Antiretroviral & Anti-Tuberculosis drug experience in children: When and what to start

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HIV/TB epidemic

- 2.1 million HIV infected children worldwide
  - 90% are found in sub-Saharan Africa

- 8.8 million new cases of TB each year
  - Over 12 of the 15 high burden countries are found in Africa

- In Africa, 10 - 60% of children with TB are also co-infected with HIV

- Concurrent Treatment of both diseases occurs frequently and is complex
Antiretroviral drug options

1\textsuperscript{st} line antiretroviral drugs in RLS
- AZT/3TC/NVP or EFV/ABC
- d4T/3TC/NVP or EFV/ABC

2\textsuperscript{nd} line ARV drug options in RLS
- DDI/ABC/LPVr
- TDF/3TC or FTC /LPVr
Overlapping toxicity of Antiretroviral and TB drugs

- d4T, AZT, INH – peripheral neuropathy
- RH, NVP – hepatitis
- PZA – hepatitis & uric acid levels
- ETH – optic neuritis
Interaction ARV’s & TB drugs

- Rifampicin stimulates cyt p450
  - Increased metabolism of NNRTI’s and PIs
  - Leading to inadequate drug levels of both NVP and LPVr which are the common 1\textsuperscript{st} and 2\textsuperscript{nd} line ARV’s for children in Africa

- EFV levels are reduced (AUC 22-26 %) so can co-administer with rifampicin

- NVP levels are reduced (AUC 31-37%) significantly
Effect of Rifampicin on NVP levels

Pharmacokinetics of NVP

- Children on NVP based HAART alone or in combination with anti-TB drugs (n=20) Dose NVP 4-8mg/kg/dose

Median NVP trough concentration

- HAART alone (13) - 4204 ng/ml (range 834-15976 ng/ml)
- HAART + TB drugs(7) - 2920 ng/ml (range 1668-9978 ng/ml)

L Barlow Mosha, et al CROI Feb 2009
Adequate NVP levels in Thai children with TB and HIV

- Fixed dose combination HAART with NVP (GPOVir) in Thai children (n=8)
  - Median age 9.7 (4.4 -11) yrs
  - Wt = 17 kg (14.5 – 23.2)
  - Average NVP levels 195 mg/m2 (149,3 -262.7 )
  - Average Rifampicin levels 11.4 mg/kg (8.3 -14.5)

- AUC for NVP was > 3.0ug/ml in all children
  - Median NVP trough = 6.34 ug/ml (3.0 – 13.8)

**Conclusion:** higher dose of NVP achieved appropriate NVP exposure in children on rifampicin

W Prasitsuebsai et al. Abstract # 908 CROI Feb2009
Adequate Immunological and virological response on NVP based HAART and Rifampicin

- **Figure 1: Immunological response**
  - There was no statistically significant difference in the immunological response between the two groups.

- **Figure 2: Virological response**
  - All children achieved a three fold drop (0.5 log$_{10}$) in viral load by 12 weeks which was sustained through 48 weeks irrespective of receiving Rifampicin.

M Kamateeka IAS Cape Town 2009
Poor virological response in children on PI based HAART and TB treatment

254 children initiated HAART with a PI, 9 months follow up

Median age 9 months  18% initiated TB treatment
- On PI based HAART and Rifampicin
  - Virological suppression 78%
- On PI based HAART and no TB treatment
  - Virological suppression 94.1%
- Those children who initiated TB treatment after HAART initiation had the worst outcome
  - Virological suppression 53%

Conclusion: Substitution of LPVr with R for children co-infected with TB did not improve virological suppression rates

Reitz C et al  CROI 2009 Abstract # 910
Inadequate LPV despite doubling the dose in children on Rifampicin

- Children > 6 months from S. Africa on LPVr HAART
- 15 with TB co-infection and 24 controls (no TB)
  - Cases LPVr dosing - 460/115mg/m2
  - Controls LPVr dosing – 230/57.5 mg/m2

<table>
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<tr>
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<th>TB/HIV</th>
<th>Controls</th>
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<td>C max (mg/L)</td>
<td>4.45 (2.51-8.22)</td>
<td>7.94(6.86 -13.4)</td>
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<td>p=0.006</td>
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Conclusion: Doubling the dose of LPVr lead to substantial reductions in children who were on rifampicin for TB treatment

McIlleron H et al CROI 2009 Abstract # 98
What ARV to start?

- HIV infected child co-infected with TB
  - If on NVP based HAART need a higher dose to maintain adequate NVP levels
    - However can switch to ABC
  - If on EFV based HAART can continue on same drug and dose
  - If on a PI, doubling the PI dose is not beneficial in increasing the PI levels while on Rifampicin
  - The best regimen if child needs a PI is not yet clear and needs further study
    - Use of newer NNRTI’s (e.g. etravirine) needs to be investigated
When to start TB treatment

- As soon as possible in the severely immunosuppressed children (2-8 weeks) CD4 % < 15% or < 250 cells

- Some data suggest use of higher dose of anti-TB drugs in co-infected children
  - Use the same drugs RHZ/E in RLS

- Where rifabutin available then can be used instead of rifampicin
What is the correct dosage of anti-TB drugs in children?

- **INH 10mg/kg & not 5mg/kg**
  - Schaaf HS et al Arch Dis Child 2005; 90: 614 - 618

- **Low levels Ethambutol & PZA in Malawian children**
  - Worse: <5y & HIV+

- **Rifampicin 15mg/kg (rather than 10mg/kg) & PZA 35- 40mg/kg (rather than 25mg/kg)**

- **Pyrazinamide 30mg/kg per day – provided adequate levels in children** – Thee S et al IJTLID 2008

Adapted from Mark Cotton slide
WHO - Recommendations

- If HIV infected child has clinical WHO stage 4 and 3 + low CD4 count and TB then
  - Need to initiate TB treatment promptly and within 2-8 weeks initiate ARV treatment

- If child has a WHO stage 3 (with high CD4 count)
  - Give TB treatment for 2 months then start HAART if child stable but monitor closely

- If child is WHO stage 1 and 2
  - If CD4 cell count above need for ART then complete TB treatment

WHO ARV therapy of HIV infection in infants and children in RLS: towards universal access 2006
WHO Recommendations cont..

- If child already on NVP or EFV based HAART and needs TB treatment
  - Switch NVP to ABC or increase NVP dose by 30%

- If child over 3 years and is on EFV then continue EFV
Multiple Questions remain

- By what % should the NVP dose be increased when TB treatment is initiated?

- If a child is on a PI and is on 2\textsuperscript{nd} line therapy what options does the child have while on TB treatment?

- Since triple NRTIs may be less effective would it be appropriate to use in severely immune suppressed infants with high viral load and co-infected with TB?

- Are they data from children to suggest the optimum time to initiate HAART in children on TB treatment in view of IRIS vs mortality?
THANK YOU