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SECTION V
Conclusions and perspectives
The development of antiretroviral therapy has been one of the greatest accomplishments of basic and translational research. In the 30 years since the discovery of the HIV virus, 31 medicines have been approved to treat HIV infection and evidence-based guidelines have been developed for their optimal use (1). Initially, in the early 1990s, drugs were administered to HIV-infected patients as monotherapy. Nucleoside monotherapy in previously untreated patients reduced plasma HIV RNA levels by 0.5 to 0.7 log10 copies/mL of plasma. These effects slowly dissipated over months even in the absence of drug resistance, thereby resulting in progressive immunologic decline (2). In the following years it was found that the combination of two antiretroviral nucleosides with relatively modest activities was beneficial in terms of the magnitude and durability of viral suppression. Several nucleoside combinations have resulted in reductions of 1 to 1.5 log10 copies/mL HIV RNA levels in plasma. Even more beneficial were the protease inhibitors (ritonavir, indinavir, and nelfinavir) that produce reductions of HIV RNA levels in the plasma of some patients by as much as 3 log10 copies/mL, with corresponding increases in CD4 levels of 300 to 500 cells/mm^3. These findings have contributed to further efforts in establishing the value of therapeutic combinations, with the use of boosted protease inhibitors in the last years, which clearly increased the probability to achieve viral suppression. At the moment, combination antiretroviral therapy with at least three drugs has resulted in substantial reductions in morbidity and mortality in both rich and poor countries. Antiretroviral therapy has been simplified to the point where treatment with a single, multidrug pill once a day is feasible with generally manageable adverse effects (3).

Despite such important improvements, a high number of patients fails to achieve viral suppression. In a marked proportion of HIV-infected individuals on treatment, the virus develops resistance to the currently available drugs. In fact, patients with circulating virus showing resistance to all three classes of conventional antiretroviral drugs is not uncommon. Children are among the group of patients who are most at risk of resistance.

The research performed in this thesis is therefore focused on the treatment of HIV-infected children, a population which presents major challenges compared to adults. Based on the current guidelines for the use of antiretroviral agents in paediatric HIV (4), the most appropriate regimen for an individual child depends on multiple factors, including 1) the age and availability of appropriate drug formulations, 2) the potency, complexity and toxicity of the regimen, 3)
the child and caregiver’s ability to adhere to the regimen, 4) the child’s personal situation at home and 5) the child’s antiretroviral treatment history. Consequently, the use of combination therapy with at least three drugs is recommended for initial treatment of HIV-infected children, including either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor and a dual nucleoside analogue reverse transcriptase inhibitor backbone. Because antiretroviral therapy will be administered lifelong, the choice of initial antiretroviral regimen should be based on considerations regarding the barriers to adherence, the complexity of schedules and food requirements for different regimens, differences in formulations, palatability problems and potential limitations in subsequent treatment options should resistance develop.

As presented in Chapter 1, another important point to consider is the dose rationale for antiretroviral therapy in children. Currently recommended doses have been derived from empirical evidence of clinical response rather than on the pharmacological (virological) properties of the combinations. In addition, the dose of antiretroviral drugs given to children is often based either on weight or body surface area without taking into account in a strictly quantitative manner the underlying physiological changes due to growth, which are known to affect drug pharmacokinetics. Inappropriate exposure, i.e., lower than optimal (sterilising) levels may promote viral mutations which mostly lead to drug resistance. With respect to the disease, an overview of viral characteristics and of the available antiretroviral drug classes currently combined to avoid development of resistance was provided. Taking into account pharmacokinetic and pharmacodynamic properties, we have shown the advantages and limitations of existing methodologies for dosing recommendation. Finally, the role of the patient was scrutinised: a detailed definition of adherence to therapy has been considered together with the main strategies used to enhance treatment compliance in children. Here we highlight the importance of adherence for the development of resistance, which has been shown to differ for each class of antiretroviral drugs.

In this thesis we have explored opportunities to support evidence generation and extrapolation across populations, with special focus on the selection of the dose, the optimisation of dosing regimens and the impact of patient behaviour towards the treatment, namely adherence to therapy. After having identified some of the challenges which need to be overcome to decrease viral failure in children, in Chapter 2 we propose the use of a model-based approach for the evaluation of covariate effects and forgiveness of non-adherence, which may allow simplification of current dosing regimens taking into consideration inadequate compliance and its implication for efficacy and drug resistance. In conjunction with clinical trial simulations, we aim to demonstrate that it is possible to evaluate relevant clinical scenarios and predict treatment outcome of simplified dosing regimens, taking into account the differences in the patterns of drug intake and the pharmacokinetic-pharmacodynamic properties of antiretroviral drugs. Such factors may all be involved in the development of resistance and thus may ultimately cause viral failure. Our work clearly shows that, even in the event of adequate dosing regimen and dosing frequency, adherence to antiretroviral therapy is crucial to achieve viral suppression.

Although the approval of medicines is primarily determined by empirical evidence generation, situations exist in paediatric diseases in which evidence cannot be generated and inferences from, e.g., underpowered trials, single arm studies, surrogate endpoints or from other populations have to be made to assess the efficacy and safety of a compound. Inferences may also be required to ensure access to treatment and availability of suitable therapeutic regimens to patients. In these circumstances, it has been demonstrated that the assessment of pharmacokinetic–pharmacodynamic relationships in conjunction with modelling and simulation concepts can support dose rationale as well as dose adjustment in specific subgroups of a population. Here we also emphasise that modelling and simulation tools are very useful when ethical issues preclude the possibility to obtain new data and historical data is used as basis for evidence synthesis (5). In fact, throughout this thesis we have used historical data and modelling and simulation to make inferences about the dose and dosing regimens for a range of antiretroviral drugs.

From a conceptual perspective, our approach expands beyond the current paradigm for the evaluation of dosage forms based primarily on pharmacokinetics; it shows how pharmacokinetic-pharmacodynamic relationships can be used as a proxy for efficacy and safety. Our approach also relies on the principles of bridging and extrapolation. As defined in the draft EMA concept paper (6), extrapolation may be generally defined as “extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product”. On the other hand, from a regulatory perspective the term bridging has been introduced to refer to the generation of data across populations when extrapolation is unsuccessful or not appropriate. Bridging studies are defined by guidelines as supplemental studies performed to provide pharmacokinetic, pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimens in a new population, region or condition. Obviously, an implicit assumption for such studies is that of pharmacokinetic non-inferiority and therapeutic equivalence when comparable pharmacodynamic effects are observed.

The scientific and clinical questions raised in the various chapters of this thesis illustrate the implementation of the concepts mentioned above. Among other things we have shown that pharmacokinetic-pharmacodynamic relationships can be used as basis for the evaluation of therapeutic equivalence. However, as illustrated for lamivudine and abacavir, a basic requirement must be satisfied, i.e., one needs to ensure the predictive performance of pharmacokinetic models. Of particular interest for paediatric drug research is the role of demographic covariates on drug disposition. In section 2 we have demonstrated that when defining dosing recommendations in children one should pay attention to the relationships between pharmacokinetic parameters and demographic covariates. The identification of the correct parameter-covariate
relationship has been shown to be particularly challenging in children, especially when the available datasets have limited sample size (i.e., number of patients) or present unbalanced covariate distribution. The role of covariates was then investigated when the model is used for simulation purposes. In particular, we have demonstrated that extrapolations beyond the covariate range used during model building are not feasible in children. Practical recommendations for the use of models for simulation purposes have been provided. In brief, it is concluded that simulations should only be performed after the predictive power of a model has been evaluated.

Based on the evidence of predictive performance, in section 3 we have presented how modelling and simulation tools can be applied for the evaluation of alternative dosing regimens in a virtual population of HIV-infected children. Such an application is particularly relevant in pediatric HIV, given that simplified dosing regimens with reduced dosing frequency have been shown to improve adherence to therapy. In this section we show that abacavir and lamivudine, two nucleoside-reverse transcriptase inhibitors, can be administered as a once or twice daily dosing regimen without the risk of under or over-exposure in children from 3 months to 12 years old. The possibility to use modelling and simulation to predict the pharmacokinetic properties of a drug in children was then extended to the evaluation of the impact of variable patterns of drug intake and adherence to therapy. In section 4, we have explored the implications of partial adherence to antiretroviral treatment outcome. In contrast to the previous section, where pharmacokinetic equivalence underpinned the use of models for bridging and extrapolation purposes, here we have highlighted the importance of pharmacokinetic-pharmacodynamic relationships as the basis for the assessment of efficacy and safety. Extrapolations were performed under the assumption that pharmacokinetic-pharmacodynamic relationships serve as proxy for therapeutic equivalence. This assumption has allowed us to evaluate forgiveness of non-adherence, an important property which reflects the ability of a drug or a regimen to achieve viral suppression despite sub-optimal adherence (7). This concept is illustrated in figures 1-4, which show indistinguishable differences in the pharmacokinetics of lamivudine and abacavir after three-day and two-week interruptions in therapy, irrespective of the dosing regimen.

Figure 1 Lamivudine pharmacokinetic profile for twice daily dosing regimen in a hypothetical group of children (n=30) aged between 3 and 12 years. Perfect adherence (a), treatment interruption of three days (b) and two weeks (c) have been simulated.
Figure 2 Lamivudine pharmacokinetic profile for once daily dosing regimen in a hypothetical group of children (n=30) aged between 3 and 12 years. Perfect adherence (a), treatment interruption of three days (b) and two weeks (c) have been simulated.

Figure 3 Abacavir pharmacokinetic profile for twice daily dosing regimen in a hypothetical group of children (n=30) aged between 3 and 12 years. Perfect adherence (a), treatment interruption for three days (b) and two weeks (c) have been simulated.
Our investigations were performed using a clinical trial simulation template, which allowed for detailed evaluation of relevant scenarios of non-adherence in children, providing important insight into the patterns of non-adherence which should be avoided by the patients. In fact, the opportunity to derive data which would not be attainable in real-life due to obvious ethical and practical reasons constitutes one of the main achievements of this thesis. Furthermore, we have shown that clinical trial simulations also allow assessment of the robustness of alternative dosing regimens in the event of partial adherence. We have found that when both drugs are administered once daily in combination with efavirenz, not only the exposures are comparable but also the forgiveness of non-adherence of the drug combination. This is illustrated in Figure 5, which depicts a clinical trial simulation scenario in which the treatment is interrupted for three consecutive days and for two consecutive weeks.

From a clinical perspective these findings dismiss the concerns regarding the use of a simplified dosing regimen in children, given that the forgiveness of non-adherence is comparable to the currently recommended one.
11.1. IMPACT OF DATASET SIZE AND COVARIATE DISTRIBUTION ON THE PREDICTIVE PERFORMANCE OF PHARMACOKINETIC MODELS IN CHILDREN

One of the primary issues in paediatric clinical pharmacology research is the management of exposure differences attributed to variation in size, age and other developmental factors. A model-based approach may be used to systematically evaluate and quantify these differences. However, one has to keep in mind that models misspecifications may lead to serious consequences when conclusions based on these models are used for clinical decision making, such as erroneous dose recommendations. In chapter 3 we performed a thorough assessment of the pharmacokinetics of lamivudine in children, with focus on the correlation between pharmacokinetic parameters and demographic covariates. A meta-analysis was performed, in which data from three clinical trials in children between 3 months and 12 years old were combined. We found that lamivudine was best described by a one compartment model with body weight exponentially correlated to clearance and volume of distribution. Interestingly, we show that such relationships can be identified only when the three datasets were analysed together. This finding emphasises a very important concept in paediatric pharmacokinetic modelling: sample size is critical when assessing parameter-covariate relationships in children. These results clearly suggest that, although a model built using a small population may be suitable for descriptive purposes its use for predictive purposes in a new population should be avoided. In addition, our findings reveal the implications of unbalanced covariate distributions. Unbalanced covariate distributions may introduce model misspecification which may easily compromise model-based predictions in a new population. Such findings were confirmed in chapter 4, in which a population pharmacokinetic analysis was performed in children receiving abacavir, an antiretroviral drug often given in combination with lamivudine. Again, in this chapter we showed the importance of a meta-analytical approach to investigate the pharmacokinetics of a drug in children. Furthermore, our work highlights the clinical application of model-based data analysis. Using simulation tools, we showed that drug exposure can be predicted even in case of very sparse sampling, which has always been a concern for drug therapeutic monitoring.

The importance of the correlation between pharmacokinetic parameters and covariates in children and its impact on the predictive performance of a model has been further evaluated in chapter 5. In this chapter we use simulations to explore whether drug exposure can be predicted for a population belonging to a different age range than the ones used for model building. Clearly, this attempt failed, indicating that pharmacokinetic models should not be used to perform extrapolations beyond the covariate range available during model building. Predictions from pharmacokinetic models are reliable only in case of interpolations involving a subgroup of the initial population. In addition, we showed that the covariate point estimates (e.g. median) used to describe the mathematical relationship between covariate and pharmacokinetic parameters should be fixed even when interpolations are referred to a subset of the initial population.

In summary, this section shows the importance of demographic factors on the pharmacokinetics of two drugs currently administered as first-line therapy in HIV-infected children. In addition, our findings highlight some critical issues for covariate selection. We recommend therefore the use of somewhat larger sample sizes than what is currently done in clinical practice. Ultimately we have shown the importance of balanced covariate distribution and its implications for the predictive performance of a pharmacokinetic model: a model in children should not be used for extrapolation beyond the covariate range explored during model building. This finding raises further questions about the widespread use of allometric scaling concepts in paediatric research.

11.2. EVALUATION OF SIMPLIFIED ANTIRETROVIRAL DOSSING REGIMENS IN CHILDREN

The possibility to administer an antiretroviral drug according to a once daily dosing regimen in children is certainly very appealing. However, one needs to be entirely confident that drug exposure achieved after once daily dosing is comparable to historical values achieved after twice daily dosing. In the third section of this thesis we show the use of a model-based approach to evaluate the feasibility of an alternative dosing regimen for lamivudine, which is currently administered as once daily in adults and twice daily in children. In chapter 6 we apply simulations to assess whether lamivudine could be administered as once daily dosing in a virtual group of children between 3 months and 12 years old. The pharmacokinetic model developed and validated previously in chapter 3 was used for this purpose. Evidently, once daily doses of lamivudine leads to AUC_{0-24} and peak concentrations comparable to historical values in children who received a twice daily dosing regimen. The same simulation exercise was performed for abacavir, which is also administered as once daily in adults and twice daily in children. In chapter 7 we used a population pharmacokinetic model developed in chapter 4 to evaluate whether the exposure of abacavir following a once daily dosing regimen was comparable to the current regimen. Again it was demonstrated that once daily doses of abacavir in children leads to AUC_{0-24} and peak concentration values comparable to those observed in historical data in children and adults.

Such results are crucial for the improvement of antiretroviral therapy in children, given that once daily doses may improve acceptability and adherence to therapy. In addition, our approach illustrates how to explore hypothetical scenarios in virtual patients. This concept is particularly useful in paediatric clinical pharmacology research. One of the main advantages is the possibility to evaluate treatment response in a large number of children, without exposing them to the actual treatment. Further details on the implementation of virtual clinical trials are discussed and expanded in the next section of this thesis.
11.3. ADHERENCE TO HIV THERAPY: “DRUGS DO NOT WORK IN PATIENTS WHO DO NOT TAKE THEM”

It is well known that the continuity of drug action derives from the continuity of execution of a prescribed dosing regimen, which is aimed at yielding pharmacologically suitable exposure to the active moiety between successive doses. Treatment interruptions can alter drug action, but the consequences of interruptions in dosing may vary according to the drug, the length of interruption and the disease being treated (9). In this context, the sentence attributed to former US Surgeon General C. Everett Koop, “Drugs don’t work in patients who don’t take them”, summarises perfectly the importance of patient adherence to therapy.

However, to fully understand the implications of the factors determining drug response and variability, one needs a comprehensive approach that takes into account the effects of developmental growth as well as other patient-specific characteristics which could modify drug pharmacokinetics. In addition, it is important to recognise how these factors interrelate with the proposed dosing regimen or interval. Current mainstream views on the use of fixed-dose combinations suggest that reduced dosing frequency improves antiretroviral therapy. Yet, evidence of therapeutic equivalence cannot be derived from bioequivalence studies or simply by comparison of pharmacokinetic data alone. In HIV therapy, the benefit of drug combinations results primarily from pharmacodynamic interactions. Accurate evaluation of changes in dosing regimen requires therefore an assessment of the impact of patient adherence on pharmacodynamics. Differences in the patterns of drug intake are a major cause of unintended variability in drug exposure, which have been associated with the failure of treatment (10). Here we have shown how to quantitatively evaluate the role of partial adherence to therapy. In other words, we have provided the framework for addressing an important clinical question: “How many doses can a patient miss without affecting treatment outcome?”

Modelling as well as other statistical approaches have been previously used to investigate the impact of adherence on therapeutics, which are worth mentioning. In fact, the consequence of partial adherence to antiretroviral therapy is one of the focus areas in this research field. For instance, Pfitzer et al. integrated adherence information as model covariate to determine its effect on drug exposure (11). Subsequently longitudinal models have been proposed to estimate the effect of patient adherence on the rate at which the patients progress through the HIV infection. Other investigators have considered the use of Markov models and other stochastic methods (12-17). Among other advantages, the approach allows the response at any time point to be conditional on that observed in the previous time period. The novelty of our work lies in the fact that for the first time the effect of imperfect adherence has been evaluated using a framework in which all the elements of a clinical trial simulation were combined. Compared to the abovementioned studies, important elements were introduced which were missing previously, including the use of combination therapy, more realistic patterns of non-adherence (random drug holidays, imperfect timing of successive doses) and a correlation between adherence and drug resistance. To illustrate the usefulness of such an integrated approach, three scenarios were selected for evaluation in this thesis: a single drug used as monotherapy, a cocktail consisting of three drugs and a fixed dose combination of three drugs administered according to a simplified dosing regimen. Our analysis also included a relationship between adherence and the probability to develop drug resistance.

This clinical trial simulation framework represents an important improvement in that it encompasses a combination of various mathematical models, allowing for the prediction of treatment outcome for scenarios that cannot be assessed empirically in a controlled, randomised manner.

In chapter 8, the forgiveness of non-adherence of the three different classes of antiretroviral drugs currently used as first-line therapy in children (NNRTI, NRTI and boosted PI) has been evaluated. This study represents the first attempt to predict treatment outcome using a combined approach in which pharmacokinetic, pharmacodynamic and disease models are applied concurrently. In addition, the use of a logistic regression to describe the relationship between the number of days in which the drug exposure remains below the expected therapeutic levels and the probability to develop drug resistance provided the basis for linking partial adherence and viral failure. For practical purposes and ease of interpretation, we have parameterised adherence in terms of the patterns of doses not taken rather than as percentage of doses taken. It is essential to mention that for predictive purposes, all the models used here have been previously evaluated and validated. Our findings provide a preliminary indication about the level of adherence required by each antiretroviral drug to prevent viral failure when used as monotherapy. In reality, these scenarios represented a starting point to characterise the implications of non-adherence or partial adherence when a combination of two or more drugs is used. Subsequently, in chapter 9, a clinical trial simulation was performed in which a cocktail of three drugs is administered to a population of HIV-infected children. Our results reveal that for an NNRTI-based regimen long periods of treatment interruption may represent a higher risk of viral failure than when the same number of doses is missed randomly.

The aforementioned findings indicate that the pharmacokinetic-pharmacodynamic relationships of antiretroviral drugs may be used to predict treatment efficacy in the investigation of forgiveness of non-adherence and, consequently, of simplified dosing regimens. In fact, pharmacokinetic-pharmacodynamic relationships may be considered a “proxy” of therapeutic equivalence in the assessment of forgiveness of non-adherence, in an analogous manner as pharmacokinetics in bioequivalence studies. Conceptually, this offers the possibility to replace efficacy trials by pharmacokinetic-pharmacodynamic studies. As shown in chapter 10, the effect of partial adherence to a simplified dosing regimen was evaluated using the underlying pharmacokinetic-pharmacodynamic relationships of lamivudine and abacavir in combination with efavirenz. Our results reveal that a once daily regimen yields comparable forgiveness of non-adherence as the currently approved twice daily in all the scenarios of non-adherence. In
practical terms, this means that a reduction in dosing frequency can ultimately reduce pill-burden in children without increasing the risk of resistance.

In summary, the clinical trial simulation framework used in chapters 8, 9 and 10, provide the opportunity to evaluate clinically relevant information about the level of adherence required to prevent viral failure and, if extended to other treatment options, may enable physicians to consider the best drug regimen based on historical adherence patterns of the patient. It is also worth mentioning that dropout information was not included in the simulations to ensure appropriate characterisation of the impact of poor adherence without the confounding effects of dropout. However, our findings suggest that poor adherence may have equal, if not more influential, effects on treatment outcome as dropout.

11.4. CONCLUSIONS, RECOMMENDATIONS AND PERSPECTIVES

The results presented in this thesis highlight the value of a model-based approach to address important issues in paediatric HIV research, which have remained unaddressed despite the ongoing scientific and clinical progress in the field. The first point regards the dose recommendation for children based on bridging concepts, rather than on body size. This implies the characterisation of developmental factors influencing drug exposure in the target population, so that exposure attained in children is comparable to adults. In addition, our work has shown the potential limitations of modelling and simulation methodologies for the prediction of pharmacokinetics in children. We have therefore delineated the following recommendations for the implementation of a model-based approach in paediatric research:

1) Population pharmacokinetic studies must consider suitable inclusion or stratification criteria to ensure balanced covariate distribution;
2) The use of meta-analysis including different population subgroups is strongly encouraged to prevent model misspecification due to the confounding effects of unbalanced covariates;
3) The predictive performance of a model is limited to interpolations. The accuracy of extrapolations beyond the range of the population used for model building cannot be warranted even when diagnostic and model validation procedures show evidence of goodness-of-fit.
4) Extrapolation across populations beyond the conditions or population under investigation requires the use of models for simulation, which are not the same as models for estimation, as in the case of models developed using the maximum likelihood.
5) Models for simulation are essential for hypothesis generation and inferences. They provide insight into conditions and scenarios which may not be observed or controlled in real life. As such, they can be parameterised in term of drug, patient and system-specific parameters, irrespective of precision or identifiability, which are data driven.

Based on the aforementioned recommendations, the use of a model-based approach can be extended beyond the issues regarding the dose rationale. It can be applied systematically for the evaluation of simplified treatment options, which is very appealing in paediatric research. Undoubtedly, in conjunction with clinical trial simulations, models become an experimental design tool.

Despite our efforts to incorporate non-adherence into the analysis, several issues were encountered, which need to be highlighted as they impose additional assumptions for model parameterisation. One of these assumptions refers to the relationship between adherence and the probability to develop resistance. We have noticed that the data on adherence available in literature are expressed as percentage of doses taken, which did not meet our objectives. Instead, we have used a logistic regression to describe that relationship. This adaptation brings to light the need for more precise and continuous data on patient adherence. In fact, this situation calls for the systematic use of medication event monitoring systems (MEMs), currently the most reliable measure of patient adherence. Moreover genotyping should be carried out more frequently to gain insight in the correlation between adherence and probability to develop drug resistance.

We are also aware about the impossibility to validate the results from our clinical trial simulation with a prospective trial. In this respect, we can conclude that forgiveness of non-adherence is better defined by means of a not-in-trial simulation (NITS), a concept which has been recently applied for the assessment of pro-arrhythmic risk (18). In contrast to typical clinical trial simulations, this methodology makes use of simulations to characterise the role of design factors which have been omitted from a randomised trial; in our case we have characterised patient adherence to therapy, which cannot be explored in a controlled manner for ethical reasons.

Not-in-trial-simulations constitute therefore a promising starting point for the evaluation of design factors or patient characteristics which cannot be reproduced in real life. Most importantly, this feature opens new opportunities for the evaluation of effectiveness of the treatment. In HIV research, we envisage the prospect for exploring the thresholds of non-adherence which should be avoided to prevent viral failure. In addition, other therapeutic areas, such as e.g., tuberculosis, oral contraceptives or hormonal replacement, would greatly benefit from the concepts presented here (19). In tuberculosis, an in vitro model was used to evaluate, for the first time, the forgiveness of a standard tuberculosis drug regimen with the objective to determine whether poor adherence, in the form of simulated drug holidays, would lead to incomplete sterilisation and/or emergence of drug resistance.

Interestingly, several attempts have been made to quantify forgiveness of non-adherence to oral contraceptive drugs. Despite the use of empirical protocols, quantitative evaluation of non-adherence in this area has been based on study designs that include controlled, blinded substitution of placebo for active drug, with frequent measurements of drug action to determine how long it takes, after the last-taken dose of active drug, for the drug’s actions to washout. Such a study design, known as the placebo substitution-for-active (PSA), has guided the first efforts to write evidence-based instructions for patients on what to do if they miss one or
more pills (9). PSA designs have also been applied in the evaluation of non-adherence in depression by Rosenbaum et al., who carried out a 5- to 8-day placebo substitution study in patients treated with fluoxetine, sertraline, or paroxetine (20).

Obviously, such a trial design could not be applied in antiretroviral therapy and other serious, fatal diseases. The use of NITS methodology, as developed in this thesis, represents a novel and alternative approach to evidence synthesis. Eventually, this will allow information on forgiveness of non-adherence to be systematically included in the summary of product characteristics, providing guidance for prescribers and patients on how to minimise the consequences of missed doses and define the course of action to correct any deviation from the prescribed dosing regimen. Another important aspect that pertains to risk management is the possibility to evaluate prospectively the forgiveness of non-adherence. In other words, NITS can be used to understand what happens in real life irrespective of the evidence derived during a clinical trial, which often shows higher degree of adherence as compared to day-to-day treatment.

The assumption that evidence generation is a sine qua non condition for regulatory approval and optimisation of the therapeutic use of medicines needs to be revisited. The hurdles for protocol implementation and feasibility issues in paediatric research and other serious infectious diseases raise questions about the relevance of evidence generated under strict controlled conditions, as they do not reproduce or reflect real life use of medicines. It should be noted that the reliance on empirical evidence is kindled by regulatory agencies, which continue to issue guidelines that outline the requirements for the approval of medicines based on evidence generation. By contrast, formal acknowledgement of the role of evidence synthesis as the basis for the evaluation of efficacy and safety has not been fully embraced in clinical therapeutic practice or by the regulatory approval process, despite its widespread application in the evaluation of effectiveness and cost–benefit analyses.

A shift in paradigm is required in which evidence synthesis is favoured, making evidence generation a confirmatory step in the continuum between assumptions and empirical evidence. Among the lessons learned from the work presented throughout this thesis, it is worth emphasising that the evaluation of efficacy and safety has not been fully embraced in clinical therapeutic practice or by the regulatory approval process, despite its widespread application in the evaluation of effectiveness and cost–benefit analyses.

We finish this thesis by evoking the very initial question in its title, i.e., does half a day make a difference to treatment outcome? Based on evidence synthesis by modelling and simulation it can be concluded that it does not. Moreover, it is our expectation that this work will contribute to consolidating the use of pharmacokinetic-pharmacodynamic relationships as the basis for inferences about therapeutic equivalence, thereby overcoming the need to perform unnecessary efficacy trials in children.

References


