Mother-To-Child Transmission of HIV

Antiretroviral interventions

Isabelle de Vincenzi

Training Course in Sexual and Reproductive Health Research

Geneva 2010

Prevention of MTCT through antiretrovirals

Mechanisms of action:

- **Maternal component:**

  Reduce viral load in mother ’s blood, genital fluids (and milk) during pregnancy, delivery (and breastfeeding)

- **Infant regimen:**

  Act as post-exposure prophylaxis (viral particles eventually transmitted during birth are eliminated)

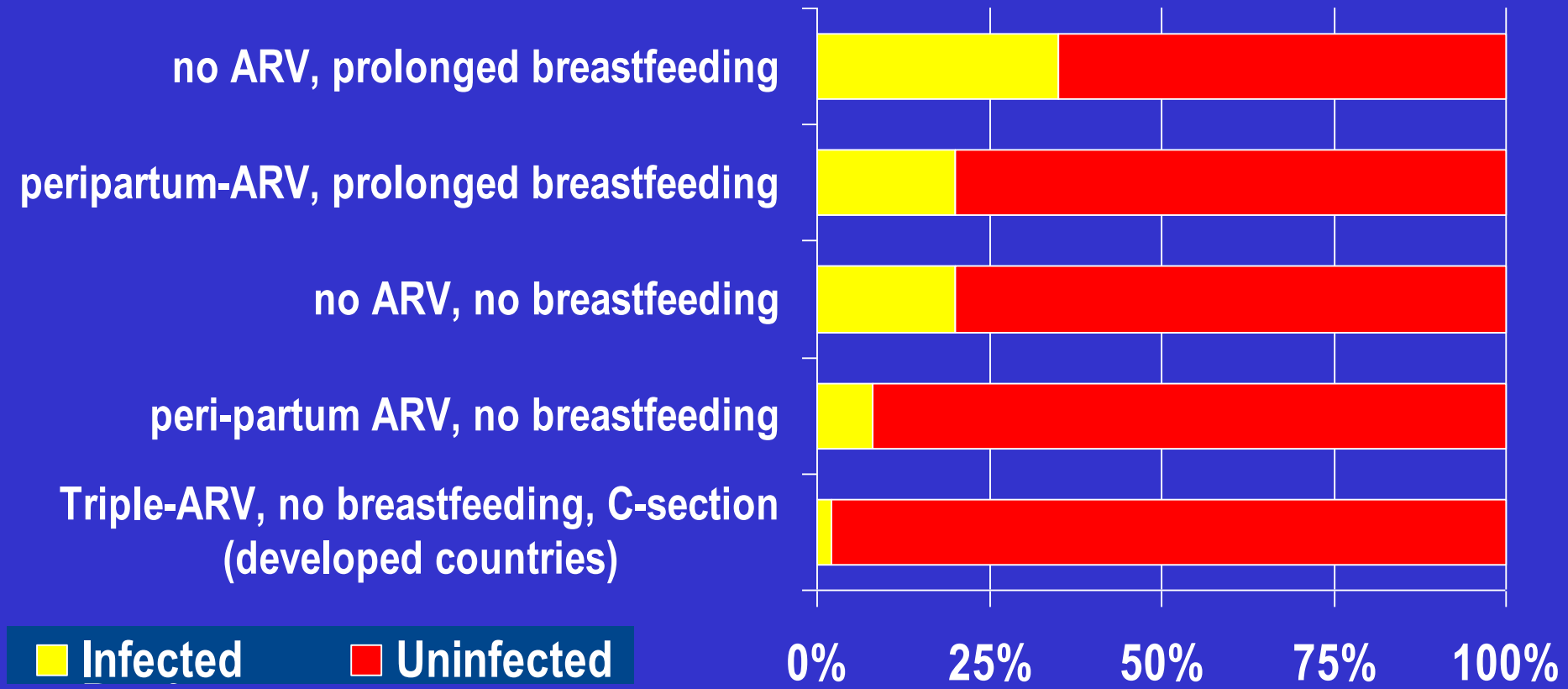
Peri-partum ARV interventions:

Late in-utero

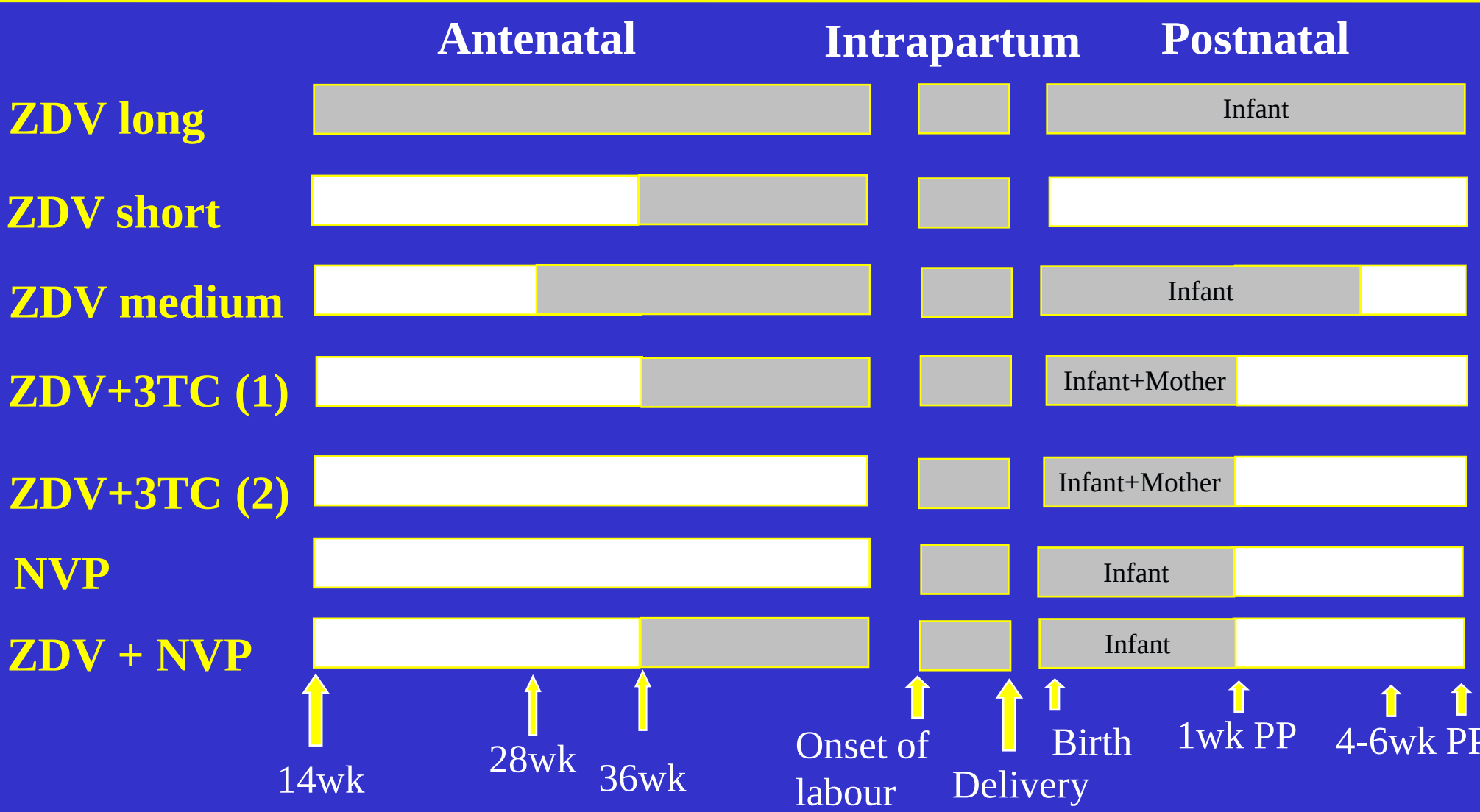
Labour and Delivery

Post-partum (1 week maximum)

The variable risk of MTCT of HIV (with and without preventive interventions)

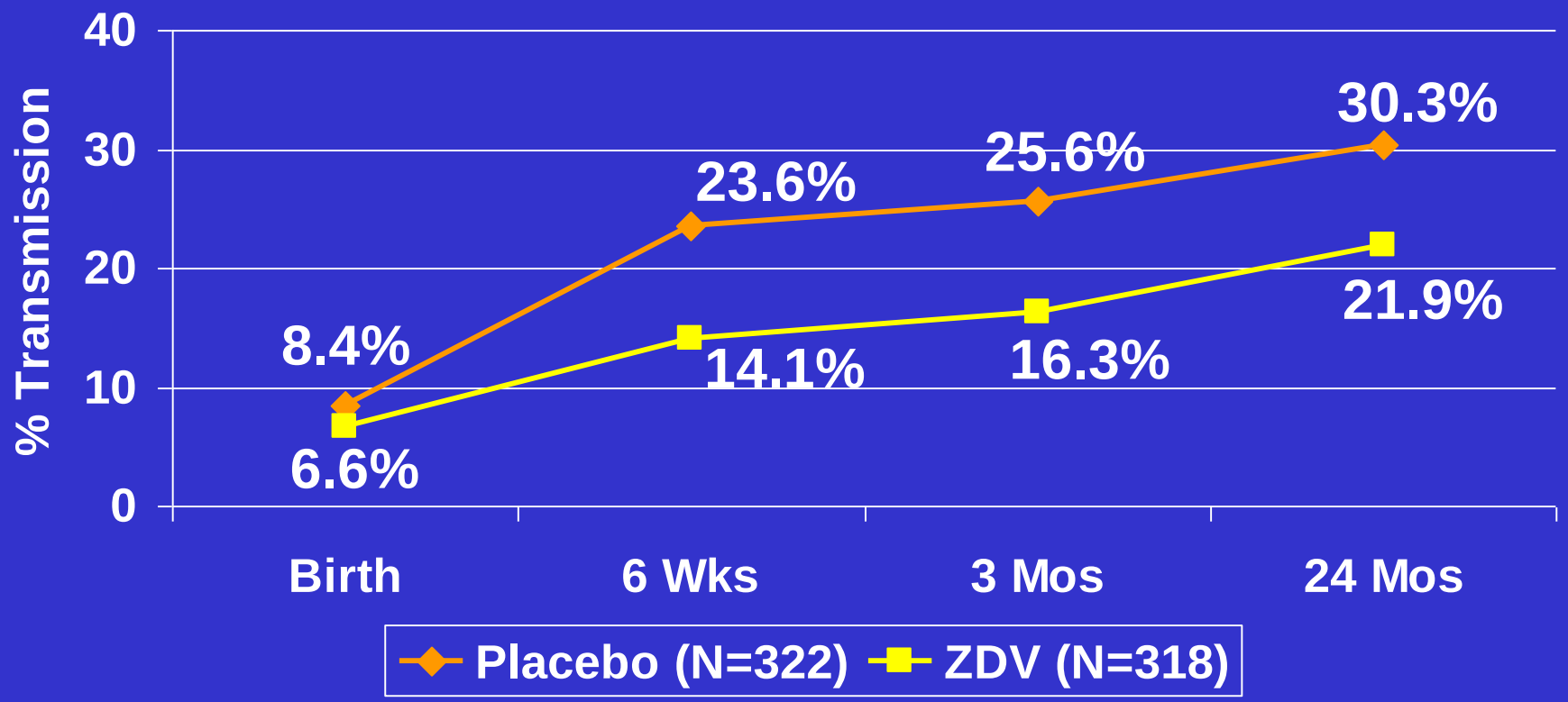


Peri-partum ARV regimen of proven efficacy
(through clinical trials)



Ivory Coast Short-Course short-ZDV Trials: Combined Analysis Through 24 Months

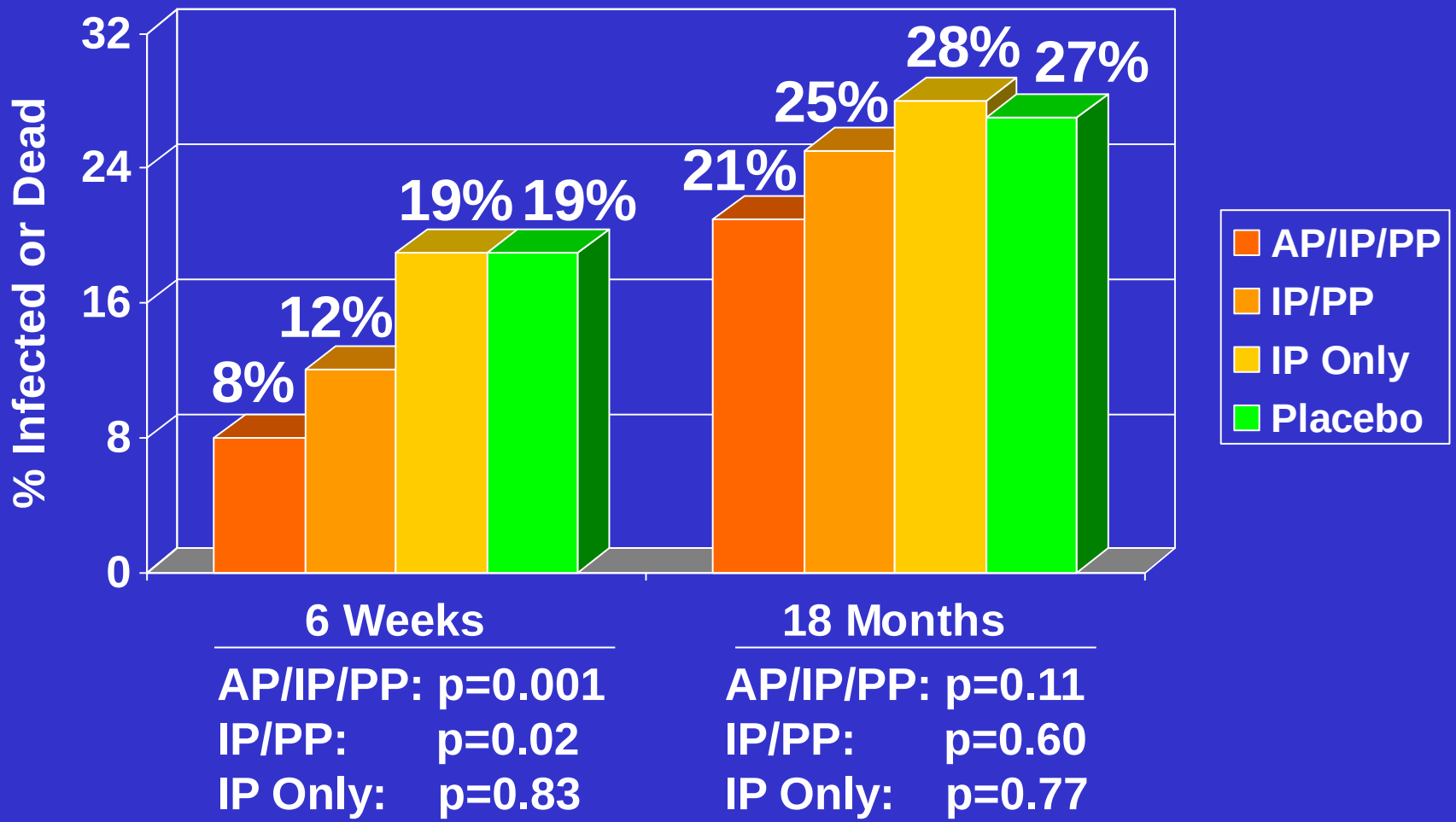
Witkor S. XIII AIDS Conf, July 2000, Durban S Africa (TuOrB354)



Risk Difference at 24 Mos: 8%, 95% CI 2.0% - 15.4%

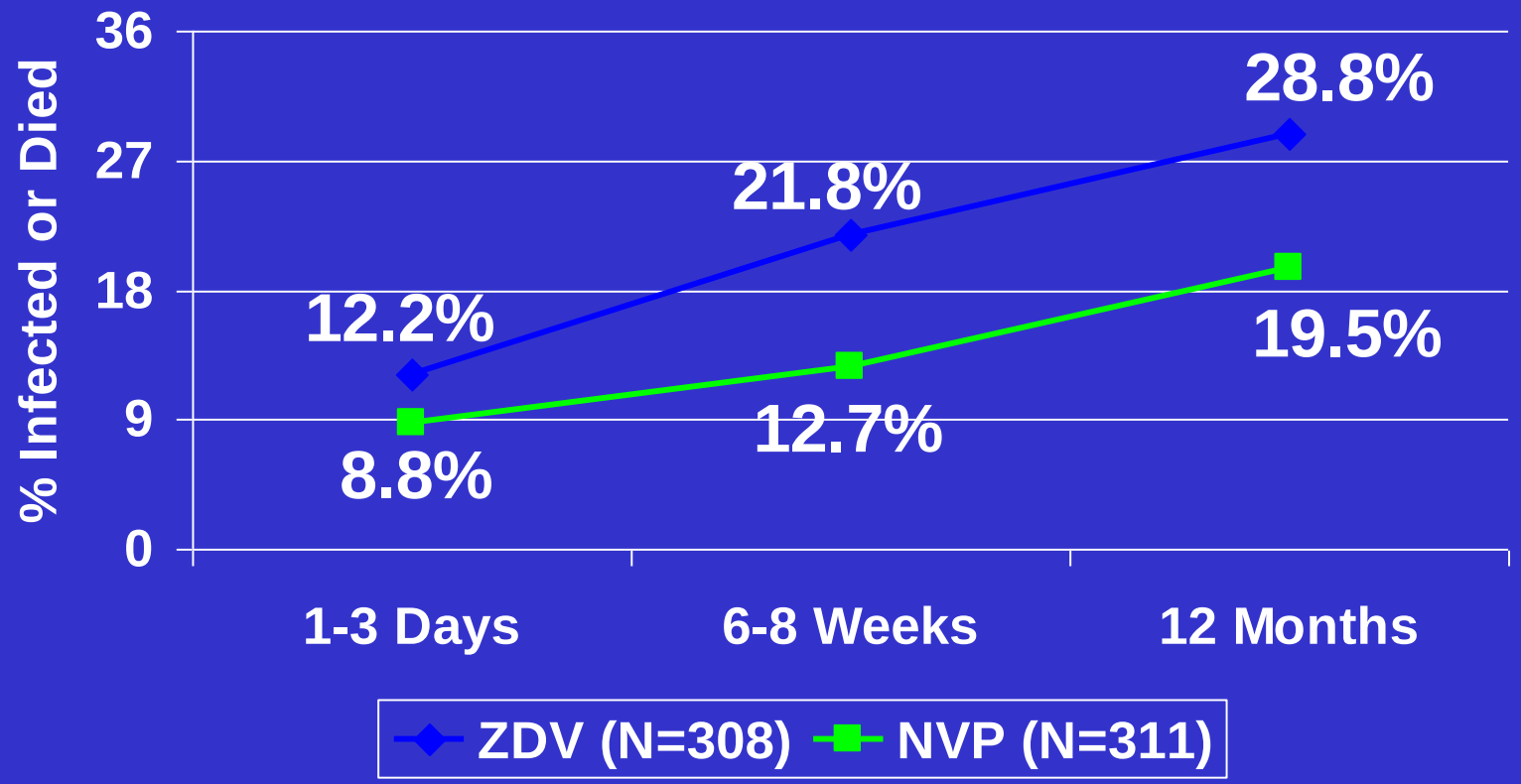
ZDV/3TC AP/IP/PP, IP/PP, or IP Only vs Placebo: PETRA, HIV Infection or Death, 6 Wks & 18 Mos

Gray G. XIII AIDS Conf, July 2000, Durban S Africa (LbOr05)



HIVNET 012, Intrapartum/Postpartum Nevirapine vs ZDV: HIV Infection or Death

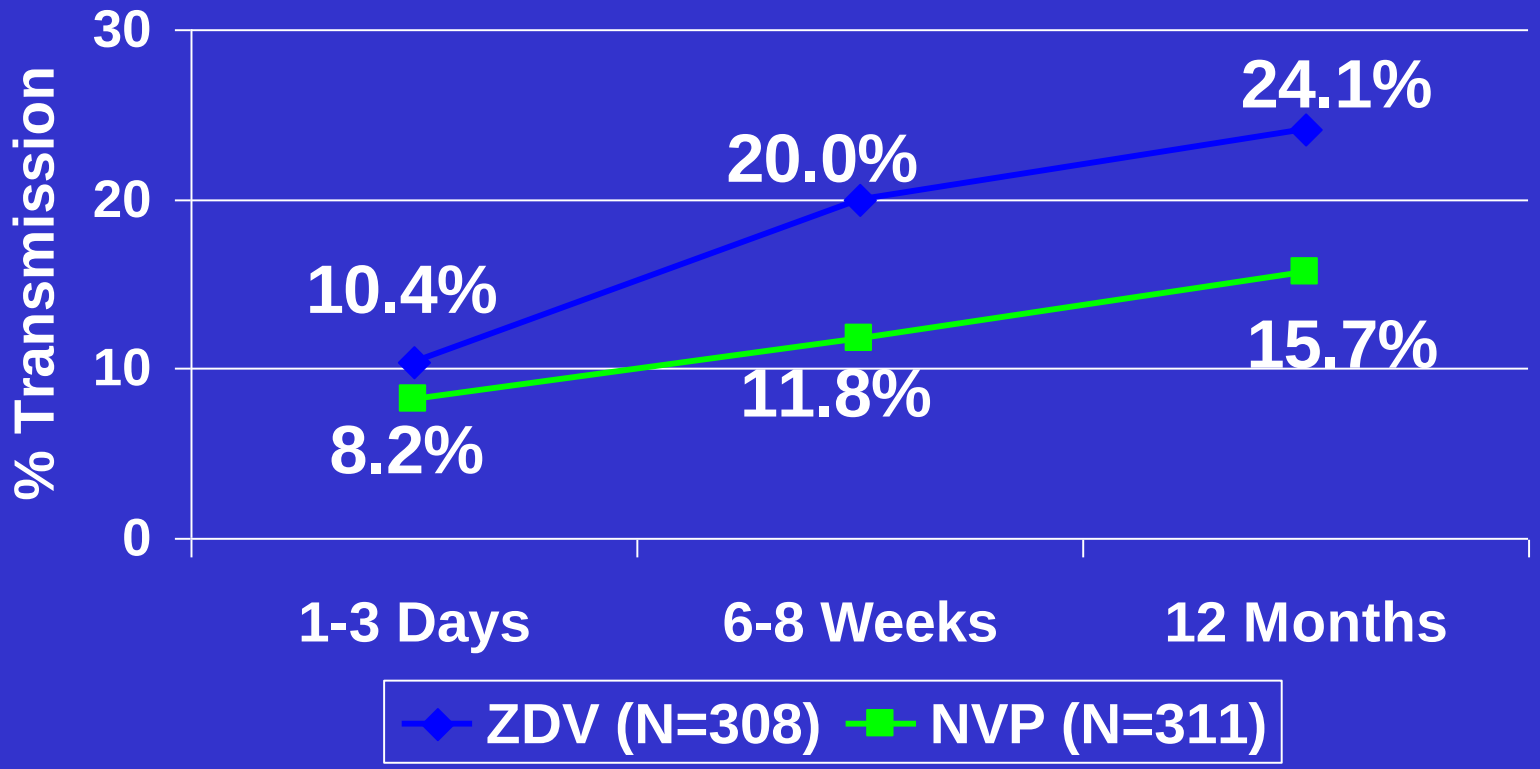
Owen M. XIII AIDS Conf, July 2000, Durban S Africa (LbOr01)



12 Month Efficacy NVP vs ZDV: p = 0.004

HIVNET 012, Intrapartum/Postpartum Nevirapine vs ZDV: HIV Transmission

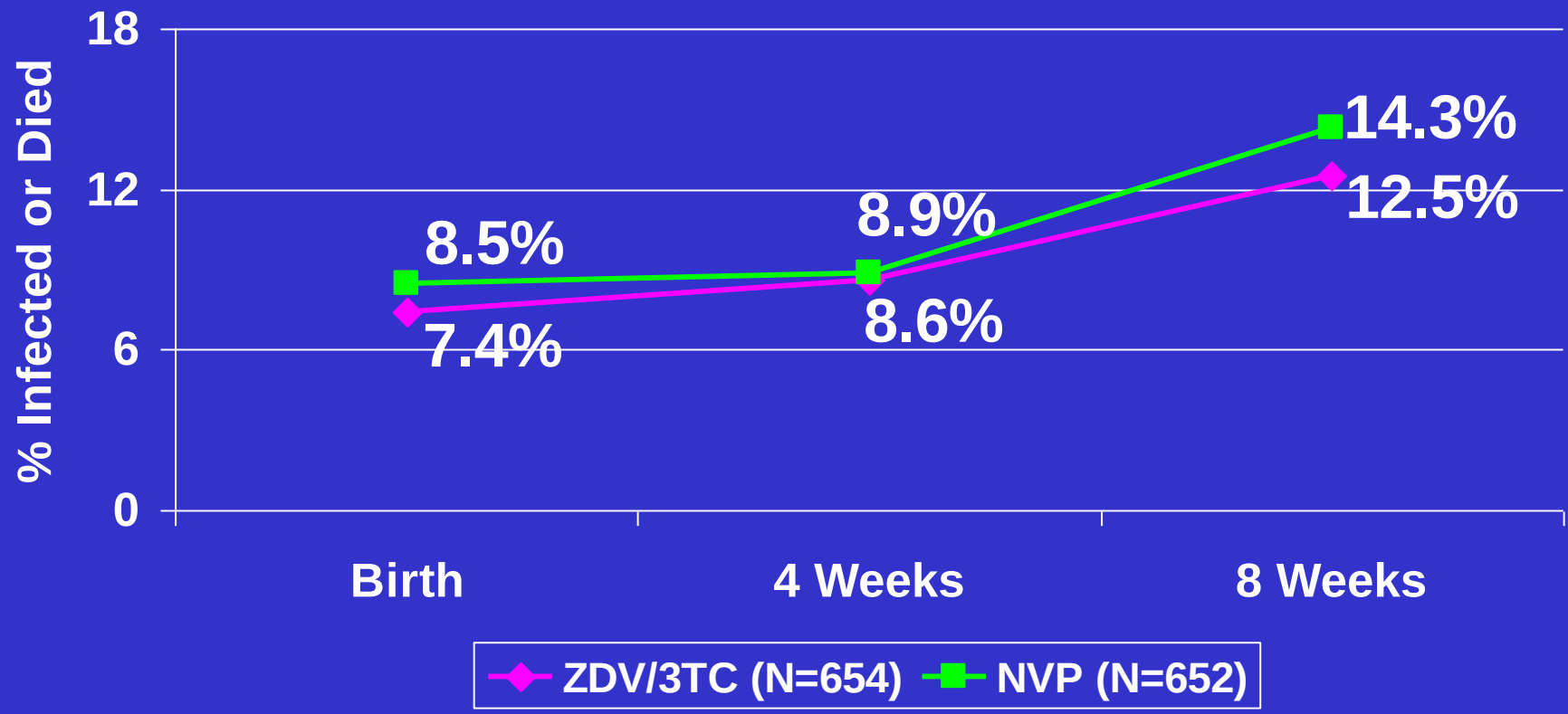
Owen M. XIII AIDS Conf, July 2000, Durban S Africa (LbOr01)



12 Month Efficacy NVP vs ZDV: p = 0.003

SAINT: Intrapartum/Postpartum ZDV/3TC vs Nevirapine: HIV Infection or Death

Moodley D. XIII AIDS Conf, July 2000, Durban S Africa (LbOr2)

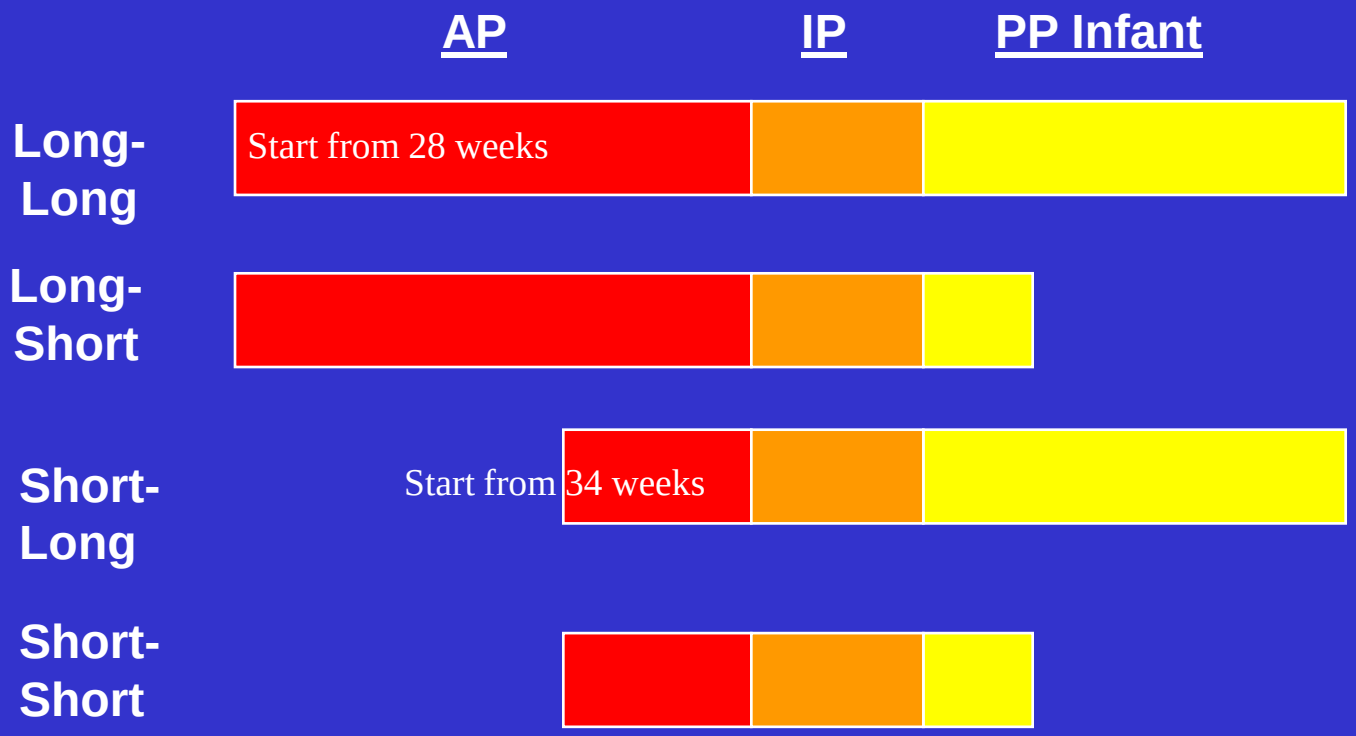


No significant difference between study arms

ANRS Abidjan - 6 wks Transmission rates

- DITRAME (ZDV 36wks-delivery) 12.8%
- DITRAME+ (ZDV + HIVNET012) 6.2%
- DITRAME++ (Combivir + HIVNET012) 4.8%

Thailand Perinatal Prevention (1) Short-Course AZT Trial Results



Most Effective (Tx 4% [vs SS])

Intermediate (Tx 5%)

Intermediate (Tx 9%)

Least Effective (Tx 11%)

No Breastfeeding

Perinatal HIV Prevention Trial – Thailand (2)

- All women received ZDV from 28weeks
- All new-borns received 1 week ZDV

Randomisation in 3 arms according to SD-NVP given to mother and child, mother only, no NVP:

- Nevirapine-Nevirapine arm - Tx rate 2.0% (1.2 to 3.4)
- Nevirapine-Placebo arm – Tx rate 2.8% (1.8 to 4.4)
- Placebo-Placebo arm – Tx rate 6.3% (4.2 to 9.5), stopped at interim analysis

No Breastfeeding

Infant PEP - Women who have not received an ante-partum regimen

- Wade (NY city) : 6 weeks ZDV started within 48h of birth
- Gray (SA) : 1 week ZDV or 1 dose NVP (equivalent)
- Taha-Taha (Malawi): 1 week ZDV + 1 dose NVP (better than NVP alone)

Risk of transmission in developed countries

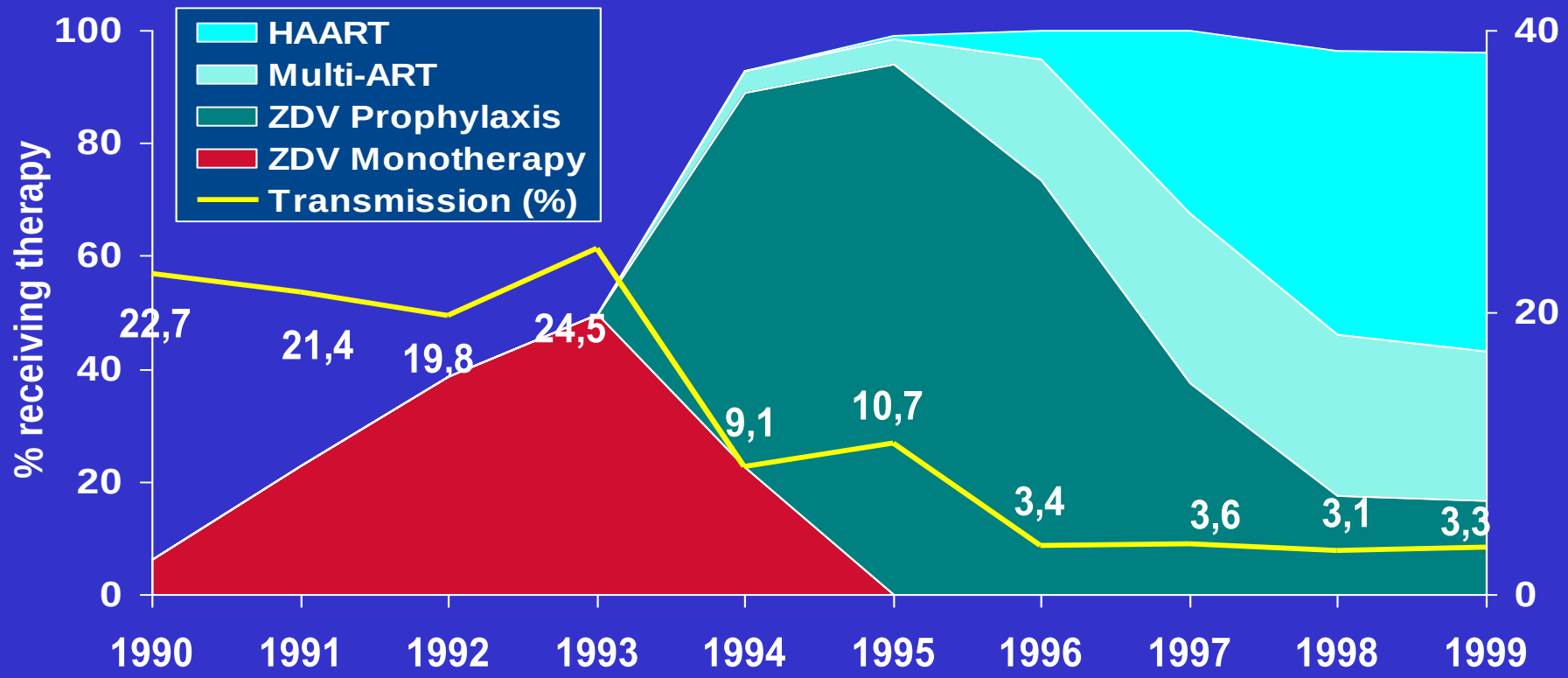
With :

Early & potent combination of ARVS,

No breastfeeding,

C-Section

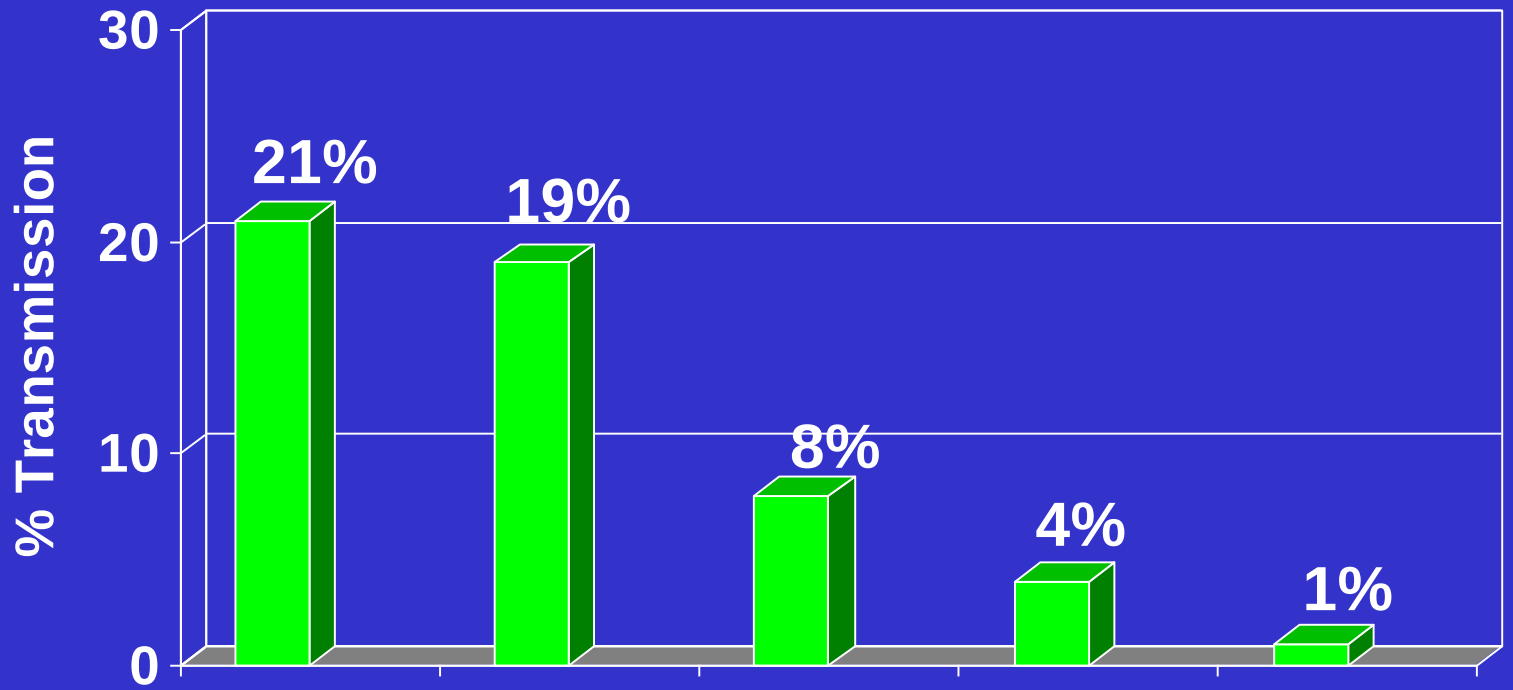
ARV Use and HIV Transmission (WITS, USA)



Source: Blattner, Durban 2000, LbOr4

Antenatal Antiretroviral Treatment and Perinatal Transmission in WITS, 1990-1999

Blattner W. XIII AIDS Conf, July 2000, Durban S Africa (LBOr4)



Type ARV vs None				
p value:	0.76	<0.01	<0.01	<0.01

Studies of Resistance in PMTCT trials using a single dose of NVP

PACTG 316, HIVNET 012,

SAINT, HIVNET 023, and Peri-3

Incidence of NVP Resistance (NVPR) at 6 Weeks PP in Women Receiving ARV in PACTG 316

Cunningham C et al. J Infect Dis 2002;186:181-8

- 16/217 women who did not have NVP resistance at delivery had NVP resistant virus detected at 6 weeks pp:
  - 14/95 (15%) in NVP arm
  - 2/122 (2%) in placebo arm (neither had received active drug or open-label NNRTI)
- K103N most common (alone in 7 and in combination in 3 women).
- All women with K103N mutation had mixture of mutant and wild-type virus.
- Not related to pre pregnancy or antenatal ARV's; or to delivery CD4, viral load, or other ARV resistance

HIVNET 012 Resistance Data

NVPR emerges by 6 wks in 25% women & 46% infants

- NVPR is more common in women with
  - high baseline VL
  - low baseline CD4 cell count
  - subtype D infection
- NVPR is not associated with increased MTCT, and transmission of NVPR virus by breast-feeding uncommon
- Different mutations are found in women vs. infants
- Different mutations found in women 7d vs. 6w post-NVP
- Complex patterns of mutations are found in some women as early as 7d after NVP exposure

Peri-3 Study in Thailand
(peripartum ZDV + SD NVP)

- **Short course ZDV starting at 34 weeks plus the 2-dose intrapartum/neonatal NVP regimen was safe and well tolerated**
- **The combined ZDV+ SD NVP regimen appeared more effective in reducing perinatal HIV transmission than short course ZDV alone**
- **Maternal resistance at 6 wks was 20% (18% NVP and 2% ZDV); Infant NVP resistance was 20%**

Clinical significance of NVP resistance acquisition: Efficacy of NVP-based ART in NVP-exposed and unexposed women

- % of women reaching undetectable Viral Load (<400 copies/ml) after 6 months of ART:

  - 68% of the 50 exposed women with at least one mutation,

  - 80% of the 92 exposed women without mutation and

  - 85% of the 27 non exposed women had a viral load <400

(p for trend = 0.057)

- NVP-exposed women who started ART > 6 months after delivery: VL<400/ml in 91% without mutation and 77% with mutation

- ART started <6 months after delivery: VL<400/ml in 69% without mutation and 58% with mutation

Treatment Options Preservation Study (TOPS)
McIntyre et al (Bangkok, abstract LbOrB09)

Supplementing NVP SD with either a 4 or a 7-day course of ZDV + 3TC for the mother and the baby

- **5-fold reduction in NVP resistance after 6 wks of follow-up PP.**
- **At interim analysis, 6 wks resistance data available for 61 mothers; Resistance was detected in :**
  - **53.3% of group 1 mothers (NVP only),**
  - **9.3% of those receiving NVP single-dose + ZDV/3TC irrespective of the duration) (p=0.001)**

Resistance to 3TC and ZDV following MTCT ARV-prophylaxis

ANRS 075: Open-Label ZDV/3TC Prophylaxis and ARV Drug Resistance at 6 wks PP (N=132)

Mandelbrot et al. JAMA 2001;285:2083-93

3TC Resistance (M184V):

- Mothers: 39% (mutant 58%; mixed, 42%)
  - Only 1 (2%) had resistance prior to 3TC dosing

- **Risk factors for maternal 3TC resistance:**
  - **CD4 lower**
  - **HIV RNA higher**
  - **Longer duration 3TC:**
    - 0% (0/12) if <1 month 3TC
    - 20% (14/70) if 1-2 months 3TC
    - 50% (37/74) if >2 months 3TC

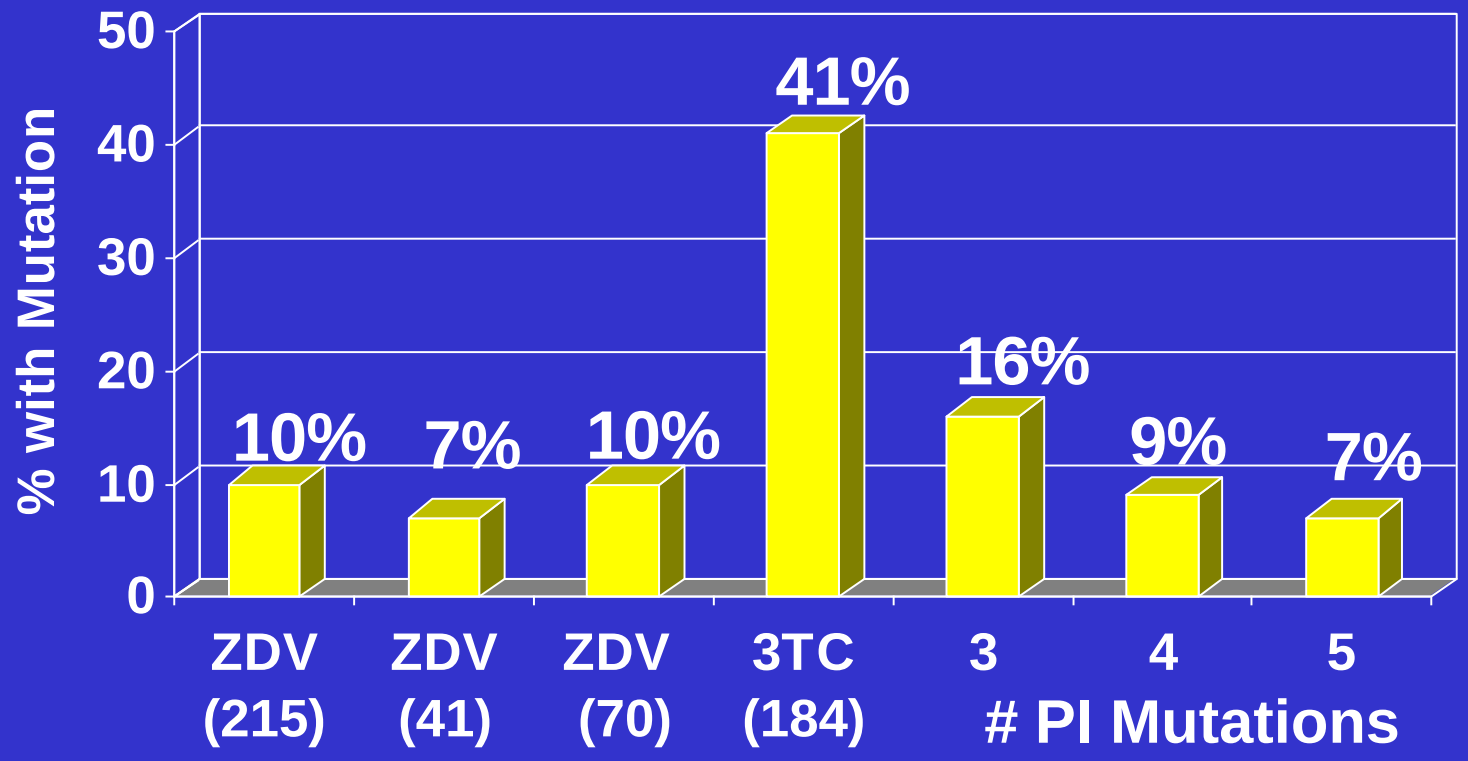
PETRA: ZDV or 3TC Antiretroviral Resistance

Giuliano M et al. AIDS 2003;17:1570-3

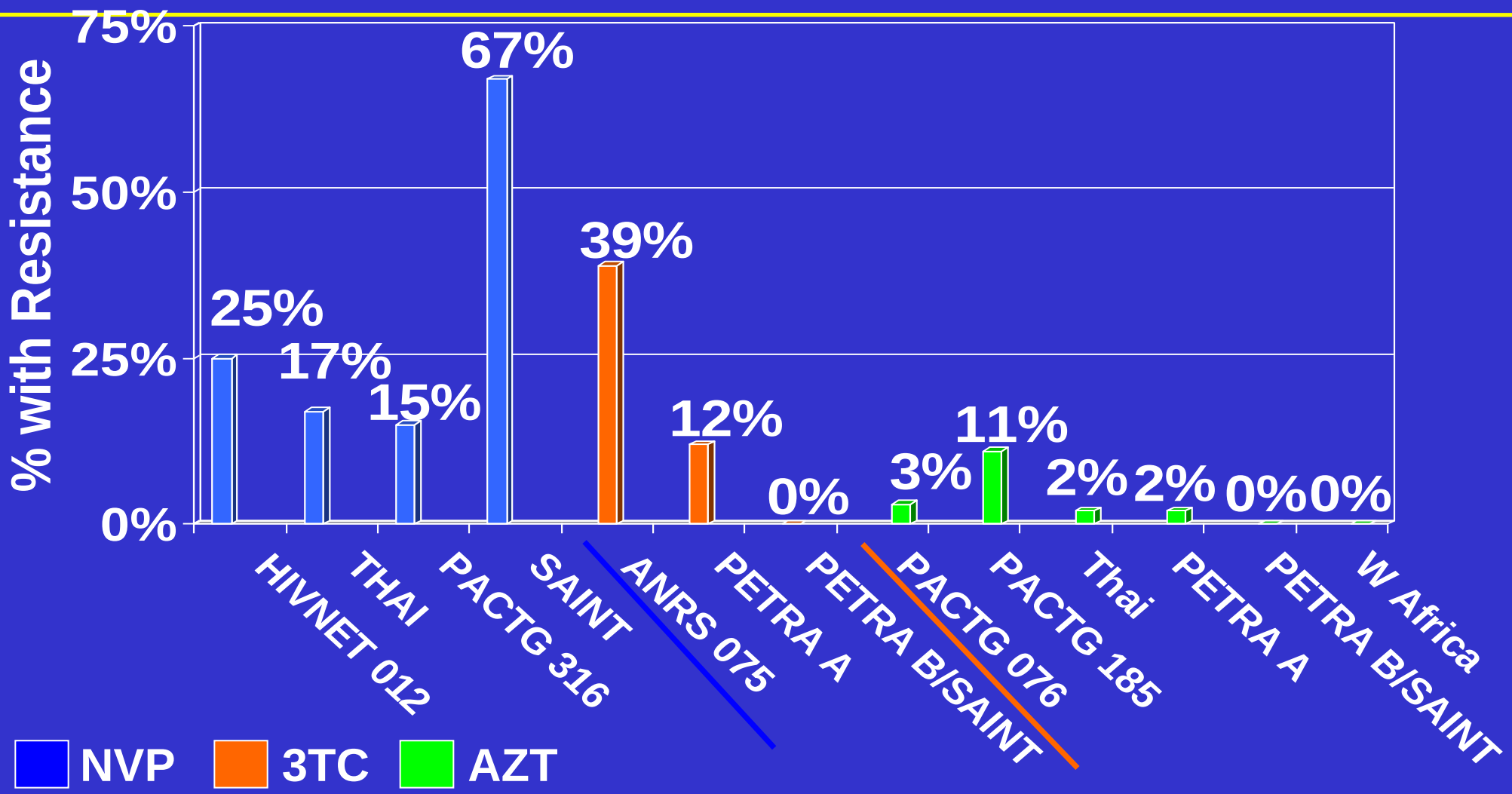
- Virus from 50 women each in arm A and B at 1 week postpartum was genotyped.
- Arm A (starting at 34wks gestation): 6/50 (12%) had 3TC resistance and 1/50 (2%) had ZDV resistance
- Transmission unrelated to presence of mutation:
- Arm B (starting in labour): 0/50 (0%) women had NRTI mutations.

PACTG 316: Resistance Mutations Present at Delivery in 70 Women with RNA >3,000

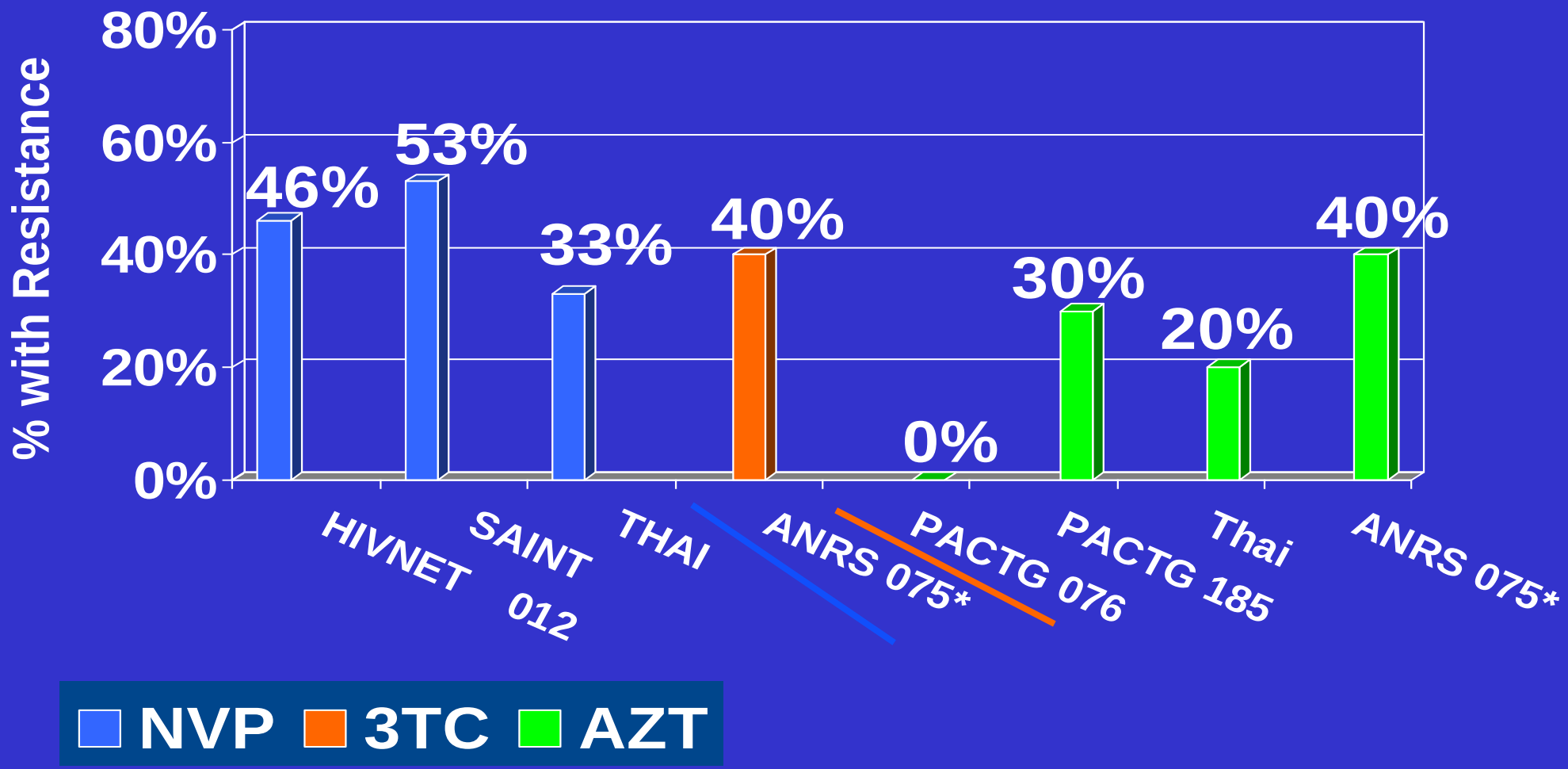
Sullivan J. XIII AIDS Conf, July 2000, Durban S Africa (LbOr014)



Summary: Acquisition of Antiretroviral Resistance in Mothers Following Antiretroviral Prophylaxis

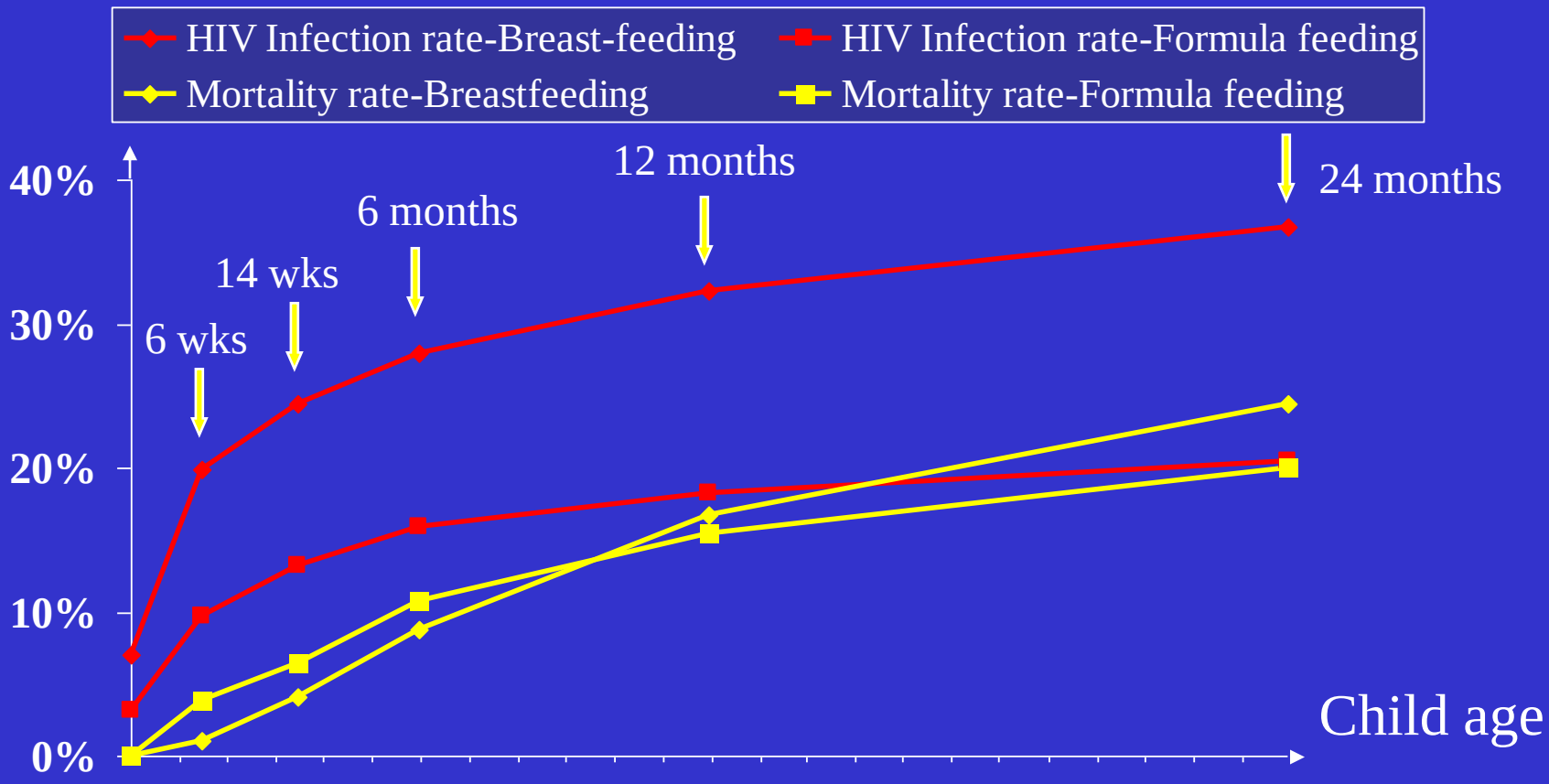


Summary: ARV Resistance at Age 6 Weeks in Infants Infected Despite ARV Prophylaxis



Transmission of HIV through Breastfeeding and its prevention

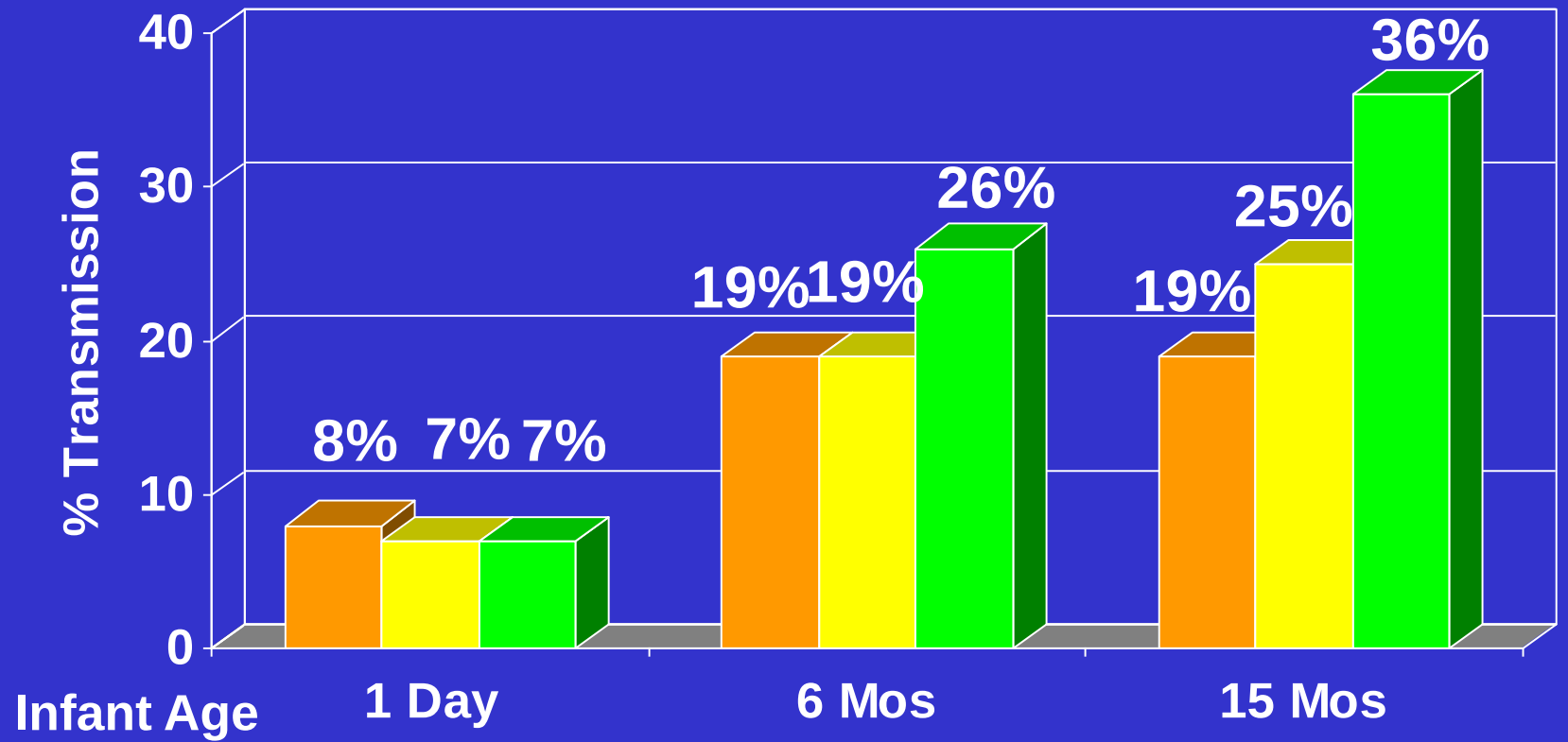
Balancing the risks of breastfeeding and formula feeding



Source: Nduati et al. JAMA 2000

Method of Infant Feeding and HIV Transmission in Breastfed Children

Coutsoudis A. XIII AIDS Conf, July 2000, Durban S Africa (LbOr6)



At 6 months:

Exclusive vs Mixed: 0.6 (0.3-1.0)

Exclusive vs Never: 1.2 (0.6-2.2)

DITRAME (peri-partum ZDV): Transmission from women with CD4 < 500mm^3

Age	ZDV (N = 50 / 137) HIV Transm. Rate	Placebo (N = 55 / 136) HIV Transm. Rate (No.)	% Efficacy	95% CI
2 weeks	20.1	26.1	23%	-27 - 53
6 weeks	25.6	32.0	20%	-18 - 46
3 mos.	27.5	34.3	20%	-17 - 45
6 mos.	29.3	35.3	17%	-19 - 42
12 mos.	38.5	38.0	-1%	-39 - 26
18 mos.				
24 mos.	39.6	41.3	4%*	-30 - 29

Late post-natal transmission (after 6 weeks) in ZDV arm = 14%

DITRAME (peri-partum ZDV): Transmission from women with CD4 > 500mm^3

Age	ZDV (N = 16 / 177) HIV Transm. Rate	Placebo (N = 38 / 179) HIV Transm. Rate (No.)	% Efficacy	95% CI
2 weeks	6.0	14.7	59%	12 - 81
6 weeks	7.7	19.3	60%	27 - 78
3 mos.	8.4	19.3	57%	23 - 76
6 mos.	8.8	19.2	54%	18 - 74
12 mos.	9.1	20.9	56%	24 - 75
18 mos.				
24 mos.	9.1	22.0	59%*	28 - 76

Late post-natal transmission (after 6 weeks) in ZDV arm = 1.4%

Maternal or Infant ARV prophylaxis during breastfeeding:

Kesho Bora, PEPI and BAN trials

Kesho Bora (Maternal prophylaxis):

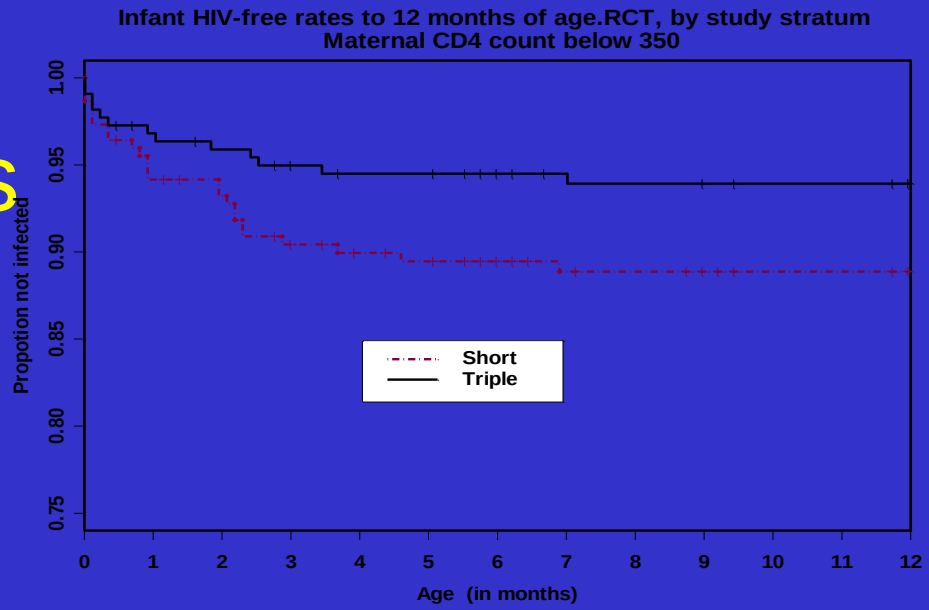
AZT/3TC/LPVr to mothers from 28-36 weeks pregnancy to 6 months post-partum

HIV Transmission in Infants born to mothers with CD4 200-500

	Triple		Short		
	Events (cum) / at risk	**Rate (95% CI)**	**Events (cum) / at risk**	**Rate (95% CI)**	**Reduc -tion**
Birth	7/395	**1.8** (0.8, 3.7)	9/401	**2.2** (1.2, 4.3)	**18%**
6 weeks	13/376	**3.3** (1.9, 5.6)	19/373	**4.8** (3.1, 7.4)	**31%**
6 months	19/337	**4.9** (3.1, 7.5)	33/329	**8.5** (6.1, 11.8)	**42%**
12 months	21/275	**5.5** (3.6, 8.4)	36/249	**9.5** (6.9, 13.0)	**42%**

P<0.04

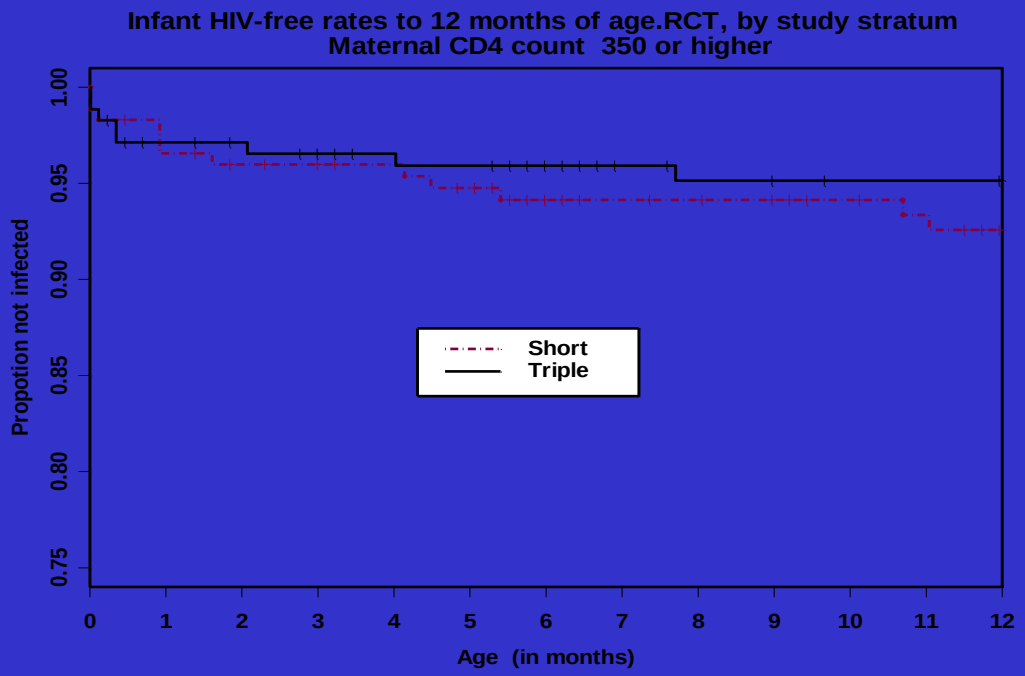
Kesho Bora
Infants born to mothers with CD4 200-350



Log rank test p = 0.044
(stratified on centre and intention to BF)

	Triple		Short		
	Events (cum) / at risk	Rate (95% CI)	Events (cum) / at risk)	Rate (95% CI)	Reduc -tion
Birth	4/220	**1.8** (0.7, 4.8)	6/224	**2.7** (1.2, 5.9)	**33%**
6 weeks	8/210	**3.6** (1.8, 7.2)	13/206	**5.8** (3.4, 9.8)	**38%**
6 months	12/189	**5.5** (3.2, 9.5)	23/182	**10.5** (7.1, 15.4)	**48%**
12 months	13/155	**6.1** (3.6, 10.3)	24/132	**11.1** (7.6, 16.2)	**45%**

Kesho Bora: Infants born to mothers with CD4 350-500



Log rank test p = 0.33

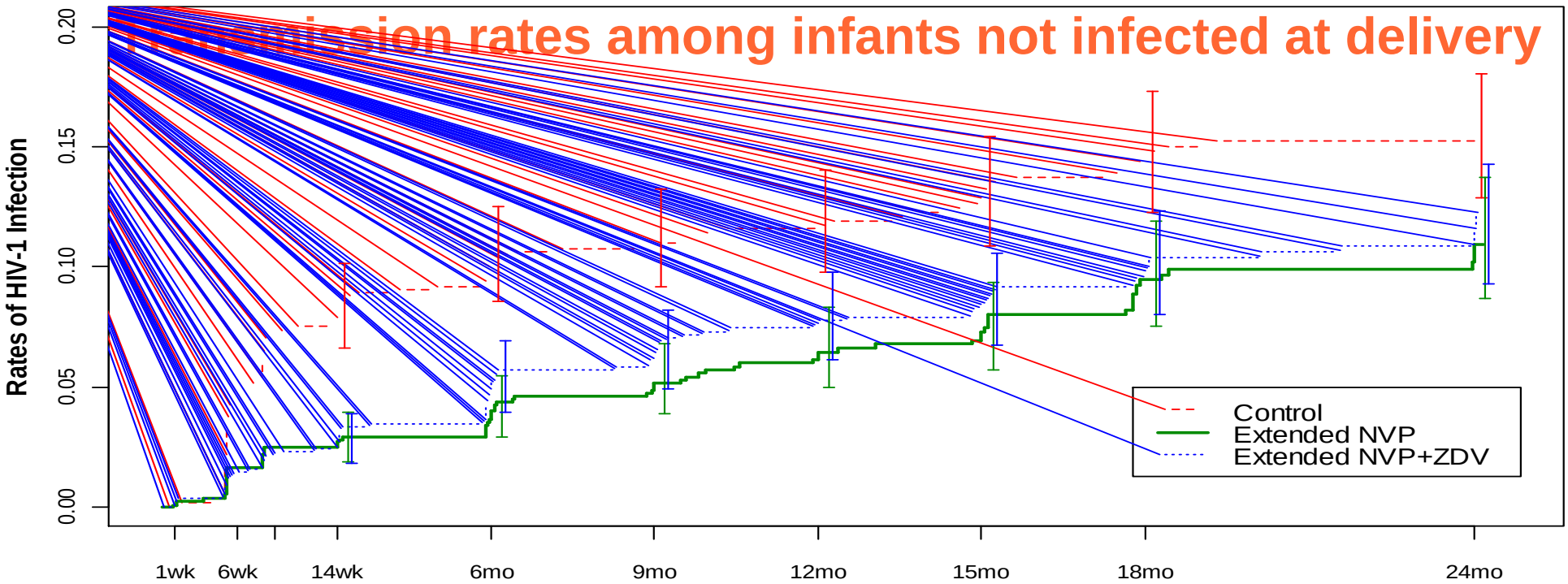
(stratified on centre and intention to BF)

	Triple		Short		
	Events (cum) / at risk	**Rate (95% CI)**	**Events (cum) / at risk)**	**Rate (95% CI)**	**Reduc -tion**
Birth	3/175	**1.7** (0.6, 5.2)	3/177	**1.7** (0.5, 5.2)	**0%**
6 weeks	5/166	**2.9** (1.2, 6.7)	6/167	**3.4** (1.6, 7.5)	**15%**
6 months	7/148	**4.1** (2.0, 8.4)	10/147	**5.9** (3.2, 10.6)	**31%**
12 months	8/120	**4.9** (2.4, 9.5)	12/117	**7.4** (4.3, 12.8)	**34%**

PEPI Malawi (Infant prophylaxis):

NVP +/- AZT to infant from birth to 3,5 months

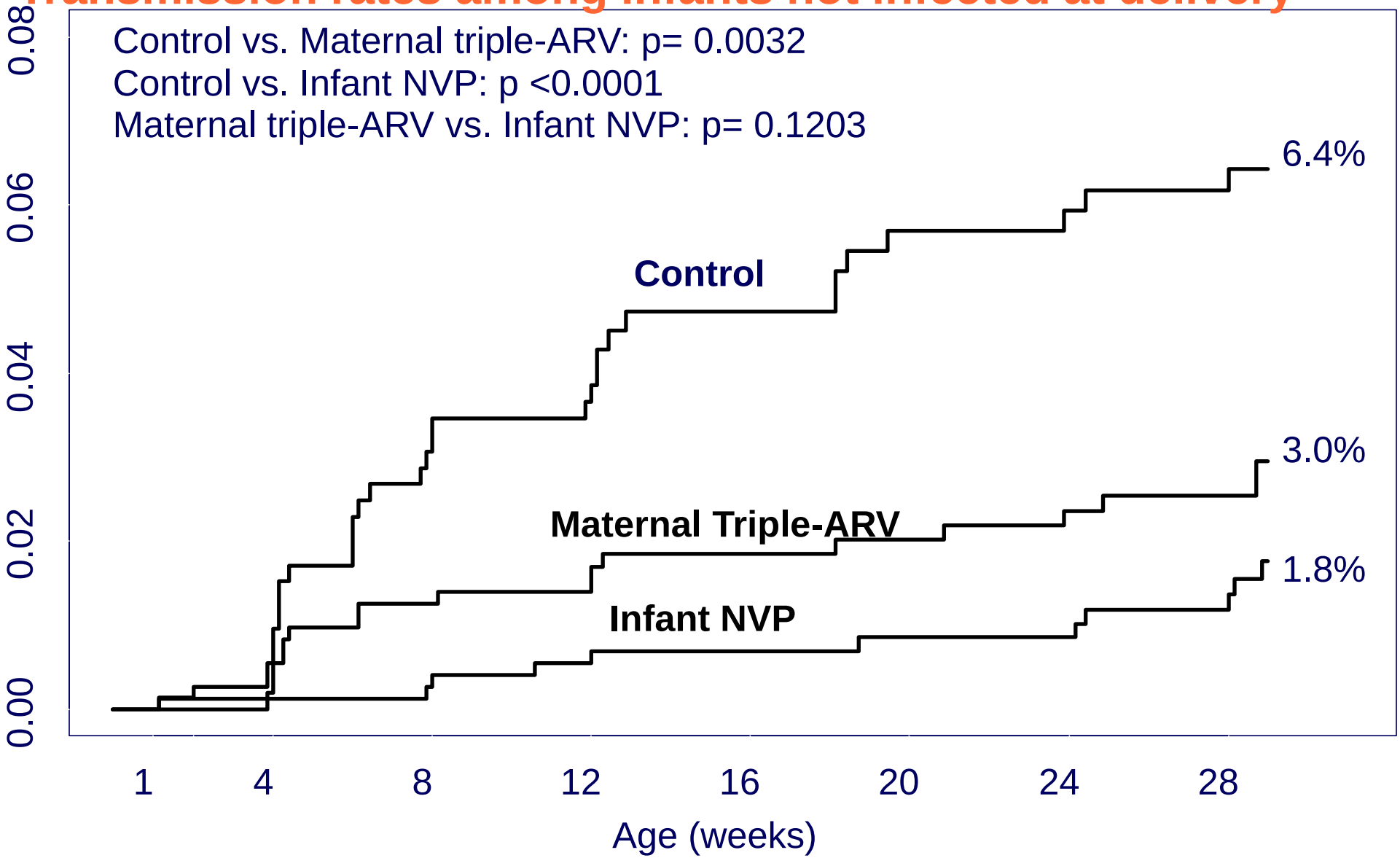
Transmission rates among infants not infected at delivery



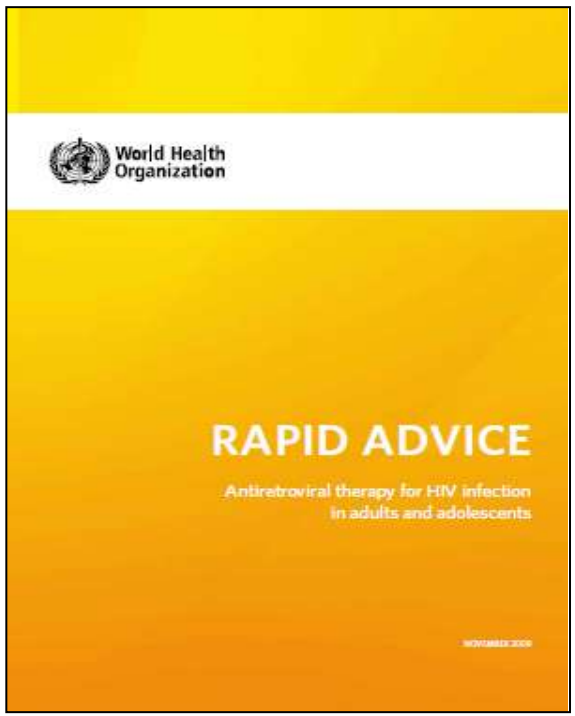
Age	1 wk	6 wks	9 wks	14 wks	6 mos	9 mos	12 mos	15 mos	18 mos	24 mos
Rate (%)										
Control	0.2	4.9	7.3	8.2	10.4	11.0	11.8	13	14.6	15.3
3,5 mths infant NVP	0.1	1.7	2.5	2.7	4.0	5.2	6.5	7.3	9.5	11.0
3,5 mths infant NVP+ZDV	0.2	1.5	2.2	2.7	5.3	6.4	7.8	8.5	10.0	11.6

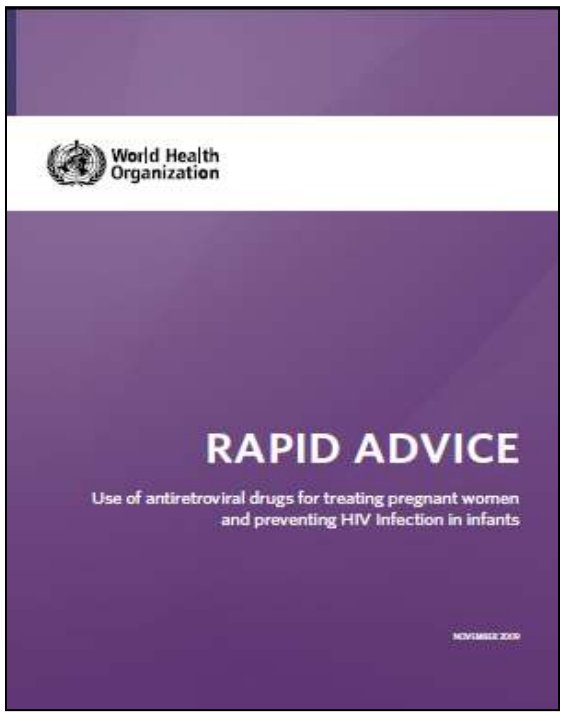
BAN Malawi : maternal (ZDV/3TC/LPVr) or infant (NVP) prophylaxis from birth to 6 months post-partum

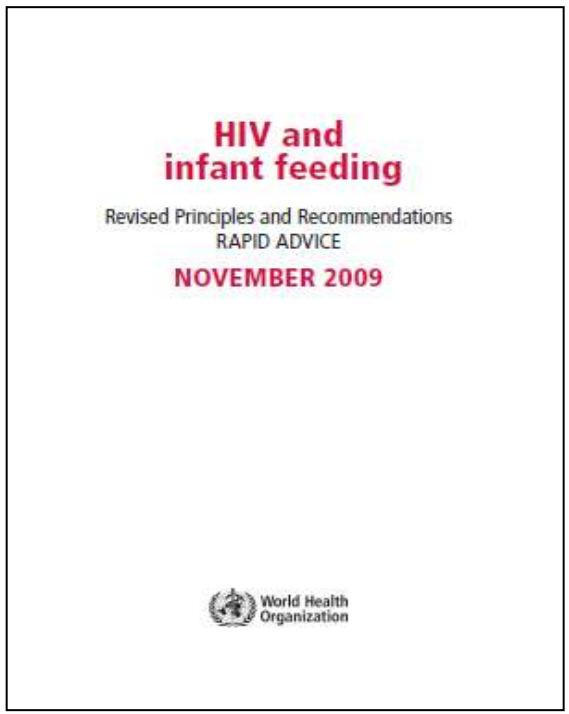
Transmission rates among infants not infected at delivery



2009 Revisions of WHO Guidelines
Coordinated in Three Rapid Advice Documents







Current guidelines available at:
http://www.who.int/hiv/en/

PMTCT ARV Recommendations Refer to Two Key Approaches

- Lifelong ART for HIV-positive pregnant women in need of treatment
- Prophylaxis, or short-term provision of ARVs, to prevent HIV transmission from mother to child
  - During pregnancy
  - During breastfeeding (if breastfeeding is the best infant feeding option)

WHO PMTCT Guidelines 2009

Initiation of ART among pregnant women

- Mothers in need of ART for their own health should get lifelong treatment
  - Initiate ART in pregnant women with CD4 < 350 regardless of clinical stage
  - Initiate ART in clinical stage 3 and 4 if CD4 not available
  - Start ART as soon as feasible
- Importance and critical need of CD4 for decision-making on ART eligibility

WHO PMTCT Guidelines 2009

ART for mother and prophylaxis for exposed infants

- **Mother**
  - **AZT + 3TC + NVP or**
  - **AZT + 3TC + EFV or**
  - **TDF + xTC + NVP or**
  - **TDF + xTC + EFV**

  (note: xTC = 3TC or FTC)

- **Strong recommendation**

- **Infant**
  - **Breastfeeding population**
    - Daily NVP from birth to 6 weeks
  - **Non-breastfeeding population**
    - AZT for 6 weeks OR
    - NVP for 6 weeks

- **Strong recommendation**

WHO PMTCT Guidelines 2009

Benefit and impact of providing ART to eligible pregnant women

Pregnant women with CD4 < 350:

- Represent about 40% of HIV+ pregnant women
- Account for > 75% of MTCT risk
- Account for > 80% of postpartum transmissions
- Account for 85% of maternal deaths within 2 years of delivery

WHO PMTCT Guidelines 2009

What ARV prophylaxis to give to non-treatment eligible pregnant women?

- Two possible options:
  - Maternal AZT
  - Maternal triple ARV prophylaxis:

- NVP-based regimens are not recommended

- Strong recommendation

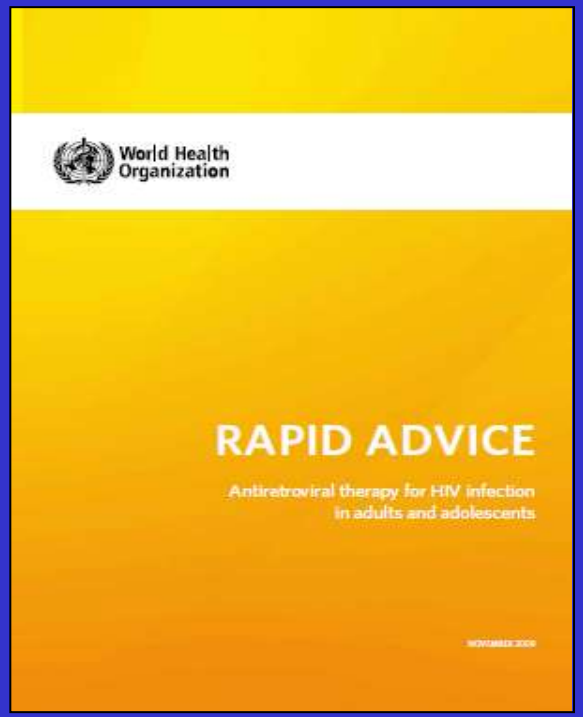
WHO PMTCT Guidelines 2009

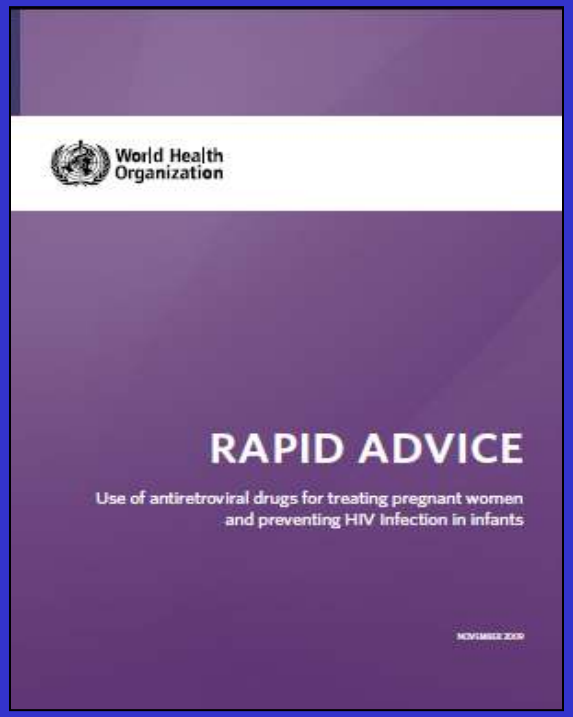
Prophylaxis options

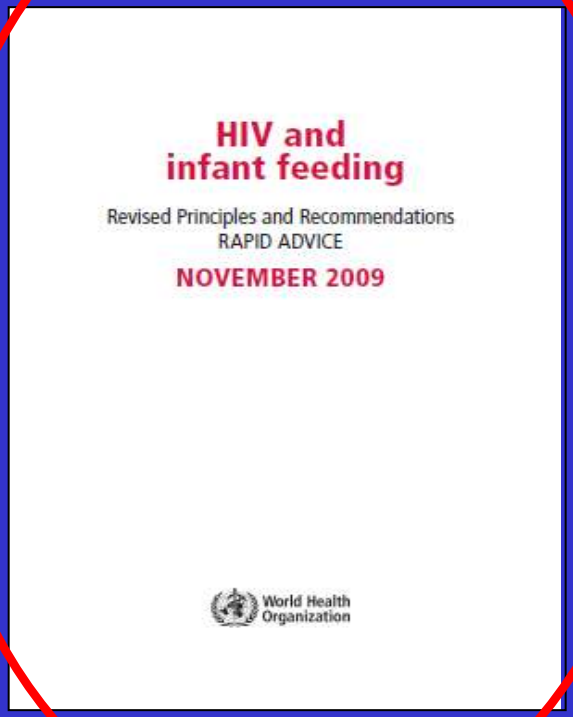
Option A: AZT	Option B: Triple ARV
Mother • Antepartum AZT (from 14 weeks) • sd-NVP at onset of labour* • AZT + 3TC during labour & delivery* • AZT + 3TC for 7 days postpartum*	**Mother** • Triple ARV (from 14 wks until one wk after all exposure to breast milk has ended) • AZT + 3TC + LPV-r • AZT + 3TC + ABC • AZT + 3TC + EFV • TDF + 3TC or FTC + EFV
Infant Breastfeeding population • Daily NVP (from birth until one wk after all exposure to breast milk had ended) Non-breastfeeding population • AZT for 6 weeks OR • NVP for 6 weeks	**Infant** Breastfeeding population • Daily NVP from birth to 6 weeks Non-breastfeeding population • AZT for 6 weeks OR • NVP for 6 weeks

*sd-NVP and AZT+3TC can be omitted if mother receives > 4 wks AZT antepartum

Revision of infant feeding recommendations in 2009







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Setting national or sub-national recommendations for infant feeding in the context of HIV

- National or sub-national health authorities should decide whether health services will principally counsel and support mothers known to be HIV-positive to
  - breastfeed and receive ARV interventions OR
  - avoid all breastfeeding

as the strategy that will most likely give infants the greatest chance of HIV-free survival

“12 months” or more?

- In the presence of ARV interventions breastfeeding can continue to 12 months
  - Avoids many of the complexities associated with stopping breastfeeding
  - Provides a safe and adequate diet for infants 6-12 months of age