


Update on Maternal-Child Transmission of HIV Infection

MILLER
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Guidelines Information

- U.S. Public Health Service's *Perinatal Guidelines Working Group* meets monthly, reviews clinical trials results, and updates the guidelines (most recently November 2, 2007)
- ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States***
- **The published text is always posted at: www.aidsinfo.nih.gov**

Improvement in prevention of maternal to child HIV transmission has been shown by utilizing.

a) Treatment of mother with HAART by third trimester of pregnancy.
b) Treatment of mother and fetus during actual birth process.
c) Consideration of Caesarian section for birth.
d) Treatment of exposed infant after birth.
e) Avoiding breast feeding of infants who are born to HIV-infected mothers.
f) All of the above.
g) I do not know, I'm coming to learn.

ARVs: Mechanisms of Action

- **ARVs reduce perinatal transmission by several mechanisms:**
  - **Decreasing maternal viral load**
  - **Pre-exposure and post-exposure infant prophylaxis**
- **Combined antepartum, intrapartum, and infant ARV prophylaxis is recommended**

HIV Transmission and Caesarean Delivery

- **Scheduled C/S at 38 weeks to reduce risk of transmission:**
  - **For women with HIV RNA levels >1000 copies/mL (whether on ARVs or not) near time of delivery**
  - **For women with unknown HIV RNA levels**
  - **Benefits of C/S not clear after rupture of membranes or onset of labor – decision based on clinical factors**
- **Benefits of C/S unclear for women with HIV RNA levels <1000 copies/mL**
  - **Scheduled C/S may not further reduce risk of transmission**

Infants Born to Mothers with Unknown HIV Infection Status

- **Rapid HIV antibody testing of mother or infant recommended**
  - ***If positive:***
    - **Initiate ARV prophylaxis for infant immediately**
    - **Perform confirmatory test (e.g. Western Blot)**
    - **Positive infant antibody test cannot distinguish maternal from infant infection – requires HIV virologic test**
    - **If confirmatory test is negative (in mother or infant), discontinue ARV prophylaxis**

Infant ARV Prophylaxis

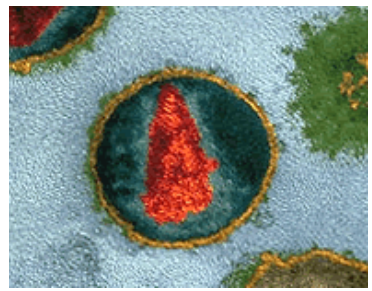
- **6-week ZDV chemoprophylaxis advised for all HIV-exposed neonates**
  - **Should be initiated within 6-12 hrs of delivery**
  - **Dose is different for premature infants; consult with pediatric HIV specialist**

Initial Management of the HIV-Exposed Neonate

- **Begin OI prophylaxis (trimethoprim-sulfamethoxazole) at 6 weeks, after completion of ZDV regimen, unless HIV has been ruled out**
- **Perform virologic tests to diagnose HIV infection in infants <18 months**

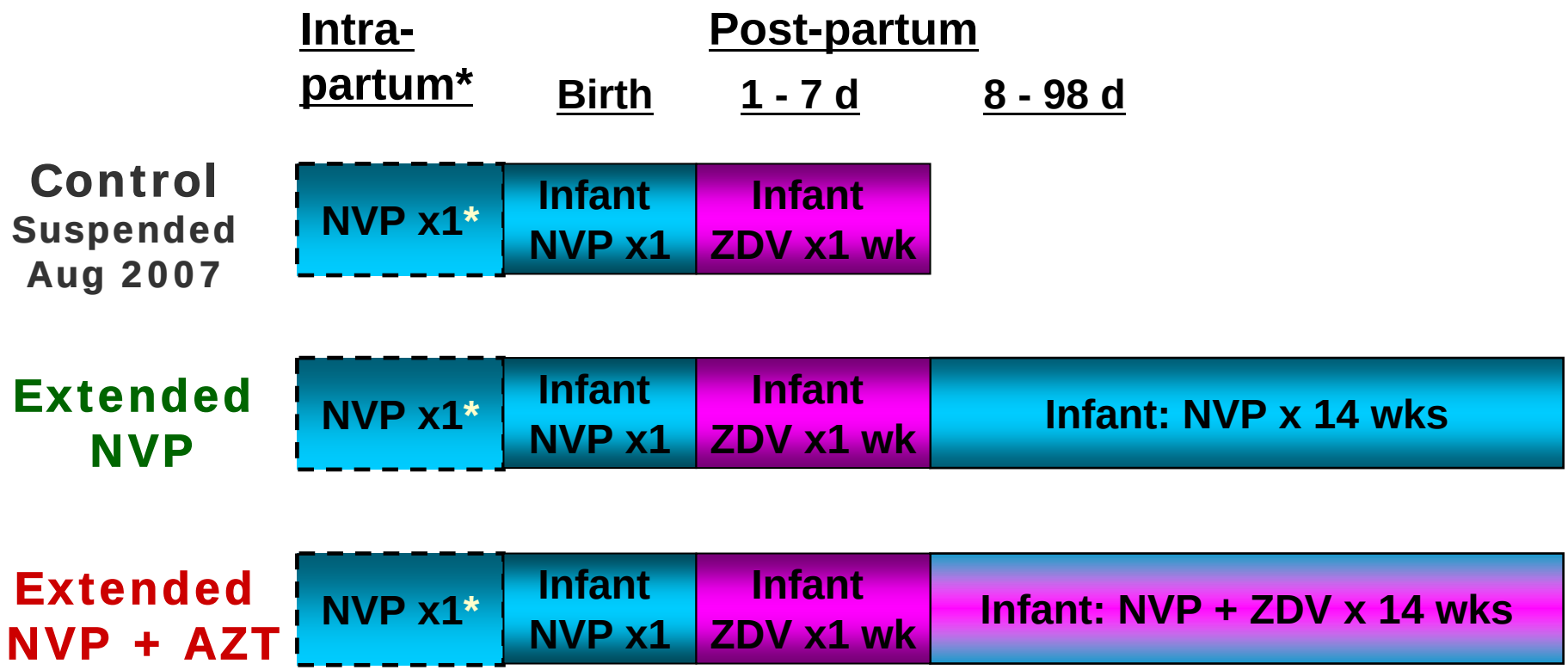
Infant Prophylaxis of Postnatal Transmission

NVP Resistance in Infants Infected Despite Infant Prophylaxis



PEPI-Malawi Study Design

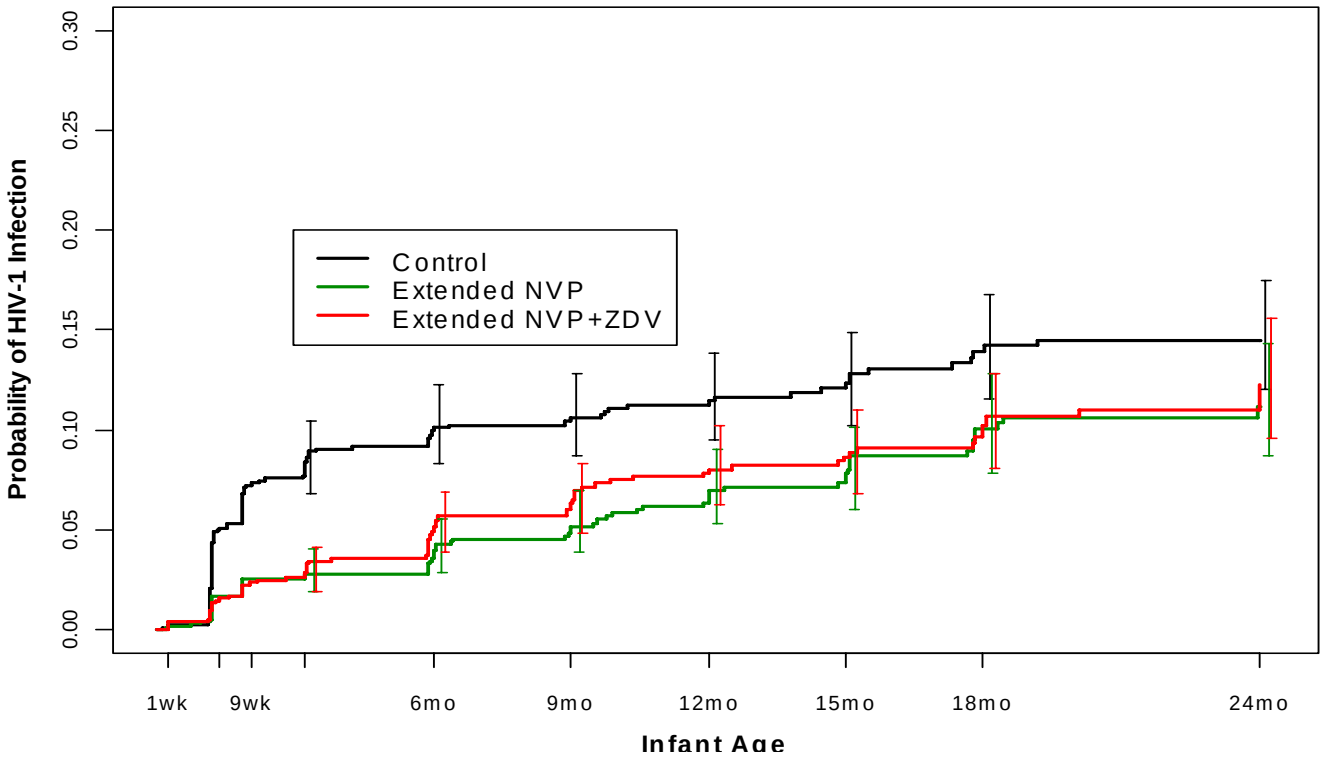
Taha TE et al. 15th CROI, Boston, MA 2008 Abs 42LB



**If mothers diagnosed in time for intra-partum prophylaxis*

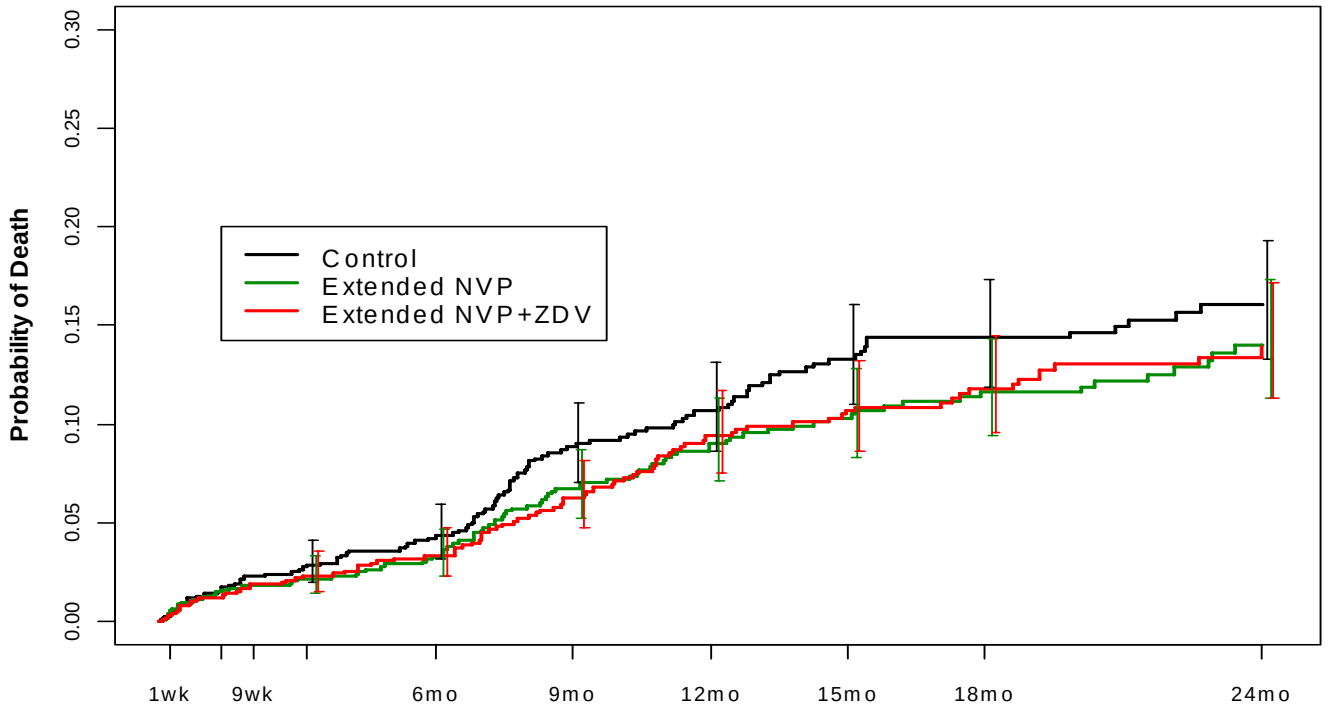
Mothers counseled to exclusively breastfeed and wean by 6 months

Probability of HIV-1 Infection in Infants Uninfected at Birth by Treatment Arm: PEPI-Malawi



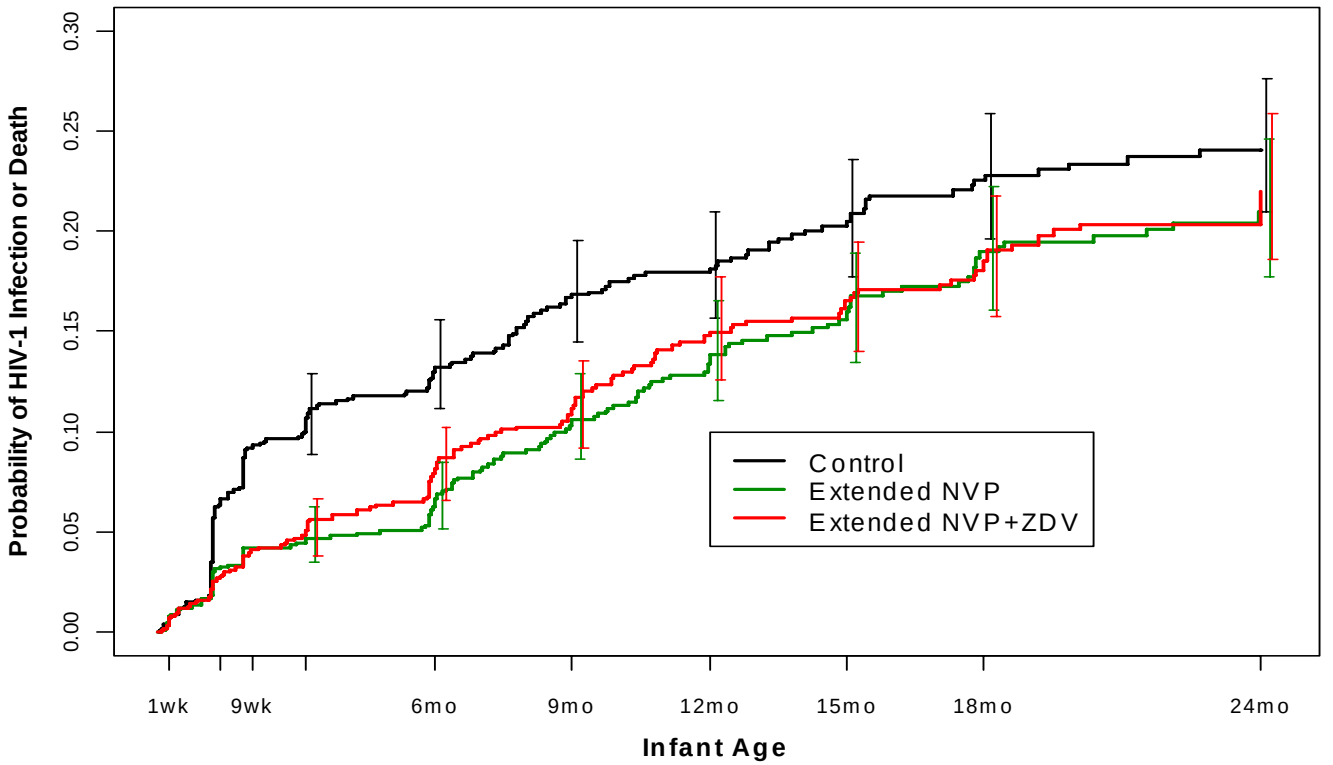
Age	1 wk	6 wks	9 wks	14 wks	6 mos	9 mos	12 mos	15 mos	18 mos	24 mos
Estimates (%)										
Control	0.3	5.1	7.4	8.4	10.1	10.6	11.5	12.4	13.9	14.5
Extended NVP	0.1	1.7	2.6	2.8	4.0	5.2	7.0	7.8	10.1	11.2
Extended NVP+ZDV	0.2	1.6	2.4	2.8	5.2	6.4	8.1	8.7	10.2	12.3

Probability of Death in Infants Uninfected at Birth by Treatment Arm: PEPI-Malawi



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	1.7	2.3	2.9	4.2	8.9	10.7	13.3	14.4	16.1
Extended NVP	0.5	1.6	1.8	2.2	3.3	6.8	9.0	10.3	11.6	14.0
Extended NVP+ZDV	0.3	1.2	1.9	2.4	3.3	6.3	9.4	10.7	11.8	13.4

Probability of HIV-1 Infection or Death in Infants Uninfected at Birth by Treatment Arm: PEPI-Malawi



Age	1 wk	6 wks	9 wks	14 wks	6 mos	9 mos	12 mos	15 mos	18 mos	24 mos
Estimates (%)										
Control	0.6	6.7	9.3	10.7	13.2	**16.8**	18.1	20.5	22.6	24.1
Extended NVP	0.6	3.3	4.2	4.7	6.6	**10.6**	13.9	16.0	19.0	20.9
Extended NVP+ZDV	0.5	2.8	4.1	5.1	8.2	**11.2**	15.0	16.5	18.6	22.0

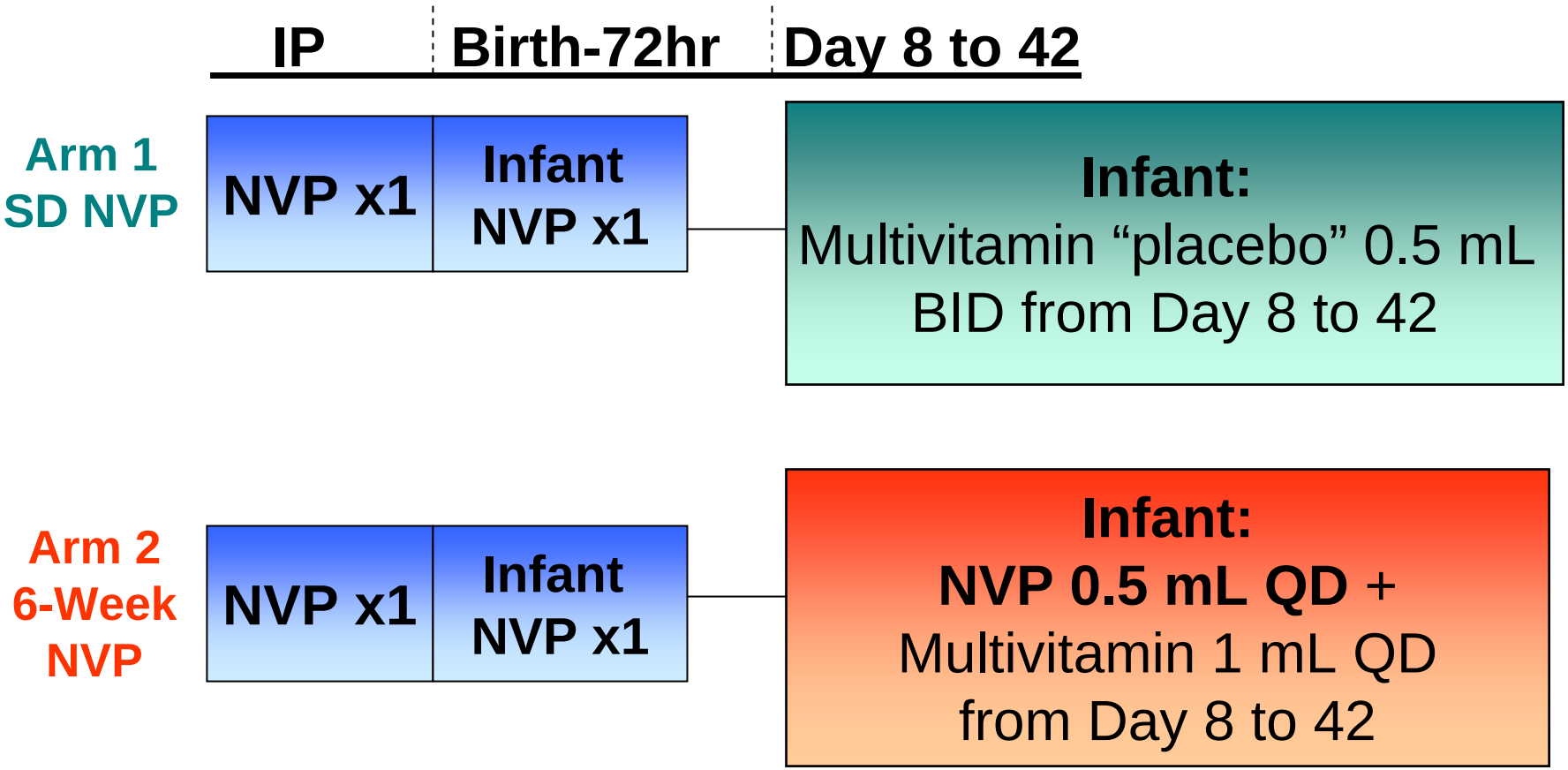
Six Week Extended NVP (SWEN) Study

Sastry J et al. 15th CROI, Boston, MA 2008 Abs 43

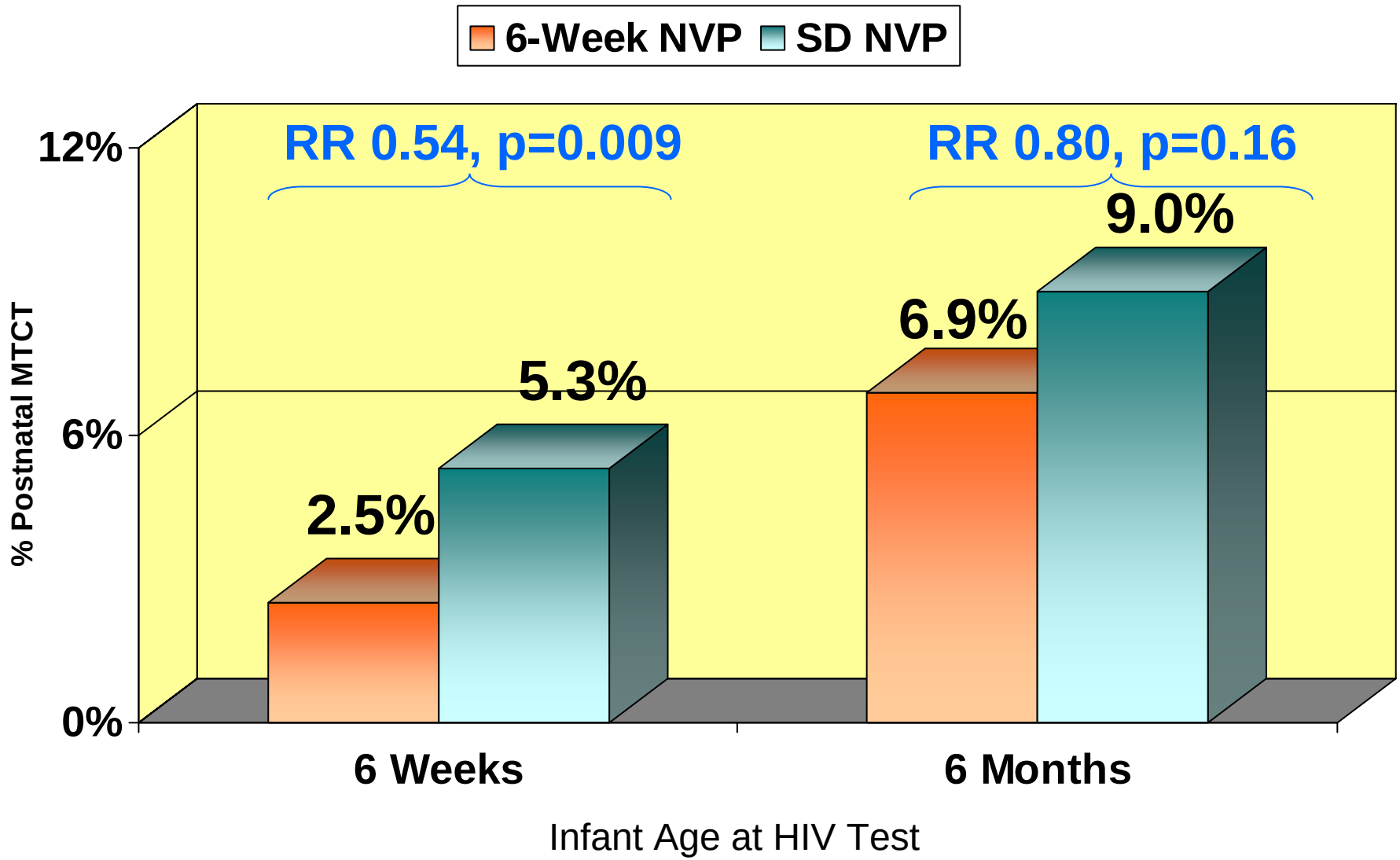
- **Combined analysis from 3 separate but coordinated randomized controlled trials in Ethiopia, Uganda, and India.**
- **Designed to assess if extended (6 week) infant NVP prophylaxis could decrease postnatal HIV transmission compared to standard SD NVP.**
- **For masking, multivitamin 'placebo' so all infants received 2 doses of study drug daily.**

Six-Week Extended Nevirapine (SWEN) Study:
Ethiopia, India, Uganda: Separate but Coordinated Trials

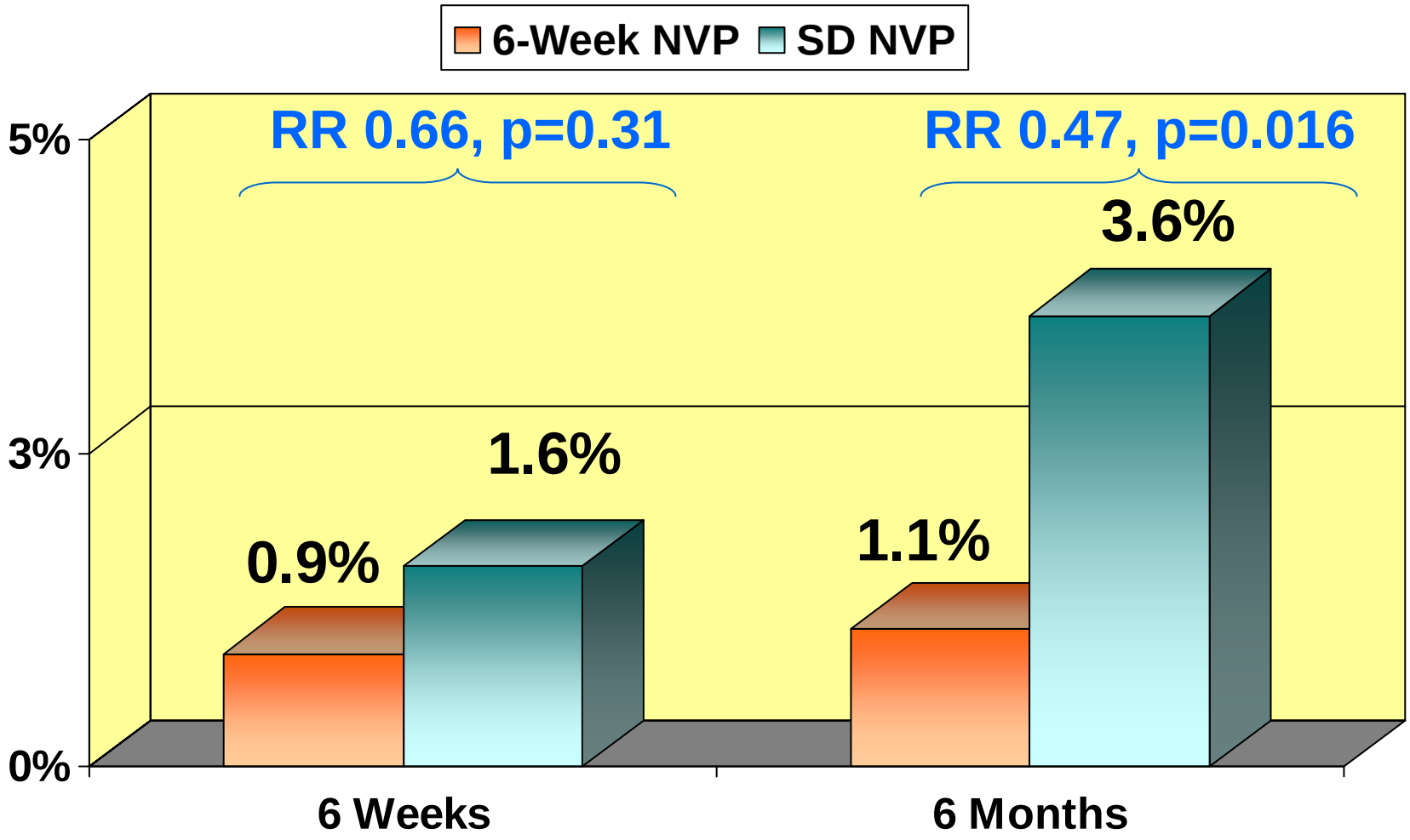
Sastry J et al. 15th CROI, Boston, MA 2008 Abs 43



SWEN: 6-Week NVP Decreases Postnatal HIV MTCT at Age 6 Wks but No Longer Significant at 6 Mos



SWEN: 6-Week NVP Reduces Risk of Death at Age 6 Mos by 53%



NVP Resistance in Breastfed SWEN Infants, India

Moorthy A et al. 15th CROI, Boston, MA 2008 Abs 44

- **Evaluated NVP resistance in 89 HIV-infected infants in India SWEN study (SD NVP vs 6 week extended NVP), all subtype C virus.**
- **83 (93%) able to be genotyped.**
- **76 infants met inclusion criteria (able to define timing infection); sample taken median 28 days since HIV diagnosis.**
- **Timing of infection defined:**
  - ***In utero* infection: <48 hrs (N=22)**
  - **Postpartum/Early BF: 1-6 wks (N=19)**
  - **Late BF: >6 wks (N=35) (Very Late: >14 wks)**

NVP Resistance in Breastfed SWEN Infants, India

Moorthy A et al. 15th CROI, Boston, MA 2008 Abs 44

- **Higher rates of NVP resistance in extended NVP infants infected within 6 weeks of birth.**
- **However, lower rates of NVP resistance in extended NVP infants infected after 6 weeks.**
- **In multivariate analysis, infants infected late (>14 weeks) were 89% less likely to have NVP resistance than those infected early (in utero, PP/EBF, LBF), and had predominantly wild type virus.**

Infants Infected Within 14 Weeks: No Difference in NVP Resistance by Maternal NVP Receipt: India SWEN Study

Moorthy A et al. 15th CROI, Boston, MA 2008 Abs 44

Maternal NVP Dose Received	% with NVP Resistance	
	SD NVP N=51	Ext NVP N=25
Yes	40%	86%
No	36%	100%

57% of women received intrapartum SD NVP

NVP Resistance in Breastfed SWEN Infants, Uganda

Church J et al. 15th CROI, Boston, MA 2008 Abs 635b

- **Evaluated NVP resistance in 69 HIV-infected infants in Uganda SWEN study (SD NVP vs 6 week extended NVP).**
- **49 (71%) able to be genotyped (24 SD NVP and 25 extended NVP).**
- **Maternal CD4, infant RNA and HIV subtypes similar between arms.**
- **At age 6 weeks: 50% in SD vs 81% in extended NVP had NVP resistance (p=0.001).**
- **Number of NVP doses received or HIV status at birth not associated with resistance.**

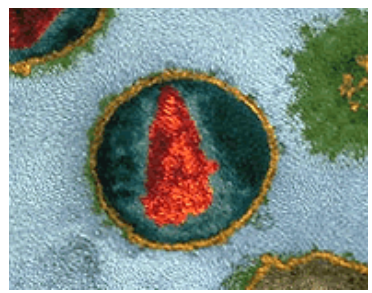
NVP Resistance in Breastfed SWEN Infants, Uganda SWEN Study

Church J et al. 15th CROI, Boston, MA 2008 Abs 635b

	SD NVP	Extended 6 week NVP	P value
Genotypic, age 6 weeks			
Viroseq assay	50% (12/24)	84% (21/25)	0.01
LigAmp assay (quantitative)	35% (7/24)	79% (19/25)	0.004
Phenotypic, age 6 weeks	45% (9/20)	86% (19/22)	0.005
Genotypic, age 6 months			
Viroseq assay	17% (1/6)	7/7 (100%)	

Maternal HAART Prophylaxis of Postnatal Transmission: Observational Studies

-- ART Resistance in Infants Infected Despite Maternal HAART Prophylaxis



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

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

- **HAART given from 34 weeks gestation to 6 months postpartum; counseled to exclusively breastfeed and wean at 6 months.**
- **HAART originally AZT/3TC/NVP; changed to AZT/3TC/NFV if CD4 >250.**
- **Infants received SD NVP at birth.**
- **Enrolled 522 women; 500 delivered 502 live born infants. Maternal parameters:**
  - **Median CD4 392; 23% had CD4 <250.**
  - **Median RNA 4.5 log.**

Cumulative MTCT through 12 Months Overall, CD4 Category, NVP vs NFV Category: KIBS

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

	0-7 Day	6 Wks	3 Mos	6 Mos	12 Mos
Overall MTCT	2.4%	3.9%	4.1%	5.0%	5.9%
Postnatal Tx		+1.5%	+1.7%	+2.6%	+3.5%
CD4 count:					
CD4 <250	3.4%	4.3%	5.2%	5.2%	6.7%
CD4 >250	2.1%	3.8%	3.8%	4.9%	5.5%
Type of ART:					
CD4 >250: NVP	1.1%	3.4%	3.4%	5.2%	5.9%
CD4 >250: NFV	3.0%	4.0%	4.0%	4.6%	5.2%

KIBS Maternal HAART Prophylaxis Study: Evaluation of ARV Resistance in Infants

Zeh C et al. 15th CROI, Boston, MA, 2008 Abs 84LB

- **29/502 infant (5.8%) were infected.**
- **24/29 infants (83%) were infected prior to 6 months (during period of prophylaxis).**
- **Maternal HAART regimen for 24 infants:**
  - **14 (58%) NVP and 10 (42%) NFV**
- **Resistance was identified in 16 (67%) infants:**
  - **43% (6/14) infants of moms on NVP**
  - **100% (10/10) infants of moms on NFV**
- **Resistance not generally present on first viral test but emerged in the breastfeeding infants of mothers on HAART by week 14-24.**

Postnatal MTCT in Infants Uninfected at Birth: Comparison Infant Prophylaxis (PEPI-Malawi, SWEN) and Maternal Prophylaxis (KIBS)

	PEPI Malawi		SWEN	Kisumu KIBS
	14 wk Ext NVP	14 Wk Ext NVP+AZT	6 Wk Ext NVP	Maternal HAART
6 weeks [1]	1.7%	1.6%	2.5%	1.5%
6 months	4.0%	5.2%	6.9%	2.6%
12 months	7.0%	8.1%	-	5.9%
Increment 6-12 mos [2]	*+3.0%*	*+2.9%*		*+3.3%*

[1] At 6 weeks, during time all regimens are being given, BF MTCT infant ~maternal prophylaxis similar.

[2] Between 6-12 months, when all prophylaxis has stopped, increment in postnatal MTCT same all groups

DREAM, Mozambique: MTCT in Women Receiving HAART During Pregnancy/Postpartum

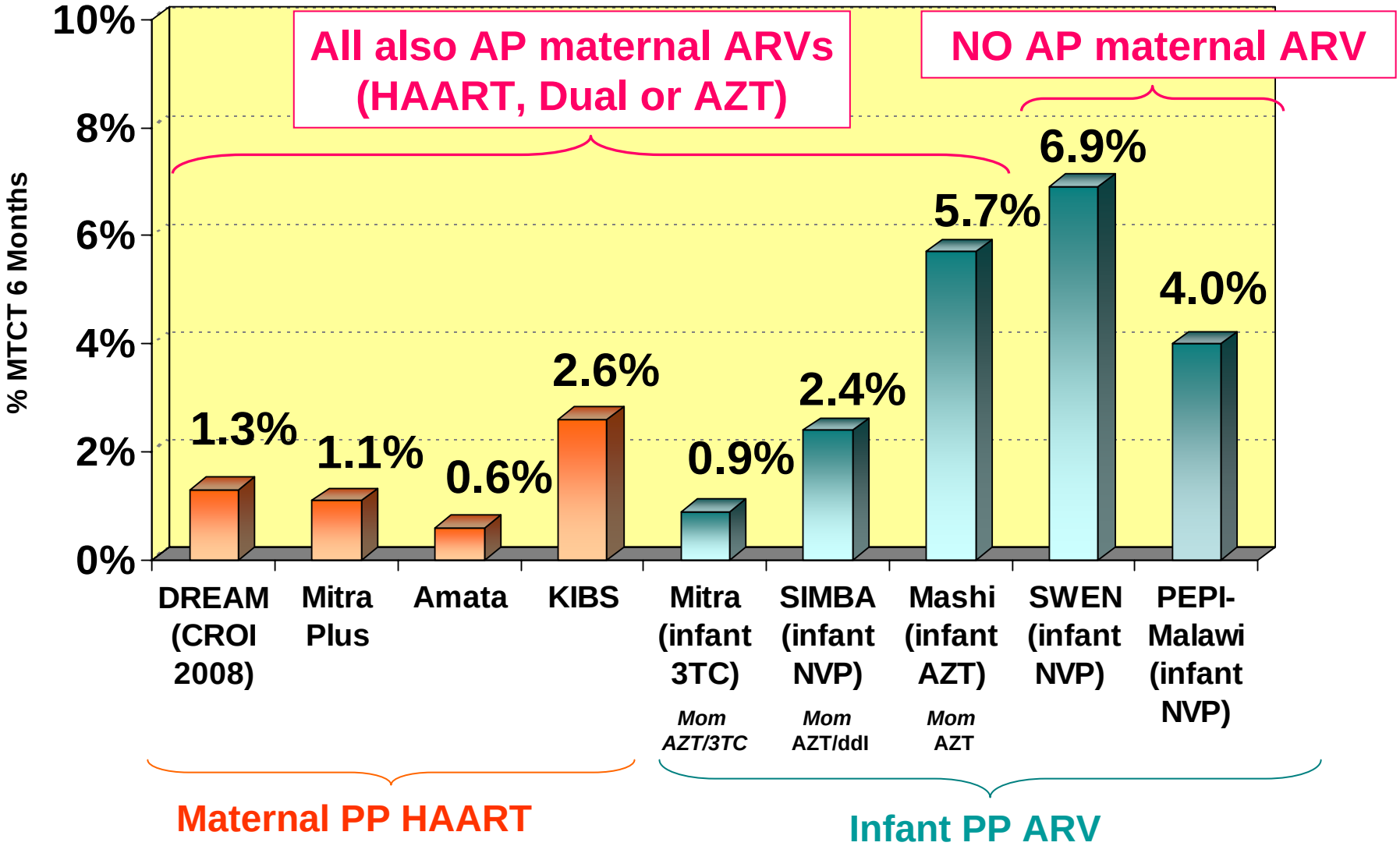
Marazzi M et al. 15th CROI, Boston, MA, 2008 Abs 639

- **Report on 341 women who started HAART during pregnancy (16% required for own health), with 12 month follow-up on 81% of 271 infants (15% loss to follow-up and 4% death by 12 months).**
- **Observed infant mortality 48.3/1,000 live birth compared to 101/1,000 in country as whole.**

	Age			
	1 mo N=341	6 mos N=313	12 mos N=276	Total
HIV infection	1.2% (4)	0.6% (2)	0.7% (2)	2.9% (8)

1.3% postnatal MTCT

ARV Prophylaxis: Postnatal Birth - 6 Month HIV Transmission Rates (uninfected at birth) Various Studies



Antiretroviral Drug Penetration into Breast Milk and Infant Plasma: BAN Study

Corbett A et al. 15th CROI Boston, MA, 2008 Abs 648

- **Sampled maternal, infant, breast milk in 20 women receiving postnatal maternal HAART at 6, 12, 24 weeks PP. Analysis of all sampling time points:**

	3TC (N=47)	NVP (N=21)	NFV (N=26)
Breast Milk/ Maternal Plasma	2.6 (1.1-3.5)	0.7 (0.5-0.9)	0.08 (0.04-0.14)
Infants Plasma/ Breast Milk	0.01 (0.004-0.03)	0.2 (0-0.3)	ND
Infants Plasma Maternal Plasma	0.06 (0.01-0.1)	0.12 (0-0.3)	ND

Antiretroviral Drug Penetration into Breast Milk and Infant Plasma: BAN Study

Corbett A et al. 15th CROI Boston, MA, 2008 Abs 648

- **While 3TC concentrations in breast milk was 2.6-fold higher than maternal plasma, infant plasma exposure was relatively low (1% of breast milk).**
- **NVP concentrations in breast milk were 70% of maternal plasma, with infant exposure 20% of breast milk.**
- **NFV concentration in breast milk is very low, 8%, with no drug found in the infant.**
- **Risk for toxicity in the infant appears low but low drug levels in infant from drug passage from breast milk for NVP (possibly 3TC) may suggest risk of resistance if infant becomes infected.**

Response to NNRTI Therapy After Single-Dose NVP for Prevention of MTCT

-- Prevention of NVP Resistance
Response to NVP-HAART

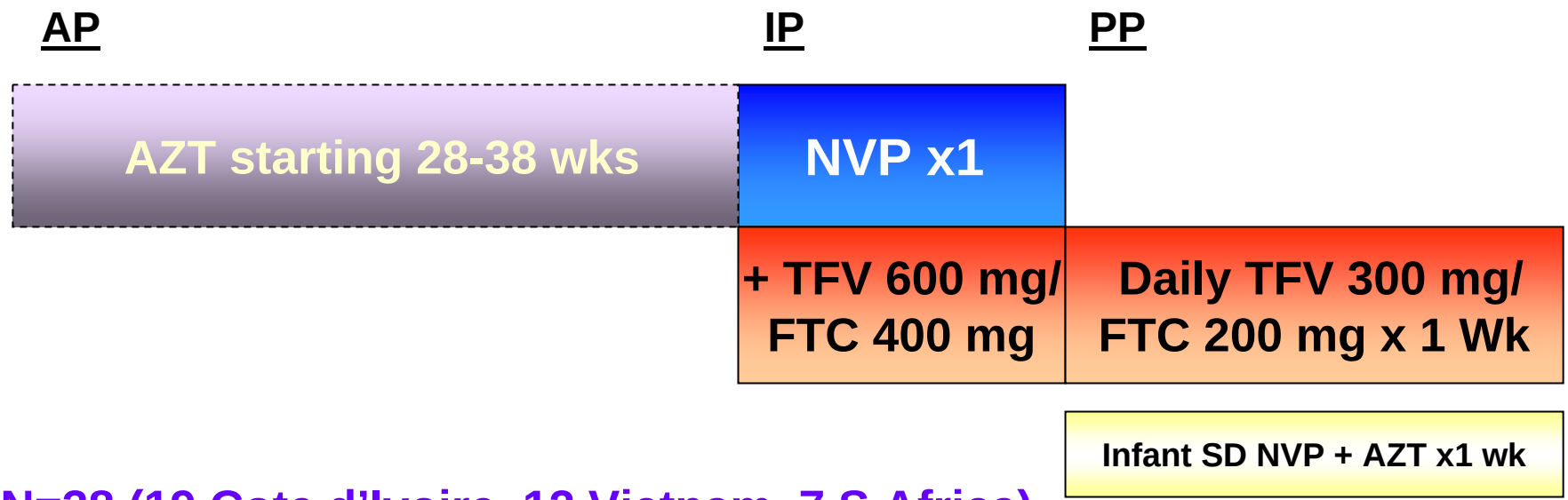
Response to NNRTI-HAART After SD NVP: Multicountry Study

Weidle P et al. 15th CROI, Boston, MA, 2008 Abs 48

- **Multi-country cohort study: Zambia (N=509), Kenya (N=152) and Thailand (N=217)**
  - **Compared response to NVP-based HAART in women with (N=355) and without (N=523) prior SD NVP exposure.**
- **High proportion of women (≥70%) responded to NVP-HAART at 24 weeks regardless of SD NVP exposure.**
- **Increased risk of failure in women with SD NVP exposure within 6 mos (possibly 12 mos) of starting HAART.**

TEmAA Study – ANRS 12109: Truvada to Reduce NVP Resistance

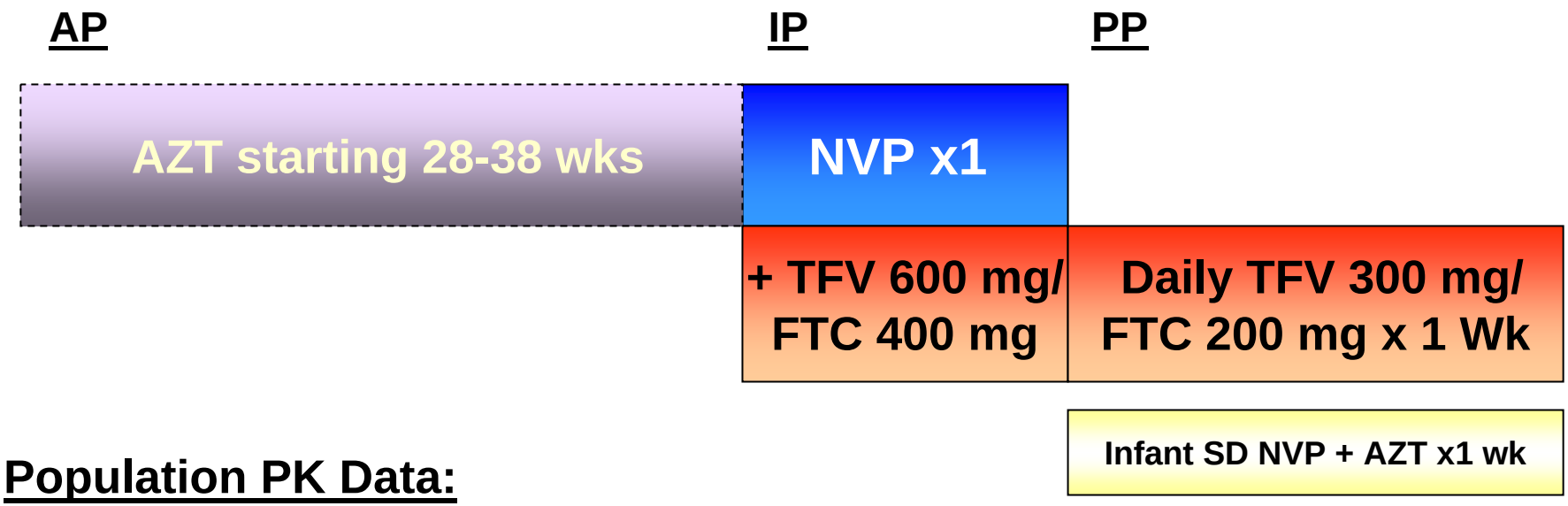
Arrive E et al. 15th CROI, Boston, MA, 2008 Abs 45b



- N=38 (19 Cote d'Ivoire, 12 Vietnam, 7 S Africa)
- Median CD4 450 (IQR 314-596)
- Median RNA 4.08
- 38 women: 24% transient grade 3 or 4 (anemia, ANC, LFT)
- 39 infants: 23% clinical SAE, 2% transient anemia
- MTCT at 4 wks: 2/39 (5.1%) (at day 3, likely in utero)
- NO AZT, NVP, TFV or FTC Resistance mom/infant at wk 4 (standard assay)

TEmAA Study – ANRS 12109: Population PK of IntrapartumTenofovir

Hirt E et al. 15th CROI, Boston, MA, 2008 Abs 47LB

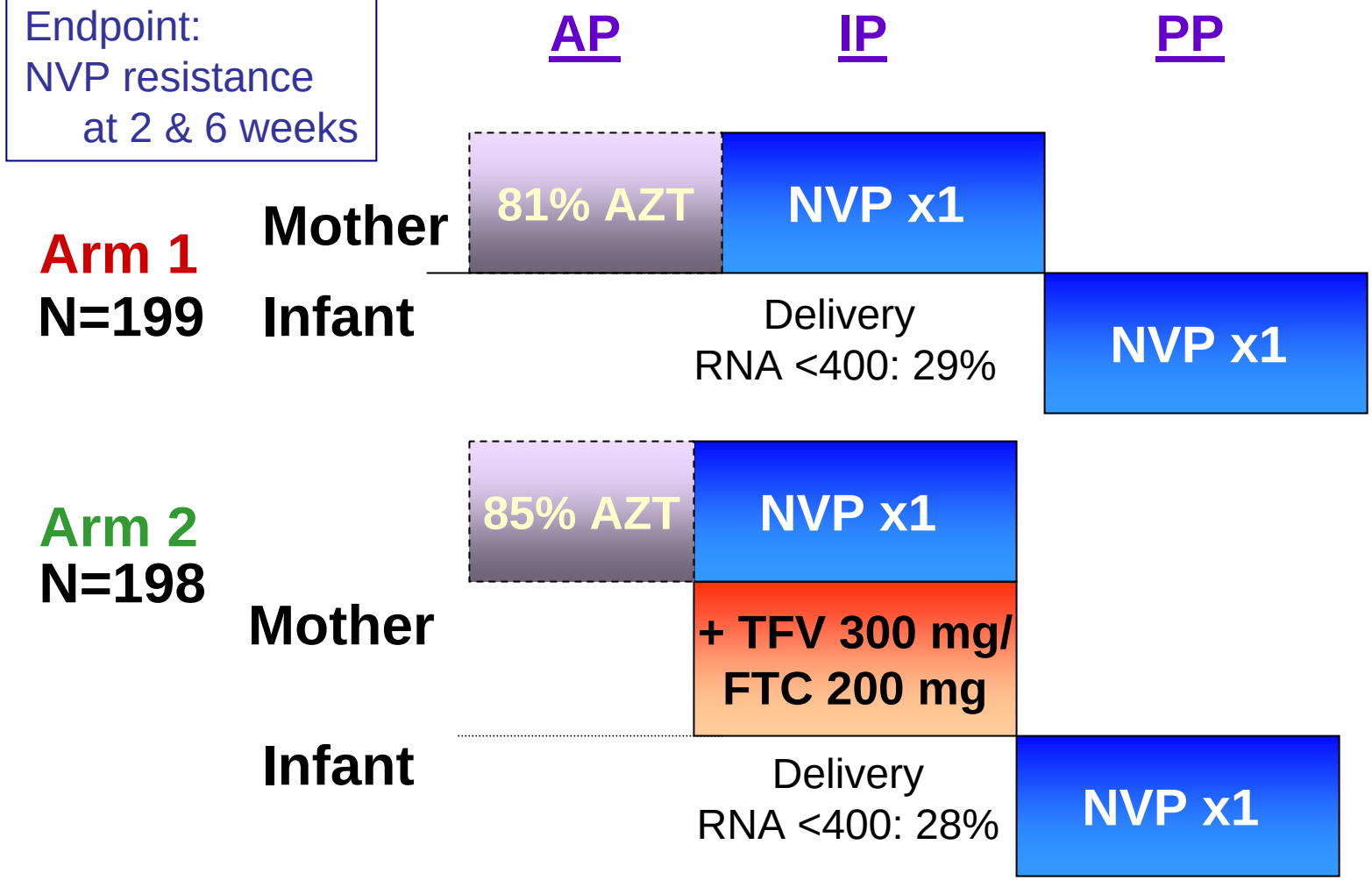


- **Population PK Data:**
  - After 600 mg IP TFV/FTC, maternal TFV median AUC 2.73 mg/L^{-1}, peak 0.31 mg/L and trough 0.056 mg/L; similar concentrations to what seen with standard 300 mg dose non-pregnant persons.
  - Absorption faster and greater for women with CS then vaginal delivery.
  - Delivery infant level 0.10 mg/mL and maternal level 0.13/L – TFV cord infant levels 76% of maternal levels, suggesting good placental transfer.
  - Neonatal half-life 8.3 hr.
  - Recommend re-administration if >12 hours since IP dose and delivery.

TD-2 Study: Truvada to Reduce NVP Resistance Ultrasensitive Assay (OLA) Analysis

Chi B et al. 15th CROI, Boston, MA, 2008 Abs 631

Endpoint:
NVP resistance
at 2 & 6 weeks



TD-2 Study: Truvada to Reduce NVP Resistance Ultrasensitive Assay (OLA) Analysis

Chi B et al. 15th CROI, Boston, MA, 2008 Abs 631

112 random maternal specimens tested using OLA assay, with sensitivity for minority subpopulations as low as 5%

Study Arm	2 Weeks
(AZT) SD NVP (N=23)	44%
(AZT) SD NVP+ TFV/FTC (N=15)	13%

Study Arm	6 Weeks
(AZT) SD NVP (N=41)	44%
(AZT) SD NVP+ TFV/FTC (N=43)	19%

69% reduction in NVP resistance at 2 weeks
RR 0.31 (95% CI 0.08-1.21)

58% reduction in NVP resistance at 6 weeks
RR 0.42 (95% CI 0.21-0.87)

Pattern of Infant Feeding and Postnatal MTCT

Risk Factors for Postnatal MTCT

Duration and Pattern of Breastfeeding and Postnatal Transmission

Becquet R et al. 15th CROI, Boston, MA, 2008, Abs 46

- **Pooled data from 2 studies: one in W. Africa (Ditrame-Plus weaning at 4 mos) and the Vertical Transmission Study in rural S. Africa (prolonged exclusive breastfeeding [EBF]).**
- **1,195 breastfeeding infants included; 90% were breastfed for at least 3 months.**
  - **W. Africa: 38% BF 6 mos, 20% BF 12 mos**
  - **S. Africa: 83% BF 6 mos, 38% BF 12 mos**
- **2/3 EBF; of non-EBF, majority predominant BF (BF+water-based drinks).**
  - **W. Africa: 55% predominantly BF to age 3 mos**
  - **S. Africa: 66% EBF to age 3 mos**

Duration and Pattern of Breastfeeding and Postnatal Transmission

Becquet R et al. 15th CROI, Boston, MA, 2008, Abs 46

- **Overall 18 month postnatal transmission was higher in S. Africa study (longer BF):**
  - **5% (CI 3-8%) W. Africa vs 9% (CI 7-11%) S. Africa, p=0.03.**
- **BF duration was major determinant of MTCT - 18 month postnatal transmission by duration:**
  - **BF <6 months: 3.9% (CI 2.3-6.5%)**
  - **BF >6 months: 8.7% (CI 6.8-11%)**
  - **Longer duration associated with 2.1-fold (CI 1.2-3.7) increased hazard postnatal MTCT.**

Duration and Pattern of Breastfeeding and Postnatal Transmission

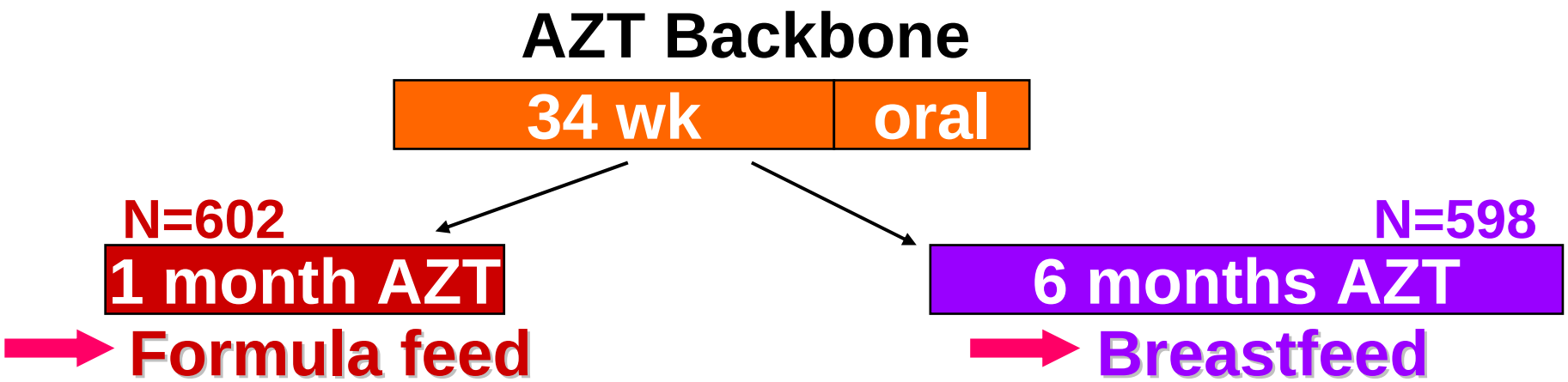
Becquet R et al. 15th CROI, Boston, MA, 2008, Abs 46

- **Risk did not vary by EBF vs predominant BF.**
- **Children exposed at least once to solids in first 2 months of life were 2.9-fold (CI 1.1-8.0) time more likely to be infected postnatally than those without such exposure (p=0.04).**

Risk Factors for Postnatal BF Transmission: Botswana (MASHI)

Shapiro R et al. 15th CROI, Boston, MA 2008 Abs 637

- **Mashi study randomized infants to formula vs breastfeed in context of short-course AZT (±SD NVP):**



Transmission in MASHI by Mode Infant Feeding and by Time of Infection

Shapiro R et al. 15th CROI, Boston, MA 2008 Abs 637

	AP AZT 34 wk Era 2: HAART 11%	**Birth** Era 1: NVP/NVP vs PL/PL Era 2: NVP/NVP vs PL/NVP	**Birth-1 month** Infant AZT x 1 mo	**>1 month** Infant AZT x 6 mos if breastfeeding (weaning by 6 mos recommended)
Breast-Fed* N=598		3.3% (19) infected at birth	1.2% (6) btn birth & 1 mo	4.4% infected after 1 month
Formula-Fed N=602		3.8% (22) infected at birth	1.1% (7) btn birth & 1 mo	0.2% infected after 1 month

No significant difference btn formula breastfed (+AZT) infants btn birth and 1 month p=1.0

In breastfed (+AZT) infants, 4.4% (24) infected after 1 mo:

15 - btn 1-4 mos (while on AZT)
6 - btn 4-7 mos (on AZT to 6 mos)
3 - >7 mos

* 2.8% (3) of 109 EBF infants became infected compared with 4.8% (20) of 400 mixed-fed infants (P=0.14).
No postnatal MTCT in 34 infants born to mothers on HAART after delivery.

Mashi: Risk Factors for Postnatal MTCT

Shapiro R et al. 15th CROI, Boston, MA 2008 Abs 637

- **No difference in MTCT between birth and 1 month by mode infant feeding (in background of infant AZT).**
- **Maternal SD NVP receipt did not predict MTCT in the 1st month or thereafter in BF arm.**
- **No difference MTCT by pattern feeding (2.8% EBF and 4.8% 400 mixed-fed infected, p=0.14).**
- **Median baseline maternal CD4 cell count for late postnatal transmitters was 225/mm^3.**
- **No late MTCT occurred when baseline maternal plasma plasma RNA was < 3,500.**

Improvement in prevention of maternal to child HIV transmission has been shown by utilizing.

a) Treatment of mother with HAART by third trimester of pregnancy.
b) Treatment of mother and fetus during actual birth process.
c) Consideration of Caesarian section for birth.
d) Treatment of exposed infant after birth.
e) Avoiding breast feeding of infants who are born to HIV-infected mothers.
f) All of the above.
g) I'm sorry, I did not learn

Guidelines Information

- ***U.S. Public Health Service*** **expert panels**
- **Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents (January 29, 2008)**
- **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (February 28, 2008)**
- **Interventions to Reduce Perinatal HIV Transmission (November 2, 2007)**
- **The published texts always posted at: www.aidsinfo.nih.gov**

Thank You For Your Attention

National Institute of Child Health and Human Development (NICHD)

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National Institutes of Health
US Department of Health and Human Services