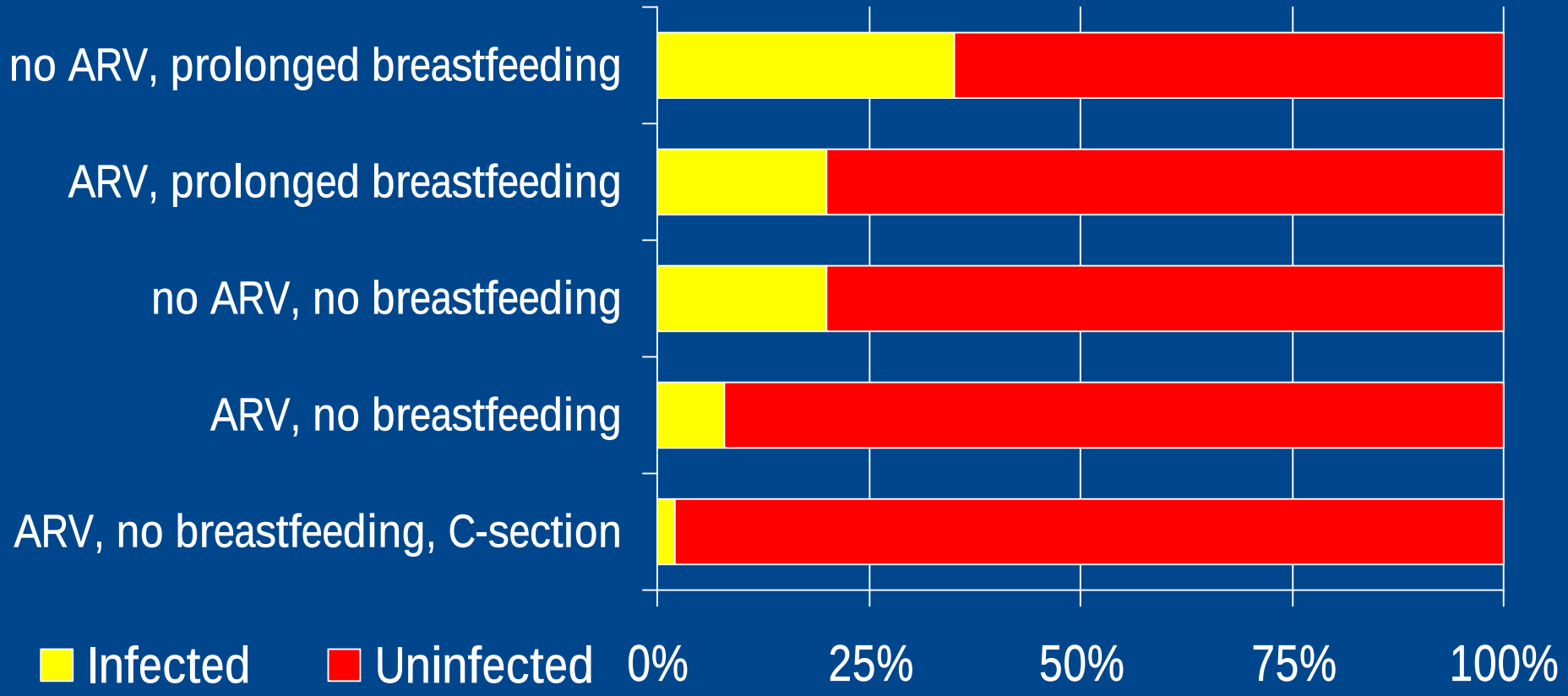
Mother-to-child transmission (MTCT) of HIV

Isabelle de Vincenzi

Training Course in Reproductive Health / Sexual Health Research
Geneva 2006

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



Prevention of MTCT through antiretrovirals

Mechanisms of action:

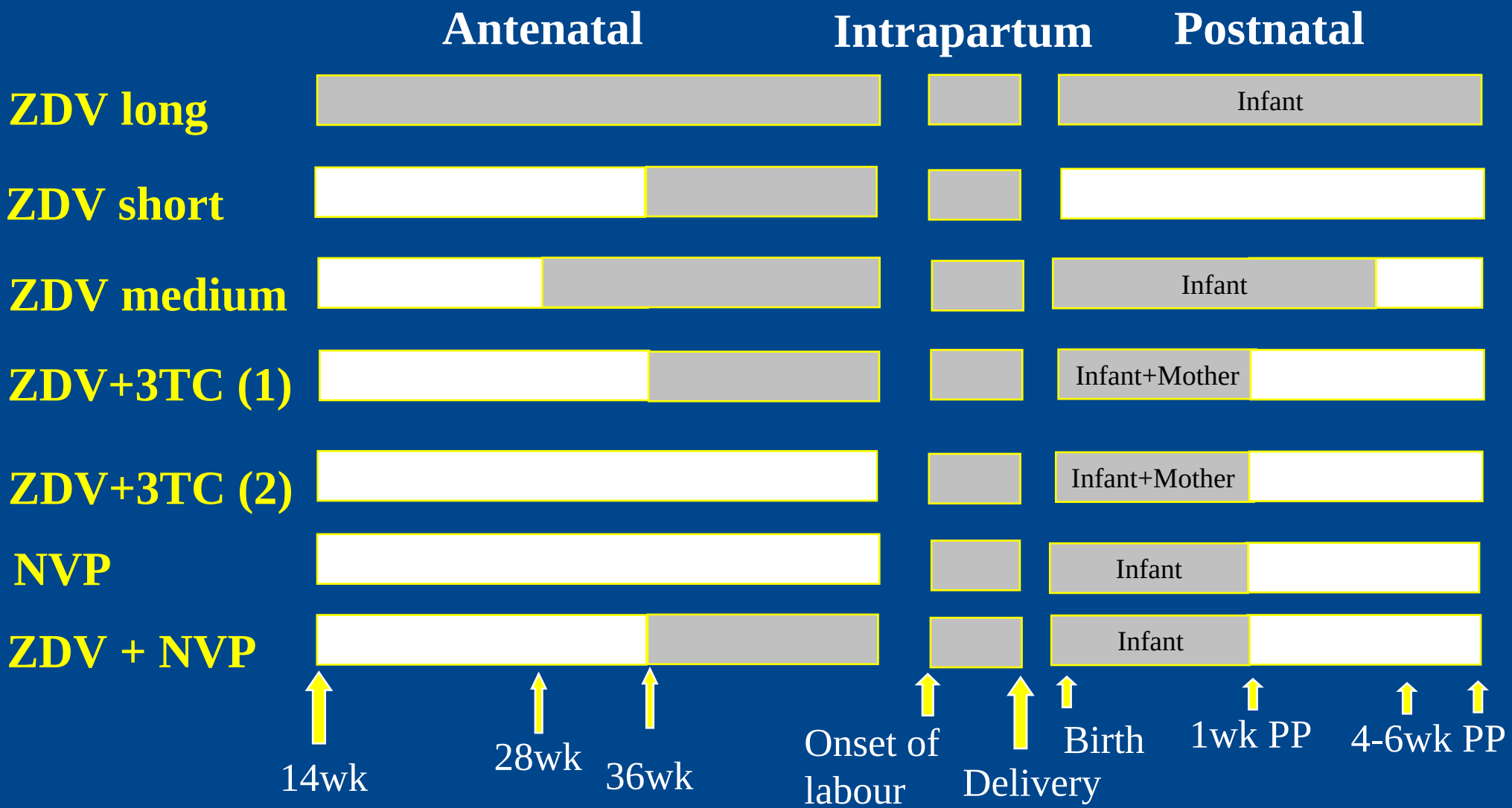
- **Maternal component:**

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

- **Infant regimen:**

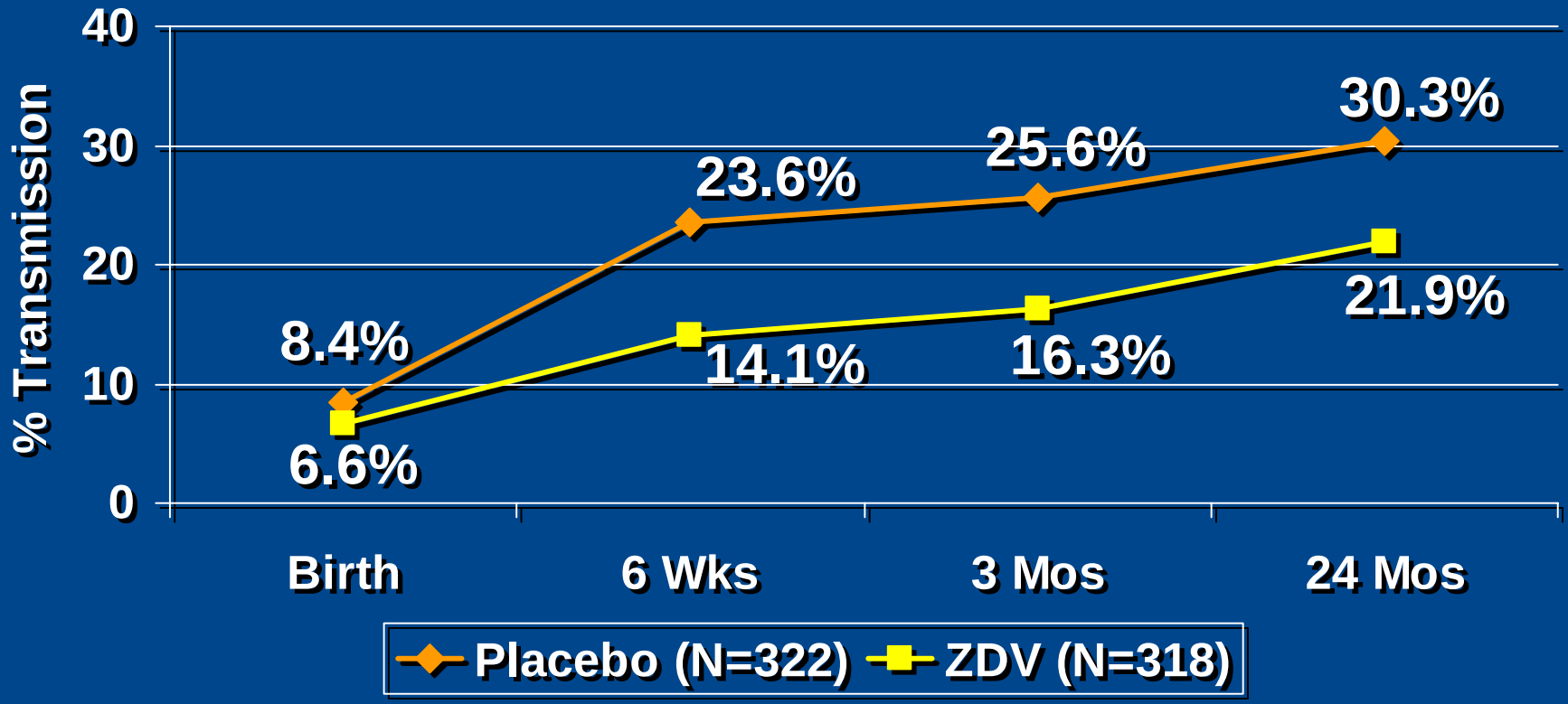
  Act as post-exposure prophylaxis (viral particles eventually transmitted during birth are eliminated)

ARV regimen of proven efficacy
(through clinical trials)



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

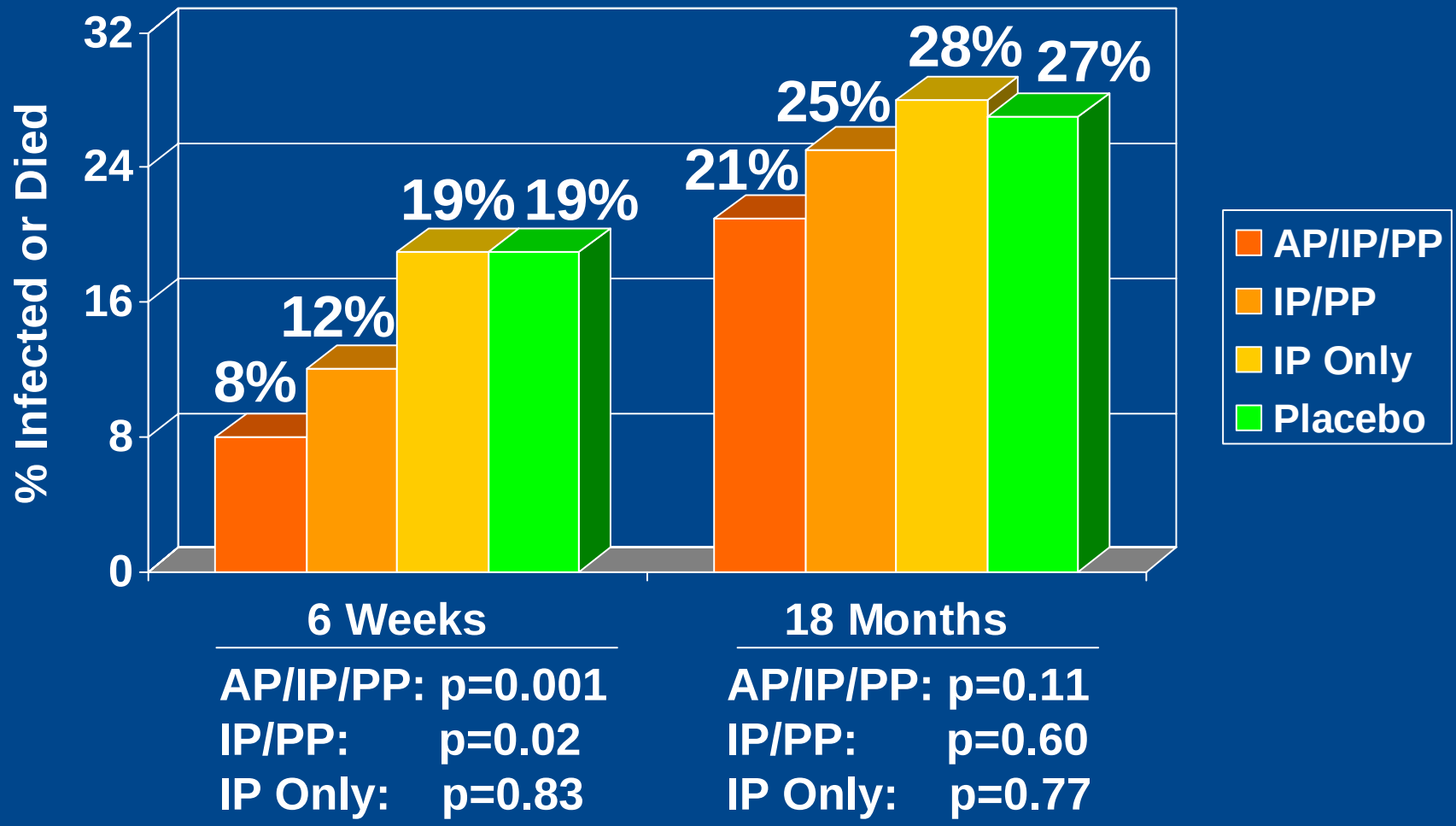
Witkor S. XIII AIDS Conf, July 2000, Durban S Africa (TuOrB354)



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

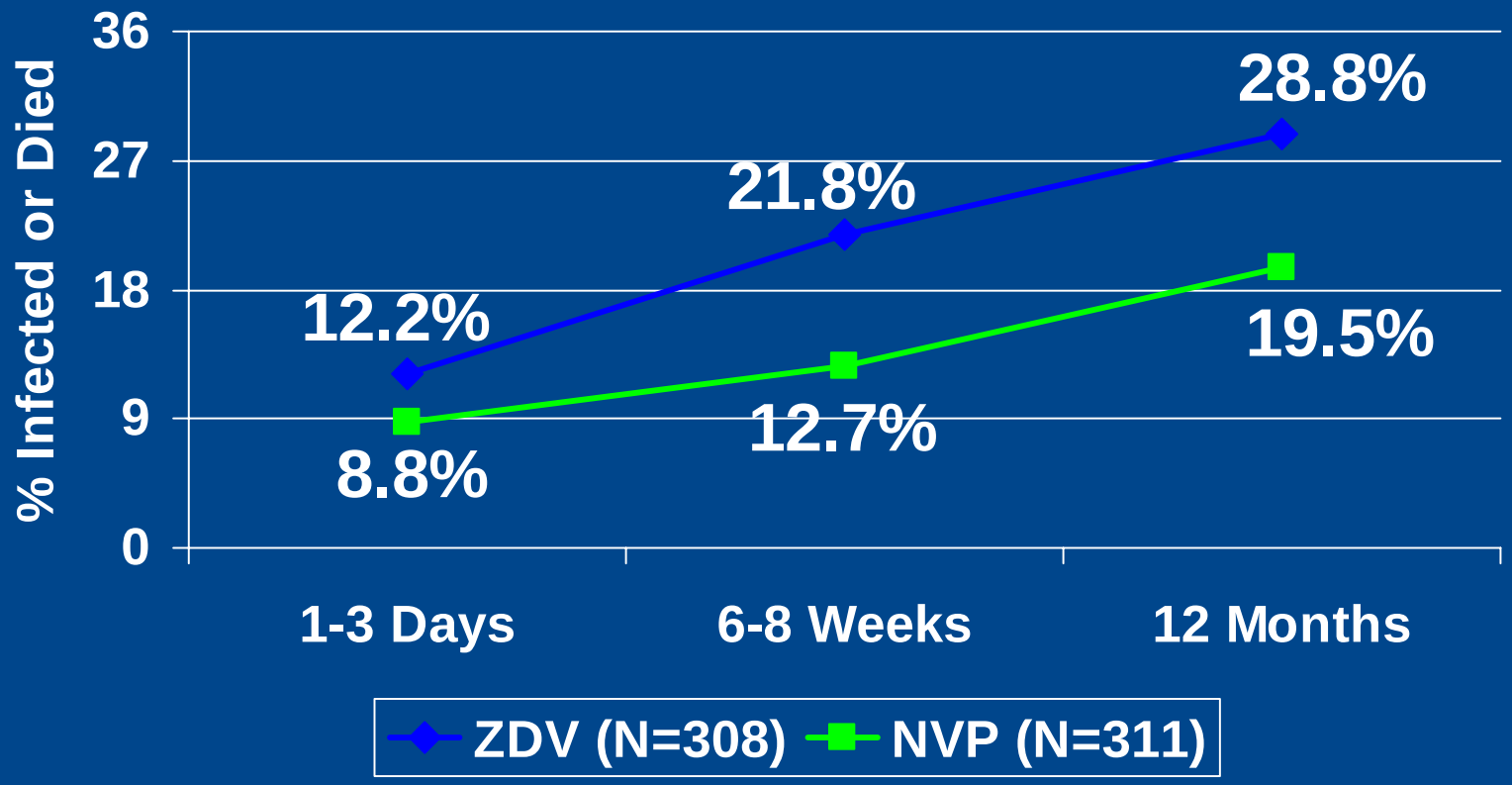
ZDV/3TC AP/IP/PP, IP/PP, or IP Only vs Placebo: PETRA, HIV Infection or Death, 6 Wks & 18 Mos

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



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

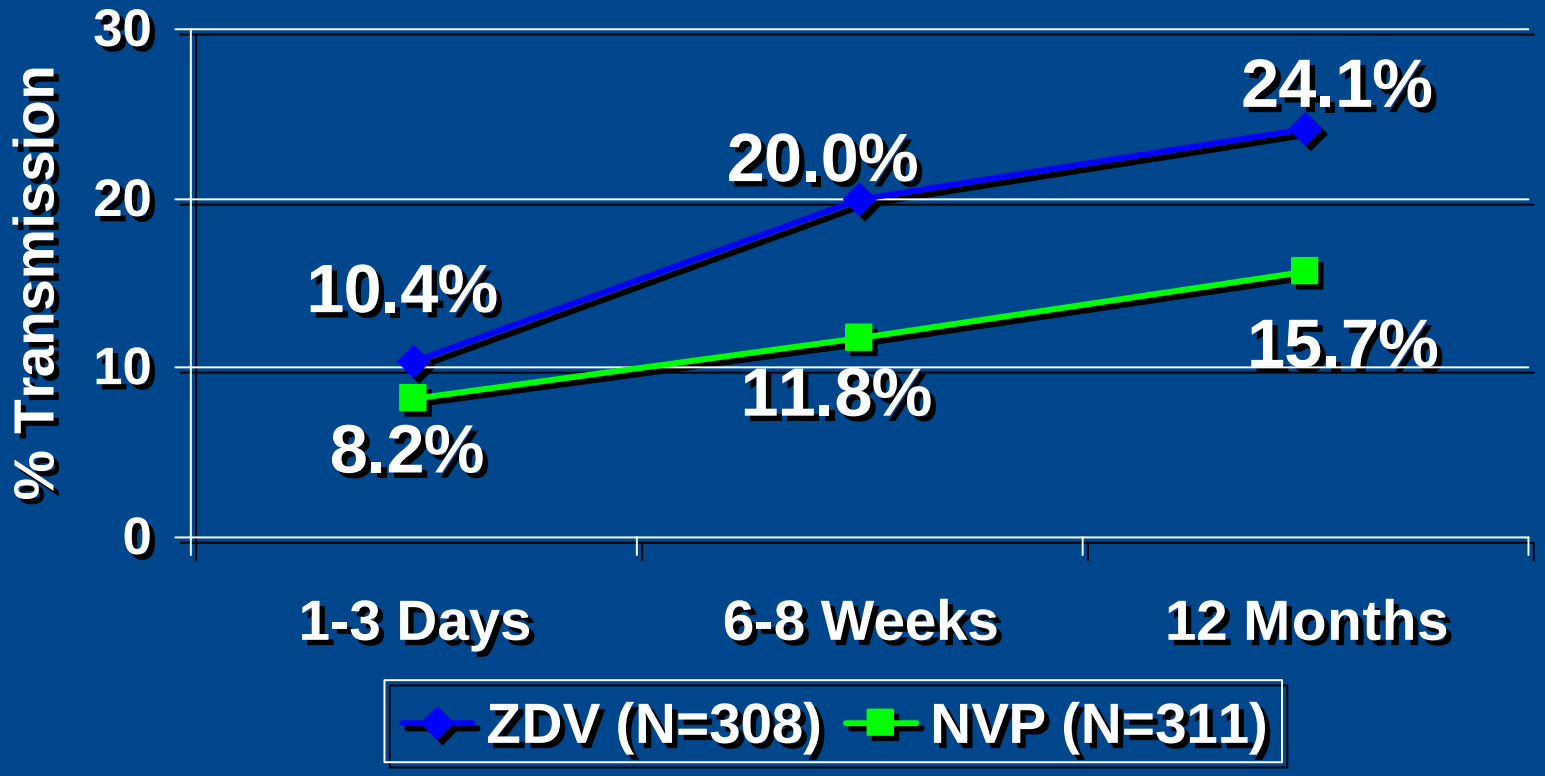
Owen M. XIII AIDS Conf, July 2000, Durban S Africa (LbOr01)



12 Month Efficacy NVP vs ZDV: p = 0.004

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

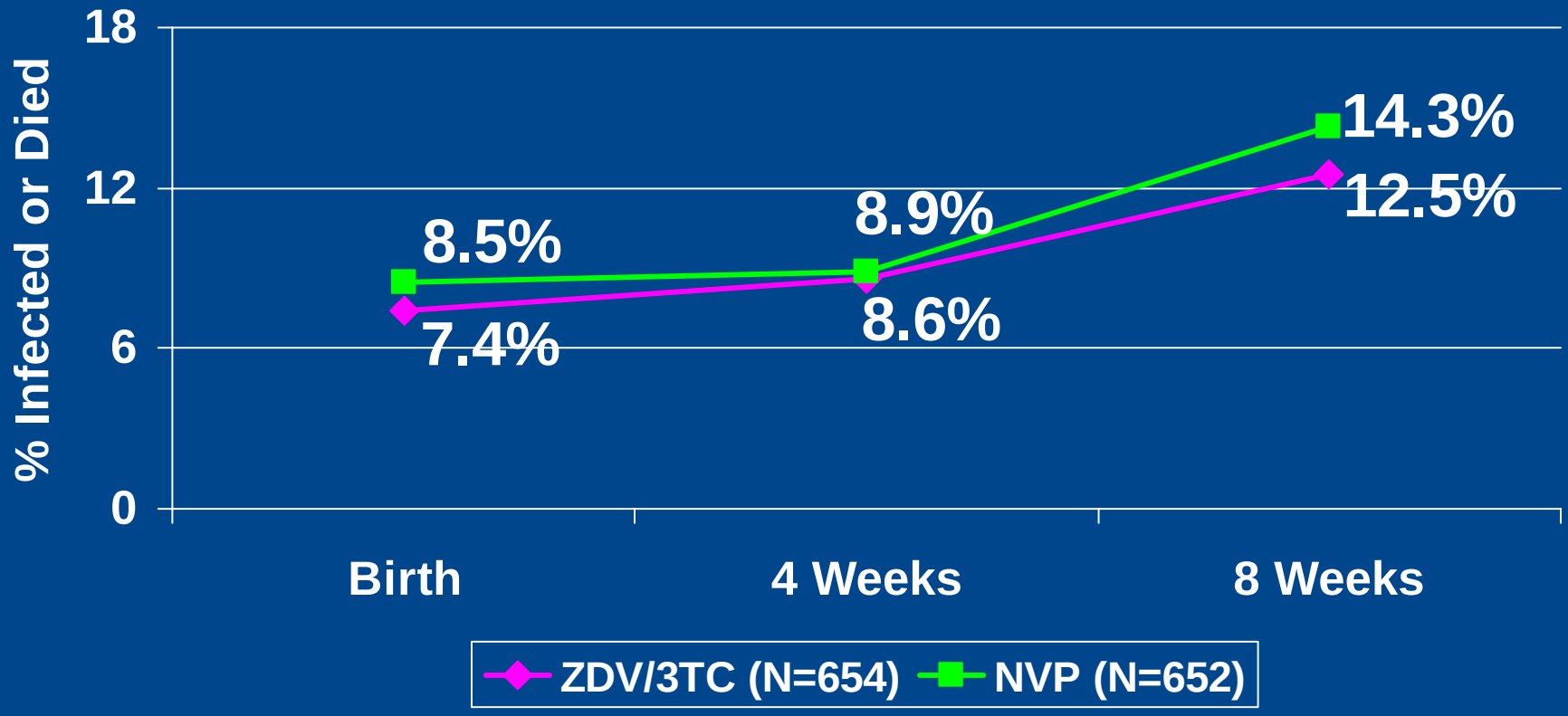
Owen M. XIII AIDS Conf, July 2000, Durban S Africa (LbOr01)



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)

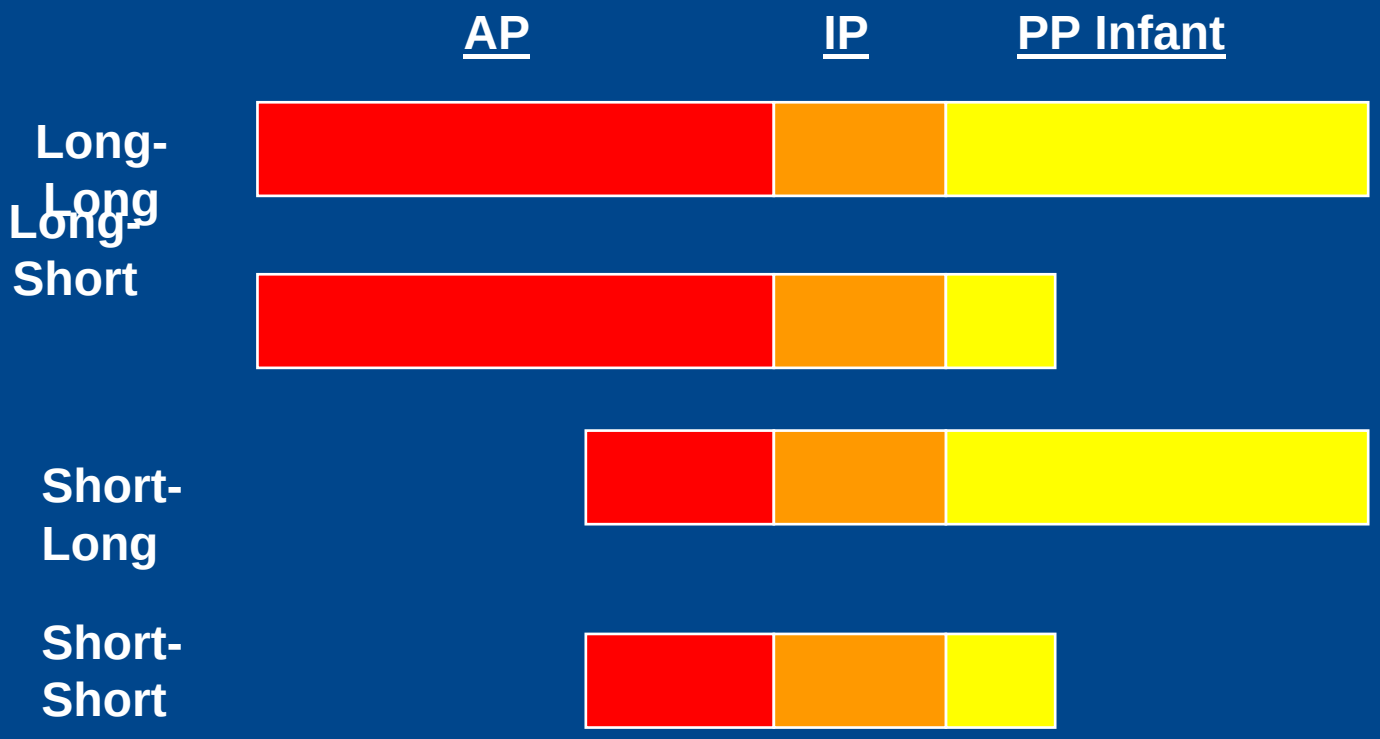


No significant difference between study arms

ANRS Abidjan - 6 wks Tx 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%)

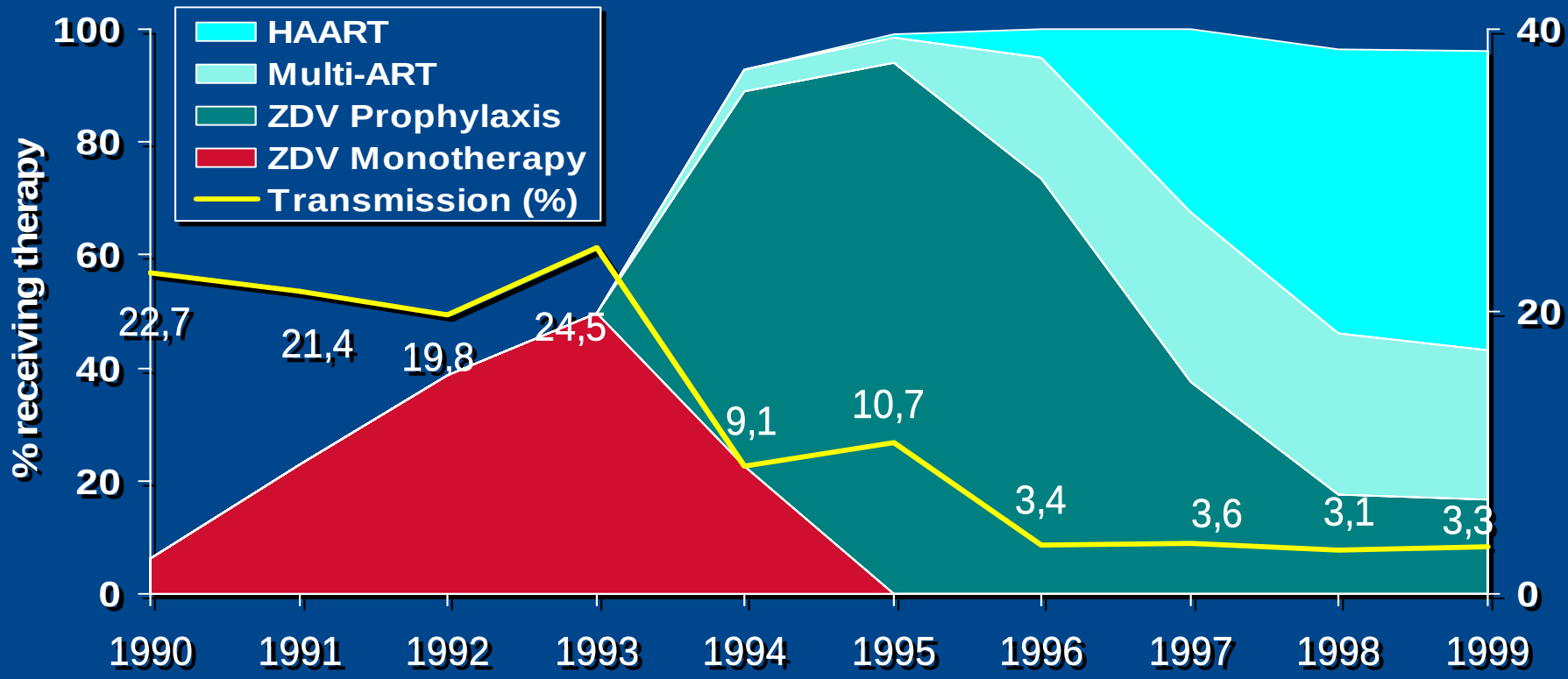
Perinatal HIV Prevention Trial – Thailand (2)

- 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

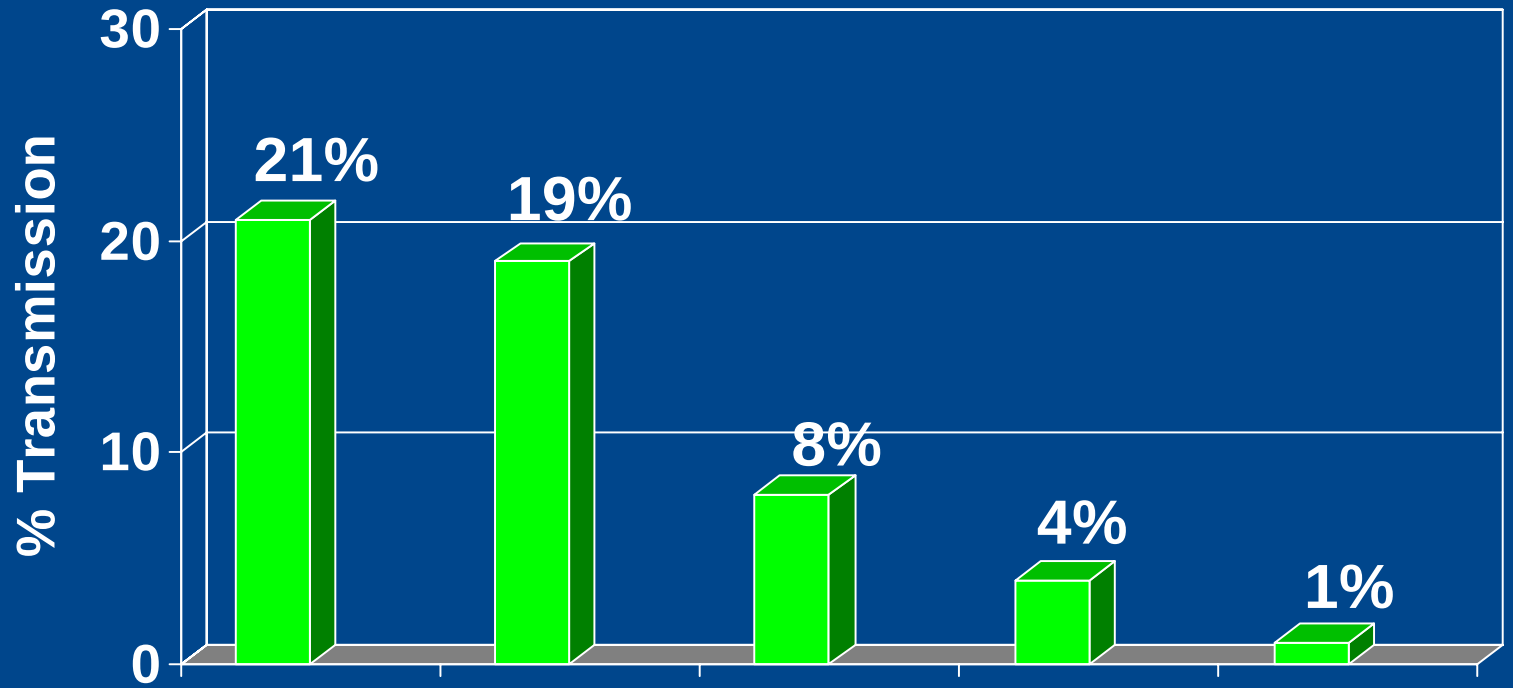
ARV Use and HIV Transmission
(WITS, USA)



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

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)**

Studies of Resistance in PMTCT trials using NVP

PACTG 316, HIVNET 012,

SAINT, HIVNET 023, and Peri-3

PACTG 316 Schema, Results : SD NVP Did Not Improve Efficacy of Longer or More Complex ARV Regimens

Dorenbaum A et al. JAMA 2002;288:189-98 [LMofenson slide]

Pregnancy	Labor	Newborn	Transmission Rates
Women receiving ARV during Pregnancy (NNRTI naïve)	Continue ARV	6 Wks AZT Perinatal Prophylaxis	
Randomize, stratified by: 1) AP ARV (no, mono, combo) 2) Entry CD4	200 mg dose of NVP	2 mg/kg dose of NVP @ 48-72 hr	1.4% (95% CI, 1-3%)
	vs	vs	
	NVP Placebo	NVP Placebo	1.6% (95% CI, 1-3%)

Incidence of NVP Resistance at 6 Weeks PP in Substudy of Women Receiving ARV in PACTG 316

Cunningham C et al. J Infect Dis 2002;186:181-8 [L Mofenson slide]

- **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 Studies in NVP arm – Sue Eshleman

Women: 200 mg NVP at onset of labor

Infants: 2 mg/kg NVP within 72 hrs of birth

Overall transmission rate 6-8 wks= **11.8%**

Overall transmission rate 18 months = 15.9%

SD NVP Relative Efficacy 42% compared to ZDV

Efficacy, simplicity and low cost make this regimen currently deliverable in resource-limited settings

NVPR in women 6-8 weeks after NVP

HIVNET 006`	**3/15 (20%)**	**AIDS (2000) 14:F111**
HIVNET 012	**21/111 (19%)*** **41/48 (T)** **70 (NT)**	**AIDS (2000) 15:1951**
	70/279 (25%)	**Final (all available samples)**

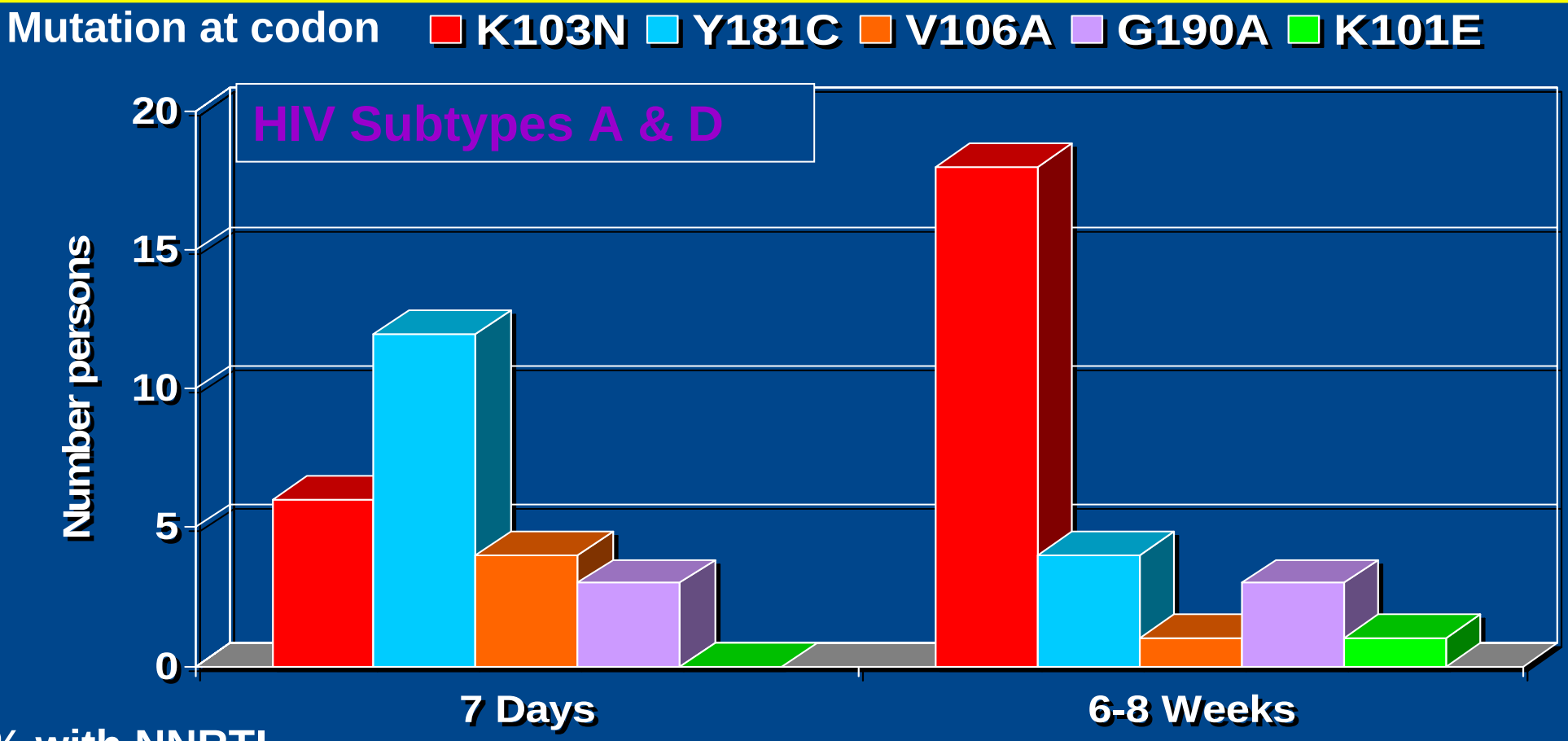
Applied Biosystems ViroSeq HIV-1 Genotyping System

***NVPR mutations faded from detection by 12-24 months in all evaluable women**

Modeling data indicates NVP levels could be >10 ng/mL (IC50=10 ng/mL) to 28 days post partum in some women who received SD NVP

Shift in Specific NNRTI-related Drug Resistance Mutations in 65 Ugandan Women in HIVNET 012

Eshleman et al. 2004 in press



% with NNRTI Mutations: 14/65 (22%) 18/65 (28%)

HIVNET 012: NVPR in infants 6-8 weeks after SD NVP

- **NVPR was detected in 11/24 (46%) of infants**
- **Majority Y181C**
- **NVPR mutations faded from detection**
  - **by 14-16 weeks in half of the infants and**
  - **by 12 months in all evaluable infants**

Eshleman, AIDS (2000) 15:1951

HIVNET 012: Comparison of NVPR mutations in women vs. infants

	Women n=70	Infants n=11
K103N	59 (84%)	2 (18%)
Y181C	26 (37%)	10 (91%)

HIVNET 012: NVPR in late-infected infants

- 12 were diagnosed with HIV-1 after age 6-8 wks (median 10 mo, range 77-550 days)
- Samples were available from 9 infants 2-9 mo after diagnosis
- 8/9 lacked NVPR mutations, including 2 whose mothers had NVPR mutations at 6-8 wks
- 1 infant diagnosed at 12 mo had K103N and Y181C at 15 and 18 mo. The mother had the same mutations at 6 wks pp

Eshleman, AIDS (2000) 15:1951

Summary: 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**

Thailand: Peri-3 Study
Collaboration Thai MOH and CDC
Phase II, Open label

Antepartum	Intrapartum	Postpartum
Initiated at 34 weeks gestation **ZDV 300mg bid**	**ZDV 300mg q 3hrs** **+** **NVP 200mg**	**Infant only** **NVP 2 mg/kg po at 48-72 hrs +** **ZDV 2mg/kg po 4x/day x 4wks**

Peri-3 Results and Conclusions

- Short course ZDV starting at 34 weeks plus the 2-dose intrapartum/neonatal NVP regimen was safe and well tolerated
- Transmission rate was 4.6%; about half that seen with short course ZDV alone
- 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%
- The clinical significance of transient detection of NVP mutation following exposure to SD NVP is unknown and needs to be evaluated

Efficacy of NVP-based HAART in NVP-exposed and unexposed women

- **After 6 months of HAART:**

  - 68% of the 50 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)

(viral load <50: 38%, 50%, 74%; p for trend = 0.0034).

- **NVP-exposed women who started therapy > 6 mths PP:**

  91% without mutation and 77% with mutation had a viral load <400,

- **Therapy started <6 months PP: 69% without mutation and 58% with mutation had a viral load <400.**

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

Supplementing NVP SD for the mother and infant with either a 4 or a 7-day course of ZDV + 3TC (given as Combivir®) for the mother and the baby

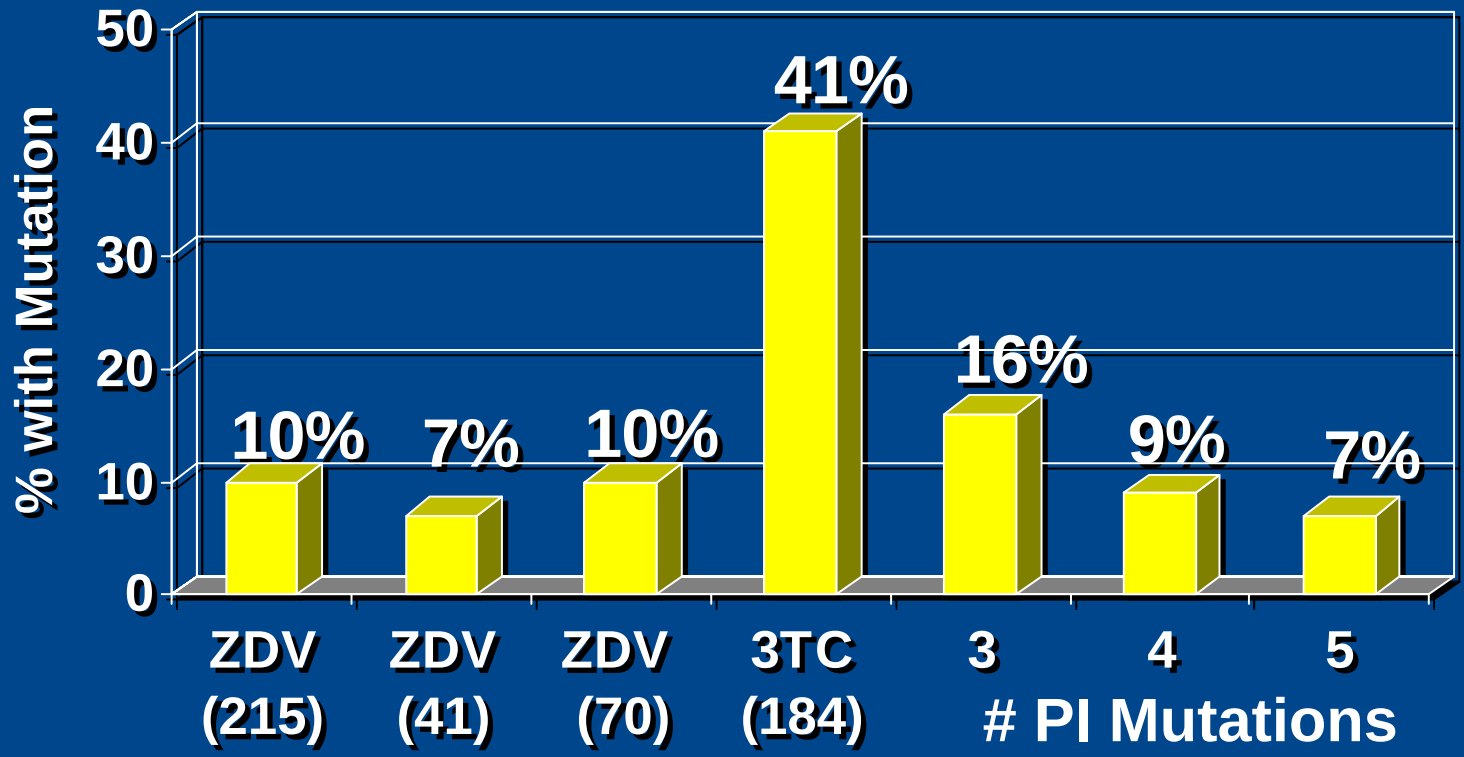
- **5-fold reduction in NVP resistance after 6 wks of follow-up PP.**
- **At interim analysis, 6 wks resistance data available for 61 mothers;**

  Resistance was detected in :
  - **53.3% of group 1 mothers (NVP only),**
  - **5.0% in group 2 (NVP + 4 days Combivir) and**
  - **13.6% in group 3 (NVP + 7 days Combivir),**

  (9.3% of those receiving NVP single-dose + Combivir® irrespective of the duration) (p=0.001)

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)



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 [adapted L Mofenson slide]

3TC Resistance (M184V):

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

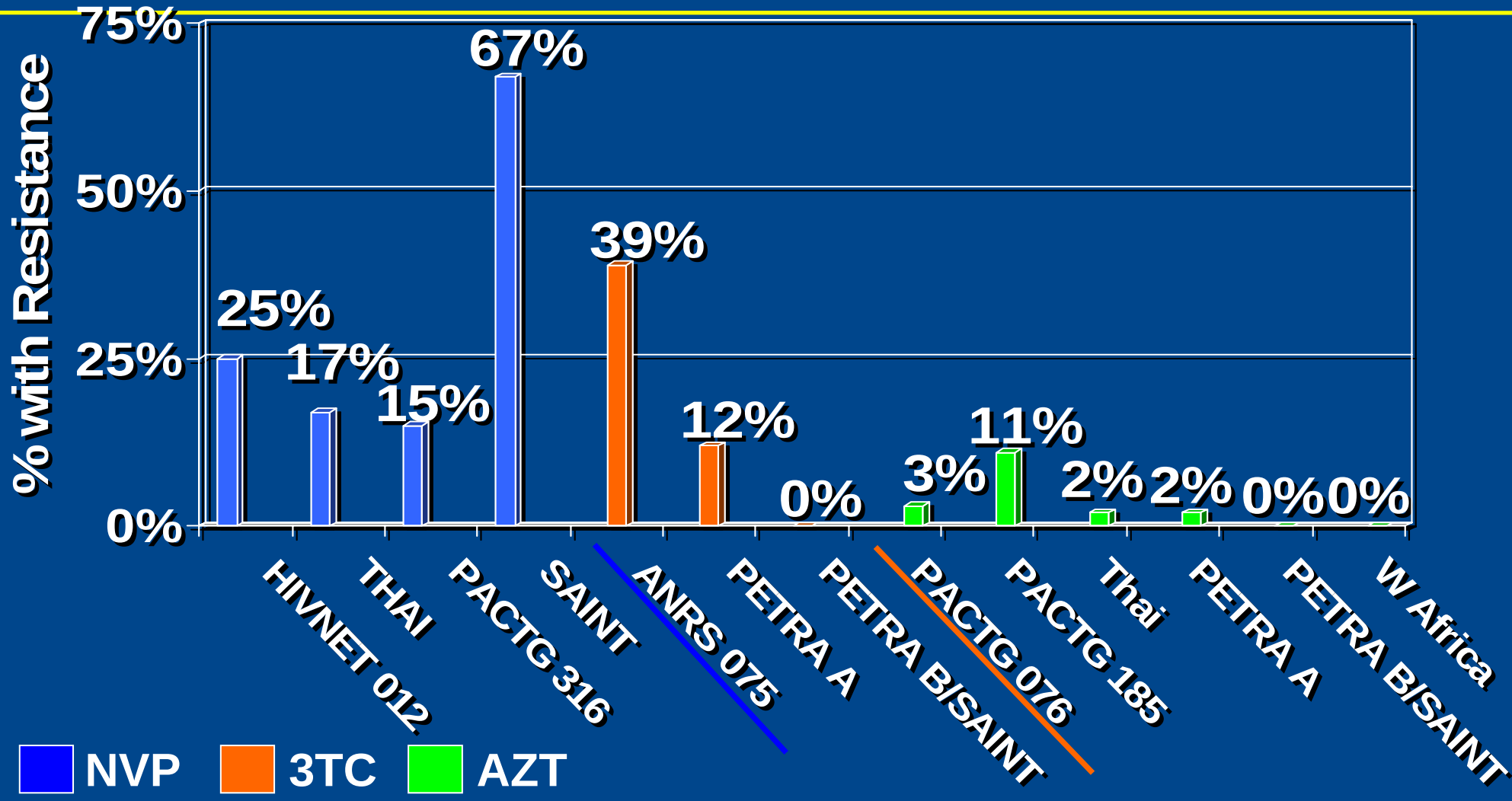
- **Risk factors for maternal 3TC resistance:**
  - **CD4 lower**
  - **HIV RNA higher**
  - **Longer duration 3TC:**
    - 0% (0/12) if <1 month 3TC
    - 20% (14/70) if 1-2 months 3TC
    - 50% (37/74) if >2 months 3TC

PETRA: ZDV or 3TC Antiretroviral Resistance

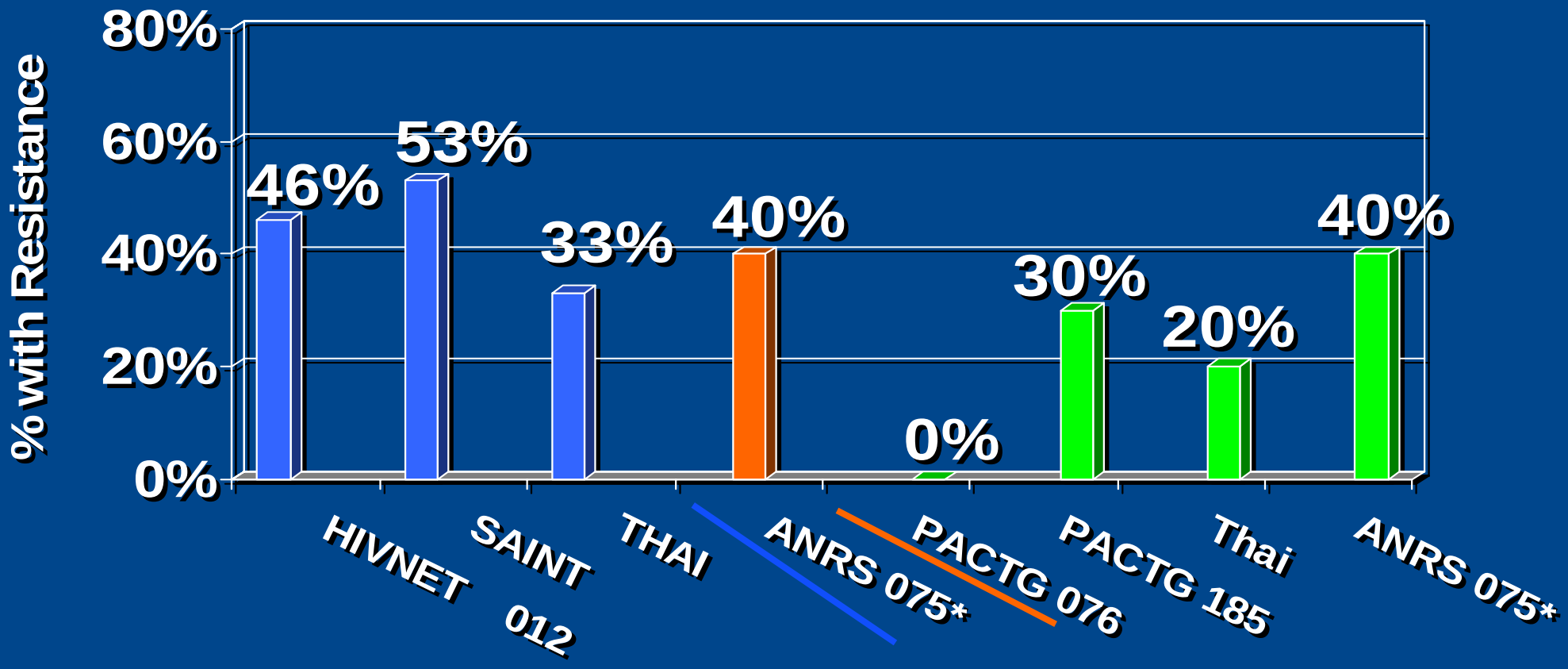
Giuliano M et al. AIDS 2003;17:1570-3 *[adapted from L Mofenson slide]*

- **Virus from 50 women each in arm A and B at 1 week postpartum was genotyped.**
- **Arm A: 6/50 (12%) had M184V (3TC) and 1/50 (2%) had M41L (ZDV) mutation**
- **Transmission unrelated to presence of mutation:**
  - **1/11 (9%) if M184V**
  - **5/39 (13%) if no M184V (NS)**
- **Arm B: 0/50 (0%) women had NRTI mutations.**

Summary: Acquisition of Antiretroviral Resistance in Mothers Following Antiretroviral Prophylaxis

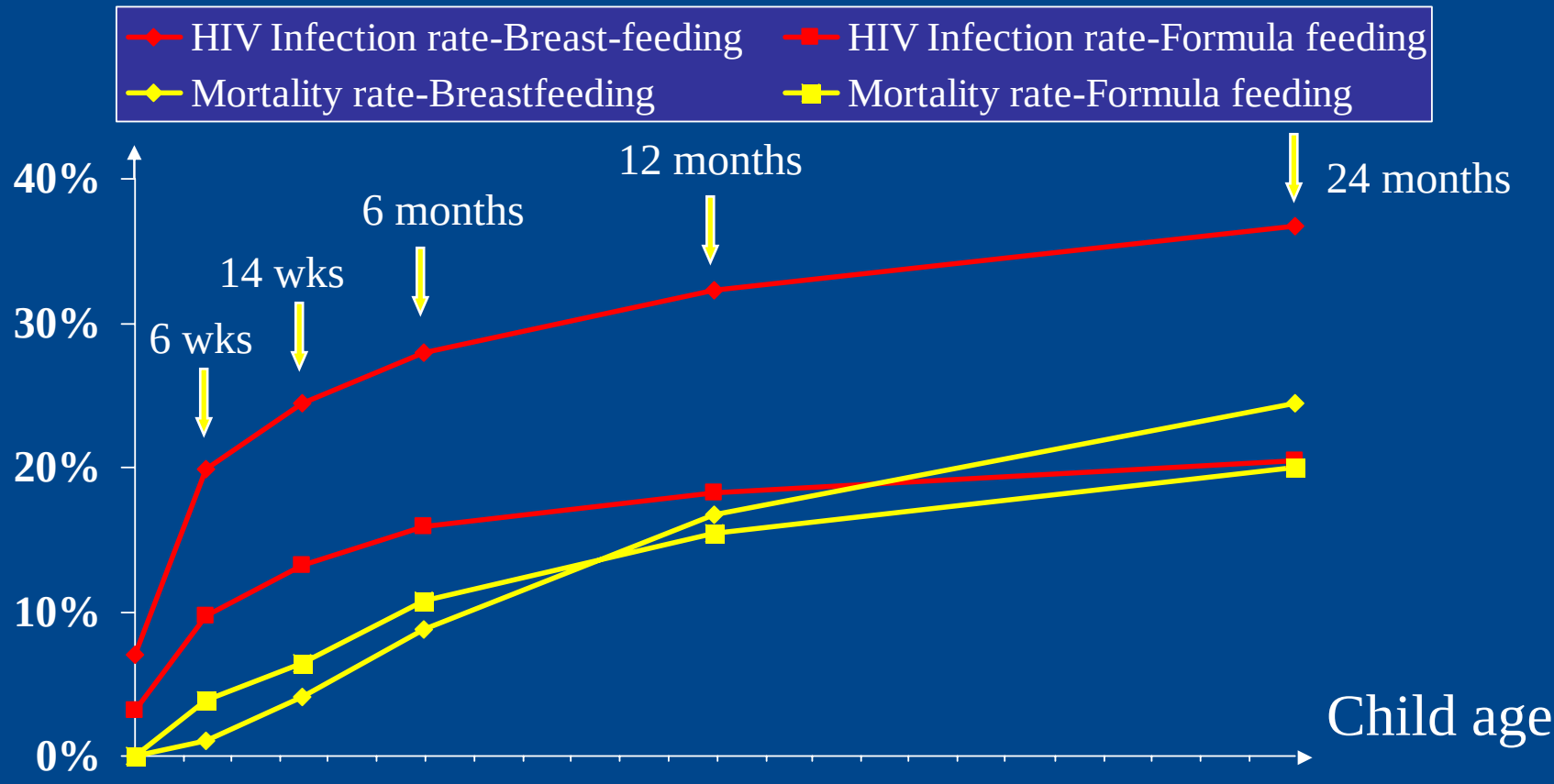


Summary: ARV Resistance at Age 6 Weeks in Infants Infected Despite ARV Prophylaxis



*ANRS 075 data on only 5 infants

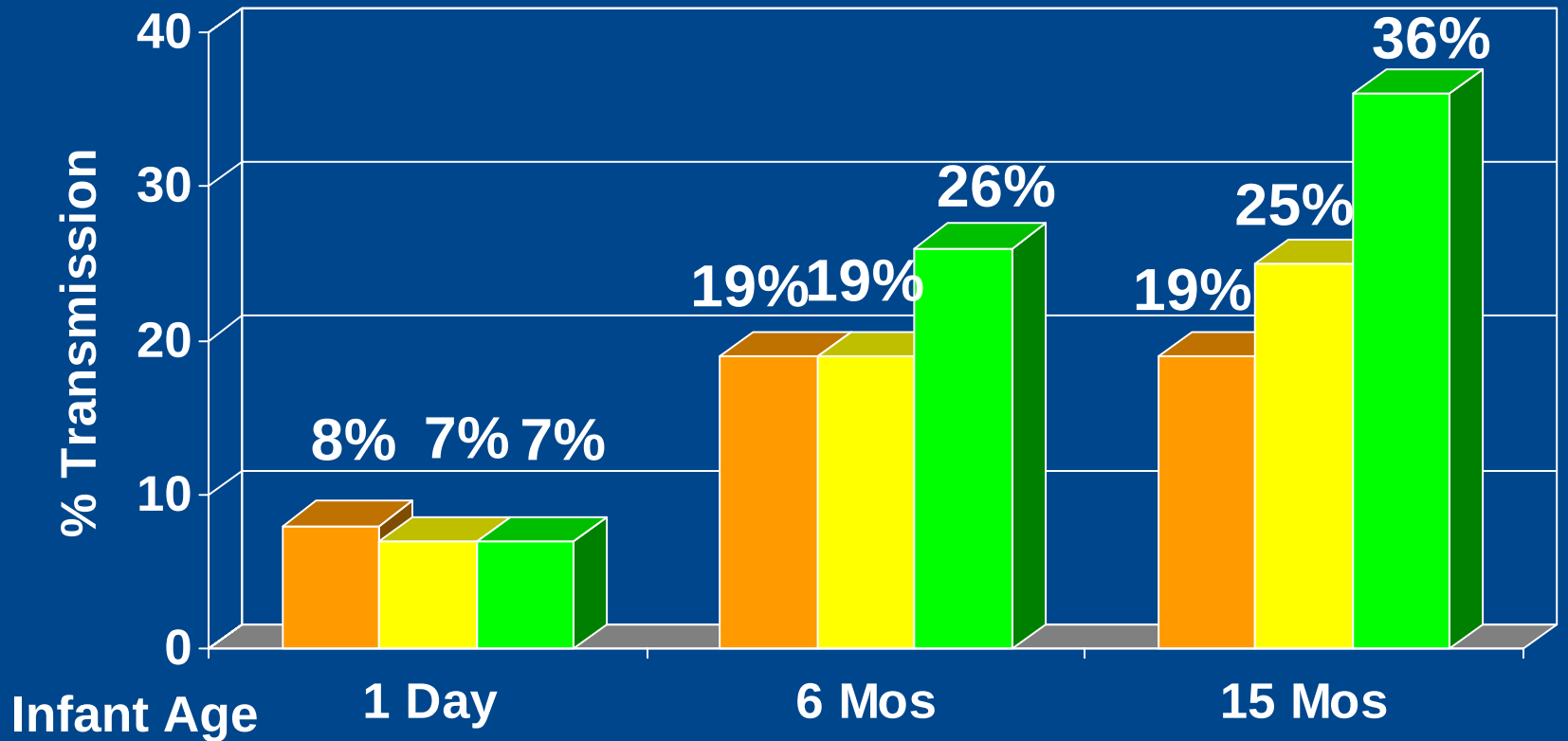
Balancing the risks of breastfeeding and formula feeding



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)



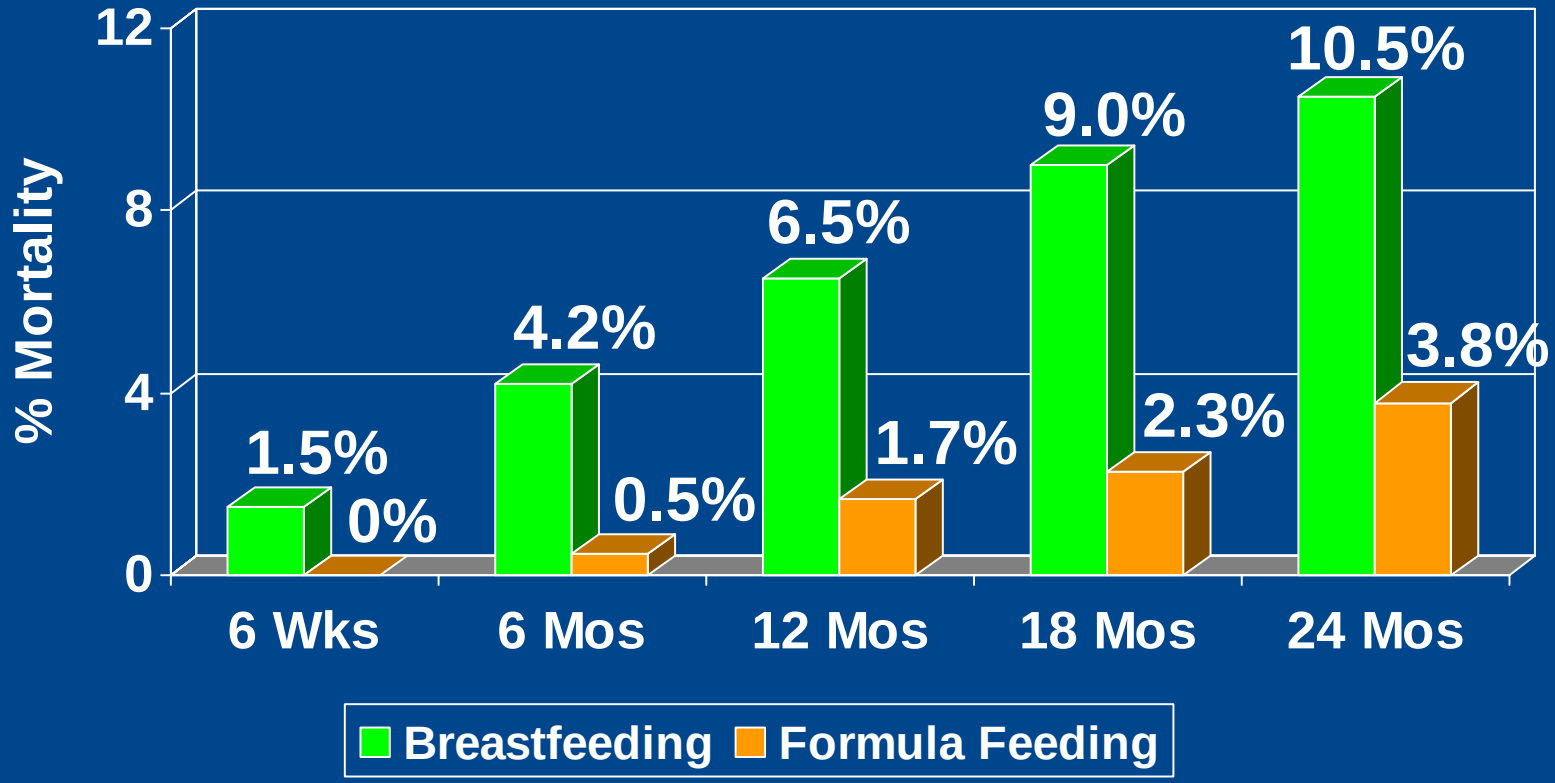
At 6 months:

Exclusive vs Mixed: 0.6 (0.3-1.0)

Exclusive vs Never: 1.2 (0.6-2.2)

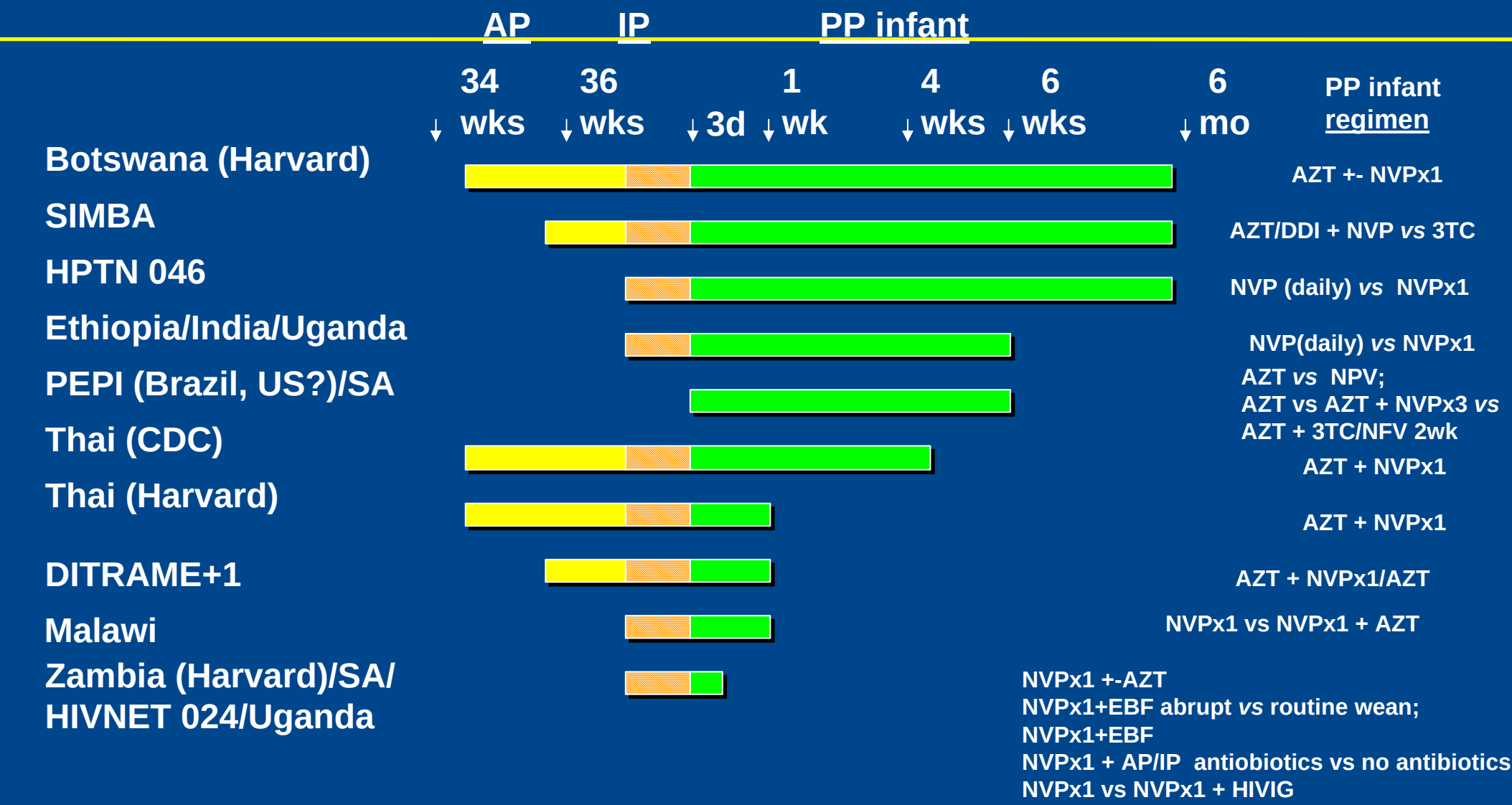
Mortality in Breast- and Formula-Feeding HIV-Infected Women, Kenya

Nduati R. XIII AIDS Conf, July 2000, Durban S Africa (WeOrC495)



RR Death (Breast vs Formula): 3.2 (95% CI 1.3-8.1%), p=0.01

Design of Ongoing/Planned Infant Prophylaxis Trials



SIMBA: Stopping Infection from Mother-to-child from Breastfeeding in Africa – Infant Prophylaxis

Vyankandondera J et al. IAS Meeting, Paris France 2003

All women get AZT+ddI "PETRA Arm A"-like 3-part regimen
Counseling exclusive breastfeeding for 3-6 months
Breastfeeding infants randomized to NVP vs 3TC

Arm 1:

AZT +ddI start 36 wks	AZT +ddI	Mother: AZT + ddI x 1 wk

Infant: 3TC x 6 months

Birth-14 days, 2 mg/kg bid; then 4 mg/kg bid

Arm 2:

AZT +ddI start 36 wks	AZT +ddI	Mother: AZT + ddI x 1 wk

Infant: NVP x 6 months

Birth-14 days, 2 mg/kg q d; then 2 mg/kg bid

SIMBA: MTCT In Utero, Intrapartum/Early Postpartum & Postnatal (Breast Milk) through 6 Mos

	3TC arm N=199	NVP arm N=198	Total N=397
Overall HIV Infection - 6 Mos	17 (9%)	13 (7%)	30 (8%)
First positive HIV test:			
Birth	13 (7%)	11 (6%)	24 (6%)
IP/Early postnatal (<4 wks)	2 (1%)	1 (0.5%)	3 (1%)
Late postnatal (4 wks-6 mos)*	2 (1%)	1 (0.5%)	3 (1%)

(No statistically significant difference between arms)

Median duration BF 3.3-3.5 mos

New HIV infections and cumulative MTCT transmission rates by age and treatment group < 500 CD4

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

* risk difference at 24 months = 2.4% (-9.9 - 14.8%)

New HIV infections and cumulative MTCT transmission rates by age and treatment group > 500 CD4

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

* risk difference at 24 months = 12.7% (5.1 - 20.3%)

Is PMTCT solved ?

HAART during late pregnancy to all HIV-infected women

- **Which HAART regimen for asymptomatic women with high CD4?**

  (toxicity/adherence/cost/interaction with food&drinks/cold chain…)
- **Risk of viral rebound during breast-feeding versus feasibility/risk/cost of replacement feeding up to 6 months PP versus risk of transmission**

Challenge (1)
Low Program Coverage* (1)

- Few good efforts:
- CEE/CIS:
  - Belarus: 87%
  - Ukraine: 49%
- LAC:
  - Uruguay: 97%
  - Belize: 70%
  - Brazil: 33%
- SSA
  - Mauritius: 100%
  - Botswana: 34%