Breastfeeding HIV Transmission and Prophylaxis

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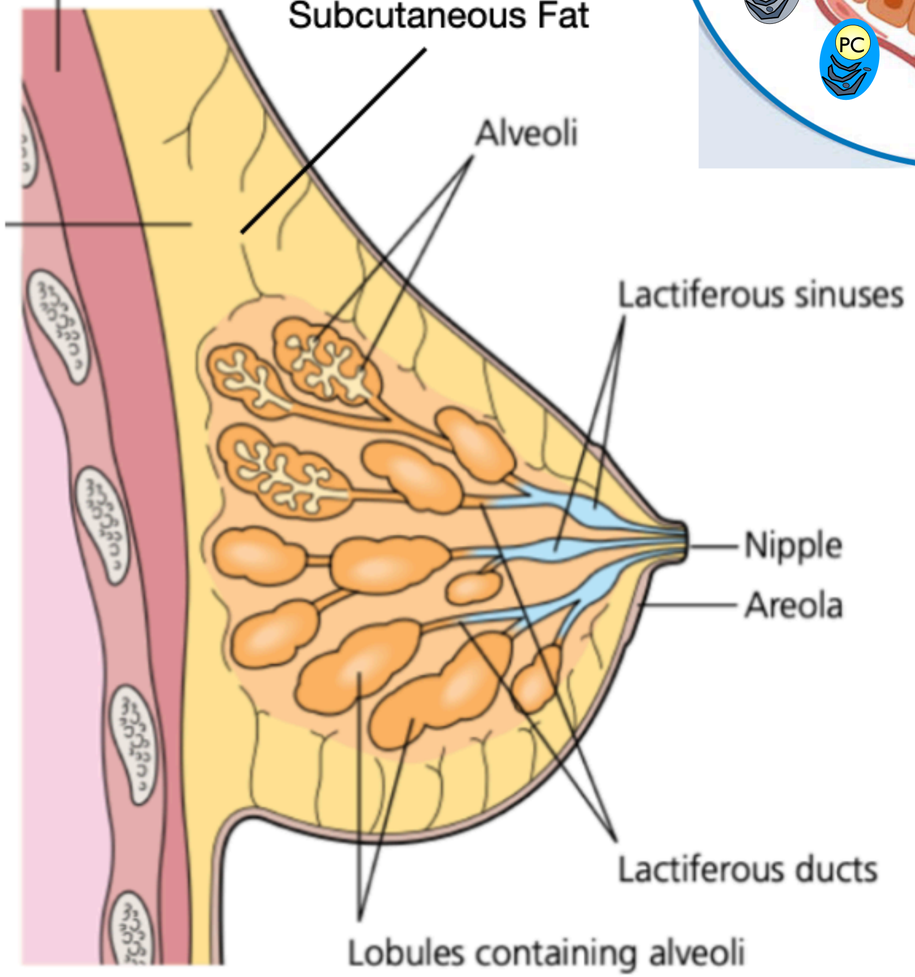
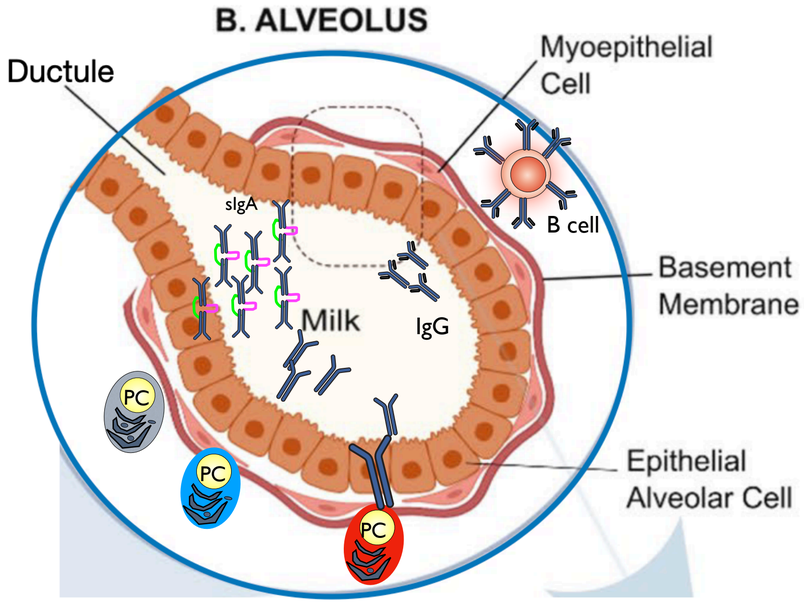
IMPAACT
Therapeutics Scientific Committee
Sept 25, 2024

Outline

- Lactation biology
- HIV breast milk transmission pre- and post-ART era
- Exclusive Breast Feeding
- bNAb vs LA vs oral

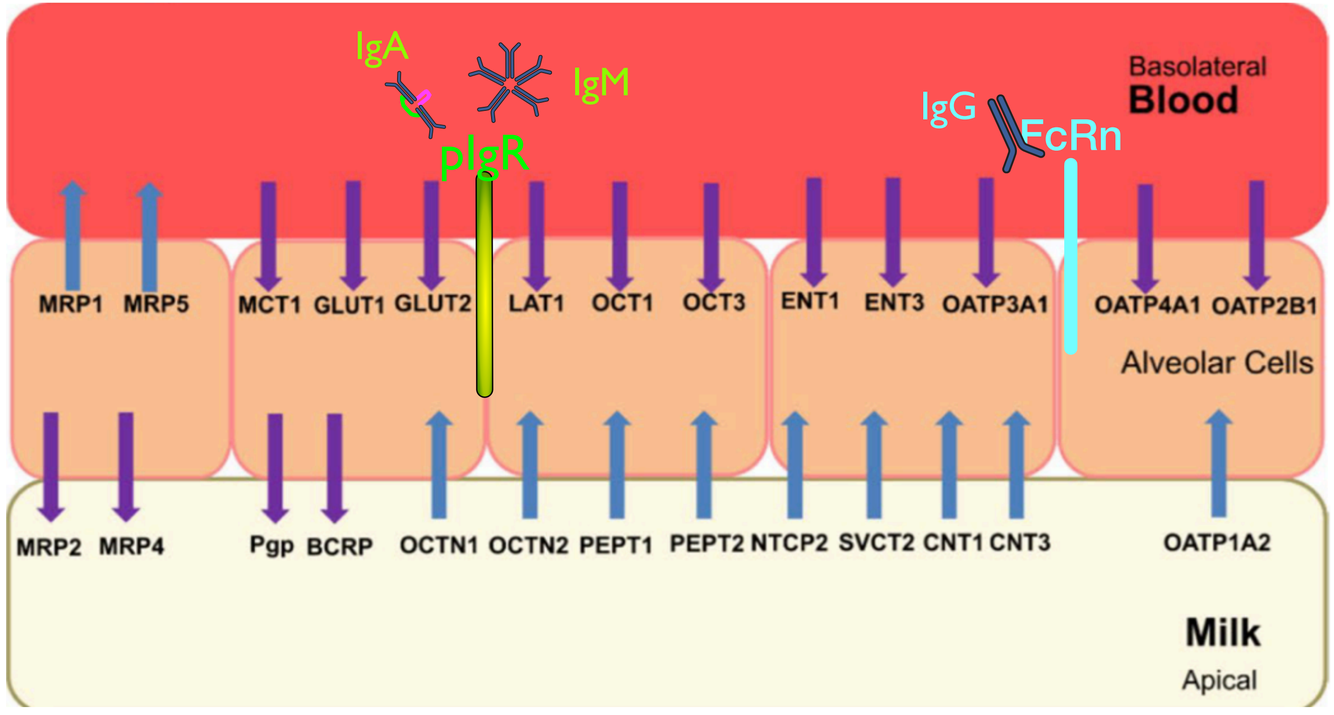




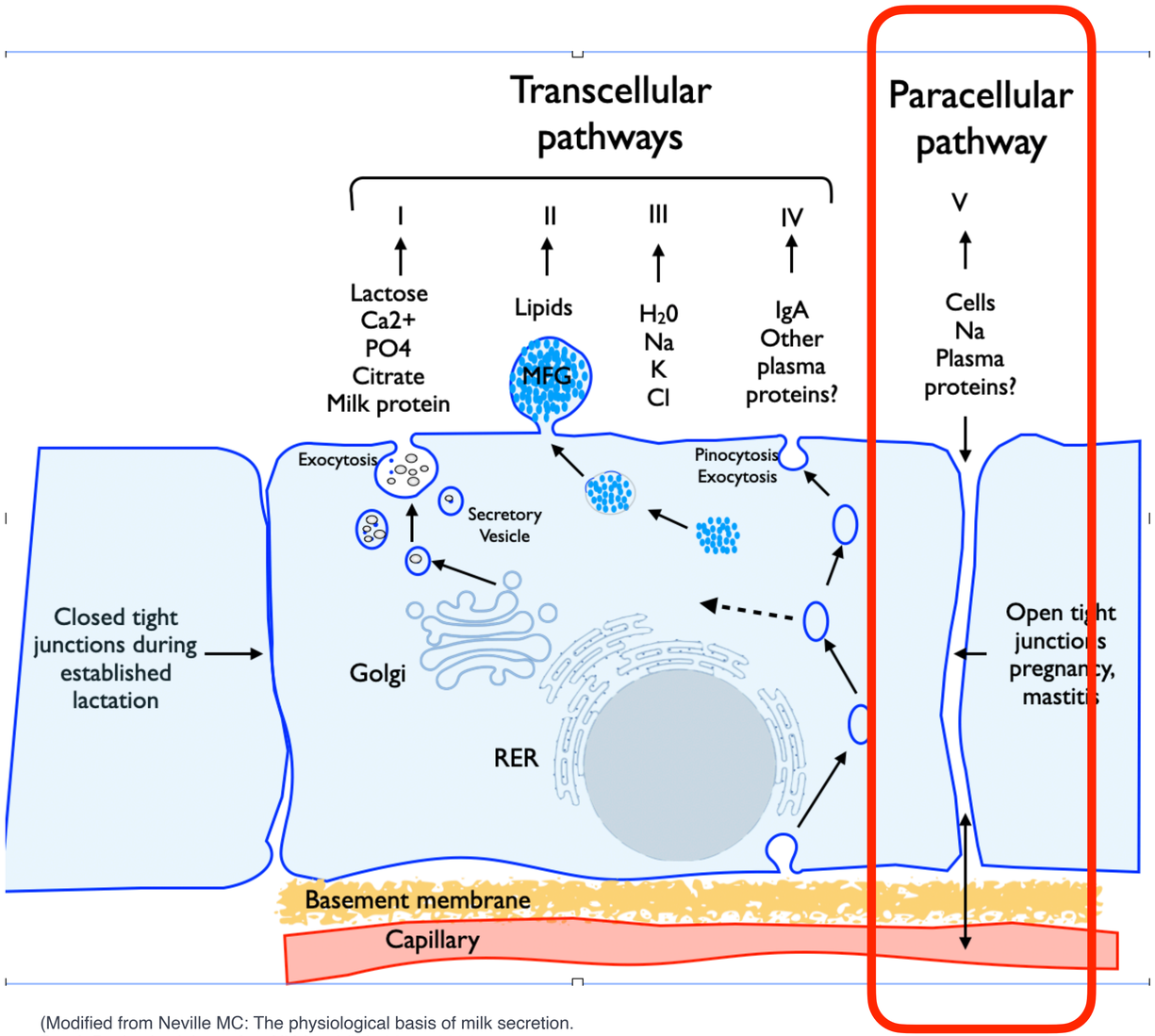
Figures Adapted from: Plastic and reconstructive surgery. 477–485 (2015)
Clinical Pharmacokinetics (2024) 63:561–588

Mammary Epithelial Transporters

(Localization of transporters may not reflect exact physiology)

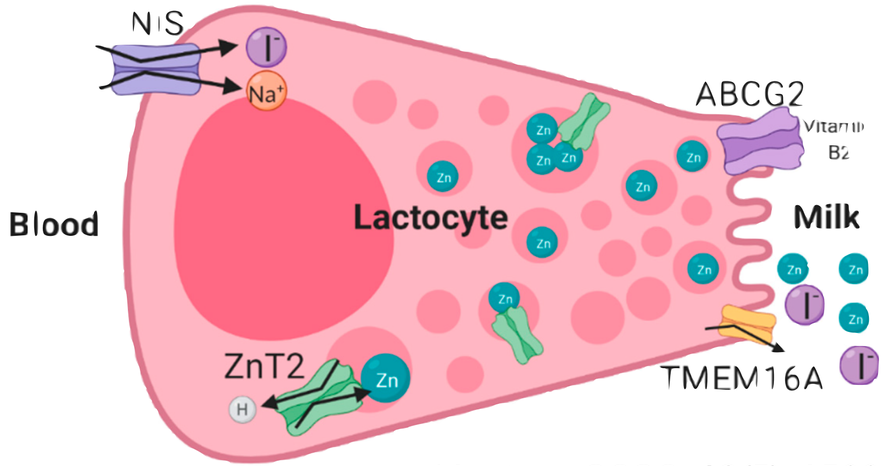


Mammary Epithelium: Not just a barrier



(Modified from Neville MC: The physiological basis of milk secretion. Part I. Basic physiology. *Ann NY Acad Sci* 586:1, 1990.)

Tightly controlled, selective entry
Local production

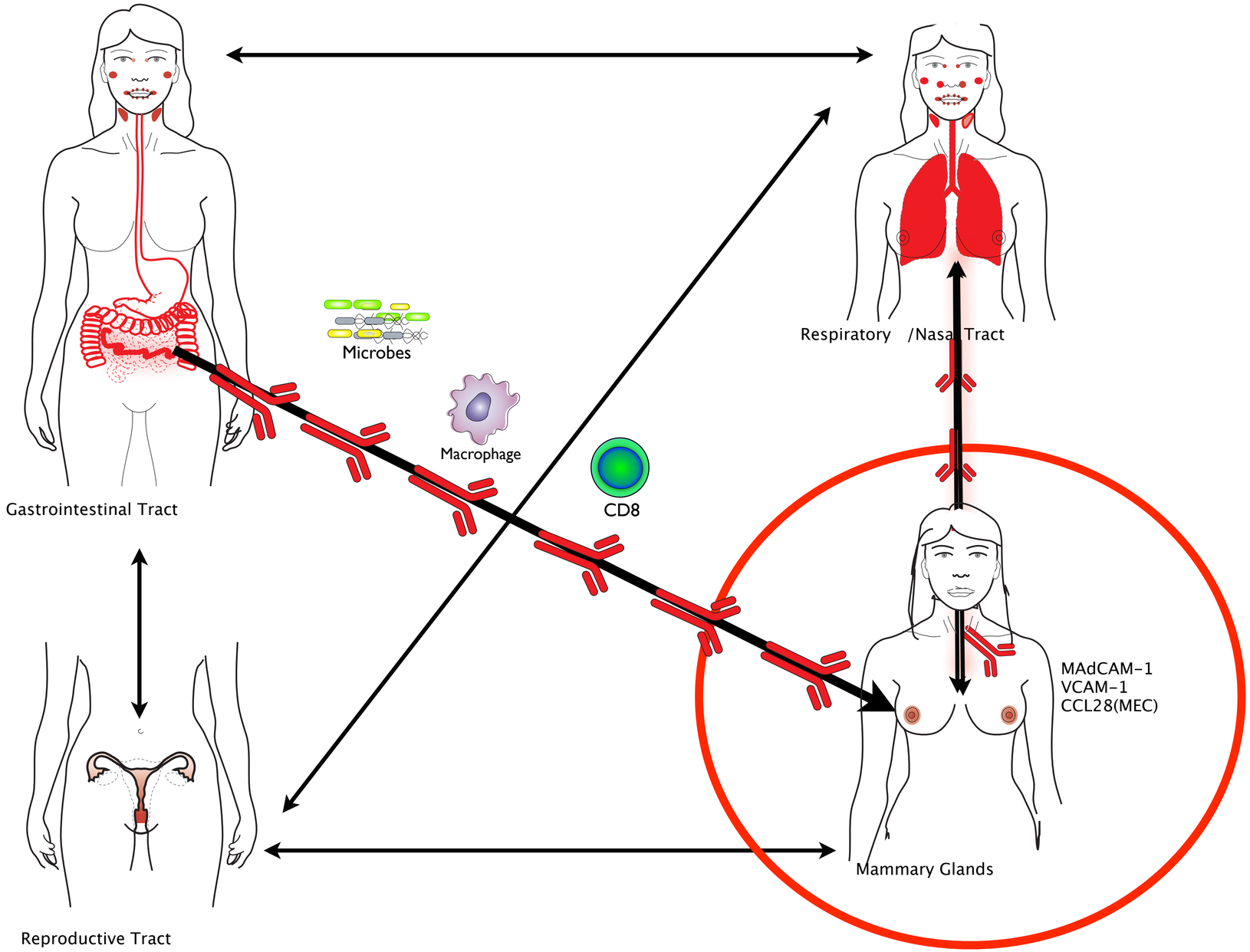


Nutrients **2020**, *12*(5), 1500

Cholesterol
Lactose
Lactalbumin
Lactoferrin

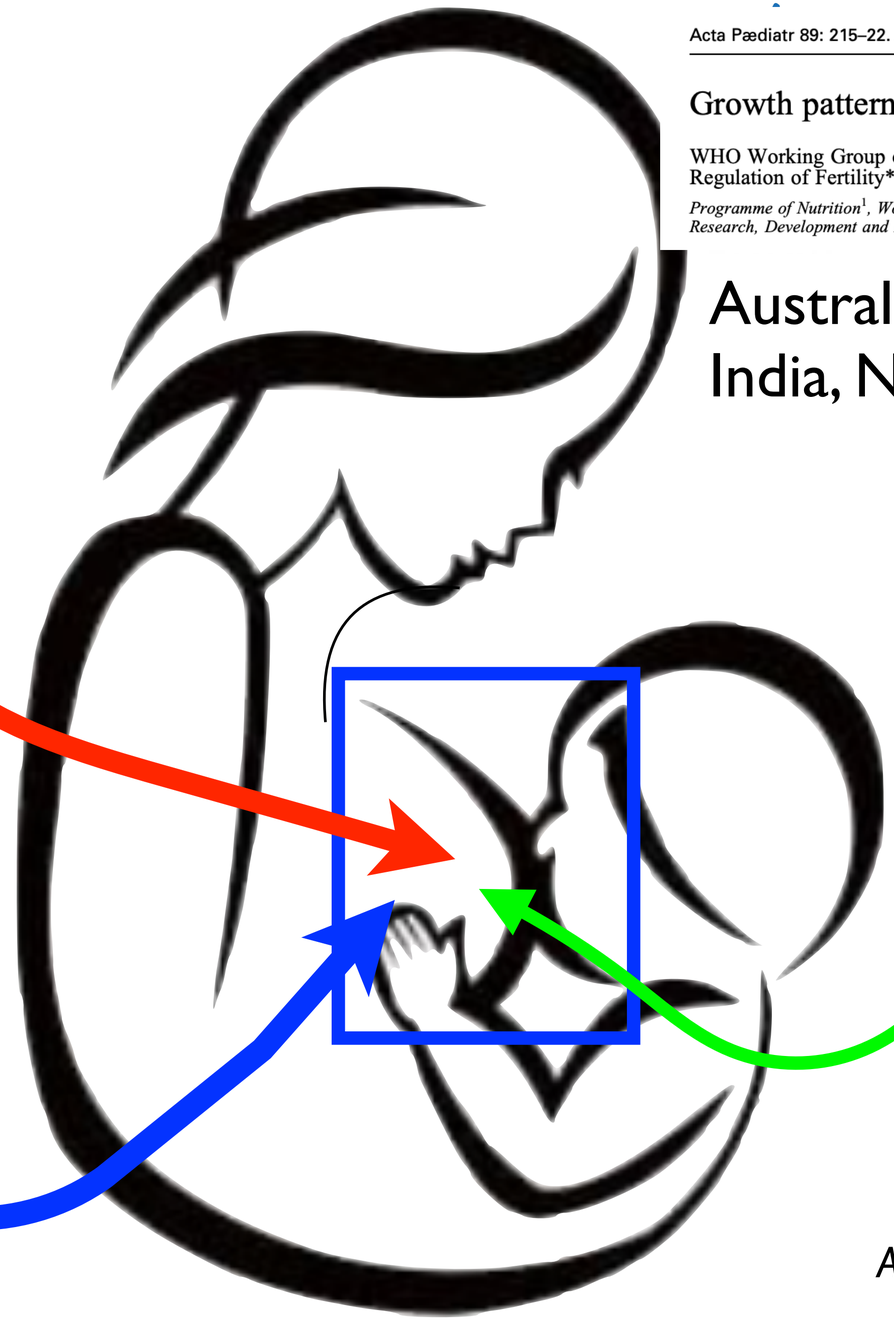
Lactocytes, are terminally differentiated milk-producing epithelial cells

Protection: mucosal immune system



Pediatr Res. 2012;71(2):220-225.
Clin Transl Immunology. 2013;2(4): e3
Pediatr Allergy Immunol. 2007;18(6): 495-502.

Genetics
Age—decrease w age
Parity
Stage of lactation
Diet
BMI
? geography
Health status
Environmental exposures



Acta Pædiatr 89: 215–22. 2000

Growth patterns of breastfed infants in seven countries

WHO Working Group on the Growth Reference Protocol*[1] and WHO Task Force on Methods for the Natural Regulation of Fertility*[2]

Programme of Nutrition[1], World Health Organization, Geneva, Switzerland; UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction[2], World Health Organization, Geneva, Switzerland

Australia, Chile, China, Guatemala, India, Nigeria, Sweden

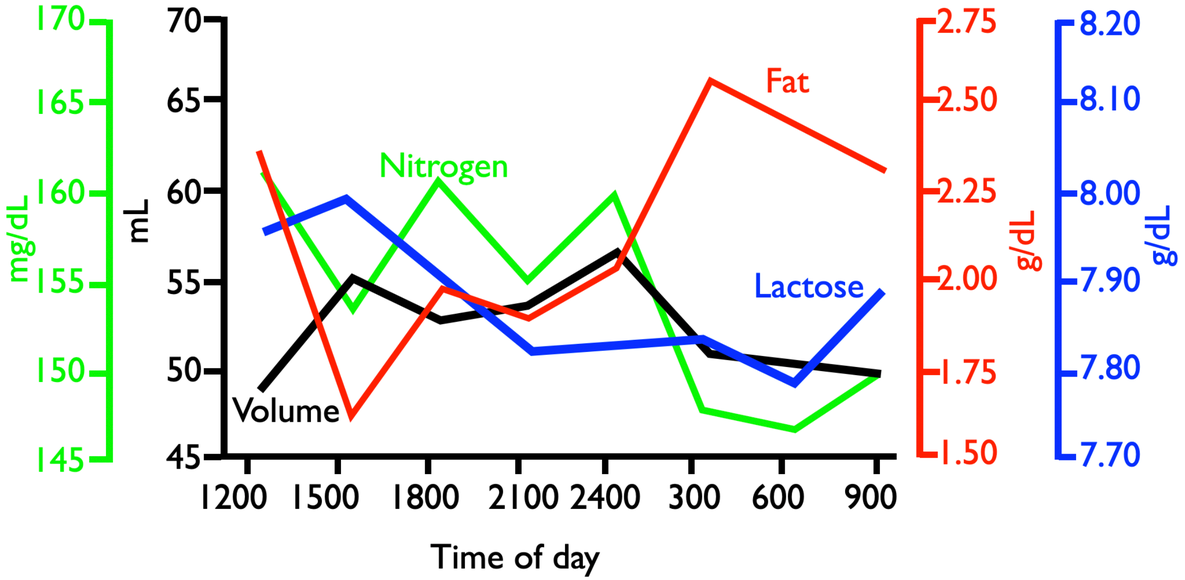
Sex
Gestational Age
Size (SGA, LGA)
Sucking ability
Genetics
Environmental exposures
Illness-infant, maternal

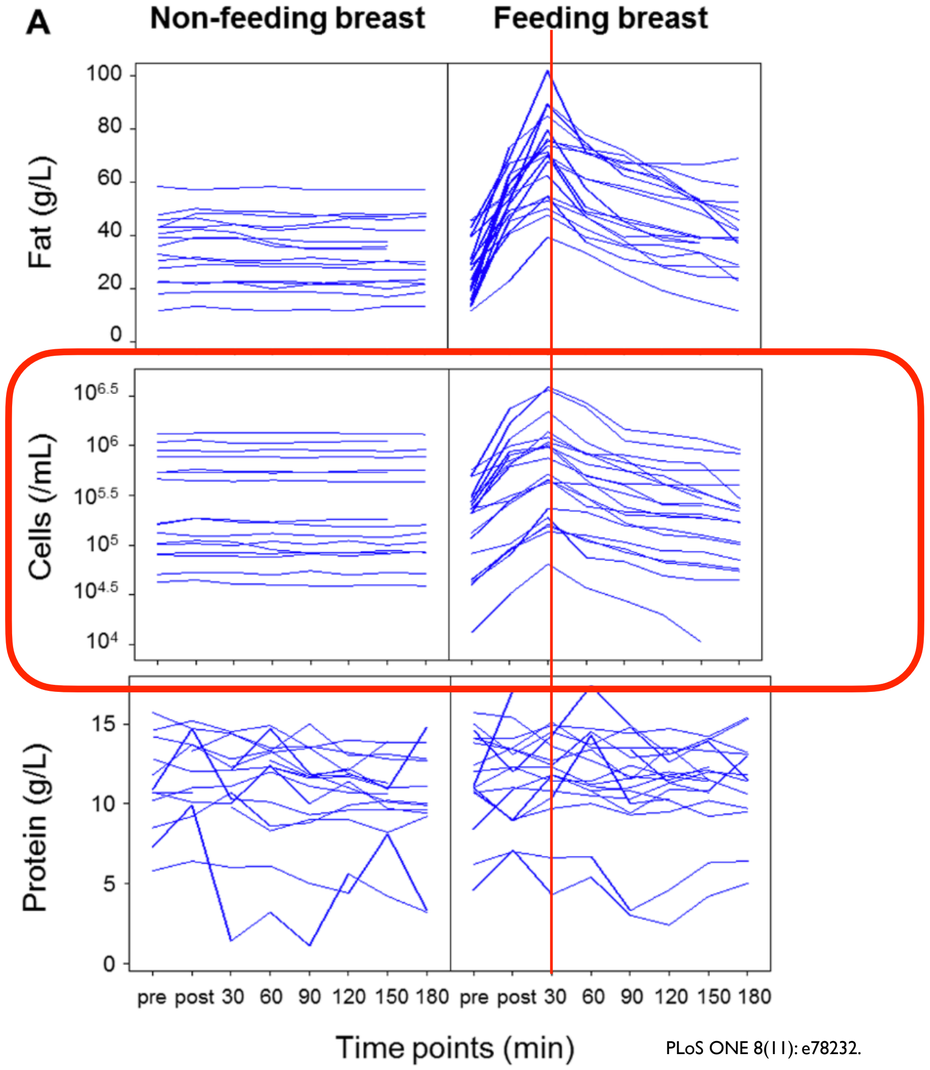
Duration of feed
Time since last feed
Breast health

Am. J. Clin. Nutr. **113**, nqab075- (2021).

Composition: dynamic & on demand

Colostrum Transitional Mature

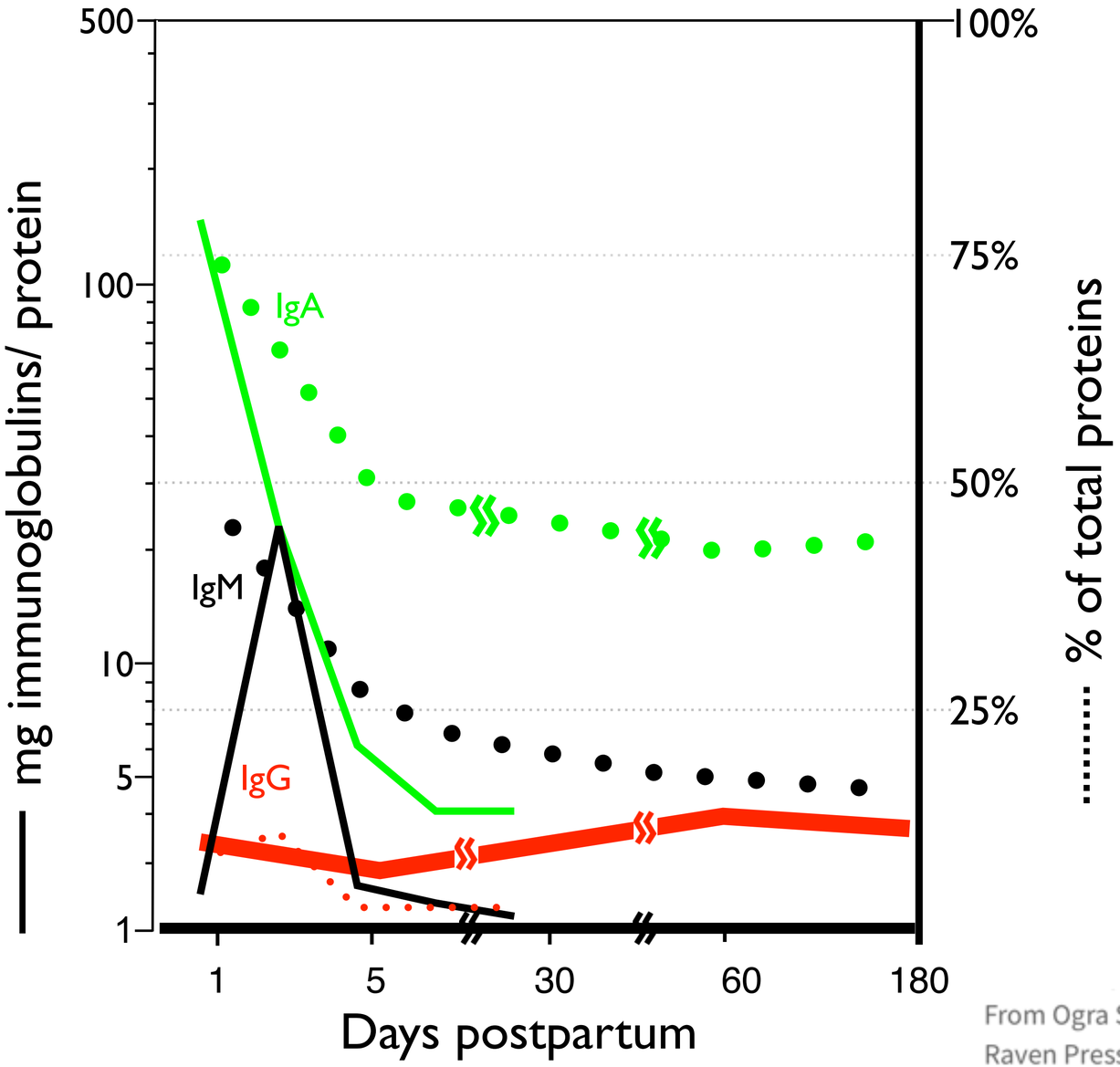


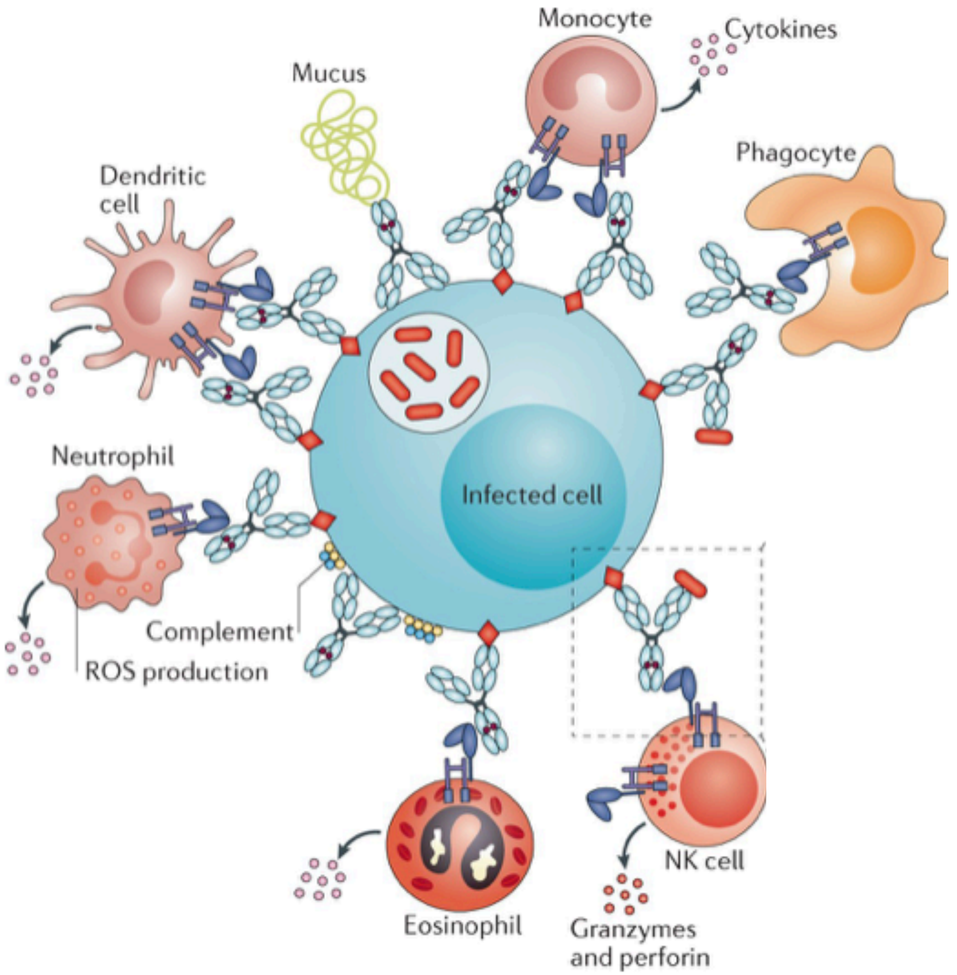


PLoS ONE 8(11): e78232.

21st century antibodies

Levels of Immunoglobulins in human milk





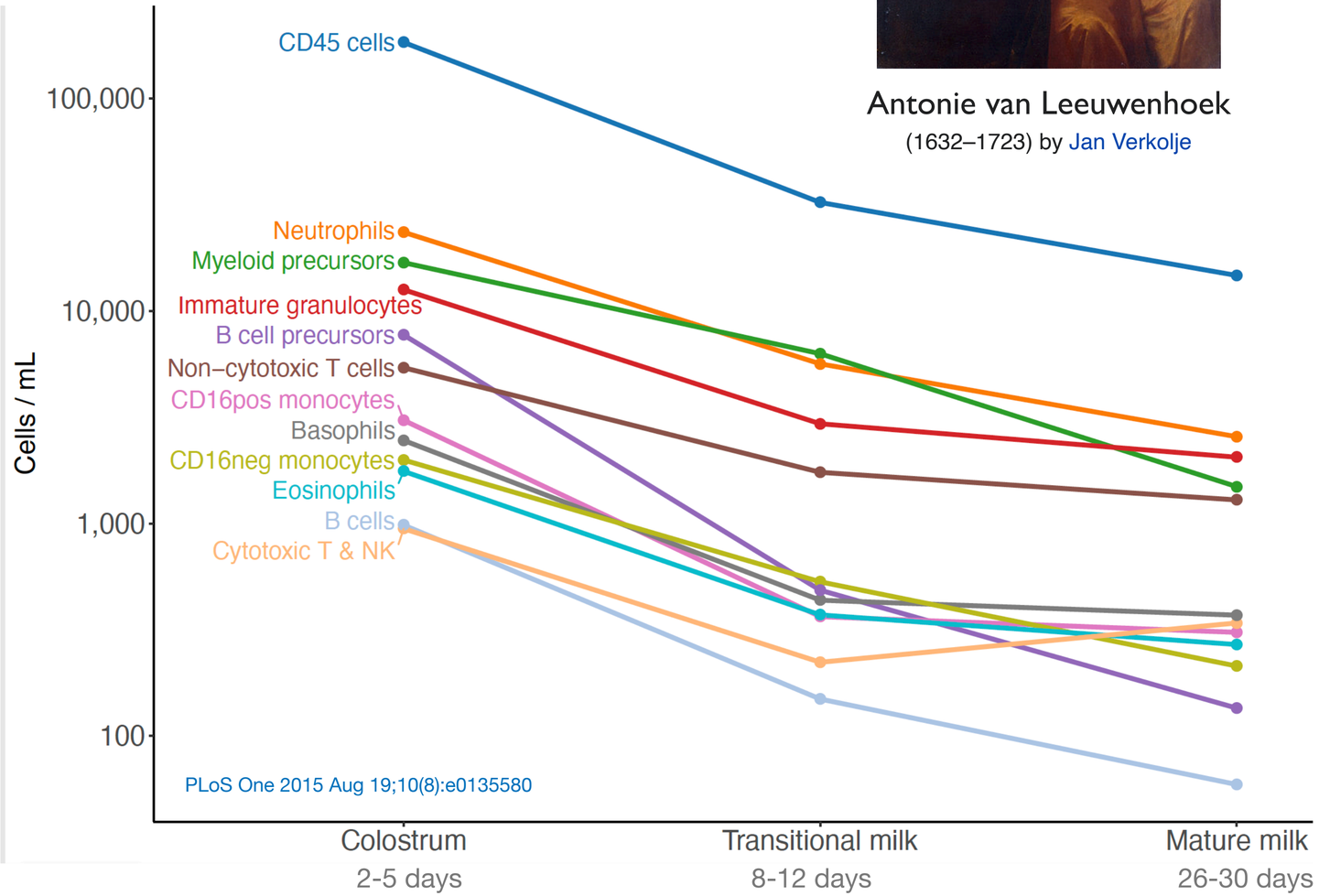
Nat Rev Immunol. 2018 Sep; 18(9): 575–589.

From Ogra SS, Ogra PL: *Components of immunologic reactivity in human colostrum and milk*, New York, 1979, Raven Press; and Losonsky GA, Ogra PL: *Mucosal immune system*, Orlando, Fla, 1984, Grune & Stratton.

Cells in human milk

Antonie van Leeuwenhoek
(1632–1723) by Jan Verkolje

- >90% are epithelial (ductal, alveolar, luminal, myoepithelial).
- Most of epithelial cells are viable, some motile and ex-vivo can form mammospheres (not just debris).



Lymphoid cells in human milk

- Breast milk T cells are phenotypically distinct from those in blood. ⬆ expression of mucosal and effector memory markers (HIV, CMV, EBV, influenza, SARS-CoV-2).
- In animal models breast milk cells traverse the infant intestinal epithelium and appear to be are functional within the infant.
- ?? breast milk cells traverse the human infant gut, are functional in infant and/or contribute to maternal microchimerism is controversial. Differentiating maternal cells transmitted via placenta vs breast milk is problematic.
- Role of these cells in transmission unclear. One group has reported "breast milk HIV reservoir".

No ART: Risk of HIV human milk transmission

- Without ART, transmission rates 15-40%, ⬆ with acute infection, duration of exposure.
- Highest risk early in lactation (also have intrapartum) and during weaning but risk is always present.
- Risk early transmission ~ 6% but have continuous risk of transmission throughout lactation (0.6 to 0.9% per month).
- Risk associated with ⬆ maternal plasma HIV RNA, ⬇ CD4, breast health (mastitis: subclinical & clinical).
- Exclusive BF significantly ⬇ risk of breast milk transmission (almost 50% in multiple studies).

No ART: Temporal and Lateral Dynamics of HIV in Human Milk

- Breast epithelium decreases HIV RNA in breast milk by ~ 100 fold
- R and L breast highly correlated (ρ 0.75 to .88)
- ~20% discordant, i.e., shedding in only one breast
- ~30% continuous shedders
- CD4 major correlate of viral shedding but women with high CD4 can transmit
- Parity and breast feeding practice (exclusive or non-exclusive)
- Shedding correlates with transmission

JAIDS 2008;47:320–328,
JAIDS 2013; 62, 348–355

No ART: Risk of HIV human milk transmission

- ZEBS: In univariable analysis, both BM HIV-1 RNA & DNA levels strongly associated with postnatal transmission (N=958 women, 24m follow-up).
  Sci Transl Med. 2013 Apr 17;5(181):181ra51
  - BUT only HIV-1 RNA concentrations remained associated with both early and late postnatal HIV transmission after adjusting for maternal CD4+ T cell counts and plasma HIV-1 RNA concentrations.

- RSA study: (36 transmitting vs 36 non-transmitting) with BM HIV RNA & DNA quantified at 6 wks and 6 m. After controlling for CD4 & plasma RNA, BM DNA levels more strongly associated with 6-week postnatal transmission while BM RNA with transmission @ 6m. *PLosOne 2012;7:e51493*

On ART: Risk of HIV human milk transmission

- Limitation of most studies of breastfeeding populations on ART:
  - focus on early transmission & do not cover the entire breastfeeding interval (18-24 months),
  - follow women who started ART during pregnancy not on life-long ART.
- With ART <1% transmission but U≠U.
- Maternal viremic control is critical, the extent to which infant prophylaxis can compensate remains to be determined.
- Even in viremic women, HIV RNA is rarely be detected in milk.
- 2 months of ART (AZT/3TC/NVP) suppressed HIV RNA but not HIV DNA breast milk (n=26)

J Infect Dis 2005;192:713-9

On ART risk of In Utero/Intrapartum/Early Breastfeeding is low

Location *ART start*	First author (Year)	Delivery Viral Load			
		Transmission at <50 c/mL	Transmission at 50-400 c/mL	Transmission at 400-1,000 c/mL	Transmission at >1000 c/mL
RSA all start during pregnancy	Myer (2017) *MTCT 6 wk*	0.25% (1/406)	2.0% (50-1,000 c/mL, 2/102)		8.5% (4/47)
Malawi *50% before pregnancy*	Landes (2019) *MTCT 4-24 wk*	0.9% (8/902)	7.0% (6/86)		14.0% (19/136)
South Africa *Likely most preconception*	Moyo (2020) *MTCT birth*	0.3% (3/946)*	3.2% (6/187)		7.9% (25/316)
Uganda, RSA >28 wk	Malaba (2022) (DolPHIN-2)	1% (3/280) started @32wks,	0.4% (1/280) Started @30 wks		
Lockman (2021)	Multi country IMPAACT 2010	0.002% (1/617) started @ 29 wks			0.002% (1/617) Started @ 26 wks

Slide adapted from slide from Dr. Lynne Mofenson, EGPAF

On ART Late Breastfeeding Transmission is rare

Three studies provided data on final infant infection status at the end of breastfeeding and maternal viral load during the postpartum period.

First Author (Year)	Study location	Findings
Flynn (2018)	Multi-country (PROMISE study)	2 infant infections: 1 mom on ART antepartum-postpartum, with VL <40 at time infant infection detected; other mom initiated ART postpartum with subsequent VL <40 cpm
Luoga (2018)	Tanzania	1 infant infection where the maternal viral load was <1,000 cpm but mother had a disruption in therapy
Giuliano (2013)	Malawi	1 infant infection, mom initiated ART during pregnancy and had a subsequent VL <37 cpm
Malaba (2022)	Uganda, RSA (DolPHIN-2)	1 infant in EFZ arm. Mom VL <50 @12, 24, 48 & 72 weeks Infant DNA neg @ birth, 6, 12 wks (missed other visits) DNA + 72 wks

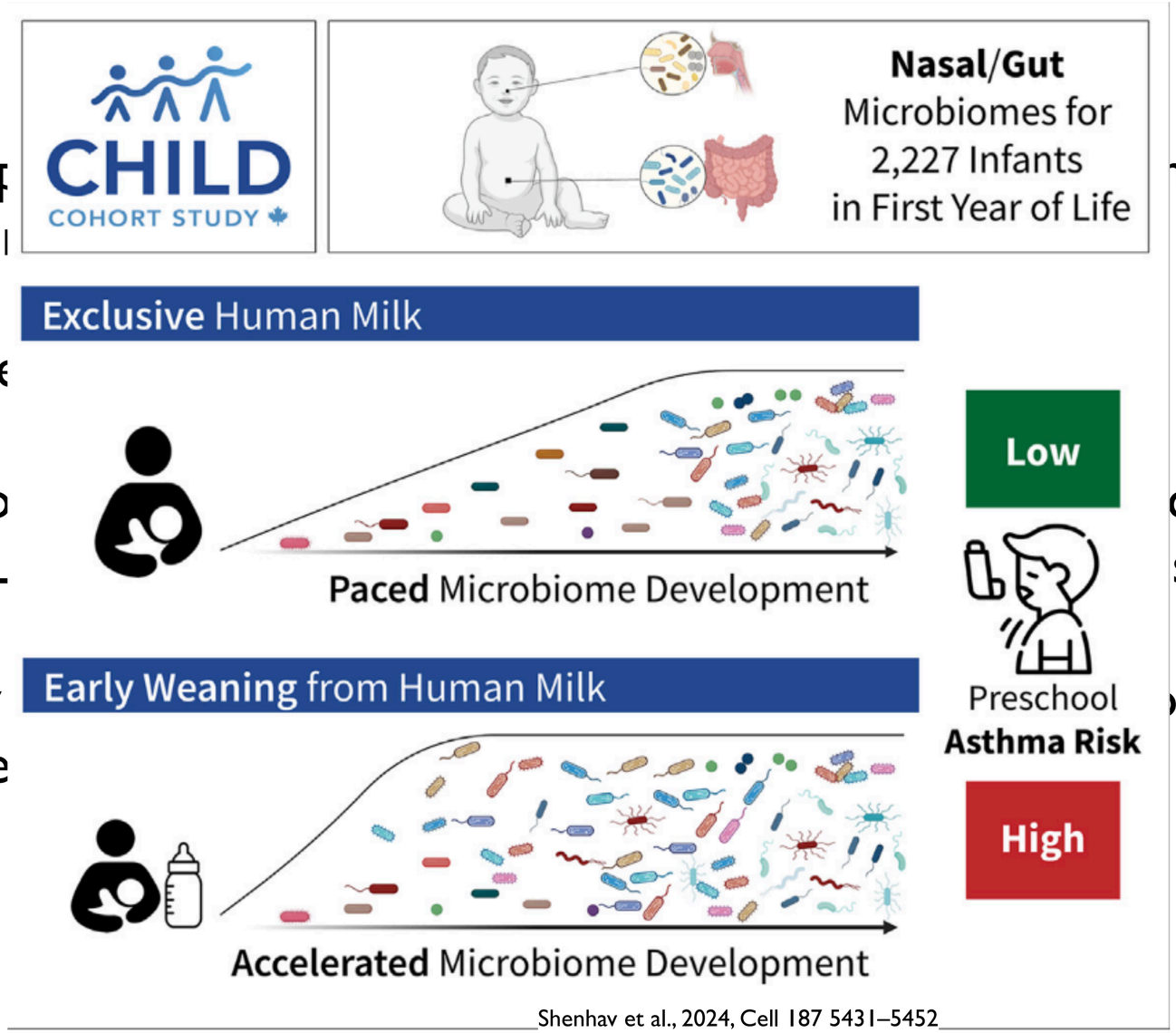
Slide adapted from slide from Dr. Lynne Mofenson, EGPAF

Why does U≠U for BMT?

- Non-adherence
- Viral blips and low level viremia occurs in virally “suppressed” and adherent persons
- ? Breast pathology
- Will duration of ART and starting ART at higher CD4 make a difference?
- Will ART regimen make a difference?

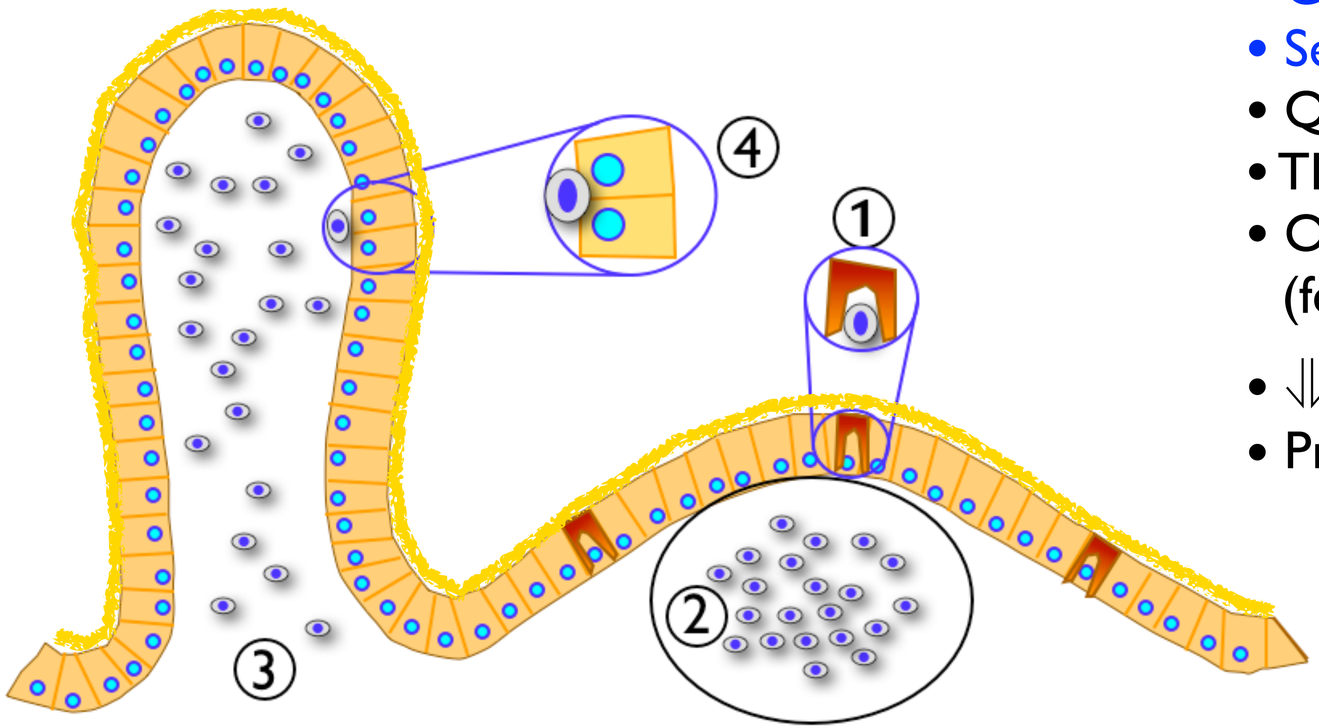
Exclusive Breast Feeding (EBF)

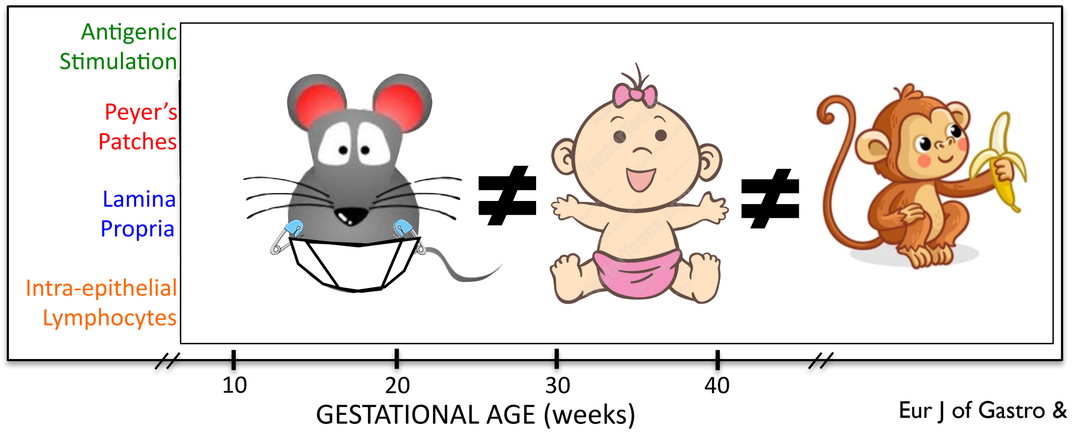
- Definition: Comp … ins and medicine preparations in fi…
- If you give tea, he…
- EBF is optimal fo… ce recommended for first 6 m of life by ALL… settings.
- Complementary … ommended after 6 m but it is not Mixed Fe…



Shenhav et al., 2024, Cell 187 5431–5452

Infant GI development





Major changes in post-natal gut:

- ⇓ permeable to macromolecules ("closure")
- Closure delayed in preterm (<33 wks)
- Seeding by microbial communities
- Quantitative & qualitative diff in mucin
- TLR expression and response to stimulus
- Oligosaccharides on intestinal epithelium (fetal sialyation⇒adult fucosylation & galactosylation)
- ⇓ gastric acid & pancreatic enzymes
- Prem gut ⇑ inflammatory response

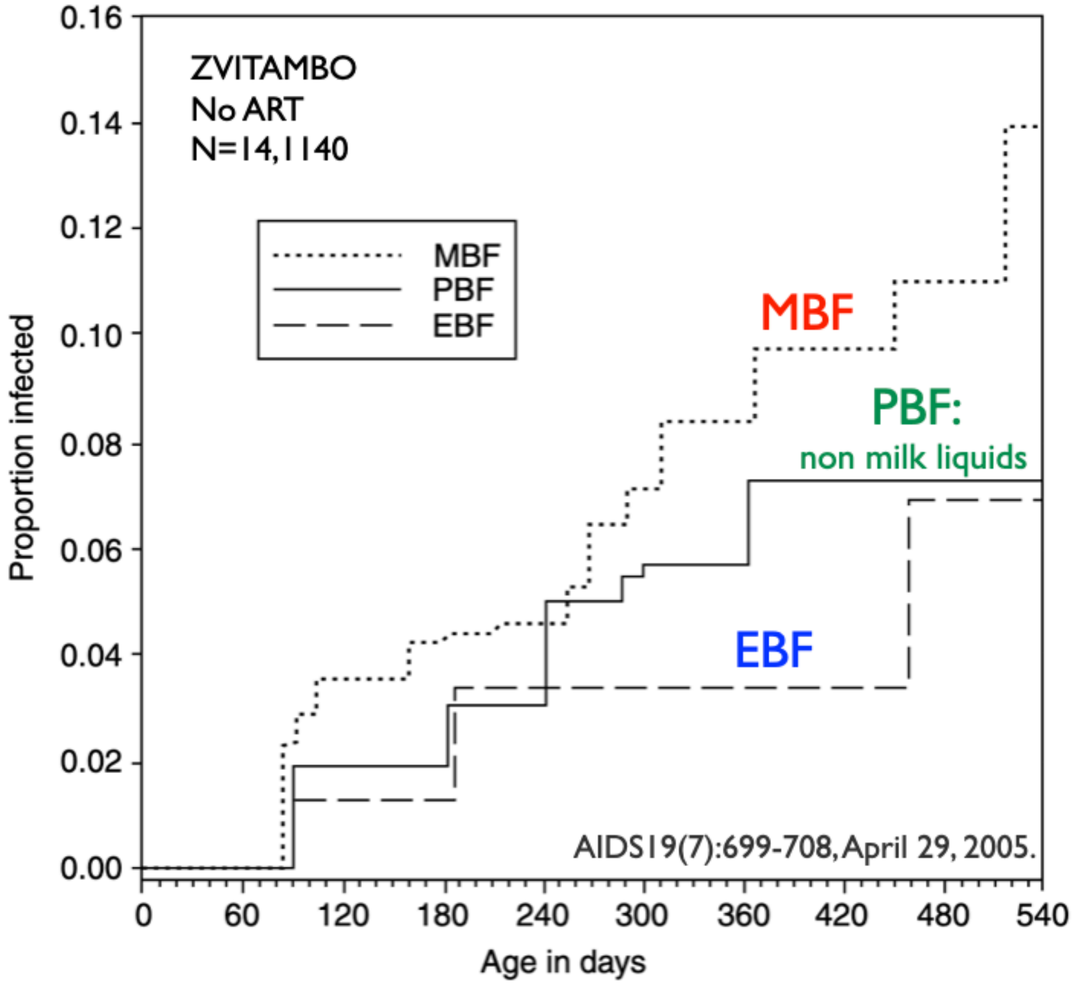
Between 4 and 6 months
MAJOR changes

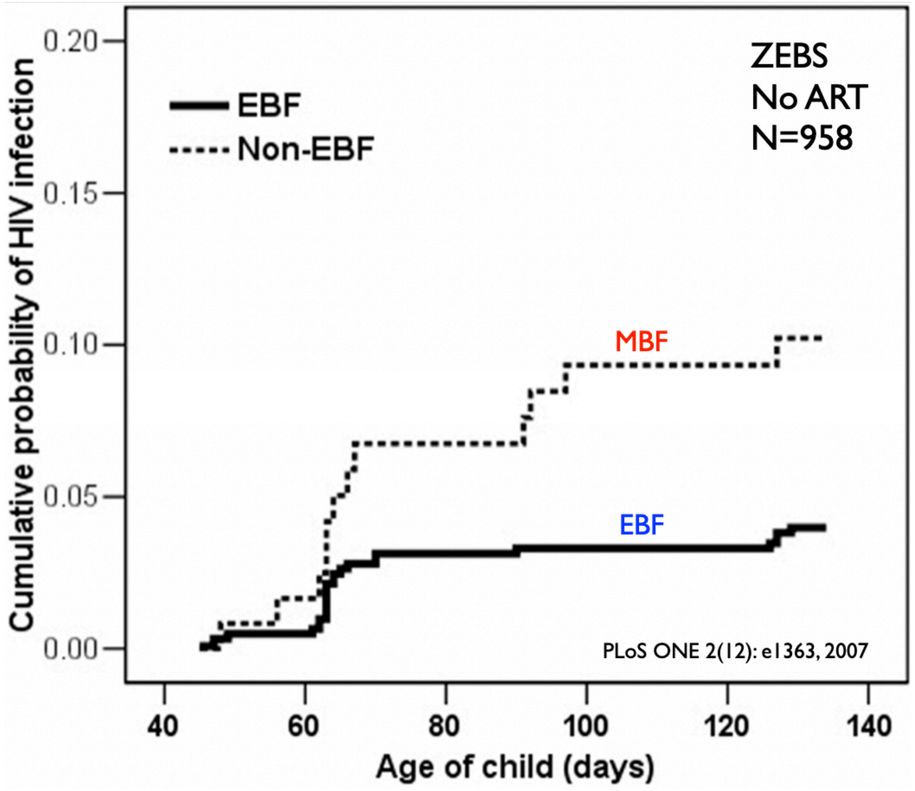
Major determinants:

- Luminal bacteria
- Dietary Antigens
- Human Milk

Eur J of Gastro & Hepatology 17:1273-1278 2005

EBF: No ART

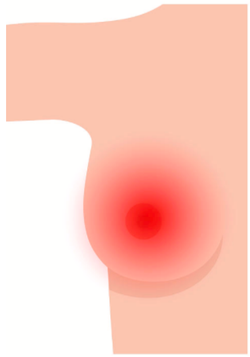




	Hazard Ratio	95% CI
Time dependent analysis	3.5	1.7-6.9
Adjust for maternal CD4, plasma RNA, infant birth wt	2.6	1.3-5.3

No association EBF with IU or IP infection (<6 wks)

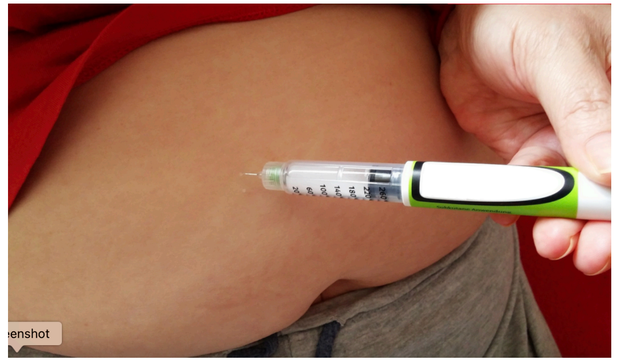
Why EBF works? Gut vs Breast



- Human gut closure and integrity:
  - breast milk ↓ gut permeability and epithelial thickness (preterm & term)
  - microbiome changes associated with BM
  - organoid systems: BM ↑ epith thickness & permeability

- Mixed feeding:
  - ↓ mammary epithelial integrity
  - ↑ risk of mastitis (subclinical & clinical)

bNAb vs LA ART vs oral



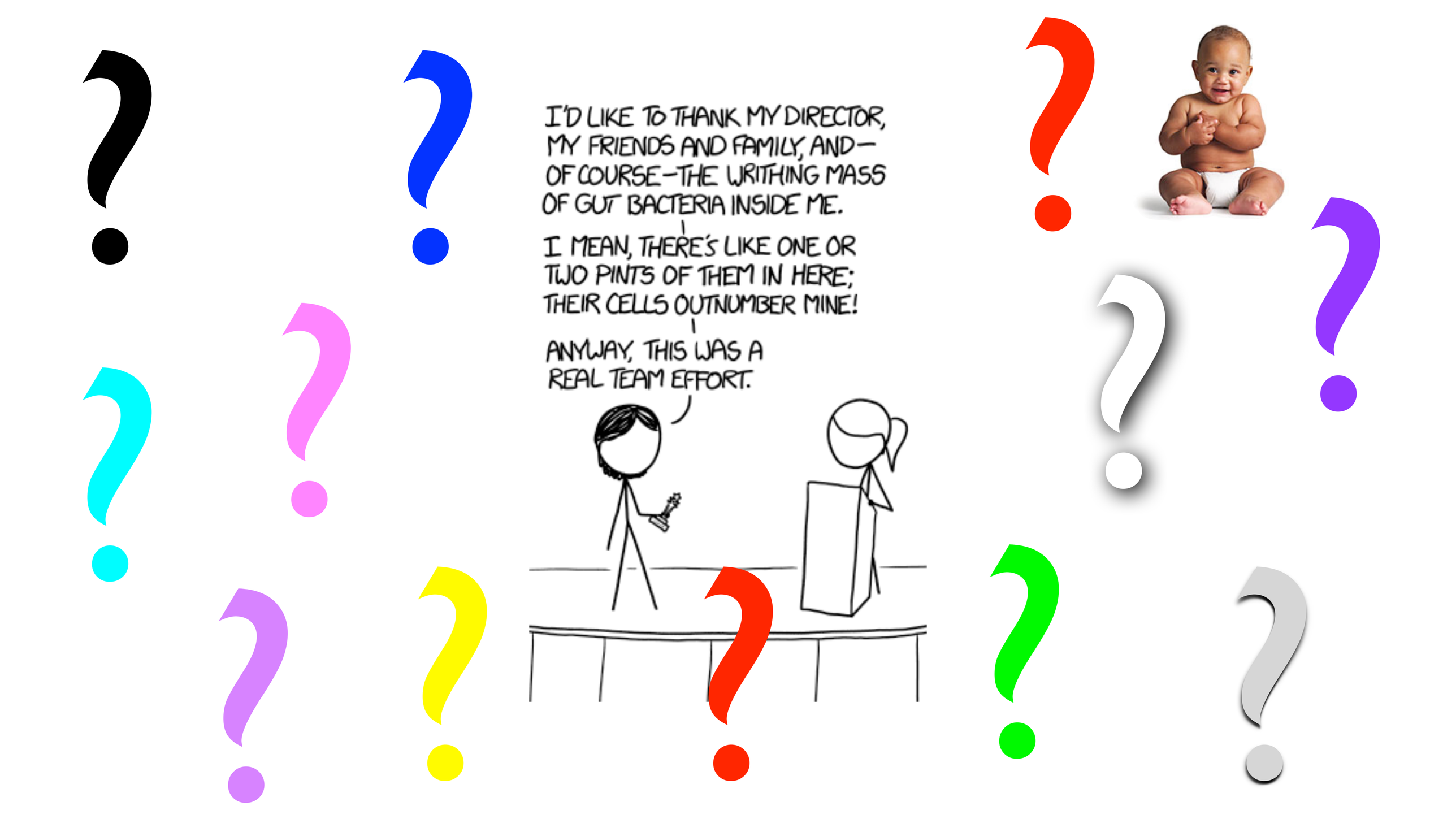
"Diagnosis of HIV in infants exposed to long-acting maternal antiretrovirals"

Edmund Capparelli, PharmD and Lisa Frenkel, MD

Salon J-K

Summary

- Breast milk HIV RNA levels are strongly associated with transmission risk.
- Breast milk HIV RNA and DNA are highly correlated in absence of ART.
- Role of breast milk HIV DNA in transmission risk is uncertain.
- Breast milk HIV transmission is rare in virologically suppressed women but U≠U.
- Correlates of immunologic protection are unknown.


I'D LIKE TO THANK MY DIRECTOR, MY FRIENDS AND FAMILY, AND— OF COURSE—THE WRITHING MASS OF GUT BACTERIA INSIDE ME.
I MEAN, THERE'S LIKE ONE OR TWO PINTS OF THEM IN HERE; THEIR CELLS OUTNUMBER MINE!
ANYWAY, THIS WAS A REAL TEAM EFFORT.