


Update on the Science of Prevention of Mother to Child HIV Transmission

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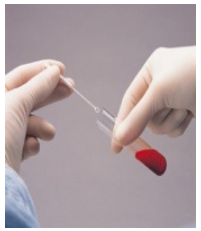
Efficacy of PMTCT Programs is Related to More than Just the PMTCT Regimen Used



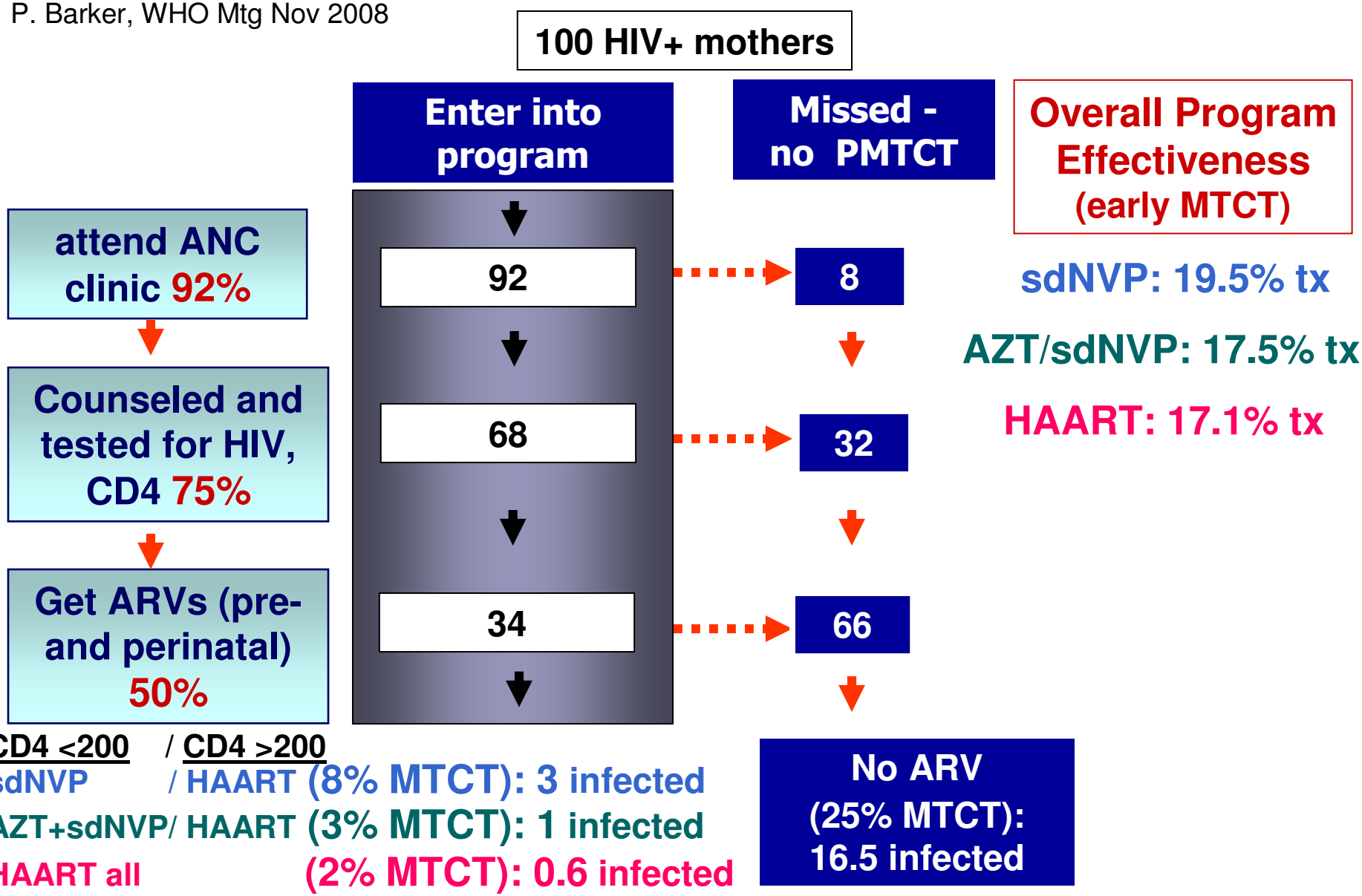
- To provide PMTCT, need to identify HIV-infected women during pregnancy.
  - In 2007, only 18% of pregnant women received HIV testing in RLC.

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

Program efficacy is as much related to PMTCT cascade efficacy as PMTCT regimen efficacy.

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

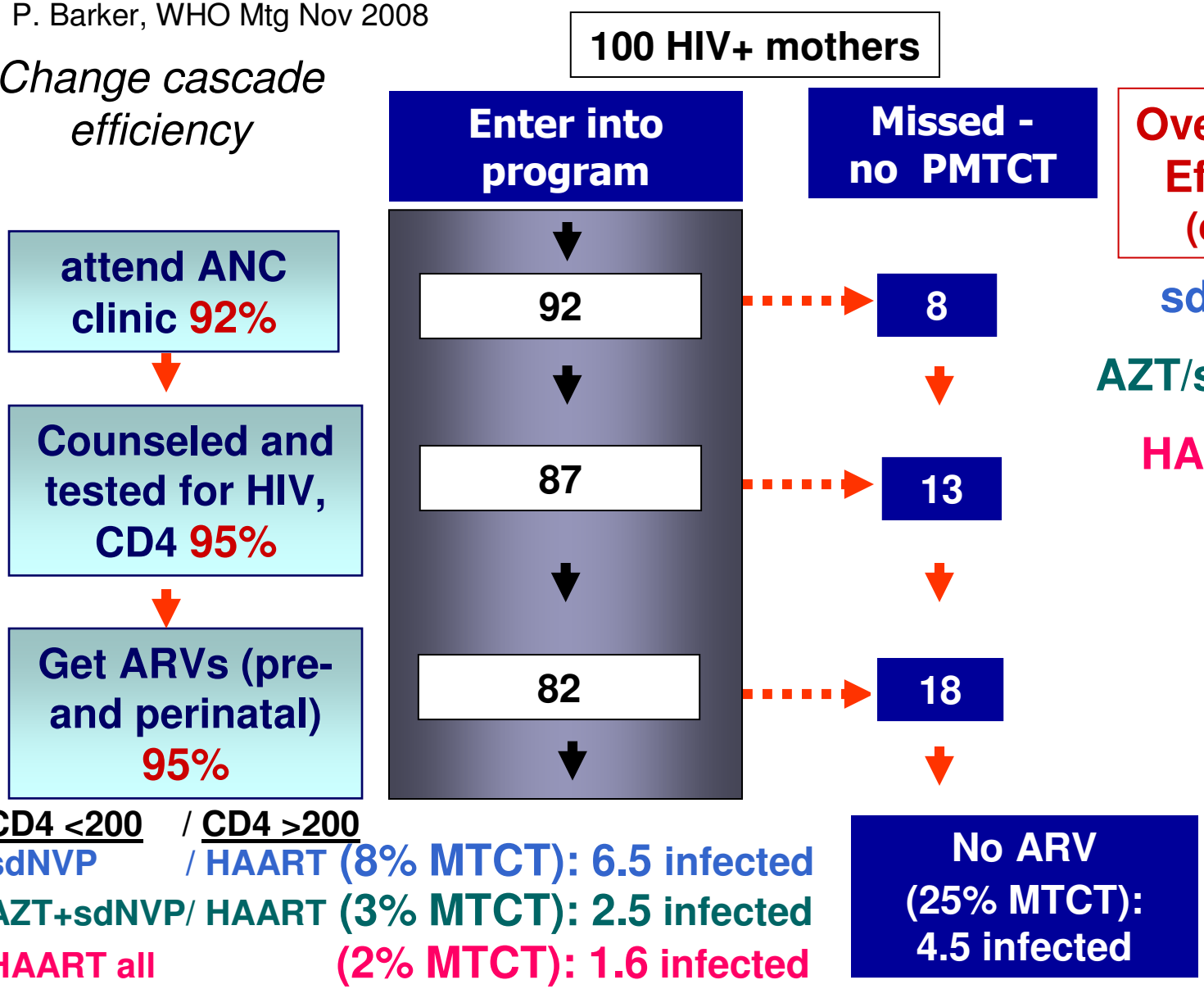
P. Barker, WHO Mtg Nov 2008



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

P. Barker, WHO Mtg Nov 2008

Change cascade efficiency



CD4 <200 / CD4 >200

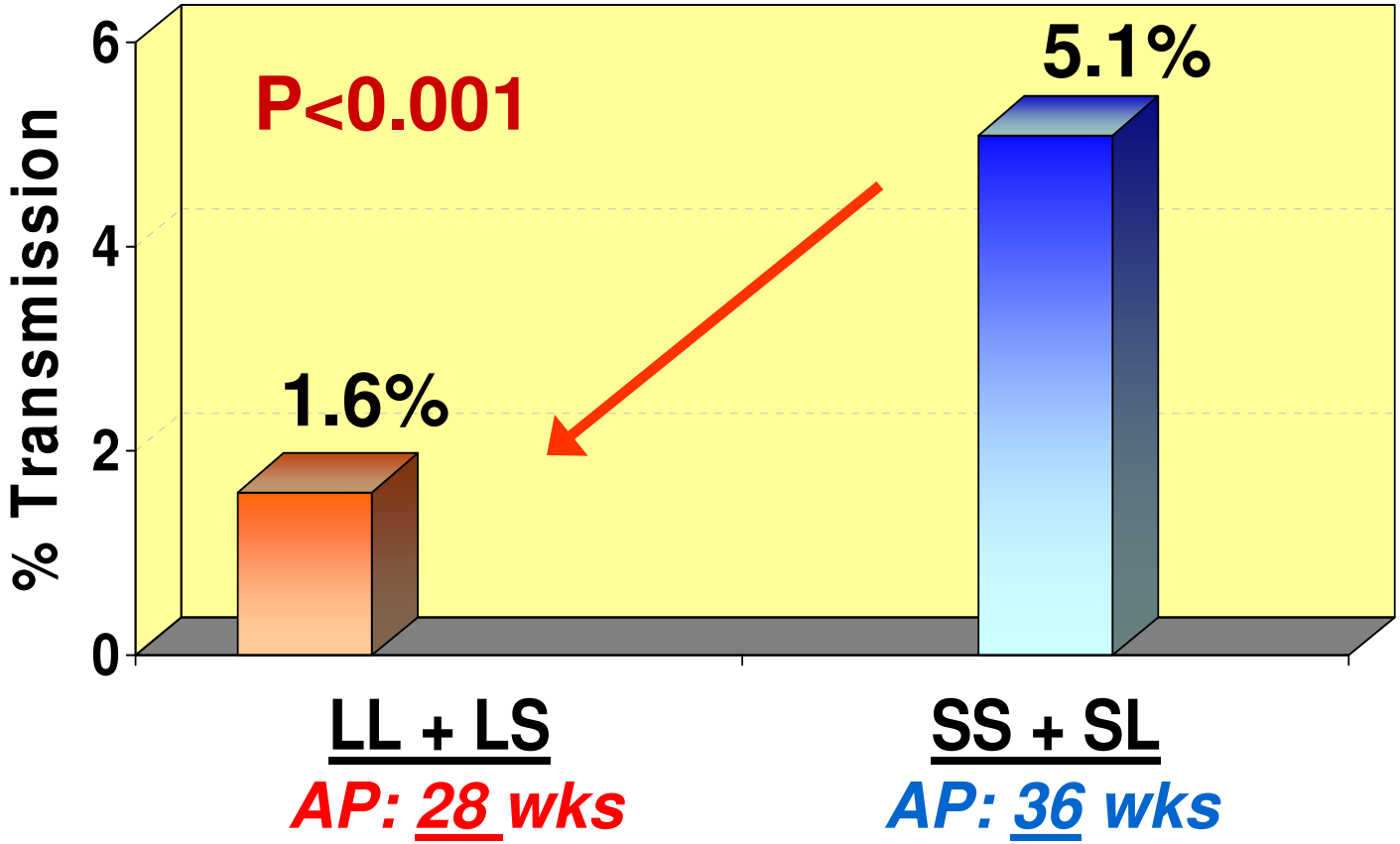
sdNVP / HAART (8% MTCT): 6.5 infected

AZT+sdNVP/ HAART (3% MTCT): 2.5 infected

HAART all (2% MTCT): 1.6 infected

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)

Current WHO (2006) PMTCT Guidelines on When to Treat Pregnant Women

Table 2. Recommendations for initiating ARV treatment in pregnant women based on clinical stage and availability of immunological markers[a]

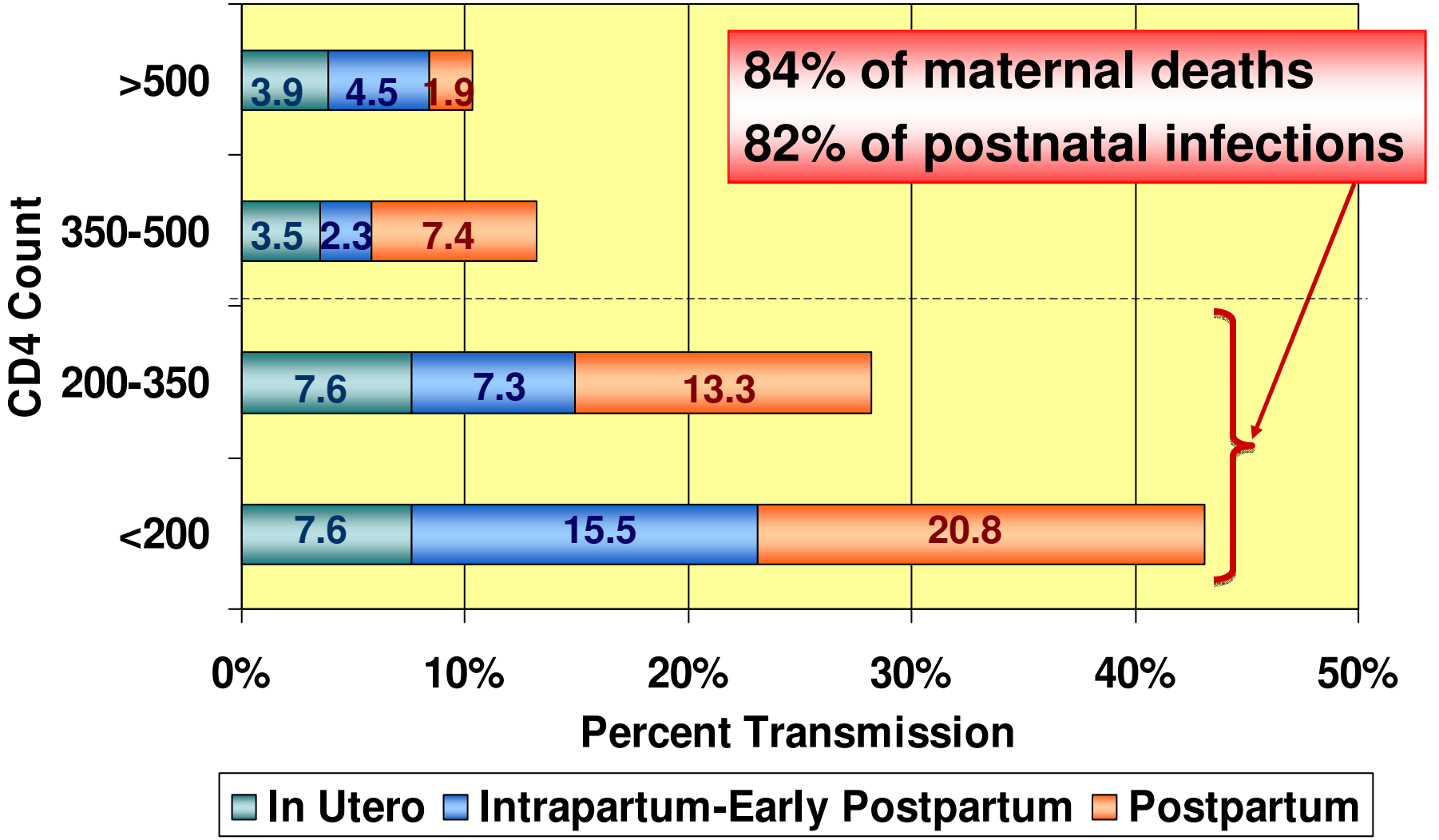
WHO CLINICAL STAGE	CD4 TESTING NOT AVAILABLE	CD4 TESTING AVAILABLE
1	Do not treat **(Level A-III recommendation)**	Treat if CD4 cell count <200 cells/mm^3 **(Level A-III recommendation)**
2	Do not treat **(Level B-III recommendation)**	
3	Treat **(Level A-III recommendation)**	Treat if CD4 cell count <350 cells/mm^3 **(Level A-III recommendation)**
4	Treat **(Level A-III recommendation)**	Treat irrespective of CD4 cell count **(Level A-III recommendation)**

[a] Women have lower CD4 cell counts during pregnancy compared to postpartum, partly due to pregnancy-related haemodilution. The impact of this on using the CD4 350 threshold in pregnant women, especially in those in clinical stage 1 or 2, is not known.

Why CD4 Threshold of <350 for Treatment?

Includes Most Maternal Deaths and Postnatal Infections

ZEBS Study – Thea D et al. 2008



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

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

For Women with CD4 >350

Antepartum/Intrapartum PMTCT

AZT/sdNVP + "tail"

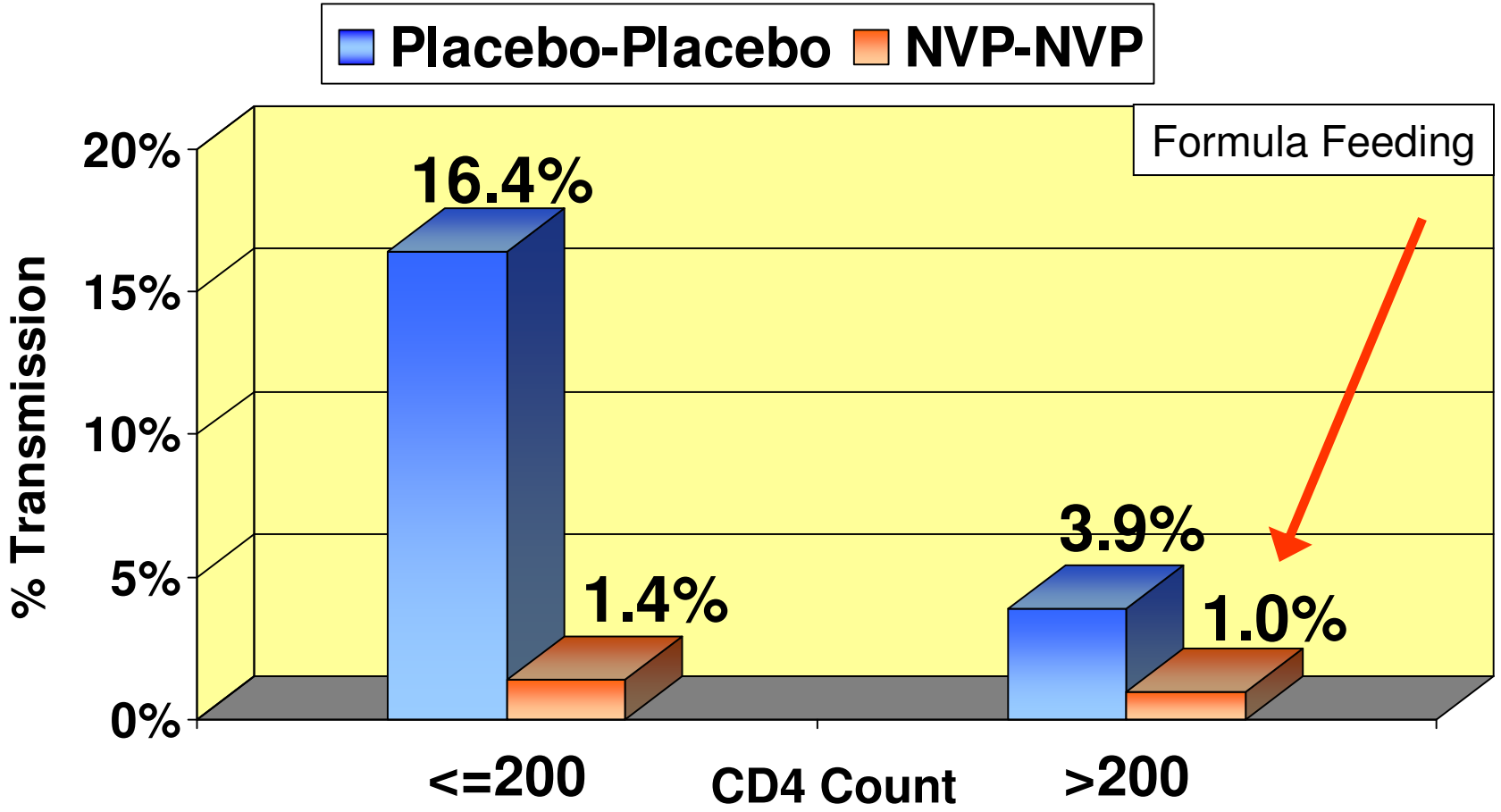
vs

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.



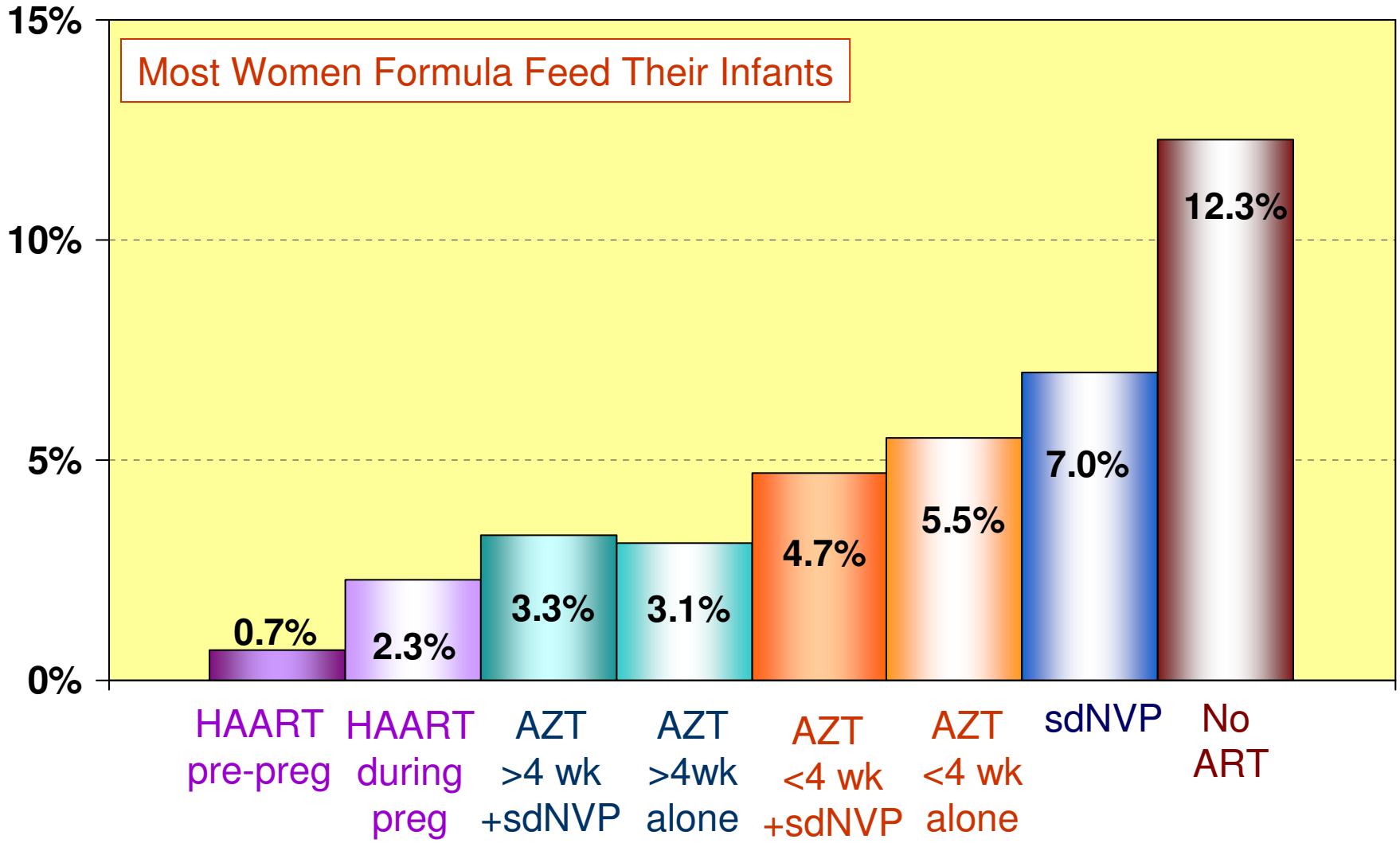
Comparing Difference in Transmission Rates Between AZT/Placebo-Placebo and AZT/NVP-NVP by CD4

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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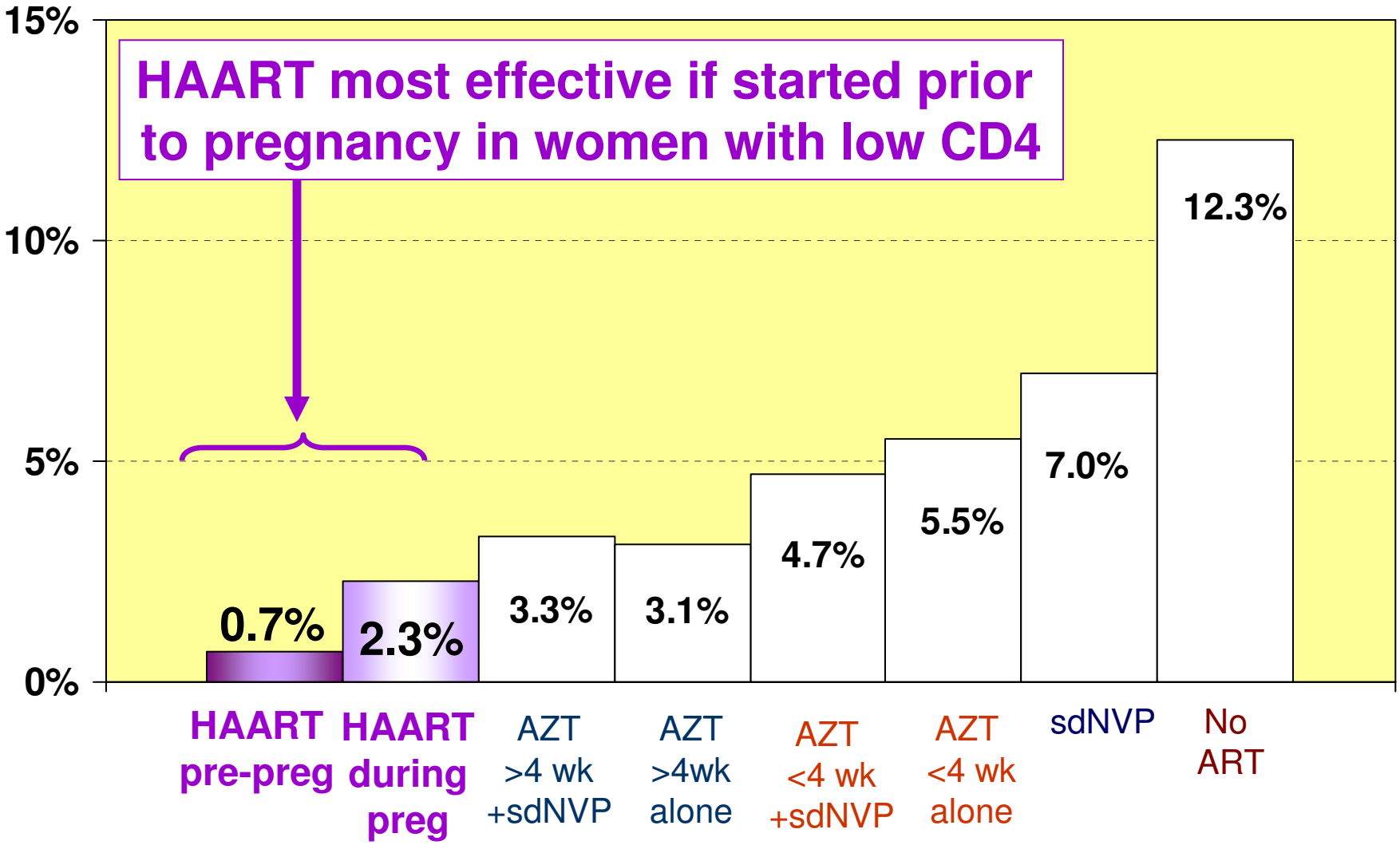

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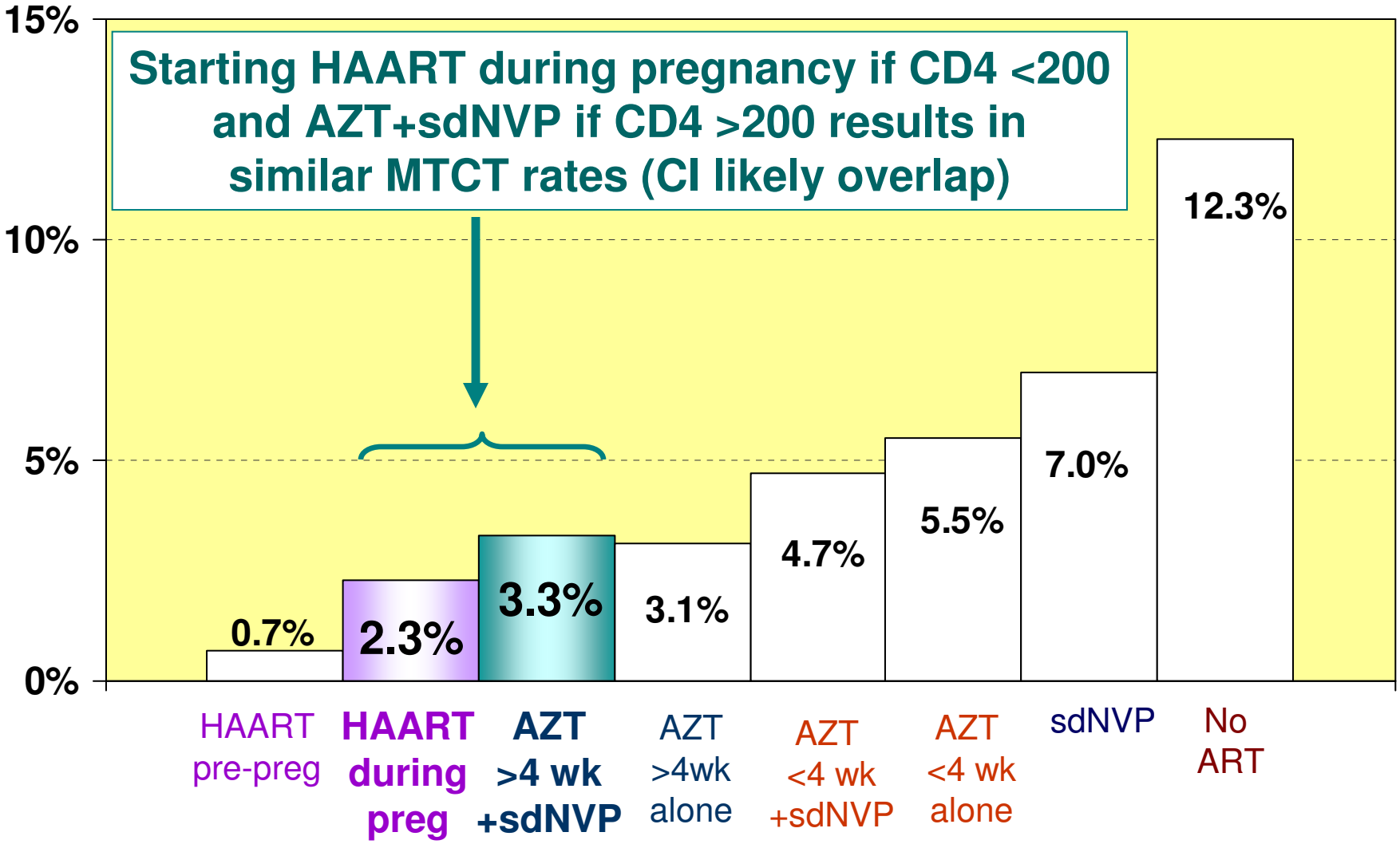

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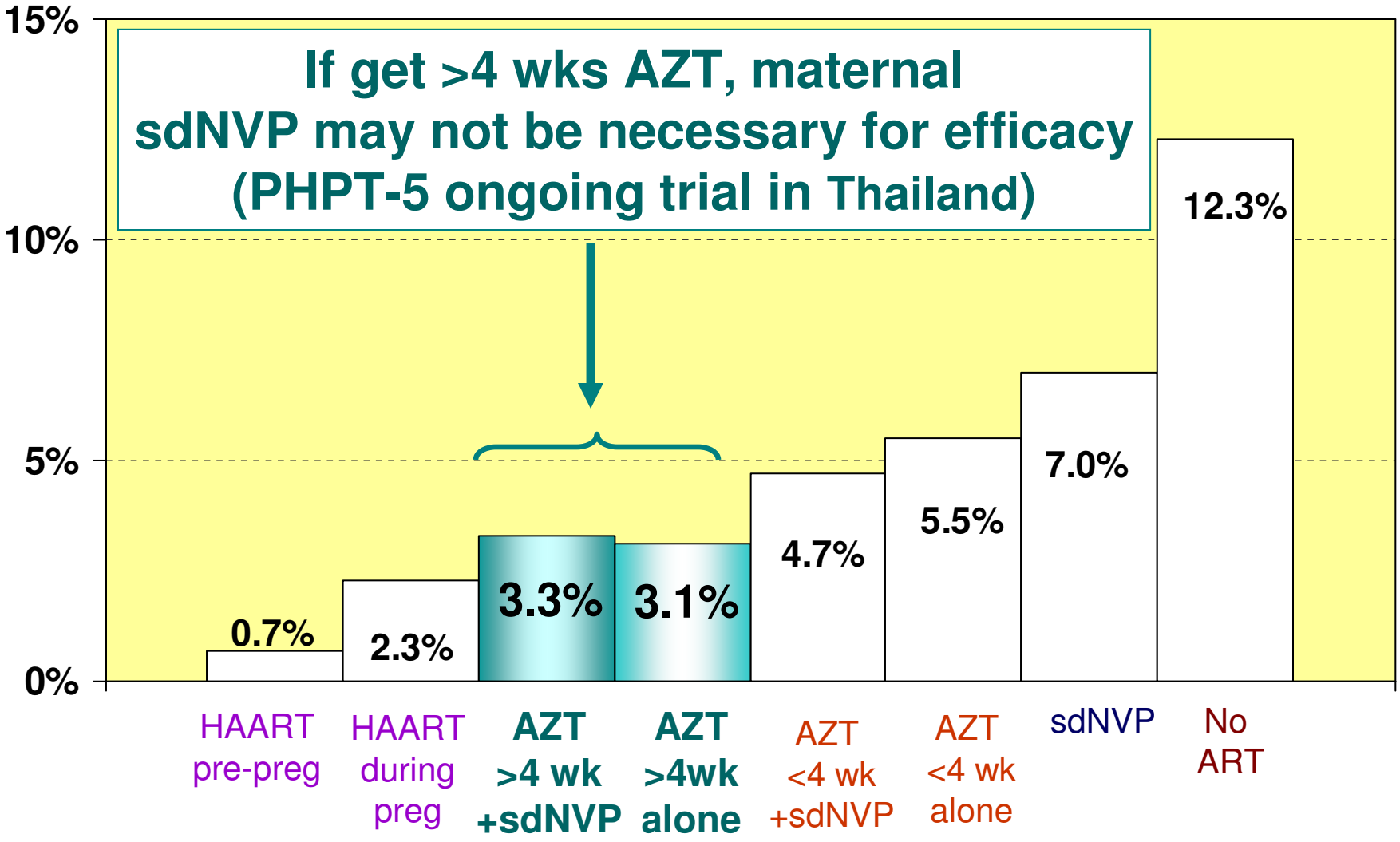

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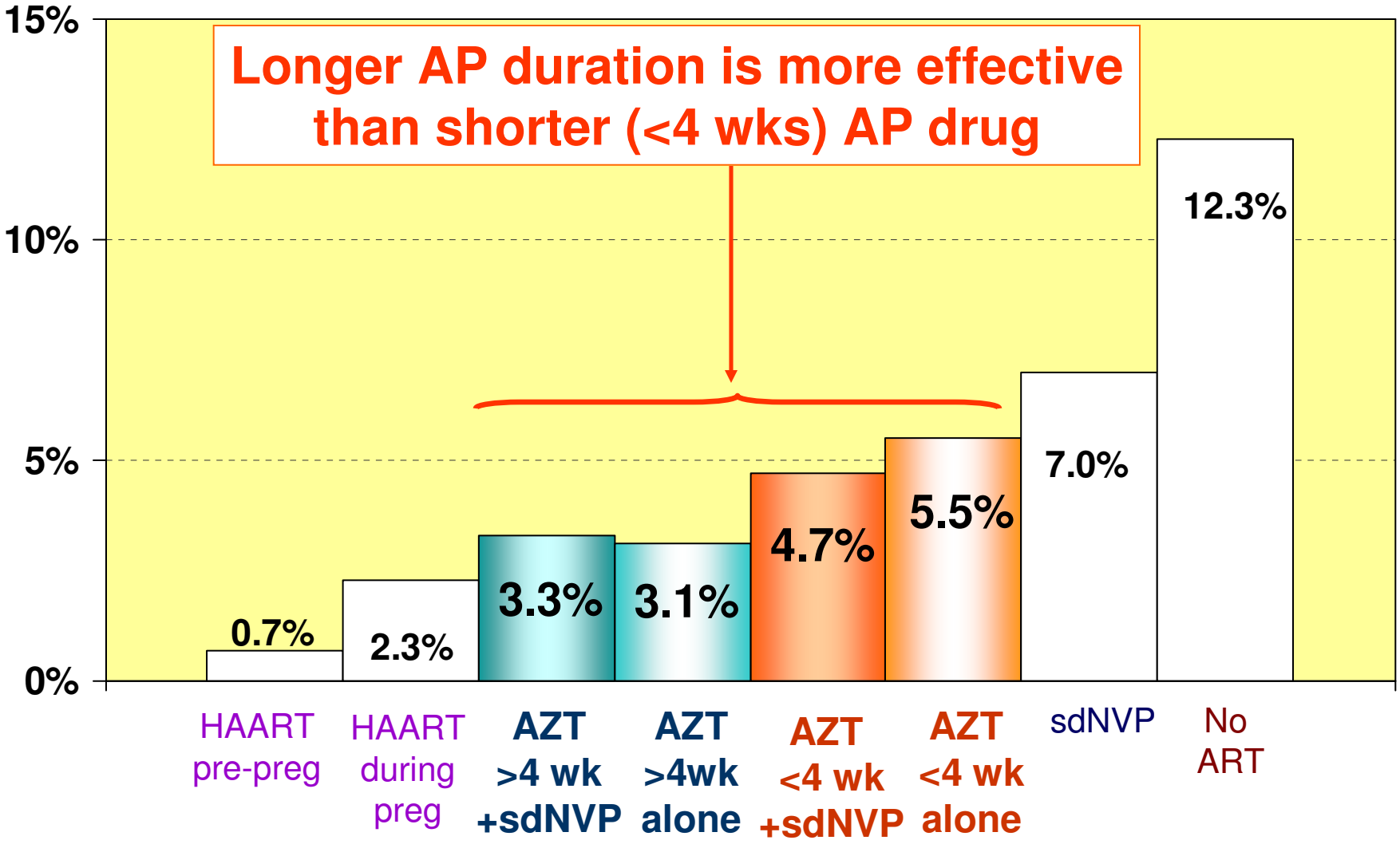

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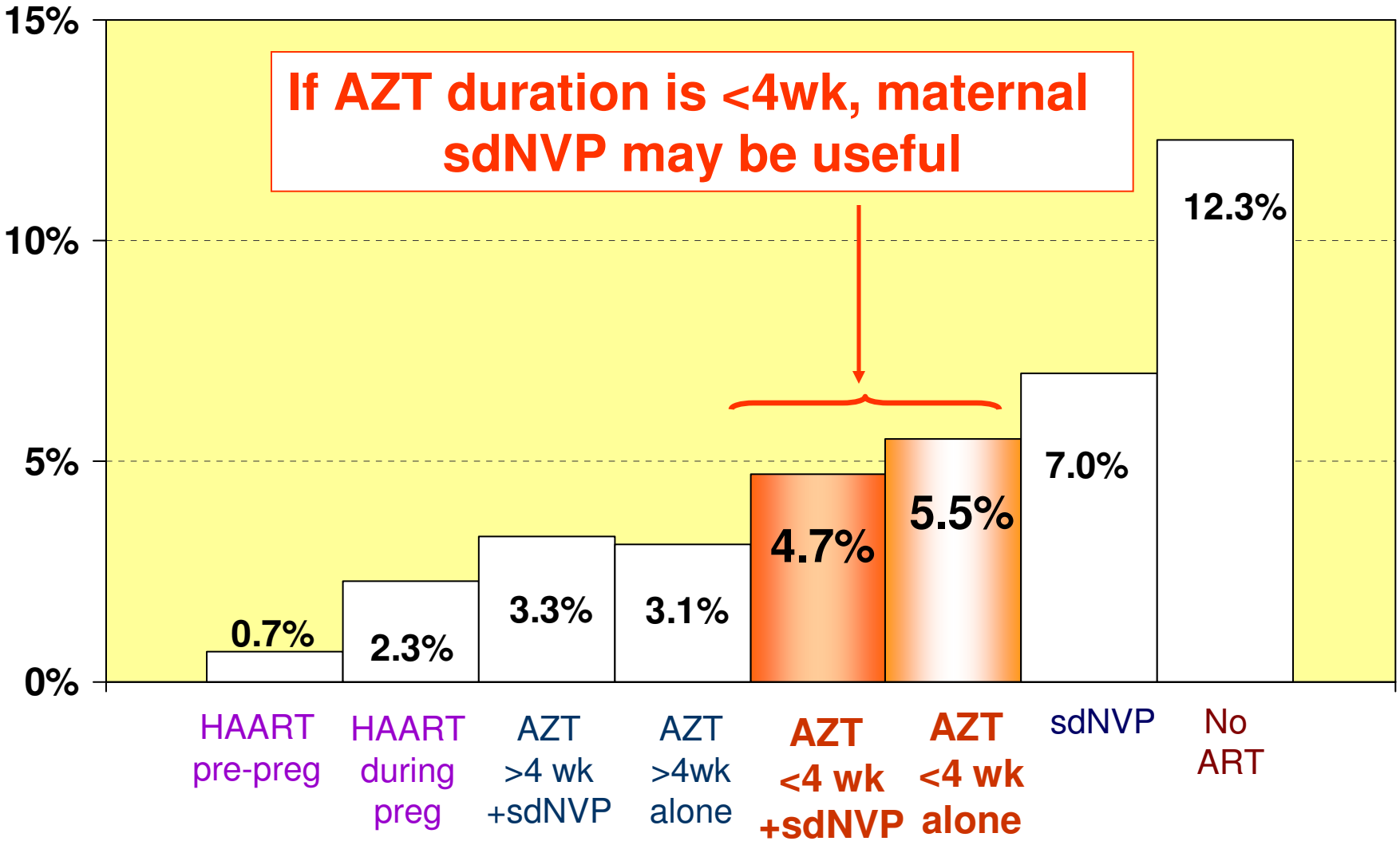

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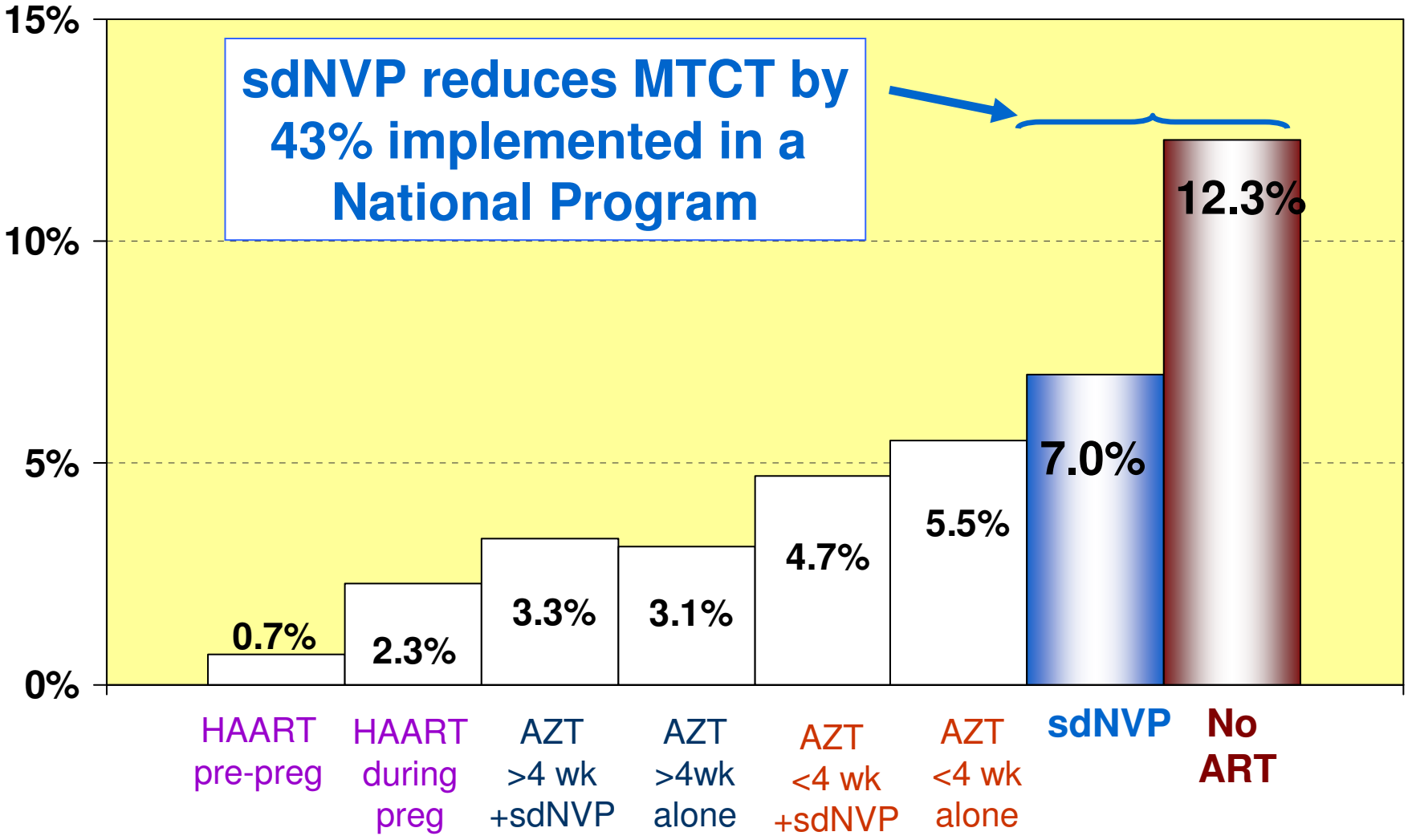


Mother to Child Transmission, 2000-2006, 5,930 Births to HIV+ Women, UK/Ireland

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%	←

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

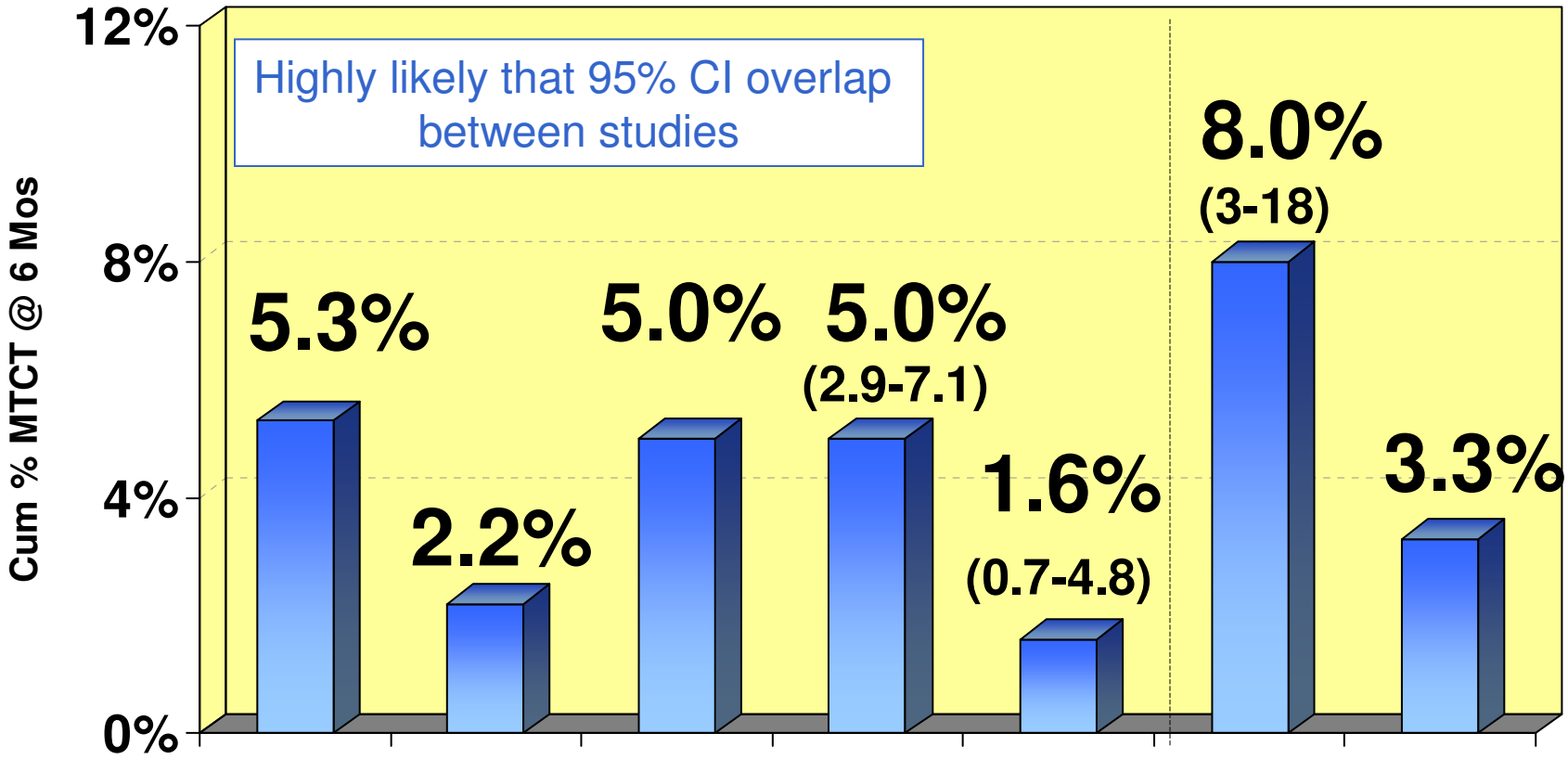
Caveats to Consider When Trying To Compare Maternal HAART and/or Infant Prophylaxis Studies

- Number studied differ tremendously; often lack 95% CI to help get range MTCT encompassed.
- Drop off in numbers tested at later periods (eg, 6 mos) important but not always specified.
- Populations not necessarily comparable (eg, CD4 count).
- Studies differ in whether there is AP intervention.
- Duration of AP ARV clearly impt in terms of *in utero* tx but not always specified.
- Duration of BF clearly impt in terms of time at risk but not specified by many.
- Birth tx rates may not be given, making difficult to differentiate IU from IP/early PP.

Abstracts/Papers on HAART for Prevention of PP MTCT

Study/ reference	Number	Median CD4	Infant feeding	MTCT at 4- 6 wks	MTCT at 6 mos (cum; increment)
DREAM (med -26.8 wk to 6 mos) Marazzi; Eur J Ped 2007	985 - 707 tested 1 mo, 467 @ 6 mo	489	Not specified BF (duration ?) and FF	3.8% (3.1-4.5) No birth data	5.3% 1.7% 4wk-6mo
DREAM (28 wk to 6 mos) Palombi; AIDS suppl 2007	FF 891- data 809 BF 341- data 251	Not specified	BF (duration?) and FF	FF: 0.9% BF: 1.2% No birth data	2.7% 2.2% 0.8% 4wk-6mo
Kibs (-34 wk to 6 mos) Thomas; CROI 2008	500 (BF)	394 (23% <250)	BF (duration?)	3.9% *2.4% at birth* 1.5% d1-6wk	5.0% 2.6% 6wk-6mo
MITRA-Plus (-34 wk to 6 mos) Kilewo; IAS 2007	501 (BF)	460 (14% <200)	BF (duration?)	4.1% (2.1-6.0) @ 6 wk No birth data	5.0% (2.9-7.1) 0.9% 6wk-6mo
AMATA (28 wk to 6 mos) Gitgea; IAS 2007	554-431 tested BF-176 FF-255	Not specified	BF and FF 59% FF 41%% BF (duration?)	*1.1% at birth* No 6 wk data	BF: 1.6% (0.7-4.8) @ 7 mos 0.5% d1-6mo
Cote d'Ivorie(-24 wks to 6 mos) Tonwe Gold; PLosMed 2007	107	189 Only CD4 <200	FF 39% BF 61% (med duration 4.7 mos)	*1.0% at birth*	3.3% 1.9% 4wk-6mo
Kesho Bora (-34-36 wks to 6 mos) De Vinenzi; CROI 2008	109 (61 BF, 48 FF)	Only CD4 <200	BF and FF 44% FF 54% BF (duration?)	No birth or 6 wk data	8% (3-18) BF 11% (3-23) FF @ 12 mos

Maternal HAART Studies in BF Populations (or BF-FF Populations): Cumulative MTCT at 6 Months

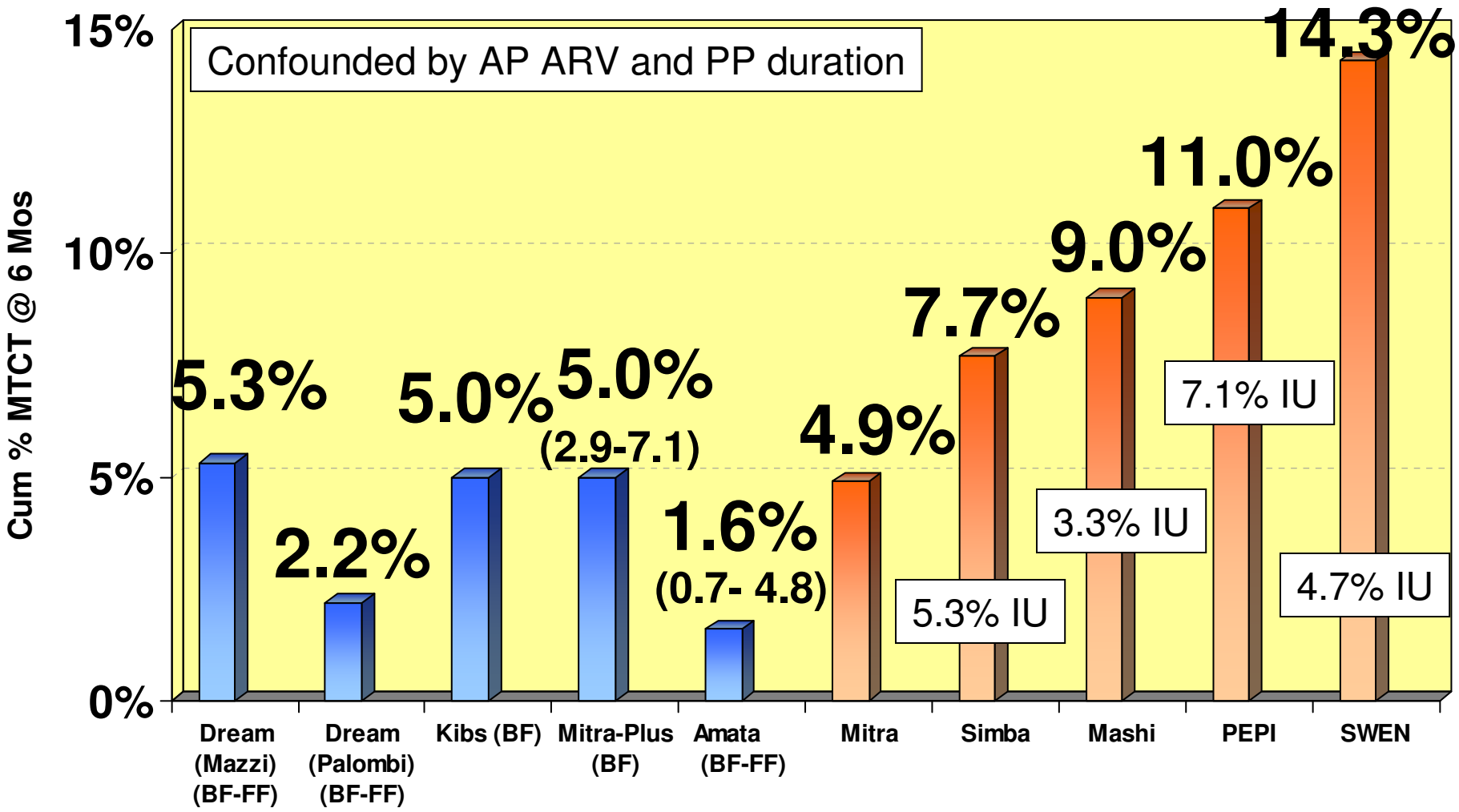


# Tested at 6 Mos:	467	251	500	501	176	61	107
GA Started:	27	28	34	34	28	34	24

Abstracts/Papers on Infant ARV for Prevention of PP MTCT

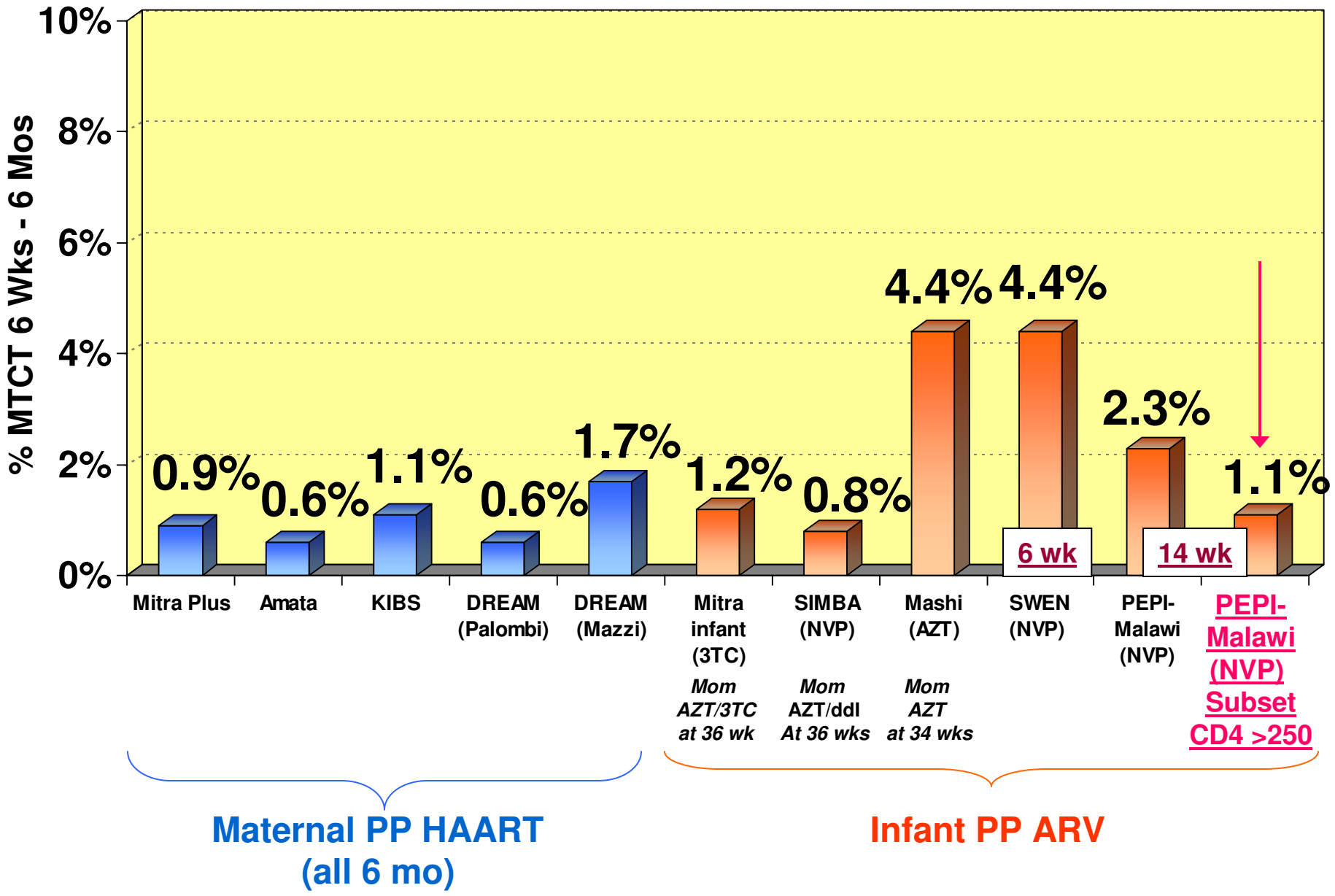
Infant Prophylaxis reference	Number	Median CD4	Infant feeding	MTCT at 4- 6 wks	MTCT 6 mos (cum; increment)
MASHI: 6 mo AZT AP (-34 wk-delivery): AZT+-sdNVP Thior; JAMA 2006	FF+ 1 mo AZT: 591 BF + 6 mos AZT: 588	366	BF (?duration) and FF	Cum: 4.6% *3.3% at birth* 1.3% d1-6wk	Cum BF+AZT: 9.0% @ 7mo 4.4% 4wk-7mo
MITRA: 6 mo 3TC AP (-36wk to 1 wk): AZT+3TC Kilewo; JAIDS 2008	398	459 (9% <200)	BF (med duration 4.5 mo)	Cum: 3.8% (2.0-5.6) No birth data	Cum: 4.9% 1.2% 6wk-6mo
SIMBA: 6 mo 3TC vs NVP AP (-36 wk to 1 wk): AZT+ddI Vyankandondera; IAS 2003	198	423	BF (med duration 3.3 mo)	Cum: 6.9% *5.3% at birth* 1.6% birth-4 wk	Cum: 7.7% 0.8% 4wk-6 mo
SWEN: 6 wk NVP NO AP Lancet 2008	831 extended 928 sdNVP	316-463	BF (most weaned btn 3-6 mos)	Cum: 7.2% *4.7% at birth* 2.5% d1-6wk	Cum: 14.3% 4.4% 6wk-6mo
PEPI: 14 wk NVP or NVP/AZT NO AP Kumwenda; NEJM 2008	800 ext NVP 801 ext NVP/AZT 788 sdNVP	379-401	BF (most weaned btn 6-9 mos)	Cum: 8.8% @ 14 wks *7.1% birth* 1.7% d1-6wk NVP	Cum: 11.1% 2.3% 6wk-6mo NVP

Maternal HAART and Infant Prophylaxis Studies
Cumulative MTCT at 6 Months



GA Started:	27	28	34	34	28	36	36	34	None	None
Duration PP:	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	14 wk	6 wk

ARV Prophylaxis: Late Postnatal MTCT Between Age 4-6 Weeks and 6-7 Months (infants uninfected at age 4-6 wks)



Overall Transmission Mitra-Plus vs Mitra

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

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

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

SMART Study

SMART Study Group. NEJM 2006;355:2283-96

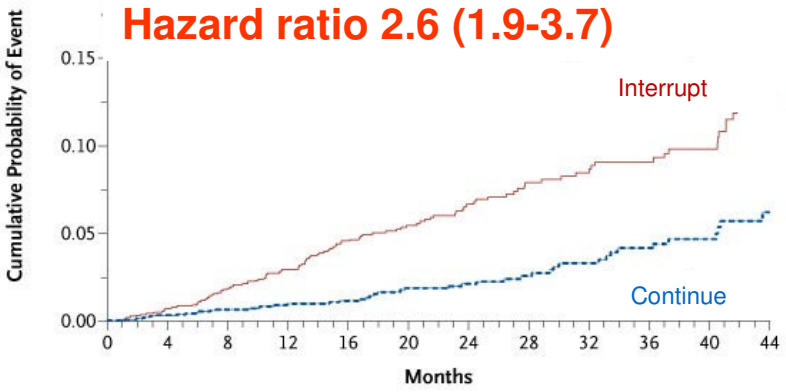
- **Enrolled 5,472 non-pregnant adults with CD4 >350 at entry (most on ART for several years, some naïve) and randomized to**
  - **Stop (drug conservation, N=2,720)**
    - **Restart when CD4 drop to <250**
  - **Continue (viral suppression, N=2,752)**
- **Terminated early because interim analysis showed more deaths, AIDS events, and serious non-AIDS events in the "Stop" arm.**

Increased Risk OI/Death/non-AIDS Morbidity with STI

SMART Study Group. NEJM 2006;355:2283-96

OI or Death from any Cause

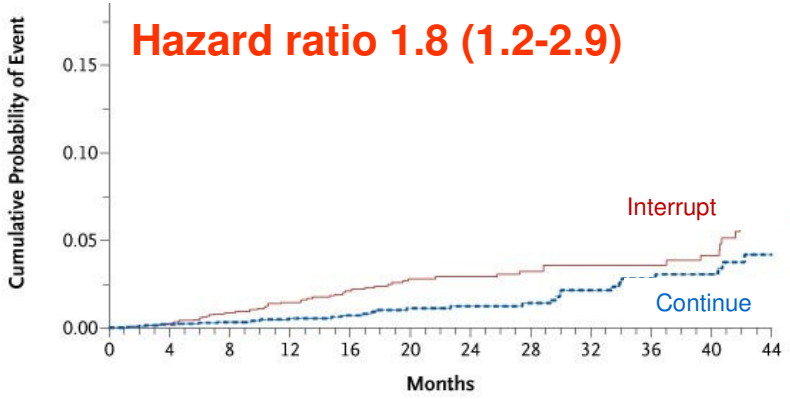
Hazard ratio 2.6 (1.9-3.7)



No. at Risk												
Drug conservation	2720	2074	1666	1301	1040	870	689	540	444	372	280	162
Viral suppression	2752	2081	1695	1310	1077	906	724	572	474	388	288	173

Death from any Cause

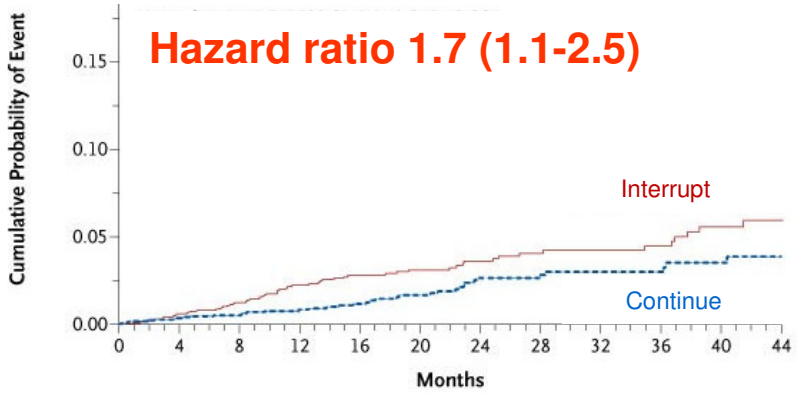
Hazard ratio 1.8 (1.2-2.9)



No. at Risk												
Drug conservation	2720	2083	1681	1321	1070	893	716	567	462	391	293	169
Viral suppression	2752	2084	1701	1317	1083	915	732	581	481	395	294	175

Major CV, Renal, Hepatic Disease

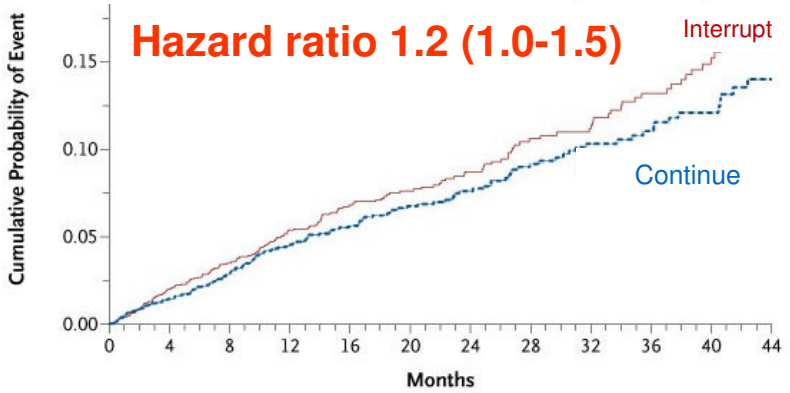
Hazard ratio 1.7 (1.1-2.5)



No. at Risk												
Drug conservation	2720	2070	1663	1292	1041	867	693	543	443	375	273	157
Viral suppression	2752	2077	1692	1307	1070	899	713	563	462	380	282	165

Grade 4 Adverse Event

Hazard ratio 1.2 (1.0-1.5)



No. at Risk												
Drug conservation	2720	2040	1625	1250	993	826	659	509	415	345	251	138
Viral suppression	2752	2053	1650	1249	1011	841	668	526	431	355	258	148

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

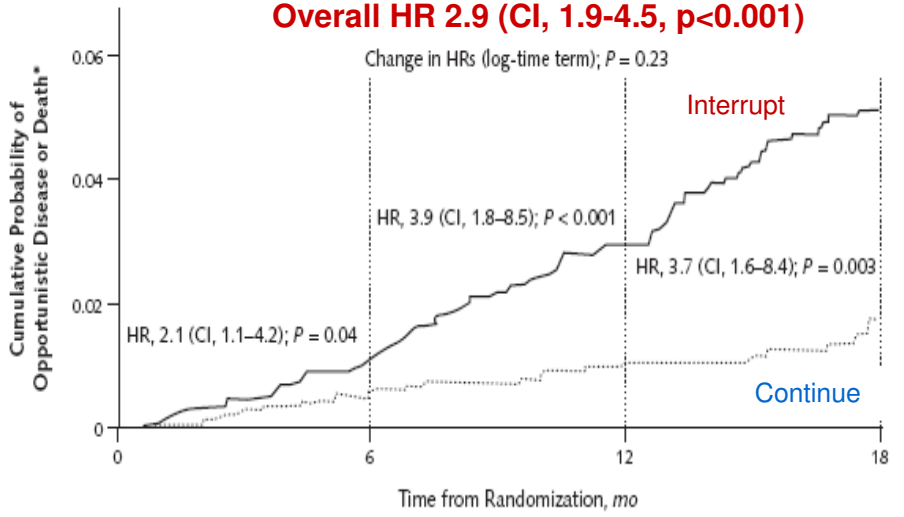
Subgroup	Interrupted ART # pt (rate 100pt-yr)	Continuous ART # pt (rate 100pt-yr)	Hazard Ratio
Baseline CD4			
350-449	24 (3.2)	18 (2.2)	1.5
→ 450-549	27 (3.7)	7 (0.9)	4.1
550-649	19 (3.5)	7 (1.3)	2.8
>650	50 (3.2)	15 (2.0)	3.2
Duration ART			
→ 0-<3 yrs	23 (2.8)	7 (0.8)	1.6
3-5 yrs	30 (2.7)	8 (1.1)	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

Continued Increase in Risk for OI and Death After Restarting Continuous HAART in Patients in Interruption Arm of SMART

The SMART Study Group. Ann Int Med 2008;149:289-99

Primary Study Period

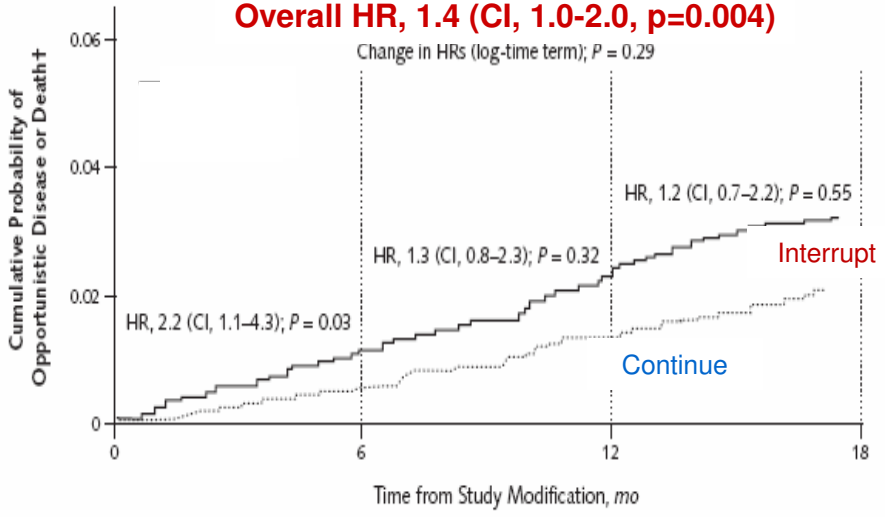
Overall HR 2.9 (CI, 1.9-4.5, p<0.001)



Participants in the risk set, *n*			
DC group	1892	1297	957
VS group	1914	1305	978

After Study Modification, All Interrupt Pts Restarted on ARV

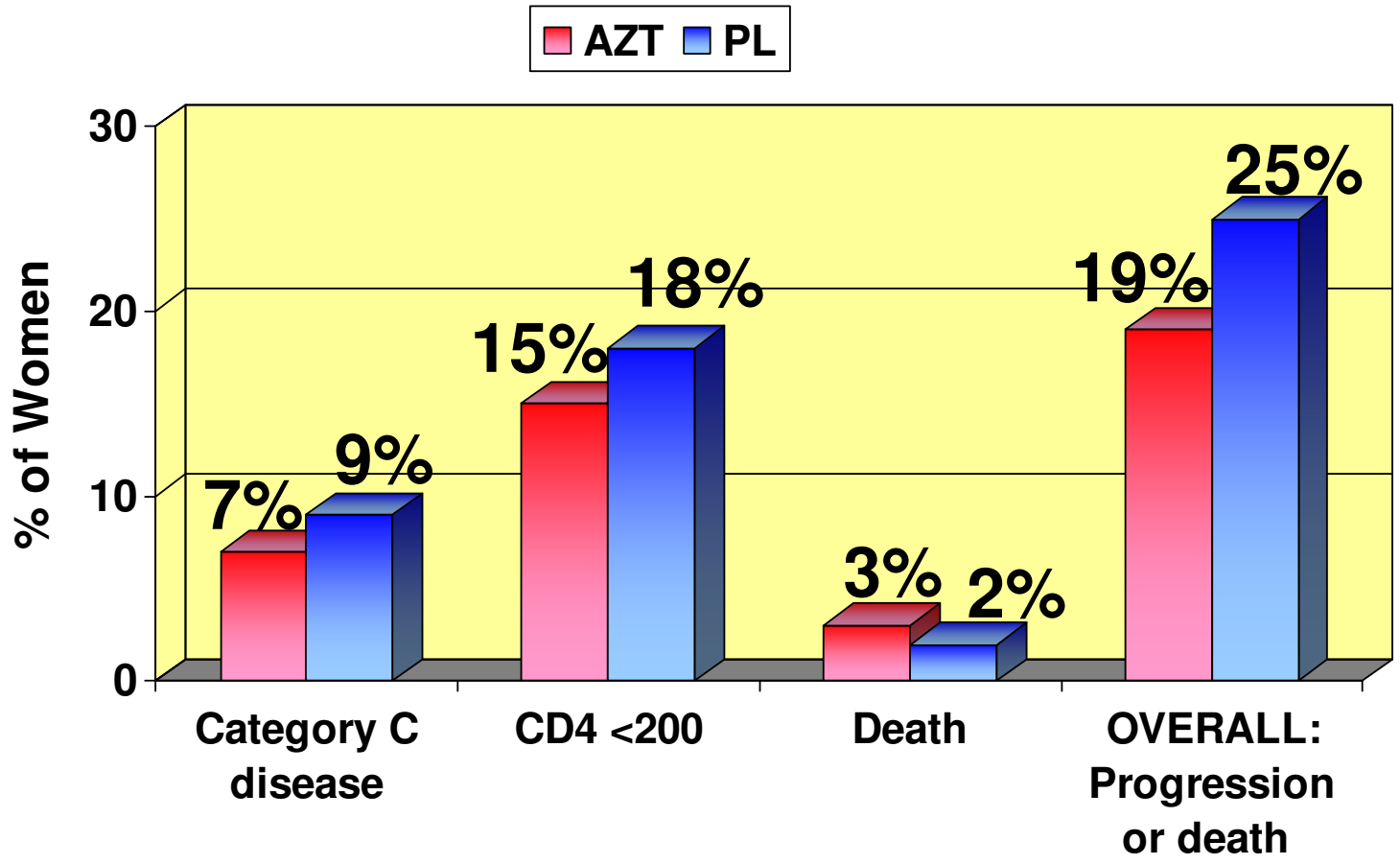
Overall HR, 1.4 (CI, 1.0-2.0, p=0.004)



Participants in the risk set, *n*			
DC group	2508	2446	2414
VS group	2617	2567	2528

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

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

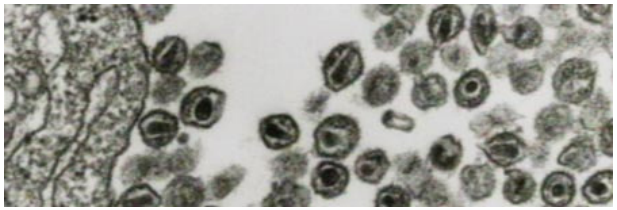


No significant differences between AZT and Placebo Groups (overall progression/death, p=0.28)

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, changes in CD4 and HIV RNA levels were similar over the 1st year postpartum among women stopping or continuing therapy after delivery.**
- **No women in either group progressed to AIDS or death during the 1st year postpartum.**
- **However, significant increase activated CD8 cells (DR+/38+) if stop; and trend to increased risk CDC Class B events in women stopping combination ART (RR 2.93, 0.64-13.4).**



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 Despite Extended NVP & Persists Longer Compared to Infants Infected Despite sdNVP

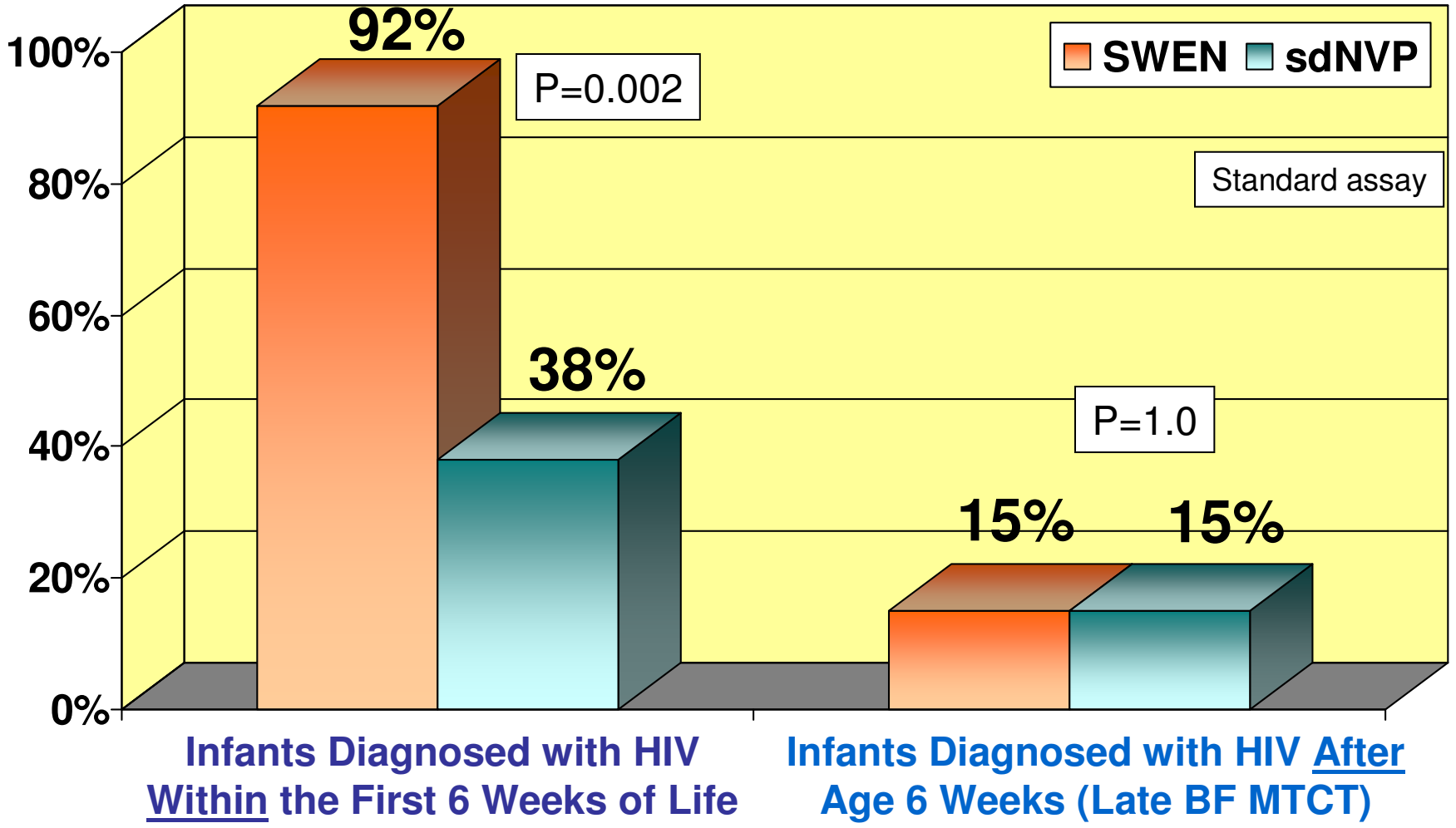
Uganda SWEN Study

Church J et al. J Infect Dis 2008;198:1075-82

	SD NVP	Extended 6 week NVP	P value
Genotypic, age 6 weeks			
Viroseq assay (standard)	50% (12/24)	84% (21/25)	0.01
LigAmp assay (quantitative)	35% (7/20)	79% (19/24)	0.005
Phenotypic, age 6 weeks	45% (9/20)	86% (19/22)	0.005
Genotypic, age 6 months			
Viroseq assay (standard)	17% (1/6)	100% (7/7)	0.005
LigAmp assay (quantitative)	50% (3/6)		

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

WHO 2008: What Initial Therapy to Start in HIV-Infected Infants <12 Months - Already Recommend PI if sdNVP Exposed

No infant or maternal ARV exposure → **NVP-based Triple ART**

Unknown infant or maternal ARV exposure → **NVP-based Triple ART**

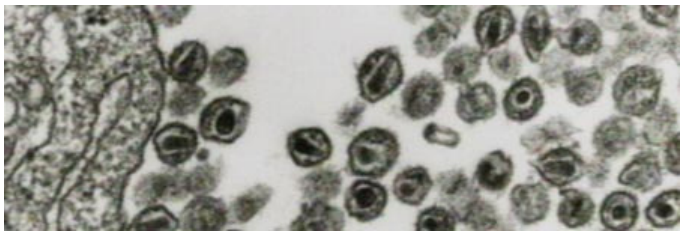
Maternal/Infant ARV exposure

- **SD NVP or NNRTI-based HAART** → **PI-based Triple ART***
- **Non-NNRTI exposure** → **NVP-based Triple ART**

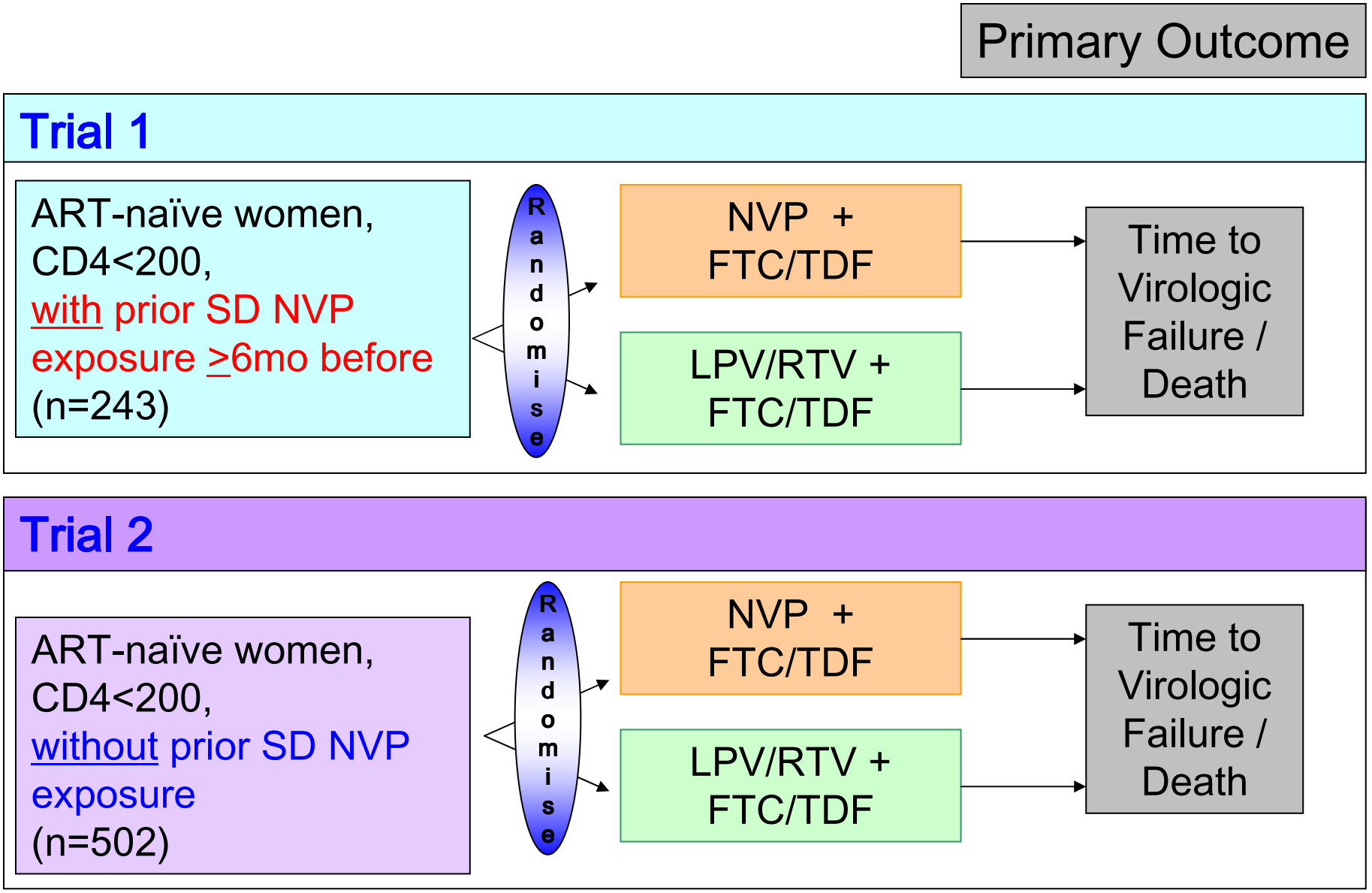
*If no PI available, use NVP-based triple ART

sdNVP, NVP Resistance, and Subsequent Maternal HAART

OCTANE (A5208)
NEVEREST



A5208 (OCTANE): Study Design



FTC: emtricitabine; TDF: tenofovir

OCTANE: Trial 1 (sdNVP Exposed Women)

- Most women exposed to sdNVP alone (89%) without "tail" to reduce resistance.
- Primary Endpoint: viral failure or death
  - Viral failure: confirmed HIV RNA <1 log below baseline 12 weeks post ART start OR HIV RNA ≥400 copies/mL at or after week 24
- Significantly more women reached a primary endpoint in the NVP arm:
  - 29 (24%) in NVP arm (25 viral, 4 death)
  - 8 (7%) in LPV/RTV arm (7 viral, 1 death)

Impact of Time Since sdNVP Exposure

- Trend toward decreasing difference (in primary endpoint) between NVP and LPV/RTV arms with increasing time between last prior sdNVP exposure and ART initiation:

Time since most recent sdNVP exposure	N (%) reaching endpoint, NVP arm	N (%) reaching endpoint, LPV/RTV arm
6 to <12 mos	**15 (37%)**	**1 (3%)**
12 to <24 mos	**11 (24%)**	**4 (8%)**
≥ 24 mos	**3 (8%)**	**3 (10%)**

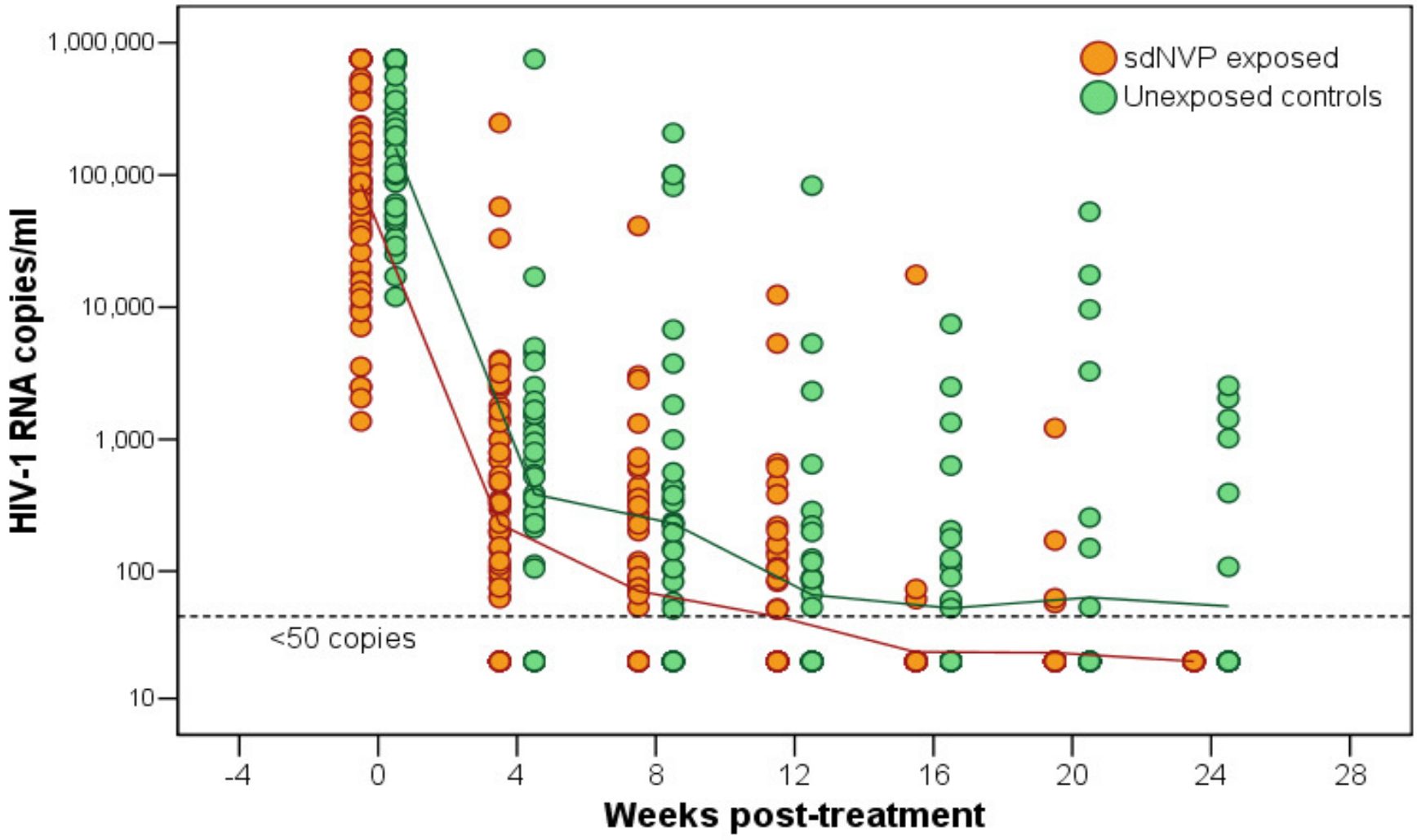
Comments on OCTANE

- **Low CD4 when sdNVP exposed: median entry CD4 was 139 at 12-18 mos post exposure: CD4 <200 likely at time of sdNVP (should have HAART)**
- **Efficacy of LPV/r higher than expected (93% <400); other studies in adults show response rate of 61-71% <400. Viral efficacy of NVP consistent with other studies, 79%. Need results of Trial 2.**
- **Relation with time since exposure present but longer than prior 6-13 mo "theshold"; likely due to low CD4 at time sdNVP. NEVEREST >18 mos since exposure no difference in viral response.**
- **Most women had only sdNVP without AZT or "tail", interventions which we know lowers resistance.**
- **Women who suppress on NVP maintain suppression (OCTANE, Mashi-Plus, Thai data).**

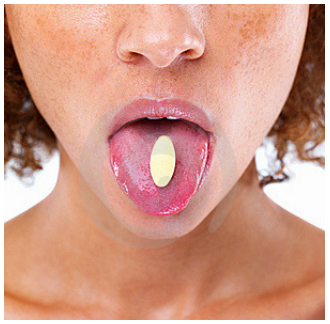
No Reduction in NNRTI-Based HAART Efficacy in Women Exposed to sdNVP 18-36 Mos Previous

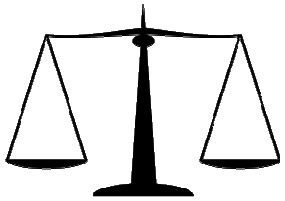
NEVEREST Results, Johannesburg

Coovadia A et al. 13th CROI, Denver, CO Abs. 641 & CID 2009 in press



Pros/Cons for Choice of PMTCT Intervention





Benefit and Risk Considerations Depend on Maternal Need for Therapy

- If mother needs treatment, benefit HAART outweighs risks/costs
- If ARV giving solely for PMTCT, other issues:
  - Comparative efficacy
  - Risk to mother/child
  - Feasability, Cost

Pros/Cons – Antepartum PMTCT Moms with CD4 >350

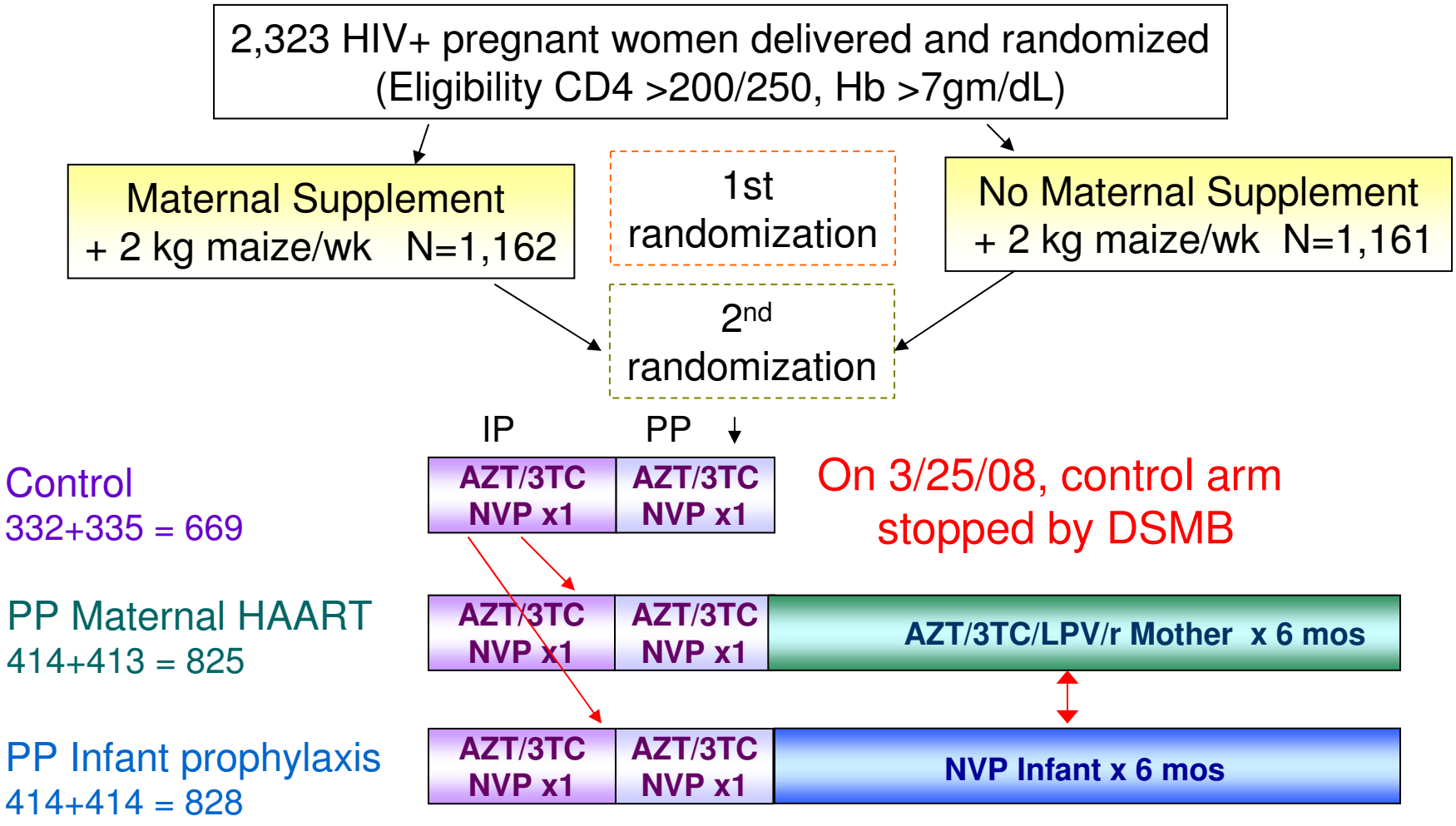
	Maternal HAART	AZT/sdNVP+tail
Comparative Efficacy	Need to assess in women with CD4 >350	
Choice of drug	Problem NNRTI; U.S. use LPV/r for pro	Complexity of sdNVP & tail (need "package")
Cost	+++ esp. if PI	+
Ease administration	If FDC easier – but can't use NVP, EFV concern PP; still need some ST infant ARV	Complexity of sdNVP & tail (need "package")
Need for mom "tail"	If NNRTI, yes when stop	Yes
Toxicity	Will need lab monitoring; safety of stopping?	AZT anemia but otherwise safe
Resistance mother	Should be low; adherence issue or low ARV level? needs to be assessed	sdNVP; need treat if CD4 <350, use AZT + tail, risk should be lower
Resistance infant – however, should be few + infants	Yes possible	Yes possible NVP (lower if AZT given); already rec PI ART

Pros/Cons – Postpartum PMTCT Moms with CD4 >350

	Maternal HAART	Infant Prophylaxis
Comparative Efficacy	Have comparative studies with weaning at 6 mos Need to compare given over longer duration of BF	
Choice of drug	Problem NNRTI; U.S. use LPV/r for pro	NVP or 3TC safe Dual drug? (↑ toxicity?)
Cost	+++ esp. if PI	+
Ease administration	Daily mom dosing – PP adherence issues	Daily infant dosing, liquid formulation
Need for mom "tail"	If NNRTI, yes when stop	No
Toxicity	Will need lab monitoring (AZT/3TC more heme tox); safety of stopping?	Safe, no difference from control in trials for NVP
Resistance mother	Should be low; adherence issue or low ARV level? needs to be assessed	No risk (only risk from sdNVP if used IP alone)
Resistance infant – however, should be few + infants	Yes	Yes – PI already rec with sdNVP, not different

Ongoing and Planned PMTCT Clinical Trials

Breastfeeding, Antiretrovirals and Nutrition (BAN) Study
Malawi – IP/PP Intervention



- Study powered to detect differences between each arm and control arm
- Study limited power (~ 60%) to detect difference between experimental arms

Breastfeeding, Antiretrovirals and Nutrition (BAN), Malawi (UNC/CDC: C Van der Horst, D Jamieson)

- **Started:** 3/2004
- **Status:** enrollment complete
- **Key data:** 7/2009 6 month F/U will be completed
- **Key questions:**
  - Compares short course IP/PP control regimen maternal HAART vs infant NVP during BF for 6 mos
  - AZT/3TC tail with sdNVP and NVP resistance
  - Nutritional support and weaning support
- **Key outcomes:**
  - Postpartum infant infection rates at 6 months
  - HIV-free survival at 48 weeks
  - NVP resistance

Kesho Bora Study: Burkina Faso, Kenya, S Africa
AP/IP +- PP

HIV-Infected Pregnant Women
Infant feeding by maternal choice: FF or BF
N= 1,136 Observational N=291; RCT N=845 (76% [638] BF)

→ CD4 <200: NVP-based HAART, Observational Cohort (N=122)

→ CD4 200-500: Randomized 2-arm clinical trial (N=845)

↓

AP (34 wks)	IP	PP	
AZT (34 wks)	AZT NVP x1	AZT NVP x1	No prophylaxis during BF

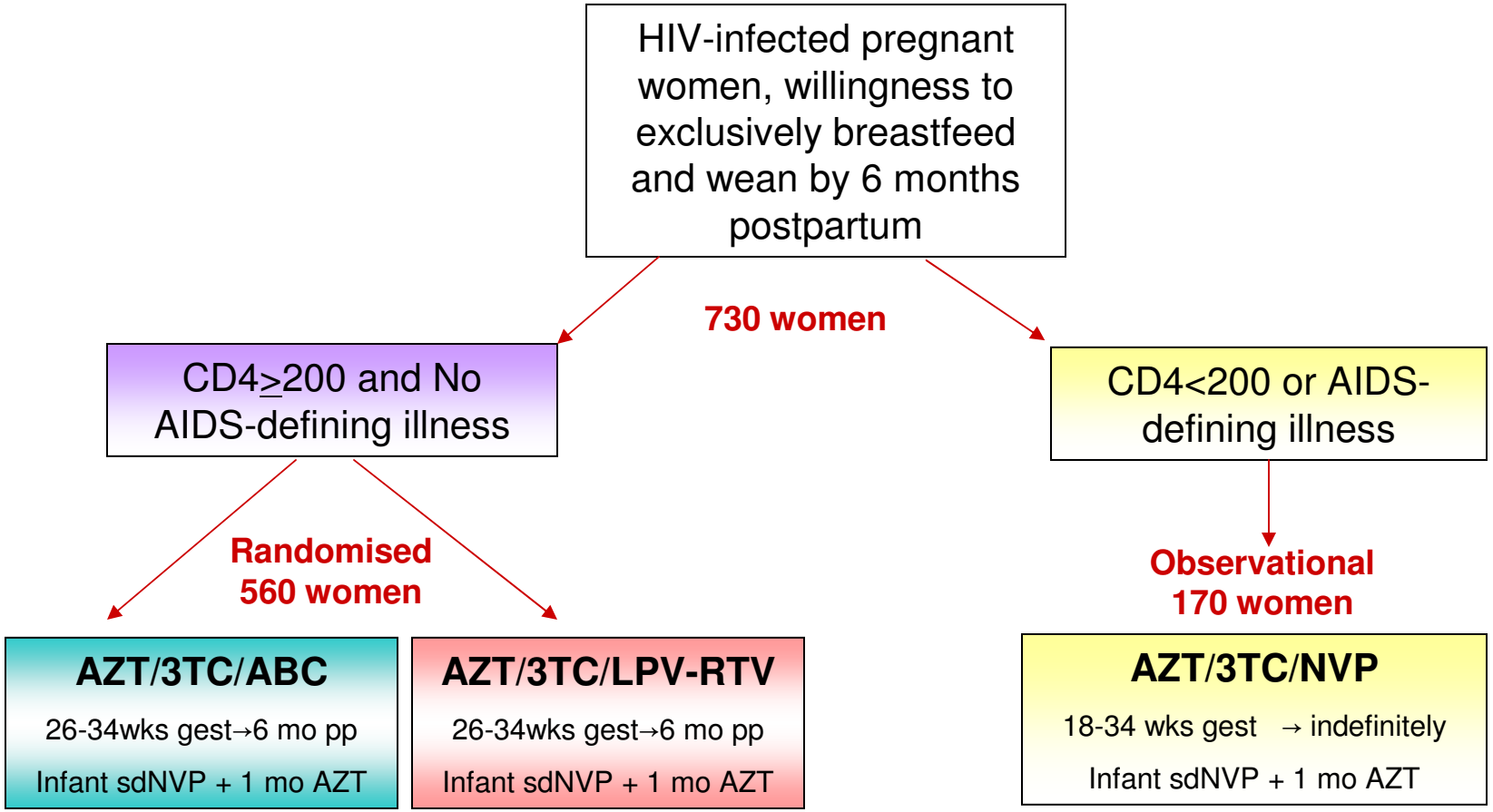
AZT/3TC/LPV/r (34 wks)	AZT/3TC/LPV/r	Mother: AZT/3TC/LPV/r Infant: NVP x 1 + AZT x 1 wk

→ CD4 <500: AZT/sdNVP, Observational Cohort (N=169)

Kesho Bora Study, Burkina Faso, S Africa, Kenya (WHO: I de Vicenzi; CDC: M Thigpen; NICHD: J Read)

- **Started:** 6/2005
- **Status:** enrollment complete
- **Key data:** late 2009 (18 mo F/U completed 5/2010)
- **Design:** Prospective cohort and nested RCT
- **Key questions:**
  - Efficacy/safety of HAART from 28-36 weeks gestation to 6 months postpartum in women with CD4 200-500 vs short course AZT/sdNVP with no infant prophylaxis
- **Key outcomes:** 18 month infant follow-up
  - HIV-free survival at 6 weeks and 12 months (all feeding patterns)
  - HIV-free survival at 12 months (BF infants)
  - AIDS-free survival of mothers at 18 mos

Mma Bana Study: 4 sites in Botswana



- Primary endpoint viral suppression in mother at delivery and at 6 mos PP
- Secondary endpoint MTCT

Mma Bana Study, Botswana: NIH grant: R Shapiro, Harvard U

- **Started:** 7/2006
- **Status:** Enrollment completed, last birth 9/2008
- **Key data:** Mar-July 2009
- **Design:** RCT for women CD4 >200, observational CD4 <200
- **Key questions:**
  - Compares maternal PI-based vs NRTI-based HAART during pregnancy and 6 mos BF
    - AZT/3TC/LPV-RTV vs AZT/3TC/ABC
- **Key outcomes:** 2 years mother/infant follow-up
  - Maternal viral suppression at delivery and 6 mo PP
  - AP, IP, PP MTCT between regimens and compare with MASHI (AZT +-NVP + infant AZT BF prophylaxis)

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
Ongoing
4 African sites
Enrolled 435 of 1,800
Results fall 2010?

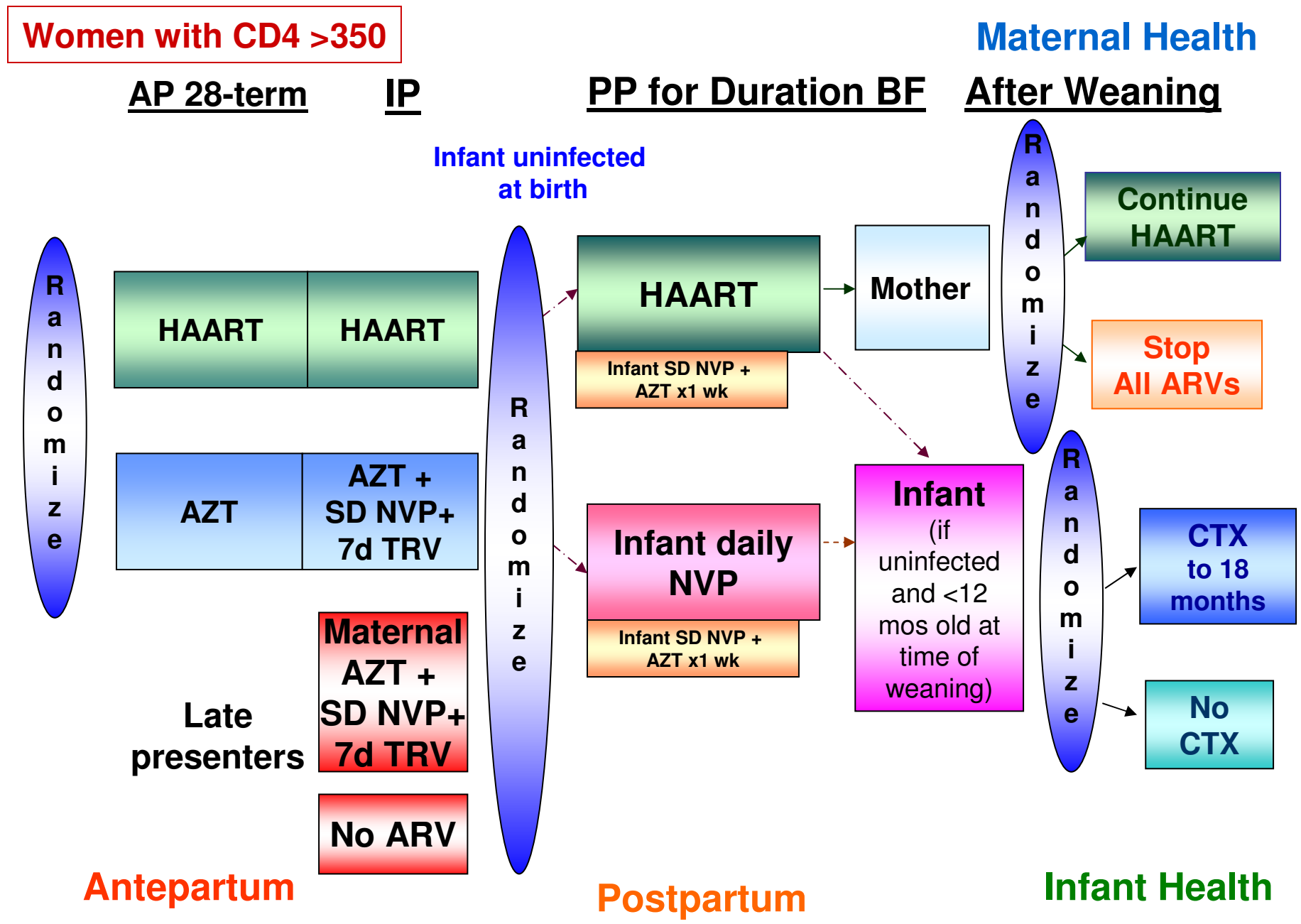
ANRS Promise PEP: Infant 3TC up to 9 Months

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**	**Placebo age 1wk to 1 mo post cessation BF (maximum 9 mos)**

PEP, Burkina Faso, S Africa, Uganda, Zambia (ANRS: P van de Perre)

- **Started:** to start in January 2009
- **Status:** to start
- **Key data:** 2012
- **Design:** RCT, 1500 mother/infant pairs
- **Key questions:**
  - Efficacy/safety of infant 3TC for 9 months to prevent BF transmission in mothers not eligible for treatment
    - 3TC or placebo once daily from day 7 to 4 weeks after weaning (maximum 38 weeks)
- **Key outcomes:**
  - HIV-free survival at 38 weeks and 12 months
  - Safety of prolonged infant 3TC, resistance, etc

PROMISE General Overview: Sequential Randomized 2x2 Factorial Trial



IMPAACT PROMISE: US and International Sites (IMPAACT and ACTG Networks)

- **Started:** to start in mid-late 2009
- **Status:** to start
- **Key data:** 2012-2014
- **Design:** sequential RCT, ~8,000 mother/infant pairs
- **Key questions:**
  - What is best AP/IP regimen for PMTCT?
  - What is best PP regimen for PMTCT?
  - Is it safe to stop maternal HAART used for PMTCT?
  - Does continuing infant CTX in uninfected babies to 18 months reduce morbidity/mortality?
- **Key outcomes:**
  - MTCT birth/1week and BF cessation; maternal AIDS/nonAIDS/death; infant morbidity/mortality.

ANRS "Universal Approach"

Under design
Non-inferiority-equivalence
Endpt: safety/efficacy
pregnancy outcome
CD4 "threshold" to stop

All women ("no" CD4 count)
randomize to one of two arms

Tenfovir/FTC/Efavirenz
From 20 wks gestation through delivery if FF, through 6 mos PP if BF

AZT/3TC/LPV-RTV ("reference regimen")
From 20 wks gestation through delivery if FF, through 6 mos PP if BF

Decision on stopping or continuing:
CD4 count done at delivery if FF, at weaning if BF (while on HAART):
If CD4 <200? 350? ?? at that time – Continue for treatment
If CD4 >200?350? ?? at that time – Stop HAART

Plan to model CD4 at start of ART to CD4 at time stop to pick "threshold"

Study	Key Design	Status	Results
Mma Bana	PI vs NRTI HAART 6 mo BF	Almost done	7/2009
BAN	Control vs 6 mos HAART or 6 mos infant NVP	Almost done	7/2009
Kesho Bora	Maternal HAART	In F/U	Late 2009
HPTN 046	BF Infant NVP 6 wks vs 6 mos	Enrolling	Fall 2010
PEP	BF Infant 3TC for 9 mo	Start early 2009	2012
IMPAACT-PROMISE	AP short vs HAART; PP HAART vs infant NVP; Mom stop vs continue; Infant CTX	Being finalized, start June 2009?	2012-14 (3-5 yrs)
ANRS	HAART: TDF/FTC/EFV vs AZT/3TC/LPV-r during pregnancy (to 6 mos if BF)	Being finalized	?

Thank You For Your Attention