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# Adaptive protocols based on predictions from a mechanistic model of the effect of IL7 on CD4 counts

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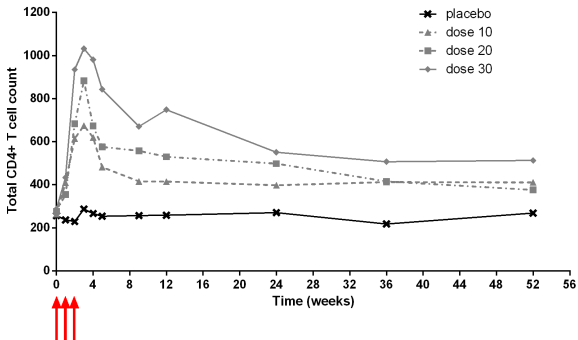
IBC, Barcelona, July 2018



# Introduction and context

- Some HIV-infected patients are unable to restore their levels of CD4 + T cells (CD4).
- IL7 is a cytokine produced by the organism (stromal cells).
- Injections of IL7 could help the reconstitution of the immune system.
- The aim is to maintain the patient above 500 CD4/ $\mu$ L of blood.

- The first clinical trial on IL7 show positive results (Sereti Blood 2009, Levy CID 2012, Levy JCI 2009).



- Repeated cycle are necessary.
- Best adaptive protocol yet to determine.

- Data from phase I / II trials : INSPIRE 1, 2 and 3.
- 138 HIV-infected patients.
- Regular measurements of immunologic markers.

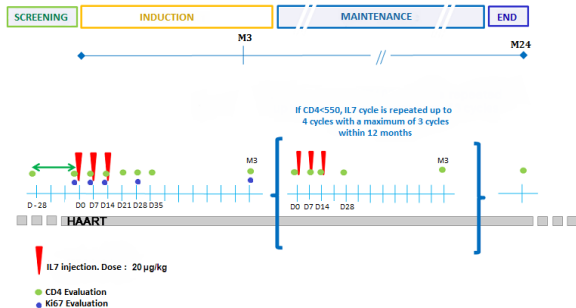


Figure – Design of INSPIRE 2 and 3 studies (**ORI** protocol)

# Mechanistic model

- Model the different cell populations, as shown in the following figure with the CD4 population.

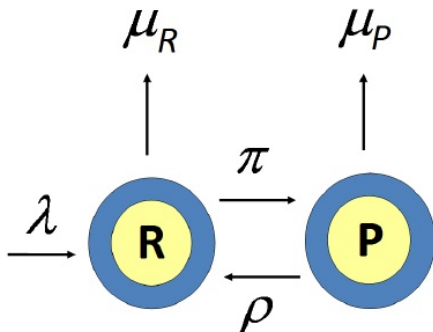


Figure – P : proliferative CD4, R : resting CD4

$$\begin{cases} \frac{dR}{dt} = \lambda - \pi R + 2\rho P - \mu_R R, \\ \frac{dP}{dt} = \pi R - \rho P - \mu_P P, \end{cases} \quad (1)$$

- $\lambda$  is the cell production rate,  $\pi$  is the proliferating rate,  $\rho$  is the return to resting state rate,  $\mu_R$  is the death rate of resting cells and  $\mu_P$  is the death rate of proliferative cells.



# Summary of the model

- **Mechanistic model** with biological parameters : one set of parameters means one trajectory
- Effect of the IL7 on the proliferation ( $\pi$ ) and cellular death ( $\mu_R$ )
- **Random effects** on the production and reversion rates ( $\lambda$  and  $\rho$ )
- There is a **measurement error**

# Estimation by NIMROD

Table – Parameters of the model and their estimation from Jarne et al. 2018

Parameter	Name	Units	Estimation
$\lambda$	Production rate	days <sup>-1</sup>	5.32 (0.33)
$\rho$	Reversion rate	cells.days <sup>-1</sup>	2.44 (0.23)
$\pi$	Proliferation rate	cells.days <sup>-1</sup>	0.058 (0.004)
$\mu_P$	Death rate of P cells	cells.days <sup>-1</sup>	0.074 (0.005)
$\mu_R$	Death rate of R cells	cells.days <sup>-1</sup>	0.077 (0.015)
$\beta_{\pi_1}$	Effect of IL7 on $\pi$ (Inj1)	days <sup>-1</sup> . $\mu\text{g}^{-1}$	0.93 (0.04)
$\beta_{\pi_2}$	Effect of IL7 on $\pi$ (Inj2)	days <sup>-1</sup> . $\mu\text{g}^{-1}$	0.707 (0.04)
$\beta_{\pi_3}$	Effect of IL7 on $\pi$ (Inj3)	days <sup>-1</sup> . $\mu\text{g}^{-1}$	0.229 (0.04)
$\beta_{\mu_R}$	Effect of IL7 on $\mu_R$	cells.days <sup>-1</sup> . $\mu\text{g}^{-1}$	-0.08 (0.006)
$\beta_C$	Cycle effect of IL7	days <sup>-1</sup>	-0.163 (0.015)
$\sigma_\lambda$	sd of the random effect on $\lambda$	days <sup>-1</sup>	0.243 (0.026)
$\sigma_\rho$	sd of the random effect on $\rho$	cells.days <sup>-1</sup>	0.515 (0.084)
$\sigma_{CD4}$	Error of measurement on CD4	cells <sup>0.25</sup>	0.289 (0.003)
$\sigma_P$	Error of measurement on P	cells <sup>0.25</sup>	0.281 (0.019)

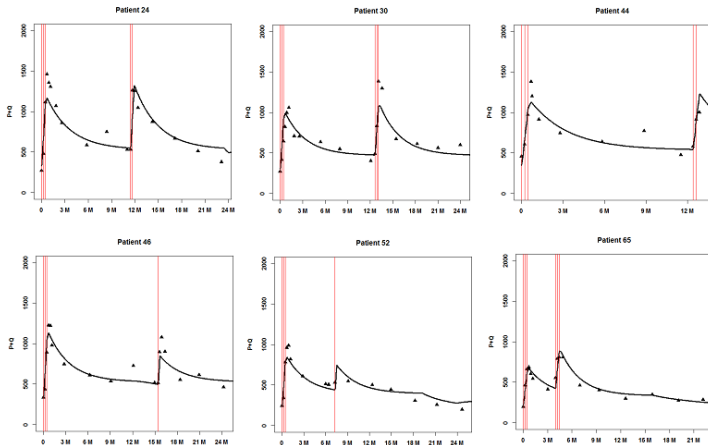


Figure – Evolution of the total number of CD4 cells ( $\text{cells}/\mu\text{L}$ ) on a patient after IL7 injections. Black line : fit predicted by NIMROD. Red dots : observations. Red lines : injections times.

# Adaptive Protocols.

The criterion of 550 CD4 for a new injection is **not adapted** to the patient :

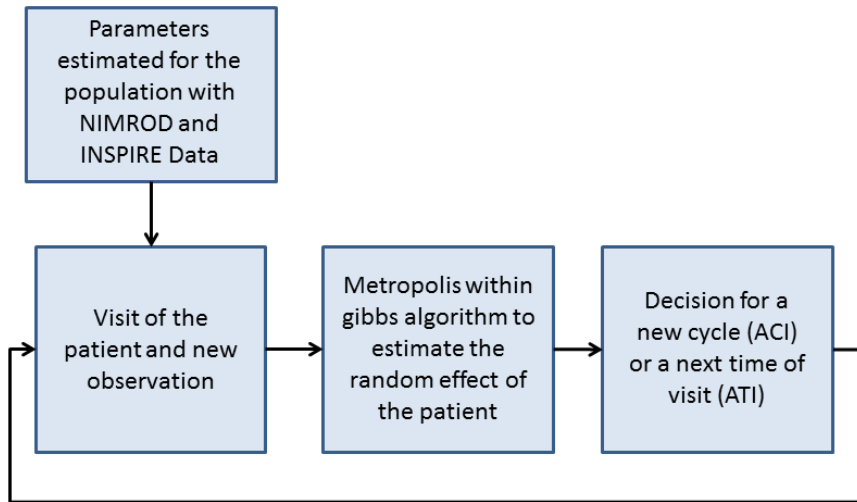
- For those with a fast decrease of CD4 after an injection, the limit might be **too low** and then they risk to spend too much **time under 500 CD4**
- For those with a slow decrease of CD4 after an injection, the limit might be **too high** and then have **unnecessary cycles of injection**

To solve those issues, we propose **four adaptive protocols**.

- We want to keep the level of CD4 **above the level of  $500\text{CD4}/\mu\text{L}$  of blood**, but without too many injections.
- A **mechanistic model** was developed to show the effect of IL7 on the population of CD4 T cells.
- With this model, we use an MCMC algorithm to estimate the **individual parameters to personalized the IL7 injections**.

We have **two ways of optimizing** :

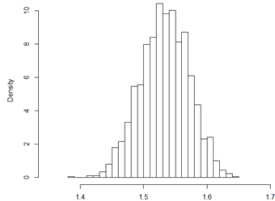
- We can still keep a **visit every 3 month** and predict the **risk to be under 500 CD4** at the next visit. (Adaptive Criterion of Injection = **ACI**).
- Or we can predict the time when the patient will be at 500 CD4 and **adapt the time of the next visit**. (Adaptive Time of Injection = **ATI**).



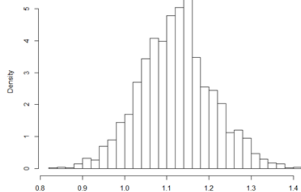


# Method

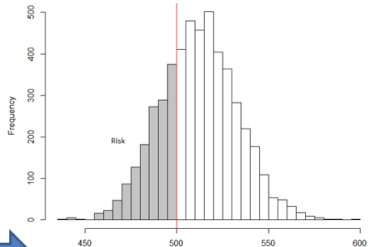
Distribution of lambda



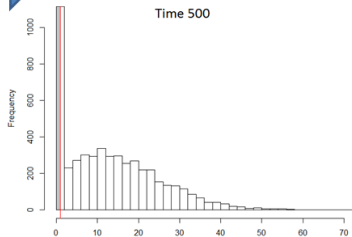
Distribution of Rho



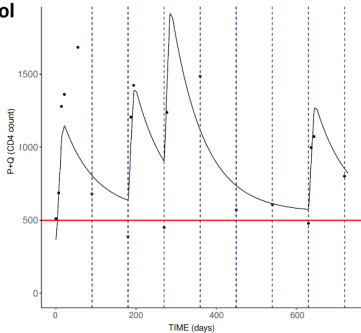
CD4 at three months



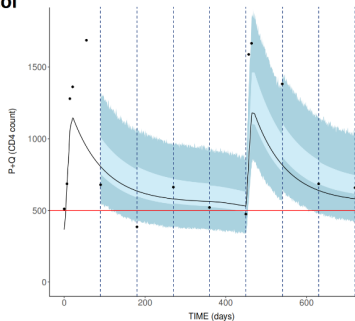
Time 500



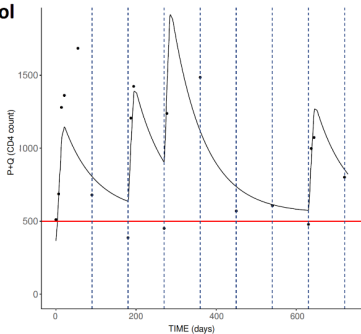
## Protocol ORI



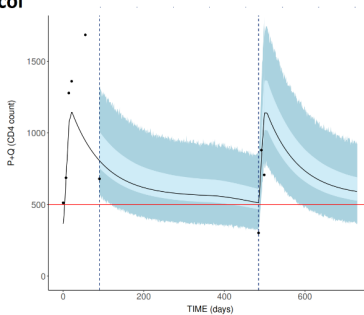
## Protocol ACI



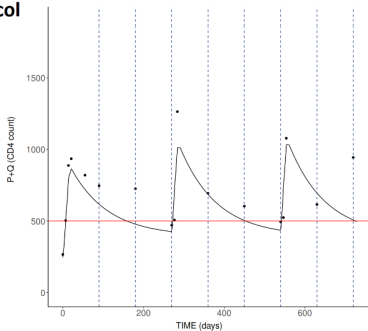
### Protocol ORI



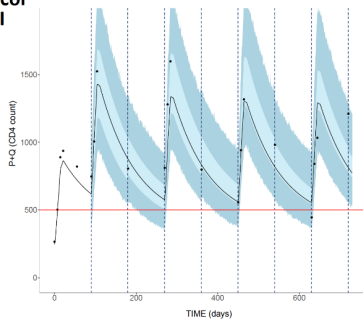
### Protocol ATI



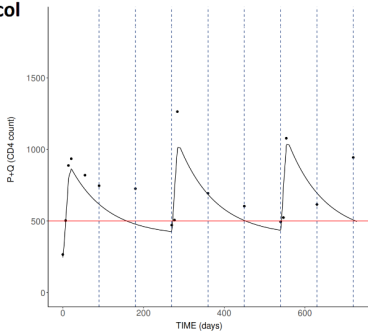
## Protocol ORI



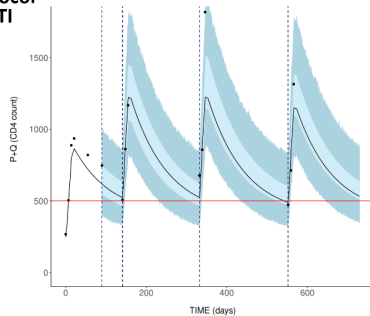
## Protocol ACI



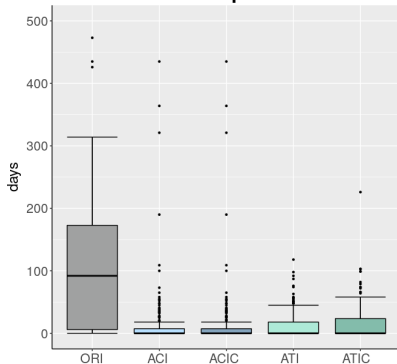
## Protocol ORI



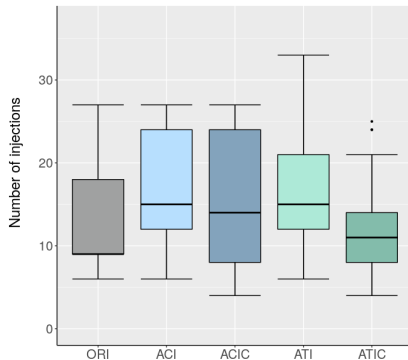
## Protocol ATI



## Time spent under 500 CD4 for each protocols



## Number of injections for each protocols



## Adaptive protocols

Data and protocols | MCMC | Protocols parameters

**Time**

**CD4**

**Ki67**

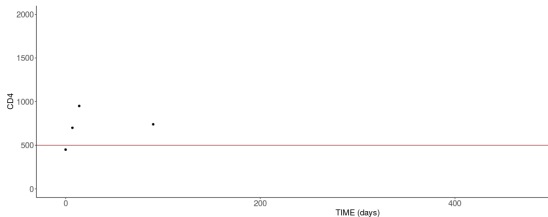
**Injections**

**UPLOAD!**

Time	CD4	Ki67	Injections
0.00	450.00	10.00	1.00
7.00	700.00	12.00	1.00
14.00	950.00	18.00	1.00
90.00	740.00	11.00	0.00

**Visit time**

**Calculate**



## Adaptive protocols

Data and protocols   MCMC   Protocols parameters

**Time**

**CD4**

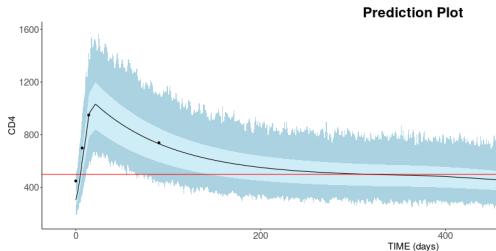
**Ki67**

**Injections**

UPLOAD!

Time	CD4	Ki67	Injections
0.00	450.00	10.00	1.00
7.00	700.00	12.00	1.00
14.00	950.00	18.00	1.00
90.00	740.00	11.00	0.00

**Visit time**



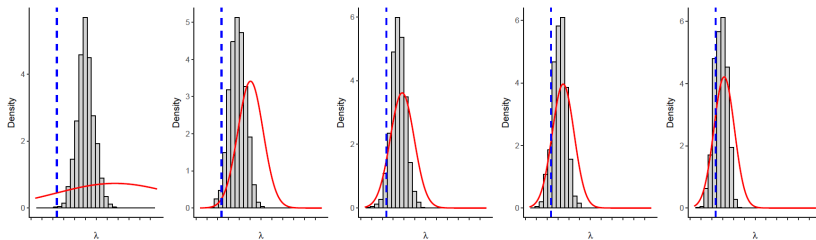
Decision ACI: Pas d'injection, prochaine visite dans 3 mois  
Decision ACIC: Pas d'injection, prochaine visite dans 3 mois  
Decision ATI: Pas d'injections, visite dans 99 jours  
Decision ATIC: Pas d'injections, visite dans 99 jours



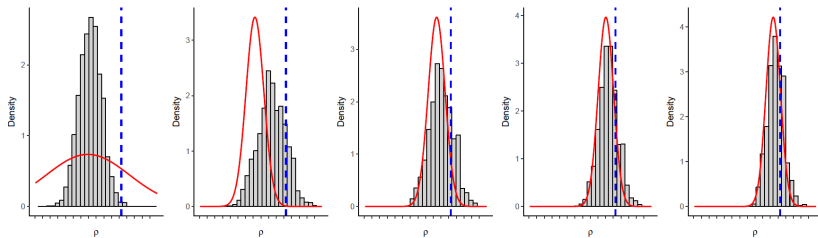
- The adaptive protocols showed a **strong diminution of the time spent under 500 without an increase of the number of injections.**
- Shiny app under development to have an easy interface.
- This protocol could be **tested in a clinical trial.**

Thank you for your attention

## Evolution of the estimation of Lambda

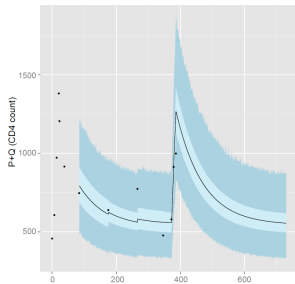
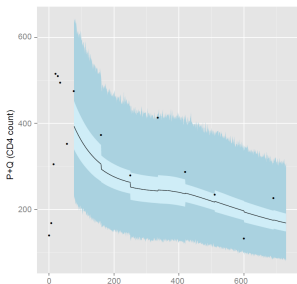
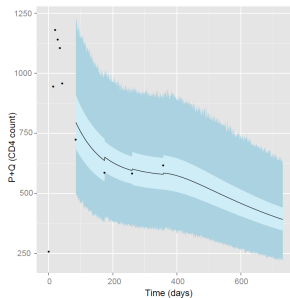
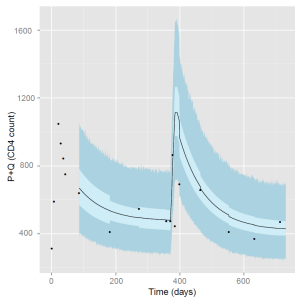


## Evolution of the estimation of rho



- For the patient  $i$ , each iteration  $q$  of the MCMC gives a couple  $(\lambda_q, \rho_q)_i$
- Each couple of parameters gives a trajectory of CD4 :  
$$CD4_{iq}(t) = [P(t, \xi^{iq}) + Q(t, \xi^{iq})]$$
- At each time point  $t_{ij}$  we have the distribution of CD4 and the distribution of the observations by adding an error of measurement :  $Y_{1jq}^i = [P(t_{ij}, \xi^{iq}) + Q(t_{ij}, \xi^{iq})]^{0.25} + \epsilon_{1jq}^i$

# Prediction ability on real patients



## QQ plot

