


Challenges in Prevention of Mother to Child HIV Transmission

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Goal:
“Eliminate pediatric HIV infection”

but also

“Maximize HIV-free survival of infant”

And

“Maximize maternal health”

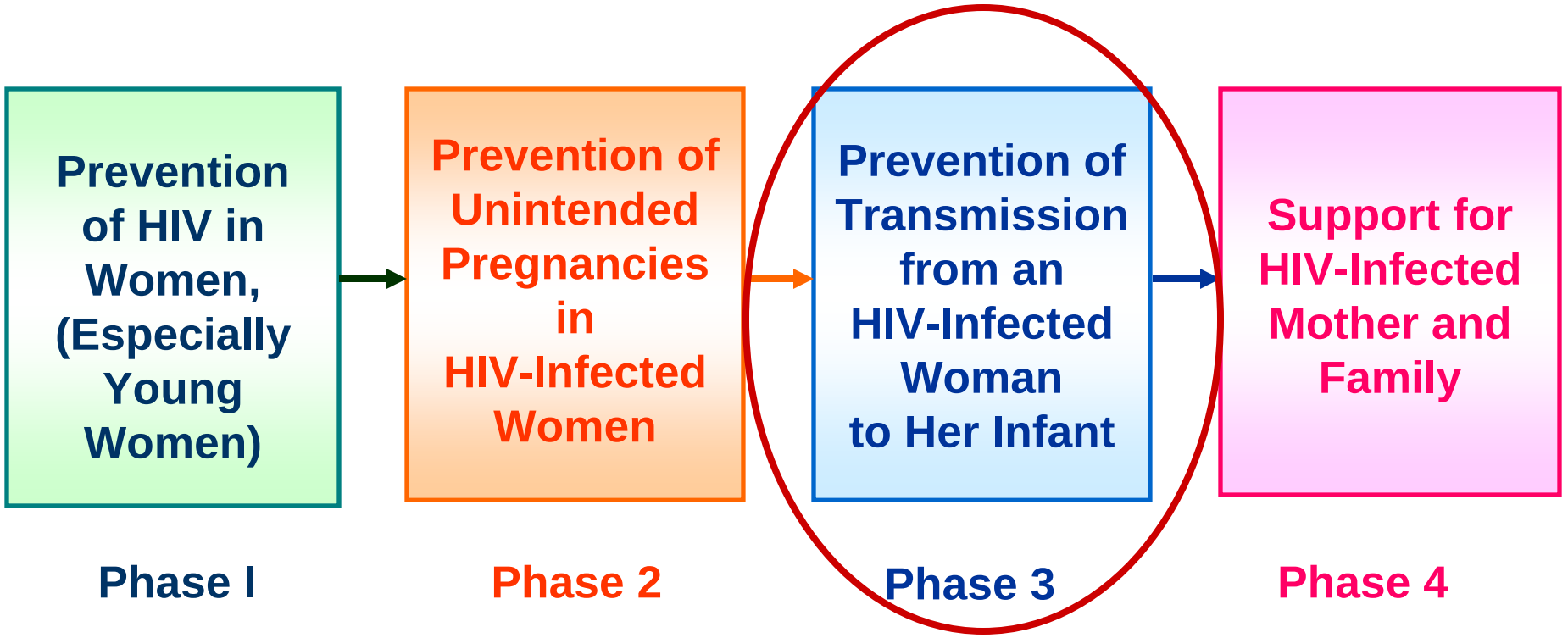
Sometimes Means of Achieving these Goals may be at Odds with Each Other (eg, early weaning and infant survival, stopping prolonged maternal HAART and mom health)

Don’t Forget
Contraception
as the Most Effective
Intervention to
Prevent MTCT

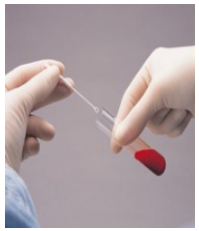
And
Prevention of HIV
in Women

Four-Phase Strategy for Prevention of Mother to Child HIV Transmission

Wilcher R et al. Sex Trans Inf 2008;84 (Suppl2):ii54-60



Efficacy of PMTCT Programs is Related to More than Just the PMTCT Regimen Used



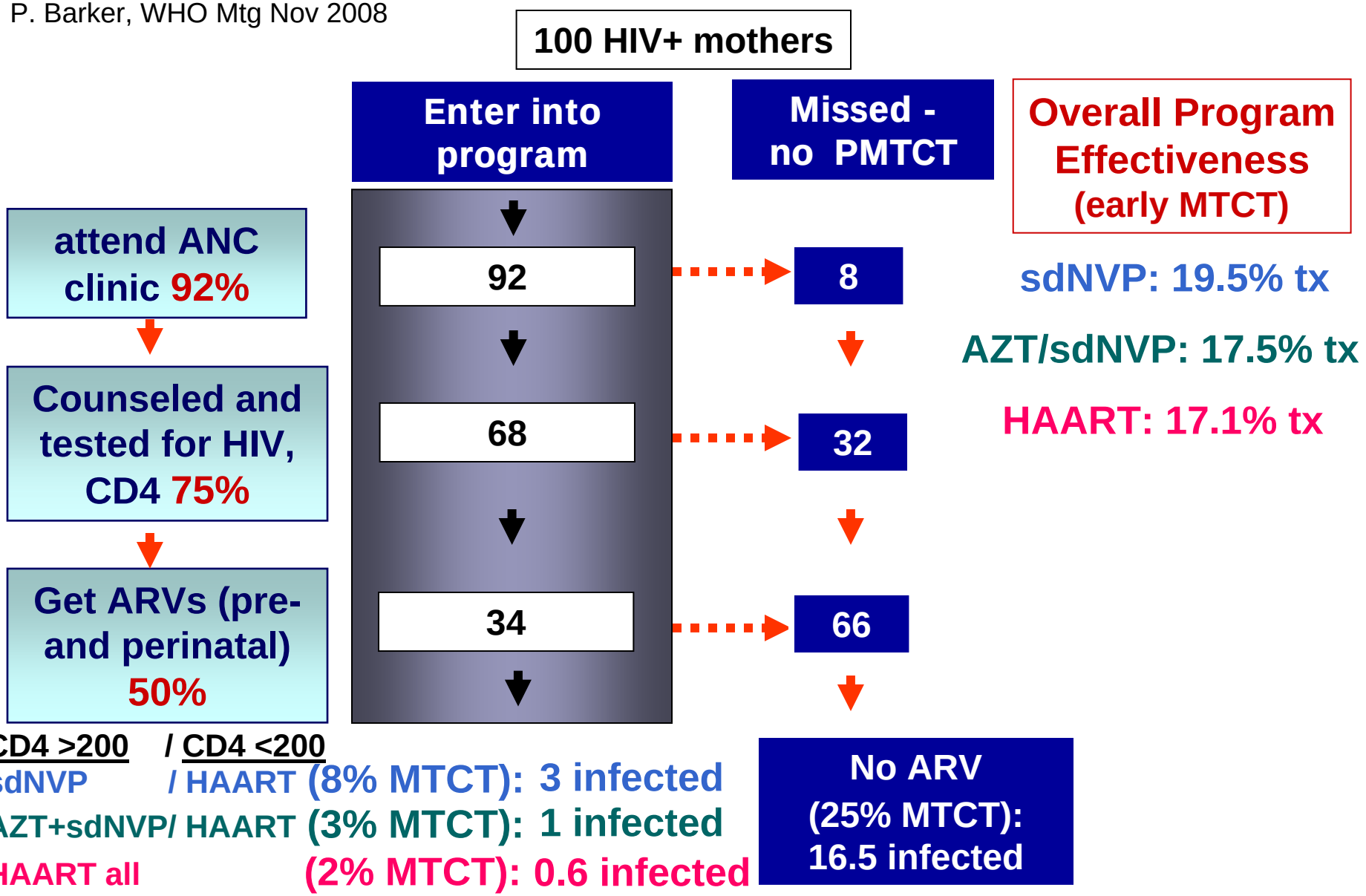
- To provide PMTCT, need to identify HIV-infected women during pregnancy.
  - In 2007, only 18% of pregnant women received HIV testing in RLC.

- Regardless of *what* PMTCT intervention, must get it to & accepted by the woman.
  - In 2007, only 33% of HIV-infected pregnant women received ARV for PMTCT in RLC.

Program efficacy is as much related to the PMTCT cascade as the specific PMTCT regimen

PMTCT Cascade: Most Critical Thing for PMTCT is Number of Women Completing Cascade

P. Barker, WHO Mtg Nov 2008



PMTCT Cascade: Most Critical Thing for PMTCT is Number of Women Completing Cascade

P. Barker, WHO Mtg Nov 2008

Change cascade efficiency

100 HIV+ mothers

Enter into program

Missed - no PMTCT

Overall Program Effectiveness (early MTCT)

attend ANC clinic 95%

Counseled and tested for HIV, CD4 95%

Get ARVs (pre- and perinatal) 95%

95 → 5

90 → 10

86 → 14

sdNVP: 10.4% tx

AZT/sdNVP: 6.1% tx

HAART: 5.2% tx

No ARV (25% MTCT): 3.5 infected

CD4 >200 / CD4 <200

sdNVP / HAART (8% MTCT): 6.9 infected

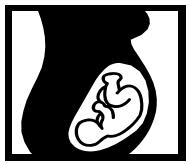
AZT+sdNVP/ HAART (3% MTCT): 2.6 infected

HAART all (2% MTCT): 1.7 infected

To Maximize Effectiveness
Need to Prevent *In Utero* Transmission

Interventions Need to Start During Pregnancy – so Need Early Identification For Early Intervention

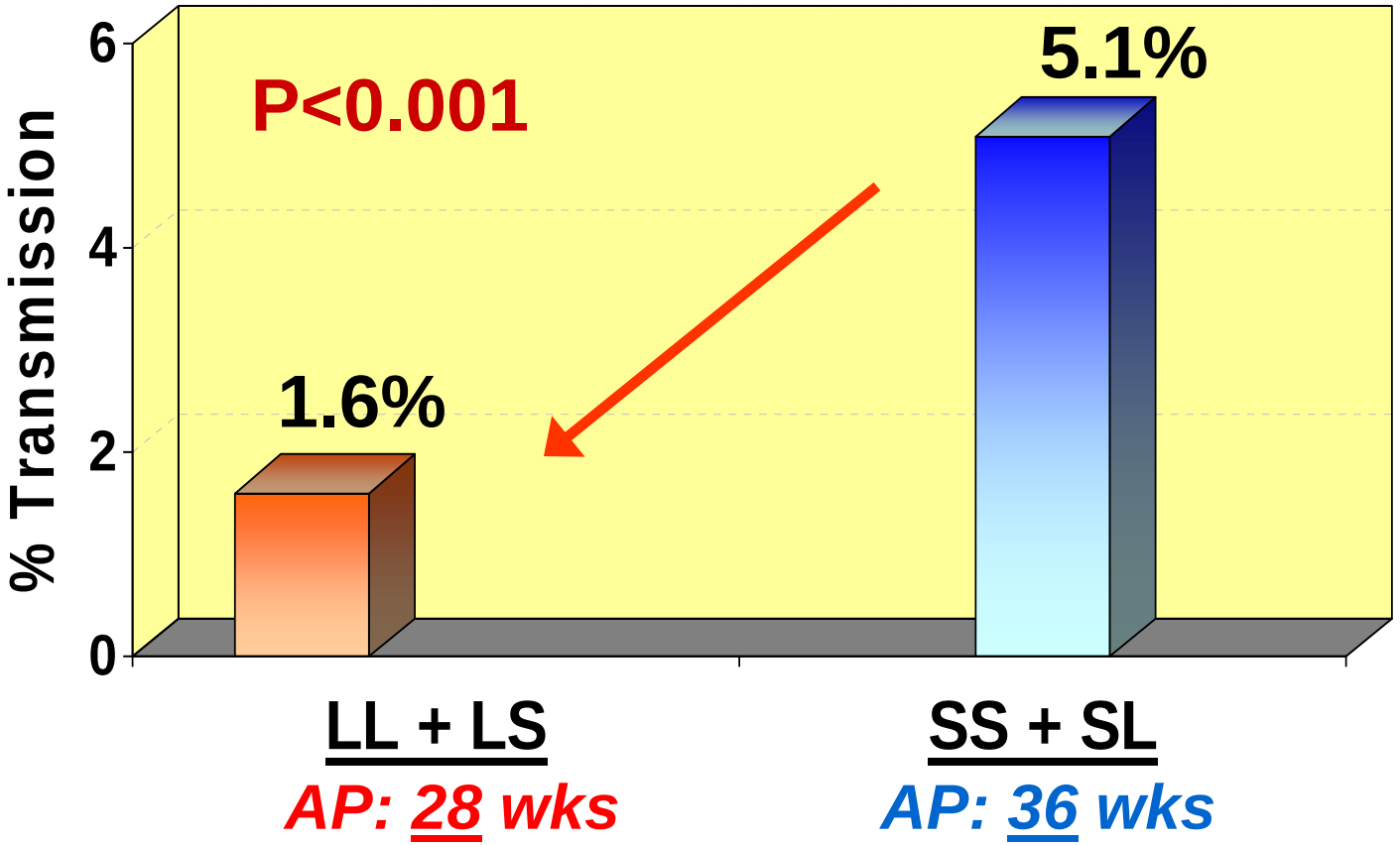
"Residual Transmission": Even if Prevent All IP and PP Transmission, When Start ARV at 28 Weeks:



1-2% *In Utero* Infection

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 for IP/PP transmission, still have “residual infection” of 1.6% starting at 28 weeks

A Key Issue:
ARV Treatment vs ARV Prophylaxis

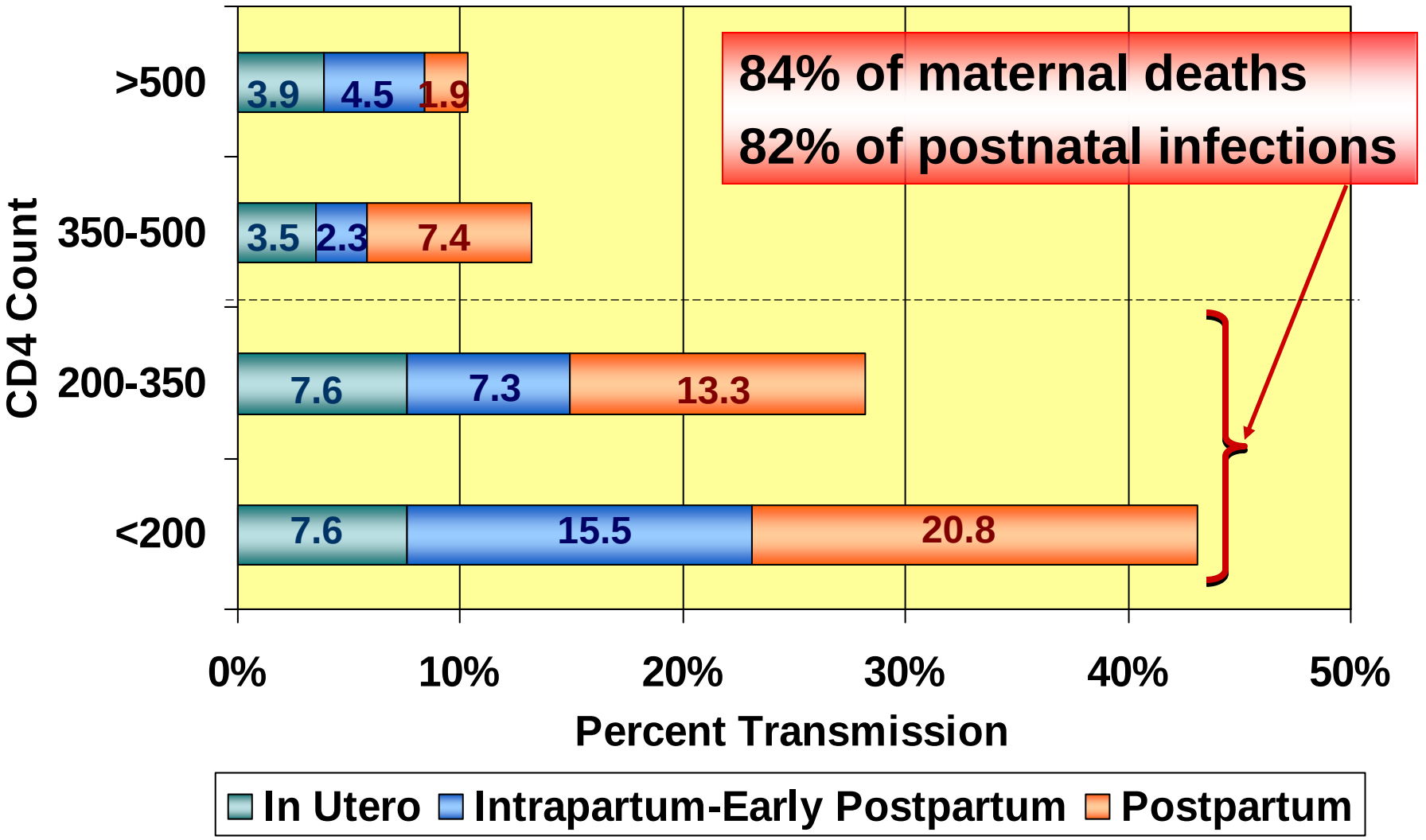
What Should CD4 Threshold for ARV Treatment be in Pregnancy?

(Treatment = HAART Started in Pregnancy and Continued "Life-Long" Even After No Further MTCT Risk Exists)

Why CD4 Threshold of <350 for Treatment?

Includes Most Maternal Deaths and Postnatal Infections

ZEBS Study – L. Kuhn personal communication 2009



CD4 < 200: 55% of maternal deaths, 47% of postnatal infections

If assume all pregnant women with CD4 <350 should be initiated on antiretroviral treatment for life

then remaining research questions revolve around

what is optimal intervention used solely for PMTCT for women with CD4 >350?

IF ASSUME TREATMENT FOR ALL WITH PREGNANT WOMEN WITH CD4 <350

For Women with CD4 >350

Antepartum/Intrapartum PMTCT

AZT/sdNVP + “tail”

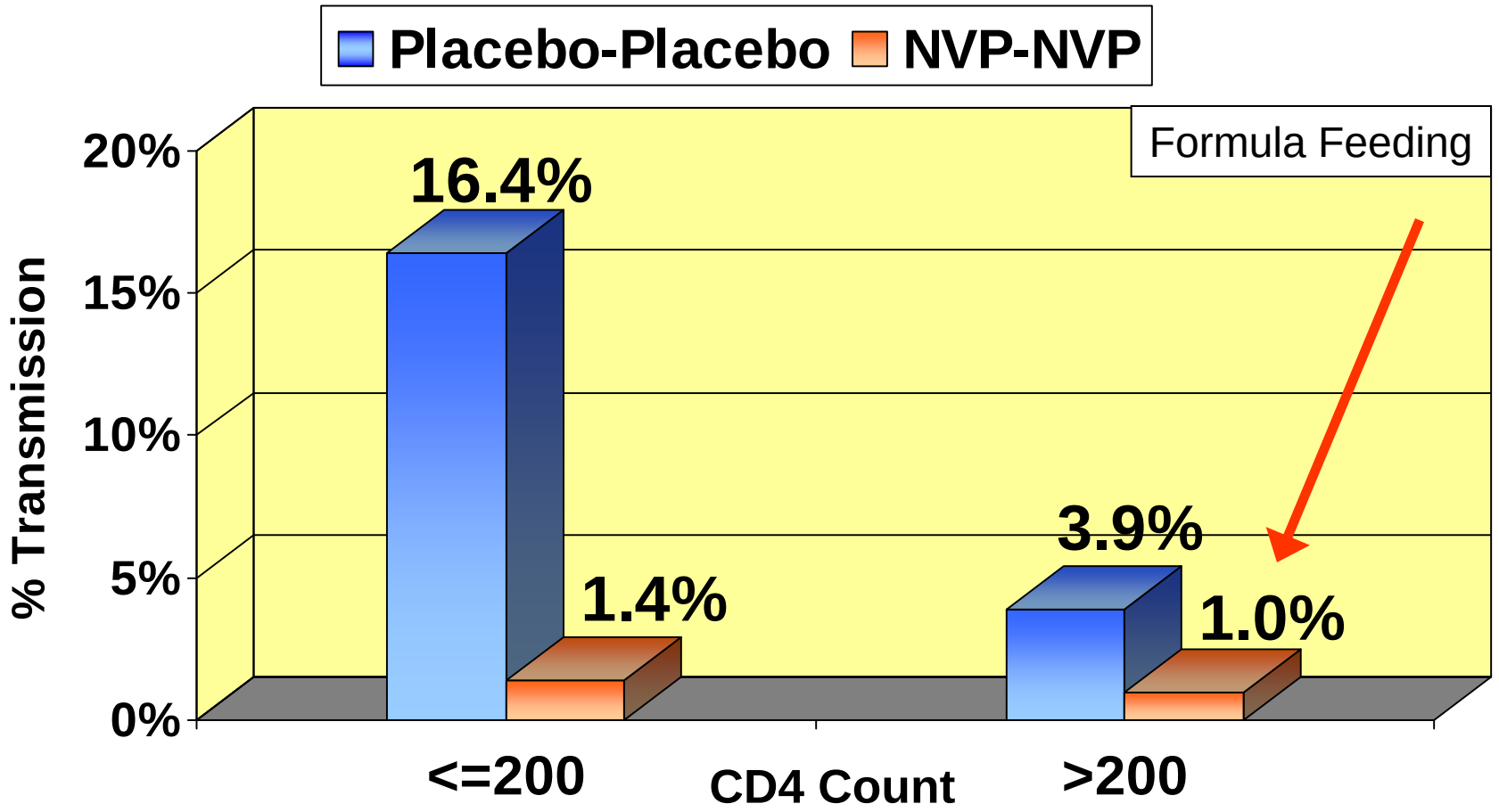
vs

Maternal HAART

May Have Comparative Efficacy in Women with Higher CD4 Counts

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

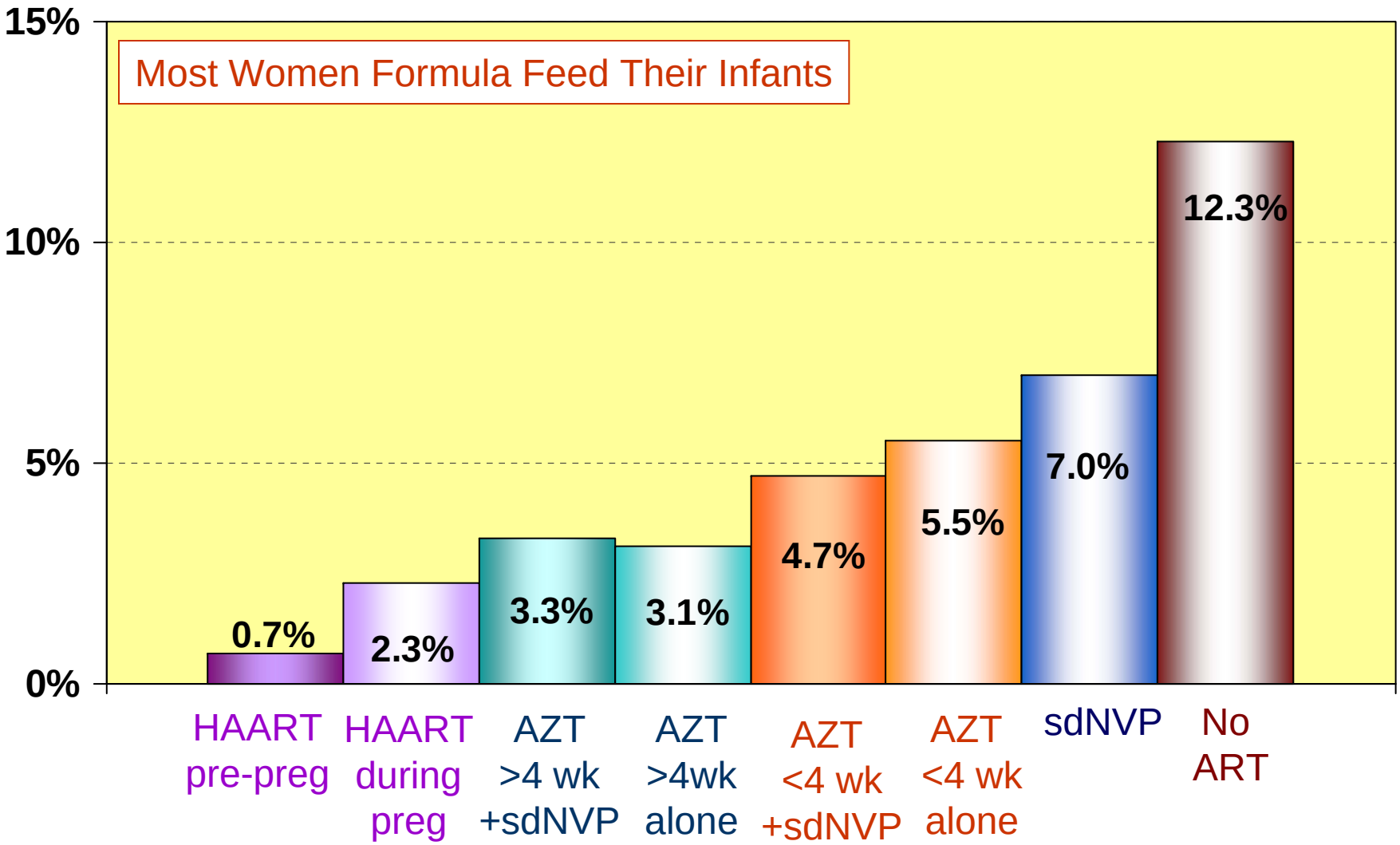
MTCT, Botswana National Data Oct 2006-Nov 2007

Tlale J et al. IAS Mexico City Aug 2008 (Abs ThAC04)

- **HIV+ pregnant women with CD4>200 are given AZT from 28 weeks through labor, and sdNVP at onset of labor.**
- **Women with CD4 ≤200 are given HAART.**
- **PMTCT uptake stood at 90% in 2007.**
- **Most women formula feed.**
- **PMTCT program data analyzed from October 2006- November 2007 on records of HIV test results of 10,516 children born to HIV-infected women from all health districts.**

MTCT at Age 6 Weeks by ARV Regimen
Botswana National Data Oct 2006-Nov 2007

Tlale J et al. IAS Mexico City Aug 2008 (Abs ThAC04)



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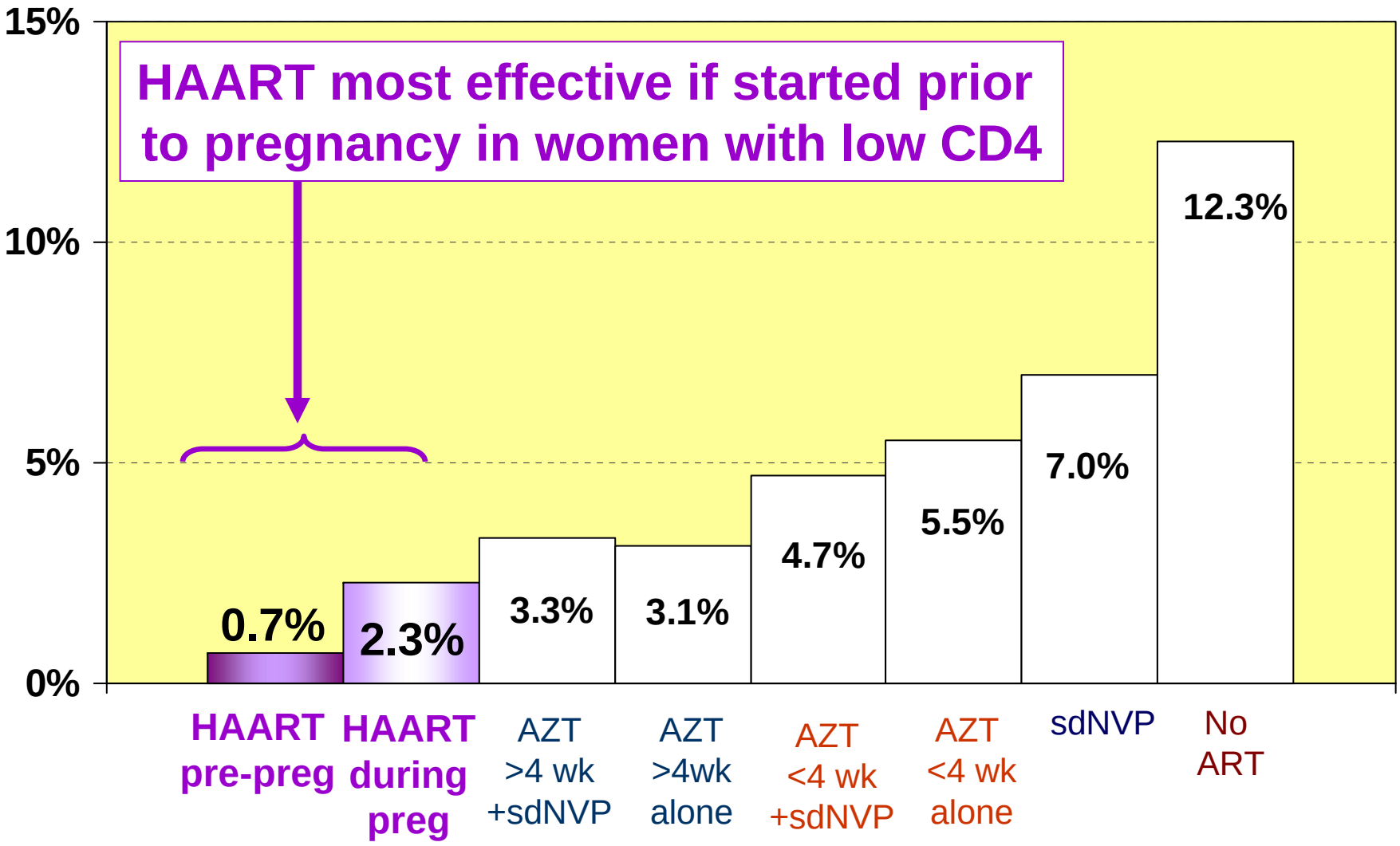

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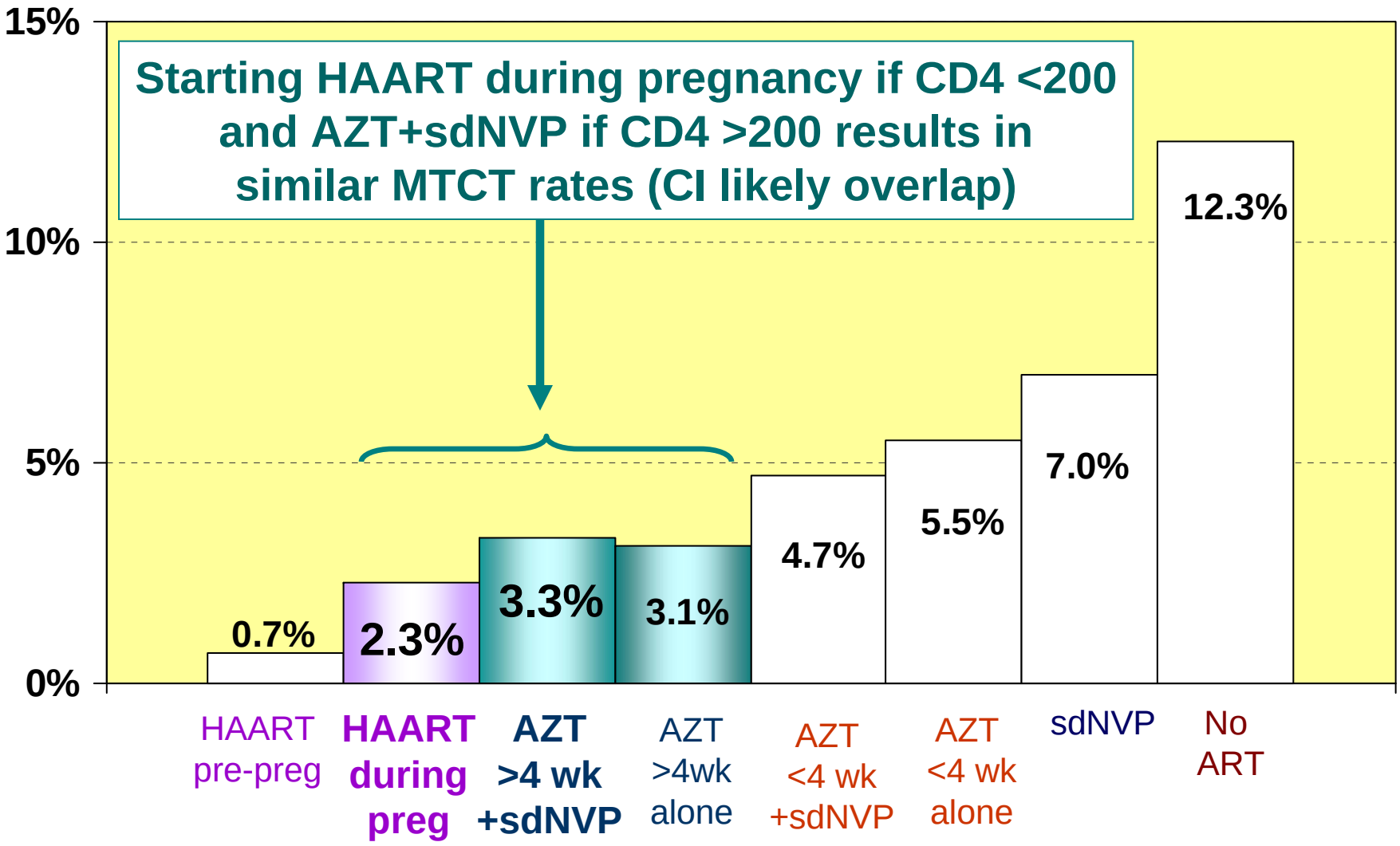

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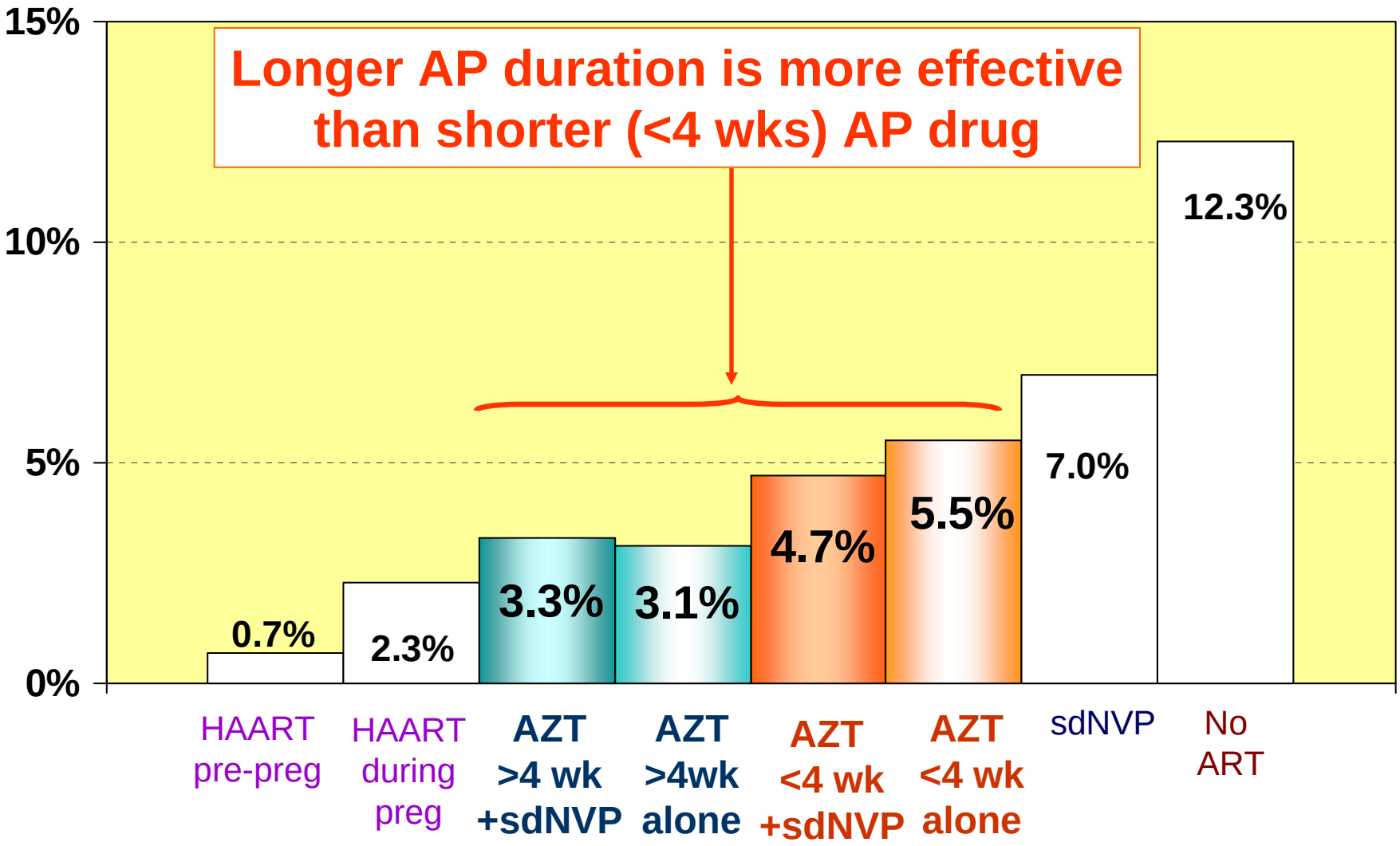

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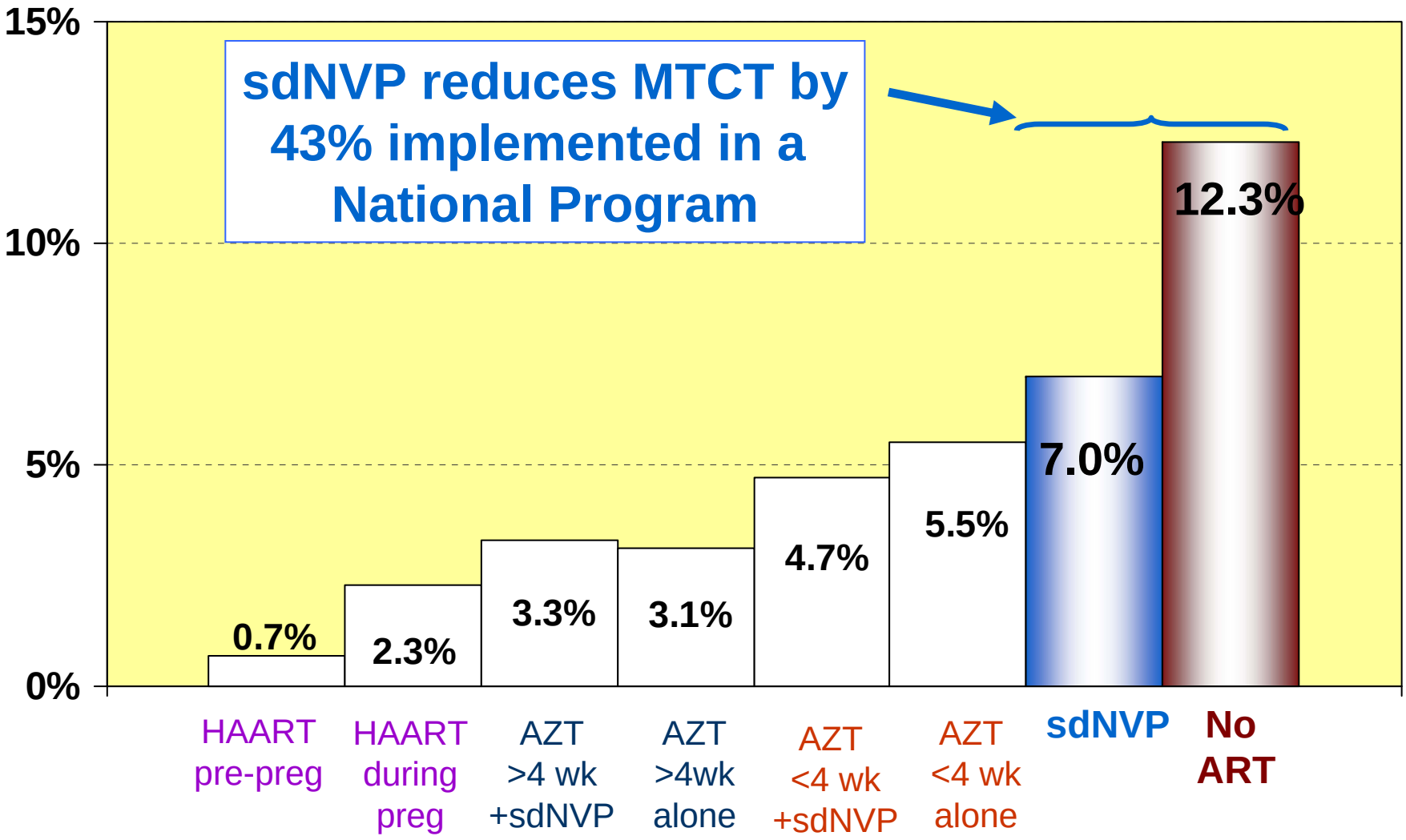


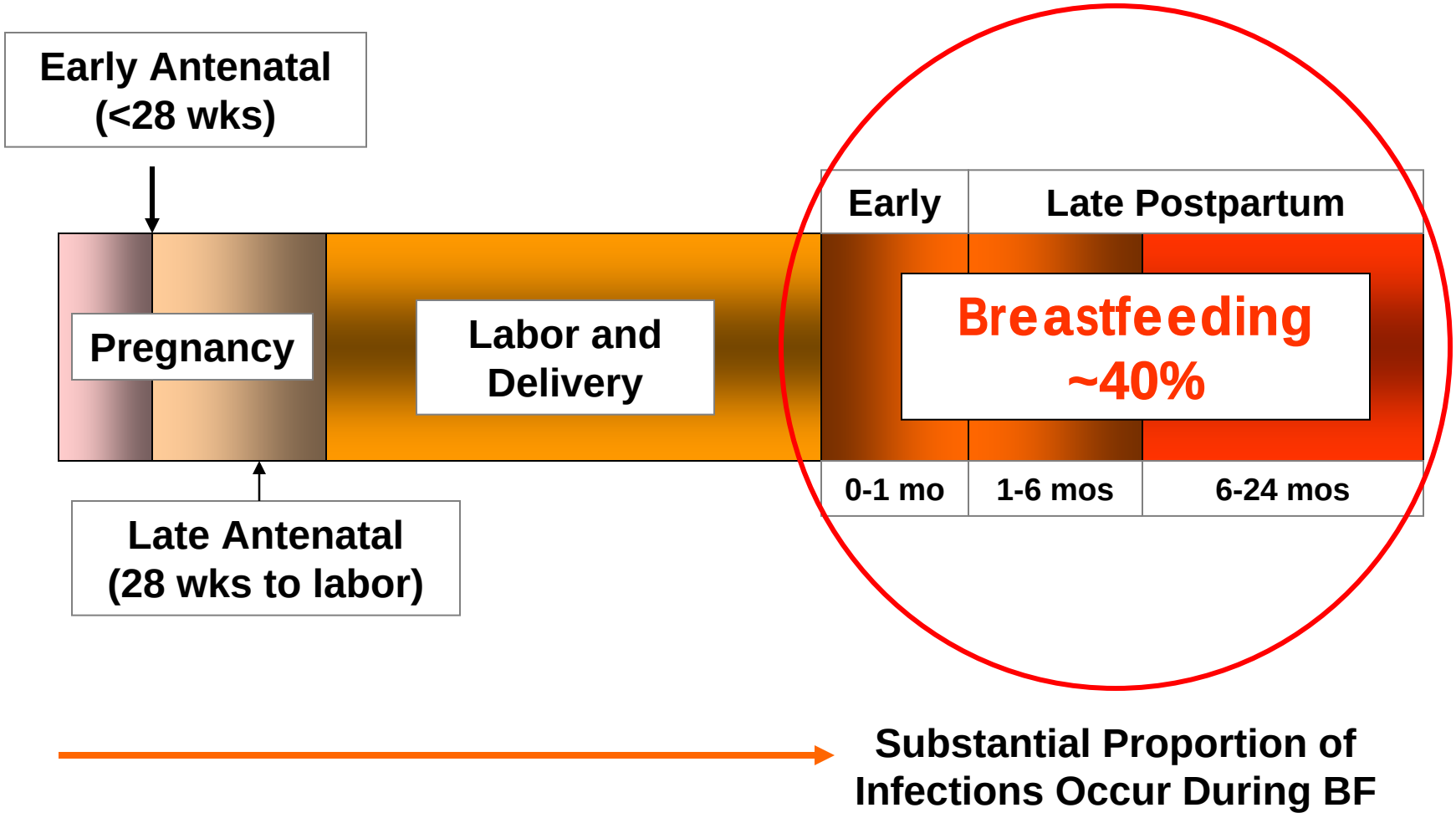
Mother to Child Transmission, 2000-2006, 5,930 Births to HIV+ Women, UK/Ireland

Townsend CL, et al. AIDS 2008;22:973-981

Prophylaxis	MTCT	Adjusted Odds Ratio (for mode delivery, sex, viral load)
Overall	1.2%	
ART >14 days	0.8%	
HAART with NNRTI	0.9%	1.31 (0.6-2.8) p=0.48
HAART with PI	1.1%	
HAART at conception	0.1%	0.18 (.02-1.3) p=0.09
HAART during pregnancy	1.3%	
HAART Elective CS	0.7%	
HAART Planned vaginal	0.7%	p=0.15
AZT Elective CS (N=464)	0%	←

In Breastfeeding Settings, ~40% of All Mother to Child Transmission Can be Attributed to Breastfeeding

10-15% of Infants with Prolonged Breastfeeding Become Infected



Prevention of Breast Milk HIV Transmission

- Hypothesized that “safer” breastfeeding, through giving antiretroviral prophylaxis during period when breast milk is most beneficial, with early weaning might reduce postnatal transmission.
- Ongoing studies are evaluating the safety and efficacy of:
  - Infant antiretroviral prophylaxis + early weaning
  - Maternal HAART during lactation + early weaning.
- However, increasing data indicate early cessation of breastfeeding at 6 months is not safe in some poor countries.

Potential Problems with Universal HAART Solely for PMTCT in Developing Countries

- Complexity – implementation issues; postnatal adherence issues (= resistance risk).
- Limited resources and cost – can't provide ART even to patients who need for own health.
- Limited regimen choice, limited by toxicity with NVP with CD4 >250 cells/uL; EFV teratogenicity; PI expense.
- Pregnancy outcome/long-term infant outcome
- Maternal health (issues of start-stop HAART).
- Differential penetration of ARV drugs into milk could result in resistant virus in milk.

If Choose to Use HAART
In Women with CD4 >350 for PMTCT:

Drug choice problematic:

- NVP toxicity

- EFV okay 3rd trimester but PP repeat pregnancy risk if prolonged?

-PI cost

NVP Liver Toxicity More Common in Pregnant than Non-Pregnant Thai Women and Women Receiving ART for PMTCT than for Treatment

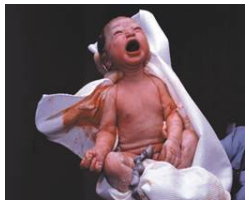
Phanuaphak N et al. HIV Med 2007;8:357-66

Rate per 100 patient-years

	Non-Preg	Preg	P value	ART for RX	ART for PMTCT	P Value
	(N=87)	(N=244)		(N=102)	(N=142)	
Median CD4	*152*	*277*		*136*	*414*	
Sx hepatitis	1.5	7.5	→ 0.02	2.5	16.0	0.0003 ←
Rash+liver	0.8	4.3	→ 0.05	0.8	10.2	0.0003 ←
Gr 1/2 liver	0.8	4.8	→ 0.04	0.8	5.8	0.02 ←
Gr 3/4 Rash	5.5	5.8	0.42	-	-	

First Trimester Efavirenz Use and Central Nervous System Defects

- Antiretroviral Pregnancy Registry prospective data do not indicate an increase in overall birth defects (10/364, overall 2.7%, 95% CI 1.3-5.0%).
- However, with *in utero* exposure in primates at doses resulting in drug levels similar to human exposure, 3/20 infant monkeys had severe central nervous system (CNS) defects (e.g., anencephaly, anophthalmia, cleft palate).
- 5 retrospective and 1 prospective human cases of CNS defects (e.g., meningomyelocele) with first trimester efavirenz exposure.
- FDA Class D (+ animal & potential human risk).



Maternal Antenatal HAART and Pregnancy Outcome

Published data	Low Birth Weight	
	HAART pre-conception	HAART start during Pregnancy
Machado Sex Tx Dis 2008 (Brazil) N=696	33.3%	16.5%

	Short AZT+-3TC+sdNVP	HAART
Ekouevi AIDS 2008 (Cote d'Ivoire) N=326	12.4%	22.3% p=0.02

Mitochondrial Dysfunction in Infants and *In Utero* ARV Exposure

- *In utero* ARV exposure has been reported to be associated with:
  - Mostly aSx transient neonatal lactic acid elevations in 50-95% (some transient neuro sx)
  - Mild, clinically aSx but persistent hematologic abnormalities
  - Rarely with clinically Sx of mitochondrial dysfunction – primarily neurologic Sx

❖ Combination ARV exposure may be associated with greater risk than single drug exposure.

Antiretroviral Drug Penetration into Human Breast Milk

	Maternal Plasma/Breast Milk Ratio
NRTI	
AZT	0.44-1.86
3TC	1.8-5.57
TDF	Low levels (non-bioavailable form - TFV, not TDF?)
NNRTI	
EFV	0.54
NVP	0.60-0.75
PI	
ATV	0.04-0.11
LPV/r	0.11
NFV	0.06-0.24

Shapiro R. JID 2005;192:720 (3TC, NVP)
Giuliano M. JAIDS 2007;44:286 (AZT, 3TC, NVP)
Mirochnick M. AAC 2009;53:1170 (AZT, 3TC, NVP)
Colebunders R. AIDS 2005;19:1912 (NVP, NFV, IDV)
Schneider S. JAIDS 2008;48:450 (EFV)
Mirochnick M. CROI 2009 Abs 940 (TDF)
Spenser L. CROI 2009 Abs 942 (AZT, 3TC, ATV)
Corbett A. CROI 2009 Abs 947 (AZT, 3TC, LPV/r)

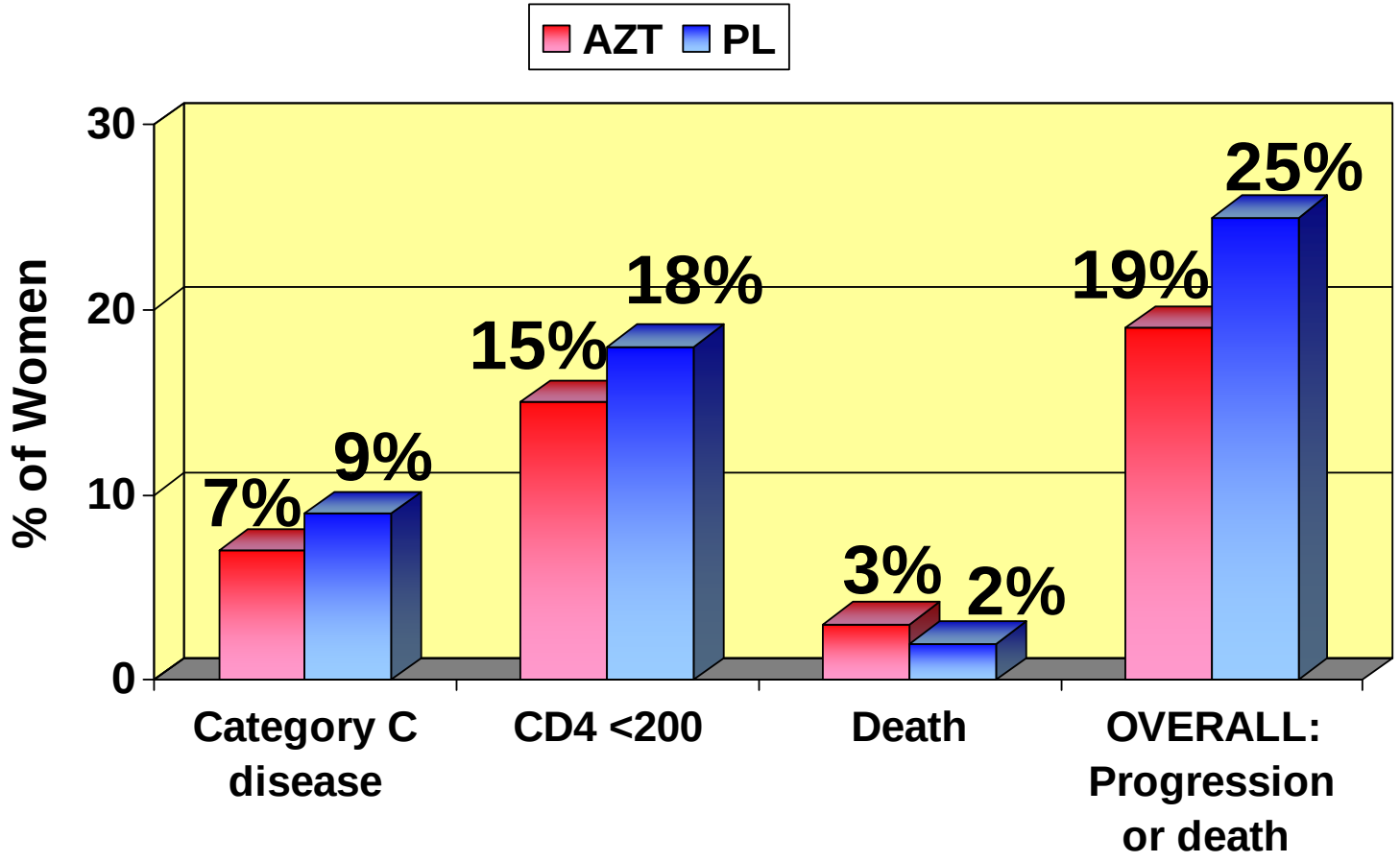
Maternal Health: Are There Long-Term Consequences in Healthy Women of Receiving HAART During Pregnancy for Prophylaxis of MTCT and then Stopping HAART?

Hazard Ratio for OI/Death Interrupted vs Continuous ART by Subgroup, SMART

Subgroup	Interrupted ART # pt (rate 100pt-yr)	Continuous ART # pt (rate 100pt-yr)	Hazard Ratio
Baseline CD4			
350-449	24 (3.2)	18 (2.2)	1.5
→ 450-549	27 (3.7)	7 (0.9)	4.1
550-649	19 (3.5)	7 (1.3)	2.8
>650	50 (3.2)	15 (2.0)	3.2
Duration ART			
→ 0-<3 yrs	23 (2.8)	7 (0.8)	1.6
3-5 yrs	30 (2.7)	8 (1.1)	1.5
5-<7 yrs	27 (3.3)	15 (1.7)	1.8
>7 yrs	40 (3.6)	17 (1.5)	2.5
Hx ART baseline			
→ No	4 (2.7)	1 (0.5)	5.2
Yes	22 (4.4)	9 (1.7)	2.6

Lack of Long-Term Adverse Effects of AZT Prophylaxis in Women in PACTG 076

Bardeguez A et al. JAIDS 2003;32:170-81.



No significant differences between AZT and Placebo Groups (overall progression/death, p=0.28)

WITS: Progression after Stopping ARV Prophylaxis

Watts DH et al. 12th CROI 2005, Los Angeles, CA, Abs S109

- Among ART-naïve women entering pregnancy with a CD4 > 350 and initiating ARV for PMTCT, change in CD4 and HIV RNA were similar over the 1st year postpartum among women stopping or continuing therapy PP.
- No women in either group progressed to AIDS or death during the 1st year postpartum.
- However, a non-significant trend to increased risk CDC Class B events (RR 2.9, 0.6-13.4) and significant increase in activated CD8 cells (CD38+, DR+) was observed among women stopping compared to continuing ART PP.

IF ASSUME TREATMENT FOR ALL WITH PREGNANT WOMEN WITH CD4 <350

For Women with CD4 >350

Postnatal PMTCT via Breastfeeding

Infant ARV Prophylaxis

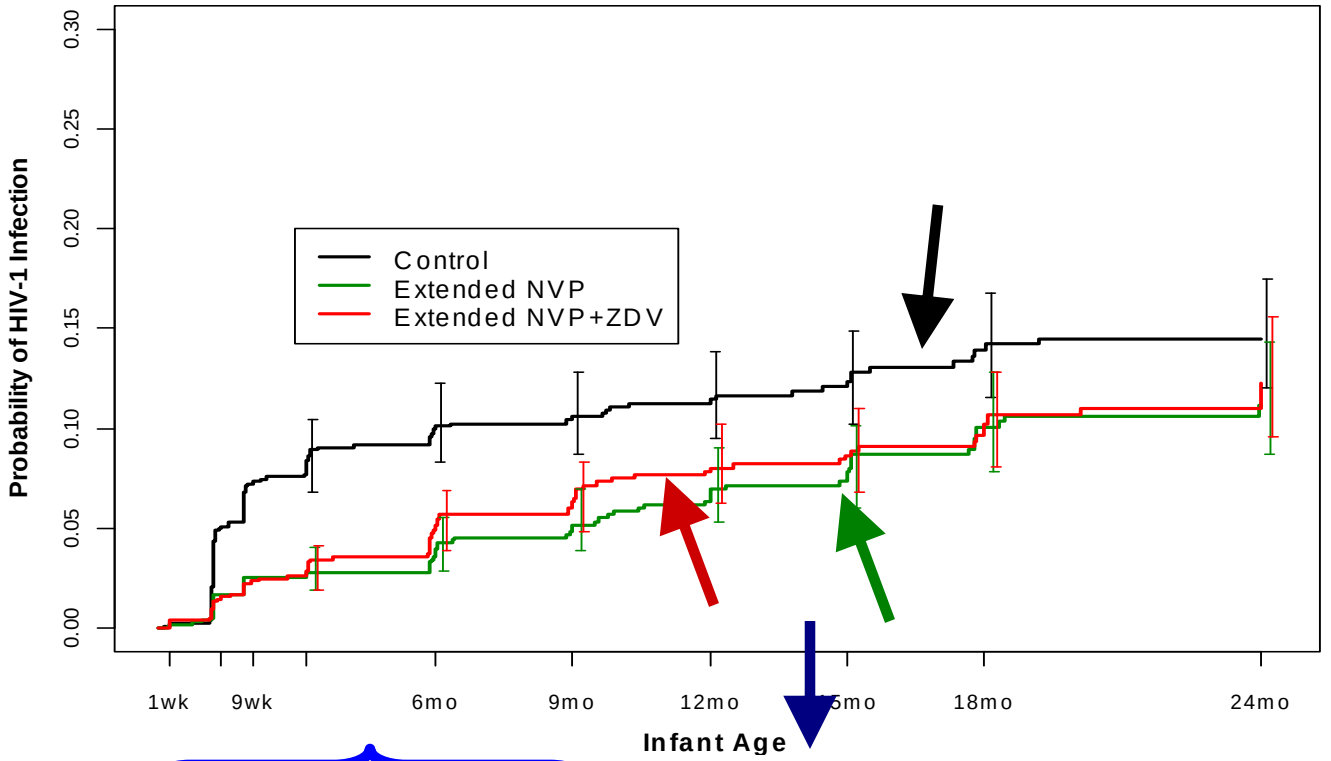
Vs

Maternal HAART

May Have Comparative Efficacy in Women with Higher CD4 Counts

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

Maternal Antiretroviral Prophylaxis of Breast Milk HIV Transmission

- Observational suggest maternal HAART during lactation may reduce transmission.
- For women who require therapy for their own health, the benefit of HAART for maternal health outweighs potential risks.
- These women are at highest risk for postnatal transmission and HAART may reduce this risk.
- NVP toxicity not a concern in women with low CD4.
- Research needed for women with high CD4.

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

Kilewo et al. 4th IAS Sydney Australia 2007 Abs. TuAX101

	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

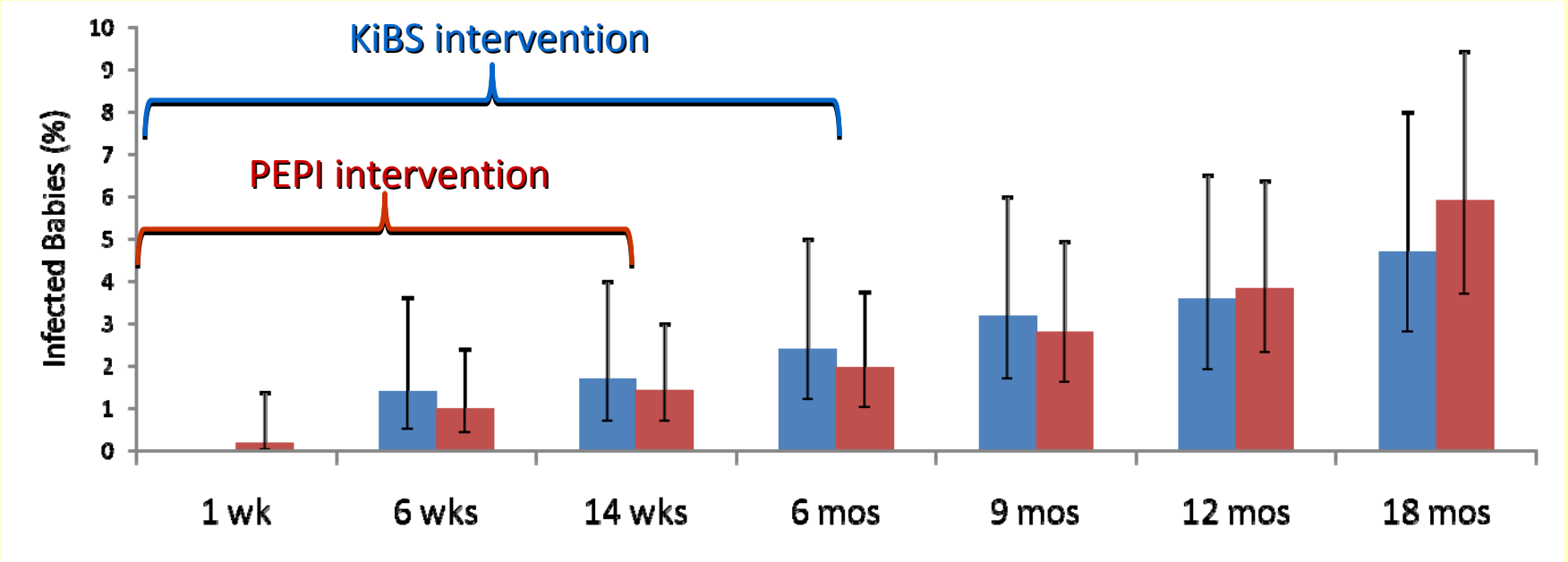
Kisumu Breastfeeding Study (KIBS): Maternal HAART for PMTCT in 500 Breastfeeding Mothers in Kenya

Thomas T et al. 15th CROI, 2008, Boston, MA Abs 45aLB

	0-7 Days	6 Wks	3 Mos	6 Mos
Overall MTCT	**2.4%**	**3.9%**	**4.1%**	**5.0%**
Postnatal Tx		**+1.5%**	**+1.7%**	**+2.6%**
By CD4 count:				
CD4 <250	**3.4%**	**4.3%**	**5.2%**	**5.2%**
CD4 >250	**2.1%**	**3.8%**	**3.8%**	**4.9%**

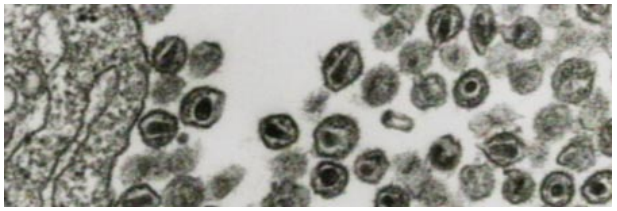
For Women with CD4 >350
No Significant Difference in Postnatal MTCT:
KiBS (Maternal HAART) vs PEPI (Infant ARV)

(infants uninfected at birth)



Thomas T, Fowler M, and KiBS study team, unpublished

Taha T, Kumwenda N, Hoover D, and PEPI study team, unpublished



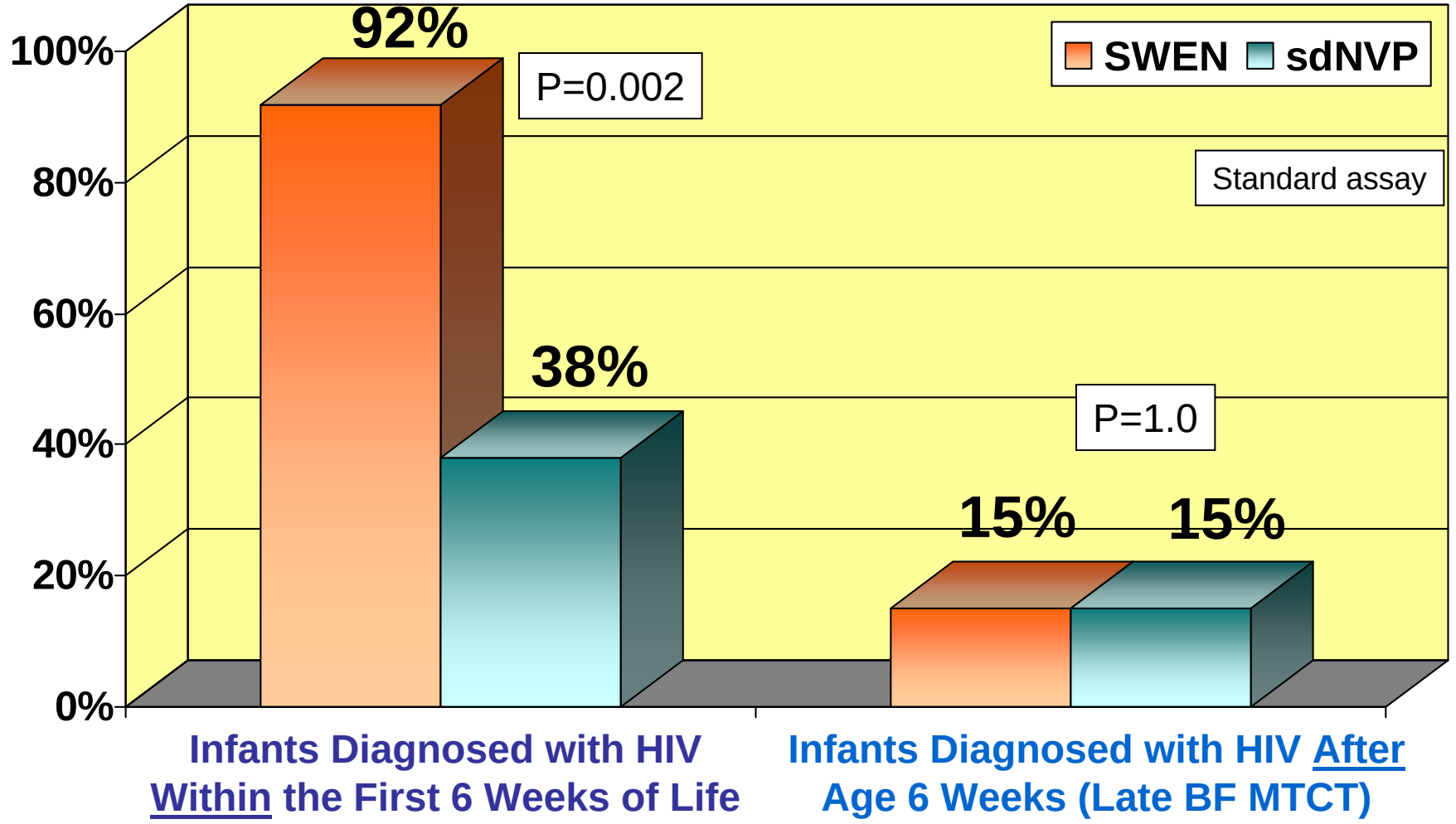
Postpartum Prophylaxis of Breast Milk MTCT

Issue of ARV Drug Resistance in Infants:

Problem with Infant NVP Prophylaxis but also with Maternal HAART

NVP Resistance More Frequent in Infants Infected While Receiving Extended NVP but Not in Infants Infected After Extended NVP was Stopped

India SWEN Study ***Moorthy A et al. PLosONE 2009;4:e4096***



Resistance in BF Infected Infants in KIBS (Maternal HAART Prophylaxis)

Zeh C et al. 15th CROI, 2008, Boston, MA Abs 45aLB

		First Positive Viral (PCR) Test		Wk 14 + 24 Specimen
Week Postpartum	**N**	**Not amplified**	**N resist/ N tested**	**N resist/ N tested**
Delivery	**12**	**3**	**0/9**	**11/12**
2 Wks	**2**	**1**	**0/1**	**1/2**
6 Wks	**6**	**0**	**1/6**	**1/6**
14 Wks	**2**	**0**	**2/2**	**2/2**
24 Wks	**2**	**0**	**1/2**	**1/2**
36 - 72 Wks	**5**	**1**	**0/4**	**NA**
Total	**29**	**10**	**3/19 (16%)**	**16/24 (67%)**

Resistance not seen on first viral test but rather appears to have emerged during breastfeeding period

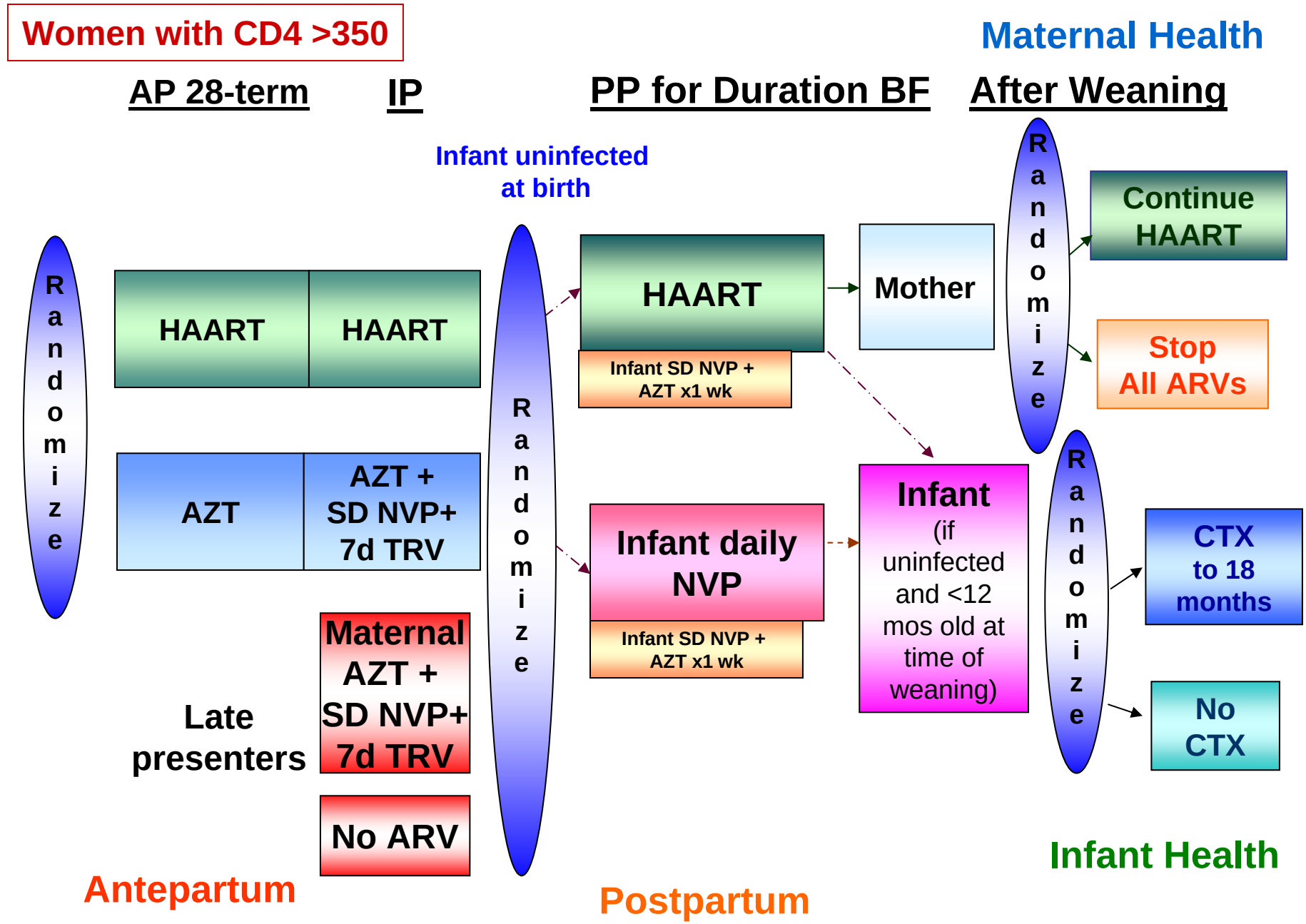
Summary: Breastfeeding and HIV Transmission

- ARV prophylaxis of infant or the mother during breastfeeding will likely both reduce postnatal MTCT, possibly to a similar extent.
- Infants who become infected in both scenarios are likely to have resistant virus.
- Women who require treatment should receive HAART, which will likely decrease PP MTCT.
- However, the risks and benefits of infant vs maternal prophylaxis need to be compared for women with higher CD4.
- Longer interventions to permit safe prolonged breastfeeding need to be assessed.

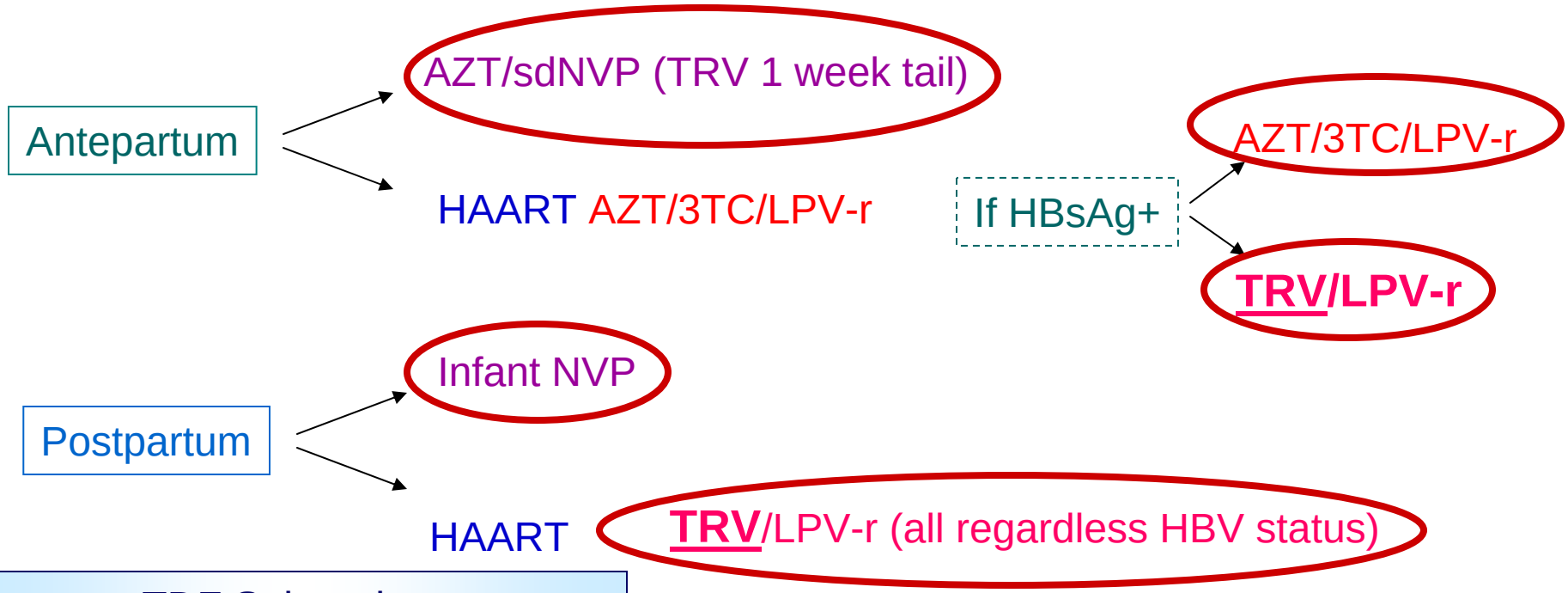
PROMISE

Promoting Maternal Infant Survival Everywhere

PROMISE General Overview: Sequential Randomized 2x2 Factorial Trial



Antiretroviral Regimens in PROMISE and Renal and Bone Safety Study of TDF



TDF Substudy:

- Dexa scans mothers and infants
- Infant growth
- Ca, P, creatinine
- Renal tubular function
- Markers of bone growth
- Inflammatory cytokines
- TDF levels in breast milk, infant

Thank You For Your Attention