Impact of disease, drug and patient adherence on the effectiveness of antiviral therapy in pediatric HIV

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Abstract

Introduction: Maintaining effective antiretroviral treatment for life is a major problem, in both resource-limited and resource-rich countries. Despite the progress observed in paediatric antiretroviral therapy, approximately 12% of children still experience treatment failure due to drug resistance, inadequate dosing and poor adherence. We explore the current status of antiretroviral therapy in children with focus on the interaction between disease, drug pharmacokinetics and patient behavior, all of which are strongly interconnected and determine treatment outcome.

Areas covered: An overview is provided of the viral characteristics and available drug combinations aimed at the prevention of resistance. In this context, the role of patient adherence is scrutinized. A detailed assessment of factors affecting adherence is presented together with the main strategies to enhance treatment response in children.

Expert Opinion: Using modeling and simulation, a framework for assessing the forgiveness of non-adherence for specific antiretroviral regimens in children is proposed in which information on pharmacokinetics, pharmacokinetic-pharmacodynamic relationships and viral dynamics are integrated. This approach represents an opportunity for the simplification of dosing regimens taking into account the interaction between these factors. Based on clinical trial simulations, we envisage the possibility of assessing the impact of variable adherence to antiretroviral drug combinations in HIV-infected children.

Keywords: pediatric HIV, antiretroviral, viral dynamics, adherence, dose rationale, forgiveness, PKPD modeling, clinical trial simulations

Article highlights box

- Paediatric HIV infection remains a worldwide public health challenge as life-long treatment is required for these patients.

- According to WHO/UNAIDS data, approximately 86% of new infections in children occur in sub-Saharan Africa, where access to therapy and treatment choice is still limited.

- The relationship between adherence, exposure to antiretroviral drugs, and resistance is more complex than "non-adherence increases the risk of drug resistance". Understanding of this relationship is a critical to reduce the risk of viral failure in highly active antiretroviral therapy (HAART).

- Forgiveness of non-adherence, defined as the ability of a drug or regimen to achieve and maintain viral suppression even in case of poor adherence, is ignored as a therapeutic criterion despite its implications for long term outcome in paediatric HIV.

- The development of a framework in which pharmacokinetic-pharmacodynamic modelling is integrated with viral dynamics may provide a powerful tool to predict the impact of variable patterns of adherence on treatment response. It also offers an opportunity to identify simplified dosing regimens for adults and children.

1. Introduction

Major advances occurred during the past 15 years in HIV therapy. Early antiretroviral treatment has dramatically modified the course of HIV infection in children, reducing mortality by fivefold or more and resulting in high survival rates into adulthood [1,2]. Through successful prevention of mother-to-child transmission programs, developed countries face few new cases of infant HIV-infection annually. Effective prophylaxis and treatment in HIV-infected women and administration of highly active antiretroviral therapy (HAART) to infected babies are just a few examples of the progresses that have been achieved in this area [3]. In fact, as a result of HAART use children who survive into adolescence are now struggling with various adherence challenges associated with long-term therapy [4]. Unfortunately, this situation is more complex in Sub-Saharan Africa, where according to WHO/UNAIDS data approximately 86% of new infections in children occur, but access to therapy and treatment choices are still limited [5].

Paediatric HIV infection remains therefore a worldwide public health challenge. Maintaining effective antiretroviral treatment for life is one of the greatest challenges for children with HIV globally. Even though HIV-infected children living in limited-resource countries clearly face more challenges compared to paediatric patients in developed country, viral failure is an issue that concerns all HIV-infected children worldwide. A European study in which more than a thousand children on antiretroviral treatment were evaluated has found that 12 % of children experience treatment failure of three classes of drugs after 5 years, i.e. over two fold the rate observed in adults [6]. Some of the reasons that lead to earlier treatment failure in children include the lack of choice of antiretroviral drugs and difficulties with adherence and inadequate dosing. In addition, one needs to consider the need for psychosocial support - particularly during adolescence and the risk of running out of drug options sooner than adults in case of drug resistance.

To better understand the problem a comprehensive overview is required of the factors which influence treatment outcome and thereby contribute to clinical failure. These factors can be clustered into three categories, namely, those involving the disease, the drug pharmacokinetics and the patient's behaviour towards therapy. Based on this classification, specific goals and strategies are proposed in clinical practice, which may help overcoming the aforementioned issues and consequently reduce the number of HIV-infected children experiencing viral failure.

2. The disease: why is combination therapy needed?

At present, a combination of at least three antiretroviral drugs from at least two drug classes is recommended for initial therapy in adults and in children. The antiretroviral classes currently approved in children are NRTIs (nucleoside reverse transcriptase inhibitors), NNRTIs (non-nucleoside reverse transcriptase inhibitors) PIs (protease inhibitors) and integrase inhibitors . Different types of drugs are used, which act in different points of the viral replication cycle in order to sufficiently prevent viral replication [7]. The mechanism of action of NRTIs and NNRTIs is based on the inhibition of reverse transcriptase, a viral DNA polymerase enzyme that retroviruses need to reproduce, while PIs block the HIV protease, an enzyme used by the virus to cleave nascent proteins for the final assembly of new virions and integrase inhibitors block the integration of the viral genetic material into human chromosomes.

There are various factors related to the mechanism of infection and replicative capacity of the virus which determine the need for drug combination in HIV treatment: (i) combination of anti-HIV drugs may overcome or delay the development of drug resistance [8,9]; (ii) given that viral replication depends on different enzymes which are the targets of antiretroviral agents, the possibility to reach two targets at the same time increases the chances of stopping

HIV and protecting new cells from infection; (iii) the virus can infect different types of cells in different parts of the body; each drug differs in how well the virus can be attacked in different tissues. As a matter of fact, drug resistance can emerge because of the replication program of HIV, which is rapid and error prone (mutation rate ca. 3×10^{-5} mutations/base/replication cycle), resulting in large and genetically diverse populations *in vivo* [10]. When HIV is allowed to replicate in the presence of antiretroviral drug concentrations, which are not sufficient to exert complete suppression, antiretroviral drug-resistance mutations will almost invariably emerge [11,12].

Depending on the site of viral mutations and their impact on viral fitness, different anti-HIV classes show higher or lower barriers to resistance. In the past years direct nucleic acid sequencing has become a common mechanism to obtain resistance information; commercial genotyping services are available; routine testing with independent panels of resistant viruses is useful to maintaining proficiency in detection of mutations [13,14]. Even though appropriate use of resistance testing may provide valuable information concerning drug options and regimens for treatment-experienced individuals with viremia during therapy, one needs to consider that this testing is not widely available in resource-limited settings where most patients live. Consequently, alternative approaches must be explored to prevent and manage resistance.

To date, two therapeutic options are suggested as first-line choice in children by the WHO guidelines: NNRTI- and PI- based regimen [15]. In addition, the NIH guidelines also recommend the use of integrase strand transfer inhibitor (INSTI)-based regimen as initial treatment [16].

Regarding NNRTI-based regimens, efavirenz (EFV) is the preferred choice in children older than 3 years because of its once daily administration, whereas nevirapine (NVP) is the preferred alternative. With respect to PI-based regimens, the WHO guidelines recommend

lopinavir/ritonavir (LPV/r) as a first line therapy in infants and children younger than 3 years of age. This drug is available as liquid formulation and appears to be safe and effective in children in relation to virological suppression and the increase in CD4 count. According to PENTA guidelines, atazanavir/ritonavir (ATV/r) is preferred over LPV/r in children older than 6 years old and either ATV/r or daruanvir/r (DRV/r) are preferred to LPV/r in children older than 12 years of age [17].

In spite of some debate about the optimal time to start HAART in children, WHO guidelines state that HAART should be initiated in all children and adolescents living with HIV, regardless of clinical stage or at any CD4 cell count. Two drugs from the NRTI class form the backbone of HAART, with seven NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, tenofovir and emtricitabine) approved for HIV-infected children younger than 13 years of age. As indicated by the WHO guidelines, combinations of lamivudine or emtricitabine plus abacavir or zidovudine are considered the preferred dual NRTIs backbone regimens for the initial therapy in children, with zidovudine or tenofovir as preferred alternatives for abacavir.

Regarding (INSTI)-based regimens, NIH guidelines recommend raltegravir as the preferred INSTI in children aged ≥2 years through 12 years who are able to take either the chewable or film-coated tablets.

Irrespective of the availability of guidelines regarding drug choices for treatment-naive patients, the selection of the initial regimen of antiretroviral drugs needs to take into account numerous other factors, such as age of the child, available formulations, comorbid conditions, potential drug interactions with other medications, results of genotypic drug resistance testing, convenience (e.g. pill burden, dosing frequency), and likely predicted adherence. Clearly, potential adverse events are also crucial in the selection of the initial antiretroviral

regimen, as they are among the most common reasons cited for switching or discontinuing therapy and for medication non-adherence [17]. Acute life-threatening events (e.g., acute hypersensitivity reaction due to abacavir, lactic acidosis due to stavudine and didanosine, liver and/or severe cutaneous toxicities due to nevirapine) usually require the immediate discontinuation of all antiretroviral (ARV) drugs and re-initiation of an alternative regimen without overlapping toxicity.

The aforementioned points to consider form the basis for the data summarised in table 1, where an overview is provided of the antiretroviral drugs currently approved in children along with their main characteristics. This overview is complemented by table 2, in which a list is given of the preferred antiretroviral combinations that should be considered as initial treatment of HIV-infected children.

3. The drug: what is the right dose for HIV-infected children?

Up to now, empirical scaling from adults to children continues to be the mainstream method for dose selection in paediatrics, with adjustment for body weight as the most common approach [43]. Although adjustment of drug pharmacokinetic parameters according to body weight or body surface area (BSA) can occasionally explain the observed differences in drug exposure between adult and paediatric patients, the direction and extent of these differences across age groups are, in general, not fully predictable. For example, some drugs are eliminated more rapidly or more slowly in younger paediatric patients, compared with adults or older paediatric patients [44]. Bioavailability may also differ between children and adults due to differences in transit time or gastrointestinal tract pH [45]. There are extensive physiological changes with pharmacological impact that occur as a child matures from infancy to adulthood, and this process does not occur with precisely predicted timing or magnitude on an individual scale [46,47]. Alternative approaches, such as the use of weight-

based methods for determining paediatric doses may not account accurately for all variables related to the different stages of maturation. Discrepancies in drug exposure may be observed in infants and toddlers, as compared to older paediatric patients. All these aspects are in strong opposition to the concept of "one dose fits all" for children [48] and to the belief of a linear relationship to scale or correct dose for the effect of body weight. From a therapeutic perspective, the rationale for dose selection involves the integration of multiple factors. Together with body weight, other confounders such as drug-drug interactions and demographic covariates, i.e. age, gender, body composition, functionality of liver and kidneys and maturation of enzymatic systems throughout the life span from neonates to adults [49] may affect the pharmacokinetics of a drug and consequently its exposure. When selecting the paediatric dose, these potential confounders must be taken into account to avoid the risk of toxicity or poor efficacy. A dosing regimen with more than the necessary doses, besides causing toxicity, might also increase the possibility of poor adherence, which is seriously related with occurrence of resistance. Suboptimal concentrations of antiretroviral drugs might as well be very dangerous because they may exert viral selection pressure and thus promote development of drug resistance.

In addition to the pharmacokinetic considerations, the dose rationale for children needs to take into account disease progression. Even though differences may exist in the underlying pathophysiology in adults and children (e.g. normal CD4 cell counts are much higher in young children than in adults and young children have immature immune systems compared to older children and adults), the pathophysiological processes subsequent to viral infection in adults do not appear to differ significantly from those observed in children. For this reason, the selection of paediatric dosing regimens based on efficacy data from adults is encouraged. Consequently, extrapolation of efficacy does impose the need for pharmacokinetic studies. Performing pharmacokinetic trials to assess optimal dosing in children is a critical step to

avoid inadequate exposure. Careful evaluation of the optimal dosing in children of different ages is also necessary to avoid under exposure or toxicity in subgroups of the patient population.

Despite the indisputable need to perform clinical trials in HIV–infected children, a major limitation of such studies must be highlighted. In patients affected by chronic diseases who are obliged to take their medication their whole life, adherence to therapy during the clinical trial may not be a realistic surrogate of patient adherence in real life, due to the limited duration of the study. Awareness is needed with regard to the implications that this may have on treatment outcome. Moreover participation to clinical trials may enhance adherence to treatment in chronic diseases [50], thus the pharmacokinetic profile of the drug might be altered in real life by different patterns of adherence.

4. The patient: adherence to HIV antiretroviral therapy

There are several reasons why antiretroviral treatment fails, of which poor adherence is a leading one [3,51-53]. It is important to emphasise that the term 'adherence' implies more than the simple concept of a 'patient's tendency to follow medical advice'. Two substituent terms must be defined to have a comprehensive understanding of patient adherence: (i) adherence and (ii) persistence [54]. The former is defined as 'the degree of correspondence between the patient's actual dosing history and the prescribed dosing regimens'. The latter is defined as 'the time elapsed between the first dose and the time of treatment discontinuation'. The term adherence includes also the degree of correspondence between the patient's actual dosing time and the prescribed dosing time. We handle this component as "quality" of adherence. Variable adherence (the patient sporadically misses some doses or takes the drug at different times) and variable persistence ("drug holiday") can have different implications on treatment outcome. It is important to mention that adherence is a critical issue in every

chronic treatment, not only in HIV. Numerous studies have investigated the effect of poor adherence in many therapeutic areas such as, hypertension [55], glaucoma [56,57] and osteoporosis [58]. Furthermore, one needs to consider that other diseases may develop in combination with HIV. For instance, tuberculosis is well known to develop in people with HIV, especially in limited-resources countries. The development of tuberculosis in association with HIV presents several issues related to adherence to therapy: patients co-infected will have more problems to adhere to treatment given the higher number of medications that they need to receive; in addition poor adherence to antiretroviral drugs may increase the probability to develop associated tuberculosis. Furthermore, the treatment of tuberculosis in association with certain antiretroviral drugs are known to result in drug-drug interactions and potentially in increased drug toxicity.

Several factors pose specific challenges for treatment adherence in children as compared to adults [59]. A summary of the main factors leading to poor adherence to HAART in children is provided in figure 1.

When considering adherence in children, it is particularly important to realise that HAART is a customised combination of different classes of drugs. Therefore, it can be very complicated for a child to comply with the prescription. Adherence in children will depend partly or entirely on a caregiver, who, especially in limited resources countries, may also be ill or may be at work when the drug has to be administered [60,61]. The identification of someone responsible for the child is difficult, especially when both parents died or are impaired. Another reason which may affect adherence in antiretroviral therapy is the heavy pill burden that sometimes needs to be administered to perinatally infected children in need of salvage therapy [62]. These complicated regimens pose greater issues in terms of adherence and therefore may lead to resistance which will create the need for even more complicated regimens.

The age of the child is also a crucial element in the evaluation of non-adherence. Usually family members have discrepant perceptions of a child's level of responsibility for medication, especially in families with older children. Older children are often unrealistically expected to take the medication independently [63]. By contrast, younger children rely exclusively on the caregiver for drug administration and might face different issues such as swallowing problems. In addition, many of the current HIV medicines have an unpleasant taste, especially in syrups and powder form. This can make it difficult for children to take their ARVs daily [64]. Another factor that may impact adherence to chronic therapy is the child's development. Children who have shown high adherence to HAART at younger ages frequently face problems during adolescence, a challenging time developmentally even without chronic illness [4]. To the list of factors highlighted so far, one needs to add safety issues, which are a known cause of non-adherence. Side effects are usually associated with irregular medication intake or discontinuation of treatment altogether [65].

To tackle these issues, several strategies aimed at improving adherence in HIV-infected children have been adopted, which rely primarily on the education of the caregivers or on peer support, self-monitoring and telephone follow-up [66,67]. A brief period of hospitalization may help to demonstrate the role of non-adherence on antiretroviral therapy and help identifying possible solutions. Particularly in developed countries, material support such as pillboxes, drug identification charts, daily schedules, diaries and educational materials are provided to explain the schedules, risks and benefits of HAART [68]. Age-specific developmental-level protocols and teaching materials (e.g., cartoons, stories and drawings) have been developed to educate children about their treatment, their HIV status, and the importance of adherence and medical follow-up, but these resources are not always widely available in resource-limited settings.

The possibility to reduce the dosing frequency of antiretroviral drugs is another important strategy to enhance adherence to treatment. It has been demonstrated that decreasing the pill burden and dosing frequency is associated with increased adherence [69-71]. Several studies have already been performed to assess the feasibility of reduced dosing frequency of some antiretroviral drugs from three times a day to twice daily or from twice to once daily [72-74]. However, deep knowledge of the pharmacokinetic and pharmacodynamic properties of a drug is required to understand whether the dosing frequency can be reduced: it has been demonstrated that missing a dose when following once daily dosing regimens may be more dangerous than missing one dose on a twice daily regimen [75].

4.1. Adherence-resistance relationship

Irrespective of the age of the patient, failure to take the prescribed dose of antiretroviral drugs leads to ongoing viral replication in the presence of drug and the development of drug-resistant HIV. However, one needs to acknowledge the fact the relationship between adherence and development of resistance is not that simple as it may seem and it differs for each class of antiretroviral drugs. Bangsberg et al. have used a cohesive model to summarise this complex relationship for each class of antiretroviral drugs currently used as first line therapy [76]. According to this model, low levels of adherence are more likely to promote development of resistance to NNRTIs due to their low genetic barriers to drug resistance. On the other hand, higher selection pressure is required for single PIs given the high genetic barriers of this class to resistance; therefore high levels of adherence are required to select for drug resistant-viruses [77]. Sporadic missed doses are unlikely to produce high risk combination of actively replicating virus and sub therapeutic levels in NNRTIs, due to their long half-lives. Conversely, sub-therapeutic levels may easily be reached after long periods of treatment interruption, increasing therefore the risk of resistance. On the other hand, boosted

PIs, which have intermediate half-lives also show a high degree of antiviral efficacy due to their potency. High potencies restrain the development of resistance in case of missed doses, whereas their half-lives are impediments to the development of resistance mutations in patients who interrupt the treatment for long periods.

In addition to the different resistance characteristics of PIs and NNRTIs, it is crucial to highlight that drugs with different half-lives used in combination therapy may lead to temporal monotherapy in case of incomplete adherence, which is particular dangerous for the development of drug resistance. A common example is the co-administration of an NNRTI with a long plasma half-life (e.g., efavirenz) with NRTIs, which generally have shorter half-lives. By contrast, the PENPACT-1 study, which assessed the long-term effectiveness in children initiating 2NRTIs+PI vs 2NRTIs+NNRTI, and switching to second-line at viral load $\geq$ 1000copies/ml or $\geq$30000c/ml, showed that resistance in NRTIs may be largely prevented by the presence of boosted PIs [78]. In fact, these findings were attributed to lopinavir/ritonavir. When resistance was observed, it was mainly associated with lamivudine. In table 3, an outline is provided of the impact of different patterns of non-adherence on the risk of resistance for different classes of antiretroviral drugs. From this outline, it becomes evident that the relationship between adherence and resistance is more complex than "non-adherence increases the risk of drug resistance". Clinicians, health care professionals and drug developers need to realise that accurate understanding of this relationship is a critical step for the choice of treatment.

5. Assessment of New Highly Active Antiretroviral Therapy

Based on the aforementioned data and considerations, optimal dosing regimen and adherence to prescribed treatment appear to be one of the main challenges in paediatric antiretroviral therapy and thus constitute an important theme for future drug development. The possibility

to develop novel drugs with different mechanisms of action, which may prevent the development of drug resistance and improve treatment outcome is an alternative solution which is beyond the scope of our investigation. Instead, we focus on practical aspects of a chronic intervention in children. Undoubtedly dosing frequency reduction may be very advantageous both for adult and paediatric patients; however the impact of poor adherence on optimised dosing regimens must be assessed along with the evaluation of efficacy and safety. In this context, the possibility to evaluate which pharmacokinetic and/or pharmacodynamic properties of an antiretroviral drug make it less susceptible to suboptimal adherence and predict treatment outcome represents an opportunity for dosing regimen optimisation.

To this purpose, an important concept, known as forgiveness of non-adherence, needs to be considered. Forgiveness of non-adherence is the ability of a drug or regimen to achieve and maintain viral suppression even in case of poor adherence [79]. A variety of pharmacological, viral and host properties determine the level of forgiveness of any specific regimen. It is generally used as comparative descriptor of different classes of antiretroviral drugs, based upon the "anchor drug" of the regimen. In 2000 Paterson et al showed that extraordinarily high rates of adherence were necessary to achieve viral suppression in a group of HIV-infected patients receiving unboosted indinavir-based regimen [52]. These findings lead to the "95% rule", which means that patients must take at least 95% of the prescribed antiretroviral doses in order to control viral replication.

More recent studies have demonstrated that more moderate levels of adherence are needed to achieve and maintain viral suppression in patients treated with NNRTIs and boosted PIs based regimens. These findings gave birth to the evidence that some antiretroviral classes are more forgiving than others. This would be the starting point for future studies and investigations which may provide further insight into clinical use of drug combinations.

A shortcoming of the empirical evidence obtained so far is that it handles forgiveness in a qualitative manner, without any specific scales or thresholds which could be used to support therapeutic choices. A quantitative and systematic definition of forgiveness is required to allow the evaluation of new dosing regimens and explore their advantages for patients without risks of inadequate efficacy and consequently drug resistance.

6. A model-based approach for the exploration of novel dosing regimens

As indicated previously, accurate prediction of the implications of forgiveness of non-adherence to treatment and evaluation of alternative dosing regimens require quantitative tools which allow for the integration of the effect of disease, drug characteristics and patient behaviour.

A model-based approach in which PKPD models for selected antiretroviral drugs are used in conjunction with a model for viral dynamics may provide a powerful tool to predict how forgiving antiretroviral drugs are and provide the scientific basis for alternative dosing regimens. In addition, the inclusion of a model for patient adherence offers the opportunity to characterise the relation between adherence, exposure and drug response as well as the impact of adherence on treatment outcome [80].

It should be clear to readers that the evaluation of adherence may not be feasible in clinical practice due to ethical reasons and protocol design issues. Thus, an *in silico* approach is critical to assess how different patterns of adherence may affect treatment outcome. Similar methods have been previously applied in different therapeutic areas, such as statin or antihypertensive therapies [81-83]. In fact, the possibility to integrate disease mechanism, drug behaviour and patient adherence to treatment in clinical trial simulations may become crucial for the exploration of simplified dosing regimens of antiretroviral drugs. In addition to obtaining quantitative estimates of the impact of different regimens on response, the use of

virtual patients overcomes ethical barriers, allowing for the assessment of hypothetical and real-life scenarios [84].

6.1. Disease models for viral dynamics

A statistical model that can accurately describe the disease in terms of viral replication and infection is the starting point to predict the response to combination antiretroviral therapy and to gain insight into possible mechanisms of treatment resistance [85] .

HIV dynamics has been widely studied in the past twenty years and several models of different levels of complexity have been developed [10,86-88]. The main advantage of this approach is the possibility to understand, quantify and parameterise viral processes such as replication, infection and viral clearance (death) over time [89]. For example, modelling of viral dynamics has shown that HIV-1 is a rapidly replicating virus and one that could respond to therapy. Furthermore, quantitative estimates of viral parameters suggest that HIV-1 is cleared from chronically infected patients at a rapid rate, with a half-life estimated to 6 hours from serum/plasma, whereas different rates apply when the virus is cleared from other tissue compartments or viral sanctuaries. Finally, modelling has shown that the HIV virus can quickly become resistant to any single drug, particularly to those that require only one mutation to generate resistance. This phenomenon can be anticipated by the fact that every single possible mutation of the viral genome can be expected to occur hundreds or thousands times each day.

An example of the basic model is commonly used for viral dynamics is depicted in figure 2. Similar models have been applied to study the dynamics of hepatitis C virus, hepatitis B virus and cytomegalovirus infections *in vivo*. The model considers a set of cells susceptible to infection, that is, target cells, T, with a birth rate of λ and a death rate of d_T, which, through interactions with virus, V, become infected at an infection rate equal to k. Infected cells, *I*, are

each assumed to produce new virus particles at a constant average rate p and to die at rate δ. The average lifespan of a productively infected cell is $1/\delta$ and so if an infected cell produces a total of N virions during its lifetime, the average rate of virus replication per cell, $p = N\delta$. Newly produced virus particles, V, can either infect new cells or be cleared from the body at rate c per virion. This model is defined by a system of three differential equations (equation 1- 3). These equations are applied to obtain minimal estimates for the parameters c and δ. From these estimates it is possible to calculate upper bounds for the half-life of virions in plasma and the half-life of productively infected cells.

$$dT/dt = \lambda - d_T T - kVT \qquad (1)$$

$$dI/dt = kVT - \delta I \qquad (2)$$

$$dV/dt = pI - cV \qquad (3)$$

This model has been expanded to include more compartments representing latently infected cells and reservoirs [90-94]. A subsequent implementation of this model has also included the effect of the antiretroviral drugs on the processes of viral infection and replication, taking into account the different mechanisms of action [95]. Such models have been validated and are widely used to predict the time course of clinical endpoints and to design novel strategies in HIV treatment [96,97]. In addition, thanks to the way viral clearance is parameterised, it is possible to link drug efficacy to long-term changes in HIV-1 viral load [95,98,99].

6.2. PKPD modelling in children

Characterisation of the pharmacokinetic-pharmacodynamic relationships is required to assess the correlation between plasma concentrations of antiretroviral drugs with changes in clinical response. In order to define such relationships detailed information on PK and potentially

also on PD of antiretroviral drugs in children need to be collected. Given ethical and practical constraints limit the number of blood samples can be obtained in paediatric subjects, non-linear mixed effect modelling parameters is the preferred approach to describe PK and PD properties [100]. The use of non-linear mixed effect modelling in paediatrics has been extensively evaluated by our group in a previous publication [101]. The term "mixed" in non-linear mixed effects modelling represents a mixture of fixed and random effects. For the fixed effects, a structural model describing the PK or PD is chosen (e.g. a two-compartment model for PK or an E_{max} model for PD). The random effects quantify the variability that is not explained by the fixed effects and include inter-subject and intra-subject random variability [102]. It is often assumed that the variability between subjects follows a log-normal distribution with a mean of zero and variance ω^2. Equation 4 is used to describe the relationship between individual and population parameter estimates:

$$\Theta_i = \theta_{mean} * e^{\eta i} \qquad (4)$$

where θ_i represents the parameter of the ith subject, θ_{mean} the population mean, and ηi the variability between subjects. The structural model uses fixed effects parameters such as clearance and volume of distribution for PK or E_{max} and EC_{50} for PD.

The residual error is generally described using a proportional error (error is dependent on the concentration, which means a higher absolute error at higher concentrations (Eq.5)) or an additive error (constant for all observations (Eq. 6)) or a combination of both. This means for the jth observed concentration of the ith individual the relation (Y_{ij}):

$$Y_{ij} = c_{pred,ij} * (1 + \varepsilon_{ij}) \qquad (5)$$

$$Y_{ij} = c_{pred,ij} + \varepsilon_{ij} \qquad (6)$$

where c_{pred} is predicted concentration and ε_{ij} is a random variable with a mean of zero and a variance of σ^2.

Non-linear mixed effects modelling also allows the evaluation of the relationships between covariates (demographic characteristics of the subject) and parameters of the structural model (e.g. influence of body weight on volume of distribution or clearance) (figure 3) [103]. Such relationships are particularly important in children, given that developmental changes (i.e. metabolising enzyme capacity, renal function, liver flow, body composition) can have profound effects on the pharmacokinetics and on the response to medications. Therefore, it is important that such changes are considered in the context of all other sources of intra- and inter-individual variability resulting from genetic, environmental and disease-related factors and drug interactions [104].

Over the last few years, it has been recognised that PKPD modelling constitutes a powerful approach to characterise PKPD relationships. As such, it has been widely applied to antiretroviral therapy to relate plasma concentration to efficacy and to identify the optimal dose of antiretroviral drugs in children [105,106].

6.3. Modelling patient adherence

In order to explore novel regimens of antiretroviral drugs or optimise existing ones, a third statistical element needs to be implemented, which describes the patients and their behaviour towards the treatment. As explained in the previous part of this review, dosing patterns may differ between patients in terms of the actual dose (adherence), the timing of doses (quality) and the duration of treatment (persistence) [107-109]. The consequences of variable

adherence on treatment outcomes are determined by the magnitude of erratic dosing about the prescribed dosing times, the number and frequency of sequentially missed doses or ''drug holidays'' (when the patient stops taking the medication(s) for a period of time) and the pharmacological properties of the drug [110]. Based on clinical data of adherence to treatment, it appears that inter-individual variability is very large for dosing times relative to the prescribed interdose interval, whereas indices of dose-taking adherence (the quantity of the drug taken per dose) are usually less variable [111].

Given the need to infer different adherence patterns when real data are not available to test their impact on treatment response, several simulation models for trial execution have been proposed in the past few years. The simplest one assumes that the prescribed number of pills is taken correctly, but at different times than the prescribed ones [112,113]. In those models, time intervals between two doses are drawn from normal distributions [114]. Other models propose to simulate the number of doses taken at each dosing time according to a multinomial distribution allowing for 0, 1, 2 or more doses taken at each dosing time [115]. Since this number may depend on the number of doses previously taken, an earlier attempt suggested the use of Markov models [116], which have great flexibility and allow the description of almost all different adherence profiles. The inclusion of covariate factors in this model also provides a mechanism to control, for example, the date at which the patient will have a "drug holiday".

In conjunction with variable adherence, patient drop-out constitutes another fundamental element in clinical trials. Two types of drop-out exist: non-informative and informative drop-outs. Non-informative drop-outs simply mean that some patients may randomly stop to be reported in the trial, this independently from the treatment they received, and this independently of efficacy or toxic effects. On the contrary, disease progression can be correlated to the marker that is being followed. In this case, the drop-out is informative to the

disease progress, and modelling the disease progression separately from the drop-out process may be inefficient and may produce biased estimates [117,118]. For example, in a trial of HIV treatment, disease progression may lead a patient to drop-out to seek other antiretroviral regimens.

7. Clinical trial simulations

Given the characteristics of the HIV-infected population, a model-based approach is a potent instrument for the evaluation of the behaviour of the patient towards the prescribed treatment, taking into account the processes underlying disease progression as well as the pharmacokinetic and pharmacodynamic properties of the drugs. Two elements need to be distinguished and defined when applying model-based approaches, namely modelling and simulation. The former enables translation of the relevant features of a system into mathematical language (i.e. model parameters), whilst the latter allows the assessment of a system's performance under hypothetical and real-life scenarios (i.e. "what-if" scenarios), yielding information about the implication of different experimental designs and quantitative predictions about treatment outcome, dosing requirements and covariate effects [119,120]. In clinical trial simulations (CTS), multiple factors can be evaluated concurrently and relevant scenarios can be defined and investigated. The great advantage of the use of CTS in paediatric drug development and clinical practice is the possibility of exploring relevant scenarios before enrolling children into a clinical protocol [121,122]. Simulations allow evaluation of a range of parameter values, including an assessment of critical scenarios, such as overdosing, that cannot be generated in real-life studies.

CTS has been widely used in the past in paediatric drug development and clinical practice [123]. Läer et al. used CTS to develop an age-specific dosing regimen for sotalol in children [124], whereas CTS was used Yim et al. [125] to get US Food and Drug Administration

approval for the dosing regimen of etanercept in juvenile rheumatoid arthritis. Another example of the use of CTS includes the selection of rufinamide doses associated with safety and efficacy in a large paediatric population [126]. In CTS three important components are characterised: a disease/placebo model, a drug model, and the implementation model (trial design and decision criteria) (figure 4). Together with a model (which describes the biological mechanisms underlying the disease [127]) and a drug-action model (which comprises pharmacokinetic and pharmacodynamic factors [128]), a trial model is required that accounts for other important aspects of the trial, such as dropout, adherence and protocol deviations [129]. Thus far, despite the widespread use of CTS in paediatrics, very few examples exist in which relevant design factors have been evaluated prospectively as part of the planning of a paediatric trial. In particular patient-related components, such as adherence and drop-out have not been encompassed in previous paediatric CTS.

In the previous paragraphs, we have advocated the advantages of model-based approaches for the characterisation of pharmacokinetics and pharmacodynamics in children. However, a previous investigation has shown that limitations exist in such approaches when extrapolations are required from different paediatric populations [130]. The use of parametric approaches must consider uncertainty in model and parameter estimates, a feature that can lead to biased predictions and potentially wrong interpretation of the results. The evaluation of adaptive protocol designs may overcome some of these limitations and ensure accurate dosing recommendations for children [131].

7.1. CTS for the assessment of forgiveness of non-adherence to antiretroviral therapy

As highlighted previously, CTS can be used to evaluate the impact of variable patterns of adherence as well as to identify the contribution of other critical factors to treatment outcome,

yielding quantitative and systematic estimates of forgiveness of non-adherence for each antiretroviral drug. Such data could be of indisputable value in the exploration of scenarios or conditions which have not been tested in reality, such as new doses, new dosing regimens or drug combinations. It is important to mention that the requirement to administer antiretroviral drugs as a combination regimen confers additional complexity to a general framework for CTS.

In particular, few mechanistic models are available that enable the prediction of the efficacy of a combination of several drugs rather than the response to each drug separately, as assessed by the PKPD relationships of individual components. Generally, the inhibitory effect of a combination is expressed through an additive equation [98]. Even though *in vitro* studies may be used to describe the inhibitory effect of a single drug, assessment of the contribution of each drug to the total inhibitory effect of a combination are usually not performed. By contrast, the use of a model-based approach may enable the evaluation of the inhibitory effects *in vivo* of different drugs administered in combination despite the lack of such information.

These models, however, were not developed with the intent of exploring the forgiveness of non-adherence to antiretroviral drugs or drug combinations. To this purpose, further integration is required in which PK, PKPD and viral dynamics models are combined. More specifically, the inhibitory effect of a drug or a combination of drugs can be predicted using available PKPD models. These data are subsequently used as input for the evaluation of viral dynamics model, allowing for the characterisation of the processes of viral infection and replication. This step yields time-varying viral load and CD4 count as output. Simulation scenarios can be evaluated by assuming perfect adherence and subsequently by introducing different patterns of non-adherence (delays in drug intake, treatment interruptions or doses randomly missed throughout the treatment period). One of the main advantages of this

approach is that specific scenarios of non-adherence can be simulated for different groups of patients. One can also evaluate the impact of different scenarios on the same group of patients. Based on simulations, differences in treatment outcome can be summarised for a range of clinically relevant scenarios of non-adherence and a threshold can be identified for forgiveness of non-adherence. Such a threshold represents the level of non-adherence allowed to the specific group of patients without compromising the outcome of the treatment. Thresholds may be similar or different for each drug or drug combination for a given population. Most importantly, such data provide important insight into the patterns of non-adherence which should be avoided in real life.

As mentioned in Section 4.1, for the accurate evaluation of forgiveness of non-adherence one also needs to consider development of resistance. An approach is to include resistance into the modelling framework by linking it to the plasma concentration levels of each specific drug. For instance, a logistic regression can be used 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, the estimates from this regression can be used subsequently link partial adherence and viral failure. Likewise, safety concerns need to be carefully assessed, as adverse events may have a direct effect the level of adherence. Also in this case, a logistic regression could be considered to establish the probability of drug-related adverse events and increasing drug levels in plasma or tissue.

An application of this concept is currently under evaluation by our group [132]. We have explored the implication of variable patterns of adherence on so-called optimised antiretroviral regimens, e.g., reduction in dosing frequency from twice-daily to once daily dosing. One of the main concerns of less frequent dosing intervals is the need for evidence of robustness or forgiveness, which means that once daily regimen should not be less forgiving than to twice daily regimens. By applying the same set of simulations to the two regimens

and including different levels of non-adherence, it is possible to compare the forgiveness of each regimen taking into account other relevant factors, such as age and body weight. Preliminary results were in agreement with clinical data, i.e., the commonly used NNRTI-based combination regimen in children appears to be more forgiving to some patterns of non-adherence (e.g. randomly missed doses) rather than to drug holidays. A similar approach can be considered for the evaluation of resistance and patient safety before enrolling the patients in the actual clinical trial. Moreover, the use of simulation scenarios also represents an opportunity for risk mitigation and risk management. Simulated data can be derived from conditions which cannot be controlled or achieved in real-life due to obvious ethical and practical reasons.

8. Conclusions

In the previous sections we have highlighted three important points of concern in antiretroviral paediatric therapy: i. the choice of the dose (dose rationale), ii. the requirements for optimisation of the dosing regimen (reduced risk of resistance to the combination) and iii. the impact of non-adherence to life-long treatment (forgiveness). The use of an approach in which PKPD relationships, viral dynamics, patient behaviour and trial execution factors are integrated provides the basis for addressing the concerns described above. Based on comprehensive clinical trial simulation scenarios, it is possible to investigate the impact of different factors as well as identify optimal experimental conditions for the evaluation of efficacy of HAART in children. The approach also offers the opportunity to explore scenarios which may not be feasible or ethically acceptable in the paediatric population. The possibility to evaluate forgiveness of non-adherence of current or future treatments in virtual patients without exposing real ones to potentially ineffective experimental conditions will strongly simplify the identification of the best dose and dosing regimens for HIV-infected children.

9. Expert Opinion

The development of HAART has been one of the greatest achievements of medical research. In both rich and poor countries, HAART combinations with at least three drugs have resulted in substantial reductions in morbidity and mortality. HAART has been simplified to the point where treatment with a single, multidrug pill once a day is feasible with generally manageable adverse effects [133].

Despite these important improvements, a significantly high number of children fail to achieve viral suppression. Inadequate dosing and poor adherence, which in turns are responsible for the development of resistance, are the major causes of this problem. Although these issues have been extensively discussed in previous scientific publications, a quantitative approach is still lacking that allows systematic evaluation of the forgiveness of non-adherence of specific antiretroviral regimens and the feasibility of simplified dosing regimens.

This review has identified three main factors which need to be considered in an integrated manner for the optimisation of antiretroviral combination treatments in children: the disease, the drug and the patient. The interaction between these factors can be characterised by a model-based approach which combines (i) pharmacokinetic-pharmacodynamic models for selected antiretroviral drugs (ii) a model for viral dynamics and (iii) a model for patient adherence. This approach provides the basis for quantifying the relation between adherence, exposure and drug response as well as the impact of adherence on treatment outcome. Moreover, it overcomes ethical and design issues involved in the evaluation of adherence in clinical practice.

The novelty of the proposed methodology relies on the fact that the outcome of an antiretroviral combination treatment may be predicted for hypothetical scenarios of non-adherence along with the thresholds of non-adherence to be avoided in clinical practice. In

conjunction with clinical trial simulations, this type of information can be used as input for the evaluation of the feasibility of simplified dosing regimens in hypothetical scenarios without enrolling the children in actual clinical trials. The feasibility of less frequent dosing (i.e., longer dosing intervals), such as the change from twice daily to once daily doses represents a typical case where this methodology could be applied. Moreover, in the future we envisage that information on the forgiveness of non-adherence may become a standard component of the summary of product characteristics. This will ensure that appropriate information is provided to prescribers, patients and caregivers on how to minimise the consequences of missed doses or treatment interruptions. In addition, it can be anticipated that the use of clinical trial simulations will be used to assess the implication of not-in-trial settings or real life conditions, which in most of the cases differ significantly from the highly controlled environment of a clinical trial.

 Whereas many of the mathematical and statistical concepts required for the implementation of the framework described here are often unfamiliar to physicians, clinical pharmacologists and drug developers in general, increased awareness is needed about the possibility that these tools represent to therapeutics. In addition to the application of the concepts in the so-called real-life clinical trials, the framework may also play an important role in the development of risk management plans through the quantitative evaluation of real-life scenarios, preventing the exposure of paediatric patients to unnecessary risks.

Declaration of interest

O Della Pasqua is Senior Director of Clinical Pharmacology at GlaxoSmithKline R&D. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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(•) **Benefits of the application of clinical trial simulation tools to clinical drug development**

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Figure 1 Main factors leading to poor adherence to antiretroviral therapy in children.
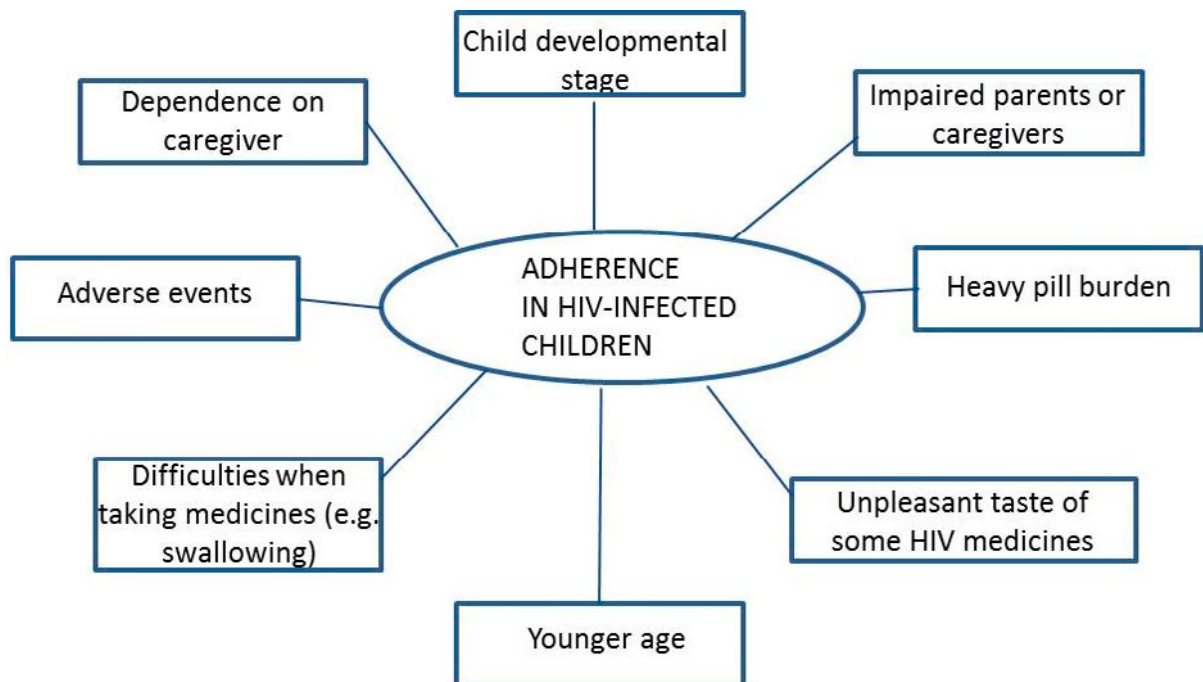

Figure 2: Schematic representation of the model developed by Bangsberg to summarise the relationship between adherence and relationship for each class of antiretroviral drugs [75].
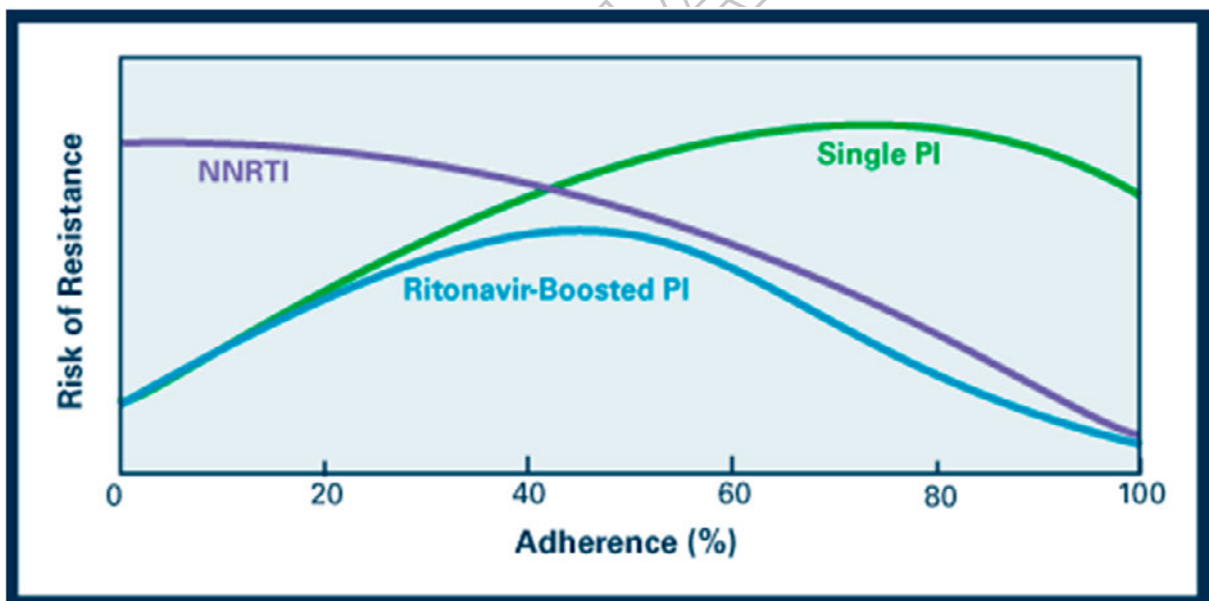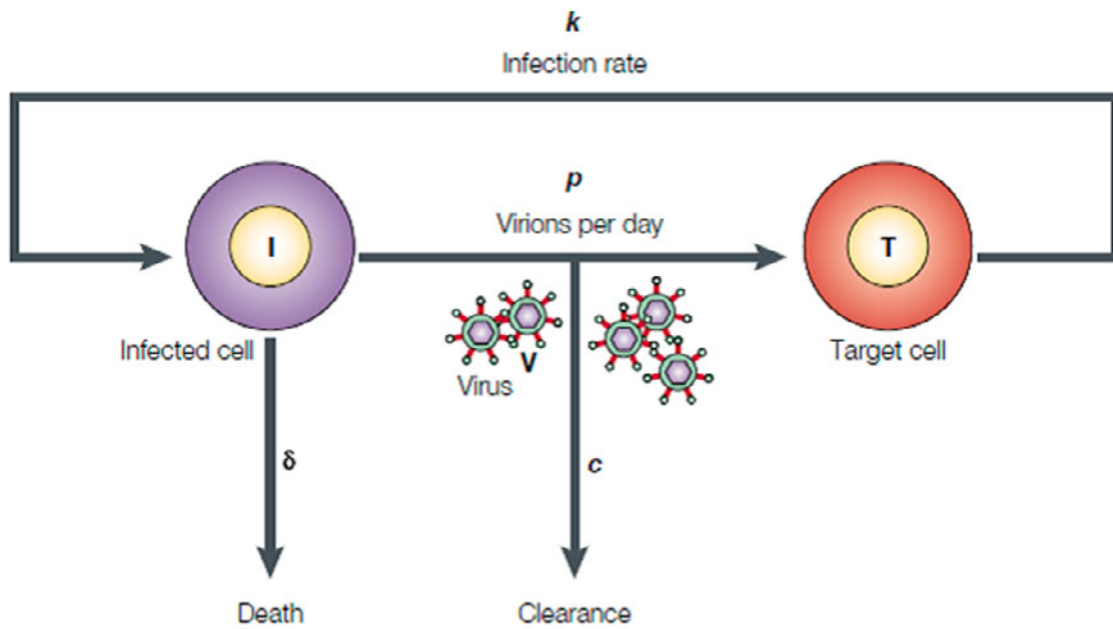
Figure 3. Basic model of viral infection by Perelson. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology [89], copyright 2016.

Figure 3. Schematic representation of the relationship between dose and concentration (pharmacokinetics, PK) and between concentration and a pharmacological (side) effect (pharmacodynamics, PD). Important covariates that may affect both the PK and/or PD are body weight, age, disease status (e.g. critically ill versus healthy children) and genetics. Reproduced with permission from [101].
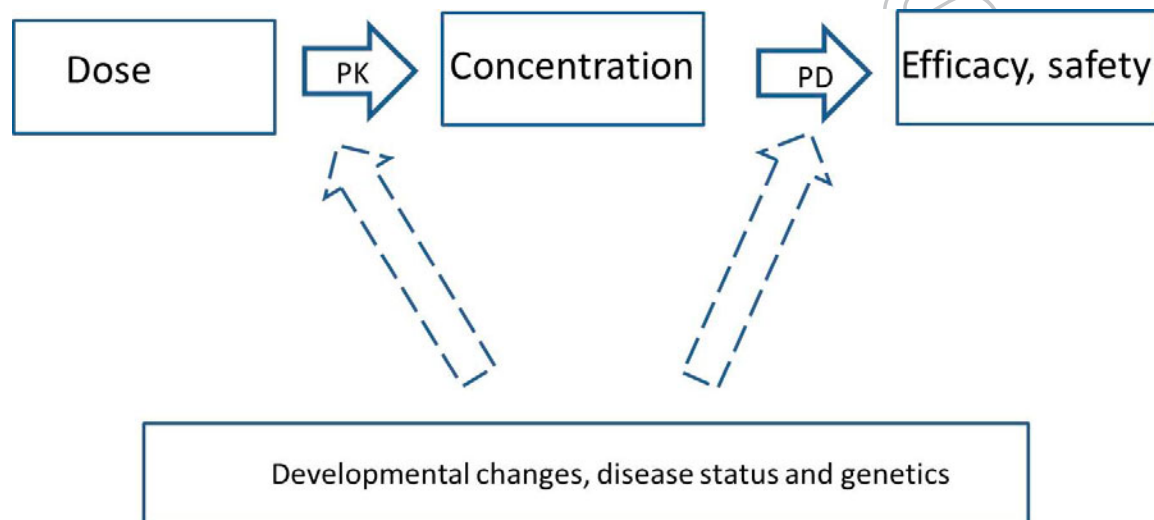
Figure 4. The diagram depicts the major components of a clinical trial simulation (CTS). In model-based drug development, CTS can be used to characterise the interactions between drug and disease, enabling among other things the assessment of disease-modifying effects, dose selection and covariate effects (e.g. age, body weight). In conjunction with a trial model, CTS allows the evaluation of such interactions, taking into account uncertainty and trial design factors, including the implications of different statistical methods for the analysis of the data. Reproduced with permission from [84].

Disease model

Biology
  Biomarker(s)/
  outcome relationship
  Natural progression

Placebo effect

Drug model

Pharmacology
  Effectiveness
  Safety

**Preclinical/Healthy/
Patient**

Product features

Trial model

Patient population

Drop-out

Adherence

Table 1 Antiretroviral drugs currently approved for the treatment of HIV infection in children.

ARV class	Drug	Half-life	IC$_{50}$	Dose
NRTI	Zidovudine	Serum 0.9-1.4 hrs Intracellular 3-4 hrs [18]	0.003-0.013 mcg/ml [19]	4-9 kg 12 mg/kg-BID 9-30 kh 9 mg/kg-BID >30 kg 300 mg-BID[20]
NRTI	Lamivudine	Serum 2-6 hrs Intracellular 10–15 hrs[21]	2 nM-15uM[22]	4mg/kg -BID [20]
NRTI	Abacavir	Serum 1.5 hrs Intracellular 12–26 hrs[23]	0.26-4.0uM [24]	8-10 mg/kg -BID[20]
NRTI	Didanosine	0.97-1.6 hrs[25]	0.49 μM[26]	20-25 kg 200 mg -QD 25-60 kg 250 mg-QD >60 kg 400 mg-QD[20]
NRTI	Stavudine	0.9-1.5 hrs[27]	0.009-4μM[28]	<30 kg 1 mg/kg-BID >30 kg 30 mg--BID[20]

Class	Drug	Half-life	Concentration	Dosing
NRTI	Emtricitabine	8-10 hrs[29]	0.0013-0.64µM[29]	<3 months 3mg/Kg-QD; >3 months 6mg/Kg-QD[20]
NRTI	Tenofovir	17 hrs[30]	0.04 – 8.5 uM[31]	17-22 kg 150 mg-QD; 22-28 kg 200 mg-QD; 28-35 kg 250 mg-QD; >35 kg 300 mg-QD[19]
NNRTI	Efavirenz	40-55 hrs after multiple doses[32]	0.51 ng/mL[33]	10-15 kg 200 mg –QD; 15-20 kg 250 mg-QD; 20-25 kg 300 mg-QD; 25-32.5 kg 350 mg QD; 32.5-40 kg 400 mg-QD; >40 kg 600 mg-QD[20]
NNRTI	Nevirapine	25-30 hrs[34]	10ng/ml[34]	150-200mg/m^2 -BID[20]
NNRTI	Rilpivirine (>12 years)	34–55 hrs [35]	0.1-2 nM [36]	25 mg-QD [20]
Boosted PI	Lopinavir/ritonavir	5-6 hrs[37]	0.04- 0.18ug/mL[37]	< 15 kg 12/3 mg/kg-BID; > 15 kg 10/2.5 mg/kg -BID[20]

Class	Drug		Half-life	Dosing
Boosted PI	Atazanavir/ritonavir	1-11 ng/ml [39]	9.9 hrs [38]	5-15 kg 200/80 mg-(powder) QD 15-20 kg 150/100 mg-QD 20-40 kg 200/100 mg-QD >40 kg 300/100 mg-QD [20]
Boosted PI	Darunavir/ritonavir	55 ng/mL [40]	6.48 hrs [38]	10-11 kg 200/32 mg-BID 11-12 kg 220/32 mg-BID 12-13 kg 240/40 mg-BID 13-14 kg 260/40-BID 14-15 kg 280/48 mg-BID 15-30 kg 375/48 mg-BID 30-40 kg 450/100 mg-BID >40 kg 600/100-BID [20]
Integrase inhibitor	Raltegravir	5 - 12 nM	9 hrs	<25 Kg chewable tablet up to 400 mg -BID >25 Kg 400 mg film-coated tablet- BID [20]
Integrase inhibitor	Dolutegravir (children older than 12 years and weighing more than 40 kg)	2.7 nM	13-14 hrs [41]	50 mg-QD [20]

Integrase inhibitor	Elvitegravir (fixed dose combination tablet containing elvitegravir/cobicistat/ emtricitabine/ tenofovir alafenamide) (children older than 12 years and weighing more than 35 kg	~9.5 hrs [42]	0.7 nM	150/150/200/10 mg-QD [20]

Table 2 Antiretroviral regimens recommended for initial therapy for HIV infection in children.

Preferred Regimens	
Children >14 days and <2 years	Two NRTIs *plus* lopinavir/ritonavir
Children >2 years and <3 years	Two NRTIs *plus* lopinavir/ritonavir
	Two NRTIs *plus* raltegravir
Children ≥3 years and <12 years	Two NRTIs *plus* efavirenz
	Two NRTIs *plus* lopinavir/ritonavir
	Two NRTIs *plus* atazanavir/ritonavir
	Two NRTIs *plus* darunavir/ritonavir
	Two NRTIs *plus* raltegravir
Adolescents aged >12 years and not sexually mature[*]	Two NRTIs *plus* atazanavir/ritonavir
	Two NRTIs *plus* dolutegravir
	Two NRTIs *plus* darunavir/ritonavir
	Two NRTIs *plus* elvitegravir in fixed-dose combination containing elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide
Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children younger than 3 months	zidovudine *plus* (lamivudine *or* emtricitabine)
Children > 3months and <12 years	abacavir *plus* (lamivudine *or* emtricitabine)
	zidovudine *plus* (lamivudine *or* emtricitabine)
Adolescents aged ≥12 years and not sexually mature[*]	abacavir *plus* (lamivudine *or* emtricitabine)

*The guidelines for adolescents and adults are applicable for adolescents aged ≥12 years and sexually mature.

Table 3. Impact of different patterns of non-adherence on the risk of development of resistance for different classes of antiretroviral drugs.

	NNRTIs	PIs	Boosted PIs
SPORADIC MISSED DOSES	low risk	high risk	low risk
LONG PERIOD INTERRUPTONS	high risk	low risk	low risk