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

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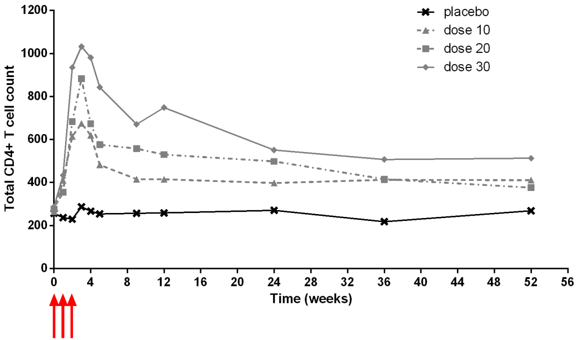
Introduction and context

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/μL of blood.

Context

- 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

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

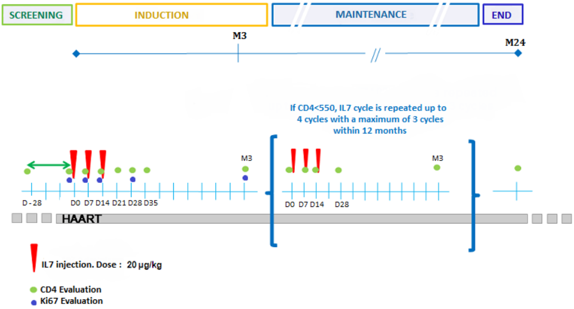


Figure – Design of INSPIRE 2 and 3 studies (**ORI** protocol)

Mechanistic model

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

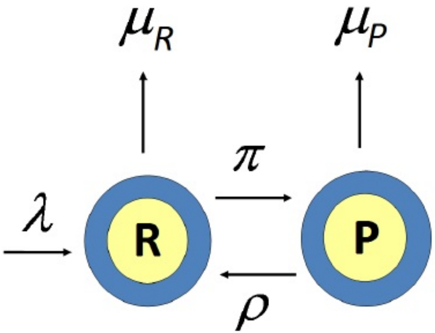


Figure – P : proliferative CD4, R : resting CD4

Mechanistic model

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

- λ is the cell production rate, π is the proliferating rate, ρ is the return to resting state rate, μ_R is the death rate of resting cells and μ_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 (π) and cellular death (μ_R)
- **Random effects** on the production and reversion rates (λ and ρ)
- 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
λ	Production rate	days^{-1}	5.32 (0.33)
ρ	Reversion rate	cells.days^{-1}	2.44 (0.23)
π	Proliferation rate	cells.days^{-1}	0.058 (0.004)
μ_P	Death rate of P cells	cells.days^{-1}	0.074 (0.005)
μ_R	Death rate of R cells	cells.days^{-1}	0.077 (0.015)
β_{π_1}	Effect of IL7 on π (Inj1)	days$^{-1}.\mu g^{-1}$	0.93 (0.04)
β_{π_2}	Effect of IL7 on π (Inj2)	days$^{-1}.\mu g^{-1}$	0.707 (0.04)
β_{π_3}	Effect of IL7 on π (Inj3)	days$^{-1}.\mu g^{-1}$	0.229 (0.04)
β_{μ_R}	Effect of IL7 on μ_R	cells.days$^{-1}.\mu g^{-1}$	-0.08 (0.006)
β_C	Cycle effect of IL7	days^{-1}	-0.163 (0.015)
σ_λ	sd of the random effect on λ	days^{-1}	0.243 (0.026)
σ_ρ	sd of the random effect on ρ	cells.days^{-1}	0.515 (0.084)
σ_{CD4}	Error of measurement on CD4	cells$^{0.25}$	0.289 (0.003)
σ_P	Error of measurement on P	cells$^{0.25}$	0.281 (0.019)

Fits

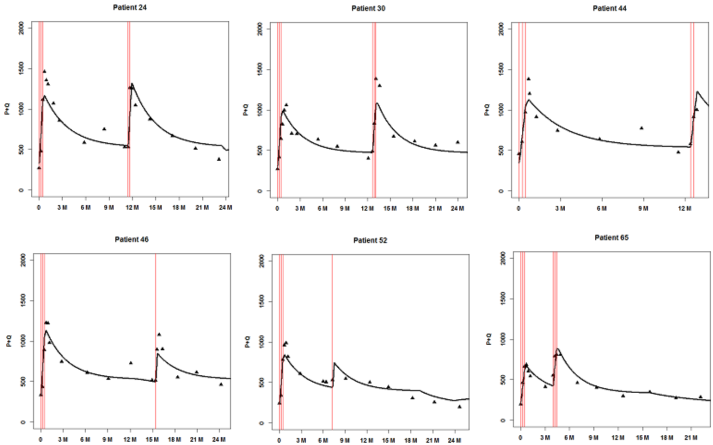


Figure – Evolution of the total number of CD4 cells (cells/μL) on a patient after IL7 injections. Black line : fit predicted by NIMROD. Red dots : observations. Red lines : injections times.

Adaptive Protocols.

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**.

Objective

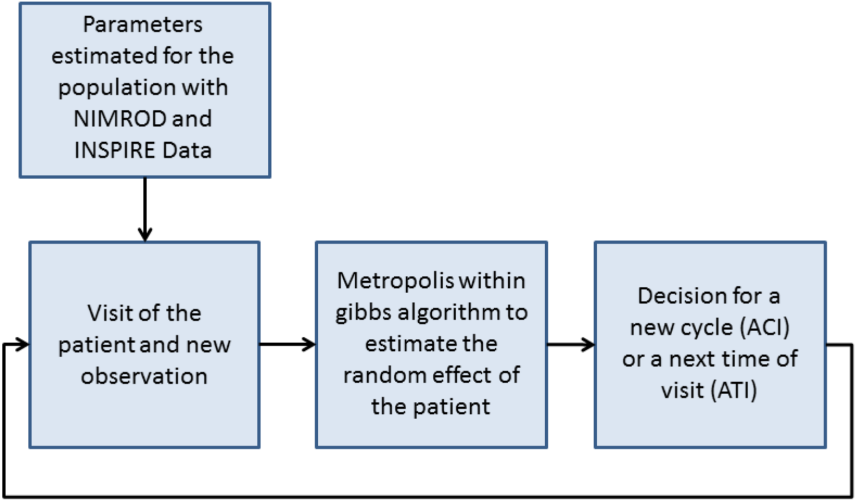
- We want to keep the level of CD4 **above the level of** $500 CD4/\mu L$ **of blood**, but without too many injections.
- A **mechanistic model** was developed to show the effect of IL7 on the population of CD4 T cells.
- With this model, we use an MCMC algorithm to estimate the **individual parameters**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

Optimization

We have **two ways of optimizing** :

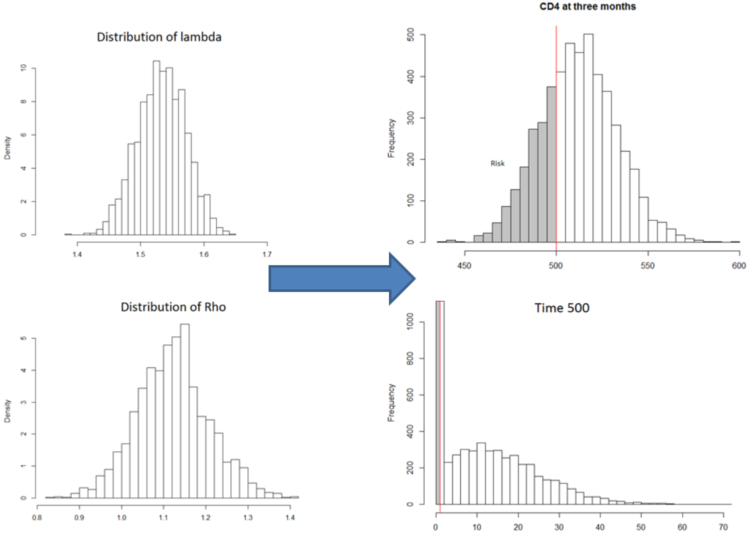
- We can still keep a **visit every 3 month** and predict the **risk to be under 500 CD4** at the next visit. (Adaptive Criterion of Injection = **ACI**).
- Or we can predict the time when the patient will be at 500 CD4 and **adapt the time of the next visit**. (Adaptive Time of Injection = **ATI**).

Method



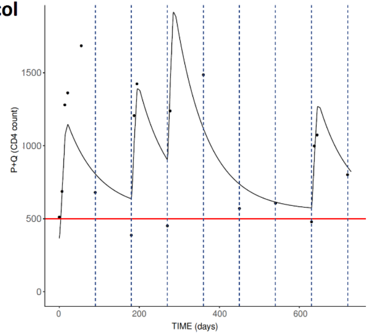
Parameters estimated for the population with NIMROD and INSPIRE Data
Visit of the patient and new observation
Metropolis within gibbs algorithm to estimate the random effect of the patient
Decision for a new cycle (ACI) or a next time of visit (ATI)

Method

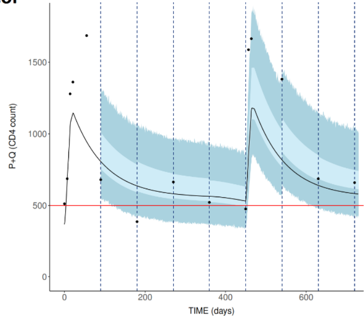

Distribution of lambda
Density
1.4
1.5
1.6
1.7
Distribution of Rho
Density
0.8
0.9
1.0
1.1
1.2
1.3
1.4
CD4 at three months
Frequency
Risk
450
500
550
600
Time 500
Frequency
0
10
20
30
40
50
60
70

Results

Protocol ORI

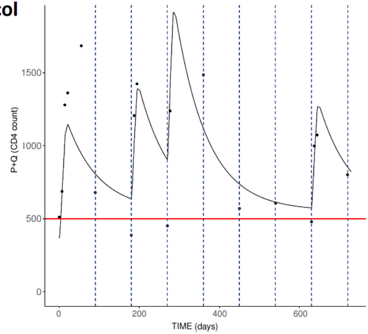


Protocol ACI

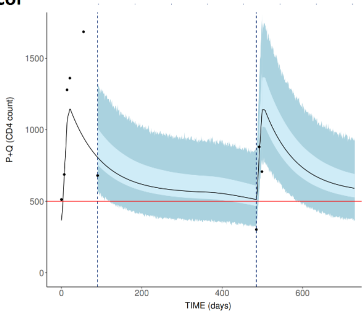


Results

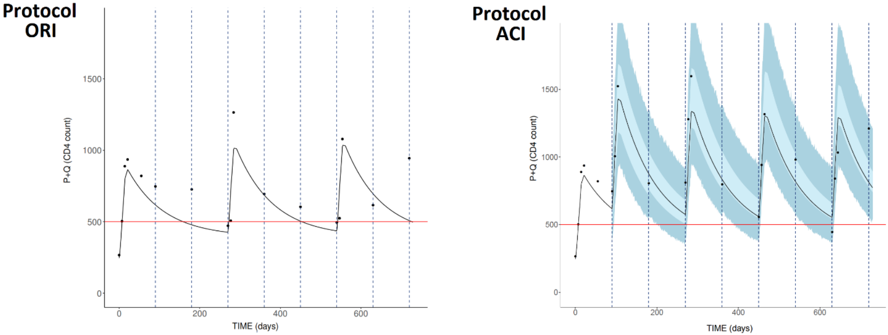
Protocol ORI



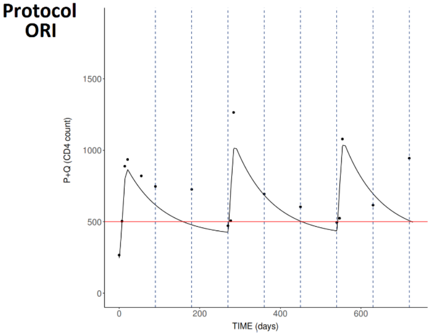
Protocol ATI



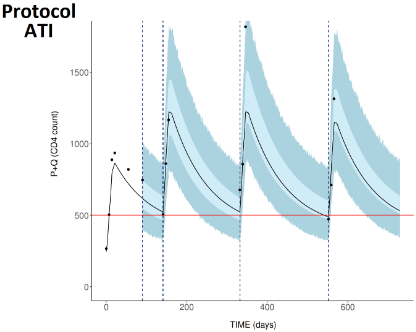
Results


Protocol ORI
P+Q (CD4 count)
1500
1000
500
0
0
200
400
600
TIME (days)
Protocol ACI
P+Q (CD4 count)
1500
1000
500
0
0
200
400
600
TIME (days)

Results

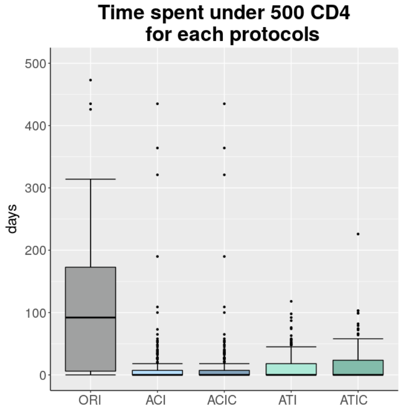


Protocol
ORI
P+Q (CD4 count)
1500
1000
500
0
0
200
400
600
TIME (days)

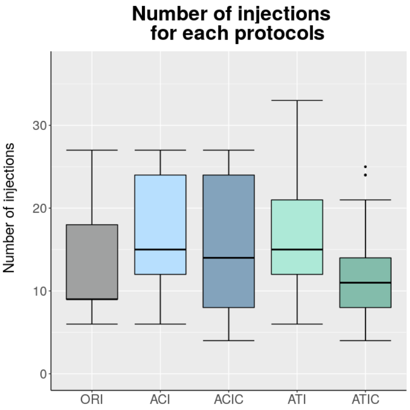


Protocol
ATI
P+Q (CD4 count)
1500
1000
500
0
0
200
400
600
TIME (days)

Results



Time spent under 500 CD4
for each protocols
days
500
400
300
200
100
0
ORI
ACI
ACIC
ATI
ATIC



Number of injections
for each protocols
Number of injections
30
20
10
0
ORI
ACI
ACIC
ATI
ATIC

Results

Adaptive protocols

Data and protocols | MCMC | Protocols parameters

Time

600

CD4

350

Ki67

9

Injections

0

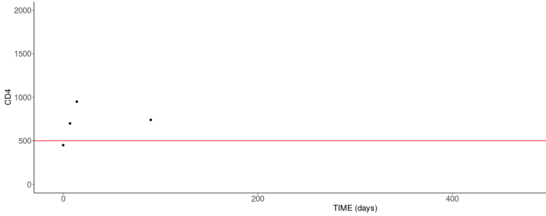
UPLOAD!

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

0

Calculate



Results

Adaptive protocols

Data and protocols | MCMC | Protocols parameters

Time

90

CD4

740

Ki67

11

Injections

0

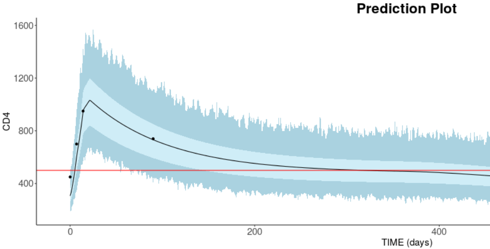
UPLOAD!

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

0

Calculate



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

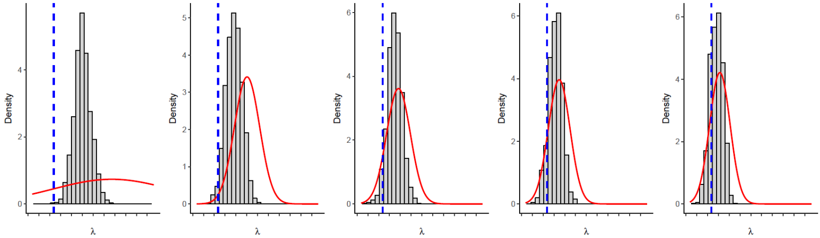
Conclusion and Perspectives

- 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**.

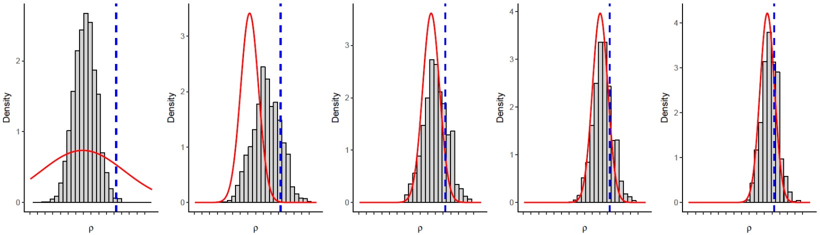
Thank you for your attention

Method

Evolution of the estimation of Lambda



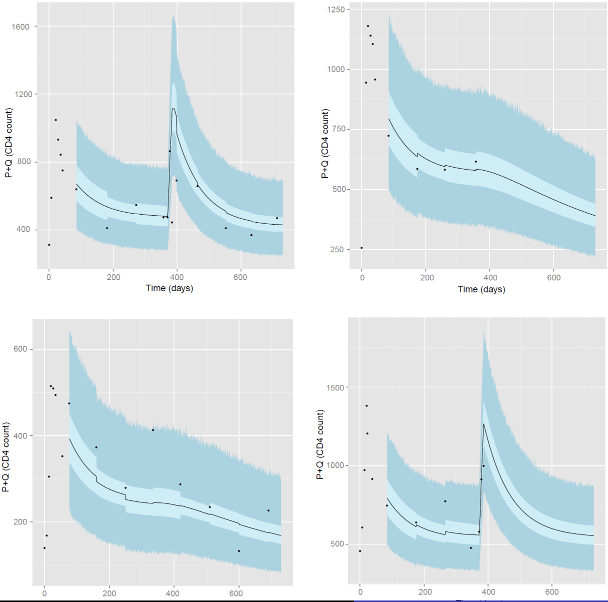
Evolution of the estimation of rho



Method

- 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 : $\mathrm{CD4_{iq}(t) = [P(t, \boldsymbol{\xi}^{iq}) + Q(t, \boldsymbol{\xi}^{iq})]}$
- At each time point t_{ij} we have the distribution of CD4 and the distribution of the observations by adding an error of measurement : $Y^i_{1jq} = [P(t_{ij}, \boldsymbol{\xi}^{iq}) + Q(t_{ij}, \boldsymbol{\xi}^{iq})]^{0.25} + \epsilon^i_{1jq}$

Prediction ability on real patients



Prediction ability on real patients