Diagnosis and treatment of common infectious diseases in severely ill sub-Saharan African patients
Bos, J.C.

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Chapter 1

General introduction
Sub-Saharan Africa and health

The challenges in health in sub-Saharan Africa (SSA) are many. Health systems deal with an enormous burden of disease and infectious diseases account for almost 50% of that burden. HIV infection and HIV related diseases, in particular tuberculosis, rank among the leading cause of death according to the WHO.\(^1\) The incidence of non-communicable diseases, of which type 2 diabetes mellitus and hypertension are well known examples, is high too.\(^2\) A large proportion of people is living below the poverty line while suffering from the effects of one or more (chronic) diseases. Admitting a febrile patient with an HIV/tuberculosis co-infection and chronic soil transmitted helminthiasis at the same time, is very common. Many enter medical care at a late stage and in a poor condition.

At the same time, SSA countries face enormous health care worker shortages.\(^3\) The majority of SSA countries is not able to meet the minimum threshold for skilled health care worker density of 230 per 100.000 as formulated by the WHO in 2006.\(^4\) It is generally believed that with a health care worker density below this minimum threshold, meeting any other health-related development goal becomes highly unlikely.\(^5\)

Mozambique, Beira and the Beira Central Hospital’s patients

Mozambique and Beira

Mozambique is a SSA country with 28 million inhabitants, located on the southeast coast of Africa, north of South Africa, facing the Indian Ocean. Maputo is Mozambique’s southern capital. It has adopted Asian, Arabic, and European influences, and is racially and religiously diverse. Mozambique is a former Portuguese colony that fought almost ten years for its independence. After gaining independence in 1975, it got caught up in a long and devastating civil war that only ended in 1992 with the signing of the Rome General Peace Accord by the civil war parties FRELIMO and RENAMO, a process that was supported by the Catholic community of Sant’Egidio. Since then, Mozambique has had a two party-, and somewhat later, a three party electoral system, and its economy has grown, despite the enormous challenges that poverty, climate extremes and epidemics continue to create.

Life expectancy at birth was 55 years in 2014, and it still has a very low rank on the United Nations Development Programme Human Development Index (HDI), a summary measure of average achievement in key dimensions of human development.\(^6\) Mozambique’s physician density was 65 per 100.000 population in
2014 and its nurses and midwifery density 94 per 100,000 population, which together still stays far below the minimum WHO threshold of 230 per 100,000.5,7

Beira, the second largest city, is situated some 1,200 kilometres north of Maputo on the Indian Ocean coast at the mouth of the Pungue river, and is the capital of the central Sofala province. Importantly, Beira is also the origin of the so called ‘Beira Transport Corridor’, an economic zone that includes the Beira port, as well as a railway line, a pipeline and a road, all linking Beira to Zimbabwe and Zambia.

**Hospital Central da Beira**

The Beira Central Hospital (*Hospital Central da Beira*; HCB), situated directly on the Indian Ocean, is a governmental referral hospital and the second largest in the country. The Catholic University of Mozambique (UCM), the creation of which resulted from the 1992 peace negotiations, opened its Faculty of Health Sciences in 2000. For the clinical training phase, FCS-UCM collaborates with the Mozambican Ministry of Health, and all UCM medical and nursing students pass through the HCB for their clinical internships, while being supervised by HCB and UCM physicians. Since 2006, the Academic Medical Centre in Amsterdam has been collaborating with UCM for medical capacity building purposes. We supported daily clinical internal medicine and infectious diseases teaching for senior medical students on the internal medicine wards of the HCB for nearly ten years through the long-term secondment of AMC and Vrije Universiteit Medical Centre (VUmc) internists, and were involved in the expansion of the national training capacity for internists. We also collaborated with UCM for the creation of the UCM Research Centre for Infectious Diseases (CIDI) that has been closely involved in a majority of studies presented in this thesis.

**Patients**

Even though a growing number of HIV infected patients is receiving antiretroviral treatment, a large proportion still is not. On top of that, the number of patients for whom antiretroviral treatment is no longer effective is increasing. In countries where the HIV prevalence as well as the absolute number of HIV infected individuals is high, the composition of hospital patient populations painfully reflects this situation: up to 75% of patients on a medicine ward may be infected with HIV and in this group, a growing proportion is admitted while already on antiretroviral treatment. Patients are generally young, underweight and bedridden. Many of them have had to travel far to get to the hospital and a substantial part of patients only speaks one of the many local languages.
Although a confirmed (microbiological) diagnosis is seldom made, roughly 50% of HIV infected patients may have TB, and up to 34% of HIV infected patients may be admitted with a bacterial bloodstream infection. The mortality rate may be as high as 30%. In a hospital environment like this, many patients have fever and pain, many have to be put through a TB diagnostic process and many are being treated empirically with antibiotics.

**Pathogens featuring in this thesis**

**Human Immunodeficiency Virus (HIV)**

‘First ask yourself: is this patient infected with HIV’. This is what we asked medical students from the Faculty of Health Sciences of the Catholic University of Mozambique (Universidade Católica de Moçambique: UCM) in Beira to do, when starting to think about what could cause a patient of roughly 35 years old to end up on the internal medicine ward in Beira. And so, not for nothing, first up is HIV.

HIV infection changes everything. The virus miraculously attacks key components of human immunologic defence: the CD4 receptor-positive T cells as well other crucial cellular components, such as macrophages. HIV puts the immune system in overdrive, with systemic inflammation and a detrimental effect on the number of T cells and the immune system’s capacity to fight disease. Patients may slowly start falling ill from diseases that they used to have a defence mechanism for: opportunistic infections. Tuberculosis is the most prominent member of this group of diseases. A rule of thumb is that the longer the patient is infected with HIV while not being on antiretroviral treatment, the more severe the decline in immunity, and the bigger the immunologic ‘scar’, the effects of which do not completely vanish during therapy, even when antiretroviral treatment has practically restored the number of T cells.

In SSA, HIV’s horizontal transmission largely occurs through sexual intercourse, whilst vertical, mother-to-child transmission may happen during pregnancy, labour and breast-feeding. Clearly, HIV infection is more likely to spread when large groups of people are unaware of the risk of infection or when they are not in a position to protect themselves sufficiently against infection. Infected individuals seeking medical assistance at a late stage may increase the spread further. SSA countries tend to have large HIV epidemics, as all three of these conditions are likely to be met. Currently, about two thirds of the global number of individuals infected with HIV live in sub-Saharan Africa, even though this part of the world is home to only 10% of the world’s population. In 2015, approximately 19 million people were living with HIV. Even though the incidence of HIV infection declined with 14% from 2010
to 2015, still an estimated 960,000 SSA individuals acquired HIV in 2015, representing roughly 46% of the global total of new infections, and 470,000 people died from AIDS-related causes.\textsuperscript{13,14} The HIV incidence is the highest in the age group of 25-45 year olds, with women being more often affected than men, but with men more likely to die once infected.

This may appear to be a dire situation, but tremendous successes have also been booked in the treatment and prevention of HIV infection over the last two decades, even though mortality rates during the first few months of treatment are very high, reflecting the relatively high proportion of patients presenting at a late stage of disease.\textsuperscript{15,16} A stunning 50-58% of all people living with HIV in SSA have accessed combination antiretroviral treatment (cART) and the response of SSA patients has shown to be similar to the one seen in HIV infected patients in Western Europe and North America.\textsuperscript{14,15} A growing body of evidence now suggests that not only individual patients benefit from early initiation of antiretroviral treatment, but the entire population as well, as with less people with a detectable viral load, less new infections occur.\textsuperscript{17} Treatment algorithms have since quickly moved from selecting patients for treatment on the basis of severity of disease, to treating all adults living with HIV, regardless of WHO clinical stage or CD4 cell count.\textsuperscript{18,19} Botswana, South Africa and Uganda have already started to implement this ‘treatment as prevention’ (TasP) strategy, and hopefully, others will follow in the nearby future.

Huge challenges do however remain. Large groups of harder to reach people, such as people living in more remote areas, prisoners and men who have sex with men tend to seek medical assistance at a late stage, or do not enter the health system at all. Stigma around HIV is significant and still creates an important barrier for sustained linkage to health care, even for people who are aware of their HIV status.\textsuperscript{20} Once on treatment, motivating patients to stay on lifelong daily treatment is difficult wherever you are in the world, and even more so when a person’s physical condition is improving. In SSA, there are many barriers to adherence to cART and retention in HIV care, but the lack of regular supportive attention from knowledgeable health care workers is certainly one of them. Non-adherence to cART may lead to incomplete viral suppression and may give rise to HIV resistance to antiretroviral drugs.\textsuperscript{21} So, even when countries will have adopted the TasP strategy, much of the success will continue to depend on the sustained comprehensive effort of local health care workers. As mentioned above, many SSA countries simply do not yet have the health care capacity to provide such care.
Tuberculosis (TB), ‘Captain Consumption with all his Men of Death’

It is a small step from HIV infection to tuberculosis. TB has had a tremendous impact on human health throughout history, but the devastating effect of HIV/TB co-infection on people’s lives is unprecedented. In 2014, Africa had 281 new TB cases per 100,000 population, which is more than twice the global average, and at least 50% of the new cases were linked to HIV infection. TB had traditionally been managed within defined disease control programs, but when an increasing number of people became relatively defenceless against TB as a result of HIV infection, TB rapidly changed from a more or less manageable, predominantly pulmonary illness into a seemingly omni-present pulmonary, as well as extra-pulmonary disease. This HIV-related ‘new tuberculosis’ was easier to overlook, linked to a deadly disease, and harder to diagnose. Huge efforts have since been made to improve TB case finding, to better time the initiation of antiretroviral treatment, to find new anti-tuberculosis drugs and especially to create and implement new diagnostic techniques and strategies that would provide a quick and unambiguous answer to the question whether or not a patient is suffering from HIV related tuberculosis. However, the potential increased yield of testing algorithms in daily practice still largely depends on a concerted, bedside effort of health care workers. This health care worker-link in the diagnostic chain is often weak, and mending it supposedly needs far more attention than it is currently getting.

Pneumococcal disease

Another hard to ignore pathogen in the SSA context is Streptococcus pneumoniae. Young children are carriers and get infected a lot. Young and middle-aged adults are only occasional carriers, but older age and compromised immune status predispose to renewed carrier state and infection. Pneumococcal infection is common worldwide, especially among children and the elderly, but in SSA, the incidence rate of infection has made a huge leap upwards during the HIV era. The most frequent presentation of pneumococcal infection is (community acquired) pneumonia, but invasive pneumococcal infections (IPD), where S. pneumoniae can be found in bodily compartments normally sterile, are common too. The risk of IPD is about 150-300 times higher in adults with an untreated HIV infection compared to non-HIV infected individuals, and although the incidence rate has come down substantially after the introduction of antiretroviral treatment and prophylactic treatment with co-trimoxazole, people with HIV infection still remain at increased risk compared to HIV uninfected individuals. IPD is associated with a high morbidity and mortality. Even though the recently widely implemented childhood pneumococcal conjugate vaccination (PCV) programs will have a significantly impact on the adult infection rate, it is highly likely that pneumococcal disease will guarantee a continued influx of patients in hospitals and health centres. At the same
time, *S. pneumoniae* has become harder to treat as a result of the worldwide increase in resistance to antibiotics. In SSA, co-trimoxazole resistance is already very common, but resistance to penicillin is present too, although there is a severe lack of data.30,31 The latter is worrying, as benzylpenicillin is a cheap and safe drug and one of the most frequently used antibiotics in SSA hospitals for the treatment of presumptive pneumococcal disease. The substitution ‘presumptive’ is important in this respect, as SSA microbiological surveillance data are scarce and a microbiologically confirmed diagnosis for individual patients an exception.

**Severe illness and pharmacokinetics of antibiotics**

Severe illness can give rise to pathophysiological changes that are able to influence pharmacokinetics of antibiotics. Studies investigating the pharmacokinetics of antibiotics in intensive care patient populations with sepsis have shown that disease-induced alterations in volume of distribution, protein binding and drug clearance may change the total drug concentration and make it hard to predict the unbound, active drug concentration.32,33 All of this may lead to underexposure, while contributing to the emergence of antimicrobial resistance. Sepsis and pre-existing chronic diseases causing organ dysfunction are estimated to be common in SSA adult hospital populations, but little is known about how this affects this population’s pharmacokinetics of commonly used antibiotics.

**Aims of this thesis**

Daily presence on a hospital medicine ward floor in Beira inspired the accomplishment of the studies presented in this thesis. Even though the HCB internal medicine ward is just one internal medicine ward out of many in SSA, it is very likely that the spectrum of problems encountered is representative of what happens in other (low-income) SSA countries with colliding HIV and TB epidemics and health care workforce restraints.6,7,34

The aim of this thesis is to describe how hospital handling of a selection of infectious diseases impacts health of a large hospital population consisting of severely ill adult patients with a high prevalence of HIV infection in a Mozambican referral hospital. The second aim is to provide information that can be used as a starting point for the improvement of care of this particular group of severely ill patients. Our hypothesis was that SSA hospitals face intertwined challenges that are likely to put individual patient care under pressure, even when existing guidelines have been nationally adopted: we supposed that the combination of weak health systems and a high continuous patient load, largely consisting of severely ill HIV infected individuals,
would create circumstances whereby patients with common infectious diseases would remain at high risk for excess morbidity and mortality.

The following six chapters (chapters 2-7) try to shed some light on this topic:

**Chapter 2** With this retrospective, cross-sectional study of medical records, we describe the TB diagnostic process of adult hospitalized patients with presumptive pulmonary and extra-pulmonary TB. We assessed how the results affected a patient’s treatment, and whether the process matched with the 2007 WHO recommendations for the diagnosis of smear-negative pulmonary TB and extra-pulmonary TB.

**Chapter 3** This chapter describes our effort to provide local SSA antimicrobial resistance data concerning the leading causative agent of community-acquired pneumonia, *Streptococcus pneumoniae*. In a pilot study, we screened adult patients presenting at the hospital with respiratory complaints for pneumococcal pneumonia, on the basis of a combination of symptoms, chest radiography, a urine pneumococcal antigen test and sputum culture. Susceptibility to penicillin, co-trimoxazole and erythromycin of isolated *S. pneumoniae* strains was subsequently tested using the disc diffusion method, as well as e-tests for the measurement of MICs. We hypothesized that penicillin non-susceptible *S. pneumoniae* strains circulated among strains causing pneumococcal pneumonia.

**Chapter 4** Data from intensive care unit patients show that severely ill and septic patients are at increased risk for changes in the pharmacokinetics of antibiotic drugs, capable of negatively impacting the attainment of desired antibiotic plasma levels, and leading to underexposure, especially in the case of β-lactams. As severe infections and/or sepsis is common among SSA hospitalized non-ICU patients, many of whom may suffer from chronic diseases at the same time, we hypothesized that hospitalized non-ICU patients treated with antibiotics are at risk for significant changes in the pharmacokinetics of antibiotics as well, including systemic underexposure. In this systematic review, we tried to summarize and evaluate existing data about pharmacokinetics of antibiotics in SSA patients in preparation for our population pharmacokinetic studies on commonly used antibiotics in a SSA hospital setting.

**Chapter 5** This chapter contains the first data from our population pharmacokinetic study of commonly used antibiotics, in which we looked at sources and consequences of variability of pharmacokinetics of ceftriaxone, a broad spectrum β-lactam antibiotic frequently used for the empiric treatment of severe
infections and sepsis. We created a population pharmacokinetic model based on measured total and unbound plasma concentrations from 88 severely ill adult non-ICU patients, as well as on documented demographic and laboratory patient variables. Using this model, we simulated the probability of various dosing regimens of reaching the (pharmacodynamic) treatment target, for different patient and dosing scenarios.

**Chapter 6** In this chapter, we present population pharmacokinetic data of another antibiotic, benzylpenicillin. Benzylpenicillin is an important β-lactam antibiotic in the SSA setting, and it is mainly used for the treatment of pneumococcal disease. This time we modeled the pharmacokinetics using total benzylpenicillin plasma concentrations from 112 patients, while making projections of the probability of target attainment with the help of a set of unbound plasma concentrations.

**Chapter 7** In a SSA hospital medicine ward, where the large majority is young, immunocompromised and severely ill, a high proportion of patients is likely to experience pain and fever, and a high proportion of patients may therefore have an oral paracetamol prescription. We assessed the occurrence of therapeutic, sub-therapeutic and toxic paracetamol concentrations in 76 patients, supposing that too low as well as too high concentrations were not unlikely to occur given the high prevalence of renal and hepatic dysfunction in this population.

**Chapter 8** This chapter summarizes the results of the different studies and we end with concluding remarks, including directions for future research.
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