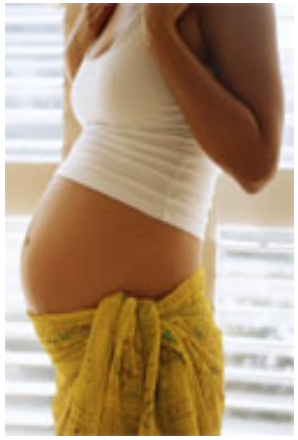
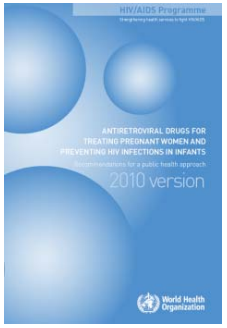


Clinical Trial Data and Transmission Data Supporting WHO 2010 Prevention of Mother-to-Child HIV Transmission Guidelines

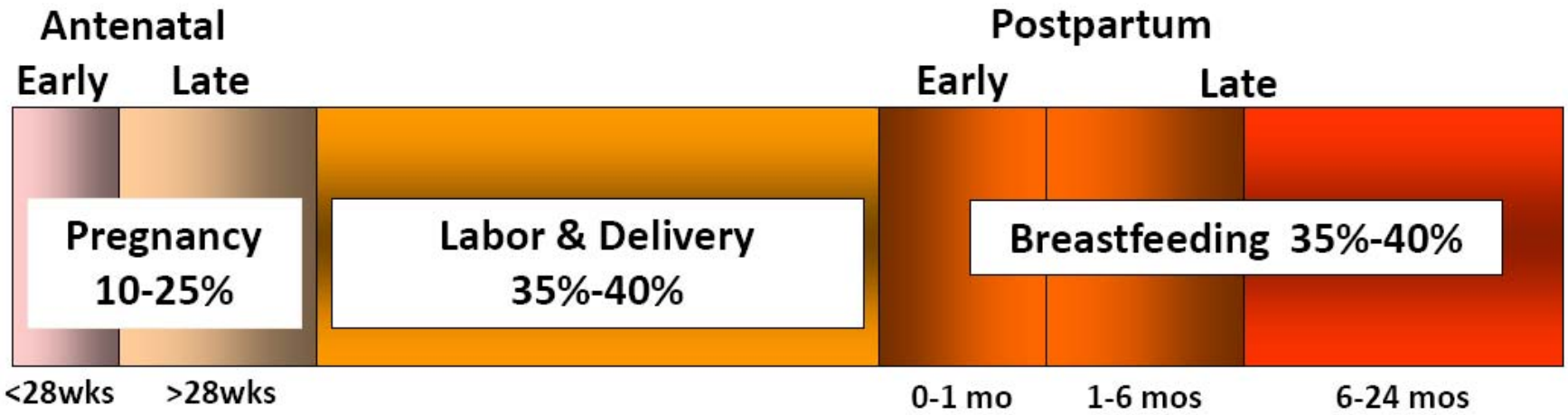
Lynne M. Mofenson, M.D.
Pediatric, Adolescent and Maternal AIDS Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Department of Health and Human Services



2010 WHO Antiretroviral Drugs Use for Treating Pregnant Women and Prevention MTCT

Two Key Approaches for PMTCT

BREASTFEEDING POPULATION



Maternal Lifelong ARV Treatment (ART)

Time-Limited Provision of ARV Prophylaxis

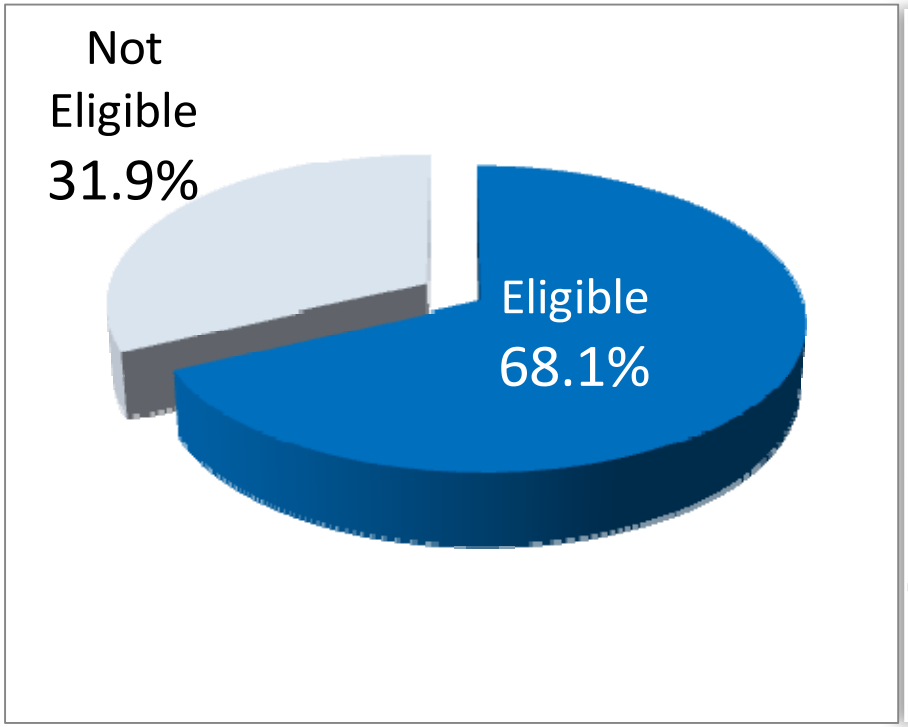
World Health Organization

2010 WHO CD4 and Clinical Criteria for Lifelong ART: Women Who Require Treatment

WHO Clinical Stage	CD4 <350 cells/uL	CD4 ≥350 cells/uL
Stage I	ART	ARV prophylaxis
Stage 2	ART	ARV prophylaxis
Stage 3	ART	ART
Stage 4	ART	ART

Women Eligible for ART Are At Highest Risk for Mother to Child HIV Transmission and Mortality

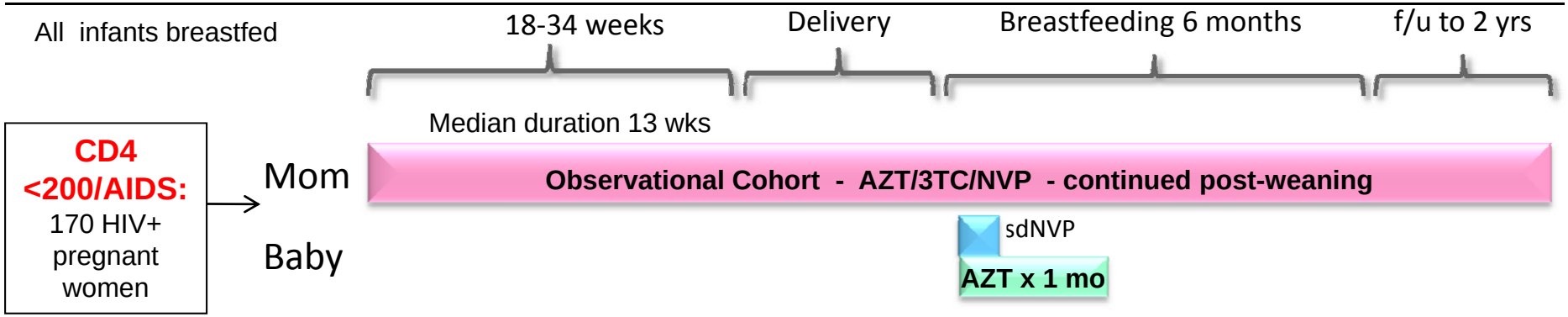
Kuhn L et al. AIDS 2010;24:1374-7



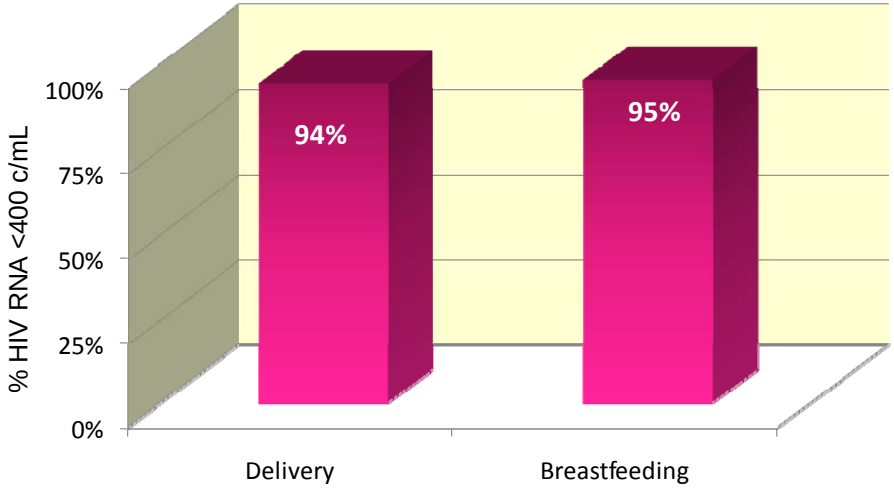
	Eligible for ART	Not eligible for ART
MTCT by 6 wk	16.7%	5.0%
Proportion of MTCT by 6 wks	87.5%	12.5%
MTCT after 6 wks	17.0%	4.2%
Proportion of MTCT after 6 wks	87.5%	12.5%
Maternal mortality 24 mo post delivery	92%	8%

- Cohort pregnant women in Zambia prior to HAART availability
- Analyzed MTCT/mortality by eligibility for ART with current WHO criteria (CD4 <350 or WHO Stage 3 or 4)

HAART is Effective in Reducing Transmission in Sick Women
Mma Bana: Observational Cohort with CD4 <200
Shapiro R et al. NEJM 2010;362:2282-94



Viral suppression

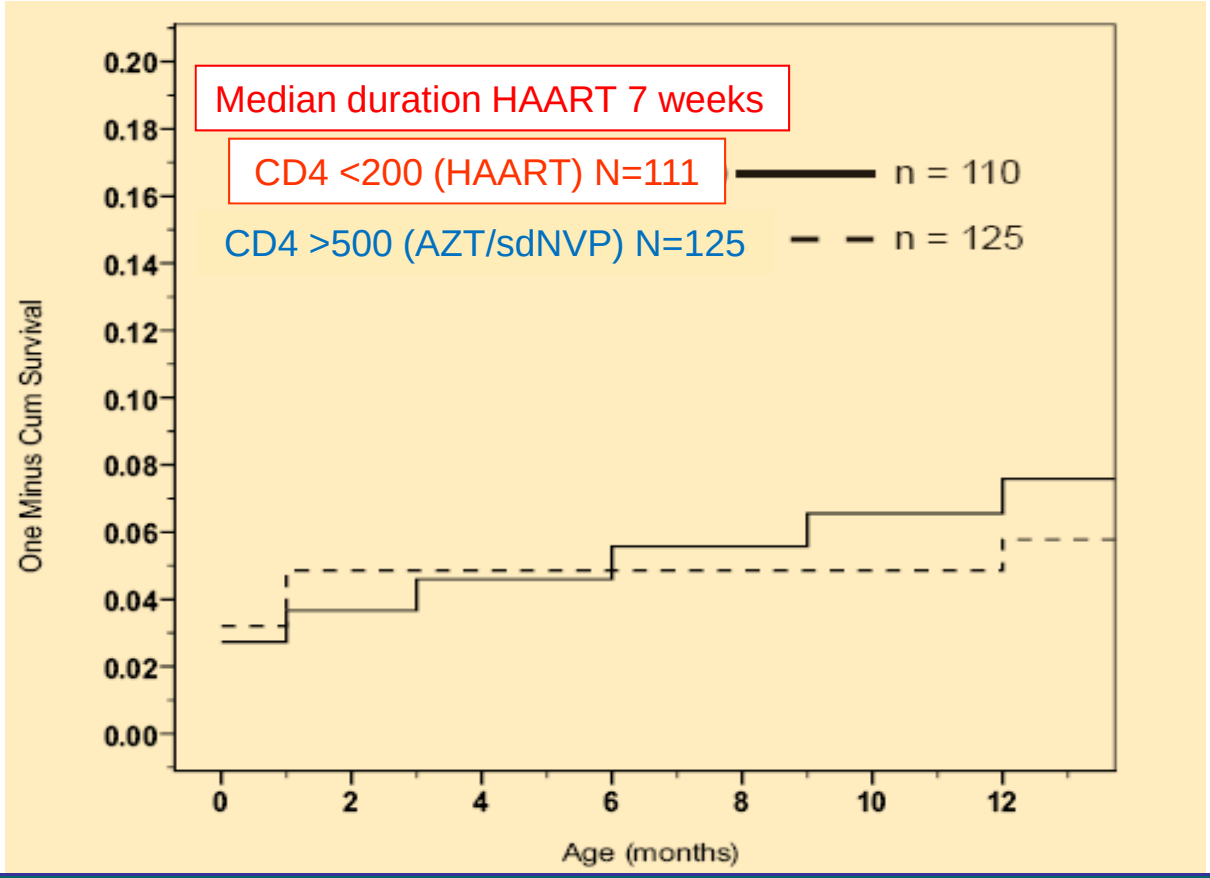


Transmission at 6 months

Infections among live-born infants, by maternal arm	Obs Arm (AZT/3TC/NVP) N=156
In utero	1 (0.6%)
Intrapartum	0
Breastfeeding	0
Total at 6 months	1 (0.6%)

Kesho Bora: HIV Infection in Observational Cohorts (CD4 <200 on HAART (infant sdNVP) &>500 on AZT/sdNVP)

Kesho Bora Study Group. JAIDS. 2010 Aug 15;54(5):533-41



Maternal CD4	MTCT at birth	MTCT at 6 wks	MTCT at 6 mos	MTCT at 12 mos
<200 (HAART)	1.8%	3.7% (peripartum 1.9%)	5.6% (postnatal 1.9%)	7.5% (late postnatal tx 1.9%)
>500 (Short course)	1.6%	4.9% (peripartum 3.3%)	4.9% (postnatal 0%)	5.8% (late postnatal tx 0.9%)

Kisumu Breastfeeding Study:
Maternal Triple ARV for Treatment or Prophylaxis (infant sdNVP)
Cumulative MTCT through 12 Months Overall & by CD4 Category

Thomas T et al. 15th CROI, Boston, MA Abs 45aLB

	Age at HIV Test				
	0-7 Day	6 Wks	3 Mos	6 Mos	12 Mos
Overall MTCT	2.4%	3.9%	4.1%	5.0%	5.9%
Postnatal Tx		+1.5%	+0.2%	+0.9%	+0.9%
CD4 count:					
CD4 <250	3.4%	4.3%	5.2%	5.2%	6.7%
CD4 >250	2.1%	3.8%	3.8%	4.9%	5.5%

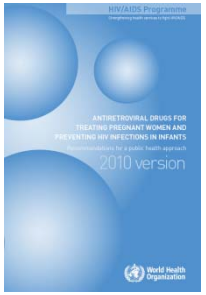
Impact HAART and Duration of Therapy on MTCT in 1,115 Pregnant Women, Johannesburg, South Africa

Hoffman R et al. IAS, Capetown, South Africa, July 2009, Abs. WePEB260

Group	% MTCT
Overall group women all on HAART (1,115) (no sig. difference NVP vs LPV/r vs EFV regimen)	4.7%
On HAART when became pregnant (median duration 93.4 weeks by delivery)	0.7%
Started HAART during pregnancy (median duration 10.7 weeks by delivery)	5.7%
Duration of HAART during pregnancy:	
Up to 4 weeks (N=137)	9.3%
Up to 12 weeks (N=450)	7.4%
Up to 28 weeks (N=661)	5.8%

p= 0.012

In women starting HAART during pregnancy, each additional week of HAART reduced odds of transmission by 8% (OR 0.92, 95% CI 0.87-0.98)



Maternal Treatment: When to Start and Recommended ART Regimens

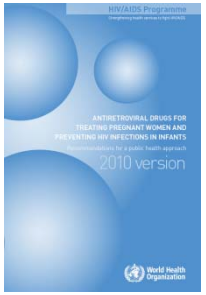
Maternal Treatment

- Start ART *as soon as possible* for women with CD4 < 350 or WHO Clinical Stage 3 or 4
- Initiate ART at any gestational age

REGIMENS

Preferred Regimen	Alternative Regimen
AZT + 3TC + NVP	TDF + 3TC(FTC) + NVP
AZT + 3TC + EFV*	TDF + 3TC(FTC) + EFV*

*EFV to be avoided in 1st trimester



Recommended Infant Prophylaxis Regimens For Infants of Eligible Women on ART

Infant ARV Prophylaxis

For breast feeding or formula feeding infants

Once daily NVP

or

Twice daily AZT from birth

until 4-6 weeks of age

Six Week Extended Nevirapine (SWEN) Study

Contribution of 6 Weeks NVP in Breastfeeding Population

Lancet 2008 Jul 26;372(9635):300-13

	IP	Birth-72hr	Day 8 to 42
Arm 1 SD NVP	NVP x1	Infant NVP x1	Infant: Multivitamin 0.5 mL placebo BID from Day 8 to 42
Arm 2 6 week NVP	NVP x1	Infant NVP x1	Infant: NVP 0.5 mL QD + Multivitamin 1 mL QD from Day 8 to 42

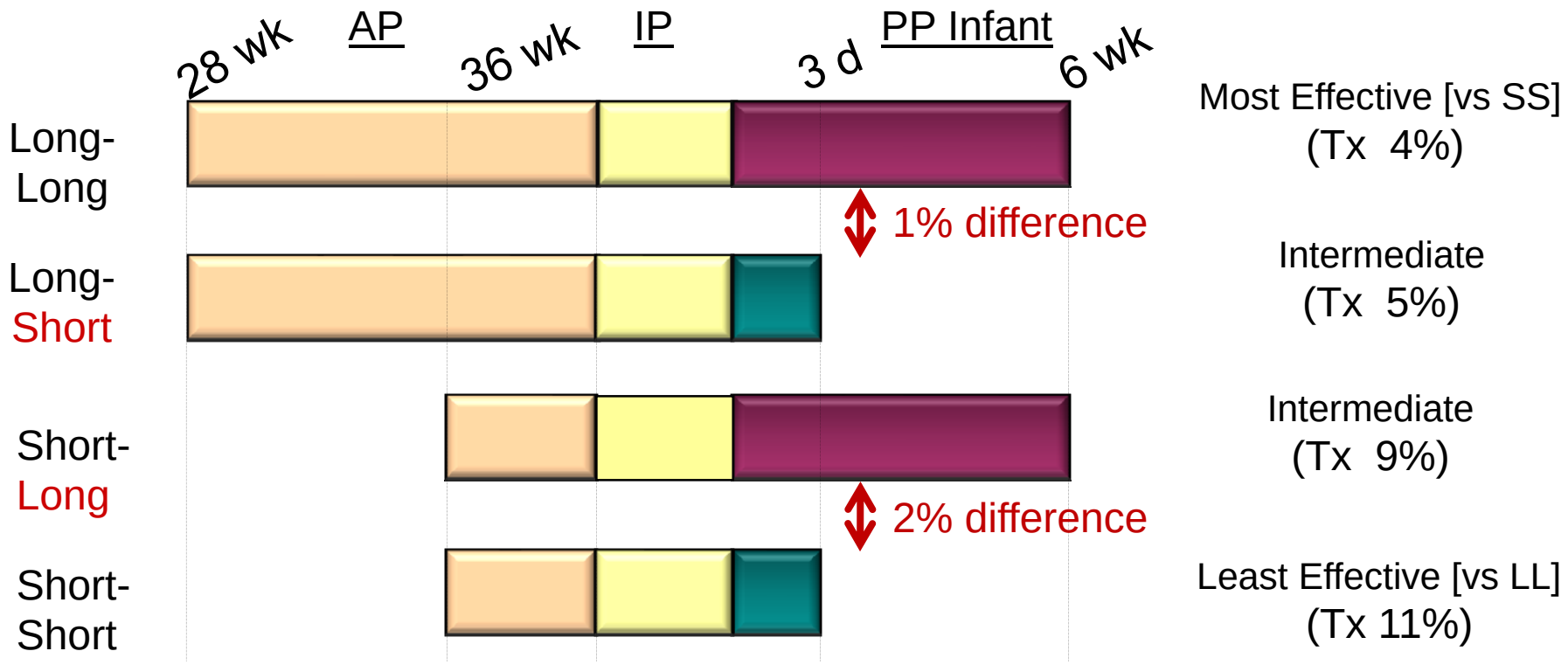
		SD NVP	6-wk NVP	RR
Postnatal	6 weeks	5.3%	2.5%	0.54 (p=0.009)

In breastfed population, 6 weeks infant NVP reduces postnatal MTCT by ~2.8% vs sdNVP (in absence of maternal HAART)

PHPT-1: Contribution of 6 Weeks of Infant AZT

Lallemant M et al. N Engl J Med 2000;343:982-91

Thailand, Formula-Feeding Population



In formula-fed population, 6 weeks infant AZT reduces postnatal MTCT by ~1-2% vs 3 days AZT (in absence of maternal HAART)

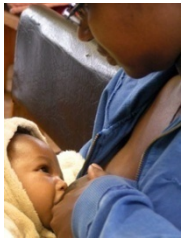
Comments on Group of Women Who Need Treatment for Own Health

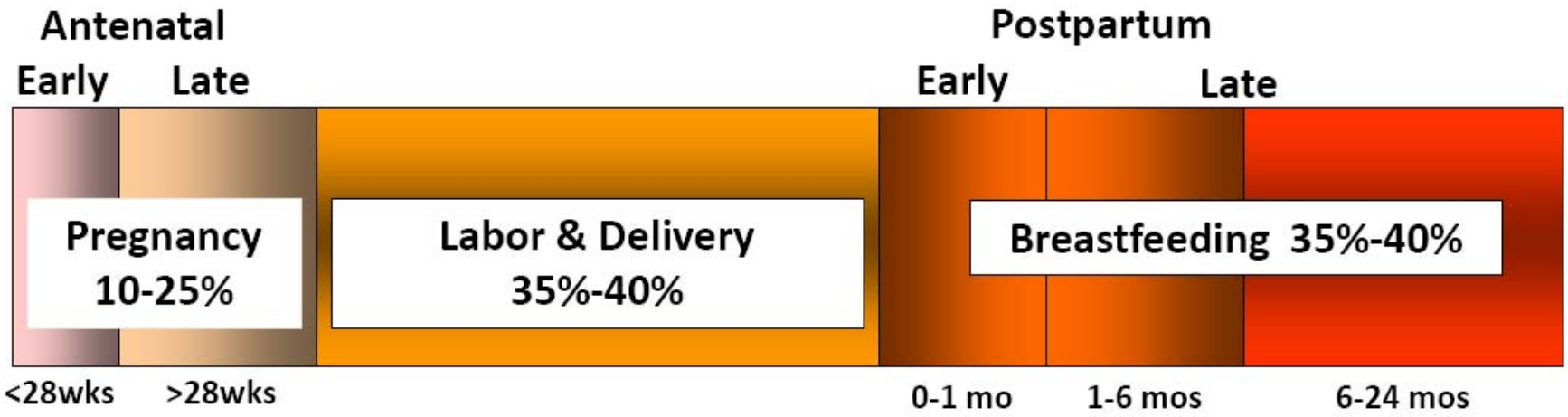
- Women who meet WHO criteria are highest risk group for MTCT – biggest impact on MTCT here.
- Treatment with HAART may reduce overall transmission to 1-5% at 6 months (depending on study).
- Extent of reduction partly depends on duration of AP HAART.
- Contribution of infant NVP or AZT in presence of maternal HAART not studied, but in absence of maternal HAART, it appears to give absolute reduction of 1-3% in MTCT.
  - Of note, Mma Bana with lowest overall rate, gave sdNVP + 4 weeks AZT, while Kesho Bora and Kibs only gave sdNVP.

2010 WHO CD4 and Clinical Criteria for Women Who Would Receive PMTCT Antiretroviral Prophylaxis

WHO Clinical Stage	CD4 <350 cells/uL	CD4 ≥350 cells/uL
Stage I	ART	ARV prophylaxis
Stage 2	ART	ARV prophylaxis
Stage 3	ART	ART
Stage 4	ART	ART

2010 WHO Guidelines:
Two Options for PMTCT Prophylaxis if Breastfeeding





AZT + sdNVP (+ tail) | Daily Infant NVP

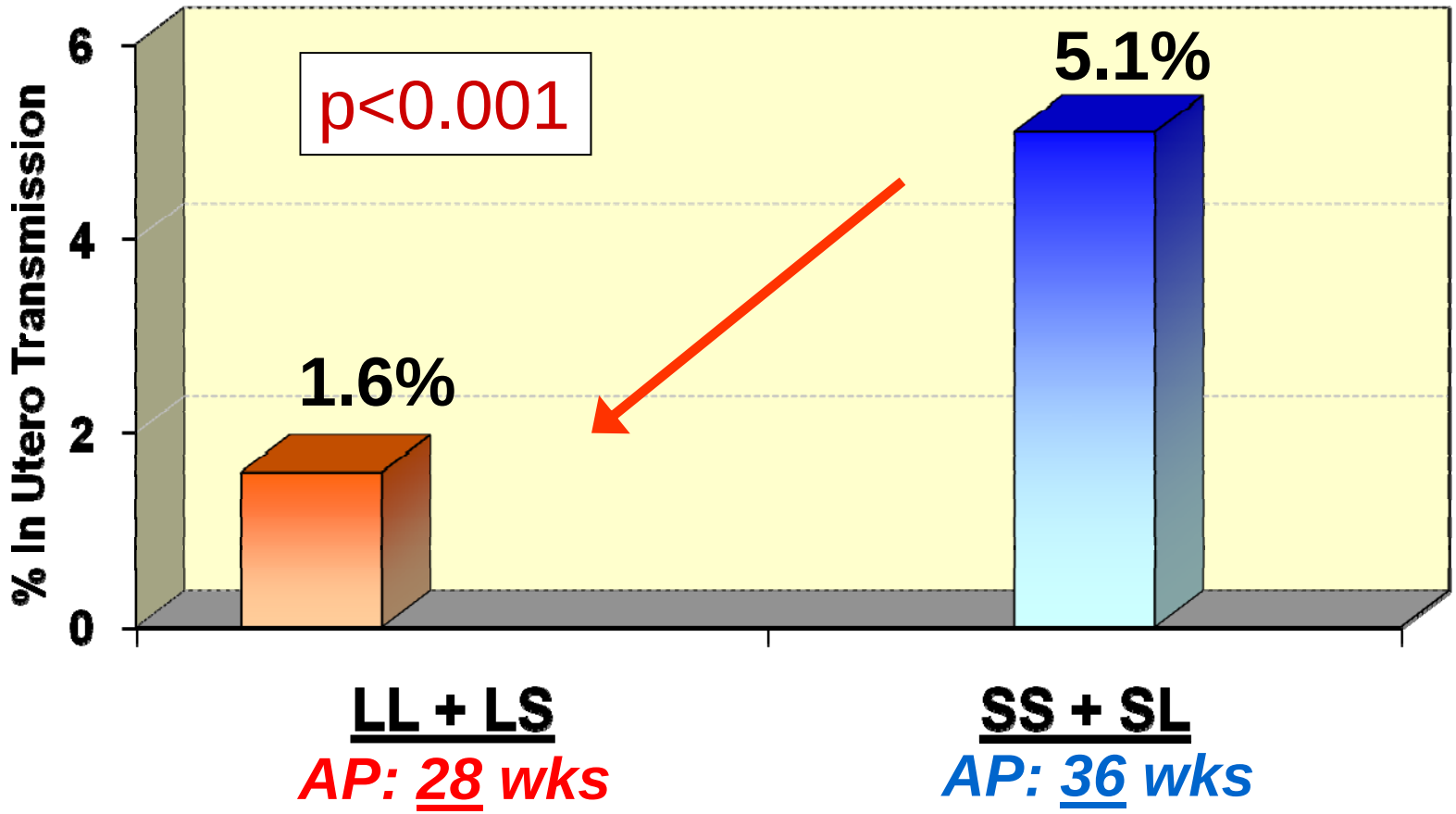
Maternal Triple Drug Prophylaxis

Why Two Options for PMTCT Prophylaxis?

- Both options offer antenatal/intrapartum/postpartum prophylaxis regimen demonstrated to decrease the risk of MTCT.
  - Linked maternal and infant regimens.
- No demonstrated superiority of one option over the other.
- Inherent risks and toxicities associated with each option.
- Takes into consideration other factors impacting effective PMTCT implementation:
  - feasibility, access, cost, equity, health system capacity, current approaches in country.

For Maximal Efficacy of Any Regimen, Need to Start Early in Pregnancy to Prevent *In Utero* Transmission

Lallemant M et al. N Engl J Med 2000;343:982-91



Even if intervention is 100% effective preventing IP/PP MTCT, still have "residual infection" of 1.6% if start at 28 weeks - Need to start earlier!

Option A: AZT/sdNVP + Infant Prophylaxis

Option A Prophylaxis Regimen for Pregnant HIV-Infected Women & Their Infants

Option A: AZT/sdNVP + Infant Prophylaxis (if breastfeeding)

MOTHER

- Start as early as 14 weeks gestation through 1 week postpartum

Antepartum	Intrapartum	Postpartum
Daily AZT from 14 wks	sd-NVP, AZT + 3TC*	AZT + 3TC for 7 days*

- If mother receives >4 wks antepartum AZT, consideration can be given to omitting sdNVP and 1 week AZT/3TC "tail"

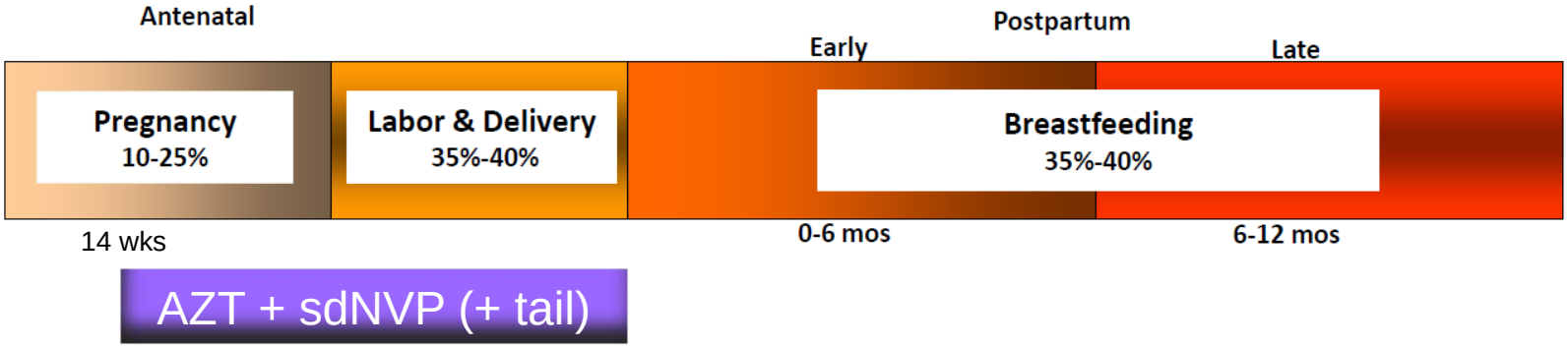
INFANT

Breastfeeding Infant

- Daily NVP until 1 week after all exposure to breast milk ceased (for a maximum of 12 months)

Non-Breastfeeding Infant

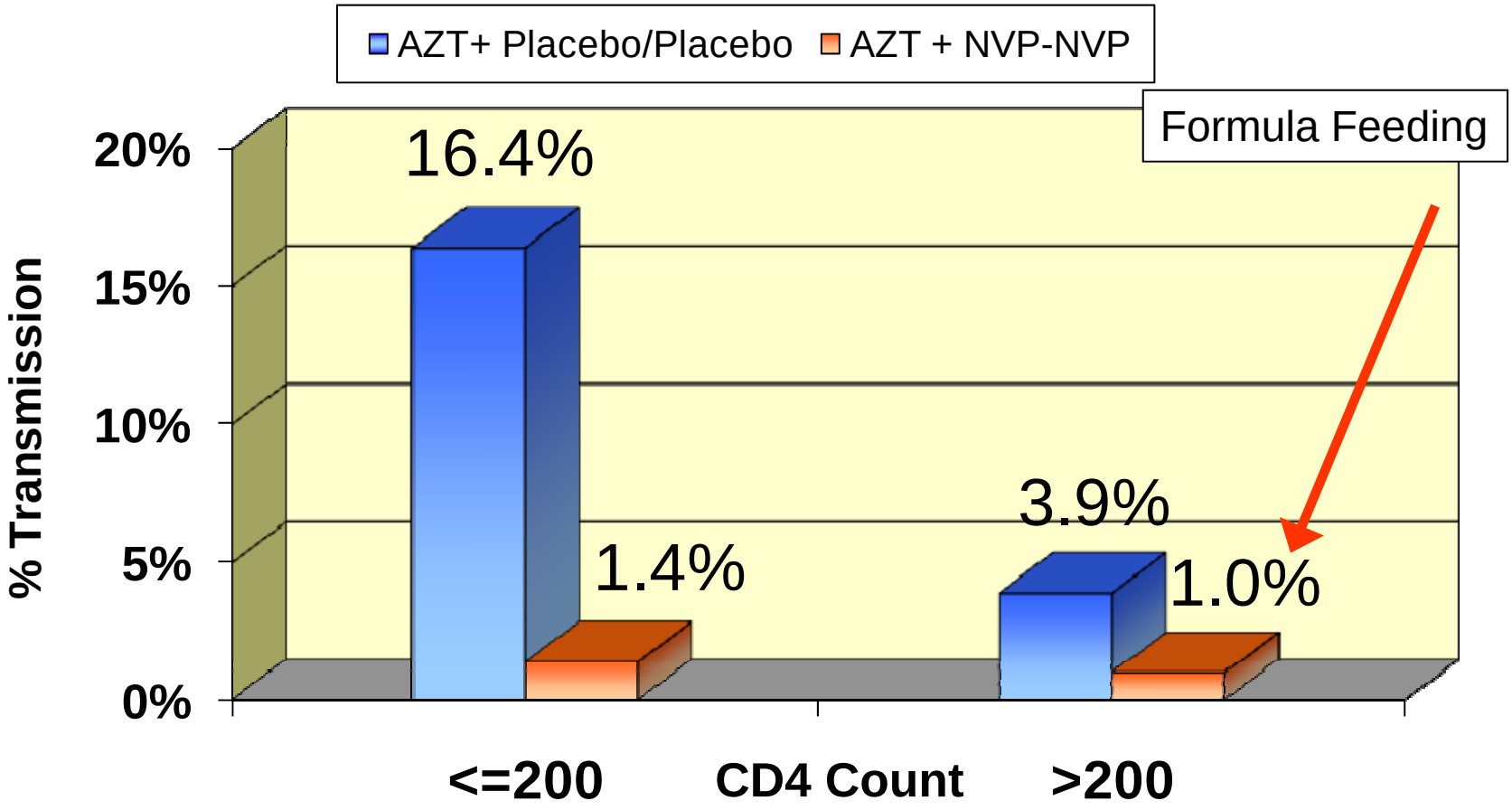
- Daily NVP or sdNVP + twice daily AZT for 4 to 6 weeks



Evidence for Efficacy of AZT/sdNVP vs Triple Drug Regimen to Prevent IU/IP Transmission in Women Not Requiring Treatment

AZT + sdNVP Results in MTCT Rates of 1% in Women with CD4 >200, Thailand

Lallemant M et al. NEJM 2004;351:217-28.



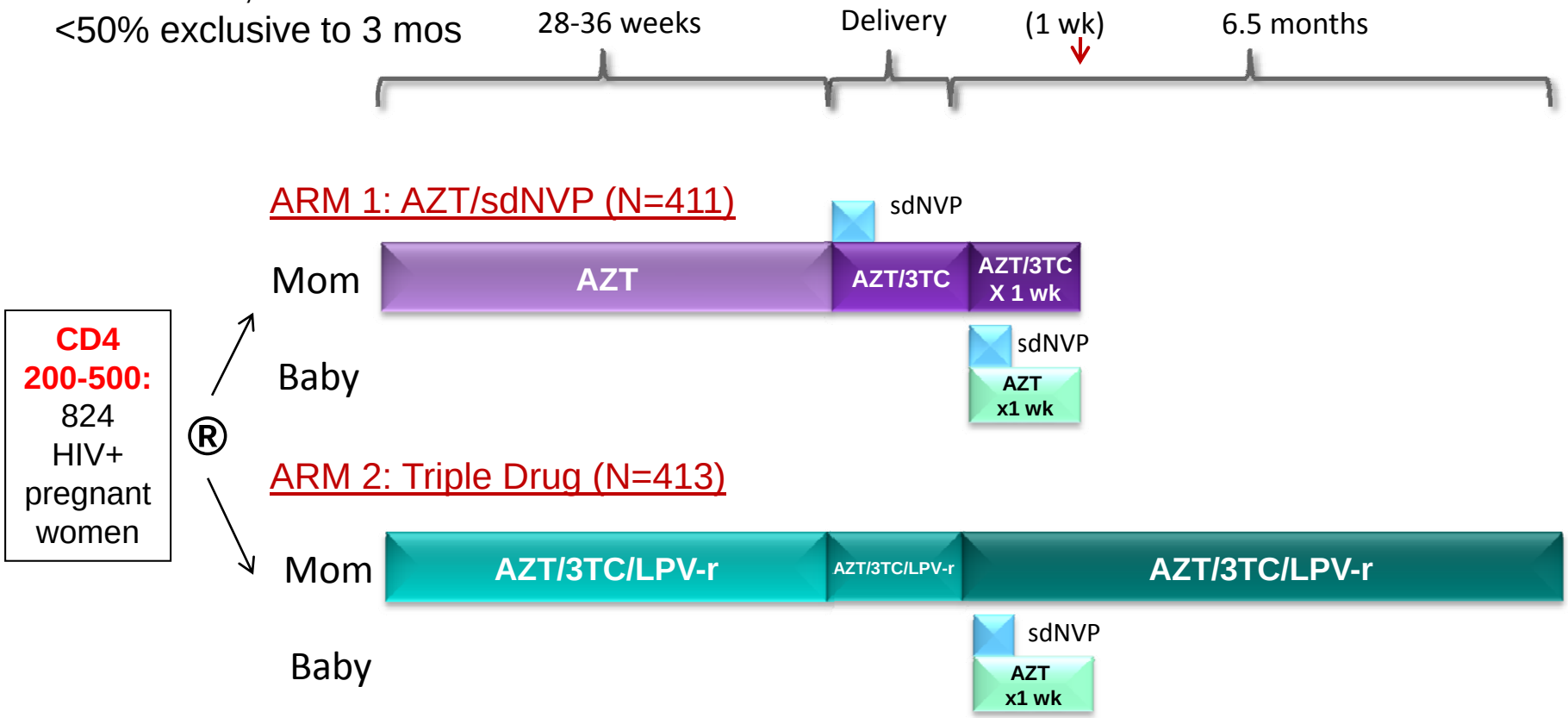
Comparing Difference in Transmission Rates Between AZT/Placebo-Placebo and AZT/NVP-NVP by CD4

Kesho Bora:

AZT/sdNVP (without Infant Prophylaxis) vs Maternal HAART

de Vincenzi I et al. IAS, Capetown, South Africa, July 2009, Abs. LB PE C01

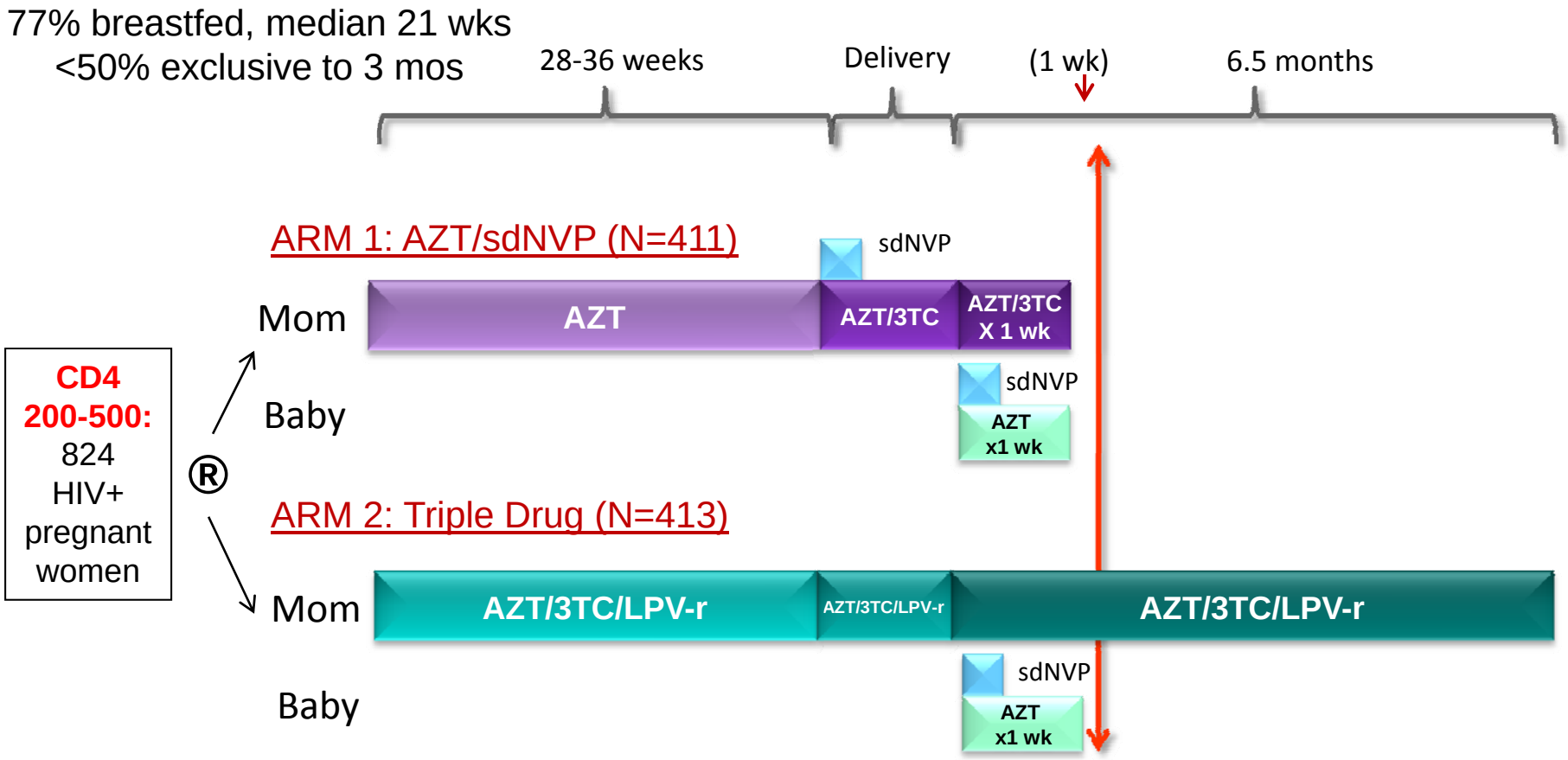
77% breastfed, median 21 wks
<50% exclusive to 3 mos



Kesho Bora: Question 1: Prevention of AP/IP Infection

de Vincenzi I et al. IAS, Capetown, South Africa, July 2009, Abs. LB PE C01

77% breastfed, median 21 wks
<50% exclusive to 3 mos

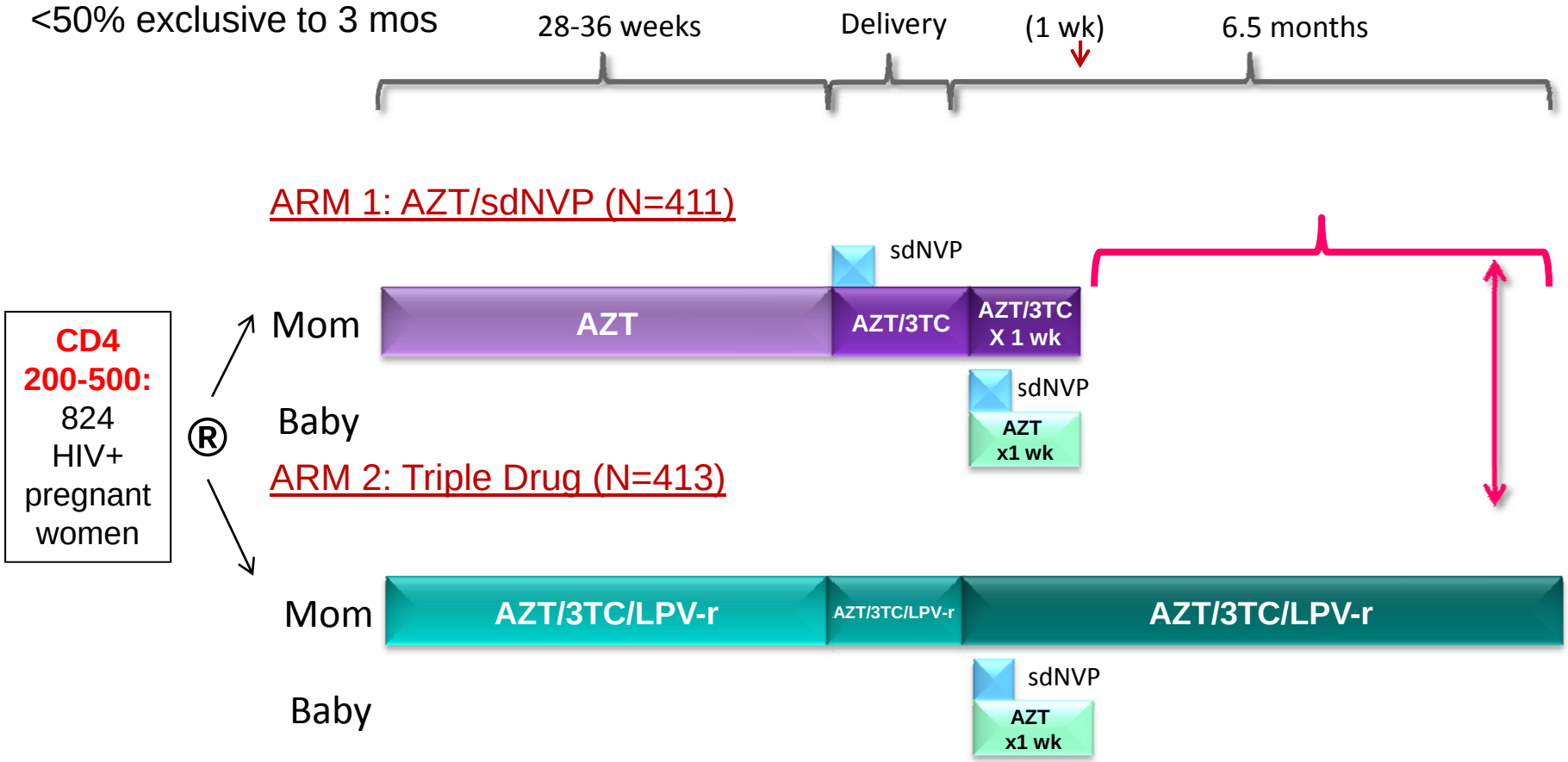


- Is administration of a maternal triple drug regimen during pregnancy and labor superior to AZT/sdNVP with AZT/3TC tail in preventing *in utero* transmission (*transmission rate around time birth-1 week*)?

Kesho Bora: Question 2: Prevention of Postnatal Infection

de Vincenzi I et al. IAS, Capetown, South Africa, July 2009, Abs. LB PE C01

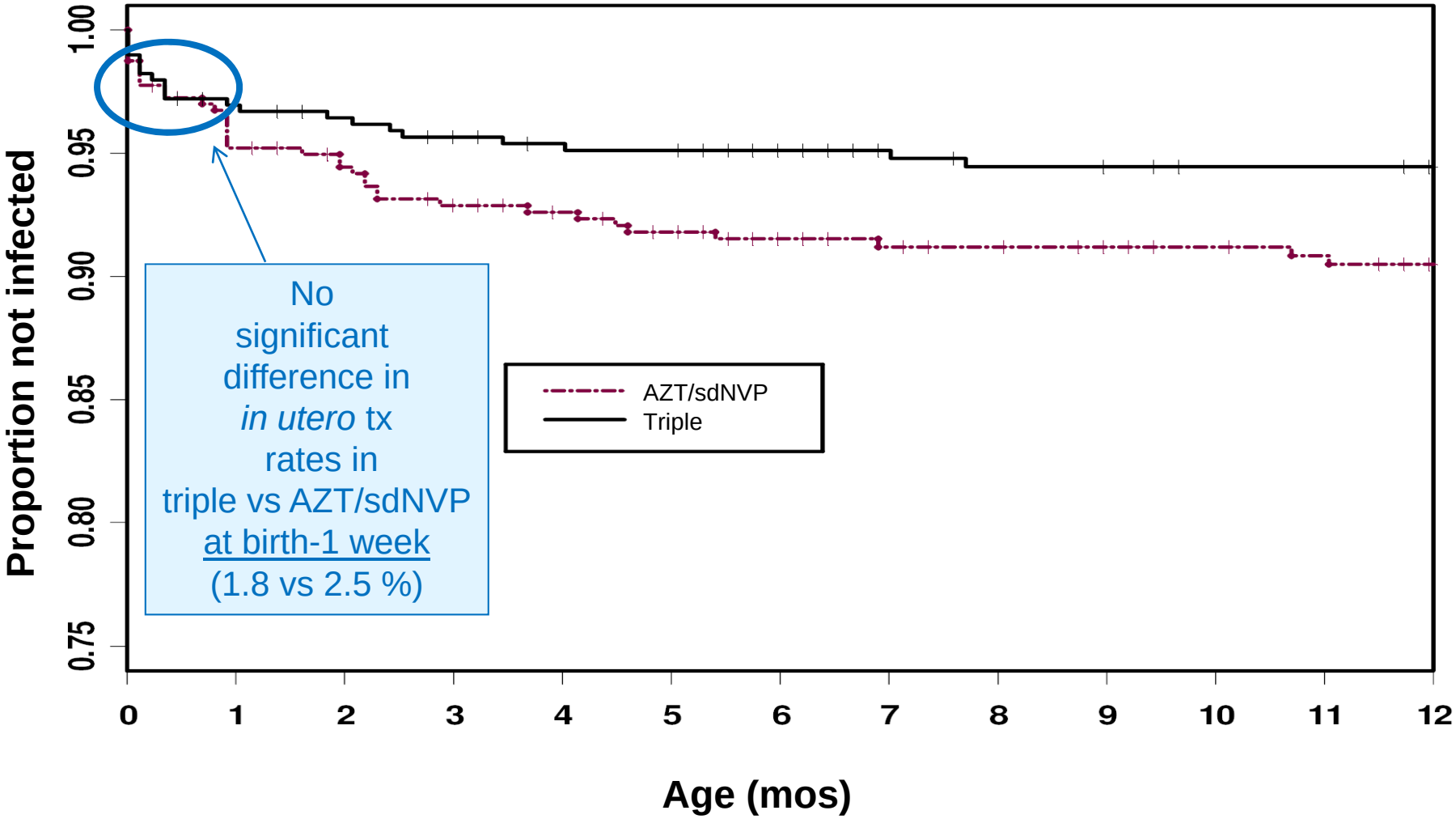
77% breastfed, median 21 wks
<50% exclusive to 3 mos



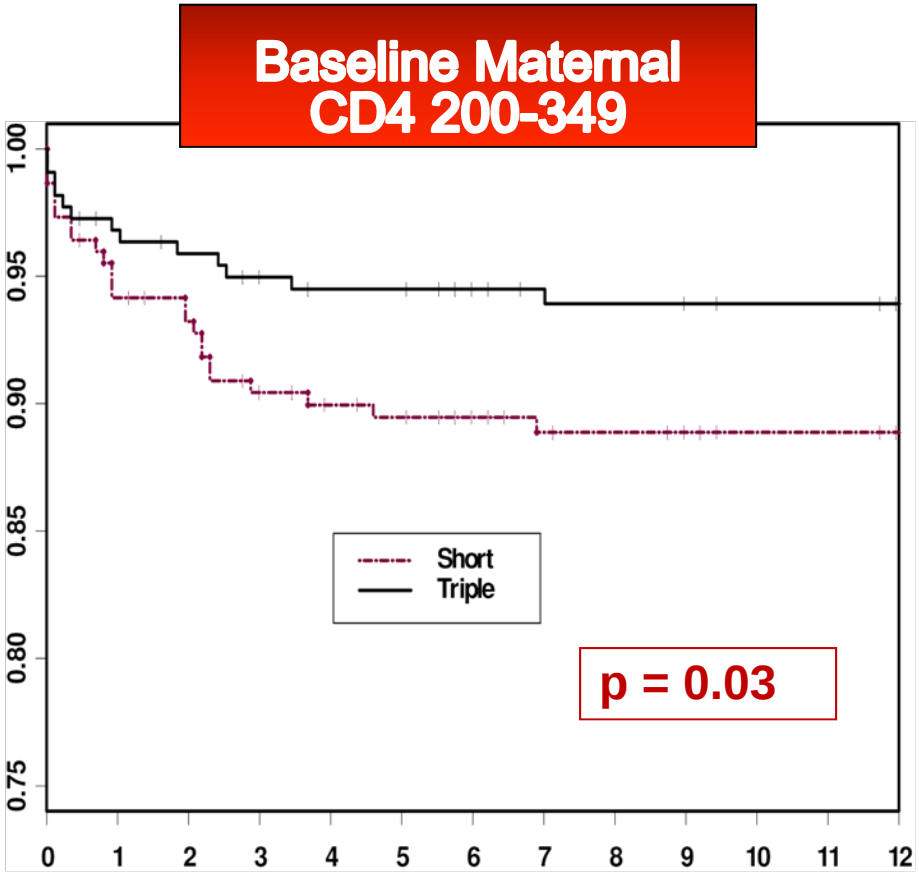
- Is administration of a maternal triple drug regimen during breastfeeding superior to sdNVP with AZT/3TC tail without extended prophylaxis for prevention of postnatal transmission *(transmission rate at 6 months)?*

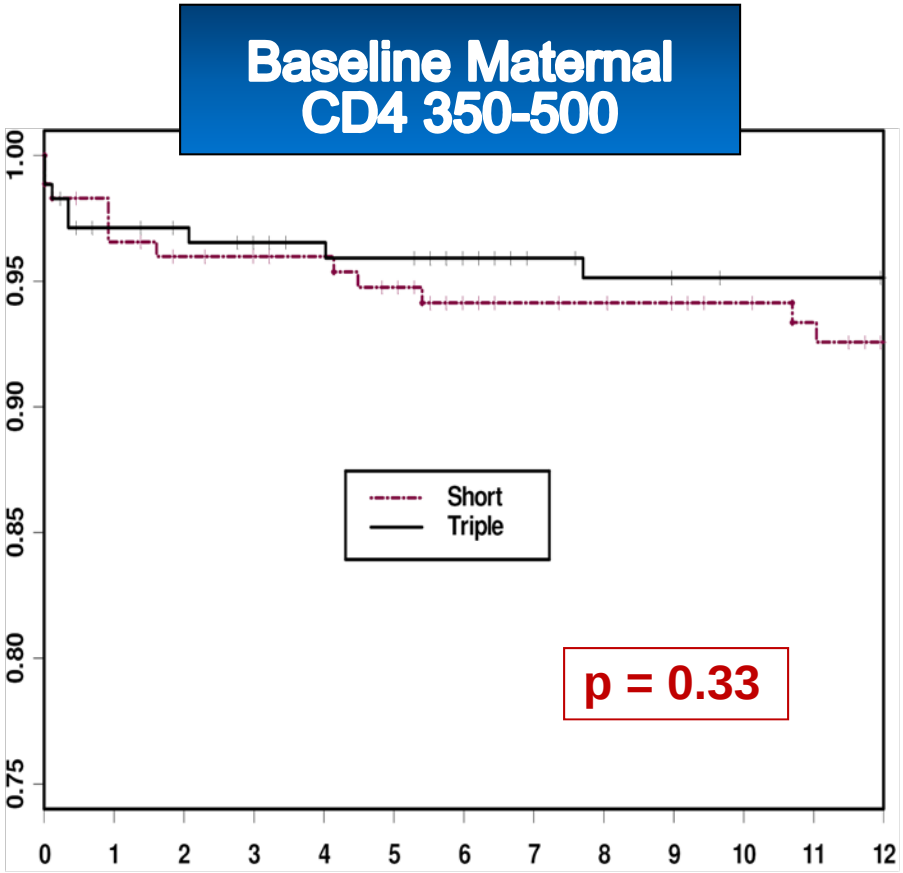
Kesho Bora: No Significant Difference in In Utero Infection with Antepartum/Intrapartum AZT/sdNVP vsTriple Drug Regimen

De Vincenzi I et al. IAS, Capetown, South Africa, July 2009 Ab LBPEC01



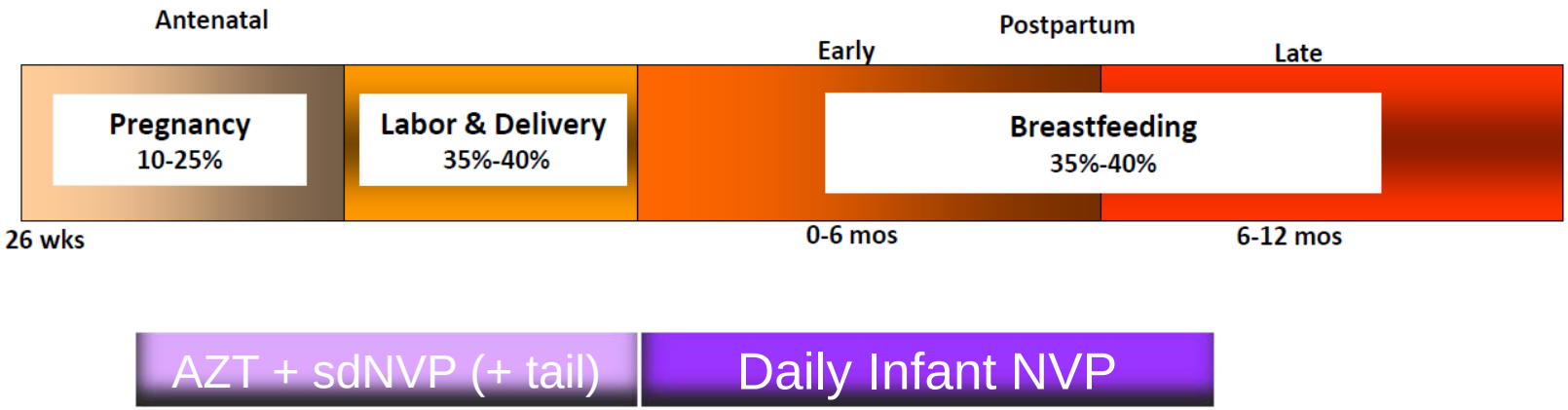
A Triple Drug Regimen through Breastfeeding was Superior to AZT/sdNVP (without Postnatal Prophylaxis) Only When Maternal CD4 200-350 but No Difference if CD4 350-500





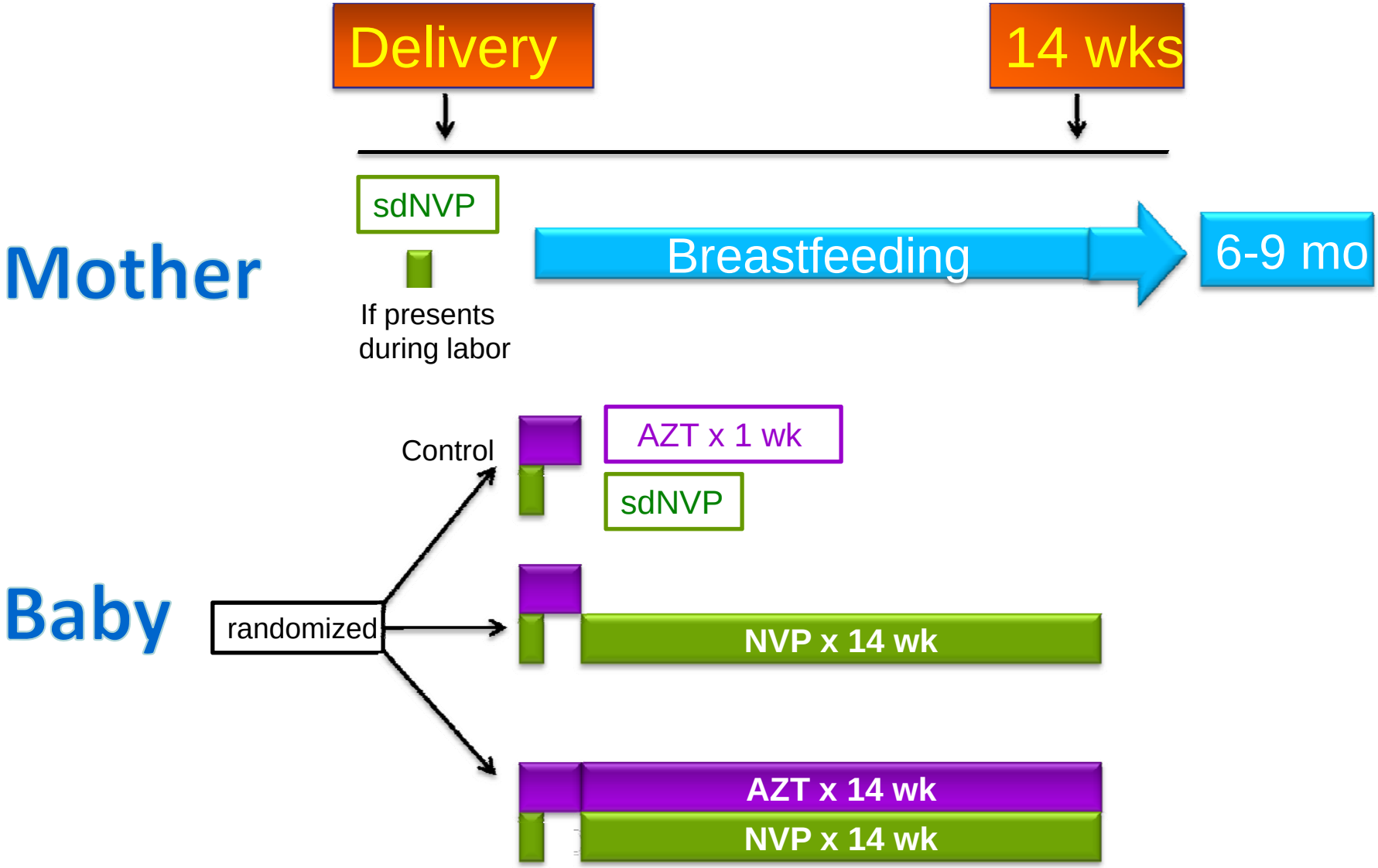
Cum HIV infection rate	Triple	AZT/sdNVP
Birth	1.8%	3.1%
6 mths	5.5%	10.5%
12 mths	6.0%	11.5%

Cum HIV infection rate	Triple	AZT/sdNVP
Birth	1.7%	1.7%
6 mths	4.1%	5.8%
12 mths	4.7%	7.1%



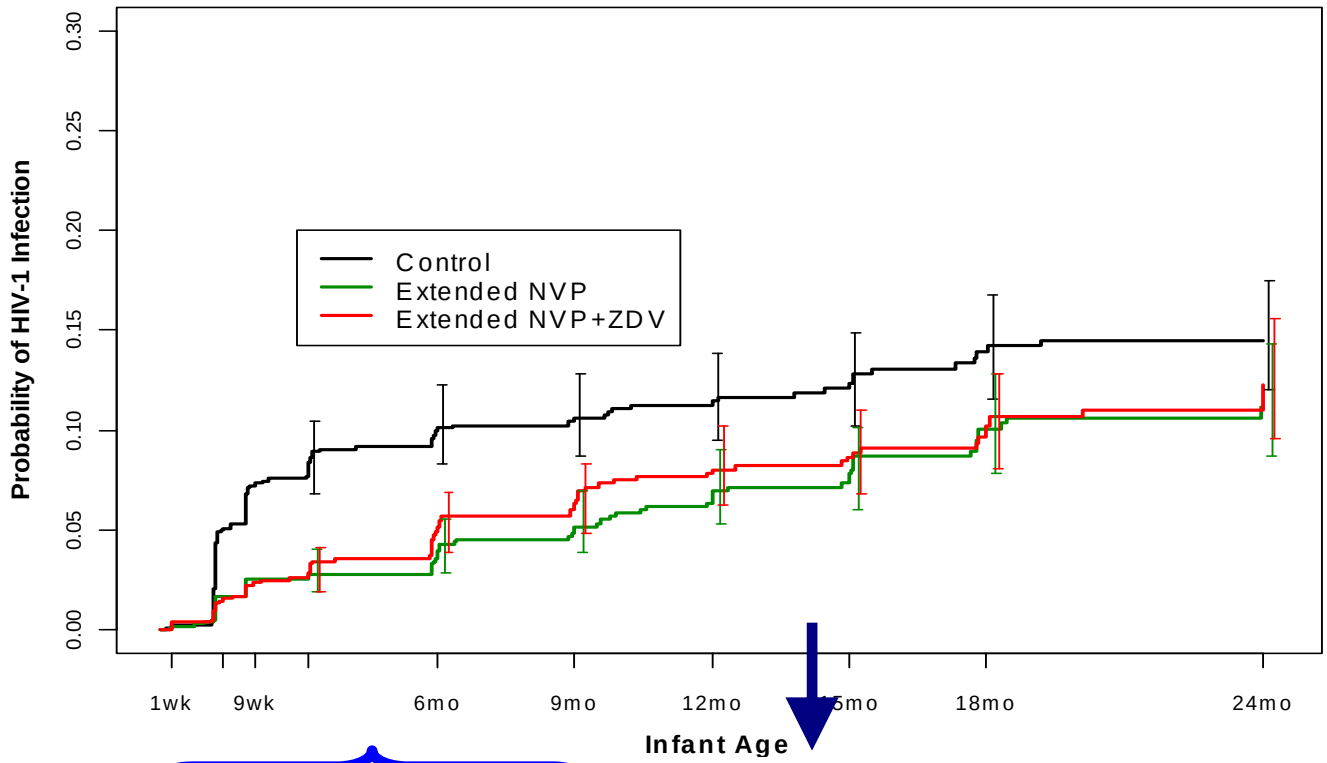
Evidence for Efficacy of Infant NVP Prophylaxis to Reduce Breast Milk HIV Transmission

BACKGROUND: PEPI-Malawi Study Design



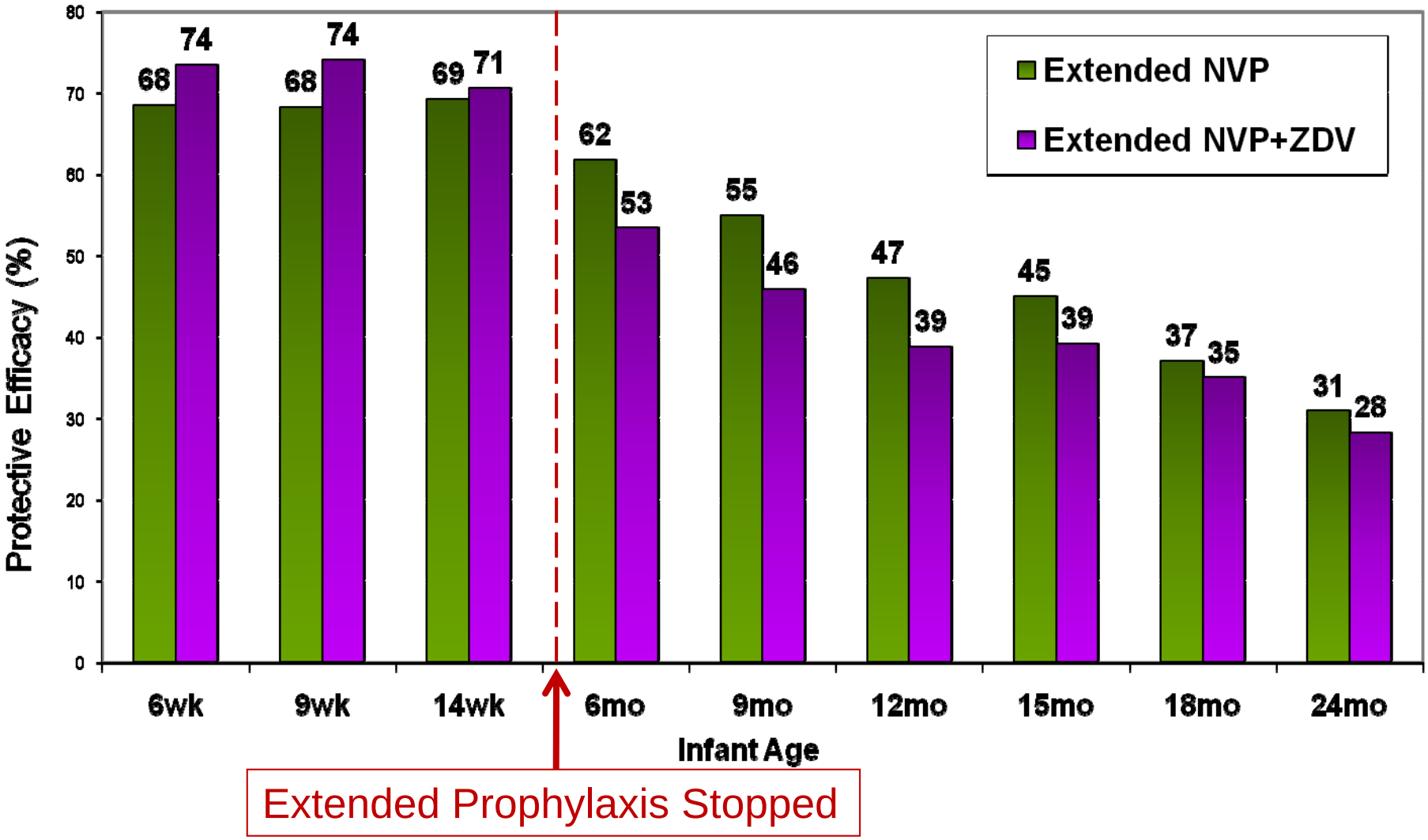
14 Week Extended ARV Prophylaxis Significantly Reduces Postnatal HIV Infection: PEPI Malawi

Kumwenda N et al. NEJM 2008:359:119-29



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

PEPI-Malawi: >70% Protective Efficacy of Extended Treatments vs. Control Arm During the Prophylaxis Period



PEPI-Malawi Infant Prophylaxis Trial:
Extended Infant Prophylaxis Reduces Postnatal MTCT in All CD4 Strata

Mofenson L et al. IAS,Capetown, South Africa, July 2009 Abs. TuPEC053

Postnatal Infection at Age 14 Weeks in Infants Uninfected at Birth

	CD4 <200		CD4 200-350		CD4 >350	
	% Postnatal infection (95% CI)	Relative Risk (95% CI)	% Postnatal infection (95% CI)	Relative Risk (95% CI)	% Postnatal Infection (95% CI)	Relative Risk (95% CI)
Control	17.6% (12.2-25.2)	1.0	9.0% (5.9-13.8)	1.0	5.5% (3.8-7.9)	1.0
Extended NVP	5.8% (3.0-10.8)	0.33 (0.16-0.68)	3.4% (1.7-6.7)	0.37 (0.17-0.84)	1.4% (0.7-3.0)	0.25 (0.12-0.59)
Extended NVP+AZT	6.1% (3.3-12.4)	0.36 (0.17-0.78)	3.2% (1.3-6.3)	0.32 (0.13-0.78)	2.3% (1.3-4.1)	0.42 (0.22-0.83)

Option B: Maternal Triple Drug Prophylaxis

Option B Prophylaxis Regimen for Pregnant HIV-Infected Women & Their Infants

Option B: Maternal Triple ARV Prophylaxis

MOTHER

- Initiate as early as 14 weeks gestation through delivery
- If breast feeding , continue until 1 week after weaning (maximum of 12 mos)

RECOMMENDED PROPHYLAXIS REGIMENS
AZT + 3TC + LPV/r AZT + 3TC + ABC AZT + 3TC + EFV TDF + ETC (FTC) + EFV

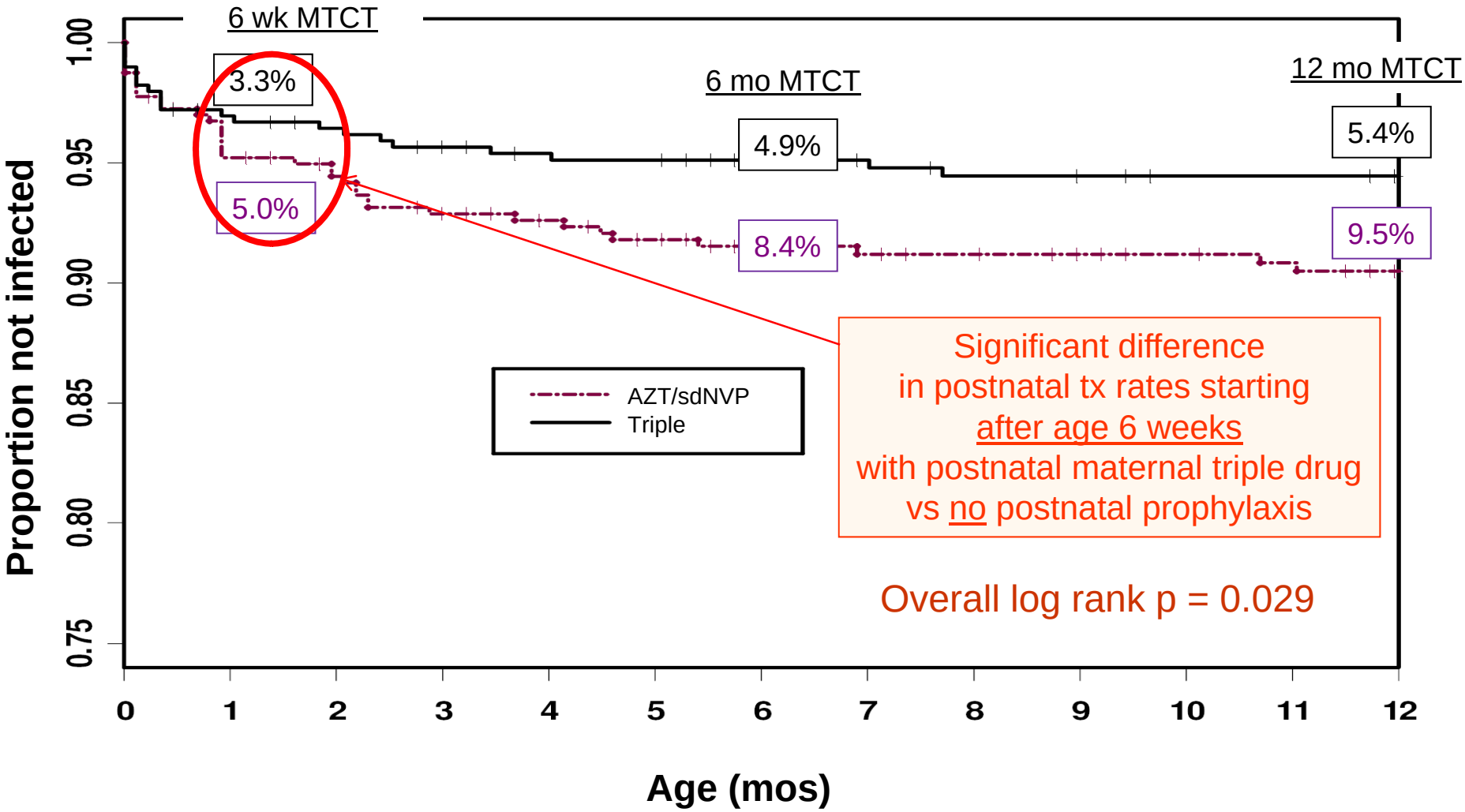
INFANT

Breastfeeding or Non-Breastfeeding Infant

- Twice daily AZT or daily NVP from birth until 4 to 6 weeks

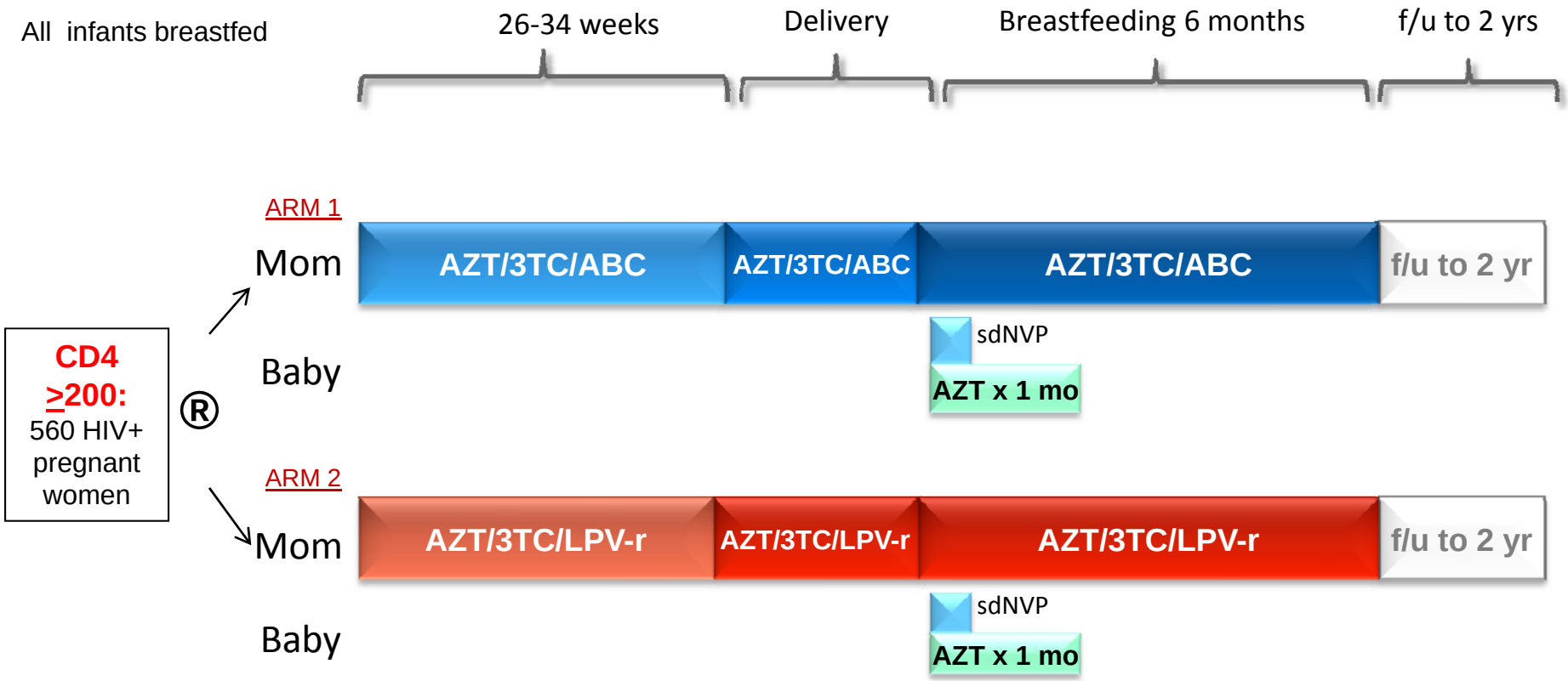
Kesho Bora: Maternal HAART Significantly Lowers Postnatal MTCT Compared to No Postnatal Prophylaxis

De Vincenzi I et al. IAS, Capetown, South Africa, July 2009 Ab LBPEC01



Triple Drugs are Effective in Reducing Postnatal Transmission
Mma Bana: Randomized Trial in Women with CD4 ≥200

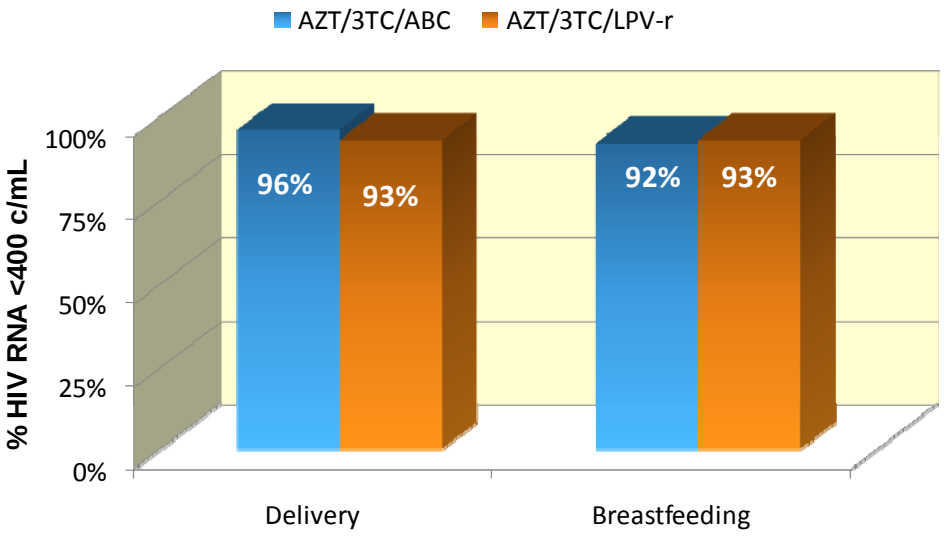
Shapiro R et al. NEJM 2010;362:2282-94



Viral Suppression and Low Postnatal Transmission Rates Are Similar Between the Two Triple Drug Regimens

Shapiro R et al. NEJM 2010;362:2282-94

Viral suppression



Transmission

Infections among live-born infants, by maternal arm	Arm A (TZV) N=283	Arm B (KAL/CBV) N=270
In utero	3 (1.1%)*	1 (0.4%)
Intrapartum	0	0
Breastfeeding	2 (0.7%)	0
Total at 6 months	5 (1.8%)*	1 (0.4%)

Overall Transmission 1%
(95% CI, 0.5-2.0%)
Through Age 6 Months
(p=0.53 between regimens)

Why Are There Differences in Overall MTCT in Women on Triple ARV in the Mma Bana Study vs Women on Triple ARV in Kesho Bora Study?

	Mma Bana	Kesho Bora
MTCT at 6 months	**1% (0.5-2.0%)**	**4.9% (3.1-7.6%)**
Differences Between the Trials		
Enrollment	26-34 wks	28-36 wks
CD4 at enrollment	393-403	336
RNA at enrollment (on no ART)	9,100-13,300	16,982
Duration AP HAART	Median 11 wks	Median 6 wks
Adherence (no missed dose)	79% (AP+PP)	73% AP, 64% PP
Exclusive BF	93% to 6 mos	only 45% to 3 mos

Kesho Bora enrollees had somewhat lower CD4/higher RNA at enrollment, shorter duration of AP HAART, lower adherence, and much lower rates of exclusive BF.

MITRA (Infant ARV) vs MITRA-PLUS (Maternal HAART) to Prevent Postnatal MTCT, Tanzania

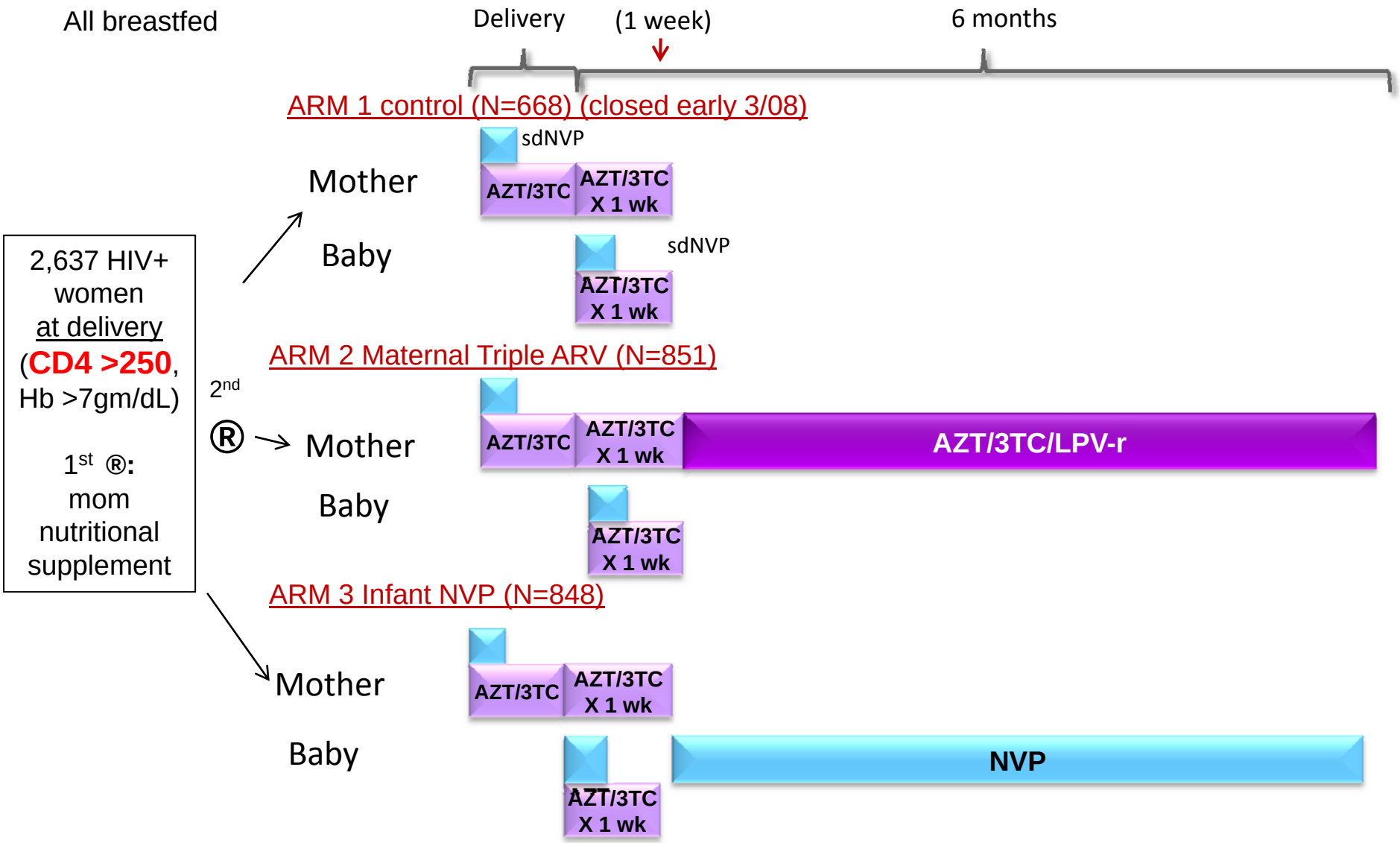
Kilewo et al. JAIDS 2008;48:315-23; JAIDS 2009 in press

	Overall Transmission	
	MITRA (Infant ART, N=398)	**MITRA-Plus** (Maternal ART, N=440)
6 Weeks	3.8% (2.0-5.6%)	4.1% (2.1-6.0%)
6 Months	4.9% (2.7-7.1%)	5.0% (3.2-7.0%)
Increment MTCT 6 weeks-6 months	1.1%	0.9%

No significant difference in terms of postnatal transmission between maternal or infant prophylaxis strategies

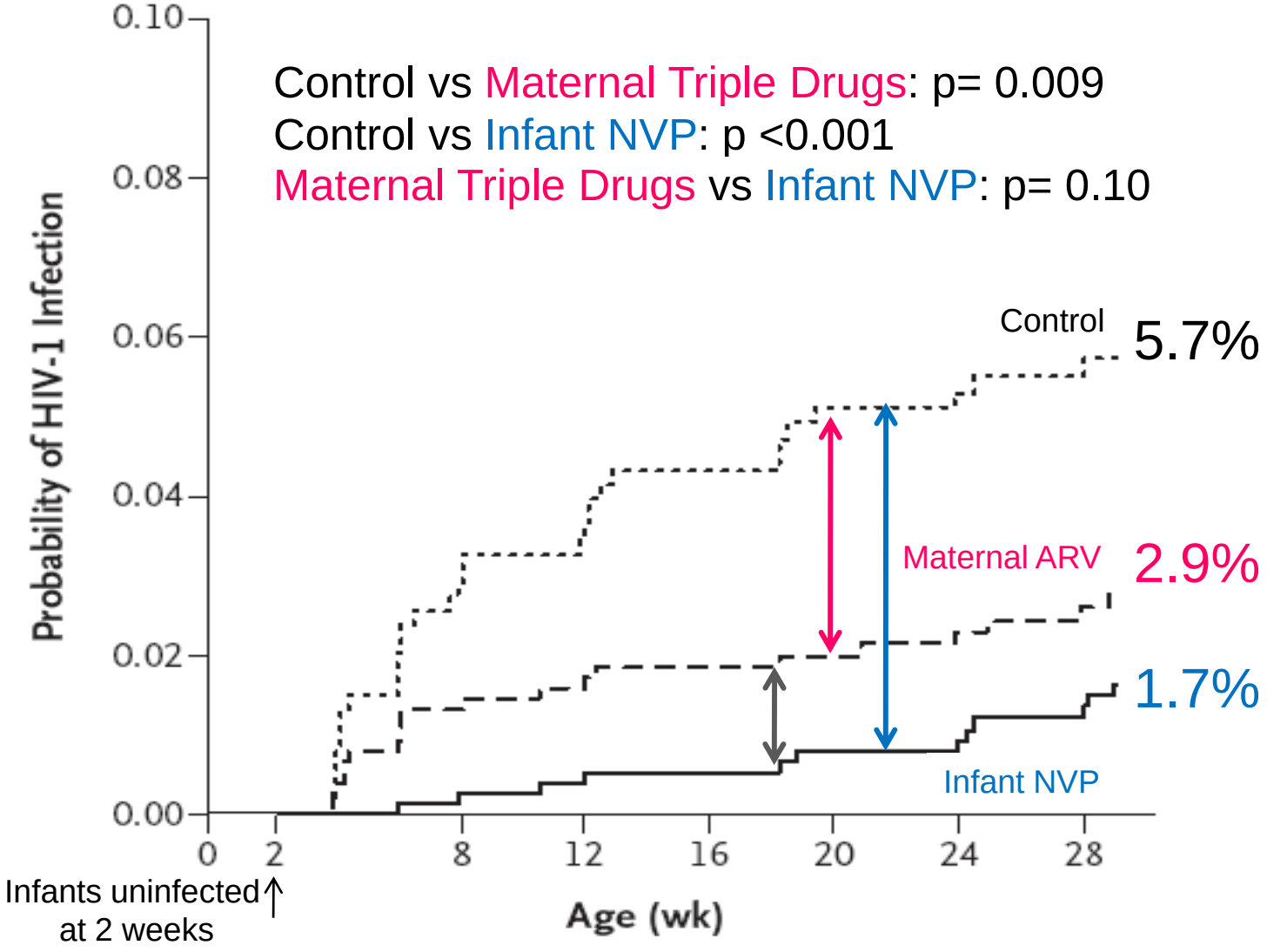
Breastfeeding, Antiretrovirals and Nutrition (BAN) Study: Postpartum Option A vs Option B

Chasela C et al. NEJM 2010;362:2271-81



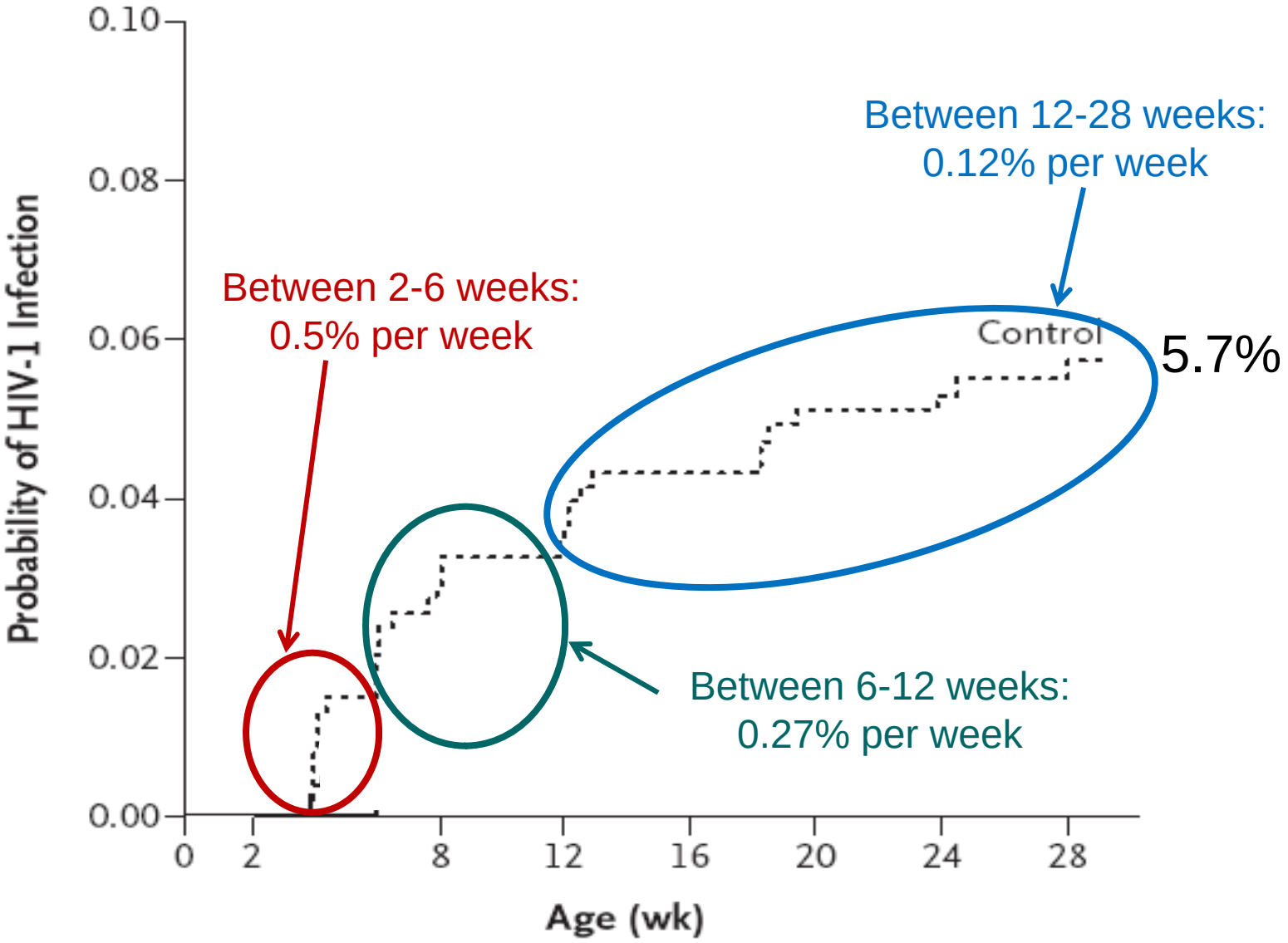
BAN: Postnatal HIV in Infants Uninfected at 2 Weeks is Reduced by Both Infant NVP and Maternal Triple ARV Prophylaxis

Chasela C et al. NEJM 2010;362:2271-81



BAN Control Group: Risk of Breast Milk Transmission is Highest in the First Weeks of Breastfeeding

Chasela C et al. NEJM 2010;362:2271-81



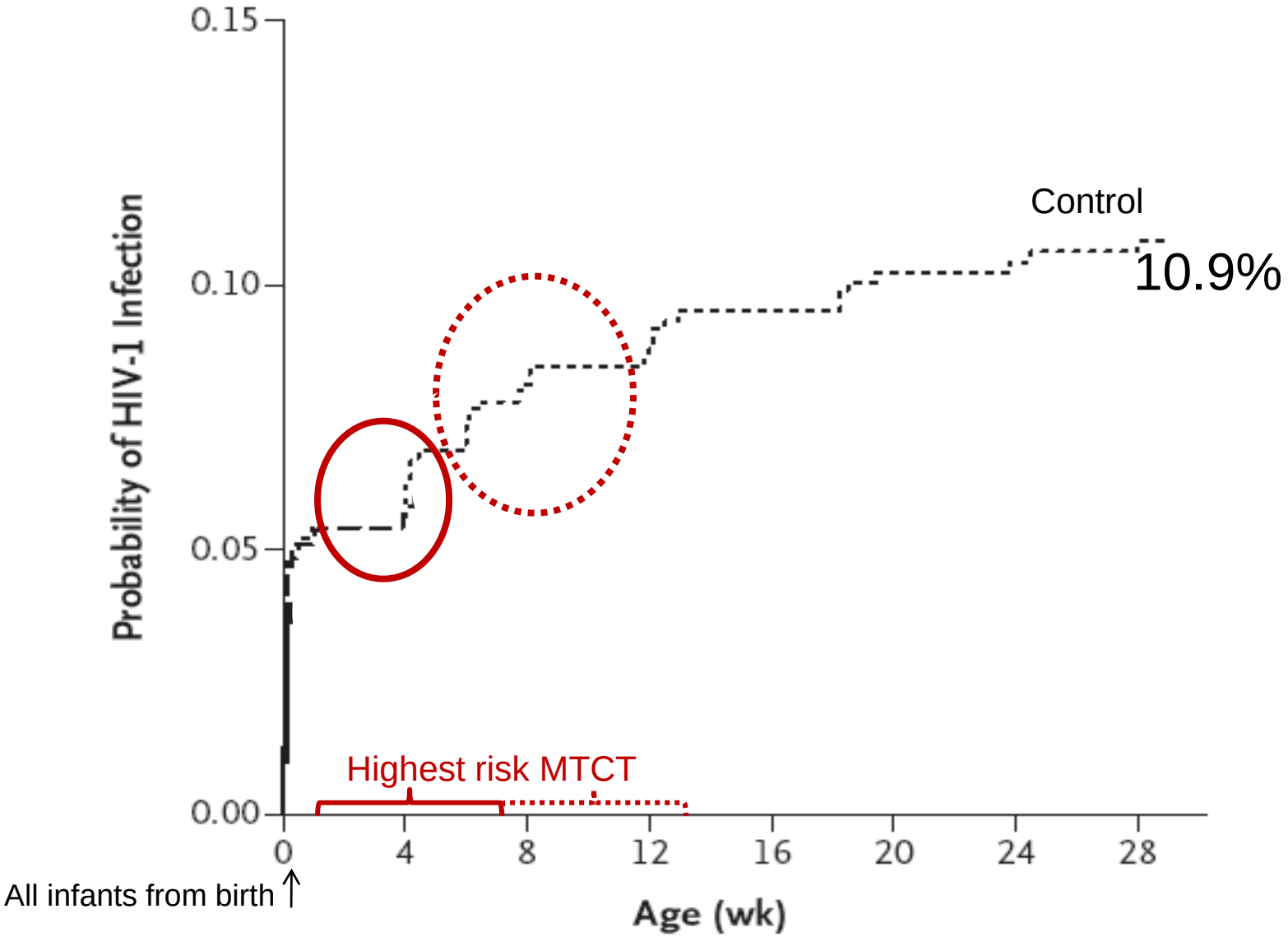
Highest Weekly Risk of Breast Milk Transmission in First 6-12 Weeks of Life: Control Group, BAN

Chasela C et al. NEJM 2010;362:2271-81

Control Group				
Time of testing	*Cumulative* postnatal tx	*Incremental* postnatal tx	Time interval (wks)	Infection rate/wk
14 d (2 wks)	Uninfected	-	-	-
42 d (6 wks)	2.0%	2.0% (btn 2-6 wks)	4 wk	0.5%/wk
84 d (12 wks)	3.6%	1.5% (btn 6-12 wks)	6 wk	0.27%/wk
203 d (29 wks)	5.7%	2.1% (btn 12-29 wks)	17 wk	0.12%/wk

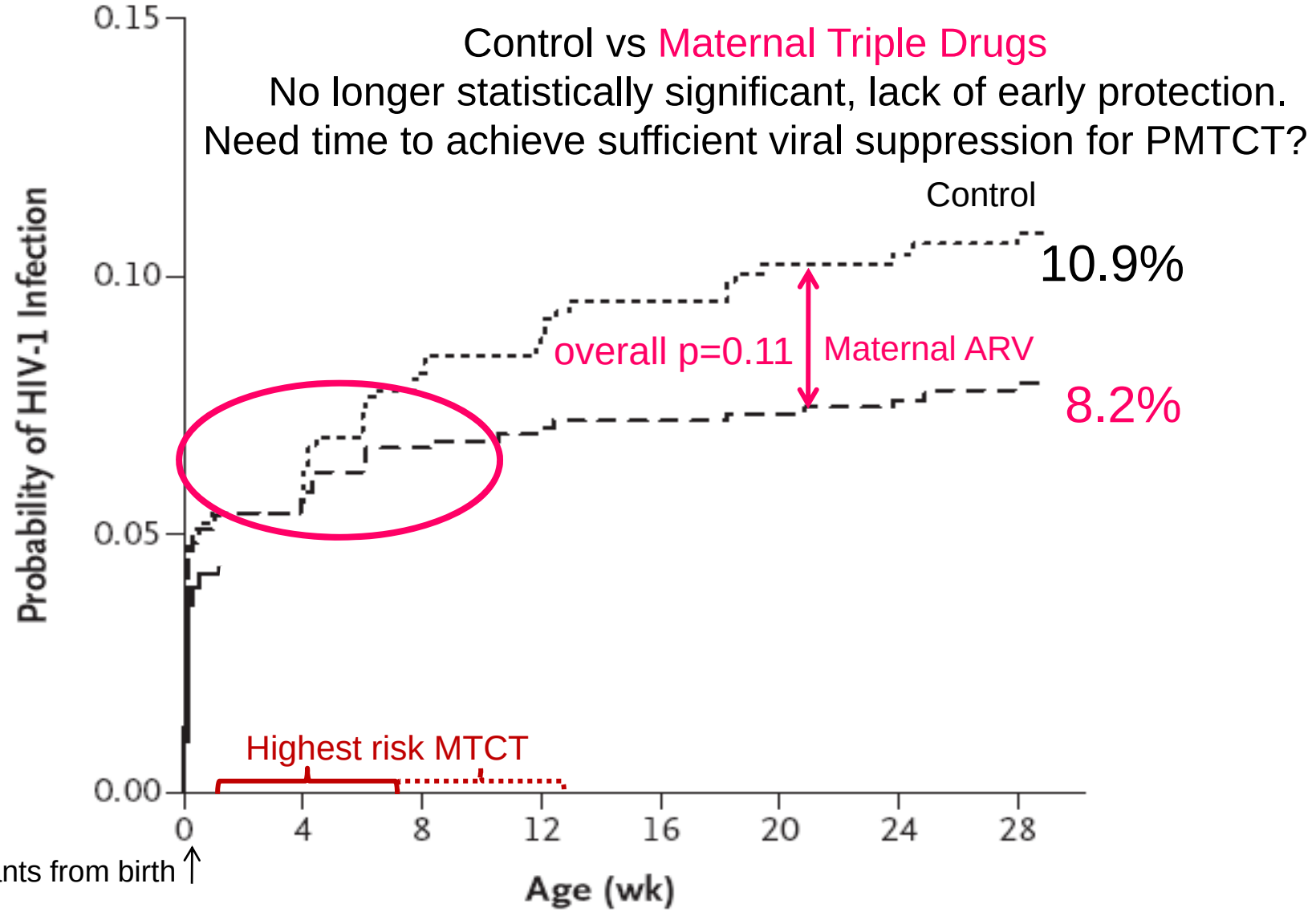
Postnatal HIV in All Infants (Regardless HIV Status at 2 Weeks): Does Efficacy Differ by Arm During Early High Risk Period For Transmission?

Chasela C et al. NEJM 2010;362:2271-81



Postnatal HIV in All Infants (Regardless HIV Status at 2 Weeks): During Early High Risk Period For Transmission, Maternal Triple ARV Prophylaxis Less Effective

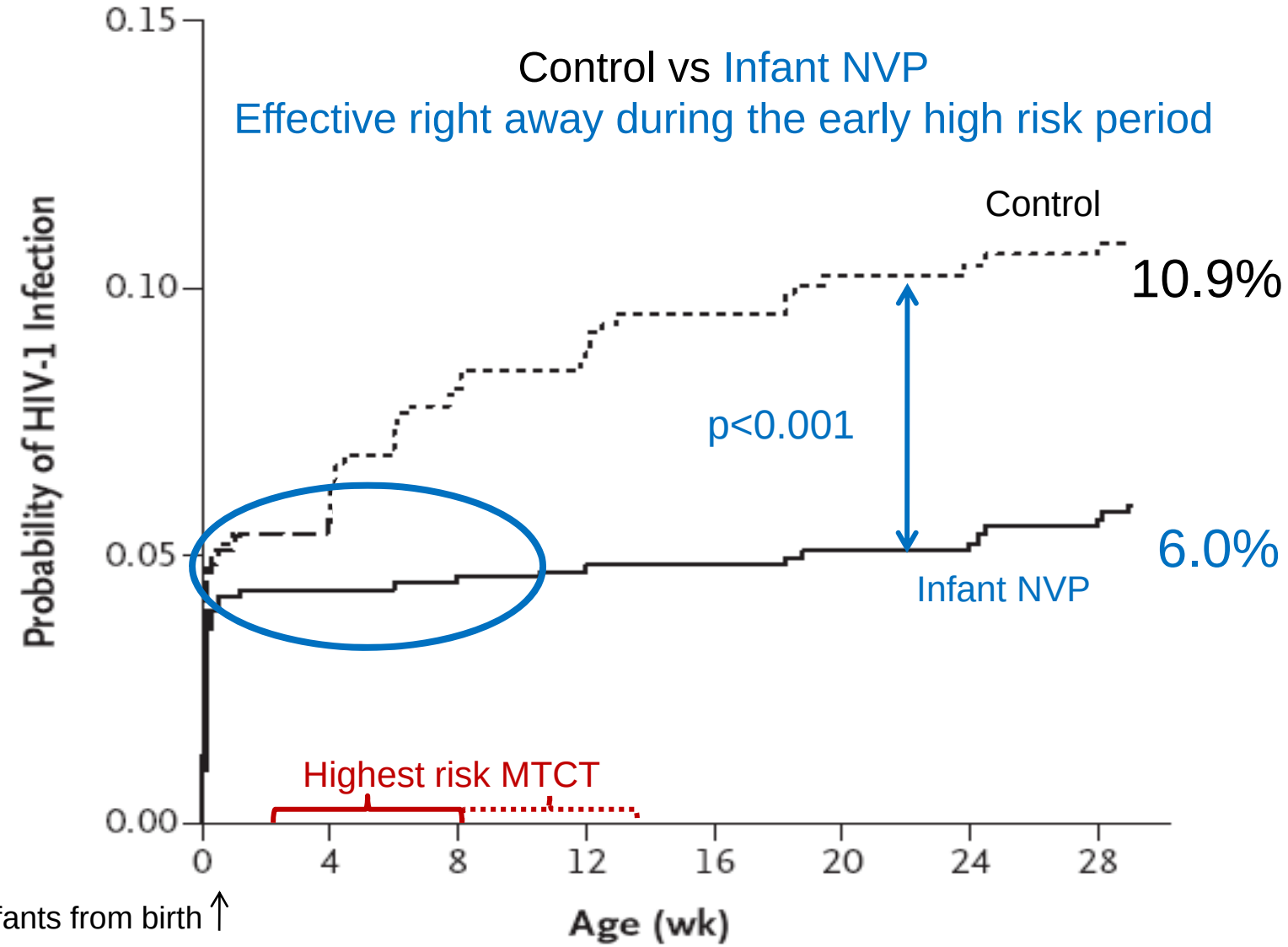
Chasela C et al. NEJM 2010;362:2271-81



All infants from birth ↑

Postnatal HIV in All Infants (Regardless HIV Status at 2 Weeks): During Early High Risk Period For Transmission, Infant NVP is Highly Effective

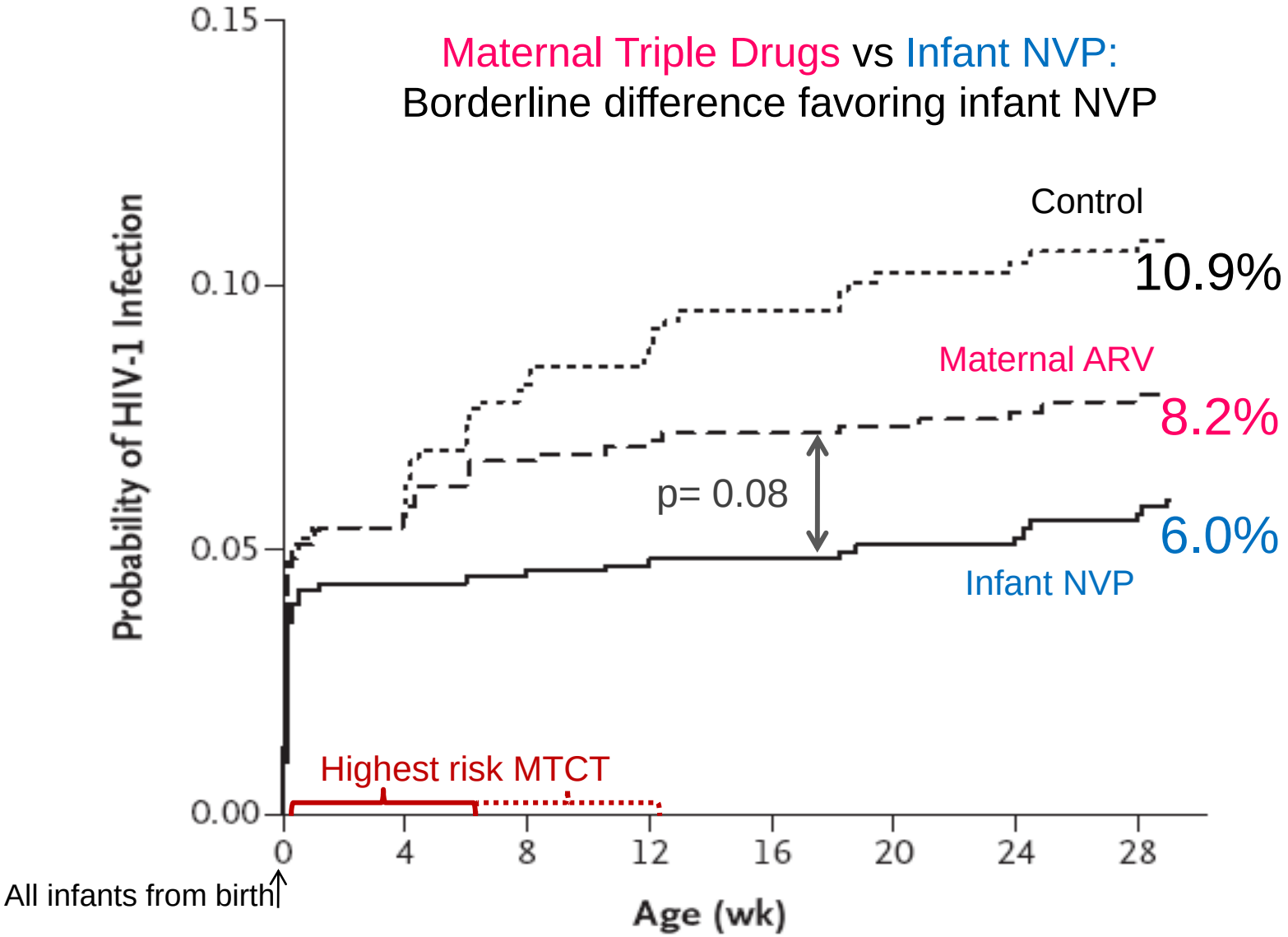
Chasela C et al. NEJM 2010;362:2271-81



All infants from birth ↑

Postnatal HIV in All Infants (Regardless HIV Status at 2 Weeks): Comparing Infant NVP to Maternal ARV Prophylaxis

Chasela C et al. NEJM 2010;362:2271-81



Incremental Infection Risk with Intervention Arms

Chasela C et al. NEJM 2010;362:2271-81

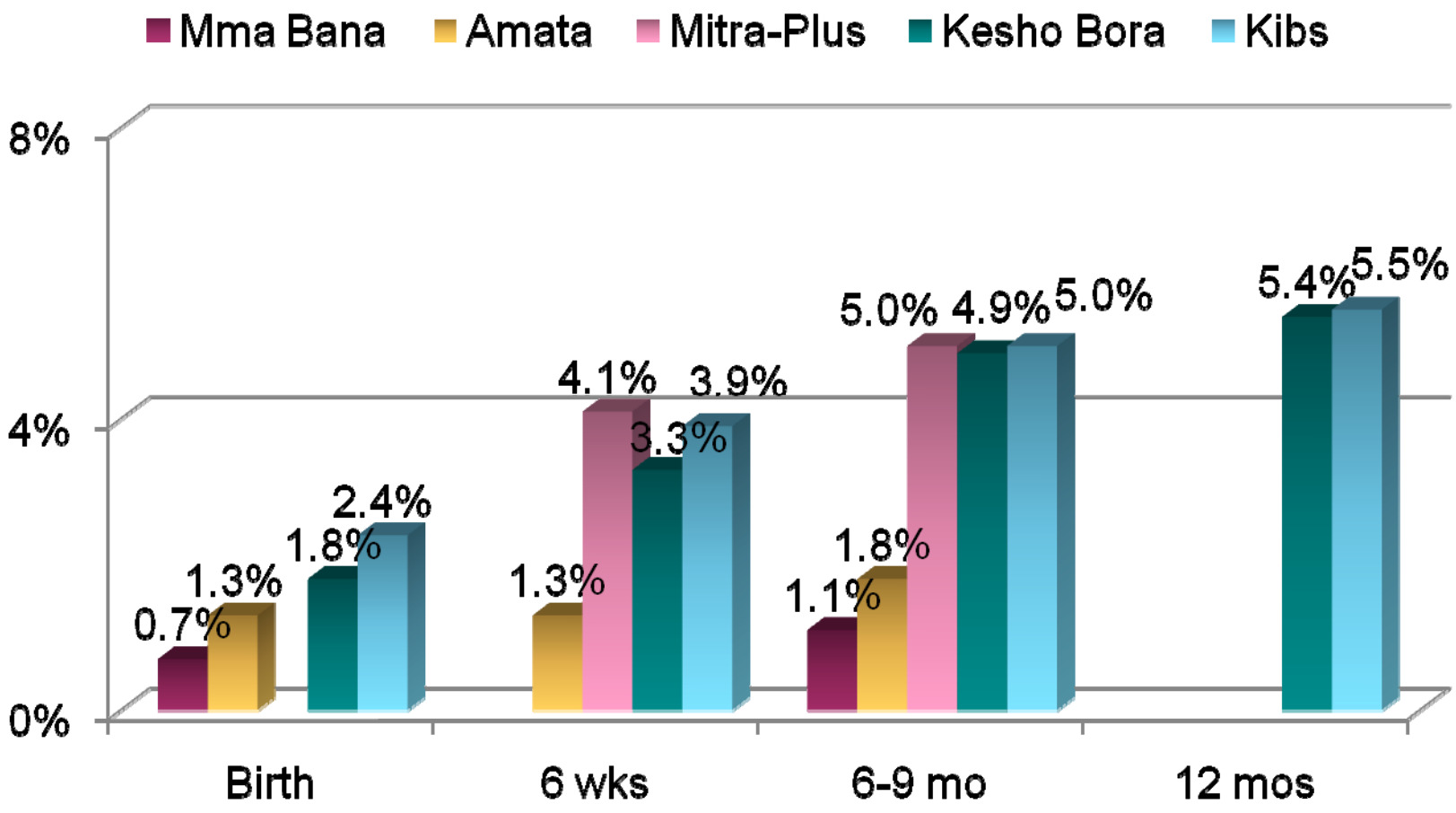
Infant NVP

Time of testing	*Cumulative* postnatal tx	*Incremental* postnatal tx	Time interval (wks)	Infection rate/wk
14 d (2 wks)	Uninfected	-	-	-
		⇕		
42 d (6 wks)	0.1%	0.1%	4 wk	0.03%/wk
		⇕		
84 d (12 wks)	0.5%	0.4%	6 wk	0.07%/wk
		⇕		
203 d (29 wks)	1.7%	1.2%	17 wk	0.07%/wk

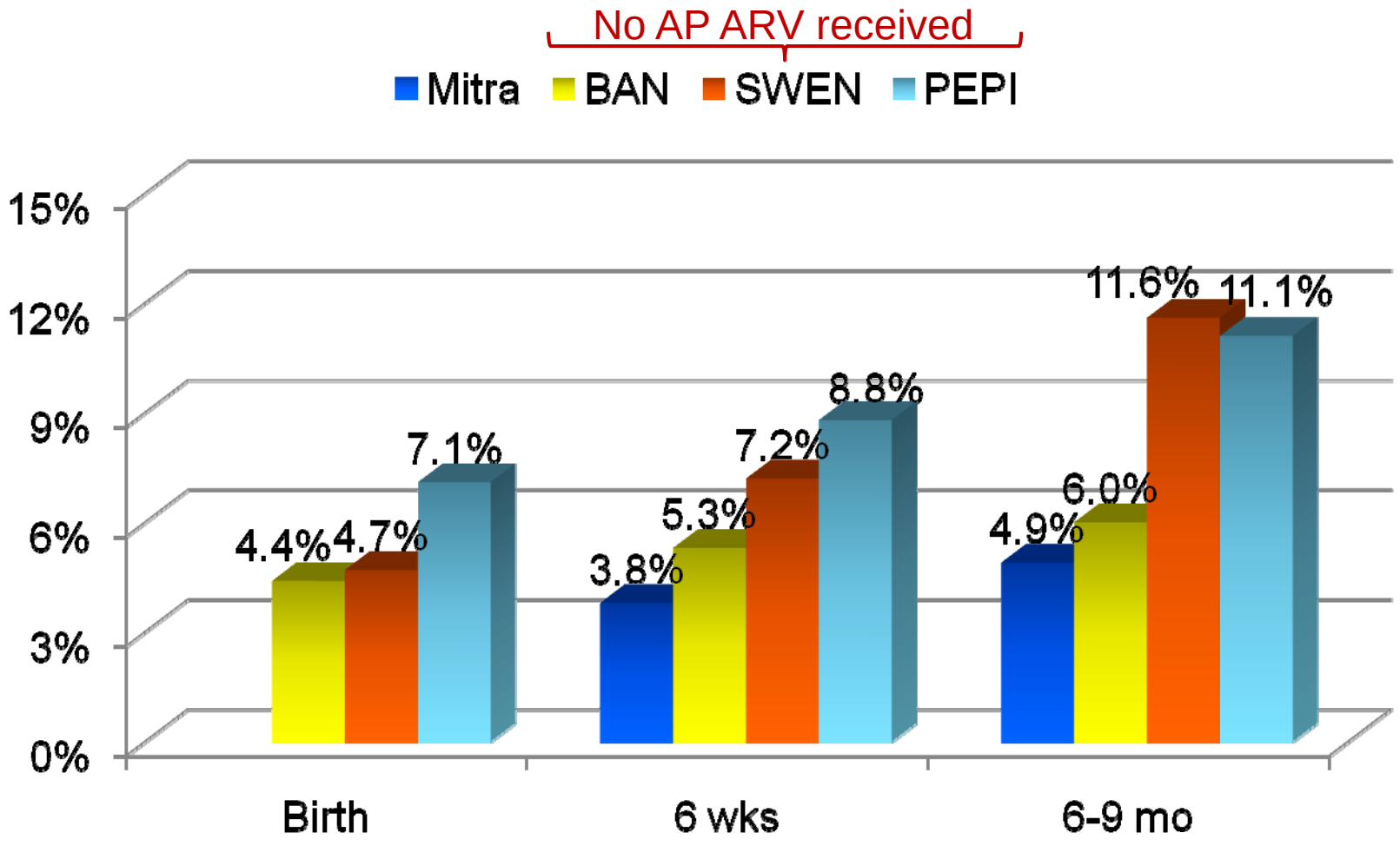
Maternal Triple ARV

Time of testing	*Cumulative* postnatal tx	*Incremental* postnatal tx	Time interval (wks)	Infection rate/wk
14 d (2 wks)	Uninfected	-	-	-
		⇕		
42 d (6 wks)	0.9%	0.9%	4 wk	0.23%/wk
		⇕		
84 d (12 wks)	1.7%	0.8%	6 wk	0.13%/wk
		⇕		
203 d (29 wks)	2.9%	1.2%	17 wk	0.07%/wk

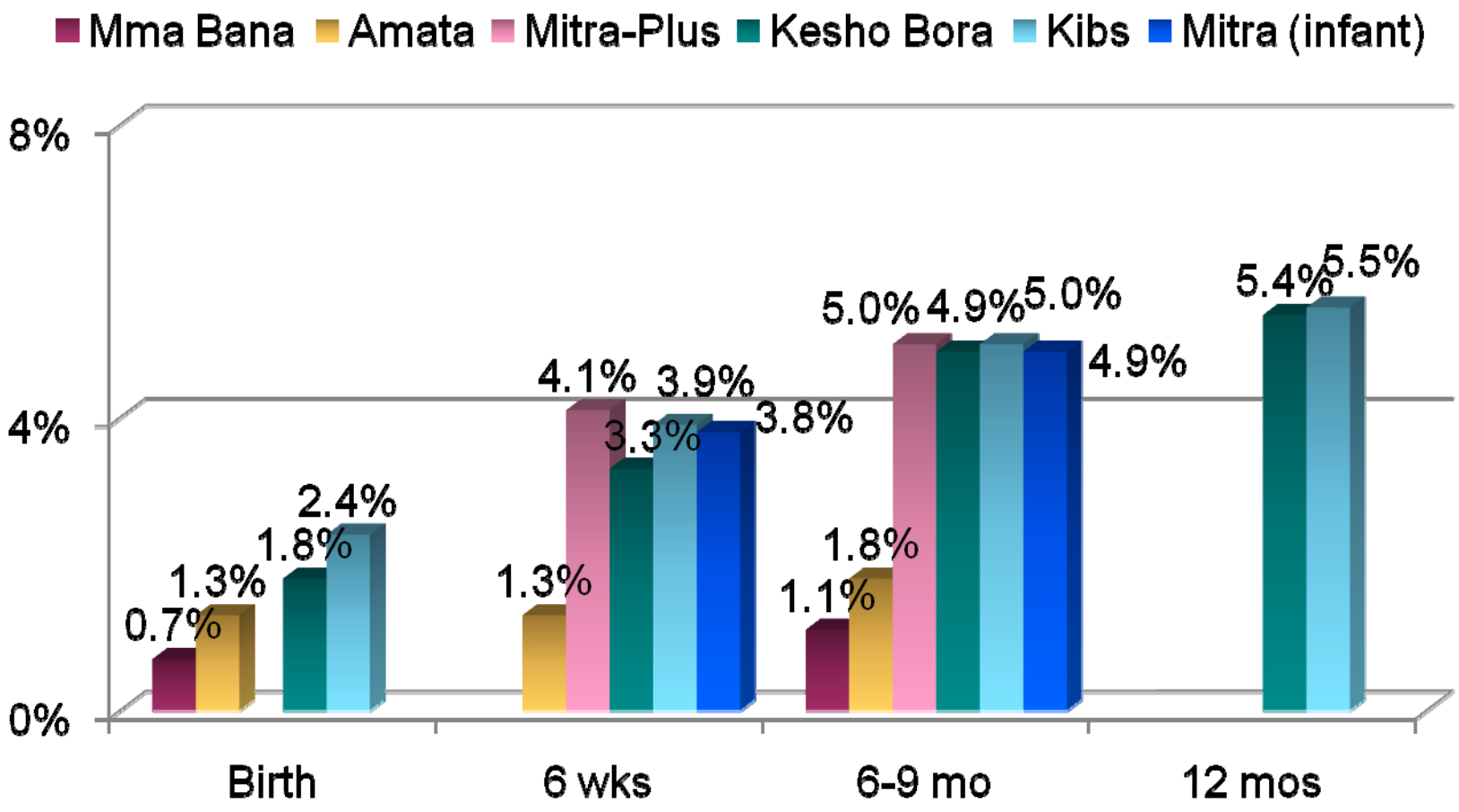
Cumulative MTCT Rates in Maternal Triple ARV Studies



Cumulative MTCT Rates in Infant ARV Prophylaxis Studies



Cumulative MTCT Rates in Maternal Triple ARV Studies & Mitra Infant Prophylaxis



Comments on ARV Prophylaxis Group of Women Who Do Not Need Treatment for Own Health

- When AP ARV (either AZT or triple ARV) given, *in utero* MTCT low (~1-2%) and similar regardless of regimen. Duration of AP ARV important in determining MTCT rate.
- Either maternal triple ARV or infant NVP prophylaxis are safe and effective in reducing postnatal MTCT. When AP ARV are given, both appear to reduce postnatal MTCT (btn 6 wk-6 mo) to about 1-2%.
- Overall MTCT rates in studies in women with CD4 >200-350 range getting AP+PP prophylaxis range from 1% (Mma Bana) to ~5% at 6-12 months.
- If maternal triple ARV started postpartum (or late AP?), it is less effective against early postnatal MTCT than infant NVP, due to time needed to lower viral load.

Ongoing and New Trials

HPTN 046: Safety and Comparative Efficacy of 6 Weeks vs 6 Months Infant NVP

Mom NVP x1	Infant NVP x1	NVP 1 wk – 6 mos	
Mom NVP x1	Infant NVP x1	Infant: NVP 1- 6 wks	Placebo 6 wk – 6 mos

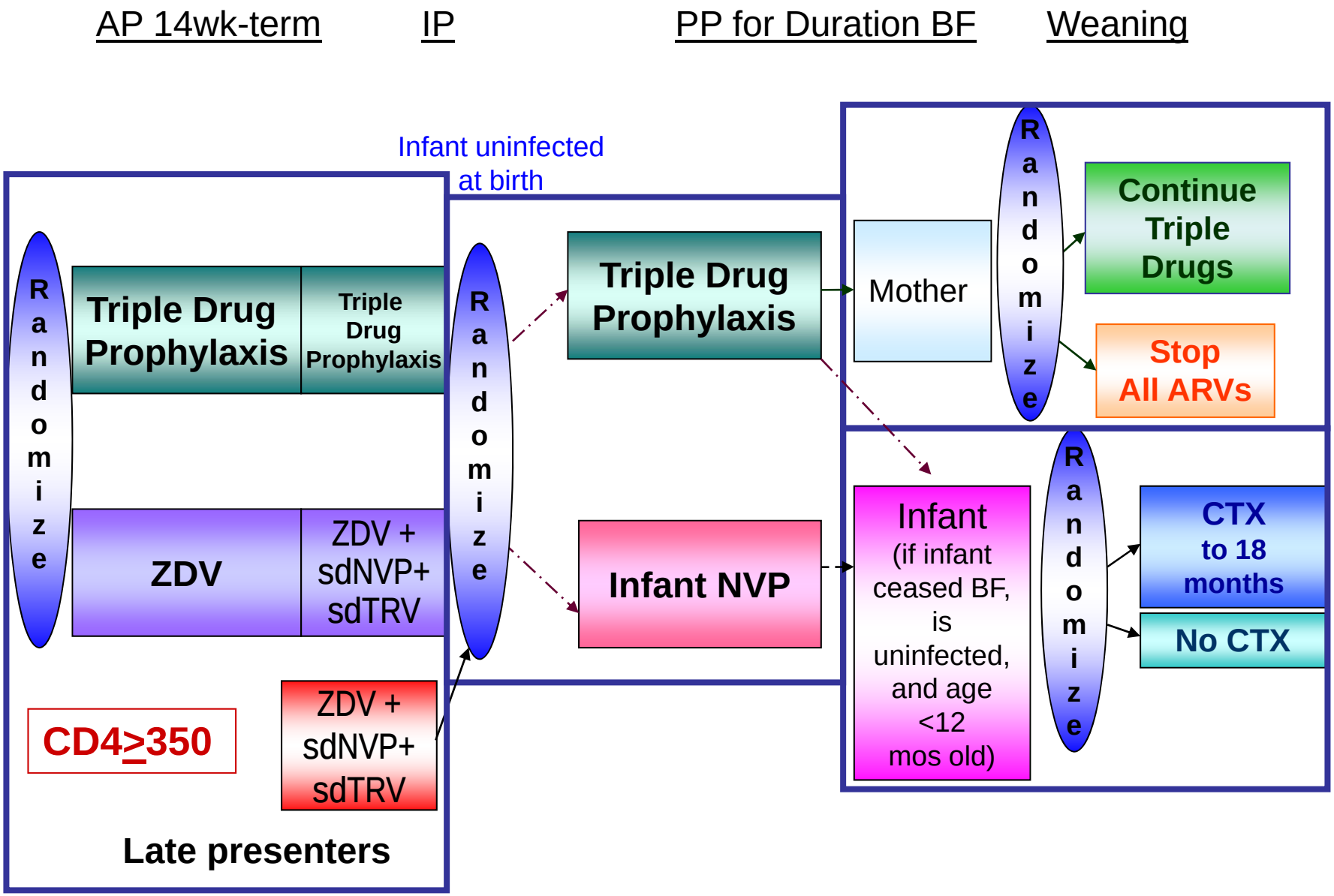
- IMPAACT trial
- All CD4
- Mom AP ARV outside study
- Fully enrolled
- 4 African sites
- Results end 2010

ANRS Promise PEP: Infant 3TC up to 9 Months

AP AZT+ sdNVP+tail?	Infant sdNVP	3TC from age 1wk to 1 mo post cessation BF (maximum 9 mos)
AP AZT+ sdNVP+tail?	Infant sdNVP	LPV-rtv age 1wk to 1 mo post cessation BF (maximum 9 mos)

- ANRS trial
- Mom CD4 >350 and WHO stage 1/2
- AP ARV outside study
- 4 African countries; 1,500 infants

PROMISE STUDY: Four Sequential Randomizations



ANRS "Universal Approach"

Non-inferiority-equivalence
Endpt: safety/efficacy
pregnancy outcome

All women regardless of CD4
randomize to one of two arms

↓

Tenfovir/FTC/Efavirenz
From 20 wks gestation through delivery if FF, through 12 mos PP if BF

AZT/3TC/LPV-RTV ("reference regimen")
From 20 wks gestation through delivery if FF, through 12 mos PP if BF

↓

ANRS trial
• 2 African countries; 1,200 mom-baby pairs
Decision on stopping or continuing based on baseline maternal CD4 and WHO stage
• If CD4 >500 at baseline and WHO 1, 2 or 3: To stop at cessation BF
• If CD4 <500 or WHO 4: To continue lifelong triple drugs

Study	Key Design	Status	Results
Mma Bana	PI vs NRTI HAART 6 mo BF	Done	Available
BAN	Control vs 6 mos HAART or 6 mos infant NVP	Done	Available
Kesho Bora	Maternal HAART	Done	Available
HPTN 046	BF Infant NVP 6 wks vs 6 mos	In F/U	Fall 2010
PEP-ANRS	BF Infant 3TC vs LPV-rtv for 9 mo	Start 2010	2013
IMPAACT-PROMISE	AP short vs HAART; PP HAART vs infant NVP; Mom stop vs continue; Infant CTX	Start end 2010	2013-15 (3-5 yrs)
ANRS	Triple ARV: TDF/FTC/EFV vs AZT/3TC/LPV-r during pregnancy (to 12 mos if BF)	Being finalized	2014