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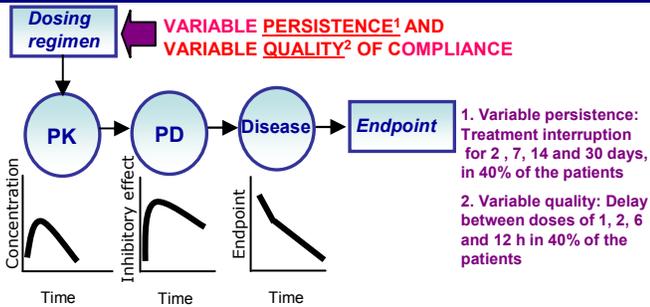
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Introduction

- Data exist showing failure of treatment with antiretrovirals due to inadequate **adherence** to the prescribed dosing regimen.
- Several studies have been performed to assess whether high rates of adherence are necessary to achieve and maintain viral suppression during the course of treatment with anti-retroviral drugs. However, none of these studies have explored compliance in a systematic manner, identifying which specific drug properties make treatment response more likely to be affected by poor adherence.

- **The aim of this investigation was to evaluate the forgiveness of antiretroviral therapy to variable compliance, taking into account the differences in pharmacokinetics and pharmacodynamic properties of currently used drugs**

Methods

VARIABLE PERSISTENCE[1] AND VARIABLE QUALITY[2] OF COMPLIANCE

1. Variable persistence: Treatment interruption for 2 , 7, 14 and 30 days, in 40% of the patients

2. Variable quality: Delay between doses of 1, 2, 6 and 12 h in 40% of the patients

❖ Hypothetical population of 100 HIV-infected children aged between 3 months and 11 years. Duration of the trial: 90 days

❖ Paradigm drug: efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor

❖ Published PK and PD models were used in conjunction with a model for viral replication to predict viral load and CD4 count after 90 days for different scenarios with variable degrees of adherence to therapy (1,2).

STEP 1

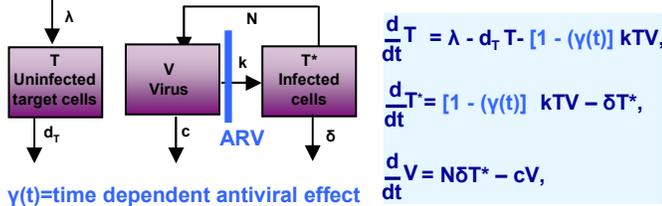Simulation of plasma concentration vs. time profiles using a two-compartment model for EFV

STEP 2

- Simulation of PD effects using a Imax model
- Inclusion of resistance development
- I_0 EFV=0.0044 mg/l
- I_r EFV=0.44 mg/L

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

$$IC_{50}(t) = \begin{cases} I_o + \dfrac{(I_r - I_o)\,t}{t_r} & \text{for } 0 < t < t_r \\ I_r & \text{for } t > t_r \end{cases}$$

STEP 3

Simulation of treatment outcome- viral load and CD4 count vs. time

$$\frac{d}{dt}T = \lambda - d_T T - [1 - (\gamma(t)]\,kTV,$$

$$\frac{d}{dt}T^* = [1 - (\gamma(t)]\,kTV - \delta T^*,$$

$$\frac{d}{dt}V = N\delta T^* - cV,$$

$\gamma(t)$=time dependent antiviral effect

Conclusions

1. Simulation scenarios can be used to explore the implications of non-adherence to treatment.

2. Our results indicates that response to treatment with efavirenz is susceptible to treatment interruptions > 1 week, despite it's long pharmacokinetic half-life.

3. Although other mechanisms and drug combinations must be considered in the evaluation of adherence, a model-based approach may provide a framework for the optimisation of the dosing regimens in paediatric HIV, enabling the identification of the pharmacokinetic and pharmacodynamic properties which determine forgiveness.

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Results

Efavirenz, a NNRTI with long half-life and high potency, appears to be insensitive to variable quality of compliance, such as delays in drug administration, whilst it is more susceptible to the interruption of therapy for long periods (2-3 weeks).

Figure 1. Median and 5% and 95% percentiles of the simulated viral load (left) and CD4 count (right) vs. time for a hypothetical population (n=100) of children, assuming perfect adherence (N=100 replicates trials).

QUALITY: 1 hour 60% · 1 hour 80% · 2 hours 80% · 12 hours 60%

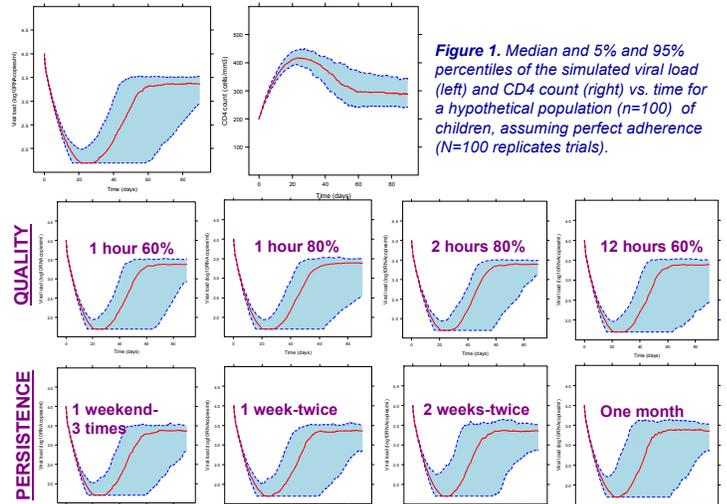**PERSISTENCE**: 1 weekend-3 times · 1 week-twice · 2 weeks-twice · One month

Figure 2. Median and 5% and 95% percentiles of the simulated viral load vs. time for a hypothetical population (n=100) of children according to different degrees of adherence. Variable quality (upper panel) and variable persistence (lower panel) (N=100 replicates trials).
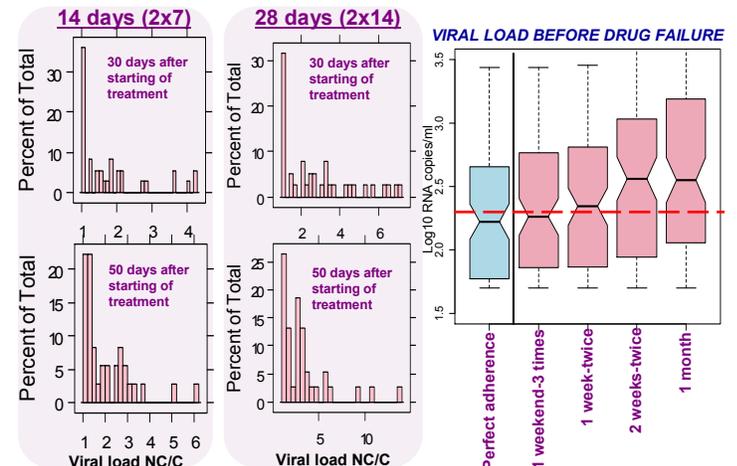

14 days (2x7) — 30 days after starting of treatment / 50 days after starting of treatment — Viral load NC/C

28 days (2x14) — 30 days after starting of treatment / 50 days after starting of treatment — Viral load NC/C

VIRAL LOAD BEFORE DRUG FAILURE — Log10 RNA copies/ml — Perfect adherence · 1 weekend-3 times · 1 week-twice · 2 weeks-twice · 1 month

Figure 3. (Left panels) Ratios between the median simulated viral load in case of non compliance (NC) and perfect compliance (C) at 30 days and 50 days after starting of treatment (n=40). The implication of poor adherence is reflected by the increase in the ratio NC/C after interruption of treatment for a period of 28 days as compared to 14 days . (Right panel) Implications of poor adherence on viral load prior to drug failure (i.e., resistance). The red line represents an arbitrary threshold for acceptable variation in response assuming perfect compliance to treatment.

References: (1) Kappelhoff et al. Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. Clin Pharmacokinet. 2005;44(8):849-61. (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

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