Parameter estimation of long-term HIV dynamic model in the COPHAR2 – ANRS 111 trial using MONOLIX

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Background

- Understanding variability in response to antiretroviral treatment in HIV patients through modelling is an important challenge.
- Several HIV dynamic models were proposed based on ordinary differential equations (ODE)
- Nonlinear mixed effect models (NLMEM) are appropriate to estimate parameters of these models and their inter-patient variability
- Most applications used a simplified model or a Bayesian approach

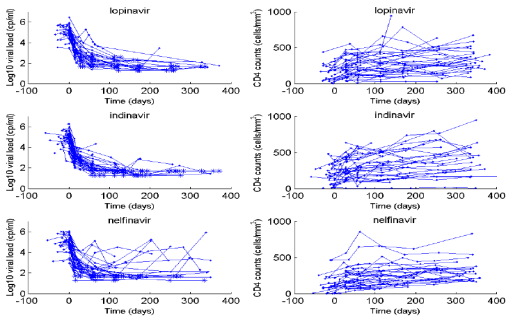
Objectives

To analyze simultaneously HIV viral load decrease and CD4 increase in patients initiating treatment using a long-term HIV dynamic model with the SAEM algorithm in MONOLIX 2.4[1]

Data

Cophar2-ANRS111 trial[2]

- Sponsor: Agence Nationale de Recherche sur le Sida (ANRS)
- 115 HIV-1 infected patients
  - Baseline plasma viral load value > 1000 copies/ml and naïve of PI
  - Initiating a treatment containing one protease inhibitor (PI) and 2 nucleoside analogs (NRTI)
  - 3 PI: Lopinavir (+ritonavir), Indinavir (+ritonavir) or Nelfinavir
  - Followed one year with measurements of viral load and CD4 cells

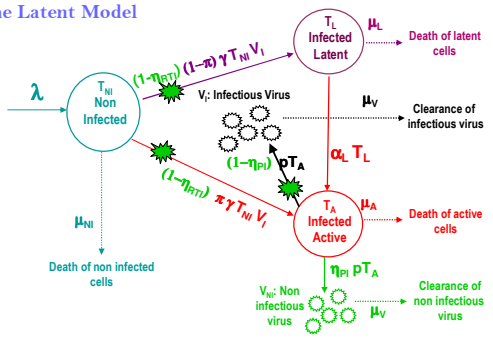


Models and Methods

Three main HIV dynamic models

- $\mathcal{M}_B$: Basic model with 8 parameters and 4 ODE[3]
- $\mathcal{M}_Q$: Quiescent Model with 11 parameters and 5 ODE[4,5]
- $\mathcal{M}_L$: Latent Model with 11 parameters and 5 ODE[6]

The Latent Model



ODE for the latent model

$$\begin{aligned}
\frac{dT_{NI}}{dt} &= \lambda - (1-\eta_{RTI})\gamma\, T_{NI} V_I - \mu_{NI} T_{NI} \\
\frac{dT_L}{dt} &= (1-\eta_{RTI})(1-\pi)\gamma\, T_{NI} V_I - \alpha_L T_L - \mu_L T_L \\
\frac{dT_A}{dt} &= (1-\eta_{RTI})\pi\gamma\, T_{NI} V_I + \alpha_L T_L - \mu_A T_A \\
\frac{dV_I}{dt} &= (1-\eta_{PI}) p\, T_A - \mu_V V_I \\
\frac{dV_{NI}}{dt} &= \eta_{PI}\, p\, T_A - \mu_V V_{NI}.
\end{aligned}$$

Implementation in MLXTRAN

```
$MODEL
COMP = (TC)
COMP = (TL)
COMP = (TA)
COMP = (VI)
COMP = (VNI)

$PSI
lambda  gamma0 fo a p0 muT
muL muA muV  etaPI etaRTI

$ODE
gamma = (1-etaRTI)*gamma0
p_I = (1-etaPI)*p0
p_NI = p0-p_I

T0 = 0
TC_0 = (muA*muV*(a+muL))/(gamma0*p0*(a+muL*fo))
VI_0 = (lambda-TC_0*muT)/(gamma0*TC_0)
TA_0 = muV*VI_0/p0
TL_0 = (1-fo)*gamma0*TC_0*VI_0/(a+muL)

DDT_TC  = lambda-gamma*TC*VI-muT*TC
DDT_TL  = (1-fo)*gamma*TC*VI-a*TL-muL*TL
DDT_TA  = fo*gamma*TC*VI+a*TL-muA*TA
DDT_VI  = p_I*TA-muV*VI
DDT_VNI = p_NI*TA-muV*VNI

$OUTPUT
OUTPUT1 = log10(max((VI+VNI)*1000,1))
OUTPUT2 = TC+TL+TA
```

Methods

- Estimation with SAEM implemented in MONOLIX 2.4 using MLXTRAN
- Analysis of Viral Load $= \log_{10}(1000(V_I + V_{NI}))$ and CD4 cells $= T_{NI} + T_L + T_A$
- Additive error for log viral load and proportional error for CD4 cells
- Lognormal distribution for positive parameters, logistic distribution for parameters between 0 and 1 (η_{RTI}, η_{PI}, π)
- Comparison of models with BIC
- Test for different efficacy of the three PI

Results

Comparison of the three dynamic models

Model	$-2\times$ log Likelihood	BIC	σ_V	σ_T
Basic model ($\mathcal{M}_B$)	9048(4)	9134(4)	0.67(0.03)	0.27(0.01)
Quiescent model ($\mathcal{M}_Q$)	8963(7)	9077(7)	0.62(0.03)	0.27(0.01)
Latently model ($\mathcal{M}_L$)	8644(6)	8758(6)	0.46(0.02)	0.25(0.01)

Test of the effect of the protease inhibitors

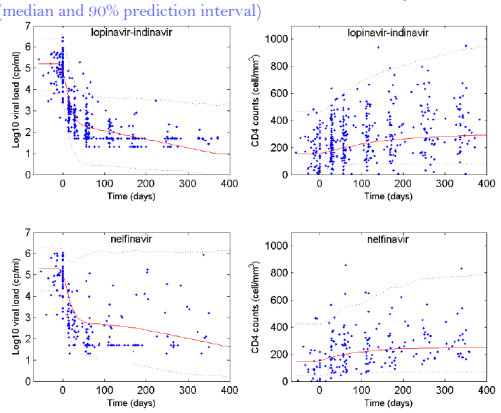
(L: lopinavir, I: indinavir, N: nelfinavir)

Model	$-2\times$ log-likelihood	BIC	β_N	p_{β_N}	β_I	p_{β_I}
LIN	8646 (6)	8741 (6)				
LI-N	8635 (6)	8734 (6)	-5.6 (2.6)	0.045		
L-I-N	8631 (6)	8735 (6)	-4.9 (2.3)	0.036	-1.1 (4.0)	0.790

Efficacy of Nelfinavir 25% lower than for Lopinavir or Indinavir ($p=10^{-12}$)

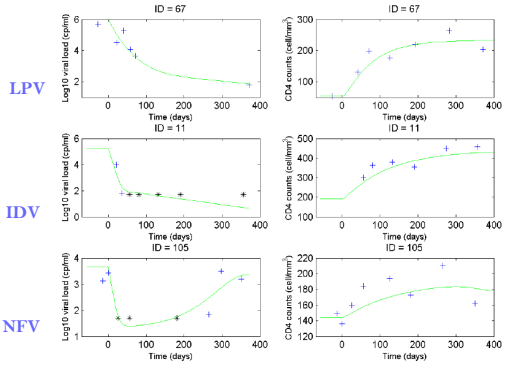
Visual Predictive Check for the latent model $\mathcal{M}_L$ with LI vs N

(median and 90% prediction interval)



Individual predictions for some individuals for the latent model $\mathcal{M}_L$

(+: observations, *: data below LOQ)



Estimated parameters for the latent model $\mathcal{M}_L$

(SD of random effect for IIV)

	Parameter (S.E.)	; Inter-patient variability (S.E.)
λ (cells/mm³/day)	2.61 (0.25)	0.55 (0.044)
γ	0.0021 (0.0009)	0 (fixed)
μ_{NI} (day^{-1})	0.0085 (0.0010)	0.44 (0.073)
μ_L (day^{-1})	0.0092 (0.0009)	0 (fixed)
μ_A (day^{-1})	0.289 (0.016)	0.399 (0.047)
μ_V (day^{-1})	30 (fixed)	0 (fixed)
p	641 (110)	0.9 (0.13)
α_L	1.6e-5 (1.7e-6)	0.678 (0.33)
π	0.443 (0.038)	0.45 (0.047)
η_{RTI}	0.90 (0.17)	2.93 (1.8)
η_{PI}	0.99 (0.003)	3.19 (2)
β_N	-5.6 (2.6)	
σ_V	0.464 (0.024)	
σ_T	0.254 (0.009)	

Conclusion

- Model with latent CD4 cells provides the best description of the data
- Accurate estimation of 10 parameters (7 with random effects) of this complex model using a maximum likelihood approach thanks to the SAEM algorithm in MONOLIX 2.4 (the final run with estimation of likelihood and SE took less than 2 hours)
- Efficient and fast estimation methods allow to evaluate and compare several models

1. www.monolix.org
2. Duval et al. *Fundamental and Clinical Pharmacology*, 2009
3. Perelson and Nelson, *SIAM review* ,1997
4. De Boer and Perelson, *Journal of Theoritical Biology*, 1998
5. Guedj et al. , *Biometrics*, 2007
6. Funk et al., *J AIDS*, 2001