

---

# Summary of Evidence

## What ART to start in infants

Martina Penazzato  
ATC HIV/AIDS Department  
WHO Geneva

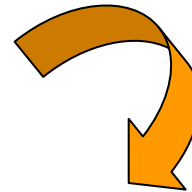
---

---

# Key Factors

➤ Safety

➤ Efficacy



ART Resistance

---

---

# Search Strategy

- Medline
- Embase
- BMJ Clinical Evidence
- The Cochrane Library
- Trip Database
- SUM search
- Bandolier
- Institute for Clinical Systems Improvement
- CROI 2005-2008 Abstract book
- IAS conferences 2005-2007 Abstract book

**Pediatric or Children or Infants**

**HIV infection**

**Antiretroviral treatment**

**Highly active antiretroviral  
therapy**

**Drug name**

**Found:** 453 clinical trials, 9 meta-analysis, 152 RCT,  
328 review, 257 multicenter studies

**Of interest: 70**

---

---

# Studies- Inclusion Criteria

- ✓ Infant subjects
  - ✓ Infants well represented
  - ✓ Outcomes stratified according to age
  - ✓ Early antiretroviral treatment
  - ✓ Specified ART regimen use
    - one regimen studies
    - cohort studies giving NVP vs PI comparison (triple nukes not included)
-

---

# References

- **Chadwick EG**, Capparelli, EV, Yogev K, Pinto J, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS* 2008, 22:249-55
  - **Chadwick EG**, Rodman JH, Britto P, Powell C, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis Journal* 2005; 24: 793-800
  - **Luzuriaga K**, McManus M, Mofenson L, Britto P, Graham B, Sullivan J. A trial of three antiretroviral regimens in HIV-1–infected children. *N Engl J Med* 2004; 350: 2471-80
  - **Faye A**, Le Chenadec J, Dollfus C, Thuret I, et al. Early versus deferred antiretroviral multidrug therapy in infants infected with HIV Type 1. *Clin Infect Dis* 2004; 39: 1692-1698
  - **Pediatric European Network for Treatment of AIDS (PENTA)**. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS*. 2004; 18:237-245
  - **Patel K**, Hernán MA, Williams PL, Seeger JD, McIntosh K, Van Dyke RB, Seage GR 3rd; Pediatric AIDS Clinical Trials Group 219/219C Study Team. Long-term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: a 10-year follow-up study. *Clin Infect Dis*. 2008 Feb 15;46(4):507-15.Bracher
  - **Abrams EJ**, Wiener J, Carter R, Kuhn L, Palumbo P, Nesheim S, Lee F, Vink P, Bulterys M; Perinatal AIDS Collaborative Transmission Study (PACTS) Group. Maternal health factors and early pediatric antiretroviral therapy influence the rate of perinatal HIV-1 disease progression in children. *AIDS*. 2003 Apr 11;17(6):867-77
  - **Berk D**, Falkovitz-Halpern MS, Hill DW, Albin C, et al. temporal trends in early clinical manifestations of perinatal HIV infection in a population-based cohort .*JAMA*. 2005; 293:2221-2231.
  - **Rouet F**, Fassinou P, Inwoley A, et al. Long-term survival and immuno-virological response of African HIV-1-infected children to highly active antiretroviral therapy regimens. *AIDS* 2006;20:2315-9.
  - **Violari A**, Cotton M, Gibb D. et al. on behalf of the CHER Study Team. Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) StudySpecial session: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Abstract no. WESS103" .Updated data still unpublished.
  - **Prendergast A**, Mphatswe W, Tudor-Williams G et al. Early immunological suppression with three-class antiretroviral therapy in HIV-infected African infants. (In Press)
  - **Eley B**, Davies M-A, Apolles P, et al. Antiretroviral treatment for children. *S Afr Med J* 2006;96 (9):988-93.
  - **Lockman S**, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 2007 Jan 11;356(2):135-47
  - **Kuhn** Personal communication, Neverest 2.
  - **Capparelli E**, Pinto J, Robbins B et al.Lopinavir Pharmacokinetic Maturational Changes and Variability in HIV-infected Infants Beginning Kaletra Therapy at <6 Weeks of Age . *CROI* 2008
-

# Outcomes

What to start in Infants		
Outcomes	Relative importance (rank 1→9 most critical)	Comments
→ Mortality (1 <sup>st</sup> year)	9	Critical
→ Mortality (5 years)	9	Critical
→ Severe/LT events	8	Critical
→ Major Adverse Events	8	Critical
→ Disease progression (clinical definition)	7	Critical
→ Detectable viral load	7	Critical
Adherence	6	
Drug Resistance	6	
CD4	6	
WAZ/HAZ	5	
Switch rate	5	

# Ranking the evidence...

<b>Comparison: NVP based VS PI based REGIMEN for EARLY ANTIRETROVIRAL TREATMENT IN INFANTS (&lt;=11 MONTHS)</b>							
<b>Outcome: EARLY MORTALITY (&lt;1<sup>ST</sup> YEAR)</b>							
<b>Population group: HIV INFECTED INFANTS (&lt;=11 MONTHS)</b>							
<b>No of studies</b>	<b>Design</b>	<b>Limitations</b>	<b>Consistency</b>	<b>Directness or generalisability</b>	<b>Imprecise or sparse data</b>	<b>Other factors</b>	<b>QUALITY RANK</b>
<b>Outcome: LATE MORTALITY (&lt;5<sup>TH</sup> YEAR)</b>							
<b>Outcome: VIRAL SUPPRESSION</b>							
<b>Outcome: DISEASE PROGRESSION</b>							

# Early mortality

<b>Comparison: NVP-BASED vs PI-BASED ANTIRETROVIRAL REGIMENS IN INFANTS (≤11 MONTHS)</b>							
<b>Outcome: EARLY MORTALITY (&lt;1<sup>ST</sup>) YEAR</b>							
<b>Population group: HIV INFECTED INFANTS (≤ 11 MONTHS)</b>							
No of studies	Design	Limitations	Consistency	Directness or generalisability	Imprecise or sparse data	Other factors	QUALITY RANK
Anyone of the following studies have been designed to compare NVP-based vs PI-based in infants, therefore the quality of evidence is ranked on studies considering the efficacy of a single regimen in infants population, and others giving a short comparison analysis in a wide children population including very few infants.							
2	RCT <b>2</b>	All the studies were not designed to assess NVP vs PI Some limitations <b>-1</b>	Direction and size of the effect appear consistent No important inconsistency	No direct comparison between NVP and PI →Indirect comparison Some uncertainty <b>-1</b>	P.small sample size but powered enough CHER good sample size	P. consider 4 drug regimen NVP +PI Any possible comparison <b>-1</b>	<b>1</b> <b>VERY LOW QUALITY</b>
8	Observational <b>2</b>	(as above) Some limitations <b>-1</b>	Direction and size of the effect appear consistent No important inconsistency	The majority of the studies haven't got a direct comparison between NVP and PI →Indirect comparison RLS vs RuLS (very different mortality background as well as different breastfeeding approach) →Indirect population Some uncertainty <b>-1</b>	Good sample sizes		<b>1</b> <b>VERY LOW QUALITY</b>

---

# Final ranking

Starting NVP based regimen compared with  
PI based regimen in infants  $\leq 11$  month  
is supported by

**VERY LOW QUALITY OF EVIDENCE**

---



---

# NVP Resistance

- ✓ Response to NVP-containing regimen affected by NVP Resistance
- ✓ NVP Resistance in Infants Infected Despite Infant Prophylaxis
- ✓ NVP Resistance in Infants Infected Despite Maternal cART Prophylaxis



---

# References

- **Arrive E**, ML Newell, D K Ekouevi et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *Int J Epidemiol*. 2007 Oct;36(5):1009-21. Review.
  - **Shapiro RL**, Thior I, Gilbert PB et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS*. 2006 Jun 12;20(9):1281-8.
  - **Jourdain G**, N Ngo-Giang-Huong, Pharm.D et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med*. 2004 Jul 15;351(3):229-40. Epub 2004 Jul 9.
  - **Lockman S**, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 2007 Jan 11;356(2):135-47.
  - **Moorthy S**, A Gupta, G Sastry et al. Timing of Infection Is Critical for Nevirapine Resistance Outcomes among Breastfed Subtype C HIV-1-infected Infants Exposed to Extended vs Single-dose Nevirapine Prophylaxis: The India SWEN Study. Abstract CROI 2008
  - **Thomas T**, R Masaba, R Ndivo et al. Prevention of Mother-to-Child Transmission of HIV-1 among Breastfeeding Mothers Using HAART: The Kisumu Breastfeeding Study, Kisumu, Kenya, 2003–2007. Abstract 45A1b CROI 2008.
  - **Church J**, S Omer, L Guay et al. Analysis of NVP Resistance in Ugandan Infants Who Were HIV-infected despite Receiving Single-dose Nevirapine vs Single-dose NVP Plus up to 6 Weeks of Daily NVP to Prevent HIV Vertical Transmission. Abstract 635 CROI 2008.
  - **Eshleman S**, T Flys, M McConnell et al. Emergence and Fading of Nevirapine Resistance after First versus Repeated Use of Single-dose Nevirapine for Prevention of Mother-to-Child HIV Transmission: Women and Infants in the Repeat Pregnancy Study in Uganda. Abstract 632, CROI 2008.
  - **Barlow-Mosha L**, P Ajunua, M Mubiru et al. Early Effectiveness of a NVP-based HAART Regimen among HIV-infected Children with and without Prior Single-dose NVP Exposure. Abstract CROI 2008.
  - **Micek M**, M Micek, A Blanco et al. Nevirapine-resistant HIV-1 among Mozambican Infants Infected in Utero vs Intra-partum or Early Postpartum. Abstract 92 CROI 2007.
-

# Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis<sup>†</sup>

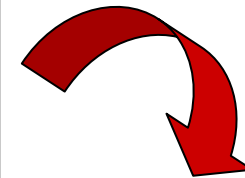
Elise Arrivé,<sup>1,2\*</sup> Marie-Louise Newell,<sup>3</sup> Didier K Ekouevi,<sup>1,4</sup> Marie-Laure Chaix,<sup>5</sup> Rodolphe Thiebaut,<sup>1,6</sup> Bernard Masquelier,<sup>7,8</sup> Valériane Leroy,<sup>1,2</sup> Philippe Van de Perre,<sup>9</sup> Christine Rouzioux<sup>5</sup> and François Dabis<sup>1,2</sup>, for the Ghent Group on HIV in Women and Children<sup>10</sup>

Eshleman et al. NVAZ N=20  
McIntyre et al. TOPS n=9  
Sullivan et al. SAINT n=40  
Martinson et al. N=50  
Eshleman et al. HIVNET012 n=24  
Gordon et al. N=30  
Loubser et al. n=25

**SD-NVP only**  
Summary estimates  
**52.6% [37.7; 67.0]**

Eshleman et al. NVAZ N=21  
Chaix et al. DITRAME plus 1.0 n=26  
Chalermchokcharoenkit et al. n=10  
McIntyre et al. TOPS n=9 arm 2  
NgoGiang Hung et al. n=29 arm 1  
Chaix et al. DITRAME plus 1.1 n=16  
NgoGiang Hung et al. n=21 arm 2  
McIntyre et al. TOPS n=7 arm 3

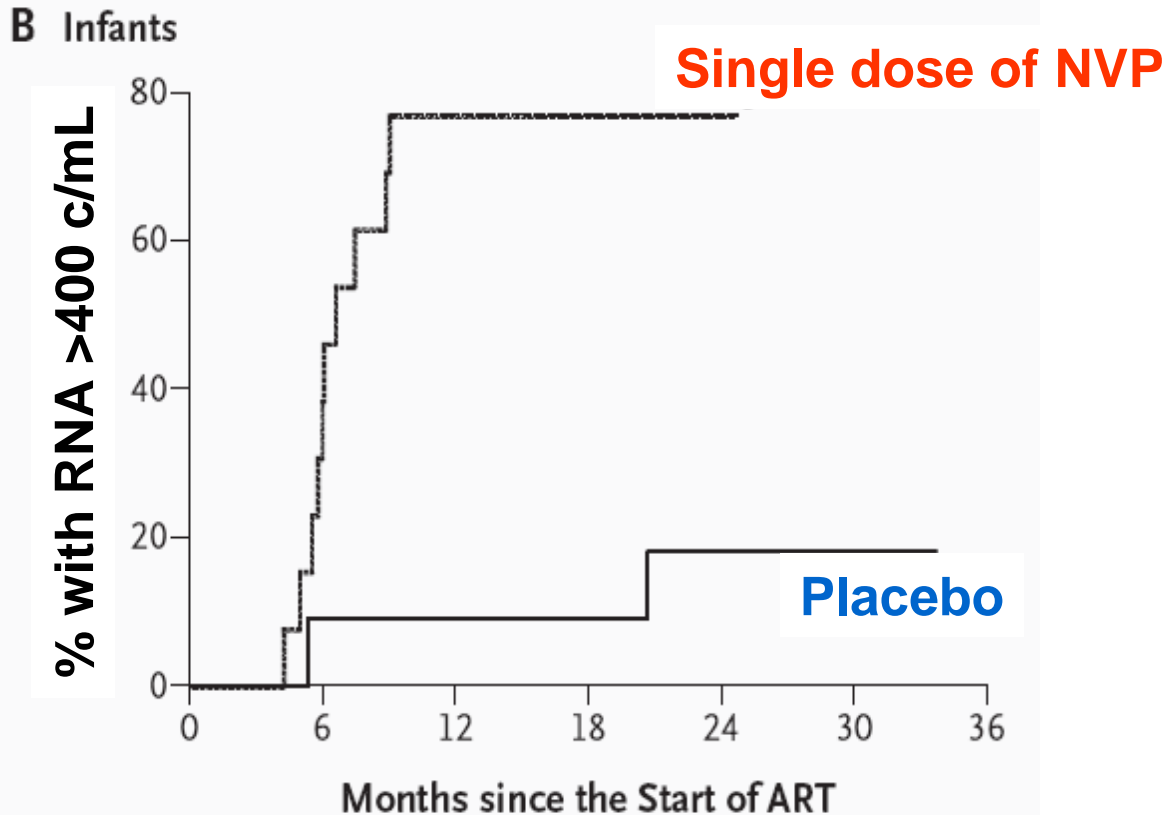
**SD-NVP supported  
by additional ARV(s)**  
Summary estimates  
**16.5% [8.9; 28.3]**



Different resistance profile described for **mother (K103N)** and **children (Y181C)**

# Response to Antiretroviral Therapy after a Single, Peripartum Dose of Nevirapine

Lockman S, et al. *NEJM* 2007;356:135-47



**Median age  
at start HAART  
8.5 months**

**Analysis after 6 months of HAART:  
10/13 in SD NVP group and 1/12 placebo group  
had HIV RNA >400 copies/mL**

---

# Quality of evidence

**GRADE**

- 5 RCTs
- No serious limitations
- No inconsistency
- No serious indirectness
- Serious imprecision (samples size are small with few events reported)

NVP exposure due to maternal and infant MTCT prophylaxis select for NVP resistant strains, which might affect the effectiveness of NVP based regimen as 1<sup>st</sup> line therapy in infants.



**MODERATE ?  
QUALITY OF EVIDENCE**

---

---

# Waiting for.....

## P1060

Multicountry  
(N=576)

Children 6-36 months enrolled



### Direct Comparison NVP vs PI

Infants with/without NVP exposure  
Randomized for LPV/r vs NVP HAART  
Endpoint: % RNA<50 at 6 mos post  
randomize

---

---

# Thank you!

