In Silico Evaluation of HIV Short-cycle Therapies with Dynamical Models

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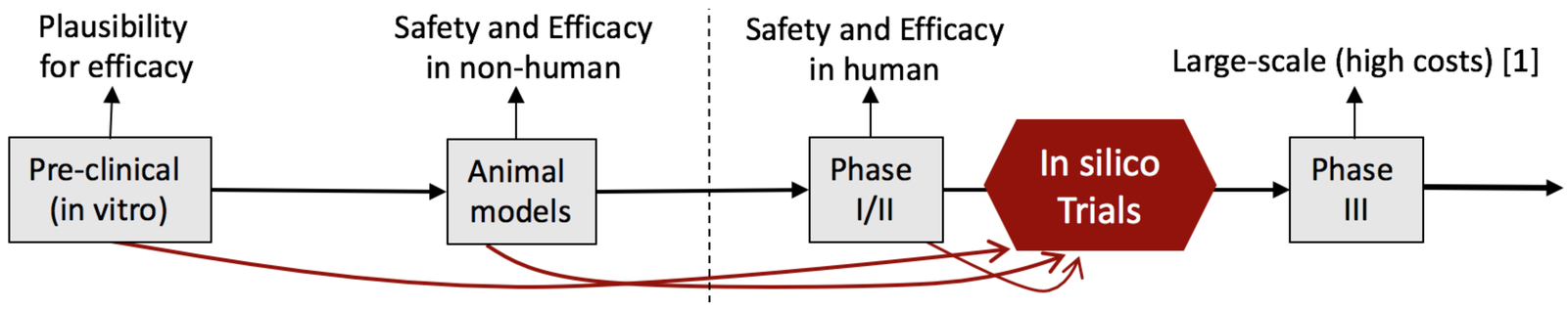
Introduction

- An **in silico clinical trial** is **an individualised computer simulation** used in the development of a medicinal product or intervention.
- Expected benefits : provide a mechanistic understanding, **optimise the strategies of delivery** and improve de clinical trials designs.



- Therapeutic relief is crucial for HIV infected patients under highly active antiretrovirals (ARVs) therapies (HAARTs). Multiple ongoing studies test **mono/bi-therapies** or **short cycle therapies** for HAARTs. **In this work, we aim at validating these strategies in silico.**

Dynamical LIM

Two-step Linear increment models (LIM):

$$\left(\frac{VL_{t+1}-VL_t}{T_{t+1}-T_t}\right)_i = \beta_{0i} + \beta_{CD4} CD4_t^i + \beta_{VL} VL_t^i + \sum_{k=1}^{n_{HAART}} \alpha_{HAART_k} HAART_k^i(t)$$

$$\alpha_{HAART_k} = \beta_0 + \sum_{j=1}^{n_{ARV}} \beta_{ARV_j} I_{ARV_j \in HAART_k}$$

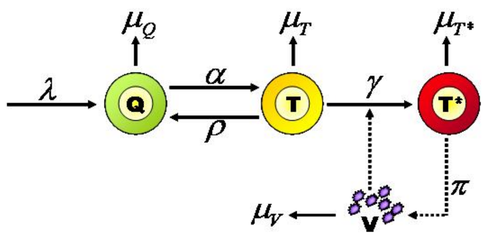
One-step LIM [2]:

$$\left(\frac{VL_{t+1}-VL_t}{T_{t+1}-T_t}\right)_i = \beta_{0i} + \beta_{CD4} CD4_t^i + \beta_{VL} VL_t^i + \sum_{j=1}^{n_{ARV}} \beta_{ARV_j} ARV_j^i(t)$$

Estimation Method: R library lme4 [3]

Mechanistic NLME-ODE

Mathematical Model: Ordinary differential equation (ODE) modeliling CD4 quiescent (Q), target (T), infected (T^*) and viruses (V).



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

Statistical Model: Transition rates modelled with non linear mixed effect models (NLME).

$$\lambda_i = \lambda_0 + u_i^\lambda \quad u^\lambda \sim \mathcal{N}(0, \sigma_\lambda^2)$$

$$\alpha_i = \alpha_0 + u_i^\alpha \quad u^\alpha \sim \mathcal{N}(0, \sigma_\alpha^2)$$

$$\gamma_i(t) = \gamma_0 + \sum_{j=1}^{n_{ARV}} \beta_{ARV_j} \mathrm{ARV}_j^i(t)$$

Observation Model: Viral load and CD4.

$$VL_{ij} = \log_{10}(V_i(j)) + \epsilon_{ij1}$$

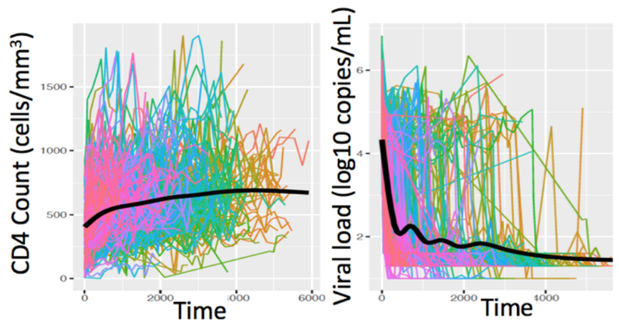
$$CD4_{ij} = (Q_i(j) + T_i(j) + T_i^*(j))^{0.25} + \epsilon_{ij2}$$

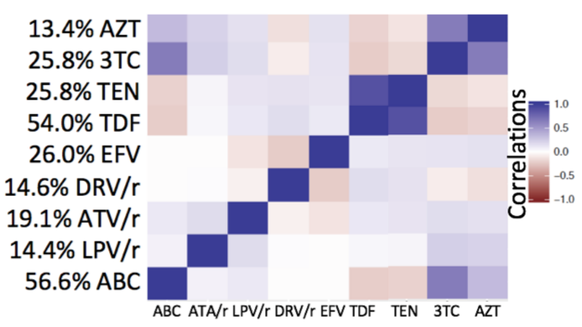
$$\epsilon_{ij1} \sim \mathcal{N}(0, \sigma_1^2) \text{ and } \epsilon_{ij2} \sim \mathcal{N}(0, \sigma_2^2)$$

Estimation Method: NIMROD, penalised likelihood maximisation for NLME-ODE [4,5]

The Aquitaine ANRS CO3 Cohort [6]

Treatment-naive patients included after 1/1/2000 with at least two follow-up and baseline viral load $> 10,000$ copies/mm^3 under investigated ARVs. Total **N=248** out of 2550 patients in the cohort.





ARVs Effects

Reasonable **concordance between in-vitro/in-vivo** indicators of efficacy.

β_{ARV_J}	Two-step LIM	One-step LIM	NLME ODE
AZT	-1.3 [-4.0; 1.6]	-1.3 [-2.5; -0.2]	-0.33 [-0.36; -0.30]
3TC	-3.8 [-7.4; -0.1]	-2.8 [-5.0; -0.7]	-0.36 [-0.40; -0.32]
FTC	-3.7 [-7.4; 0.1]	-3.2 [-5.3; -1.0]	-0.40 [-0.45; -0.34]
ABC	-1.5 [-3.9; 1.1]	-1.6 [-2.7; -0.4]	-0.29 [-0.32; -0.26]
TEN	-1.1 [-3.6; 1.5]	-1.5 [-2.7; -0.4]	-0.30 [-0.35; -0.24]
EFV	-3.8 [-5.9; -1.4]	-2.4 [-3.6; -1.2]	-0.34 [-0.36; -0.32]
LPV/r	-3.5 [-5.6; -1.2]	-1.9 [-3.1; -0.7]	-0.28 [-0.33; -0.23]
ATA	-3.0 [-5.8; -0.1]	-2.3 [-3.4; -1.1]	-0.35 [-0.36; -0.34]
DRV/r	-3.4 [-6.0; -0.5]	-2.5 [-3.6; -1.3]	-0.34 [-0.36; -0.32]
Reg.	-2.1 (p=0.003)	-5.3(p<0.001)	-13.6 (p=0.005)
Model fitted $\beta\times$ IIP, p-values are for R^2 adequation			
p-value	0.097	0.097	0.463
Spearman Corr. Instantaneous Inhibitory Potential (IIP) [7]			

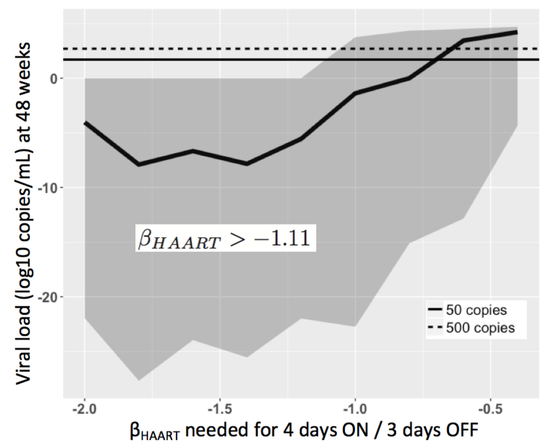
In silico ARVs relief

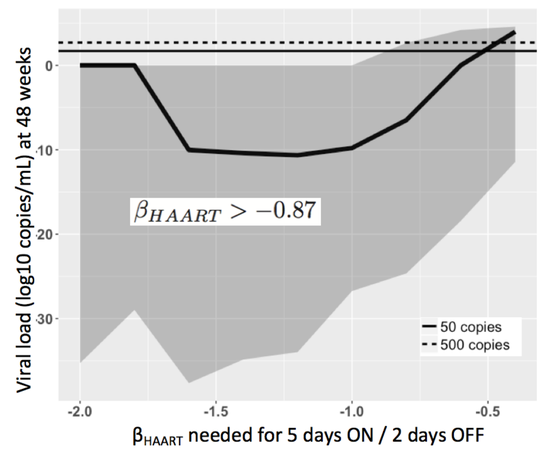
Reduction of the number of ARV: The OLE trial [8], the SALT study [9] and the MADRID cohort [10] show that regarding viral control at 48 weeks, DRV/r+3TC (98%) lead to more successes than LPV/r+3TC (91%), which is more powerful than ATV+3TC (84%). **We investigate in silico the probability of viral control at 48 weeks.**

In silico Short-cycle therapies

Predictive ability of NLME-ODE [1] are used to predict the probability to have viral control at 48 weeks under various On/off strategies.

$$\gamma_i(t) = \gamma_0 + \sum_{j=1}^{n_{ARV}} \beta_{ARV_j} \mathrm{ARV}_j(t) I_{\{t=\text{dayON}\}}$$





This is consistent with on-going studies. Strategies such as in 4D ANRS 162 [11] shows 96% fo viral control at 48 weeks with PI or NNRTI + 2NRTI and BREATHER trial [12] shows 94% of viral control at 48 weeks with EFV + 2NRTI.

Conclusion

- **Proof-of-concept**, need to add virus mutations & pharmacological modeling
- **Optimal design for patient/regimen-specific strategies** using Bayesian control [5]

References

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