Summary of Evidence

What ART to start in infants

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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

**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 nuckes not included)
References

- 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
- Kuhn Personal communication, Neverest 2.
- Capparelli E, Pinto J, Robbins B et al.Lopinavir Pharmacokinetic Maturational Changes and Variability in HIV-infected Infants Beginning Kàletra Therapy at <6 Weeks of Age . CROI 2008
### Outcomes

#### What to start in Infants

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative importance (rank 1→9 most critical)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (1st year)</td>
<td>9</td>
<td>Critical</td>
</tr>
<tr>
<td>Mortality (5 years)</td>
<td>9</td>
<td>Critical</td>
</tr>
<tr>
<td>Severe/LT events</td>
<td>8</td>
<td>Critical</td>
</tr>
<tr>
<td>Major Adverse Events</td>
<td>8</td>
<td>Critical</td>
</tr>
<tr>
<td>Disease progression (clinical definition)</td>
<td>7</td>
<td>Critical</td>
</tr>
<tr>
<td>Detectable viral load</td>
<td>7</td>
<td>Critical</td>
</tr>
<tr>
<td>Adherence</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Drug Resistance</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>WAZ/HAZ</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Switch rate</td>
<td>5</td>
<td></td>
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</table>
Comparison: NVP based VS PI based REGIMEN for EARLY ANTIRETROVIRAL TREATMENT IN INFANTS (<=11 MONTHS)

Outcome: EARLY MORTALITY (<=1ST YEAR)
Population group: HIV INFECTED INFANTS (<=11 MONTHS)

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness or generalisability</th>
<th>Imprecise or sparse data</th>
<th>Other factors</th>
<th>QUALITY RANK</th>
</tr>
</thead>
</table>

Outcome: LATE MORTALITY (<=5TH YEAR)

Outcome: VIRAL SUPPRESSION

Outcome: DISEASE PROGRESSION
# Early mortality

## Comparison: NVP-BASED vs PI-BASED ANTIRETROVIRAL REGIMENS IN INFANTS (≤11 MONTHS)

### Outcome: EARLY MORTALITY (<1ST YEAR)

### Population group: HIV INFECTED INFANTS (≤ 11 MONTHS)

<table>
<thead>
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</tr>
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<tbody>
<tr>
<td>2</td>
<td>RCT</td>
<td>All the studies were not designed to assess NVP vs PI Some limitations</td>
<td>Direction and size of the effect appear consistent No important inconsistency</td>
<td>No direct comparison between NVP and PI →Indirect comparison Some uncertainty -1</td>
<td>P.small sample size but powered enough CHER good sample size</td>
<td>P. consider 4 drug regimen NVP +PI Any possible comparison -1</td>
<td>1 VERY LOW QUALITY</td>
</tr>
<tr>
<td>8</td>
<td>Observational</td>
<td>(as above) Some limitations -1</td>
<td>Direction and size of the effect appear consistent No important inconsistency</td>
<td>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 -1</td>
<td>Good sample sizes</td>
<td>1 VERY LOW QUALITY</td>
<td></td>
</tr>
</tbody>
</table>

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.
Final ranking

Starting NVP based regimen compared with PI based regimen in infants ≤11month 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


Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis

Elise Arrivé, Marie-Louise Newell, Didier K Ekouevi, Marie-Laure Chaix, Rodolphe Thiebaut, Bernard Masquelier, Valérie Leroy, Philippe Van de Perre, Christine Rouzioux and François Dabis, for the Ghent Group on HIV in Women and Children

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

Eshleman et al. NVAZ N=21
Chaix et al. DITRAME plus 1.0 n=26
Chalermachokcharoenkit 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 only
Summary estimates
52.6% [37.7; 67.0]

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


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

- 5 RCTs
- No serious limitations
- No inconsistency
- No serious indirectness
- **Serious imprecision** (sample 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 1st line therapy in infants.

**Mildly Low**

QUALITY OF EVIDENCE
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!