507 - In Silico Clinical trials for Evaluation of HIV Short-cycle Strategies

Mélanie Prague[1,2,5], **Chloé Pasin**[1,2,5], **Linda Wittkop**[2], **Pierre Duffau**[4], **Estibaliz Lazaro**[4], **Charles Cazanave**[4], **Marc Vareil**[3], **Fabrice Bonnet**[4], **Rodolphe Thiébaut**[1,2,4,5]

[1]*Inria, Project Team SISTM, Bordeaux, France* [2]*Inserm U1219 (BPH), ISPED, Bordeaux University, France* [3]*Centre Hospitalier de Bayonne, France*

[4]*Centre Hostitalo-Universitaire de Bordeaux, France* [5]*Vaccine Research Institute, Créteil, Paris, France* ***(contact: rodolphe.thiebaut@u-bordeaux.fr)***

Objectives

1) To build a predictive model of the response to combination of antiretroviral therapies (c-ART) using data from an observational cohort,
2) To predict the results of existing trials.

Mechanistic Model

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

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

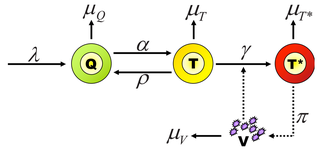

Fig. 1: Target cells model

Statistical Model: Transition rates are modelled with non linear mixed effect models (NLME). For patient $i = 1, \ldots, N$:

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

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

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

Observation Model: Viral load and CD4 are measured with errors. For patient $i = 1, \ldots, N$ at observation timepoints $k = 1, \ldots, K$:

$$VL_i(t_{ik}) = \log_{10}(V_i(t_{ik})) + \epsilon_{ik1}$$

$$CD4_i(t_{ik}) = (Q_i(t_{ik}) + T_i(t_{ik}) + T_i^*(t_{ik}))^{0.25} + \epsilon_{ik2}$$

$$\epsilon_{ik1} \sim \mathcal{N}(0, \sigma_1^2) \text{ and } \epsilon_{ik2} \sim \mathcal{N}(0, \sigma_2^2)$$

Estimation Method:

$$\theta = (\lambda, \mu_Q, \alpha, \rho, \mu_T, \gamma, \mu_{T^*}, \pi, \mu_V, \beta_{ARV\,1}, \ldots, \beta_{ARV\,n_{ARV}}, \sigma_\lambda, \sigma_\alpha, \sigma_1, \sigma_2)$$

Get $(\hat{\theta}, \widehat{H(\hat{\theta})})$ with NIMROD, using a penalised likelihood maximisation algorithm for NLME-ODE [2,3].

Acknowledgement & References

We thanks all the PIs ans participants in cited trials.

[1] Prague et al. Biometrics 2017 [2] Prague et al. Comp. Meth. Prog. Biomed. 2013 [3] Prague et al. Biometrics 2012 [4] Jarne et al. AoAS 2017

In Silico Pipeline

An **in silico clinical trial** is **a computer simulation** used in the development of a medicinal product or intervention. It is based on a **mathematical model with good predictions abilities**. See [4] for an example.

Generate pseudo-patients:
Sample (r = 1, ... N) parameters from the posterior distribution of θ
$\theta_r \sim N(\hat{\theta}, \widehat{H(\hat{\theta})})$

In silico data:
Simulate trajectories under various treatment and target population $(X, ARV_j^i(t))$
$Y_r = ODE(\theta_r, ARV_j^i(t), X, t_{ij})$

Evaluate in silico outcomes :
Virological failure at 48 week $P\left(V_r > 50 \frac{\text{copies}}{\text{mL}}\right)$

Additional features: Basic reproduction number
$R_{0_r} = \frac{\lambda_r \pi_r \alpha_r \gamma_r}{\mu_{T^*r} \mu_{V_r} (\rho_r \mu_{Q_r} + \alpha_r \mu_{T_r} + \mu_{Q_r} \mu_{T_r})}$, if <1, $V_r(\infty) \to 0$

$P(Y \leq x) = \int_{-\infty}^{x} f(t)dt$

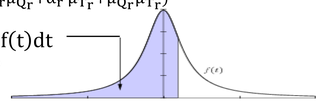

Fig. 2 : Simulations algorithm

The Aquitaine ANRS CO3 Cohort [1]

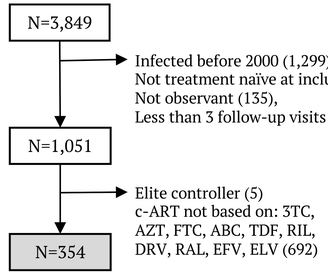

Fig. 3 : Flowchart of patient selection

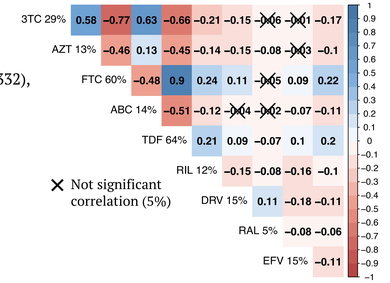

Fig. 4 : ARV significantly associated in c-ART

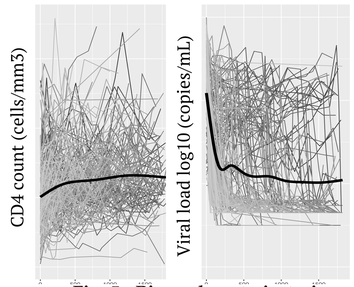

Fig. 5 : Biomarkers trajectories

Review of Short-cycle therapies trials

Short-cycle therapies (SCT) as opposed to continuous therapies (CT) is a type of regimen in which the patient takes combination of antiretroviral (ARV) therapies (c-ART) only x consecutive days in the week (x<7).

	Cohen et al. 2009	Reynolds et al. 2010	Butler et al. 2016	Rudy et al. 2009	Leibowitch et al. 2015	De Truchis et al. 2016	De Truchis et al. 2018
Names	FOTO	NCT00339456	BREATHER	ATN 015	ICARRE	ANRS-4D	ANRS-QUATUOR
Type	5/7 randomized	5/7 randomized	5/7 randomized	4/7 Single arm	4/7 Single arm	4/7 Single arm	4/7 randomized
N	60 ($n_{SCT} = 30$)	146 ($n_{SCT} = 57$)	199 ($n_{SCT} = 99$)	$n_{SCT} = 32$	$n_{SCT} = 94$	$n_{SCT} = 100$	640 ($n_{SCT} = 320$)
Country	USA	Uganda	11 countries	USA	France	France	France
Pop.	Adult (83% men)	Adult (47% men)	8-24yr (53% men)	14-24yr (51% men)	Adult (83% men)	Adult (82% men)	Adult
c-ART	EFV/TDF/FTC	2NRTI+PI/EFV	2NRTI+EFV	2NRTI+PI	2NRTI+PI/NNRTI	2NRTI+PI/NNRTI	2NRTI+PI/NNRTI/II
Failure CT	14%	21.6%	7%	-	-	-	
Failure SCT	10%	11.5%	6%	37.5%	0%	4%	**On going**
Conclu.	Promising	Non-inferiority	Non-inferiority	Failure	Promising	Promising	

Tab. 1: List of funded SCT trials

Predicting 5/7

	Virological Failure 1 cp/mL	50 cp/mL	R_0
EFV+TDF+3TC	0.9% [0%; 5%]	0.5% [0%; 4%]	0.77 [0.59; 0.92]
EFV+ABC+3TC	1.1% [0%; 14%]	0.6% [0%; 11%]	0.82 [0.64; 0.99]
EFV+AZT+3TC	2.4% [0%; 19%]	1.0% [0%; 16%]	0.84 [0.65; 1.02]
BREATHER trial	1.7% [0%; 15%]	1% [0%; 11.9%]	0.82 [0.63; 0.99]

Tab. 2: In silico trial for 5/7 SCT design

In BREATHER, the observed failure rate at 50 cp/mL is 6% [2%; 10%], the prediction confidence band overlaps the results of the trial.

Predicting 4/7

	Virological Failure 1 cp/mL	50 cp/mL	R_0
EFV+TDF+3TC	5.3% [2.2%; 9.0%]	2.0% [0.0%; 4.0%]	0.91 [0.71; 1.11]
EFV+ABC+3TC	17.1% [11%; 23%]	11.9% [6%; 17%]	0.96 [0.74; 1.16]
EFV+AZT+3TC	21.4% [16%; 28%]	16.4% [10%; 23%]	0.97 [0.75; 1.18]
TDF+FTC+RIL	2.8% [0.2%; 6.6%]	1.2% [0%; 3%]	0.90 [0.70; 1.09]
TDF+FTC+DRV	1.4% [0%; 3.8%]	0.7% [0%; 3%]	0.88 [0.69; 1.04]
More potent (DOL-based?)	0.2% [0%; 1.2%]	0.1% [0%; 1%]	0.82 [0.63; 0.99]

Tab. 3: In silico trial for 4/7 SCT design

Projections for SCT are encouraging with high potency c-ART. However, for some c-ART it remains a risk of low-level viral replication. This low replication may however remain smaller than 1cp/mL.

Conclusion & Going further

We conclude that we have :

- Good prediction abilities of existing trials,
- Encouraging results for ongoing trial.

Extensions include:

- Modelling of pharmacometric & **viral mutations** .
- Development of SCT optimal design for patient/regimen-specific strategies using Bayesian control
- Definition of ethical risk to predict on-going trials