TRANSMISSION OF HIV IN BREASTMILK

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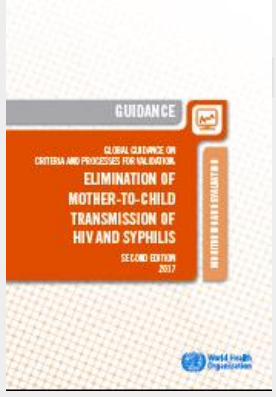
SAHIV Clinicians Society Conference
24-27 October 2018



ELIMINATING MTCT AS A PUBLIC HEALTH PROBLEM: IMPACT CRITERIA

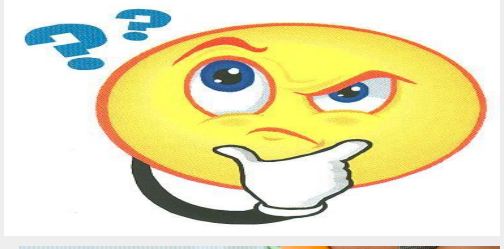
- <50 new paediatric infections per 100 000 live births
- MTCT <5% in breastfeeding populations

Both achieved for 1 year at a lowest sub-national level

World Health Organisation: http://www.who.int/hiv/pub/emtct-validation-guidance/en/

OUTLINE OF PRESENTATION

Road travelled



Dilemmas

Infant PEP options

Future possibilities

ROAD TRAVELLED

Breastfeeding 1

Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect

Cesar G Victora, Rajiv Bahl, Aluísio J D Barros, Giovanny V A França, Susan Horton, Julia Krasevec, Simon Murch, Mari Jeeva Sankar, Neff Walker, Nigel C Rollins, for The Lancet *Breastfeeding Series Group**

The importance of breastfeeding in low-income and middle-income countries is well recognised, but less consensus *Lancet* 2016; 387: 475-90

Never before in the history of science has so much been known about the complex importance of breastfeeding for both mothers and children

Scaling up breastfeeding to a near universal level would prevent 823 000 annual deaths in children<5 and 20 000 annual deaths from breast cancer

- Children who are breastfed for longer periods have lower infectious morbidity and mortality, fewer dental malocclusions, and higher intelligence than do those who are breastfed for shorter periods, or not breastfed. This inequality persists until later in life. Growing evidence also suggests that breastfeeding might protect against overweight and diabetes later in life.

BREASTFEEDING

It Rocks!

Estimated Timing and Risk of Mother-to-Child Human Immunodeficiency Type 1 Transmission without Antiretroviral Interventions and with Minimal ARV Prophylaxis

	Without Antiretroviral Cover				With Minimal Antiretroviral Cover	
	No Breastfeeding		Breastfeeding through 18–24 Months		Breastfeeding through 18–24 Months	No Breastfeeding
Timing	Relative Proportion	Absolute Rate	Relative Proportion	Absolute Rate	Absolute Rate	Absolute Rate
Intrauterine	25–35%	5–10%	20–25%	5–10%	3.5%[a]	<0.5%[c]
Intrapartum	65–75%	10–20%	35–50%	10–15%	2.6%[b]	
Breastfeeding	—	—	25–45%	15–20%	Cumulative risk 4% (3–6%) on triple ART or infant prophylaxis by 48 weeks[d]	0
Overall	—	15–30%	—	30–45%	3–6%	<0.5%

Source: De Cock, K.M. et al., *JAMA*, 283(9), 1175–82, 2000; Coutsoudis, A. et al., *AIDS*, 15(3), 379–87, 2001.

Note: Population-level MTCT under 2008 PMTCT guidelines (dual prophylaxis).

[a] Goga et al. (2015).

[b] Population-level MTCT using zidovudine from 14 weeks gestation with single-dose nevirapine to mother and baby peri-partum with daily infant nevirapine or maternal antiretroviral therapy if maternal CD4 cell count ≤ 350 cells/μL.

[c] Forbes et al. (2012), Townsend et al. (2014).

[c] Jamieson et al. (2012).

Published in final edited form as:
Clin Perinatol. 2010 December ; 37(4): 787–ix. doi:10.1016/j.clp.2010.08.005.

Immune-Based Approaches to the Prevention of Mother-to-child-Transmission of HIV-1: Active and Passive Immunization

Barb Lohman-Payne[1,2], **Jennifer Slyker**[2], and **Sarah L. Rowland-Jones**[3]
[1]Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Kenya 00202
[2]Departments of Medicine and Global Health, University of Washington, Seattle, WA 98104
[3]Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, OX3 9DS, UK

In the absence of PMTCT 55-80% of HIV exposed infants remain uninfected

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Breastmilk characteristic	Protection conferred
sIgA	Local immunity against entry of HIV
T and B lymphocytes	Antiviral activity
Oligosaccharides	Form viral ligands to prevent mucosal entry of free HIV.
Glycoconjugates	
ά Defensins	reduces risk of intrapartum and postnatal MTCT.
IFN-γ cellular immune responses	associated with ≈70% reduction in early MTCT

Lohman-Payne B et.al. Clin Perinatol 2010
Cheynier R et.al. Euro J. Immunol 1992
Kuhn L et.al. J Pediatr 2004
Kuhn L et.al. AIDS 2001
Aldhous M et.al. Clin Exp Immunol 1994
Bode L et.al. Am J Clin Nutr 2012

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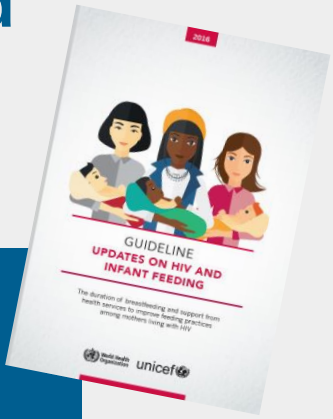
World Health Organization unicef

In settings where lifelong ART is provided and supported (incl. adherence counselling) and breastfeeding is promoted and supported, an HIV+ mother



- **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**

(*Strong recommendation; Quality of evidence: up to 12 m – Low; to 24 m – Very low*)

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Before 2011

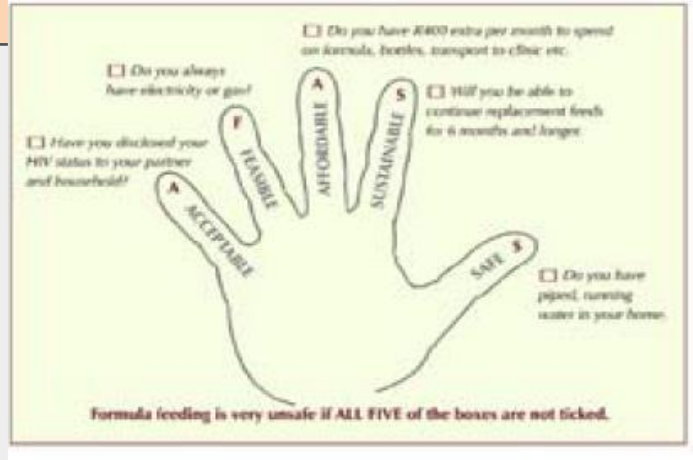
Individual approach:

Individual counselling of mothers living with HIV for individual decision making

From 2011

Public health approach:

National or local authorities recommend infant feeding method for children of mothers living with HIV with extended NVP/ART



It is your right to make your own choice,
but, **it is a baby's right to be fed safely.**

IYCF POLICY 2013 AMENDMENT

3. RECOMMENDED INFANT AND YOUNG CHILD FEEDING PRACTICES

3.1 The main infant and young child feeding recommendations are summarised in the table below.

Main Feeding Recommendation				
HIV-negative women	Exclusively breastfeed their infants during the first 6 months of life.	Introduce adequate, safe and appropriate complementary foods at 6 months	Continue breastfeeding for 2 years or longer.	Breastfeeding cessation needs to occur gradually over one month. Abrupt cessation is discouraged.
HIV-positive mothers *(and whose infants are HIV uninfected or of unknown HIV status)* **On ~~lifelong~~ ART**			Continue breastfeeding for ~~12~~ **24** months (recommended) **while being fully supported for ART** adherence (as outlined in the current PMTCT guidelines). The infant should receive prophylactic ARVs ~~**from birth until six weeks of age as prescribed**~~ in accordance with current PMTCT guidelines.	
~~**HIV-positive mothers *(and whose infants are HIV uninfected or of unknown HIV status)***~~ ~~**Not on lifelong ART**~~			~~**Continue breastfeeding for the first 12 24 months of life (recommended) while being fully supported for ART adherence.**~~ ~~**The mother and/or infant should receive ARVs as prescribed in accordance with current PMTCT guidelines. This should continue for one week after all breastfeeding has stopped.**~~ **This section is no longer relevant as all HIV-infected women should receive ART.**	
HIV-positive mothers and whose infants are HIV infected			Continue breastfeeding for 2 years or longer **while being fully supported for ART adherence for mother and infant.**	

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

HEADS OF PROVINCIAL HEALTH DEPARTMENTS
PROVINCIAL AND DISTRICT MCWH, EPI, NUTRITION, HAST AND PMTCT MANAGERS
DISTRICT CLINICAL SPECIALIST TEAMS
DISTRICT AND PHC MANAGERS
HEALTH FACILITY MANAGERS

CIRCULAR MINUTE NO. 3 OF 2017/18 HIV/AIDS, TB & MCWH

AMENDMENT OF THE 2013 INFANT AND YOUNG CHILD FEEDING (IYCF) POLICY

The 2013 Infant and Young Child Feeding (IYCF) policy recommendation on the duration of breastfeeding for HIV infected women has been amended to align with the updated 2016 WHO/UNICEF guidelines.

The policy recommendation that HIV-infected women should stop breastfeeding at 12 months is revised. HIV-infected women who are breastfeeding should be supported to adhere to antiretroviral therapy (ART), and should be counselled and supported to exclusively breastfeed their infants for the first 6 months of life, to introduce complementary foods thereafter, and to continue breastfeeding for at least 2 years (pg 14 of the IYCF policy indicating the amendment is attached). This means that infant and young child feeding recommendations for HIV negative and HIV positive mothers are fully aligned. All healthcare workers are reminded of the importance of ensuring that all pregnant and breastfeeding HIV-infected mothers receive ART, together with adherence support.

The remainder of the IYCF policy, which emphases that breastfeeding should be protected, supported and promoted, remains unchanged.

It would be appreciated if the contents of this circular are communicated to all relevant officials.

DR Y PILLAY
DEPUTY DIRECTOR-GENERAL: HIV/AIDS, TB & MCWH
DATE: 07/06/17

7 June 2017

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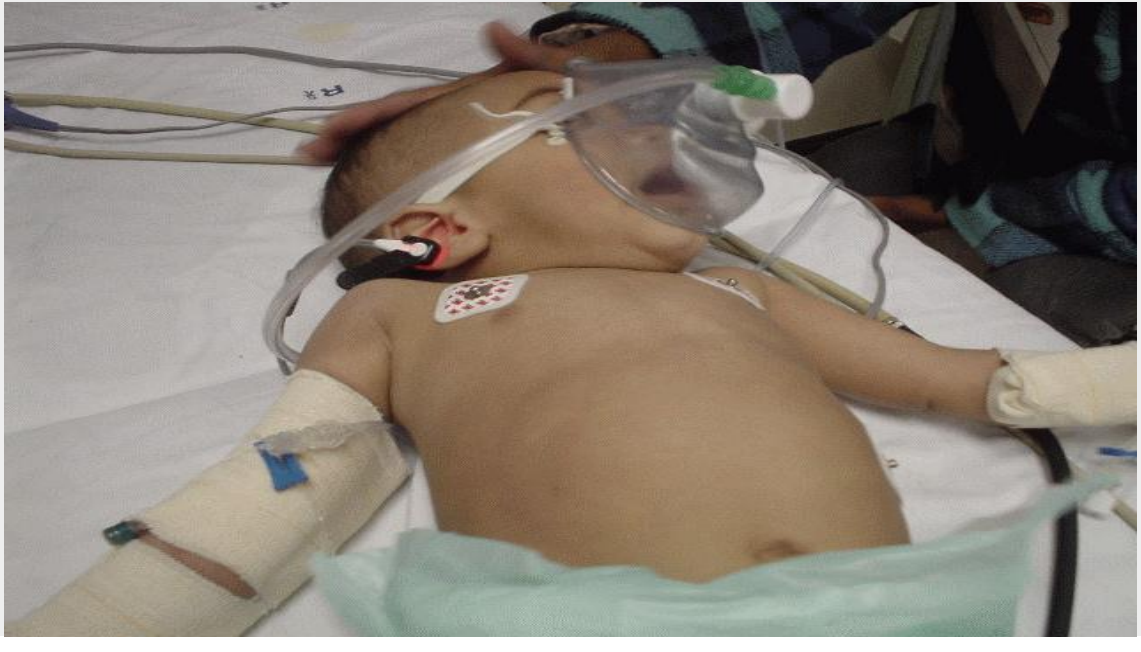
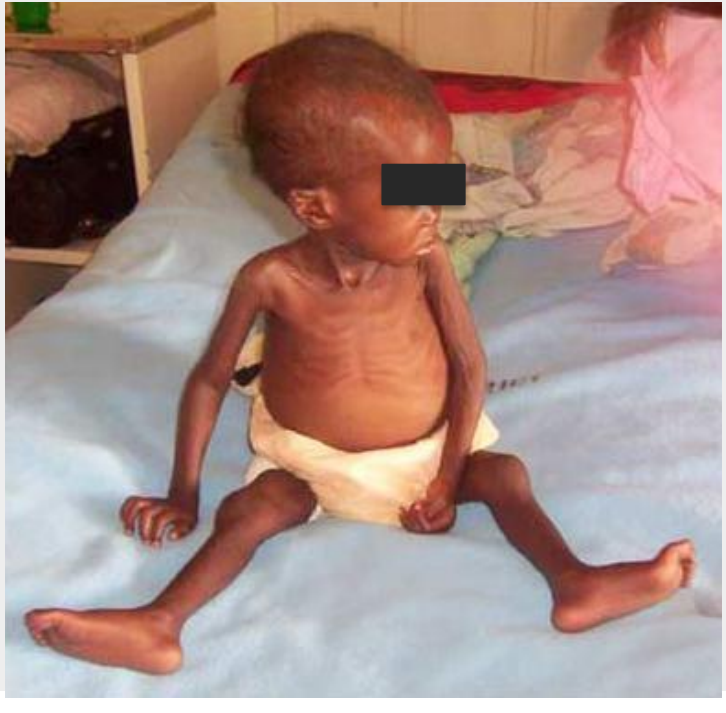
PROMOTING HIV-FREE SURVIVAL, THRIVING AND TRANSFORMING FOR CHILDREN





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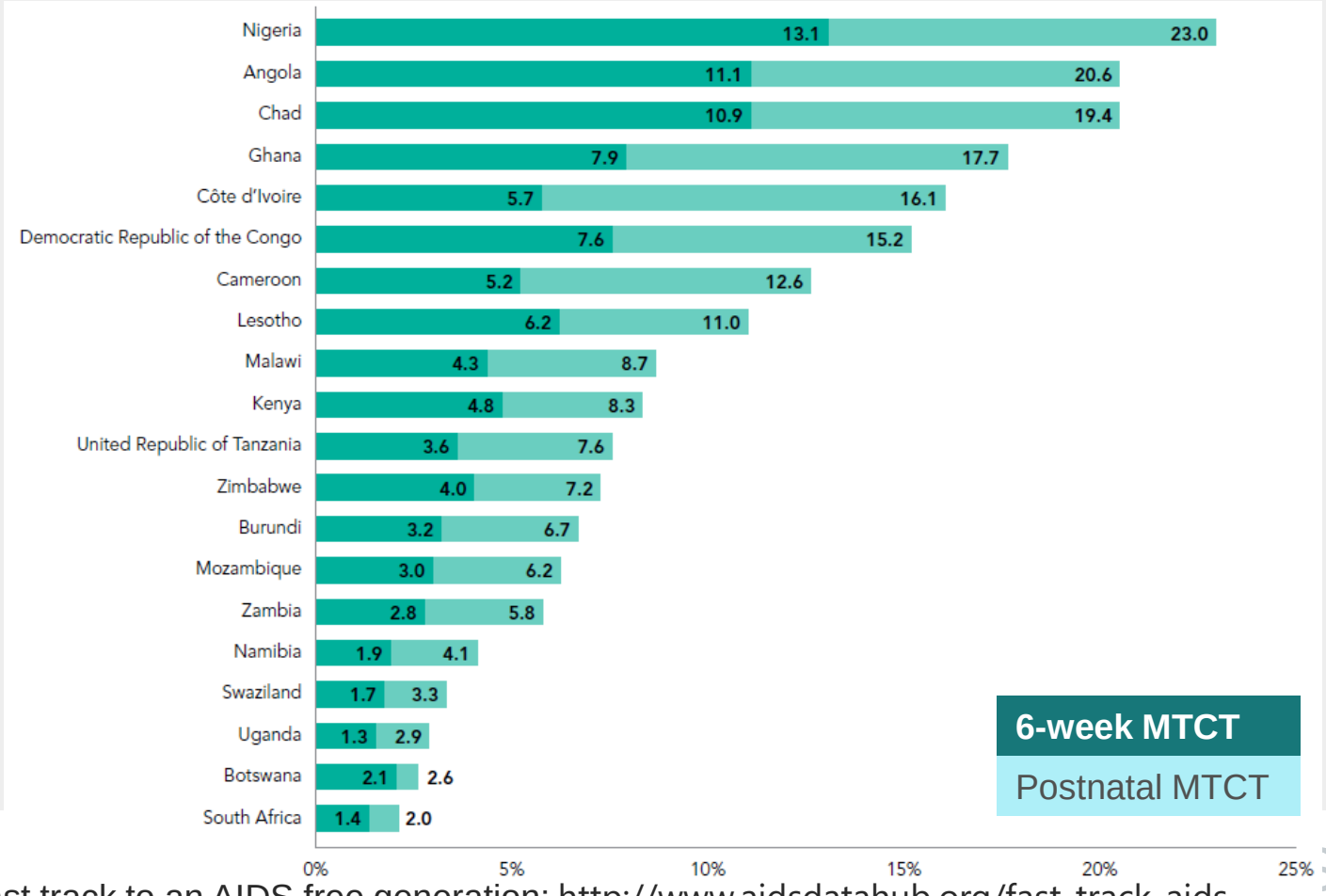
DILEMMAS: CAN WE ELIMINATE BREASTMILK TRANSMISSION OF HIV?

BY 2015: OVERALL MTCT HAS REDUCED, BUT BREASTMILK CONTRIBUTES TO >50% MTCT IN SOME COUNTRIES



UNAIDS: On the fast track to an AIDS free generation: http://www.aidsdatahub.org/fast-track-aids-free-generation-unaids-2016

Viewpoint

Does U=U for breastfeeding mothers and infants? Breastfeeding by mothers on effective treatment for HIV infection in high-income settings

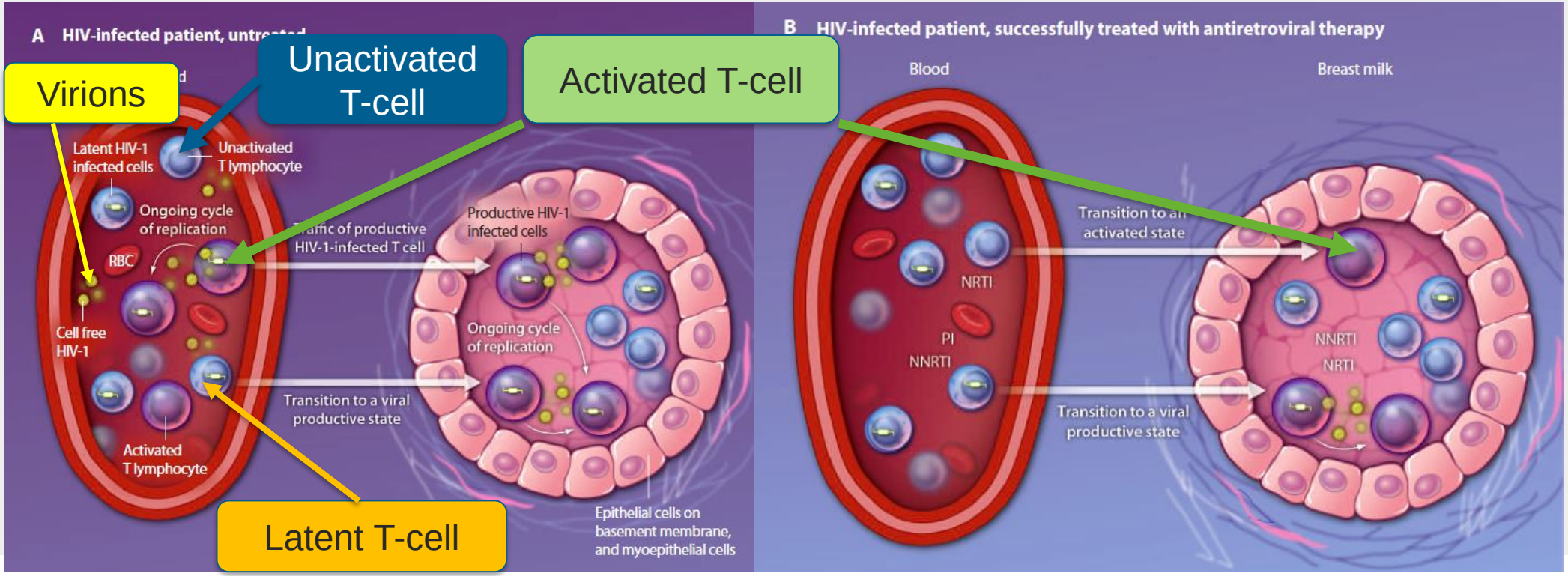
Catriona Waitt, Nicola Low, Philippe Van de Perre, Fiona Lyons, Mona Loutfy, Karoline Aebi-Popp

Can the campaign Undetectable=Untransmittable (U=U), established for the sexual transmission of HIV, be

Lancet HIV 2018; 5: e531–36

NO

BLOOD AND BREASTMILK OF TREATED AND UNTREATED HIV INFECTED PATIENTS

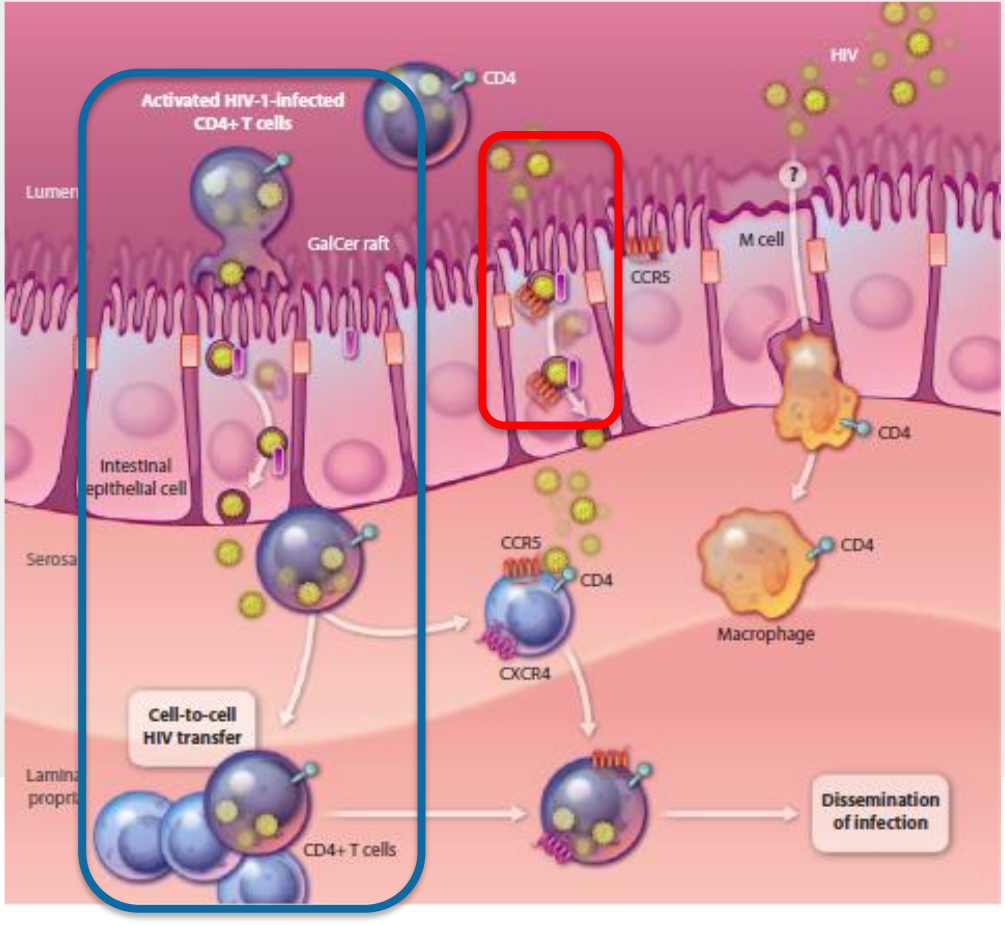


Untreated Patient

Treated Patient

Van de Perre et.al Science Translational medicine 2012

CELL-CELL TRANSFER - CENTRAL ROLE IN CELL-ASSOCIATED MTCT THROUGH GUT



Entry of free virions and cell-associated virus

Van de Perre et.al Science Translational Med 2012

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BREASTMILK HIV TRANSMISSION

- Before 9 months postpartum, most MTCT is associated with cell-associated virus
- Breast tissue might be seeded with a lineage of latently infected resting cells
- ART typically reduces breastmilk HIV RNA but not DNA

Koulinska, JAIDS, 2006
Shapiro JID, 2005

Danaviah, Plos ONE, 2015

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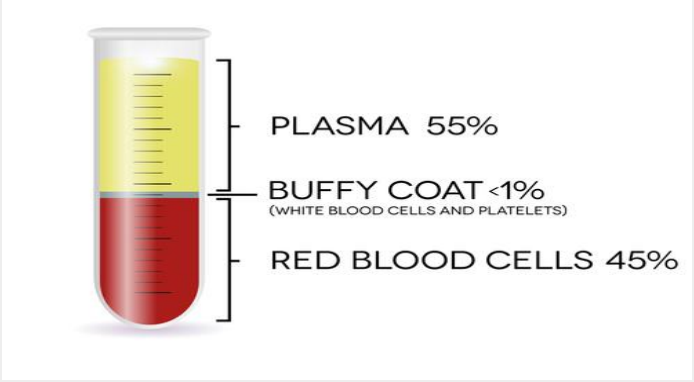
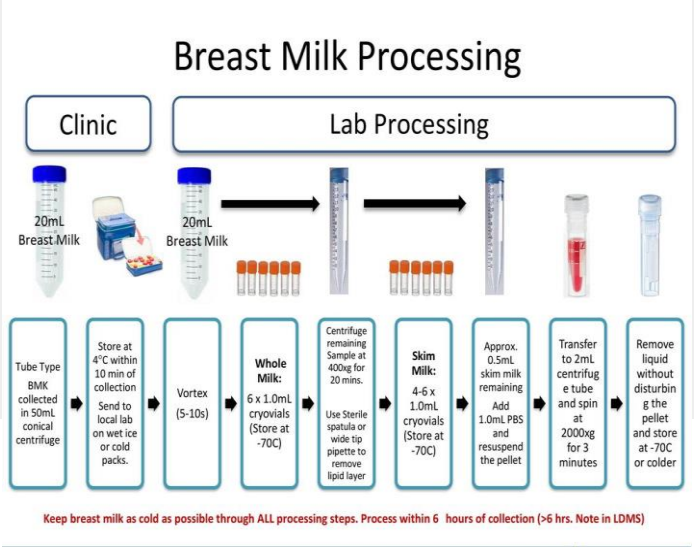
CONCERNS





A safe threshold of plasma and breastmilk viral load has not been established **AND**

We do not routinely measure breastmilk viral load

RISKS OF BREASTMILK TRANSMISSION

UNAIDS mathematical modelling:

- Among mothers who initiated ART pre-delivery: 1 in 625 probability (0.16%) of MTCT

MTCT WITH ART

Published in final edited form as:
N Engl J Med. 2010 June 17; 362(24): 2282–2294. doi:10.1056/NEJMoa0907736.

Antiretroviral Regimens in Pregnancy and Breast-Feeding in Botswana

R.L. Shapiro, M.D., M.P.H., M.D. Hughes, Ph.D., A. Ogwu, M.B., B.S., D. Kitch, M.S., S.

ART initiated between 26 and 34 weeks
Plasma VL at baseline, delivery, 1, 3, 6, months
One BM VL measurement post-hoc

MTCT HAS BEEN REPORTED IN WOMEN WITH UNDETECTABLE BASELINE PLASMA VL

Maternal and Breastmilk Viral Load: Impacts of Adherence on Peripartum HIV Infections Averted—The Breastfeeding, Antiretrovirals, and Nutrition Study

Nicole L. Davis, MPH, PhD,†‡ William C. Miller, MD, PhD, MPH,† Michael G. Hudgens, PhD,§ Charles S. Chasela, PhD,‖ Dorothy Sichali, BSc,¶ Dumbani Kayira, MBBS,¶ Julie A. E. Nelson, PhD,# Susan A. Fiscus, PhD,# Gerald Tegha, BSc,¶ Deborah D. Kamwendo, MSc,¶ Joseph Rigdon, PhD,§ Jeffrey S. A. Stringer, MD,** Jonathan J. Juliano, MD, MSPH,† Sascha R. Ellington, MSPH,†† Athena P. Kourtis, MD, PhD, MPH,†† Denise J. Jamieson, MD,†† and Charles van der Horst, MD,† for the BAN study team*

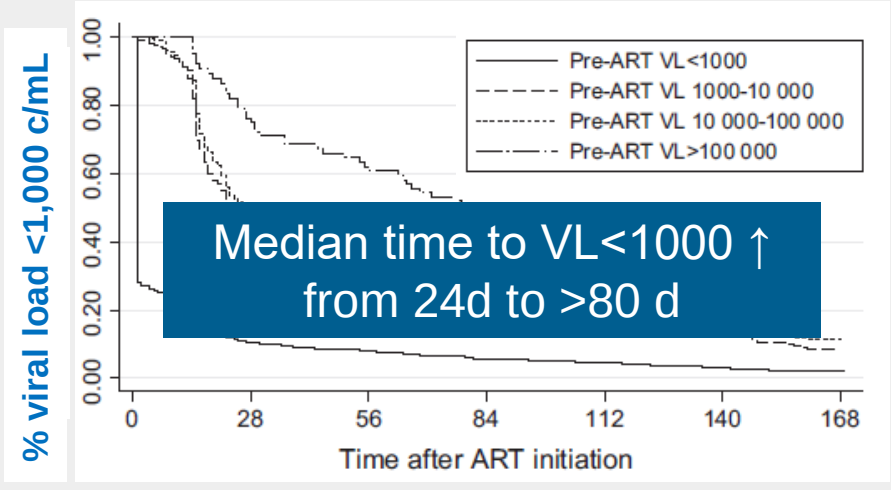
J Acquir Immune Defic Syndr • Volume 73, Number 5, December 15, 2016

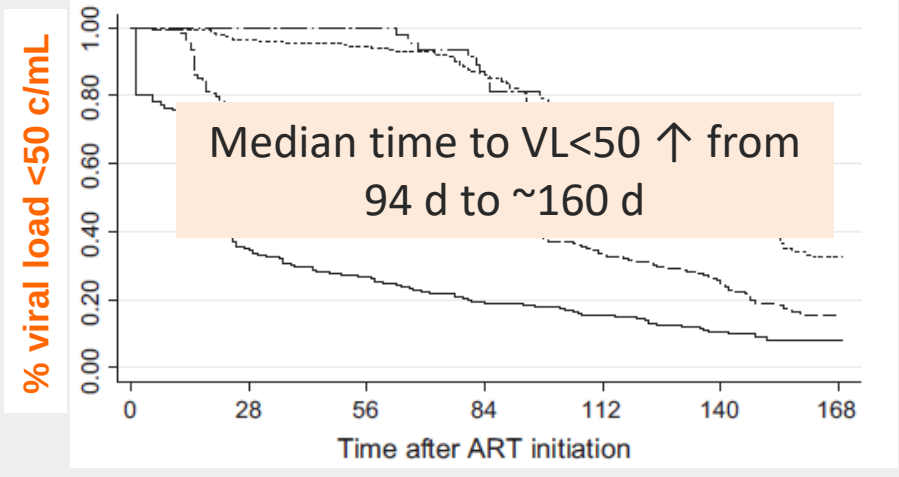
BAN STUDY

- ✓ Better adherence ⟶ lower breastmilk HIV RNA ⟶ lower MTCT
- ✓ 90% vs 100% ART adherence: same MTCT
- ✓ No MTCT if plasma VL consistently <100

TIME TO SUPPRESSION AFTER ART INITIATION

If pre-ART VL>100 000

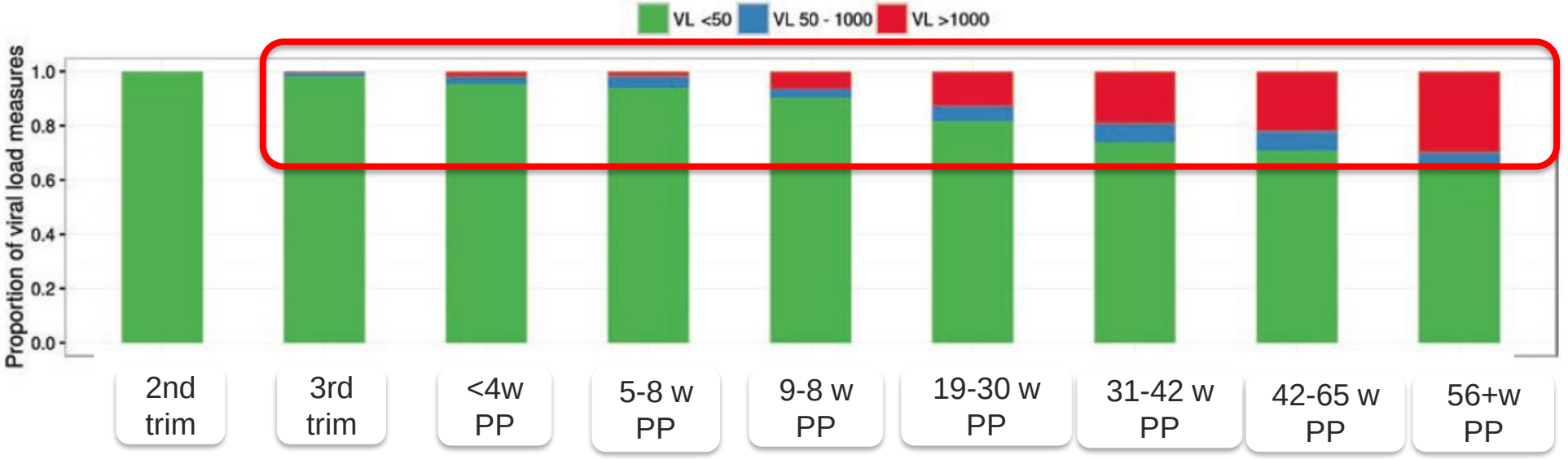




Myer L et al. HIV Med 2017;18:80-8 n=620

FREQUENCY OF VIREMIC EPISODES IN HIV-INFECTED WOMEN ACHIEVING VIRAL SUPPRESSION

523 HIV+ women initiating antenatal ART with initial suppression. 85% breastfeeding

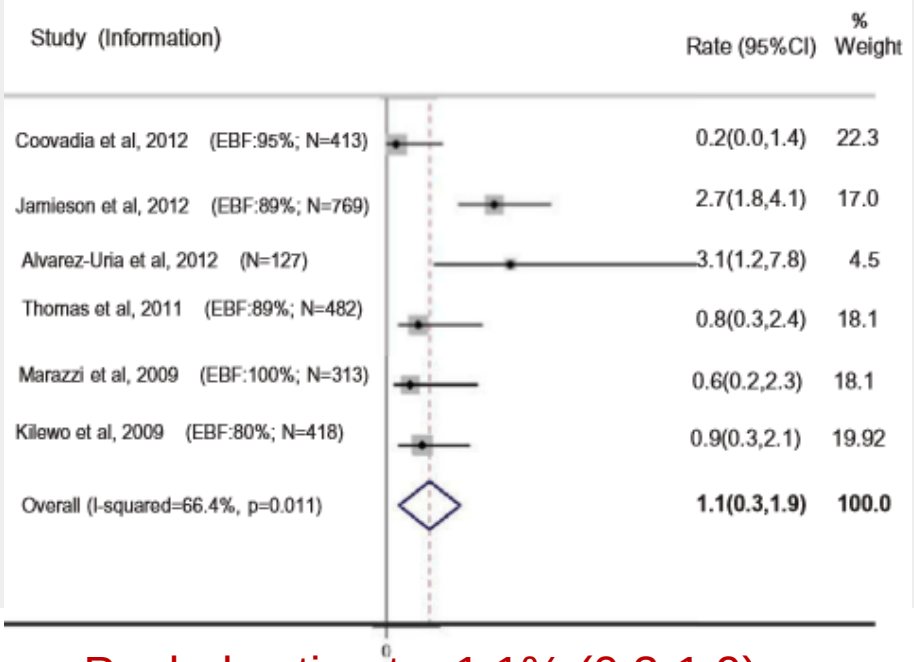


Myer L et al. Clin Infect Dis 2017 n=523

POSTNATAL MTCT IN BREASTFED INFANTS OF WOMEN ON ART

11 studies - all clinical trial settings – mothers on ART for 6 months. Rapid weaning advised

Postnatal MTCT between 4-6 weeks and 6 months: 6 studies



Pooled estimate: 1.1% (0.3-1.9)

If maternal HIV prev is 20% translates into 220 new infections per 100 000 live births

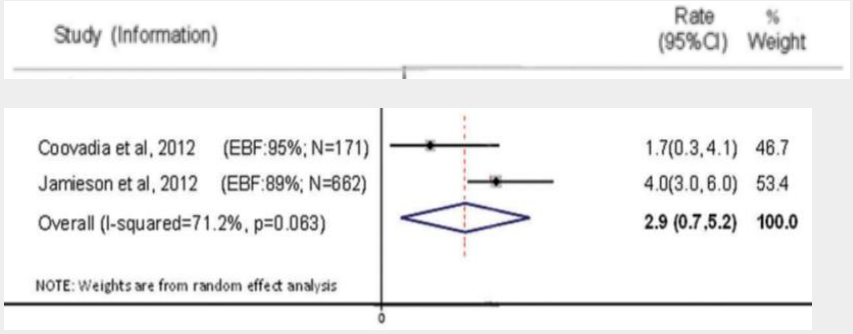
Bispo S et al. JIAS 2017;20:21251

POSTNATAL MTCT IN BREASTFED INFANTS OF WOMEN ON ART

11 studies - all clinical trial settings – mothers on ART for 6 months. Rapid weaning advised

Postnatal MTCT

4-6 weeks and 12 months: 2 studies



Pooled estimate 2.9% (0.7-5.5%)

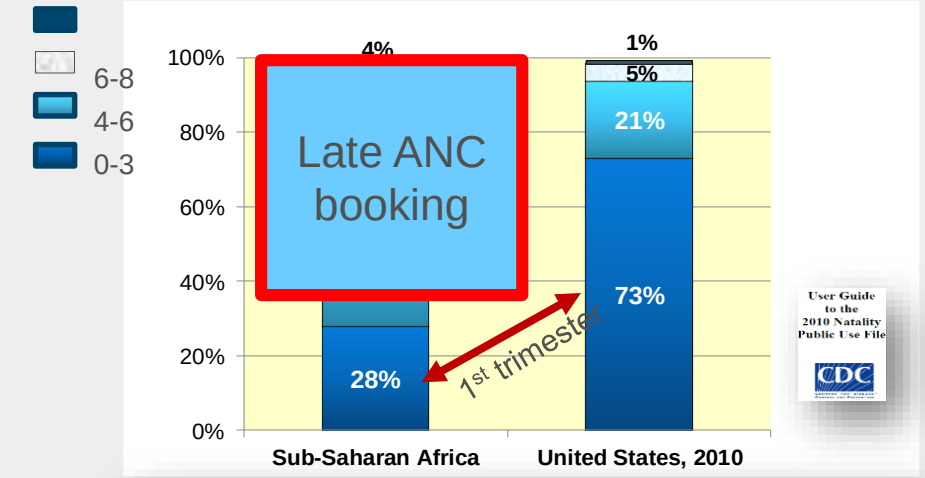
If maternal HIV prev is 20% translates into 580 new infections per 100 000 live births

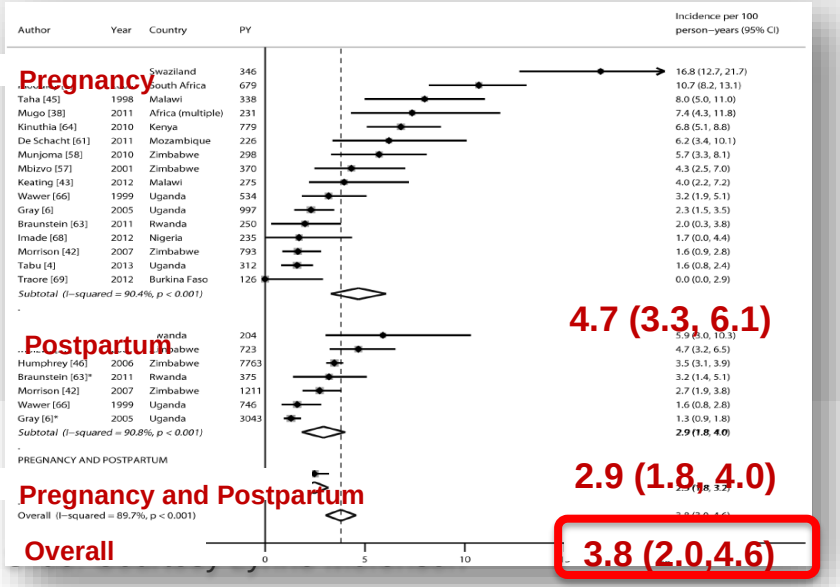
Bispo S et al. JIAS 2017;20:21251

OUR REALITIES

	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5
Mum	Misses doses No transport VL 2 million cpml **Non-adherent: resistance unlikely**	Newly diagnosed when baby admitted to ICU **Resistance unlikely** **VL very high**	VL never done Reports adherence **Poor VL monitoring: resistance unlikely**	Stopped ART after delivery **Non-adherent: resistance unlikely**	VL never done. Reports adherence **Poor VL monitoring: resistance unlikely**
BF Baby	3 months HIV neg EBF	3 months PCP pneumonia EBF	4 months Mixed feeding	7 months HIV neg	13 months Mixed feeding

Resource-constrained settings: 5 issues





Late ANC booking

Incident HIV infections during pregnancy / BF

Drug stock-outs

Poor VL Monitoring/ delayed return of results

High maternal HIV prevalence

CDC, Drake AL et al. PLosMed 2014;11:e1001608

INFANT PEP OPTIONS

USA GUIDELINES OCT 2017

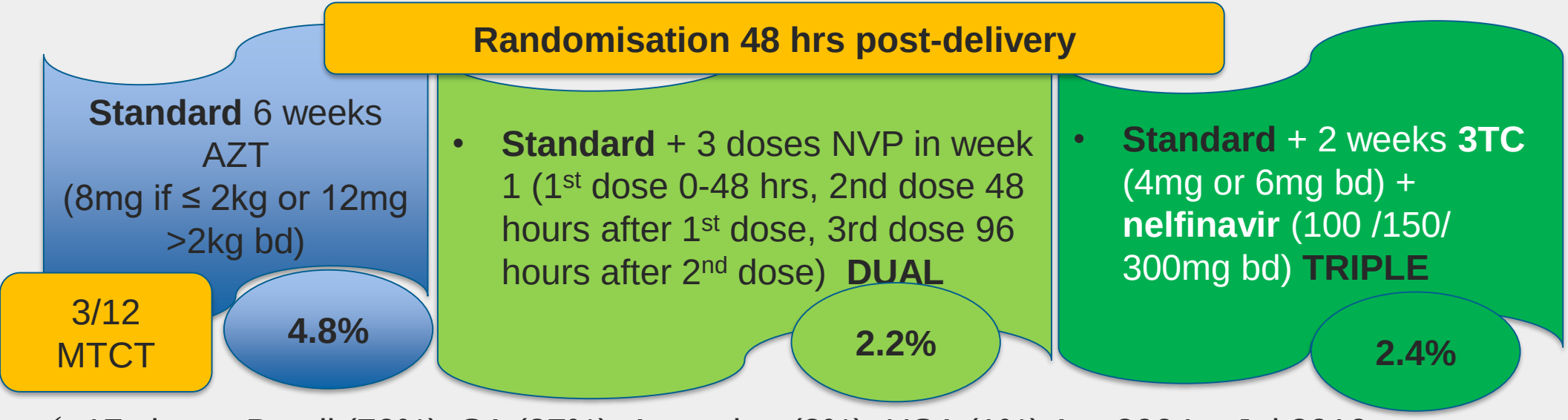
1. Full viral suppression in breast milk takes several weeks to months

2. Thus, hypothetically, maternal ART may be less effective than infant prophylaxis if initiated postpartum or late in pregnancy

https://aidsinfo.nih.gov/guidelines/html/3/perinatal/448/appendix-a--review-of-clinical-trials-of-antiretroviral-interventions-to-prevent-perinatal-hiv-transmission

NICHD-HPTN 040/P1043: NO MATERNAL ANC ARVS

Nielsen-Saines K et.al. ***N Engl J Med.*** 2012;366(25):2368-2379.



- ✓ 17 sites – Brazil (70%), SA (27%), Argentina (2%), USA (1%) Apr 2004 – Jul 2010
- ✓ 9% BF at birth. <1% BF at 2 weeks **96% ARV adherence (diaries)**
- ✓ **Dual -** and triple-combination regimens reduced risk of intrapartum MTCT by ≈ 50% at 3 months compared with **Standard (n=1684)**
- ✓ Triple - more hematologic toxicity (neutropaenia) + difficult to administer
- ✓ **Resulted in USA moving to DUAL INFANT ARV prophylaxis**

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WHO 2016 guidance for extended postnatal prophylaxis (ePNP)

All HIGH RISK <u>newborns</u>: daily AZT + NVP for 6 weeks
HIGH RISK <u>breastfeeding infants</u> continue **either AZT and NVP or NVP alone for an *additional* 6 weeks**

High risk assessed at delivery or later

Known HIV+ mother:

1. **not on ART** OR
2. **on ART with VL>1000 OR**
3. **ART duration<5 weeks**

Newly identified HIV+ mother within 72 hours of delivery

2016 guidance f extended postnatal pro s (ePNP)

All HIGH RISK n ZT + NVP for 6 weeks

HI AZT and NVP

Dilemmas:

1. Diagnosed during BF
2. Not virally suppressed & BF
3. Mother refuses ART or
4. Poor adherence

1. not on ART OR
2. on ART with VL>1000 **OR**
3. ART duration<5 weeks

ewly identified HIV+ mother within 72 hours of delivery

AZT dosing is tricky since AZT clearance increases between birth and 6 weeks so the dose goes up 4-fold

Infant age (and birthweight)		Dosing of NVP	Dosing of AZT
0- 6 weeks	BW 2000−2499g	10 mg once daily	10 mg twice daily
	BW ≥ 2500g	15 mg once daily	15 mg twice daily
6 to 12 weeks		20 mg once daily	60 mg twice daily

Doses are for term infants >35 weeks gestation

World Health Organization

Are we making life complicated?

1. Who is high risk? Assessing risk is difficult and time-consuming in busy clinics

2. Do you use two drugs or one drug from week 6 to 12? It seems easier to use 2 drugs but the jump in AZT dose is challenging

3. Formulations… Syrups are difficult to use and there is no FDC tablet for infant prophylaxis

ePNP – What are countries doing?

COUNTRY	ePNP DURATION	REGIMEN
Cote D'Ivoire	4 wks	NVP for HIV-1, AZT for HIV -2 or mixed
Angola, Cameroon Malawi, Mozambique	6 wks	NVP
Ethiopia	6 or 12 wks	NVP, duration based on timing of diagnosis and feeding
Uganda	12 wks	NVP
Tanzania	6 wks	AZT + NVP
Nigeria	6 wks	NVP if VL<1,000; AZT+ NVP for HIGH RISK infants
Kenya	12 weeks	6 wks AZT + NVP then 6 weeks NVP
Ghana	12 weeks	AZT + NVP
South Africa, Zimbabwe	6 weeks 12 wks	NVP AZT+ NVP for HIGH RISK
Zambia	6 wks AZT+ NVP for LOW RISK: Mother>12 wks on ART / complicated mother on ART>12wks, home delivery with arrival at HF <72h 12 wks AZT+ NVP for HIGH RISK : <12 wks on ART /VL>1,000/ Identified at delivery or during BF until infant's final outcome: AZT+ NVP if mother refuses ART	

ePNP – What are countries doing?

COUNTRY	ePNP DURATION	REGIMEN
Cote D'Ivoire	4 wks	P for HIV-1, AZT for HIV -2 or mixed
Angola, Cameroon Malawi, Mozambique	6 wks	NVP
Ethiopia		losis and feeding
Uganda		
Tanzania		P
Nigeria		P for HIGH RISK infants
Kenya	1	n 6 weeks NVP
Ghana		P
South Africa, Zimbabwe		ISK
Zambia	6 wks AZT+ N mother on ART> 12 wks AZT+ NVP at delivery or during AZT+ NVP if mother re s ART	Mother>12 wks on ART / complicated elivery with arrival at HF <72h SK : <12 wks on ART /VL>1,000/ Identified nfant's final outcome:

No programme/ pragmatic trial data on ePNP effectiveness

FUTURE POSSIBILITIES

POSSIBLE SA OPTIONS

VL monitoring and Management 	Check if the mother has had a VL result in the last 3 months and categorize the risk of the mother: • VL < 400c/ml = Low risk • VL> 400 c/ml = High risk • No VL result in the last 3 months = High risk **All women must have a VL test done at the time of delivery.** Although this VL result will mostly still be unknown when infant prophylaxis is initiated, remember to insert the laboratory barcode sticker into the postnatal discharge form and/or the RTHB. The results of the delivery VL must be checked at the 3-6-day postnatal visit, and the management of the mother-infant pair adjusted accordingly

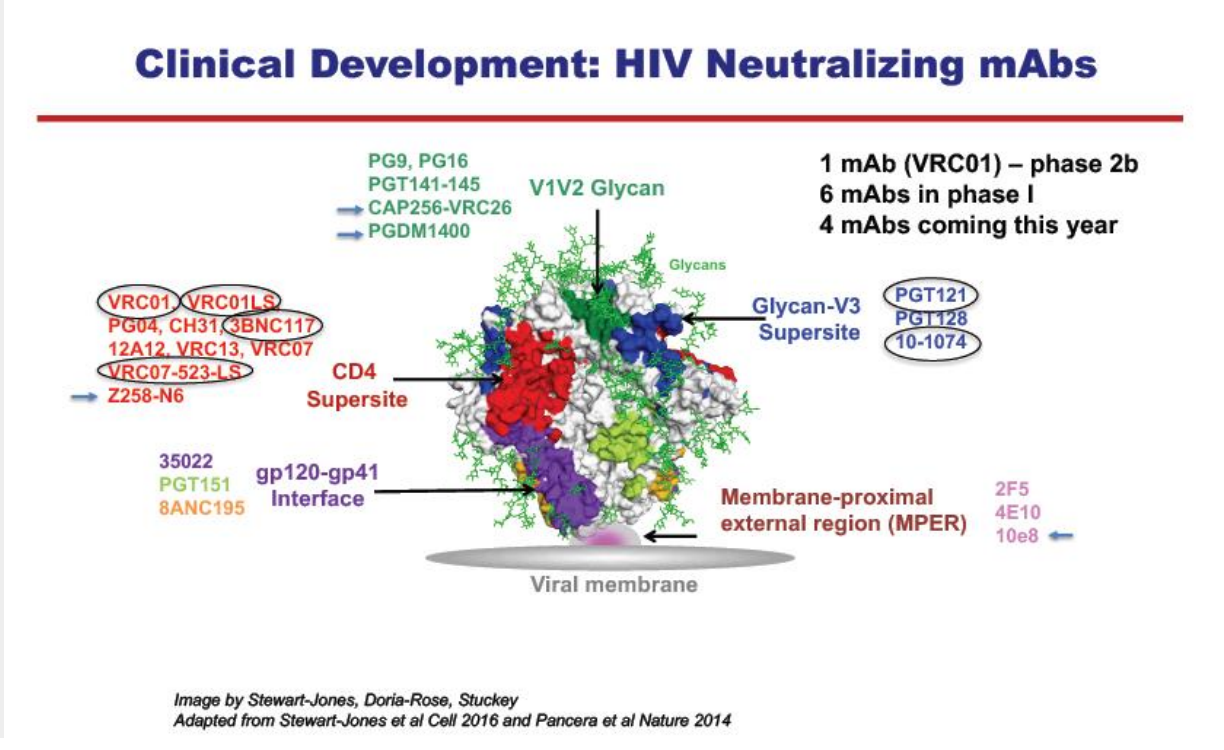
An elevated viral load at delivery Increases the risk for poor maternal outcomes and MTCT during labour and through breastfeeding.

- NVP for baby for 6 weeks or until mother virally suppressed or breastfeeding has stopped

2 PLANNED TRIALS OF RESCUE THERAPY

Randomisation to infant ePNP (3TC) at 6-8 weeks immunization if maternal VL>1000

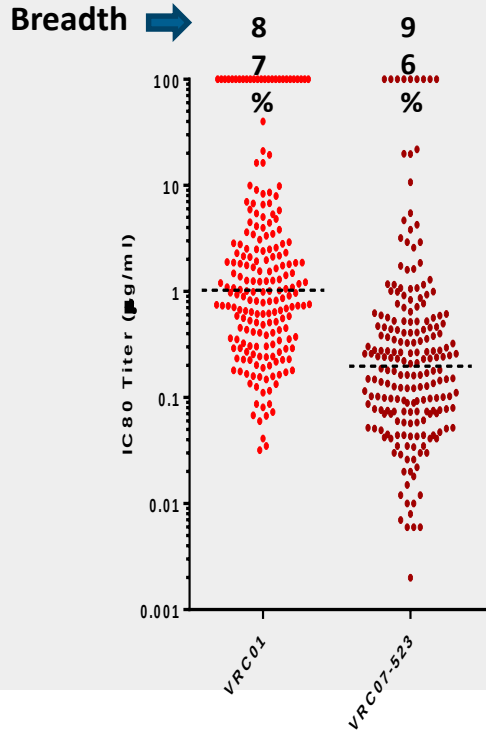
WHAT ABOUT NEUTRALIZING ANTIBODIES



bNAbs

Slide from Philippe van de Perre

Improved Neutralization Potency
VRC01 ➡ VRC07-523-LS



- 10 fold more potent
- Coverage improves to 96%
- Particularly good vs clade C (Seaman, Williamson et al, PlosPath 2016)
- Improved in vivo protection (SHIV) (Rudicell et al, J Virol 2014)

Panel of 206 Env-pseudoviruses:
Doria-Rose, Louder, Bailer et al.

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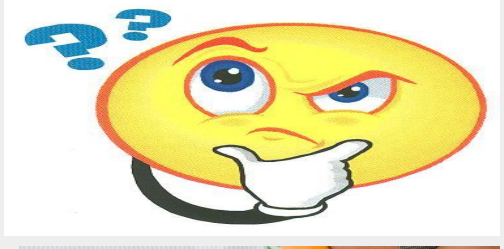
SUMMARY

Road travelled



Dilemmas

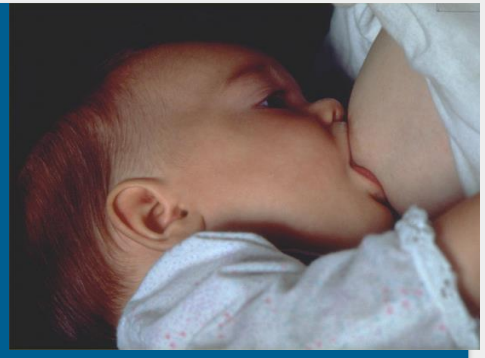
Infant PEP options

Future possibilities

We know:

- **Cell-associated MTCT**
- **Viral suppression:** 1-3 mo to < 1000, 5-6 mo to <50
- **Postpartum rebound viraemia**
- **Increased mastitis/breast inflammation** with ART
- In **high HIV prev settings**, case rates are>50 despite low MTCT %

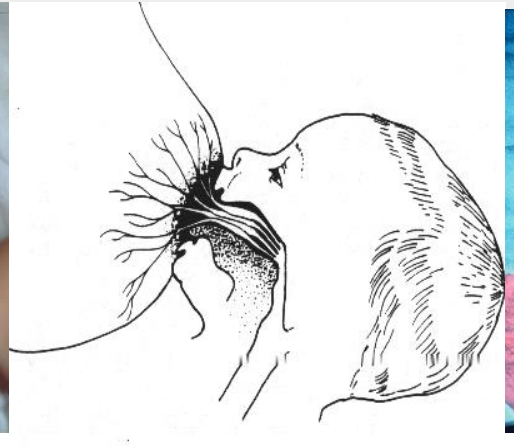
Gaps

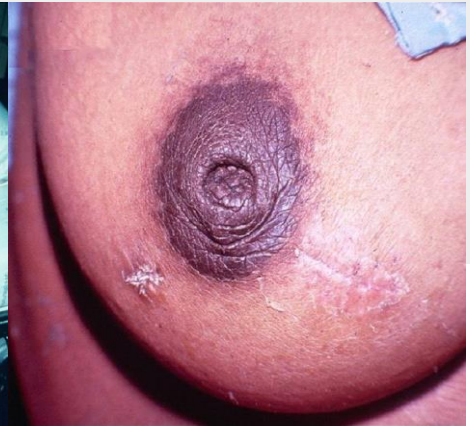


- Do newer dugs influence cell-associated HIV?
- Registry to track MTCT
- Clinical monitoring and pharmacokinetics
- Mastitis during ART?
- Optimal prophylaxis for infants – what combinations? Neutralising antibodies?
- Health systems issues and differential models of care

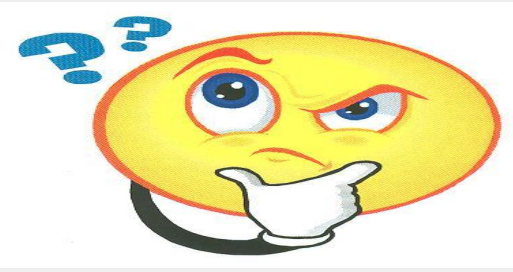
DO WE KNOW HOW TO SUPORT BREASTFEEDING?

- Back to basics: attachment, positioning, breast health
- But also important to monitor viral load!!!!



Can we eliminate breastmilk MTCT?



Perhaps with:

- maternal ART + infant ePNP OR
  maternal ART + infant ePNP + infant bNAb OR
  maternal ART + maternal bNAb +infant ePNP + infant bNAb AND
- Viral load monitoring AND
- Breastfeeding monitoring AND
- Reducing maternal HIV incidence and prevalence

THANK YOU!

- Lynne Mofenson
- Hoosen Coovadia
- Landon Myer
- Hermione Lyall
- Shaffiq Essajee
- Philippe van der Perre
- SAMRC:
  - Vundli Ramokolo
  - Nobubelo Ngandu
  - Witness Chirinda
  - Duduzile Nsibande

Breastfeeding rocks!
Let's make it risk free!

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