**Bachelor’s thesis**

TuberXpert

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**Authentication**

The undersigned, Melvyn Herzig, hereby certifies that he alone carried out this work and did not use any other source than those expressly mentioned.

Yverdon, the Friday, March 4, 2022

Melvyn Herzig

**Table of contents**

[1 Introduction 6](#_Toc97296588)

[1.1 What is therapeutic drug monitoring 6](#_Toc97296589)

[1.2 Actual situation in Tanzania 6](#_Toc97296590)

[1.3 Goal of this work 6](#_Toc97296591)

# Introduction

## What is therapeutic drug monitoring

Nowadays, many drugs or antibiotics are used to treat diseases such as tuberculosis and HIV. Usually, the doctors prescribe generic doses that are suitable for the general population. Unfortunately, everyone’s metabolism reacts differently which makes generic dosages often ineffective.

Some people will have insufficient circulating drug exposure caused by an underdose. Thus, the treatment will be ineffective, and the patient may become drug resistant. Conversely, an overdose may result in intoxication. This would force an interruption of the treatment in order not to worsen the patient's health.

To avoid such situations, therapeutic drug monitoring (TDM) has been developed. TDM is a precision medicine that prescribes a personalized dosage to each patient based on the monitoring of the evolution of the drug concentration in the blood.

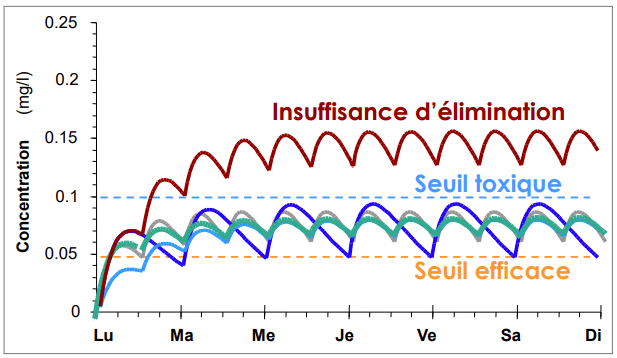


Figure 1 - Dosage Scheme (BUCLIN Thierry, 2022, Les Bases de la pharmacocinétique clinique [PDF document])

The purpose of TDM is to measure the concentration of the drug regularly and accurately in order to know its evolution. After examination, an expert in pharmacology can determine how to adjust the dosage to be above the threshold of inefficiency and below the threshold of toxicity.

## Actual situation in Tanzania

Tanzania has a high burden of Tuberculosis (TB). Over the last decade Tanzanian health authorities estimate an incidence of 120’000 – 150’000 patients per year for TB. The global community, through the END TB strategy, has declared its willingness to end TB by 2035, and a central component of the arsenal for this includes resorting to the correct use of anti-TB drugs, in particular the first-line agents: isoniazid, rifampicin, ethambutol, and pyrazinamide.

However, the problem is that only 60’000 – 75’000 patients are notified and receive a treatment. In addition, studies have reported that rifampicin dosages are insufficient most of the time. For example, investigations by Heysell et al. (2011) and Tostmann et al. (2013) in the Kilimanjaro region showed that one to two thirds of uncomplicated TB patients had maximum concentrations below the reference range of 8-24 mg/L, defined two hours after last dose intake.

Moreover, a significant proportion of individuals with TB are coinfected with HIV. It represents 25 to 40% of the monitored people. Administering antiretroviral drugs with first line antitubercular drugs lower furthermore the rifampicin concentration.

On top of that, TB patients have an increased risk to get affected by diabetes mellitus (DM). It represents 4-16% of the TB population. Unluckily DM may alter the pharmacokinetics (PK) of various drugs which include antitubercular. Mtabho et al. observed that DM predicted low levels of rifampicin in TB Tanzanian patients. Sadly, evidence have shown that individuals with TB and DM have a 5-fold risk of death compared to those without DM.

At this point, we easily understand that the risk of treatment failure or unfavorable outcome is real if the dosages are kept unsuitable.

## Goal of this work

The need to end tuberculosis is real and urgent in Tanzania. Unfortunately, TDM is a long and complicated process. In addition, the number of experienced pharmacologists is not sufficient to provide well established interpretation and recommendation everywhere their expertise is needed.

Currently, Professor Yann Thoma and his team have developed Tucuxi. It is a software intended for the practice of TDM. Already developed for several years, the software offers many features:

* Drug concentration predictions based on population and patient data (covariates) as well as on previous measurements.
* Suggestion of dosage adjustments to reach an optimal drug concentration state.
* Generation of printable reports.
* Integration with Electronics Health Record (EHR) systems.

Although it greatly simplifies the TDM process, Tucuxi is intended for experienced pharmacologists.

TuberXpert comes at the beginning of a large project between Switzerland and Tanzania led by Prof. Thoma Yann, Prof. Mpagama Stellah, and Prof. Mpagama Stellah. The aim is to develop a Clinical Decision Support System (CDSS) to fight tuberculosis. Thus, TuberXpert is a software layer that adds to the existing Tucuxi computing core. By receiving complete information from a patient, the system assesses the relevance of the data provided and then determines whether an adjustment of rifampicin dosage is necessary. All interpretations made by the program will then be provided to the user in the form of a simplified report compared to the original software. The main purpose of TuberXpert is to simplify the “Interpretation and recommendation” phase of TDM for non-experts

Figure 2 -TDM process (BUCLIN Thierry, 2022, Les Bases de la pharmacocinétique clinique [PDF document])

In other words, TuberXpert is a turnkey solution for rifampicin TDM. The software developed during this Bachelor's thesis is a first step. It will then be taken over by three PhD students in charge of the development and the concrete application of the project.

**Bibliography**

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