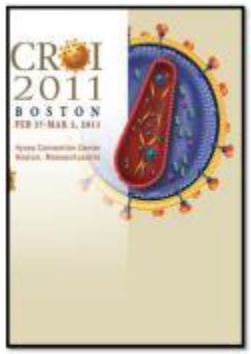


CROI 2011 Update

18th CROI, Boston, MA, Feb 27-Mar 2, 2011

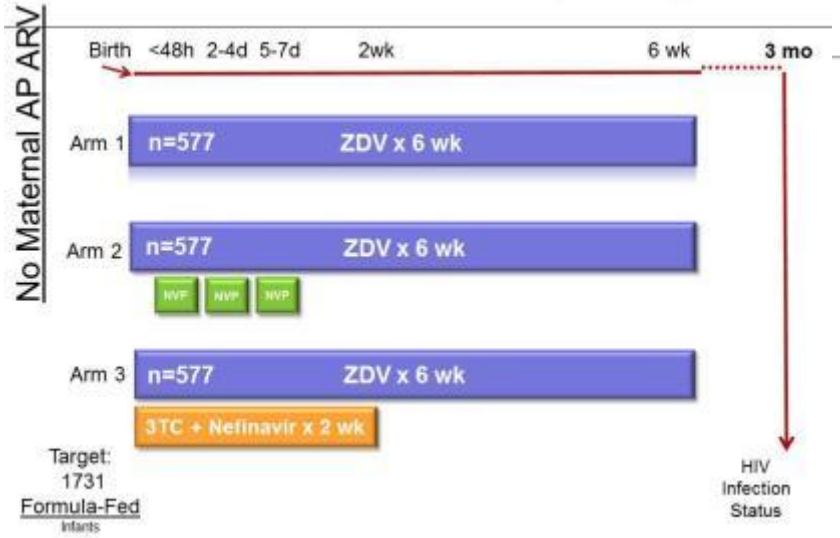
Selected PMTCT, Pregnancy, and Pediatric Presentations

Lynne Mofenson MD
Pediatric, Adolescent and Maternal AIDS Branch
National Institute of Child Health and Development
National Institutes of Health

4/20/11

Prevention of Mother to Child HIV Transmission

NICHD/HPTN 040 Study Design



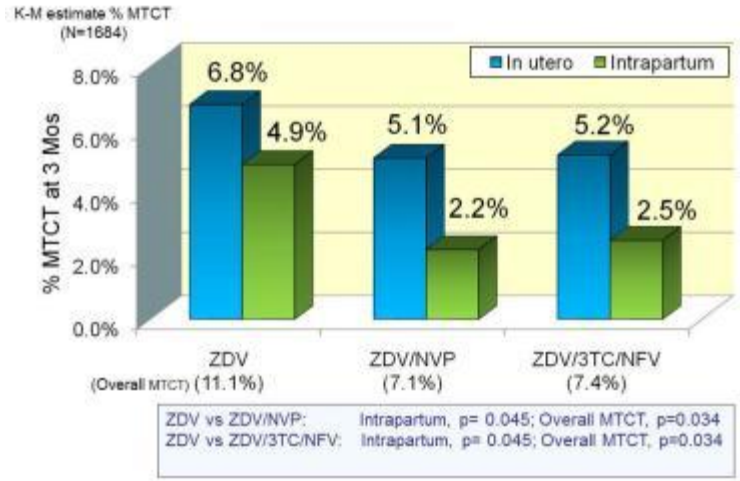
NICHD/HPTN 040: Study Regimens and Dosing

Nielsen-Saines K et al. 18th CROI, Boston, 2011 Abs 124LB

Group	N	Study Drug Regimen Started Within 48 Hrs of Birth
1 (ZDV control)	557	• ZDV x 6 weeks 12 mg po BID if BW >2 kg 8 mg po BID if BW ≤2 kg
2 (ZDV/ NVP)	557	• ZDV as above • NVP: 1st dose within 48 hr of birth (birth-48 hrs) 2nd dose 48 hrs after 1st 3rd dose 96 hrs after 2nd –NVP dose: 12 mg po if BW >2 kg 8 mg po if BW ≤2 kg
3 (ZDV/ 3TC/ NFV)	557	• ZDV as above • 3TC + NFV daily for 2 weeks –3TC dose: 6 mg po BID if BW >2 kg 4 mg po BID if BW ≤2 kg –NFV dose: 200 mg po BID if BW >3 kg 150 mg po BID if BW >2 and <3 kg 100 mg po BID if BW ≤2 kg

NICHD/HPTN 040: *In Utero* & Intrapartum MTCT at 3 Mos

Nielsen-Saines K et al. 18th CROI, Boston, 2011 Abs 124LB



NICHD/HPTN 040: *In Utero* & Intrapartum MTCT at 3 Mos

Nielsen-Saines K et al. 18th CROI, Boston, 2011 Abs 124LB

NICHD / HPTN 040: Trong TC & MTCT trong chuyển dạ tại 3 Mos Nielsen-Saines K et al. 18 CROI, Boston, 2011 Abs 124LB

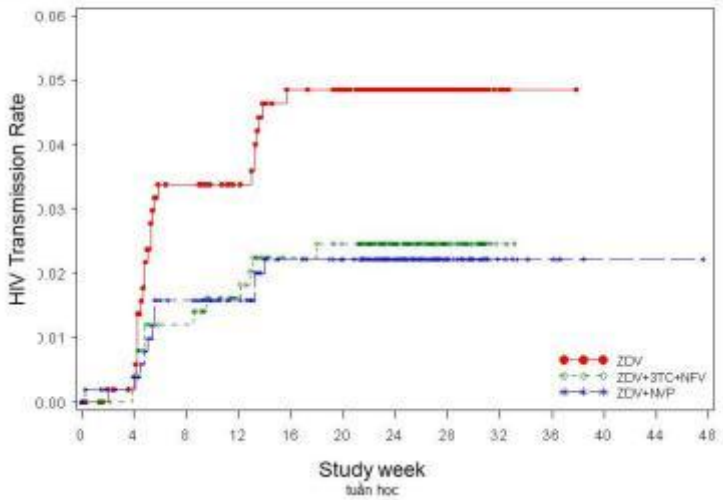
Infant HIV Status Trẻ SS nhiễm HIV	ZDV N = 566	ZDV/NVP N = 562	ZDV/ 3TC/ NFV N = 556	Total N = 1684	p Value Giá trị
Infected *In Utero* nhiễm trùng trong TC	N = 37	N = 28	N = 28	N = 93	
KM Rate (IU) 95% CI KM giá (IU) 95% CI	6.8% 5.0 - 9.3	5.1% 3.5 - 7.3	5.2% 3.6 - 7.4	5.7% 4.7 - 7.0	0.243
Infected Intrapartum Nhiễm trùng trong chuyển dạ	N = 24	N = 11	N = 12	N = 47	
KM Rate (IP) 95% CI KM giá (IU) 95% CI	4.9% 3.3-7.2	2.2% 1.2 – 4.0	2.5% 1.4 - 4.3	3.2% 2.4 - 4.2	0.045*
Infected Overall Nhiễm trùng tổng thể	N = 61	N = 39	N = 40	N = 140	

*To comparison of each experimental arm to control

NICHD/HPTN 040: HIV Infection Timing for Infants Uninfected at Birth (IP MTCT Only) by Treatment Arm

Nielsen-Saines K et al. 18th CROI, Boston, 2011 Abs 124LB

NICHD / HPTN 040: Nhiễm HIV Timing cho trẻ không bị lây nhiễm khi sinh (IP MTCT Chỉ) của Arm Điều trị



NICHD/HPTN 040: Risk Factors for MTCT

Adjusted Multivariate Logistic Regression Analysis

NICHD / HPTN 040: Các yếu tố rủi ro cho MTCT

Phân tích điều chỉnh hồi quy Logistic đa biến

Nielsen-Saines K et al. 18 CROI, Boston, 2011 Abs 124LB

	OR (95% CI)	*p Value* Giá trị
Treatment arm điều trị cánh tay		
ZDV	1.0	
ZDV+NVP	0.41 (0.19 - 0.82)	0.017
ZDV+3TC+NFV	0.48 (0.24 - 0.99)	0.045
Log_{10} HIV RNA (continuous)	2.09 (1.42 - 3.09)	0.0002
CD4 count (per 100 cells/uL)	0.96 (0.86-1.07)	0.428

Not associated
Age
Race
Prenatal care
ZDV in labor
Maternal Syphilis
Region of birth
Mode of delivery
Gestational age
CD4 cell count
Không liên quan
Tuổi
Chủng tộc
Chăm sóc trước khi sinh
ZDV trong lao động
Giang mai mẹ
Khu vực sinh
Phương thức giao hàng
Tuổi thai

đếm tế bào CD4

NICHD/HPTN 040: Number Infants with Grade 3/4 Laboratory Adverse Events by Treatment Arm

Trẻ sơ sinh với số lượng Lớp 3 / 4 phòng thí nghiệm tác dụng phụ kiện của Arm Điều trị

Nielsen-Saines K et al. 18th CROI, Boston, 2011 Abs 124LB

Lab Abnormality XN bất thường	ZDV	ZDV/NVP	ZDV/3TC/ NFV	Total	p Value Giá trị
Anemia thiếu máu	153	131	147	431	0.31
Neutropenia Bạch cầu giảm	93	84	153	330	<0.0001
Elevated AST AST tăng	18	11	14	43	0.43
Thrombocytopenia Tiểu cầu giảm (< 75,000)	9	7	10	26	0.75

NICHD/HPTN 040: Summary tóm tắt

- *Intrapartum* MTCT significantly reduced in 2 & 3-drug arms compared to ZDV alone.
- Overall HIV MTCT (*in utero* + *intrapartum*) also significantly lower in the 2 & 3-drug arms vs ZDV.
- MTCT risk factors were study arm and maternal RNA.
- Infants at high risk of HIV infection (i.e., born to mothers who received no ARV during pregnancy) should receive a 2 or 3-drug ARV regimen starting as soon as possible after birth to reduce HIV infection risk.
- Toxicity profile (less neutropenia) and ease of use suggests a 2-drug regimen ZDV/NVP may be preferable (resistance testing is ongoing).
- Trong chuyển dạ MTCT giảm đáng kể ở 2 & 3-thuốc cánh tay so với ZDV một mình.
  Nhìn chung MTCT HIV (trong chuyển dạ + tử cung) cũng thấp hơn đáng kể trong 2 & 3-thuốc tay vs ZDV.
  MTCT yếu tố nguy cơ đã được nghiên cứu cánh tay và mẹ RNA.
  Trẻ sơ sinh có nguy cơ nhiễm HIV cao (ví dụ, được sinh ra từ các bà mẹ không nhận được điều trị ARV trong khi mang thai) sẽ nhận được một phác đồ điều trị ARV 2 hoặc 3 thuốc bắt đầu càng sớm càng tốt sau khi sinh để giảm nguy cơ nhiễm HIV.
  Độc tính cá nhân (ít giảm bạch cầu) và dễ sử dụng cho một chế độ 2-thuốc ZDV / NVP có thể được ưa chuộng hơn (kháng thử nghiệm đang được tiến hành).

HPTN 046 Study Design

thiết kế nghiên cứu

Phase III, randomized, double-blind, placebo-controlled study in breastfeeding infants born to HIV-infected mothers

Giai đoạn III, ngẫu nhiên, mù đôi, kiểm soát giả dược

HPTN 046: Randomized Infants & Maternal Characteristics

Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB

- 1,522 breastfed, uninfected infants born to 1,505 HIV-infected mothers randomized at age 6 weeks:
  - N=759 extended nevirapine
  - N=763 placebo
- Mothers on ART for own health:
  - at randomization: 29% in each study arm
  - at 6 months: 31% in extended NVP; 32% in placebo arm
- Median maternal CD4+ count at randomization (6 wks PP):
  - Extended NVP arm: 560 cells/mm^3
  - Placebo arm: 528 cells/mm^3
- Most infants weaned between ages 6 and 12 mos.

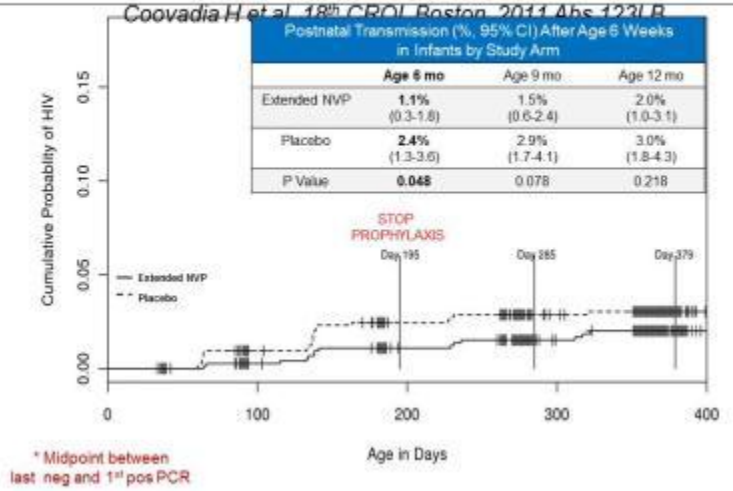
* 1.522 bú sữa mẹ, không nhiễm 1.505 trẻ sinh ra từ bà mẹ nhiễm HIV ngẫu nhiên ở độ tuổi 6 tuần:
N = 759 mở rộng nevirapine
N = 763 giả dược
* Bà mẹ về ART cho sức khỏe của riêng:
tại ngẫu nhiên: 29% trong mỗi cánh tay nghiên cứu
6 tháng: 31% trong mở rộng NVP; 32% ở cánh tay giả dược
* CD4 + trung bình của mẹ đếm tại ngẫu nhiên (6 wks PP):
* Mở rộng cánh tay NVP: 560 tế bào/mm3
* Placebo cánh tay: 528 tế bào/mm3
* Hầu hết trẻ cai sữa ở độ tuổi từ 6 đến 12 m

% Infants Still Breastfeeding, by Study Arm			
	6 mo	9 mo	12 mo
Extended NVP	85.2%	48.5%	4.6%
Placebo	86.2%	50.7%	4.5%

HPTN 046: Time to Infant HIV Infection*

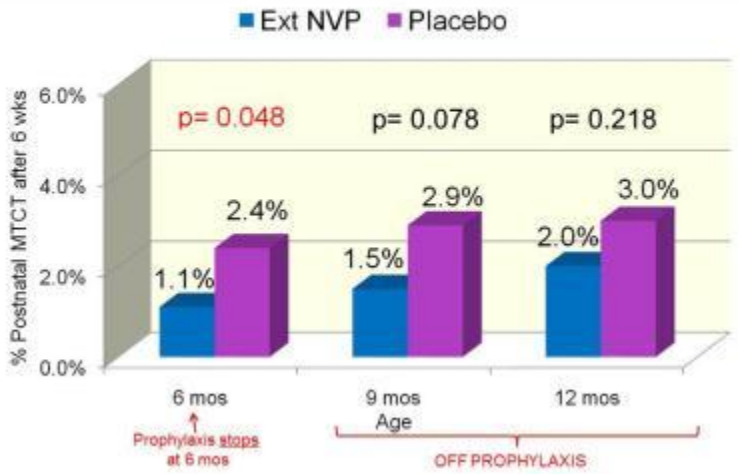
(Infants Uninfected at 6 Wks: Kaplan Meier Plot) **Thời gian đến * trẻ sơ sinh nhiễm HIV (không bị nhiễm bệnh tại 6 Wks Trẻ sơ sinh: Kaplan Meier Lô)**

Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB



HPTN 046: Cumulative % Postnatal MTCT in Infants Uninfected at Age 6 Weeks

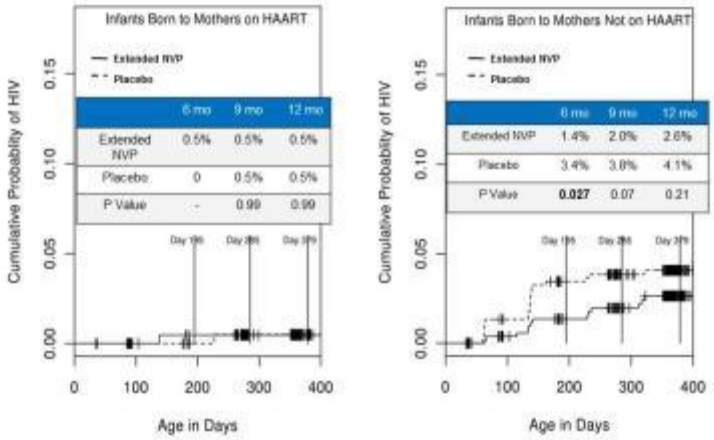
Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB



HPTN 046: Infant HIV Infection Stratified by Maternal ART Status at Randomization

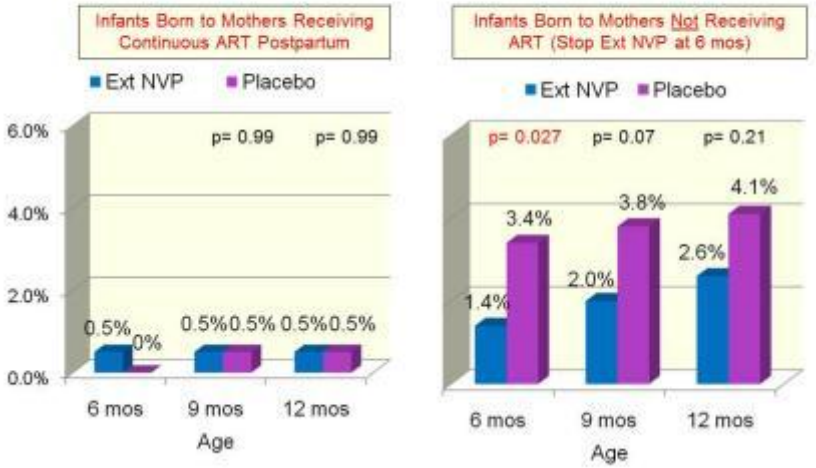
(Infants Uninfected at 6 Wks: Kaplan Meier Plot)

Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB



HPTN 046: HIV Infection in Infants of Mothers Receiving and Not Receiving ART by Arm

Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB



HPTN 046: HIV Infection in Infants of Mothers Not on HAART by CD4 count and Study Arm

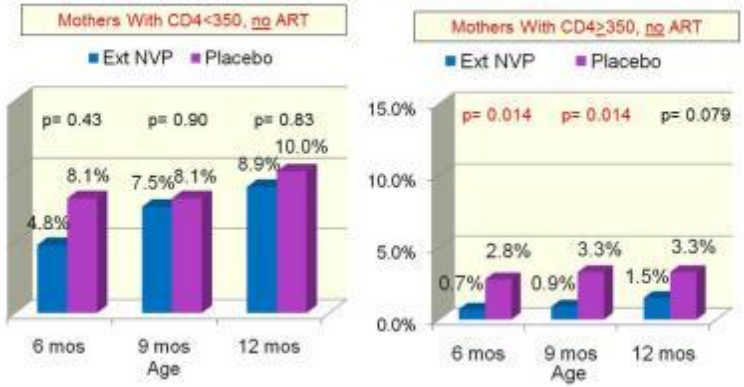
Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB

	% Postnatal Transmission (95% CI) after Age 6 Weeks					
	Age 6 mos		Age 9 mos		Age 12 mos	
	CD4 <350	CD4 ≥350	CD4 <350	CD4 ≥350	CD4 <350	CD4 ≥350
Extended NVP	4.8% (0.2-9.4)	**0.7%** (0-1.5)	7.5% (1.7-13.3)	**0.9%** (0-1.9)	8.9% (2.5-15.2)	**1.5%** (0.3-2.7)
Placebo	8.1% (1.3-14.8)	2.8% (1.3-4.4)	8.1% (1.3-14.8)	3.3% (1.7-4.9)	10.0% (2.4-17.6)	3.3% (1.7-4.9)
P Value	0.438	**0.014**	0.901	**0.014**	0.831	**0.079**

WHO Guidelines: CD4 <350: ART-Eligible for Own Health (ARV for treatment)
CD4 ≥350: ART-Ineligible (ARV use for prophylaxis only)

HPTN 046: HIV Infection in Infants of Mothers Not on HAART by CD4 count and Study Arm

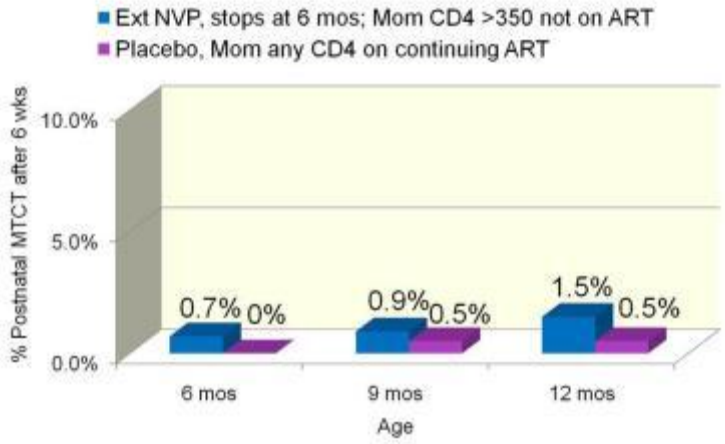
Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB



WHO Guidelines: CD4 <350: ART-Eligible for Own Health (ARV for treatment)
CD4 ≥350: ART-Ineligible (ARV use for prophylaxis only)

Cumulative Postnatal MTCT in Infants Uninfected at 6 Wks: Born to Mothers on Continued ART vs Receiving Ext NVP Stopped at 6 mos with Mother with CD4 >350

Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB



HPTN 046: Infant Mortality After Age 6 Weeks

Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB

	% Mortality (95% CI) after Age 6 Weeks in Infants by Study Arm		
	Age 6 mos	Age 9 mos	Age 12 mos
Extended NVP	1.2% (0.4-2.0)	2.2% (1.1-3.3)	3.1% (1.7-4.5)
Placebo	1.1% (0.3-1.8)	2.6% (1.5-3.8)	3.7% (2.3-5.2)
P Value	0.81	0.59	0.54

Most Infant Mortality Occurred After Age 6 Months (post-weaning)

HPTN 046: Safety

Coovadia H et al. 18th CROI, Boston, 2011 Abs 123LB

	Extended NVP N=758	Placebo N=761
Overall Adverse Events (AE)	83%	83%
AE probably or definitely related to study drug	12 infants (1.6%)	8 infants (1.1%)
Serious Adverse Events (SAE)*	19%	17%
SAE: Gr 3/4 Neutropenia	1 infant	2 infants
SAE: Gr 3/4 Increased ALT	1 infant	1 infant
SAE: Gr 3/4 Skin rash	0	0

* Most common SAEs: gastroenteritis (6%), malaria (5%), pneumonia (3%), sepsis (1%), with no difference between study arms

LPV/r Single Drug PMTCT During Pregnancy: PRIMEVA/ANRS 135, France

Tubiana R et al. 18th CROI, Boston, 2011 Abs. 125LB

- 105 women (PI-naïve except prior pregnancy) with RNA <30,000/ CD4 ≥350 randomized at 26 wks gestation 2:1 to:
  - LPV/r 400/100 BID alone
  - LPV/r 400/100 + AZT/3TC 300/150 BID
- All women got IP AZT and all infants got 4-6 wks AZT
- "Efficacy": defined as >75% with RNA<200 at 8 wk ARV

	LPV/r (n=69)	LPV/r+ZDV+3TC (N=36)	P
Baseline HIV RNA (median; c/mL)	2952	2928	NS
Baseline CD4 (median; cells/mm3)	525	523	NS
Previous ARVs	57%	36%	0.05
HIV-1 RNA<200 c/mL at 8 wks	88% (95%CI 78-95)	94% (95%CI 81-99)	0.18
Change ARV due to intolerance	1.4%	11.1%	0.046
HIV-1 RNA<50 c/mL at delivery	80% (95%CI 63-88)	97% (95%CI 86-100)	0.01
Infant HIV infection	0 (0%)	1 (2.8%)	NS

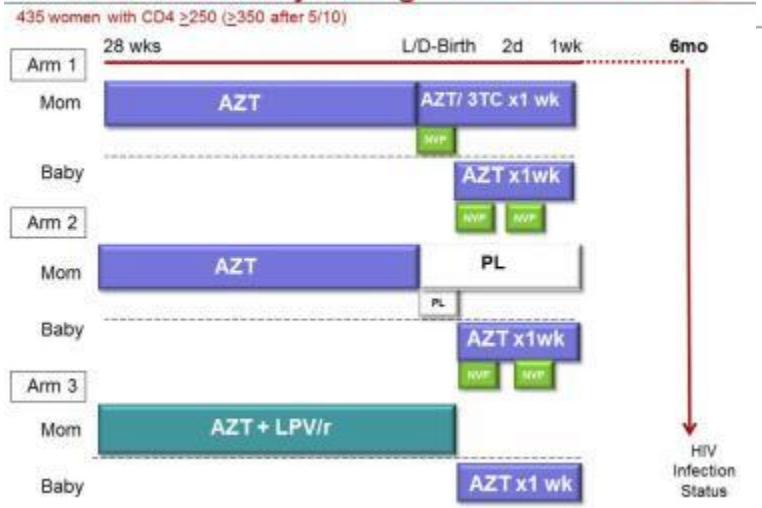
HPTN 046 Summary

- At age 6 months, extended NVP through 6 months compared to 6 weeks was more effective in preventing postpartum HIV infection.
- Reduction in postpartum infection with extended infant NVP was primarily seen among infants of mothers *not* on ART *and* with CD4 counts ≥350 cells/mm^3 (i.e., not meeting current WHO guidelines for treatment).
- These data support the benefits and safety of extended NVP for infants of mothers who do not yet require ART for their own health.

Conclusions: LPV/r Alone for PMTCT

- LPV/r alone achieved satisfactory viral efficacy after 8 weeks of ARV based on definition (75% with <200 c/mL) and had lower rates of intolerance than triple drugs.
- However, at delivery, significantly lower rate suppression to <50 with single-drug.
- MTCT was very low in both arms.
- Minimal transplacental passage of LPV/r raises concern regarding adequacy of pre-exposure prophylaxis (but all mothers got IP AZT which crosses placenta well).

PHPT-5 Study Design (Thailand, Formula Feeding)



PHPT-5: AZT + Maternal/Infant NVP, Infant NVP Only, or LPV/r for PMTCT, Thailand

Lallemant M et al. 18th CROI, Boston, 2011 Abs. 741

- 435 pregnant women had 430 live-born infants.
- Baseline characteristics similar between arms: median entry CD4 459 (368-578); HIV RNA 4.0 (3.4-4.4); entry gestation age 28.6 weeks (28.1-30.4).
- Study stopped early when Thailand guidelines changed to 3 drugs regardless of CD4. MTCT rates at that time:

Study Arm	MTCT at 6 Mos (ITT)	P Value	
AZT-NVP/NVP	3.6% (1.2-8.2%)	p=0.3	p=0.5
AZT-Placebo/NVP	1.6% (0.2-5.5%)		
AZT/LPV-r	1.4% (0.2-4.9%)		

- Factors independently associated with MTCT: duration of AP ZDV (aOR 1.8/week decrease); viral load at delivery (aOR 2.3 per log increase)

Pregnancy, ARV, and Pregnancy-Outcome Related Abstracts

Low Risk of MTCT Among Women on HAART Prior to Conception: ANRS French Perinatal Cohort

Tubiana R et al. 18th CROI, Boston, 2011 Abs.735

- ~1,900 HIV-infected women in ANRS cohort who took antepartum HAART and delivered live-born non-breastfeeding infants with known infant HIV status, 2000-2008

MTCT Rate According to Time HAART Initiation

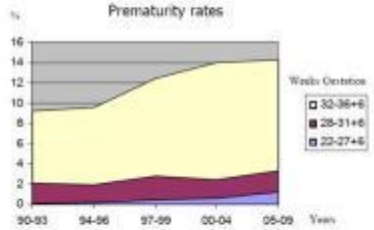
RNA close to delivery	Before conception	1st trimester <14 weeks	2nd trimester 14-27 weeks	3rd trimester >28 weeks	P value
Overall	0.5%	0.6%	1.2%	2.6%	< 0.01
<400 cp/mL	0.1%	0.4%	0.9%	1.8%	< 0.01
<50 cp/mL	0	0	0.5%	0.8%	0.045

Conclusion: Very low MTCT risk if HAART started before 14 wks, especially if suppressed HIV RNA; but what is optimal timing of initiation if start before 2nd trimester?

Increase in Prematurity between 1990 and 2009 in HIV-infected Women in France

Sibiude et al. 18th CROI, Boston, 2011 Abs. 743

- Preterm delivery increased significantly over time in French ANRS Perinatal Cohort (n=~11,500), from 9.2% in 1990-93 to 14.3% in 2005-09; sharp rise between 1997 and 2004:



- Among women who received ARV, preterm delivery risk was related to the *type of ARV received* and was *higher for women already on ARV at conception* compared to women starting ARV during pregnancy.

Increase in Prematurity between 1990 and 2009 in HIV-infected Women in France

Sibiude et al. 18th CROI, Boston, 2011 Abs. 743

Regimen/Timing	N	% with Preterm Delivery
NRTI mono-prophylaxis	2,904	9.6%
NRTI dual-prophylaxis	1,664	11.3%
HAART	6,738	14.7% aOR 1.7 (1.4-2.1)
ARVs started during pregnancy	7,413	11.2%
ARVs started before pregnancy	3,893	15.9% aOR 1.3 (1.1-1.6)

- HAART was associated with 1.7-fold increase prematurity
- ARVs before pregnancy associated with 1.3-fold increase prematurity
- In 1,253 women starting antepartum PI's, preterm rate higher with *RTV-boosted* than non-boosted PIs: 14.4% vs 9.1% (aHR = 2.0, 95% CI 1.1 -3.9) and also more metabolic/liver toxicity

Higher Rate of Premature Deliveries Among Mothers Randomized to LPV/r/ZDV/3TC vs. Trizivir: MmaBana Trial

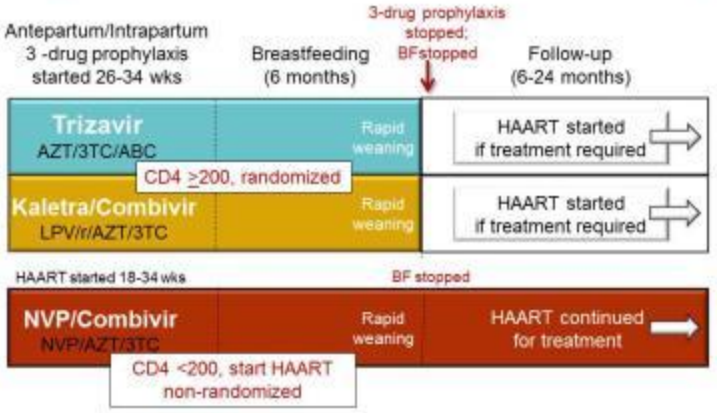
Powis K et al. 18th CROI, Boston, 2011 Abs. 746

- 530 pregnant ARV-naive HIV+ women with CD4>200 randomized to LPV/r/ZDV/3TC vs. Trizivir at 26-34 wks gestation (median 27.1 wks)
- Preterm delivery: spontaneous delivery live singleton at <37 wks
- LPV/r arm significantly higher preterm rate (21.4%) than TZV arm (11.8%) [p= 0.003], regardless of gestational age at ART start (including after adjustment for income, CD4, HIV RNA)
- Preterm (but not regimen) more infant resp. disease, hosp, and death

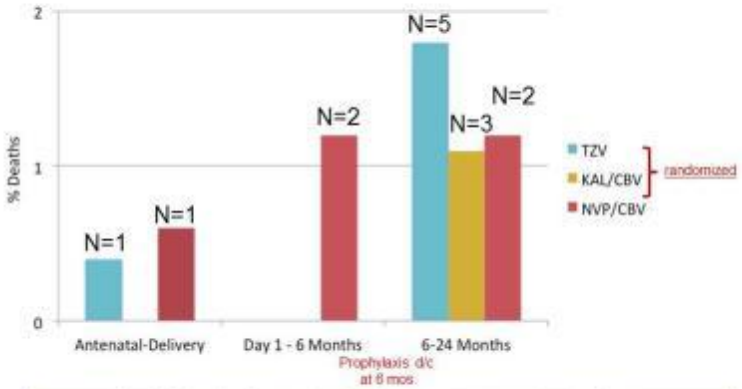
Infant Morbidity/Mortality to 6 Months by Preterm Status & ARV Regimen

Event	Preterm (N,%)	Term (N, %)	p-value[1]	TZV (N, %)	CBV-KAL (N, %)	p-value[1]
Resp Tract Infect	8 (9.1%)	9 (2.0%)	**0.003**	10 (3.8%)	7 (2.6%)	0.47
Diarrheal Disease	0 (NA)	12 (2.7%)	0.23	9 (3.4%)	3 (1.1%)	0.09
Meningitis	1 (1.1%)	4(0.9%)	1.0	5 (1.9%)	0 (NA)	**0.03**
Sepsis	4(4.6%)	11 (2.5%)	0.29	10 (3.8%)	5 (1.9%)	0.20
Hospitalization	20 (22.7%)	56 (12.7%)	**0.02**	40 (15.2%)	36 (13.5%)	0.62
Death	6 (6.8%)	6 (1.4%)	**0.002**	5 (1.9%)	7 (2.6%)	0.77

Mma Bana Study Design: Longer-Term Follow-Up Infant and Maternal Mortality

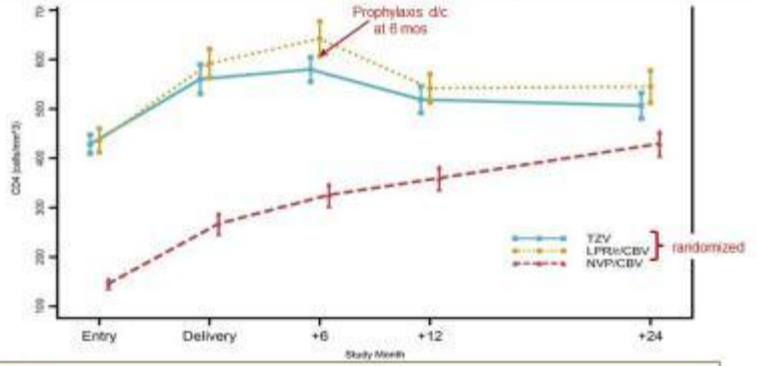


Mma Bana:
Maternal Mortality by Study Arm Through 24 Months
Shapiro RS et al. 18th CROI, Boston, MA, 2011 Abs. 747



➢8 of 9 deaths in randomized women occurred after 6 mos (after 3-drug prophylaxis stopped; 5 had not restarted ART after stopping) p=0.18 for overall deaths <6 mos vs >6 mos postpartum

Mma Bana:
CD4 Count by Study Arm and Time
Shapiro RS et al. 18th CROI, Boston, MA, 2011 Abs. 747



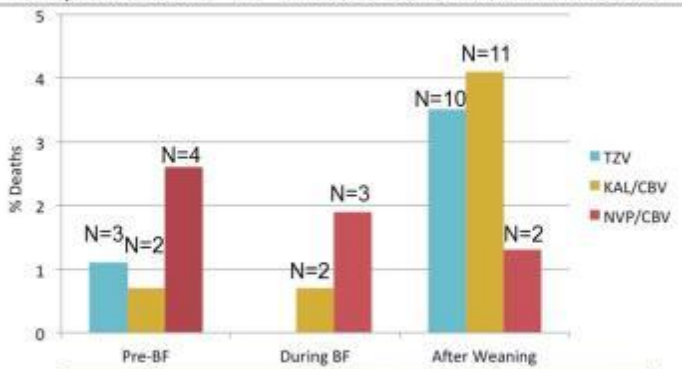
➢ Mean CD4 increased all women (15% randomized women restarted ART after stopping postpartum)
➢ For women with CD4 >250, CD4 increase more with LPV/r (+86) then TZV (+46) (p=0.04)

Mma Bana:
Maternal Outcomes
(ART Status, CD4 Change, Mortality) at 24 Months
Shapiro RS et al. 18th CROI, Boston, MA, 2011 Abs. 747

		Randomized, CD4 ≥200		CD4 <200
	Total (N=730)	AZT/3TC/LPV-r (N=285)	AZT/3TC/ABC (N=275)	AZT/3TC/NVP (N=170)
D/C 3 drugs ≤6 mo	75%	95%	97%	4%
Continue 3 drugs >6 mo for ART	25%	5%	3%	96%
Restart 3 drugs for ART	9%	11%	12%	-
Mean baseline CD4	366	429	436	146
Mean CD4△ at 24 mos	+134	+68	+98	+283
Maternal death	14 (1.9%)	6 (2.1%)	3 (1.1%)	5 (2.9%)

While maternal mortality low, 89% deaths in randomized arms occurred >6 months (after prophylaxis stopped)

Mma Bana:
Infant Mortality by Study Arm and Time
Shapiro RS et al. 18th CROI, Boston, MA, 2011 Abs. 747



➢ 23 of 28 (82%) infant deaths occurred after weaning
➢ Death rates during BF 1.76/100 pt-yrs vs within 6 mos of weaning 5.71/100 pt-yrs, p=0.02

Mma Bana:
Infant Outcomes (HIV Infection or Death) in Live-Born Infants at 24 Months

Shapiro RS et al. 18th CROI, Boston, MA, 2011 Abs. 747

		Randomized, CD4 ≥200		CD4 <200
Infant death/HIV through 24 mos	Total (N=709)	AZT/3TC/LPV-r (N=283)	AZT/3TC/ABC (N=270)	AZT/3TC/NVP (N=156)
Death	37 (5.2%)	13 (4.6%)	15 (5.6%)	9 (5.8%)
HIV+	8 (1.1%)	6 (2.1%)	1 (0.3%)	1 (0.6%)
Death or HIV+	43 (6.2%)	18 (6.4%)	16 (5.9%)	9 (5.8%)

High infant mortality despite low HIV transmission with weaning at age 6 months

5 deaths (0.7%) while BF vs 23 (3.2%) deaths post stop BF(14/23 <3 mos stop BF)

CD4 Decline in Women Receiving 3-Drug PMTCT Stopped Postpartum – MTCT-Plus Programs in 9 Countries

Ekouevi DK et al. 18th CROI, Boston, 2011 Abs 753

- Data from MTCT-Plus programs in 9 countries in Africa and Thailand in women not eligible for ART (CD4 >250) who received PMTCT stopped postpartum.
- Objective: describe CD4 decline in 1,583 HIV+ women not eligible for ART receiving 3-drug PMTCT during pregnancy & stopping PP vs other PMTCT regimens.
  - 33.6% received short-course AZT or AZT/3TC
  - 43.5% received sd-NVP
  - 10.9% received 3-drug ARV PMTCT
- 80.7% were WHO Stage 1 at enrollment; median CD4 469; median follow-up, 26.1 months.

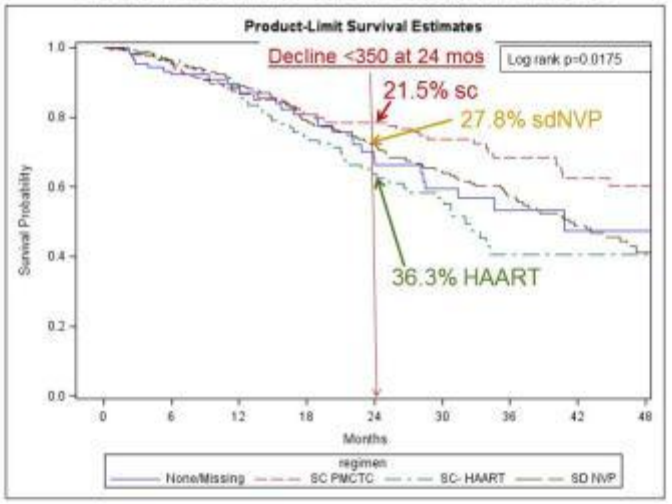
CD4 Decline in Women Receiving 3-Drug PMTCT Stopped Postpartum – MTCT-Plus Programs in 9 Countries

Ekouevi DK et al. 18th CROI, Boston, 2011 Abs 753

- Of women with CD4 >250 at enrollment:
  - 11.6% had CD4 decline to <200 by 24 mos PP
- Of women with CD4 >400 at enrollment:
  - 28.0% (24.6,31.6) had CD4 decline to <350 by 24 mos
    - Entry level associated with decline to <350:
      - If CD4 400-499, overall 47.8% (41.2, 54.8) declined
      - If CD4 >500, overall 18.3% (14.9, 54.8) declined
- CD4 decline was significantly associated with:
  - 3-drug PMTCT prophylaxis
  - Age 25-35 years
  - Enrollment CD4 count

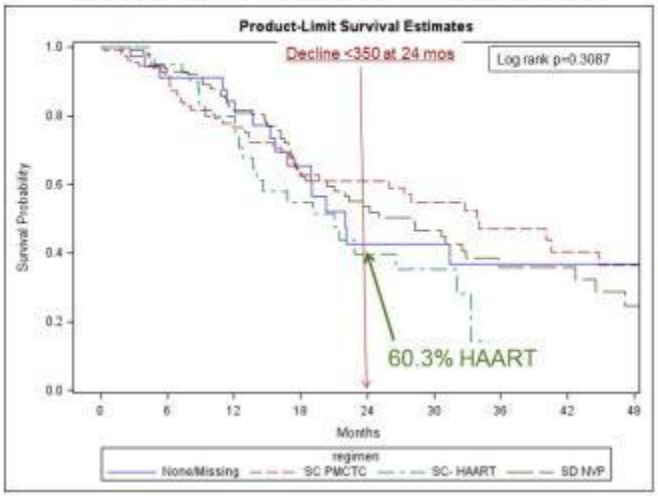
(K-M) Probability CD4 <350 by 24 Mos by PMTCT Regimen in1,027 HIV+ Pregnant Women with Baseline CD4 >400

Ekouevi DK et al. 18th CROI, Boston, 2011 Abs 753



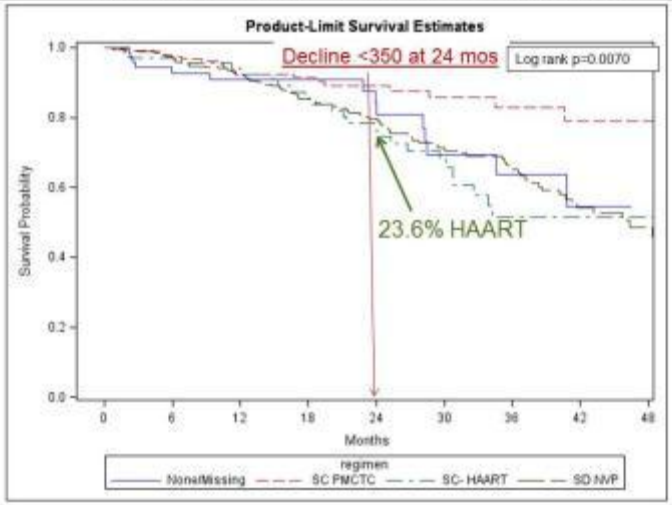
(K-M) Probability CD4 <350 by 24 Mos by PMTCT Regimen in 332 HIV+ Pregnant Women with Baseline CD4 400-499

Ekouevi DK et al. 18th CROI, Boston, 2011 Abs 753



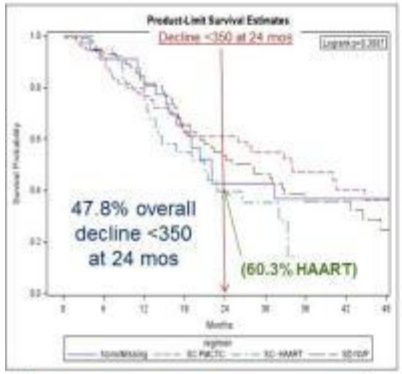
(K-M) Probability CD4 <350 by 24 Mos by PMTCT Regimen in 695 HIV+ Pregnant Women with Baseline CD4 ≥500

Ekouevi DK et al. 18th CROI, Boston, 2011 Abs 753

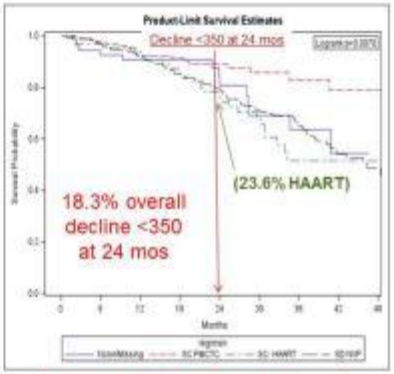


(K-M) Probability CD4 Decline <350 by 24 Mos PP in HIV+ Women by PMTCT Regimen and Baseline CD4 Count

Ekouevi DK et al. 18th CROI, Boston, 2011 Abs 753



Baseline CD4 400-499 (N=332)



Baseline CD4 ≥500 (N=695)

Multivariate Analysis: Variables, including PMTCT Regimen, Associated with Progression to CD4 <350 in HIV+ Pregnant Women with Enrollment CD4 >250

Ekouevi DK et al. 18th CROI, Boston, 2011 Abs 753

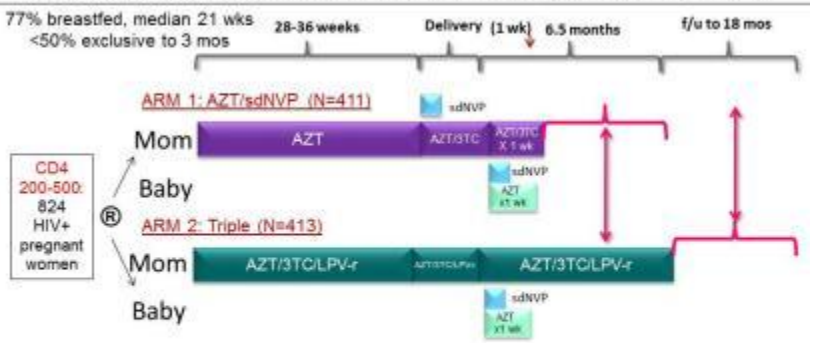
Variable		Adjusted HR	P Value
PMTCT regimen:	None/not documented	1.7 (1.1-2.6)	0.02
	sdNVP	1.7 (1.2-2.3)	0.001
	Short-course ARV	1.0	-
	Triple drugs	2.2 (1.5-3.3)	<0.0001
Age (yrs):	<25	1.0	-
	25-30	1.4 (1.1-1.9)	0.02
	31-35	1.6 (1.1-2.3)	0.01
	36-40	1.4 (0.9-2.2)	0.16
Enrollment CD4 (cells/uL):	400-499	1.0	-
	500-650	0.5 (0.4-0.7)	<0.0001
	>650	0.3 (0.2-0.4)	<0.0001
Enrollment WHO Stage:	Stage 1	1.0	-
	Stage 2	1.3 (0.9-1.8)	0.11
	Stage 3	1.6 (0.9-2.7)	0.09

Summary: CD4 Decline in Women Receiving 3-Drug PMTCT Stopping Postpartum

- Pregnant women with CD4 >400 receiving antepartum triple ARV PMTCT (stopped PP) had 2.2-fold increase in decline to CD4 <350 at 24 mos than those on other PMTCT regimens (36% triple ARV vs 22% AZT/sdNVP and 28% sdNVP).
- Regardless of PMTCT regimen, women with CD4 400-499 were at higher risk of CD4 decline than those with CD4 >500 (48% vs 18% respectively).
- CD4 decline was independently associated with triple ARV PMTCT, baseline CD4 and age 25-35 yrs.
- While needing confirmation, these data suggest pregnant women with baseline CD4 <500 would benefit from initiating lifelong ART.

Kesho Bora Study

Kesho Bora Study Group. XVIII IAS Conf, Vienna, July 2010 Abs ThLB B105

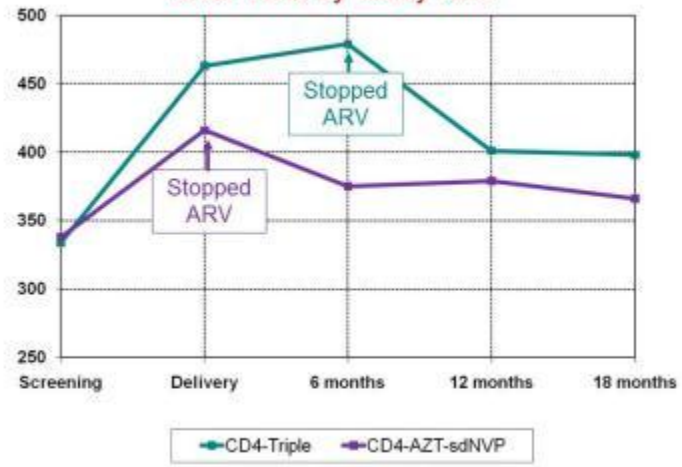


- Comparison of progression from delivery to 18 months – compares 6 mos postpartum drugs in triple ARV group to no postpartum drugs in AZT group
- Comparison from time of stopping triple ARV allows a comparison of progression in both groups off ARVs.

Kesho Bora: Mothers' Characteristics

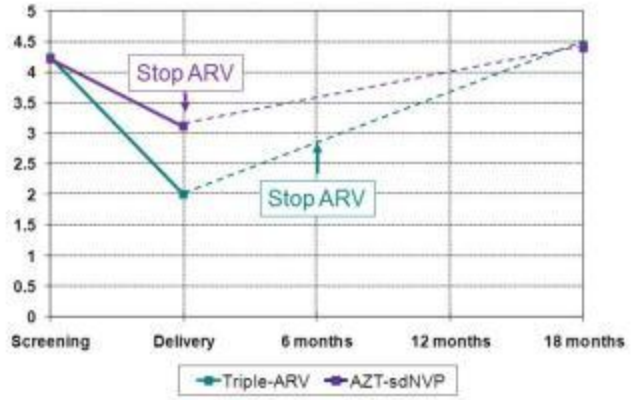
	Triple n=412	AZT/sdNVP n=412
Age (mean years)	27	27
Primigravid (%)	18.0	18.0
At least primary education (%)	85.4	84.7
Working (%)	32.8	27.7
Married/regular partner (%)	95.2	97.1
Enrollment CD4 (median cells/mm^3)	336	339
Enrollment viral load (log_{10} copies/ml)	4.23	4.21
Duration of ARV prophylaxis (median weeks)		
- before delivery	6.0	6.4
- after delivery	19.0	NA

Kesho Bora: Maternal Median CD4 Changes Over Time by Study Arm*



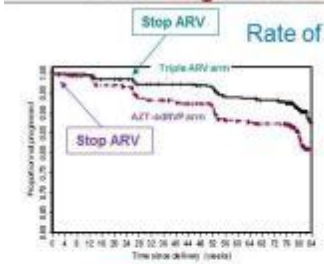
* Data censored at ART initiation

Kesho Bora: Median Maternal Log_{10} Viral Load Changes Over Time by Study Arm*



* Data censored at ART initiation

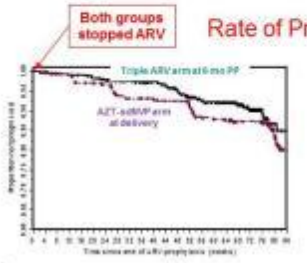
Kesho Bora: Rates of Maternal Progression to WHO Stage 4 or CD4<200 - All women (CD4 200-500)



Rate of Progression From Delivery

	6 months	12 months	18 months
AZT-sdNVP	(408) 6.4%	(362) 11.8%	(303) 19.6%
Triple-ARV	(405) 2.8%	(376) 6.1%	(332) 12.4%

P=0.003

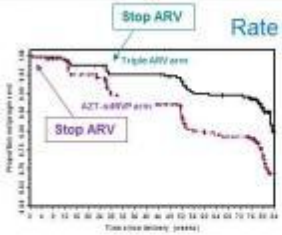


Rate of Progression From Stopping ARV Prophylaxis

	6 months	12 months	18 months
AZT-sdNVP	(408) 6.4%	(362) 11.8%	(303) 19.6%
Triple-ARV	(386) 2.6%	(358) 7.9%	(213) 14.7%

P=0.159

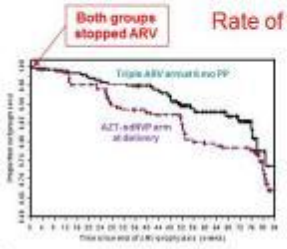
Kesho Bora: Rates of Maternal Progression to WHO Stage 4 or CD4<200 – Women with Entry CD4 200-349



Rate of Progression From Delivery

	6 months	12 months	18 months
AZT-sdNVP	(226) 10.6%	(192) 20.0%	(152) 32.4%
Triple-ARV	(226) 4.9%	(209) 10.1%	(186) 20.4%

P=0.002



Rate of Progression From Stopping ARV Prophylaxis

	6 months	12 months	18 months
AZT-sdNVP	(226) 10.6%	(192) 20.0%	(152) 32.4%
Triple-ARV	(217) 4.7%	(199) 12.0%	(107) 25.9%

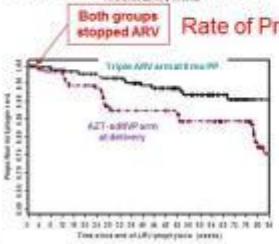
P=0.107

Kesho Bora: Rates of Maternal Progression to WHO Stage 3 or CD4<350- Women with Entry CD4 350-500

Rate of Progression From Delivery

	6 months	12 months	18 months
AZT-sdNVP	(182) 12.0%	(151) 15.7%	(129) 24.1%
Triple-ARV	(179) 2.9%	(162) 6.1%	(138) 10.4%

P=0.002



Rate of Progression From Stopping ARV Prophylaxis

	6 months	12 months	18 months
AZT-sdNVP	(182) 12.0%	(151) 15.7%	(129) 24.1%
Triple-ARV	(168) 3.7%	(152) 8.2%	(98) 9.5%

P=0.013

Kesho Bora vs MTCT-Plus

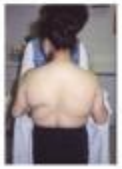
- Both studies showed baseline CD4 significantly affected time for CD4 progression after stopping ARV prophylaxis.
- But significantly different rates of decline to <350 after stopping triple ARV prophylaxis between studies:
  - Kesho Bora: if baseline CD4 350-500, only 10% progressed to <350 in 18 mos.
  - Ekouevi MTCT-Plus: if baseline CD4>400, 36% progressed to <350 in 24 mos (if CD4 400-499, 60% vs CD4 >500, 24% progressed)
- Using above baseline CD4 categories, in Kesho Bora, stopping triple ARV prophylaxis *may* have slower progression than AZT/sdNVP (10% vs 24% at 18 mos), while in Ekouevi/MTCT-Plus, triple ARV had more rapid progression than short AZT (36% vs 22%).

Kesho Bora vs MTCT-Plus

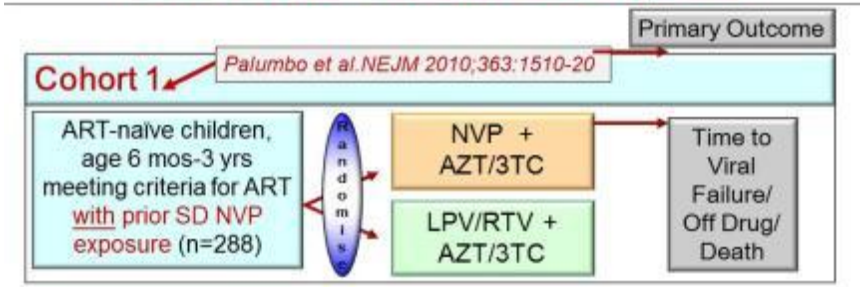
- In Kesho Bora, 26-32% women with baseline CD4 200-349 declined to <200 within 18 months of stopping ARV regardless of PMTCT regimen.
  - Reinforces WHO recommendations to start ART when CD4 <350
- MTCT-Plus data suggest the threshold to start life-long therapy in pregnant women might need to be even higher (CD4 <500).
- The safety of stopping triple ARV when used solely for PMTCT in women with high CD4 count requires specific evaluation (as in the P1077 PROMISE randomized trial).

Miscellaneous Pediatric Infection

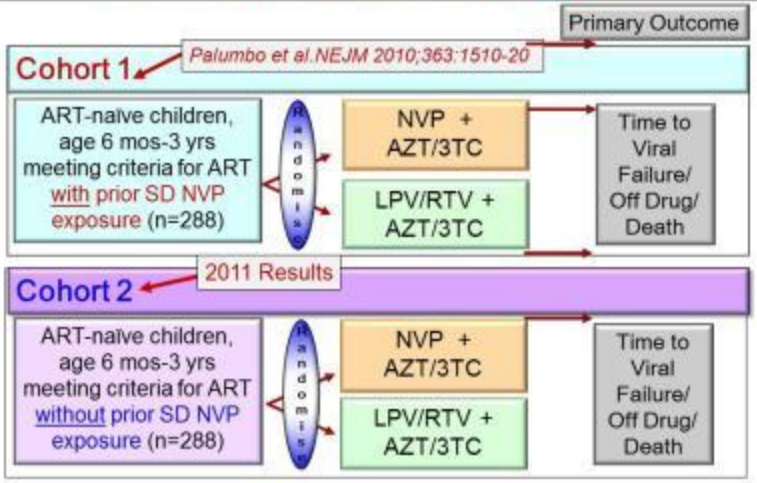
Treatment



P1060: NVP vs LPV-r HAART in HIV-Infected Infants With and Without sdNVP Exposure



P1060: NVP vs LPV-r HAART in HIV-Infected Infants With and Without sdNVP Exposure

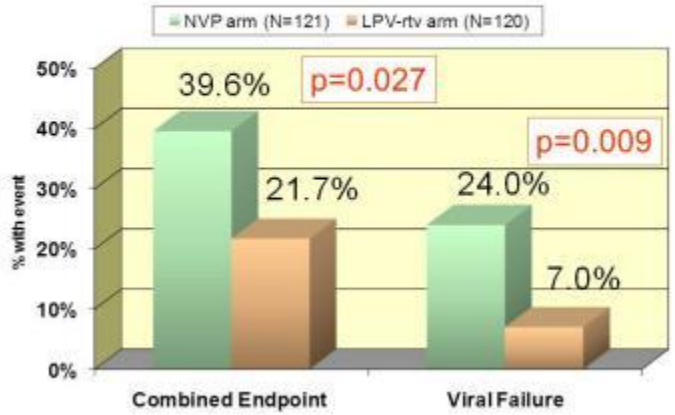


P1060: Comparison of Cohort 1 (NVP-Exposed) and Cohort 2 (Not NVP-Exposed) Characteristics

Characteristic	Cohort 1 (NVP-exp)	Cohort 2 (No NVP-exp)
Number	164	287
Entry Age	0.7 yrs	1.7 yrs
Median Entry CD4%	19-20%	15%
Median Entry HIV RNA	>750,000	536,000
Entry WHO stage III/IV	50-62%	
Median F/U	48 wks	72 wks

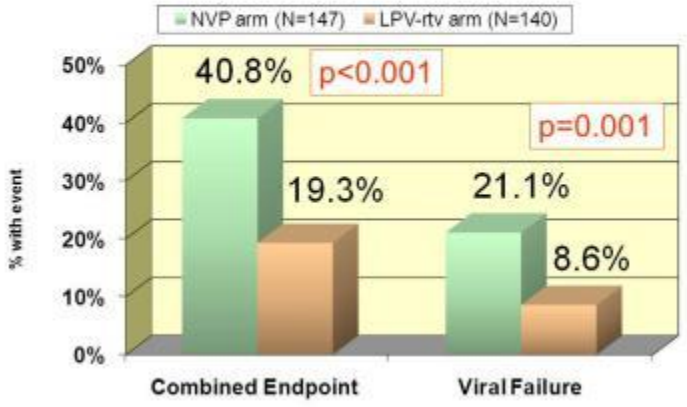
P1060 Cohort 1: Infants Infected Despite sdNVP Exposure have Higher Rates of Viral Failure, Off Study Drug, or Death with NVP than LPV-rtv Therapy

Palumbo P et al. NEJM 2010;363:1510-20



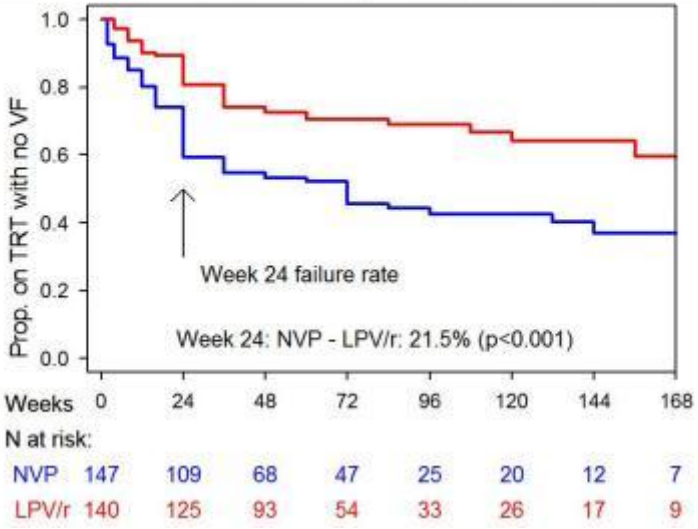
P1060 Cohort 2: Infants Without sdNVP Exposure Also have Higher Rates of Viral Failure, Off Study Drug, or Death with NVP than LPV-rtv Therapy

Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB



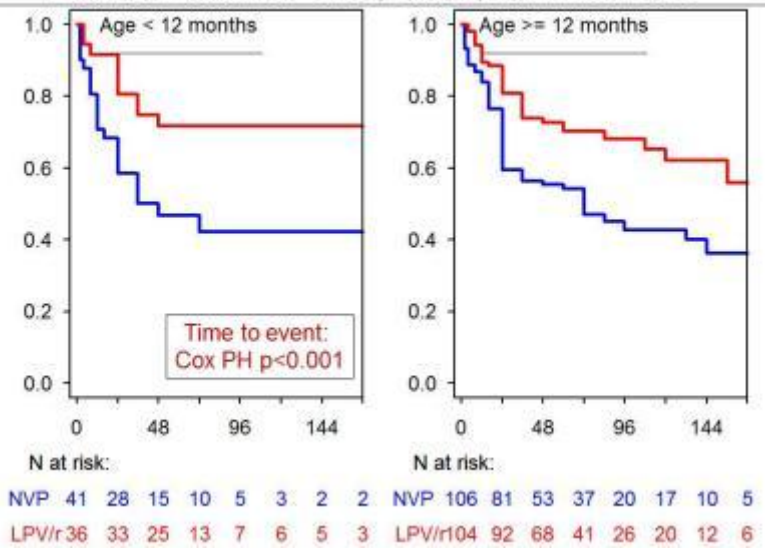
P1060 Cohort 2: Time to Off Study Treatment/Viral Failure

Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB



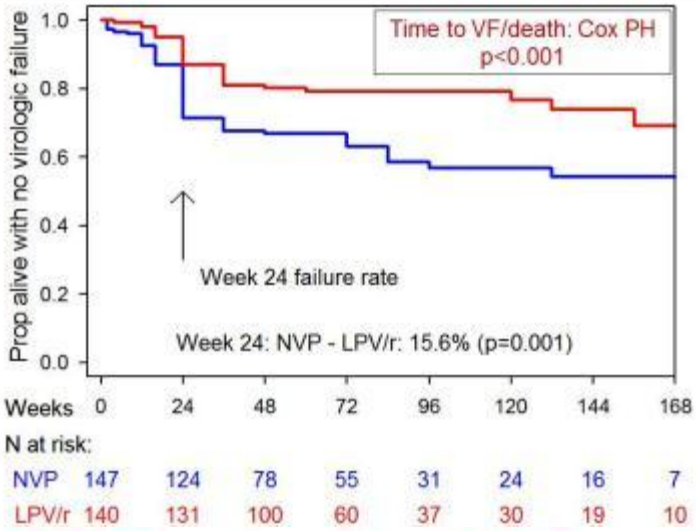
P1060 Cohort 2: Time to Off Study ARV/Viral Failure by Age

Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB



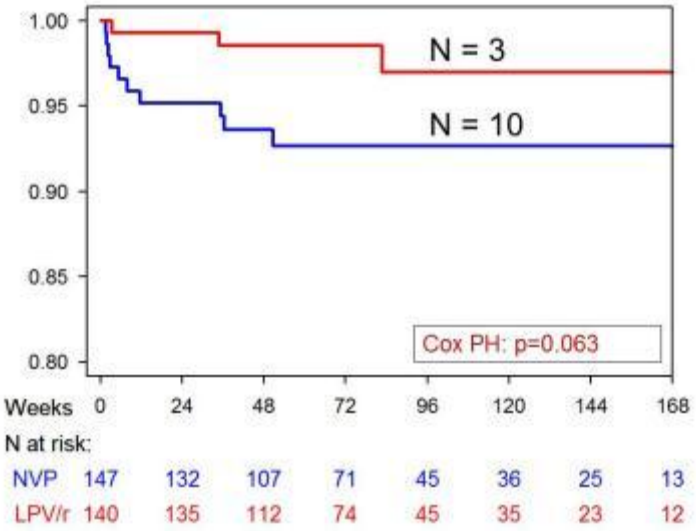
P1060 Cohort 2: Time to Viral Failure or Death

Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB



P1060 Cohort 2: Time to Death

Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB



P1060: Comparison of Cohort 1 (NVP-Exposed) and Cohort 2 (Not NVP-Exposed) Results

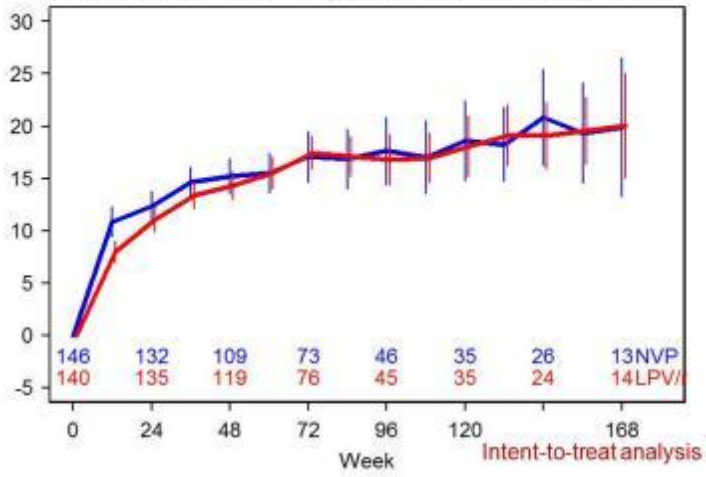
Cohort 1: Palumbo P et al.NEJM 2010;363:1510-20

Cohort 2: Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB

Result (at 24 wks)	Cohort 1 NVP	Cohort 2 NVP	Cohort 1 LPV/r	Cohort 2 LPV/r
Number	82	147	82	140
Primary endpoint	40%	40%	22%	19%
Viral failure/death	27%	29%	10%	12%
Viral failure	24%	20%	7%	4%
Protocol-Defined Toxicity	(N=2) 2%	(N=15) 10%	(N=1) 1%	(N=5) 4%
Death	N=4	N=10	N=3	N=3

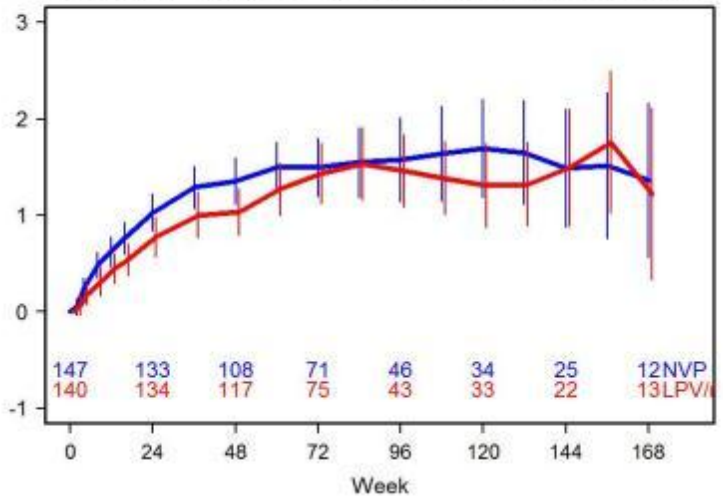
P1060 Cohort 2: Mean (95% CI) Change from Baseline: CD4%

Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB



P1060 Cohort 2: Mean (95% CI) Change from Baseline: Weight z-score (CDC)

Palumbo P et al. 18th CROI, Boston, 2011 Abs 129LB

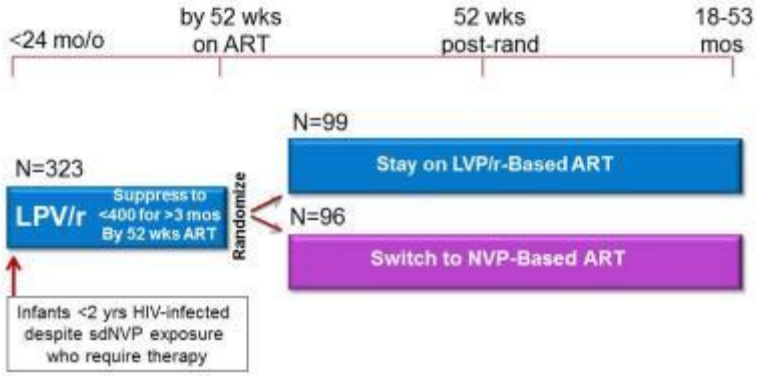


P1060 Cohort 2 Implications

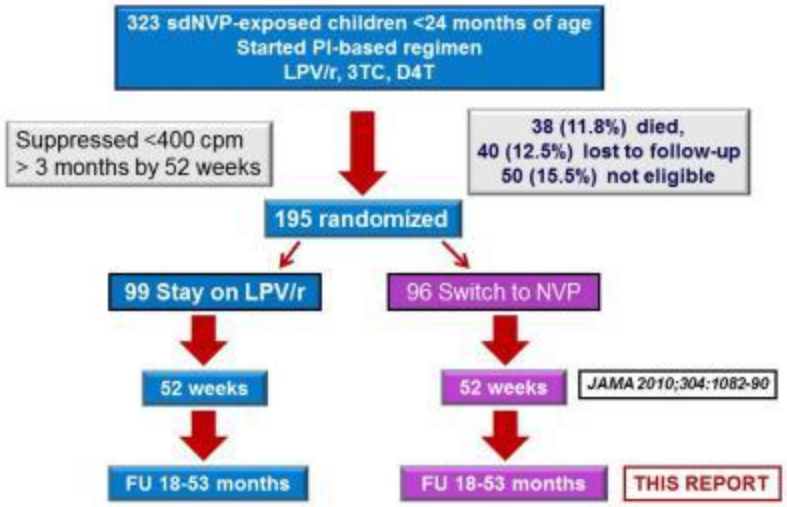
- Different results – OCTANE in women/P1060 in children
  - ART chronic HIV in women vs early pediatric HIV
  - High baseline viral load in infants
- CD4 and growth observations
  - ? Real phenomenon
  - ? Metabolic effects of ritonavir +/- PIs
- Issues with access to PI first line ARV therapy for infants exposed to sdNVP and based on Cohort 2 for all infants <3 years.
- Development of new 1st & 2nd line ARV options.
- WHO deliberations – NVP vs LPV/r for first line.

NEVEREST Study Design

Phase III, randomized study in sd-NVP exposed HIV-infected infants <2 yr successfully suppressed with LPV/r treatment and randomized to switch to NVP-based treatment or stay on LPV/r

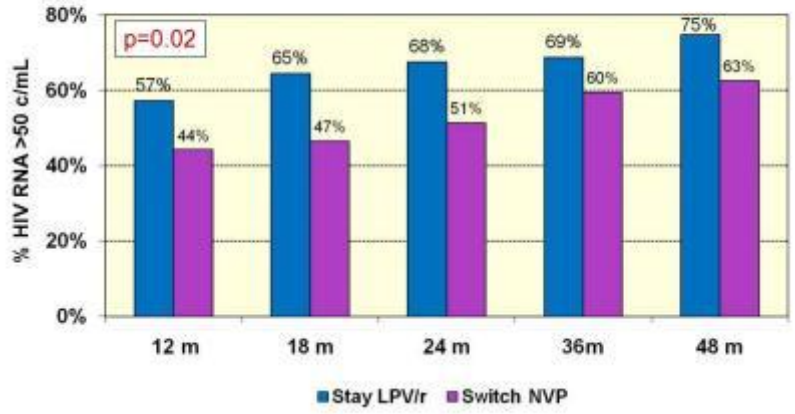


NEVEREST Enrollment



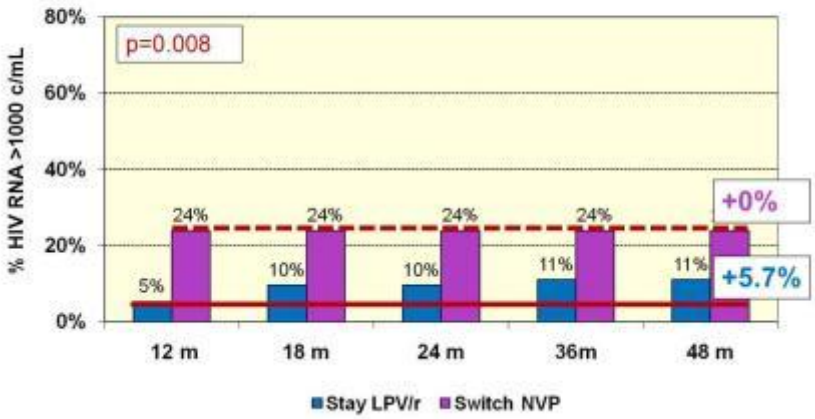
Post-Randomization HIV RNA > 50 copies/ml Probability *Ever Reaching* this Endpoint by Study Arm

Kuhn L et al. 18th CROI, Boston, MA, 2011, Abs.xxx



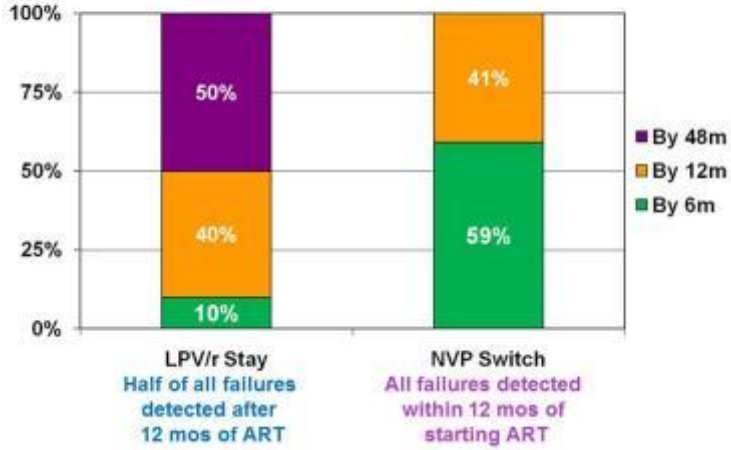
Post-Randomization Confirmed HIV RNA >1000 copies/ml Probability *Ever Reaching* this Endpoint by Study Arm

Kuhn L et al. 18th CROI, Boston, MA, 2011, Abs.xxx



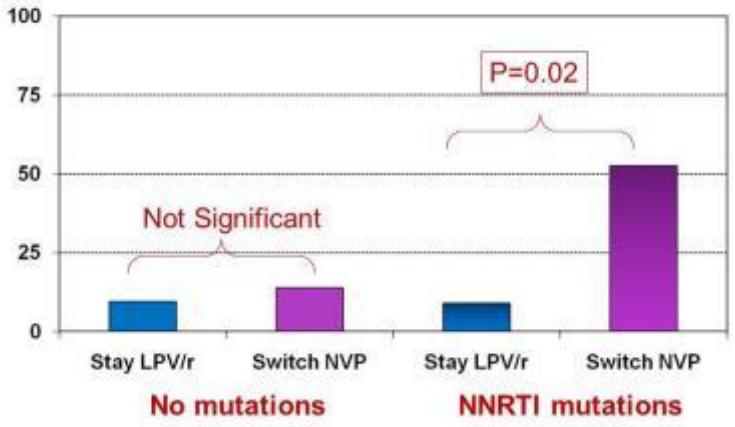
Percent of All "Failures" (Confirmed >1000cp/mL) Occurring by Different Time Points Post-Randomization

Kuhn L et al. 18th CROI, Boston, MA, 2011, Abs.xxx



Post-Randomization Confirmed HIV RNA > 1000 copies/ml by 48 Weeks by Study Arm and Pre-Treatment Drug Resistance Genotype

Kuhn L et al. 18th CROI, Boston, MA, 2011, Abs.xxx

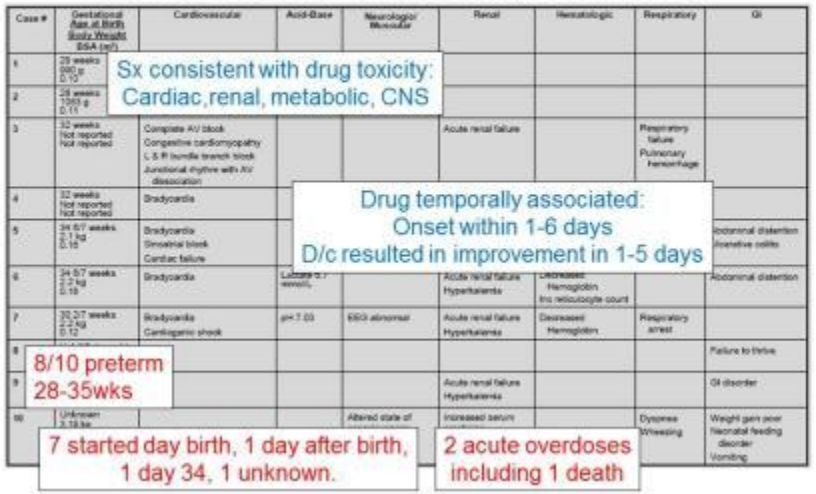


NEVEREST Long-Term Follow-Up Conclusions

- Viral load testing can identify all switch failures in need of return to PI regimens.
- Majority failures early (by 6 mos) and all by 12 mos.
- Switching to an NNRTI regimen in NVP-exposed children can be accomplished safely if adequate viral monitoring is in place.
- Pre-treatment screening for drug resistance can optimize the switch strategy to identify those who could benefit.
- Switch strategy allows drug resistance testing to be used in novel ways.

10 Serious Toxicity Reports of LPV/rtv in FDA AERS in Neonates/Preterm Infants

Boxwell D et al. 18th CROI, Boston, 2011 Abs. 708



Toxicity of LPV/rtv in Neonates/Preterm Infants

Boxwell D et al. 18th CROI, Boston, 2011 Abs. 708

- LPV/r oral solution: 42% ethanol (E),15.3% propylene glycol (P).
- Metabolism LPV by CYP3A, E and P initially by alcohol dehydrogenase (and E inhibits metabolism of P).
- Reduced hepatic metabolism, renal clearance neonates, especially preterms, can lead to accumulation of all.
- Toxicities:
  - Propylene glycol: cardiac arrhythmia, bradycardia, CNS depression, renal failure, lactic acidosis;
  - Ethanol: AV block, cardiac arrhythmia, CNS depression, lactic acidosis
  - LPV associated with heart block and QT prolongation

Toxicity of LPV/rtv in Neonates/Preterm Infants

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- Based on these data, LPV/r oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities.
- Label change: LPV/r oral solution should not be administered to neonates:
  - before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks;

  and
  - a postnatal age of at least 14 days has been attained.