

**Efavirenz 600mg daily leads to
therapeutic concentrations in a majority
of patients when combined with
rifampin: preliminary data from the
CAMELIA clinical trial**

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INTRODUCTION

- The CAMELIA (ANRS1295-CIPRA KH001) trial started to enrol HIV-infected patients with TB in January 2006
- Enrolled patients received concomitantly a Rifampin (Rifampicine) 10 mg/kg/d based TB regimen plus d4T, 3tC and efv.
- R. is a potent drug metabolizing enzymes inducer, the efv dose to be coadministered is not well established.
- CAMELIA, all patients were randomized to receive efv 600mg QD either 2 weeks or 2 months after the onset of TB treatment.

INTRODUCTION

- EFV, first line ARV treatment in naïve patients
- Pharmacokinetic characteristic :
 - $F=50\%$,
 - $T_{max} = 2-5h$
 - Protein binding = 99.5%
 - Elimination by liver metabolism (CYP 2B6)
 - $T_{1/2} = 50 h$
 - Therapeutic window for trough concentration 1000-5000ng/mL

MATERIAL AND METHODS

■ Patients and treatments

- Patients enrolled in the CAMELIA-ANRS1295-CIPRA KH001 trial,

- Coinfected with tuberculosis and HIV,

- Treatment:

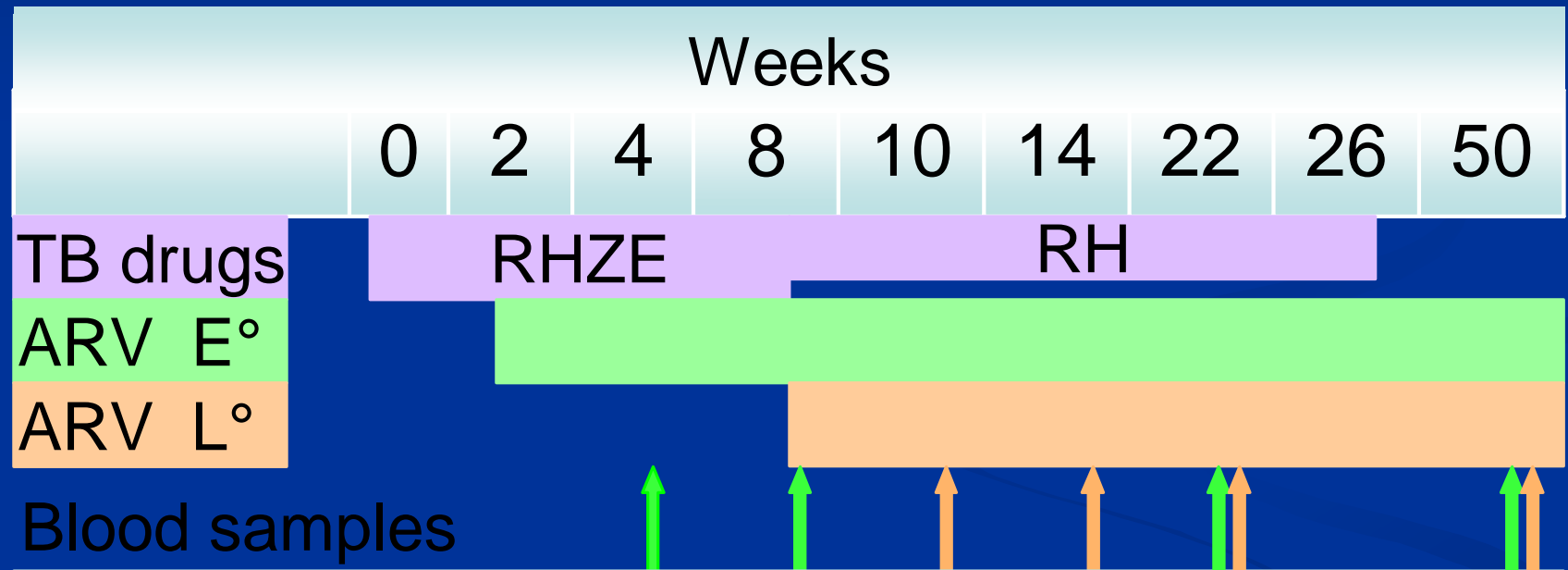
- ARV : 3tC 150 mg bid, d4T 30 or 40mg bid, (generic fixed dose combination from India) and EFV 600 mg qd (Merck);
- All patients took their regimen at night
- TB : H (4-5mg/kg/d), E (15-20mg/kg/d), Z (20-30mg/kg/d) and R (10 mg/kg/d) up to week 8 and R, H up to week 26.

MATERIAL AND METHODS

■ Study design

- A total of 4 blood samples for EFV assay were drawn
- 12h after drug intake at weeks 2 (W+2) and 6 (W+6) after the onset of HAART
- and at weeks 22 and 50 (after R discontinuation) after the onset of TB treatment.

MATERIAL AND METHODS



°randomisation E (early) L (late)

MATERIAL AND METHODS

- Efavirenz assay
 - EFV was assayed by a validated HPLC method:
In brief : plasma 100 μ l + ACN 200 μ l with IS;
centrifugation and 25 μ l of the supernatant injected onto
a C18 column.
 - Mobile phase ACN/ H₂O mixture (45/55 v/v)
 - RT: EFV 10 min and IS 13.5 min
 - LLQ 50ng/mL
 - Day-to-day quality controls variability below 15%.

MATERIAL AND METHODS

- Statistics
 - All data are presented as median (ranges) or as box-plots;
 - Coefficient of correlation was used to assess relationships between weight and efavirenz plasma concentration.

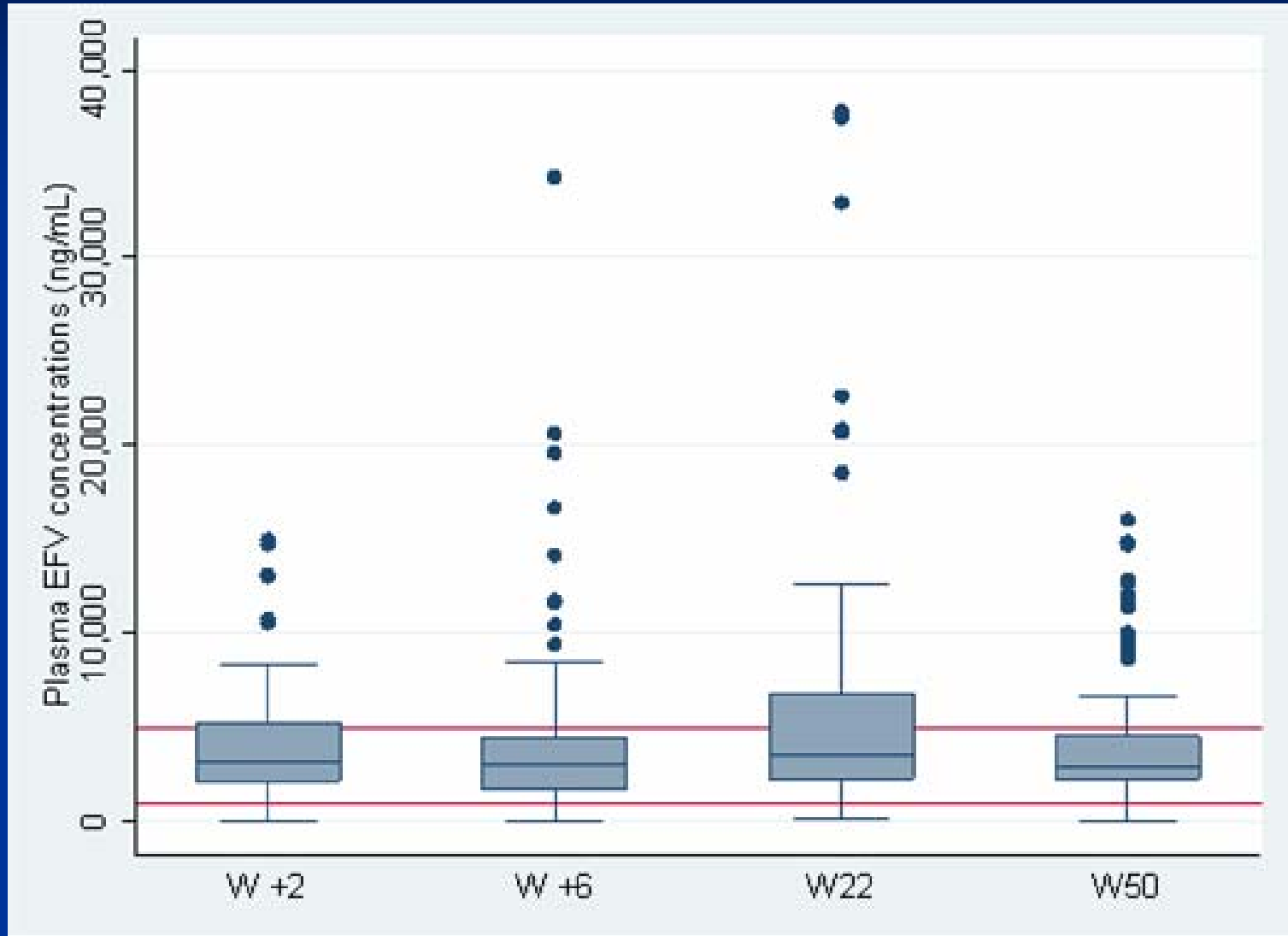
RESULTS

■ Patients characteristics

- 90 patients reached week 50 at time of analysis.
- 86 patients had plasma samples for efavirenz assay drawn in the morning 12 to 16 h post dosing.

<i>Age - years</i>	<i>36 (21-58)</i>	
<i>Weight - kg</i>	<i>Week +2 : 44(28-65)</i>	<i>n=80</i>
	<i>Week +6 : 45 (25-63)</i>	<i>n=85</i>
	<i>Week 22 : 50 (34-68)</i>	<i>n=80</i>
	<i>Week 50 : 52 (37-74)</i>	<i>n=86</i>

■ Efavirenz concentrations



Number of patients per concentration ranges

Weeks	+2	+6	22	50
% pts with plasma efv 1000 -5000 ng/mL	65.0	70.6	65.0	79.1
% pts with plasma efv > 5000 ng/mL	26.3	23.5	32.5	19.8

CONCLUSION

- ◆ Only 1 patient (at week 50) had EFV concentrations below effective threshold (1000 ng/ml);
- ◆ A high proportion of patients have EFV concentrations within the therapeutic range (1000-5000 ng/mL) despite the rifampin coadministration;
- ◆ Interestingly 15.7 % of the concentrations are very high and above 8000ng/mL;
- ◆ EFV concentrations were found to be highly variable and the only correlation with body weight was at week 22 ($r=-0.3$ $p=0.007$);
- ◆ Further studies are ongoing to validate the safety and efficacy of a standard 600mg EFV regimen during TB treatment.

■ Thanks to

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