Pharmacokinetics and doses of antituberculosis drugs in children

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Declarations

• I have no conflict of interest
• I am only a clinician, not a pharmacologist
• The reason for our/my interest in this area is to determine the best doses for the different anti-TB drugs in children
• As a general approach, the recommended dose of anti-TB drugs in children should lead to a PK profile that approximates the adult exposures associated with efficacy and safety
In Considering Treatment of Childhood TB

• Mainly paucibacillary disease compared to adult pulmonary TB (less cavities in the lungs)

• More extrapulmonary TB (EPTB) including severe and disseminated TB (TBM and miliary TB) especially in the young (<3 yr)

• Bacillary load and type of TB may influence effectiveness of Rx regimens

• Rx outcome in children is generally good provided that Rx starts promptly
Main objectives of TB treatment

Intensive phase

• To rapidly kill most bacilli in order to:
  - prevent disease progression
  - prevent transmission of infection
  - prevent development of drug resistance

Continuation phase

• To effect cure and prevent relapse (eliminate dormant bacilli)

To do all of the above with minimal adverse effects
Current First-Line Regimen

Bacterial intensive phase
INH, RMP
PZA (EMB, SM)

Sterilising continuation phase
INH, RMP

85–95% Sputum culture negative

Percentage organisms killed

Percentage patients cured

Time (months)
Why has first-line anti-TB drug doses changed?

In 2006 WHO published a literature review on ethambutol:

• “Peak serum EMB concentrations in both children and adults increase in relation to dose, but are significantly lower in children than adults receiving the same mg/kg body weight dose.”

• It was recommended that the dose for children should be 20 mg/kg (15-25 mg/kg)

Pharmacokinetics (PK) of first-line anti-TB drugs in children

• Recent studies and reviews on PK of first-line anti-TB drugs in children showed:
  - in general, children achieved lower serum concentrations of drugs than adults at the same mg/kg dose
  - however, this was variable – e.g. PZA maximum concentrations were the same in adults and children
  - children eliminated drugs faster than adults at the same mg/kg body weight doses
Pharmacokinetics of INH

Several PK “benchmarks” have been associated with optimal INH efficacy (in adults):

- A 2 h serum concentration of approximately 3.0 µg/ml
  (Mitchell & Bell 1957, Gangadharam et al 1961)

- A 2 h post-dose serum concentration of 3-5 µg/ml
  (Peloquin 1992)

- A 2 h post-dose serum concentration of 2-3 µg/ml
  (Donald et al 2004 & 2007)
2-hr INH concentration vs. dose. The 2-hour INH serum concentration associated with the EBA90 is 2.19 µg/ml.
INH Pharmacokinetics in Children
(4-6mg/kg dose)
McIlion et al CID 2009
Pharmacokinetics of Isoniazid in Low-Birth-Weight and Premature Infants

LBW infants receiving 10 mg/kg of INH had desirable blood drug concentrations, .... However, a prolonged half-life and reduced elimination of INH were noted in smaller and younger infants, especially in ... slow acetylators. ...we caution against exceeding a dosage of 10 mg/kg in this population.

Bekker et al. AAC 2014;58:2229
INH study results

• Studies found, taking into account the NAT2 genotype (i.e. acetylation type – fast, intermediate or slow, which is responsible for eliminating INH), that younger children eliminate INH faster than older children, and children, as a group, faster than adults

• WHO and IUATLD previously recommend 5 mg/kg (4-6) INH for children and adults. However, AAP and BTS recommend an INH dose of 10-15 mg/kg/dose

• New WHO recommendation: 10mg/kg (7-15mg/kg)
Mean age
- HIV+: 3.73 yrs;
- HIV-: 4.05 yrs

Mean dose RMP:
9.6 mg/kg

Mean 2 h RMP Concentrations:
- HIV+: 3.90 ug/ml
- HIV-: 4.78 ug/ml

Dosage 8-12 mg/kg
Rimcure & Rimactazid
(Sandoz SA Pty)

Not reaching $C_{\text{max}}$ target of 8μg/mL
Thee S et al. Pharmacokinetics of isoniazid, rifampicin and pyrazinamide in children younger than two years of age with tuberculosis: evidence for the implementation of revised World Health Organization recommendations. Antimicrob Agents Chemother 2011; doi1128/AAC.05429-11

Rifampin

- 15 mg/kg
- 10 mg/kg
Simulations based on our models predict that the newly recommended weight band-based doses in WHO guidelines for children result in rifampicin exposures in our paediatric population that are similar to those in adults. However, when dosed in pragmatic weight bands, there is wide variability in drug exposure.
Recommended PZA serum concentrations


Target: $C_{\text{max}}$ 20-60 µg/ml


A study of HIV-infected and HIV-uninfected adult tuberculosis patients from Botswana found a poor outcome to be associated with: PZA $C_{\text{max}}$ of $<35$ µg/mL
Pyrazinamide PK in adults and children


Courtesy Prof PR Donald
Simulations based on our models suggest that with the new WHO dosing guidelines and utilizing available paediatric fixed-dose combinations, pyrazinamide and isoniazid exposures in many children will be lower than in adults. Further studies are needed...
## WHO doses first-line anti-TB drugs

<table>
<thead>
<tr>
<th>Drug (Abbrev)</th>
<th>Recommended dose in mg/kg BW (range)</th>
<th>Daily (new WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>10 (7-15)</td>
<td>max 300/d</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>15 (10-20)</td>
<td>max 600/d</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>35 (30-40)</td>
<td>max 2000/d</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>20 (15-25)</td>
<td>max 1600/d</td>
</tr>
</tbody>
</table>
Delayed-Release Granules
4 g p-aminosalicylic acid

Store in a refrigerator (2 °C – 8 °C). Avoid excessive heat.

PASER packets may be stored at or below 25°C for not longer than 7 days.

KEEP OUT OF REACH OF CHILDREN

Pharmplan (Pty) Ltd
Treatment of drug-resistant childhood TB

• Most second-line anti-TB drug dosages in current TB treatment guidelines are inferred from adult data
• Pharmacokinetic studies of first-line drugs in general (but not all) higher mg/kg doses required in children than in adults to achieve same $C_{\text{max}}$ and / or AUCs
• **However**: efficacy studies in children almost impossible and optimal PK parameters are therefore difficult to establish, therefore adult reference values used
• Almost no pharmacokinetic studies on second-line drugs in children
• New (novel) drugs – only starting dose seeking and safety studies in children
Changes during growth

• height and weight, body surface
• Relative size of body compartments / organs
• Ability to absorb, metabolize and excrete drugs
PK of ethionamide (ETH) in adults

• Complete absorption from the intestine unaffected by food or antacids

• Distributes well in body compartments (incl. CSF)

• Metabolised in the liver to metabolites also active against *M. tb*

• Metabolites are excreted mainly by the kidney

• $C_{\text{max}}$ 1.9 to 2.5µg/ml after 500mg dose [Zhu 2002, Auclair 2001]

• $T_{\text{max}}$ after approximately 2h [Zhu 2002]

• **Recommended ETH serum $C_{\text{max}}$ for clinical purposes 2.5µg/ml** [Heifets 1991]

ETH PK studies in children

• 2 separate PK studies in children
• Study 1: children 0-12 years:
  Age groups: 0-2 yrs; 2-5 yrs; 6-12 yrs with 10 in each group
  ETH dose 15-20 mg/kg daily
  PK time points: 0, 1, 2, 3, 4 and 6 hrs
  PK done at months 1 and 4 on treatment
• Study 2: children 0-15 years (part of large PK study)
  Age groups: 0-2 yrs; 2-5 yrs; 6-15 yrs (34 children)
  ETH dose 20mg/kg daily
  PK time points: 0, 1, 2, 4, 6, 8 hrs
  Once only between 1-2 months on Rx
ETH serum concentrations in children of different age groups after oral intake of ETH 15-20mg/kg (n=31 children)

C\textsubscript{max} higher in children >2y than in those <2y of age (Mann Whitney p=0.003)

T\textsubscript{max} shorter in children <2y than in those >2y of age (Mann Whitney p= 0.001)
Relationship between age and area under the curve \( (AUC_{0-6}) \) after oral intake of ETH 15-20mg/kg
(children with and without RMP)

\[ \text{AUC}_{0-6} \text{ increases with age (Spearman Rho correlation } p=0.001) \]

Courtesy Steffi Thee
**ETH 2\textsuperscript{nd} study by age and HIV status (N=34)**

<table>
<thead>
<tr>
<th>Age group</th>
<th>$C_{\text{max}}$ ((\mu\text{g/ml}))</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$AUC_{0.8}$ ((\mu\text{g} \cdot \text{h/ml}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (IQR)</td>
<td>p-value</td>
</tr>
<tr>
<td>0-2 years</td>
<td>10</td>
<td>7.66 (6.01 - 9.38)</td>
<td>0.119</td>
</tr>
<tr>
<td>2-5 years</td>
<td>11</td>
<td>5.10 (4.37 - 7.48)</td>
<td></td>
</tr>
<tr>
<td>6-15 years</td>
<td>13</td>
<td>4.97 (4.35 - 6.27)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV status</th>
<th>$C_{\text{max}}$ ((\mu\text{g/ml}))</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$AUC_{0.8}$ ((\mu\text{g} \cdot \text{h/ml}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (IQR)</td>
<td>p-value</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>9</td>
<td>4.86 (4.31 - 6.01)</td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>25</td>
<td>6.37 (4.93 - 8.01)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions: Ethionamide studies

• Mean ETH $C_{\text{max}}$ in all age groups were above recommended serum $C_{\text{max}}$ of 2.5µg/ml for clinical effectiveness in adults at 15-20 mg/kg dose

• More rapid absorption with earlier peak concentration in younger children – possible effect of crushing tablets

• AUC and $C_{\text{max}}$ was not consistently different in the age groups in the two studies, but high inter- and intraindividual variability was found

• Lower concentrations in HIV-infected children?

• Larger analysis planned with PK modeling of +/- 100 children
# Amikacin by age & HIV status (N=28)

## Amikacin dose: 20mg/kg IMI

<table>
<thead>
<tr>
<th>Age group</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-8&lt;/sub&gt; (μg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (IQR)</td>
<td>p-value</td>
</tr>
<tr>
<td>0-2 years</td>
<td>6</td>
<td>43.65 (42.20 - 49.20)</td>
<td></td>
</tr>
<tr>
<td>2-5 years</td>
<td>7</td>
<td>49.10 (40.70 - 59.20)</td>
<td></td>
</tr>
<tr>
<td>6-15 years</td>
<td>15</td>
<td>49.60 (40.30 - 56.40)</td>
<td>0.845</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-infected</td>
<td>10</td>
<td>47.05 (42.20 - 54.40)</td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>18</td>
<td>46.85 (40.70 - 53.00)</td>
<td>0.719</td>
</tr>
</tbody>
</table>

Courtesy AC Hesseling
Early Bactericidal Activity of Amikacin

(EBA) of an anti-TB agent is defined as the fall in log(10) colony forming units (cfu) of M. tuberculosis per ml sputum per day during the first 2 days of treatment.

Table 3  The early bactericidal activity (EBA) of amikacin in relation to the dose of amikacin (mg/kg/body weight) and mean plasma amikacin concentrations at 1, 2, 3 and 4 hours after amikacin administration*

<table>
<thead>
<tr>
<th>Amikacin dosage mg/kg</th>
<th>Mean EBA</th>
<th>Mean amikacin plasma concentrations μg/ml (SD); hours after dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0.0405</td>
<td>13.5 (±2.7)</td>
</tr>
<tr>
<td>10</td>
<td>0.0450</td>
<td>26.7 (±5.5)</td>
</tr>
<tr>
<td>15</td>
<td>0.0533</td>
<td>39.2 (±9.0)</td>
</tr>
</tbody>
</table>

* The minimal inhibitory concentration of amikacin for M. tuberculosis on Löwenstein-Jensen solid media is reported to vary from 2-4 μg/ml.6,7

Donald,  Int J Tuberc Lung Dis, 2001
Amikacin: Discussion

- Adult target values: $C_{\text{max}}$: 35-45 μg/ml*
- Adult dose: 1 gram (750 mg range)
- All children exceeded adult recommended $C_{\text{max}}$

- Lower exposures (AUC) in younger age groups: distributed to body water; unpredictable PK
- Correlation: PK and toxicity? Especially important as causes irreversible hearing loss
- Role for Therapeutic Drug Monitoring? Not possible in most high-burden areas
- Dose reduction to 15 mg/kg now implemented – awaiting results
- Follow-up PK and safety at lower dose

*Peloquin, Antimicrob Agents Chemother, 2002
The Fluoroquinolones

- Later generation FQNs (levofloxacin/moxifloxacin) more active against *M. tb* than ofloxacin
- Easily and rapidly absorbed after oral administration. Bioavailability >85-99% following oral administration
- $C_{\text{max}}$ and AUC increase linearly with dose
- Distributed widely with good tissue & CSF penetration
- Food delays absorption, but has no effect on the AUC
- Absorption is decreased by co-administration of vitamins and minerals (often vitamin syrups mixed with tablets given to children!)

The Fluoroquinolones

- *In vitro*, the development of *M.tb* resistance depends on the FQN concentration. Low FQN concentration produces low-level resistance mutants.
- Ofx and Lfx: half-life ~5 hours in adults - eliminated mainly unchanged by the kidney (70-90%). Mfx: long half-life in adults ~6-12 hours; 50% undergoes phase II biotransformation in the liver, while 45% is excreted unchanged in urine and faeces.
- Rifampicin reduces MFX concentration by 30% due to induction of hepatic enzymes.
Ofloxacin and levofloxacin

- Pharmacodynamic targets (adults) of FLQs
  - $f\text{AUC}_{0-24}/\text{MIC}$ primary PD index (target 100)
  - $C_{\text{max}}/\text{MIC}$ (target 8-10)
  - $C_{\text{max}}$ (target 8-12 µg/ml) – most important?
Summary PK measures of Ofx and Lfx in children
Cross-over design – PK in same children <8 years of age

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Ofloxacin</th>
<th>N</th>
<th>Levofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 mg/kg</td>
<td></td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</td>
<td>23</td>
<td>9.67 (7.09 - 10.90)</td>
<td>23</td>
<td>6.71 (4.69 - 8.06)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>23</td>
<td>1.61 (0.72)</td>
<td>23</td>
<td>1.44 (0.51)</td>
</tr>
<tr>
<td>k&lt;sub&gt;el&lt;/sub&gt; (1/h)</td>
<td>22</td>
<td>0.22 (0.19 - 0.25)</td>
<td>23</td>
<td>0.22 (0.20 - 0.26)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>22</td>
<td>3.20 (2.84 - 3.57)</td>
<td>23</td>
<td>3.18 (2.68 - 3.51)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-8&lt;/sub&gt; (μg∙h/ml)</td>
<td>23</td>
<td>43.34 (36.73 - 54.46)</td>
<td>23</td>
<td>29.89 (23.81 - 36.39)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; SD, standard deviation.
All parameters are reported using median and IQR, except for T<sub>max</sub> which was reported using mean and SD.
Pharmacodynamic parameters using published MICs of M. tb. for ofloxacin and levofloxacin in children (n=23)

<table>
<thead>
<tr>
<th></th>
<th>Ofloxacin 20mg/kg</th>
<th>Levofloxacin 15mg/kg</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC for M. tb,</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>published (µg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean AUC(_{\text{inf}})/MIC (SD) (target 100)</td>
<td>23.13 (7.2)</td>
<td>46.3 (14.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean C(_{\text{max}})/MIC (SD) (target 8-10)</td>
<td>4.5 (1.5)</td>
<td>9.6 (3.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

* Paired t-test
OFX & LFX: Discussion

- Following a dose of Ofx 20mg/kg and Lfx 15mg/kg, drug exposure (AUC) in children is less than half of that in adults following a standard oral dose (Ofx 800mg, Lfx 750mg)
- There were no significant differences in $C_{\text{max}}$, $T_{\text{max}}$ or AUC by age, weight for age or HIV status with Lfx (small numbers)
- Pharmacodynamic indices were in favour of Lfx compared to Ofx
- No QTc prolongation (QTc>450ms) occurred (data not shown)
- More PK and PD data on FQNs in children are needed
Pharmacokinetics and Safety of Moxifloxacin in Children With Multidrug-Resistant Tuberculosis

Stephanie Thee,1,2 Anthony J. Garcia-Prats,1 Heather R. Draper,1 Helen M. McIlneron,3 Lubbe Wiesner,3 Sandra Castel,3 H. Simon Schaaf,1,a and Anneke C. Hesseling1,a

Table 2. Summary Statistics for Pharmacokinetic Measures in Children Following an Oral Moxifloxacin Dose of 10 mg/kg

<table>
<thead>
<tr>
<th>Pharmacokinetic Measure</th>
<th>No.</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$, µg/mL</td>
<td>23</td>
<td>3.08 (2.85–3.82)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, h</td>
<td>23</td>
<td>2.0 (1.0–8.0)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>12</td>
<td>10.53 (7.23–14.14)</td>
</tr>
<tr>
<td>Vd, L</td>
<td>12</td>
<td>70.61 (57.53–77.70)</td>
</tr>
<tr>
<td>$C_{0}$, µg/mL</td>
<td>12</td>
<td>4.27 (3.38–4.86)</td>
</tr>
<tr>
<td>$T_{1/2}$, h</td>
<td>12</td>
<td>4.14 (3.45–6.11)</td>
</tr>
<tr>
<td>AUC$_{0–24}$, µg × h/mL</td>
<td>23</td>
<td>17.24 (14.47–21.99)</td>
</tr>
<tr>
<td>AUC$_{0–24}$, µg × h/mL</td>
<td>12</td>
<td>23.31 (19.24–42.30)</td>
</tr>
</tbody>
</table>

All pharmacokinetic measures are reported as median and interquartile range, except for $T_{\text{max}}$, which is reported as median and range.

Abbreviations: AUC$_{0–8}$, area under the curve from 0–8 hours; AUC$_{0–24}$, area under the curve from 0–24 hours; $C_{0}$, concentration at time 0; CL, clearance; $C_{\text{max}}$, maximum serum concentration; F, fraction absorbed; $T_{1/2}$, half-life; $T_{\text{max}}$, time until $C_{\text{max}}$; Vd, volume of distribution.

Figure 1. Individual serum concentrations in children 7–15 years of age following an oral moxifloxacin (MFX) dose of 10 mg/kg/day.
MFX - Pharmacodynamic indices

• \( \text{MIC}_{90} \) used = 0.5 mg/L  Sirgel et al. JAC 2012

• Mean \( \text{AUC}_{0-24}/\text{MIC} \) (IQR): 56.1 (SD 25.1)
  – Target: 100

• Mean \( \text{C}_{\text{max}}/\text{MIC} \) (IQR): 6.5 (SD 1.5)
  – Target: 8-10
Discussion MFX in children 7-15 years of age receiving 10mg/kg MFX

- PK: Shorter $t_{1/2}$ and lower AUC relative to published values in adults receiving 400mg MFX despite this being an older paediatric population

- PD indices (adult targets) not achieved
  - Efficacy of Mfx in adults with TB shown in several studies

- $C_{\text{max}}$ was higher than the mutant prevention concentration 90% ($\text{MPC}_{90}$) of in vitro studies for MFX (1.2μg/mL)

- Limited data on Mfx use in children with MDR-TB, but current recommended dose of 7.5-10mg/kg may be too low. Studies in younger children essential
<table>
<thead>
<tr>
<th>Second-line anti-TB drug</th>
<th>Current recomm dose</th>
<th>Suggested dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (Kanamycin/Capreomycin?)</td>
<td>15-30 mg/kg/day IM or IV</td>
<td>15-20 mg/kg/day IM / IV</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>7.5-10 mg/kg once daily</td>
<td>15-20 mg/kg once daily</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>7.5-10 mg/kg once daily</td>
<td>10 mg/kg once daily – higher?</td>
</tr>
<tr>
<td>Ethionamide/Prothionamide</td>
<td>15-20 mg/kg once daily</td>
<td>15-20 mg/kg once daily</td>
</tr>
<tr>
<td>Cycloserine/Terizidone</td>
<td>10-20 mg/kg once daily</td>
<td>15-20 mg/kg once daily</td>
</tr>
<tr>
<td>PAS (para-aminosalicylic acid)</td>
<td>150 mg/kg granules daily in two doses</td>
<td>150-200 mg/kg as single or divided dose daily</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>3-5 mg/kg once daily (max 100mg)</td>
<td>3-5 mg/kg once daily or every second day? (max 100mg)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>10 mg/kg once or twice daily</td>
<td>10 mg/kg twice daily &lt;10 years 300-600 mg once daily &gt;10 yrs</td>
</tr>
</tbody>
</table>
Future research directions in treatment?

Current drugs
• Optimising dosing of drugs (further PK/PD studies)

Prevention
• Shorter course prevention of DS-TB in children
• Rational evidence-based prevention of MDR-TB in children

Treatment
• Shorter course, injectable sparing regimens of MDR-TB
• Shorter course treatment of DS-TB in children
• Optimizing the treatment of TBM in children (FQN, hd Rif)

New drugs
• PK and safety studies of new drugs required early on in children
• Develop child-friendly formulations – new and 2nd line drugs
Thank you!

Acknowledgements:

• Anneke Hesseling, Peter Donald, Steffi Thee, Tony Garcia-Prats, Adrie Bekker and the Desmond Tutu TB Centre PK Team!
• Financial support for studies presented: NIH, SA MRC and SA NRF