P1060

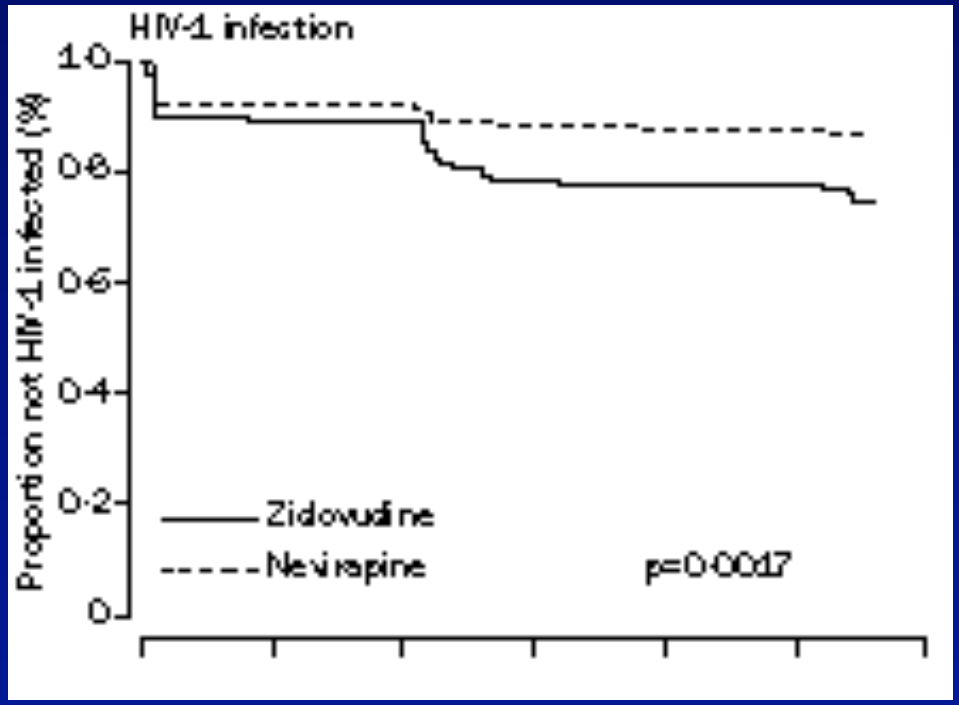
Paul Palumbo

IAS – Industry Liaison Forum

February 27, 2011

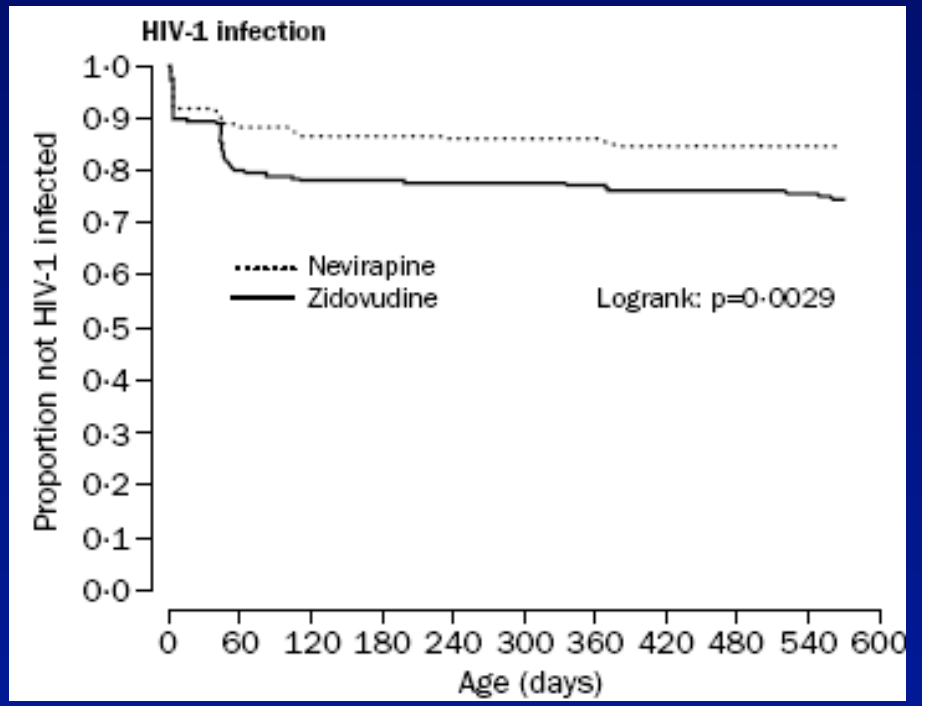
HIVNET 012

16 wk Data



Guay LA etal Lancet
1999; 354: 795

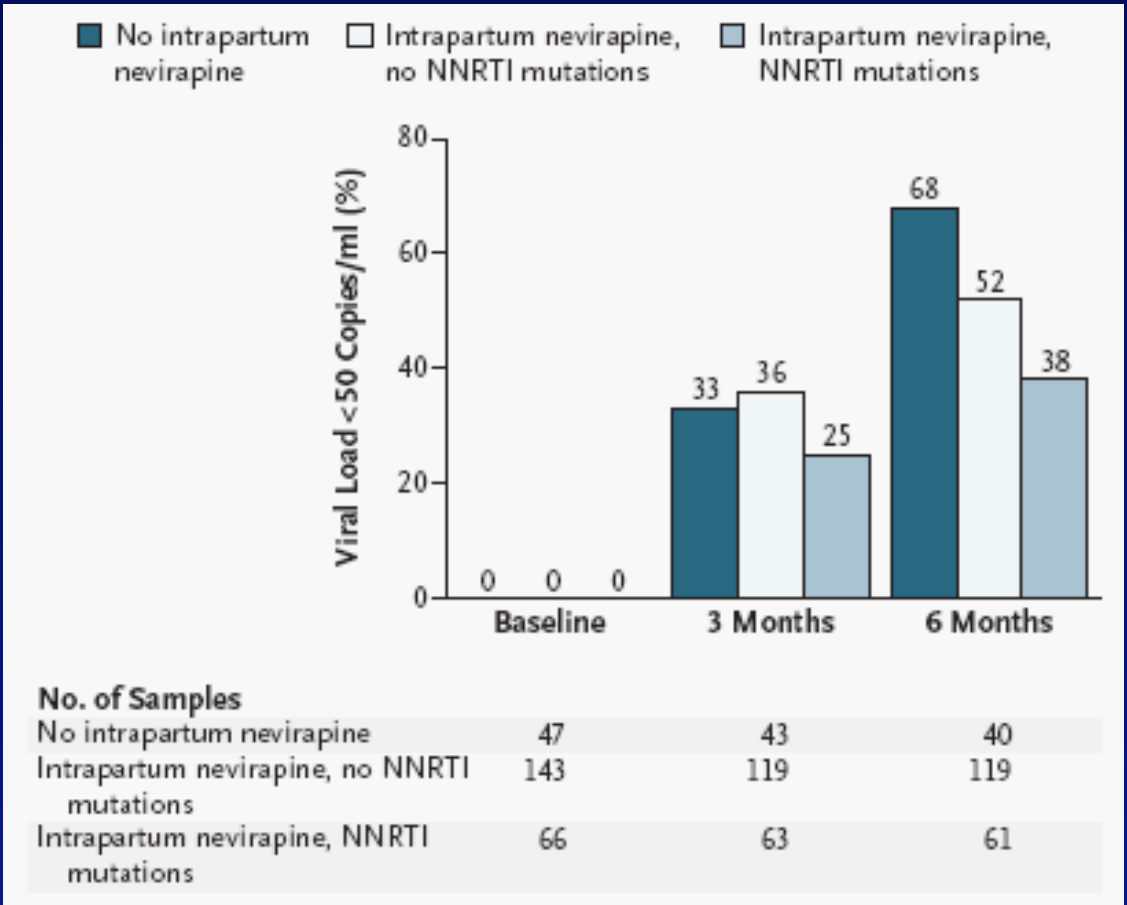
LTFU



Jackson JB et al
Lancet 2003; 362: 859

NVP Resistance post sdNVP

- Parade of reports began in 2000
- K103N and Y181C
- Mothers and Infants
- Persistence and Fading

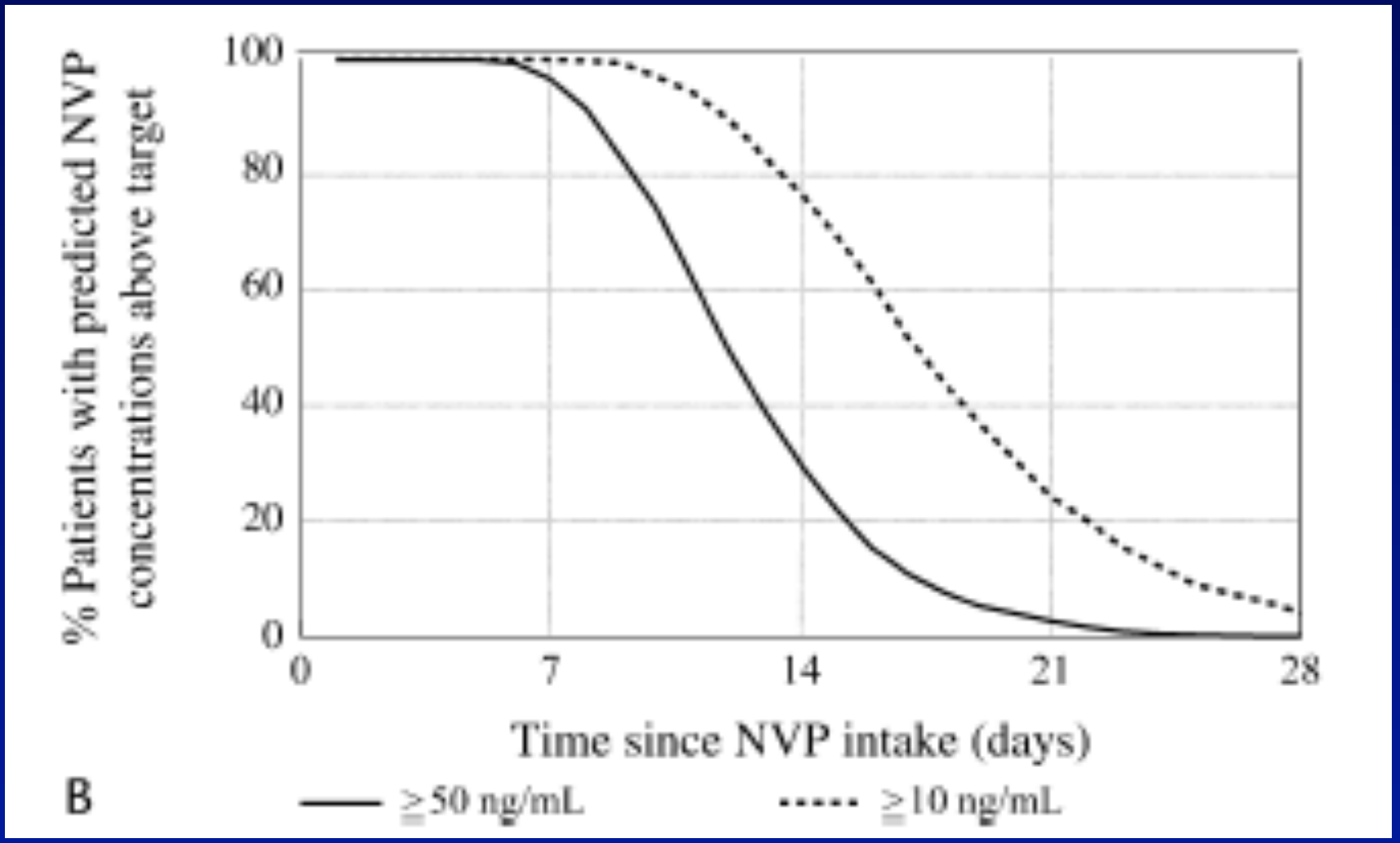


No. of Samples			
No intrapartum nevirapine	47	43	40
Intrapartum nevirapine, no NNRTI mutations	143	119	119
Intrapartum nevirapine, NNRTI mutations	66	63	61

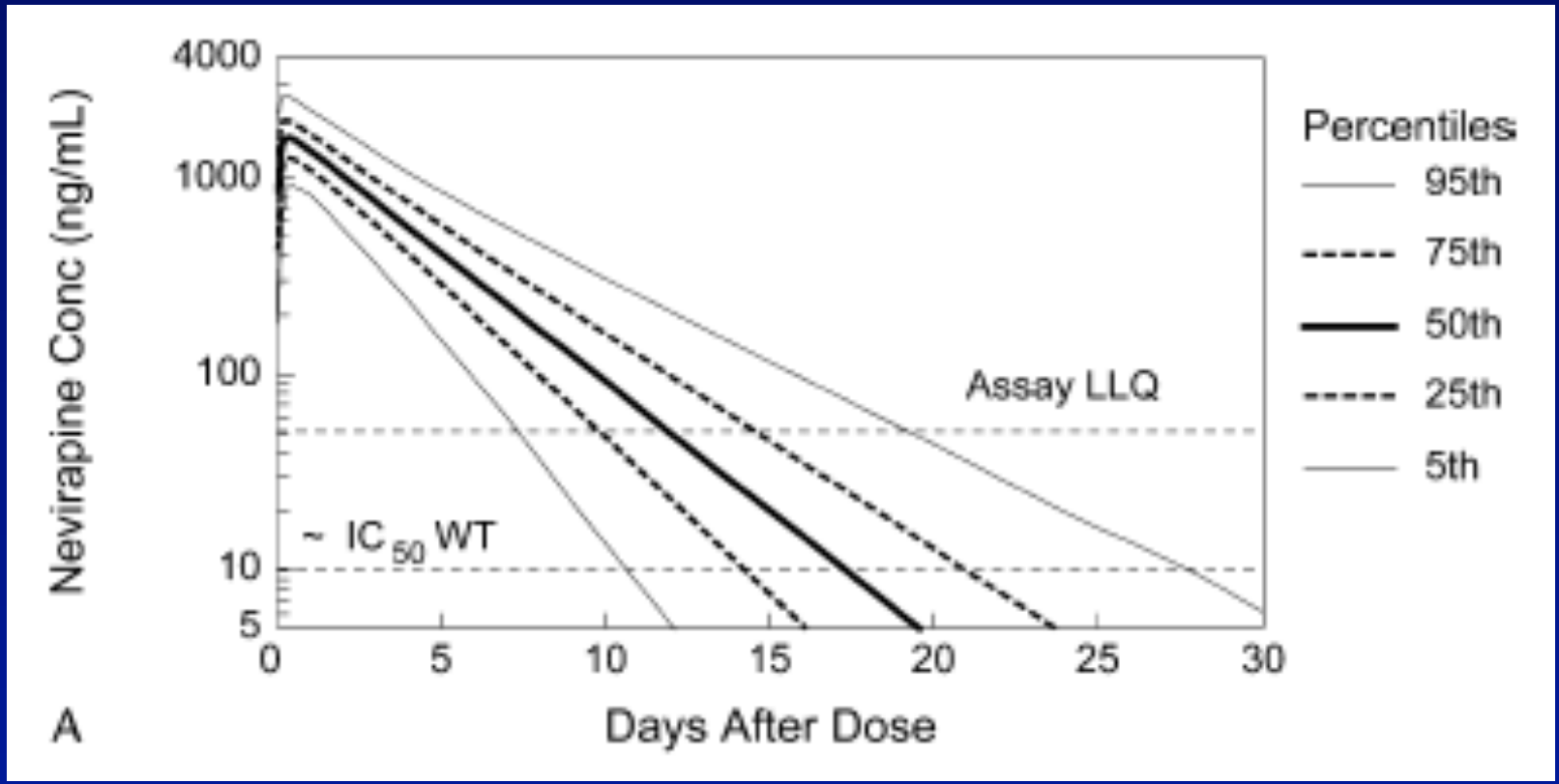
Jourdain G et al NEJM 2004;351:229 PHPT

MASHI Study/Botswana NEJM 2007; 356:135

Lockman S et al



Cressey TR et al; JAIDS 2005;38:283–288



Cressey TR et al; JAIDS 2005;38:283–288

Tail Theory

- AZT
- Combivir
- Truvada
- HAART

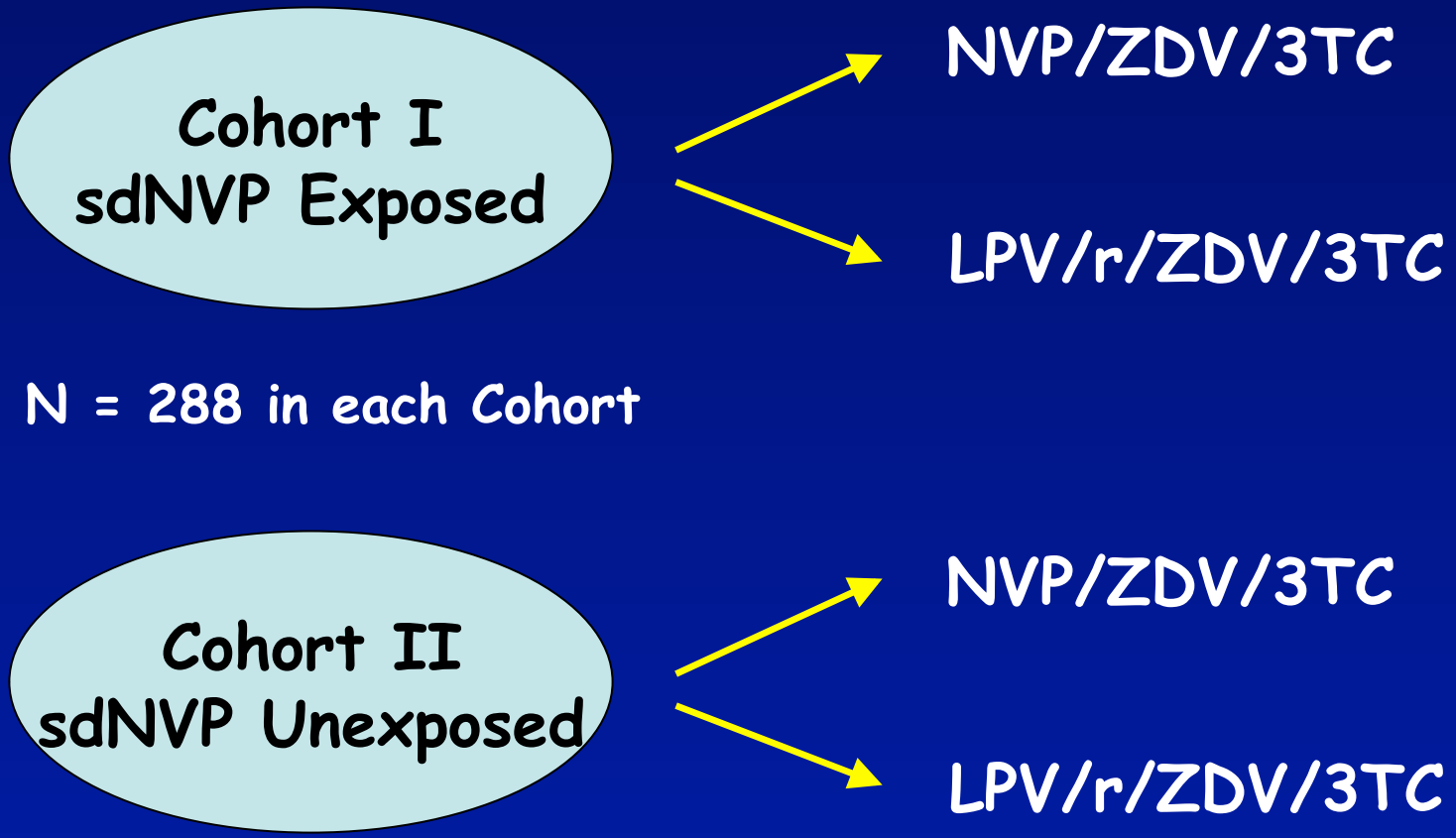
DAIDS Summit

- Prevention of resistance
  - P1032
  - A5207
- Treatment Strategies
  - A5208
  - P1060

IMPAACT P1060

Phase II parallel, randomized, clinical trials comparing the responses to initiation of NNRTI-based versus PI-based antiretroviral therapy in HIV-infected infants who have and have not previously received single dose nevirapine for prevention of mother-to-child transmission

Study Design



Study Design

- 6 months to 3 years of age
- Stratified by age (<12 months vs ≥ 12 months)
- Eligible for treatment by WHO criteria
- Baseline RNA > 5,000
- Cohort I
  - Documentation of sdNVP exposure
  - HIV diagnosis by 60 days of age (or)
  - Strict formula feeding (or)
  - AIDS-defining event by 60 days

Study Design – Primary Endpoint

- Primary 24 week <u>treatment failure</u> endpoint:
  - Virologic failure at ≤ 24 weeks OR
  - Permanent discontinuation of NVP or LPV/r at ≤24 weeks
  - Death
- Virologic failure defined as confirmed:
  - < 1 log10 decline from baseline after 12-24 weeks
  - >400 copies/ml at week 24
  - >4000 copies/ml after week 24
  - Death

Trial Issues

- Cohort I sdNVP Exposure
  - Mandate documented exposure in infant
- Breastfeeding
  - Infant diagnosis by 60 days of age
- TB and rifamycin drugs
  - Enrollment Ineligibility Criteria
  - Trial Endpoint
- Tails – no more than 1 week AZT

Trial Challenges – Clinical Environment

- CHER – all infants < 12 months eligible for treatment regardless of CD4
- WHO NVP dosing vs FDA-approved
- 7 kg minimum for Kaletra dosing
- Abbott RealTime HIV RNA
- WHO recommendations: PI-based therapy
- A5208 – Oct 2008 DSMB recs

Third Full DSMB Review
20April2009

Data published
NEJM 2010;363:1510

Accrual to Apr 20 2009: n=164

Site	N
Tygerberg, SA	61
Chris Hani HIV, SA	29
Durban, SA	28
Chris Hani, SA	18
Harare, Zimbabwe	13
Lusaka, Zambia	6
Kampala, Uganda	5
Lilongwe, Malawi	2
Moshi, Tanzania	2
Total (% < 12 months)	164 (75%)

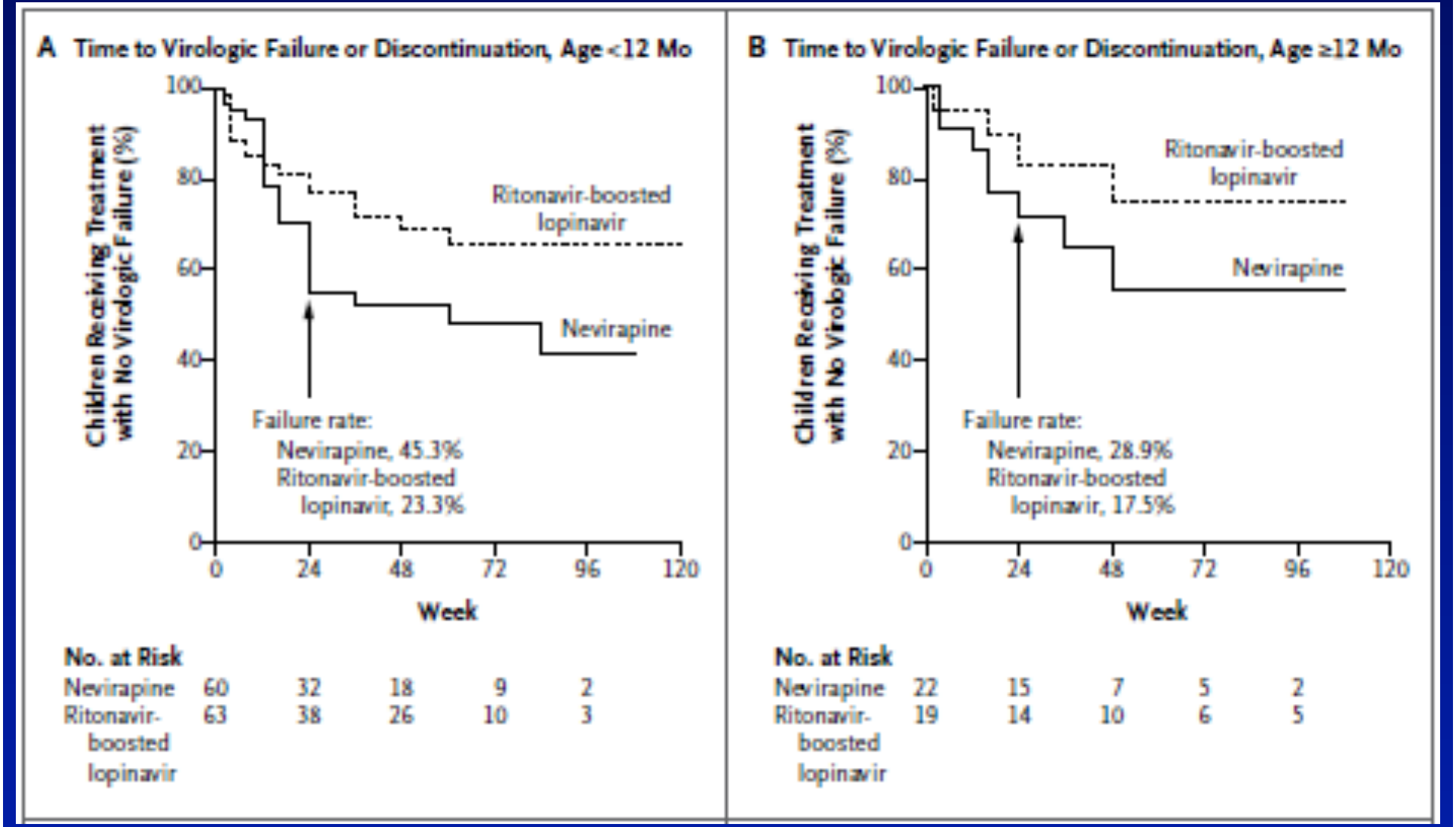
Median follow-up = 48 weeks [0 - 125]

Baseline Characteristics

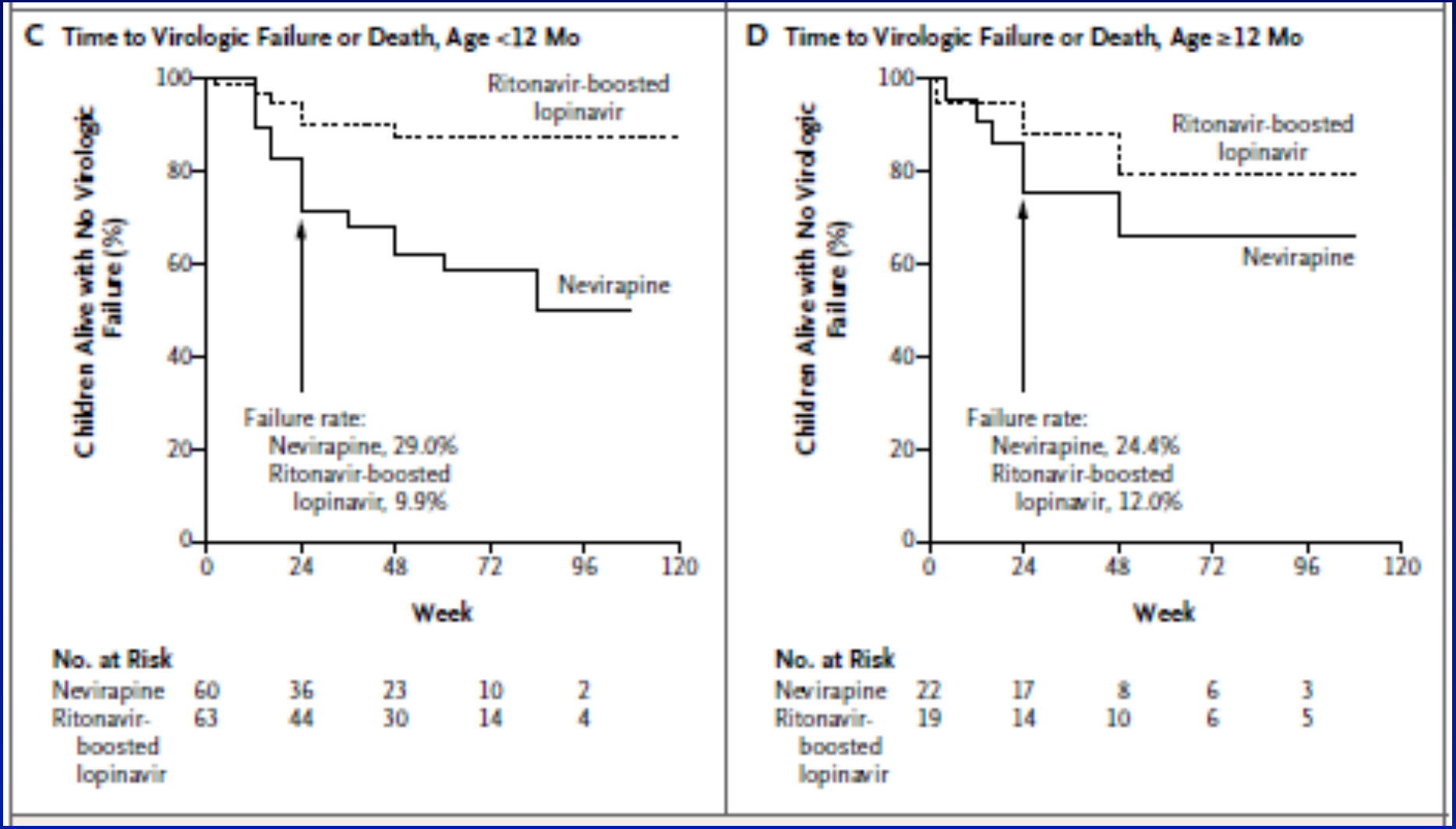
	Treatment	
Median	NVP (n=76)	LPV/r (n=77)
Age (yrs)	0.7	0.7
CD4%	19%	19%
CD4 count (cells/mm^3)	1240	1082
HIV-1 RNA (copies/ml)	>750K	>750K
WHO stage ≥ III (%)	62%	50%

73% had medical record verification of infant SD NVP exposure

Primary Endpoints at 24 Weeks



Secondary Endpoints



Rates of the Primary End Point and One Secondary End Point at 24 Weeks

End Point	Nevirapine Group		Ritonavir-Boosted Lopinavir Group		Between-Group Difference (95% CI)†	P Value
	Subjects	Rate of End Point	Subjects	Rate of End Point		
	no.	%	*no.*	%	*percentage points*	
Virologic failure or discontinuation of treatment						
Children <12 mo	60	45.3	63	23.3	22.0 (3.9 to 40.0)	0.02
Children ≥12 mo	22	28.9	19	17.5	11.4 (−15.3 to 38.0)	0.40
All children						
Unweighted analysis	82	40.2	82	21.9	18.3 (3.2 to 33.4)	0.02
Weighted analysis	82	39.6	82	21.7	18.6 (3.7 to 33.6)	0.02
Virologic failure or death						
Children <12 mo	60	29.0	63	9.9	19.1 (3.4 to 34.8)	0.02
Children ≥12 mo	22	24.4	19	12.0	12.3 (−12.1 to 36.8)	0.32
All children						
Unweighted analysis	82	27.4	82	10.4	17.1 (4.0 to 30.1)	0.01
Weighted analysis	82	27.4	82	10.4	17.1 (3.9 to 30.3)	0.01

Adverse Events - Deaths

NVP (4):
- Sepsis (2)
- Gastroenteritis
- Suspected pneumonia

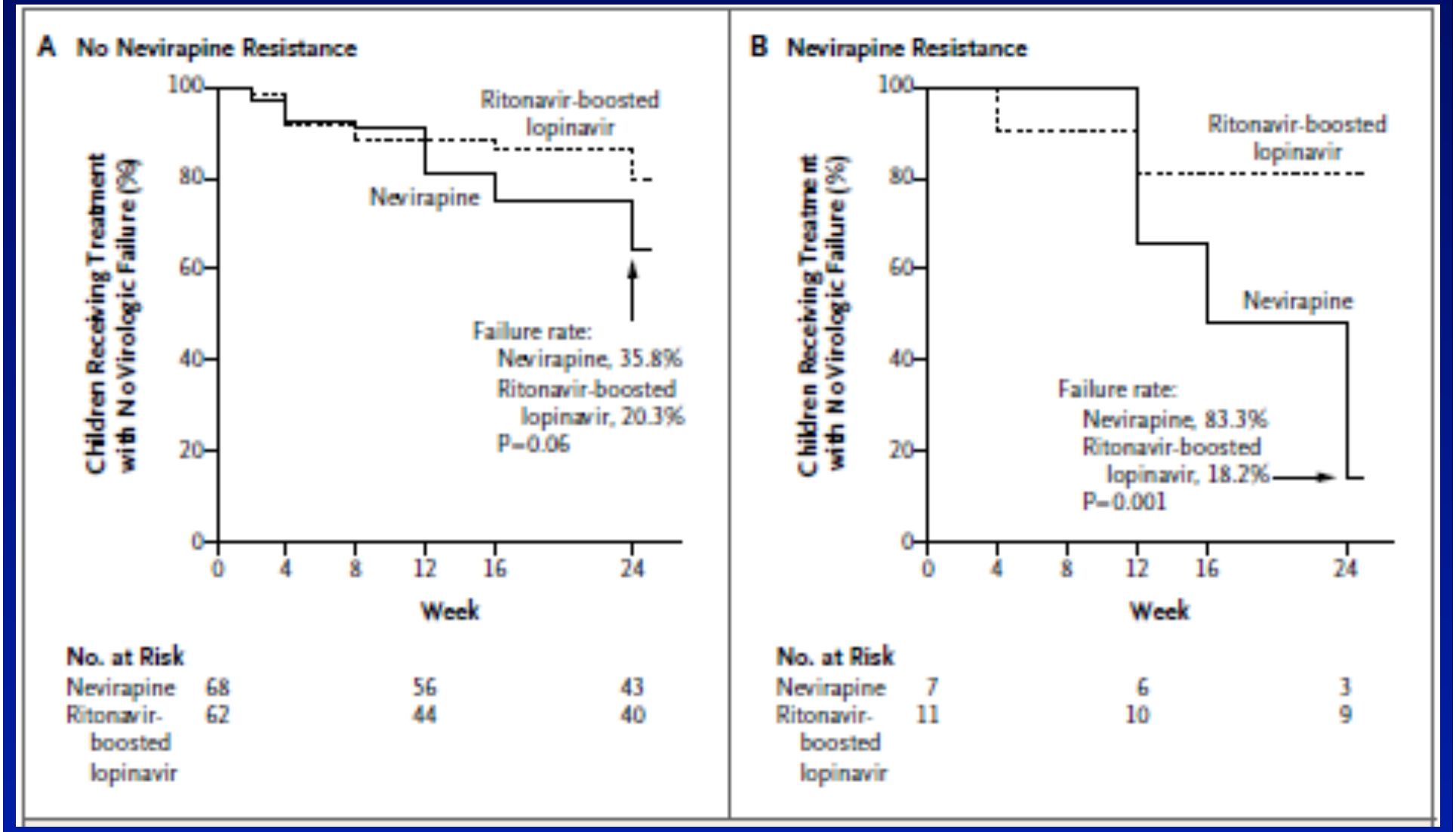
LPV/r (3):
- Pneumonia
- Burns
- Cardiac/respiratory arrest

None assessed by sites to be related to study treatment

Baseline NVP Resistance (standard assay)

- Available on 148/164
  - 18 (12%) NVP resistant (4 > 12 months)
- Y181C – 15; K103N - 3
- 141/148 (95%) HIV subtype C

Endpoints and Baseline NVP Resistance



Genotypic Resistance Data for 25/27 w VF

Treatment	Baseline resistance mutations	Failure NNRTI resistance Mutations	Failure NRTI resistance mutations	Week of Virologic Failure
NVP	None	None	None	24
	None	None	None	48
	None	None	None	12
	None[2]	None	M184V [FTC 3TC]	48
	K103N T215I [DLV EFV NVP (d4T) (AZT)]	K103N [DLV EFV NVP]	M184V T215I [(ABC) FTC 3TC]	16
	V118I Y181C [DLV (EFV) NVP]	K101E V118I Y181C [DLV EFV NVP]	M184V [FTC 3TC]	24
	A98G V118I Y181C [DLV (EFV) NVP]	A98G V118I Y181C [DLV (EFV) NVP]	D67N M184V [FTC 3TC]	12
	T69N L74V Y181C [DLV (EFV) NVP (ABC) ddI]	V108I Y181C [DLV (EFV) NVP]	T69N K70R M184V K219E [FTC 3TC]	24
	None	Y181C [DLV (EFV) NVP]	None	12
	None	K103N Y181C [DLV EFV NVP]	M184V [FTC 3TC]	24
	None	K101E G190A [(DLV) EFV NVP]	M184V [FTC 3TC]	16

	None	K101E G190A [(DLV) EFV NVP]	D67N T69N K70R M184V [FTC 3TC]	48
	None	K101E G190A [(DLV) EFV NVP]	M184V [FTC 3TC]	24
	None	K103N [DLV EFV NVP]	M184V [FTC 3TC]	36
	None	K103N [DLV EFV NVP]	M184V [FTC 3TC]	24
	None	Y181C [DLV (EFV) NVP]	A62V M184V [FTC 3TC]	16
	None	K103N [DLV EFV NVP]	M184V [FTC 3TC]	24
	V118I M184V [FTC 3TC]	K103N V118I Y188H Y188L [DLV EFV NVP]	M184V [FTC 3TC]	12
	T69N L74V [(ABC) ddI]	(A98G) Y181C [DLV (EFV) NVP]	K70R L74V M184V [ABC ddI FTC 3TC]	84
	Unable to genotype	K103N Y181C [DLV EFV NVP]	M184V [FTC 3TC]	16

4/20: baseline and VF NNRTI resistance
4/20: WT at baseline and VF
12/20: new NNRTI resistance at baseline

6.1.1 Infants

1.For infants not exposed to ARVs:

NVP + 2 NRTIs.

(Strong recommendation, moderate quality of evidence)

2. For infants exposed to maternal or infant NVP/other NNRTIs:

LPV/r + 2 NRTIs.

(Strong recommendation, moderate quality of evidence)

3. For infants w unknown ARV exposure:

NVP + 2 NRTIs.

(Conditional recommendation, low quality of evidence)

WHO 2010

6.1.2 Children

4. For children 12 - 24 months of age exposed to maternal or infant NVP/other NNRTIs:

LPV/r + 2 NRTIs

(Conditional recommendation, low quality of evidence)

5. For children 12 - 24 months of age, not exposed to NNRTIs:

NVP + 2 NRTIs.

(Strong recommendation, moderate quality of evidence)

6. For children > 24 months and < 3 years of age:

NVP + 2 NRTIs.

(Strong recommendation, moderate quality of evidence)

WHO 2010

Implications

- Next generation strategies for pMTCT
  - ARV tails
  - Maternal HAART
- Creative access to PI first line ARV therapy for infants exposed to sdNVP
- Concerns about second line therapy options
  - role for new agents [first & second line]
  - NEVEREST: ?return to NNRTI after PI
- Prioritization of resources for mother-infant pairs

P1060 Team Members

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- Deborah Persaud
- Charlotte Hobbs
- Jen Gardella/Beth Sheeran/Kim Hudgens
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- Emily Barr/Joan Coetzee
- Tamara Kuryla
- Laura Dooley/James Tutko/Don Decker
- Lauren Petrella/Carolyn Conner - Boehringer-Ingelheim
- Marisol Martinez – Abbott
- Edde Loeliger/Elke Loschel; Navdeep Thoofer/Wendy Snowden-GlaxoSmithKline

- Mark Cotton – Tygerburg
- Avy Violari – PHRU
- Tammy Meyers – Chris Hani
- Raziya Bobat – Durban
- Mutsawashe Bwakura-Dangarembizi – Harare
- Philippa Musoke/Linda Barlow – Kampala
- Ben Chi – Lusaka
- Portia Kamthunzi - Lilongwe
- Werner Schimana – Moshi
- Gowri Sastry – Pune
- George Kafulafula/Taha Taha - Blantyre

The families and their infants/toddlers

Adverse Events (cont.)

New event ≥ grade 3	NVP (n=76)	LPV/r (n=77)	Total (n=153)
Hemoglobin	1	2	3
Cholesterol	0	0	0
ANC	13	10	23
SGOT	2	1	3
SGPT	3	3	6
Potassium	1	0	1
Any labs	17	14	31
Any signs/symp	6	4	10