A quest to optimize the clinical pharmacology of tuberculosis and human Immunodeficiency virus drug treatment
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General Discussion and Future Perspectives
General Discussion

In this thesis we aimed to provide insight in the treatment of drug-susceptible TB in TB/HIV co-infected patients and to reveal potential knowledge gaps in this area. We have shown that there is a need for a consistent and homogeneous approach to studies regarding the effect of HIV infection on the PK of first-line TB drugs and that a uniform quality assessment tool specifically for PK studies is currently lacking. Furthermore, we have identified drug-induced liver injury as a significant independent predictor of extended TB treatment. Another issue we addressed in this thesis is personalized medicine from clinical practice perspective. For the development and registration of new drugs large and expensive clinical trials are needed to convince registration authorities like European Medicine Agency (EMA) and Food and Drug Administration (FDA) that the efficacy and safety of these novel compounds are sufficient for release on the European and American market. While this clearly is an improvement compared to decades ago, we believe that the effect of the drugs in the individual patient is often overlooked. We aimed to not only investigate the effect of HIV infection on the PK of first-line TB drugs, but also to investigate these issues from a daily clinical practice perspective. As there might be an even higher inter- and intra-individual variability in certain subpopulations we included letters to the editor and a case-report providing insight in the effect of TB drugs in the individual patient.

The second major focus of this thesis is providing tools for a tailor-made antiretroviral treatment by investigating the PK of darunavir in real-life outpatient settings. In order to do this we developed and validated a LC-MS/MS method for the simultaneous determination of 14 antiretrovirals and we developed a robust one-compartment population pharmacokinetic model to support TDM of darunavir in a daily outpatient setting by collaborating in an international setting. Combining these two tools provided the opportunity to determine darunavir blood samples and to estimate darunavir trough concentrations. One important finding was that there was no relation between the reported food intake and darunavir trough concentrations in patients at the outpatient clinic. Therefore we advise to avoid unnecessarily high caloric intake which may result from the instruction to take darunavir with food to improve drug exposure. Unnecessarily high food intake is undesirable, especially in people living with HIV as they already have an increased risk of cardiovascular disease due to their HIV infection. We have also found that younger patients with a higher than average eGFR more frequently have a darunavir plasma concentration below median population pharmacokinetic values and that simultaneous intake of tenofovir might have an impact in darunavir PK.

Scientific, financial and political balance

Despite the high mortality rates, TB can be considered as a disease for which there is little public and political attention in major parts of the world. When drug companies develop
General Discussion and Future Perspectives

Drugs a market analysis is often carried out aiming to maximize the financial return of the investments made. Indeed, drug development is fuelled by marked-driven principles that intrinsically ignore low-resourced population. As an example, novel products like the development and the utilization of the expensive PD-1 inhibitor nivolumab which is used as immunotherapy in different forms of cancer\(^1\), typically target wealthy patient populations. Although the development of such drugs provides new hope for patients and present a leap forward in cancer therapy, the balance between health gains and costs however, is highly skewed; as immunotherapy drugs often are highly expensive\(^2\), but result in a relatively short elongation of life-expectancy\(^1,3\). In contrast, TB is an infectious disease which often can be well treated and even cured when caregivers are equipped with adequate (diagnostic) tools and drugs. Sadly, in 2016 1.7 million people died worldwide due to TB; 0.4 million of whom HIV co-infected\(^4\). Despite the high burden of TB in high endemic areas a relatively low amount of funding is available for TB in relation to its impact\(^4\).

After the introduction of rifampicin in 1968 and a three drug (HRZ) sterilizing treatment regimen of limited duration (six months) for TB, almost half a century ago, the TB mortality rates dropped. The WHO estimated that 53 million lives around the world have been saved between 2000 and 2016 as a result of short course TB treatment around the world\(^5\). At the same time, perhaps due to this very success, the interest in TB research, including the development of new therapeutic and prophylactic regimens diminished\(^6,7\). As TB mortality rates dropped rapidly in high income countries, where TB drugs were previously developed, a feeling that TB was already a defeated enemy prevailed and therefore less attention and funding became available for TB research and drug development\(^8\). In addition, due to the reduced mortality rates for TB and the emergence of other illnesses (notably HIV) there was a lack of financial incentive for the pharmaceutical industry to invest in TB drug development\(^9\). Perhaps more importantly, TB patients, who at that point in time predominantly were people living in resource limited settings\(^10\), could not lobby and were unable to put TB on the political agenda; no lessons were learned from the lobby of people living with HIV/AIDS in order to enforce research and development of better, less toxic and simpler treatments\(^11\). Zidovudine, the first ever drug developed to combat HIV, was developed and brought to the market in no more 20 months\(^12\), whereas most drugs would take close to a decade for this entire process. In the absence of lobbyists, TB therefore continued to claim lives, especially in resource limited countries\(^10\). It was only in 1992 when TB was declared a global emergency that this situation changed.

**TB/HIV co-infection**

With the emergence of the HIV epidemic and the rise of MDR-TB in the eighties and nineties of the past century, the number of TB cases increased in major parts of the world, even in high resource countries\(^13,14\). In 1995, the WHO started to roll out the Directly Observed Treatment Short course (DOTS) program in order to fight TB\(^15\). This change in recognizing
the importance of TB research due to TB/HIV co-infection (also in high-income countries) is also demonstrated in the systematic review we conducted investigating the effect of HIV infection on the PK of first-line TB drugs [chapter 2]. The first studies warning for potential reduced exposure of first-line TB drugs in TB/HIV co-infected people were published mid-nineties\textsuperscript{16,17}. As we demonstrated in our quality assessment however, the methodology of many studies was not optimal. The majority of the studies included in our systematic review were investigator initiated research conducted by committed caregivers in high endemic areas in often resource-limited settings. Due to a lack of funding and due to practical reasons often TB control groups were not included and the PK of first-line TB drugs in TB/HIV co-infected patients were compared with published reference ranges \textsuperscript{18-21}. Due to the varying methodology of the conducted studies highly varying results were presented and still no clear cut conclusions can be drawn. Partly due to the varying results published earlier and partly due to lack of funding and political will, to date still no thorough research has been conducted investigating whether HIV infection leads to reduces first-line TB drug exposures and combining this data with clinical outcomes. Potential reduction of TB drug exposure should be strongly avoided as we postulate that reduced exposure could lead to sub-therapeutic drug levels and subsequently to sub-optimal treatment and drug resistance \textsuperscript{22}.

Regarding DOTS, the predominant consensus was that a programmatic approach would be the winning scenario: one size fits all; and most if not all TB related problems were traced back to poor adherence to therapy\textsuperscript{23}. Due to the lack of solid evidence regarding the effect of HIV infection on the PK of first-line TB drugs, only weight-band dosing was recommended and the HIV status was not taken into account in dosing. Despite the DOTS program TB currently is the number one infectious killer\textsuperscript{24}. Recent studies show that pharmacokinetic variability can occur under DOTS\textsuperscript{25} and that socio-economic aspects in high endemic areas still can contribute to higher TB rates\textsuperscript{26}. Moreover, a systematic review of randomized clinical trials and a recent meta-analysis both did not find any difference between DOTS and self-administered therapy in terms of cure rates and treatment completion rates \textsuperscript{27,28}. This inversely affects the contribution and the current role of DOTS in TB control. Two decades later, in 2015, the WHO again set up a target for TB, the ‘End-TB strategy’; which aims to achieve a 95% reduction in TB mortality in 2035\textsuperscript{29}. Although this aim is ambitious and admirable, for many highly endemic areas like South Africa, it does not seem an attainable goal\textsuperscript{30}. There is a huge funding gap of 1.4 billion U.S. dollars for implementation of existing TB interventions\textsuperscript{29} and more importantly, the healthcare systems in highly endemic countries and regions are not equipped and cannot cope with such high numbers of patients and huge projects.

There is a need to define risk factors which predispose to an increased risk of sub-therapeutic levels. This would aid healthcare providers in resource limited settings in defining which patients are eligible for TDM or which patients are at risk for extended therapy and
therefore need additional attention. In order to aid caregivers in resource-limited settings in better recognizing patients at risk for extended TB treatment by assessing simple patient characteristics, we conducted a retrospective analysis and identified drug-induced liver injury as contributor to prolonged treatment. We believe that more studies taking the resource-limited settings of high endemic areas into account are needed. Healthcare providers have to deal with the daily practice, which in high endemic areas unfortunately often means that few diagnostic tools are available.

In recent years TB research teams have explored the PK of TB drugs; in repurposing old antimicrobials\(^1\)\(^2\) for the treatment of TB; and new antimicrobials such as delamanid\(^3\) and bedaquiline\(^4\) have been developed and brought to the market. Other improvements investigated which could provide a solution in resource-limited settings are dried blood spot analysis\(^5\),\(^6\). In addition to these hopeful developments a renaissance is needed in TB drug development (and likely also in TB vaccine development) to impact on the global burden of TB.

An alternative approach

The rapid developments in HIV treatment have shown that if there is a political will accompanied by sufficient funding, major steps forward can be made in controlling infectious diseases. While three decades ago HIV infection was a virtual death sentence it has now turned into a chronic illness with an often good prognosis and near-normal life expectancy\(^8\) provided that antiretroviral treatment is available and adequately used.

These rapid improvements in HIV drug treatment have been achieved by the huge investments made by pharmaceutical companies. It has been estimated that the costs for development of effective and safe antiretrovirals to ultimately bring these products to the market amounts to 1 – 2 billion U.S. dollars\(^9\),\(^10\). With the market-driven mechanisms in place, both company management boards and shareholders ultimately demand return of investments made. Small and medium-sized companies and academia are important players in screening for potentially effective compounds. Due to the large financial investments that are required, big pharmaceutical companies ultimately dominate drug research. As a result, political will and collaboration between international not-for-profit organisations like UNICEF, MSF and WHO on the one hand, and the big pharmaceutical companies on the other hand, are required to attract large sums to be invested in drug development needed for TB-affected populations in poor-resourced settings.

An alternative approach would be a system with a more dominant role for governments and international bodies like the European Union (EU), to regulate and support drug research. Currently, EU and other sponsors like the Bill and Melinda Gates Foundation have systems in place to sponsor and support international consortia of academia together with small
and medium-sized companies\textsuperscript{39,40}. This would require a change in legislation and change in government funding in order to help universities and small innovative drug research companies to contribute more independently to drug development. This would provide the opportunity for promising and fundamental drug research, as typically conducted in universities, to upgrade to the next phases and thereby giving “financially less attractive” morbidities, such as TB, the attention they deserve. The rapid developments in antiretroviral treatment show that the pharmaceutical industry are a valuable partner, even though one might argue that humanitarian principles should dominate financial motives for drug development for those that cannot afford paying for the medical care they need.

Challenges in HIV research

The rapid improvements facilitated by the emergence of antiretroviral therapy are hopeful and the knowledge gained in terms of lobbying, funding and political interest can be supportive and may provide valuable lessons for the battle against TB. Despite the improvements made, the treatment of HIV still faces challenges. In addition to the social-economic there are psycho-social challenges including stigma experienced by people living with HIV. In low resourced, highly burdened regions stigma and insufficient knowledge about HIV/HIV transmission are important as well as huge logistical challenges. Specific (newer, less toxic and more expensive) antiretroviral drugs are not always available under the umbrella of national programs and supportive tools such as bioanalytical measurements and pharmacokinetic modelling likewise not readily available. Furthermore, due to the use of combined drug groups, the pill burden often is high and drug-drug interactions may occur. Due to the high pill burden and the stigma toward people living with HIV adherence to therapy also may be compromised.

In order to optimize HIV treatment we have developed and extended tools to investigate the PK of antiretrovirals, darunavir in particular, in daily clinical practice. Information about the PK of an antiretroviral might aid in the treatment as it can provide (indirect) information about the efficacy or toxicity and treatment adherence of drugs. We have described a bioanalytical method to measure concentrations of antiretrovirals in blood and we developed a pharmacokinetic model to interpret the measured concentrations. These tools have been used in our outpatient clinical to examine the darunavir blood levels and food intake in our patient and data from these tools has been used to perform a retrospective study. Although the developed tools could aid care providers, the techniques; knowledge and devices required for these tools are often not widely available in high endemic areas, as HIV transmission currently mainly occurs in resource limited settings. It is therefore of the utmost importance that the techniques and devices that make the investigation of the PK of drug possible are made more affordable and that additional tools are developed such as dried blood spot analysis and optimal sampling strategies to make TDM more cost efficient in the areas where this is most needed. The primary objective obviously is making adequate
antiretroviral therapy available in resource limited settings, before tools such as TDM can be used. Major improvements have already been made as in 2017 20.7 million people were using antiretroviral therapy.

**Future perspectives**

People living with HIV are often already burdened by the socio-economic and clinical aspects of HIV and, if sufficient resources are available, need to take many drugs daily. Even with adequate viral suppression some immune compromise persists and even with a relatively high CD4+ count, they still have an increased risk to contract TB. Specifically patients burdened with both TB and HIV were our target group in this thesis. This thesis provides data on both the PK of first-line TB drugs as on the antiretroviral darunavir. The systematic review investigating the effect of HIV infection on the PK of first-line TB drugs revealed current knowledge gaps. Data on treatment outcome in studies investigating the PK of first-line TB drugs in people co-infected with HIV-TB is needed. Data in this thesis can be used as a starting point for the design of a prospective study with both an HIV-positive- and HIV-negative TB group, including data on treatment outcome. The systematic review also revealed that both the quality and the data of available studies was highly heterogeneous.

In order to sufficiently grade papers specifically investigating PK a quality assessment tool is needed for pharmacokinetic studies. We have designed an initial quality assessment tool for pharmacokinetic studies, but this tool has to be further developed in the future and validated.

In order to free ourselves from the dogma of “one size fits all” we have to accept that each patient is unique and that standardized treatment will lead to suboptimal therapy in some cases and to toxicity in others. Personalizing the therapy could possibly be the next step in combating resistance and eventually, TB itself. Currently there is little to no in vivo data relating antibiotic targets to treatment outcome. Some studies have shown in murine and in vitro models that AUC/MIC is the antibacterial target for first-line TB drugs, but this has not been clearly confirmed in human studies. A well designed study relating PK/PD data of the several first-line TB drugs could shed light in terms of which antibacterial target (AUC/MIC, C$_{max}$/MIC or T/MIC) is most predictive for treatment outcome. Using these PK/PD data would give care givers more guidance in combating TB, rather than solely using weight-band dosing and omitting both patient- and mycobacteria-related factors. Other hopeful developments are the WHO (and other) TB and HIV programs that contribute to education, availability of drugs and to gaining scientific data. Closer collaboration is needed between the different TB and HIV programs as this could lead to better understanding of TB-HIV co-infection and resources could be spend more efficiently.

Another development which is currently already starting to take shape is the reduction of the pill burden in the treatment of HIV. For those who still experience treatment adherence
problems, long acting drugs which require a less frequent administration (once a week or even once a month) could provide a solution. The development of a vaccine against HIV would ultimately be ideal. In the meantime clinical tools such as TDM could be improved and made financially more attractive in order to optimize antiretroviral treatment. More research is needed in order to make currently expensive clinical tools such as TDM and optimal sampling strategies available for resource limited settings. Therefore innovative drug concentration measurements and, for TB, MIC determinations are required with limited financial investments. Further development of Dried Blood Spot analysis is needed, in order to facilitate simple utilization and transportation to a centralized laboratory possible. In addition, alternative methods have to be developed for quantifying drug concentrations in other, less invasive, body fluids. On-site drug determination in saliva may provide a solution but the applicability in daily practice has to be investigated.

In order to manage drug resistance, to optimize treatment in terms of efficacy and toxicity and ultimately to achieve the End TB strategy goals of 95% reduction in TB mortality in 2035, personalized treatment is essential. Accepting that personal treatment strategies are required for different patients could herald the beginning of the end of the era of HIV and (MDR and XDR)TB.
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