The challenges posed by Tuberculosis in HIV-infected children

Helena Rabie
2020

THE TREATMENT TARGET

- 90% diagnosed
- 90% on treatment
- 90% virally suppressed
REACH. TREAT. CURE EVERYONE

Every year 9 million people get sick with TB.

3 million don’t get the care they need. Help us to reach them.

World TB Day 24 March 2015
Tuberculosis in childhood

Risk of Disease progression post infection:

- **Age**
  - 43% of infants (children < 1 year)
  - 25% of children aged 1-5
  - 15% of adolescents
- Recent infection (1-2 years)
- Malnutrition
- HIV
- Measles
Epidemiology of TB and HIV

[Maps showing the estimated HIV prevalence in new and relapse TB cases, 2015, and the estimated TB incidence rates, 2015.]
HIV exposed and infected children live with HIV-infected adults.
Where there is TB in pregnant HIV infected women

- 795/100 000 of pregnant women 201/100 000 if no HIV
- 27% of deaths in women who died of AIDS-related complications during pregnancy, childbirth, puerperium
- Maternal mortality in HIV infected woman
  - 12 170/100 000 Where there is TB
  - 3 850/100 000 Where there is NO TB

- Increased the risk of HIV transmission to the infant
- Risk of TB to the infants
In P1041 – TB prevention trial

- 229 contact occasions
  - 83% household
  - 53 + microbiologically assessment
    - 81% positive
- 49% of source case contact identified at or AFTER child diagnosed with TB

- 48% with confirmed TB
- 58% probable
- 43% possible
- 8% deaths

Maritz IUTBLD 2012
Increased ART coverage & decreased TB in RSA
**cART**

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Restoration of CD4-cell counts and functional immune responses to <em>Mycobacterium tuberculosis</em>¹⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlate</td>
<td>CD4-cell count</td>
</tr>
<tr>
<td>Effect on endogenous reactivation</td>
<td>Likely sustained reduction in patients with increasing CD4-cell counts;</td>
</tr>
<tr>
<td>Effect on exogenous re-infection</td>
<td>Likely sustained reduction in patients with increasing CD4-cell counts; however, exogenous re-infection may be proportionately more important</td>
</tr>
<tr>
<td>Efficacy with isoniazid resistant</td>
<td></td>
</tr>
<tr>
<td>Risk of generating drug resistance</td>
<td></td>
</tr>
<tr>
<td>Exclude active tuberculosis before starting treatment</td>
<td>Unmasking of tuberculosis or unmasking of tuberculosis immune-reconstitution disease</td>
</tr>
</tbody>
</table>

Adapted from Lawn LancetID 2010
Tuberculosis in 1st year of life (per 100 patient years)

IPT for HIV+ children?

• 2 Studies:
  – Madhi: Primary Isoniazid Prophylaxis against Tuberculosis in HIV-Exposed Children. NEJM 2011
  
cART and IPT

- INH alone - 0.22 (95% CI 0.09 to 0.53)
- ART alone - 0.32 (95% CI 0.07 to 1.55)
- INH & ART - 0.11 (95% CI 0.04 to 0.32)
South African guideline

Post-exposure IPT 10 mg/kg daily for 6 months is recommended in the following children after exclusion of TB disease

• HIV-uninfected children less than 5 years of age

• HIV-infected children irrespective of age or ART status.
IPT will not select resistance

- Must take a good history of the contact
- Try to find the culture result of the contact
- Failure of IPT
  - Resistance in the contact
  - Non adherence
This is nice BUT

- In the DNDi Superboosting study
  - TB treatment started 1st: 70 (73%) of children in the DNDi superboosting study
  - < 3 Months ART Before TB: 12 (12.5%)
6 year old with confirmed TB PCR positive in early live
Mom and dad defaulting ART

10 month old with confirmed TB PCR positive after initially testing negative
Mom defaulting ART
High rates of TB in HIV-infected infants and children

• Rates:
  – 53.3 cases/100 patient years in children not on HAART
  – 1596 per 100 000 HIV-infected infants
  – 25-60% of children hospitalized with TB HIV infected

• Mortality:
  – TB-related deaths in 18.8% of HIV-infected Zambian children

## Incidence of culture-confirmed TB in HIV-infected and uninfected South African infants (per 100 000 infant population)

<table>
<thead>
<tr>
<th></th>
<th>All infants</th>
<th>HIV-uninfected</th>
<th>HIV-infected</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All tuberculosis</strong></td>
<td>83.1</td>
<td>65.9</td>
<td>1595.9</td>
<td>24.2</td>
</tr>
<tr>
<td></td>
<td>(72.9-93.7)</td>
<td>(56.7-75.3)</td>
<td>(1151.3-2131.5)</td>
<td>(16.9-33.6)</td>
</tr>
<tr>
<td><strong>Pulmonary tuberculosis</strong></td>
<td>78.7</td>
<td>62.5</td>
<td>1505.6</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>(68.6-89.0)</td>
<td>(53.3-71.7)</td>
<td>(1075.2-2022.8)</td>
<td>(16.7-33.7)</td>
</tr>
<tr>
<td><strong>Extra pulmonary tuberculosis</strong></td>
<td>28.2</td>
<td>22.9</td>
<td>481.8</td>
<td>21.0</td>
</tr>
<tr>
<td></td>
<td>(22.2-34.4)</td>
<td>(17.5-28.6)</td>
<td>(257.0-750.8)</td>
<td>(10.7-35.0)</td>
</tr>
<tr>
<td><strong>Disseminated tuberculosis</strong></td>
<td>16.6</td>
<td>14.1</td>
<td>240.9</td>
<td>17.1</td>
</tr>
<tr>
<td></td>
<td>(11.9-21.2)</td>
<td>(9.7-18.3)</td>
<td>(86.6-431.7)</td>
<td>(6.0-33.7)</td>
</tr>
<tr>
<td><strong>Miliary tuberculosis</strong></td>
<td>10.9</td>
<td>9.3</td>
<td>150.6</td>
<td>16.2</td>
</tr>
<tr>
<td></td>
<td>(7.2-14.7)</td>
<td>(5.8-12.7)</td>
<td>(30.8-301.0)</td>
<td>(3.4-37.1)</td>
</tr>
<tr>
<td><strong>Tuberculosis meningitis</strong></td>
<td>9.2</td>
<td>7.9</td>
<td>120.1</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td>(5.8-12.6)</td>
<td>(4.7-11.1)</td>
<td>(27.7-257.9)</td>
<td>(2.9-38.7)</td>
</tr>
</tbody>
</table>
Can we screen for and diagnose TB?

1. Contact with an index case
2. Positive TST
3. History of symptoms
4. Suggestive signs on the chest radiograph
5. Xpert and culture of respiratory and other specimens
Can we screen for and diagnose TB?

1. Contact with an index case
   1. Time and space sensitive

2. Positive TST
   1. Understanding negative results
   2. Understanding positive results

3. History of symptoms
   1. HIV vs TB symptoms

4. Suggestive signs on the chest radiograph
   1. View all images

5. Xpert and culture of respiratory and other specimens
Shifting Paradigm of TB

CHILD

MOM
It is important to contextualize Xpert MTB/RIF for tuberculosis in children

For every 100 children on therapy

- Clinical grounds
- Xp + / Cul -
- Cul +

For the 30 culture confirmed children

- Cul + / Xp - / Sm -
- Cul + / Xp + / Sm +
- Cul + / Xp + / Sm -
Will LAM Help?

• lipoarabinomannan glycolipid component of the cell wall of M. tuberculosis and other mycobacteria

• Only 1 study showed value
  – Hospitalized adults
  – Low CD4
  – Not in SA

• No study in children showing any effect

Peter PlosOne
Therapeutic considerations in co-infected children

1. Timing of ART
2. Choice of drug regimens
3. Duration of TB treatment
4. Monitoring
# Drug Interactions

<table>
<thead>
<tr>
<th>Rifamycin</th>
<th>Interaction with antiretroviral drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>NNRTI ↓60%</td>
</tr>
<tr>
<td></td>
<td>PIs ↓90%</td>
</tr>
<tr>
<td></td>
<td>Maraviroc ↓60-70%</td>
</tr>
<tr>
<td></td>
<td>Raltegravir ↓40%</td>
</tr>
<tr>
<td></td>
<td>ABC/AZT ↓50%</td>
</tr>
<tr>
<td>Rifapentin</td>
<td>Less potent activator</td>
</tr>
<tr>
<td></td>
<td>No data on ART interaction</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Interaction with PI and EFV that require dose adjustments</td>
</tr>
</tbody>
</table>
Which anti-tuberculosis drugs to use

Rifampicin
- Maximum induction 1 week dose dependent

Rifabutin
- Least induction Phase 1 enzymes and p glycoprotein
- Induce own metabolism
- Substrate CYP3A
- Dosing in adults?
- Dosing in children?
Timing in relation to TB therapy?

“Any child with active TB disease [not yet on ART] should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of the CD4 count and clinical stage”

*(Strong recommendation, very low quality of evidence).*
Delaying HAART

• Increased mortality
• Increased risk of virological failure
• Important in specific conditions ie meningitis

• Decreased risk of IRIS
• Decrease pill burden
• Lower risk of adverse drug reactions

Early HAART

• Increase IRIS
• Increased pill burden
• Increase risk drug reactions

• Reduced mortality
EFAVIRENZ

- Doses were low regardless of RMP exposure and suggested weight based doses where modified
- FDA approved for children<3 years
- Resistance risk in low resource settings
Effectiveness of Efavirenz-Based Regimens in Young HIV-Infected Children Treated for Tuberculosis: A Treatment Option for Resource-Limited Settings

Janneke H. van Dijk¹,², Catherine G. Sutcliffe³, Francis Hamangaba¹, Christopher Bositis⁴, Douglas C. Watson⁵, William J. Moss³

- Mortality similar
- Adherence similar
- EFV: better viral control
- ?A/E

Van Dijk, PLoS One 2013
## Boosted PI: double dose LPV/r

<table>
<thead>
<tr>
<th></th>
<th>TB/HIV-double LPV/r</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.25</td>
<td>1.59</td>
<td>0.60</td>
</tr>
<tr>
<td>Cpre (mg/L)</td>
<td>0.63</td>
<td>4.25</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>4.45</td>
<td>7.94</td>
<td>0.006</td>
</tr>
</tbody>
</table>

McIlleron, Antivir Ther 2011
Boosted PI: Super-boosted LPV

n=15 per cohort

Ren, JAIDS 2008
Modeled PK n=80, non inferiority

**Visual predictive check:** the model was used to re-simulate the dataset

- **Observed concentrations**
- **Modeled from simulation**
  - 50th centile
  - 5th & 95th centiles

- Normal scale
- Log scale
Super-boosting is not without issues

- Taste
- Logistics
  - Shelve life

- Consequences of not super-boosting
  - Failure WITH resistance
What about resistant TB and the “newer” ART
ART and RIF

• Atazanvir – Use rifabutin
• Dolutegravir – no pediatric data BD in stead of daily dose
• Raltegravir – No pediatric data doubling the daily dose
<table>
<thead>
<tr>
<th>Estimated total TB cases in children</th>
<th>1 million (10% global total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB deaths</td>
<td></td>
</tr>
<tr>
<td>• HIV-</td>
<td>81 000</td>
</tr>
<tr>
<td>• HIV+</td>
<td>55 000</td>
</tr>
<tr>
<td>TB infections</td>
<td>6.6 million</td>
</tr>
</tbody>
</table>

WHO 2013 Global TB report
www.who.int
What is needed for novel pediatric MDR-TB treatment?

• Injectable sparing shorter regimen: 6-9 months
• Data on optimal use of 2\textsuperscript{nd} line drugs: FQN, clofazamine, PAS, Linezolid?
• Adult PK targets defined
• Inclusion of novel drugs: data on dosing, safety needed (bedaquiline, delamanid, PA-824) – need for phase I studies
• Formulations: SLD, novel drugs
Short course - Drug resistance

• Who
  – Probable or confirmed MDR-TB in which resistance to second-line drugs is unlikely
  – Probable or confirmed MDR-TB with no previous second-line drug treatment in the child or source case

• Not in
  – Children with known resistance to any component of the shortened regimen except isoniazid
  – Children whose source cases have known resistance to any component of the shortened regimen except isoniazid
Short course - Drug resistance

4-6 months intensive phase
1. Kanamycin / Amikacin
2. Moxifloxacin / Levofloxacin
3. Prothionamide
4. Clofazaimine
5. Pyrazinamide
6. High dose INH
7. Ethambutol

5 months continuation phase
1. Moxifloxacin / Levofloxacin
2. Clofazamine
3. Pyrazinamide
4. Ethambutol
Other drugs

Repurpose
• Terizidone
• PAS
• Linizolid
• Meropenem
• Co-amoxiclavlanic acid

New
• Delamanid
• Bedaquilin
Delamanid: 6 more than 20kg

• Who
  – Confirmed MDR-TB when a four-drug regimen plus pyrazinamide cannot be constructed owing to resistance or significant intolerance
  – Probable MDR-TB with a source case with known or suspected additional resistance to second-line agents
  – Confirmed or probable MDR-TB with a high risk of treatment failure

• Dose
  – >35 kg: 100 mg twice daily
  – 20–34 kg: 50 mg twice daily

• Monitoring
  – Baseline: ECG to assess QTc interval and albumin in addition to standard MDR-TB assessments
  – Follow-up: Monthly ECG to assess for QTc prolongation

• Safety with ART not studies in children – DDI possibly not important
Bedaquiline > 12 years > 33 kg

• Who > 12 and > 33 kg
  – Confirmed MDR-TB in whom a four-drug regimen plus pyrazinamide cannot be constructed because of resistance or significant intolerance and where delamanid is not available
  – Probable MDR-TB with a source case with known or suspected additional resistance to second-line agents and where delamanid is not available

• Dose
  – 400 mg daily for 14 d followed by 200 mg given three times weekly for an additional 22 weeks

• Monitoring with ECG
### Results: -30% in CL of HIV

<table>
<thead>
<tr>
<th>parameter</th>
<th>mean</th>
<th>stddev</th>
<th>95%CI_low</th>
<th>95%CI_upp</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLOCL</td>
<td>0.2700</td>
<td>0.078</td>
<td>0.1169</td>
<td>0.422</td>
</tr>
<tr>
<td>ALLOV</td>
<td>0.992</td>
<td>0.064</td>
<td>0.8671</td>
<td>1.117</td>
</tr>
<tr>
<td>HIV.effect.on.CL</td>
<td>-0.300</td>
<td>0.076</td>
<td>-0.447</td>
<td>-0.15</td>
</tr>
</tbody>
</table>

Power: 88% found a statistically significant effect of HIV on CL when simulating 30% lower CL
N=54 total children, minimum 18 HIV-infected

Simulating BDQ and M2 PK in paediatric patients with/without HIV

Elin Svensson, Mats Karlsson
Linizolid

• Who
  – Some MDR cases especially meningitis
  – Confirmed or probable MDR-TB as part of the core second-line regimen

• Dose - entire course of treatment as long as the child tolerates it
  – Children >12 yr: 10 mg/kg once daily
  – Children ,12 yr of age: 10 mg/kg twice daily

• Monitoring
  – FBC and peripheral nervous system
Clofazimine

• **Who**
  – Confirmed or probable MDR-TB as part of the core second-line regimen

• **Dose**
  – 2–3 mg/kg given daily for a maximum daily dose of 100 mg or every other day in smaller children (gelcaps cannot be split)

• **Monitoring**
  – Skin
  – ECG
Amikacin

• Recommended WHO dose – 15-30mg/kg IM
• Preliminary data from our group on amikacin PK in 28 children: IM dose of 20mg/kg: median $C_{\text{max}}$ of 47.1 μg/mL, higher than proposed adult target $C_{\text{max}}$ of 35-45 μg/mL* in >70% of children
• We evaluated PK of once daily IM amikacin at 20 vs. 15 mg/kg
• Analyses on safety and clinical outcomes with higher and lower dose pending

*Peloquin CA. 2002;62(15):2169-83
Amikacin median concentration (IQR) in different age groups at doses of 15mg/kg and 20mg/kg IM daily

<table>
<thead>
<tr>
<th>Age Group</th>
<th>15 mg/kg</th>
<th>20 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>2-5 years</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>6-15 years</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

*Note: Cmax (g/mL) per dose (15 mg/kg vs 20 mg/kg) and age (0-2 years vs 2-5 years vs 6-15 years).*
Amikacin: Conclusions

• Age had a significant influence on IM amikacin by total exposure; not by $C_{\text{max}}$; no effect by HIV or nutritional status
• To achieve target adult $C_{\text{max}}$ of at least 35 $\mu$g/mL: amikacin dose 18-20mg/kg
• Majority of children achieved a $C_{\text{max}}$ of >35 $\mu$g/mL at 20mg/kg daily: care not to exceed this dose unless TDM is available. Hearing loss is associated with cumulative amikacin exposure
• Previous studies showed 25% children had hearing loss*

Seddon, ITLD 2012
Levofloxacin

- FQN cornerstone of MDR-TB regimens
- Active enantiomer of ofloxacin
- Fast and complete absorption - F is high: 99%
- Low protein binding 24-38%
- Elimination half-life 6-8 hours in adults
- Mainly renally cleared, very little metabolism
- Toxicity: hepatic
- Few earlier popPK studies in children

Fish DN, Chow AT. Clinical Pharmacokinetics, 1997
Levofloxacin: Conclusions

• 20mg/kg dose more closely approximates adult exposures than 15mg/kg
  – But still low
  – Safety data at this dose being analyzed
• Despite low exposures, outcomes good
• More optimal doses may improve outcomes further or facilitate shorter or injectable sparing regimens
  – Important for bridging to novel regimens
Levofloxacin – 100mg dispersible tablet
Pharmacokinetics of moxifloxacin

Summary pharmacokinetic parameters of moxifloxacin in children with multidrug-resistant TB (n=23), and published values in adults with TB

<table>
<thead>
<tr>
<th></th>
<th>( C_{\text{max}} ) (μg/ml)</th>
<th>( \text{AUC}_{0-24} ) (μg·h/ml)</th>
<th>( t_{1/2} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (IQR)</td>
<td>N</td>
</tr>
<tr>
<td>Children 7-15y (10mg/kg dose)</td>
<td>23</td>
<td>3.08 (2.85 - 3.82)</td>
<td>12</td>
</tr>
<tr>
<td>Adult summary (400 mg dose)</td>
<td></td>
<td>3.3 - 6.1</td>
<td></td>
</tr>
</tbody>
</table>

Thee S. Clin Infect Dis. 2015
<table>
<thead>
<tr>
<th>Grade of AE</th>
<th>Gr 0</th>
<th>Gr 1</th>
<th>Gr 2</th>
<th>Gr 3-4</th>
<th>Any AE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint, muscle or bone pain</td>
<td>122</td>
<td>11</td>
<td>2</td>
<td>2 (1.5)</td>
<td>15 (10.9)</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>104</td>
<td>30</td>
<td>2</td>
<td>1 (0.7)</td>
<td>33 (24.1)</td>
</tr>
<tr>
<td>Itchy skin</td>
<td>110</td>
<td>24</td>
<td>2</td>
<td>1 (0.7)</td>
<td>27 (19.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>120</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>17 (12.4)</td>
</tr>
<tr>
<td>Sleep/mood problem</td>
<td>124</td>
<td>9</td>
<td>3</td>
<td>1 (0.7)</td>
<td>13 (9.5)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>118</td>
<td>17</td>
<td>1</td>
<td>1 (0.7)</td>
<td>19 (13.9)</td>
</tr>
<tr>
<td>Visual problem</td>
<td>132</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5 (3.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>113</td>
<td>20</td>
<td>3</td>
<td>1 (0.7)</td>
<td>24 (17.5)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>125</td>
<td>10</td>
<td>1</td>
<td>1 (0.7)</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>133</td>
<td>1</td>
<td>2</td>
<td>1 (0.7)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>↓Appetite/nausea</td>
<td>118</td>
<td>14</td>
<td>3</td>
<td>1 (0.7)</td>
<td>18 (13.1)</td>
</tr>
<tr>
<td>Hearing loss (n=142)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25 (17.6)</td>
</tr>
<tr>
<td>Thyroxine supplementation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32 (22.5)</td>
</tr>
</tbody>
</table>

Seddon, Clin Infect Dis 2013
Acknowledgements

- Anneke Hesseling