Dose-Timing Information Improves the Clinical Explanatory Power of Data on Patient Adherence to Antiretroviral Drug Regimens

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Motivation

- Plasma viral load is the strongest predictor of the risk of progression to AIDS and death [Mellors et al. 1996, Hughes et al. 1997, Marchner et al. 1998, Delta Coordinating Committee 1999]
- New treatments (PI's) are very effective in suppressing the virus but are not a cure for HIV disease
- Many patients receive clinical benefit from treatment; however, others do NOT or only temporarily receive clinical benefit
- Poor patient adherence to therapy is one of the most cited reasons for treatment failure [Montaner et al. 1998, Paterson et al. 2000]

PK sampling design

Dose

On site

C C C C C C C C C C C C

+2 4 6 8 12 (24) hours

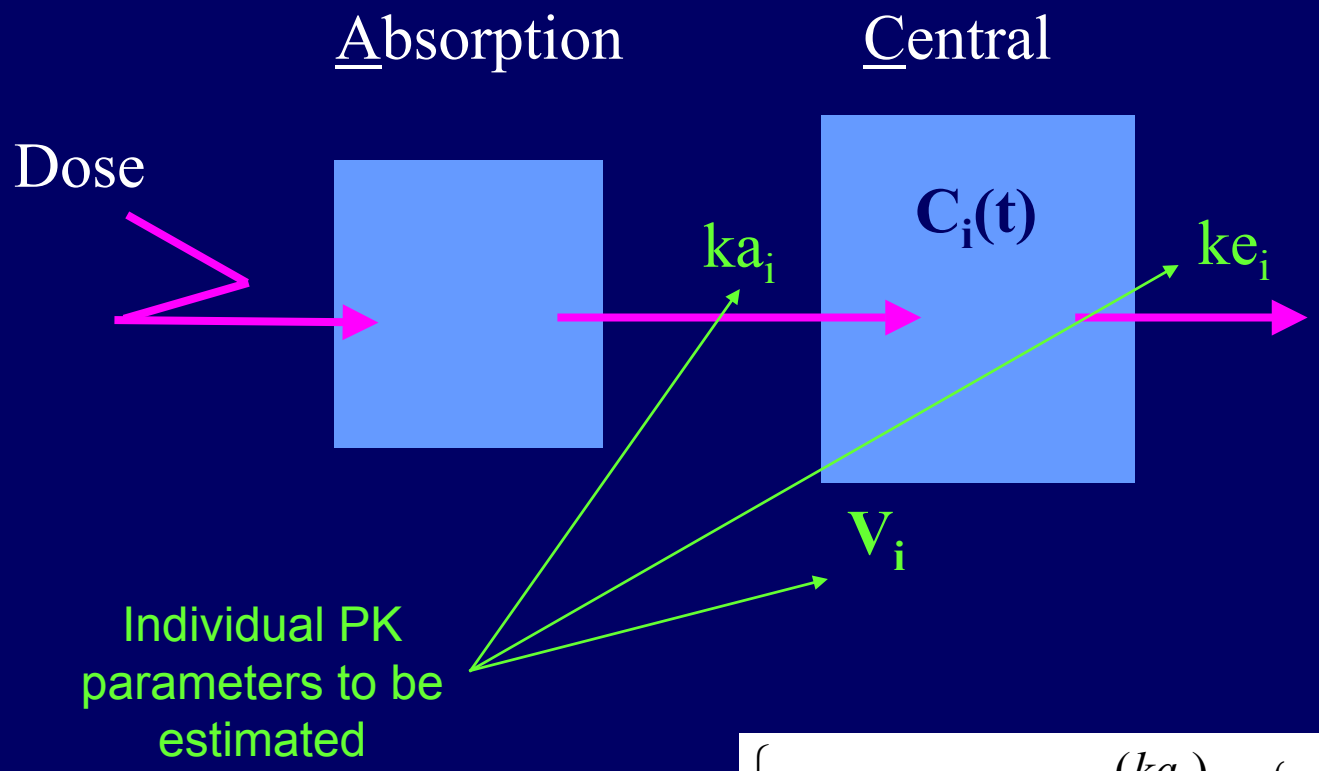
Day 21

Week 8 16 24 48

: Last reported dose

Lopinavir/ritonavir (QD: 800/200 mg or BID: 400/100 mg), stavudine, and lamivudine.

Modeling PI concentrations



Differential equations leading to

$$\begin{cases} C_i(t) = Ca_i(t_d)\dfrac{(ka_i)}{(ka_i - ke_i)}\left\{e^{-(ke)_i t} - e^{-(ka)_i t}\right\} \\ \qquad + C_i(t_d)e^{-(ke)_i t} \\ Ca_i(t_d) = Ca_i(t_{d-1})e^{-(ka)_i t_d} + \dfrac{Dose}{V_i} \end{cases}$$

First step

Estimation of the individual PK parameters : ka_i, ke_i, V_i

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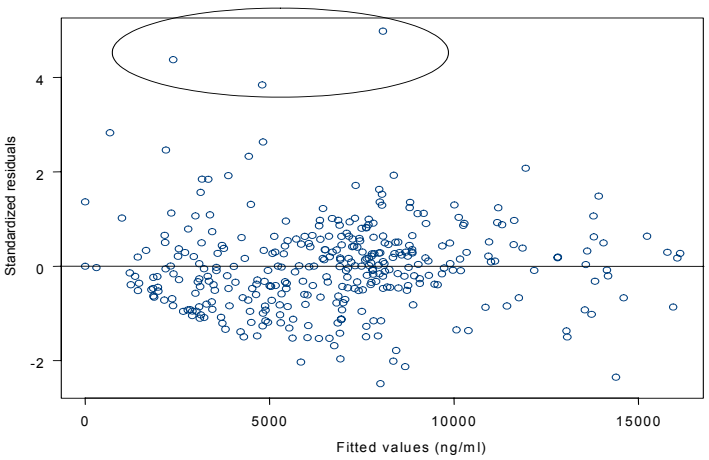
Estimation based on a population approach

First Order Conditional Estimates (FOCE)

The model did not converge when using the last reported dose and the assumption of steady state !

More complex model with additional compartments



Same model introducing dosing history

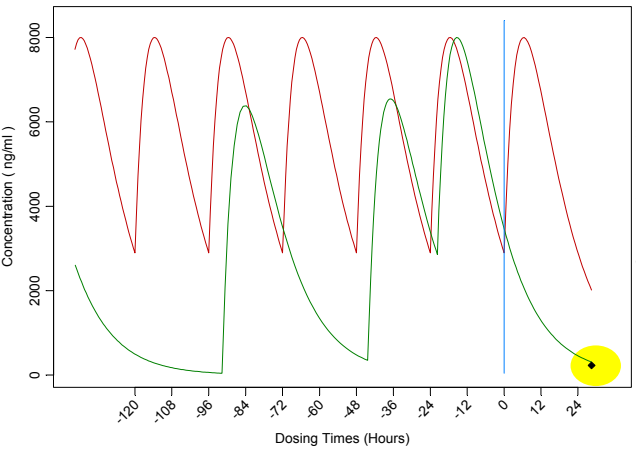
Convergence

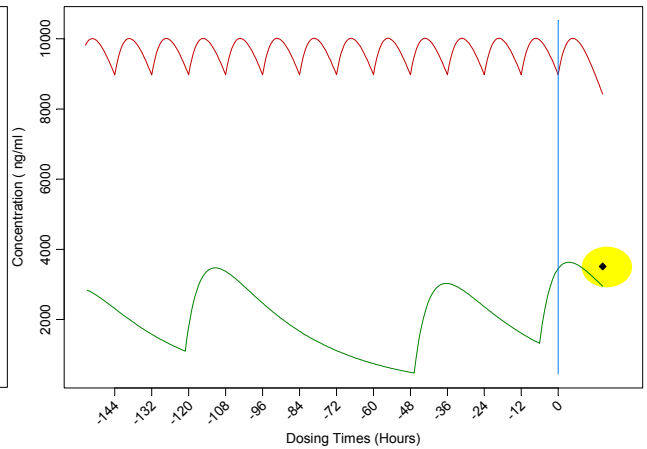
Individual expected values

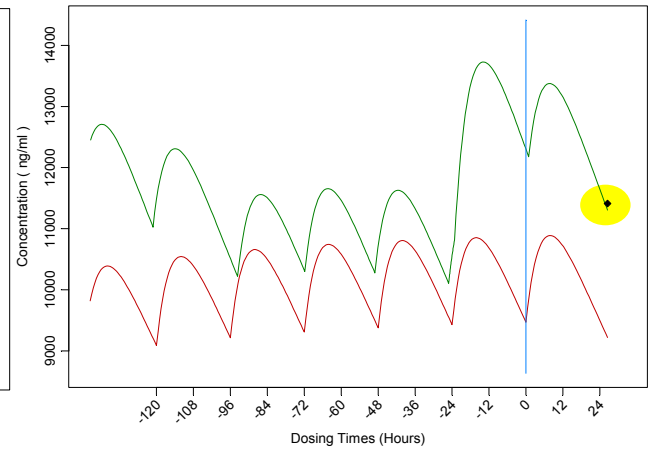
of the parameters :

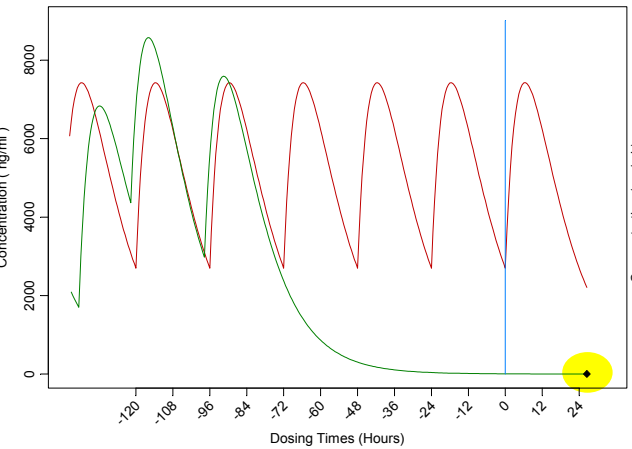
$\hat{ka}_i$, $\hat{ke}_i$, $\hat{V}_i$ (expected a posteriori values)

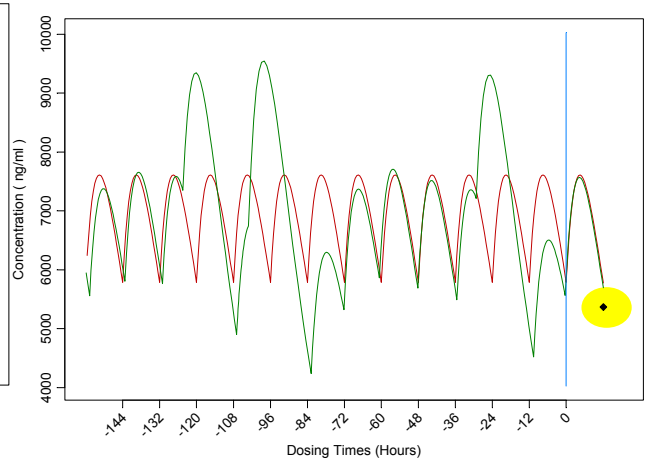
Steady-State assumption vs Electronically Monitored dosing histories

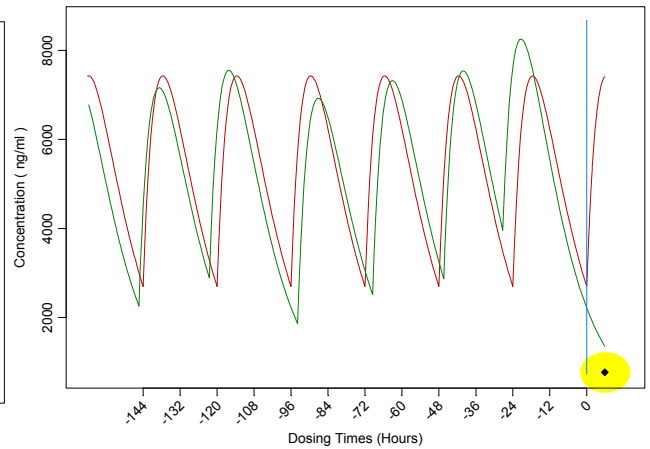




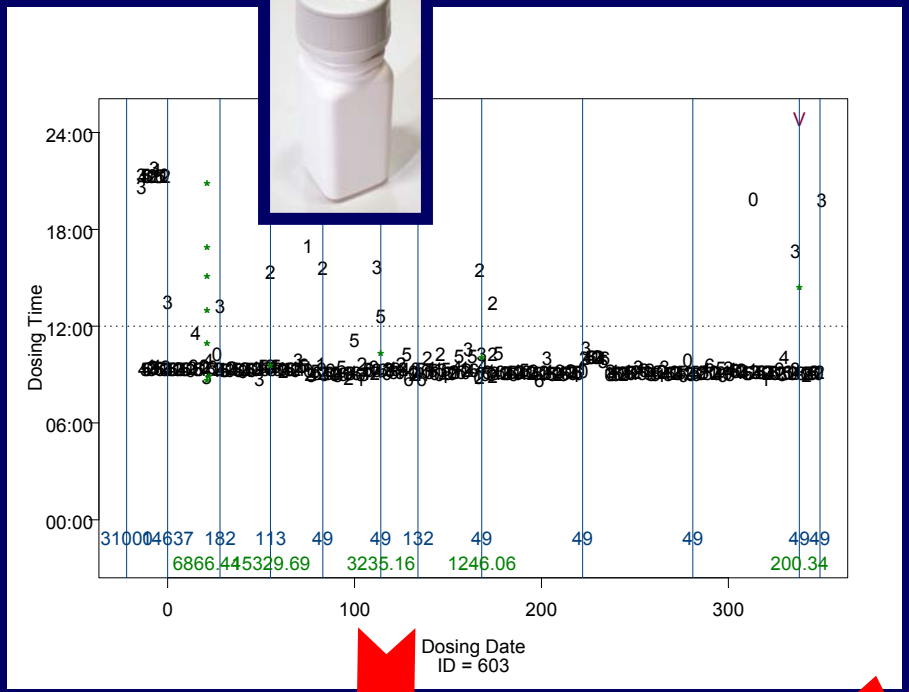








Internal exposure



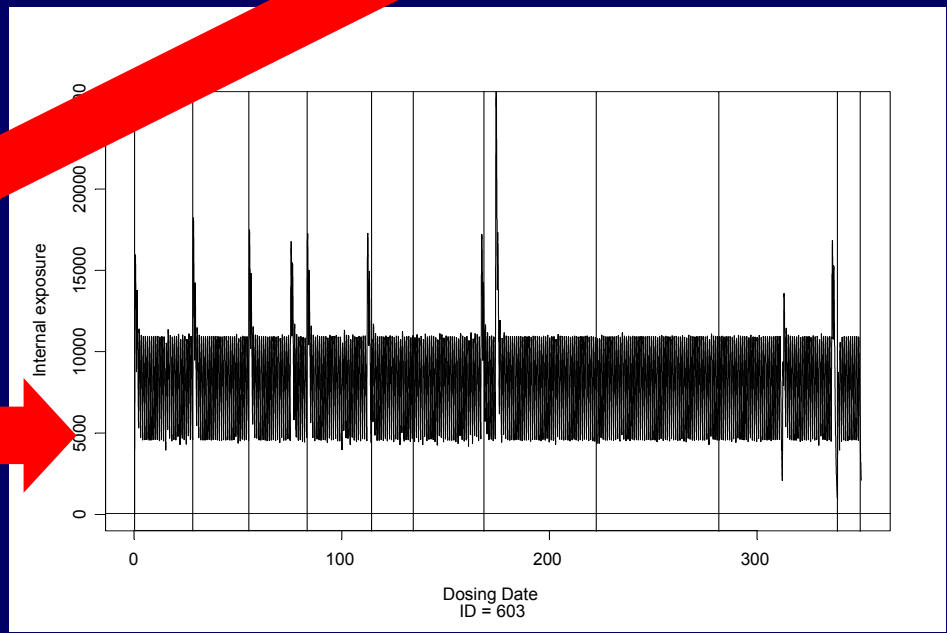
Dosing regimen

$\hat{ka}_i$

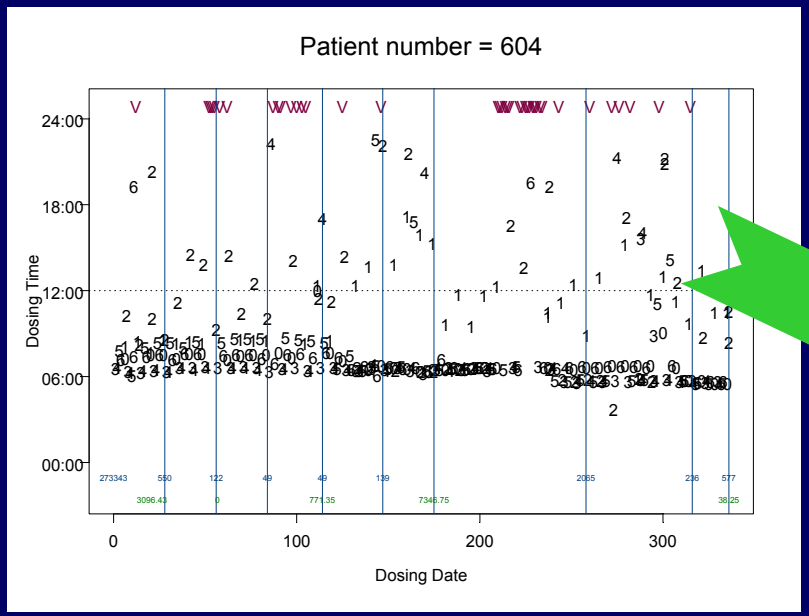
$\hat{ke}_i$

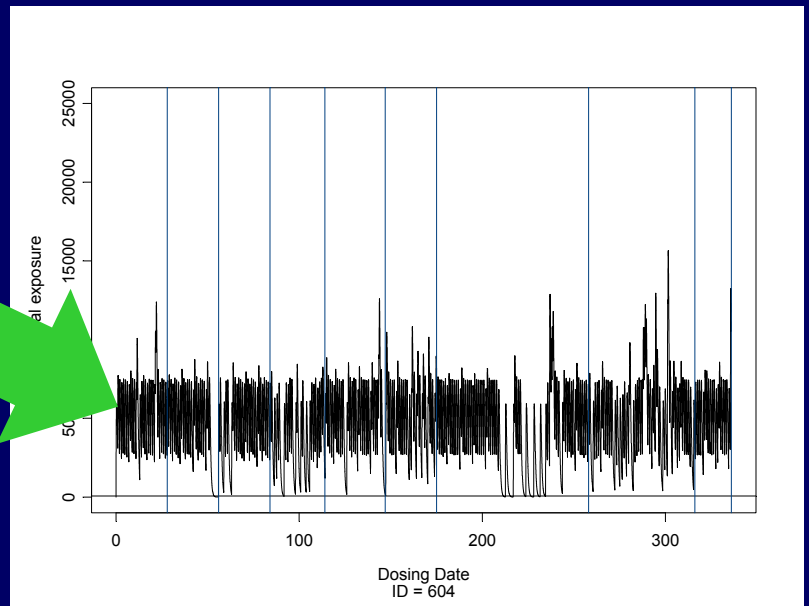
$\hat{V}_i$

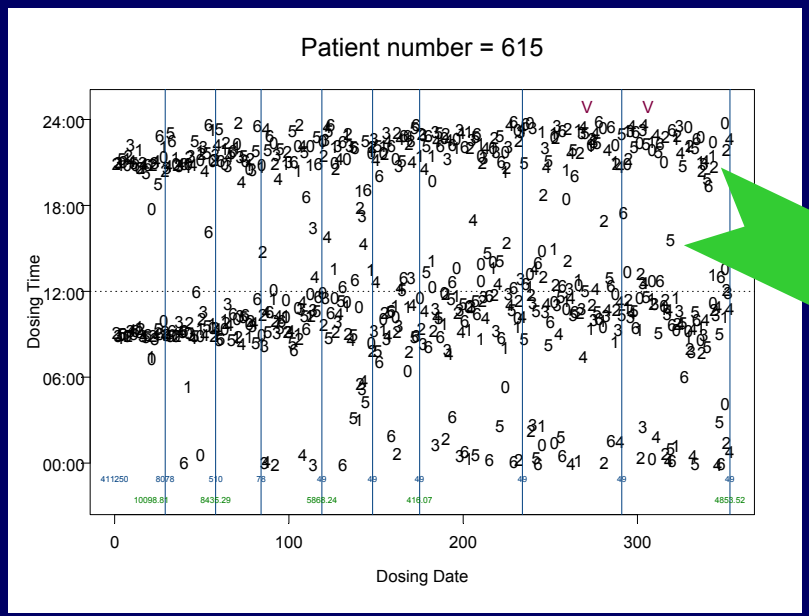
$$\begin{cases} C_i(t) = Ca_i(t_d)\dfrac{(ka_i)}{(ka_i - ke_i)}\left\{e^{-(ke)_i(t-t_d)} - e^{-(ka)_i(t-t_d)}\right\} \\ \qquad + C_i(t_d)e^{-(ke)_i(t-t_d)} \\ Ca_i(t_d) = Ca_i(t_{d-1})e^{-(ka)_i(t_d - t_{d-1})} + \dfrac{Dose}{(V)_i} \end{cases}$$

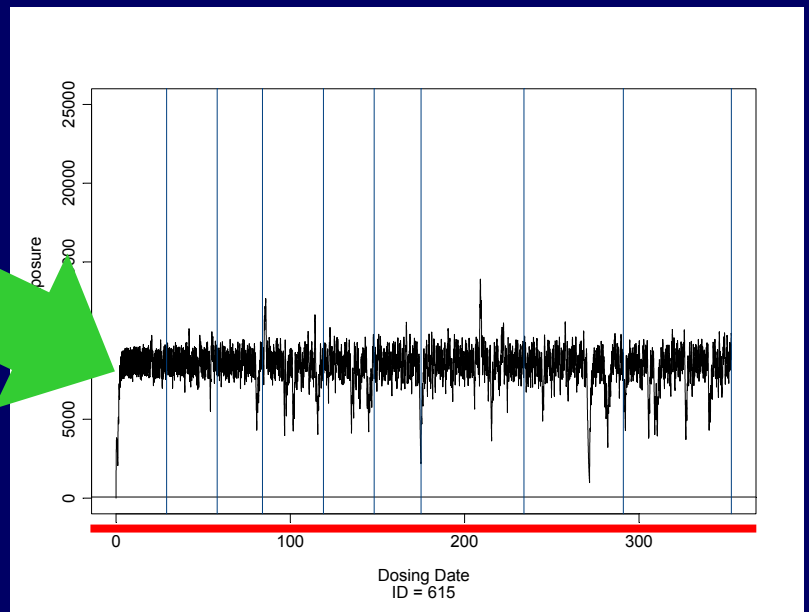


Examples (QD vs BID)

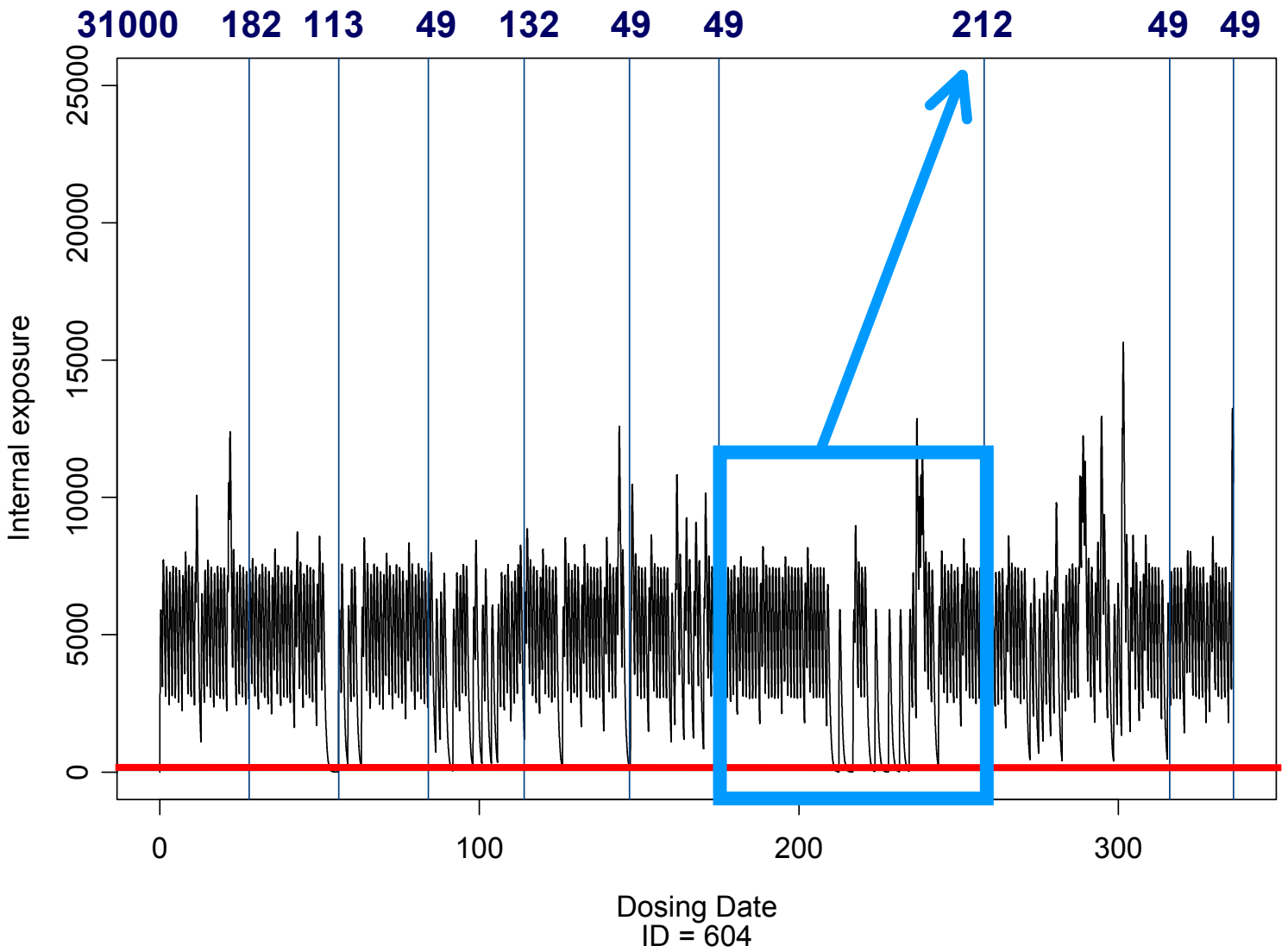








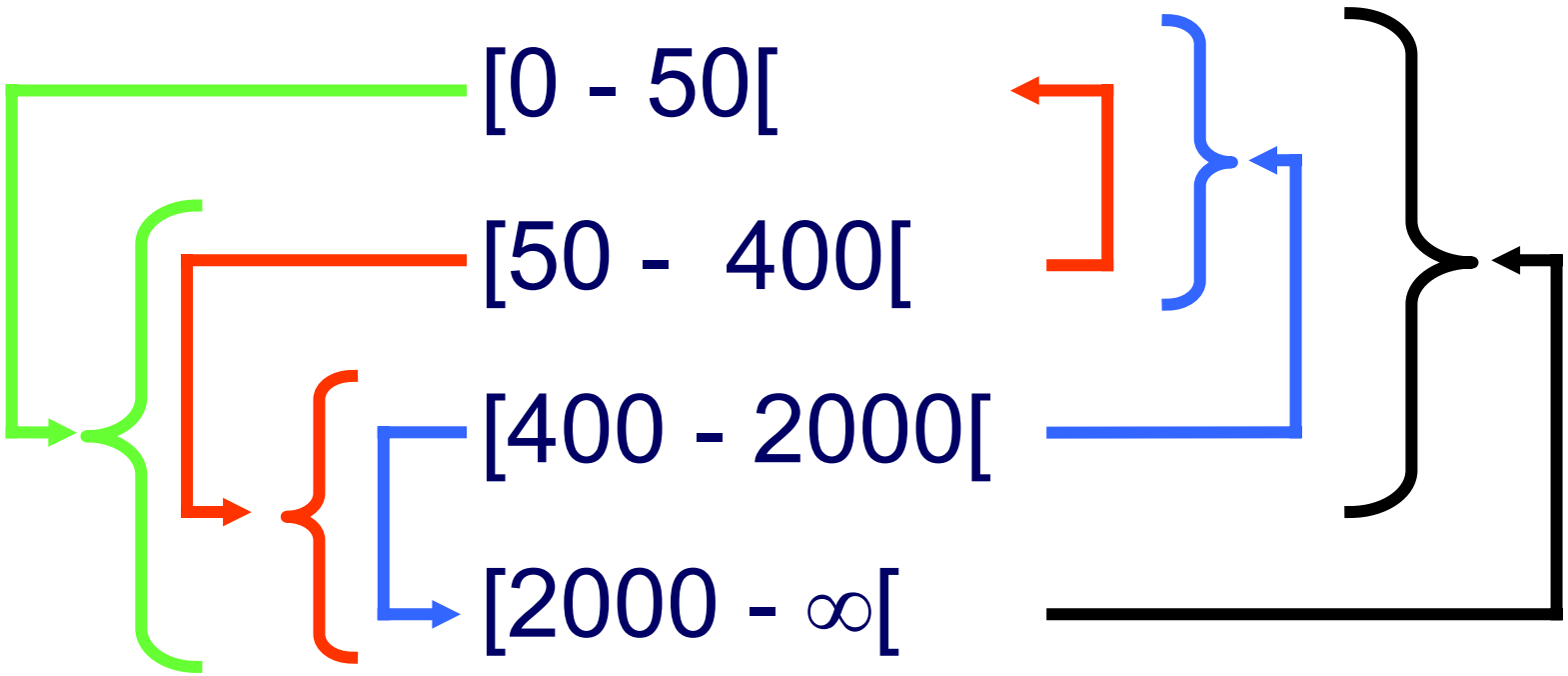
Viral load observation



Model for repeated ordered ordinal variables

Probability of

Deterioration *Improvement*



Internal exposure summary between visits

- Mean concentration
- Median concentration
- Percent of time IE < EC50
- Actual time IE < EC50

Note: IE = Internal Exposure
EC50 = 70 ng/ml

Model comparison

Deviance table

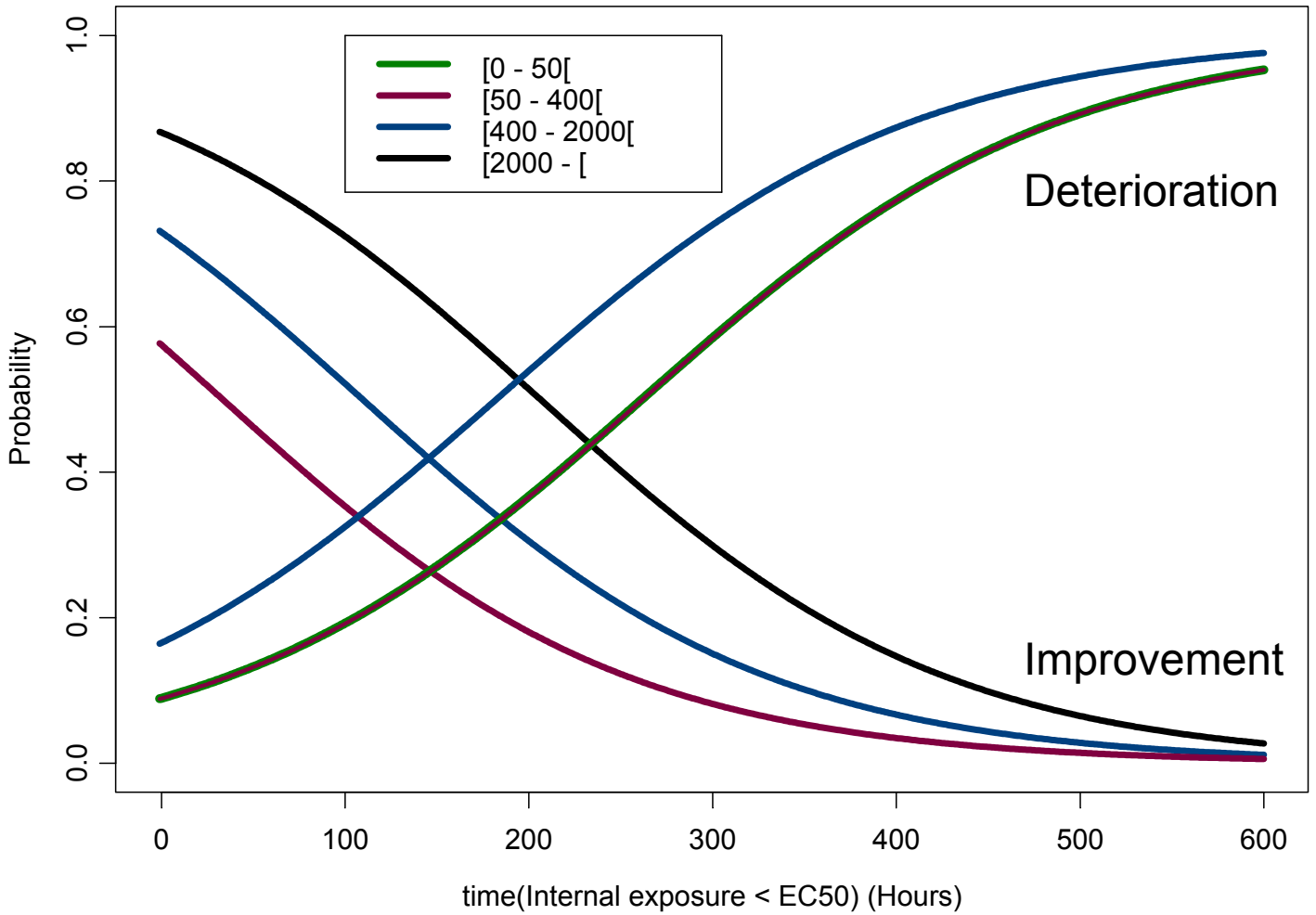
Model deviance	Deterioration	Improvement
Null model	418.1	404.5
Mean	405.5 *	397.5 *
Median	402.0 *	395.7 *
% time(IE<EC50)	392.9 *	392.1 *
time(IE<EC50)	390.6 *	389.2 *

*comparisons against the null model
p-values < 0.05

Parameter estimation

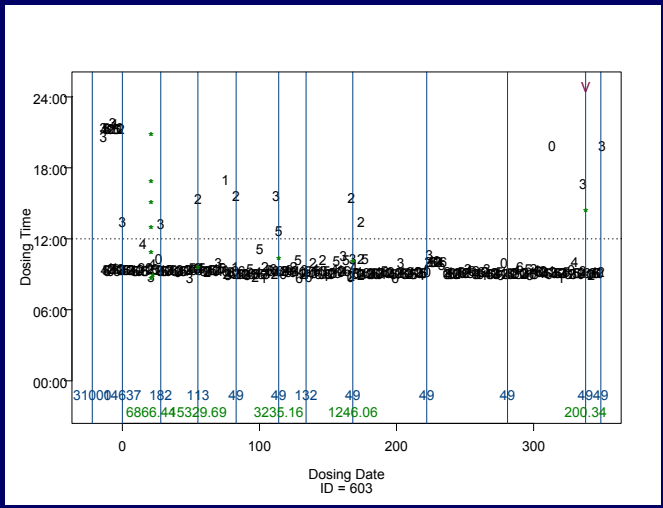
	Deterioration			Improvement		
	Value	Std	t	Value	Std	t
Intercept	-2.32	0.28	-8.3	6.74	0.55	12.2
[0-50[	*	*	*	*	*	*
[50-400[	2.20	0.35	6.3	-2.18	0.36	-6.0
[400-2000[	4.06	0.48	8.4	-4.21	0.50	-8.4
[2000- ∞[	4.81	0.48	10.1	-4.87	0.49	-9.9
Sub table 1	*	*	*	*	*	*
Sub table 2	-2.21	0.37	-6.0	-1.53	0.43	-3.6
Sub table 3	-3.35	0.53	-6.3	-4.26	0.49	-8.7
time(IE<EC50)	0.009	0.003	3.5	-0.009	0.002	-3.7

Results



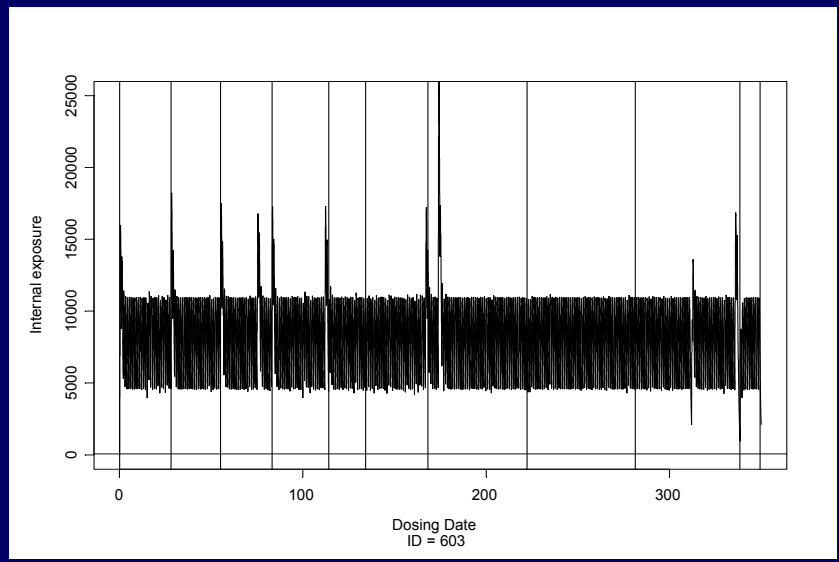
Direct relationship?

Dosing histories



Viral load

VL



Timing Error (TE)

- δ_{ik} = the k^{th} dosing interval for the i^{th} patient
- δ_0 = prescribed dosing interval (12 h or 24 h)
- $\delta^*_{ik}=(\delta_{ik} - \delta_0) / \delta_0$: standardized dosing interval

$$TE_i = \sqrt[3]{\frac{1}{n_i}\sum_k (\delta^*_{ik})^3}$$

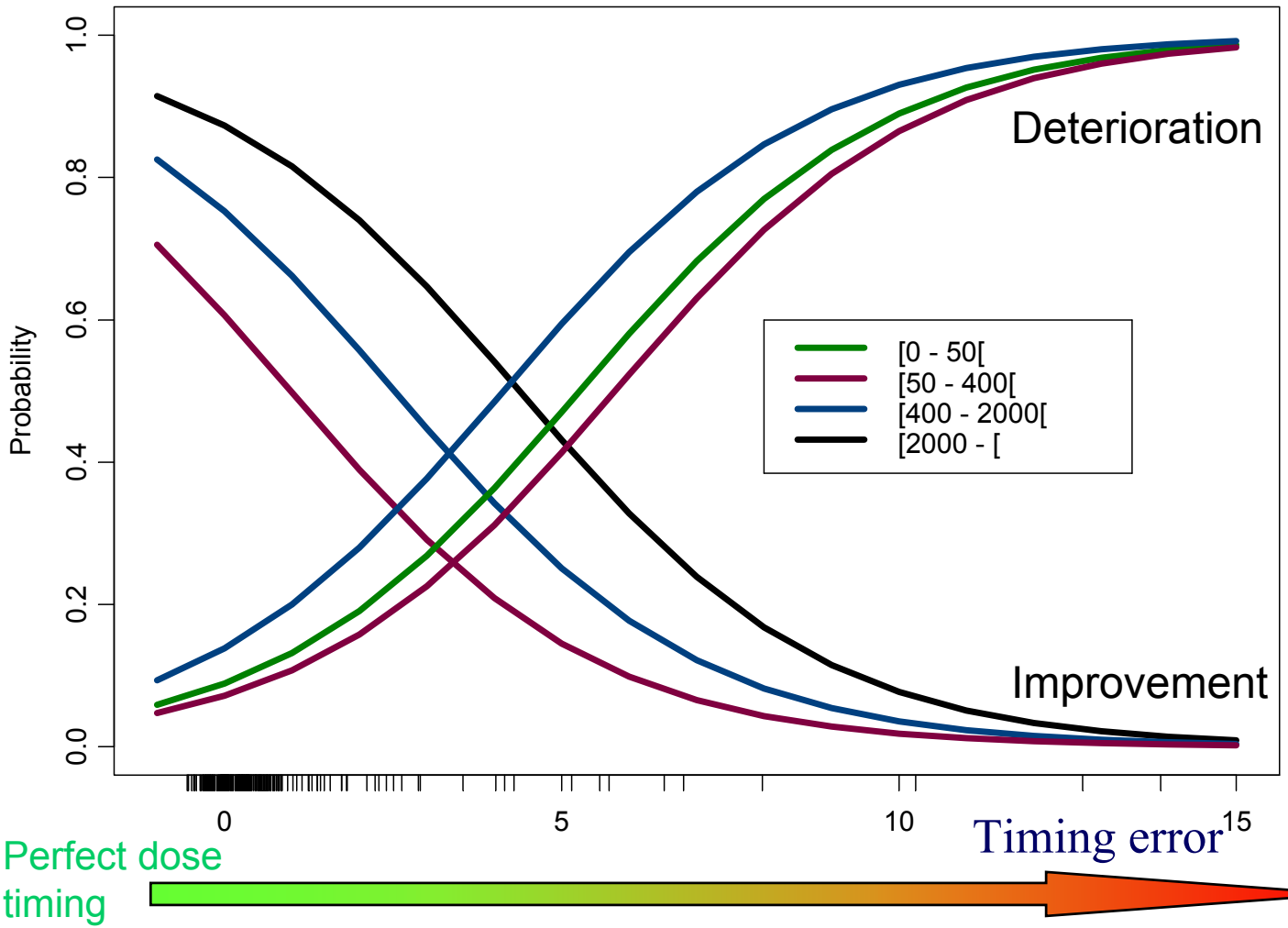
Adherence variables

Deviance table

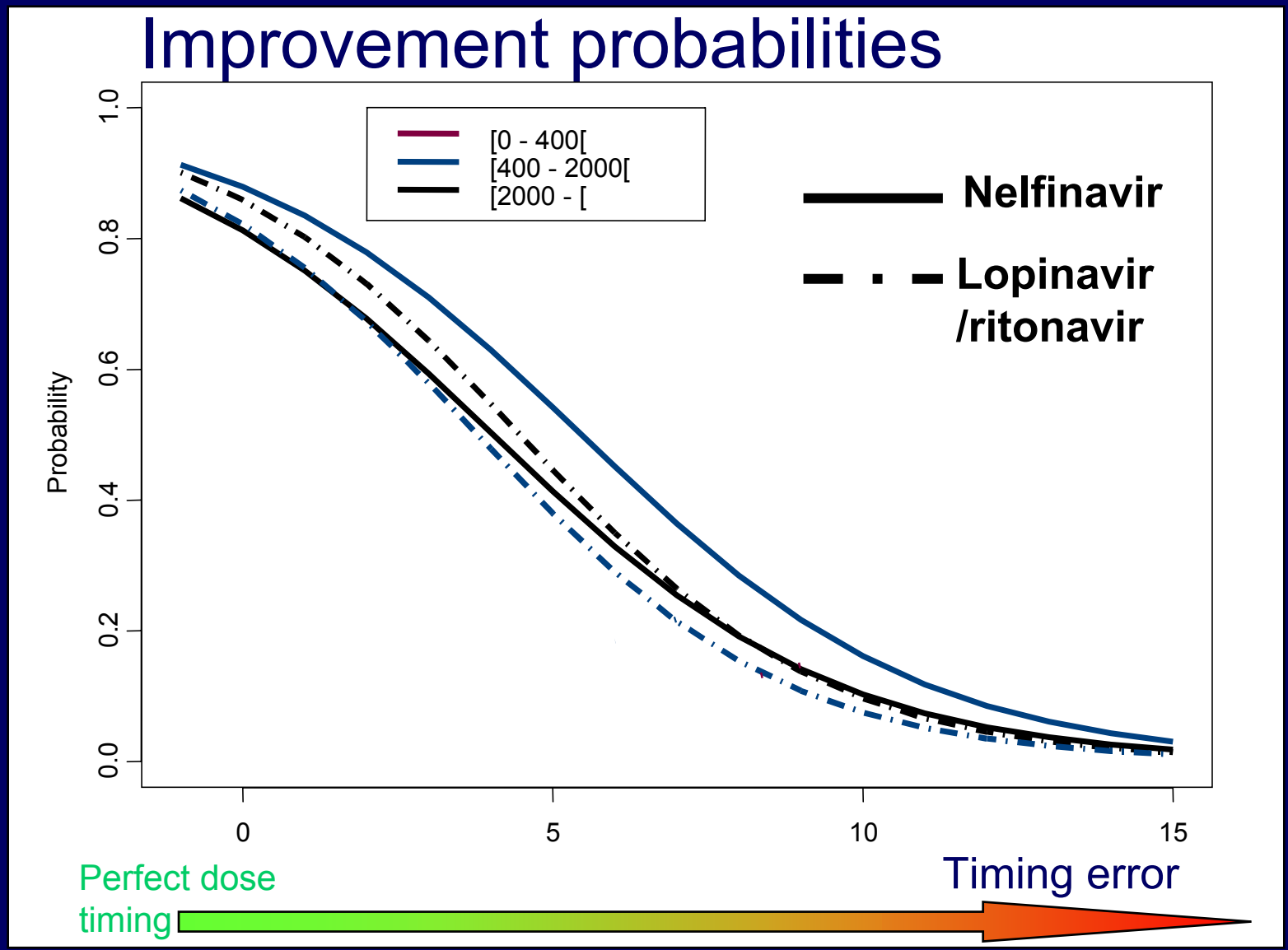
	Deterioration	Improvement
Null model	418.1	404.5
Timing compliance	414.9	403.8
Correct dosing	411.4 *	402.8
Taking compliance	401.5 *	396.6 *
Timing error	389.1 *	388.9 *
Time(IE<EC50)	390.6 *	389.2 *

* comparisons against the null model
p-values < 0.05

Results

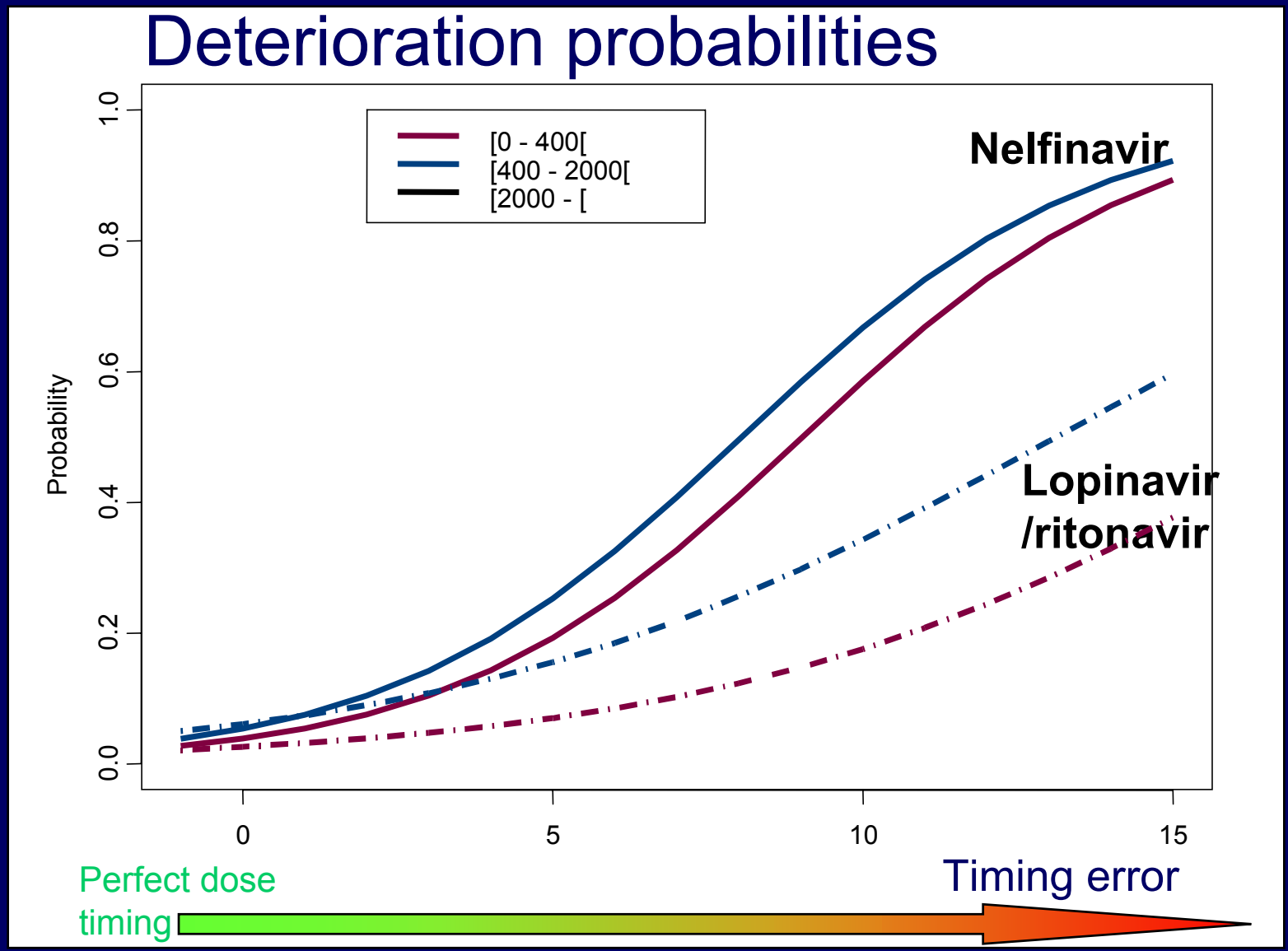


Comparison between PIs



Data from a cross-study comparison

Comparison between PIs



Data from a cross-study comparison

Conclusions

- PK estimates can be improved by using electronically monitored dosing histories obtained prior to blood sampling as model input.
- Dose timing information increases the explanatory power of patient adherence data and its association with antiretroviral treatment outcomes.
- The proposed methodology allows separate study of the “on” and “off” processes (improvement vs deterioration)
- After initial viral suppression, an antiretroviral regimen containing lopinavir/ritonavir was not highly dependent on timing errors.

Making it simple for the patient

Patient adherence → Model → Viral Load → Patient care

Timing error