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Title: Adherence to antiretroviral combination therapy in children: what a difference half a day makes...
Issue Date: 2013-10-31
SECTION IV
Forgiveness to poor adherence
The aim of this investigation was to evaluate the forgiveness of antiretroviral therapy to variable adherence, taking into account the differences in pharmacokinetic and pharmacodynamic properties of the drugs currently administered to HIV-infected children as first-line therapy.

Simulation scenarios were evaluated using a hypothetical population of HIV-infected children (n=100) between 3 and 12 years. Three drugs, belonging to the three antiretroviral classes approved as first-line therapy in children, were selected: efavirenz (NNRTI), lamivudine (NRTI) and lopinavir/ritonavir (boosted PI). Published pharmacokinetic and pharmacodynamic models were integrated with an established model for viral replication to predict treatment outcome based on different degrees of adherence to therapy for each drug. Simulations were performed in NONMEM7 and R 2.13.0 was used for data manipulation, statistical and graphical summaries.

Despite its long half-life, efavirenz may be susceptible to viral failure for treatment interruptions longer than one week. Due to its short half-life, lamivudine appears to be forgiving only to very short periods and few missed doses. Similarly, forgiveness of non-adherence to treatment with lopinavir/ritonavir is limited to short treatment interruptions and few missing doses. Based on the current dosing regimens, no relevant clinical effect is observed for delays in drug intake of up to six hours for the three drugs.

Our results show that simulations can be applied as a tool to explore non-adherence to treatment. The use of a model-based approach provides a framework for the optimisation of the dosing regimens for antiretroviral drugs, unravelling the set of pharmacokinetic and pharmacodynamic properties that determine forgiveness.
8.1. INTRODUCTION

The goal of antiretroviral therapy is to delay disease progression by minimizing viral replication and preserving immune function, with minimal drug-toxicity effects. Several antiretroviral drugs are currently approved in children. They are classified by their target in the HIV life-cycle as nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) (1). Yet, children with HIV represent a highly complex population. In fact, despite the available drugs, viral failure remains a serious issue in paediatric HIV. A previous study has shown that 24% of children followed up over 4 years were triple-class exposed, and 10% had triple-class viral failure (2).

These failure rates may be explained by the chronic nature of the disease, which requires the use of drug combinations throughout adolescence and adulthood. During growth, time varying developmental factors that affect the pharmacokinetics of antiretroviral drugs are often ignored, which leads to inappropriate exposure levels. Secondly, young children must rely on a caregiver to receive their medications. Given the social and economic constraints, caregivers may be busy during the day, causing dosing frequency to be variable and making adherence to treatment rather challenging. Although simplified treatments are highly advantageous, currently only few antiretroviral medications are available as a once daily dosing regimen in children. Indeed, fewer than 50% of the children/caregivers report an adherence of 100% to their treatment (3).

Reasons of non-adherence include: forgetting doses, changes in routine, being too busy, and child refusal. In some cases, however, the cause of poor adherence is unrelated to the patient; it is due to the environment: patients in limited resource countries do not always have access to antiviral drugs as drug supplies may be limited or they cannot afford the cost of treatment. Therefore, even when a child receives the optimal dose and has access to simplified dosing regimens, the impact of poor adherence to treatment still needs to be considered carefully: compliance to the prescribed regimen is very difficult to achieve in practice. It has been demonstrated that the risk of viral failure increases as the amount of missed doses increases (4–6). Imperfect adherence can lead to sub-therapeutic drug levels, which may boost the development of drug resistance to one or several drugs in the treatment. In fact, it is estimated that a degree of adherence equal or higher than 95% is required for a successful viral treatment (95 rule) (7). More recent studies with new classes of antiretroviral drugs show that a degree of adherence lower than 95% may be sufficient to maintain viral suppression, but these findings result from empirical experimental protocols and as such may not be generalisable (8).

Given that HIV therapy is usually a lifelong treatment it is critical to understand whether a drug allows for such patterns of poor adherence. The objective of our analysis is therefore to investigate the forgiveness of non-adherence of each class of antiretroviral drugs currently used as first-line therapy in children based on their pharmacokinetic and pharmacodynamic properties such as half-life and potency. For the sake of clarity, the forgiveness of a drug is defined as the ability to achieve and maintain viral suppression despite sub-optimal adherence to the prescribed dosing regimen. This may depend on many factors, such as drug, viral and host properties. Forgiveness of non-adherence may be a powerful factor in the selection of the most suitable treatment in resource limited countries.

In contrast to empirical protocols, here we propose a model-based approach to evaluate forgiveness of drug to treatment interruptions and deviations from the prescribed regimen, which cannot be assessed in a real-life randomised controlled trial due to obvious ethical and clinical reasons. We assess adherence as a covariate effect on drug exposure using a range of scenarios. Similar approaches dealing with adherence have been proposed before (9). However, an integrated analysis of the impact of adherence on pharmacodynamics has not been performed so far. Instead, Markov models have been developed to estimate the effect of patient adherence on the rate at which patient progress through the HIV infection (10–12). More recently, Genberg et al (13) have shown the implication of treatment interruptions on the outcome of antiretroviral therapy, but their work has not explored how pharmacokinetic-pharmacodynamic properties contribute to or prevent treatment failure.

8.2. METHODS

Hypothetical population and paradigm drugs

A hypothetical population consisting of 100 HIV-infected between 3 and 12 years old was selected with individuals evenly spread across two groups based on body weight (15–40kg and >40kg). Three paradigm drugs were evaluated as monotherapy: efavirenz (NNRTI), lamivudine (NRTI) and boosted lopinavir/ritonavir (boosted PI). The drugs were selected to represent the antiretroviral classes presently approved as first-line therapy in children (6). Each drug was administered according to the currently recommended dose (table 1), as indicated in the latest Summary of Product Characteristics. The duration of the treatment in this hypothetical trial was 90 days. Viral load was considered the measure of interest in the study. Further details of the proposed experimental protocol are summarised in table 2.

Models for drug pharmacokinetics, drug resistance and drug efficacy

In order to explore the effect of a range of sub-optimal adherence scenarios on treatment outcome, including that of drug holidays, three mathematical models were used for simulation purposes during the analysis. First a pharmacokinetic model was used to predict the time course of plasma concentrations for each drug. Subsequently a pharmacodynamic model was applied to predict the time varying inhibitory effect of the drugs and ultimately a disease model for viral replication and infection was employed to predict the time varying clinical endpoints (viral load).
Forgiveness of non-adherence of antiretroviral drugs in children

Table 1: Doses of antiretroviral drugs administered to the hypothetical population of HIV-infected children based on current guidelines

<table>
<thead>
<tr>
<th>Antiretroviral drug</th>
<th>Dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>250 mg once daily (14-20 kg)</td>
</tr>
<tr>
<td></td>
<td>300 mg once daily (20-25 kg)</td>
</tr>
<tr>
<td></td>
<td>350 mg once daily (25-32 kg)</td>
</tr>
<tr>
<td></td>
<td>400 mg once daily (32-39 kg)</td>
</tr>
<tr>
<td></td>
<td>600 mg once daily (&gt;39 kg)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>150 mg twice daily (14-21 kg)</td>
</tr>
<tr>
<td></td>
<td>225 mg twice daily (21-30 kg)</td>
</tr>
<tr>
<td></td>
<td>300 mg twice daily (&gt;30 kg)</td>
</tr>
<tr>
<td>Boosted lopinavir/ritonavir</td>
<td>15/40 mg/Kg twice daily (15-40 kg)</td>
</tr>
<tr>
<td></td>
<td>400/100 mg twice daily (&gt;40 kg)</td>
</tr>
</tbody>
</table>

Table 2: Details of the hypothetical clinical protocol

<table>
<thead>
<tr>
<th></th>
<th>EFV</th>
<th>3TC</th>
<th>LPV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of virtual patients</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Treatment duration (days)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Sampling frequency</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Assumed failure time (days)</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

The pharmacokinetic profiles over time for each drug were simulated based on validated models available in literature (14, 15).

The median inhibitory concentration (IC_{50}) was used to quantify agent-specific drug susceptibility. To model within-host changes over time in IC_{50} attributable to the emergence of new-drug resistant mutations the function depicted in equation (1) was used (16).

$$IC_{50}(t) = \begin{cases} \frac{I_0}{1 + \frac{I_{\text{IC50}}}{C}} & \text{for } 0 < t < t_r \\ \frac{I_0}{1 + \frac{I_{\text{IC50}}}{C}} & \text{for } t \geq t_r \end{cases} \tag{1}$$

where $I_0$ and $I_{\text{IC50}}$ are respective values of IC_{50}(t) at baseline and at time point $t_r$ at which the resistant mutations dominate. If $I_0 = I_{\text{IC50}}$ no new drug resistant mutation is developed during treatment. More complicated models for IC_{50} are available in literature (17, 18); however in clinical practice it is common to collect IC_{50} values only at baseline and failure time (19).

In our investigation the failure time was fixed at 40 days after the start of the treatment given that antiretroviral drugs are administered in monotherapy resistance usually develops within few weeks after the start of treatment. The values of IC_{50} for the drugs explored in this analysis were obtained from literature (20–22), such as the values of $I_0$ based on phenotypic resistance tests for each drug.

Efficacy was considered to be constant over time in several viral dynamic studies (23–25). However, treatment response may vary because of differences in drug concentration and other factors or conditions (i.e. development of resistance), which may change during treatment. A pharmacodynamic additive sigmoid $I_{\text{max}}$ model was used to describe the concentration-effect relationship:

$$I = \frac{I_{\text{max}}C}{IC_{50} + C} \tag{2}$$

where $I_{\text{max}}$ is the maximal inhibitory effect that can be achieved and equals to 1, $C$ is the drug concentration, and IC_{50} is the drug concentration that induces an effect equivalent to 50% of the maximal inhibitory effect.

Given that during our analysis the three drugs were administered as monotherapy, the time-varying efficacy or response to treatment equals the effect of the drug at each time point, as calculated in equation 2. Time-varying efficacy $γ(t)$ ranges from 0 to 1 and is referred to as the drug efficacy index (the inhibition rate of viral replication) in the viral dynamic model (Equation 3-5). If $γ(t) = 1$, the drug is 100% effective, whereas if $γ(t) = 0$, the drug has no effect.

Mathematical models for HIV dynamics

A widely used model for viral infection and replication was used to simulate the time course of the clinical endpoints (viral load and CD4 count) (19). As depicted in figure 1, the model consists of 3 compartments: uninfected target cells (T), free virions (V) and infected target cells (T*). Although more complex models for viral replication were available in literature, this simple model showed characteristics of stability and robustness deemed suitable for the purpose of our analysis.
The model for viral replication is defined by three differential equations (equation 3-5). Several parameters are required to describe the viral and immunological processes: \( \lambda \) (day\(^{-1}\) mm\(^{-2}\)) is the birth rate of new T cells appearing in the body, \( d_t \) (day\(^{-1}\)) is the death rate of the T cells, \( N \) is the amount of virions produced by each of the infected target cells, \( c \) (day\(^{-1}\)) is the clearance of the free virions, \( k \) (day\(^{-1}\) mm\(^{-3}\)) is the infection rate, \( \delta \) (day\(^{-1}\)) is the death rate of infected target cells; \( \gamma(t) \) is the time varying efficacy of the drug, predicted by the pharmacodynamic model depicted in equation (2).

\[
\begin{align*}
\frac{dT}{dt} & = \lambda - d_t - [1-\gamma(t)] kTV \\
\frac{dT^*}{dt} & = [1-\gamma(t)] kTV - \delta T^* \\
\frac{dV}{dt} & = N\delta T^* - cV
\end{align*}
\]

**Simulation scenarios of variable adherence to treatment**

The diagram in figure 2 depicts all the scenarios which were simulated for different patterns of non-adherence to treatment (treatment interruption, delay in drug intake or single doses randomly missed throughout the clinical trial).

Based on average adherence in clinical trials derived from objective measures (4, 26, 27), a pre-defined fraction of patients (40%) was randomly selected to be non-adherent to the prescribed dosing regimen. For each scenario the period of non-adherence was randomly assigned to each subject across the duration of the trial as shown in figure 3. 100 replicates were simulated for each scenario. Simulations were performed with NONMEM v7 and R (v 2.13.0) was used to produce the datasets for each simulation scenario and to numerically and graphically summarise the results. A comparison between treatment outcome for the full population in case of perfect and imperfect adherence was made to evaluate the forgiveness of non-adherence for each drug and explore which drug-specific properties have to be considered to achieve viral success.

**Pharmacodynamic vs. clinical forgiveness**

Given the lack of quantitative measures to characterise forgiveness of non-adherence, two thresholds were defined in our study. The first threshold corresponds to an increase of 20% in the median value of viral load compared to perfect adherence. Such a threshold, which indicates a variation in drug response, was selected to account for the inter-individual variability defined in the models. If the viral load is below this threshold, we consider that the drug allows for pharmacodynamic forgiveness.
The second threshold corresponds to an increase in median viral load equal to 0.5 log10 copies/mL. Such an increase, which was selected to account for essay variability (28), can be considered clinically relevant and indicate viral failure. If the viral load is below this threshold we consider that the drug allows for clinical forgiveness.

Two main assumptions were required to implement the simulations presented here. First of all, we have assumed the same failure time for the three drugs (day 40). This was done to avoid additional variability in the study and evaluate adherence as the only variable in our analysis. Secondly, the selection of discrete scenarios of non-adherence was deemed necessary to evaluate the forgiveness of each drug. Nevertheless, these scenarios reflect the most common patterns of non-adherence and were defined according to a more detailed taxonomy for compliance, based upon which treatment interruptions, random missingness of doses or delays in drug intake can be characterised.

8.3. RESULTS

Viral load and CD4 counts were derived by simulations for all three drugs. Given that both endpoints appeared to be equally affected by varying patterns of compliance, only viral load data will be presented and summarised in the next paragraphs.

The boxplots in figure 4-6 show the median viral load for the children non-adherent to therapy (n=40) for each simulated scenario of non-adherence at the last time point before resistance dominates. After this time point the treatment is no longer effective due to resistance. As indicated previously, the evaluation of the effects of poor adherence according to a model-based approach requires a more detailed taxonomy. Therefore, our results will be presented in terms of treatment interruptions, random missingness and delays in drug intake.

Figure 4: Boxplots show the implications of poor adherence on viral load prior to drug failure (i.e., resistance) for variable persistence of compliance. On the x-axis the duration of the treatment interruption is displayed. In parenthesis the number of interruptions is illustrated. The lines represent two thresholds for variation in response assuming perfect adherence to treatment: the dashed line indicates the threshold for pharmacodynamic forgiveness; the solid line indicates the threshold for clinical forgiveness.

a. efavirenz, b. lamivudine, c. lopinavir/ritonavir
Figure 5 Boxplots show the implications of poor adherence on viral load prior to drug failure (i.e., resistance) for randomly missed doses. On the x-axis the percentage of doses missed is displayed. For lamivudine and lopinavir/ritonavir, administered twice daily, the scenarios in which only the morning dose is missed are illustrated as well. The lines represent two thresholds for variation in response assuming perfect adherence to treatment: the dashed line indicates the threshold for pharmacodynamic forgiveness; the solid line indicates the threshold for clinical forgiveness.

a. efavirenz, b. lamivudine, c. lopinavir/ritonavir

Figure 6 Boxplots show the implications of poor adherence on viral load prior to drug failure (i.e., resistance) for variable quality of compliance. On the x-axis the number of hours of delay in drug intake is depicted. In parenthesis the percentage of days of treatment in which the delay happens is displayed. The lines represent two thresholds for variation in response assuming perfect adherence to treatment: the dashed line indicates the threshold for pharmacodynamic forgiveness; the solid line indicates the threshold for clinical forgiveness. The lower dashed line in panel c represents the quantification limit for viral load.

a. efavirenz, b. lamivudine, c. lopinavir/ritonavir
TREATMENT INTERRUPTIONS

Median viral load values are presented separately for each of the three drugs. In figure 4 an increase in median viral load is clearly visible between scenarios with variable treatment interruptions. However, significant differences in the effect on poor adherence can be observed for the different drugs. Median viral load values above the threshold of clinical forgiveness are reached for efavirenz after repeated treatment interruptions of one week (7x3) or two weeks (14x2). On the other hand less frequent treatment interruptions (7x2) for lamivudine and boosted lopinavir/ritonavir are sufficient to raise median values of viral load. Moreover, our analysis shows that repeated treatment interruptions of three days do not seem to alter treatment response for efavirenz, while similar interruptions may lead to treatment failure for lamivudine and lopinavir/ritonavir.

DOSES RANDOMLY MISSED

Different patterns of response were observed for each of the drugs when doses are missed randomly, as shown in figure 5. Missing a dose twice a day for 20% of the days of treatment and missing one dose a day for 40% of the days of treatment (the amount of total doses missed is the same) leads to different median viral load values but overlapping confidence interval. In the case of efavirenz, viral failure may be caused by 40% of the doses randomly missed during the trial, whilst for lamivudine and boosted lopinavir/ritonavir 20% of the daily dose or 40% of half-daily dose missed may cause viral failure. In addition, we have found that the median viral load increases as the amount of missed doses increases. The difference between missing a dose once or twice a day appears to be important. For lopinavir/ritonavir when a dose is missed once a day for 20% of the days of treatment the median viral load does not reach the threshold of clinical forgiveness while missing a dose twice a day for 20% of the days causes an increase in median viral load above the threshold for clinical forgiveness.

DELAYS IN DRUG INTAKE

Based on the box plots in figure 6, no variations were observed in median viral load for the three drugs for delays in drug intake up to six hours. Although the 10th and 90th percentiles show small changes, the median values of viral load for efavirenz, lamivudine and boosted lopinavir/ritonavir remain very similar to the value observed in the case of perfect adherence for each scenario of delay in drug intake. Given that median viral load values for lopinavir/ritonavir stay below the limit of quantification for all the scenarios, in figure 6 c the values of viral load below the quantification limit are also shown. Such values can be predicted by the model but are not quantifiable in clinical practice.

8.4. DISCUSSIONS AND CONCLUSIONS

Using a model-based approach, we have shown that integration of pharmacokinetic and pharmacodynamic models to a disease model for viral replication and infection can provide the basis for a framework for the evaluation of patient behaviour during a clinical trial. Our analysis clearly shows a relationship between the duration of treatment interruption and increase in viral load for the three classes of antiretroviral drugs evaluated. For NNRTIs the risk for viral failure is statistically significant starting at interruptions between 7 and 14 days, whilst for PI-based regimens, the risk of viral failure is statistically significant at 2–7 days. This findings are in agreement with a previous investigation which shows the impact of treatment interruptions on treatment outcome (13).

Despite its long half-life (40-55 hours), efavirenz seems to be completely forgiving only to very short interruptions. Longer or repeated interruptions may lead either to change in treatment outcome or to viral failure, depending on the duration and frequency of such interruptions. These findings are in agreement with previous publications which show that, despite its pharmacokinetic and pharmacodynamic properties, high levels of adherence to NNRTIs are needed to control viral replication (5, 29).

Published data also confirm our findings with boosted PIs. According to these studies, an adherence rate of at least 80% is required to achieve viral suppression (30–34). In addition, longer half-life and increased PI concentrations produced by the boosting effect of ritonavir can increase the forgiveness of PIs. However, higher levels of adherence are needed to the boosted PIs compared with the NNRTIs in order to obtain the same virologic suppression.

Very little information was available in literature about the impact of non-adherence to NR-TIs. Based on our findings, lamivudine seems to be less forgiving than efavirenz due to its shorter half-life. Yet, despite its pharmacokinetic profiles, delays in drug intake do not seem to affect treatment outcome (as depicted in figure 6 b).

CLINICAL RELEVANCE

From a clinical perspective, knowledge of the level of adherence necessary to achieve virologic suppression can be extremely valuable as it may help to determine when adherence counselling is most necessary as well as whether alternative antiretroviral drugs need to be administered given a patient’s adherence pattern (30). Furthermore, quantitative measures of forgiveness of non-adherence and class-specific thresholds may represent a powerful tool for patients and clinicians. In fact, we envisage that the availability of a methodology that allows correlation of the forgiveness to the pharmacokinetic and pharmacodynamic properties of a drug may be used during the development of novel antiretroviral drugs and in the evaluation of the robustness of existing drugs not yet approved in children.

Furthermore, it may be used to explore the behaviour of new antiretroviral compounds in children for which little empiric data exists.
We reiterate that the importance of our analysis relies mainly on the fact that the use of a model-based approach allows one to evaluate critical scenarios which cannot be investigated in real-life or controlled in a randomised protocol. In fact, it appears to be the only way to generate drug-specific thresholds of forgiveness of non-adherence. In conjunction with simulation techniques, this approach can provide the basis for improved dose rationale and better dosing regimens in children.

From a drug development perspective, the integration of pharmacokinetic-pharmacodynamic models with a viral dynamics model also offers an opportunity to predict the efficacy of antiretroviral combinations. Estimates of pharmacokinetic-pharmacodynamic relationships in vivo are often challenging because of the use of combination therapy, which prevents detailed evaluation of the contribution of each drug to the overall inhibitory effect on viral load. Yet, scenarios can be considered in which drug effects are explored under the assumption of additivity and taking into account differences in pharmacokinetics (35).

Limitations in our approach
We are aware that the clinical setting depicted in our simulation exercise does not fully reflect clinical practice, in that each drug is not administered as monotherapy. Antiretroviral drugs have been always administered in combination. In fact, monotherapy has been avoided mainly because of the rapid development of drug resistance. However this setting was required to investigate which properties determine the forgiveness of non-adherence to an antiretroviral drug. On the other hand, we have considered the implications of drug resistance, which has been observed for monotherapy with antiretroviral drugs. However, we have not been able to identify a clear relationship between poor adherence and increased probability to develop drug resistance, particularly for NNRTIs. In fact, it has been shown that despite their long half-life, such drugs may remain for long time at sub-therapeutic levels, which may lead to a higher risk of resistance.

Given that our primary aim was to explore which pharmacological properties determine forgiveness, we do not anticipate any bias due to this limitation. We acknowledge however that the inclusion of a correlation between non-adherence and development of resistance may improve the assessment of the time to viral failure and consequently the impact of poor adherence.

Conclusions
In summary, we have evaluated the impact of non-adherence for three drugs used in first line therapy in children. Undoubtedly, our methodology offers the opportunity to explore the liability of novel compounds to variable patterns of drug intake, which are often unfeasible in experimental protocols. Although generalisation of the findings cannot be warranted without further investigations, we envisage that other mechanisms and drug combinations can be evaluated in a similar manner. In fact, the use of a model-based approach may provide a framework for the optimisation of the dosing regimens in paediatric HIV.

References


