Pharmacological approaches to optimize TB treatment
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General discussion and future perspectives
The treatment success rate for drug-susceptible TB has been estimated to be around 83 percent globally [1]. For MDR-TB, this percentage is only 54 and for XDR-TB it is even as low as 30 percent [1]. The goal set by the WHO is to have a global overall treatment success rate of 90 percent or more before 2025, for drug-susceptible as well as for drug-resistant TB [1]. The treatment success rates have only been increasing slightly, which shows the need for new treatment strategies to attain the WHO set targets [1]. In this thesis we studied and discussed new treatment strategies to individualize and optimize TB treatment.

In chapter 2 we discussed the possible role of TDM. Pharmacokinetic variability has been shown to be one of the most important drivers of therapeutic failure [2]. We argued that this supports the case for an individualized approach. No large prospective randomized trials have been conducted to prove that TDM leads to better outcomes in the treatment of TB. Also no cost-effectiveness analysis has been performed for TDM in the context of TB treatment. The rationale of TDM is to increase efficacy and decrease toxicity, although toxicity of anti-TB drugs is not always dose-dependent. For example, the hepatotoxicity of pyrazinamide is partially idiosyncratic [3]. Which means that the toxicity is unpredictable and independent of the dose. Indeed, host pharmacogenetics and genetically determined drug (in)tolerance confound drug toxicity profiles of individual patients. We therefore cannot assume that performing TDM can prevent all adverse effects. The question remains, can we increase the efficacy of the anti-TB drugs with TDM? Plasma drug concentration is not the only determinant of treatment efficacy, also the penetration of the drug to the site of infection plays an important role [4]. Measuring plasma drug concentrations is actually an indirect method of determining the amount of drug that could be effective, since we measure the concentration in blood and not in tissue. In order to solve this discrepancy, ratios can be used such as the epithelial lining fluid/plasma ratio. However, ratios are not known for all drugs and all lesions and intracellular sites of infection [4].

The anti-TB drug will never be effective, if the *M. tuberculosis* strain is resistant to that drug. Whole genome sequencing, and not only analyzing dominant mutations in e.g. *katG*, *inhA* and *rpoB* genes, would enable personalized treatment to avoid exposure to ineffective drugs [5]. As stated in chapter 2, an integrated approach of whole genome sequencing in combination with the measurement of plasma drug concentrations is needed to further optimize anti-TB treatment.

One of the focuses of the World Health Organization is to optimize the diagnosis of TB including drug susceptibility or resistance. For this cause multiple new
techniques are being tested and evaluated, which could help define more accurate breakpoints [1]. The implications of more accurate breakpoints need to be discussed. Lower breakpoints would ultimately result in a policy to ‘condemn’ many patients to second-line drugs with prolonged treatment [6]. In turn, higher breakpoints would lead to increased use of first-line TB drugs, which could cause antimicrobial pressure on the *M. tuberculosis* population to select increasingly resistant strains to these first-line anti-TB drugs [7]. This could eventually result in decreased effectiveness of the first-line anti-TB drugs, that have been shown to be clearly much less toxic than many of the second-line anti-TB drugs [8-11].

In chapter 3a we showed that using a higher dose of the first-line anti-TB drugs isoniazid, rifampicin and pyrazinamide could be an alternative to lowering the susceptibility breakpoints, which were thought to be too low based on the ability to reach the pharmacokinetic/pharmacodynamic target in a hollow-fiber infection model [6]. We proposed to define the area between the old and the newly suggested lower breakpoints, “intermediate-susceptibility dose-dependent”.

In chapter 3b it was shown that this approach might be cost-effective in low- and middle-income countries with a high MDR-TB burden. These studies showed that this approach could be preferred over current treatment and should be validated in a prospective study in TB patients. Despite the fact that hollow-fiber infection models have only recently been introduced and accepted by the European Medicine Agency to explore the correlation between drug concentration over time and efficacy [12], these models do not address the tolerability of high-dose first-line anti-TB drugs. As a result, the issue of high dosing for first-line anti-TB drugs is still subject of debate. Although there have been clinical studies showing that high-dose rifampicin, isoniazid and rifampicin are well tolerated, the evidence remains very limited [8-11]. Some argue that the safety evidence is too weak to support a strong recommendation to increase the dose. Because the use of high-dose first-line anti-TB treatment is not widely accepted, the only alternative would be second-line anti-TB treatment. Our approach should be tested in a prospective randomized controlled trial, the exact design would be dependent on the funding, in which the adverse events and the microbiological outcomes of giving a higher dose is compared to continuation on a normal-dose.

The first-line anti-TB drugs exist in fixed-dose combinations (FDC), effectuating a considerable reduction in pill burden, a reduction in the risk of monotherapy and subsequent acquired resistance [13]. FDCs are available as isoniazid/rifampicin,
Isoniazid/rifampicin/pyrazinamide and isoniazid/rifampicin/pyrazinamide/ethambutol [13]. The formulations are based on adult weight-banded dosing [13]. One of the aims of this thesis was to individualize anti-TB treatment, which makes the use of FDCs counterintuitive, because they are based on the weight-banded ‘one size fits all’ dosing.

In chapter 4 we showed that this is not necessarily true. We suggested a strategy to combine TDM and FDCs, which is an option because there are multiple FDC combinations that can be used to adjust the dose in a way that all drugs are dosed in the therapeutic range - still effective and not yet toxic. By performing TDM on FDCs, dose adjustments occur for all anti-TB drugs simultaneously. In case of a dose increase, this could result in a significant increase in plasma drug concentrations. The question remains if the plasma drug concentration would be considered too high. The answer is not straightforward and depends on several different factors; is the toxicity dose-dependent, what exactly is the tolerability of the first-line anti-TB drugs in the target population and what is the bioavailability of rifampicin in FDCs in the target population [13]? A prospective implementation study could help find the answer to our questions.

In chapter 5a we discussed dried blood spot sampling (DBS), which is a way to perform TDM by using a finger prick to obtain a blood drop on a DBS card instead of a venous sample. Because this technique has several advantages over venous sampling, such as a reduced total volume of blood drawn; and generally reducing patient discomfort, it might make TDM more acceptable and feasible [14]. DBS also has the advantage of being less of a bio-hazard, which is especially helpful in the case of HIV, HBV or HCV co-infection. This is not only an advantage over venous sampling but also over saliva sampling, since saliva could also contain TB bacteria and in case of hemoptysis these blood-borne viruses could conceivably be transmitted. Similar to venous sampling, DBS sampling needs to be validated for all drugs in order to estimate the plasma drug concentration correctly [14]. However, for DBS analysis an expensive LC-MS/MS system is required that requires a lot of maintenance and an un-interrupted power supply, which is not feasible in remote areas. Then again, DBS samples are more stable than regular samples and could be send via regular mail to a central laboratory contrary to venous samples, which need to be send on ice [14].

Another problem with DBS sampling as discussed in chapter 5a, is that DBS sampling might not be as easy as initially thought. In the end 46% of all DBS cards were rejected for analysis based on their quality. This was mostly due to inaccurate sampling. Obviously, inaccurate sampling causes incorrect results. This study
showed that more than written instructions alone are needed to be able to produce DBS of sufficient quality. Clearly, more research on the influence of incorrect sampling on the outcome of the analysis is needed. In addition to research on the efficacy of different tools for DBS sampling, such as video instructions or in-person training [15]. Maybe, we should look at other sampling techniques, which are easier to do at home. Saliva sampling might be an option; with this non-invasive technique, plasma concentrations can be estimated by using a saliva-plasma ratio [16]. This technique also has drawbacks at the moment because the salivary concentrations of some of the anti-TB drugs cannot be determined, and therefore this technique is not applicable for all TB patients [16]. More importantly, some drugs do not penetrate into saliva, which makes determination of the plasma drug concentrations from saliva impossible [17]. Even if DBS could be applicable at home, the question remains if it would be feasible to train patients for self-sampling, as limited training of health care workers was not successful [15]. Since regular contact with a healthcare worker is inevitable during TB treatment it would be preferred to train them and let them perform TDM at patients’ homes [2].

In chapter 5B, we discussed DBS sampling for MDR-TB patients with HIV co-infection. Multiple anti-HIV drugs and blood tests have been validated for DBS in addition to the second-line anti-TB drugs, but not all. Some tests can be performed with sputum sampling, instead of venous sampling but it remains a burden on the patient. This study also showed that more research needs to be performed before TDM can be considered feasible in the treatment of MDR-TB with HIV co-infection. As MDR-TB patients can harbor *M. tuberculosis* bacilli with additional resistance to some of the second-line anti-TB drugs, molecular resistance testing is needed to individualize the treatment. Additional resistance limits the treatment options even further. Therefore, exploring more treatment options for MDR-TB is warranted. A search for new types of antimicrobial agents or repurposing of existing antimicrobials, which are currently not in use for TB, should be considered. Before repurposing existing drugs can be accepted for MDR-TB, studies are needed to determine the pharmacokinetics/pharmacodynamics of these agents to be able to select the optimal dose for these new drugs. Should dosing appear to be overwhelmingly effective, such studies might indicate that TDM is unnecessary; if however, breakpoints appear to be in the intermediate susceptibility range, TDM would clearly be advantageous [18].

In chapter 6 we discussed the carbapenems. The conclusion of the systematic review on carbapenems in chapter 6a was that much information is lacking. Even though imipenem and meropenem have been added to TB treatment guidelines, ertapenem
has not yet been included [19]. In chapter 6b we made a pharmacokinetic model for ertapenem, to be able to perform TDM for ertapenem. Ertapenem has favorable characteristics; one being that it has a long half-life allowing once daily treatment [20]. The downside is, that it is only available for intravenous use. This limits its use for home-based treatment. This is shared by other injectable drugs, such as amikacin and kanamycin, that are considered key components in the treatment of TB. Ertapenem has shown to be effective in the hollow fiber infection model of TB in a simulated dose of 2000 mg, and in chapter 6c we described the pharmacokinetics of 2000 mg ertapenem [21]. We propose ertapenem as an attractive option for the treatment of TB, if only limited treatment options are available. The pharmacokinetic model and limited sampling strategy described in chapter 6b can be used in a phase 2 trial, where 2000 mg ertapenem, in combination with clavulanic acid, can be tested for the early bactericidal activity. This is needed to strengthen our hypothesis that 2000 mg ertapenem might be a valuable asset for the treatment of MDR-TB.

Mutations in the \textit{rrs} and \textit{eis} genes of \textit{M. tuberculosis} can cause resistance to amikacin and kanamycin, eliminating them as options for the treatment of (pre)-XDR-TB [22]. Carbapenems may be an attractive solution. However, \textit{M. tuberculosis} does possess the BlaC gene, encoding a beta-lactamase that hydrolyzes the beta-lactam ring of, among others, carbapenems [22]. This inactivates the carbapenems, but this can be overcome by combining them with clavulanic acid, a beta-lactamase inhibitor [22]. We hypothesize that ertapenem could be a good alternative for amikacin and kanamycin, because of once daily dosing and the possibility of circumventing inactivation with a beta-lactamase inhibitor. However, clavulanic acid is not available on the market as a single agent; it is only available as a co-formulated drug added to a beta-lactam. The combination of ertapenem and clavulanic acid is also not available at this point in time. The lack of availability of clavulanic acid not necessarily limits the use of ertapenem, as amoxicillin/clavulanic acid might simply be added to ertapenem in the framework of an efficacy study. After efficacy and safety of ertapenem in a dose of 2000 mg has been demonstrated in a phase 2 trial, the next step would be a phase 3 randomized superiority trial in order to determine if ertapenem can actually replace amikacin in the treatment of MDR-TB.

In this thesis we showed that TDM could tailor the dose to the individual patient to reach target concentrations expected to be related to better outcome. Even though this thesis contributed in making the implementation of TDM in the treatment of TB more feasible, more research is needed. More prospective pharmacokinetic/pharmacodynamics studies need to be performed in order to better understand the relationship between the plasma drug concentration and clinical outcome. Many
data is still lacking to determine the role of TDM for the second-line anti-TB drugs. Additionally, more anti-TB drugs need to be validated for DBS sampling and other sampling options must be explored to facilitate pharmacokinetic studies and TDM to reduce patient burden and costs, especially in middle and low-income countries.

Ultimately, with optimized technology, only randomized controlled trials of different designs can answer the question to what extent, and for which patients TDM has added value in terms of management and improved outcome. Studies should be powered to provide meaningful answers. As an outcome parameter the time to sputum smear conversion can be used as well as treatment outcomes after the predefined treatment duration in addition to the number of adverse events and interventions, including concentration-driven dose adjustments, in both groups.

In conclusion, the knowledge gap has been reduced with this thesis, but more research is needed to close it entirely.

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