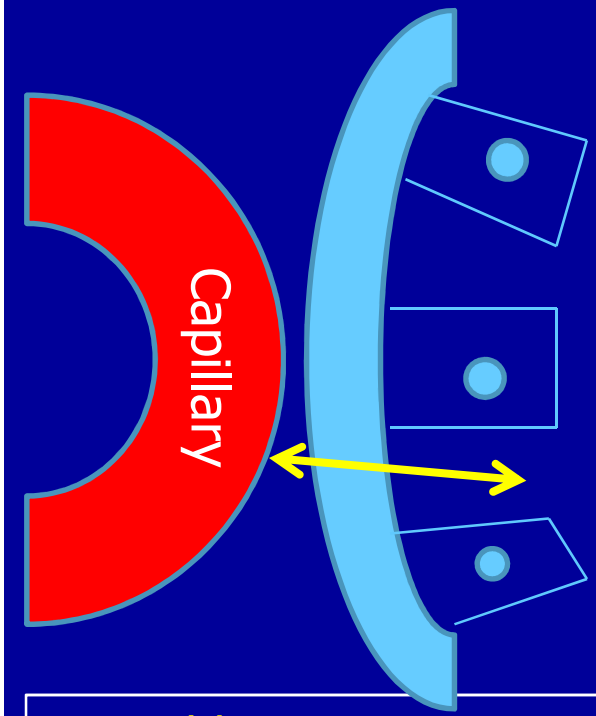
- Lipase to assist with fat digestion
- Amylase
- Bile-acid stimulating esterase
- Bile-acid stimulating lipase
- Lipoprotein lipas

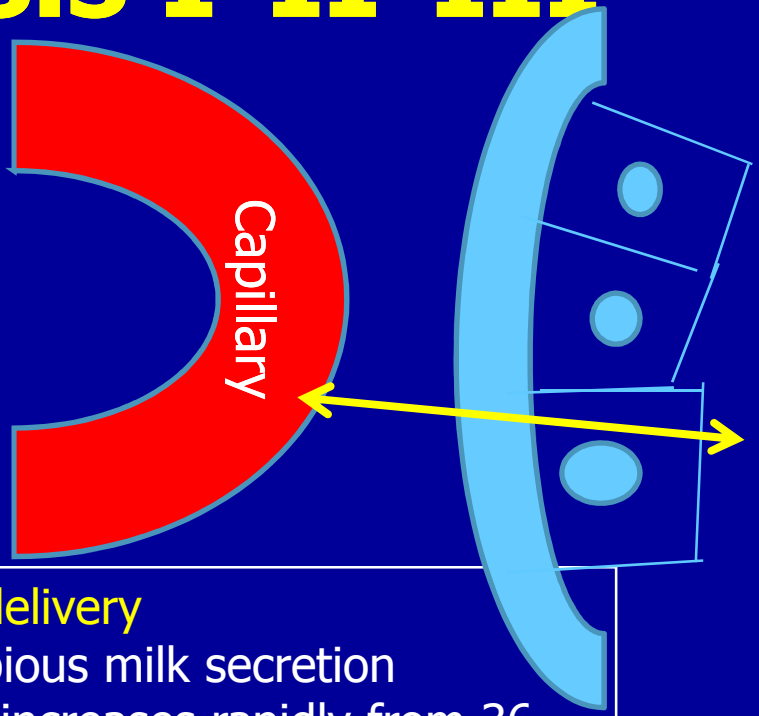
Immune-related constituents

- sIgA***, IgM, IgG
- Lactoferrin
- Lysozyme
- C3
- Leucocytes
- Bifidus factor
- Lipids and fatty acids
- Antiviral mucins
- oligosacharides

- When? How? Why? does it transmit infections (CMV, Hep C, HTLV1, HIV)?
- Can we harness the benefits of breastmilk while eliminating the risk of disease transmission?

Lactogenesis I-II-III





LI: mid-late preg-D2-3pp

1. Alveoli epithelial cells differentiate into secretory cells
2. Fat droplets accumulate
3. [lactose and □lactalbumin]↑

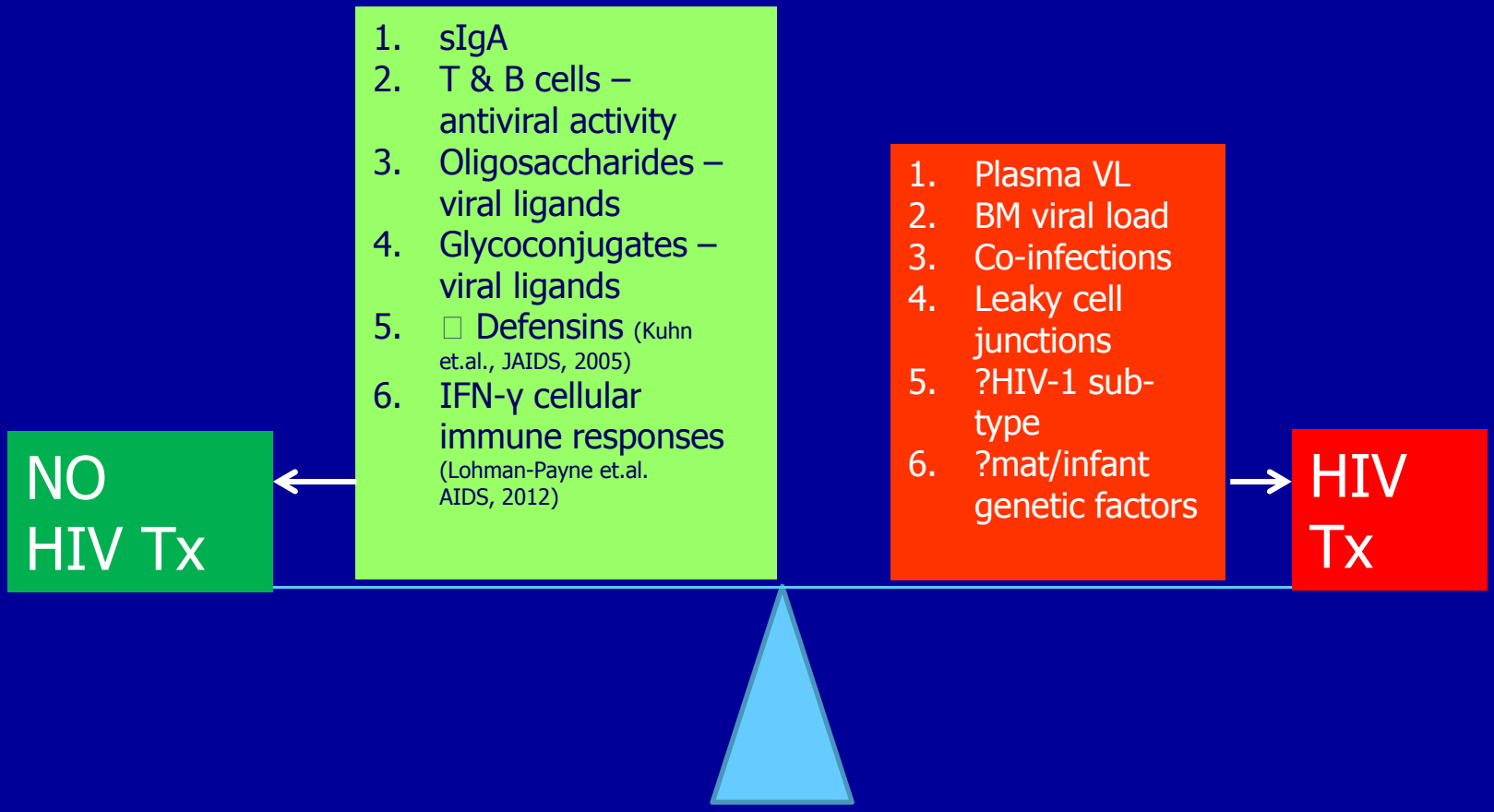
LII: D2-8 post-delivery

1. Onset of copious milk secretion
2. Milk volume increases rapidly from 36-96hrs pp – then abruptly levels off
3. Triggered by placental delivery → ↓ serum progesterone and oestrogen
4. Intracellellar junction complexes close ⟶ tight junctions
5. ↓BM NaCl & prot; lactose & ↑ lipids
6. Release of prolactin and oxytocin
7. ↑maternal metab. & mammary blood flow

LIII: pp

Autocrine regulation of galactopoesis

A balance between protection and transmission



Population Attributable Fractions for Late PN MTCT in SSA

- PAF measures the public health impact attributed to being exposed to a risk factor e.g. PAF of 15% ≈ RF would account for 15% of the population disease incidence, and dx incidence would be reduced by 15% if the RF were removed from the population:
- Malawi, Tanzania and Zambia (HIVNET 024)

RF	Late PN period	Total incidences	Expected incidences	PAF	95% CI
VL>50 000	42-365 days	78	49.5	37	22-51
CD4<200		77	57.2	26	12-36
CD4<200 AND VL>50000		73	61.1	16	6-25

A substantial proportion of LPT is accounted for by high-risk women with low CD4 and high VL. ART by high risk women is essential. Additional strategies to reduce LPT for those not meeting ART criteria should be implemented

Other factors and BF Transmission

- sIgA does not appear to be a protective factor against HIV transmission through breastmilk [Kuhn et.al. J Pediatr, 2006 Nov; 149(5): 611-6].

- Breastmilk IL-7 may be necessary for effective HIV transmission [Walter J et.al. JAIDS 2007 Oct 1; 46(2): 200-7]

- Consistent viral shedding and high breastmilk viral load are strong predictors of MTCT. Although sodium concentrations later in BF correlate with breastmilk VL, increased breastmilk sodium is normal in early lactation and does not predict HIV transmission [Semrau K et.al. JAIDS 2008 Mar 1; 47(3):320-8]

Other factors and BF Transmission

- Postnatal Acquisition of HIV-1 is more strongly associated with cumulative exposure to cell-free particles in breastmilk than with feeding mode. Allowing for maternal antenatal CD4 cell count, plasma HIV-1 load, child sex and duration of mixed BF the association between HIV RNA exposure and infection remained statistically significant. Reducing BM VL through ART may further reduce PN MTCT [Neveu et.al. CID 2011:52 (6): 819-825

- A higher concentration of human milk oligosaccharides (HMOs) was associated with a reduced odds of BF transmission after adjusting for CD4 cell count and BM HIV VL (OR 0.45; 95%CI: 0.21,0.97 P=0.06).
  - The proportion of 3'-siallyllactose was higher amongst transmitting than among non transmitting women (p=0.003) and correlated with higher plasma and BM HIV RNA and lower CD4 cell counts [Bode L et.al. Am J Clinical Nutrition. 2012 Oct; 96(4):831-9. e-pub 2012 Aug 15

Other factors and BF Transmission

- IFN-g responses were associated with breast milk viral load, levels of macrophage inflammatory protein (MIP)
- Breast milk IFN-g responses were associated with an approximately 70% reduction in infant HIV infection [adjusted odds ratio (aOR) 0.29 (0.092–0.91)] (Lohman-Payne et.al. AIDS, Aug 2012)

Vaccines and postnatal MTCT

- Mum or baby?
- Mucosal vaccine - could exploit the common mucosa associated lymphoid tissue - oral or nasal delivery. An attenuated canarypox vector (vCP 205) and Salmonella vaccine vector (CKS257) vaccine platforms - well-tolerated in humans but with less than expected mucosal immunogenicity
- A phase III randomized clinical trial - HIVIGLOB – Uganda with pooled analysis from Ethipia and India – safety and tolerability but no effect on transmission
- PACTG 326 - Immunization of neonates was well tolerated and induced lymphoproliferative and/or cytotoxic T cell responses in vaccinees:
- An MVA-vectored vaccine is also currently under evaluation in an open randomized phase I/II study

Summary and Way Forward

- Too many questions.. Few answers
- Maternal and breast health seems to be the biggest driver of breastmilk HIV transmission ----- ↓ breastmilk VL & ↑maternal CD4 cell count
- Reduce co-infections
- How to make breastmilk safer:
  - increase 'good' factors:
    - enhancing the immune responses to HIV-1 through immunotherapeutic strategies in uninfected infants could confer protection against breast milk infection.
    - Vaccine? To mother? To infant? Both?

We have an ethical obligation to change the epidemiology of HIV transmission through breastfeeding so that HIV-free child survival is maximised