Linezolid pharmacokinetics in South African patients with drug resistant tuberculosis and a high prevalence of HIV co-infection

Running title: Linezolid pharmacokinetics in drug-resistant tuberculosis

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ABSTRACT

WHO recently recommended linezolid should be prioritized in treatment regimens for drug-resistant tuberculosis (TB), but there are limited data on its pharmacokinetics (PK) in this population. We conducted an observational study to explore covariate effects on linezolid PK and to estimate the probability of PK/pharmacodynamic target attainment in South African patients with drug-resistant TB. Consecutive adults on linezolid-based regimens were recruited in Cape Town and underwent intensive PK sampling at steady-state. Non-compartmental analysis was performed. Thirty participants were included: 15 HIV-positive, 26 on the initial dose of 600 mg daily and 4 participants on 300 mg daily after dose reduction for linezolid-related toxicity. There was a negative correlation between body weight and exposure with 17.4% (95% confidence interval [CI], 0.1 to 31.7) decrease in area under the concentration-time curve (AUC_{0-24}) per 10 kg weight increment after adjustment for other covariates. Age was an independent predictor of trough concentration, with an estimated 43.4% (95% CI, 5.9 to 94.2) increase per 10-year increment in age. The standard 600 mg dose achieved the efficacy target of free AUC/minimum inhibitory concentration (MIC) > 119 at wild type MIC values (≤ 0.5 mg/L), but the probability of target attainment dropped to 61.5% (95% CI, 40.6 to 79.8) at the critical concentration of 1 mg/L. When dosed at 600 mg daily, trough concentrations were above the toxicity threshold of 2 mg/L in 57.7% (95% CI, 36.9 to 76.6). This confirms the narrow therapeutic index of linezolid and alternative dosing strategies should be explored.

INTRODUCTION

Drug-resistant TB is an ongoing global public health crisis; there were over half a million incident cases in 2017 with a case fatality ratio of approximately 40%, more than double that of drug-sensitive TB (1). New and repurposed drugs offer the hope of improved outcomes. One such agent, the oxazolidinone linezolid, has an impressive impact on treatment outcomes when added to multidrug regimens for multidrug- (MDR) and extensively drug-resistant (XDR) TB (2, 3). As a result, linezolid has been promoted to the list of priority 'Group A medicines' in the new WHO antituberculosis drug categorization (4) and is included in the experimental arms of multiple trials of novel regimens for drug-resistant TB. However, linezolid use is limited by dose- and duration-related toxicity, and the optimal dosing strategy that balances efficacy and toxicity is unknown (5).

The pharmacokinetics (PK) that underpins linezolid dosing is poorly defined in patients with TB, particularly at the most commonly used dose of 600 mg daily and amongst patients in sub-Saharan Africa where there is a high burden of HIV co-infection (6). Understanding linezolid PK is important for several reasons. First, PK variability of antituberculosis agents has been associated with unsuccessful treatment outcomes (7), which may also lead to treatment-emergent drug resistance where drug exposure falls below PK/pharmacodynamic (PD) targets (8). Population-specific factors, including genetic polymorphisms, may influence drug disposition and drug effects (9), and it is therefore essential to perform PK studies in diverse populations. Second, the myelosuppression and neuropathy associated with linezolid use, which is often

treatment-limiting (3), correlates with dose and trough concentrations (10). Linezolid toxicity may be increased amongst HIV-positive patients (11), which is especially relevant in sub-Saharan Africa where up to 60% of patients with drug-resistant TB are co-infected with HIV. Third, linezolid has limited selectivity for its ribosomal target in bacteria and binds to a homologous site in human mitochondria (12). Because of these shared linezolid targets in the pathogen and host, there is a narrow therapeutic window for which the optimal PK targets and dose have not been defined (5), but which is likely to be sensitive to PK variability. Finally, efficacy targets of antituberculosis drugs are influenced by minimum inhibitory concentration (MIC) distributions for *M tuberculosis*, but there are limited data on linezolid MICs in populations with drug-resistant TB (13). Applying observed linezolid drug exposures to putative PK/PD parameters for efficacy and toxicity may inform policy decisions around dose optimization until more robust clinical targets are defined.

We aimed to describe the PK of linezolid in a population of patients with drug-resistant TB and a high burden of HIV in South Africa. We also explored the effect of key covariates on PK parameters and estimated the probability of PK/PD target attainment corrected for the *M tuberculosis* MIC distribution in this cohort.

MATERIALS AND METHODS

Study population

We conducted a prospective observational PK/PD study of linezolid in adults treated with linezolid containing regimens for drug-resistant TB in South Africa. We enrolled

participants from two studies: an observational cohort study of patients with pre-XDR and XDR-TB on bedaquiline containing regimens (PROBeX); and from the intervention arm of an open label clinical trial examining a shortened injection-free regimen for MDR-TB (NExT; ClinicalTrials.gov NCT02454205). The initial dose of linezolid used in both studies was 600 mg daily but was reduced to 300 mg daily in the event of toxicity at the discretion of local clinicians or trial staff. Consecutive participants enrolled in the intervention arm of the NExT trial and those receiving linezolid as part of standard of care in PROBeX were approached to provide informed consent for intensive PK sampling. Eligible participants were over the age of 18 years, had a known HIV test result, and had culture-confirmed drug-resistant TB. Most of the participants in PROBeX were inpatients at the time of the intensive sampling visit, and all of the NExT participants attended as outpatients.

The study was approved by the ethics committees at the University of Cape Town (refs 264/2015 and 920/2015) and Albert Einstein College of Medicine (ref 2014-4348).

Data collection

Participants underwent PK sampling on a single occasion pre-dose and at 1, 2, 3, 4, 5, 6, and 24 hours after a standardized meal and observed linezolid administration. Some participants in the PROBeX cohort had an additional sample taken at 8 and 48 hours as part of other study procedures. The sampling visit was scheduled at Month 2 of linezolid treatment and was thus performed at steady-state. Blood draws were done through a peripheral intravenous catheter placed for the duration of the first day of the visit.

Samples were collected into 10 mL K3EDTA Vacutainer tubes and centrifuged (1,500 x *g* for 10 minutes) within 30 minutes of collection. At least 1.5 mL of plasma was pipetted into polypropylene tubes and immediately frozen at -80°C. Linezolid concentrations were measured in Division of Clinical Pharmacology at the University of Cape Town using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Using a deuterated internal standard, the LC-MS/MS method for linezolid was validated over a calibration range of 0.100 mg/L to 30 mg/L. Over the period of sample analysis (n = 8 batches), a mean percentage accuracy of 98.8 was achieved, with a mean precision of 5.93 (%CV).

Because the 24-hour dose was unobserved and may have been administered prior to the 24-hour sample, concentration-time profiles were inspected for each subject to compare pre-dose and 24-hour concentrations. The 24-hour concentration was considered highly unlikely to represent the true trough value where it exceeded the pre-dose concentration and was > 50% of the concentration at the prior sampling time point (6- or 8-hours). This was based on the published elimination half-life of linezolid of ~6 hours (14, 15), and the assumption that the 24-hour concentration would therefore fall below the 6- or 8-hour concentration in the absence of additional dosing. In these cases, the 24-hour concentration was imputed from either the pre-dose concentration or the mean of the pre-dose and 48-hour concentrations where available (and when the 48-hour concentration satisfied the same criteria in relation to the pre-dose value). Pre-dose concentrations reported as below the limit of assay quantification (BLQ) were imputed as 50% of the lower limit of detection (i.e. 0.05 mg/L), unless there was a

history of missed doses prior to the PK visit, in which cases BLQ was replaced by a value of '0.'

Demographic and clinical data were collected from participants at the time of the PK visit, as well as from other visits as part of the parent studies. Data included HIV status, linezolid dose and duration, concomitant antituberculosis drugs and antiretrovirals, and most recent serum creatinine. Timing of administration of linezolid and other antituberculosis drugs was recorded.

Linezolid MIC testing was performed on *M tuberculosis* isolates collected at the time of entry into the parent studies using the mycobacterial growth indicator tube (MGIT) system and continuous growth monitoring with Epicenter software (16). Dilutions ranged from 0.25 mg/L to 2 mg/L based on the epidemiological cut off (ECOFF) value of 0.5 mg/L (17) and the critical concentration of 1 mg/L (13).

Analysis

Demographic and clinical characteristics were summarized and compared using the Wilcoxon rank-sum test for continuous variables and χ^2 test for dichotomous variables. Non-compartmental analysis was used to estimate linezolid PK parameters from observed concentrations. The area under the concentration-time curve over the 24-hour dosing period ($AUC_{0\text{-}24}$) was computed using the cubic splines method. The trough concentration was defined as the plasma concentration 24 hours after observed intake (actual or imputed as described above). The elimination rate constant (k_e) was

assessed by linear regression analysis of the last three concentrations in the terminal log-linear period. The apparent clearance of the drug (CL/F) and the volume of distribution after oral administration (Vd/F) were calculated using standard equations.

We performed linear regression to explore associations between clinically relevant covariates and linezolid exposure. AUC_{0-24} and trough concentrations were log-transformed and regressed versus weight, age, sex, ethnicity, HIV status, estimated creatine clearance (calculated using the Cockcroft-Gault formula), and concurrent use of ritonavir-boosted lopinavir. This latter parameter was included to explore a possible drug-drug interaction with linezolid, which may be a substrate of the drug transporter P-glycoprotein (18) that is inhibited by HIV protease inhibitors. Parameters with a P value < 0.5 were retained in the multivariable model, using a backward stepwise approach. Regression coefficients were exponentiated and transformed into a value reflecting percentage change $((e^{\beta} - 1)\cdot 100)$ for ease of interpretation.

The PK/PD target for efficacy was defined as free AUC_{0-24}/MIC (*f*AUC/MIC) of 119, based on findings from a hollow fiber infection model (19). Protein binding of 30% was used to calculate *f*AUC (15). The PK/PD parameter for toxicity was a trough concentration of 2 mg/L, based on clinical data showing increased mitochondrial and clinical linezolid toxicity above this threshold (10). The probability of target attainment was calculated as the proportion of subjects with PK exposures above the efficacy and toxicity targets. Probability distributions were constructed using kernel densities of PK

parameters, stratified by MIC. Statistical analysis, including non-compartmental analysis, was performed using Stata version 14.2 (StataCorp).

RESULTS

Study population

Thirty-eight participants were screened between June 2016 and April 2018, and 30 underwent intensive PK sampling. Reasons for exclusion were discontinuation of linezolid prior to the sampling visit (n = 4), withdrawal of consent (n = 2), loss to follow up (n = 1), and failed intravenous access (n = 1). The demographic and clinical characteristics at the time of linezolid sampling are summarized in Table 1. All participants were ambulant at the time of evaluation, including the 21 participants hospitalised for the PROBeX study. Five participants were on lopinavir-ritonavir-based ART. Four participants were on 300 mg daily after undergoing dose reduction for suspected linezolid-related toxicity, one of whom was switched to the 300 mg dose on the day of the study visit and therefore was not at steady state.

PK parameters

Trough concentrations were imputed for 6 participants due to extreme outlying results from presumed unobserved dosing prior to the 24-hour sample. The pre-dose concentration was BLQ in 4 participants. The full dataset showing original and imputed linezolid concentrations is available in the supplementary material (Table S1), along with the respective concentration-time profiles for each subject (Figures S1a and S1b).

As shown in Figure 1, concentration-time profiles demonstrated high inter-individual variations in plasma concentrations, with an overall coefficient of variation (%CV) of 40.1%. There was a rapid attainment of peak concentrations, which was similar for both doses, but concentrations at early time points appeared to be highly variable. Table 2 summarizes the estimated PK parameters from observed linezolid concentrations, disaggregated by linezolid dose. Clearance was significantly lower amongst subjects who had undergone dose reduction to 300 mg daily (1.8 L/h (IQR 1.7 to 21) versus 3.1 L/h (IQR 2.4 to 4.3) in those remaining on 600 mg daily; P = 0.012), which resulted in a longer half-life in the 300 mg group. There was a linear correlation between linezolid trough concentrations and $AUC_{0\text{-}24}$; $\rho = 0.5$, P = 0.005 (Figure S2).

Covariate effects on PK parameters

Linear regression only included participants receiving the 600 mg dose (n = 26) since the sample size of those receiving 300 mg (n = 4) was too small to allow for a meaningful evaluation at that dose. There was no association between HIV infection or the use of lopinavir-ritonavir and linezolid exposure on univariable or multivariable analysis. The final multivariable model described 33% of the variability associated with $AUC_{0\text{-}24}$ (Table 3). After adjustment for age, sex, race, and HIV status, there was a negative correlation between body weight and linezolid exposure, with an estimated 17.4% (95% CI, 0.1 to 31.7) decrease in $AUC_{0\text{-}24}$ per 10 kg increment. Age was significantly associated with higher trough concentrations, and remained an independent predictor on multivariable analysis, with an estimated 43.4% (95% CI, 5.9 to 94.2) increase in trough concentrations per 10-year increment in age (Table 4).

Probability of PK/PD target attainment

MIC results were available for the baseline isolates of 16 participants. The median MIC was 0.5 mg/L, range 0.25 to 0.5 mg/L. At this MIC distribution, the probability of efficacy target attainment, defined as a *f*AUC/MIC of 119, was 100% (95% CI, 87 to 100) for the 600 mg dose of linezolid. This finding was consistent after performing a sensitivity analysis using the original outlier trough concentrations. The *f*AUC distributions across four MIC strata are shown in Figure 2. Although the PK/PD target would be achieved in almost all subjects at the ECOFF value of 0.5 mg/L, only 61.5% (95% CI, 40.6 to 79.8) of patients would exceed an *f*AUC/MIC of 119 at the critical concentration of 1.0 mg/L (13). Trough concentrations exceeded the toxicity threshold of 2 mg/L in 57.7% (95% CI, 36.9 to 76.6) of those on 600 mg daily, and in 75% (95% CI, 19.4 to 99.4) of those who had undergone dose reduction to 300 mg daily. In a sensitivity analysis the proportions exceeding the toxicity threshold were similar when original trough concentration data were used: 67.7% (95% CI, 47.1 to 82.7) versus 60% (95% CI, 40.6 to 77.3) with imputed data at all doses.

DISCUSSION

We characterized the PK of linezolid in 30 South African participants with drug-resistant TB and a high prevalence of HIV co-infection. We showed that age and weight were the most important predictors of linezolid exposure. A major finding was that the standard 600 mg dose resulted in exposures that reached efficacy targets, but a substantial proportion of individuals were exposed to concentrations exceeding the known toxicity

threshold. Of concern, at the critical concentration (1 mg/mL) efficacy targets would only be achieved in 61.5%, which has implications for the programmatic use of linezolid as resistance is expected to increase with more widespread use.

Despite its growing importance as a key drug for the treatment of drug-resistant TB, the optimal dose and duration of linezolid for this indication is unknown. There are very limited published PK data for linezolid in TB patients to help inform an effective dosing strategy that minimizes both mitochondrial toxicity and the emergence of resistance. Eight clinical studies reporting linezolid PK in TB treatment were identified in a recent systematic review (6) but these studies had four different dosing strategies and mostly did sparse sampling PK schedules, limiting their generalizability. Only two studies (n = 48) (2, 20) have evaluated linezolid PK at the standard dose for TB of 600 mg daily; all were HIV-negative and full PK profiles were only done in 10 participants (20). Our study provides a comprehensive description of plasma linezolid concentrations at the recommended dose of 600 mg daily for drug-resistant TB and is the first to include HIV-positive patients.

We found high interindividual PK variability, as has been observed in patients with Gram-positive infections (21), particularly at early sampling time points, suggesting variable absorption delay. Most of the PK variability was unexplained by the covariates included in the regression model and was likely due to stochastic effects; however, this needs to be quantified with formal population PK modelling, possibly incorporating an absorption lag phase. Linezolid clearance was lower amongst participants who

underwent dose reduction to 300 mg, which could be explained by channeling bias, as patients with lower linezolid clearance would have higher exposure and be more susceptible to toxicity, necessitating a dose reduction. Although the sample size was small, the median trough concentration with the reduced 300 mg daily doses exceeded the toxicity threshold of 2 mg/L in three of four participants. This finding emphasizes the need for toxicity monitoring with linezolid therapy, even after dose reduction for adverse events.

The median trough concentrations were higher in our cohort compared with the two previous studies of linezolid 600 mg daily in TB therapy (2, 20). Although there is substantial interstudy heterogeneity in linezolid PK parameters (6), our finding may suggest a longer terminal half-life with an attendant increased risk of toxicity in our population. A small clinical study found a trend towards an association between HIV infection and higher rates of linezolid toxicity (11); if this association is confirmed in larger prospective cohorts, it is likely to be explained by predisposition to the high prevalence of neuropathy and limited bone marrow reserve in people with advanced HIV disease rather than higher linezolid exposure, which we did not find. We explored the potential PK drug-drug interaction between linezolid and lopinavir-ritonavir as an additional contributing factor to increased linezolid exposures and toxicity in HIV. An association between the use of lopinavir-ritonavir and linezolid trough concentrations was not detected in our cohort, but this needs confirmation with a larger sample size.

In a previous study, increasing age accounted for a small reduction (2%) in linezolid clearance in patients with Gram-positive infection (22), but did not contribute to the development of a population PK model of linezolid in TB (23), and did not influence linezolid exposures in a study of healthy volunteers (24). By contrast, we showed a significant correlation between increasing age and linezolid trough concentrations, where every 10-year increment in age was associated with 43% higher trough concentrations; this finding needs to be validated in similar populations. We also found a significant association between weight and lower linezolid exposure in the multivariable model, an association previously reported (25). These observations have implications for dose selection and could inform therapeutic drug monitoring (TDM) strategies for linezolid; for example, by targeting TDM to older patients and those with lower weights to prevent toxicity.

PK targets for efficacy have not been established for linezolid in TB treatment. Although C_{max}/MIC (26) and trough/MIC (27) have been associated with bacterial killing using *ex vivo* and *in vitro* models, the PK/PD index most consistently linked to linezolid activity in *M tuberculosis* is the *f*AUC_{0-24}/MIC ratio (19, 28, 29). A hollow-fiber infection model, which recapitulates human drug exposure, showed that optimal mycobacterial kill was achieved at a *f*AUC_{0-24}/MIC ratio of 119 (19); this was used as the PK/PD parameter in a recent simulation of published linezolid PK data to determine the probability of efficacy target attainment at wild type MIC values (6). Using data from 10 patients with full PK profiles, with an estimated median AUC_{0-24} of 98.6 mg.h/L (23), those simulations predicted that 45% would fail to achieve the target at a daily dose of 600 mg.

Reassuringly, in our participants linezolid exposures were higher (median AUC_{0-24} 200.2 mg.h/L), translating into probability of target attainment of 100% across the MIC distribution in baseline isolates and 96% at the population wild type MIC cut-off of 0.5 mg/kg, supporting the efficacy of the 600 mg daily dose. However, linezolid exposures did not exceed the putative efficacy threshold at the critical concentration of 1 mg/L in 38% of our subjects. With the expanding use of linezolid for TB treatment it will be essential to monitor for evidence of 'MIC creep' in the population.

Unlike the PK/PD parameter for efficacy, the linezolid toxicity threshold is relatively well-defined as a trough concentration of 2 mg/L, supported by clinical evidence (10) as well as data from pre-clinical models showing that mitochondrial toxicity is related to trough concentrations (27). Although a 600 mg daily dose was likely to reach the efficacy target in our cohort, almost 58% also exceeded this threshold concentration for linezolid toxicity, clearly illustrating the narrow therapeutic window of linezolid. In murine models, linezolid's sterilizing ability is dose-related and can occur within 2 months of effective combination therapy (30, 31). In TB patients, neurological toxicity tends occur late, usually after 2 months of therapy (32). Based on these observations, an appealing dosing strategy could be to provide higher linezolid doses (1,200 mg daily) for an initial 'intensive phase' of treatment, followed by either discontinuation, dose reduction, or intermittent dosing (33) that allows longer periods within the PK safety window. This strategy needs to be evaluated in prospective studies.

We acknowledge a number of limitations of our study, including the inability of non-compartmental analysis to assess intra-individual PK variability, evaluation at only a single time point during treatment, an incomplete PK profile and non-steady state dosing for one participant each, and small numbers of participants receiving the reduced 300 mg dose. Importantly, we had to impute the trough concentrations for six participants due to extremely high values after suspected unobserved dosing prior to the 24-hour sample. If anything, inclusion of the original data would have biased the results towards higher trough concentrations and overall exposures. Thus, our reported findings may represent a conservative estimate of both efficacy and toxicity target attainment.

In conclusion, we found substantial variability in linezolid drug concentrations in this cohort of patients with drug-resistant TB and a high prevalence of HIV infection. Much of this variability was unexplained, but age and weight were identified as predictors of trough concentrations and exposure, respectively. The standard 600 mg dose is likely to achieve efficacy targets for *M tuberculosis* isolates with linezolid wild type MICs. The clinical impact of this needs to be evaluated by linking linezolid PK to toxicity and efficacy endpoints. In the meantime, the expanding use of linezolid 600 mg daily for drug-resistant TB should be supported by programmatic surveillance of MICs and adverse events. Alternative dosing strategies and TDM should be explored to optimize the use of this important but toxic antituberculosis agent.

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512 **FIGURE LEGENDS**

513

514 **Figure 1. Plasma free concentration-time data for 30 subjects on linezolid.**

515 The grey lines represent concentration-time profiles for individual subjects; green dotted

516 line is the median for the 600 mg dose, blue dotted line is the median for the 300 mg

517 dose. The horizontal red line on the y-axis represents the critical concentration of

518 linezolid of *M tuberculosis* (1 mg/L).

519

520 **Figure 2. Probability density distributions for efficacy target attainment of**

521 **linezolid for subjects on 600 mg daily.**

522 The solid vertical line on the x-axis represents the experimentally-derived efficacy target

523 *f*AUC/$MIC_{0\text{-}24}$ of 119. Note the log-scale on the x-axis.

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526

527 **TABLES**

528

529 **Table 1. Demographic and clinical characteristics**

Variable	**N = 30**
Age, years	33 (27 – 44)
Male sex	19 (63)
Weight, kg	58.5 (49.8 – 67.6)
Height, cm	164.5 (158 – 172)
BMI, kg/m^2	20.2 (18.1 – 25.5)
Ethnicity	
Black	14 (47)
Mixed	16 (53)
Baseline resistance pattern	
MDR-TB	9 (30)
XDR-TB	21 (60)
HIV positive	15 (50)
Current ART	15 (100)
Current LPV/r	5 (33)
Creatinine, µmol/L	65 (53 – 71)
Creatinine clearance, mL/min	116 (103 – 139)
Duration on linezolid, days	59 (55 – 63), range (20 – 95)
Daily dose 600 mg	26 (87)
Dose, mg/kg	10.0 (8.3 – 11.5)

530 Data are median (IQR) or n (%). BMI, body mass index; ART, antiretroviral therapy;

531 LPV/r, lopinavir-ritonavir.

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533

534 **Table 2. PK parameters**

Variable	600 mg (n = 26)	300 mg (n = 4)	Overall (n = 30)
AUC_{0-24}, mg·h/L	200.2 (139.9 – 250.8)	165.8 (144.3 – 173.7)	178.9 (139.9 – 244.4)
CV (%)	41.0	13.2	40.1
K_e, h^{-1}	0.08 (0.07 - 0.11)	0.06 (0.06 – 0.09)	0.08 (0.07 – 0.11)
$T_{1/2}$, h	8.4 (6.3 – 9.8)	11.2 (8.6 – 11.9)	9.1 (6.3 – 10.3)
C_{max}, mg/L	14.6 (13.4 – 18.1)	8.4 (8.2 – 9.8)	14.0 (12.0 – 17.4)
T_{max}, h	3 (2 – 4)	2 (2 – 2)	3 (2 – 4)
Trough, mg/L	3.4 (1.6 – 5.1)	2.4 (1.9 – 2.6)	2.9 (1.6 – 5.1)
	74.0	47.7	73.0
CL/F, L/h*	3.1 (2.4 – 4.3)	1.8 (1.7 – 2.1)	2.6 (2.3– 4.1)
CV (%)	69.4	14.7	71.4
V_d/F, L#	37.8 (24.4 – 54.8)	31.2 (21.6 – 35.9)	36.8 (25.4 – 45.3)

535 Data are median (IQR). AUC_{0-24}, area under the 24-hour concentration-time curve; K_e,
536 elimination constant; $T_{1/2}$, elimination half-life; C_{max}, maximum concentration; T_{max}, time
537 of maximum concentration; Trough, 24-hour/pre-dose concentration; CL/F. clearance;
538 V_d, volume of distribution; CV, coefficient of variation. *Dose/AUC, #CL/k_e

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540

541 **Table 3. Univariable and multivariable linear regression models describing**
542 **associations between the AUC_{0-24} for linezolid 600 mg daily and selected**
543 **covariates.**

	Univariable		Multivariable	
n = 26	**AUC_{0-24} change* % (95% CI)**	**P value**	**AUC_{0-24} change* % (95% CI)**	**P value**
Male sex	-13.0 (-42.2 – 30.9)	0.488	-24.9 (-49.9 – 12.6)	0.156
Age Per 10-year increase	7.3 (-11.2 – 29.6)	0.452	18.7 (-2.1 – 43.9)	0.078
Black African	9.6 (-26.5 – 63.5)	0.641	-17.3 (-33.1 – 2.2)	0.075
Weight Per 10 kg increase	-11.9 (-25.8 – 4.4)	0.136	-17.4 (-0.1 – -31.7)	0.049
BMI, kg/m^2	-1.6 (-5.9 – 2.9)	0.458		
HIV positive	-14.3 (-42.3 – 27.5)	0.430	-27.2 (-53.5 – 13.8)	0.154
Current LPV/r	-18.9 (-50.9 – 43.1)	0.399		
Dose, mg/kg	7.5 (-2.3 – 18.2)	0.132		

Creatinine clearance, mL/min	-0.5 (-1.1 – 0.1)	0.108	

*Percentage change in AUC_{0-24} calculated as $[(e^{\beta} - 1)\cdot 100]$. BMI, body mass index. BMI, body mass index; LPV/r, lopinavir-ritonavir. Variables were excluded from the final multivariable model due to collinearity or as a result of backward elimination after exceeding the P-value inclusion threshold.

Table 4. Univariable and multivariable linear regression models describing associations between linezolid 600 mg daily trough concentrations and selected covariates.

	Univariable		Multivariable	
n = 26	**Trough change % (95% CI)**	**P value**	**Trough change % (95% CI)**	**P value**
Male sex	10.7 (-41.5 – 109.9)	0.744		
Age Per 10-year increase	37.4 (5.4 – 79.2)	0.021	43.4 (5.9 – 94.2)	0.022
Black African	26.1 (-31.9 – 133.3)	0.445	-13.8 (-37.4 – 18.7)	0.346
Weight Per 10 kg increase	9.3 (-17.1 – 43.9)	0.514		
BMI, kg/m^2	1.0 (-5.8 – 8.4)	0.770		
HIV positive	16.1 (-37.7 – 116.2)	0.625	-27.9 (-66.9 – 56.4)	0.389
Current LPV/r	11.5 (-49.4 – 145.5)	0.778	37.1 (-42.9 – 229.6)	0.463
Dose, mg/kg	-4.3 (-17.9 – 11.6)	0.560		
Creatinine clearance, mL/min	-0.2 (-1.2 – 0.8)	0.650		

*Percentage change in trough concentrations calculated as $[(e^{\beta} - 1)\cdot 100]$. BMI, body mass index; LPV/r, lopinavir-ritonavir. Variables were excluded from the final

multivariable model due to collinearity or as a result of backward elimination after exceeding the P-value inclusion threshold.

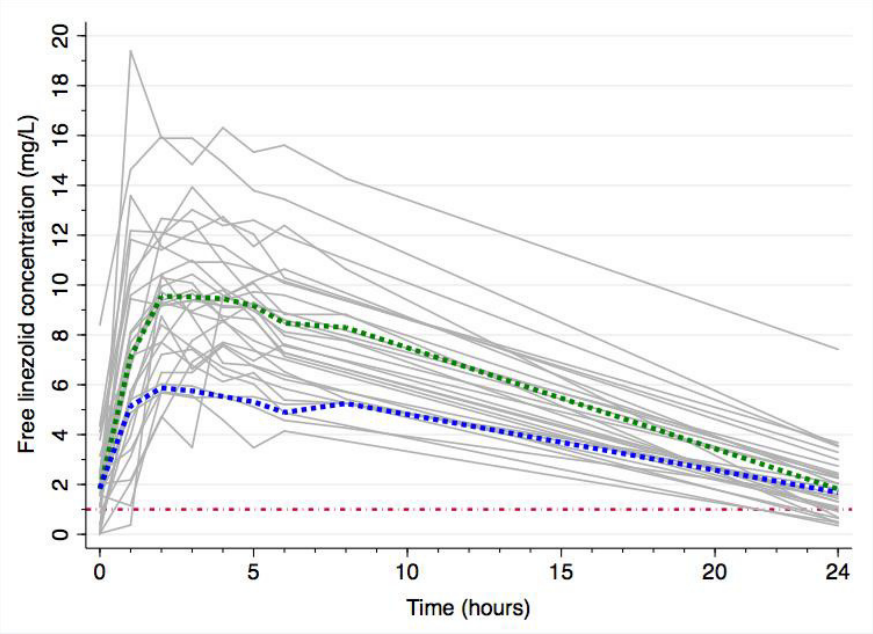

Figure 1. Plasma free concentration-time data for 30 subjects on linezolid.
The grey lines represent concentration-time profiles for individual subjects; green dotted line is the median for the 600 mg dose, blue dotted line is the median for the 300 mg dose. The horizontal red line on the y-axis represents the critical concentration of linezolid of M tuberculosis (1 mg/L).

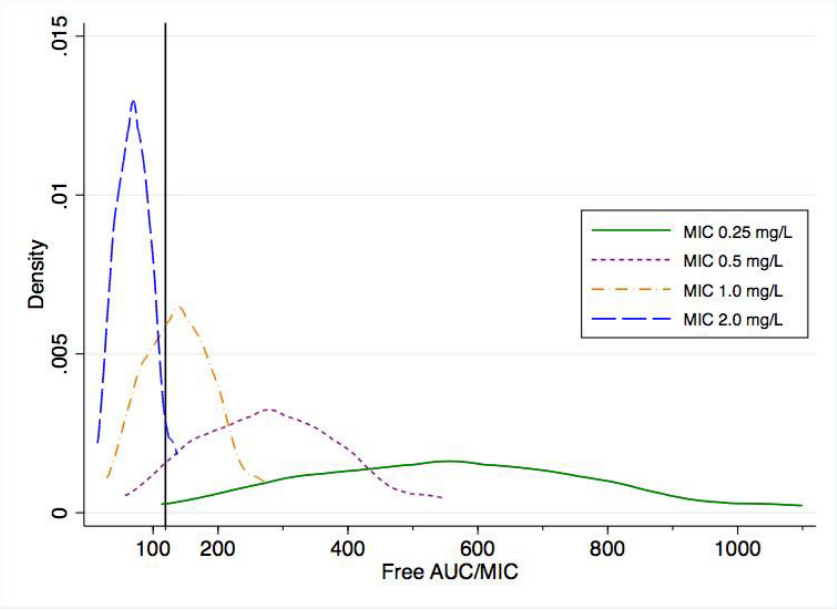

Figure 2. Probability density distributions for efficacy target attainment of linezolid for subjects on 600 mg daily.

The solid vertical line on the x-axis represents the experimentally-derived efficacy target fAUC/MIC0-24 of 119. Note the log-scale on the x-axis.