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

- 1st line antiretroviral drugs in RLS
  - AZT/3TC/NVP or EFV/ABC
  - d4T/3TC/NVP or EFV/ABC
- 2nd 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 1st and 2nd 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

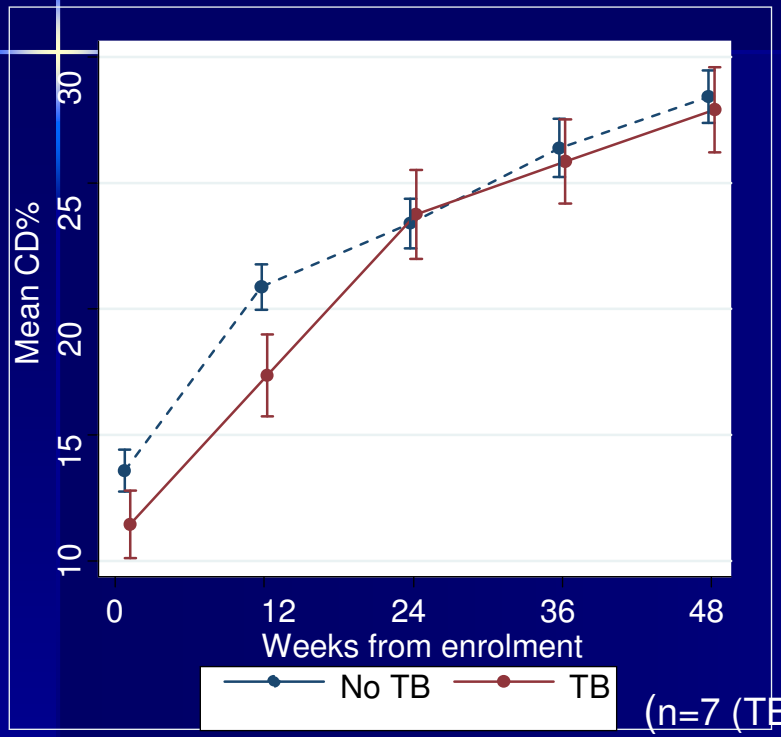
- Fixed dose combination HAART with NVP (GPOVir) in Thai children (n=8)
  - Median age 9.7 (4.4 -11) yrs
  - Wt = 17 kg (14.5 – 23.2)
  - Average NVP levels 195 mg/m2 (149,3 -262.7)
  - Average Rifampicin levels 11.4 mg/kg (8.3 -14.5)
- AUC for NVP was > 3.0ug/ml in all children
  - Median NVP trough = 6.34 ug/ml (3.0 – 13.8)

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

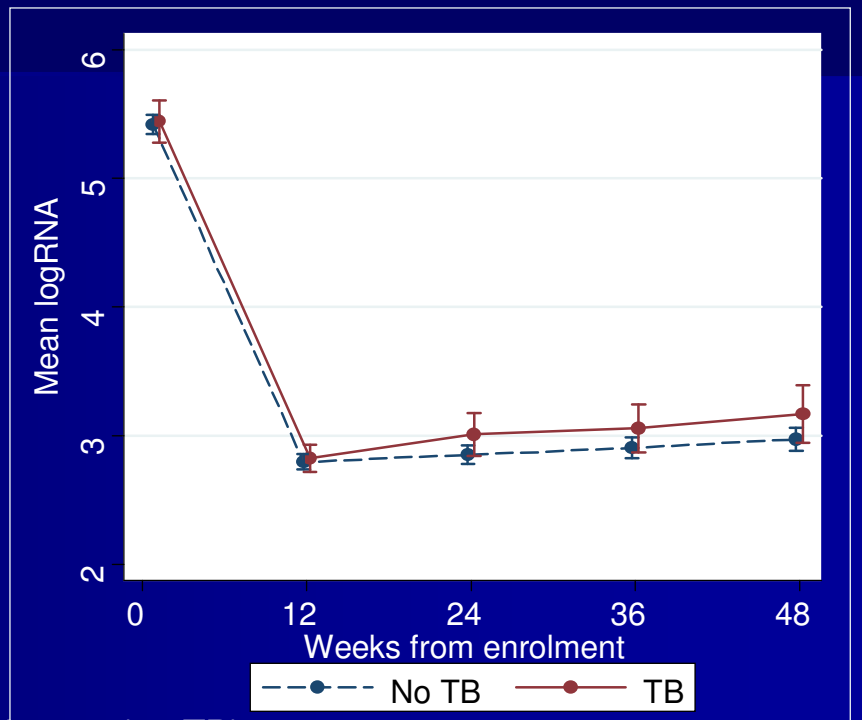
W Prasitsuebsai et al. Abstract # 908 CROI Feb2009

Adequate Immunological and virological response on NVP based HAART and Rifampicin

- *Figure 1: Immunological response*



- *Figure 2: Virological response*



(n=7 (TB) and n=13 (no TB)

- There was no statistically significant difference in the immunological response between the two groups.
- 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

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

LPV concentrations

	TB/HIV	Controls
C max (mg/L)	4.45 (2.51-8.22)	7.94(6.86 -13.4)

p=0.006

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
  - Graham et al Antimicrob Agents Chemother 2006; 50: 407 - 413
  - 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 IJTLD 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

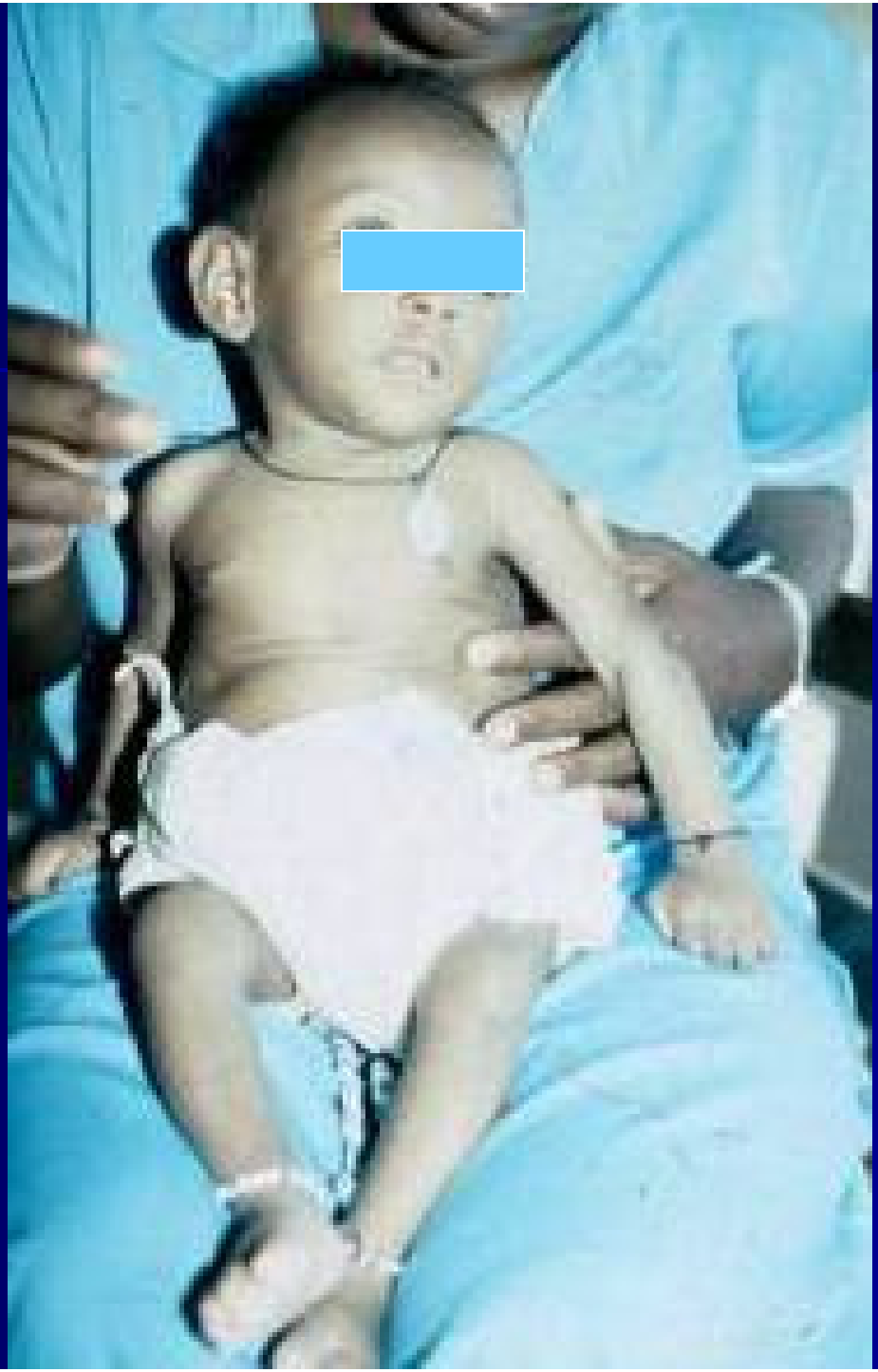
WHO Recommendations cont..

- 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 2nd 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 ?

MARASMUS



THANK YOU