

PMTCT: A REVIEW OF THE PAST TWO YEARS AND THE WAY FORWARD.

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**THE TERESA GROUP SYMPOSIUM. CHILDREN AND
HIV/AIDS: “ACTION NOW, ACTION HOW” SYMPOSIUM.**

AUGUST 1ST 2008. 2.55-3.25 pm. HOTEL NIKKO

MOTHER TO CHILD TRANSMISSION OF HIV: GENETIC FACTORS

- Higher infant CCL3L1 gene copies = reduced transmission of HIV in absence of NVP
- Reduction in CCL3L1 production with NVP exposure.
- Therefore NVP has contradictory roles modifying the CCR5 ligand CCL3 in MTCT

Kuhn L et al AIDS 2007; 21: 1753-1761

A FRAMEWORK FOR ACTION TO PREVENT HIV INFECTION IN INFANTS

**Prevention of
HIV in women**

(by 1.25%)

**Prevention of
unintended
pregnancies in
HIV-infected
women**

(by 16%)

**Prevention of
transmission
from an HIV-
infected
woman to her
infant**

**Care and support for HIV-infected women, their
infants and their families**

Data from 8 African countries: Sweat MD et al. AIDS 2004;18:1661

COMPREHENSIVE PMTCT PROGRAMME- WHO

Programme Costs [average,annual]	\$4.8m
Infant HIV infections averted [average]	1898
Costs; per HIV infection averted	\$2517
per Daly averted	\$84
Equivalents to total HIV infections averted:	
*lowering female HIV prevalence	by 1.25%
*reducing unintended pregnancies in HIV infected women	by 16%

Data from 8 African countries: Sweat MD et al.AIDS 2004;18:1661

DECLINING MATERNAL HIV PREVALENCE RATHER THAN PMTCT DECREASES MTCT OF HIV IN ZIMBABWE.

MTCT of HIV decreased from 8.2% in 2000 to 6.2% in 2005, **predominantly attributable to declining maternal HIV prevalence rather than to the PMTCT program.**

Between 2002 and 2005, the single-dose NVP PMTCT program may have averted 4600.

In 2005, **32%** and **4.0%** of infections were attributable to **breast-feeding** and maternal seroconversion

Twice as many infections could have been averted had a more efficacious but logistically more complex NVP + zidovudine regimen been implemented with similar coverage (50%) and acceptance (42%).

MTCT and Integration of Services

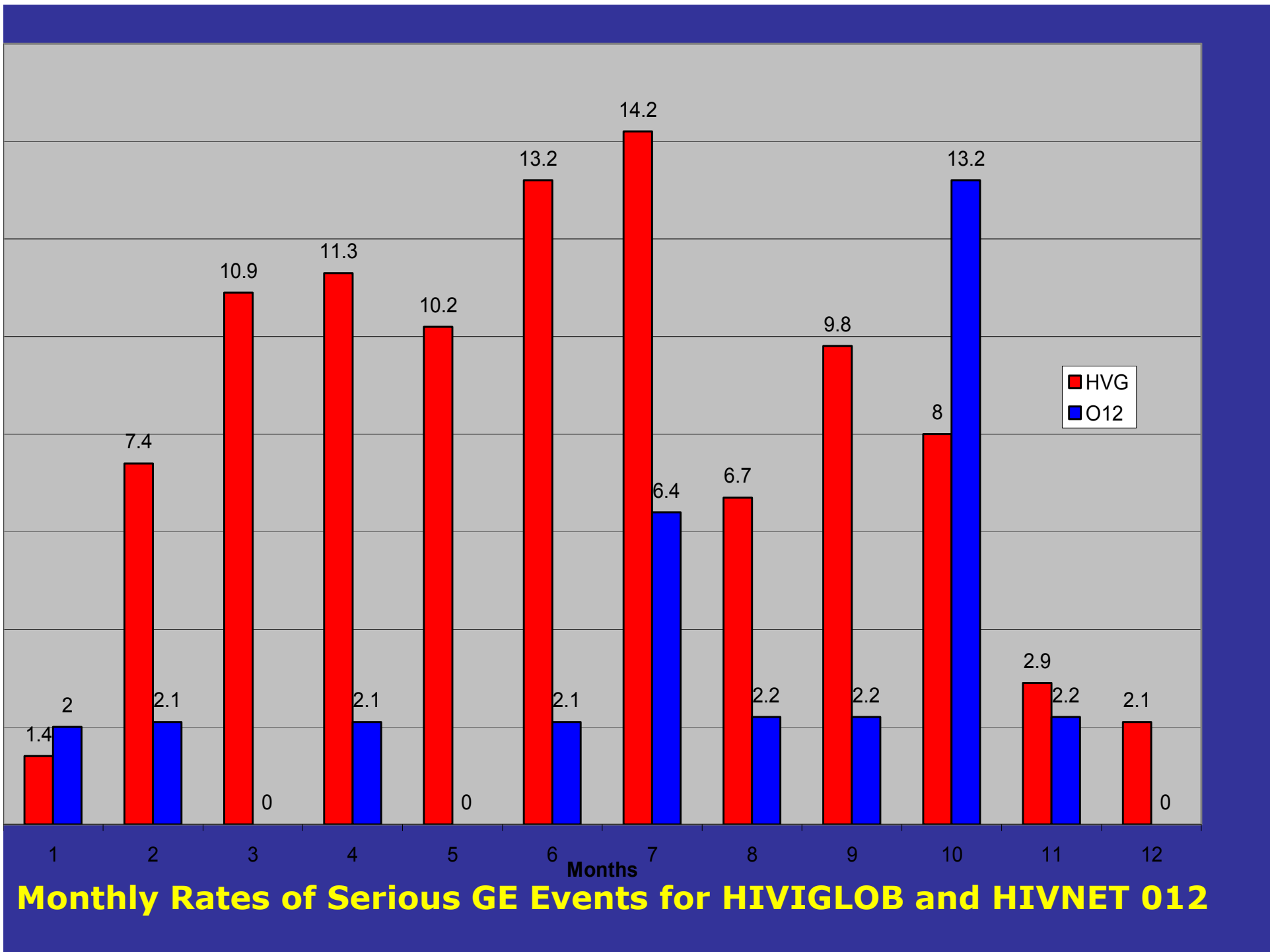
Integrating antenatal clinic services with ARV treatment facilities

- In facilities with ARV therapy **4.3%**
- In facilities for only sdNVP **10.7%**

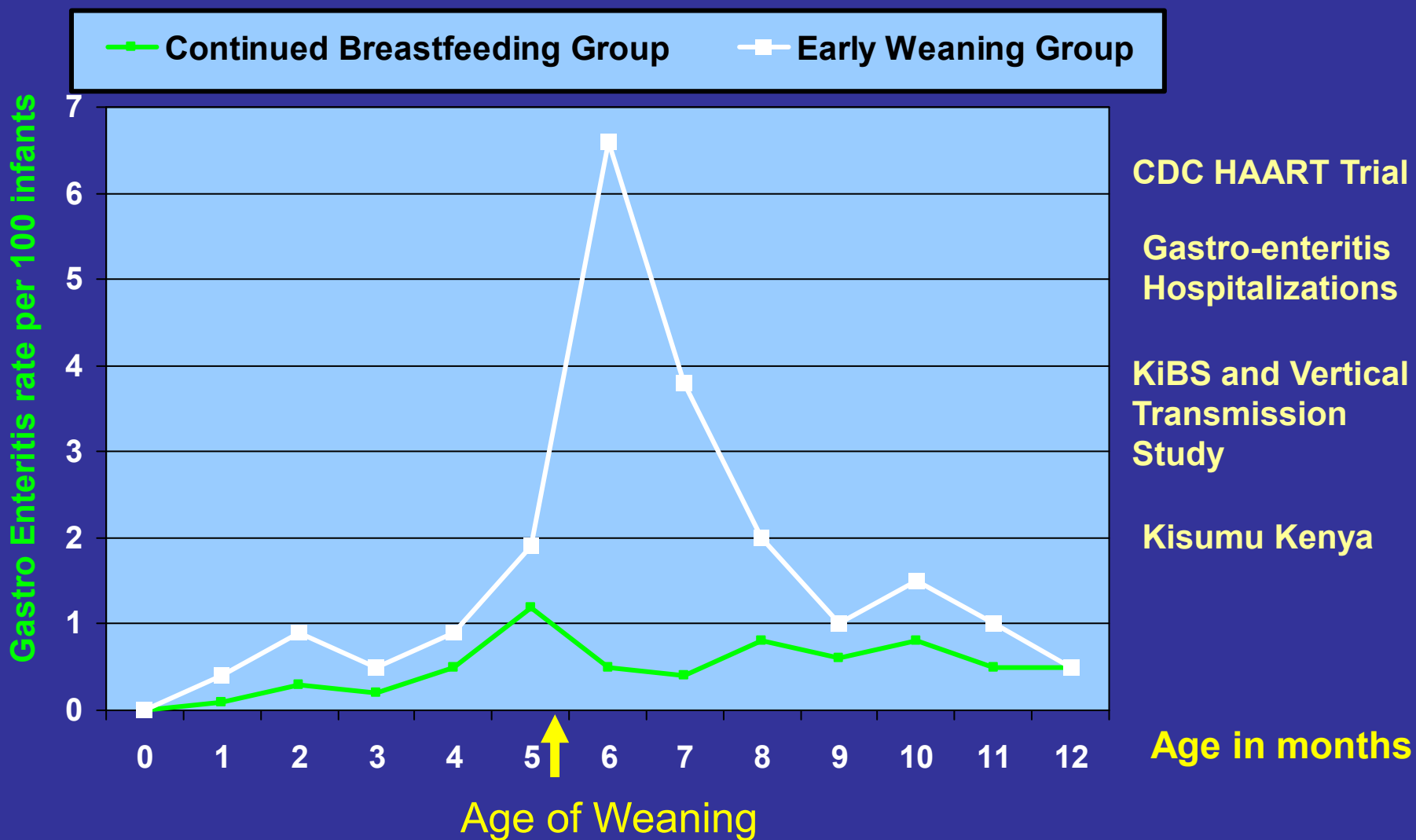
Coovadia Ashraf et al. Coronation Hospital, SA. JAIDS
2006;43;5

Summary from 3 Ongoing Trials Re Serious GE Events following BF Cessation among HIV Uninfected Infants

- The trials in Blantyre Malawi, Kisumu Kenya, and Kampala Uganda all include counselling to stop breast feeding by 6 months of age as part of the study design
- In each of these studies, **a rise in serious GE adverse events has been documented during the period immediately following early Breastfeeding cessation**
 - Each of these trials was able to compare data to earlier studies at the site where there was not an emphasis on early cessation of BF
 - The findings raise concerns that early BF cessation is associated with significant morbidity/mortality for HIV exposed uninfected infants



GASTRO-ENTERITIS RATES IN EARLY WEANING GROUP COMPARED WITH CONTINUED BREASTFEEDING GROUP



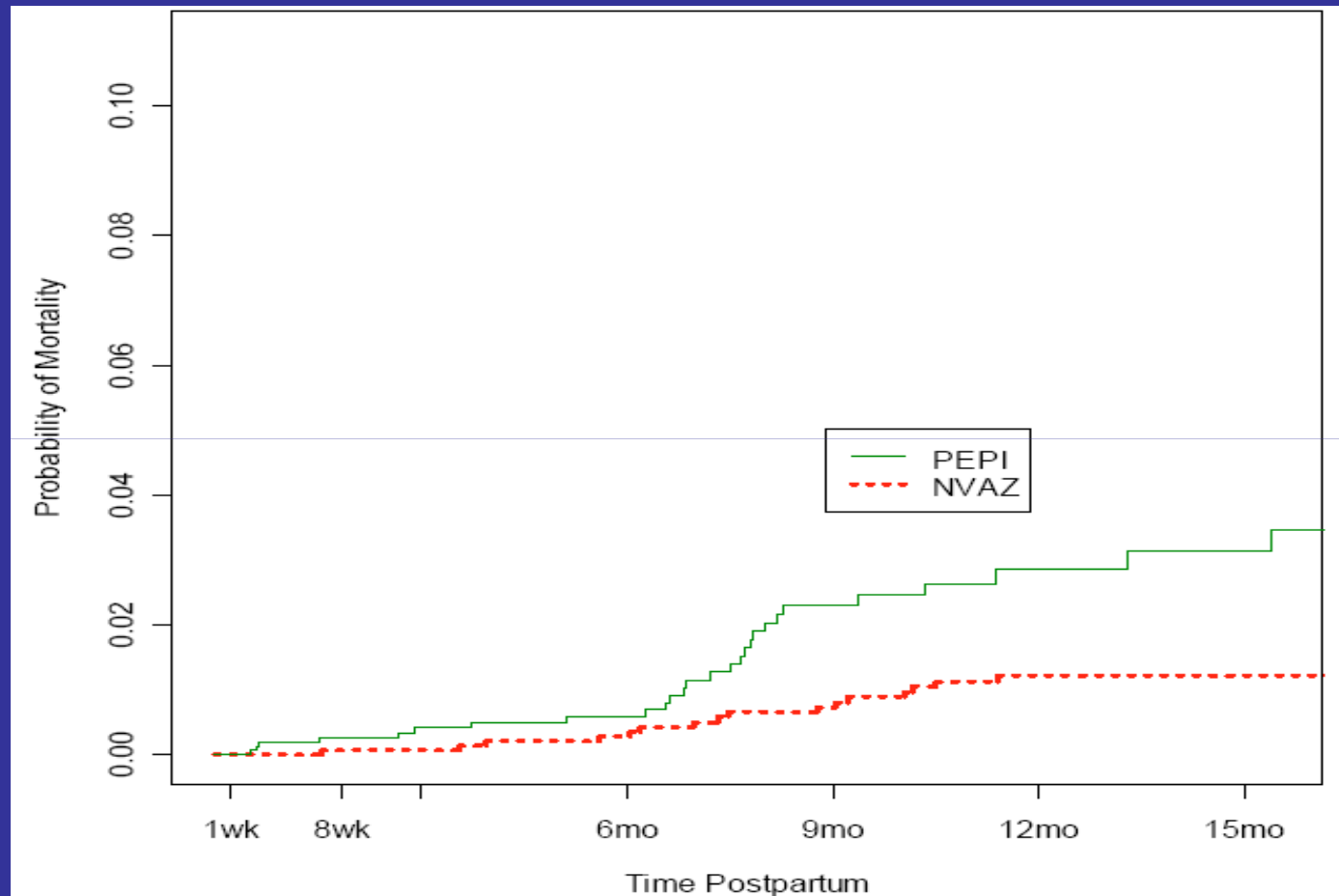
CDC HAART Trial

Gastro-enteritis Hospitalizations

KiBS and Vertical Transmission Study

Kisumu Kenya

GE Related Mortality Among HIV UNINFECTED Babies in PEPI versus NVAZ



	1 wk	8 wks	3 mos	6 mos	9 mos	12 mos
<u>PEPI</u>	0/1000	3/1000	4/1000	6/1000	23/1000	28/1000
<u>NVAZ</u>	0/1000	1/1000	1/1000	3/1000	7/1000	12/1000

Log-rank test for GE related mortality comparing PEPI and NVAZ $p = .0003$

Reduced Mortality Associated With Breastfeeding-Acquired HIV Infection in Zambia.

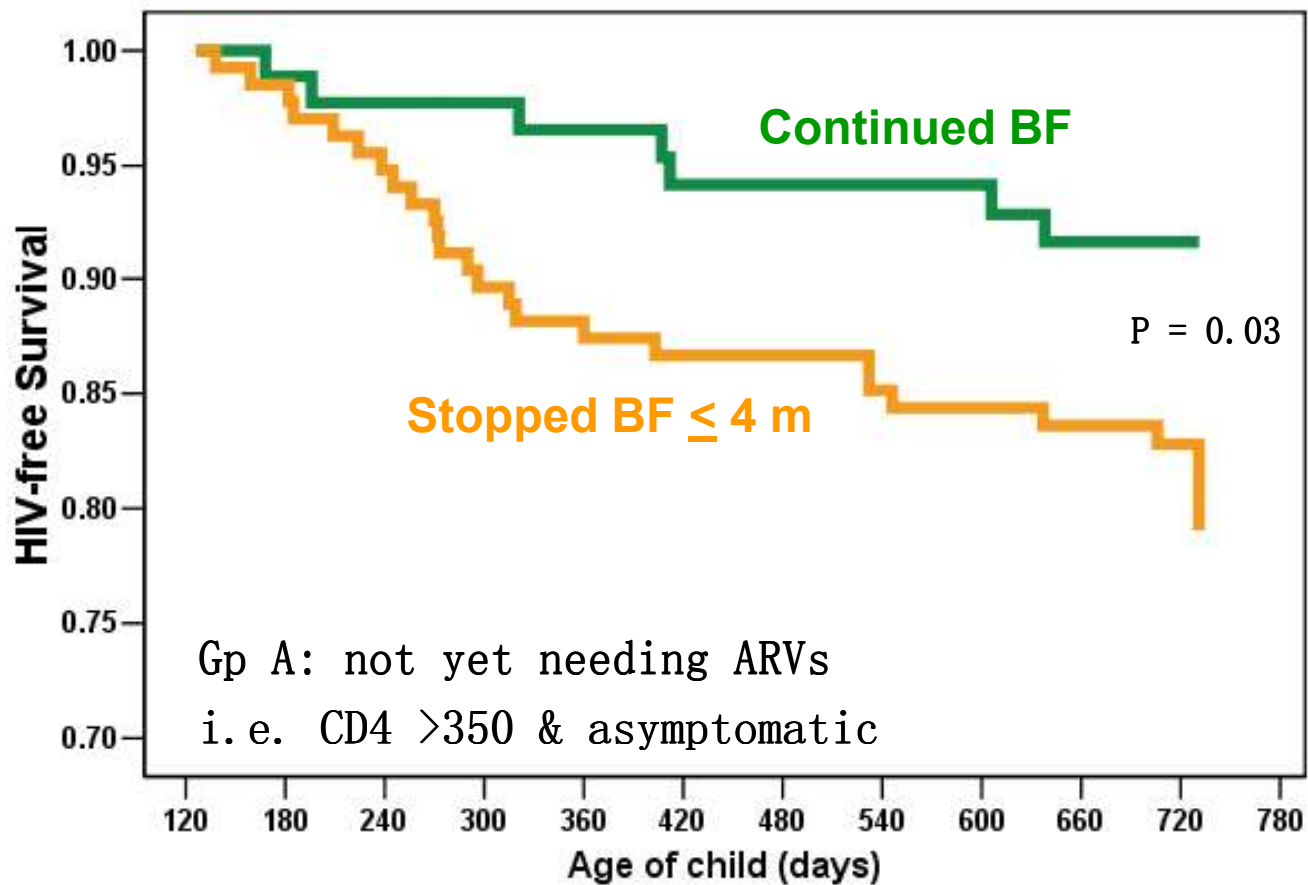
Children with intrauterine [IU] or intrapartum/early postpartum [IP/EPP] transmission had higher mortality over the first 12 months after infection than children with postpartum transmission (P = 0.001 and P = 0.006, respectively)

Nearly 20% of the IU and IP/EPP groups vs 10% of the PP group died by 100 days after infection.

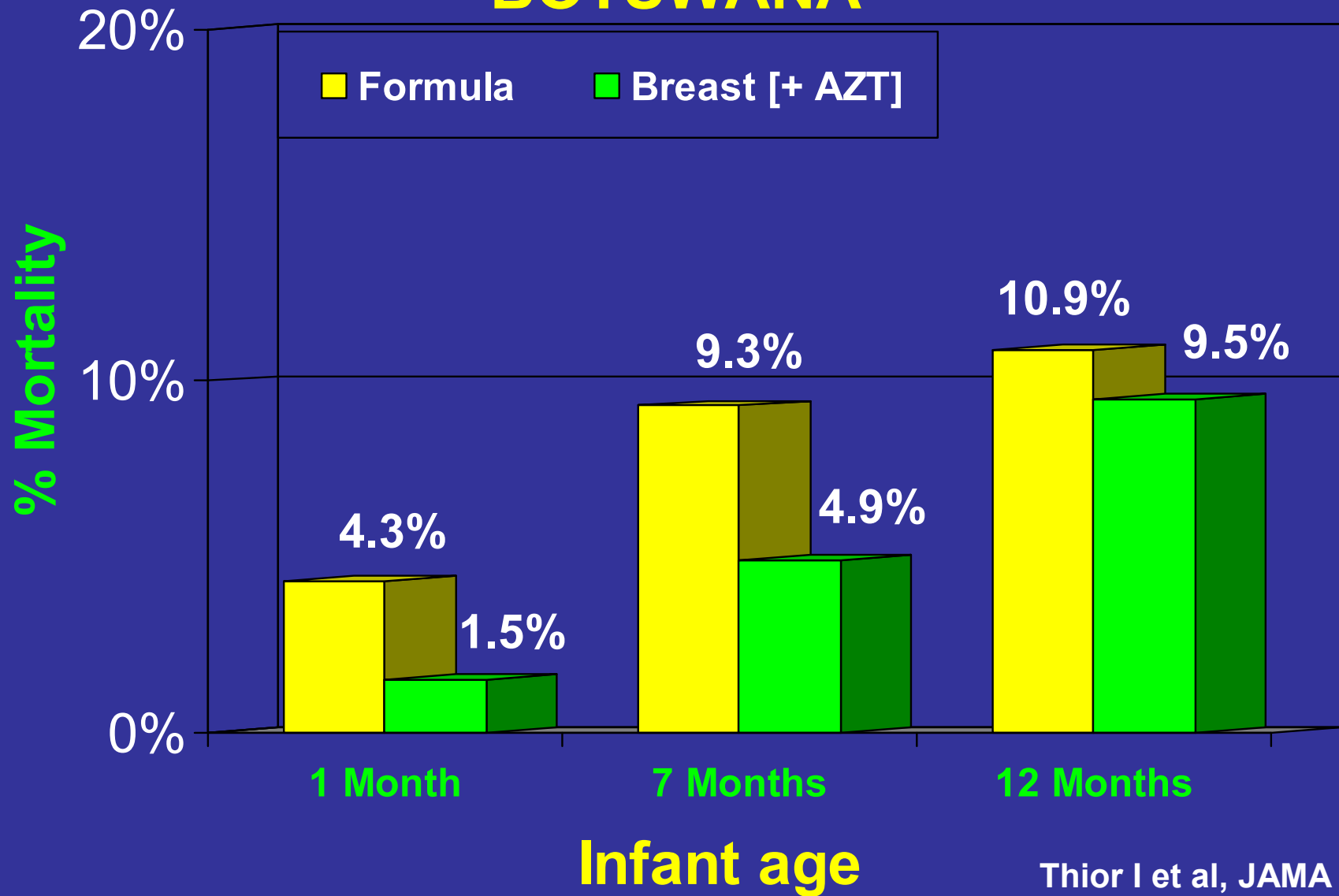
Children infected postpartum had one quarter the mortality rate (HR = 0.27) of those infected IU.

Stopping breast-feeding increased mortality in infected children (HR = 3.1, 95% CI: 1.8 to 5.3).

Net HARM of early breastfeeding cessation if maternal CD4 count is higher >350

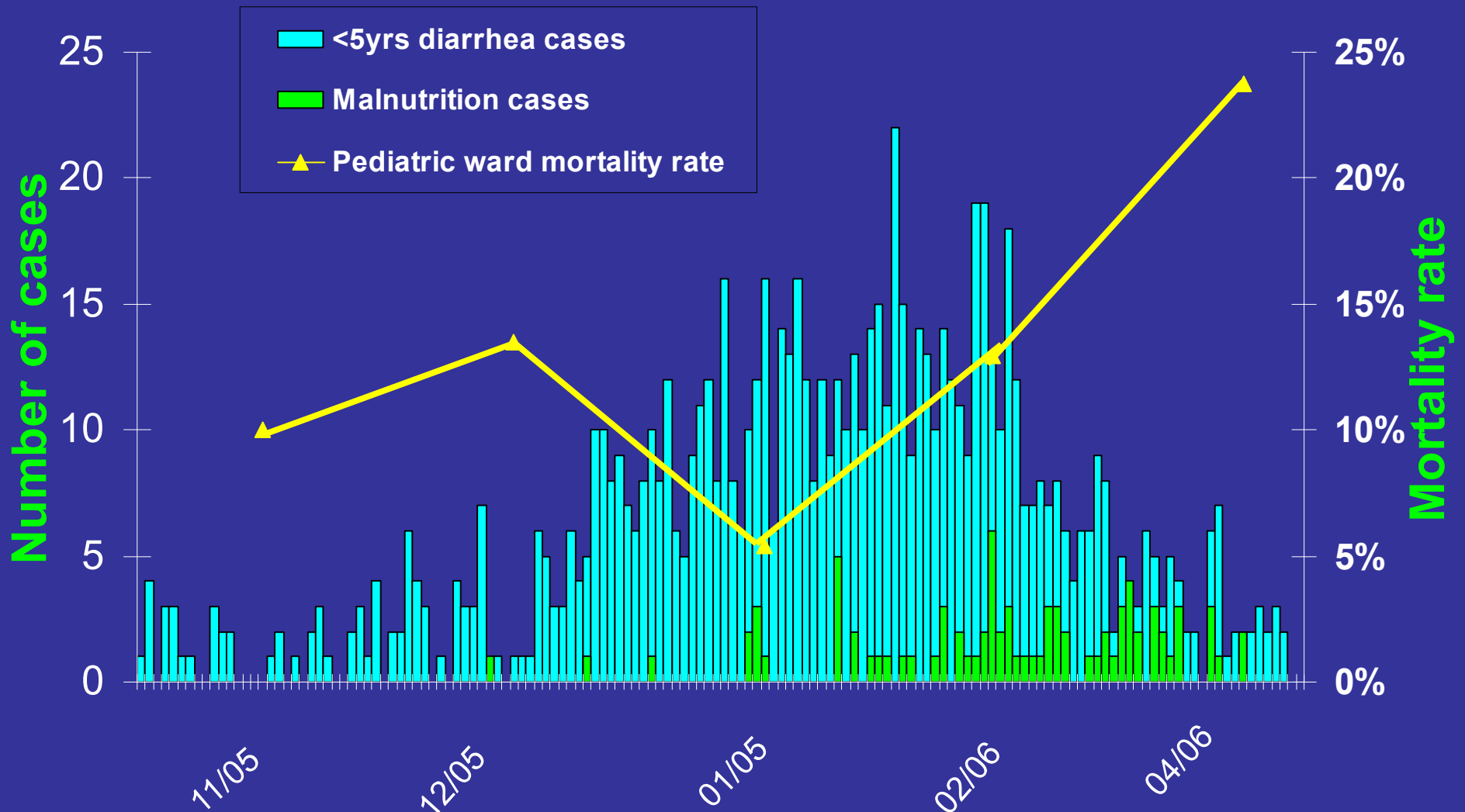


EARLY MORTALITY IS HIGHER IN FORMULA-FED THAN BREASTFED [+ AZT] INFANTS: BOTSWANA



DIARRHOEA; MALNUTRITION; CHILD MORTALITY

Francistown, Botswana, Nov 2005-April 2006



BOTSWANA. EMERGENCY ROOM FINDINGS: CDC

CHARACTERISTIC

AOR*(95% CI)

- | | |
|------------------------------|----------------------|
| • Not breastfeeding | 50.0[4.5-100] |
| • Storing drinking water | 3.7[1.5-9.1] |
| • Overflowing latrines | 3.0[1.1-8.6] |
| • Stagnant water near home | 2.6[1.1-6.3] |
| • Unwashed hands: caregivers | 2.5[1.1-5.0] |

*adjusted for socio-economic status, age, mothers HIV status

SUMMARY:
**PREVENTING BREASTFEEDING
ASSOCIATED HIV TRANSMISSION**

- ◆ **Primary Prevention**
- ◆ **Infant Feeding Options**
- ◆ Immunisation
- ◆ **Chemoprophylaxis**
- ◆ **Policy Options**

LOW CD4 CONSISTENTLY SHOWN TO BE AN IMPORTANT RISK FACTOR

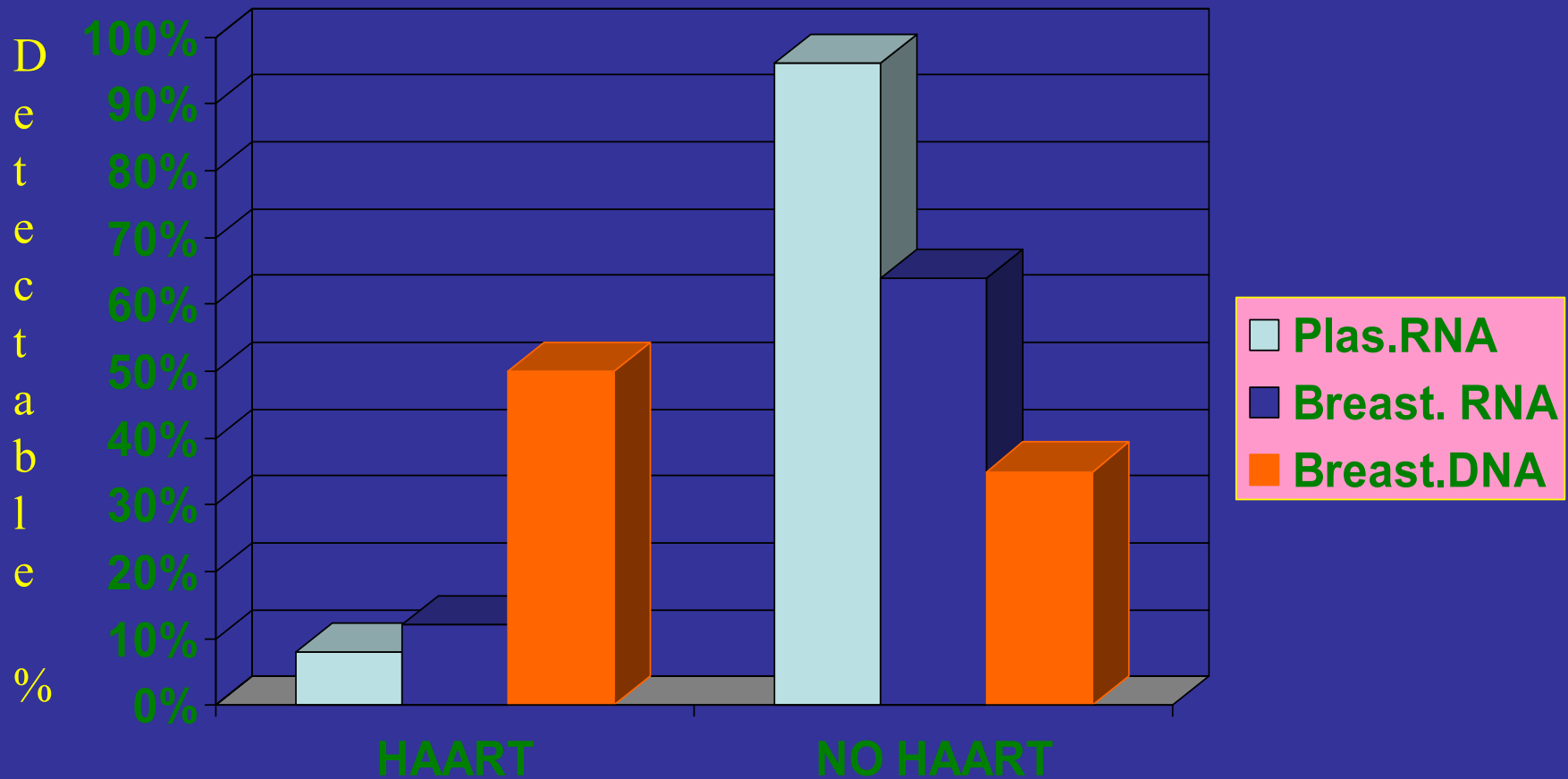
Vertical Transmission Study [VTS]– South Africa

6-month Transmission in Exclusively Breastfed Infants	
Maternal CD4 count	
<200	34.1%
>200	17.0%

Zvitambo Study Transmission 5 times higher in CD4<200 compared to CD4>500 cells

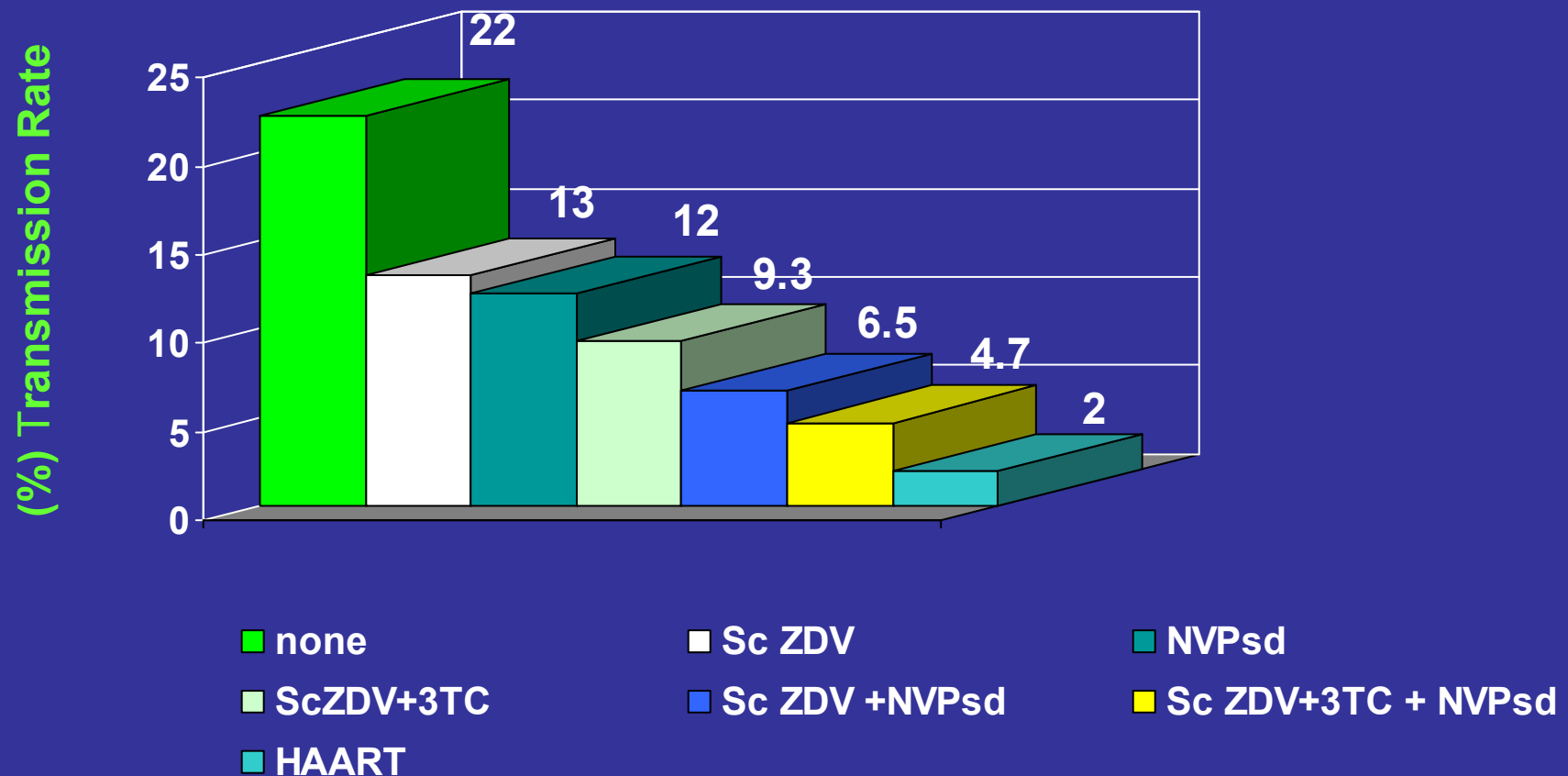
HAART SUPPRESSES BREASTMILK HIV RNA BUT NOT DNA

DETECTABLE%



Shapiro RL et al.JID.2005;192:713-19

HOW EFFICACIOUS ARE SHORT-COURSE ARVs IN MOTHER-TO-CHILD-TRANSMISSION AT ABOUT 6 WEEKS IN BREASTFEEDING AFRICAN WOMEN. 1995-2005?



**ANTENATAL HAART FOR ALL HIV+ PREGNANT
WOMEN :BREASTFEEDING WITH HAART
COMPARED TO FORMULA FEEDING WITH
WATER FILTERS AND FREE FORMULA
THE DREAM STUDY**

- All HIV+ pregnant women got HAART from 25th week.
- Formula + water filters for 6 months. Infant PEP. n=809 evaluated at 6 months.[2004-2006]
- Breastfeeding option group, postnatal HAART. 251 infants evaluable at 6 months.[2005-2006]

Palombi L et al. AIDS 2007;21:[Supplement 4] S65-S71

THE DREAM STUDY

HIV transmission:	@ 1 mth:	b/f 1.2%	ff 0.8%
	@ 6 mths:	b/f 0.8%	ff 1.8%
Cumulative Incidence	6 mths:	b/f 2.2%	ff 2.7%
Mortality	@ 6 mths:	b/f 28.5/10 ³	py
		ff 27/10 ³	py
	[Mocambique]	101/10 ³	py

Growth

weight[<2.0 Z scores]	bf 11.1%	ff 11.4%
Hb [<8gms/dl]	bf 6.8%	ff 4.9%

Palombi L et al. AIDS 2007;21:[Supplement 4] S65-S71

HAART, BREASTFEEDING, AND MTCT MITRA-PLUS TANZANIA

- Open-label, prospective, non-randomised study
- All HIV+ pregnant women enrolled, counselled on Exclusive Breastfeeding, AZT+3TC+NVP during late pregnancy and breastfeeding, stopped at 6 months except those who required HAART for their own treatment.
- Infants: AZT+3TC for one week; n=441;
- Breastfeeding; median =24weeks
- **MTCT @ 6 weeks= 4.1% [95%CI 2.1%-6.0%]**
- **MTCT @ 6 months= 5.0% [3.2%-7.0%]**
- **Breastfeeding Transmission = 0.9%**

Kilewo C et al .Abs TUAX101.4th IAS Conference on HIV Pathogenesis, Treatment and Prevention., incorporating the 19th ASHM

Conference.22-25 July,2007,Sydney,Australia. www.ias2007.org

Kaplan-Meier Estimated Transmission of HIV-1, Mortality, and HIV-Free Survival in the Mitra Study and in the Breast-Feeding Population in the Petra Trial Arm A

	HIV-1 infection % (95% CI)		Mortality % (95% CI)		HIV-1 infection or death % (95% CI)	
	Mitra	Petra	Mitra	Petra	Mitra	Petra
6 weeks	3.8 % (2.0 - 5.6)	5.4 % (2.7 - 8.1)	0.8 % (0 - 1.6)	0.4 % (0 - 1.1)	4.5 % (2.4 - 6.5)	8.7 % (5.4 - 11.9)
6 mnths	4.9 % (2.7 - 7.1)	11.9 % (7.9 - 15.8)	3.7 % (1.9 - 5.6)	4.7 % (2.1 - 7.3)	8.5 % (5.7 - 11.4)	15.5 % (11.1 - 19.9)

Kilewo C et al. JAIDS 2008; Vol 48, No. 3

HAART, BREASTFEEDING, AND MTCT. AMATA STUDY, RWANDA

- All HIV+ pregnant women enrolled, NNRTI HAART after 2nd trimester for breastfeeders; choice of breast or formula, HAART until one month after cessation of breastfeeding.
- Results for 419 infants @ 6 weeks, 236 @ 7 months
- Only 6 HIV+ [1.4%] at birth.
- **Breastfeeding transmission @ 7 months = 0**
- **No significant differences between FF and BF for psychomotor development; morbidity [1.23 episodes in FF vs 1.21 in BF], mortality [2.9% in FF vs 1.3% in BF]**

Arendt V et al .Abs TUAX102.4th IAS Conference on HIV Pathogenesis, Treatment and Prevention., incorporating the 19th ASHM

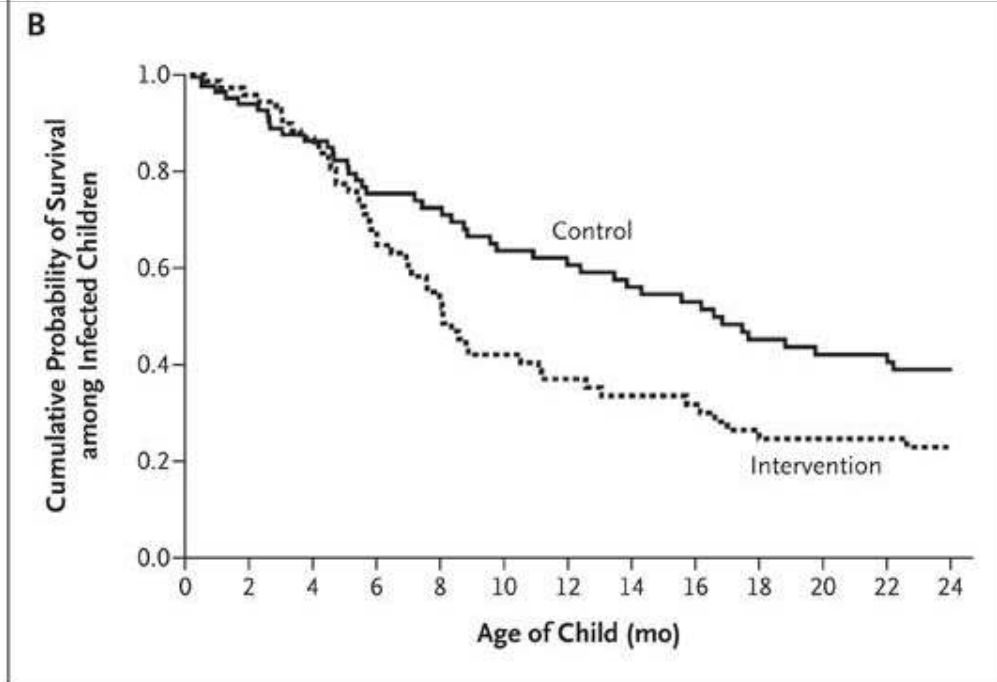
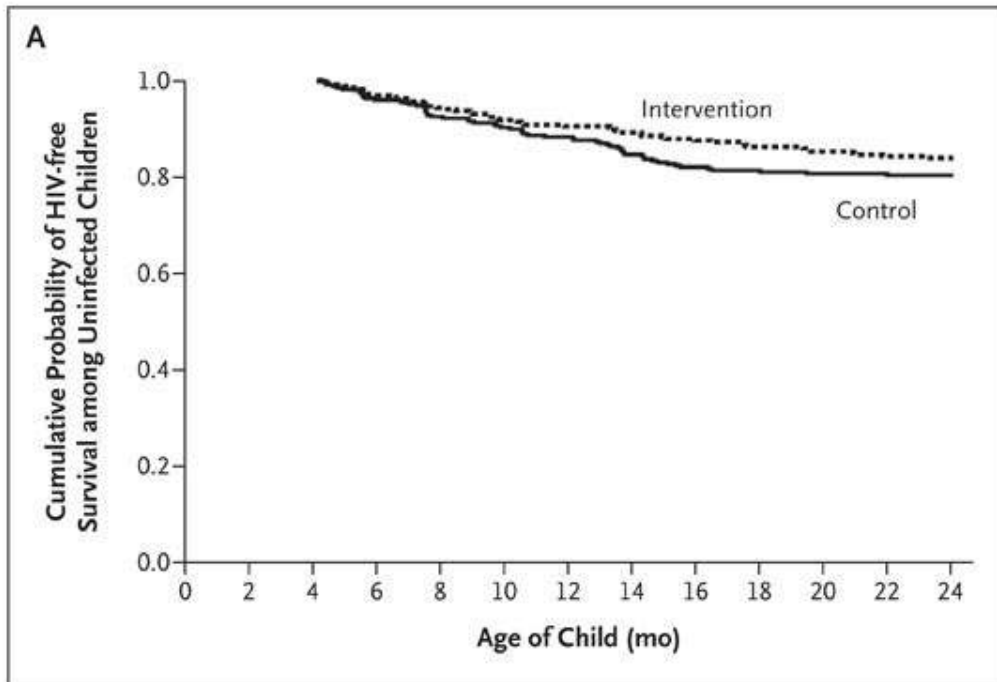
Conference.22-25 July,2007,Sydney,Australia. www.ias2007.org

ADJUVANT TRUVADA DOES NOT REDUCE MTCT IN WOMEN ON scAZT+sdNVP

- ZDV and NVP in all: intrapartum/early postpartum transmission was **1.6%** among infants whose mothers received TDF/FTC , compared with **2.8%** among those who did not ($p = 0.67$).
- Mothers :no antenatal ZDV but confirmed NVP ingestion, transmission similar (**0 of 19 vs.1 of 26**)

Chi, Benjamin et al. JAIDS. 2008;48:220-223

Cumulative Probability of HIV-Free Survival among Uninfected Children and of Survival among Infected Children, According to Study Group



Kuhn L et al. N Engl J Med 2008;10.

PEPI-Malawi Study Design

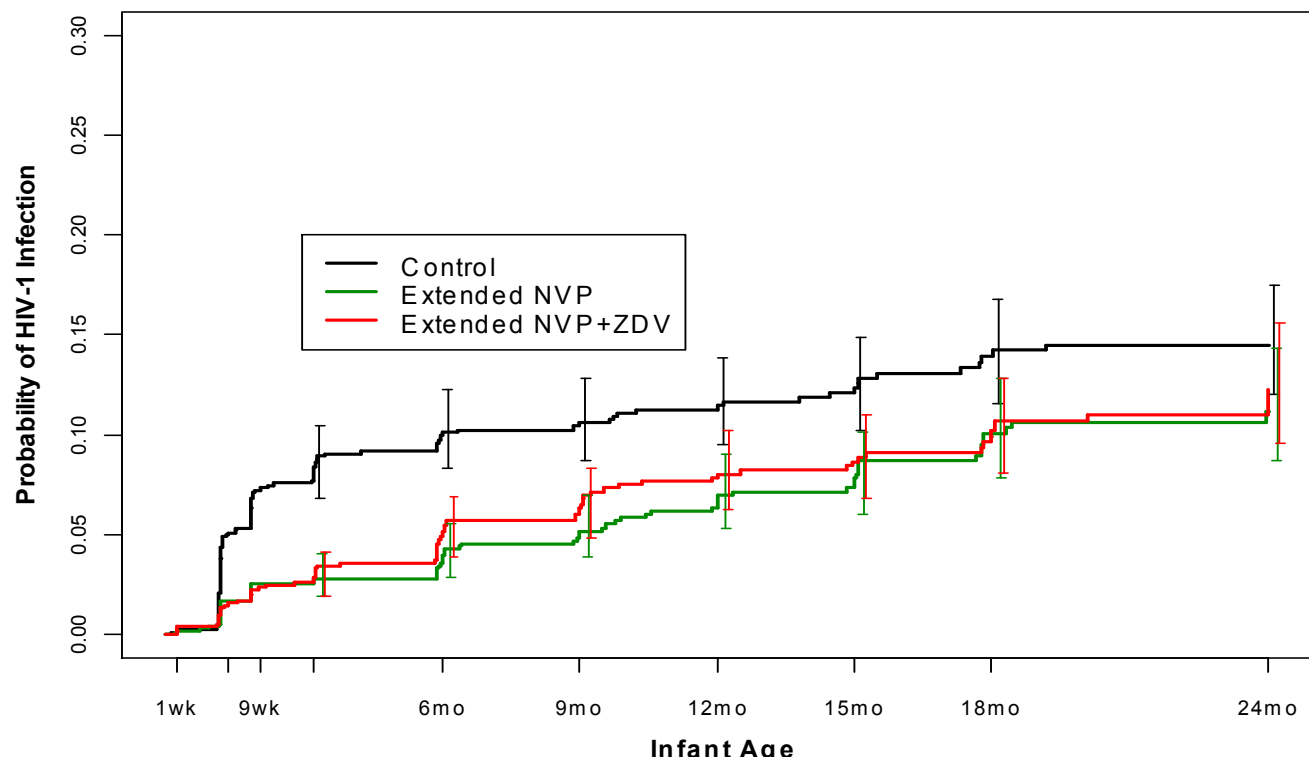
Taha TE et al. 15th CROI, Boston, MA 2008 Abs 42LB

	<u>Intra-partum*</u>	<u>Birth</u>	<u>Post-partum</u>	
			<u>1 - 7 d</u>	<u>8 - 98 d</u>
Control Suspended Aug 2007	NVP x1*	Infant NVP x1	Infant ZDV x1 wk	
Extended NVP	NVP x1*	Infant NVP x1	Infant ZDV x1 wk	Infant: NVP x 14 wks
Extended NVP + AZT	NVP x1*	Infant NVP x1	Infant ZDV x1 wk	Infant: NVP + ZDV x 14 wks

Mothers counselled to exclusively breastfeed and wean by 6 months

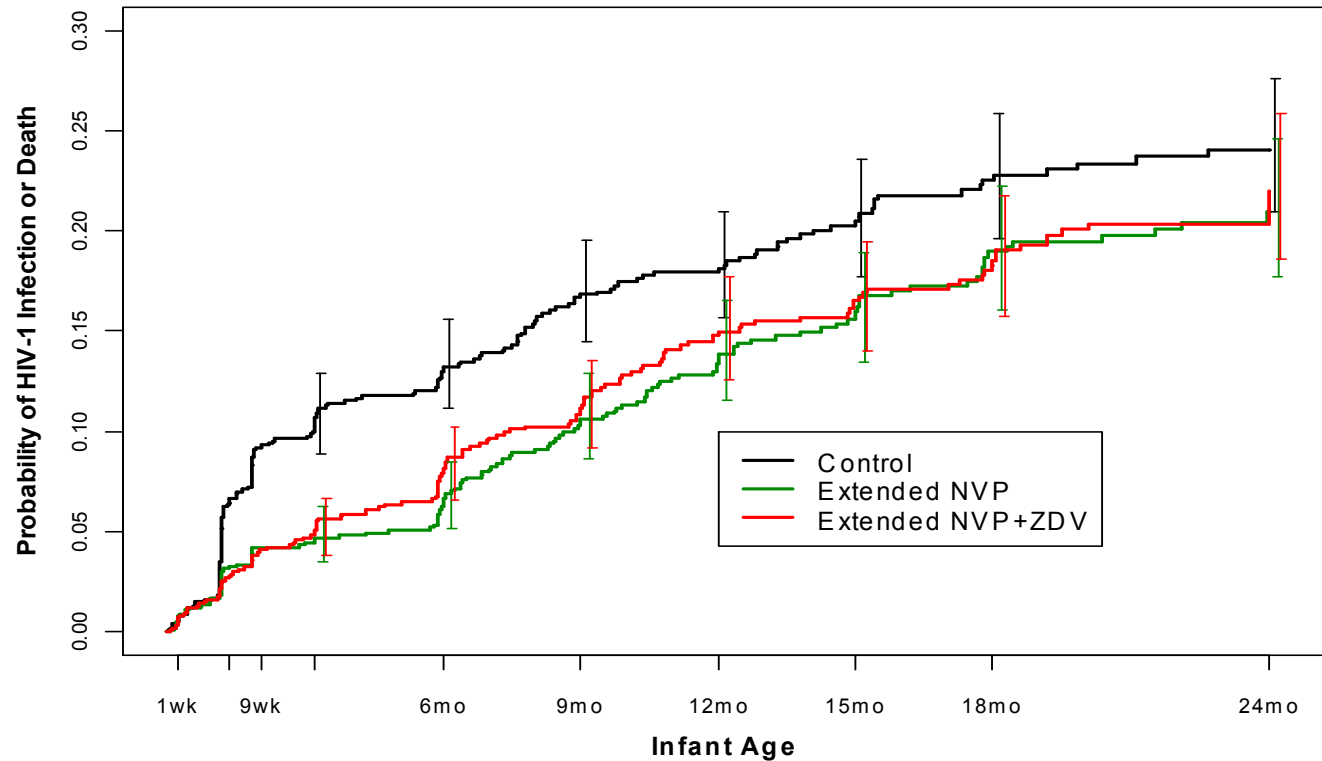
Kumwenda et al NEJM. 2008 June 4th. www.nejm.org

Probability of HIV-1 Infection in Infants Uninfected at Birth by Treatment Arm: PEPI-Malawi



Age	1 wk	6 wks	9 wks	14 wks	6 mos	9 mos	12 mos	15 mos	18 mos	24 mos
Estimates (%)										
Control	0.3	5.1	7.4	8.4	10.1	10.6	11.5	12.4	13.9	14.5
Extended NVP	0.1	1.7	2.6	2.8	4.0	5.2	7.0	7.8	10.1	11.2
Extended NVP+ZDV	0.2	1.6	2.4	2.8	5.2	6.4	8.1	8.7	10.2	12.3

Probability of HIV-1 Infection or Death in Infants Uninfected at Birth by Treatment Arm: PEPI-Malawi



Age	1 wk	6 wks	9 wks	14 wks	6 mos	9 mos	12 mos	15 mos	18 mos	24 mos
Estimates (%)										
Control	0.6	6.7	9.3	10.7	13.2	16.8	18.1	20.5	22.6	24.1
Extended NVP	0.6	3.3	4.2	4.7	6.6	10.6	13.9	16.0	19.0	20.9
Extended NVP+ZDV	0.5	2.8	4.1	5.1	8.2	11.2	15.0	16.5	18.6	22.0

Six-Week Extended Nevirapine (SWEN) Study:

Ethiopia, India, Uganda: Separate but Coordinated Trials

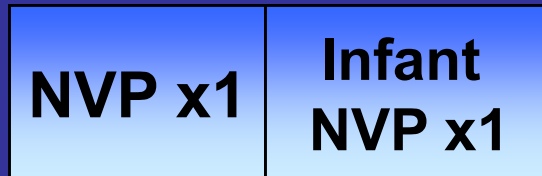
IP Birth-72hr Day 8 to 42

Arm 1
SD NVP



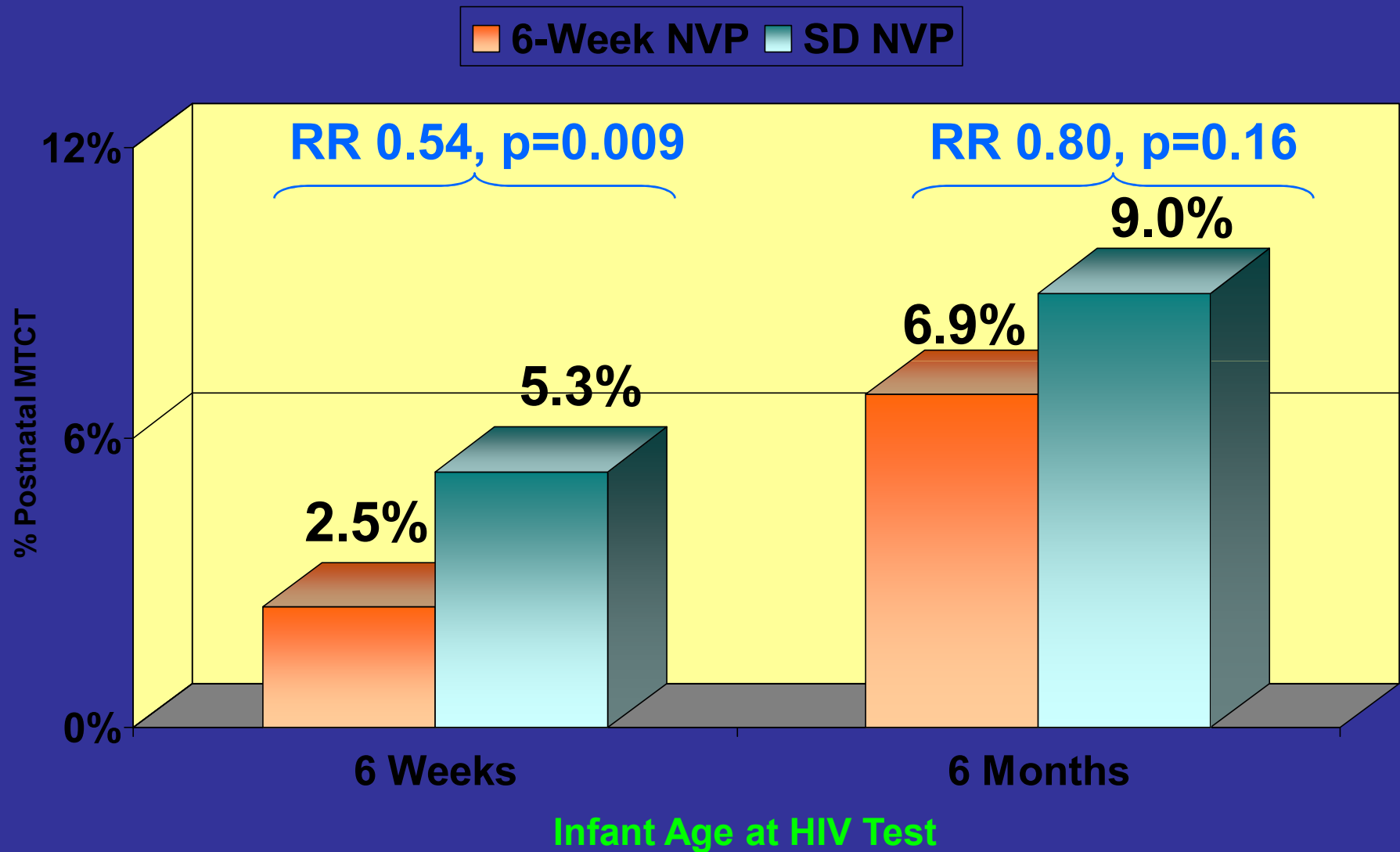
Infant:
Multivitamin “placebo” 0.5 mL
BID from Day 8 to 42

Arm 2
6-Week
NVP

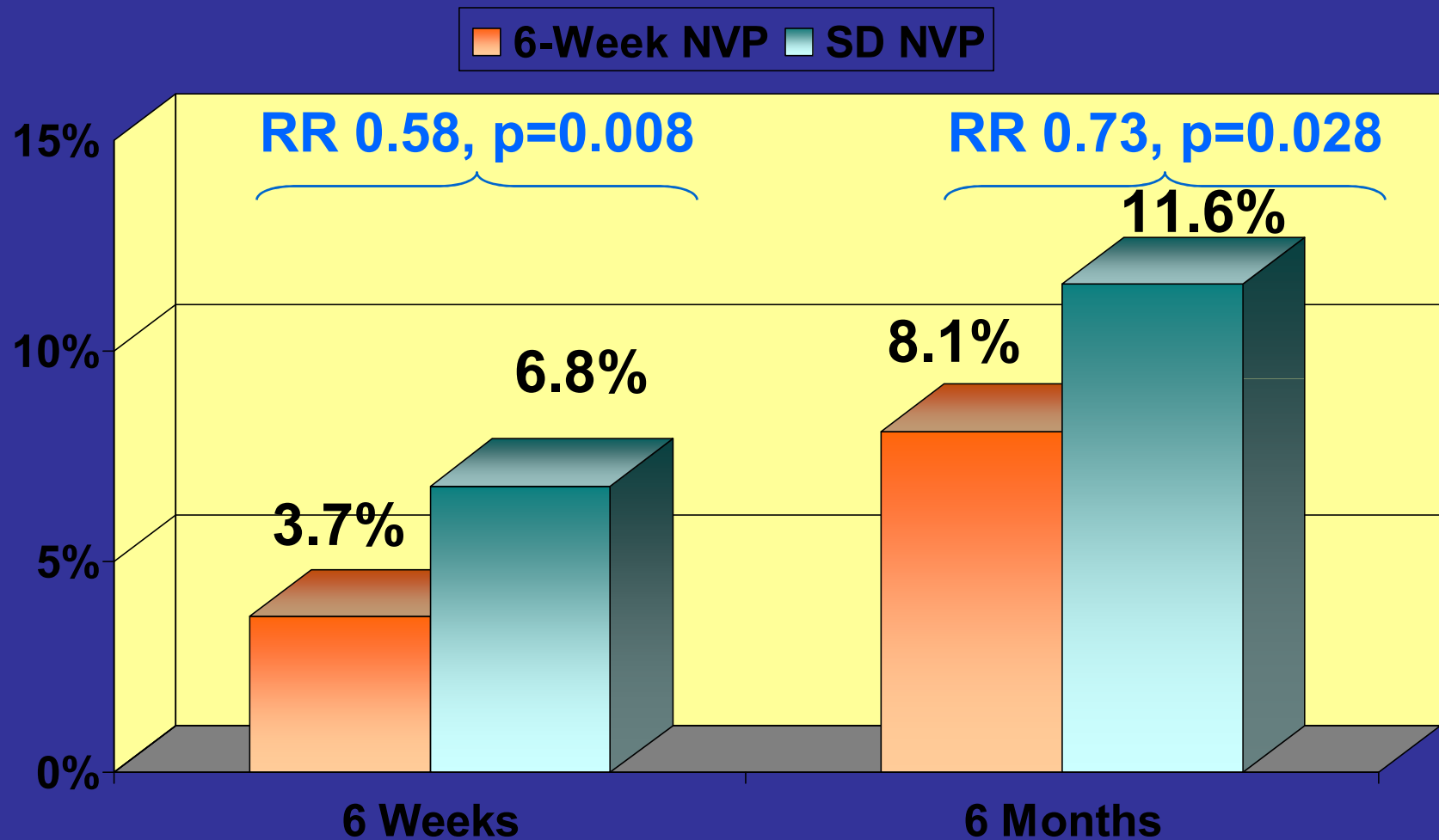


Infant:
NVP 0.5 mL QD +
Multivitamin 1 mL QD
from Day 8 to 42

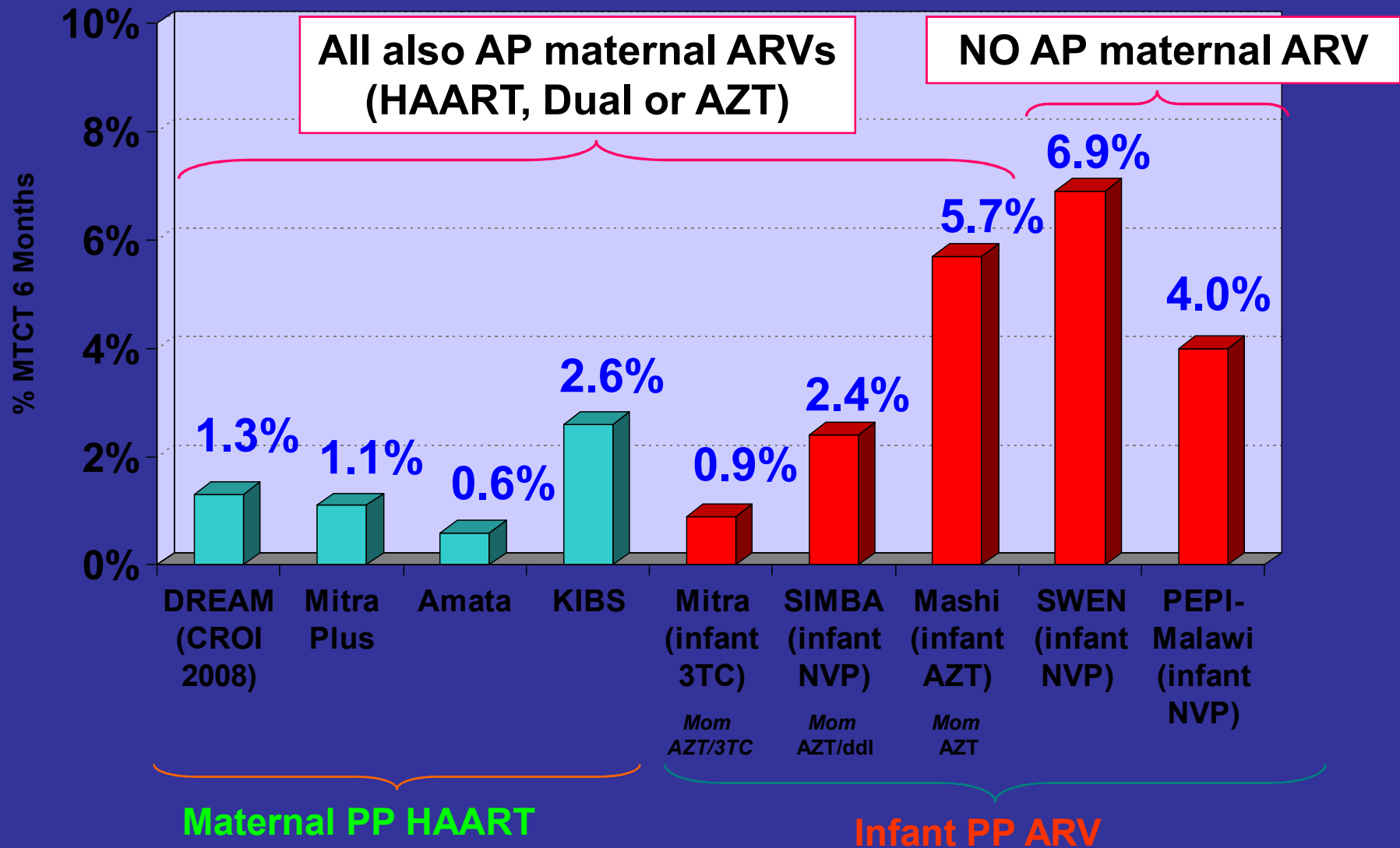
SWEN: 6-Week NVP Decreases Postnatal HIV MTCT at Age 6 Wks but No Longer Significant at 6 Mos



SWEN:6-Week NVP Reduces Risk of HIV Infection or Death at 6 Wks and 6 Mos

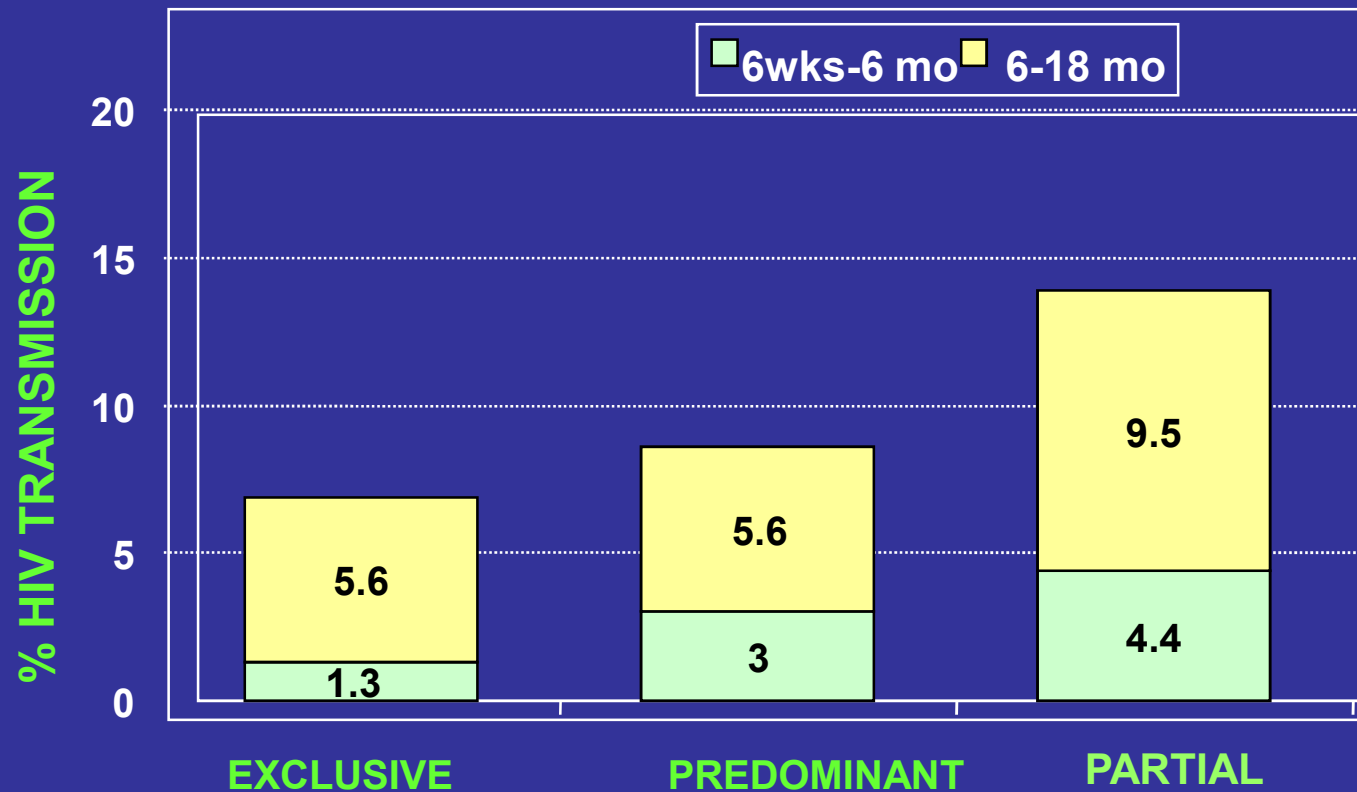


ARV Prophylaxis: Birth - 6 Month HIV Transmission Rates (uninfected at birth)

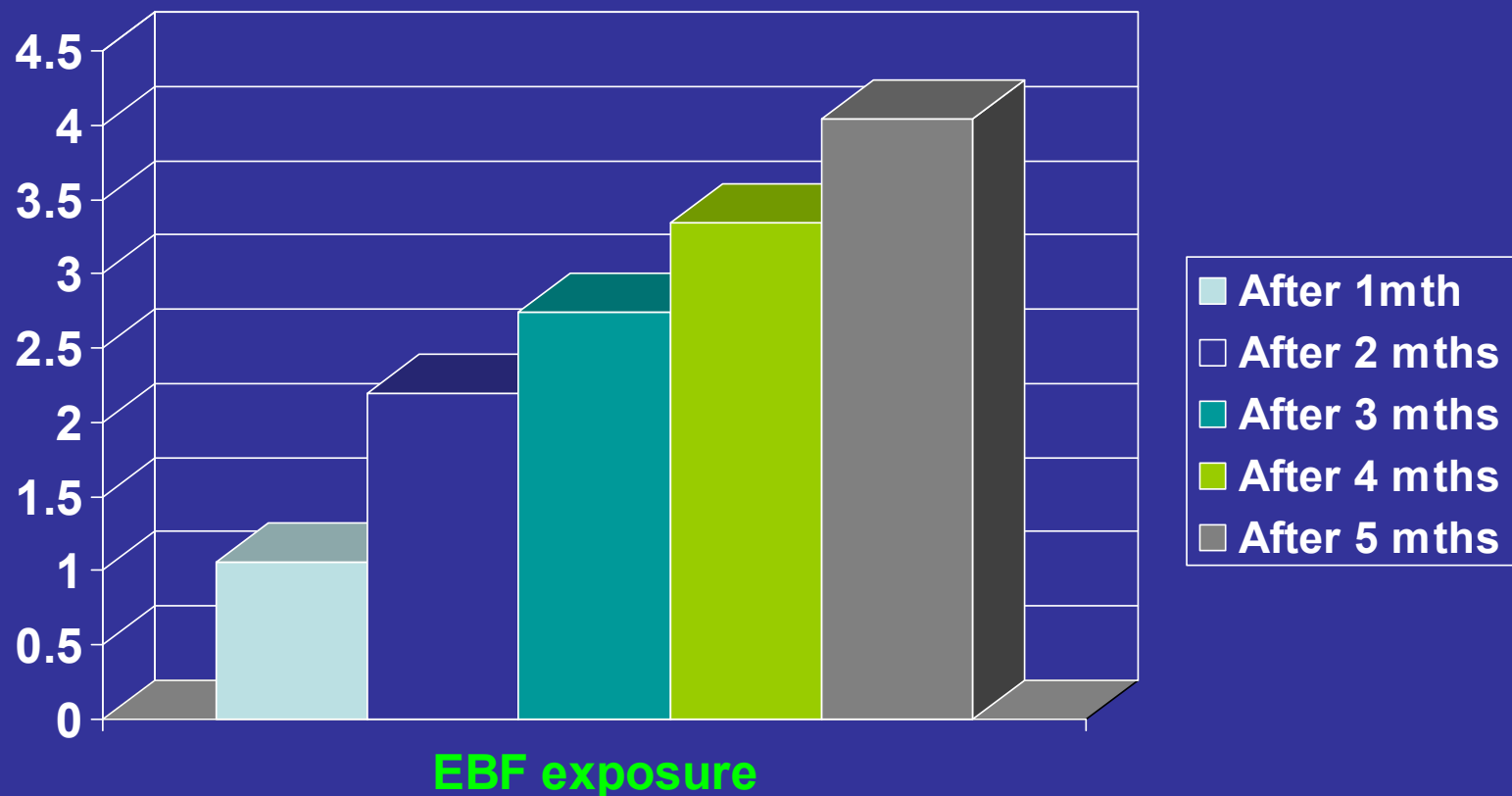


2. EXCLUSIVE BREASTFEEDING

CUMULATIVE RISK OF POSTNATAL HIV TRANSMISSION RATE BY EARLY FEEDING PATTERN & AGE



ESTIMATED KAPLAN-MEIER CUMULATIVE HIV TRANSMISSION RISK. VTS



Estimated risk per 100 child years of EBF exposure = 10.72

**0.89 per month EBF exposure

**MIXED- BREASTFEEDING IS ASSOCIATED
WITH A HIGHER RISK OF HIV
TRANSMISSION THAN EXCLUSIVE-
BREASTFEEDING. VTS**

Breastfeeding Type

Hazard Ratio

Exclusive Breastfeeding:

1.00

Breastmilk + Solids:

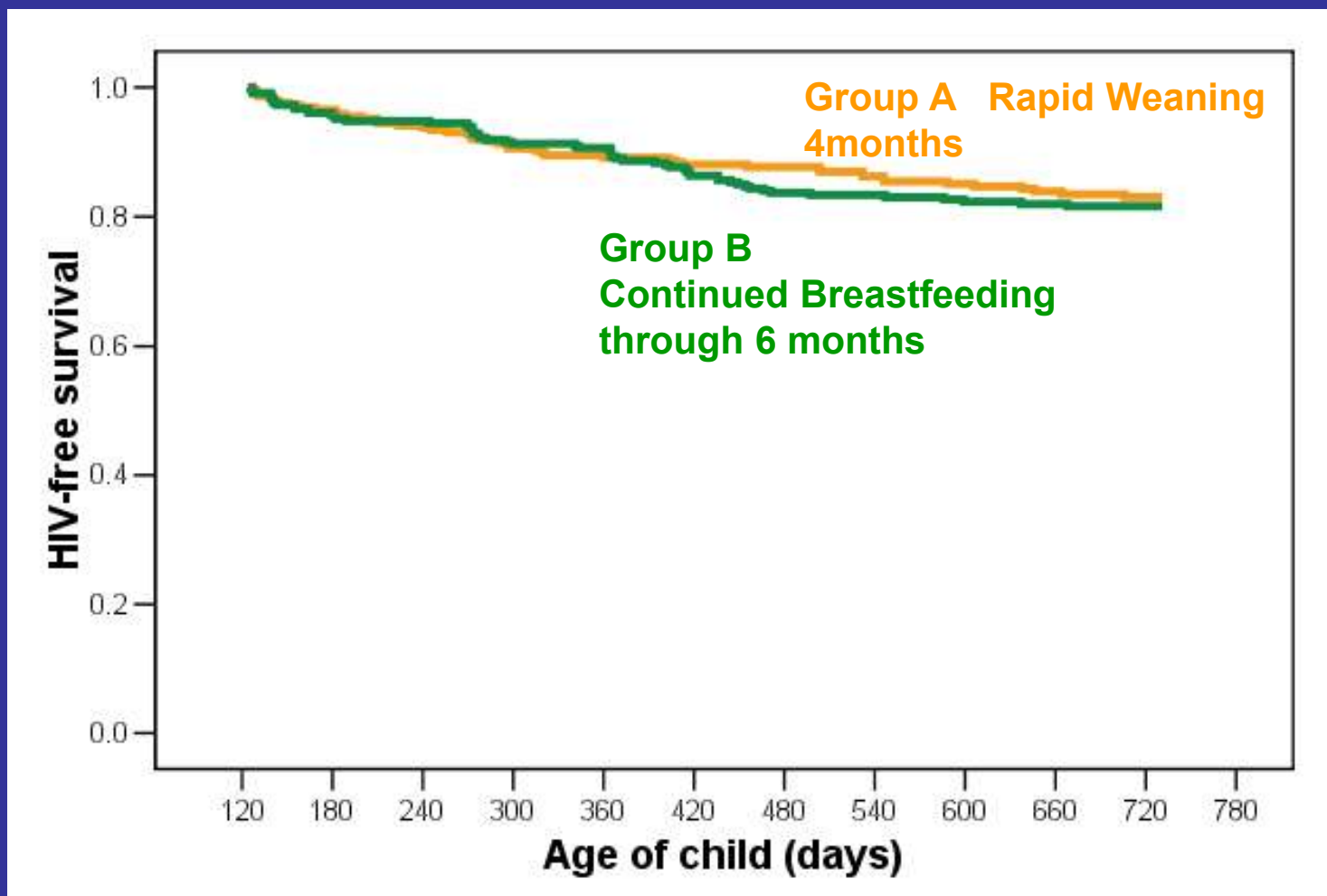
10.84*

Breastmilk + Formula :

1.80

IS THERE BENEFIT TO EARLY BREASTFEEDING CESSATION[GR.A] vs CTD BREASTFEEDING[GR.B]

ZAMBIA



Duration and Pattern of Breastfeeding and Postnatal Transmission

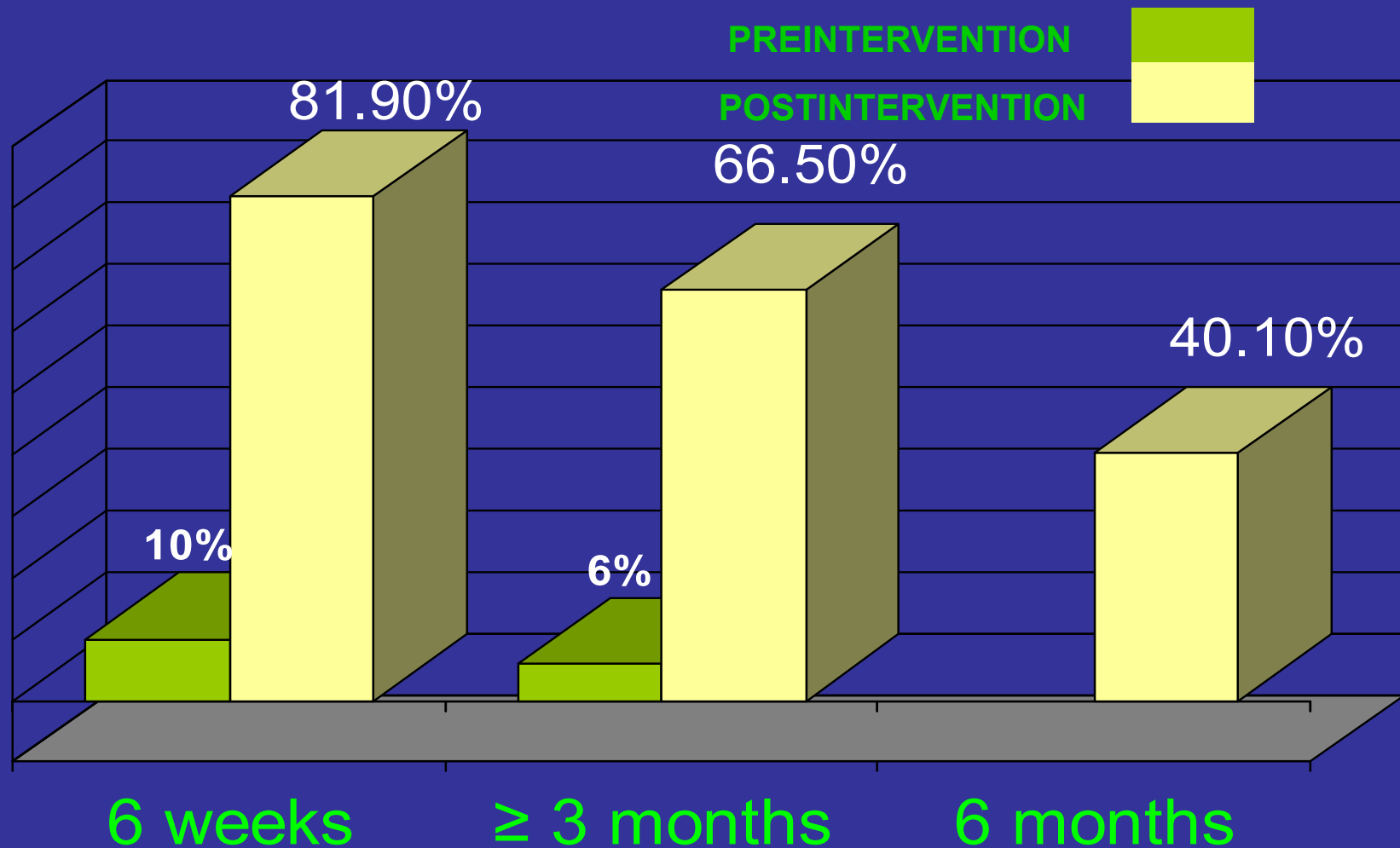
WEST AFRICA, COTE D'IVOIRE

SOUTH AFRICA, KWAZULU/NATAL

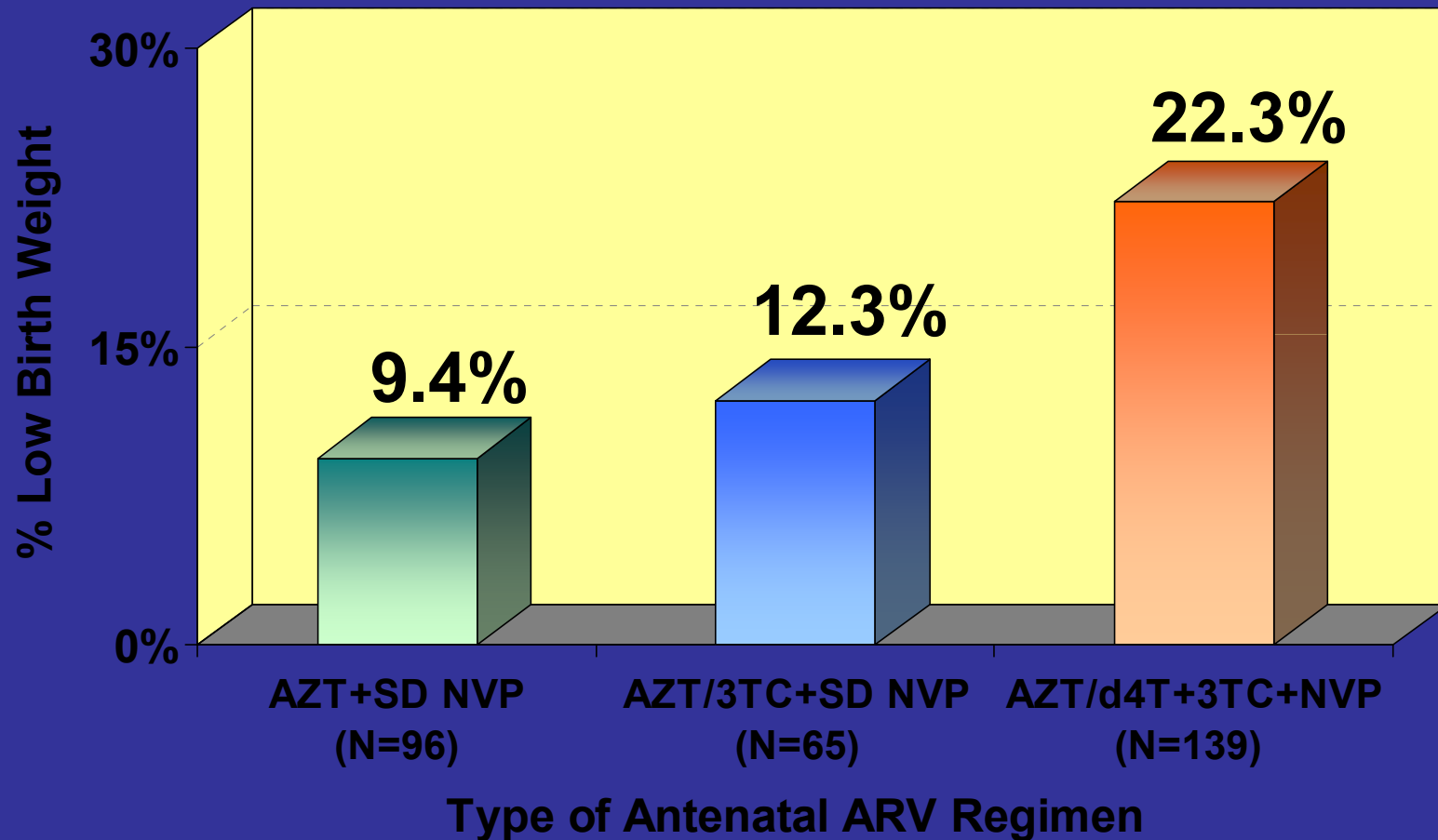
- Overall 18 month postnatal transmission was higher in S. Africa study (longer BF):
 - 5% (CI 3-8%) W. Africa vs 9% (CI 7-11%) S. Africa, $p=0.03$.
- BF duration was major determinant of MTCT - 18 month postnatal transmission by duration:
 - Longer duration associated with 2.1-fold (CI 1.2-3.7) increased hazard postnatal MTCT.

CAN WE CHANGE BREASTFEEDING BEHAVIOUR?

DURATION OF EXCLUSIVE BREASTFEEDING



Low Birth Weight and ARV Regimen Used During Pregnancy: Cote d'Ivoire



PROMISE General Overview: Sequential Randomized 2x2 Factorial Trial

Women with CD4 >350

Maternal Health

AP 28-term

IP

PP for Duration BF

After Weaning

Infant uninfected at birth

