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Impact of Non-Adherence to Antiretroviral Combination Therapy in HIV-Infected Children

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Summary

Sub-optimal adherence to therapy is among the main causes of failure in the treatment of HIV. In children, such issue is particularly serious given that they rely on caregivers to receive their medications. The aim of this study is to evaluate the impact of different patterns of non-adherence for a widely used NNRTI-based regimen in children.

Clinical trial simulations (CTS) were performed in R 2.14. A hypothetical population of HIV-infected children between 3 and 12 years old was simulated (n=100). Published pharmacokinetic and pharmacodynamic models were integrated with an established model for viral replication to predict treatment outcome based on various degrees and different patterns of non-adherence to therapy. A logistic regression was used to incorporate the relation between sub-therapeutic drug levels and the probability of developing resistance. The duration of the hypothetical trial was 48 weeks and the primary efficacy endpoint was the proportion of patients with HIV-1 RNA <50 copies/mL at week 48.

Treatment interruptions of two weeks to NNRTI-based regimens may extensively increase the proportion of children experiencing viral failure compared to perfect adherence (76% vs. 90% of the children achieving a viral load <50 copies/mL at week 48), as well as 10% of doses randomly missed during the 48-weeks trial (78% vs. 90% of the children achieving viral load <50 copies/mL at week 48). Delays in drug intake up to 4 hours do not impact the outcome of the treatment.

Based on our findings, treatment interruptions to a NNRTI-based regimen may pose more risk for virologic rebound than the same number of randomly missed doses. Clinical trial simulations can be applied as a tool to explore the impact of different patterns of non-adherence to combination treatment in children, which could not be evaluated in clinical practice due to obvious ethical reasons.
9.1. INTRODUCTION

In the last decades considerable progress has been made in the delivery of antiretroviral therapy. Among other things, the use of fixed-dose combinations has been proven to be a powerful approach to improve patient adherence. However, these improvements are not always equally applicable to children, who will be subjected to lifelong treatment and who most likely will face the burden of disease in resource limited areas, where the access to the medication may be inadequate. Such challenges are further compounded by the fact that paediatric patients also have to rely on the availability of caregiver for the administration of the drugs.

As shown in previous studies, adherence is the strongest predictor of HIV-RNA suppression among individuals infected with HIV (1). In fact, many studies have been performed to investigate the role of adherence in HIV therapy, however in most cases adherence has been measured as the percentage of prescribed doses taken. Such a definition of adherence is outdated and has been shown to have important limitations (2). Today, it is acknowledged that differences in individual patterns of non-adherence can have different implications for the treatment outcome.

Thus far no quantitative assessment has been made of the patterns of non-adherence in children, in which the role of extrinsic factors and intrinsic properties of the drugs used in combination therapy are distinguished. Such data may allow further understanding of the forgiveness of poor adherence to treatment and consequently provide guidance for the evaluation of alternative dosing regimens as well as improved recommendations for prescribers and patients. In the previous chapter we have proposed a model-based approach to evaluate forgiveness of drug to treatment interruptions and deviations from the prescribed regimen using an integrated approach in which the pharmacokinetic characteristics and the potency of the drug were integrated with the properties of the viral system in order to predict treatment outcome. Herein, the same concept is applied to a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and the pharmacokinetic-pharmacodynamic relationships of antiretroviral (ART) drugs are used to evaluate the effect of partial adherence to combination therapy. NNRTI-based regimens are widely administered as combination therapy in children, as recommended by the revised WHO guidelines (3). According to the guidelines, first-line antiretroviral therapy for HIV-infected children older than 3 years of age should include two nucleoside reverse transcriptase inhibitors (NRTI) and a non-nucleoside reverse transcriptase inhibitor. At the moment, the combination between abacavir, lamivudine and efavirenz (ABC-3TC-EFV) is one of the most commonly prescribed to the paediatric population (4). In addition, it has been established that high levels of adherence to NNRTI-based regimens are required in order to achieve and maintain viral suppression (1). However, further investigation is needed to establish in a quantitative and systematic manner what is the clinical relevance of different levels of adherence.

The objective of this study was therefore to evaluate different scenarios of poor adherence in a hypothetical population of 100 HIV-infected children between 3 and 12 years old receiving abacavir, lamivudine and efavirenz according to the currently recommended doses. Using clinical trial simulations we evaluate relevant scenarios of poor adherence, whilst discriminating the contribution of pharmacokinetic and pharmacodynamic factors from patient behaviour as determinants of variability in treatment response. Moreover, our approach allows scrutiny of the aforementioned factors without subjecting children to the burden of an actual clinical protocol, which in many cases might not be feasible due to ethical reasons. In contrast to the empiricism that has prevailed in the development of antiretroviral therapies, we envisage that our work will shed light on how adherence concepts can be used in conjunction with pharmacokinetic-pharmacodynamic relationships to evaluate the efficacy of drug combinations in HIV-infected children.

9.2. METHODS

Clinical trial simulation

Clinical trial simulations were performed in R (v 2.14.0) using a general template for clinical trial simulation previously developed by our group (5). In figure 1 an overview of the different simulation steps required to implement a clinical trial simulation able to assess the impact of different patterns of non-adherence for a combination of three drugs is presented.
Population demographics and treatment

A hypothetical population consisting of 100 HIV-infected children between 3 and 12 years old was selected with individuals evenly spread across the body weight range relevant to this group. Body weight has been simulated from an empirical distribution represented by two clinical trials in which HIV-infected children were enrolled, namely PENTA 13 (6) and ARROW part 1 (7). Simulations of body weight using a multivariate distribution were performed in R (v 2.14.0) according to the method described by Tannenbaum et al (8).

Patients in this population were given a combination of three drugs: abacavir (NRTI), lamivudine (NRTI) and efavirenz (NNRTI), which is the currently recommended first-line therapy for HIV-infected children (9). The doses used for each compound were based on the latest Summary of Product Characteristics (table 1). The duration of the hypothetical trial was 48 weeks, with viral load at week 48 as the primary endpoint for evaluation of efficacy. A measure of viral load < 50 copies/mL (detection limit) at week 48 was assumed to be treatment success.

Table 1 Doses of antiretroviral drugs currently recommended for the treatment of HIV-infected children, which were used in the simulation scenarios

<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>Abacavir</td>
<td>300 mg twice daily (14-21 kg)</td>
</tr>
<tr>
<td></td>
<td>450 mg twice daily (21-30 kg)</td>
</tr>
<tr>
<td></td>
<td>600 mg twice daily (&gt;30 kg)</td>
</tr>
</tbody>
</table>

Models for drug pharmacokinetics, drug sensitivity and drug efficacy

Three mathematical models were subsequently used to predict the effect of sub-optimal adherence on treatment outcome. 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 endpoint (viral load).

The pharmacokinetic profiles over time for each drug were simulated based on validated models available in literature (10–12). The median inhibitory concentration (IC50) was used to quantify agent-specific drug susceptibility. To model within-host changes over time in IC50 attributable to the emergence of new-drug resistant mutations the function described in equation (1) was used (13):

$$ IC_{50}(t) = \begin{cases} I_0 + \frac{I_r - I_0}{t_r} t & \text{for } 0 < t < t_r \\ I_r & \text{for } t \geq t_r \end{cases} $$

where \(I_0\) and \(I_r\) are, respectively, the values of IC\(_{50}\) (t) at baseline and time point tr at which the resistant mutations dominate. If \(I_r = I_0\), no new drug resistant mutation is developed during treatment. More complicated models for IC\(_{50}\) are available in literature (14, 15), however in clinical practice it is common to collect IC\(_{50}\) values only at baseline and failure time (16). The values of IC\(_{50}\) for the drugs included in our analysis were obtained from literature, such as the values of \(I_0\), which is based on phenotypic resistance tests for each drug (17–19).

Drug efficacy was considered to be constant over time in several viral dynamic studies (20–22). However, drug efficacy may vary because of the differences in drug concentration and other factors (i.e. development of resistance), which may vary during treatment. A pharmacodynamic sigmoidal additive Imax model was used to describe the concentration-effect relationship of three drugs and subsequently predict time-varying efficacy during the course of therapy with the drug combination:

$$ y(t) = \frac{\text{ConcEFV}(t)/IC_{50,EFV}(t) + \text{Conc3TC}(t)/IC_{50,3TC}(t) + \text{ConcABC}(t)/IC_{50,ABC}(t) + \Phi + \text{ConcEFV}(t)/IC_{50,EFV}(t) + \text{Conc3TC}(t)/IC_{50,3TC}(t) + \text{ConcABC}(t)/IC_{50,ABC}(t)}{\Phi + \text{ConcEFV}(t)/IC_{50,EFV}(t) + \text{Conc3TC}(t)/IC_{50,3TC}(t) + \text{ConcABC}(t)/IC_{50,ABC}(t)} $$
Time varying efficacy $\gamma(t)$ of the treatment ranges from 0 to 1 and is referred to as the treatment efficacy index (the inhibition rate of viral replication) in the viral dynamic model (Equation 3-5). If $\gamma(t) = 1$, the treatment is 100% effective, whereas if $\gamma(t) = 0$, the treatment 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 viral load (16). The model is basic and 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 which were suitable for the purpose of our analysis.

The model for viral replication is defined by three differential equations (equation 3, 4 and 5). Several parameters are used to describe the viral and immunological processes: $\lambda$ (day$^{-1}$ mm$^{-3}$) is the birth rate of new T cells created 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 inhibitory effect of the combination, predicted using the pharmacodynamic model depicted in equation (2).

\[
\frac{dT}{dt} = \lambda - d_T - [1-\gamma(t)] kTV \tag{3}
\]
\[
\frac{dT^*}{dt} = [1-\gamma(t)] kTV - \delta T^* \tag{4}
\]
\[
\frac{dV}{dt} = N \delta T^* - cV \tag{5}
\]

Adherence-resistance relationship

A correlation between adherence and resistance in antiretroviral drugs has been previously established by Bangsberg et al (23). Despite their initial findings, different correlations appear to exist for different classes of antiretroviral drugs (24). For example, most of the NNRTI and lamivudine mutations occurred in patients showing low adherence, suggesting that these two drugs have different adherence–resistance relationships compared to PIs and NRTIs. In our investigation a relationship between adherence and resistance was considered for efavirenz and lamivudine, given that these drugs are known to be more susceptible to resistance than abacavir (25, 26). Such a relationship was described in terms of a logistic regression (figure 2), in which the probability of resistance is linked to the number of days during which the levels of efavirenz remain below the target therapeutic level or lamivudine remains below the quantification limit. The final model describing the correlation and the corresponding parameter estimates used in the simulations were derived from published data (27, 28).

Simulation scenarios of variable adherence to treatment

The diagram in figure 3 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 (29–31), a predefined 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. Dropout rates were considered to be zero for the purpose of this analysis. 100 replicates were simulated for each scenario. Simulations were performed with NONMEM v7 and R (v 2.14.0) 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 and for the subject non-compliant in case of perfect and imperfect adherence was made for each scenario of non-adherence in order to evaluate the forgiveness of non-adherence of a NNRTI-based regimen in HIV-infected children.
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9.3. RESULTS

Under assumption of constant resistance rate, our simulations show that viral success is 10% for patients who show perfect adherence. Our simulations reveal that delays in drug intake do not affect treatment outcome of ABC/3TC-EFV combination in HIV-infected children between 3 and 12 years old. As can be seen in figure 4, the proportion of children who achieve viral success at week 48 in case of a delay in drug intake up to 4 hours in 20% or 40% of the days of treatment is not significantly different from the group showing perfect adherence. A closer evaluation of the viral load profiles also shows that delays in drug intake do not affect treatment outcome considering either the full population of 100 HIV-infected children or only the children who were not compliant to the prescribed dosing regimen. On the other hand, interruptions to the NNRTI-based regimen (i.e., simultaneous interruption of the three drugs) seem to have important implications for the outcome of antiretroviral therapy in this population of children. The treatment appears to be forgiving to interruptions of three days, whilst interruptions of one week may decrease the proportion of children experiencing treatment success at the end of the treatment from 90% to 87%, as compared to perfect adherence. A higher effect is observed for treatment interruptions of two weeks, which lead to a decrease the proportion of patients experiencing viral success from 90% to 78% (figure 5). In addition, treatment interruptions of 30 days caused a decrease in the proportion of children achieving viral failure from 90% to 58%.

By contrast, randomly missing 30 doses (i.e., 10% of the prescribed doses during the trial) resulted in a reduction in viral success from 90 to 80% (figure 6).

Figure 3 Diagram depicting the simulation scenarios of non-adherence to treatment investigated during the analysis.

Figure 4 Proportion of subjects achieving viral success (HIV RNA<50 copies/mL) at week 48 based on different delays in drug intake. 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.

Figure 5 Proportion of subjects achieving viral success at week 48 based on different duration of treatment interruption. On the x-axis the duration (days) of the treatment interruption is depicted.
9.4. DISCUSSIONS AND CONCLUSIONS

This is the first attempt to describe in a quantitative manner the impact of poor adherence to a NNRTI-based regimen when evaluating efficacy in a paediatric population. Given that high levels of adherence in paediatric antiretroviral therapy are very difficult to reach, efforts to identify which conditions represent a higher risk for viral failure is essential for ensuring positive treatment outcome. 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. In fact, our results are in agreement with a previous investigation (32) which showed that in patients with incomplete adherence, missing doses over a continuous and sustained interval may pose more risk for virologic failure than interspersed missed doses.

The possibility to identify the duration of treatment interruptions that pose more risk for virologic rebound in a specific population and for a specific drug combination represents a powerful tool for mitigation strategies during drug development and risk management after drug approval. 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. In fact, our results are in agreement with a previous investigation (32) which showed that in patients with incomplete adherence, missing doses over a continuous and sustained interval may pose more risk for virologic failure than interspersed missed doses.

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Optimisation of antiretroviral therapy

The possibility to simplify antiretroviral therapy is crucial to improve patient adherence and consequently the proportion of patients achieving viral success. In fact, the use of fixed-dose combinations has been a huge success in antiretroviral treatment in adults. However, new optimised dosing regimens are still required given that poor adherence to therapy remains a determinant of resistance. The methodology developed here may be used to test the forgiveness of poor adherence for new simplified dosing regimens, which may not necessary be higher. In other words, a simplified regimen may improve compliance to treatment, but may not always lead to improved forgiveness in those patients who remain non-adherent. Thus far, this issue has not been evaluated in a systematic manner before enrolling the patients into a clinical trial with a fixed-dose combination.

Pharmacokinetic-pharmacodynamic relationship as a “proxy” for efficacy

Fixed-combination medicinal products have been increasingly used either to improve compliance or to benefit from the added effects of the two or more medicinal products given together. According to the current EMA guideline on fixed-dose combinations (33), the proposed combination should always be based on valid therapeutic principles. In addition, it is necessary to assess the potential advantages (e.g. product rapidly effective, higher efficacy or equal efficacy and better safety) in the clinical situation against possible disadvantages (e.g. cumulative toxicity), for each fixed-combination product and for each dose of the fixed-combination product. In fact, the effectiveness of a simplified dosing regimen has been assessed through the use of pharmacokinetic, efficacy and safety trials (34–36). Given that switching to a simplified dosing regimen may be considered as a particular scenario of forgiveness of non-adherence, we anticipate that the use of this type of in silico evaluation will offer the advantage of using pharmacokinetic-pharmacodynamic relationships as a proxy for efficacy, preventing the need for costly and often complex efficacy trials in which it is not the efficacy (and safety) of the drugs or dose levels that are scrutinised, but rather the implications of the alternative dosing regimen. Analogously,
a similar situation exists when pharmacokinetics is used as “proxy” for efficacy in bioequivalence studies.

Potential limitations

The main limitation in our analysis is that toxicity was not taken into account in the simulation scenarios. It is well known that adverse events may influence the level of adherence of the patient. Taking into account the safety profile of abacavir and lamivudine and the mild adverse events that they seem to cause, efavirenz is the only drug for which toxicity should have been a concern. However, no association was found between efavirenz plasma concentrations and the risk of treatment discontinuations because of adverse events or toxicity (37).

Another potential limitation is the fact that we have deliberately chosen to use a basic model of viral dynamics. More complicated models are available that describe viral infection and replication, including different steps and physiological compartments associated with immune response and viral resistance. We do not expect that these models would lead to significantly different results. On the other hand, it is important to point out that in our methodology the inhibitory effect of each single drug could not be evaluated separately. Rather, it was expressed through an additive equation. Although in vitro studies may be used to evaluate 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. Here we show that despite the lack of such information, the use of a model-based approach enables the evaluation of the inhibitory effects in vivo of three drugs administered in combination.

Conclusions

In summary, we have shown that for similar levels of compliance treatment interruptions may pose a higher risk for viral rebound, as compared to randomly missed doses when using NNR-TI-based regimens. Our analysis also illustrates how mathematical and statistical models can be used to investigate adherence scenarios which cannot be evaluated in clinical practice in paediatric HIV due to obvious ethical and practical reasons. This methodology offers the opportunity for the development of patient-tailored treatments taking into account differences in compliance pattern. Further investigation of the impact of non-adherence to different antiretroviral combination treatments (e.g. boosted protease inhibitor-based regimens) is required to confirm the generalisability of the approach used here.

References


