

---

# **Mother-To-Child Transmission of HIV**

## **Antiretroviral interventions**

**Isabelle de Vincenzi**

**Training Course in Sexual and Reproductive Health Research**

**Geneva 2012**

# 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)

---

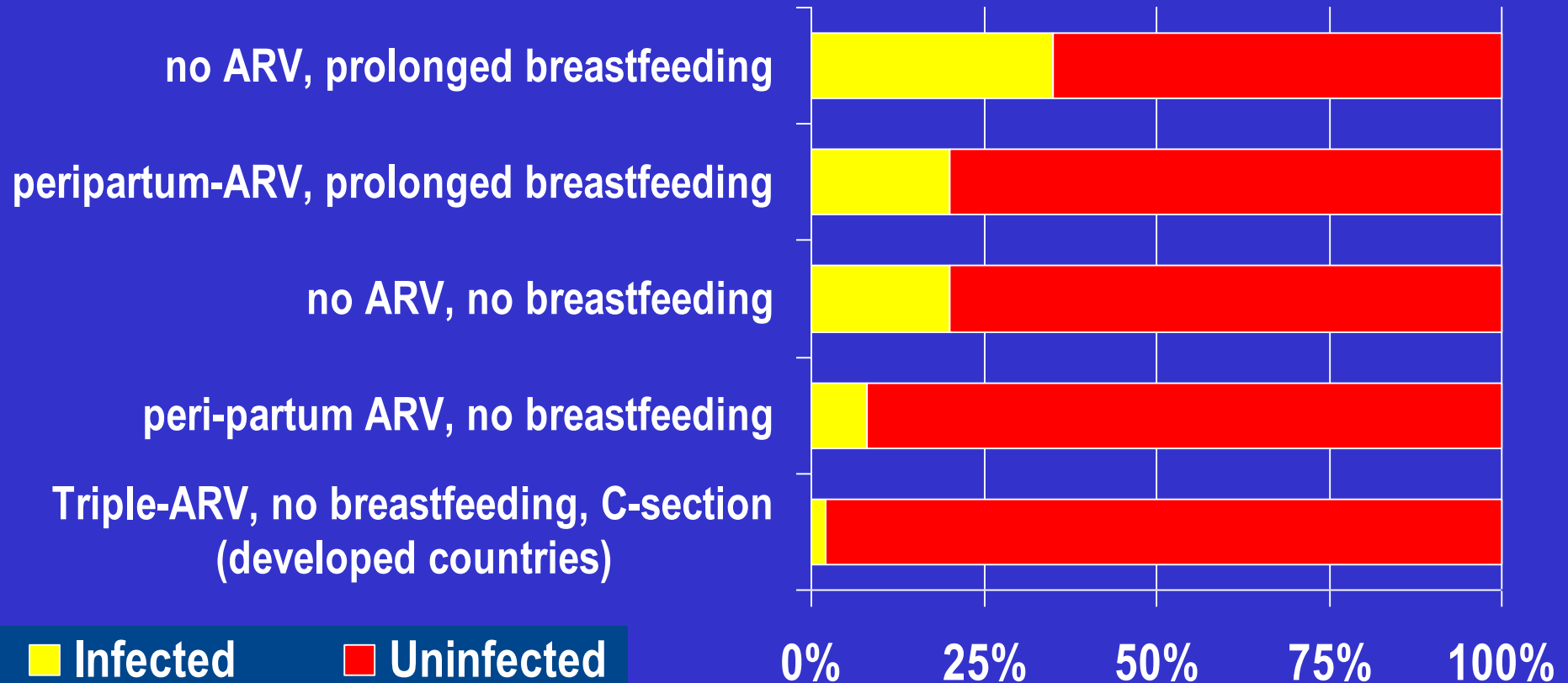
# Peri-partum ARV interventions:

Late in-utero

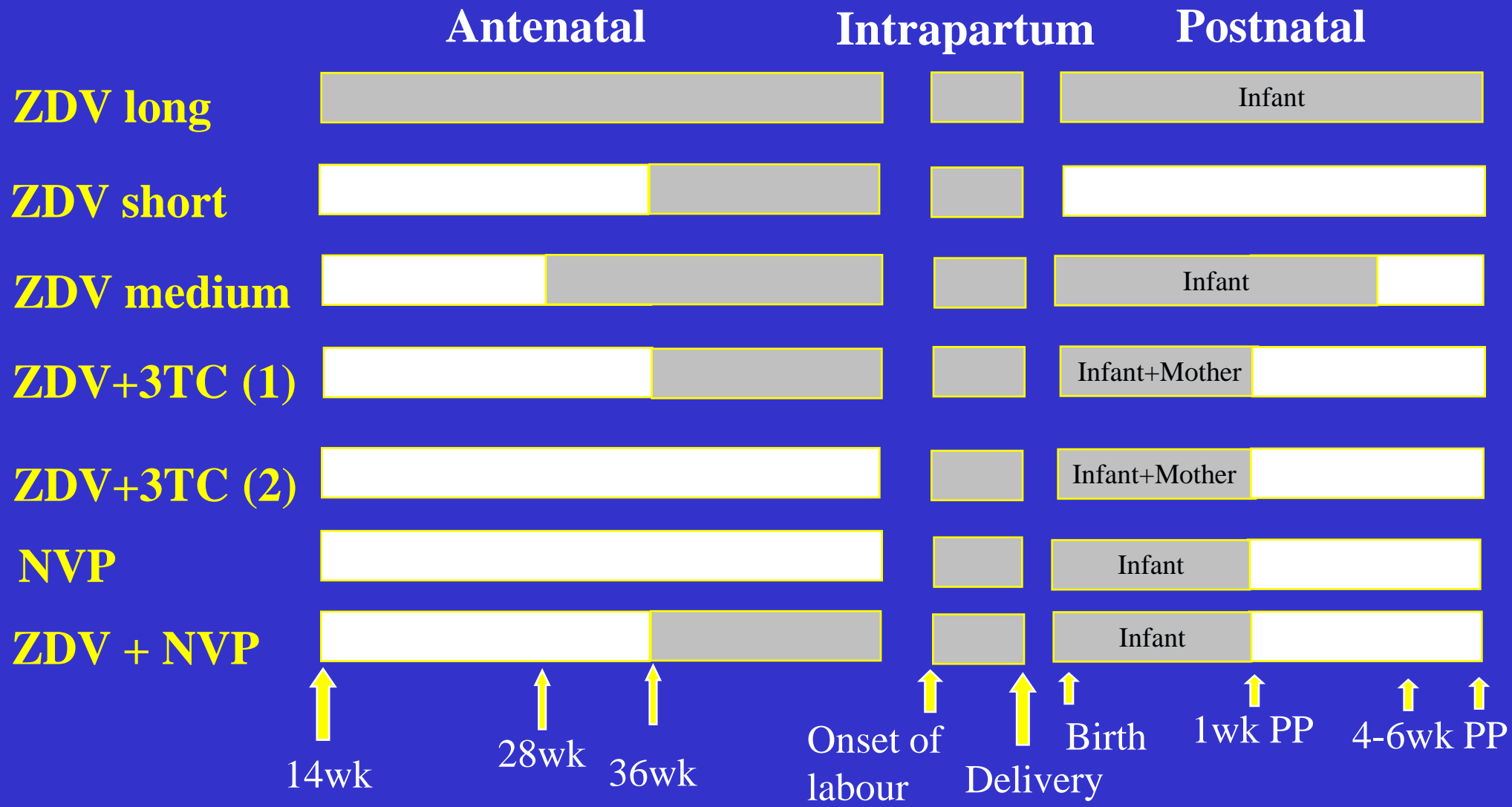
Labour and Delivery

Post-partum (1 week maximum)

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

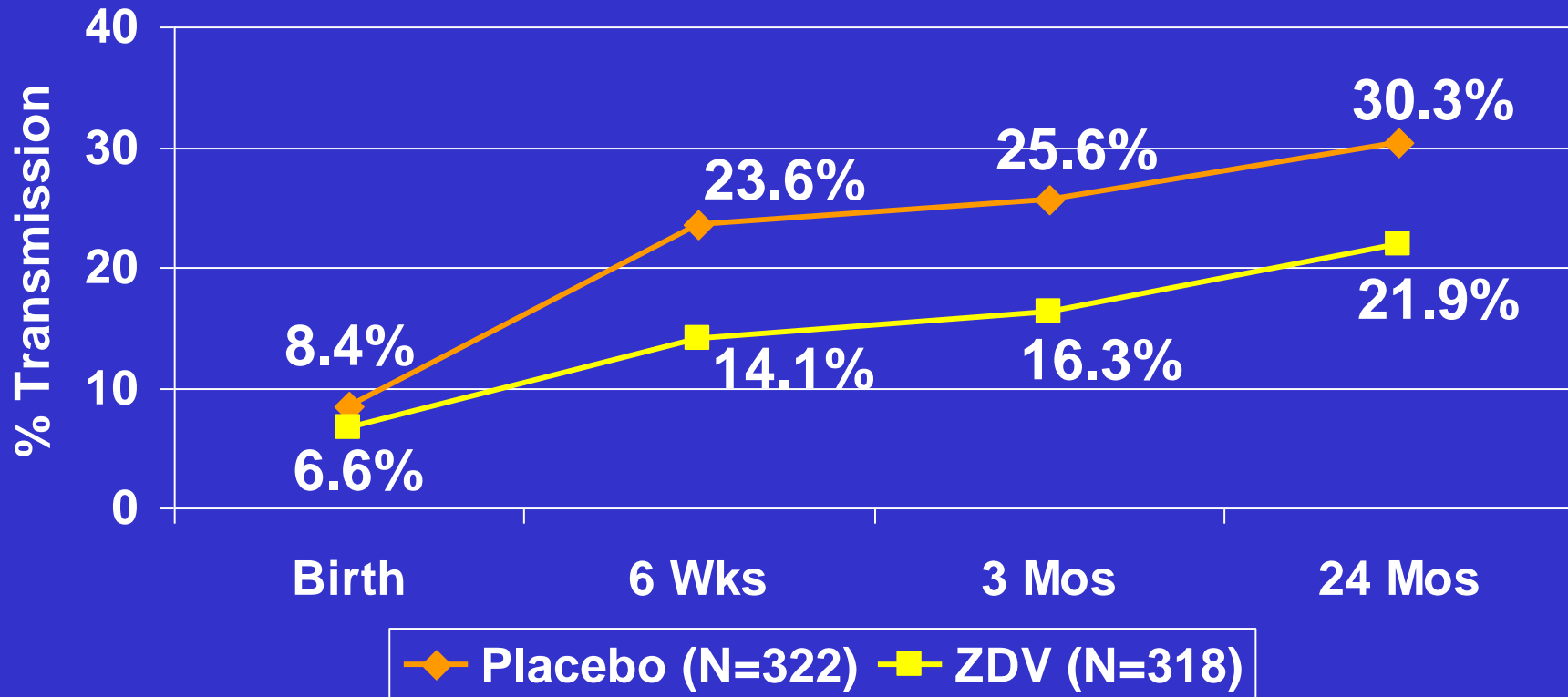


# Peri-partum ARV regimen of proven efficacy (through clinical trials)



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

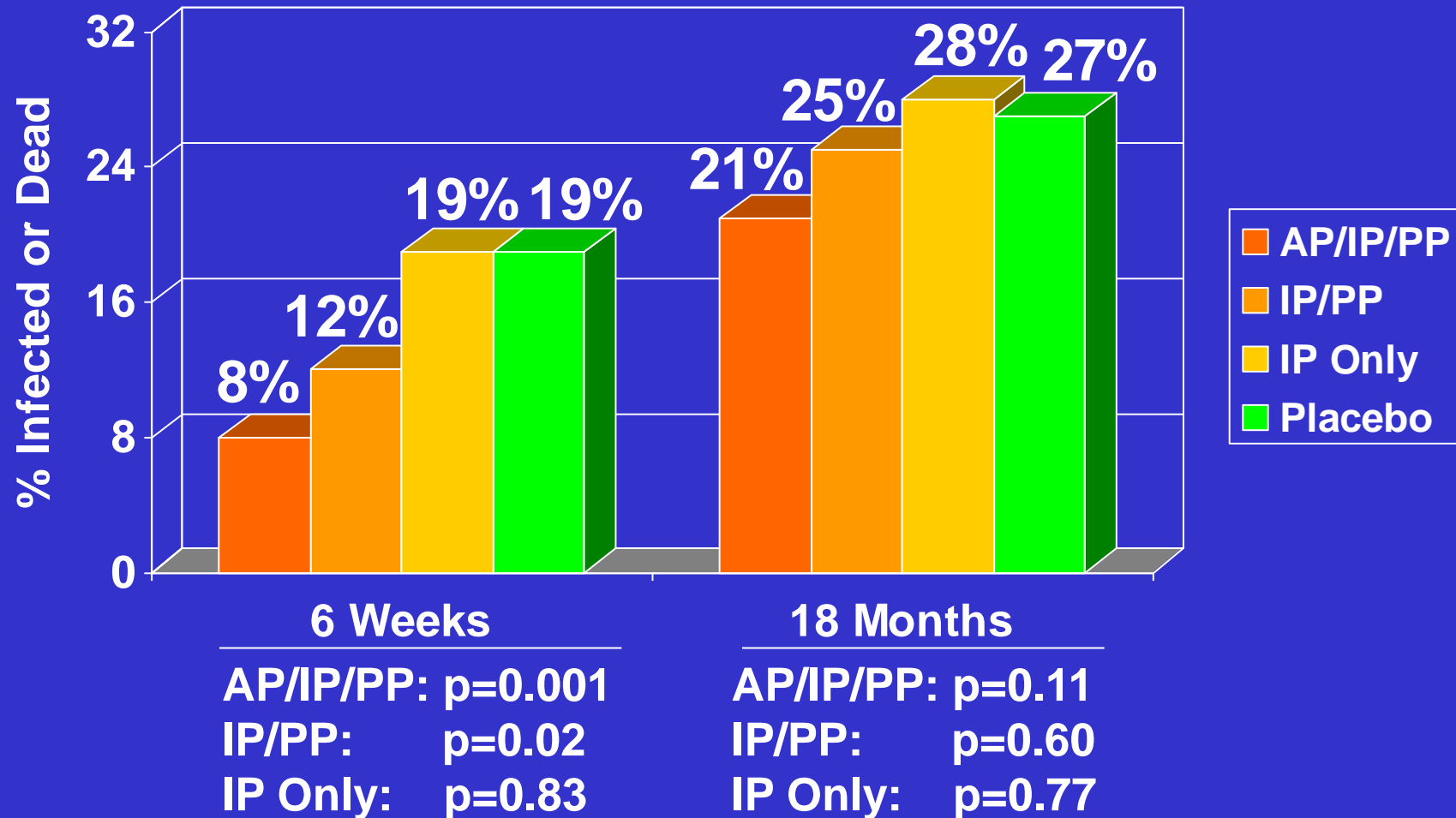
Witkor S. XIII AIDS Conf, July 2000, Durban S Africa (TuOrB354)



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

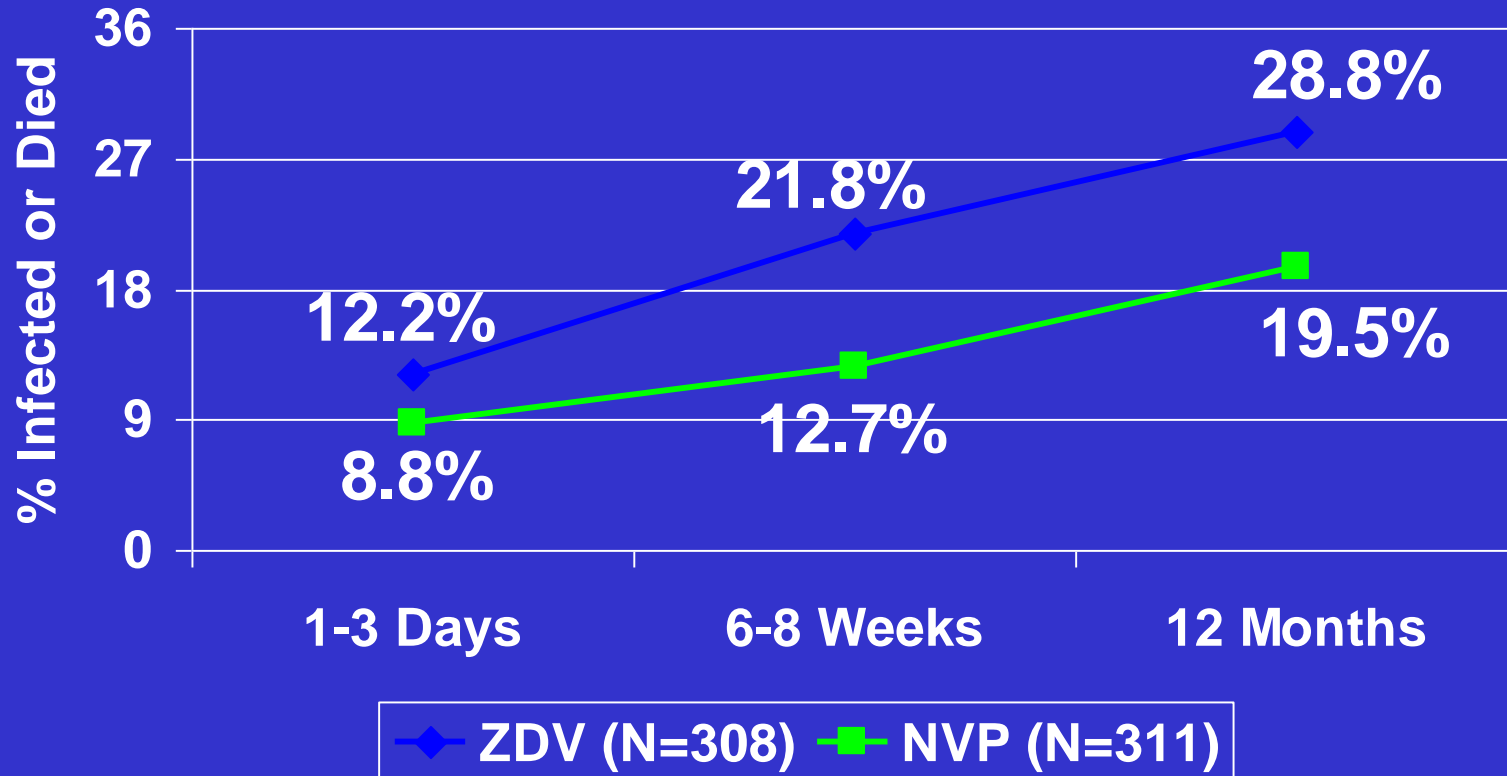
# ZDV/3TC AP/IP/PP, IP/PP, or IP Only vs Placebo: PETRA, HIV Infection or Death, 6 Wks & 18 Mos

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)

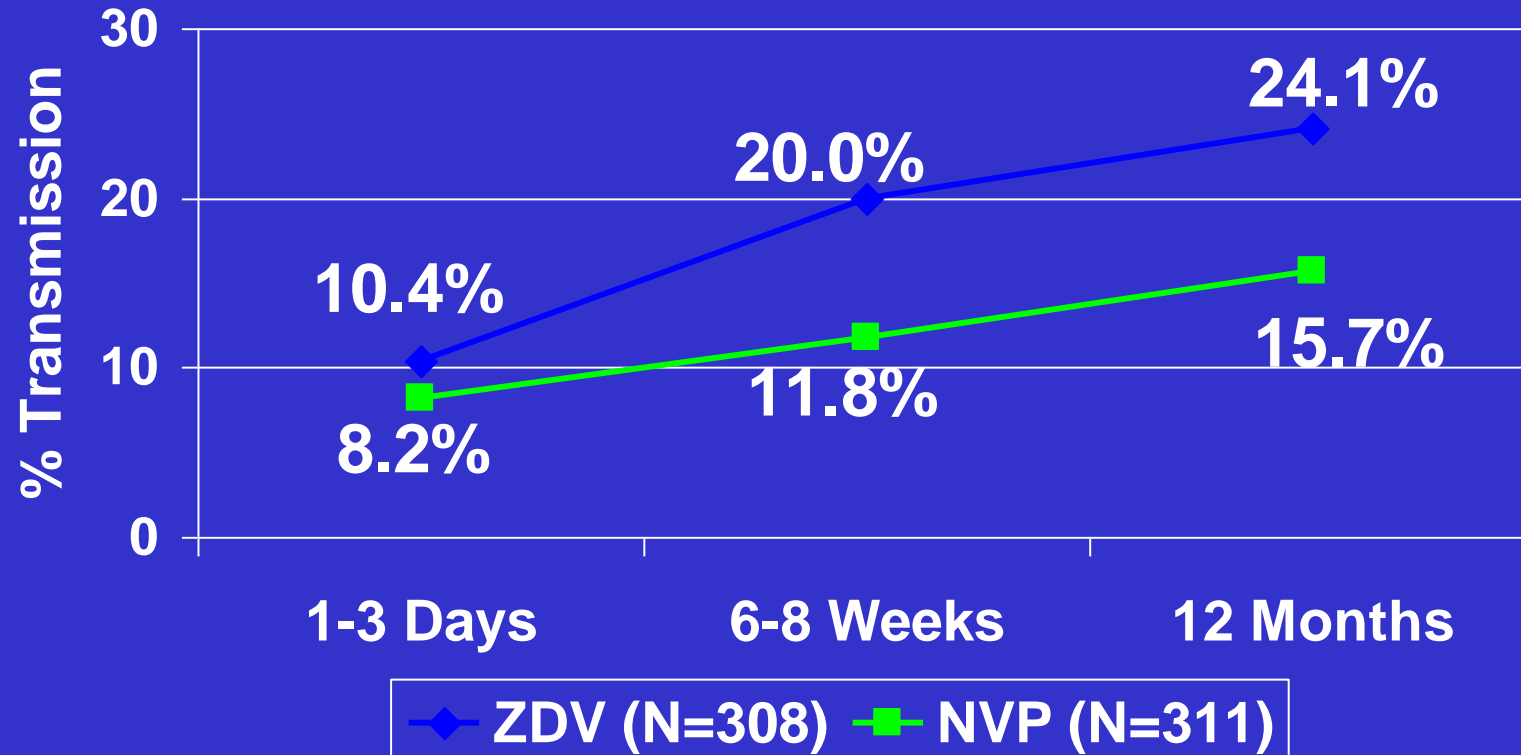


**12 Month Efficacy NVP vs ZDV:  $p = 0.004$**



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

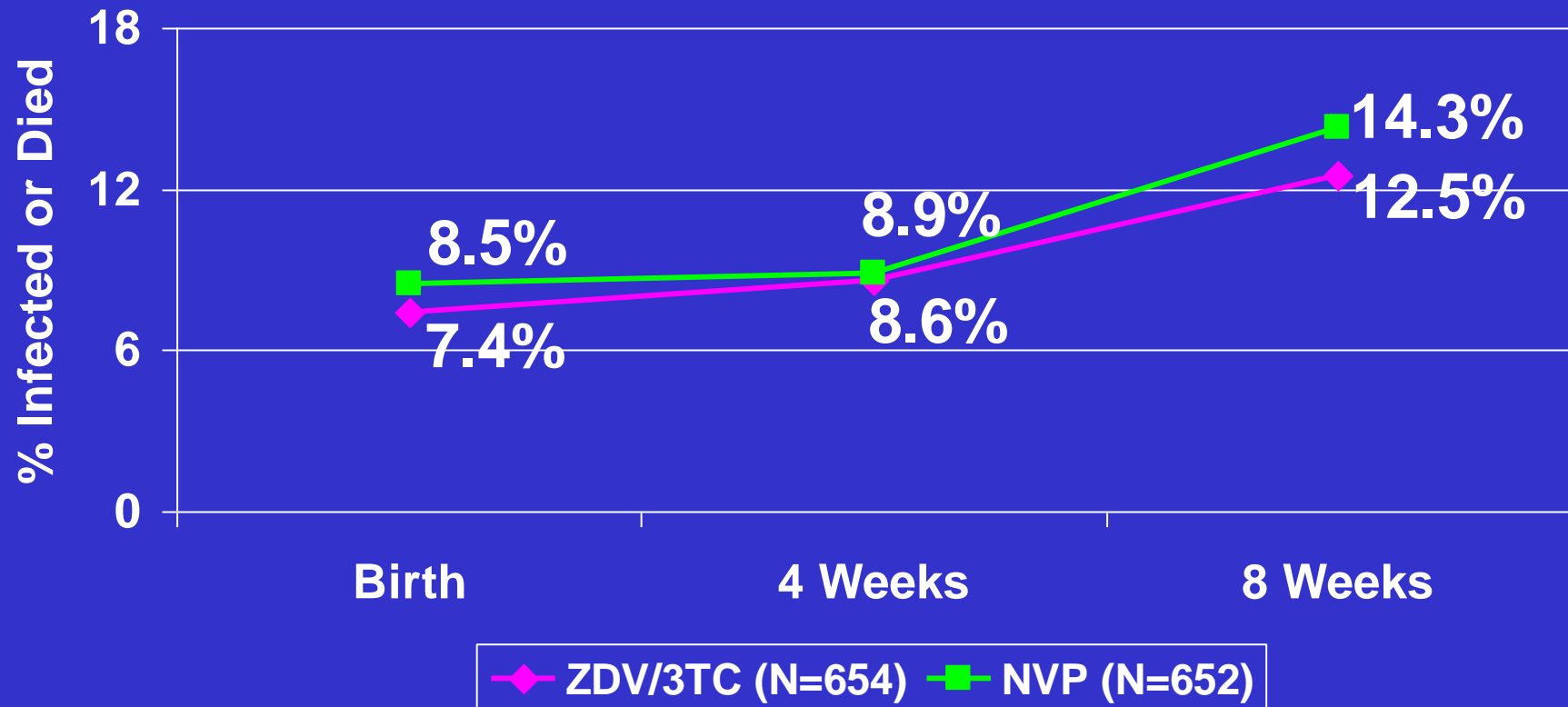
Owen M. XIII AIDS Conf, July 2000, Durban S Africa (LbOr01)



**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)



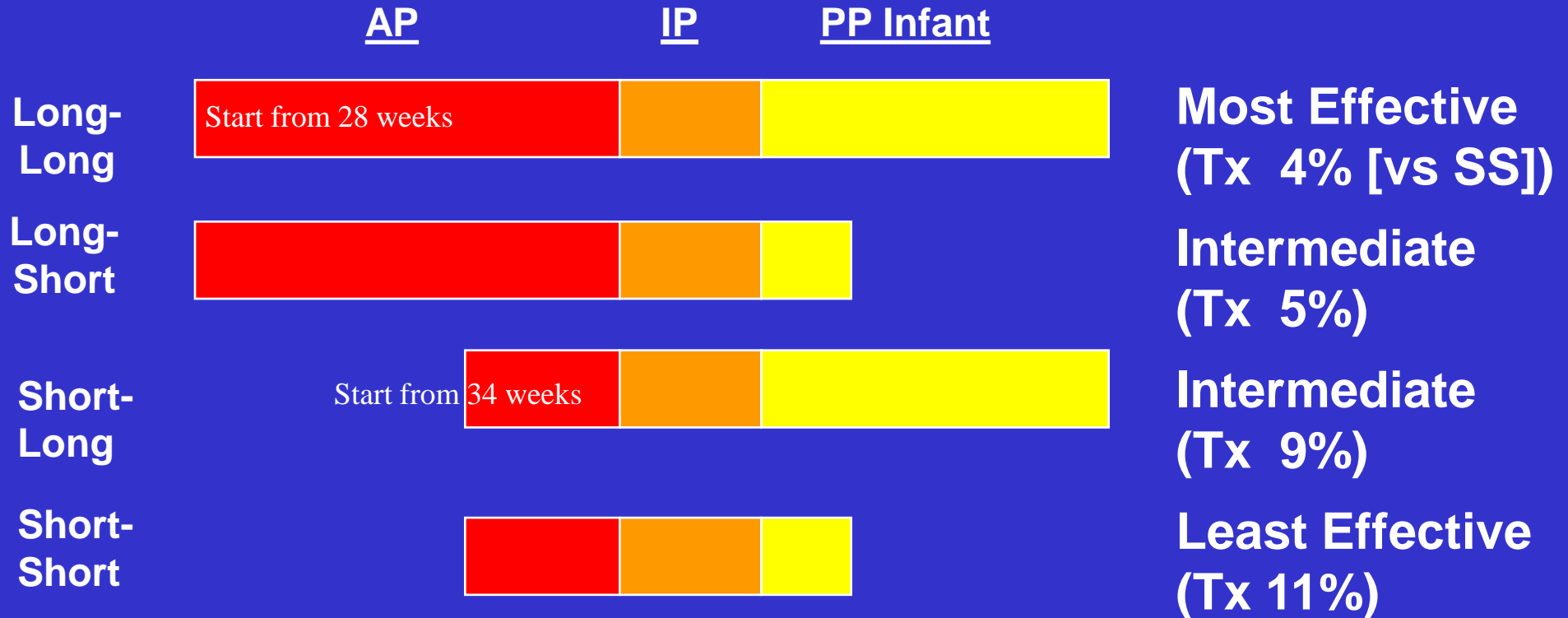
**No significant difference between study arms**

# 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



No Breastfeeding

# Perinatal HIV Prevention Trial – Thailand (2)

- All women received ZDV from 28 weeks
- 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**

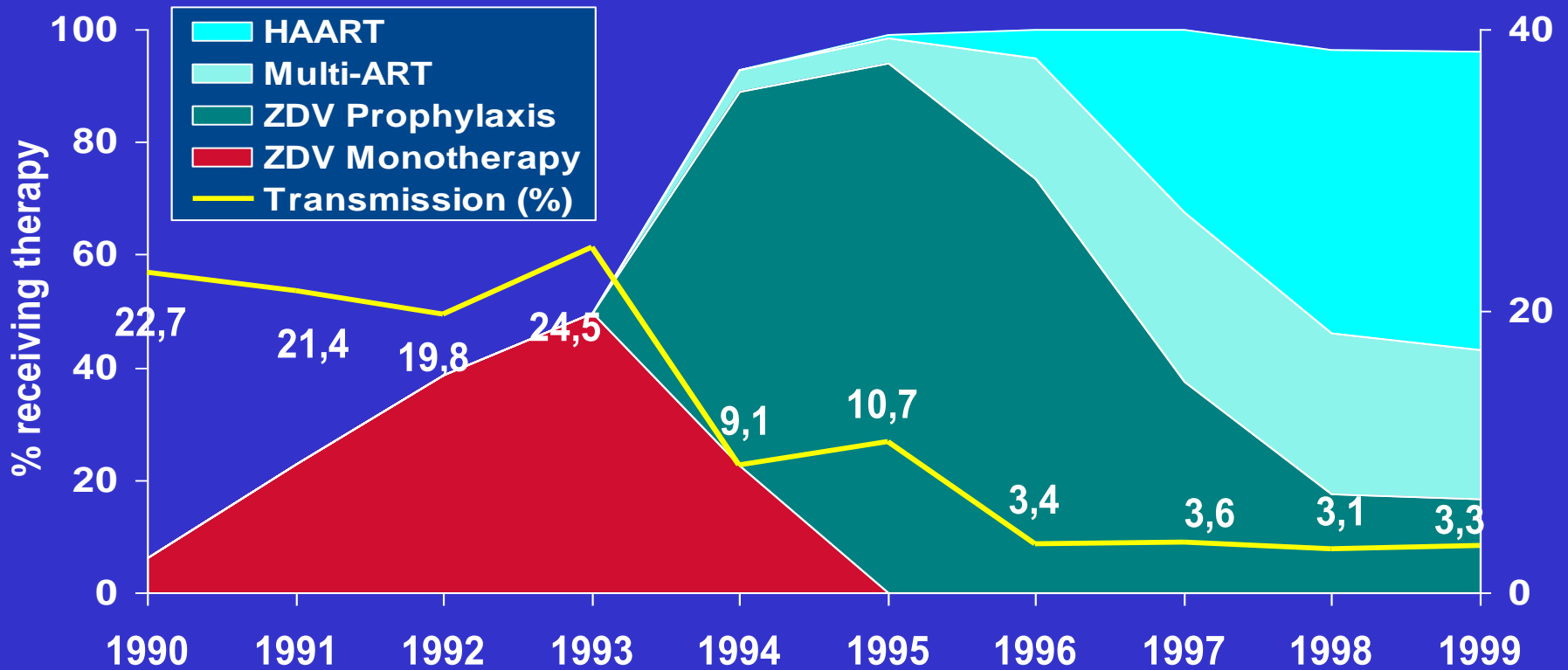
**With :**

**Early & potent combination of ARVS,**

**No breastfeeding,**

**C-Section**

# ARV Use and HIV Transmission (WITS, USA)

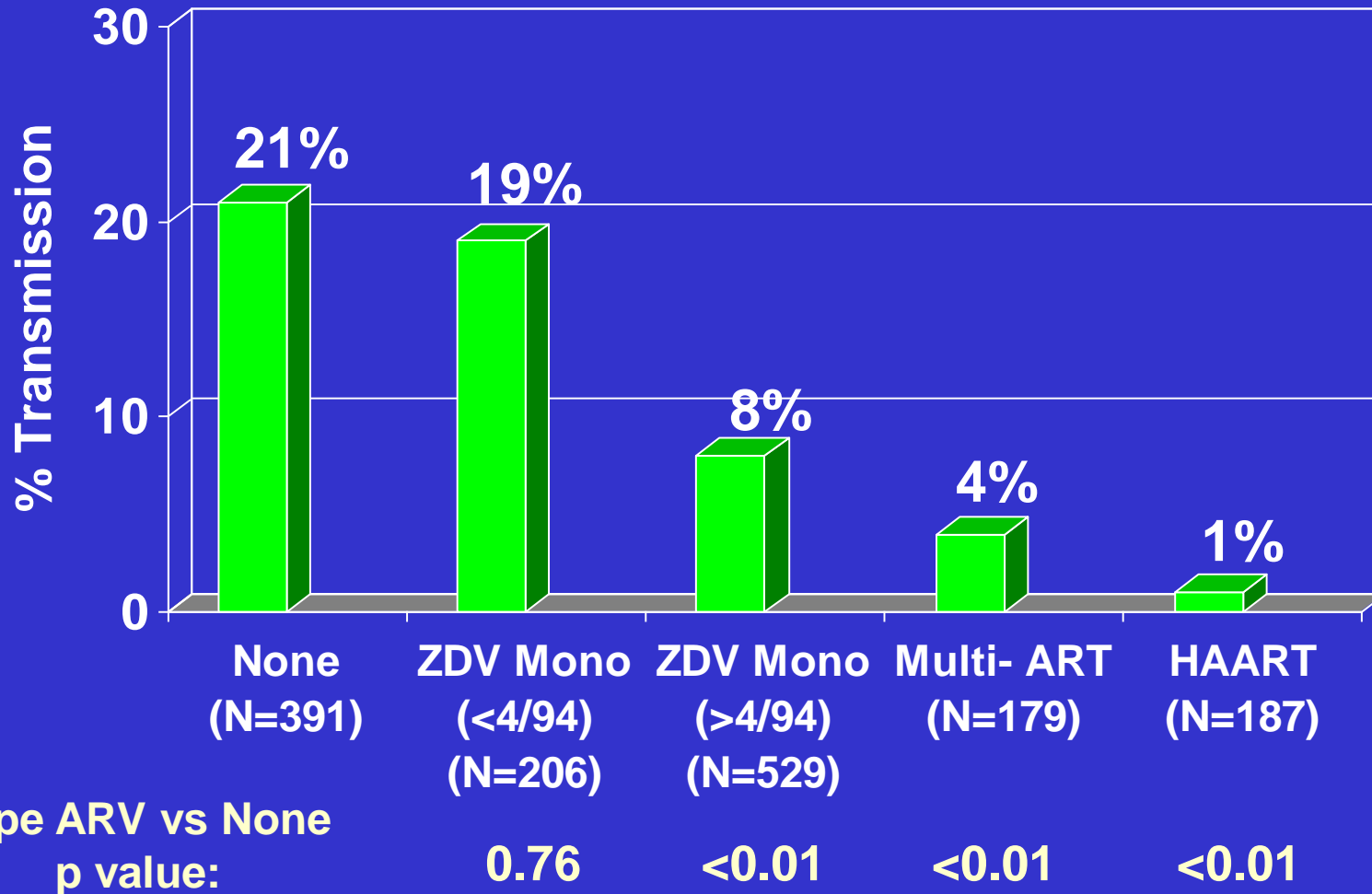


Source: Blattner, Durban 2000, LbOr4



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

Blattner W. XIII AIDS Conf, July 2000, Durban S Africa (LBO4)



---

# **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

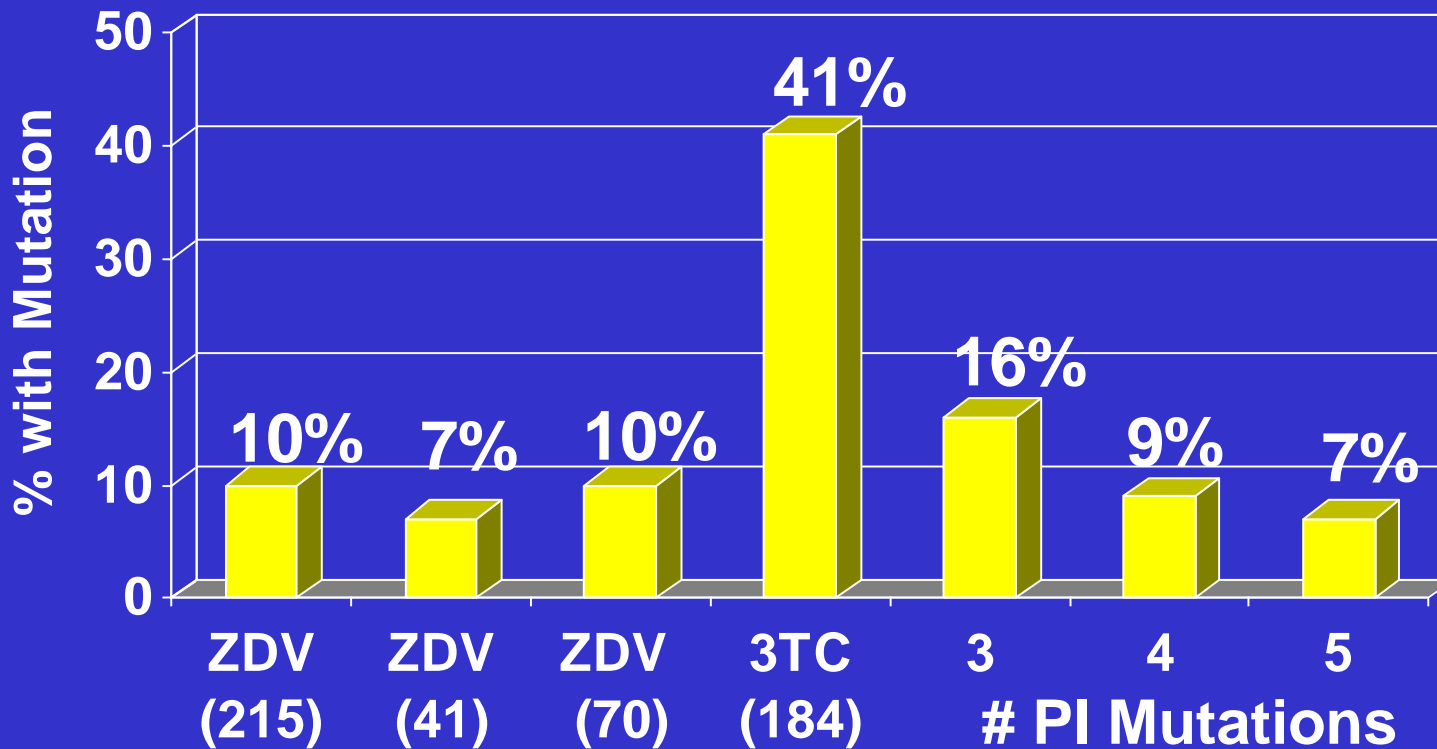
# **PETRA: ZDV or 3TC Antiretroviral Resistance**

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

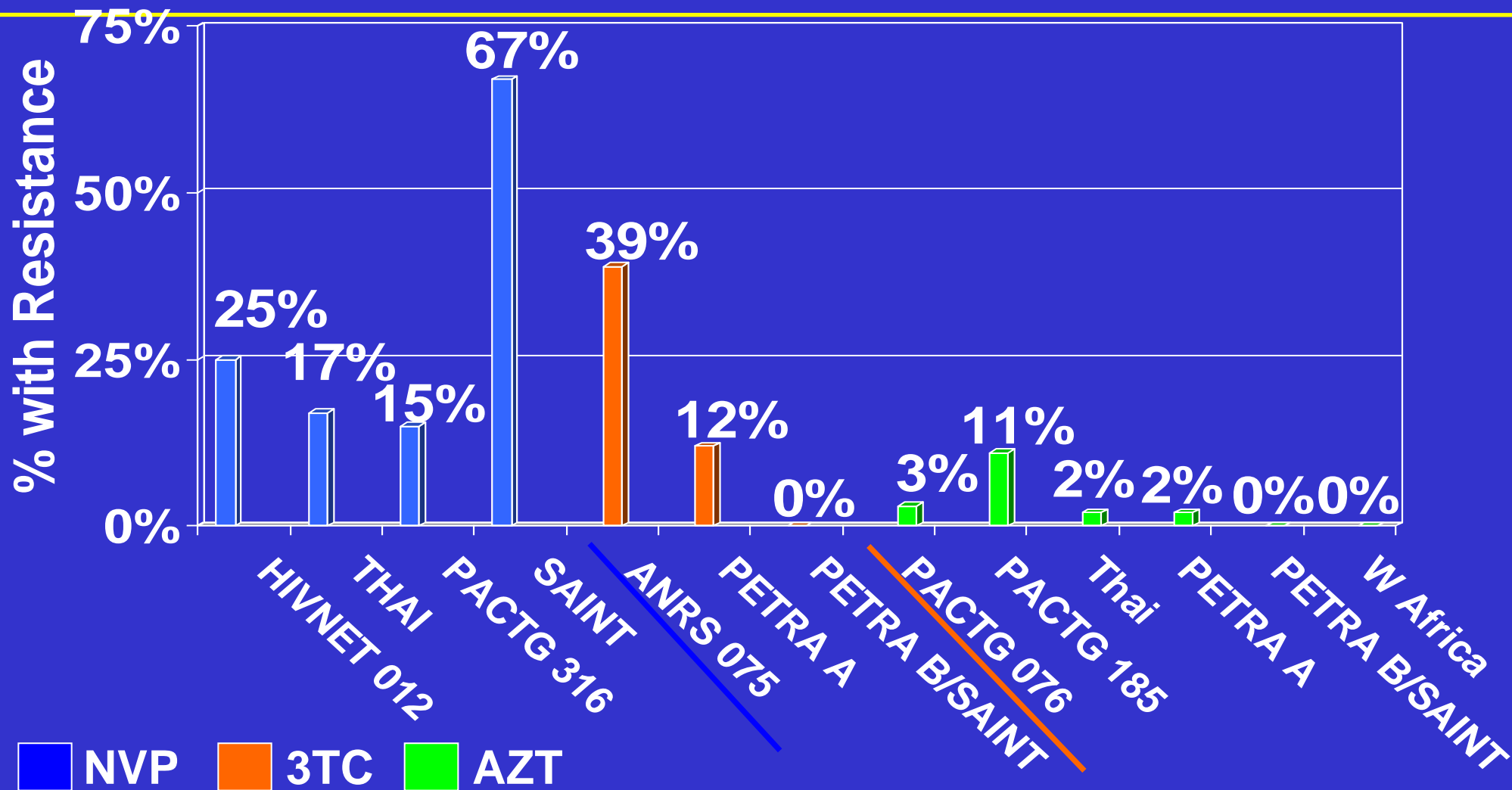
- **Virus from 50 women each in arm A and B at 1 week postpartum was genotyped.**
- **Arm A (starting at 34wks gestation): 6/50 (12%) had 3TC resistance and 1/50 (2%) had ZDV resistance**
- **Transmission unrelated to presence of mutation:**
- **Arm B (starting in labour): 0/50 (0%) women had NRTI mutations.**

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

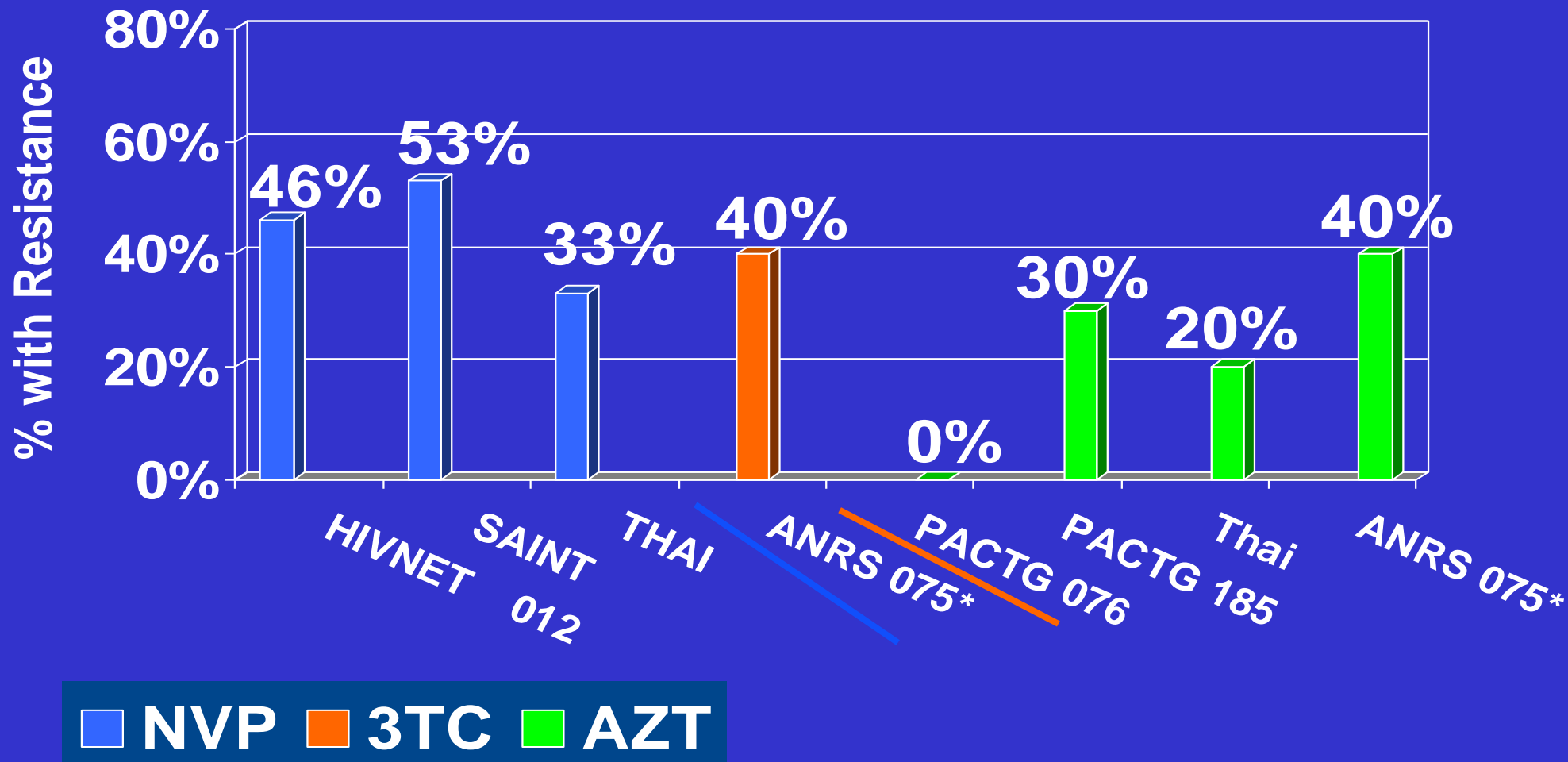
*Sullivan J. XIII AIDS Conf, July 2000, Durban S Africa (LbOr014)*



# Summary: Acquisition of Antiretroviral Resistance in Mothers Following Antiretroviral Prophylaxis



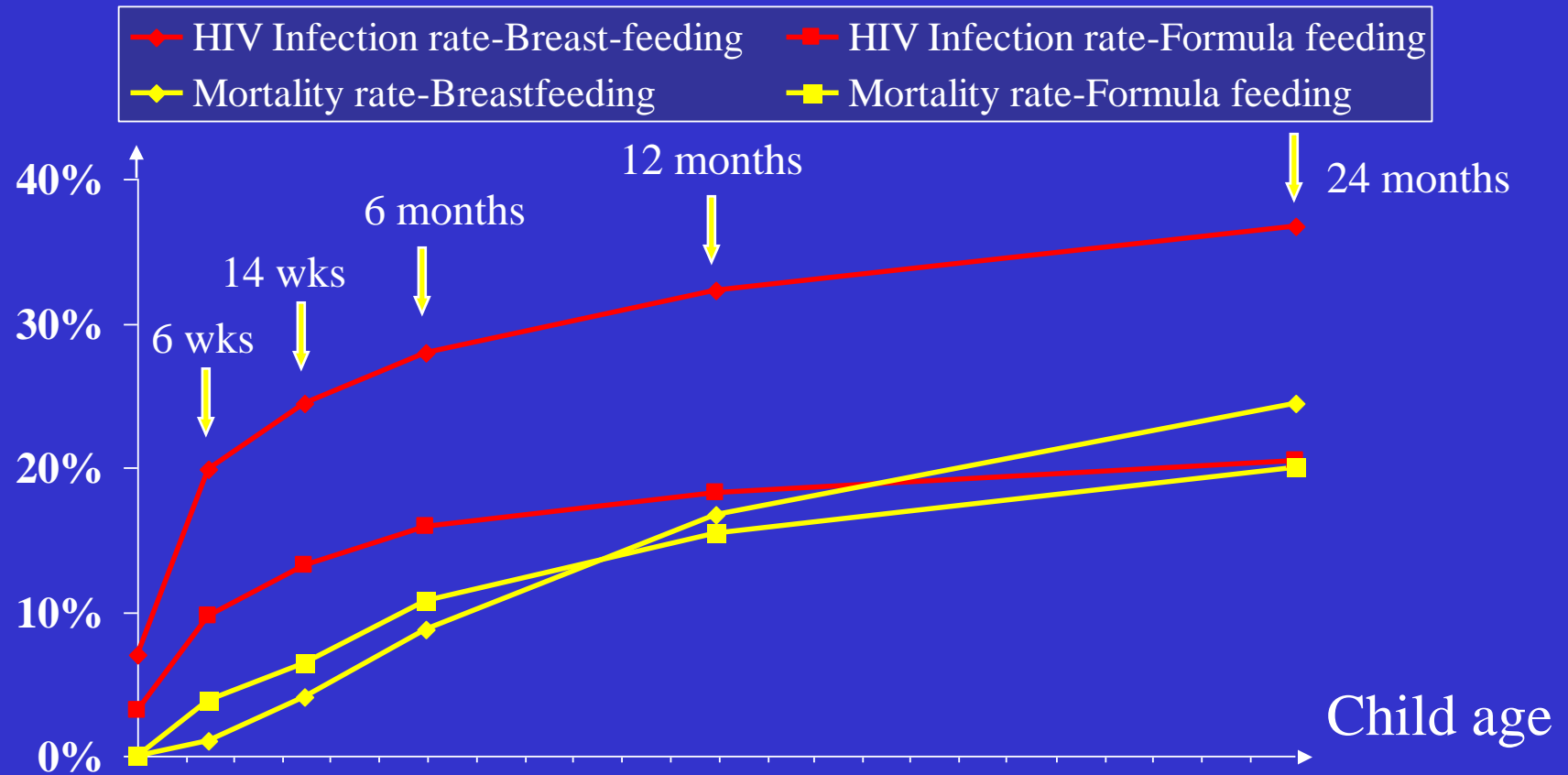
# Summary: ARV Resistance at Age 6 Weeks in Infants Infected Despite ARV Prophylaxis



---

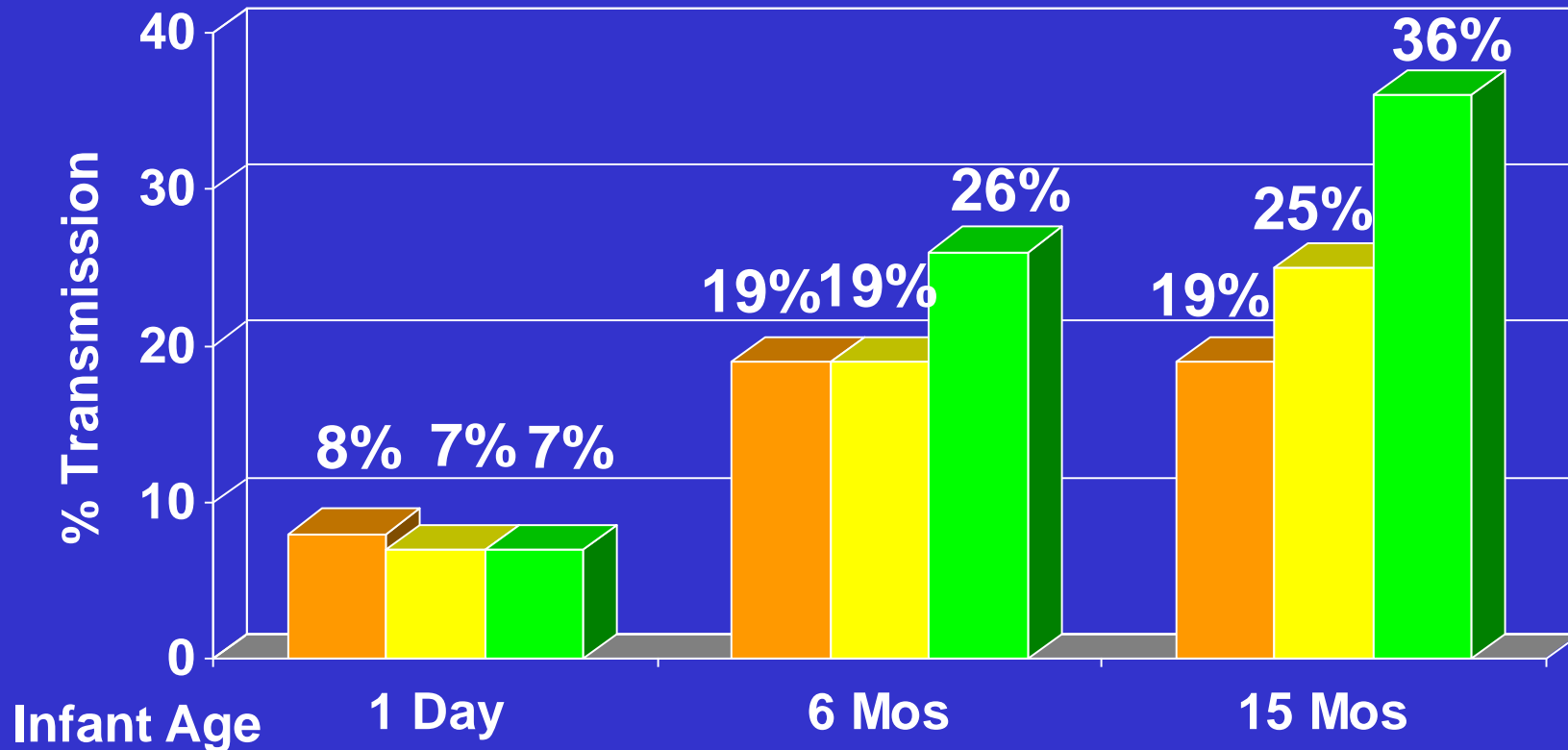
# **Transmission of HIV through Breastfeeding and its prevention**

# Balancing the risks of breastfeeding and formula feeding



# Method of Infant Feeding and HIV Transmission in Breastfed Children

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



■ Never Breastfed (N=157)  
■ Exclusive Breastfed (N=118)  
■ Mixed Feeding (N=276)

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<sup>3</sup>

Age	<u>ZDV</u> (N = 50 / 137) HIV Transm. Rate	<u>Placebo</u> (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<sup>3</sup>

Age	<u>ZDV</u> (N = 16 / 177) HIV Transm. Rate	<u>Placebo</u> (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

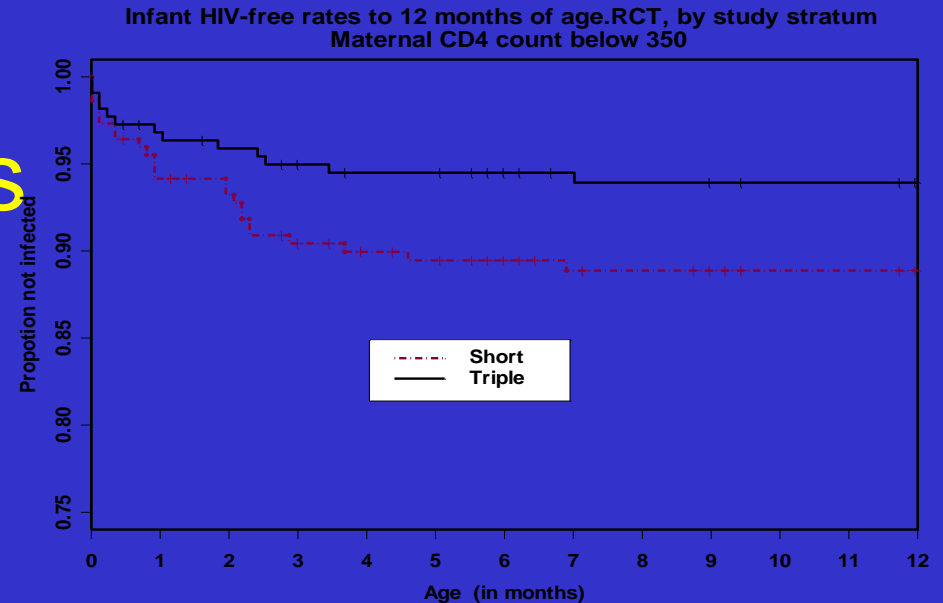
	Triple Events (cum) / at risk	Rate (95% CI)	Short Events (cum) / at risk	Rate (95% CI)	Reduc- -tion
<b>Birth</b>	7/395	1.8 (0.8, 3.7)	9/401	2.2 (1.2, 4.3)	18%
<b>6 weeks</b>	13/376	3.3 (1.9, 5.6)	19/373	4.8 (3.1, 7.4)	31%
<b>6 months</b>	19/337	4.9 (3.1, 7.5)	33/329	8.5 (6.1, 11.8)	42%
<b>12 months</b>	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)

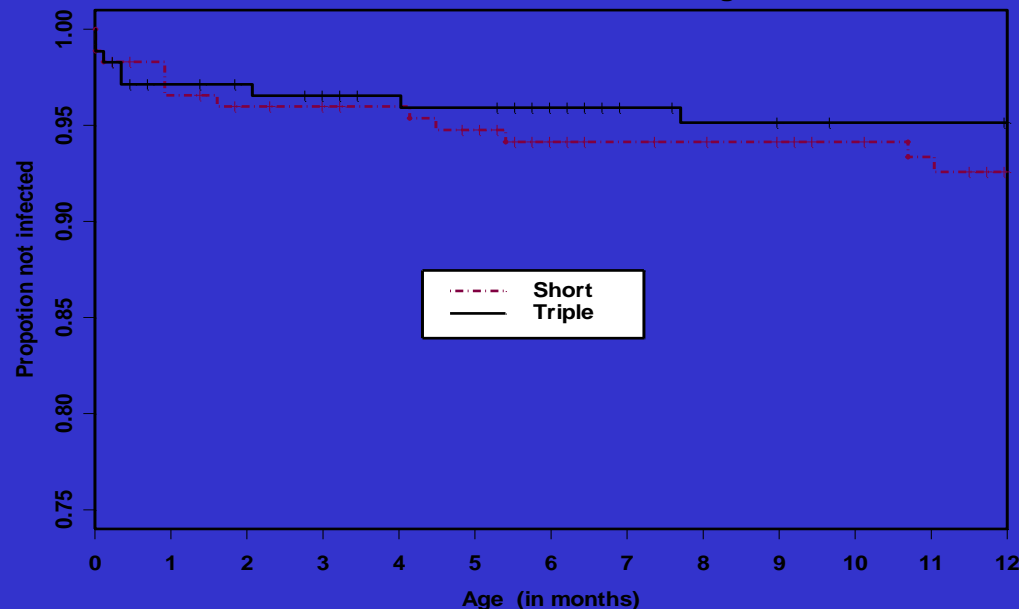


	Triple		Short		Reduction
	Events (cum) / at risk	Rate (95% CI)	Events (cum) / at risk	Rate (95% CI)	
Birth	4/220	1.8 (0.7, 4.8)	6/224	2.7 (1.2, 5.9)	33%
6 weeks	8/210	3.6 (1.8, 7.2)	13/206	5.8 (3.4, 9.8)	38%
6 months	12/189	5.5 (3.2, 9.5)	23/182	10.5 (7.1, 15.4)	48%
12 months	13/155	6.1 (3.6, 10.3)	24/132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

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

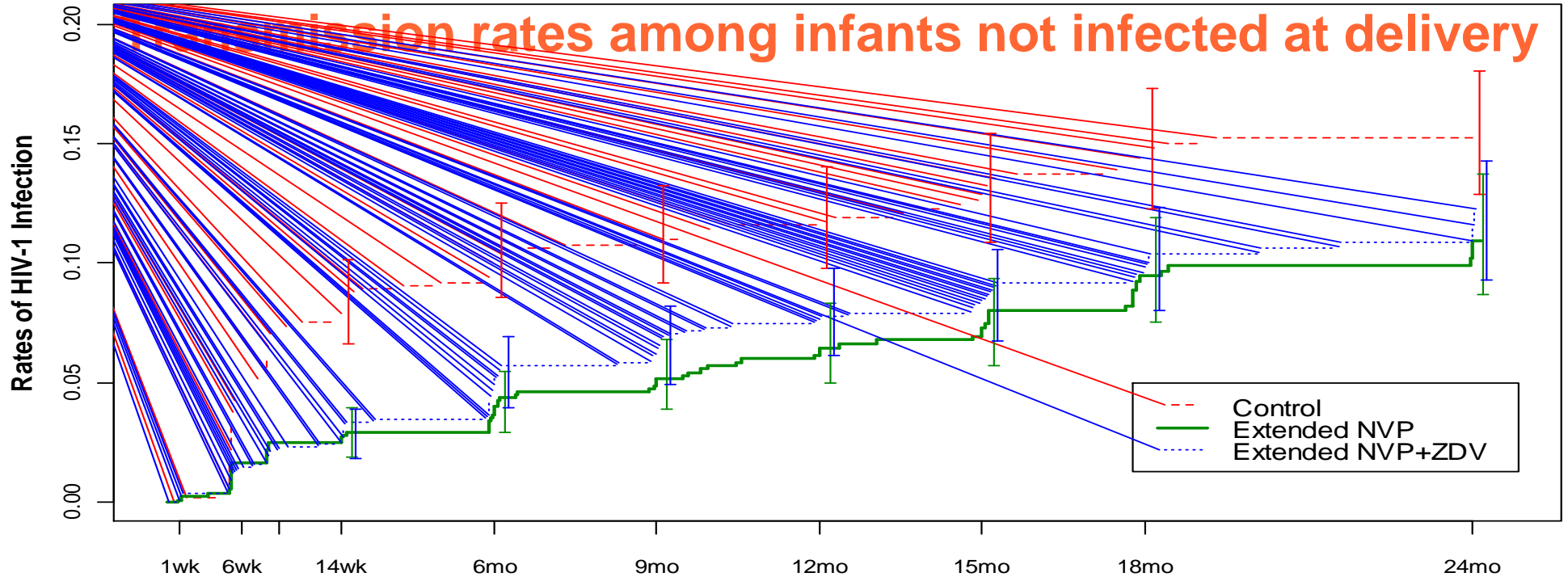
Log rank test  $p = 0.33$   
(stratified on centre and intention to BF)

Infant HIV-free rates to 12 months of age.RCT, by study stratum  
Maternal CD4 count 350 or higher



	Triple		Short		
	Events (cum) / at risk	Rate (95% CI)	Events (cum) / at risk	Rate (95% CI)	Reduction
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%

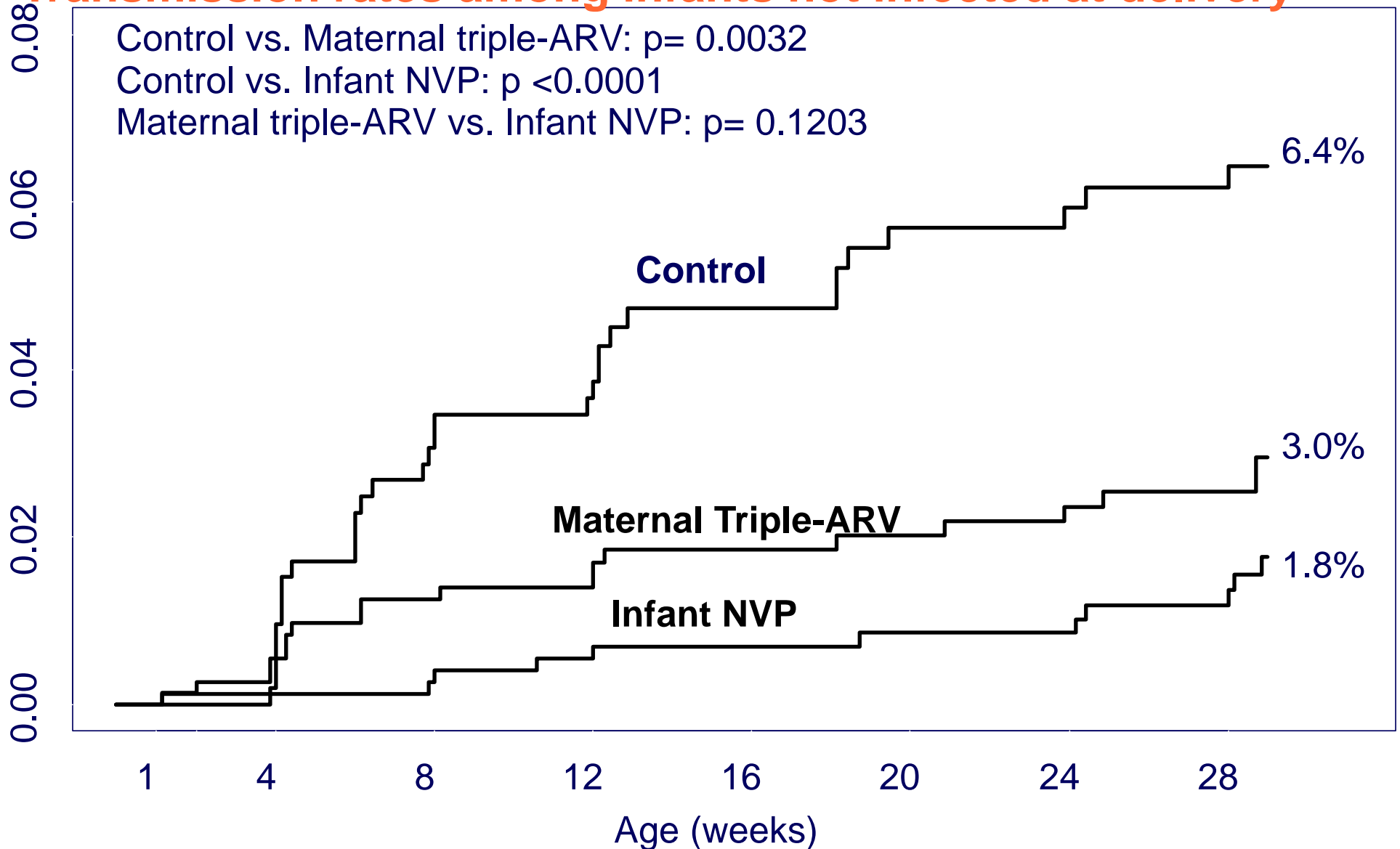
# PEPI Malawi (Infant prophylaxis): NVP +/- AZT to infant from birth to 3,5 months



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

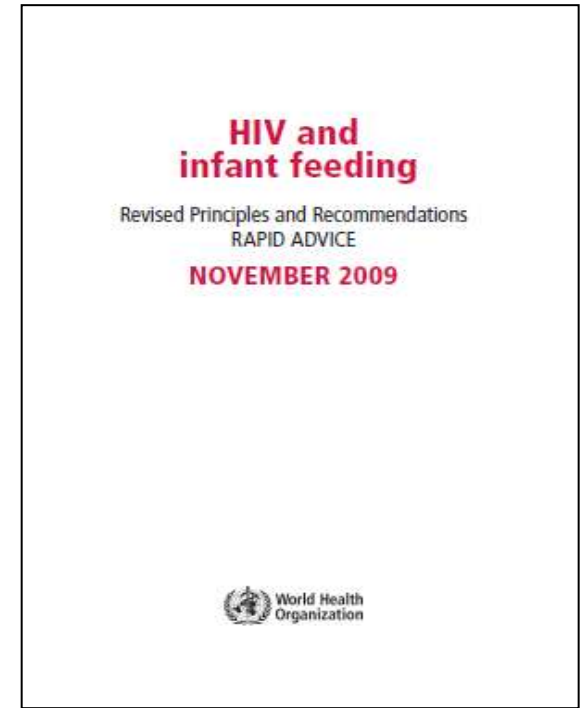
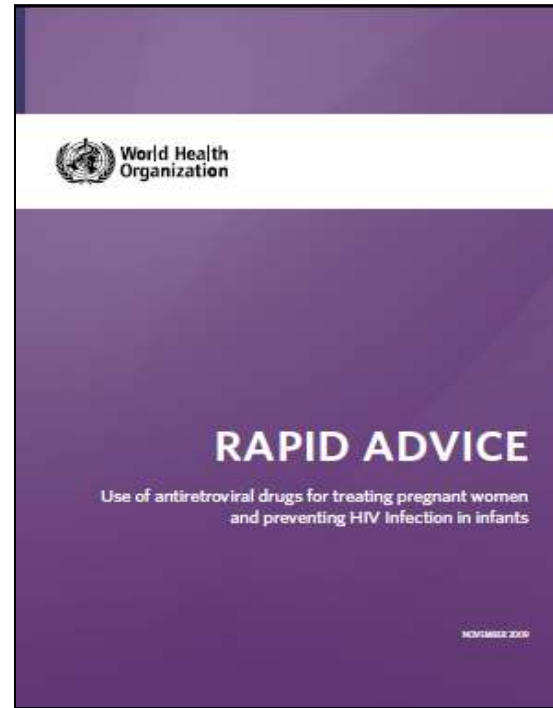
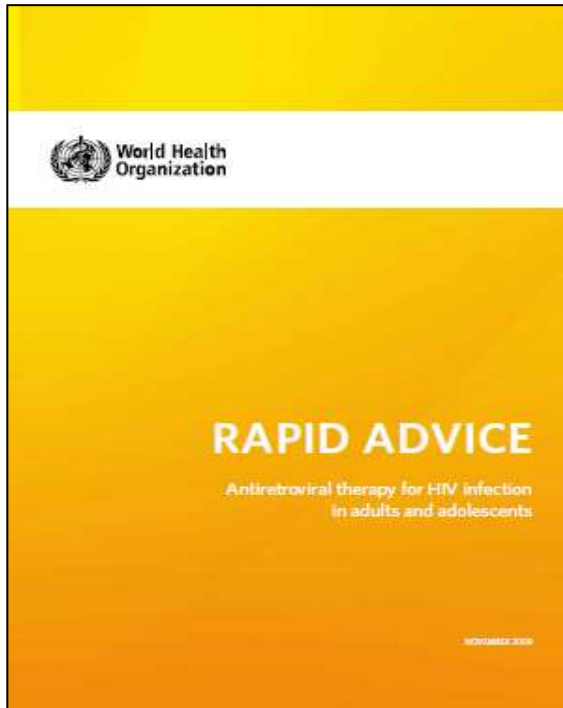
**BAN Malawi : maternal (ZDV/3TC/LPVr) or infant (NVP)  
prophylaxis from birth to 6 months post-partum**

**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)**

# 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**

# 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**

# **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**

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

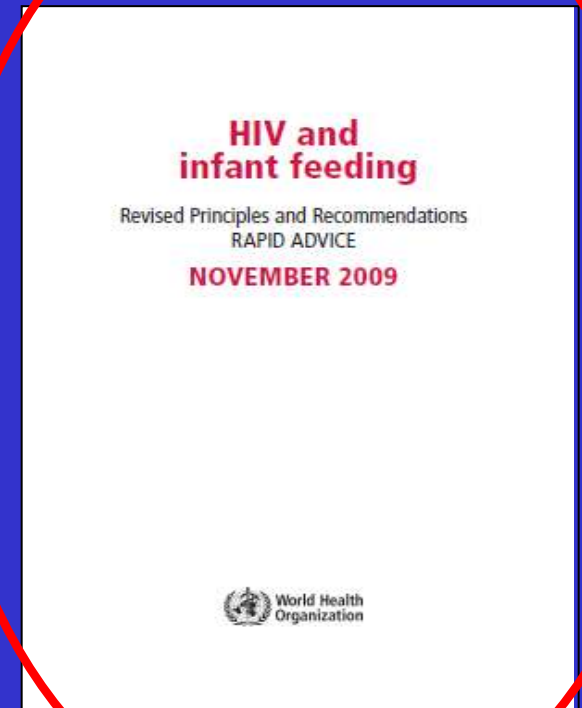
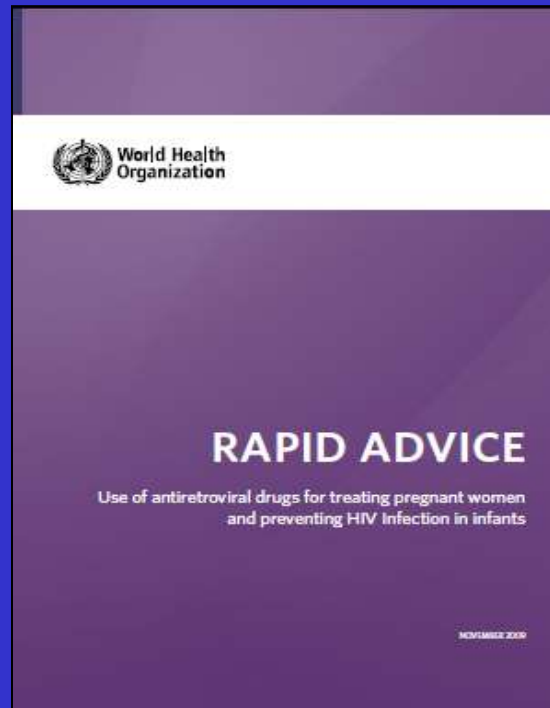
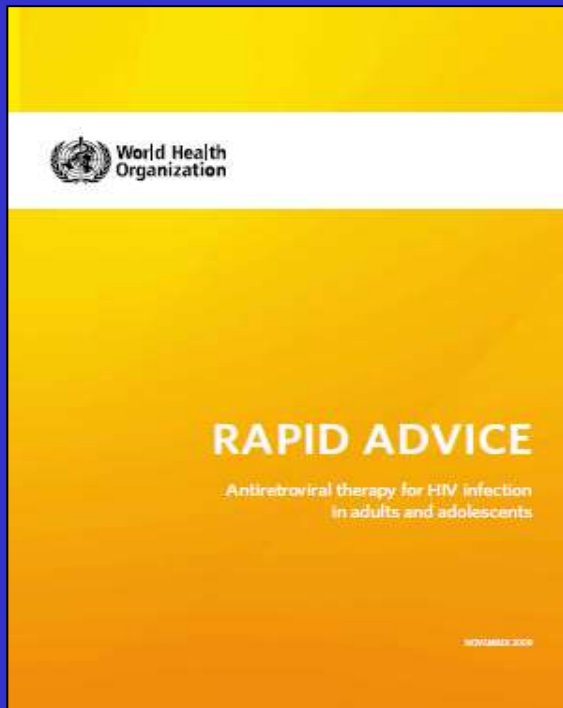
- **Two possible options:**
  - **Maternal AZT**
  - **Maternal triple ARV prophylaxis:**
- **NVP-based regimens are not recommended**
- **Strong recommendation**

# Prophylaxis options

Option A: AZT	Option B: Triple ARV
<p><b>Mother</b></p> <ul style="list-style-type: none"><li>• Antepartum AZT (from 14 weeks)</li><li>• sd-NVP at onset of labour*</li><li>• AZT + 3TC during labour &amp; delivery*</li><li>• AZT + 3TC for 7 days postpartum*</li></ul> <p><b>Infant</b></p> <p>Breastfeeding population</p> <ul style="list-style-type: none"><li>• Daily NVP (from birth until one wk after all exposure to breast milk had ended)</li></ul> <p>Non-breastfeeding population</p> <ul style="list-style-type: none"><li>• AZT for 6 weeks OR</li><li>• NVP for 6 weeks</li></ul>	<p><b>Mother</b></p> <ul style="list-style-type: none"><li>• Triple ARV (from 14 wks until one wk after all exposure to breast milk has ended)<ul style="list-style-type: none"><li>• AZT + 3TC + LPV-r</li><li>• AZT + 3TC + ABC</li><li>• AZT + 3TC + EFV</li><li>• TDF + 3TC or FTC + EFV</li></ul></li></ul> <p><b>Infant</b></p> <p>Breastfeeding population</p> <ul style="list-style-type: none"><li>• Daily NVP from birth to 6 weeks</li></ul> <p>Non-breastfeeding population</p> <ul style="list-style-type: none"><li>• AZT for 6 weeks OR</li><li>• NVP for 6 weeks</li></ul>

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

# Revision of infant feeding recommendations in 2009



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



# 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

