FROM *IN VITRO* TO *IN VIVO* QUANTIFICATION OF ANTIRETROVIRAL DRUGS EFFECTS BASED ON DYNAMICAL MODELS OF HIV.

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Outline of the talk

Motivation :

- Quantify antiretroviral effects **on clinical data**,
- Extrapolate cART effects.

***In vivo* Modeling :**

- Dynamic models (ODE-based),
- Intrinsic antiviral activity,
- Pharmacokinetics,
- Drug-drug interactions,
- Genetic barrier to resistance.

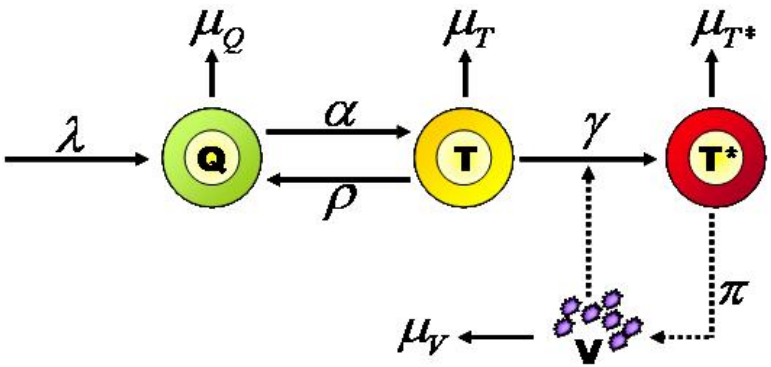
} use of ***in vitro*** **knowledge**

Model assessment on clinical data :

- Evaluate the model quality and reliability,
- Evaluate the model predictive abilities.

In vivo Dynamical model of HIV

Activated T-cell model [1]



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

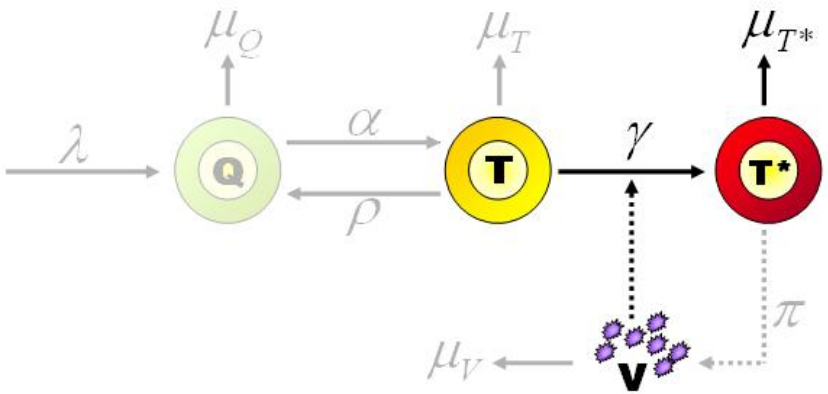
Compartment	Meaning
Q	Quiescent cells
T	Activated cells
T^*	Activated Infected cells
V	HIV circulating Viruses

Parameters	Meaning
λ	Rate of Q cells production
μ_{Q,T,V,T^*}	Death rate of $Q/T/T^*/V$
α	Activation rate of Q cells
ρ	Rate of reversion to the Q state
γ	Infectivity : Infection rate of T cells per virion
π	Rate of virions per T^* cells

1. Prague et al. (2013) *Adv. Drug Deliv. Rev.*

From *in vitro* to *in vivo*

Dynamic of the infected T-cells compartment :



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

Treatments plays on infectivity parameters :

$$\tilde{\gamma}(t) \quad = \quad \tilde{\gamma}_0 - \mathrm{f}_{\mathrm{PKPD}}(d_1(t), \ldots, d_{n_{cART}}(t))$$

Summarizing *in vitro* knowledge : f_{PKPD} definition

IIP quantifies the antiviral activity [2] :

$$\mathrm{IIP}(d_j(t)) \quad = \quad \log\left(1 + \left(\frac{d_j(t)}{\mathrm{IC}_{50}^{j}}\right)^{m_j}\right)$$

Bliss independence [3] is assumed :

$$\mathrm{IIP}(d_1(t), \ldots, d_{n_{cART}}(t)) \quad = \quad \sum_{j=1}^{n_{\mathrm{cART}}} \mathrm{IIP}(d_j(t))$$

Estimated drug-specific *in vitro* to *in vivo* conversion factor :

$$\tilde{\gamma}(t) \quad = \quad \tilde{\gamma}_0 + \underbrace{\sum_{j=1}^{n_{\mathrm{cART}}} \beta_j \mathrm{IIP}(d_j(t))}_{f_{PKPD}(d_1(t),\ldots,d_{n_{cART}}(t))} \qquad \text{(expected } \beta_j < 0\text{)}$$

2. Shen et al. (2008) *Nature Medecine*
3. Jilek et al. (2012) *Nature Medecine*

Statistical model : the populational approach

There is an inter-individual variability of parameters that justifies the use of random effects :

- Immune systems Q-cells input can vary :

$$\tilde{\lambda}^i = \tilde{\lambda}_0 + u_\lambda^i \text{ with, } u_\lambda^i \sim \mathcal{N}(0, \sigma_\lambda)$$

- CD8 response can vary :

$$\tilde{\mu_{T^*}}^i = \tilde{\mu_{T^*}}_0 + u_{\mu_{T^*}}^i \text{ with, } u_{\mu_{T^*}}^i \sim \mathcal{N}(0, \sigma_{\mu_{T^*}})$$

- Sampah et al.[4] evaluated *in vitro* that mutations result in mutation/patient-specific IIP reductions :

$$\tilde{\gamma}^i(t) = \tilde{\gamma}_0 + \sum_{j=1}^{n_{\text{cART}}} \beta_j \text{IIP}(d_j^i(t)) + u_\gamma^i \text{ with, } u_\gamma^i \sim \mathcal{N}(0, \sigma_\gamma)$$

4. Sampah et al. (2011) *PNAS*

Dataset : Population description

Study name	nb. pat.	Duration (weeks)	**AZT**	**3TC**	**d4T**	**ddI**	**LPV/r**	**APV/r**	**DRV/r**
			(at least one intake - % of patients)						
ALBI [5]	148	24	66	66	68	68	-	-	-
PUZZLE [6]	22	26	23	86	46	68	86	86	-
ZEPHIR [7]	116	12	22	56	3	11	10	100	-
PREDIZISTA [8]	64	12	3	17	3	20	2	-	100
ALL	**350**	**19**	**37**	**55**	**33**	**41**	**9**	**39**	**18**

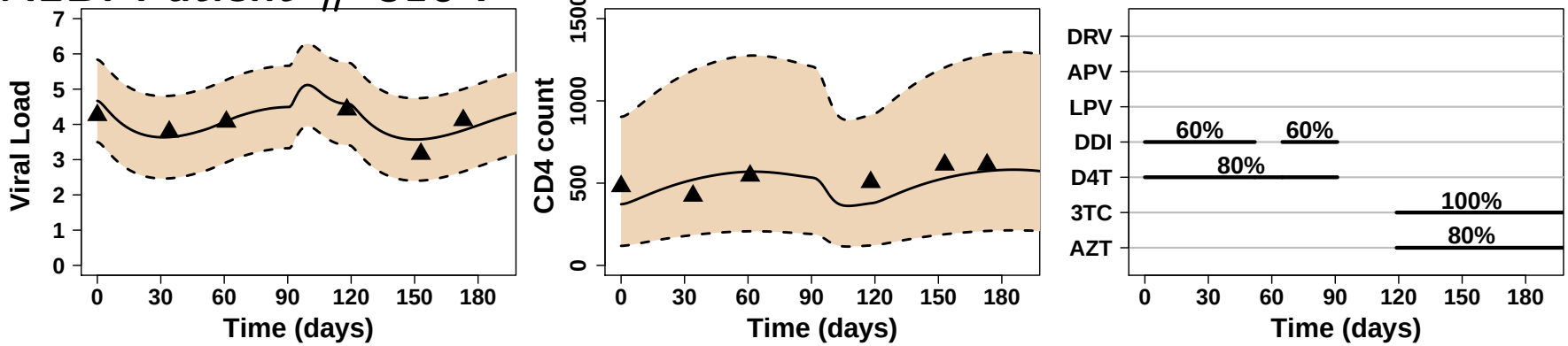
5. ANRS 70 : Molina et al. (1999) *J. Infect. Dis.*
6. ANRS 104 : Raguin et al. (2004) *Antiviral therapy*
7. ANRS Co3 Aquitaine Cohort : Pellegrin et al. (2007) *Antimicrob. Agents Chemo.*
8. ANRS Co3 Aquitaine Cohort : Pellegrin et al. (2008) *Antiviral therapy*

Data fits - MAP Bayesian Approach (NIMROD) [9]

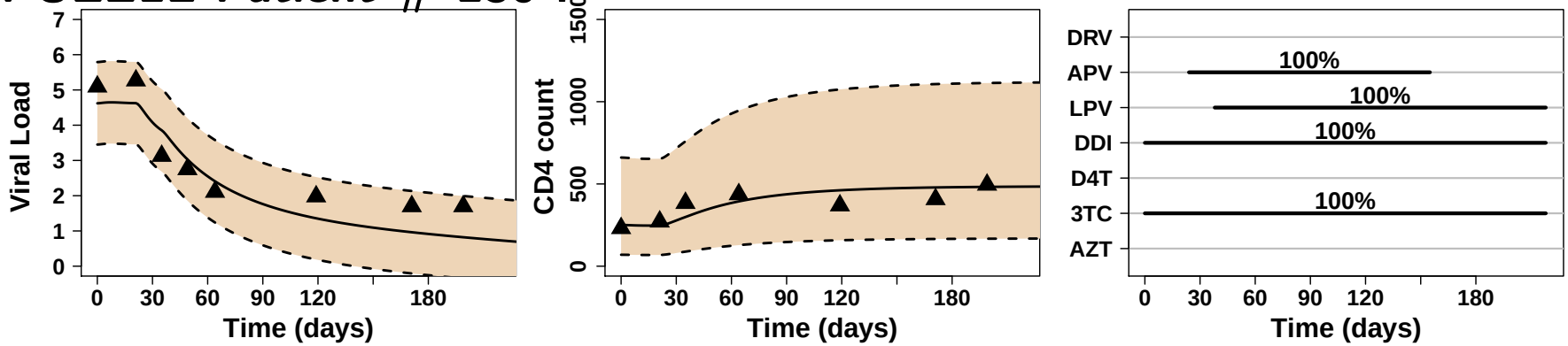
Observed Biomarkers and data :

Viral Load ($\log_{10}(V)$) , CD4 count ($Q+T+T^*$) and treatment designs.

ALBI Patient # 316 :



PUZZLE Patient # 230 :

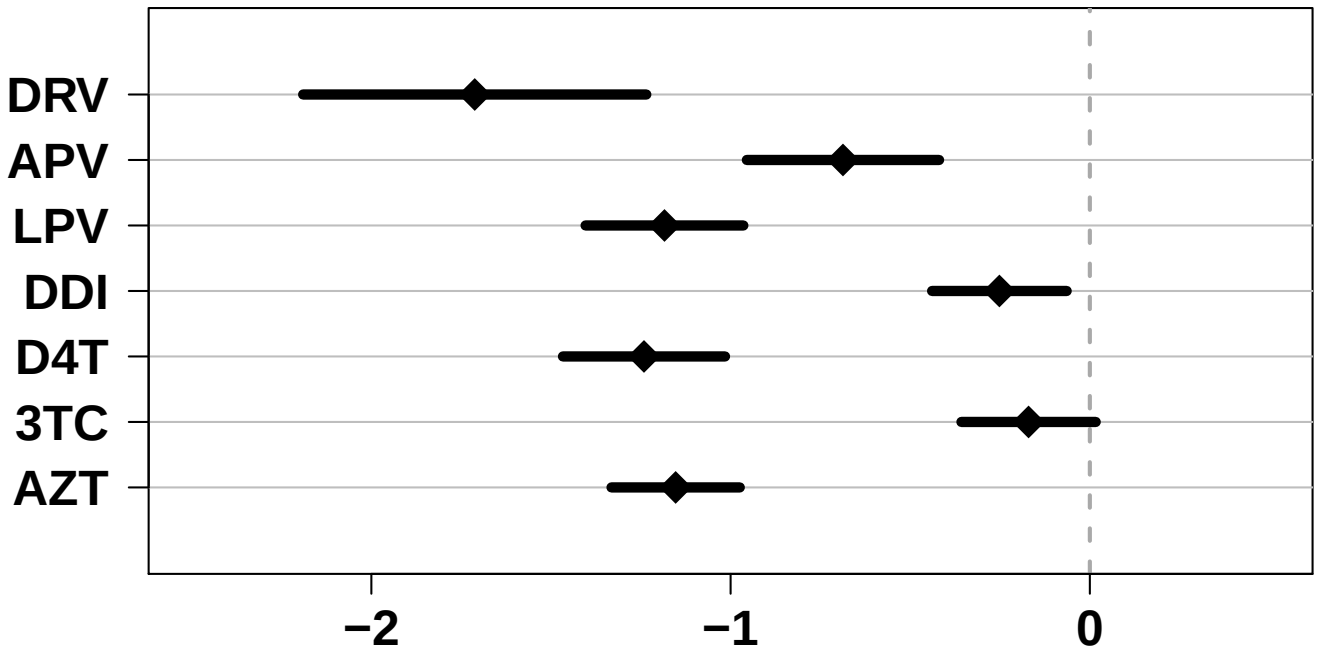


9. Prague et al. (2013) *Comp. Methods Programs Biomed.*

Effect of Antiretrovirals : Estimation on *in vivo* data

Antiretroviral Effects :

$$\tilde{\gamma}^i(t) = \tilde{\gamma}_0 + \sum_{j=1}^{n_{\text{cART}}} \boxed{\beta_j \text{IIP}(d_j^i(t))} + u_\gamma^i$$



-> Each antiretroviral has a distinguishable effect : estimated on data.

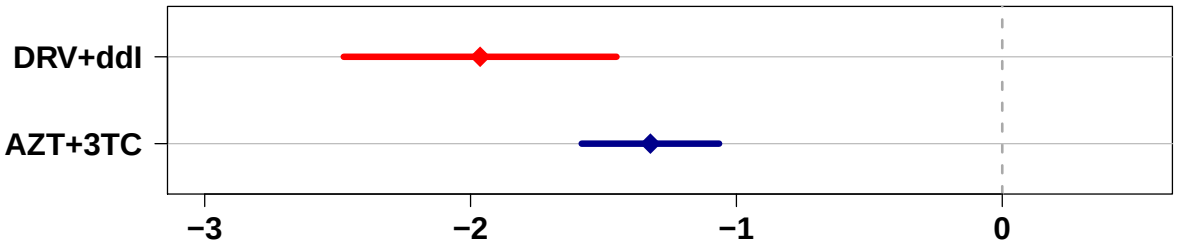
-> Small standard errors with Separate CIs.

-> Consistent with *in vitro*

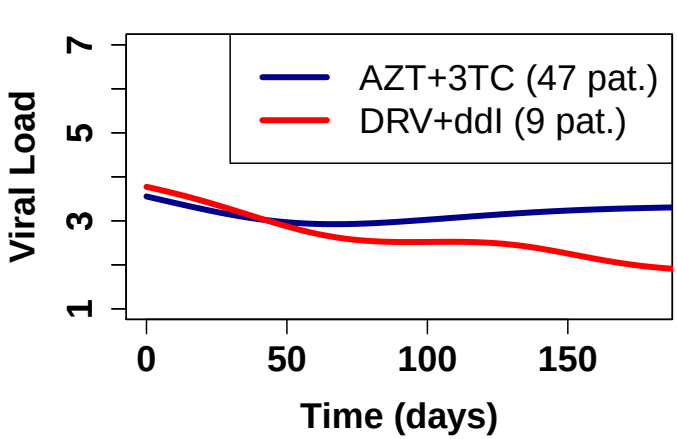
Effect of cART : Estimation on *in vivo* data

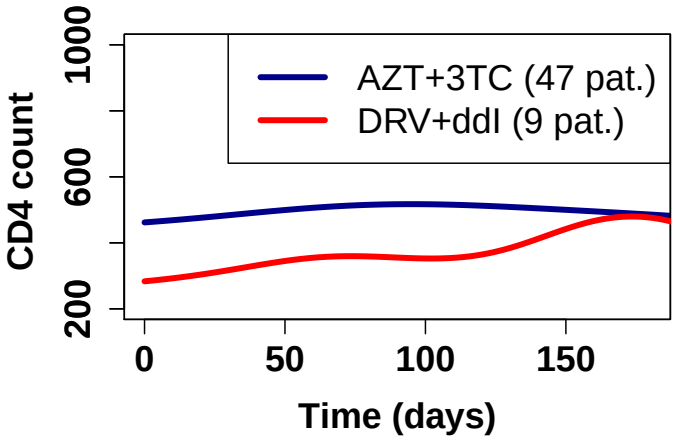
cARTs Effects :

$$\tilde{\gamma}^i(t) = \tilde{\gamma}_0 + \boxed{\sum_{j=1}^{n_{\text{cART}}} \beta_j \text{IIP}(d_j^i(t))} + u_\gamma^i$$



Observed Biomarkers profiles on data for different cARTs :

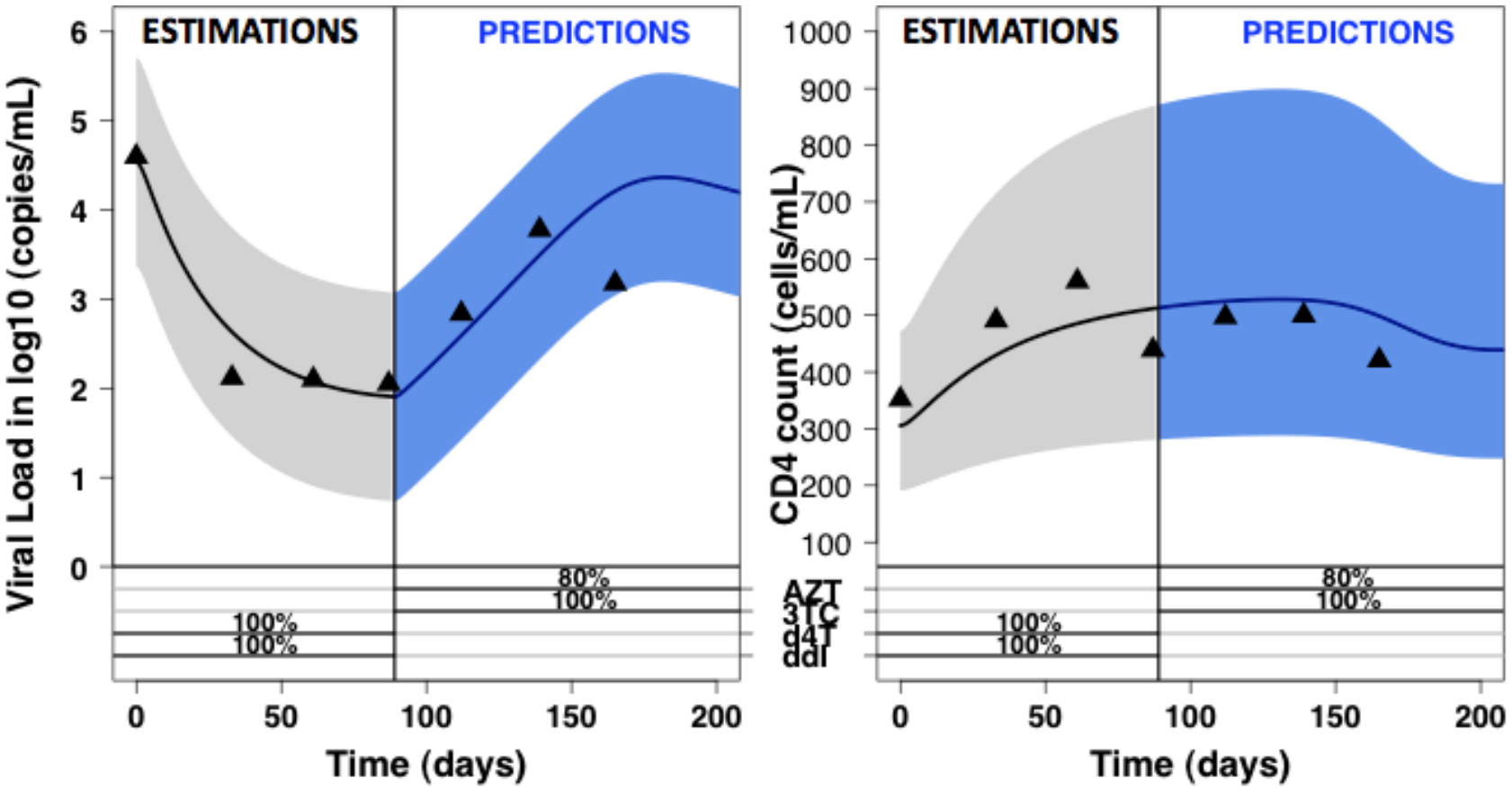




Predictive Abilities : from d4T+ddI to AZT+3TC

We are able to forecast the response of the patients to a new cART [10].

ALBI Patient # 41 :



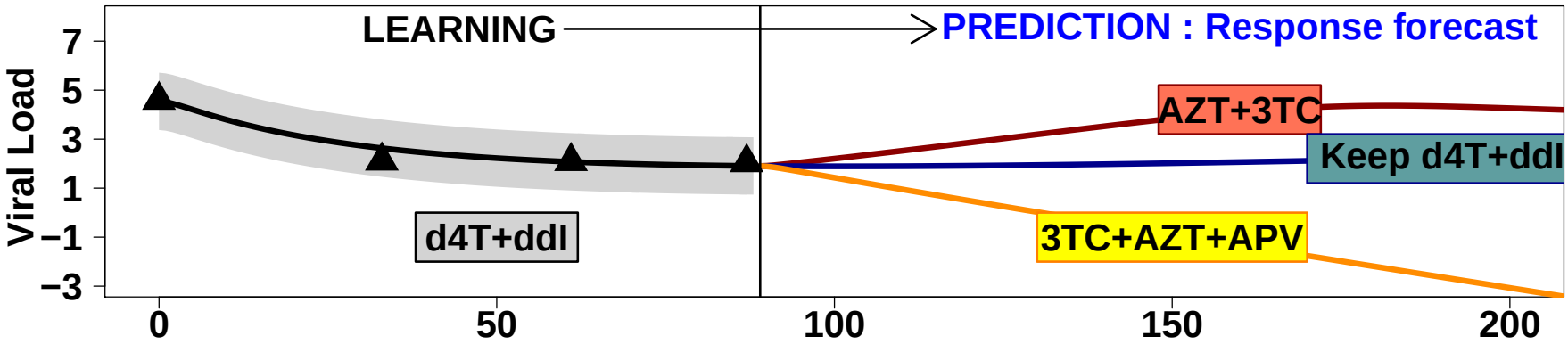
10. Prague et al. (2012) *Biometrics*

Perspectives and long-term prospects

This model could be a tool to :

-> Design new cART clinical trial,

-> Help in personalized medicine.



Ongoing works :

-> Stronger modeling (mutations, more antiretrovirals, ...)

-> Extend analyses to other trials and cohorts (eg. Aquitaine cohort).

Acknowedgements

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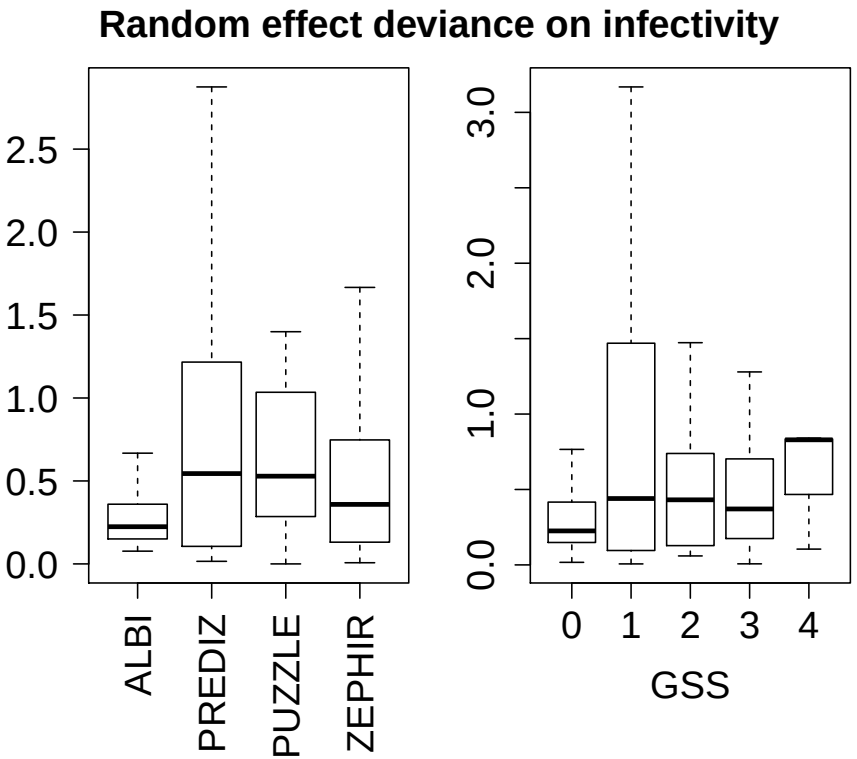
- All the patients and heath-care providers that articipated in these studies,
- All fundings institutions.

Further readings :

- **Concerning parameters estimation methods :**
  Prague et al. (2013) *Comp. Methods Programs Biomed.*
  http ://www.isped.u-bordeaux2.fr/NIMROD/documentation.aspx
- **Concerning HIV dynamical models in personalized medecine :**
  Prague et al. (2013) *Adv Drug Deliv Rev*
  Prague et al. (2012) *Biometrics*

Effect of Mutations : Estimation on *in vivo* data

$$\tilde{\gamma}^i(t) = \tilde{\gamma}_0 + \sum_{j=1}^{n_{\text{cART}}} \beta_j \text{IIP}(d_j^i(t)) + \boxed{u_\gamma^i}$$



-> Random effects on infectivity is greater when :

- Patients are heavily pretreated (PUZZLE, ZEPHIR, PREDIZISTA)
- Genotypic susceptibility Score (GSS) is different from 0.

-> Both ANOVA : $p < 0.001$