Introduction to pharmacokinetics and pharmacodynamics of TB drugs

Xiith International Child TB Training Course
Goudini Spa, South Africa, September 12, 2017

Presented by: Kelly Dooley MD, PhD
Johns Hopkins University School of Medicine
Part I
Clinical Pharmacology
An Overview of Vocabulary and Tools
The Context: **What’s wrong with TB therapy?**

- 6 months is not “short-course”
- Only a minority of pts completes TB therapy in 6 mos
  - < 90% complete in 12 months
- We extrapolate drugs/dosing from adult pulmonary TB to other populations and other forms of TB
- Adverse drug reactions cause morbidity & mortality
- Drug-drug interactions create challenges
- Resistance happens

Better understanding and application of PK/PD science can help
PK or PK/PD Studies: Role in Optimizing Treatment

- **Phase I studies**
  - Determine PK characteristics of a drug, maximal tolerated dose, food effect

- **Drug-interaction studies**
  - Evaluate pharmacokinetic drug interactions, assess overlapping toxicities

- **Phase II dose-finding**
  - Understand dose-concentration-effect (PK/PD) relationships to pick dose to take forward

- **Pharmacogenomics**
  - Helps explain variability in pharmacokinetics and treatment response

- **Establishing dosing for special populations**
  - children, pregnant women, patients with disease in a pharmacologically less-accessible site

- **Phase III trials**
  - Determine the reasons that treatment was not effective in some subpopulations
The ‘magical journey’ of a medicine in your body

Or, alternatively, ‘a pharmacologist’s view of the world’

The 'magical journey' of a medicine in your body

[Diagram showing the journey of a medicine through the body, starting in the Gut, entering the Blood, and then reaching the Site of Action, with processes involving Liver and Kidney.]
Pharmacokinetics & Pharmacodynamics: linking events, concentrations, and time

- Pharmacodynamics (PD)
  - What the drug does to the body
  - Variation of drug effects with varying drug amount
  - Concentration-response
  - Deciding on the target

- Pharmacokinetics (PK)
  - What the body does to the drug
  - Variation in drug concentration in space and time
  - Concentration-time data
  - Hitting the target

Adapted slide from Craig Hendrix, MD
Jogging your memory: audience response #1

Matching

- Bioavailability, F
- Absorption rate constant, $K_a$
- Volume of distribution, $V_d$
- Oral clearance, $CL/F$
- Area under the concentration-time curve (AUC)
- Maximum concentration, $C_{max}$
- Half-life, $t_{1/2}$

The right answers, in order are: AGBFEDC

True=A; False=B
Pharmacokinetic Parameters

- Area under the curve, AUC
- Maximum concentration, Cmax
- Bioavailability, F
- Volume of distribution, Vd
- Clearance, Cl
- Half-life, $t_{1/2}$

MEC=minimum effective concentration; MSC=maximum safe concentration
Some terms…

**Bioavailability (F)**
Fraction of a dose of drug that reaches the systemic circulation after an extravascular dose (oral, intramuscular, etc.) (unitless, %)

**Clearance (Cl)**
Rate at which a volume of fluid is completely cleared of drug (mL/min)

**Volume of Distribution, Vd**
Volume into which a dose “appears” to have been uniformly distributed

\[
\text{Dose (mg)} \div \text{Vd (mL)} = \text{Concentration (mg/mL)}
\]
<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume of distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>8L (high protein binding)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>30L (distribution in total body water)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>15,000L (highly lipophilic, sequesters into fat)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>60 L</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>540 L</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>1470 L</td>
</tr>
</tbody>
</table>
Pharmacokinetics: (Understanding) **Variability** is important

### Determinants

- Genetic differences in drug transporter enzymes\(^1\)
- Patient-specific characteristics
  - Large body mass\(^3,4\)
  - Diabetes mellitus\(^3,4\)
  - HIV infection\(^2,3\)
  - Childhood\(^5\)
- Food effect and other causes of dose-to-dose variability\(^2\)
- Non-dose-proportional PK\(^3\)

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1. Antimicrob Agents Chemother (2007); 51:2861
3. Drugs (2002); 62:2169
6. Am J Respir Crit Care Med (2015); 191:333
Pharmacodynamics: Optimizing Rx for efficacy and safety

• **Concentration-dependent activity**
  - Effect of the drug increases as you increase the concentration at the site of infection
  - Parameter associated with best kill: $C_{\text{max}}/\text{MIC}$

• **Time-dependent activity**
  - Major killing effect against an organism is produced by the time that the drug at the binding site
  - Parameter associated with best activity: **Time above MIC**

• **Therapeutic margin**
  - The ratio between the toxic dose and the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment
TB is a complex disease: multiple “effect” compartments

- Metabolic state of bacteria may vary by lesion type
- Drug activity may be different depending on microenvironment
- TB is both an intracellular and extracellular disease
Differential vascularization of lesions in the LUNG

Diffusion of drugs into necrotic lesions with poor blood supply
### Do TB Drugs get to the site of infection: TB meningitis?

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF:serum ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.04-0.11</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>0.79-1.05</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Negligible (&lt;MIC even with meningitis)</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Good</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>0.7-0.8</td>
</tr>
</tbody>
</table>

*Depends on lipid solubility, ionization, molecular weight, protein binding, meningeal inflammation, etc.
Part II

New and Old TB drugs

Using clinical pharmacology to inform treatment optimization
Which PK/PD parameter correlates best with INH activity?

AUC/MIC has best correlation with bactericidal effect

Jayaram et al, AAC 2004; 48:2951
Audience response #2
The first time the term ‘Pharmacogenetics’ was used in a PubMed-cited article was by geneticists at JHU in reference to genetically-determined differences in the metabolism of which anti-TB drug?

A. Isoniazid
B. Rifampicin
C. Pyrazinamide
D. Ethambutol
E. Amikacin
Pharmacokinetics of Isoniazid

- Metabolized by n-acetyltransferase 2 (NAT2)
- Half-life depends on acetylator status, or NAT2 genotype
- Slow acetylator prevalence varies geographically:
  - 67% USA
  - 12% China
  - 83% Egypt
Pharmacokinetics of Isoniazid: the birth of Pharmacogenetics

• In 1960, McCusick and colleagues report genetically determined difference in the metabolism of isoniazid – slow metabolism is an autosomal homozygous recessive trait

• Evans, a co-investigator on this publishes article: Pharmacogenetics (1961). Br Med Bull 17: 234-40
Isoniazid Pharmacogenetics

![Histogram showing half-life distribution for slow and fast acetylators.](image-url)
Maximum EBA achieved with dose of 300 mg (~5 mg/kg) for drug-sensitive TB

n.b. There is measurable activity against DS isolates even with doses as small as 18.75 mg (0.38 mg/kg).
Isoniazid: What’s the right dose for patients with MDR-TB?

**Design of A5312**

**INH-resistant TB**

- **Group 1:** Dose-ranging
  - M. tuberculosis with \textit{inhA} mutation
  - Apply treatment INH 5, 10, or 15 mg/kg (drug)
  - NAT2 metabolizer genotype (host)
  - Measure 7-day Early Bactericidal Activity (EBA)

- **Group 2:** Positive Control Arm
  - Standard INH dosing

- **Group 3:** MIC only
  - M. tuberculosis with \textit{katG} mutation
  - Gather MIC data

**Drug-sensitive TB**

- Apply treatment INH 5mg/kg (drug)
- Measure 7-day Early Bactericidal Activity (EBA)

**Treatment response**

- **Define Target AUC/MIC** (based on positive control arm, max effect in experimental arms)
- Monte Carlo simulation using MIC, NAT2, AUC to determine dose required to achieve targets.
Why it’s important to get it (dosing, esp. rifampin) right
What happens when drug concentrations are too low?

Serum Drug Concentrations Predictive of Pulmonary Tuberculosis Outcomes

Jotam G. Pasipanodya,1 Helen McIlleter,2 André Burger,3 Peter A. Wash,3 Peter Smith,3 and Tawanda Gumbo1,4

1Office of Global Health, University of Texas Southwestern Medical Center, Dallas, Texas; 2Division of Pharmacology, Department of Medicine, University of Cape Town, Observatory; and 3The Brewelskloof Hospital, Worcester, South Africa; and 4Department of Medicine, University of Texas Southwestern Medical Center, Dallas

Results. Drug concentrations and pharmacokinetics varied widely between patients. Poor long-term outcomes were encountered in 35 (25%) patients. The 3 top predictors of poor long-term outcome, by rank of importance, were a pyrazinamide 24-hour area under the concentration–time curve (AUC) ≤ 363 mg·h/L, rifampin AUC ≤ 13 mg·h/L, and isoniazid AUC ≤ 52 mg·h/L. Poor outcomes were encountered in 32/78 patients with the AUC of at least 1 drug below the identified threshold vs 3/64 without (odds ratio = 14.14; 95% confidence interval, 4.08–49.08). Low rifampin and isoniazid peak and AUC concentrations preceded all cases of acquired drug resistance.

Conclusions. Low drug AUCs are predictive of clinical outcomes in tuberculosis patients.
Why is rifampin special? What is “sterilizing activity”?

SUMMARY Model systems were set up in vitro to explore the reasons why rifampin is a better sterilizing drug than isoniazid in short-course chemotherapy of tuberculosis. When the growth rate of *Mycobacterium tuberculosis* strain H37Rv was reduced uniformly by lowering the incubation temperature or the pH of the culture medium, the bactericidal activity of rifampin and isoniazid decreased to a similar extent. However, when a culture was maintained at 8°C and incubated for daily periods of 1 or 6 h at 37°C, rifampin killed more rapidly than isoniazid. Maintenance of control cultures without antimicrobials at 8°C with or without periods at 37°C, had little or no effect on their viability, ability to commence logarithmic growth at 37°C, or to incorporate [14C]uridine. Old cultures left undisturbed or to which small additions of fresh culture medium were regularly added were killed more rapidly by rifampin than by isoniazid. These experiments supported the view that the special part of the bacterial population that is killed more rapidly by rifampin than by isoniazid during short-course chemotherapy consists of bacilli dormant much of the time but occasionally metabolising for short periods.

Dickinson & Mitchison 1981

AM REV RESPIR DIS 1981; 123:367-371
‘Everyone does fine’ – or do they?

Among successfully treated patients with TB, incidence risk of relapse is 2,836/100,000 in first year following treatment.
Effects of HIV infection on:

**TB drug concentrations** and treatment outcomes

McIlver et al AAC 2006:
- HIV infection associated with 39% reduction in rifampin exposures
- Formulation was determinant of rifampin bioavailability

Rockwood et al AAC 2016

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Comparison of Treatment Outcomes of New Smear-Positive Pulmonary Tuberculosis Patients by HIV and Antiretroviral Status in a TB/HIV Clinic, Malawi

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Percentage</th>
<th>Adjusted Odds Ratio (95% CI) for treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td>1,275</td>
<td>56%</td>
<td>1.00</td>
</tr>
<tr>
<td>HIV negative</td>
<td>989</td>
<td>44%</td>
<td>1.49 (1.14–1.94)</td>
</tr>
</tbody>
</table>

*P-value*
Higher-dose rifamycins in patients with advanced HIV

Patients with HIV and low CD4 count

AIDS 2016: High-Dose Rifampicin for TB May Improve Survival of HIV+ People with Low CD4 Counts

More aggressive tuberculosis (TB) treatment using a high dose of rifampicin, in addition to antiretroviral therapy (ART), could reduce mortality among people with HIV/TB coinfection who are severely immunocompromised, according to results from the 3-arm RAFA trial presented at the 21st International AIDS Conference (AIDS 2016) last month in Durban.

[Produced in collaboration with Aidsmap.com]

TB remains the leading infectious cause of death among people living with HIV. Even when a person with HIV develops drug-susceptible TB that appears to respond to the standard 6-month treatment, 12-month mortality is often poor. To improve outcomes, the World Health Organization recommends initiating ART as soon as possible after starting TB treatment.

RAFA trial

• Immediate ART (2 wks) vs.
• Delayed ART (8 wks) vs.
• Delayed ART but RIF 15 mg/kg (intensive phase)

IAS 2016
Mortality for patients with less than 100 CD4: RAFA Trial results

Slide, adapted, from http://programme.aids2016.org/Programme/Session/962
**Current use of rifampin: might higher doses be better?**

**Pharmacodynamics in mice**

Jayaram et al, AAC (2003); 47:2118

<table>
<thead>
<tr>
<th>RIF dose</th>
<th>n</th>
<th>EBA_{0.2} (log CFU/ml/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td>600 mg</td>
<td>8</td>
<td>0.19</td>
</tr>
<tr>
<td>1200 mg</td>
<td>8</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Jindani et al, ARRD 1980; 121:939
## PanACEA MAMS results

<table>
<thead>
<tr>
<th></th>
<th>Control( (R_{10}^{\text{HZE}})) N=123</th>
<th>R(_{35}^{\text{HZE}}) N=63</th>
<th>RQHZ N=58</th>
<th>R(_{20}^{\text{QHZ}}) N=56</th>
<th>R(_{20}^{\text{MHZ}}) N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12 weeks (MGIT)</strong></td>
<td>% cx conversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.1%</td>
<td>79.9%</td>
<td>65.2%</td>
<td>58.6%</td>
<td>78.7%</td>
</tr>
<tr>
<td></td>
<td>aHR (CI)</td>
<td>1.78 (1.22-2.58)</td>
<td>0.85 (0.57-1.27)</td>
<td>0.76 (0.50-1.17)</td>
<td>1.42 (0.98-2.05)</td>
</tr>
<tr>
<td><strong>8 weeks (MGIT)</strong></td>
<td>% cx conversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32%</td>
<td>49%</td>
<td>34.5%</td>
<td>27.8%</td>
<td>46.2%</td>
</tr>
<tr>
<td></td>
<td>aHR (CI)</td>
<td>2.06 (1.26-3.38)</td>
<td>1.04 (0.59-1.81)</td>
<td>0.91 (0.49-1.67)</td>
<td>1.67 (1.01-2.67)</td>
</tr>
<tr>
<td><strong>8 weeks (LJ)</strong></td>
<td>% cx conversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80.9%</td>
<td>88.0%</td>
<td>83.9%</td>
<td>82.6%</td>
<td>82.7%</td>
</tr>
<tr>
<td></td>
<td>aHR (CI)</td>
<td>1.17 (0.83-1.64)</td>
<td>1.00 (0.70-1.42)</td>
<td>1.06 (0.74-1.52)</td>
<td>0.76 (0.54-1.07)</td>
</tr>
</tbody>
</table>

PK-PD analysis is coming soon....

Boeree et al Lancet ID 2016
Impact of bedaquiline exposure
On time to sputum culture conversion

Perpetrator drug  Effect on BDQ $C_{ave,ss}$

- Efavirenz: -52%
- Rifampicin: -79%
- LPV/r: +188%

Next steps: DDI

Audience response
Match each drug to its important PK or PK/PD characteristic

- Rifapentine
- Bedaquiline
- Delamanid
- Amikacin
- Linezolid

A. Mitochondrial toxicity related to cumulative exposure
B. Potent inducer of metabolizing enzymes
C. Cytochrome P450 substrate, therefore victim of many DDI
D. Extremely slow half-life of disappearance from inner ear tissues
E. Low bioavailability, must be dosed separately from other drugs
Part III
Pharmacology of TB Drugs in Children
When are efficacy trials required for children (vs. PK/safety alone)?

Minimal disease?  
Severe disease?  
LTBI -> active disease?

Modified, from FDA Guidance
Developmental pharmacology:

A Moving Target, role of ontogeny

Pediatric TB ≠ Adult TB: What does pediatric TB look like?

It depends (on how old you are)!

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>No disease</th>
<th>Pulmonary dz</th>
<th>TBM/miliary dz</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>50</td>
<td>30-40</td>
<td>10-20</td>
</tr>
<tr>
<td>1-2</td>
<td>70-80</td>
<td>10-15</td>
<td>2-5</td>
</tr>
<tr>
<td>2-5</td>
<td>95</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>5-10</td>
<td>98</td>
<td>2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>80-90</td>
<td>10-20</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

Table 4. Average age-specific risk for disease development following primary infection (immune-competent children)*

*Adapted from Marais et al 2004 IJTLD.
The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era
“Drug must be present \textit{at the site of disease} at sufficient concentrations for sufficient duration to effect functional cure”

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Where the bacilli live</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated</td>
<td>Intracellular</td>
</tr>
<tr>
<td></td>
<td>Note the role of cell-mediated immunity</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>Brain, meninges, cerebrospinal fluid</td>
</tr>
<tr>
<td></td>
<td>Drugs must cross BBB, BCSF barriers; not be PGP substrate</td>
</tr>
<tr>
<td></td>
<td>CNS Multiparameter Optimization desirability score</td>
</tr>
<tr>
<td>Minimal disease</td>
<td>Lymph nodes, intrathoracic lymph nodes or bronchi</td>
</tr>
<tr>
<td>Adult-type cavitary lung disease</td>
<td>Necrotic, caseous content of cavity</td>
</tr>
<tr>
<td></td>
<td>Drugs must diffuse through caseum</td>
</tr>
</tbody>
</table>

Tucker et al (2017) IJTLD, in press
Revised WHO dosing for children—

*Are we achieving target concentrations?*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Revised dose</th>
<th>2-hour target</th>
<th>Mean concentration</th>
<th>% achieving target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>10-15 mg/kg</td>
<td>3 mcg/mL</td>
<td>4.5 mcg/mL</td>
<td>65%</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10-15 mg/kg</td>
<td>8 mcg/mL</td>
<td>2.9 mcg/mL</td>
<td>6%</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
<td>20 mcg/mL</td>
<td>23 mcg/mL</td>
<td>55%</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-25 mg/kg</td>
<td>2 mcg/mL</td>
<td>1.1 mcg/mL</td>
<td>15%</td>
</tr>
</tbody>
</table>

PHATISA Study (n=23, Durban, SA): Hiruy et al JAC doi:10.1093/jac/dku478
Mean plasma rifampin (RMP) concentrations (μg/ml) after the intake of a mean dose of 12.9 mg/kg for RMP formulation 1 (n = 14) and of a mean dose of 16.7 mg/kg for RMP formulation 2 (n = 25).
Yes, but do TB drug concentrations in children matter? “they all do well…”

**TABLE 3.** Multiple Regression Analysis Showing Factors Significantly Influencing Peak Concentration and Exposure of RMP, INH and PZA

<table>
<thead>
<tr>
<th>Factor</th>
<th>( \beta )</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} )</td>
<td>0.881</td>
<td>0.065 to 1.697</td>
<td>0.035</td>
</tr>
<tr>
<td>Serum albumin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.305</td>
<td>0.154 to 0.455</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV infection</td>
<td>-1.698</td>
<td>-2.796 to -0.600</td>
<td>0.003</td>
</tr>
<tr>
<td>AUC (_{0-48h} )</td>
<td>-12.883</td>
<td>-16.878 to -8.889</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.472</td>
<td>0.752 to 2.192</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ramachandran et al PIDJ 2016 35:530

**Figure 3.** The logistic regression model predictions of the probability of unfavorable treatment outcome \((P_{\text{unfavorable}})\) as a function of the rifampin exposure at steady state over a 48-h period \((\text{AUC}_{\text{RIF,0–48h,ss}})\).
The Indian experience

Predicted probability of unfavorable treatment outcome ($P_{\text{unfavorable}}$) under the current (left panel) and future (right panel) revised national tuberculosis control program (RNTCP) dosing recommendations.

Based on NIRT data from children with TB mono-infection and TB/HIV co-infection
What about second-line drugs for children? Example of Levofloxacin: What is the right dose? Is it safe? How about LFX 15 mg/kg daily (NICHD R01 PI=Hesseling)?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Target value</th>
<th>Mean (sd) PK value/MIC if MIC is 0.5</th>
<th>Mean (sd) PK value/MIC if MIC is 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ /MIC</td>
<td>8-10</td>
<td>13.1 (4.0)</td>
<td>6.5 (2.0)</td>
</tr>
<tr>
<td>AUC/MIC</td>
<td>100</td>
<td>65.3 (18.4)</td>
<td>32.6 (9.2)</td>
</tr>
</tbody>
</table>

QTc interval in children on levofloxacin (n=22)

<table>
<thead>
<tr>
<th>Levofloxacin 15mg/kg</th>
<th>Mean QTc in ms (SD)</th>
<th>QTc ≥450 ms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>369.1 (21.9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

15 mg/kg likely not quite enough for children > 2 years of age

*Thee, Antimicrob Agents Chemother, 2013*
# TB/HIV Co-Treatment: Limited Options for Children

## Table 2b. Recommendations for coadministering antiretroviral drugs with rifampin in children – 2013

<table>
<thead>
<tr>
<th>Antiretroviral drug regimen choices</th>
<th>Recommended change in dose of antiretroviral drug</th>
<th>Recommended change in dose of rifampin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Super-boosted&quot; lopinavir / ritonavir + 2 NRTIs</td>
<td>Pediatric weight-adjusted dosing for lopinavir/ritonavir* (Kaletra™) PLUS added ritonavir to reach mg to mg parity of lopinavir and ritonavir doses</td>
<td>No change</td>
<td>Preferred.</td>
</tr>
<tr>
<td>Zidovudine/lamivudine/ abacavir</td>
<td>None (standard pediatric weight-adjusted dosing*)</td>
<td>No change</td>
<td>Alternative for children &lt;3 years</td>
</tr>
<tr>
<td>Efavirenz + 2 NRTIs</td>
<td>None (standard pediatric weight-adjusted dosing*)</td>
<td>No change</td>
<td>Efavirenz AUC ↓ by 20-30% on average, though effect is highly variable. Alternative for children age &gt;3 years. Careful monitoring of virologic response; therapeutic drug monitoring of efavirenz levels if available</td>
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</table>

Rifabutin dosing for children with TB/HIV co-infection taking PI-based ART

Pharmacokinetics and safety of rifabutin in young HIV-infected children receiving rifabutin and lopinavir/ritonavir

Harry Moultrie¹*, Helen McIlleron², Shobna Sawry¹, Tracy Kellermann², Lubbe Wiesner², Gurpreet Kindra¹, Hermien Gous¹ and Annelies Van Rie³

RBT 5 mg/kg three times a week in children < 5 years of age taking LPV/r
Study stopped after 6 participants by IRB because of severe, transient neutropenia
Tuberculous meningitis: starting with adults…

Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis

Lindsey te Brake, Sofiati Dian, Ahmad Rizal Ganiem, Carolien Ruesen, David Burger, Rogier Donders, Rovina Ruslami, Reinout van Crevel, Rob Aarnoutse

Note:
Rifampicin bioavailability: 60%
CSF:plasma ratio: 0.082
Then, from adult and pediatric data, predict (then confirm) doses children need to achieve targets…

Figure 3. Range of recommended rifampicin doses for children with TB meningitis, by weight and age, to achieve AUC target of 92 mg*h/L. Black bars represent the range for intravenous dosing and grey bars represent the range for oral dosing.

At least 30 mg/kg orally (or 15 mg/kg IV)

Collaborative effort: Rada Savic; Rovina Ruslami; Jenn Hibma; Anneke Hesseling; Geetha Ramachandran; A Rizlam Ganiem; Soumya Swaminathan; Helen McIlleron; Amita Gupta; Reinout van Crevel; Robert Aarnoutse; Kelly E. Döbley
New drugs for TB: dosing for kids

(1) Start with knowledge of age-to-weight distribution of children w TB, clearance/metabolic pathway, all available PK info
(2) Build model, decide weight bands, simulate likely PK
(3) Test the doses to make sure they achieve targets and are safe

<table>
<thead>
<tr>
<th>WT-band1</th>
<th>WT-band2</th>
<th>WT-band3</th>
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<th>WT-band6</th>
<th>WT-band7</th>
<th>Adult dose</th>
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</table>

1), 2), 3) and 6) refer to the pediatric formulation

Work of Maria Kjellsson, Elin Svensson, Mats Karlsson

Figure 3: Exposure, dosing strategy 1) [age < 6 yrs]
Summary

• Doses of most first-line drugs are suboptimal, and are particularly low in certain populations, including young or HIV-infected children

• Clinical pharmacology and its tools can help us explain variability in drug exposures, PK-efficacy, and PK-toxicity relationships (which may differ in adults and children)– this can help us choose right drugs and doses

• One size does NOT fit all

• Mathematical modeling (pharmacometrics) in design and analysis phases of studies can increase yield and efficiency of trials, especially in children

• Lots of work to do to improve treatment for drug-sensitive TB, drug-resistant TB, TB meningitis, TB/HIV co-infection, LTBI in children
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  • Tuberculosis Trials Consortium
  • AIDS Clinical Trials Group
  • IMPAACT Network

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