

# IMPACT OF NON-ADHERENCE TO ANTIRETROVIRAL COMBINATION THERAPY IN HIV-INFECTED CHILDREN

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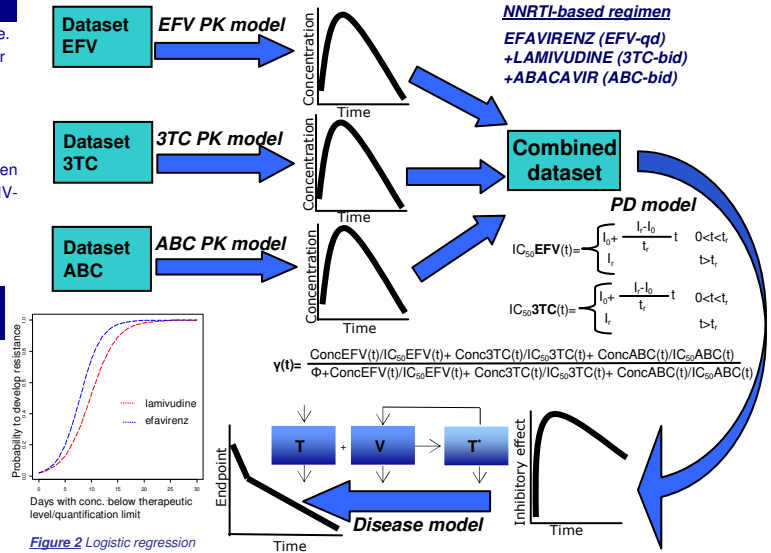
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## Introduction

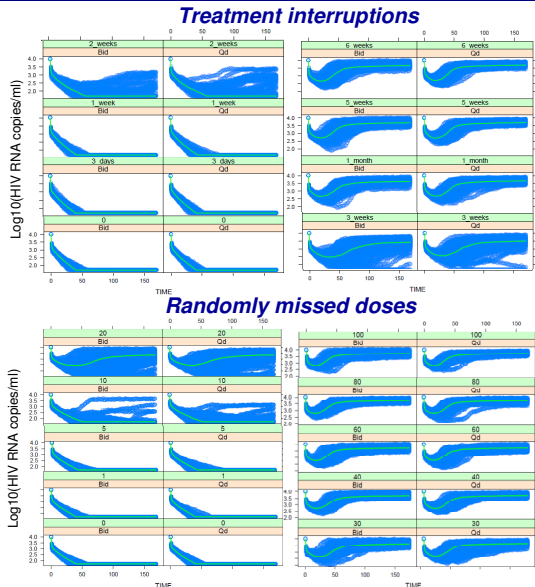
- Suboptimal adherence to antiretroviral therapy is the most common cause of viral resistance. Despite the magnitude of this problem, precise measures of forgiveness of non-adherence for antiretroviral combination treatments are still lacking.
- A distinction between the impact of different patterns of non-adherence has never been performed in a systematic manner.
- The aim of this analysis is to assess the impact of non-adherence for a NNRTI-based regimen (efavirenz (qd) + lamivudine (bid) + abacavir (bid)), as currently used in first-line therapy in HIV-infected children
- In addition, we intend to assess forgiveness to a simplified regimen in which all drugs are given once daily, which may be preferable for this patient group.

## Methods

- Published pharmacokinetic and pharmacodynamic models were integrated with a model for viral replication to predict treatment outcome, as defined by drop in viral load (fig.1)
- A logistic regression was used to describe the relation between sub-therapeutic drug levels and the probability of developing resistance (fig.2)
- Different scenarios of non-adherence (treatment interruption, randomly missed doses and delays in drug intake) were simulated. 100 clinical trials were simulated for each scenario of non-adherence.
- 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=30) in each scenario.
- The primary efficacy endpoint was the proportion of patients with HIV-1 RNA <50 cp/ml at week 48.



## Results

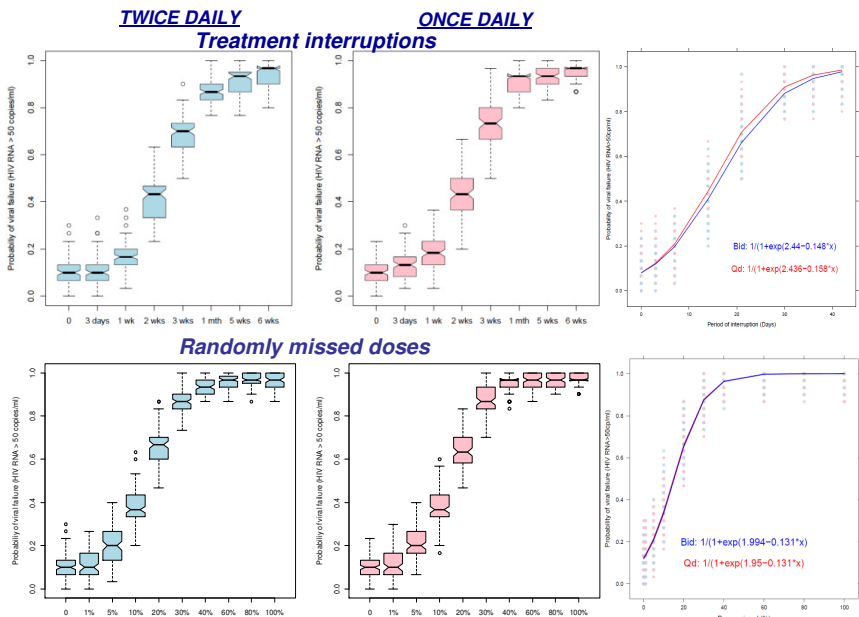


**Figure 3** Median profiles of viral load vs. time for each scenario of non-adherence for bid and qd dosing regimens. The blue lines represent the median profile for each trial, the green line represents the median of the median profiles of viral load vs. time for 100 trials.

## Conclusions

- Clinical trial simulations can be applied as a tool for the evaluation of non-adherence to combination treatment in children. Such an evaluation would not be feasible in clinical practice due to ethical reasons and design issues.
- Based on the simulated results, treatment interruptions to a NNRTI-based regimen may pose more risk for virologic rebound than the same number of randomly missed doses.
- Once daily doses of abacavir and lamivudine appear to show efficacy and forgiveness comparable to what is observed after the licensed bid dosing regimen

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**Figure 4 (left)** Boxplots showing the probability of viral failure for each scenario of non-adherence after bid and qd dosing regimens.

**Figure 5 (above)** Fitting of the probability of viral failure vs. duration of treatment interruption and vs. the percentage of randomly missed doses during the trial.

**References:** (1) Teutonico, D. et al. Multivariate patient simulation for clinical trial optimization in COPD. Poster presented at PAGE Conference 2011  
 (2) Wu et al. Modeling long-term HIV dynamics and antiretroviral response: effect of drug potency, pharmacokinetics, adherence and drug resistance. J Acquir Immune Defic Syndr. 2005 Jul 1;39(3):272-83

