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Undoubtedly, considerable advancements have been made in the last decades in terms of efficacy and availability of treatment options for HIV. Cocktails containing three or more antiretroviral drugs are now available, as well as fixed-dose combinations which may significantly improve patient’s quality of life. However, there are other issues that are still unresolved when dealing with paediatric HIV. Despite the abovementioned advancements, an estimated 2.5 million children worldwide are infected with HIV; 90% of them live in sub-Saharan Africa (SSA), where annually 330,000 new infections occur (1). HIV remains a disease widely spread in limited-resource areas where the access to the medication is inadequate and monitoring of antiretroviral therapy is challenging if not impossible in clinical practice. In addition, the pill burden for patients and the potential for drug-drug interactions that can compromise the outcome of the treatment continue to be high.

The chronicity of the treatment implies the administration of several drugs throughout childhood. Furthermore, dose adjustment is often necessary to ensure that appropriate exposure is achieved and maintained during the course of therapy. Among other factors, physiological growth and development in the paediatric patients can significantly affect ADME processes, in particular drug absorption and elimination. Immature renal function, altered hepatic enzyme activity and differences in drug absorption lead to variations in the systemic exposure of antiretroviral drugs among children (2).

From a therapeutic perspective, growing evidence also reveals that treatment adherence in HIV-infected children is complex and current levels are often suboptimal. Poor adherence to therapy may compromise the outcome of the treatment, even when the administered dose takes into account demographic characteristics and growth-related changes. It can lead to the development of drug resistance towards most medications, which ultimately results in viral failure. Adherence is influenced by many factors, which may be categorised as characteristics of the child, the caregiver(s) and family, the formulation and the regimen (3). Paediatric patients usually rely on a caregiver to receive their medication, which may be a challenge when frequent dosing is required. In this context, a reduction in dosing frequency has been considered critical for the optimisation of antiretroviral therapy. Yet, one should bear in mind that simplified
dosing regimens should not increase the risk of under or over exposure. Such an evaluation is complicated by the fact that efficacy and safety in patients must be assessed for combination therapies, in which the contribution of each single drug is often not well defined.

Based on the aforementioned, it is hard to understand why the choice of the dose and dosing regimens for the treatment of paediatric HIV continues to be driven by empirical decisions. An integrated approach is required in which the evaluation of efficacy and safety is driven not only by the evidence arising from paediatric clinical trials, but also by inferences from historical data and quantitative pharmacology concepts.

The aim of this thesis is therefore to explore opportunities to support evidence generation and extrapolation across populations, with special focus on the selection of the dose and dosing regimens in HIV-infected children. Here we propose the use of a model-based approach to identify and quantify the potential causes of variation in drug pharmacokinetics in children, taking into account the interaction between patient adherence and the pharmacokinetic-pharmacodynamic properties of antiretroviral drugs. Furthermore, given the known challenges in running clinical trials in children, we will also show the utility of clinical trial simulations and role of simulation scenarios to assess the implications of changes in pharmacokinetics and pharmacodynamics associated with different doses, dosing regimens and variable adherence patterns, which cannot be controlled or evaluated in an ethically acceptable manner in clinical practice.

Three central questions will form the basis for the work to be presented in the subsequent chapters of this thesis:

1. How to select the appropriate dose(s) for children given that changes in exposure due to developmental growth are often nonlinearly correlated with body size and evidence from clinical trials is limited to small, imbalanced cohorts?
2. Can changes in dosing regimen be assessed by a model-based approach taking into account the concepts of pharmacokinetic and pharmacokinetic-pharmacodynamic bridging?
3. Can pharmacokinetic-pharmacodynamic relationships be used to evaluate the impact of variable patterns of adherence to therapy on treatment outcome in a quantitative manner, given that this cannot be formally tested in clinical practice due to ethical constraints?

It is our endeavour to show how the use of a model-based approach offers an opportunity to assess the impact of pharmacokinetic differences on pharmacodynamics and consequently enables prediction of treatment outcome (i.e., viral failure) in children before exposing them to a clinical protocol. Ultimately, we will demonstrate that the assumption of similar exposure-response relationships between adult and children enables one not only to account for differences in physiological processes due to developmental growth when selecting the dose, but also provides the basis for evaluating the impact of changes in dosing regimen.

In Chapter 1, we provide an overview about the current status of antiretroviral (ART) therapy in children. In fact, we examine the three main elements which undeniably contribute to the outcome of the treatment: the disease, the drug and the patient. First, we explore the concept of drug resistance, the need for drug combination therapy in HIV and the progress achieved in terms of novel interventions, which prevented the development of treatment resistance in the last decades. In addition we introduce the use of mathematical modelling as a tool for characterising infection and viral dynamics in humans. In a subsequent section, we focus on the relevance of statistical population models to characterise the pharmacokinetics and the pharmacodynamics of antiretroviral drugs in children and to quantify the effect of developmental factors on drug exposure and efficacy. Of particular interest is the possibility to apply model-based methodologies to describe and discriminate different sources of variability in pharmacokinetic and pharmacodynamic parameters even when only sparse samples are available. Lastly, we look at the role of the patient in antiretroviral therapy. Different methods are presented, which enable the evaluation of adherence to treatment and how this information can be used to explore variability in treatment outcome. Lastly, we introduce the concept of clinical trial simulations as a tool that allows scrutiny of a variety of factors associated with the drug, the disease, the patient population and the clinical study design prior to enrolment of actual patients into a clinical protocol. Of interest is the possibility to investigate the implications of dose adjustment, titration algorithms and changes in dosing regimen under different scenarios taking treatment adherence into account, rather than considering as a random effect.

Based on the review of the requirements for evidence synthesis in paediatric research, specific issues have been identified in the accepted strategy for the evaluation of the dose and dosing regimens in HIV-infected children which will underpin the scope and intent of the investigations described here in Chapter 2 and detailed in the subsequent sections of this thesis. From a methodological perspective we highlight the need for accurate parameter estimation, the identification of differences in parameter distributions and formal evaluation of the performance of pharmacokinetic-pharmacodynamic models when scaling of the dose and dosing regimens across populations. These principles are then used to support the rationale for extrapolating efficacy across dosing regimens, an approach which is currently not possible according to existing regulatory guidelines. Our work is then extended to include uncertainty and patient-related factors in pharmacokinetic-pharmacodynamic bridging, providing a framework for inferential analysis and evidence synthesis in paediatric drug development.
2.2. Sample size, covariate distribution and predictive performance of pharmacokinetic models

Pharmacokinetic and pharmacokinetic-pharmacodynamic models must be predictive to be used for the purposes of bridging and extrapolation (4). Therefore, uncertainty and bias in parameter estimates need to be assessed accordingly to ensure potential limitations minimised. The predictive performance of a model implies its ability to accurately describe the effects of developmental growth, physiological function and disease across the populations of interest. In this context, the use of small sample sizes has been assumed to be acceptable for data extrapolation, which entails that differences in pharmacokinetics and/or pharmacodynamics are primarily driven by the magnitude of parameter estimates, rather than by distinct structural components (fixed effects) determining drug disposition across populations. This assumption also imposes that a common relationship between parameter and covariates must hold across the various age groups and most likely that common biological substrates are involved from birth throughout to adolescence. Clearly, these considerations may not always be plausible. In fact, available data reveal that pharmacokinetic variability may be caused by different factors at different stages of life (4).

To overcome the potential for bias in the inferences from a pharmacokinetic or pharmacokinetic-pharmacodynamic model, attention must be given to the identification of the mechanisms (and influential factors) underlying differences across populations. Most importantly, one needs to consider which model parameterisation will support accurate dose selection when using models for extrapolation purposes.

It has been previously shown that small samples may increase the probability to introduce bias in the selection of the correct covariate during a stepwise covariate selection (5), which in turns leads to erroneous dosing recommendations. Therefore, in Chapter 3, we investigate the impact of sample size on parameter uncertainty and model parameterisation, emphasising the importance of identifying the causes of variability and quantifying their relative contribution (i.e., covariate effect) across populations prior to any inferential analysis. From a methodological perspective, we scrutinise the use of small populations when performing covariate analyses, a common practice which is often justified by ethical and practical limitations in paediatric research. The impact of imbalanced samples across a wide distribution of occurring values and co-linearity between covariates (e.g., age, body weight and height) are investigated.

We perform a meta-analysis in which pharmacokinetic data from three small clinical trials in children aged between 3 months and 12 year old receiving lamivudine are pooled, with a total of 77 children available after combining the three studies. A population pharmacokinetic model is developed taking into account the imbalanced data distribution of reduced sample size on covariate selection. To illustrate the clinical implications of bias in covariate selection, a separate analysis is performed using a subset of the population and the results are subsequently compared with the findings of the meta-analysis. Here we also take the opportunity to demonstrate the importance of comprehensive validation procedures to assess the predictive performance of a model. Such procedures are often omitted in the reporting of population pharmacokinetic and/or pharmacodynamic models (6). We show that a shift in paradigm is needed to allow the use of nonlinear mixed effects modelling not only as a statistical data analysis method, but rather as an inferential tool. In addition, we highlight that the availability of parameter estimates does not automatically translate into dosing regimen recommendations. This represents one of the main shortcomings of model-based analysis of paediatric data. Without comprehensive use of simulations in which variables of interest rather than model parameters are taken into account, one cannot select the correct dose for children and concomitantly assess whether a proposed dosing regimen meets extrapolation or bridging requirements. Given that the main application of models should be the prediction of drug exposure and/or efficacy across different populations, we apply a range of diagnostic tools to explore model performance, including visual predictive check, posterior predictive check, bootstrap, mirror plots and normalised prediction distribution error (NPDE).

Despite the availability of population pharmacokinetic models for abacavir in the published literature, in Chapter 4 we apply the same meta-analytical approach to this nucleoside reverse transcriptase inhibitor (NRTI) commonly used in combination with lamivudine. In contrast to previous studies, which were based on either a small number of patients or included only a limited, imbalanced sample of the patient population, our analysis shows that accurate characterisation of covariate factors is critical for further assessment of the individual dosing requirements across different age groups. In this context, the use of meta-analysis is proposed as a requirement to ensure that insight is gained into the processes determining maturation and metabolic capacity. Our analysis also shows the potential implication of co-linearity and confounders during covariate model building, which may affect the underlying (true) parameter-covariate correlations. These points are pre-requisites for subsequent use of the model as an inferential tool for predicting drug exposure and/or effect both in individual patients and extrapolation across groups or populations.

Whilst covariate model building and validation procedures are important scientific steps in the implementation of a model-based approach in paediatric drug research, attention should also be paid to the clinical relevance. One should note that the possibility of applying population pharmacokinetic models to predict drug exposure across an age range different from the population used during model building is very appealing, but challenging (7). In fact, evidence from a previous investigation suggests that pharmacokinetic models developed from subsets of the overall population may not be predictive beyond the range of covariates available during model building (8). Given the meta-analytical nature of our approach, in Chapter 5 we investigate the requirements for the use of simulations in the extrapolation of data across populations. Here we assess the feasibility of extrapolating the variable(s) of interest in a new population...
beyond the covariate range explored during model building and the role of covariate-parameter correlations in this process. Different pharmacokinetic models for a hypothetical drug will be used in which the influential demographic factors are linearly or exponentially correlated with clearance. In addition, we explore how the presence of multiple covariate factors affects model parameter estimation and consequently causes bias and confounding with regard to the contribution of each individual. Each model will be used to predict drug exposure in a virtual population of children. Subsequently, two subgroups of children will be identified and the data from the two subgroups will be used to fit a pharmacokinetic model, which in turn will be used to predict drug exposure in the other population. The accuracy and precision of model predictions will be considered as diagnostics of the predictive performance of the model. It will become clear to the readership of this thesis, that the use of simulation tools is crucial to explore the predictive performance of models when investigating the possibility of extrapolating beyond the covariate range explored during model building. This requirement needs to be considered for subsequent application of the models for bridging and extrapolation purposes.

Another methodological issue to be investigated in this chapter is the so-called “centring” on the median or the mean value of the covariate in the population when expressing the covariate-parameter relationship in a model. Thus far, it has been unclear whether the median of the covariate must be kept when the model is used for simulation purposes in a new population or must be adjusted to reflect the covariate distribution in the new population. Again, simulation tools will help us quantifying the accuracy and precision of model predictions when extrapolating across populations.

From a statistical perspective, the modelling issues described here also illustrate the limitations of maximum likelihood methods. Model parameter (fixed and random effects) and covariate selection are determined by diagnostic tools (e.g., goodness-of-fit) which assess model performance relative to the available data, making models primarily descriptive, rather than predictive.

### 2.3. SIMPLIFIED DOSING REGIMENS IN CHILDREN

In the previous section of this thesis special attention is given to the use of model-based methodologies as a tool for the selection of the appropriate dose(s) for children given that evidence from clinical trials is limited and often derived from small, imbalanced cohorts. Clearly, one needs to account for the effect of developmental growth on pharmacokinetics if the right dose is to be recommended using bridging and extrapolation methods. This also implies accurate identification of the sources of variability and assumptions about the relevance of pharmacokinetic-pharmacodynamic relationships as a proxy for efficacy and safety.

In this context, a second important application of modelling and simulation is the evaluation of changes in dosing regimen. Together with the selection of the optimal dose, dosing frequency is another challenging aspect in antiretroviral therapy. Reduced dosing frequency, such as once daily administration, may be very appealing for patients and may increase adherence to therapy, as shown previously in various studies (9). Many antiretroviral drugs have been approved in adults for their use as oncedaily dosing. However, fewer options are available in children. In a paediatric population, where adherence can be compromised because of the patients’ young age, poor palatability of the medications, and dependence on caregivers, a oncedaily regimen is preferred (10). In this section, we will evaluate the feasibility of oncedaily dosing for lamivudine and abacavir, which are currently approved in adults, but are still recommended according to a twicedaily dosing regimen in children. Despite the favourable pharmacokinetic properties of these drugs and the availability of clinical trials which show comparable pharmacokinetics between once and twice daily dosing, an extensive evaluation in a large paediatric population is required. In Chapters 6 and 7 the pharmacokinetic models previously developed and validated for lamivudine and abacavir will be used to assess whether the exposure levels achieved after once daily dosing in a hypothetical population of 180 HIV-infected children is comparable to historical values in children and adults. Here it is also assumed that similar efficacy can be inferred based on evidence of comparable exposures between dosing regimens.

In contrast to the typical bridging studies in which pharmacokinetic data is used to simply generate evidence of comparable drug exposure (figure 1), changes in dosing regimen require an additional assumption, i.e., that the underlying pharmacokinetic-pharmacodynamic relationships are dose and concentration-independent. Unfortunately, little has been done in this area to demonstrate that such a requirement is biologically plausible in most diseases where pharmacokinetic processes do not represent the rate limiting step for the onset and maintenance of response. According to the ICH guidelines, in these circumstances studies aimed at the evaluation of the pharmacological effects would usually be expected and the dose recommendations in children may be defined based on the biomarker response if established biomarkers are available, which can then be correlated with efficacy. This means that the use of pharmacokinetic-pharmacodynamic bridging in paediatric trials implies that even when pharmacodynamics cannot be used as a direct proxy for efficacy, it should suffice to demonstrate that the changes in viral load are correlated with systemic exposure.
Figure 1 Paediatric study decision tree (adapted from FDA's Guidance to industry: exposure-response relationships - study design, data analysis, and regulatory applications; 1993). First, the disease and its time course or progression must be similar in adults and children. Second, the pharmacokinetic-pharmacodynamic relationships need to be comparable across the two populations. The third requirement refers to the use of efficacy endpoints in trial protocols which can be compared across population or for which a correlation has been demonstrated. If these three prerequisites are met, PK and safety studies are sufficient to infer efficacy. By contrast, evidence of efficacy and safety must be generated in the paediatric population when one or more requirements cannot be satisfied. PK: pharmacokinetic; PD: pharmacodynamic.

From a clinical perspective, our approach offers the opportunity for applying pharmacokinetic-pharmacodynamic relationships as the basis for the dose rationale. The availability of such data also offers the opportunity to explore hypothetical scenarios in large populations without the need to expose the patients to the actual protocol, thereby characterising in a quantitative manner the impact of drug-, disease- and patient-specific factors.

### 2.4. FORGIVENESS TO POOR ADHERENCE

In the previous sections of this thesis we have dealt with general issues regarding the predictive value of population models for bridging and extrapolation purposes and consequently for paediatric dose selection. We make clear that whilst the changes in pharmacokinetics due to developmental growth may be easily characterised as long as covariate factors are included in a balanced manner, the use of pharmacokinetic-pharmacodynamic bridging based on inferences about comparable efficacy and safety imposes an additional assumption, i.e., that fluctuation in exposure levels are truly random in the population and that pharmacokinetic-pharmacodynamic relationships are time and concentration-independent. This assumption may be confounded by variable adherence patterns. Yet, one needs to keep in mind that perfect adherence to antiretroviral therapy is very difficult to achieve, especially in children (11). In fact, numerous studies have shown that non-adherence to antiretroviral therapy is one of the main causes of viral failure (12). In addition, it has been demonstrated that imperfect adherence can lead to sub-therapeutic drug levels, which may boost the development of drug resistance to one or several drugs in the treatment.

Here we propose a model-based approach to evaluate forgiveness of drug to treatment interruptions and deviations from the prescribed regimen, which cannot be assessed in a randomised controlled experimental protocol due to obvious ethical and clinical reasons. From a methodological standpoint, we show for the first time how clinical trial simulations can be used as a framework to evaluate complex adherence patterns and explore in a strictly quantitative manner its implications for efficacy and safety. Different mathematical and statistical models are combined together to describe the interaction between drug properties, disease characteristics and patient behaviour. Most importantly, we envisage the use of such a framework for virtual, rather than real populations.

The main objective of this section is therefore to assess adherence as a covariate effect on drug exposure using a range of scenarios. The forgiveness of a drug is the ability to achieve and maintain viral suppression despite sub-optimal adherence to the prescribed dosing regimen. This may depend on many factors, such as drug, viral and host properties. In Chapter 8, we investigate which properties of an antiretroviral drug might be related with its degree of forgiveness using a putative population of HIV-infected children (n=100). Three paradigm drugs belonging to different antiretroviral classes currently approved in children will be investigated, including a variety of patterns of non-adherence, which corresponds to the most common deviation(s) observed in protocol execution. Despite the somewhat complex framework, which involves pharmacokinetic, pharmacodynamic and disease models, the impact of poor adherence will be limited to the evaluation of the effects on viral load after monotherapy. In Chapter 9, the concept will be subsequently expanded to allow characterisation of the effects of poor adherence to a NNRTI-based regimen (efavirenz, lamivudine, abacavir). The probability to experience viral failure will be assessed in each scenario of non-adherence and a correlation between adherence and probability for the virus to mutate and become drug resistant will be included in the clinical trial simulation framework. In this chapter, we will also explore the feasibility to use pharmacokinetic-pharmacodynamic relationships as “proxy” for efficacy in the investigation of forgiveness of non-adherence. It is envisaged that evidence of comparable pharmacokinetic...
ic-pharmacodynamic relationships could be treated in a similar manner to pharmacokinetics in bioequivalence studies, i.e., a “proxy” for efficacy and safety.

The predictive value of pharmacokinetic-pharmacodynamic relationships as a proxy for efficacy will be evaluated for a range of adherence patterns. A clinical trial simulation will be performed to simulate treatment outcome in a virtual population (n=30) of children. Of interest is the relevance of changes in dosing regimen to pharmacokinetics and viral load. Based on this concept, in Chapter 10 the forgiveness of non-adherence to a simplified dosing regimen (efavirenz, lamivudine and abacavir, all administered once daily) is compared with the forgiveness of non-adherence of the currently approved dosing regimen.

2.5. CONCLUSIONS AND PERSPECTIVES

A summary of the results and conclusions drawn from the various chapters is provided in Chapter 11. Here we show that three main topics regarding the development of antiretroviral paediatric therapy are intertwined, namely the dose, the dosing regimen and patient adherence to treatment. As such, they all contribute to success or failure of treatment. Despite the challenges in characterising such a complex interaction, throughout the various chapters, we highlight the relevance of evidence synthesis in paediatric drug development, as opposed to evidence generation as the basis for treatment optimisation in children. Pharmacokinetic-pharmacodynamic relationships can be used in conjunction with modelling and simulation to make inferences about efficacy and safety, overcoming many if not most of the ethical and technical constraints associated with clinical studies in children.

We also attempt to provide practical recommendations regarding the evaluation of models for the purposes of bridging and extrapolation of pharmacokinetic and pharmacodynamic data across populations. As highlighted in the first section of the thesis the challenge is to identify the factors that accurately describe the changes associated with developmental growth. Once the predictive performance of a model has been evaluated, its application in subsequent simulation scenarios must be considered carefully. The availability of a framework for clinical trial simulations offers not only the possibility to investigate the benefits and risks of a simplified dosing regimen, it also provides the basis for evaluating the role of patient behaviour. In this context we highlight that the importance of our investigation mainly relies on the use of an in silico approach to evaluate critical scenarios which could not be investigated in real-life due to obvious ethical issues. The possibility to derive quantitative measures of forgiveness may become critical for the development of novel antiretroviral compounds. Special attention is also given to the novelty of an in silico methodology for the exploration of non-adherence to therapy and to its potential applications to other chronic diseases.

References
