

# **Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis**

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## Abbreviations and acronyms<sup>1</sup>

ADME	absorption, distribution, metabolism and elimination
ADR	adverse drug reaction
aDSM	active TB drug safety monitoring and management
AE	adverse event
ART/ARV	antiretroviral therapy
ATP	adenosine triphosphate
AUC	area under the concentration curve
Bdq	bedaquiline
CC	critical concentrations for TB medicines
CLSI	Clinical & Laboratory Standards Institute
Cm	capreomycin
DBS	dried blood spot
DDI	drug-drug interaction
Dlm	delamanid
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
E	ethambutol
EBA	early bactericidal activity
ECG	electrocardiography
ECOFF	epidemiological cut-off points for TB medicines
EMA	European Medicines Agency
FA	fast acetylator (of isoniazid)
FDA	US Food & Drug Administration
FDC	fixed-dose combination formulation
GDF	Global Drug Facility
Gfx	gatifloxacin
GI	gastrointestinal
GTB (or WHO/GTB)	WHO Global TB Programme of the World Health Organization
H	isoniazid
HFIM	hollow fibre infection models
HIV	human immunodeficiency virus
HR-TB	rifampicin-susceptible, isoniazid-resistant TB (i.e. non MDR-TB)
HREZ	isoniazid, rifampicin, pyrazinamide, ethambutol (medicines of 1st line TB regimens)
IPD	individual patient data
Km	kanamycin
Lfx	levofloxacin
LJ	Löwenstein-Jensen (solid) medium
LPA	line probe assay

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<sup>1</sup> See also the definitions of PK/PD terms in Annex 3

LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
Mfx	moxifloxacin
mg/L	milligram per litre (equivalent to microgram per millilitre - mcg(µg)/ml)
MIC	minimum inhibitory concentration
NAT2	N-terminal acetyltransferase 2
NMDA	N-methyl-D-aspartate receptor
P5P	pyridoxal 5'-phosphate
PD	pharmacodynamics
PK	pharmacokinetics
PMDT	programmatic management of drug-resistant TB
QTcF	Fridericia's correction formula to the QT interval of an electrocardiography trace
R	rifampicin
RR-TB	rifampicin-resistant TB (including MDR-TB)
S (or Sm)	streptomycin
SA	slow acetylator (of isoniazid)
SAE	serious adverse event
SD	standard deviation
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Xpert MTB/RIF	an automated real-time nucleic acid amplification technology for rapid and simultaneous diagnosis of TB and of mutations conferring rifampicin-resistance to TB strains
Z	pyrazinamide

THIS MEETING REPORT WILL SERVE AS A BACKGROUND DOCUMENT FOR THE WHO TB TREATMENT POLICY REVIEWS BEING UNDERTAKEN IN 2018. IT IS NOT A WHO GUIDELINE. UNLESS ALREADY PART OF CURRENT WHO GUIDANCE THE EXPERT POSITIONS ON KEY QUESTIONS DESCRIBED IN THIS DOCUMENT WILL REQUIRE FURTHER ASSESSMENT BY A WHO GUIDELINE DEVELOPMENT GROUP FOR BENEFITS, HARMS AND OTHER CONSIDERATIONS, AND FOR THE CERTAINTY IN THE EVIDENCE, BEFORE CHANGES ARE RECOMMENDED TO WHO GUIDANCE.



## Executive Summary

With an estimated 1.7 million deaths attributed to it each year, tuberculosis (TB) is the single leading infectious cause of death in the world. Combined chemotherapy has been the cornerstone of TB treatment for seven decades and has helped to save more than 50 million lives between 2000 and 2016 alone. Although the vast majority of the 10.4 million new cases of TB emerging worldwide remain curable with a standardised 6-month course of antimicrobials, the spread of multidrug-resistant TB (MDR-TB; combined resistance to at least isoniazid and rifampicin, the two most powerful first-line anti-TB medicines) threatens to reduce treatment effectiveness, increase drug-safety concerns and defies the prospect of global TB control.

In the absence of direct evidence from outcomes of patients involved in clinical trials, knowledge about the expected effect of a medicine on an organism or a human (pharmacodynamics; PD), from how the human body handles a medicine (pharmacokinetics; PK), and from the field of microbiology can help clinicians address critical questions on how to optimise dosage, duration and design of regimens; which formulations to use and when; how best to treat children, HIV-associated TB and other sub-groups; and how to avert and manage drug-drug interactions.

In April 2017, WHO held a technical consultation in Geneva to discuss priority clinical issues related to the clinical management of drug-resistant TB. The conclusions drawn in this report reflect the extensive discussions during and after the consultation based on the latest research findings on PK/PD of TB medicines, as well as *in vitro* microbiological data, up until the end of 2017. **The findings of this report do not represent WHO recommendations at this point.** Any changes to current recommendations will require further evaluation by a WHO Guideline Development Group in accordance with WHO requirements using the GRADE approach before they become part of future guidance.

Ahead of the technical consultation, and on the basis of feedback received from stakeholders, WHO identified a set of priority clinical questions and used them to guide evidence reviews on the PK/PD of key medicines recommended for use in drug-resistant TB regimens. In response to these questions the following salient points were concluded<sup>2</sup>:

	<b>Clinical question 1:</b> In which situations and patient subgroups would a higher dose of later-generation fluoroquinolones be useful (including dosage in children and adults)?
	<b>Conclusion:</b> At high-dose (400-800mg/day, depending on body weight-band), the effect of moxifloxacin appears to be maximised in both the shorter and longer MDR-TB regimens, but requires regular and repeated monitoring for prolongation of the QT-interval using electrocardiography. The frequent concomitant use of other QT-interval prolonging drugs such as clofazimine, bedaquiline and delamanid may add to the risk of cardiotoxicity. For levofloxacin, the current dose of 10–15 mg/kg once daily in adults and children over 5 years and 15–20 mg/kg in children <6 years does not need to be changed.
	<b>Clinical question 2:</b> Is there any reason why levofloxacin cannot replace moxifloxacin or gatifloxacin in a shorter MDR-TB regimen?
	<b>Conclusion:</b> No routine substitution of levofloxacin for moxifloxacin in the shorter MDR-TB regimen is currently advised. End-of-treatment results from two observational studies in which levofloxacin substituted moxifloxacin are expected later in 2018. Substitution of moxifloxacin by levofloxacin may be considered in special situations e.g. clinically significant QT-interval prolongation due to moxifloxacin.

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<sup>2</sup> In addition to these responses, no changes to the recommended dosage of pyrazinamide, bedaquiline and delamanid were proposed.

	<b>Clinical question 3:</b> Is intermittent dosing of an injectable agent (amikacin, kanamycin, capreomycin) as effective as a daily dose?
	<u>Conclusion:</u> When given three times a week at 25 mg/kg body weight as part of a <u>longer</u> MDR-TB regimen, second-line injectable agents - amikacin and kanamycin - are likely to be still effective and less toxic on the basis of known PK/PD properties of these agents.
	<b>Clinical question 4:</b> Is there any reason why capreomycin cannot replace amikacin or kanamycin in a shorter MDR-TB regimen?
	<u>Conclusion:</u> Capreomycin should not routinely substitute kanamycin or amikacin in the shorter MDR regimen, as it has more potentially serious adverse drug reactions and data remain limited. In the presence of certain mutations conferring resistance to kanamycin (like <i>eis</i> C14T), capreomycin and amikacin may still be active and can therefore replace kanamycin in both the shorter and longer MDR regimens.
	<b>Clinical question 5:</b> Can prothionamide or ethionamide still have a therapeutic benefit in a regimen for patients infected with TB strains bearing the <i>inhA</i> promoter mutation or “thiamide” resistance?
	<u>Conclusion:</u> Given the number of medicines in the standardised shorter MDR-TB regimen the presence of the <i>inhA</i> mutation by itself (i.e. without any other mutations or phenotypic drug resistance) should not automatically disqualify a patient from receiving this regimen. However, if there is concomitant resistance to other components of the shorter MDR-TB regimen, or the presence of the <i>katG</i> mutation, a longer regimen in which the thiamide is replaced by another agent likely to be more effective is advised.
	<b>Clinical question 6:</b> Are prothionamide and ethionamide interchangeable in a shorter MDR-TB regimen?
	<u>Conclusion:</u> Ethionamide and prothionamide can be used interchangeably in the shorter regimen, as well as the longer regimens.
	<b>Clinical question 7:</b> What dose of isoniazid could still have a therapeutic benefit in a regimen for patients infected with TB or MDR-TB strains bearing the <i>katG</i> mutation?
	<u>Conclusion:</u> If the <i>katG</i> mutation is present, a number of isolates would be expected to resist isoniazid even when used at the upper end of the high dose (i.e. 15mg/kg/day), therefore rendering it ineffective. High-level resistance to isoniazid is more likely if the <i>inhA</i> promoter mutation is also present.
	<b>Clinical question 8:</b> What is the range/maximum dose of isoniazid considered as “high dose” and still tolerated in children and adults?
	<u>Conclusion:</u> In both children and adults, high-dose isoniazid for use in shorter and longer MDR-TB regimens is defined as 10-15 mg/kg/day (the normal dose being 4-6mg/kg/day). In settings like northern Asia, where the majority of the population has the fast acetylator genotype, a dose of 15 mg/kg may be more effective.
	<b>Clinical question 9:</b> Are cycloserine and terizidone interchangeable in an MDR-TB regimen?
	<u>Conclusion:</u> Cycloserine and terizidone are considered interchangeable (equivalent), although there are much less PK/PD data on terizidone, for which no formal bioequivalence studies exist.

	<b>Clinical question 10:</b> What is the optimal dosing frequency (divided daily; daily; alternate day) of cycloserine in an MDR-TB regimen?
	<i>Conclusion:</i> Twice daily dosing for cycloserine would be favoured, based on PK principles and the mechanism of action. Terizidone, with its longer half-life, can be given once daily. In many patients a dose higher than 500mg/day would not be tolerated.
	<b>Clinical question 11:</b> What is the optimal daily dose and dosing frequency of linezolid in an MDR-TB regimen?
	<i>Conclusion:</i> When there is an adequate number of effective companion medicines and the strain is susceptible to fluoroquinolones, linezolid can be used at 600 mg/day and the dose decreased to 300 mg/day in case of toxicity (temporary interruption may be necessary). If the number of effective companion medicines is lower than recommended or the strain is resistant to fluoroquinolone (confirmed or suspected), linezolid 600 mg can be given twice daily for the initial 2 to 4 weeks and 600mg once daily thereafter. Close clinical and laboratory monitoring is necessary to quickly identify adverse drug reactions during linezolid administration.
	<b>Clinical question 12:</b> What optimal dosage regime of clofazimine is required when it is used in longer and shorter MDR-TB regimens?
	<i>Conclusion:</i> Available data preclude a conclusive position regarding the optimal dose and dosing frequency of clofazimine for shorter and longer MDR-TB regimens. Most of the experience in its use has been from observational studies of the shorter MDR regimens, in which most patients received 100mg/day. There is no evidence for improved benefit-to-harm to support changes to the current recommended dose of 100 mg/day (50mg/day for individuals <40kg body weight), without a loading dose, in MDR-TB patients.
	<b>Clinical question 13:</b> In which patients on treatment for active, drug-susceptible tuberculosis is a higher dose of rifamycins indicated?
	<i>Conclusion:</i> This question was beyond the immediate focus of the technical consultation (on MDR-TB regimens). A full evidence review was not conducted but emerging PK/PD data and findings of ongoing trials on the dose and duration of rifampicin treatment were briefly presented. While a change to WHO policy on the currently recommended weight-based dosing of rifampicin would require additional trial evidence, the point was made that a higher rifampicin dose may be needed to achieve therapeutic concentrations, particularly in younger children, underweight adults, patients with TB meningitis and immunocompromised HIV-infected TB-patients. A full evidence review on the optimal use of rifampicin in terms of efficacy and safety would be important once more data become available.
	<b>Clinical question 14:</b> For which TB patients, regimens or medicines is the monitoring of blood or urine levels useful to assess therapeutic and/or toxic effects?
	<i>Conclusion:</i> Therapeutic drug monitoring (TDM) is likely to help in the case of medicines with a narrow therapeutic index and for which it is difficult to develop a dosing regimen that applies universally owing to individual variations in PK/PD (e.g. injectable agents, cycloserine, linezolid). Studies quantifying the value that TDM adds to clinical outcomes - efficacy, safety, quality and cost-effectiveness - are lacking. Likewise the best-suited methods to test and optimal sampling strategies still need to be determined.



## Report objectives

Studies of pharmacokinetics (PK; what the human body does to a medicine) and pharmacodynamics (PD; the effect of a medicine on an organism or a person) are key to establish the most appropriate dose of tuberculosis (TB) medicines. Due to variability in drug concentrations between patients and differences in the drug susceptibility patterns of *Mycobacterium tuberculosis* strains, the dosages required to maximise effectiveness at tolerable toxicity can differ substantially. In order to define the most appropriate dosage for TB treatment, PK/PD studies need to relate as much as possible to TB patients (rather than healthy volunteers) and the infecting bacteria.

A technical consultation was convened by WHO in Versoix, Switzerland from 24 to 26 April 2017 to address key clinical questions that could not be answered by the systematic reviews of patient outcomes which underpin the 2016 WHO policy recommendations on shorter and longer MDR-TB regimens (see Table 1 and Annexes 1-2)<sup>3</sup>. Evidence reviews were commissioned to inform the dose recommendations for the second-line medicines used to compose these regimens (cycloserine, clofazimine, linezolid, bedaquiline, delamanid, aminoglycosides and fluoroquinolones). Experts were invited to review other first-line medicines (rifampicin, isoniazid and pyrazinamide) and cross-cutting issues of interest in drug administration (children versus adult PK/PD, drug-drug interaction, and lesion distribution, alternative methods of drug delivery). The PK/PD of ethambutol, *p*-aminosalicylic acid, thioacetazone, carbapenems and clavulanic acid were not covered by the consultation. The findings were discussed during the three-day meeting and subsequently by e-mail and webinar. The end objective was to update drug information sheets in use in WHO guidance (1), and to agree upon areas and directions for future work.

The conclusions drawn in this report reflect the extensive discussions during and after the consultation based on the latest research findings on PK/PD of TB medicines, as well as *in vitro* microbiological data<sup>4</sup>, up until the end of 2017. **The findings of this report do not represent WHO recommendations at this point.** Any changes to current recommendations will require further evaluation by a WHO Guideline Development Group in accordance with WHO requirements using the GRADE approach before they become part of future guidance.

The experts involved in the discussions leading to this report acknowledged that numerous gaps remain in our understanding of the relationship between PK/PD and clinical-relevant end-points, such as culture conversion, cure and relapse. This still limits the quest for the optimal dose, frequency and duration of each medicine to maximise efficacy and minimise harm. A number of ongoing studies will provide useful insights in some critical questions, such as the dose-ranging Phase II study of levofloxacin (3), dose-ranging EBA study for linezolid (4),(5), efficacy and safety of higher-dose moxifloxacin in the shorter MDR-TB regimen (6), and pharmacokinetic optimization of levofloxacin, moxifloxacin and linezolid doses in children (7).

## Acknowledgements

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The writing of this report was led by Rada Savic (University of California San Francisco, USA), Dennis Falzon and Ernesto Jaramillo (WHO/GTB), under the supervision of Karin Weyer, Coordinator of the Laboratories, Diagnostics and Drug Resistance Unit of WHO/GTB.

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<sup>3</sup> Slides presented at the consultation available at : <https://www.dropbox.com/sh/ruu7pru9xzxw6vo/AABOLNL-FrzLVM3243CFSLfja>

<sup>4</sup> Concomitant discussions on the critical concentrations of linezolid, bedaquiline, delamanid, aminoglycosides and fluoroquinolones, are summarized in a separate WHO meeting report (2).

**Table 1.** Priority clinical questions for the pharmacokinetic and pharmacodynamics (PK/PD) reviews

In which situations and patient subgroups would a higher dose of later-generation fluoroquinolones be recommended (including dosage in children and adults)?
Is there any reason why levofloxacin cannot replace moxifloxacin or gatifloxacin in a shorter MDR-TB regimen?
Is intermittent dosing of an injectable agent (amikacin, kanamycin, capreomycin) as effective as a daily dose?
Is there any reason why capreomycin cannot replace amikacin or kanamycin in a shorter MDR-TB regimen?
Can prothionamide or ethionamide still have a therapeutic benefit in a regimen for patients infected with TB strains bearing the <i>inhA</i> promoter mutation or “thiamide” resistance?
Are prothionamide and ethionamide interchangeable in a shorter MDR-TB regimen?
What dose of isoniazid could still have a therapeutic benefit in a regimen for patients infected with TB or MDR-TB strains bearing the <i>katG</i> mutation?
What is the range/maximum dose of isoniazid considered as “high dose” and still tolerated in children and adults?
Are cycloserine and terizidone interchangeable in an MDR-TB regimen?
What is the optimal dosing frequency (divided daily; daily; alternate day) of cycloserine in an MDR-TB regimen?
What is the optimal daily dose and dosing frequency of linezolid in an MDR-TB regimen?
What dosage regime of clofazimine is required when it is used in longer and shorter MDR-TB regimens?
In which patients on treatment for active, drug-susceptible tuberculosis is a higher dose of rifamycins indicated?
For which TB patients, regimens or medicines is the monitoring of blood or urine levels useful to assess therapeutic and/or toxic effects?

## Methods<sup>5</sup>

### Search terms

The following search terms were used to query PubMed and Web of Science (“DRUG NAME” OR “ALTERNATIVE DRUG NAME”) AND (“tuberculosis” OR “TB” OR “Mtb”) AND (“pharmacokinetics” OR “concentration” OR “therapeutic drug monitoring” OR “TDM” OR “drug exposure” OR “drug monitoring” OR “pharmacology” OR “pharmacodynamics” OR “pharmacol\*” OR “pharmacod\*”). The date of the last search was recorded. The search was performed by two reviewers independently. In case of differences, agreement was reached by discussion. Descriptive retrospective or prospective PK studies in TB patients were included in

<sup>5</sup> See also the Methods sections of the individual PK/PD reviews (Annex 4)

the review. Removal of duplicates was followed by screening of titles and abstracts. The full text of eligible studies selected was read and articles referenced in them were furthermore searched for original data. A PRISMA diagram was prepared for each review. Target attainment in the population was calculated by using weighted median exposure and quartiles.

## Main study types

The most common type of human study used to evaluate the effect of an anti-TB drug in TB patients is the **early bactericidal activity** (EBA; see Annex 3) study, which is considered an early Phase IIa study in drug development. The measurement of bacterial killing rate has recently been divided into (i) an early EBA (between days 0 and 2) and (ii) an extended EBA (between days 2 and 7, at times extended up to 14 days). Extended EBA is proposed as an early measure of sterilizing activity, the ability of a drug to kill slowly replicating, persistent bacilli in tissues. EBA data were included in this review whenever available.

However, the most informative and relevant studies to evaluate the effect of anti-TB drugs are Phase III trials that include a long-term assessment of relapse-free cure (12-18 months of follow up) in patients who are usually randomised to different treatment groups. Second in line are Phase IIb studies with time to (stable) culture conversion as the main endpoint and with other data of efficacy surrogates collected during treatment. Follow up after the end of treatment usually plays no part in Phase IIb studies. The time to stable (or sustained) culture conversion is generally considered a solid indicator of sterilizing potential of the regimen.

In conclusion, the efficacy endpoints of different types of trials can be ranked by order of decreasing importance in following way: relapse-free cure>time to stable culture conversion>EBA.

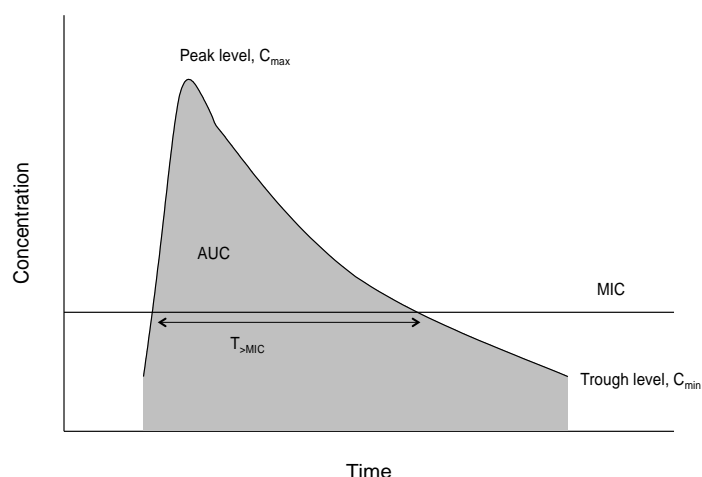
**The mouse preclinical infection model** is the main *in vivo* preclinical model of tuberculosis treatment and most commonly used to assess efficacy of drug regimens before they enter clinical development.

**Hollow fibre infection models** (HFIM) have been introduced in the field of TB since the early 2000s. These *in vitro* systems are of particular interest for studying PK/PD because they can mimic closely human PK. Moreover, the systems can be sampled frequently to study bacterial growth and drug PK. HFIM has recently been endorsed by European Medicines Agency (EMA) for use in anti-TB drug development as an additional and complementary tool to methods currently used to inform the selection of dose and treatment regimen, including the combination of TB medicines, to maximize bactericidal effects and minimize the emergence of drug resistance (8). HFIM studies can be used to determine whether efficacy is driven by AUC/MIC,  $C_{max}/MIC$  or  $\%T > MIC$ , by comparing the efficacy/effectiveness of a single dose ( $C_{max}$ ) with the dose divided in two or three dosages ( $\%T > MIC$ ) (see Figure 1 for a graphic representation of the main PK/PD indices and Annex 3 for a more extensive glossary). If HFIM data were available, they were included in the review. It is important to be aware of the drug susceptibility testing (DST) method used when interpreting or comparing PK/PD parameters that relate to an MIC.

Standard dose and higher dose were investigated to judge whether PK sampling was performed at steady state. Assay parameters for analysis were assessed for compliance with EMA, US Food and Drug Administration (FDA) and/or CLSI guidelines for bioanalytical validation. In the PK/PD studies, studies on outcome or development of resistance were selected with data on:

1. EBA studies with single drug in TB patients,
2. Animals studies with single drug, data on PK, MIC and outcome (including relapse where possible).
3. HFIM

Reviews, case reports and studies in healthy volunteers were excluded. Data found by reviewers to have been cited in different publications were only included once. Data extraction was verified by a second reviewer. The data were reported in tables and plotted (e.g. Forest plots) where possible. Conclusions were drafted as short statements, identifying knowledge gaps. The members of the review team peer-reviewed the final report.



**Figure 1:** The main pharmacokinetic / pharmacodynamic (PK/PD) parameters for anti-TB drugs.

AUC, area under the concentration-time curve;  $C_{min}$ , minimum concentration;  $C_{max}$ , maximum concentration; MIC, minimum inhibitory concentration;  $T_{>MIC}$ , time during which the drug blood concentration is above the MIC (see also Annex 3).

## Findings and conclusions – priority questions

This section summarises the salient points made in the evidence reviews, the presentations and the resulting discussions. The full text of the literature reviews are appended to this report (Annex 4) and the presentations themselves are available online<sup>3</sup>. Some of the main references are cited at the end of this report, but for a full listing of the literature used in the reviews the reader is referred to the citations in Annex 4.

### *Fluoroquinolones (levofloxacin (Lfx), moxifloxacin (Mfx), gatifloxacin (Gfx))*

#### Clinical questions:

- In which situations and patient subgroups would a higher dose of later-generation fluoroquinolones be recommended (including dosage in children and adults)?
- Is there any reason why levofloxacin cannot replace moxifloxacin or gatifloxacin in a shorter MDR-TB regimen?

#### Discussions

In addressing the two key clinical questions relating to the fluoroquinolones, the PK/PD review and the experts structured their discussion around the following questions:

- What is the optimal dose of fluoroquinolones for treatment of MDR-TB, including special populations (children)?
- What is the comparative clinical efficacy of fluoroquinolones
- What is the comparative safety of fluoroquinolones

#### Optimal fluoroquinolone dose

While later generation fluoroquinolones play a key role in contemporary regimens for drug-resistant TB, there is concern about the development of resistance and suboptimal efficacy. Higher drug exposures may prevent the acquisition of additional resistance and improve outcomes in certain patients, however an increase in the fluoroquinolone dose may increase safety concerns. The effectiveness of later generation fluoroquinolones in susceptible strains has been observed to be lower in the presence of resistance to earlier generation fluoroquinolones such as ofloxacin (9).

Up to now, there has been no publication of dose-ranging studies in DR-TB patients for any of the fluoroquinolones that could provide data and clinical evidence for exposure-response relationship to guide an

optimization of dose. Two trials that have been finished recently will provide important insights into the dosing of moxifloxacin and levofloxacin once published, namely:

- stage 1 of the Phase III STREAM trial that used moxifloxacin doses ranging from 400mg-800mg based on weight bands as part of the 9-month shorter MDR-TB regimen (6);
- Opti-Q : a formal dose-ranging study of levofloxacin using time to stable culture conversion as an endpoint (9).

Provisional results from the STREAM trial announced in October 2017 have indicated that QTcF-interval prolongation was higher in the intervention arm (10% of subjects exceeded the 500ms threshold on automated ECG reading) than in controls on a longer MDR-TB regimen (4.7%) (10). Preliminary results from Opti-Q trial were also presented in October 2017 and showed dose-proportional PK up to the 20 mg/kg dose of levofloxacin (11). Efficacy data (time to sustained culture conversion) are still pending for this trial and are expected to inform further on the optimal dose of levofloxacin.

Currently, PK/PD targets are lacking for gatifloxacin and levofloxacin, and these are only available for moxifloxacin based on murine studies and HFIM. These models are limited as there are gaps in their translation to patients, with scanty knowledge about the free-drug concentrations and drug activity at the microbe-drug interface in patients and unknown effects of companion drugs within a multidrug regimen. Moreover, PK thresholds for efficacy would vary with different forms of TB (e.g. meningitis, pericarditis) and disease severity (e.g. cavitation). Nonetheless, experts agreed that in the absence of clinical exposure-response data, the AUC/MIC ratio provides an important correlate of activity. Hence the distribution of both MICs and the AUCs for the individual fluoroquinolones amongst TB patients are useful when discussing optimal dose. Wide variability of both of these indices is observed (e.g. geographical variation) and limited clinical evidence amongst patients with fluoroquinolone-susceptible TB suggests that relatively high MICs are associated with a risk of worse outcomes. More evidence is needed to support the safety of higher doses of these fluoroquinolones, particularly in the presence of companion medicines in a regimen and other risk factors for toxicity.

#### Comparative efficacy of fluoroquinolones

Koh et al (12) suggested that daily 750mg doses of levofloxacin have very similar 3-month efficacy and safety to 400mg of moxifloxacin. Similarly, an EBA study found similar activity for levofloxacin 1000 mg, gatifloxacin 400 mg and moxifloxacin 400 mg (13). A dose of 1500 mg/day of levofloxacin may be equivalent to 800mg of moxifloxacin in the typical adult patient and has less QT-interval prolongation effects. However, these relatively short-term outcomes may not adequately reflect sterilizing activity of the regimen in patients with MDR-TB, and may not have had sufficient power. Murine studies suggest that moxifloxacin 400mg may have superior sterilizing activity to levofloxacin 1000mg, and *in vitro* studies suggest better accumulation in macrophages of moxifloxacin than levofloxacin (14). Substitution of moxifloxacin or gatifloxacin with levofloxacin cannot therefore be recommended with confidence, especially as doses of moxifloxacin or gatifloxacin higher than 400mg may be needed for optimal effect. On the other hand, levofloxacin appears to display superior penetration of cerebrospinal fluid (CSF), and has less propensity to prolong the QT-interval (15),(16),(17). However it has been reported to show some CNS toxicity in young children when receiving increased doses (Hesseling A, personal communication, 2017). Moxifloxacin is associated with better penetration into cavitary lesions in patients, suggesting better activity in patients with these features (18).

Two sites (Bangladesh, Viet Nam) are known to be using high-dose levofloxacin as part of the shorter MDR-TB regimen under programmatic conditions. Final outcomes from these cohorts are expected in early 2018.

#### Comparative safety of fluoroquinolones

Increased doses of fluoroquinolone carry safety concerns, namely prolonged QT-interval (moxifloxacin) and dysglycaemia (gatifloxacin), however since data on exposure-response and exposure-safety are lacking, it is not clear how benefit/risk ratio might be impacted by replacing one medicine with another, and further studies are still needed.

Drug-drug interactions may be unanticipated. Within regimen interactions and interactions with drugs used to treat common comorbidities should be evaluated. Moxifloxacin is metabolized by glucuronosyltransferase and sulphotransferase and is a putative substrate of P-glycoprotein. A recent study reported a 30% reduction in moxifloxacin AUC associated with concomitant use of efavirenz (19). If this effect is confirmed it could impact outcomes in HIV-infected individuals and alternative drug/dosing strategies would need to be considered. PD

interactions with other QT-interval prolonging agents - or agents that might increase moxifloxacin concentrations thereby indirectly prolong further the QT - are a particular safety concern. Rifampicin induces the metabolism of moxifloxacin, resulting in a 31% reduction in the AUC of moxifloxacin (20),(21). A reduction of up to 30% in moxifloxacin AUC has also been reported when it was co-administered with low dose of rifapentine (22). A similar effect has been described for gatifloxacin (23). Less has been published about levofloxacin, which in addition to MDR-TB regimens is also recommended for use in combination regimens with rifampicin for the treatment of isoniazid-resistant tuberculosis (24).

Dairy products, which are rich sources of the divalent ions calcium and magnesium, have been reported to interfere with the absorption of ciprofloxacin or norfloxacin when given concomitantly (25),(26). However, this has not been shown for levofloxacin and moxifloxacin and restriction of milk products from the diet of children on MDR-TB regimens may not therefore be justified on these grounds alone (27).

#### Conclusions:

1. High-dose moxifloxacin (i.e. 400-800mg/day depending on body weight) may maximise its effect in both the shorter and longer MDR-TB regimens. However, ECG monitoring for clinically significant prolongation of the QT-interval is advised when moxifloxacin is used at this dose. The concomitant use of other QT-interval prolonging drugs like clofazimine, bedaquiline and delamanid is now becoming more likely and may add to the risk of cardiotoxicity.
2. For levofloxacin, the current recommendation is to use 10–15 mg/kg once daily in adults and children over 5 years and 15–20 mg/kg split into two doses in children <6 years old (1). The optimal dose of levofloxacin in adults and children is being studied; until results are made public the current recommended dose of levofloxacin is best left unchanged.
3. On the basis of PK/PD data from animal models, no routine substitution of levofloxacin for moxifloxacin in the shorter MDR regimen is proposed. The substitution may be considered in special situations (e.g. significant QT-interval prolongation due to moxifloxacin) but ideally this should await the publication of results of observational studies in which levofloxacin was used in the shorter MDR-TB regimen under programmatic conditions.

#### *Second-line injectable agents (amikacin (Am), capreomycin (Cm), kanamycin (Km))*

##### Clinical questions:

- Is intermittent dosing of an injectable agent (amikacin, kanamycin, capreomycin) as effective as a daily dose?
- Is there any reason why capreomycin cannot replace amikacin or kanamycin in a shorter MDR-TB regimen?

##### Discussions:

In addressing the two key clinical questions relating to the injectable agents, the PK/PD review and the experts structured their discussion around the following questions:

- What is the rationale for use of injectable agents in MDR-TB treatment regimens and can they be avoided?
- What is the clinical comparative efficacy of injectable agents and in which instances is the exchange of drugs justified?
- What is the optimal dose and dosing schedule for amikacin and kanamycin given their toxicity profiles?
- What is the status of development of inhaled therapies for aminoglycosides?

##### What is the rationale for use of injectable agents in MDR-TB treatment regimens and can they be avoided?

In a careful review of early studies carried out by the British Medical Research Council, streptomycin appeared to have limited sterilizing activity as measured by relapse rates in some studies, but which never reached statistical significance (28). Further, reviews of clinical outcomes of MDR-TB patients treated with regimens including injectable agents have not yielded consistent results. The analyses are limited by the observational nature of studies, small numbers of patients treated, and by residual confounding from factors that cannot be fully accounted for. For example, in a large, individual patient data meta-analysis including 9,153 patients, the use of kanamycin, amikacin, or capreomycin vs. no injectable was not associated with a successful treatment

outcome (29). The analysis from this study was limited by the small number of patients who did not receive an injectable agent. In another meta-analysis, treatment success was achieved in 64% of patients with MDR-TB only, 56% of patients with MDR-TB with additional resistance to injectable agents, 48% in patients with MDR-TB with resistance to fluoroquinolones, and 40% among patients with XDR-TB (30). This probably indicated that fluoroquinolones are more important than injectable agents in a regimen, even if better outcomes are obtained in patients who are susceptible to an injectable agent and who receive one in their treatment (albeit not statistically significant). Similarly, another study including 337 patients showed that baseline fluoroquinolone resistance was associated with a 4-fold higher odds of unfavourable outcome in MDR-TB patients on treatment whereas baseline resistance to the injectable agents was not associated with a higher risk of unfavourable outcome (31). Children with mild forms of MDR-TB<sup>6</sup> appear to do equally well with and without injectable agents, and WHO-recommended regimens no longer propose the inclusion of these agents in such cases (33).

Dose-ranging studies of amikacin (15mg/kg/day) showed that it has *no early bactericidal activity* (34),(35). However, amikacin is presumed to have sterilizing activity because members of this class of medicines show this property at later time points. *In vitro* studies show that amikacin is weakly bactericidal and that kanamycin is bacteriostatic (36). Evidence from the HFIM indicates that  $C_{max}/MIC$  is the best PK/PD index and a  $C_{max}/MIC$  ratio of 10 (in lung tissue) has been proposed as a target from HFIM system (37). The penetration of aminoglycosides into the lung tissue is known to vary and is not well defined. This has an important bearing on the correlation between the measurable plasma levels and those that can be achieved in the lungs as the target organ (conversion of the  $C_{max}/MIC$  ratio).

Overall, in cohort studies, patients with MDR-TB strains resistant to the injectable agents seem to respond slightly worse than patients with strains susceptible to injectable agents. It is unclear if this is due to the microbiologic activity of the injectable, or confounded by accompanying resistance to companion drugs (that may be undetected), greater likelihood of treatment observation by health care workers when injectable agents are part of a regimen, or other factors that are associated with both higher risk of drug resistance and poor outcomes (poor absorption, malnutrition, adherence challenges). It was also noted that the relative contribution of injectable agents to regimen efficacy may be diminished when potent companion medicines are used. The experts agreed that the fundamental question about the place of the injectable agents in future regimens needs further examination.

#### What is the clinical comparative efficacy of injectable agents and in which instances is the exchange of drugs justified?

There are no formal studies evaluating comparative efficacy of second-line injectable agents. In one observational study of the shorter MDR-TB regimen supported by Médecins Sans Frontières in Uzbekistan, capreomycin was used in 30 patients with kanamycin resistant MDR-TB strains [du Cros P, personal communication, 2017]. Success rates in these patients were comparable to patients with kanamycin-susceptible strains treated with kanamycin.

In the absence of other comparative patient outcome data, exchangeability was discussed mainly in light of the relative toxicity and with respect to the strain mutations associated with resistance. The expert panel agreed that capreomycin should not routinely substitute kanamycin or amikacin in the shorter MDR regimen, as capreomycin has more electrolyte disturbances and was associated with an increased risk of life-threatening metabolic abnormalities in TB patient series (38),(39).

The presence of the two most important mutations conferring resistance to second-line injectable agents - and which can be detected by second-line LPA - has important implications on the effectiveness of these agents in MDR-TB treatment regimens:

- If the *rrs* A1401G mutation is present, none of the injectable agents (amikacin, kanamycin or capreomycin) is likely to work;
- Some mutations (like *eis* C14T, detectable using the Hain second-line LPA) confer resistance to kanamycin, but both amikacin and capreomycin may still retain activity.

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<sup>6</sup> Severity was determined by bacteriologically confirmed disease, which was associated with HIV infection, malnourishment, severe forms of extrapulmonary disease and advanced changes on chest radiography (32)

### What is the optimal dose and dosing schedule for amikacin and kanamycin given their toxicity profiles?

The PK/PD review and expert discussion acknowledged that there is limited knowledge and clinical studies that can provide a sound basis for the optimisation of the dose and administration schedule for any of the second-line injectable agents.

Injectable agents carry a number of serious safety concerns, most importantly ototoxicity, which appears to be dependent on cumulative dose/exposure, and nephrotoxicity, which is associated with trough levels.

Aminoglycosides interact in a time- and dose-dependent manner with the sensory structures of the inner ear and the cumulative ototoxicity appears to be due to drug accumulation in the perilymph. Ototoxicity seems to be related to penetration into deep compartments from which the half-life of disappearance is extremely slow and not necessarily correlated with measureable plasma levels.

These are important considerations in the choice of the dose and regimen. There is a rapid uptake of aminoglycosides, early saturation, and long exposure due to long tissue/plasma half-life. Dosing strategies associated with less accumulation of an injectable agent in the body would therefore be preferred and daily dosing may not be necessary. An alternate-day dosing scheme achieved kill slopes similar to those for daily dosing as long as the  $C_{max}$  was matched, which means that more intermittent injections would possibly work as well as daily injections (37). However, this concept has not been proven in patient studies. No difference in toxicity was shown between intermittent and daily dosing (40). Monte Carlo simulations of an alternate day dosing of amikacin at 25mg/kg/day appears to exceed an MIC of 2mg/L in a larger group of patients than the more usual 15mg/kg dose when given daily (Gumbo T, personal communication, 2017). The risk of ototoxicity would be lower at this dose given that the mean exposure to amikacin in the body would be reduced.

Based upon these considerations, intermittent use of injectable agents, such as 3 times a week (e.g. Mon-Wed-Fri), is likely to be equally efficacious but less toxic and discomforting for the patient than daily administration.

### What is the status of development of inhaled therapies for aminoglycosides?

Alternative routes of administration for injectable agents would be of interest given that the regular administration of painful intramuscular injections over many months represents one of the most inconvenient features of MDR-TB regimens. The emergence of drug-resistant disease requiring complicated regimens has motivated the quest for alternative strategies of drug administration.

The application of inhaled therapy in TB has been evaluated at intervals over the last 80 years (41). A wide variety of medicines commonly employed in MDR-TB regimens has been assessed for their potential as inhaled therapies. Early studies involved nebulizer delivery of compounds. Simple, inexpensive unit-dose dry powder inhalers have been adopted more recently, which may be a more practical option for use in remote locations including patients' homes. Several drugs are commercially available in aerosol dosage forms, most notably nebulized kanamycin. Others are in various stages of development. Inhaled therapy has been explored for aminoglycosides in an effort to avoid injections and to try to achieve higher concentrations of the active agent in the lungs and thus limit ototoxicity and nephrotoxicity. The results of a series of studies of inhaled, spray-dried capreomycin sulphate powder were focused upon during the consultation (42),(43). The key finding is that substantially higher doses can be concentrated in the lungs by direct inhalant delivery than by the conventional intramuscular route. The concentrations in bronchoalveolar fluid and lung tissue following administration of ~4mg/kg doses by inhalation to guinea pigs (n=6) was 4-100 fold higher than a 20mg/kg intramuscular dose (44),(45). Moreover, the drug concentrations remain above MIC in the lungs for an extended period of time. A single escalating dose PK study in healthy volunteers showed that the aerosol was well tolerated up to a dose of 300mg. This may be a useful supplement to conventional therapy. However, within the design parameters of the studies described, a large lung dose is required to achieve systemic levels of the compound within the therapeutic ranges and that can also reach sanctuary sites (e.g. lymph nodes).

### Conclusions:

- The PK/PD review indicated that when given three times a week at 25mg/kg body weight, second-line injectable agents - amikacin and kanamycin - are likely to remain effective but be less toxic. While this could be an option in the longer MDR-TB regimen, the effect of intermittent administration of the injectable agent throughout the intensive phase of the shorter MDR-TB regimen cannot be predicted and is therefore not yet advised.
- Capreomycin should not routinely substitute kanamycin or amikacin in the shorter MDR regimen, as it has more potentially serious adverse drug reactions and empirical data remain limited.



- With respect to genetic mutations and use of second-line injectable agents:
  - If the *rrs* A1401G mutation is present, the shorter MDR regimen is not to be used and the injectable agent is replaced with another agent in the longer MDR regimen (to achieve the minimum number of effective agents).
  - In the presence of certain other mutations (like *eis* C14T), capreomycin and amikacin may still be active and can therefore replace kanamycin in both the shorter and longer MDR regimens.
- In children with non-severe disease, MDR-TB can be treated without a second-line injectable.
- Promising developments on alternative routes of administering aminoglycosides and capreomycin could avoid the inconvenience of injection and deliver the active agent more effectively to the lung. More studies are needed to clarify the future utility of these methods and their applicability to other TB medicines that present challenges to administration (particularly agents that are poorly absorbed or tolerated when given by mouth).

### Thiamides (*ethionamide (Eto)*, *prothionamide (Pto)*<sup>7</sup>)

#### Clinical questions:

- Can prothionamide or ethionamide still have a therapeutic benefit in a regimen for patients infected with TB strains bearing the *inhA* promoter mutation or “thiamide resistance”?
- Are prothionamide and ethionamide interchangeable in a shorter MDR-TB regimen?

#### Discussions:

The expert discussions focused on the comparative efficacy of ethionamide and prothionamide (i.e. interchangeability) and on the use of the agents in the presence of resistance (as inferred, primarily, from the presence of *inhA* mutations).

Ethionamide and prothionamide are derivatives of isonicotinic acid, structurally similar to isoniazid. They act against *inhA* products and mycolic acid production. Some consider ethionamide and prothionamide to have bactericidal activity and have similar effectiveness. Low tolerability is the major limiting factor in using those agents. They have low to very low tolerability at current doses needed to achieve some efficacy, mostly as a result of gastrointestinal (GI) toxicity, but also subclinical hypothyroidism and neurotoxicity. Theoretically, higher doses might achieve better efficacy, however GI tolerability is an important dose-limiting factor for thiamides. Prothionamide has shown lower GI toxicity (nausea and vomiting) than ethionamide at equivalent doses across several blinded trials in the 1960s (46). Similarly, lower rates of treatment discontinuation with prothionamide have been reported as compared to ethionamide. To improve its tolerability, there is a desire for new formulation and/or alternative administration routes. Suppositories have been reported to be 50% absorbed relative to oral tablets. Inhaled therapy could address GI intolerance. From the efficacy standpoint, use of prothionamide has been associated with slightly improved culture conversion, which may also be related to improved GI tolerability.

Ethionamide MIC is 1-2 orders of magnitude higher than for isoniazid. If TB strains bear the *inhA* promoter mutation or have other genetic (e.g. *ethA*) or phenotypic characteristics suggestive of “thiamide” resistance, the thiamide is unlikely to be effective in an MDR-TB regimen (high-dose isoniazid may still have activity). If only the *katG* mutation is present, thiamides retain activity, while isoniazid is unlikely to be effective, even at a high-dose (see also next section and Table 2). In the presence of both *inhA* and *katG* mutations, it is likely that both isoniazid and thiamides will not work and could thus jeopardise the effectiveness of a MDR-TB regimen which depends upon these two agents.

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<sup>7</sup> A literature review specific to the thiamides was not undertaken ahead of the meeting

### Conclusions:

- If solely the *inhA* mutation is present, the shorter MDR-TB regimen – inclusive of the thiamide<sup>8</sup> - can still be used unless there is evidence of resistance to other components of the regimen (e.g. presence of the *katG* mutation renders isoniazid ineffective). If a longer MDR-TB regimen is prescribed then thiamide should be replaced by another agent likely to be more effective.
- If solely the *katG* mutation is present, ethionamide and prothionamide can still be used. Table 2 summarises how thiamides and isoniazid are best used and how regimens may be modified based on a combination of strain and host characteristics.
- Ethionamide and prothionamide are likely to be equally effective and can thus be used interchangeably. Prothionamide has shown less GI toxicity (nausea and vomiting) than ethionamide in some studies.

### *Isoniazid (H)*<sup>9</sup>

#### Clinical questions:

- What dose of isoniazid could still have a therapeutic benefit in a regimen for patients infected with TB or MDR-TB strains bearing the *katG* mutation?
- What is the range/maximum dose of isoniazid considered as “high dose” and still tolerated in children and adults?

#### Discussions:

The expert discussions focused on the isoniazid dosage that demarcates between “normal” (most commonly 4-6mg/kg/day) and “high” (most commonly 10-15mg/kg/day), and the host and strain characteristics that can determine if isoniazid can still be effective, and if so, which dose would be expected to attain the optimal benefit-to-harm ratio.

Isoniazid is an inhibitor of mycolic acid biosynthesis. It is a prodrug and peroxidative activation of isoniazid by the mycobacterial enzyme *katG* generates reactive species that form adducts with NAD(+) and NADP(+) that are potent inhibitors of lipid and nucleic acid biosynthetic enzymes. *InhA*, the enoyl-ACP reductase of the fatty acid synthase type II system, leads to further inhibition of mycolic acid biosynthesis. Mutations in *inhA* and *katG* genes account for approximately 90% of isoniazid resistance detected by phenotypic DST. There are regional differences in the distribution of different mutations but globally about 2/3 of isoniazid mutations are *katG* and many of these may have accompanying *inhA* mutations as well. *katG* mutations are usually associated with higher MICs and mutations in both *katG* and *inhA* locations are expected to lead to higher MICs. Mutations in the promoter region of the *inhA* gene are normally associated with low-level resistance to isoniazid and with cross-resistance to the thiamides(47),(48). The presence of a *katG* 315 mutation alone is associated with elevated MICs(49),(50). Although resistance associated with *katG* is almost always encoded by the same mutation - Ser315Thr - MICs vary considerably.

In the host, isoniazid is metabolized by N-terminal acetyltransferase 2 (NAT2), and a mutation in the NAT2 genotype leads to substantial differences in isoniazid metabolism, and individuals are classified as either “slow” or “fast” acetylators. The prevalence of NAT2 mutations differ geographically, with for example slow acetylator status being prevalent in Egypt (83%) and USA (67%). In contrast, the slow acetylator mutation is rare in the north Asia (e.g. 12% in China) but higher elsewhere.

Isoniazid efficacy is concentration driven, with AUC/MIC followed by the  $C_{max}/MIC$  being reported as having the best correlation with efficacy(51). EBA studies of dose-ranging isoniazid in drug-susceptible TB shows clear dose-response relationship indicating saturation of the effect at the doses  $\geq 300mg$ (52). In both slow and fast acetylators, a daily isoniazid dose of 5 mg/kg for drug-susceptible TB can achieve the target levels in adults and higher doses would only predispose to toxicity(53). In the presence of the *inhA* mutation, the same dose may suffice in slow acetylators but fast acetylators may require 15mg/kg/day to reach the threshold. In the

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<sup>8</sup> Although the thiamide may add more toxicity than effectiveness to the standardized shorter MDR-TB regimen it is not clear what negative effect on the synergic action of the combined drugs in the regimen its removal would incur.

<sup>9</sup> A literature review specific to isoniazid was not undertaken ahead of the meeting

presence of the *katG* mutation, it was predicted that even at a dose of 15mg/kg/day the effectiveness levels could not be achieved even in the individuals with a slow acetylator status.

In the context of MDR-TB, a higher isoniazid dose may be needed to overcome resistance and elevated MICs. In a randomized controlled trial of MDR-TB patients in India the use of isoniazid at 16-18 mg/kg/day when compared with low dose (5 mg/kg) or placebo was associated with better 6 month culture conversion rates and shorter time to culture conversion (at the expense of more peripheral neuropathy in the high dose group although vitamin B6 was not given as part of therapy)(54). Isoniazid was also observed to be an important determinant of success in the studies which studied the composition of the shorter MDR-TB regimens in Bangladesh (55). Most studies of these regimens used an isoniazid dose closer to 10mg/kg, which is at the lower end of what is usually referred to as a “high-dose” range (56),(57).

Optimal isoniazid dose in context of MDR-TB is likely to be a function of both host genetics and the type of mutation. The MIC, if determined correctly, will capture strain resistance not directly inferable from the mutations detected. As discussed in the previous section on thiamides, an algorithm such as the one in Table 2 can help users decide when to use the shorter regimen and what modifications to make to a longer regimen that can be individualised to maximise effectiveness and reduce risk of harms.

#### Conclusions:

- If the *katG* mutation is present, MICs may be too high to achieve benefit from isoniazid even when used at the upper end of the high dose and in slow acetylators.
- If only the *inhA* mutation is present, high-dose isoniazid is likely to be effective even in fast acetylators.
- If both *katG* and *inhA* mutations are present then isoniazid is probably useless and the shorter MDR-TB regimen should not be used (because of the reduced thiamide efficacy; see also section on thiamides and Table 2)
- In both children and adults, high-dose isoniazid for use in shorter and longer MDR-TB regimens is defined as 10-15 mg/kg/day (the normal dose being 4-6mg/kg/day)<sup>10</sup>. In settings like northern Asia, such as China, where the majority of the population is a fast acetylator, a dose of 15 mg/kg needs to be considered, so long as the medicine is tolerated.

#### Cycloserine (Cs) and Terizidone (Trd)

##### Clinical questions:

- Are cycloserine and terizidone interchangeable in an MDR-TB regimen?
- What is the optimal dosing frequency (divided daily; daily; alternate day) of cycloserine in an MDR-TB regimen?

##### Discussions:

Cycloserine and terizidone are partial N-methyl-D-aspartate (NMDA) receptor agonists and antagonists of pyridoxal 5'-phosphate (P5P) reactions. Terizidone converts into cycloserine, likely by hydrolysis of imine groups in terizidone to cycloserine and para-phthalate, although the precise pathway of bio-transformation has not been characterised. Their primary route of elimination is renal (~70% excreted unchanged), although the metabolic pathway and products are not characterised. There is potential for enhanced neurotoxicity with isoniazid (especially when given at “high dose”) and with thiamides. Given their narrow therapeutic window, these DDIs may limit any further attempt at dose optimisation.

PK/PD data for cycloserine are extremely sparse and based on outdated bioanalytical methods. There are very limited PK data on terizidone, which may not have distinguished separately between the activity of terizidone *per se* from that of cycloserine as its breakdown product. No results from HFIM studies have been published. Furthermore, there have not been preclinical or clinical studies performed to identify a correct PK/PD target, however cycloserine is cell-wall active, suggesting that duration of exposure in excess of the MIC (%T>MIC) might be the appropriate index. Distribution of clinical strains appears to be bimodal, with poor separation at

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<sup>10</sup> Pyridoxine at 10-25 mg/day may protect against neurological effects when high dose isoniazid is used (dose may need to be increased if other agents like cycloserine and thiamides are used concomitantly; see also (1))

the older critical concentration on LJ media,<sup>11</sup> which was based on three different MICs. A ceiling for peak concentrations and TDM of 35 mg/L has been proposed although the basis for this level is not clear (58). This is close to cycloserine  $C_{max}$  with  $C_{max}/CC$  ratios <2. The therapeutic index is therefore narrow and there is little room for dose adjustment.

**Table 2:** Potential implications of strain and host factors on the effectiveness of isoniazid and thiamides in MDR-TB treatment regimens<sup>12</sup>

FA=fast acetylator of isoniazid; SA=slow acetylator of isoniazid; NAT2=gene coding for N-terminal acetyltransferase 2, an isoniazid activator

Mutations	Host acetylator (NAT2) status	Isoniazid	Ethionamide / Prothionamide
<i>inhA</i>	Not known	Higher dose in shorter and longer regimens	Replaced in longer regimens Shorter regimen can still be used
<i>inhA</i>	FA	Higher dose in shorter and longer regimens	Replaced in longer regimens Shorter regimen can still be used
<i>inhA</i>	SA	Higher dose in shorter and longer regimens	Replaced in longer regimens Shorter regimen can still be used
<i>katG</i>	Not known, SA	Higher dose in shorter regimen and replaced in the longer regimens	Can still be used in longer regimens Shorter regimen can still be used
<i>katG</i>	FA	Higher dose in shorter regimen and replaced in the longer regimens	Can still be used in longer regimens Shorter regimen can still be used
Both <i>katG</i> and <i>inhA</i>	Not known, FA, SA	Not used in longer regimens Shorter regimen not recommended	Not used in longer regimens Shorter regimen not recommended

The expert discussions focused on the optimal dosing regimen of cycloserine and terizidone and on the relative effectiveness of the two agents.

#### Interchangeability of cycloserine and terizidone

There have not been any bioequivalence or mass balance studies of terizidone so equivalence of dosing is not established. In one study, it appears that cycloserine showed less than a stoichiometric increase in plasma than terizidone (59). However, recent data suggest near-complete conversion of terizidone to cycloserine (McIlleron H, personal communication 2017). The approach to formulate a pro-drug could increase tolerability to these medicines but there have been few direct comparisons (60).

#### What is the optimal dose and dosing frequency of cycloserine in an MDR-TB regimen?

The optimal dose of cycloserine in an MDR-TB regimen is not known and data to support when to use cycloserine/terizidone in a regimen are lacking. The limited PK/PD data available need to be interpreted with caution if used to support dosing strategies. Inter-person variability in PK of cycloserine is not clear but may be substantial. No relevant primary or bridging studies are available to inform dosing in children.

<sup>11</sup> The older WHO critical concentration for cycloserine in L-J media (30 mcg/ml) will be discontinued with the current revision(57)

<sup>12</sup> This information is based on the expected likelihood of effectiveness of the two anti-TB agents. It is not a guideline for use

Even if exposures achieved from doses higher than 500mg were not proportional to dose they may still increase concentrations. Concentrations peaked at about two hours after intake in most MDR-TB patients on treatment in one small study (61). The current once-daily dosing is not likely to achieve a plasma  $C_{max}$  greater than the critical concentration of 30 mg/L, although some recent work suggests that 500 mg/day has a more favourable PK/PD than 250 mg twice daily (62). Estimates of cycloserine half-life range from 5-8 hours and therefore accumulation may be expected with twice daily dosing (accumulation ratio is 1.8 for 12h and 2.4 for 8h dosing, therefore more frequent dosing might be suitable to meet these targets). If %T>MIC is important then this would favour twice daily dosing of cycloserine. Terizidone has a longer half-life which may make it more suitable for once daily dosing.

#### Conclusions:

- Cycloserine and terizidone are considered interchangeable (equivalent), although there is much less PK/PD data on terizidone and no formal bioequivalence studies exist.
- Dose ranging PK data for cycloserine and terizidone are incomplete, pathways of biotransformation are not well-characterised, therefore any projections of clinical PK are limited
- PK/PD support for current dosing is very weak in terms of efficacy and narrow therapeutic index and potentially significant DDIs may limit further the scope for dose optimisation.
- The presumed importance of %T>MIC for the effectiveness of cycloserine favours twice daily dosing based on PK principles and mechanism of action. This might also lower risk for ADRs if the dose is maximised to >500mg/day based on individual patient tolerance. The longer half-life of terizidone would make it more suitable for once daily dosing than cycloserine, a clear advantage in clinical practice.

#### Linezolid (Lzd)

##### Clinical question:

- What is the optimal daily dose and dosing frequency of linezolid in an MDR-TB regimen?

##### Discussions:

The expert discussions focused on the PK/PD parameter and target for linezolid; the optimal dose and dosing schedule for linezolid in adults and children, considering its toxicity profile; the potency of companion agents in the regimen, and the repurposing of its use in TB from its original indication to treat Gram-positive bacterial diseases.

Linezolid is an oxazolidinone developed for infections with doubling times of roughly 30 minutes. A 12-hourly dosing in adults and, often, 8 hourly in children is thus predicated upon this indication. Linezolid is considered to be an important drug for treating MDR- and XDR-TB. Linezolid is one of the Group C agents recommended by WHO for use in longer M/XDR-TB regimens and is listed as a TB medicine in the current WHO Model Lists of Essential Medicines for adults and children(19),(39),(40). Access to linezolid has improved in recent years, with more generic suppliers and a notable price drop.<sup>13</sup> Linezolid is not a cytochrome P450 substrate, inducer or inhibitor. It does undergo morpholine ring oxidation by non – P450 pathways. Linezolid is a weak, non - selective, reversible inhibitor of monoamine oxidase. Caution is advised when co-administered with adrenergic, vasopressor, or dopaminergic agents.

Although initially considered bacteriostatic, linezolid activity in TB EBA trials was modest at best and it may only have modest bactericidal activity against dividing TB bacilli(63). However initial activity in TB clinical treatment experience appeared to exceed expectations(64). *In vitro* data suggest that its efficacy is driven by  $C_{min}/MIC$  and  $AUC/MIC$ (65). Limited data and clinical experience points toward an  $AUC/MIC$  with a target of 100 based on exposure of 600mg twice daily and MIC of 2mg/L (non-species related). The main EBA study included in the review concluded that although drug exposure was lower in once daily dosing than in twice daily dosing, T>MIC and  $AUC/MIC$  appeared similar to and adequate for the management of other resistant bacterial infections(63). Preclinical data suggest that linezolid has a different effect in infection murine models (e.g. kill is T>MIC driven for actively dividing bacteria) while no difference for slowly dividing bacteria. This

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<sup>13</sup> The Global Drug Facility (GDF) now has two suppliers and the price of a box of 10 tablets of 600mg ranges from USD13.79 to USD15.21 (<http://www.stoptb.org/gdf/drugsupply/pc3.asp?PID=698>; accessed 17 November 2017)

suggests that dosing schedules could differ at the start and later into treatment to maximise the effect of the medicine.

#### Optimal dose and dosing schedule for linezolid

The optimal dose, regimen schedule and duration of use of linezolid in M/XDR-TB regimens is not known and there are no clinical PK/PD data relating PK of linezolid to outcomes such as cure and/or time to culture conversion. However, new clinical data are emerging from different linezolid EBA and Phase IIB/Phase III studies evaluating different doses and durations of linezolid (e.g. NixTB (66); NEXT (67); TB-PRACTECAL (68); ZeNIX(69)).

The major concern limiting the increase of dose, frequency or duration of use is toxicity. Serious neuropathies (e.g., peripheral and optic neuropathies), myelosuppression, and hyperlactatemia have been observed and are probably related to the inhibition of mitochondrial protein synthesis (64),(70),(71). Bone marrow toxicities appear to be concentration driven, while neuropathy is cumulative dose/AUC driven. Duration of use in MDR-TB regimens is usually much longer than the maximal period of use recommended by the manufacturer for non-TB indications (28 days) (72); TB practitioners tend to keep it in the regimen for as long as the individual patient can tolerate it.

Current experience suggests that once daily dosing of 600mg linezolid strikes an uneasy balance between efficacy and toxicity. Intermittent dosing could reduce toxicity, but the dose has yet to be determined. Observations from HFIM suggest that 300 mg of linezolid every 12 hours generates more bacterial kill but also more toxicity than 600 mg given once daily (with no influence on acquisition of resistance) (4); however a linezolid dose of 300 mg/day still performs well but has yet to be compared with 600 mg/day or 1,200 mg/day or every other day in clinical trials (65). Recent data suggest that patients in NixTB trial experiencing haematological toxicities after receiving 1,200 mg/day recovered well if linezolid was withdrawn or its dose was decreased to 300 mg/day (TB Alliance, unpublished data, October 2017;(66)).

There are insufficient data on the use of linezolid in children. It is not clear if there should be a different dosing strategy between adults and children because the PK/PD target is not clearly defined. It is known that children clear linezolid faster than adults (73). The slower doubling time of TB bacilli in children would support once daily dosing, although twice daily dosing could achieve AUC values closer to those seen in adults. However data are lacking regarding the long-term safety of this approach.

The dosing of linezolid might be conditional upon the number of effective companion agents in the M/XDR-TB regimen and their dosing frequency. For instance when linezolid is part of a regimen with an adequate number of effective companion drugs and the strain is still susceptible to the fluoroquinolone, 600 mg per day can be used initially and the dose decreased to 300 mg daily (or temporarily interrupted) in the case of toxicity. In contrast when linezolid is the major drug in the regimen (e.g. fluoroquinolone resistance) then dosing may need to be increased especially in the beginning.

The combination of moxifloxacin and linezolid may be synergic or antagonistic in children, depending on the concentrations (74). Rifampicin may reduce linezolid concentrations. When combined with rifampicin to model the possibility of reducing regimen duration, a linezolid AUC/MIC ratio of 99 was found to be adequate corresponding with a linezolid dose of 600 mg once daily (75). This thus seems to be sufficient to effectively kill *M. tuberculosis* and prevent the selection of resistant mutants, provided linezolid is combined with another agent at sufficient exposure

Companion medicines in a regimen are important in averting the emergence of linezolid resistance. Resistance amplification when linezolid is used in monotherapy has been shown in HFIM(4). This risk cannot be suppressed by increasing the dose of linezolid owing to its toxicity. A clear understanding of clinical isolate MICs could assist in dose selection. The more variable the clinical MICs, the less likely it is that a single linezolid dose will be appropriate across a population of patients. To prevent development of drug resistance, an AUC/MIC ratio of 100 (based on exposure of 600mg twice daily and MIC of 2mg/L (non-species related)), in the presence of a companion drug at relevant exposure, is required. Because of its very narrow therapeutic window, linezolid treatment may benefit from the measurement of actual MIC values and could be prioritised for TDM (see separate section on TDM below). The monitoring of haemoglobin and other correlates of toxicity is important (see relevant sections on aDSM in (1)).

### Conclusions:

- When there is an adequate number of effective companion medicines and the strain is susceptible to fluoroquinolones, linezolid can be used at 600 mg/day and the dose decreased to 300 mg/day in case of toxicity (temporary interruption may be necessary).
- When linezolid is part of a regimen with a questionable number of effective companion medicines or and the strain is confirmed/suspected to be fluoroquinolone resistant, 600 mg can be given twice daily for the initial 2 to 4 weeks and 600mg once daily thereafter.
- Dosing in children can be slightly modified to allow twice daily dosing
- Linezolid may be a suitable candidate to prioritise for TDM. The monitoring of haemoglobin and other correlates of toxicity is important (see relevant sections on aDSM in (1)).
- The imminent publication of trial results is expected to provide further guidance on dosing and optimal duration of use.

### Clofazimine (Cfz)

#### Clinical questions:

- What dosage regime of clofazimine is required when it is used in longer and shorter MDR-TB regimens?

#### Discussions:

The expert discussions focused on the optimal dose and dosing schedule for clofazimine, including the rationale for a loading dosage, based on knowledge about clofazimine effectiveness and safety (e.g. relationship between clofazimine PK and QT-interval prolongation).

Clofazimine is an anti-mycobacterial agent first approved in 1969 in Switzerland for the treatment of lepromatous leprosy and its complication, *erythema nodosum leprosum*. Clofazimine has been used off-label as a second-line TB drug in a multidrug regimen for drug-resistant tuberculosis (TB) for several years and it is listed as one of the Group C agents for use in designing M/XDR-TB regimens in the 2016 WHO drug-resistant tuberculosis treatment guidelines and in the current WHO Model Lists of Essential Medicines (33),(76),(77). Clofazimine is also a critical component of the intensive and continuation phases of the WHO-recommended shorter MDR-TB regimen (78). Despite this, knowledge about how to optimise its dosing to increase benefit over harm remains incomplete.

Clofazimine is very lipophilic and incompletely absorbed from the GI tract (45-62% of dose in a capsule) (79). Food increases rate and extent of absorption. It predominantly distributes and accumulates in the macrophage-rich organs such as the lungs, liver, spleen, brain, and bone marrow. In patient studies, clofazimine has shown good penetration in tissue but not in cavities. Target tissue concentrations may be much higher than can be inferred from plasma measurements (with the exception of caseating tissue in a cavity).

Much is unknown about the mechanism of action and PK/PD of clofazimine. Clofazimine may interfere with the proton-motive force and bacterial ATP production by membrane interaction with the respiratory chain or phospholipids(80). The delayed activity might therefore be due to the need to saturate the lipid-rich bacterial membrane, the time needed to disrupt the proton-motive force and/or the need to deplete energy stores before antimicrobial activity is observed.

Based on knowledge from leprosy patients the PK of clofazimine appear to be rather complex. Recent data indicated substantial differences however between clofazimine PK parameters in TB patients compared with those in leprosy patients (81),(82). The properties of clofazimine appear to resemble those of bedaquiline, with high tissue levels, low and stable serum levels, and long half-life (the terminal half-life of clofazimine in leprosy patients is reportedly about 25 days). As for other medicines with a very long half-life like bedaquiline, one concern is that its persistence in tissues outlasts the presence of companion medicines in the multidrug-regimen, which could favour the acquisition of resistance to it. In one study of TB patients,  $C_{max}$  and  $AUC_{0-24}$  varied hugely when clofazimine was given alone or in combination with another 2-3 TB drugs, in a dose of 300 mg on days 1-3 followed by 100mg on days 4-14 (83).

There are no clinical data relating clofazimine PK/PD indices to a clinical endpoint (cure, time to culture conversion, time to positivity or EBA)<sup>14</sup>. Not much evidence is available in preclinical models due to lack of well-designed experiments correlating the PK and activity of clofazimine in a drug resistant model of TB. No studies of HFIM testing of clofazimine for TB have been published (these experiments may not be feasible owing to the lipophilic nature of clofazimine).

Despite its high protein binding and extensive distribution in the body, and in absence of well-defined concentration-response relationship, the dose rationale for clofazimine is focused on maintaining levels above MIC. The MIC of clofazimine against MDR-TB strains ranges from 0.25-1 mg/L on MGIT. However, the majority of strains tested across studies showed MIC value of  $\leq 0.5$  mg/L for clofazimine (pooled estimate of strains with MIC  $\leq 0.5$  mg/L = 73.5%; 95% CI 12.1%-98.2%). These findings are also in alignment with the clinical resistance breakpoint reported for clofazimine (84),(82)<sup>15</sup>. Based on simulations from a population PK model with 100mg daily dosing, the trough plasma concentration is predicted to reach the anticipated efficacious level of 0.5 mg/L within 2 months of the treatment initiation (85), and therefore T>MIC (in plasma) should be longer than 7 months in a 9-month treatment regimen. Of note, these simulations are based on PK data modelled in leprosy patients; recent observations indicate that PK parameters may behave differently in TB patients and this question thus warrants further examination (Savic R, 2017, unpublished data).

In mice, the administration of clofazimine-containing dry powder microparticles reduced numbers of colony-forming units in the lung much more than oral clofazimine (86). It was concluded that spray-dried clofazimine is suitable for deep lung delivery, retained the *in vitro* kill characteristics of the native compound and demonstrated superior efficacy in preliminary *in vivo* experiments. Inhalant delivery of clofazimine could also, conceivably, lower adverse reactions.

#### Optimal clofazimine dose and dosing schedule

Clofazimine is commonly used in MDR-TB regimens at a daily dose of 50-100mg/day, depending on body weight. It has been suggested that a clofazimine “loading” dose of 200mg/day in the first weeks of treatment could reduce the time needed to reach MIC and help hasten steady-state. There is a lack of empirical evidence showing superiority of a loading dose; if clofazimine acts primarily as a sterilizing agent, as *in vitro* and animal studies suggest(87),(88), then its role should be less important in the first part of treatment. A high initial dose may also increase the risk of adverse reactions. There has been some recent clinical evidence of incidental *torsade de pointes* after receiving a dose >100 mg(79). Therefore, caution should be exercised when using a higher dose and when combining clofazimine with other drugs that might have a similar effect because of risk of additive toxicity (e.g. bedaquiline, delamanid and moxifloxacin). The association between clofazimine and QT-interval prolongation has yet to be quantified in a standard PK-QTc study.

#### Conclusions:

- Available data preclude any conclusive position regarding the optimal dose and dosing frequency of clofazimine for MDR-TB treatment.
- The promising results obtained in observational studies of shorter MDR regimens were achieved with 100 mg clofazimine per day (50mg/day for individuals <40kg body weight). In the absence of other evidence showing improved benefit to harm, this should remain the recommended dose for the time being. Even if a loading dose is expected to help achieve steady-state faster it is not routinely justified.
- Formal PK-QTc studies and effectiveness studies, especially in combination with other drugs, should be pursued as a research priority, in order to inform dose optimization (e.g. use in small children and infants). Inhalant delivery of clofazimine could also be an important area for future research.

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<sup>14</sup> Addition of clofazimine to HRZE or HPZE has been reported to reduce time to relapse-free cure to less than 3 months in drug-susceptible TB (Nuermberger E, personal communication, 2017).

<sup>15</sup> The revised critical concentration recommended for susceptibility testing of clofazimine in MGIT960 is 1mg/L (57)



## Bedaquiline (Bdq)

### Clinical questions:

None of the key questions addressed bedaquiline specifically given that much of the data on this medicine had been reviewed by WHO in mid-2016 when considering whether an update of the interim policy was in order(89),(90). Nonetheless, the latest available data were reviewed to inform the consultation.

### Discussion:

Bedaquiline has been shown to add substantial benefit to the regimens of patients with multidrug-resistant TB (91). The review of current knowledge and literature on bedaquiline PK/PD demonstrated that the exposure-response relationship is insufficiently characterized (Annex 4). There are no HFIM data available for bedaquiline and *M tuberculosis*. Data from mice experiments have primarily been evaluated in terms of dose-response and not in terms of exposure-response, but a dose-fractionation study indicated that total exposure rather than peak concentrations seems to drive the effectiveness (92). Given that the M2 metabolite is formed faster from bedaquiline in mice than in humans, it may be difficult to conduct reliable exposure-response analysis in this model.

Bedaquiline PK is fairly well described in typical adult patients (93),(91),(94),(95), and DDIs with several important ARTs have been studied (96),(97),(98). Non-compartmental analysis and geometric mean ratios underestimate the actual impact of interactions, which has generated misleading information for the bedaquiline-lopinavir/ritonavir case (98),(99),(100). More information is needed on potential interactions between bedaquiline and e.g. clofazimine (101) and delamanid(102). Bedaquiline is not recommended in children (90); no data from children are available yet but studies are ongoing or about to start. A child-friendly dispersible formulation of bedaquiline has been developed by Janssen, and a recent health-volunteer cross-over study demonstrated bioequivalence between dissolved and whole bedaquiline tablets (BDQ CRUSH study, TASK Applied Sciences), providing an alternative means of administration to children in future until a paediatric formulation is produced. No PK data from pregnant women are available.

In phase IIa studies of 7- or 14-day EBA investigating doses of bedaquiline up to 400mg (700mg loading dose day 1 and 2) a delayed response has been documented. Higher doses generally lead to a stronger EBA, but the statistical significance varied with the biomarker (CFU or time to positivity) and between which days EBA was calculated (0-2, 2-7, 0-14, 7-14) (103),(104),(81). Generally, the statistical analyses have been conducted through comparisons between dose-groups, instead of by evaluation of a continuous exposure-response relationship. Plots of log AUC vs EBA showed increasing EBA with increasing log AUC without any indication of a maximal effect being reached(104). For longer treatment durations, the PK/PD relationship has been evaluated by comparing time to sputum culture conversion for exposure quartiles, but no significant relationship could be detected(105). Using quantitative culture data from the same study, a model-based analysis could identify a relationship between decline of bacterial load and average weekly bedaquiline concentration(106). No maximal effect could be derived and the estimated EC50 was lower than the median observed exposure, indicating that higher exposures might give additional benefit. However, the safety of higher exposures must be studied. A link between the concentration of the M2 metabolite and QT-prolongation has been observed (105).

The high protein binding (>99.9%) and extensive tissue distribution of bedaquiline (107) makes direct comparison between plasma exposure and CC or MIC difficult. In the pivotal study C208 average bedaquiline plasma concentrations at week 24 ranged from 0.2-2 µg/mL (95); MIC values in the same patients were 0.01-0.25 mg/L in Middlebrook 7H11 agar (91). Hence, the expected average free concentration of bedaquiline was much lower than the MIC, but still the patients benefitted from the treatment (91). No clear relationship between baseline bedaquiline MIC and culture conversion, or treatment outcome could be detected in the pivotal bedaquiline studies (108).

### Conclusion:

- The current recommended dose of bedaquiline in adults (400mg/day for the first 2 weeks followed by 22 weeks of 200mg three times per week) remains unchanged.
- Studying alternative bedaquiline dosing in future regimen trials is important.
  - The currently recommended regimen includes the highest doses ever tested on top of longer MDR-TB treatments, and is not well supported by exposure-response analyses. However, PK/PD data indicate that higher exposures may help clear the bacterial load faster.
  - Intermittent dosing may lead to adherence issues and makes it difficult to include bedaquiline in future fixed-dose combinations.
- There are insufficient data on the use of bedaquiline beyond 6 months or in combination with delamanid. WHO has issued a best practice statement on the use of bedaquiline (and delamanid) beyond the one envisaged by its current evidence-based interim policy (109).

### *Delamanid (Dlm)*

#### Clinical questions:

None of the key questions addressed delamanid specifically, given that much of the data available until mid-2016 had been reviewed by WHO in preparation for its interim policy on delamanid use (110),(111). Nonetheless, a PK/PD review was conducted to inform discussion at the consultation.

#### Discussions:

Most of the available evidence on the dose-exposure-response relationships derives from data on file with the innovator or data that are publically accessible in connection with the European Medicines Agency (EMA) review (112). All data were provided by the manufacturer and mainly derive from preclinical studies or from healthy volunteers. PK data of TB patients are available from only two studies (113),(114), making it difficult to extrapolate to other patient populations with different characteristics.

No HFIM data have been published on delamanid. In an ascending dose study of healthy adults there were no differences in exposure between the 50mg and 100mg dosing groups and a less than dose-proportional increase in exposure at dose levels through 400mg. The lack of linearity in dose-exposure was reproduced in adult patients with uncomplicated, sputum smear-positive, drug-susceptible TB (114). To evaluate EBA, four doses of delamanid - 100mg, 200mg, 300mg, or 400mg - were administered once daily, as monotherapy for 14 days (12 patients per treatment arm). Mean steady state  $\pm$  SD  $AUC_{0-24h}$  values were  $2,500 \pm 1,454 \mu g \cdot h/L$  for 100 mg,  $3,551 \pm 1,551 \mu g \cdot h/L$  for 200 mg,  $5,489 \pm 1,484 \mu g \cdot h/L$  for 300mg and  $4,877 \pm 2,103 \mu g \cdot h/L$  for 400 mg once daily. Delamanid was evaluated in MDR-TB patients in a 3-month randomized, double-blind, placebo-controlled trial that included a 2-month treatment period and a 1-month follow-up (Trial 204, n=481)(113),(115). The doses explored were 100 mg twice daily and 200mg twice daily. Reported mean steady state  $AUC_{0-24h}$  values were  $7,925 \pm 2,972 \mu g \cdot h/L$  (n=144) and  $11,837 \pm 3,977 \mu g \cdot h/L$  (n=145) for 100 mg and 200 mg twice daily respectively.

Initial pharmacokinetic analyses indicate that  $C_{max}$  and  $AUC_{0-24h}$  values in 13 children (median age 13 years, range 7–17 years) treated with delamanid in the Philippines and South Africa (100 mg twice daily in ages 12–17 years; and 50 mg twice daily in ages 6–11 years) were within the ranges observed in adult clinical trials (111),(115). There was no discernible relationship between weight-adjusted dose and exposure; however, this may reflect the small sample size, the presence of age-effects, and the influence of pre-existing malnutrition [Abdel-Rahman S, personal communication, 2017].

Findings from these early reports are also relevant for the clinical utilization of delamanid under programmatic conditions. These include the risk of variable exposures depending upon concurrent food intake and with low body mass index z-score, and the possibility of increased exposures with decreasing age in children (although the observed age effects may be confounded by the underlying nutritional status). It has been recommended to administer delamanid with, or just after, a meal given that absorption is increased with a standard meal. Of note, exposures in children aged 6-17 years more closely resemble those of adults receiving 200 mg twice daily rather than the labelled 100 mg twice daily dose, raising the question of whether the current paediatric dosing strategy requires re-evaluation.

Importantly, a PK/PD target for delamanid (e.g. AUC/MIC, T>MIC,  $C_{max}/MIC$ ) has not been identified and efficacy thresholds for non-pulmonary TB have not been defined. Preliminary data suggest an exposure dependency, and combined with the dose-limited absorption and non-linear PK, this would favour twice daily instead of once daily dosing. Data from phase 1 modelling showed that the preliminary target of AUC<sub>0-24h</sub> of at least 4,000  $\mu\text{g}\cdot\text{h}/\text{L}$  would be reached by more than 95% of patients dosed 200 mg twice daily (112). PK data from trial 204 appear to support this (113).

The EBA of delamanid was monophasic and not significantly different between dosages. The average early EBA (between 0-2 days) of all dosages combined was  $0.069 \pm 0.208 \log_{10} \text{CFU/ml sputum/day}$  compared to  $0.553 \pm 0.379 \log_{10} \text{CFU/ml sputum/day}$  for the control group that was treated with HREZ. The extended EBA (between 2-14 days) was  $0.035 \pm 0.062 \log_{10} \text{CFU/ml sputum/day}$  compared to  $0.100 \pm 0.156 \log_{10} \text{CFU/ml sputum/day}$ , for all delamanid dosages and the control group respectively. The lack of early EBA and little extended EBA suggests a limited role if any for delamanid as a sterilizing agent. A moderate correlation was found between  $C_{max}$  and EBA and between AUC and EBA, indicating exposure dependence. Delamanid exposure was less than dosage-proportional, reaching a plateau at 300 mg, partially due to dose-limited absorption.

Although the proposed PK surrogate for delamanid (steady-state AUC<sub>0-24</sub> between 3,500-5,500  $\text{ng}\cdot\text{hr}/\text{mL}$  (116)) arises from a weak relationship between exposure and response (112), these putative surrogates are attained in the vast majority of adults at 100 mg twice daily and exceeded in essentially all children aged 6-11y and 12-17y at 50mg and 100mg twice daily, respectively.

In studies delamanid has been well tolerated without significant toxicity (114),(115). Prolongation of the QTc are uniformly observed in adults and children receiving delamanid, though there have been no clinical safety signals in the absence of concurrent electrolyte abnormalities (117),(118),(119),(120). Notably, sponsored PK studies have not permitted concomitant administration of other medications that prolong the QTc interval, and thus the question of whether additive toxicity may be expected when medicines with the same properties are administered concomitantly remains to be shown. Since pre-exposure ECG monitoring will not detect at-risk patients, and may be impractical in selected clinical settings, risk-to-benefit assessments and mitigation strategies should be considered when utilizing delamanid in a regimen or patient population where there exists the risk for cardiac conduction abnormalities. Of note, putative neurotoxicities have not been adequately characterized in all populations and thus the impact of concentrations above the therapeutic limit (as observed in children) is unclear.

*In vitro* data suggest that perturbation of the cytochromes P450, BSEP, BCRP, P-gp OCT1, OAT1/3, and OATP1B1/3 appears to be low with delamanid, implying that it is unlikely to alter the disposition of concurrently administered medications (121),(122). *In vivo* data suggest that lopinavir/ritonavir can be expected to increase delamanid exposure with no effect of tenofovir and efavirenz on the disposition of delamanid (112),(123),(124).

#### Conclusion:

- The current recommended duration (6 months) and dose of delamanid remains unchanged (100mg twice daily for patients >11 years; 50mg twice daily for patients 6-11 years).
- To ensure optimal absorption, added instructions on dosing delamanid in relationship to food and other medicines will be updated in the forthcoming revision of the implementation handbook(1).
- There are insufficient data on the use of delamanid beyond 6 months or in combination with bedaquiline. WHO has issued a best practice statement on the use of delamanid (and bedaquiline) beyond the one envisaged by its current evidence-based interim policy (94).

#### Pyrazinamide (Z)

##### Clinical questions:

None of the priority questions prepared for the consultation addressed pyrazinamide specifically. However, pyrazinamide is a crucial component of current and future regimens for both drug-resistant and drug-susceptible TB.

### Discussions:

Two aspects relating to pyrazinamide were discussed given their relevance to drug-resistant TB regimen effectiveness: (1) whether the currently recommended dose of pyrazinamide achieves the best balance in benefit-to-harm and (2) when and how results from pyrazinamide DST should be used in clinical decision-making.

### Dose optimization

The mechanism of action of pyrazinamide is still not fully clear. Pyrazinamide is a prodrug and requires enzymatic activation of pyrazinamidase/nicotinamidase (encoded by the *pncA* gene) inside the bacterial cells. The active compound (pyrazinoic acid) works in an acidic environment by disrupting bacterial membrane permeability, inhibiting transport(125).

Preclinical and clinical evidence (based on culture conversion data) suggests that the current dose in standard use is not optimised (20-30mg/kg/d). The PK/PD parameter linked to sterilizing effect is AUC/MIC ratio, with an optimal value of 210 at site of effect(126). Monte Carlo simulations indicate that at the current standard dose of pyrazinamide only about 57% of patients achieve optimal AUC/MIC; doubling the dose has been shown to have a higher sterilizing effect in animal models(127). In a study of patients with drug-susceptible TB (69% HIV positive), low pyrazinamide  $C_{max}$  was the only measured factor strongly associated with a poor outcome(128). In another observational study, optimal outcomes were associated with a serum AUC >363 mg·h/L(129) - albeit the association only became statistically significant when levels of accompanying rifampicin, and especially rifampicin and isoniazid, exceeded a threshold which can usually be achieved with the doses recommended for these two medicines. This work suggests that a proportion of patients on standard first-line treatment achieve low drug concentrations, which may predispose to unfavourable outcome. However any further consideration of increasing the pyrazinamide dose needs to be considered in light of increasing liver toxicity. Systematic review of pyrazinamide-induced toxicities would be instrumental in assessing appropriate risk-to-benefit ratio for this drug.

### DST and resistance testing for clinical decision-making

Based on evidence of its effectiveness, pyrazinamide has been recommended for use in longer MDR-TB regimens and is one of the four medicines used throughout the shorter MDR-TB regimen(29),(33),(55), (130). The concern is that resistance to pyrazinamide - which has been reported to be high among MDR-TB patients in different settings worldwide(131) – would impact upon the effectiveness of these regimens. Resistance would be reason to replace pyrazinamide in a longer MDR-TB regimen with another medicine with similar properties, and could determine whether a shorter MDR-TB regimen can be offered (pyrazinamide resistance is associated with failure of shorter regimens(132)).

In most settings there is no reliable means to detect pyrazinamide resistance and no rapid molecular diagnostics for this agent. Phenotypic DST for pyrazinamide presents a number of challenges. The detection of enzymatic activity critical to the pro-drug conversion has not been officially endorsed as a valid proxy of resistance. MGIT is available but considered difficult to perform and outside quality controlled laboratories the results may be unreliable because of poor specificity(133)<sup>16</sup>. Future diagnostic efforts are likely to focus on molecular diagnostics. Mutations in the *pncA* region identify around 85-90% of all existing resistance associated with pyrazinamide (*rpsA* and *panD* are additional genes involved in resistance to pyrazinamide). The *pncA* region is highly variable and mutations may be scattered across the gene coding for the enzyme responsible for the pro-drug activation. The large majority of mutations confer an elevated MIC but some do not. A line probe assay for pyrazinamide has been assessed(134) and a new assay is under development. Methods like Next-Generation DNA sequencing of the *pncA* coding region can be performed from smear positive samples or from isolated strains; these would be the techniques of choice for surveillance. Mono-resistance to pyrazinamide is extremely rare, with the exception of *M.bovis* and *M.canettii* that are always resistant.

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<sup>16</sup> CLSI recommends repeated testing (<https://clsi.org/standards/products/microbiology/documents/m24/>)

### Conclusion:

- In the absence of information on accompanying MICs, the undisputed detection of mutations in the *pncA* region may be sufficient to consider replacing pyrazinamide with a more effective agent in a longer regimen. Given the uncertainties on the effect of pyrazinamide resistance on the effectiveness of the shorter regimen it is proposed not to use this regimen if these mutations are detected(132)
- Increasing the dose of pyrazinamide could probably improve effectiveness in certain patients but is expected to increase toxicity to unacceptable levels if this is applied in all patients. This subject deserves further study.
- Molecular diagnostics appear to be the diagnostic of choice for pyrazinamide resistance testing in future. One could envisage that sequencing would be offered at national reference laboratory setting and other methods (e.g. LPA, automated sequencing) more peripherally.

### Rifampicin (R)

#### Clinical question:

- In which patients on treatment for active, drug-susceptible tuberculosis is a higher dose of rifamycins indicated?

#### Discussion:

A specific review for rifampicin was not undertaken ahead of the consultation. The discussions followed a presentation by one of the experts attending the consultation. They focused on the rationale for the choice of the current standard dose, would a higher dose improve efficacy and at what risk of added toxicity and if efficacy could be improved, under which circumstances and at which dose?

Apart from being an essential component of first-line TB regimens, rifampicin is probably the most critical agent when treating TB strains resistant to one or more of the other first-line agents (e.g. isoniazid(24), pyrazinamide). The medicine has been recommended for use in these regimens by WHO since many years, including the 2017 guidelines which were updated using the GRADE method (1),(24),(135). Rifampicin is also included in both the adult and children Model Lists of Essential Medicines as a TB medicine (76),(77), as solid, liquid and dispersible tablets, and in single dose formulation or as part of fixed-dose combinations with other first-line anti-TB agents.

#### Rationale for the current standard dose of rifampicin

The dose of rifampicin currently recommended by WHO for TB treatment regimens is 10 mg/kg/d (8-12 mg) in adults and 15 mg/kg (10-20 mg) in children, given once daily (136),(137). These doses were introduced in 1971 when rifampicin was approved by the US FDA (138). Rifampicin-containing regimens were very effective against drug-susceptible TB in clinical trials and they allowed a considerable reduction of treatment duration to 6 months when used in combined therapy. Most of these trials used rifampicin at a single dose of 600mg/d, based on PK, toxicity, and cost considerations (139). The prohibitive cost of rifampicin at the time probably weighed significantly upon the decision to run trials using the lowest possible dose considered necessary to achieve the therapeutic range in most patients. More recent PK/PD data suggest that by increasing the dose of rifampicin efficacy can be improved with little risk of added toxicity (140).

#### An optimised rifampicin dose

A disproportional - nine-fold - increase in rifampicin exposure, which was safe and well tolerated, was reported when rifampicin doses were increased up to 35 mg/kg in pulmonary TB patients (141). At this dose, the time to stable sputum culture conversion (in liquid culture) was reduced (HR 2.06 for 8 weeks, 1.78 for 12 weeks; Boeree M, personal communication, 2017). However, the extent to which target exposure is increased and the treatment duration reduced at a higher dose of rifampicin have yet to be established.

Clinical predictors of poor long-term outcome were studied using a HFIM and clinical and PK data collected prospectively from 142 TB patients in South Africa on HRZE regimens for drug-susceptible TB and followed for up to 2 years (129). Drug concentrations and PK varied widely between patients. The three top predictors of poor long-term outcome, by rank of importance, were a pyrazinamide 24-hour AUC  $\leq 363$  mg·h/L, rifampicin AUC  $\leq 13$  mg·h/L, and isoniazid AUC  $\leq 52$  mg·h/L. Low rifampicin and isoniazid peak and AUC concentrations preceded all cases of acquired drug resistance. A 4-month regimen in which moxifloxacin and 900 mg of

rifapentine were administered twice weekly during the continuation phase had a significantly higher relapse rate in drug-susceptible TB than the standard 6-month regimen (daily dosing) (142). A rifampicin dose-ranging study aimed at reducing the duration of first-line regimens for drug-susceptible TB by increasing the rifampicin dose compared with the standard 6-month regimen is underway (143). More data are required on the potential of shortening treatment duration by increasing the rifampicin dose.

Toxicity studies and clinical experience using rifampicin for treatment of other diseases showed no increased toxicity or tolerability problems when daily doses used were two or three times higher than those currently recommended. Based upon known pharmacological properties of rifampicin, induction of CYP450 and P-glycoprotein is expected to be dose-dependent, although little is known about the maximum inductive capacity. In one study daily doses of 900mg and 1200mg rifampicin caused no additional induction of propranolol (a substrate of CYP1A2, CYP2D6 and CYP2C19) in comparison with a daily dose of 600 mg rifampicin (144). Trials are planned to study this (e.g. (145)).

#### Situations favouring a higher dose of rifampicin

Sufficient studies of patient subgroups that could benefit more from a higher dose of rifampicin are still lacking. A higher dose was reported to reduce mortality in a small study of TB meningitis patients and survival was observed to be closely related to exposure (146),(147). In this patient group AUC ( $AUC_{0-6h}$  of ca. 70 mg/L·h or  $AUC_{0-24h}$  of ca. 116 mg/L·h) and  $C_{max}$  (of ca. 22 mg/L) were deduced as minimum target values. In another study of TB meningitis treated with a 9-month regimen, a rifampicin dose of 15mg/kg in the first 8 weeks of treatment (accompanied by levofloxacin) did not have an impact on mortality when compared with a 10mg/kg rifampicin throughout (148).

In children the recommended dose is higher than in adults (10-15mg/kg/d), but may still be suboptimal (149). Low rifampicin levels have been reported to increase the risk of poor outcomes in children (150),(151). Weight-band dosing also needs to be reviewed to ensure appropriate concentrations, especially in lower-weight adults (McIlleron H, personal communication, 2017).

High-dose rifampicin, in addition to ART, could reduce mortality among HIV-infected individuals who are severely immunocompromised (e.g. baseline CD4 cell-count of less than 100 cells/mm<sup>3</sup>)(152). Studies testing high-dose rifampicin and rifapentine to optimise or shorten treatment regimens are underway and could help improve policy in a near future (153),(154).

Finally it was noted that in patients weighing >60kg, the current 600mg maximal allowance of rifampicin per day would be exceeded at the recommended dose of 10mg/kg/day (p30 of (136)), at the risk of systematically under-dosing patients in this weight-band.

#### Conclusion:

- A number of trials have and are studying the dose and duration of rifampicin. A full discussion on the optimal use of rifampicin in terms of efficacy and safety would be important once all of these data are available for review.
- A higher dose of rifampicin may be indicated particularly in younger children, underweight adults, patients with TB meningitis and immunocompromised HIV-infected TB-patients, who are reported to achieve low concentrations.
- While a WHO policy decision to increase the current weight-based dose of rifampicin requires additional trial evidence, taking into account patient outcomes, removing the 600mg “ceiling” for the maximum daily dose from current guidance would allow patients who weigh >60kg on the standard 6-month treatment regimen for drug-susceptible TB to attain the recommended dose (8-12 mg/kg/d).
- To effect changes to rifampicin dosage in treatment programmes, new fixed-dose combinations would be needed to permit appropriate dosing of all the component drugs without increasing ADRs. Giving >4 tablets of the current FDC would exceed the maximal daily dose of isoniazid, which is capped at 300mg/day. For instance, 5 tablets of the FDC formulation “rifampicin 150mg / isoniazid 75mg / pyrazinamide 400mg / ethambutol 275mg” given to a 65kg adult would provide 750mg of R and 375mg of H. The bioequivalence and bioavailability of new preparations would also need to be shown.

## Therapeutic Drug Monitoring (TDM)

### Clinical question:

- For which TB patients, regimens or medicines is the monitoring of blood or urine levels useful to assess therapeutic and/or toxic effects?

### Discussion:

The expert discussions reviewed the evidence and recent developments in therapeutic drug monitoring (TDM) methods and discussed whether TDM would be a helpful additional routine diagnostic option for TB health care providers to avail of.

### About TDM

TDM is a multi-disciplinary clinical specialty aimed at improving patient care by individually adjusting the dose of drugs for which clinical experience or clinical trials have shown it improved outcome in the general or special populations. It can be based on an *a priori* pharmacogenetic, demographic and clinical information and/or on the *a posteriori* measurement of blood concentrations of drugs (pharmacokinetic monitoring) and/or biomarkers (pharmacodynamics monitoring)(155).

The three main reasons which underpin TDM are:

- i. an experimentally determined and validated relationship between plasma drug concentration and the pharmacological effect (efficacy & toxicity);
- ii. the substantial inter and/or intra-patient PK variability; and
- iii. a difficulty to monitor the clinical effect of a given medicine.

Other important good practices in TDM are that samples taken for PK testing are optimally timed; that the analysis method used is adequate; and that the intake of the medicine tested is recorded precisely for the 5 days before sampling along, with other relevant clinical information, to allow the proper interpretation of results. For optimal use of TDM, a sound therapeutic window needs to be defined with clear targets associated with optimal efficacy and safety. One important limitation of TDM is that the levels of a substance as measured in plasma do not necessarily correlate with concentrations obtained at the target site of action, due to differential distribution of drug in tissues and the variability of lung pathology.

One of the challenges in TDM is that the implementation and recurrent expenses are high. A single test in the US would typically cost about USD80, excluding shipping charges which may be substantial. In the Netherlands, a typical test would cost about EUR44, about 75% of which represent labour costs.

Recent developments in the area of TDM were discussed. The testing of saliva may be an attractive approach to avoid the inconvenience of repeated blood testing: it still needs further validation. Available data suggest that for drugs with narrow ranged saliva-plasma and saliva-serum ratios (e.g. linezolid), salivary testing could be useful in future (many TB medicines e.g. isoniazid, rifampicin, moxifloxacin, ofloxacin, have wide ranges). Collection of samples on a card as dried blood spots (DBS), which can then be forwarded by post to the analysis laboratory under ambient temperature, is an emerging technology which could also simplify logistics (156).

### Conditions under which TDM may be helpful

The ATS/CDC/IDSA guidance summarised the situations under which TDM may be of particular help in TB care (157). These are

- Poor response to tuberculosis treatment despite adherence and fully drug-susceptible TB strain
- Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhoea with malabsorption
- Drug–drug interactions
- Impaired renal clearance: renal insufficiency, peritoneal dialysis, critically ill patients on continuous renal replacement
- HIV infection
- Diabetes mellitus
- Treatment using second-line drugs MDR-TB

One approach to operationalising TDM is to focus on critical components of a regimen that are known for their variability in drug exposure. In a first-line regimen, rifampicin, isoniazid and pyrazinamide are the obvious choice; in a second-line regimen the preferred agents could be the fluoroquinolones, the injectable agents, cycloserine and linezolid.

#### Evidence for TDM

Historically, TDM of anti-TB medicines has focused on malabsorption, altered metabolism or clearance and drug-drug interactions influencing drug exposure, and thereby, potentially, treatment outcome. More recently, acquired drug resistance has been added to the list of indications for TDM. Up to now no RCT has compared the added value of TDM on the standard of care. To evaluate the effect of TDM on outcome the study would need to include:

- an appropriate measure for drug exposure that assesses the most relevant PK parameter (AUC,  $C_{max}$  or  $T > MIC$ );
- an appropriate measure for drug susceptibility of the pathogen given that MIC is part of the PK/PD equation;
- an appropriate measure of outcome: time to sputum conversion or even better a follow-up period which is long enough to detect relapse;
- an appropriate measure to distinguish between relapse and reinfection

Many current studies lack more than one of these parameters. A recent review of published data on TDM of first-line anti-TB medicines concluded that the evidence does not currently support routine measurement of drug concentrations (158). Another review found that across a wide variety of studies, a high proportion of patients on first-line TB treatment had 2h drug concentrations below the accepted normal threshold although this does not necessarily imply that TDM would have a positive impact on patient outcomes (159). The reviews concluded that the studies were not designed properly, that sample sizes were small and that outcome data were often lacking.

The current consultation identified numerous knowledge gaps concerning lack of clear PK/PD relationships for the majority of the drugs used in MDR-TB. Furthermore, TDM operates on optimization of plasma drug levels. Urine and saliva are alternative fluids, but in general less specific and require further validation.

#### Conclusion:

- TDM is likely to play the most important role in the case of medicines with a narrow therapeutic index and for which it is difficult to develop a dosing regimen that applies universally owing to individual variations in PK/PD (e.g. injectable agents, cycloserine).
- Akin to other clinical tests (e.g. blood counts, radiology), TDM aims to assess a patient on treatment and support clinical decision-making. There is no guarantee that its results will influence outcomes. Studies quantifying the value that TDM adds to clinical outcomes - efficacy, safety, quality and cost-effectiveness - are lacking. Likewise the best suited methods e.g. salivary testing, optimal sampling strategies, would need to be worked out.
- As TDM becomes more widely available given more access to testing and advancements such as dried blood spot, more clinicians are inclined to use it and guidance may therefore be in increased demand. Given the substantial resources needed to implement and sustain TDM, particularly in places where it is not yet established, programmatic use needs to balance carefully the opportunity costs and potential gains from investing in it.



## Findings and conclusions – other issues in PK/PD

During the consultation a number of cross-cutting issues of relevance to the key clinical questions were also discussed separately.

### PK/PD of children versus adults

Some of the main issues discussed included

- whether target exposures for children are the same as in adults;
- whether the recommended doses achieve target exposures; and
- about the optimal delivery of the medicines (formulations, preparations and administration).

A commonly held principle is that an effective response to treatment can be achieved in children if a medicine achieves concentrations and total exposures comparable to those that have demonstrated safety and efficacy among adults. However, it is not clear if this is always justified in the case of TB e.g. minimal disease, no extensive pathology and cavitation or preventive treatment. Provided that children tolerate their recommended doses well, it would make more sense to investigate the shortening of treatment regimens in children with minimal disease by using current doses rather than to reduce dosage at a risk of lowering efficacy. Moreover, there are indications that children tolerate higher maintenance doses per kg body weight of TB medicines than adults given their faster metabolism or clearance.

There is an urgent need for a PK/PD evaluation of target exposures that achieve optimal treatment responses and safety profiles in adults. Model-based pharmacometric analyses facilitate efficient studies, pooling of data across different studies, and prediction of pragmatic dosing approaches.

In the absence of evidence-based targets, normal exposures achieved in adults on standard doses become the target for children, based on a key premise that disease progression is the same in children and adults. However, even typical exposures in adults can be contentious, given the fragmented data from different studies, often reporting very variable exposures across populations. Pooled data analyses can play a role, and evidence from different geographic and patient settings need to be considered.

Children generally require a higher mg/kg dose of a medicine to achieve the same AUC as in adults. This notion follows allometric theory and assumes that metabolic capacity is proportional to size of the organs involved in drug elimination (liver, kidney). Children weighing about 10 kg at about 1 to 2 years of age have roughly twice the clearance of the average adult, requiring twice the mg/kg dose. Allometric scaling techniques can be applied to estimate the nonlinear increase in clearance associated with weight and can be used to improve predictions of dose by weight band in children down to about 2 years of age. However, immaturity of drug metabolizing enzymes, kidney function and transporters reduces clearance in children <2 years. The maturation process is specific for different metabolizing enzymes and it needs to be studied separately for each medicine of interest. Data from a recent, unpublished PK study of levofloxacin in South African children with TB given a 20 mg/kg dose of the oral solution were used to illustrate this effect (McIlleron H, personal communication, 2017). The 20 mg/kg dose, which is at the top end of the currently recommended range, did not achieve an AUC comparable to adults on a fixed 750 mg dose regardless of age and body weight albeit peak concentrations were better preserved. Higher doses than expected from allometric scaling for size would thus be needed, suggesting that formulation, or other factors, may play a role (simulations suggested that doses of up to 40 mg/kg would reach the target AUC). A definition of the appropriate PK measures for safety and toxicity targets are important.

There is a pressing need for more appropriate child-friendly formulations. These should not be bulky and should be stable under storage conditions in the field. This needs to be matched with simplified dose scaling based on pragmatic weight-bands. Palatability is fundamental, and proper attention is advised at the stage of administration given that the bioavailability of certain medicines may be altered when tablets are crushed and their contents mixed with other substances. PK studies and safety monitoring need to validate doses and formulations in paediatric TB patients. Modelling with simulations can be used to revise weight band dosing which can achieve better the PK targets. Data-sharing platforms can accelerate evidence to support optimal dosing efficiently.

New data relevant to the paediatric dosing of levofloxacin, moxifloxacin, linezolid, bedaquiline, and delamanid are expected shortly from controlled PK studies. Importantly, however, there are no known paediatric data or studies planned for clofazimine.

### Differential distribution & granuloma penetration

TB is characterized by a very broad range of possible pathologies, with intricate immune-system contributions to its clinical manifestations and to its progression. TB is both an intracellular and extracellular disease. Lesions have different levels of blood supply (e.g. no vascularization in a necrotic, caseating focus but much better blood supply elsewhere in the lesion). The metabolic state of TB bacteria may vary by the type of lesion and the activity of medicines may depend on the microenvironment (e.g. moxifloxacin cannot penetrate a caseating centre because of its poor vascularization).

When designing regimens and planning their optimal delivery it would be helpful to know which bacilli are killed by which medicines and where are they located. There are a number of TB regimens being evaluated for which PK/PD relationships and PK targets are ill-defined for almost all component TB agents. There is also a shortage of good microbiological markers to assess effectiveness. It would be desirable to know how a drug distributes into the respective compartments over the dosing interval, and about the “site-of-action PK/PD” and how this changes in the course of treatment. Mass spectrometry of tissue samples can, for instance, compare the distinct spatial distribution of different TB medicines over time after dosing.

Preclinical models may give an idea of the tissue distribution of a substance that may help determine the ideal time lapse until specimen collection. Extrapolation of these observations to the clinical situation may nonetheless be limited, although knowledge of the plasma/lesion penetration ratio (how much?) and uptake (how quickly?) are very useful in understanding how a substance is expected to distribute in the target tissue. Clinical studies can quantify the actual concentrations of medicines at steady state in diseased human lung, but they typically represent single sampling time/person, small numbers of observations and usually for more severe forms of disease. Future innovations could usefully map the localization of both the medicines and microorganisms; the time effects, including evolution of lesions during the course of treatment and the “site-of-action PK/PD” (what PK is needed for maximal efficacy, and is it achieved?).

### DDI to ART and other common companion medicines

PK drug interactions can occur at the point of absorption, distribution, metabolism and elimination (“ADME”). Moreover, medicines taken concomitantly may have overlapping toxicities. A particular concern is the co-administration of ART with TB medicines. Table 3 highlights some important known or potential drug-drug interactions associated with medicines currently recommended by WHO when composing a second-line TB treatment regimen.

Isoniazid inhibits CYP2A6, which is important in the metabolism of efavirenz and may thus potentiate its adverse drug reactions if alternative pathways for efavirenz metabolism are not well developed (e.g. CYP2B6 genotype). The relationship between isoniazid dose and efavirenz-related adverse drug reactions is unknown (160),(161). The isoniazid inhibitory effect on CYP3A appears to bear no clinically significant effects on nevirapine and lopinavir/ritonavir levels when used at standard dose but it remains unclear whether this becomes clinically significant at a higher dose of isoniazid. Induction of CYP2B6 by rifampicin can lower the AUC of efavirenz, an effect that appears to be independent of the rifampicin dose (based on simulations of dose from 10mg/kg to 35mg/kg).

Efavirenz is a CYP3A inducer itself, and it might impact upon the metabolism of CYP3A substrates such as bedaquiline. Different population PK models predict that when administered with efavirenz, a doubling of the usual bedaquiline dose of 200mg 3 times weekly is needed to achieve the levels observed in the absence of efavirenz. Lopinavir/ritonavir is also predicted to alter the average steady state concentrations of bedaquiline and could cause clinically relevant interactions (this is less clear for nevirapine).

Rifampicin exerts a significant lowering effect on delamanid levels, which may be due to reductions in absorption with co-administration, rather than enzyme induction. Tenofovir disoproxil fumarate (TDF) also lowers the peak concentration of delamanid while lopinavir/ritonavir increases delamanid levels throughout the time trace. The extent of these changes however does not suggest a need for delamanid dose adjustment. Efavirenz shows no effect.

A number of medicines used in the treatment of MDR-TB have QT-interval prolonging effects, namely bedaquiline, delamanid, clofazimine and moxifloxacin/levofloxacin. Ritonavir may also prolong the QT-interval. In addition, TB patients may also be predisposed to cardiotoxicity because of electrolyte imbalances caused by nephrotoxic injectable agents, or diarrhoea and vomiting induced by thiamides or by the disease process itself.

**Table 3:** Summary of the main DDIs to ART and other common companion medicines

Agent	Substrate of / metabolized by	Induces/inhibits	Notes
Moxifloxacin / levofloxacin	Sulfation, glucuronidation None	None	Attention to moxifloxacin with rifamycins Increased risk of tendon rupture with steroids Avoid with iron, magnesium, aluminium
Amikacin / kanamycin	None, renally cleared	None	Renally cleared; care with nephrotoxins
Ethionamide/ prothionamide	Multiple metabolites	Inhibits CYP2C8 Inhibits CYP2B6, CYP2C19, CYP2C8	Caution with drugs metabolized by listed enzymes? (e.g. efavirenz)
Cycloserine	65% excreted in urine; rest “apparently metabolized to unknown substances”	None?	Attention to overlapping toxicities- CNS side effects
Clofazimine	??	Inhibits CYP3A	QT-interval prolongation with BDQ
Linezolid	P450?	None	Caution with drugs that cause bone marrow suppression or neuropathy; Avoid use with monoamine oxidase inhibitors (MAOI) Rifampicin expected to lower linezolid concentration
High-dose isoniazid	NAT2	Inhibits CYP2A6, CYP3A	?clinically relevant effect on any CYP2A6 or CYP3A substrates? (e.g. EFV or BDQ)
Bedaquiline	CYP3A	None	Caution with CYP3A inhibitors / inducers
Delamanid	Albumin; CYP3A - minor pathway	None	Low bioavailability; space dosing

**Conclusion:**

- Most drug interactions involving second-line TB medicines are either modestly or poorly characterized (e.g. prothionamide, clofazimine). Particular attention is needed for potentially overlapping toxicities and predisposing factors, particularly the risk of cardiotoxicity.
- The dose-exposure-inhibition relationships of isoniazid, an inhibitor of CYP2A6 and CYP3A4 are not well characterized (e.g. effects on efavirenz-related adverse events).
- Bedaquiline is a CYP3A substrate, so inducers and inhibitors of CYP3A can significantly affect its concentrations. The therapeutic margin may be better-defined as more robust safety data become available.
- The interaction of medicines with foods is often ignored but may be important. Administration of delamanid is best separated in time from other medications, although it otherwise has a low metabolic drug interaction liability.
- Physiologically-based PK modelling can help predict which drug interactions are likely to be clinically-relevant and require assessment.

### Implications of PK/PD for the surveillance of drug-resistant tuberculosis

The Global Project on Anti-TB Drug Resistance Surveillance is the oldest and largest project on surveillance of antimicrobial resistance in the world (131). Since 1994, data on the frequency of MDR-TB have been collected from 160 countries, representing more than 97% of the world's population and estimated TB cases (162). Since 2006, data on resistance to second-line anti-TB medicines in patients with MDR-TB have also been collected from 91 countries. A multi-country project was started in 2014 to generate data on the prevalence of resistance to additional medicines such as pyrazinamide and fluoroquinolones among all TB cases and to explore the role of genome sequencing technologies for the surveillance of drug resistance (163). As part of this project, phenotypic DST is being performed in parallel with genome sequencing. Surveillance of drug resistance is gradually moving away from phenotypic testing towards the use of molecular technologies, including genome sequencing. The use of genotypic testing promises to provide better standardization and comparability of resistance surveillance data between countries and over time and could overcome the problems associated with modifications of critical concentrations for phenotypic testing.

The conclusions of this report, and the associated discussions on critical concentrations (57), have two major implications for the future surveillance of drug-resistant TB. Firstly, the modification of critical concentrations at which TB medicines are tested will influence the levels of resistance detected in a population. Given this change in the surveillance parameters, the time trends in the frequency of drug resistance would need to be reconsidered given that the earlier estimates in particular relied exclusively on phenotypic testing. Secondly, most experts involved in the production of this report suggested that epidemiological cut-off values (ECOFF) be used for surveillance rather than clinical breakpoints, when investigating resistance to fluoroquinolones (57).

## References

1. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2014.11) [Internet]. Geneva, World Health Organization; 2015. Available from: [http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf)
2. Technical report on the critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis (WHO/CDS/TB/2018.5) [Internet]. Geneva, World Health Organization; 2017. Available from: [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/) (future site)
3. Efficacy and Safety of Levofloxacin for the Treatment of MDR-TB - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Sep 6]. Available from: <https://clinicaltrials.gov/show/NCT01918397>
4. Brown AN, Drusano GL, Adams JR, Rodriquez JL, Jambunathan K, Baluya DL, et al. Preclinical Evaluations To Identify Optimal Linezolid Regimens for Tuberculosis Therapy. *mBio* [Internet]. 2015 Nov 3 [cited 2017 Sep 4];6(6). Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4631805/>
5. A Phase 2 Trial to Evaluate the Efficacy and Safety of Linezolid in Tuberculosis Patients. (LIN-CL001) - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Sep 6]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02279875>
6. Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PPJ, Chiang C-Y, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. *Trials*. 2014;15:353.
7. Garcia-Prats A, Savic R. Optimizing and operationalizing pediatric drug-resistant tuberculosis treatment. *Grantome* [Internet]. [cited 2017 Sep 6]; Available from: <http://grantome.com/grant/NIH/R01-HD083047-03>
8. Qualification Opinion In-vitro (HFS-TB)\_\_\_049-1-QO-2014 final for publication - WC500181899.pdf [Internet]. [cited 2017 Aug 30]. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2015/02/WC500181899.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/02/WC500181899.pdf)
9. Lee H, Ahn S, Hwang NY, Jeon K, Kwon OJ, Huh HJ, et al. Limited Effect of Later-generation Fluoroquinolones in the Treatment of Ofloxacin-resistant and Moxifloxacin-susceptible Multidrug-resistant Tuberculosis. *Antimicrob Agents Chemother*. 2017 Dec 4;AAC.01784-17.
10. Nunn A. Preliminary efficacy results of STREAM stage 1. In: STREAM trial (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis): preliminary stage 1 results [Internet]. Guadalajara, Mexico: UNION; 2017. Available from: <http://www.professionalabstracts.com/theunion2017/iplanner/#/person/3892>
11. 10th International Workshop on Clinical Pharmacology of Tuberculosis Drugs - Presentations - InfectiousDiseasesOnline [Internet]. [cited 2017 Oct 25]. Available from: <http://www.infectiousdiseasesonline.com/10th-international-workshop-clinical-pharmacology-tuberculosis-drugs-presentations/>
12. Koh W-J, Lee SH, Kang YA, Lee C-H, Choi JC, Lee JH, et al. Comparison of Levofloxacin versus Moxifloxacin for Multidrug-Resistant Tuberculosis. *Am J Respir Crit Care Med*. 2013 Oct;188(7):858–64.
13. Johnson JL, Hadad DJ, Boom WH, Daley CL, Peloquin CA, Eisenach KD, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2006 Jun;10(6):605–12.

14. Ahmad Z, Tyagi S, Minkowski A, Peloquin CA, Grosset JH, Nuermberger EL. Contribution of moxifloxacin or levofloxacin in second-line regimens with or without continuation of pyrazinamide in murine tuberculosis. *Am J Respir Crit Care Med*. 2013 Jul 1;188(1):97–102.
15. Mandell LA, Ball P, Tillotson G. Antimicrobial safety and tolerability: differences and dilemmas. *Clin Infect Dis*. 2001 Mar 15;32 Suppl 1:S72–79.
16. Noel G. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther*. 2003 Apr;73(4):292–303.
17. Briasoulis A, Agarwal V, Pierce WJ. QT Prolongation and Torsade de Pointes Induced by Fluoroquinolones: Infrequent Side Effects from Commonly Used Medications. *Cardiology*. 2011;120(2):103–10.
18. Prideaux B, Via LE, Zimmerman MD, Eum S, Sarathy J, O'Brien P, et al. The association between sterilizing activity and drug distribution into tuberculosis lesions. *Nat Med*. 2015 Oct;21(10):1223–7.
19. Naidoo A, Chirehwa M, McIlleron H, Naidoo K, Essack S, Yende-Zuma N, et al. Effect of rifampicin and efavirenz on moxifloxacin concentrations when co-administered in patients with drug-susceptible TB. *J Antimicrob Chemother*. 2017 May;72(5):1441–9.
20. Balasubramanian V, Solapure S, Gaonkar S, Mahesh Kumar KN, Shandil RK, Deshpande A, et al. Effect of Coadministration of Moxifloxacin and Rifampin on Mycobacterium tuberculosis in a Murine Aerosol Infection Model. *Antimicrob Agents Chemother*. 2012 Jun 1;56(6):3054–7.
21. Nijland HMJ, Ruslami R, Suroto AJ, Burger DM, Alisjahbana B, Crevel R van, et al. Rifampicin Reduces Plasma Concentrations of Moxifloxacin in Patients with Tuberculosis. *Clin Infect Dis*. 2007;45(8):1001–7.
22. Conde MB, Mello FCQ, Duarte RS, Cavalcante SC, Rolla V, Dalcolmo M, et al. A Phase 2 Randomized Trial of a Rifapentine plus Moxifloxacin-Based Regimen for Treatment of Pulmonary Tuberculosis. *PLoS One*. 2016;11(5):e0154778.
23. Smythe W, Merle CS, Rustomjee R, Gninafon M, Lo MB, Bah-Sow O, et al. Evaluation of Initial and Steady-State Gatifloxacin Pharmacokinetics and Dose in Pulmonary Tuberculosis Patients by Using Monte Carlo Simulations. *Antimicrob Agents Chemother*. 2013 Sep 1;57(9):4164–71.
24. WHO treatment guidelines for isoniazid-resistant tuberculosis. Supplement to the WHO treatment guidelines for drug-resistant tuberculosis (WHO/CDS/TB/2018.7) [Internet]. Geneva, World Health Organization. 2018. Available from: <http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/en/>
25. Neuvonen PJ, Kivistö KT, Lehto P. Interference of dairy products with the absorption of ciprofloxacin. *Clin Pharmacol Ther*. 1991 Nov;50(5 Pt 1):498–502.
26. Kivistö KT, Ojala-Karlsson P, Neuvonen PJ. Inhibition of norfloxacin absorption by dairy products. *Antimicrob Agents Chemother*. 1992 Feb;36(2):489–91.
27. Harausz EP, Leigh J, Garcia-Prats AJ, Furin J, Peloquin CA. Stability of Second-Line Tuberculosis Medications Mixed With Milk or Yogurt. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2017 Aug 15;65(4):704–5.
28. Streptomycin Treatment of Pulmonary Tuberculosis: A Medical Research Council Investigation. *BMJ*. 1948 Oct 30;2(4582):769–82.
29. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med*. 2012;9(8):e1001300.

30. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox H, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. *Eur Respir J*. 2013;42(1):156–68.
31. Jeong B-H, Jeon K, Park HY, Kwon OJ, Lee KS, Kim HK, et al. Outcomes of pulmonary MDR-TB: impacts of fluoroquinolone resistance and linezolid treatment. *J Antimicrob Chemother*. 2015 Nov;70(11):3127–33.
32. Harausz E. Treatment and outcomes in children with multidrug-resistant tuberculosis: a systematic review and individual patient data meta-analysis. *PLOS Med*. 2017;under review.
33. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.4) [Internet]. Geneva, World Health Organization. 2016. Available from: <http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf>
34. Donald PR, Sirgel FA, Venter A, Smit E, Parkin DP, Van de Wal BW, et al. The early bactericidal activity of amikacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2001 Jun;5(6):533–8.
35. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *Am Rev Respir Dis*. 1980 Jun;121(6):939–49.
36. Sanders WE, Hartwig C, Schneider N, Cacciatore R, Valdez H. Activity of amikacin against *Mycobacteria* in vitro and in murine tuberculosis. *Tubercle*. 1982 Sep;63(3):201–8.
37. Srivastava S, Modongo C, Siyambalapitiyage Dona CW, Pasipanodya JG, Deshpande D, Gumbo T. Amikacin Optimal Exposure Targets in the Hollow-Fiber System Model of Tuberculosis. *Antimicrob Agents Chemother*. 2016 Oct;60(10):5922–7.
38. Holmes AM, Hesling CM, Wilson TM. Capreomycin-induced serum electrolyte abnormalities. *Thorax*. 1970 Sep;25(5):608–11.
39. Steiner RW, Omachi AS. A Bartter's-like syndrome from capreomycin, and a similar gentamicin tubulopathy. *Am J Kidney Dis Off J Natl Kidney Found*. 1986 Mar;7(3):245–9.
40. Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clin Infect Dis*. 2004 Jun 1;38(11):1538–44.
41. Hickey AJ, Durham PG, Dharmadhikari A, Nardell EA. Inhaled drug treatment for tuberculosis: Past progress and future prospects. *J Control Release Off J Control Release Soc*. 2016 Oct 28;240:127–34.
42. Fiegel J, Garcia-Contreras L, Thomas M, VerBerkmoes J, Elbert K, Hickey A, et al. Preparation and in vivo evaluation of a dry powder for inhalation of capreomycin. *Pharm Res*. 2008 Apr;25(4):805–11.
43. Dharmadhikari AS, Kabadi M, Gerety B, Hickey AJ, Fourie PB, Nardell E. Phase I, single-dose, dose-escalating study of inhaled dry powder capreomycin: a new approach to therapy of drug-resistant tuberculosis. *Antimicrob Agents Chemother*. 2013 Jun;57(6):2613–9.
44. Garcia-Contreras L, Fiegel J, Telko MJ, Elbert K, Hawi A, Thomas M, et al. Inhaled large porous particles of capreomycin for treatment of tuberculosis in a guinea pig model. *Antimicrob Agents Chemother*. 2007 Aug;51(8):2830–6.
45. Garcia-Contreras L, Muttill P, Fallon JK, Kabadi M, Gerety R, Hickey AJ. Pharmacokinetics of sequential doses of capreomycin powder for inhalation in guinea pigs. *Antimicrob Agents Chemother*. 2012 May;56(5):2612–8.

46. Scardigli A, Caminero JA, Sotgiu G, Centis R, D'Ambrosio L, Migliori GB. Efficacy and tolerability of ethionamide *versus* prothionamide: a systematic review. *Eur Respir J*. 2016 Sep;48(3):946–52.
47. Vilchèze C, Wang F, Arai M, Hazbón MH, Colangeli R, Kremer L, et al. Transfer of a point mutation in *Mycobacterium tuberculosis* *inhA* resolves the target of isoniazid. *Nat Med*. 2006 Sep;12(9):1027–9.
48. Morlock GP, Metchock B, Sikes D, Crawford JT, Cooksey RC. *ethA*, *inhA*, and *katG* Loci of Ethionamide-Resistant Clinical *Mycobacterium tuberculosis* Isolates. *Antimicrob Agents Chemother*. 2003 Dec 1;47(12):3799–805.
49. Kambli P, Ajbani K, Sadani M, Nikam C, Shetty A, Udwadia Z, et al. Defining multidrug-resistant tuberculosis: correlating GenoType MTBDR plus assay results with minimum inhibitory concentrations. *Diagn Microbiol Infect Dis*. 2015 May;82(1):49–53.
50. Böttger EC. The ins and outs of *Mycobacterium tuberculosis* drug susceptibility testing. *Clin Microbiol Infect*. 2011 Aug;17(8):1128–34.
51. Jayaram R, Shandil RK, Gaonkar S, Kaur P, Suresh BL, Mahesh BN, et al. Isoniazid Pharmacokinetics-Pharmacodynamics in an Aerosol Infection Model of Tuberculosis. *Antimicrob Agents Chemother*. 2004 Aug 1;48(8):2951–7.
52. Donald PR, Sirgel FA, Botha FJ, Seifart HI, Parkin DP, Vandenplas ML, et al. The early bactericidal activity of isoniazid related to its dose size in pulmonary tuberculosis. *Am J Respir Crit Care Med*. 1997 Sep;156(3 Pt 1):895–900.
53. Peloquin CA, Jaresko GS, Yong CL, Keung AC, Bulpitt AE, Jelliffe RW. Population pharmacokinetic modeling of isoniazid, rifampin, and pyrazinamide. *Antimicrob Agents Chemother*. 1997 Dec;41(12):2670–9.
54. Katiyar SK, Bihari S, Prakash S, Mamtani M, Kulkarni H. A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2008 Feb;12(2):139–45.
55. Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010 Sep 1;182(5):684–92.
56. Study Protocol for the evaluation of the tolerance and effectiveness of a short 9 months treatment for multi-drug resistant tuberculosis patients [Internet]. Paris, UNION; 2012. Available from: [http://www.theunion.org/what-we-do/technical-assistance/tuberculosis-and-mdr-tb/body/2013\\_04\\_25\\_protocol\\_MDR\\_ENGLISH\\_rev.pdf](http://www.theunion.org/what-we-do/technical-assistance/tuberculosis-and-mdr-tb/body/2013_04_25_protocol_MDR_ENGLISH_rev.pdf)
57. Research Protocol - Effectiveness of a simplified short regimen for Multidrug Resistant Tuberculosis treatment in Karakalpakstan, Uzbekistan - MSF Field Research [Internet]. Available from: <http://fieldresearch.msf.org/msf/handle/10144/322296>
58. Curry International Tuberculosis Center, California Department of Public Health. Drug-resistant Tuberculosis: A survival guide for clinicians [Internet]. Third. 2016. 304 p. Available from: <http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition>
59. Zítková L, Tousek J. Pharmacokinetics of cycloserine and terizidone. A comparative study. *Chemotherapy*. 1974;20(1):18–28.
60. Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. *Int J Tuberc Lung Dis*. 2013 Oct;17(10):1257–66.



61. Yew WW, Cheung SW, Chau CH, Chan CY, Leung CK, Cheng AF, et al. Serum pharmacokinetics of antimycobacterial drugs in patients with multidrug-resistant tuberculosis during therapy. *Int J Clin Pharmacol Res.* 1999;19(3):65–71.
62. Abdullah Alsultan, Michael Neely, Wael A. Alghamdi, Mohammad Alshaer, Scott K. Heysell, Russell R. Kempker, Stellan G. Mpagama, Maia Kipiani, Anna Chongolo, Eric R. Houpt, Guohua An, Charles Peloquin. Population pharmacokinetics of cycloserine. In Atlanta, GA, USA; 2017. Available from: <http://www.infectiousdiseasesonline.com/10th-international-workshop-clinical-pharmacology-tuberculosis-drugs-presentations/>
63. Dietze R, Hadad DJ, McGee B, Molino LPD, Maciel ELN, Peloquin CA, et al. Early and extended early bactericidal activity of linezolid in pulmonary tuberculosis. *Am J Respir Crit Care Med.* 2008 Dec 1;178(11):1180–5.
64. Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis. *New Eng J Med.* 2012;367(16):1508–18.
65. Srivastava S, Magombedze G, Koeuth T, Sherman C, Pasipanodya JG, Raj P, et al. Linezolid Dose That Maximizes Sterilizing Effect While Minimizing Toxicity and Resistance Emergence for Tuberculosis. *Antimicrob Agents Chemother* [Internet]. 2017 Jul 25 [cited 2017 Aug 31];61(8). Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5527615/>
66. A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Jan 31]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02333799>
67. An Open-label RCT to Evaluate a New Treatment Regimen for Patients With Multi-drug Resistant Tuberculosis - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Sep 4]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02454205>
68. Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Sep 4]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02589782>
69. Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNiX) - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Nov 1]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03086486>
70. Nagiec EE, Wu L, Swaney SM, Chosay JG, Ross DE, Brieland JK, et al. Oxazolidinones Inhibit Cellular Proliferation via Inhibition of Mitochondrial Protein Synthesis. *Antimicrob Agents Chemother.* 2005 Sep 1;49(9):3896–902.
71. Song T, Lee M, Jeon H-S, Park Y, Dodd LE, Dartois V, et al. Linezolid Trough Concentrations Correlate with Mitochondrial Toxicity-Related Adverse Events in the Treatment of Chronic Extensively Drug-Resistant Tuberculosis. *EBioMedicine.* 2015 Oct 9;2(11):1627–33.
72. Approval Package for application numbers: NDA 21-130/S-012, NDA 21-131/S-012, NDA 21-132/S-012 [Zyvox (linezolid); sponsor: Pfizer Global Pharmaceuticals] [Internet]. CENTER FOR DRUG EVALUATION AND RESEARCH; 2007. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2007/021131Orig1s012.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021131Orig1s012.pdf)
73. Jungbluth GL, Welshman IR, Hopkins NK. Linezolid pharmacokinetics in pediatric patients: an overview. *Pediatr Infect Dis J.* 2003 Sep;22(9 Suppl):S153-157.

74. Deshpande D, Srivastava S, Nuernberger E, Pasipanodya JG, Swaminathan S, Gumbo T. Concentration-Dependent Synergy and Antagonism of Linezolid and Moxifloxacin in the Treatment of Childhood Tuberculosis: The Dynamic Duo. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2016 Nov 1;63(Suppl 3):S88–94.
75. Drusano GL, Neely M, Van Guilder M, Schumitzky A, Brown D, Fikes S, et al. Analysis of combination drug therapy to develop regimens with shortened duration of treatment for tuberculosis. *PloS One*. 2014;9(7):e101311.
76. WHO Model List of Essential Medicines. 20th List [Internet]. Geneva, World Health Organization; 2017. Available from: [http://www.who.int/medicines/publications/essentialmedicines/20th\\_EML2017.pdf](http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf)
77. WHO Model List of Essential Medicines for Children. 6th List [Internet]. Geneva, World Health Organization; 2017. Available from: [http://www.who.int/medicines/publications/essentialmedicines/6th\\_EMLc2017.pdf](http://www.who.int/medicines/publications/essentialmedicines/6th_EMLc2017.pdf)
78. WHO | Frequently asked questions (FAQ) about the shorter MDR-TB regimen [Internet]. [cited 2018 Feb 12]. Available from: [http://www.who.int/entity/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter\\_MDR\\_regimen.pdf](http://www.who.int/entity/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter_MDR_regimen.pdf)
79. Novartis Pharmaceuticals Corporation. LAMPRENE- clofazimine capsule, gelatin coated [Internet]. 2016. Available from: <https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=222267>
80. Ammerman NC, Swanson RV, Tapley A, Moodley C, Ngcobo B, Adamson J, et al. Clofazimine has delayed antimicrobial activity against *Mycobacterium tuberculosis* both in vitro and in vivo. *J Antimicrob Chemother*. 2017 Feb;72(2):455–61.
81. Diacon AH, Dawson R, von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet*. 2012 Sep 15;380(9846):986–93.
82. Zhang S, Chen J, Cui P, Shi W, Zhang W, Zhang Y. Identification of novel mutations associated with clofazimine resistance in *Mycobacterium tuberculosis* : Table 1. *J Antimicrob Chemother*. 2015 Sep;70(9):2507–10.
83. Diacon AH, Dawson R, von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. *Am J Respir Crit Care Med*. 2015 Apr 15;191(8):943–53.
84. van Ingen J, Simons S, de Zwaan R, van der Laan T, Kamst-van Agterveld M, Boeree MJ, et al. Comparative Study on Genotypic and Phenotypic Second-Line Drug Resistance Testing of *Mycobacterium tuberculosis* Complex Isolates. *J Clin Microbiol*. 2010 Aug 1;48(8):2749–53.
85. Ganesan S, Sunkara G, McNeeley D, Hughes D. Poster : Identification of optimal dose and dosing regimen of clofazimine for the treatment of multi-drug resistant tuberculosis (MDR-TB) based on pharmacokinetic modeling. In Cape Town, South Africa; 2015.
86. Verma RK, Germishuizen WA, Motheo MP, Agrawal AK, Singh AK, Mohan M, et al. Inhaled Microparticles Containing Clofazimine Are Efficacious in Treatment of Experimental Tuberculosis in Mice. *Antimicrob Agents Chemother*. 2013 Feb 1;57(2):1050–2.
87. Xu J, Lu Y, Fu L, Zhu H, Wang B, Mdluli K, et al. In vitro and in vivo activity of clofazimine against *Mycobacterium tuberculosis* persisters. *Int J Tuberc Lung Dis*. 2012 Aug 1;16(8):1119–25.
88. Williams K, Minkowski A, Amoabeng O, Peloquin CA, Taylor D, Andries K, et al. Sterilizing Activities of Novel Combinations Lacking First- and Second-Line Drugs in a Murine Model of Tuberculosis. *Antimicrob Agents Chemother*. 2012 Jun;56(6):3114–20.

89. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Interim policy guidance (WHO/HTM/TB/2013.6) [Internet]. Geneva, World Health Organization. 2013. Available from: [http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf)
90. Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis (WHO/HTM/TB/2017.01) [Internet]. Geneva, World Health Organization. 2017. Available from: <http://apps.who.int/iris/bitstream/10665/254712/1/WHO-HTM-TB-2017.01-eng.pdf>
91. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. *N Engl J Med*. 2014 Aug 21;371(8):723–32.
92. Rouan M-C, Lounis N, Gevers T, Dillen L, Gilissen R, Raoof A, et al. Pharmacokinetics and pharmacodynamics of TMC207 and its N-desmethyl metabolite in a murine model of tuberculosis. *Antimicrob Agents Chemother*. 2012 Mar;56(3):1444–51.
93. Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother*. 2012 Jun;56(6):3271–6.
94. McLeay SC, Vis P, van Heeswijk RPG, Green B. Population Pharmacokinetics of Bedaquiline (TMC207), a Novel Antituberculosis Drug. *Antimicrob Agents Chemother*. 2014 Sep 1;58(9):5315–24.
95. Svensson EM, Dosne A-G, Karlsson MO. Population pharmacokinetics of bedaquiline and metabolite M2 in drug-resistant tuberculosis patients – the effect of time-varying weight and albumin. *CPT Pharmacomet Syst Pharmacol*. 2016; Epub ahead of print.
96. Dooley KE, Park J-G, Swindells S, Allen R, Haas DW, Cramer Y, et al. Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS Clinical Trials Group Study A5267. *J Acquir Immune Defic Syndr* 1999. 2012 Apr 15;59(5):455–62.
97. Svensson EM, Aweeka F, Park J-G, Marzan F, Dooley KE, Karlsson MO. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfecting with HIV and tuberculosis. *Antimicrob Agents Chemother*. 2013 Jun;57(6):2780–7.
98. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. 2014 Nov;58(11):6406–12.
99. Brill MJE, Svensson EM, Pandie M, Maartens G, Karlsson MO. Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug-resistant tuberculosis. *Int J Antimicrob Agents*. 2017 Feb;49(2):212–7.
100. Pandie M, Wiesner L, McIlleron H, Hughes J, Siwendu S, Conradie F, et al. Drug-drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB. *J Antimicrob Chemother*. 2016 Apr;71(4):1037–40.
101. Maartens G, Brill MJE, Pandie M, Svensson EM. Pharmacokinetic interaction between bedaquiline and clofazimine in patients with drug-resistant tuberculosis. *Int J Tuberc Lung Dis* [Internet]. 2017 [cited 2017 Dec 22]; Available from: <http://www.ingentaconnect.com/content/10.5588/ijtld.17.0615>
102. Migliori G, Pontali E, Sotgiu G, Centis R, D'Ambrosio L, Tiberi S, et al. Combined Use of Delamanid and Bedaquiline to Treat Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: A Systematic Review. *Int J Mol Sci*. 2017 Feb 7;18(2):341.

103. Rustomjee R, Diacon AH, Allen J, Venter A, Reddy C, Patientia RF, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2008 Aug;52(8):2831–5.
104. Diacon AH, Dawson R, Von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2013 May;57(5):2199–203.
105. US FDA Center for drug evaluation and research. Application number 204384Orig1s000, Clinical Pharmacology and Biopharmaceutics review(s) [Internet]. 2012. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/204384Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/204384Orig1s000ClinPharmR.pdf)
106. Svensson EM, Karlsson MO. Modelling of mycobacterial load reveals bedaquiline's exposure–response relationship in patients with drug-resistant TB. *J Antimicrob Chemother*. 2017 Dec 1;72(12):3398–405.
107. van Heeswijk RPG, Dannemann B, Hoetelmans RMW. Bedaquiline: a review of human pharmacokinetics and drug-drug interactions. *J Antimicrob Chemother*. 2014 Sep;69(9):2310–8.
108. Pym AS, Diacon AH, Tang S-J, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J*. 2016 Feb;47(2):564–74.
109. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis (WHO/HTM/TB/2017.20) [Internet]. Geneva, World Health Organization; 2017. Available from: <http://apps.who.int/iris/bitstream/10665/258941/1/WHO-HTM-TB-2017.20-eng.pdf>
110. The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance (WHO/HTM/TB/2014.23) [Internet]. Geneva, World Health Organization. 2014. Available from: [http://apps.who.int/iris/bitstream/10665/137334/1/WHO-HTM-TB\\_2014.23\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/137334/1/WHO-HTM-TB_2014.23_eng.pdf)
111. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance (WHO/HTM/TB/2016.14) [Internet]. Geneva, World Health Organization. 2016. Available from: <http://apps.who.int/iris/bitstream/10665/250614/1/9789241549899-eng.pdf>
112. European Medicines Agency Committee for Medicinal Products for Human Use. Assessment report Deltyba [Internet]. 2013. (Procedure No.: EMEA/H/C/002552). Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/002552/WC500166234.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002552/WC500166234.pdf)
113. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for Multidrug-Resistant Pulmonary Tuberculosis. *N Engl J Med*. 2012;366(23):2151–60.
114. Diacon AH, Dawson R, Hanekom M, Narunsky K, Venter A, Hittel N, et al. Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. *Int J Tuberc Lung Dis*. 2011 Jul;15(7):949–54.
115. Gupta R, Wells CD, Hittel N, Hafkin J, Geiter LJ. Delamanid in the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2016 Dec 1;20(12):33–7.
116. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J*. 2013 Jun;41(6):1393–400.

117. Hafkin J, Frias M, De Leon A, Gler M, Hittel N, Wells C, Geiter L, Mallikaarjun S. Long-term Safety, Tolerability and Pharmacokinetics of Delamanid in Pediatric MDR-TB Patients, Ages 12-17 Years. 46th Union World Conference on Lung Health, Cape Town, South Africa. 2015.
118. Hafkin J, Frias M, Hesselning A, Garcia-Prats AJ, Schaaf HS, Gler M, Hittel N, Wells C, Geiter L, Mallikaarjun S. Pharmacokinetics and Safety of Delamanid in Pediatric MDR-TB Patients, Ages 6-17 Years. ICAAC. 2015.
119. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, Hewison C, Centis R, Schaaf HS, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. *Eur Respir J*. 2016 Sep;48(3):938–43.
120. Geiter L. Delamanid Global Clinical Database and Phase 3 Trial Results [Internet]. 2017. Available from: <http://www.professionalabstracts.com/theunion2017/iplanner/#/session/378>
121. Sasabe H, Shimokawa Y, Shibata M, Hashizume K, Hamasako Y, Ohzone Y, et al. Antitubercular Agent Delamanid and Metabolites as Substrates and Inhibitors of ABC and Solute Carrier Transporters. *Antimicrob Agents Chemother*. 2016 Jun;60(6):3497–508.
122. Shimokawa Y, Sasahara K, Yoda N, Mizuno K, Umehara K. Delamanid does not inhibit or induce cytochrome p450 enzymes in vitro. *Biol Pharm Bull*. 2014;37(11):1727–35.
123. Paccaly A, Petersen C, Patil S, Bricmont P, Kim J, Harlin M, Wells C. Absence of clinically relevant drug interaction between delamanid, a new drug for multidrug-resistant tuberculosis (MDR-TB) and tenofovir or lopinavir/ritonavir in healthy subjects [AIDS 2012, July 22-27, Washington DC].
124. Petersen C, Paccaly A, Kim J, Roth S, Stoltz R, Wells C. Delamanid, a new drug for multi-drug resistant tuberculosis (MDR-TB), and efavirenz do not show clinically relevant drug interactions in healthy subjects. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy: Abstract A- 1255.
125. Miotto P, Cirillo DM, Migliori GB. Drug Resistance in Mycobacterium tuberculosis: Molecular Mechanisms Challenging Fluoroquinolones and Pyrazinamide Effectiveness. *Chest*. 2015 Apr 1;147(4):1135–43.
126. Gumbo T, Siyambalapitiyage Dona CSW, Meek C, Leff R. Pharmacokinetics-Pharmacodynamics of Pyrazinamide in a Novel In Vitro Model of Tuberculosis for Sterilizing Effect: a Paradigm for Faster Assessment of New Antituberculosis Drugs. *Antimicrob Agents Chemother*. 2009 Aug;53(8):3197–204.
127. Ahmad Z, Fraig MM, Bisson GP, Nueremberger EL, Grosset JH, Karakousis PC. Dose-Dependent Activity of Pyrazinamide in Animal Models of Intracellular and Extracellular Tuberculosis Infections. *Antimicrob Agents Chemother*. 2011 Apr;55(4):1527–32.
128. Chideya S, Winston CA, Peloquin CA, Bradford WZ, Hopewell PC, Wells CD, et al. Isoniazid, Rifampin, Ethambutol, and Pyrazinamide Pharmacokinetics and Treatment Outcomes among a Predominantly HIV-Infected Cohort of Adults with Tuberculosis from Botswana. *Clin Infect Dis*. 2009 Jun 15;48(12):1685–94.
129. Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. *J Infect Dis*. 2013 Nov 1;208(9):1464–73.
130. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 Update. (WHO/HTM/TB/2011.6) [Internet]. Geneva, World Health Organization. 2011. Available from: [http://whqlibdoc.who.int/publications/2011/9789241501583\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf)
131. Zignol M, Dean AS, Falzon D, van Gemert W, Wright A, van Deun A, et al. Twenty years of global surveillance of antituberculosis-drug resistance. *N Engl J Med*. 2016 Sep 15;375(11):1081–9.

132. Ahmad Khan F, Salim MAH, du Cros P, Casas EC, Khamraev A, Sikhondze W, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *Eur Respir J*. 2017 Jul;50(1):1700061.
133. Whitfield MG, Soeters HM, Warren RM, York T, Sampson SL, Streicher EM, et al. A Global Perspective on Pyrazinamide Resistance: Systematic Review and Meta-Analysis. Mokrousov I, editor. *PLOS ONE*. 2015 Jul 28;10(7):e0133869.
134. Sekiguchi J-I, Nakamura T, Miyoshi-Akiyama T, Kirikae F, Kobayashi I, Augustynowicz-Kopec E, et al. Development and evaluation of a line probe assay for rapid identification of *pncA* mutations in pyrazinamide-resistant mycobacterium tuberculosis strains. *J Clin Microbiol*. 2007 Sep;45(9):2802–7.
135. Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update. (WHO/HTM/TB/2017.05) [Internet]. Geneva, World Health Organization. 2017. Available from: <http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf>
136. Guidelines for treatment of tuberculosis. 4th ed. (WHO/HTM/TB/2009.420) [Internet]. Geneva, World Health Organization. 2009. Available from: [http://whqlibdoc.who.int/publications/2010/9789241547833\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf)
137. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. (WHO/TB/2014.03) [Internet]. Geneva, World Health Organization; 2014. Available from: [http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf)
138. Drugs@FDA: FDA Approved Drug Products (Rifampin 300mg capsule; oral) [Internet]. [cited 2017 Sep 1]. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=050420>
139. van Ingen J, Aarnoutse RE, Donald PR, Diacon AH, Dawson R, Plemper van Balen G, et al. Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment? *Clin Infect Dis*. 2011 May;52(9):e194-199.
140. Hiruy H, Rogers Z, Mbowane C, Adamson J, Ngotho L, Karim F, et al. Subtherapeutic concentrations of first-line anti-TB drugs in South African children treated according to current guidelines: the PHATISA study. *J Antimicrob Chemother* [Internet]. 2014 Dec 11 [cited 2017 Sep 1]; Available from: <https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dku478>
141. Boeree MJ, Diacon AH, Dawson R, Narunsky K, du Bois J, Venter A, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med*. 2015 May 1;191(9):1058–65.
142. Jindani A, Harrison TS, Nunn AJ, Phillips PPJ, Churchyard GJ, Charalambous S, et al. High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis. *N Engl J Med*. 2014 Oct 23;371(17):1599–608.
143. Phillips PPJ, Dooley KE, Gillespie SH, Heinrich N, Stout JE, Nahid P, et al. A new trial design to accelerate tuberculosis drug development: the Phase IIC Selection Trial with Extended Post-treatment follow-up (STEP). *BMC Med* [Internet]. 2016 Mar 23 [cited 2017 Sep 4];14. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4804526/>
144. Herman RJ, Nakamura K, Wilkinson GR, Wood AJ. Induction of propranolol metabolism by rifampicin. *Br J Clin Pharmacol*. 1983 Nov;16(5):565–9.
145. Interaction Between High Dose Rifampicine and Efavirenz in Pulmonary Tuberculosis and HIV Co-infection - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Sep 4]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01986543>

146. Ruslami R, Ganiem AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. *Lancet Infect Dis*. 2013 Jan;13(1):27–35.
147. Te Brake L, Dian S, Ganiem AR, Ruesen C, Burger D, Donders R, et al. Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis. *Int J Antimicrob Agents*. 2015 May;45(5):496–503.
148. Heemskerk AD, Bang ND, Mai NTH, Chau TTH, Phu NH, Loc PP, et al. Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis. *N Engl J Med*. 2016 Jan 14;374(2):124–34.
149. Bekker A, Schaaf HS, Draper HR, van der Laan L, Murray S, Wiesner L, et al. Pharmacokinetics of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Dosed According to Revised WHO-Recommended Treatment Guidelines. *Antimicrob Agents Chemother*. 2016 Apr;60(4):2171–9.
150. Ramachandran G, Kumar AKH, Kannan T, Bhavani PK, Kumar SR, Gangadevi NP, et al. Low Serum Concentrations of Rifampicin and Pyrazinamide Associated with Poor Treatment Outcomes in Children with Tuberculosis Related to HIV Status. *Pediatr Infect Dis J*. 2016 May;35(5):530–4.
151. Swaminathan S, Pasipanodya JG, Ramachandran G, Hemanth Kumar AK, Srivastava S, Deshpande D, et al. Drug Concentration Thresholds Predictive of Therapy Failure and Death in Children With Tuberculosis: Bread Crumb Trails in Random Forests. *Clin Infect Dis*. 2016 Nov 1;63(suppl 3):S63–74.
152. HIV & AIDS Information: High-dose rifampicin for TB treatment regimen may improve survival in people with low CD4 cell counts [Internet]. [cited 2017 Sep 4]. Available from: <http://www.aidsmap.com/High-dose-rifampicin-for-TB-treatment-regimen-may-improve-survival-in-people-with-low-CD4-cell-counts/page/3074652/>
153. PanACEA kicks off new clinical trials programme for TB-drug evaluation - EDCTP [Internet]. [cited 2017 Sep 6]. Available from: <http://www.edctp.org/news/panacea-consortium-kicks-new-clinical-trials-programme-accelerate-tb-drug-evaluation/>
154. TBTC Study 31: Rifapentine-containing Tuberculosis Treatment Shortening Regimens - Full Text View - ClinicalTrials.gov [Internet]. [cited 2017 Sep 6]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02410772>
155. Definitions of TDM & CT [Internet]. [cited 2017 Sep 4]. Available from: <https://www.iatdmct.org/about-us/about-association/about-definitions-tdm-ct.html>
156. Vu DH, Alffenaar JWC, Edelbroek PM, Brouwers JRBJ, Uges DRA. Dried blood spots: a new tool for tuberculosis treatment optimization. *Curr Pharm Des*. 2011;17(27):2931–9.
157. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016 Oct 1;63(7):e147–95.
158. Wilby KJ, Ensom MHH, Marra F. Review of Evidence for Measuring Drug Concentrations of First-Line Antitubercular Agents in Adults. *Clin Pharmacokinet*. 2014 Oct;53(10):873–90.
159. Mota L, Al-Efraij K, Campbell JR, Cook VJ, Marra F, Johnston J. Therapeutic drug monitoring in anti-tuberculosis treatment: a systematic review and meta-analysis. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2016 Jun;20(6):819–26.

160. Bertrand J, Verstuyft C, Chou M, Borand L, Chea P, Nay KH, et al. Dependence of Efavirenz- and Rifampicin-Isoniazid-Based Antituberculosis Treatment Drug-Drug Interaction on CYP2B6 and NAT2 Genetic Polymorphisms: ANRS 12154 Study in Cambodia. *J Infect Dis.* 2014 Feb 1;209(3):399–408.
161. Dooley KE, Denti P, Martinson N, Cohn S, Mashabela F, Hoffmann J, et al. Pharmacokinetics of Efavirenz and Treatment of HIV-1 Among Pregnant Women With and Without Tuberculosis Coinfection. *J Infect Dis.* 2015 Jan 15;211(2):197–205.
162. Global tuberculosis report 2017 (WHO/HTM/TB/2017.23) [Internet]. Geneva, World Health Organization; 2017. Available from: <http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf>
163. ReSeqTB [Internet]. [cited 2017 Nov 9]. Available from: <https://platform.reseqtb.org/>



# Annex 1. Agenda of the technical consultation on the pharmacokinetics and pharmacodynamics (PK/PD) of tuberculosis medicines

**PLN**=plenary session

**CC**=critical concentrations parallel session

**PK**=pharmacokinetics/pharmacodynamics parallel session

**Day 1 - Monday 24<sup>h</sup> April 2017**

<u>Chair:</u> Karin Weyer		
8:30 – 9:00	Registration	
9:00 – 9:15	Welcome & opening Declarations of interest	Karin Weyer
9:15 – 9:45	Meeting objectives, agendas, cross-cutting issues PLN1. Definitions for critical concentrations (CC), PK/PD and priority clinical questions	Chris Gilpin (CC), Dennis Falzon (PK/PD)
9:45-10:20	PLN2. Scope and methodology for the systematic reviews for CC and PK/PD	Claudio Köser, J-W C Alffenaar
10:20-11:00	PLN3. Can we use current diagnostics for pyrazinamide resistance in clinical decisions?	Daniela Cirillo
11:00-11:20	<i>Coffee</i>	
<u>Chair:</u> Chris Gilpin / <u>Co-chair:</u> Tom Shinnick		
11:20–13:00	CC1. Main findings of systematic review on critical concentrations for Second Line Injectable Drugs (SLIDs): Amikacin (AMK), Capreomycin (CM), Kanamycin (KM) Discussion	Claudio Köser  Discussant: Tom Shinnick
13:00-14:00	<i>Lunch</i>	
14:00-15:00	CC2. Main findings of systematic review on critical concentrations for delamanid (DLM) and linezolid (LZD)  Discussion	Claudio Köser  Discussant: Daniela Cirillo
15:00-16:00	CC3. Main findings of systematic review on critical concentrations for bedaquiline (BDQ) and clofazimine (CFZ)  Discussion	Claudio Köser  Discussant: Nazir Ismail
16:00-16:15	<i>Coffee</i>	
16:15-16:45	CC4. Main findings of systematic review on CC for cycloserine (CS)  Discussion	Claudio Köser Discussant: Francis Drobniowski

16:45-17:15	CC5. Main findings of systematic review on CC for ethionamide/prothionamide (ETO/PTO) Discussion	Claudio Köser Discussant: Chris Coulter
17:15-17:30	Summary of the discussions of Day 1	
<u>Chair:</u> Dennis Falzon / <u>Co-chair:</u> Tawanda Gumbo		
11:20-12:15	PK1. Review of PK/PD of linezolid (LZD) and delamanid (DLM) Discussion	J-W C Alffenaar Discussants: Charles Peloquin (LZD); Susan Abdel-Rahman (DLM)
12:15-13:00	PK2. Review of PK/PD of 2nd line injectable agents Discussion	J-W C Alffenaar Discussant: Tawanda Gumbo
13:00-14:00	<i>Lunch</i>	
14:00-14:30	PK2 (ctd). Discussion of 2nd line injectable agents (on alternative methods of delivery of injectable agents)	Tawanda Gumbo, Anthony Hickey
14:30-15:30	PK3. Review of PK/PD of bedaquiline (BDQ) and clofazimine (CFZ) Discussion	J-W C Alffenaar Discussants: Elin Svensson, Stewart Cole (BDQ), Bernard Fourie (CFZ)
15:30-16:00	PK4. Review of PK/PD of cycloserine/terizidone (Cs/Trd)	J-W C Alffenaar Discussant: Gerry Davies
16:00-16:15	<i>Coffee</i>	
16:15-17:15	PK5. Key clinical questions relating to isoniazid (H) and ethionamide/prothionamide (Eto/Pto) that could be informed by PK/PD	Discussants: Kelly Dooley, Payam Nahid
17:15-17:30	Summary of the day & plan for Day 2	Chair

**Day 2 - Tuesday 25<sup>h</sup> April 2017**

<u>Chair:</u> Karin Weyer / <u>Co-chair:</u> Helen McIlleron		
08:30-09:00	PLN4. Summary of the day 1	Chris Gilpin (CC); Dennis Falzon (PK/PD)
09:00-09:30	PLN5. Main findings of systematic review on a CC for isoniazid & clinical breakpoints Discussion (including the discussion on ethionamide/prothionamide from session CC5)	Claudio Köser Discussant: Chris Coulter
09:30-10:30	PLN6. PK/PD issues on isoniazid (from session PK5) Discussion	Kelly Dooley
10:30-11:00	<i>Coffee</i>	
11:00-12:30	PLN7. Main findings of the systematic reviews on critical concentrations for levofloxacin (LFX), moxifloxacin (MFX), gatifloxacin (GFX) & clinical breakpoints (+ relevant findings on ofloxacin) Discussion	Claudio Köser Discussants: Jamie Posey, Leen Rigouts
12:30-13:30	<i>Lunch</i>	
13:30-15:45	PLN8. Main findings from PK/PD reviews of fluoroquinolones Discussion	J-W C Alffenaar Discussants : John Horton, Helen McIlleron
15:45-16:00	<i>Coffee</i>	
<u>Chair:</u> Chris Gilpin / <u>Co-chair:</u> Daniela Cirillo		
16:00-17:45	CC6. Review of updated critical concentration tables	Chris Gilpin
17:45-18:00	Summary of the day	Chair
<u>Chair:</u> Dennis Falzon / <u>Co-chair:</u> Bernard Fourie		
16:00-17:00	PK6. Miscellaneous issues in PK/PD <ul style="list-style-type: none"> <li>• Issues in PK/PD of children vs. adults</li> <li>• Differential distribution &amp; granuloma penetration</li> <li>• DDI to ART and other common companion drugs</li> </ul>	Discussants : Helen McIlleron, Kelly Dooley
17:00-18:30	PK7. Implications of PK/PD findings on the design of longer and shorter MDR-TB regimens	Discussants: M Rich, G Maartens

### Day 3 - Wednesday 26 April 2017

<u>Chair:</u> Chris Gilpin / <u>Co-chair:</u> Daniela Cirillo		
8:15-9:30	CC6 (continued). Review of updated critical concentration tables	Chris Gilpin
<u>Chair:</u> Dennis Falzon / <u>Co-chair:</u> Bernard Fourie		
8.30-9.30	PK8. TDM: its value, its priority application in TB care	Discussants: C Peloquin, G Davies, J W Alffenaar
<u>Chair:</u> Karin Weyer / <u>Co-chair:</u> Payam Nahid		
9:30–10:00	PLN9. Updated critical concentration table (from CC.6)	Chris Gilpin
10:00-10:30	PLN10. Cross-cutting issues between CC and PK/PD for prothionamide/ethionamide and cycloserine/terizidone	Discussants: Gerry Davies, Payam Nahid
10:30-11:00	PLN11. Cross-cutting issues between CC and PK/PD for 2nd line injectable agents	Discussants: Tawanda Gumbo
11:00–11:30	<i>Coffee</i>	
11:30–13:00	PLN12. Main concerns and issues relating to rifamycins and pyrazinamide	Martin Boeree; Tawanda Gumbo; Rada Savic
13:00-14:00	<i>Lunch</i>	
14:00-14:45	PLN13. Cross-cutting issues between CC and PK/PD for bedaquiline, clofazimine, delamanid and linezolid	Discussants: Elin Svensson, Susan Abdel-Rahman, Charles Peloquin
14:45-15:30	PLN14. Implications for DR-TB surveillance	Matteo Zignol
15:30–16:00	<i>Coffee</i>	
16:00-18:30	PLN15. Review of the clinical questions and way forward (e.g. update of the relevant sections of the companion handbook)	Bernard Fourie, Michael Rich, Rada Savic
18:30-19:00	Conclusion, any changes to the CCs & next steps	Chair (Karin Weyer)

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## Annex 3. Definitions of terms used in pharmacokinetics and pharmacodynamics (PK/PD)

This brief glossary is intended to improve the common understanding of certain terms, abbreviations and acronyms used in this Report. For more details please refer to the resources listed under **Further Reading** at the end of this Annex, from which this glossary has been inspired.

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Pharmacodynamics (PD): describes the effects of a compound on the body or on a micro-organism or a combination of the two

Pharmacokinetics (PK): describes the disposition of a compound in the body over time. The processes of absorption, distribution, metabolism and excretion, which govern disposition, are quantified by the *primary PK parameters* specific to each compound. These include the absorption rate constant, volume of distribution, and clearance

Population pharmacokinetics refers to the study of the extent, sources, and correlates of variability in PK parameters within a patient population

PK/PD analysis: an assessment of pharmacokinetic-pharmacodynamic (PK-PD, or concentration-effect) relationships. PK/PD analyses describe the associations between the concentration or exposure of a drug and an effect of interest (e.g. bacterial killing, sterilizing effect, adverse events, emergence of drug resistant populations of bacteria)

In essence, PK refers to how the human body handles a medicine, and PD is about the effect of a medicine on an organism or a person.

Pharmacogenetics (PG): the effect of genetics on the metabolism of a substance (e.g. isoniazid)

Pharmacovigilance: the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of any other drug-related problems. The application of the principles of active pharmacovigilance to tuberculosis treatment is referred to as active TB drug-safety monitoring and management (aDSM(4))

### Basic terms

Absorption, distribution, metabolism, and excretion (ADME): the processes which determine drug disposition, which, in turn, influence plasma and tissue exposures and hence the effects of a medicine. Differences in these processes between individuals contribute to pharmacokinetic variability. The value and magnitude of these elements are termed PK parameters

Bactericidal: a substance that kills bacteria rather than just arresting their growth (bacteriostatic). This is usually defined on the basis of preclinical assessments of a compound. In PK/PD science this is defined as at least 10-fold kill by colony-forming units (CFU) per millilitre of bacteria (or  $1.0 \log_{10}$  CFU/mL) compared to baseline bacterial burden in dynamic models (animal models of TB, hollow fibre models, etc)

Bacteriostatic: a substance that arrests the replication of bacteria without killing them (bactericidal)

Colony-forming unit (CFU): a quantifiable measure of viable bacteria based on their ability to replicate on culture into discrete groups ("colonies") which can be enumerated

Drug interaction: when a drug, food, or other substance affects the PK, the toxicity, or the effects of another drug. The sum of the interaction could have a synergic, additive, or inhibitory effect

Early Bactericidal Activity (EBA): is a quantitative measure of the potency of a compound to kill viable bacteria in the initial period of treatment; when applied to *M. tuberculosis* this is usually estimated by measuring the reduction in colony-forming units (CFU) observed in sputum samples collected serially over time among patients with microscopy smear-positive pulmonary TB being administered an anti-TB medicine(s). EBA studies are generally performed over 2-14 days. The method is commonly used to inform dose selection for subsequent, longer-duration clinical trials(5),(6),(7)

Sterilizing activity: the capacity of a compound to kill the slowly replicating ("persistent") bacteria. Regimen components which are effective sterilizers are considered important in shortening treatment duration.

Therapeutic drug monitoring (TDM): is a specialized activity focused on the measurement of concentrations of a substance in body fluids, with the aim to improve patient outcome by adjusting the dose of medicines to increase efficacy of treatment whilst minimizing toxicity.

### *PK/PD parameters and indices*

50% Effective concentration (EC50): the concentration required to obtain 50% of the maximum effect

50% Effective dose (ED50) (or 50% effective PK/PD index (EI50)): the dose, dosing regimen or exposure required to obtain 50% of the maximum effect

Absorption rate constant ( $k_a$ ): The absorption rate constant is the rate of absorption of a substance from the site of administration (e.g. following oral administration) into the systemic circulation

Accumulation ratio: is the ratio of drug concentrations observed during a dosing interval at steady-state divided by drug concentrations seen during the dosing interval after a single (first) dose

Area under the concentration-time curve (AUC): is used to express the exposure to a substance following its administration over a defined period. It is usually depicted as an area graph plotting the time after administration (usually either over 24h or over a dosing interval) on the horizontal axis and the plasma concentration of the substance on the vertical axis. AUC is a function of the amount of a substance absorbed, divided by clearance ( $AUC = \text{fraction absorbed} \times \text{dose} / \text{clearance}$ ). The AUC can also be estimated by integration of the points on the concentration-time graph. AUC is expressed in units such as  $\text{mg} \cdot \text{h} / \text{L}$  ( $[\text{dose (mg)} / \text{clearance (L/hr)}] = \text{mg} \cdot \text{h} / \text{L}$ ). The subscript denotes the time period over which the AUC is calculated (e.g.  $AUC_{0-24}$  is the AUC over 24 hours;  $AUC_{0-T}$  is the AUC over the dosing interval, for instance over 12 hours if the drug is given twice daily). At times AUC is expressed in relation to other relevant metrics:

AUBC: is the area under the bactericidal curve at steady-state (usually during 24 h)

AUC/MIC: is the AUC divided by the MIC

AUIC: is the area under the inhibitory curve at steady-state (usually during 24 h)

fAUC: is the AUC of the free fraction of a given medicine (i.e. the proportion which is not bound to protein)

Bioavailability (F): Fraction of a dose of drug that is absorbed from its site of administration and reaches, in an unchanged form, the systemic circulation

Clearance (CL or CL/F): This is the rate of elimination of a medicine from the body. Clearance is the volume of plasma in litres from which a substance is completely removed per hour (units=L/h). It is determined by both the metabolism as well as the excretion of the medicine into urine or faeces. Oral clearance, as a function of bioavailability, is denoted CL/F

$C_{\text{max}}$  (concentration maximum or peak): the highest concentration reached or estimated in the plasma, or other relevant body organ or 'compartment' such as the lung

$C_{\text{max}}/\text{MIC}$ : the maximum concentration achieved during the dosing interval in relation to MIC (i.e. the peak level divided by the MIC)

$C_{\text{min}}$  (concentration minimum or trough): the lowest concentration reached or estimated in the plasma, or other relevant body organ or 'compartment' such as the lung

$C_{\text{min}}/\text{MIC}$  (or "trough drive"): the minimum concentration achieved during the dosing interval in relation to MIC (i.e. the trough level divided by the MIC)

Extraction ratio: rate of drug removal from plasma by an organ of elimination (like the kidney or liver), divided by the rate at which it is presented to this organ

First-order rate constant: is a numerical multiplier which does not change and which determines the rate of a reaction, taking into account the concentration of only one substance (reactant)

Free fraction (prefix "f"; e.g. fAUC,  $f T_{>\text{MIC}}$ ): the proportion of a given substance which is not bound to protein. Only the free fraction of a medicine is available to exert pharmacologic effects

Growth rate: The rate at which bacteria, viruses, and other micro-organisms grow per unit time

Growth rate constant ( $k_0$ ): the first-order rate constant that describes growth

Half-life ( $t_{1/2}$ ): the time needed for the concentration of a substance in a body compartment, such as the plasma or lung tissue, to be reduced by one half

Kill rate: The rate at which bacteria, viruses, and other micro-organisms are killed per unit time

Kill rate constant: the first-order rate constant (i.e., dependent only on concentration of the one substance/drug) that describes the kill rate

Maximum effect of a drug ( $E_{max}$ ): the maximum effect that can be achieved when determining a dose–effect or concentration–effect relationship for a given medicine

Maximum kill rate (MKR): the maximum rate at which organisms are killed

Maximum kill rate constant ( $k_{max}$ ): the rate constant that describes the maximum kill rate

Minimum inhibitory concentration (MIC): the lowest concentration of an antimicrobial agent that prevents growth of more than 99% a microorganism in a solid medium or broth dilution susceptibility test (alternatively, a subscript on the MIC refers to the percentage of bacteria in a culture dish that are inhibited from growing (e.g.  $MIC_{90}$ )). The MIC may vary from strain to strain but the critical concentration is usually set at the highest MIC of the wild type distribution or one dilution higher and is defined so that it clearly differentiates resistant strains from susceptible strains. As the MIC rises, the ability of a medicine to kill the bacteria may be reduced in laboratory animal models and in patients receiving the medicine. It is important to be aware of the DST method used when interpreting or comparing PK/PD parameters which relate to an MIC.

Mutation prevention concentration (MPC): concentration of a medicine required to prevent growth at a high ( $> 10^9$ ) inoculum using agar dilution methodology

Mutation prevention index (MPI): the ratio between MPC and MIC

Mutant selection window (MSW): difference between MIC and MPC for a given micro-organism

PK/PD indices: Since the bacterial kill rate of a given medicine is determined by both the concentration achieved and the MIC of the organism, it is useful to calculate PK/PD indices that take both into account. This can be done by dividing a PK parameter of interest (like  $C_{max}$  or AUC) by the MIC and then these values can be used to explore exposure-response relationships

Post-antibiotic effect (PAE):

*In vitro* PAE : the period of suppression of bacterial growth after exposure of the micro-organisms to an antimicrobial following removal of the antimicrobial agent from the culture medium

*In vivo* PAE : Comparing treated animals versus untreated control animals, the difference in time required for the number of bacteria in a tissue to increase  $1 \log_{10}$  CFU/mL after drug concentrations in serum or the infection site fall below the MIC. The *in vivo* PAE thus includes the effects of sub-MIC concentrations

Post-antibiotic sub-MIC effect (PA SME): the effect of sub-MIC drug concentrations on bacterial growth following serial exposure to drug concentrations exceeding the MIC

Post-MIC effect (PME): the difference in time for the number of antibiotic-exposed bacteria versus controls to increase  $1 \log_{10}$  over values after drug concentrations in serum, the infection site or an *in vitro* pharmacokinetic model fall below the MIC. The PME thus includes the effects of sub-MIC concentrations and includes the *in vivo* PAE

Sub-MIC effect: Any effect of an antimicrobial on a micro-organism at concentrations below the MIC

Steady state: is achieved when the rate of input of a substance (e.g. from absorption) equals the rate of elimination (via metabolism and excretion). This happens after five half-lives and is generally independent of the dosing schedule

Static dose: the dose, dosing regimen, or value of a PK/PD index required to obtain a net static effect over a period of time (usually 24 h unless otherwise stated), in other words to just hold the bacterial burden constant (no net kill or growth of the bacteria)

Sterilizing effect: rates of kill of semi-dormant and non-replicating tubercle bacilli by a drug

Stationary concentration: the concentration of antimicrobial at which growth equals kill, i.e. no net growth or kill

Time interval within mutant selection window (tMSW): in settings where bacteria are exposed to changing concentrations of drug over time, tMSW represents the time (over a dosing interval) during which concentrations stay within the MSW

Time to peak concentration ( $T_{max}$ ): the time to reach the maximum plasma concentration ( $C_{max}$ ) following the administration of a medicine.

%T>MIC: the duration for which the concentration of a medicine exceeds the MIC over the dosing interval (usually expressed as a percentage)

Volume of distribution ( $V_d$ ): This is the theoretical fluid volume that would be required to contain the amount of a substance present in the body at the same concentration that it is observed in the plasma

### Analytic and modelling terminology

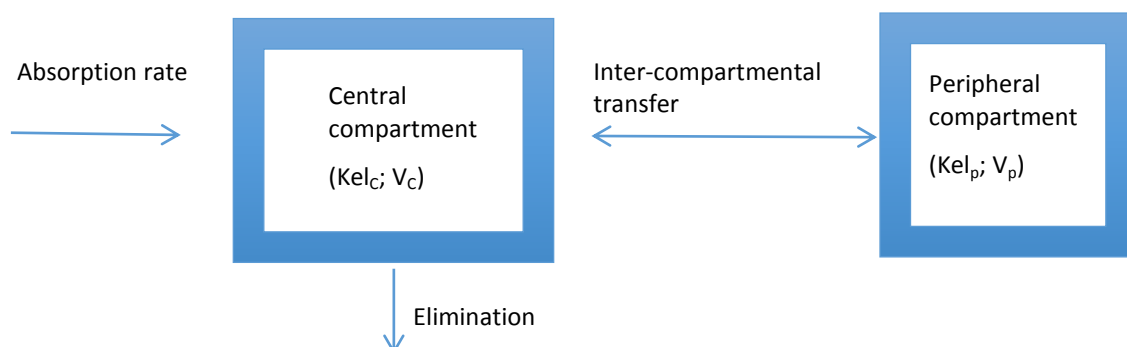
Models are used to describe the processes involved in the interaction between a medicine, the host, and the micro-organism and to estimate the parameters. In addition to the quantitative and time-bound indices mentioned above, some special terms commonly used in modelling and simulation (abbreviated as “M&S”) are defined here.

Allometric scaling: describes the variation of a characteristic (e.g. exposure following a dose) with the body weight

Bacterial kill kinetics: a model to explain the lethal properties of a substance on bacteria based on PK/PD properties (concentration, time)

Compartmental kinetics: a model describing drug disposition in the body, which is represented as one or several compartments (see graphic next page). Each compartment is described by having a different clearance rate and volume of distribution of the drug from the other compartment. Thus, a two compartment model means two different elimination rates and volumes in the same patient; these compartments are linked to each other by inter-compartmental rate constants

Cumulative fraction of response (CFR): the expected population probability of attainment of a particular PK/PD target for a specific drug dose if it were given to thousands of patients, taking into account inter-individual variability in PK as well as the MIC distribution



Hollow fibre infection models (HFIM): (otherwise known as *in vitro* pharmacodynamics systems (IVPDS)(8),(9),(10),(11)), have thousands of small tubular fibres that run through a cartridge into which drug and nutrients are delivered. The bacteria are contained within the fibres in the ‘peripheral’ compartment, and the fibres have pores that allow for nutrients, bacterial waste, and drug delivered into the ‘central compartment’ to pass, reaching equilibrium, but are not large enough for the organisms to pass. These HFIM are designed to mimic (i) the dynamic changes in drug concentration over time that occur after a human or animal is administered a dose, and (ii) the different metabolic profiles of *Mycobacterium tuberculosis* (log-phase or fast growing, semi-dormant, non-replicating “persisters”, and intracellular bacteria). This model, together with Monte Carlo simulations, was shown to have good forecasting accuracy of clinical therapeutic

outcomes (12)

Linearity: refers to the gradient of the relationship between drug-dose and a specific PK parameter. Dose proportionality occurs when a specific increase in drug dose results in a proportional increase in drug concentration (e.g.  $C_{\max}$  or AUC). Deviations from linearity result from saturable processes such as absorption, drug transport (e.g. efflux pumps), or elimination

Monte Carlo method (simulations): a modelling approach which uses repeated sampling of data plus information about the characteristics of a certain population to simulate an effect in that population. In this context, the data may include PK parameters and PD measures, as well as covariate factors, to make predictions of, for instance, exposures to or effects of certain medicines

Physiological-based PK model (PBPK): describes drug absorption, distribution and elimination in the body using a series of organs or tissue spaces for representation

Probability of target attainment (PTA): in Monte Carlo simulations, the probability that at least a specific value of a pharmacodynamic index (e.g. 30%  $fT_{>MIC}$ ;  $fAUC/MIC$  of 100) is achieved at a certain drug dose

Sampling strategies: for collection of PK samples in a study include sparse sampling (few samples per person requiring a larger group of patients) or intensive sampling (larger number of samples per person in a – usually - small number of participants). Optimal sampling strategies (OSS) aim to collect serial specimens at particular intervals in order to make the best possible inferences based on the goals of the particular study.

### *Further reading (for Annex 3)*

1. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2014.11). Geneva, World Health Organization. 2015. Available from: [http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf)
2. Mouton JW. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother. 2005 Apr 8;55(5):601–7.
3. PHARMACOKINETICS: An Online resource for students. Available from: <http://sepia.unil.ch/pharmacology/index.php?id=100>
4. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation.(WHO/HTM/TB/2015.28). Geneva, World Health Organization; 2015. Available from: [http://apps.who.int/iris/bitstream/10665/204465/1/WHO\\_HTM\\_TB\\_2015.28\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf)
5. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis. 1980 Jun;121(6):939–49.
6. Dietze R, Hadad DJ, McGee B, Molino LPD, Maciel ELN, Peloquin CA, et al. Early and extended early bactericidal activity of linezolid in pulmonary tuberculosis. Am J Respir Crit Care Med. 2008 Dec 1;178(11):1180–5.
7. Diacon AH, Donald PR. The early bactericidal activity of antituberculosis drugs. Expert Rev Anti Infect Ther. 2014 Feb;12(2):223–37.
8. Cadwell J. The Hollow Fiber Infection Model for Antimicrobial Pharmacodynamics and Pharmacokinetics. Adv Pharmacoepidemiol Drug Saf. 2012;01(S1). Available from: [http://www.fibercellsystems.com/wp-content/uploads/2015/07/FiberCellSystems\\_PkPd\\_Omics.pdf](http://www.fibercellsystems.com/wp-content/uploads/2015/07/FiberCellSystems_PkPd_Omics.pdf)
9. Hamzeh FM, Lietman PS. Dosage modeling system. 2001 Sep 11; Available from: <https://www.google.ch/patents/US6287848>
10. Gumbo T, Lenaerts AJ, Hanna D, Romero K, Nuermberger E. Nonclinical Models for Antituberculosis Drug Development: A Landscape Analysis. J Infect Dis. 2015 Jun 15;211(suppl 3):S83–95.
11. Gumbo T, Angulo-Barturen I, Ferrer-Bazaga S. Pharmacokinetic-Pharmacodynamic and Dose-Response Relationships of Antituberculosis Drugs: Recommendations and Standards for Industry and Academia. J Infect Dis. 2015 Jun 15;211(suppl 3):S96–106.
12. Gumbo T, Pasipanodya JG, Romero K, Hanna D, Nuermberger E. Forecasting Accuracy of the Hollow Fiber Model of Tuberculosis for Clinical Therapeutic Outcomes. Clin Infect Dis. 2015 Aug 15;61(suppl 1):S25–31.

## Annex 4. Reviews of individual medicines and therapeutic drug monitoring (TDM)

accessible at:

[https://www.dropbox.com/sh/ruu7pru9xzx6vo/AABOLNL-FrzLVM3243CFSLfja?dl=0&preview=Annex+4.+Reviews+of+individual+medicines+and+therapeutic+drug+monitoring+\(TDM\).pdf](https://www.dropbox.com/sh/ruu7pru9xzx6vo/AABOLNL-FrzLVM3243CFSLfja?dl=0&preview=Annex+4.+Reviews+of+individual+medicines+and+therapeutic+drug+monitoring+(TDM).pdf)

