Treatment monitoring of HIV infected patients : optimal drug dose control

M. Prague, D. Commenges, J. Drylewicz and R. Thiébaut

ISPED Bordeaux 2 University
Inserm U897 - Epidemiology and Biostatistics Research Center Biostatistics Team

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HIV Background

HAART : Keep most patients controlled (Dray-Spira et al., AIDS, 2007)

$\rightarrow$ short-term and long-term adverse effects exist

Treatment interruption : SMART study, interrupted clinical trial & Increased risks of adverse events (Silverberg et al., AIDS, 2007)

- Arm 1, continuous HAART treatment
- Arm 2, stop and go HAART treatment depending on CD4 count

$\rightarrow$ Possibility of adapting the dose: not seriously attempted yet.

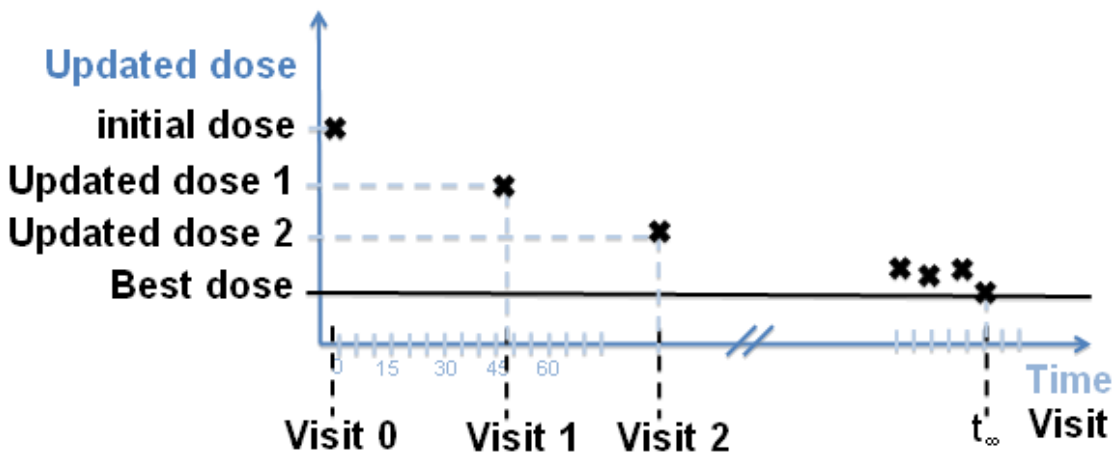
Main Issue

Optimal treatment :

Murphy (JRSS-B, 2003) formalized the theory of optimal treatment regimes in terms of maximizing a "potential outcomes".

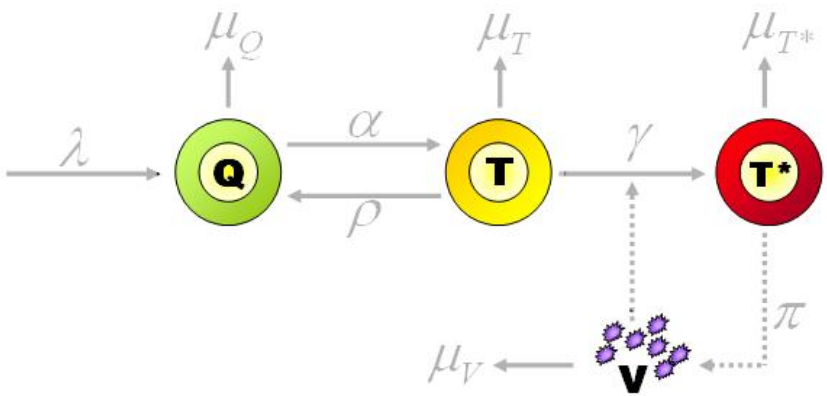
Reduce treatment dose in an adaptive strategy scheme :

- → Observe biomarkers of a HIV-infected patient ($\mathcal{H}^i_{t_k}$),
- → Link dose and effect in ODE (Kirschner et al., JMB, 1997)
- → Forecast an optimal dose $d(\mathcal{H}^i_{t_k})$ which maximizes $\mathbb{E}[Y(d)]$,
- → Continue in an iterative manner at time t_{k+1}.



Biological model : dynamical system

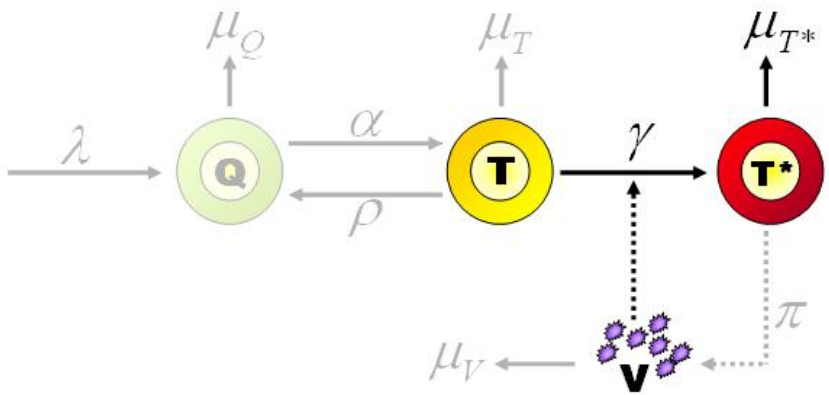
Biological compartments



Compartments	Meaning
Q	Quescient CD4
T	Non infected activated CD4
T^*	Infected CD4
V	Virions

Biological model : dynamical system

T^* cells (infected CD4) dynamic

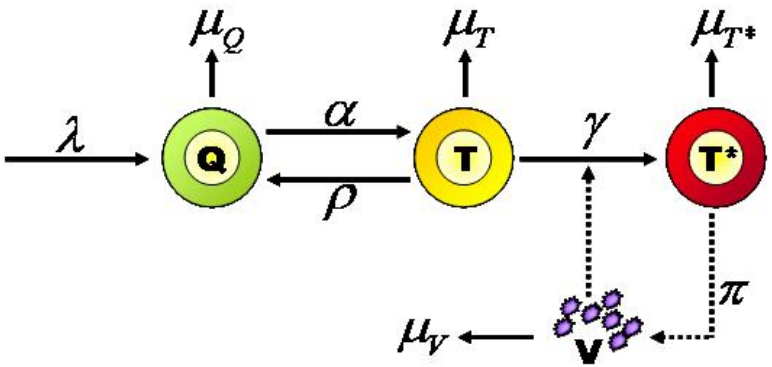


$$\frac{dT^*}{dt} = \gamma VT - \mu_{T^*} T^*$$

Parameter	Meaning
μ_{T^*}	T^* cells death rate
γ	Infectivity rate of T cells by virions

Biological model : dynamical system

Activated T-cells model



$$\begin{cases} \frac{dQ}{dt} &= \lambda - \mu_Q Q - \alpha Q + \rho T \\ \frac{dT}{dt} &= \alpha Q - \rho T - \mu_T T - \gamma V T \\ \frac{dT^*}{dt} &= \gamma V T - \mu_{T^*} T^* \\ \frac{dV}{dt} &= \pi T^* - \mu_V V \end{cases}$$

Dose Introduction :

$$\tilde{\gamma} = \log(\gamma) = \tilde{\gamma}_0 + \beta\psi(d(t)) \quad | \quad \beta < 0 \text{ and } \frac{\partial \psi}{\partial d} > 0$$

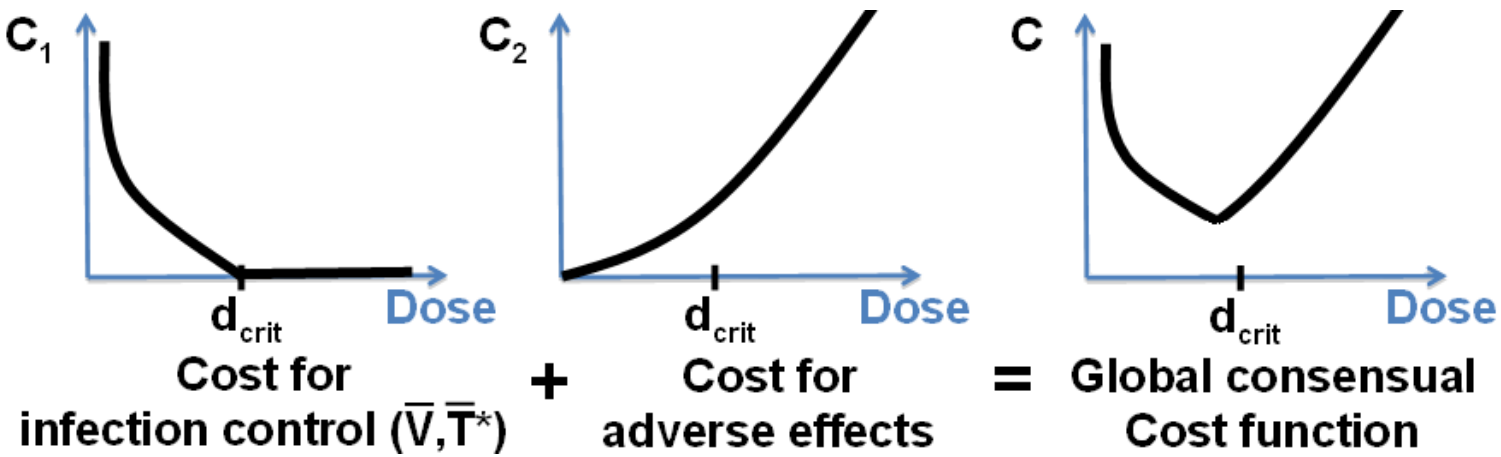
Equilibrium and Optimal dose

Reproductive Number : $R0 = \frac{\pi\alpha\lambda\gamma_0 \exp^{\beta\psi(d(t))}}{\mu_V\mu_{T^*}(\alpha\mu_T+\rho\mu_Q+\mu_T\mu_Q)}$

If $R0 > 1$, Non-trivial equilibrium ($\bar{V} \neq 0$ and $\bar{T}^* \neq 0$)

→ Absolutely control : $R0(\xi, d) \leq 1$

→ Optimal dose d_{crit}: $R0(\xi, d_{crit}) = 1$



→ $\tilde{\xi}^i = \left(\tilde{\alpha}^i, \tilde{\lambda}^i, ..., \tilde{\gamma_0}^i, \tilde{\mu}_V^i\right)$ are unknown : **Bayesian approach**

Prior Elicitation by MAP

Observation Model

$$\text{Viral Load :} \quad Y_{ij1} = \log_{10}(V(t_{ij}, \tilde{\xi}^i)) + \epsilon_{ij1}$$

$$\text{CD4 count :} \quad Y_{ij2} = (Q(t_{ij}, \tilde{\xi}^i) + T(t_{ij}, \tilde{\xi}^i) + T^*(t_{ij}, \tilde{\xi}^i))^{0.25} + \epsilon_{ij2}$$

Variability Model

$$\tilde{\xi}^i_l = \underbrace{\phi_l + z^i_l(t)\beta_l}_{\text{Fixed effects}} + \underbrace{\omega^i_l(t)u^i}_{\text{Random effects}}$$

→ Analysis of the ALBI data (9 biological parameters, 2 treatment effects, 2 random effects and 2 measurement errors)

→ MAP Estimation : Penalized Maximum Likelihood using a Newton-like algorithm. (Guedj et al., Biometrics, 2007)

Posterior Construction and Dose optimisation

Update information about the patient : Given $\mathcal{H}^i_{t_k}$, $\tilde{\xi}^i$ has a posterior distribution, then $R0(\tilde{\xi}^i, (d))$ too.

$\rightarrow$ Metropolis-Hastings algorithm

Control the probability that the proposed dose is too low : We propose to choose $(d_{opt})_{t_k}$ as the minimum dose which gives a high posterior probability that R0 is below 1

$$(d_{opt})_{t_k} | \quad \mathbb{P}\left(R0(\tilde{\xi}^i, (d_{opt})_{t_k}) < 1 \middle| \mathcal{H}^i_{t_k} \right) = \omega$$

$\rightarrow$ Robins-Monro algorithm

$$(d_{n+1})_{t_k} = (d_n)_{t_k} + \frac{1}{n^s}(\omega - \mathbb{1}_{R0(\tilde{\xi}^i, (d_n)_{t_k} | \mathcal{H}^i_{t_k}) < 1})$$

$(d_n)_{t_k}$ converges in $L2$ (and hence also in probability) to $(d_{opt})_{t_k}$

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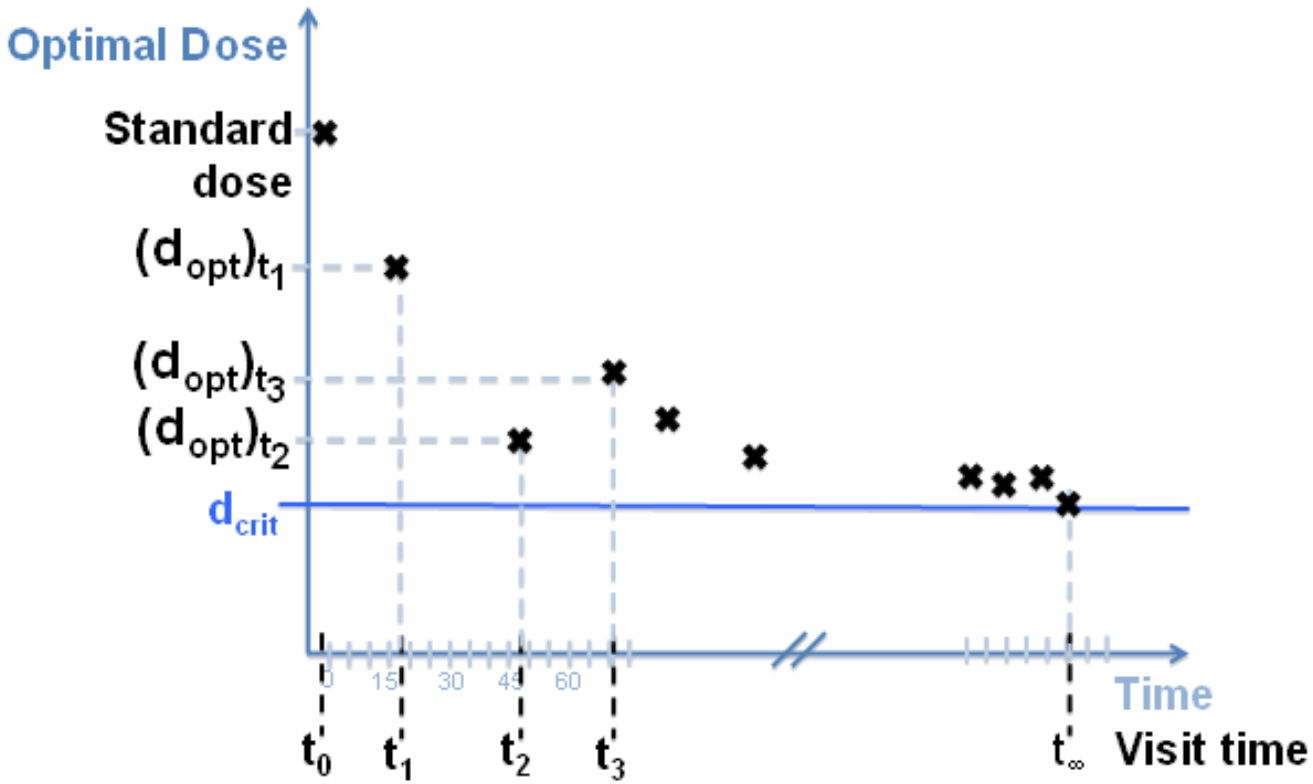
Global idea : adaptive dose reduction strategy

Hypothesis :

- $\mathcal{H}^i_{t_0} \subset \mathcal{H}^i_{t_1} \subset ... \subset \mathcal{H}^i_{t_\infty}$
- Enought time between dose adjustements (t_k, t_{k+1}) to reach system equilibrium (so that $R0$ is meaningful)

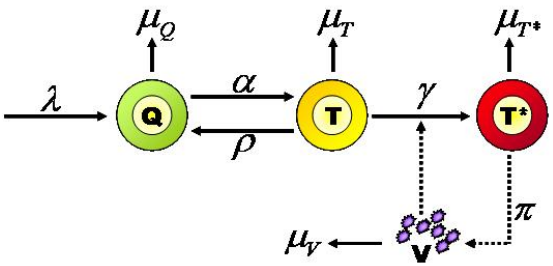


ALBI data analysis

149 patients : 51 d4T+ddI, 49 AZT+3TC, 49 Switch

Biological Parameters	Natural scale Mean	Log-transformed scale Mean	Sd.
α	0.05	-2.99	0.13
μ_{T*}	0.67	-0.41	0.10
λ	14.77	2.69	0.11
μ_T	0.10	-2.29	0.09
π	66.7	4.31	0.18
ρ	0.016	-4.12	0.12
μ_V	29.96	3.4	-
γ_0	0.005	-5.3	-
μ_Q	0.0001	-8.9	-

Parameter	Natural scale Mean	Sd.
σ_α	0.38	0.03
$\sigma_{\mu_{T*}}$	0.04	0.01
$\beta_{\text{AZT+3TC}}$	-0.92	0.09
$\beta_{\text{d4T+ddI}}$	-0.97	0.005
σ_{VL}	0.50	0.009
σ_{CD4}	0.20	0.004



Simulation of biomarkers for a specific subject

Parameters choice :

	Natural scale	Log-transformed scale	
Parameter	Real Value	Real Value	Prior=ALBI posterior
α^*	0.04	-3.15	$\mathcal{N}(-2.99, 0.51)$
μ_{T*}^*	0.74	-0.3	$\mathcal{N}(-0.41, 0.11)$
λ^*	12.2	2.5	$\mathcal{N}(2.69, 0.11)$
μ_T^*	0.11	-2.2	$\mathcal{N}(-2.29, 0.09)$
π^*	66.7	4.2	$\mathcal{N}(4.31, 0.18)$
ρ^*	0.015	-4.2	$\mathcal{N}(-4.12, 0.12)$
μ_V^*	33.12	3.5	$\mathcal{N}(3.4, 0.1)$
γ_0^*	0.007	-5.0	$\mathcal{N}(-5.3, 0.1)$
μ_Q^*	0.0001	-9.0	$\mathcal{N}(-8.9, 0.1)$
$\beta_{\text{d4T+ddI}}$	-0.97	-	$\mathcal{N}(-0.97, 0.1)$
ω	90%	-	-

Observations perturbation :

$\epsilon_{VL} \sim \mathcal{N}(0, 0.5)$

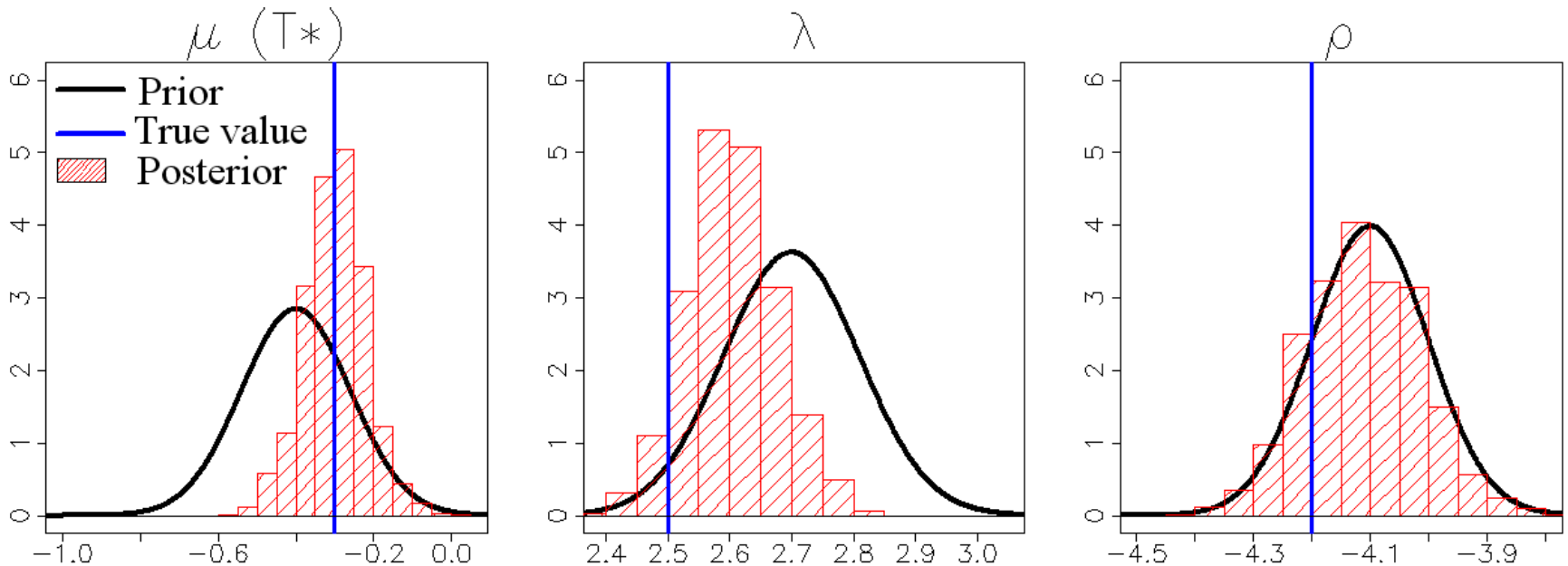
$\epsilon_{CD4} \sim \mathcal{N}(0, 0.2)$

Time Schedule for simulation :

Simulation time : 0 (before treatment),7 , 14

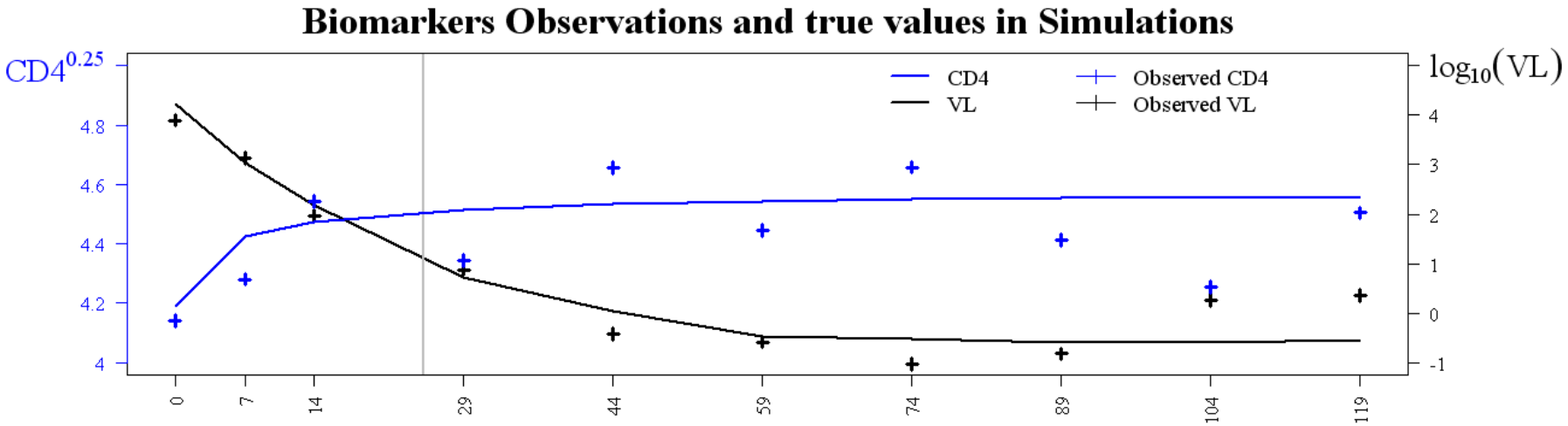
Dose readjustement time : 29, 44, 59, 74, 89, 104, 119

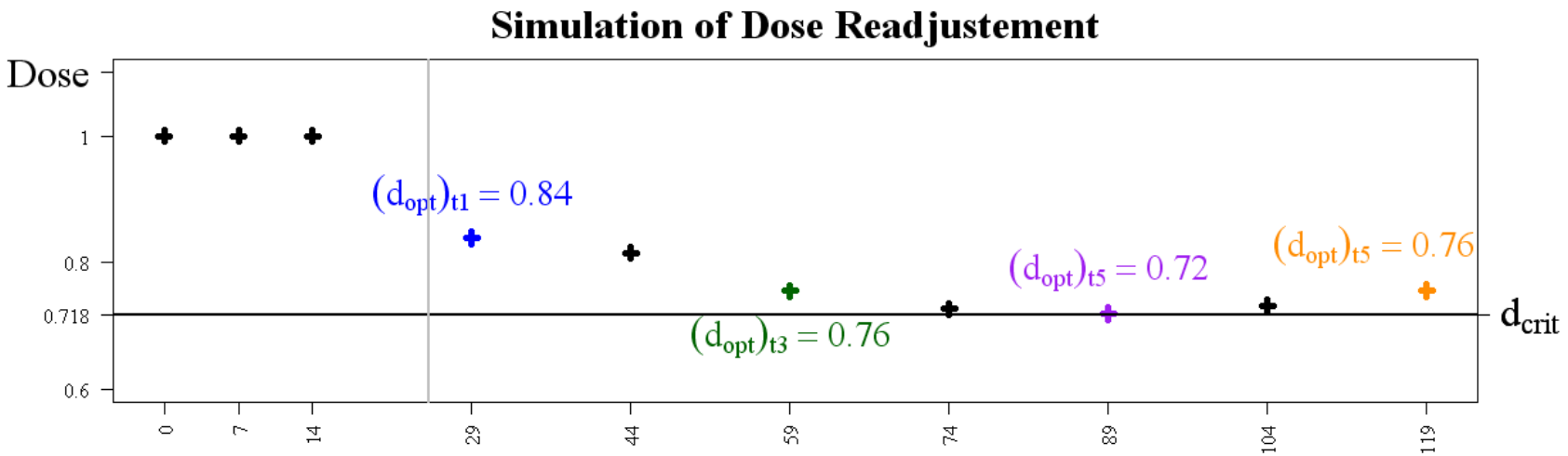
Posterior distribution of parameters for first dose readjustement (time 29)



Burning size 100000, Posterior sample size = 500000

Simulation of 7 dose readjustements for a specific subject





Making up, prospects

Does it works ? Yes ! Optimal drug dose finding seems to be possible

- Convergence mathematically proved
- Large sample simulation : RMSE decreases when $\mathcal{H}^i$ increases [1]

Current concerns and perspectives

- Computation time : Potential low rates of acceptation/rejection
- Reduced information in real data due to misspecification or censorship
- Pharmacokinetic specification of ψ
- Use of real data
- Problems of virus mutation due to reduced dose

[1] 100-sample; same schedule as before; ξ^* drawn from normal laws; $RMSE_{t_1} = 0.34$, $RMSE_{t_2} = 0.19$, $RMSE_{t_3} = 0.13$, $RMSE_{t_4} = 0.09$ ...

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