Is U=U Applicable to Breastfeeding?

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Is U=U

Applicable to Breastfeeding?

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JAMA. 2019 Feb 5;321(5):451-452. doi: 10.1001/jama.2018.21167.

HIV Viral Load and Transmissibility of HIV Infection: Undetectable Equals Untransmittable

Robert W Eisinger [1], Carl W Dieffenbach [2], Anthony S Fauci [1]

Elizabeth Glaser Pediatric AIDS Foundation

Until no child has AIDS.

Undetectable = Untransmittable

JAMA. 2019 Feb 5;321(5):451-452. doi: 10.1001/jama.2018.21167.

VIEWPOINT

HIV Viral Load and Transmissibility of HIV Infection

Undetectable Equals Untransmittable

Robert W Eisinger [1], Carl W Dieffenbach [2], Anthony S **Fauci** [1]

- U=U signifies that an HIV-infected individual on antiretroviral therapy who achieves and maintains an undetectable viral load cannot transmit HIV to their partner.

Principles of U=U

- In order for antiretroviral therapy (ART) to provide maximum benefit, taking medication as prescribed is essential.
- Achieving an undetectable viral load can take up to 6 months of ART. Once achieved, continued adherence is required.
- According to guidelines from the Department of Health and Human Services, viral load testing should be performed every 3-4 months after the plasma HIV-1 RNA level reaches undetectable (<200 copies/mL). If viral suppression and stable immunologic status are maintained for >2 years, the viral load testing can be extended to every 6 months thereafter.
- Stopping therapy negates the validity of assuming that U = U.

→ Consistent adherence to ART required

→ Achieving suppression takes time - undetectability is not immediate on ART

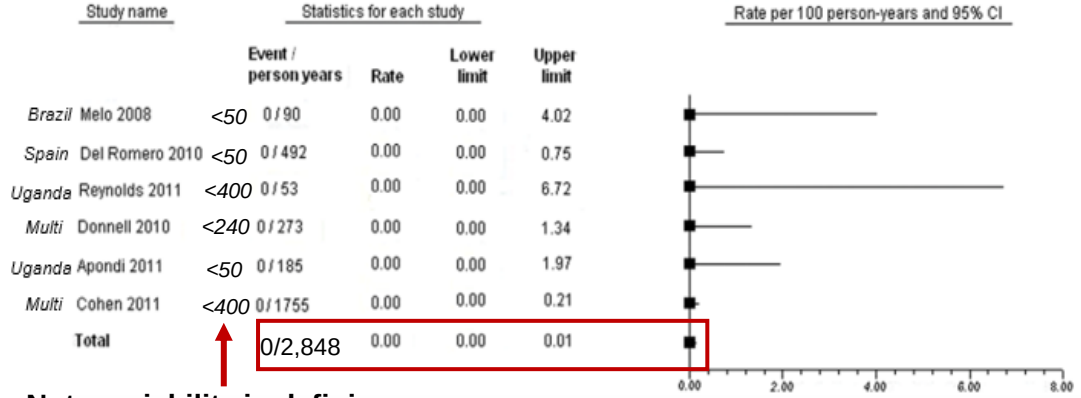
→ Monitoring to verify remains undetectable (what defines undetectable?)

→ Risk of stopping - U=U invalid if non-adherent

Evidence Supporting U = U Comes From Studies of Sexual Transmission

- HPTN 052, PARTNER1, PARTNER 2, Opposites Attract, and other studies followed thousands of MSM and heterosexual HIV discordant couples.

6 Studies in 2,848 Heterosexual Discordant Couples
Metaanalysis HIV Transmission/100 Person-Years
Excluding those with Unconfirmed Suppressed Viral Load



Note variability in defining undetectable RNA threshold

Loutfy MR et al. PLosOne 2013;8: e55747

3 Studies in 1,126 Homosexual Discordant Couples

Author/Journal/Year	Threshold	N	Event/PY	Rate	Upper Limit
Rodger AJ. JAMA 2016 *PARTNERS1 (MSM part)*	<200	330	**0**/439	0.00	0.84
Bavinton BR. Lancet HIV 2018 *Opposites Attract*	<200	343	**0**/588	0.00	0.63
Rodger AJ. Lancet 2019 *PARTNERS2*	<200	783	**0**/1,593	0.00	0.23

- No genetically-linked transmissions occurred when HIV+ partner on ART had stable virally suppression (defined as HIV RNA <50 to <400 copies/mL depending on study).
- Provides robust evidence that individuals *do not* **sexually** transmit HIV if they are virally suppressed/ have an undetectable viral load.

Undetectable = Untransmittable
Evidence Limited to Sexual Transmission

World Health Organization

Dear Colleague: September 27, 2017

Dear Colleague

INFORMATION FROM CDC'S DIVISION OF HIV/AIDS PREVENTION

When ART results in viral suppression, defined as less than 200 copies/ml or undetectable levels, it prevents sexual HIV transmission. Across three different studies, including thousands of couples and many thousand acts of sex without a condom or pre-exposure prophylaxis (PrEP), no HIV transmissions to an HIV-negative partner were observed when the HIV-positive person was virally suppressed. ***This means that people who take ART daily as prescribed and achieve and maintain an undetectable viral load hav[illegible] effectively no risk of sexually transmitted the virus [illegible]o an HIV-negative partner.***

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HIV/AIDS

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- Data and statistics
- About us
- World AIDS Day

Viral suppression for HIV treatment success and prevention of sexual transmission of HIV

July 2018 – The World Health Organization (WHO) leads the health sector response to HIV as part of the Joint United Nations Programme on HIV/AIDS. WHO works to increase access to HIV testing, antiretroviral therapy (ART) and viral load monitoring, to improve the clinical management of HIV as an urgent public health priority to prevent HIV-related morbidity and mortality.

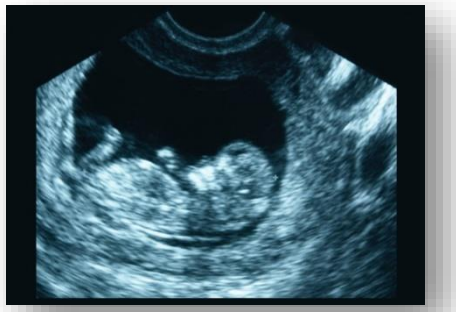
The science related to the use of ART as an additional prevention tool is clear: there is no evidence that individuals who have successfully achieved and maintained viral suppression through ART transmit the virus sexually to their HIV-negative partner(s)

and prevention programmes.

Undetectable = Untransmittable
Evidence Limited to Sexual Transmission

World Health Organization

Does This Apply to Postnatal Breast Milk Transmission?



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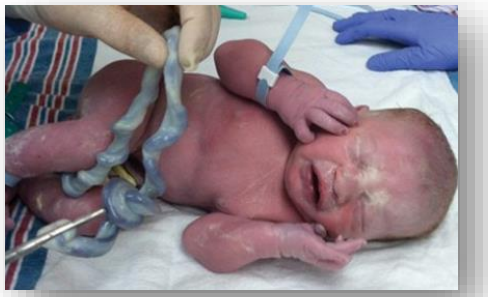


Does U=U Apply to Peripartum (*In Utero*/Intrapartum) MTCT in Non-Breastfeeding Women?

In Utero/Intrapartum MTCT (Formula-Feeding)
Starting ART During Pregnancy

Cohort (Location)	First author (Year)	Viral Load at Delivery			
		Transmission at <50 c/mL	Transmission at 50-400 c/mL	Transmission at 400-1,000 c/mL	Transmission at >1000 c/mL
France	Mandelbrot* (2015)	0.5% (14/2,694)	2.0% (17/873)	3.1% (≥400 copies/mL, 18/588)	
United Kingdom & Ireland (NSHPC)	Townsend* (2014)	0.1% (2/1,965)	2.2% (≥50 copies/mL, 17/783)		
Total		**0.3% (16/4,659)**	**2.3% (52/2,244)**		

*In both studies, MTCT risk associated with **duration of ART** prior to delivery

→ While risk MTCT is low, it is <u>not</u> zero with delivery VL <50 c/mL when first initiating ART during pregnancy, and even higher using <400 c/mL.

Mandelbrot L et al. *Clin Infect Dis.* 2015;61:1715-25
Townsend CL et al. *AIDS* 2014;28:1049-57

In Utero/Intrapartum MTCT (Formula-Feeding) ART Preconception *and* During Pregnancy

Cohort (Location)	First author (Year)	Viral Load at Delivery			
		Transmission at <50 c/mL	Transmission at 50-400 c/mL	Transmission at 400-1,000 c/mL	Transmission at >1000 c/mL
France	Mandelbrot* (2015)	0% (0/2,651) *95% CI 0 - 0.1%*	0.3% (1/301)	2.2% (≥400 copies/mL, 5/230)	
United Kingdom & Ireland (NSHPC)	Townsend (2014)	0% (0/1,894) *95% CI 0 - 0.2%*	2.0% (≥50 copies/mL, 3/151)		
Total		**0% (0/4,545)** 95% CI 0 - 0.8%	**1.3% (≥50 copies/mL, 9/682)**		

*312 women on preconception ART had **ART interruption** in first trimester; 4/312, 1.3%, transmitted to infant, **despite** 2/4 having VL <50 at delivery.

Mandelbrot L et al. *Clin Infect Dis.* 2015;61:1715-25
Townsend CL et al. *AIDS* 2014;28:1049-57

Significant Limitations of Evidence Considering U=U for MTCT, Particularly Postnatal MTCT

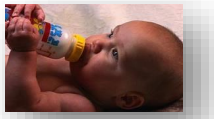
- Evidence for U=U for MTCT comes from developed world and formula-fed population
  - Supporting evidence is from France, UK/Ireland
- Limited breastfeeding data
  - Many studies in breastfeeding populations exclude the full breastfeeding period and only address early transmission
  - Breastfeeding data available primarily limited to women started on ART during pregnancy and not those on life-long ART

What Do We Know About Breast Milk HIV Transmission?

Differences in Early vs Late (After Age 1 Month) Transmission Risk

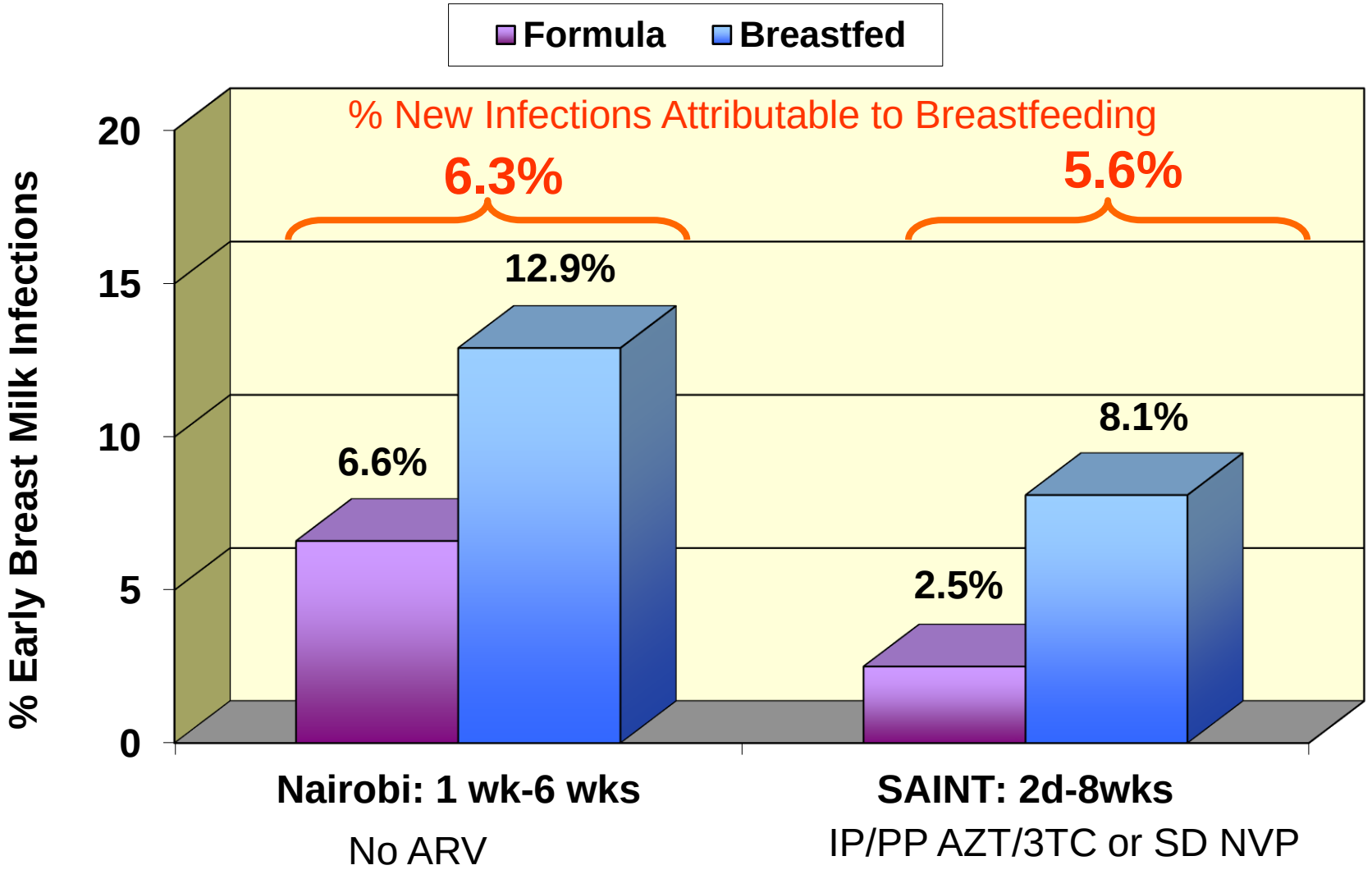
Timing of Breast Milk Transmission
(in the Absence of ART)

- Several studies suggest a substantial proportion of breast milk transmission occurs early, before 1-2 month of age – as high as an absolute risk of 6%.
- This may be due to high T-cell content of colostrum/early breast milk, which could theoretically increase risk of HIV transmission.
- However, there appears to be a continuous risk throughout lactation, with low monthly risk, on average about 0.6-0.9% per month.
- Thus, for women not on ART who breastfeed for 18-24 months, overall risk of postnatal transmission can be as high as 21-27%.



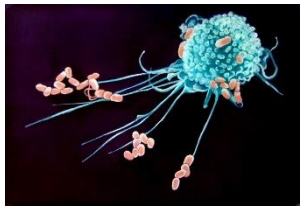
Substantial Early Breast Milk HIV Transmission:

Nairobi & SAINT Trials: Difference Between Formula & Breast-Fed Infants



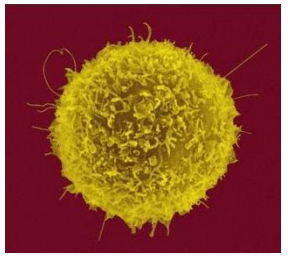
Nduati R, et al. JAMA 2000;283:1167-74

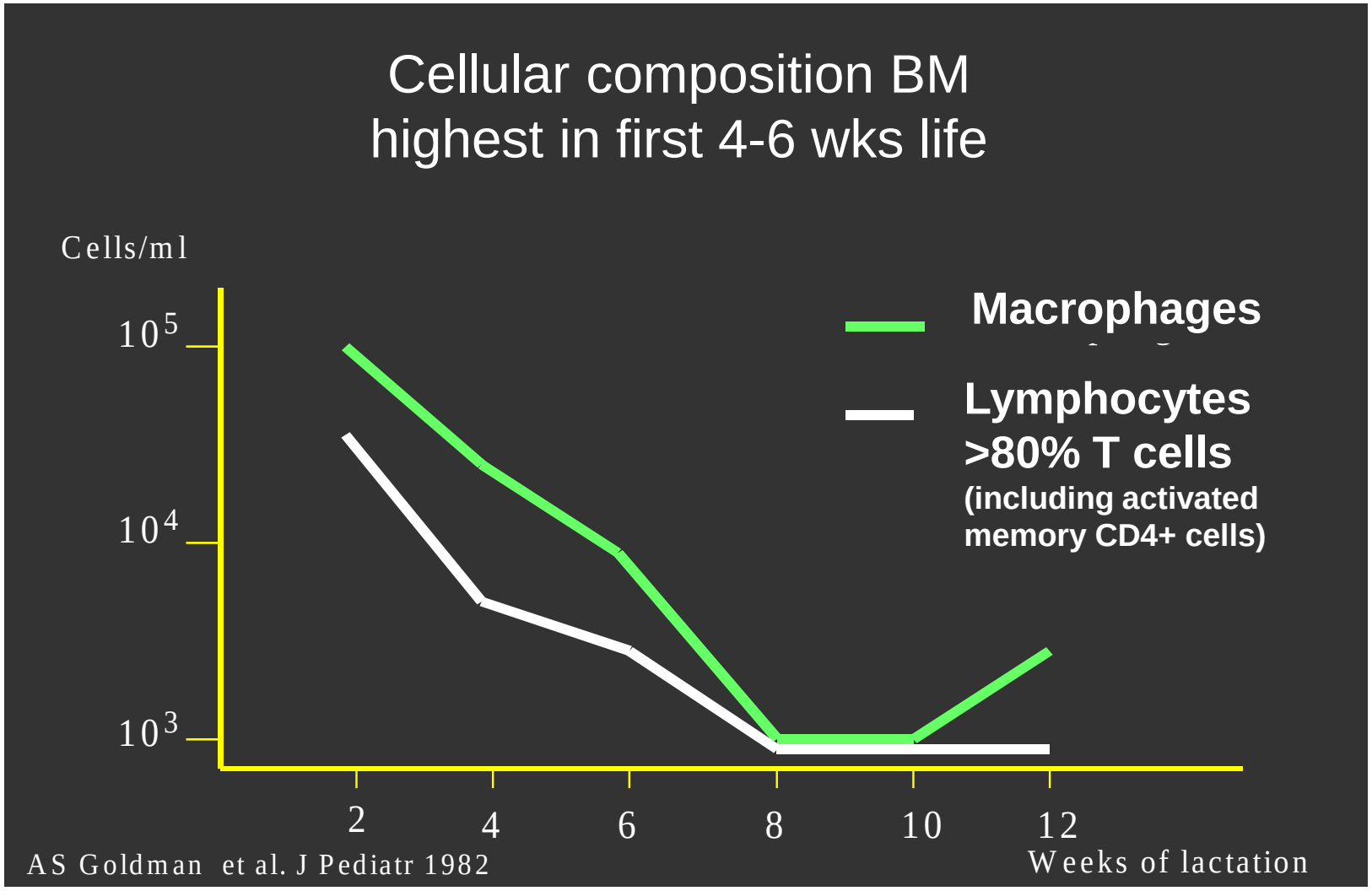
Moodley D, et al. J Infect Dis. 2003;187:725-35

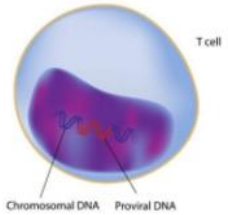


Cellular Composition of Breast Milk During Lactation: Highest Cellular Content First Month of Life

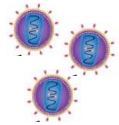
Goldman AS et al. J Pediatr 1982;100:563-7







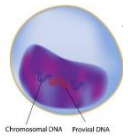
Cell-Associated HIV DNA and Cell-Free HIV RNA and Early Postnatal Transmission

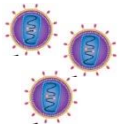


Ndirangu J et al. PLosOne 2012;7:e51493

36 mothers with postnatal MTCT and 36 control non-transmitters, S Africa

Breast Milk	MTCT risk and BM sample age **6 weeks=EARLY**		MTCT risk and BM sample age **6 months=LATE**	
	Adjusted OR*	P value	Adjusted OR*	P value
Cell-associated HIV DNA (/log ↑)	**2.47** (1.3-4.6)	0.004	1.73 (0.9-3.2)	0.077
Cell-free HIV RNA (/log ↑)	1.52 (1.2-2.0)	0.002	**2.53** (1.7-3.9)	<0.001



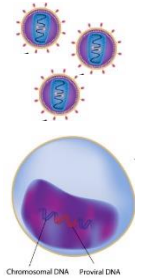


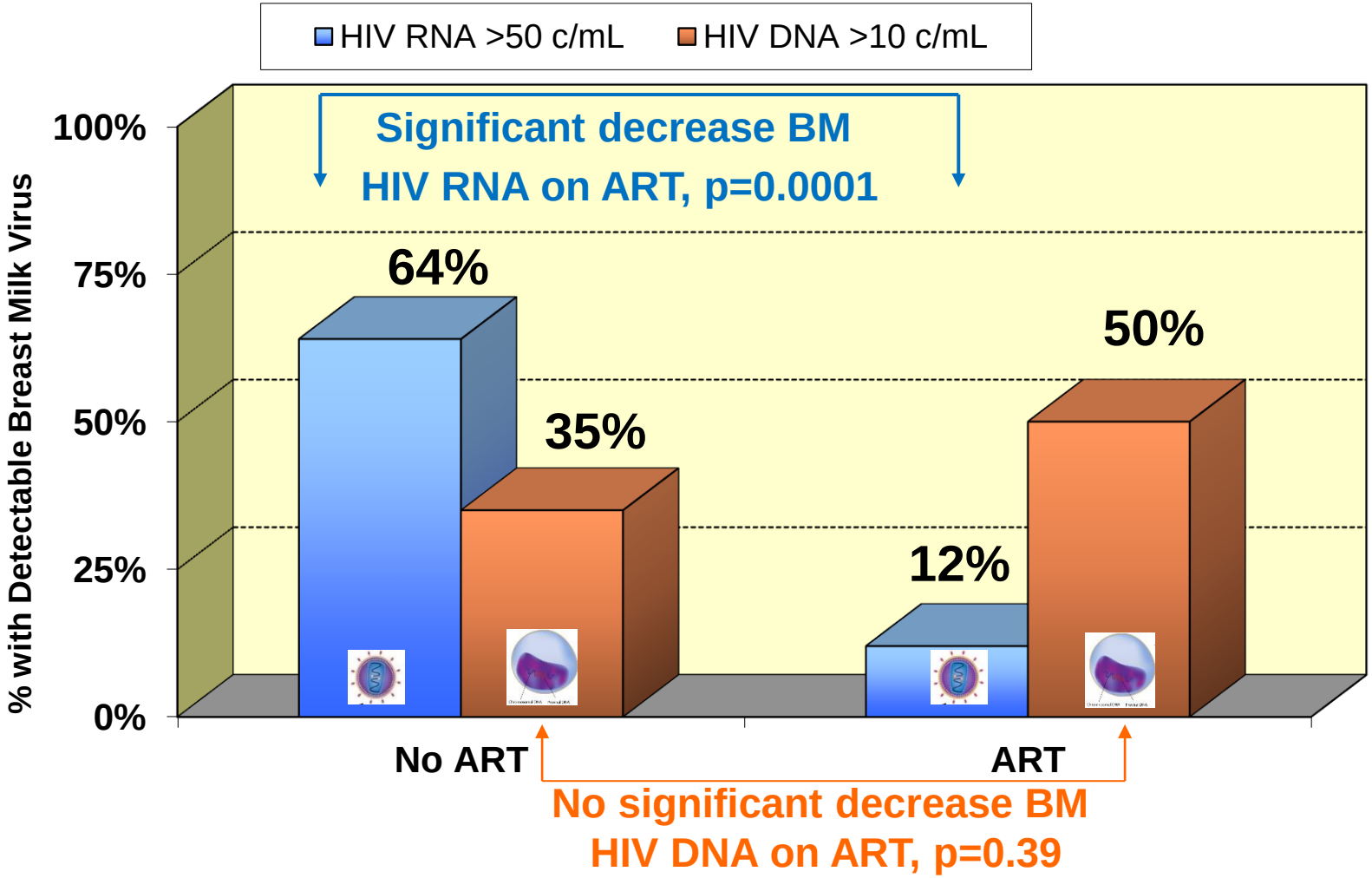
* Adjusted for maternal CD4 count and viral load at delivery

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.

Association of Early Postnatal MTCT with Cell-Associated Virus is Important Because ART Reduces Breast Milk HIV Cell-Free (RNA) But Not HIV Cell-Associated (DNA) Viral Load

Shapiro R et al. J Infect Dis 2005;192:713-9

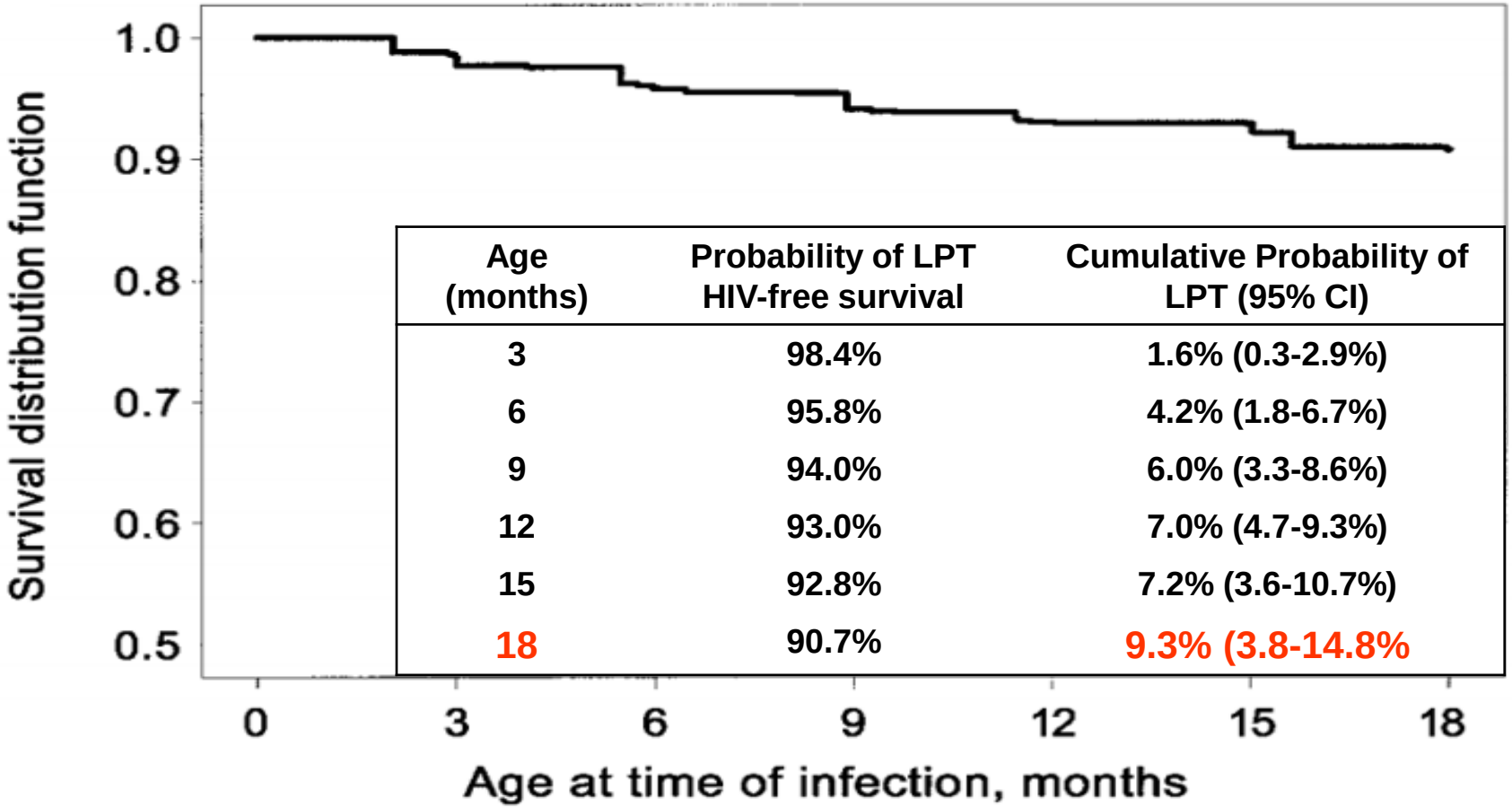




After Age 1 Month, Risk of Late Postnatal Transmission is Constant

BHITS JID 2004;189:2154-66

- Evaluated postnatal infection rate in 4,085 breastfed children uninfected at age 1 month

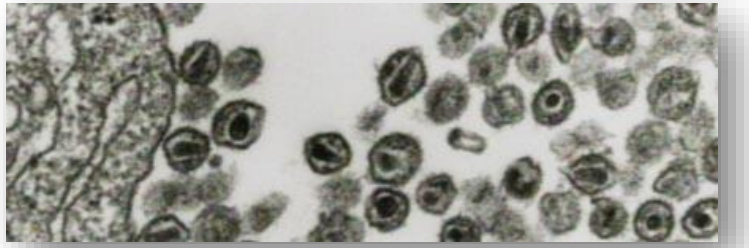


Age (months)	Probability of LPT HIV-free survival	Cumulative Probability of LPT (95% CI)
3	98.4%	1.6% (0.3-2.9%)
6	95.8%	4.2% (1.8-6.7%)
9	94.0%	6.0% (3.3-8.6%)
12	93.0%	7.0% (4.7-9.3%)
15	92.8%	7.2% (3.6-10.7%)
18	90.7%	9.3% (3.8-14.8%

Late postnatal transmission 0.74%/month breastfeeding (8.9 per 100 child-years)

What Do We Know About Breast Milk HIV Transmission?

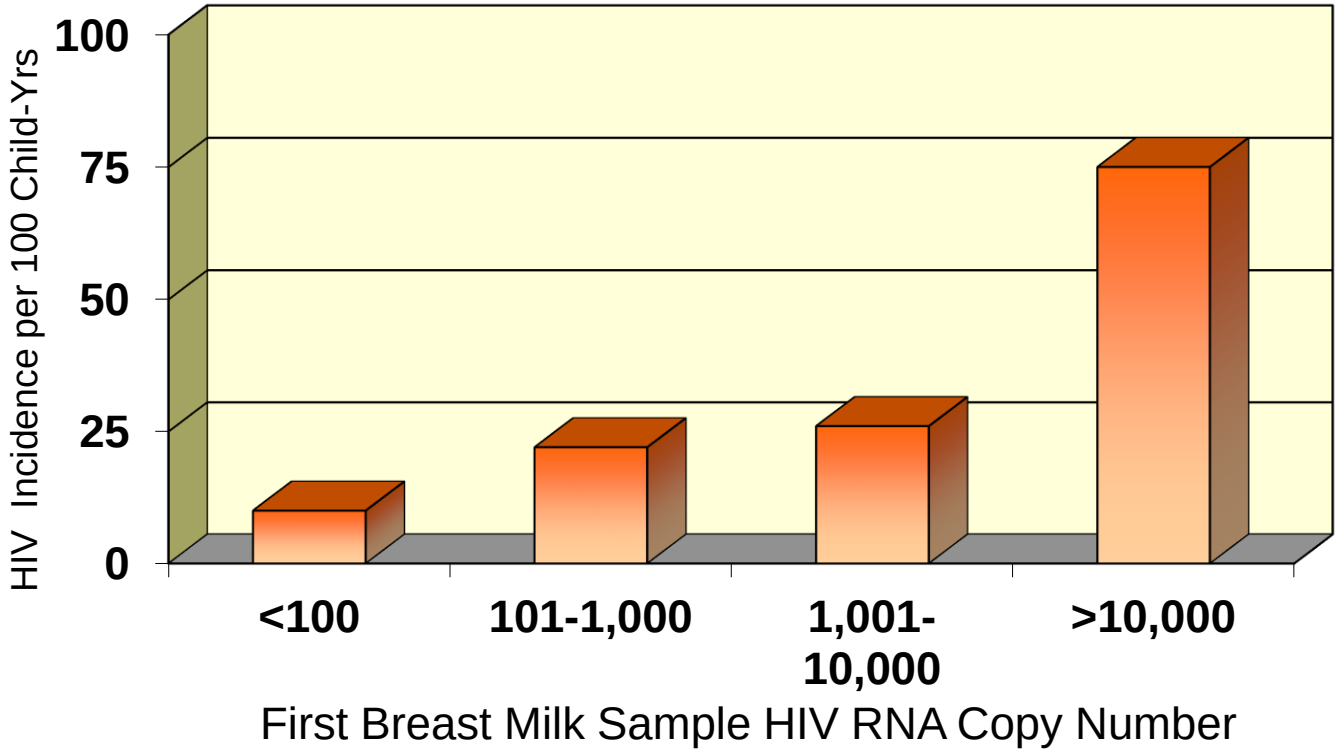
Breast Milk Viral Load vs Plasma Viral Load And Postnatal Transmission

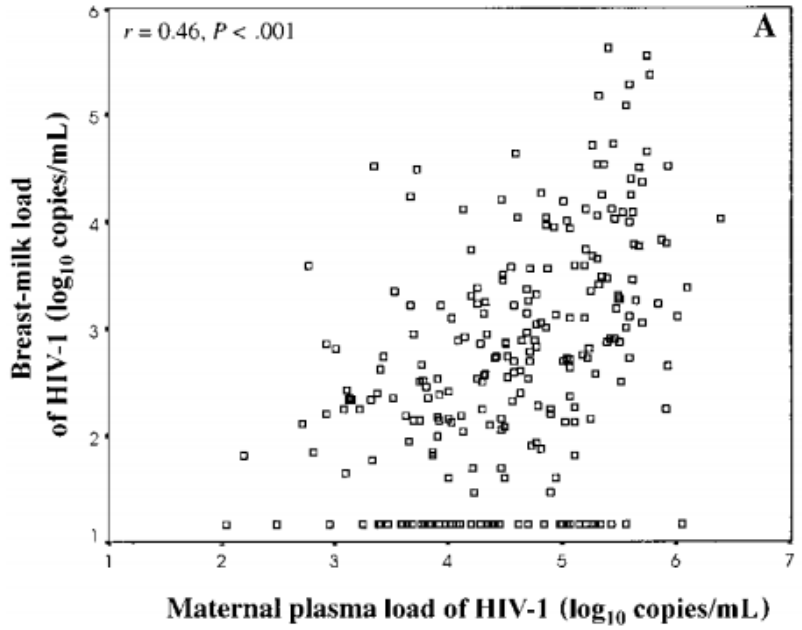


Quantitative Breast Milk HIV RNA Viral Load is Associated with Risk of Postnatal Transmission

Rousseau CM et al. J Infect Dis 2003;187:741-7

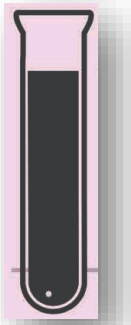
Evaluation breast milk RNA in 275 women over 2 years Kenya





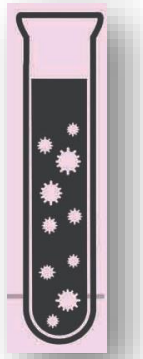
Women who consistently have HIV RNA in milk more likely to transmit to the infant than those with intermittent or no RNA in milk.

Maternal plasma RNA VL correlated with breast milk RNA VL, although breast milk RNA is lower. For every 1 log ↑ in plasma VL there was estimated 0.58 log ↑ breast milk VL.



Does Undetectable Plasma Viral Load Mean Undetectable Breast Milk Viral Load?

Davis NL et al. JAIDS. 2016;73:572-80



- BAN study: Postnatal maternal ART vs infant NVP vs single-dose NVP for prevention of postnatal transmission (maternal ART and infant NVP similar significant efficacy).
- 221 mothers had paired plasma and breast milk specimens.
- Mothers with detectable plasma VL has adjusted 40-fold increased odds of detectable breast milk VL (95% CI 15-108).
- However, 2 (**0.9%**) had **undetectable plasma VL** at 6 weeks postpartum but **detectable breast milk VL** (56 and 77 c/mL).

Does U=U for Postnatal Breast Milk Transmisision?

In Utero/Intrapartum/Early Breastfeeding MTCT

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
South Africa *100% 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)
Kenya *100% start PP*	Davies (2016) *MTCT 2-24 wk*	Undetectable** all time points 2-24 wk 0% (0/5)	-	-	-

Myer L et al. HIV Med. 2017;18:80-88
Landes M et al. JIAS. 2019;22:e25290
Moyo et al. JAIDS.2020;83:390-6
Davies NL et al. JAIDS. 2016;73:572-80

*2 no prior VL, 1 VL >1,000 3 mo before delivery

** Undetectable plasma and breast milk RNA

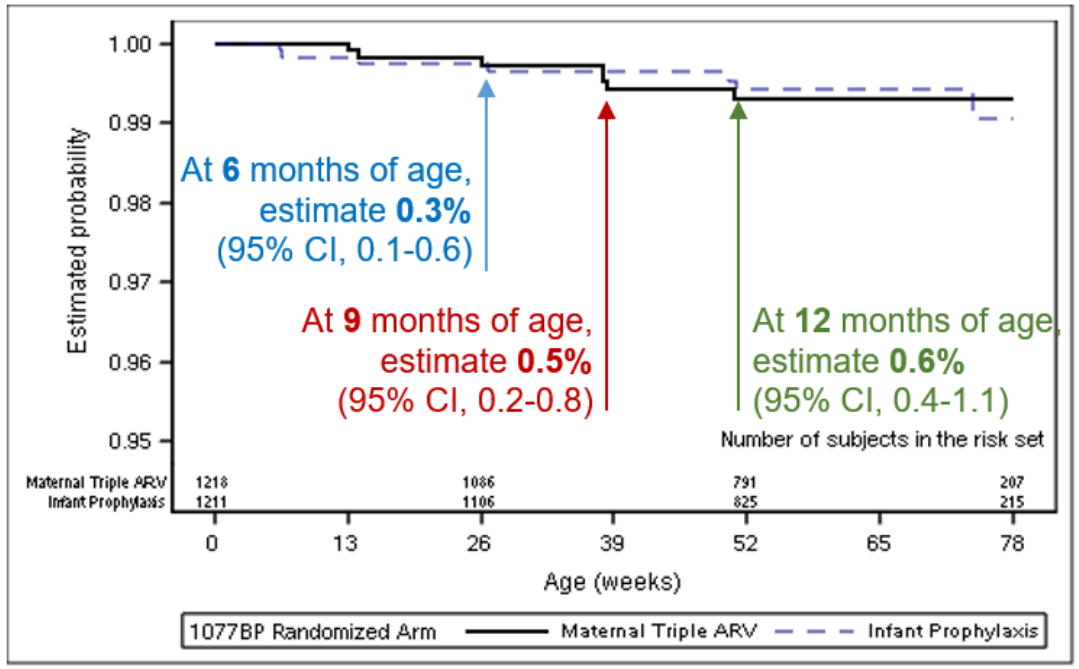
Late Breastfeeding Transmission, ART, and Maternal VL

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 in mothers who initiated ART postpartum with subsequent viral load <40 copies/mL
Luoga (2018)	Tanzania	1 infant infection where the maternal viral load was <1000 copies/mL but mother had a disruption in therapy
Giuliano (2013)	Malawi	1 infant infection where mother initiated ART during pregnancy and had a subsequent viral load <37 copies/mL

PROMISE Randomized Trial – Postpartum Component

- HIV+ mothers with CD4 ≥350 cells/mm3 and their uninfected breastfeeding infants randomized to start either maternal ART (n=1220) or infant NVP (n=1211) at 6-14 days postpartum at 14 sites in 7 countries.
- Plasma viral load measured at baseline and 6, 14, 26, and 50 weeks postpartum.



No statistically significant difference in probability of MTCT of HIV by study arm
Overall infant infections: 7 maternal ART, 7 infant NVP

Flynn P et al. JAIDS. 2018;77:383-92

- Time-varying maternal viral load was significantly associated with infant infection in the **maternal ART** arm (HR 11.0, 95% CI 2.5-56.1) but not the infant NVP arm.
- Of 7 postnatal infections in the maternal ART arm, **2 had plasma VL <40 c/mL in the visit closest to infection** (1 week 36: <40 at all visits; 1 week 14, <40 at week14 but but 50-1000 at week 6).

1,220 mothers on ART

VL <40 copies/mL

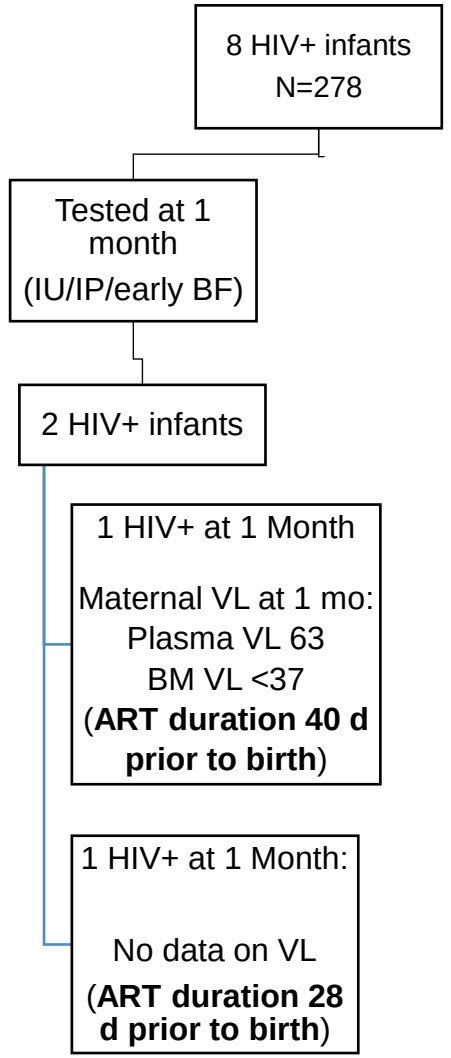
2 cases of MTCT
1 at Week 14
1 at Week 36

Flynn et al. 22nd IAS Conference, Amsterdam, July 2018, Abs. THPEB115

DREAM project, MTCT during breastfeeding - Malawi

- 311 HIV+ pregnant women started ART during pregnancy and breastfed their infants (median duration 6.5 months); if CD4 >350, dc ART after cessation BF at 6 months.
- Infant PCR, plasma VL tested at 1, 3, 6, and 12 months, BM VL 1, 3 and 6 months (not all had)
- HIV status available for 278 infants.

- 1 month: 2 infections
  - Both **short duration of maternal ART prior to delivery** (28-40 days)



Giuliano M et al. PLoS One. 2013;8:e68950.

DREAM project, MTCT during breastfeeding - Malawi

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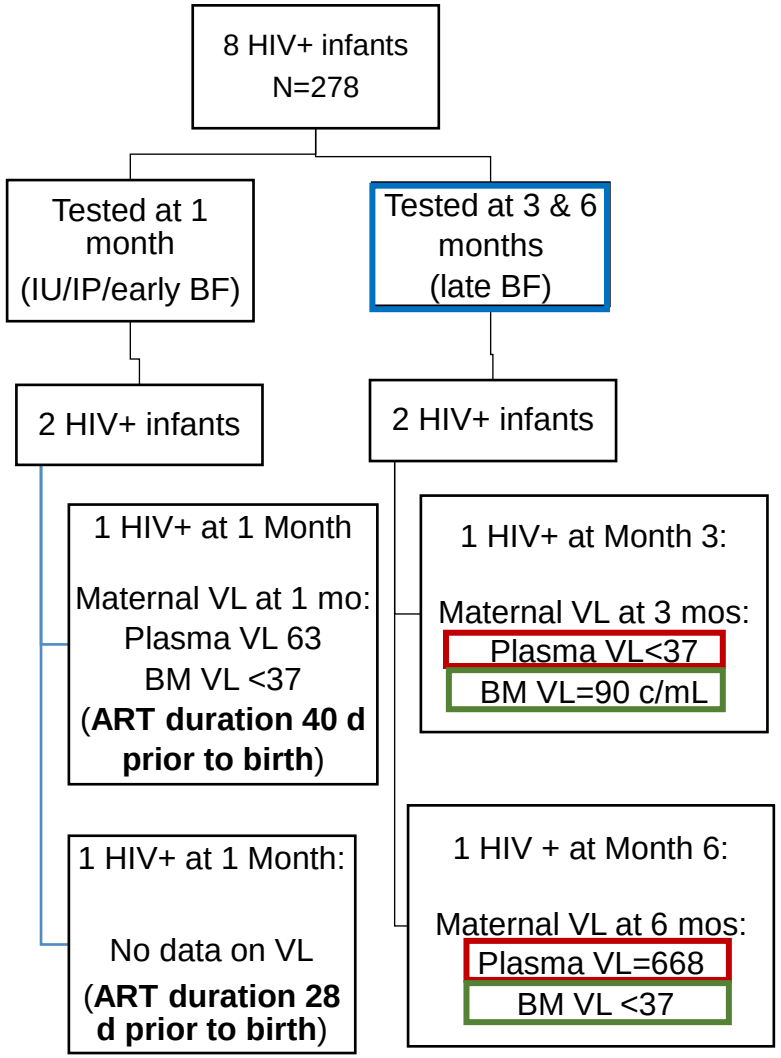
- Infant PCR, plasma VL tested at 1, 3, 6, and 12 months, BM VL 1, 3 and 6 months (not all had)
- HIV status available for 278 infants.

- 1 month: 2 infections
  - Both **short duration of maternal ART prior to delivery** (28-40 days)
- **1-6 months (all mothers on on ART):** 2 postnatal infections (0.7%)
  - 1 undetectable plasma VL, low level BM VL;
  - 1 low level plasma VL, undetectable BM VL



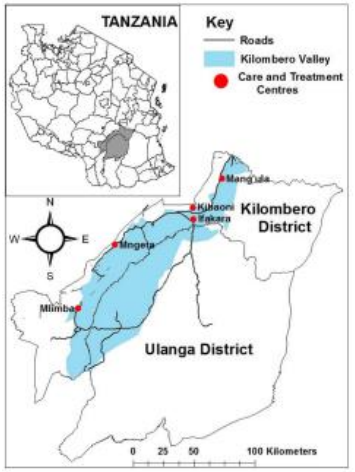
Giuliano M et al. PLoS One. 2013;8:e68950.

Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) - Tanzania

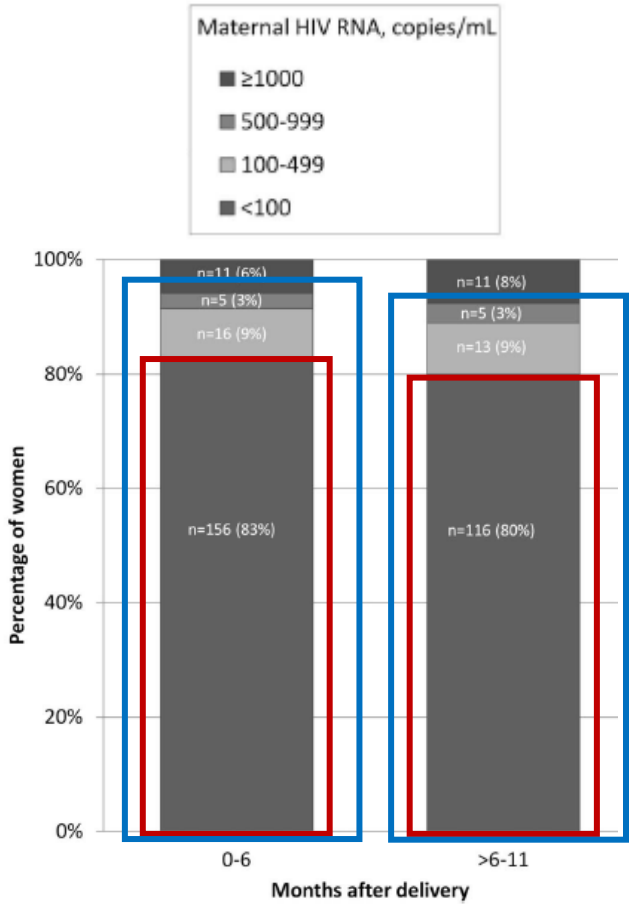
J Acquir Immune Defic Syndr • Volume 79, Number 1, September 1, 2018

No HIV Transmission From Virally Suppressed Mothers During Breastfeeding in Rural Tanzania

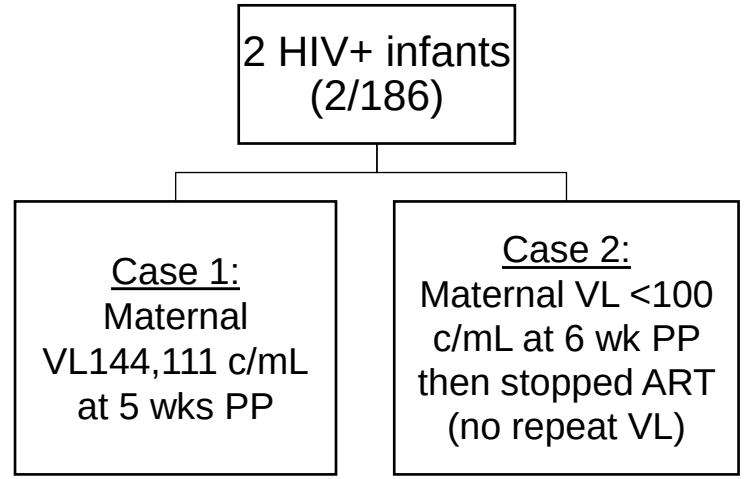
Ezekiel Luoga, MD, Fiona Vanobberghen, PhD,†‡ Rahel Bircher, MD,†‡ Amina Nyuri, BSc,* Alex J. Ntamatungiro, BSc,* Dorcas Mnzava, BSc,* Getrud J. Mollel, MD,* Emilio Letang, MD, PhD,*†‡§ Manuel Battegay, MD,‡‖ Maja Weisser, MD,*†‡ and Anna Gamell, MD, PhD,*†‡ on behalf of the KIULARCO Study Group*



- HIV+ patients attending HIV clinic in Tanzania.
- 228 infants who were *uninfected* at 4-12 wks born to HIV+ mothers on ART median 23 mos (IQR 4-52), breastfed for median 1 year; final HIV status on 186 infants (median age 14 mos).
- Maternal plasma viral load measured at least once within 11 months of delivery (53% had measured twice).



- 2/186 infant postnatal infections (1%)
- No infections if undetectable VL and consistently on ART



– VL <100 in 80-83%

– VL<1000 in 92-94%

Luoga E et al. JAIDS. 2018; 79: e17-e20.

So – Where are We with U=U for Postnatal MTCT?

- U = U is based on data showing persons on ART achieving consistent undetectable VL (defined as <200 c/mL by CDC) have essentially no **sexual** transmission to HIV-negative sexual partners.
- Data clearly show that a viral load threshold of 200 cannot be used when referring to peripartum and postpartum MTCT; the threshold must be 50 c/mL.
- In formula-feeding populations, data indicate that there is likely a zero risk of transmission if a mother is on ART and achieved viral suppression <50 c/mL prior to pregnancy and maintains ART and suppression through delivery – so U=U may apply here.

So – Where are We with U=U for Postnatal MTCT?

- Data on breast milk transmission and viral load are more limited and complex as our measure is virus in plasma rather than milk.
  - Plasma VL generally correlates with breast milk VL but rarely virus may be undetectable in plasma but present in low levels in milk – and visa versa.
  - Breast milk cell-associated virus is important in early transmission, and is less affected by ART.
  - For early breast milk transmission, limited data suggest U ≠ U in women who *start ART during pregnancy*, even if delivery VL is <50.

So – Where are We with U=U for Postnatal MTCT?

- Late breast milk transmission will likely require *both* plasma and breast milk virus to be undetectable from before pregnancy and through the entire breastfeeding period.

- However, data on women on preconception ART and consistently suppressed throughout pregnancy and breastfeeding are not yet available.

- However, even if residual risk, it appears extremely low (<1%).

SUMMARY

Non-breastfeeding populations

If define “undetectable” = VL <50 c/mL

AND: Start ART prior to conception and plan pregnancy for after viral suppression is achieved

AND: Maintain ART and viral suppression throughout pregnancy

MAY

Breastfeeding populations

(or have extremely low risk, <1)

IF: Viral suppression <u>before</u> and <u>during</u> pregnancy <u>and</u> breastfeeding

Thank you for your attention!