Influence of pharmacogenetics on pharmacokinetic interindividual variability of indinavir and lopinavir in HIV patients (COPHAR2 - ANRS 111 trial)

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Introduction

- COPHAR2 - ANRS 111 trial
  - non comparative, prospective, open trial
  - sponsor: Agence Nationale de Recherche sur le Sida (ANRS)
  - objective: to evaluate feasibility and impact of early dose adaptation in HIV positive patients naive of protease inhibitors (PI) starting a PI containing HAART treatment
- Two of the three groups studied in this trial are presented here*
  - indinavir/ritonavir (IDV)
  - lopinavir/ritonavir (LPV)
- Role of genetic polymorphisms on PK of PI not yet completly defined

* The results for the nelfinavir group are presented in poster PI.3

Objectives

- Analysis of the concentrations collected at week 2 (W2) using a population approach
- Evaluation of the inter-individual variability in the PK of the 2 PI
- Evaluation of the effect of genetic polymorphisms
- Study of the link between concentrations and short term efficacy and toxicity

Methods

Population study

- HIV-1 infected patients
  - with a baseline plasma viral load value > 1000 copies/mL and naive of PI
  - initiating a treatment containing either
    - IDV / ritonavir 400 to 800 mg / 100 mg bid: 40 patients
    - LPV /ritonavir 400 mg / 100 mg bid: 34 patients

Plasma concentration measurements

- Four samples collected at W2 before and at 1, 3 and 6h after drug administration
- Concentrations determined by HPLC

Pharmacokinetic model

- One compartment model
  - first order absorption parameterized in k_a plus absorption delay (T_{lag}) if necessary
  - apparent volume of distribution V/F
  - first order elimination parameterized in apparent clearance Cl/F

Population analysis

- Exponential model for the random effects
- Proportionnal error model
- Estimation of the mean parameters and their variabilty using the SAEM algorithm implemented in the MONOLIX V2.1 software (http://www.monolix.org/)

Genetic data

- Genotype of the gene coding for
  - the CYP3A4 and CYP3A5 cytochromes
  - the P-glycoprotein (exon 26 and 21 of the ABCB1 gene)
- Categorization in 2 or 3 classes
- Non parametric tests on EBE of the individual parameters from the basic model
- Forward LRT selection of the covariate model for polymorphisms having an effect on EBE

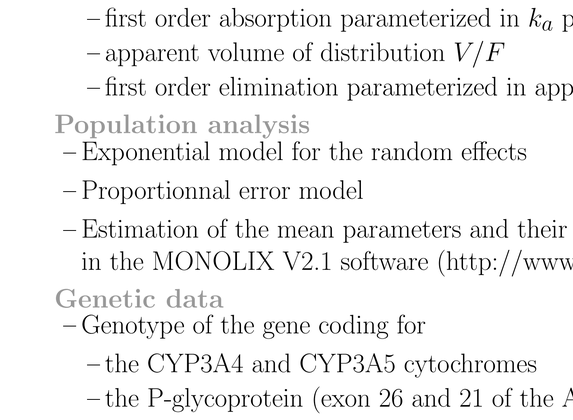
Concentrations/short term efficacy or toxicity relationship

- Efficacy: decrease in log viral load after 2 weeks of treatment
- Toxicity: change in biological constants (glycemia, total cholesterol total, triglycerides), measured 4 weeks before and after treatment initiation
- Concentrations: derived from the individual PK parameters estimates
  - C_{trough}: trough individual concentrations
  - C_{mean}: mean individual concentrations
  - C_{max}: maximal individual concentrations
- Correlation using non parametric test between concentrations and efficacy/toxicity

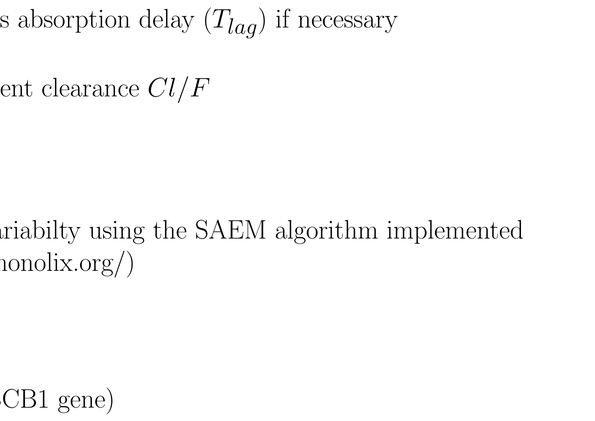
Results

Observed concentrations and model predicted curve

IDV



LPV



Population pharmacokinetics

PK parameters of the basic model

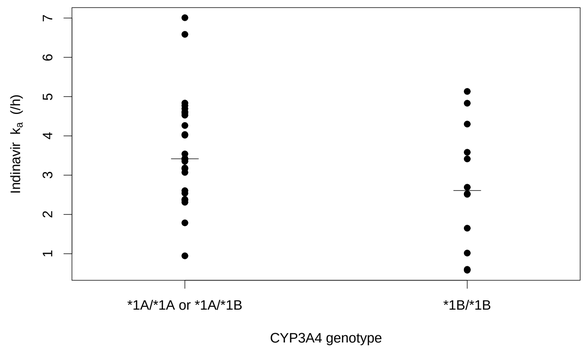
	IDV		LPV	
Parameters	Estimates	RSE (%)	Estimates	RSE (%)
T_{lag} (h)	-	-	0.7	50.0
k_a (/h)	1.3	33.7	0.7	37.1
Cl/F (L/h)	21.9	6.9	4.6	5.3
V/F (L)	93.9	8.2	68.7	1.6
$\omega_{T_{lag}}$ (%)	-	-	123.0	24.1
ω_{k_a} (%)	118.0	22.9	-	-
$\omega_{Cl/F}$ (%)	34.4	15.0	19.1	72.7
$\omega_{V/F}$ (%)	19.3	66.8	66.5	12.4
σ (%)	44.5	8.9	18.8	9.2

Effect of genetic polymorphisms

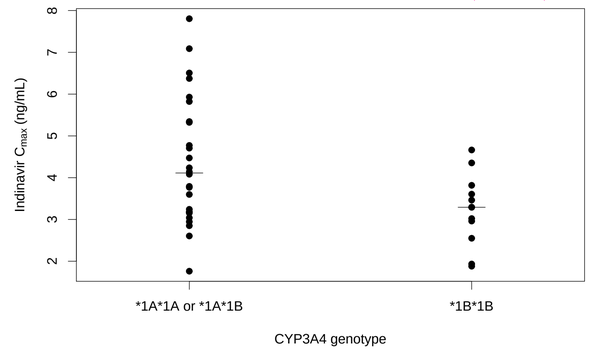
- IDV: k_a is divided by 3.45 (LRT p=0.02) in patients *1B/*1B vs *1A/*1B or *1A/*1A for CYP3A4

  → impact on the individual C_{max} (p=0.04)
- LPV: no genetic effects found on the PK parameters

IDV absorption constant (k_a)



IDV maximal concentration (C_{max})



Short term efficacy and toxicity

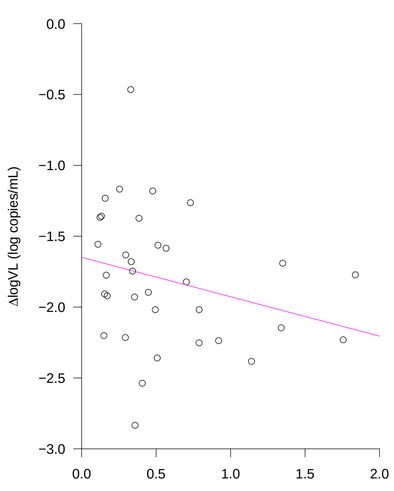
Median	IDV	LPV
Efficacy		
Δ log viral load between D0 and W2 ($\log_{10}$ cp/mL)	-1.8*	2.0*
Toxicity		
Δ total cholesterol between W-4 and W4 (mmol/L)	0.8*	0.3
Δ glycemia between W-4 and W4 (mmol/L)	0.2*	0.2
Δ triglycerides between W-4 and W4 (mmol/L)	0.4*	0.4*

* significant change from baseline

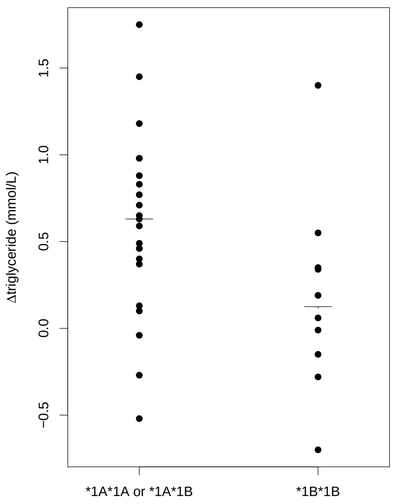
Correlation with concentrations

- IDV: C_{mean} and C_{trough} with the log viral load decrease at W2 (p=0.02 et 0.03)
- IDV: higher increase in triglycerides at W4 in patients *1A/*1A or *1A/*1B vs *1B/*1B for CYP3A4 (p<0.04)

Δ log viral load for IDV



Δ triglyceride for IDV



- LPV: no correlation found between concentrations and short term efficacy or toxicity

Conclusion

- Important PK variability for indinavir and lopinavir in HIV patients of the COPHAR2 - ANRS 111 study
- For indinavir
  - role of CYP3A4*1B polymorphism in PK variability and consequences on short term toxicity
  - confirmation of the link between concentrations and short term efficacy and toxicity
- For lopinavir there is no evidence in this study of neither genetic effect on PK nor link between concentrations and short term efficacy and toxicity

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