A pharmacokinetic/pharmacodynamic analysis of drug-resistant tuberculosis therapy in Durban, South Africa

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Analysis

- Outcome:
  - Time to positivity (TPP) in mycobacterial growth indicator tubes (MGIT) measured
  - Baseline and change in $\log_{10}$ 1/TTP modelled
  - Non-linear mixed effects models (NLME) in NONMEM

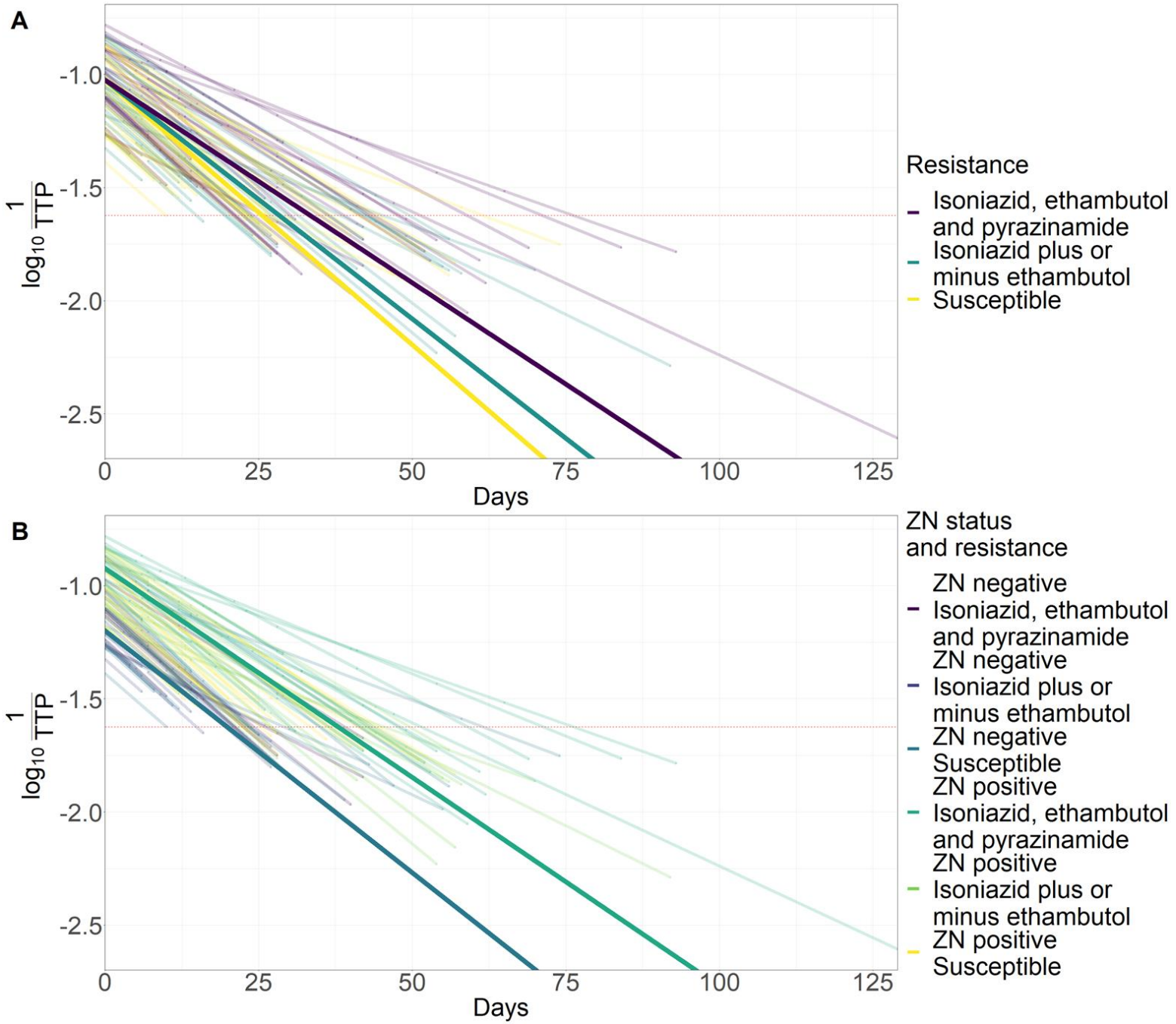
- Area under the curve ($AUC_{0-\infty}$) derived from population pharmacokinetic (popPK) models built in NONMEM

- Covariates included on the basis of biological plausibility
- The impact of covariates on baseline bacillary load, elimination rate or both assessed

Results

- 140 participants recruited
  - 108/140 (77.1%) culture positive
  - 88/108 (81.5%) culture positive and received a bedaquiline- and levofloxacin-based regimen

- Heterogeneity of PK exposures i.e. $AUC_{0-\infty}$
- Isoniazid resistance 66.7%, Pyrazinamide resistance 50%
- Linear model of change in $1/\log_{10}TTP$
  - Baseline bacillary load
    - Sputum smear microscopy - Higher
    - CXR score – Higher
    - Cavitation - Higher
  - Bacillary elimination
    - Isoniazid resistance – Slower
    - Pyrazinamide resistance – Slower


A
-1.0
-1.5
-2.0
-2.5
1
log10 TTP
0
25
50
75
100
125
Days
Resistance
Isoniazid, ethambutol and pyrazinamide
Isoniazid plus or minus ethambutol
Susceptible
B
-1.0
-1.5
-2.0
-2.5
1
log10 TTP
0
25
50
75
100
125
Days
ZN status and resistance
ZN negative
Isoniazid, ethambutol and pyrazinamide
ZN negative
Isoniazid plus or minus ethambutol
ZN negative
Susceptible
ZN positive
Isoniazid, ethambutol and pyrazinamide
ZN positive
Isoniazid plus or minus ethambutol
ZN positive
Susceptible

$$\log_{10} \frac{1}{TTP} = \alpha + \beta \cdot time$$

Parameter	Parameter estimate	SE	RSE (%)
fixed effects for intercept (A)	-1.2	0.04	3.2
fixed effects for ZN	0.8	0.03	3.8
fixed effects for slope (alpha) - EMB/PZA/INH sens	0.02	0.004	17.05
fixed effects for INH +/- EMB res	0.9	0.1	14.28
fixed effects for EMB/PZA/INH res	0.8	0.1	13.58
random effect on intercept	0.1	0.02	18.94
random effect on slope	0.008	0.003	37.75
SD / SIG1	0.2	0.02	13.45
Sigma	1		

Intercept (A) represensts baseline bacillary load, slope (Beta) represents bacillary elimination, sigma resepresents ths standard deviation of the residual error and was fixed to 1. SE = Standard error, RSE = relative standard error

Discussion points

- Power of PK/PD analysis

- First line drugs remain important in DR-TB – setting specific?
- Stratified treatment based on rapid identification of baseline bacillary load, isoniazid and pyrazinamide resistance?

- Model follows the data – e.g. can't assess effect of pyrazinamide resistance alone

- No effect of PK covariates

- Assessment of impact of e.g. bedaquiline resistance on clearance

Covariate	Relationship	Estimate	RSE (%)	delta OFV	delta random effect
CXR score	Additive	0.1	22.5	-15.4	-0.02
CXR score	Power	-0.05	38.5	-9.5	-0.01
CXR cavitation	Additive	0.1	33.8	-5.8	-0.01
CXR cavitation	Proportional	0.9	4.7	-5.8	-0.01
Age	Power	-0.05	194.9	-0.3	
Male sex	Proportional	0.9	5.4	-4.9	-0.007
Smoking (pack years)	Power	-0.009	184.4	-0.3	-9e-04
Recent TB*	Proportional	1	17.1	0.0	-1e-04
HIV infection	Proportional	1	5.6	-0.7	-0.001
ZN positive	Proportional	0.8	3.8	-38.5	-0.06
ZN grade	Proportional			-41.2	-0.06
scanty/1+		0.8	4.4		
2+		0.8	8.7		
3+		0.7	4.8		

Covariate	Relationship	Estimate	RSE(%)	delta OFV	delta random effects
CXR score	Additive	-0.003	83.6	-2.8	0.000587
CXR score	Power	-0.009	603.3	-0.1	0.000114
CXR cavitation	Additive		1,121.0	0.0	0.000022
CXR cavitation	Proportional	1	13.8	0.0	0.000020
Age	Power	0.4	51.9	-3.8	-0.000378
Male sex	Proportional	1.1	14.1	-0.7	-0.000369
Smoking (pack years)	Power	-0.1	38.1	-7.1	-0.000867
Recent TB*	Proportional	1	24.3	0.0	0.000004
HIV infection	Proportional	1	12.7	0.0	0.000020
ZN positive	Proportional	0.8	13.9	-2.7	-0.000006
ZN grade	Proportional			-4.3	-0.000771
scanty/1+		0.9	14.9		
2+		0.6	32.3		
3+		0.8	16.2		
Baseline TTP	Power	0.05	231.0	-0.2	0.000142
Isoniazid resistance	Proportional	0.8	11.8	-4.5	-0.000730
Isoniazid $AUC_{0-\infty}$ (μg·hr/ml)	Power	-0.07	58.5	-3.4	0.000079
Isoniazid AUC:MIC	Power	0.04	86.3	-1.6	-0.000452
Pyrazinamide resistance	Proportional	0.7	11.9	-7.5	-0.000586
Pyrazinamide $AUC_{0-\infty}$ (μg·hr/ml)	Power	-0.04	93.4	-1.1	-0.000333
Pyrazinamide $AUC_{0-\infty}$:MIC	Power	0.06	70.0	-2.8	-0.000039
Ethambutol resistance	Proportional	0.8	12.0	-3.1	-0.000110
Ethambutol $AUC_{0-\infty}$ (μg·hr/ml)	Power	0.03	165.1	-0.5	-0.000284
Ethambutol $AUC_{0-\infty}$:MIC	Power	0.02	275.9	-0.2	-0.000136
Clofazimine $AUC_{0-\infty}$ (μg·hr/ml)	Power	0.03	211.5	-0.3	-0.000044
Clofazimine $AUC_{0-\infty}$:MIC	Power	0.03	201.6	-0.3	-0.000027
Levofloxacin $AUC_{0-\infty}$ (μg·hr/ml)	Power	0.03	204.2	-0.2	-0.000020
Levofloxacin $AUC_{0-\infty}$:MIC	Power	-0.01	405.5	-0.1	0.000070
Average daily linezolid dose	Power	0.02	158.1	-0.4	-0.000128
Bedaquiline $AUC_{0-\infty}$ (μg·hr/ml)	Power	0.06	221.9	-0.7	-0.000151
Bedaquiline $AUC_{0-\infty}$:MIC	Power	0.04	172.1	-0.6	-0.000078
Attainment of pyrazinamide $AUC_{0-\infty}$ > 363μg·hr/ml target	Proportional	1	13.3	0.0	-0.000066
Attainment of pyrazinamide $AUC_{0-\infty}$:MIC > 11.3 target	Proportional	1.3	16.7	-2.7	-0.000262
Attainment of isoniazid $AUC_{0-\infty}$:MIC > 500 target	Proportional	1.3	13.3	-3.9	-0.000283

Table 4.14: Overall drug susceptibility patterns based on phenotypic and genotypic drug susceptibility testing

Resistance pattern	n	%
Fully susceptible (DS-TB)	7	6.5
Injectable monoresistance	1	0.9
Rifampicin monoresistance (RR-TB)	25	23.1
Rifampicin and pyrazinamide resistance (RR-TB)	1	0.9
Rifampicin and isoniazid resistance (MDR-TB)	14	13.0
Rifampicin, isoniazid and ethambutol resistance (MDR-TB)	14	13.0
Rifampicin, isoniazid and pyrazinamide resistance (MDR-TB)	1	0.9
Rifampicin, isoniazid, pyrazinamide and ethambutol resistance (MDR-TB)	34	31.5
Rifampicin and injectable resistance (pre-XDR-TB)	1	0.9
Rifampicin and fluoroquinolone resistance (pre-XDR-TB)	1	0.9
Rifampicin, isoniazid and injectable resistance (pre-XDR-TB)	1	0.9
Rifampicin, isoniazid, ethambutol and injectable resistance (pre-XDR-TB)	3	2.8
Rifampicin, isoniazid, ethambutol, injectable and fluoroquinolone resistance (XDR-TB)	1	0.9
Rifampicin, isoniazid, pyrazinamide, ethambutol, injectable and fluoroquinolone resistance (XDR-TB)	4	3.7