

Pharmacokinetic Parameters of Efavirenz in patients receiving an intermittent efavirenz-based antiretroviral treatment: a Substudy of WINDOW- ANRS 106 Trial

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ABSTRACT

Background : The ANRS 106 WINDOW trial is an open randomized 96-week (w) trial comparing intermittent therapy (IT: 8 w on / 8 w off) to continuous therapy (CT) among 400 patients with chronic HIV-1 infection, stable HAART, HIV-1 RNA (VL) < 400 cp/ml and CD4 > 450/mm³ for at least 6 months ; primary endpoint is immunologic. When the patients receiving an efavirenz (EFV)-based IT regimen came off therapy, they stopped EFV straightaway and the other drugs 7 days later.

Methods : Pharmacokinetic study was planned in a subgroup of patients receiving an EFV-based IT regimen. The objective was to evaluate the pharmacokinetics of EFV plasma concentrations during the interruption phase. Blood samples were drawn on day 1, 12h after last EFV dosing, then on days 3, 7 and 10. EFV concentrations were measured by a validated HPLC assay. The lower limit of quantification (LLQ) was 50 ng/ml. PK was repeated at a next interruption phase in 9 pts with EFV concentrations < 312 at day 3 or > 625 ng/ml at day 7. EFV half-life was calculated from the concentrations versus time mono-exponential decline.

Results : 21 patients (15 males) were evaluated (mean 39 years). EFV-associated ARV drugs included NRTI in all patients plus a protease inhibitor in 3 patients. Median [range] EFV concentrations (ng/ml) on days 1, 3, 7 and 10 were : 1962 [728-4146], 416 [95-1390], 112 [<50-749] and 50 [<50-631] respectively. EFV half-lives ranged from 27h up to 136h (median : 47h, coefficient of variation 54%). In contrast, intra-subject variability was low in the 6 patients who experienced a second complete PK evaluation. After 8 weeks of HAART resumption following the considered interruption phase, VL decreased to < 400 cp/ml in 19/21 patients.

Conclusions : EFV half-life was highly variable among patients without influence on the short-term viral response after treatment resumption. Data suggest that closer and individualized drug monitoring of patients undergoing EFV treatment interruptions should be recommended. Virologic impact, including resistance remains to be deeply investigated.

BACKGROUND

The ANRS 106 WINDOW trial is an open randomized 96-week trial comparing intermittent therapy (IT: 8 w on / 8 w off) to continuous therapy (CT) among 400 patients with chronic HIV-1 infection, stable HAART, HIV-1 RNA (VL) < 400 cp/ml and CD4 > 450/mm³ for at least 6 months ; primary endpoint is immunologic. When the patients receiving an efavirenz (EFV)-based IT regimen came off therapy, they stopped EFV straightaway and the other drugs 7 days later.

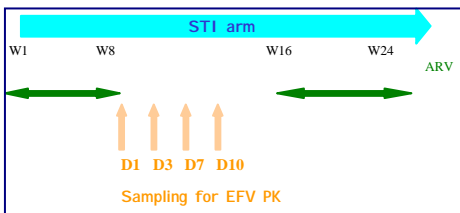
OBJECTIVE

To assess the rate of efavirenz concentrations decline and the pharmacokinetic parameters of efavirenz, after stopping efavirenz therapy at the beginning of an interruption phase.

METHODS

> STUDY DESIGN :

- Patients receiving an efavirenz-based regimen and randomized in the interruption group
- Blood samples drawn on day 1, 12h after last efavirenz dosing, then on days 3, 7 and 10.



> DRUG ASSAYS IN PLASMA

- EFV concentrations were measured by a validated HPLC assay
- Interlab quality controls variation : 11% (target 203 ng/mL), 5,8% (target 811 ng/mL), 6,1% (target 2434 ng/mL)
- Day-to-day variability: 4%, 5% and 10% respectively

> PHARMACOKINETIC CALCULATIONS

- Concentrations: experimental values
- Half-lives: log-linear decline of concentrations vs times

PATIENT CHARACTERISTICS AT BASELINE

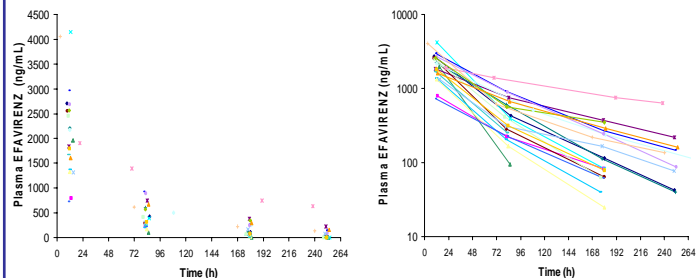
•21 patients included		
•15 males		
• weight 66 ± 19 kg		
• HIV-RNA level <400 copies/ml (inclusion criteria)		
	<u>Median</u>	<u>(Min. Max)</u>
Age (years)	38.6	23.8 59.9
CD4 cell count/µl	648	435 1151

RESULTS

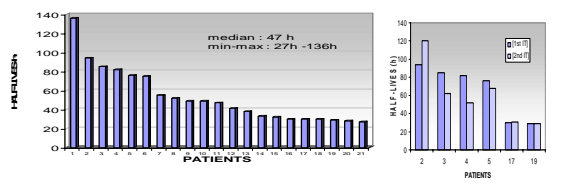
EFV concentrations decline after stopping EFV treatment (A)

Days post Treatment	EFV plasma median concentrations-ng/ml	range
D 1	1962	[728-4146]
D3	416	[95-1390]
D7	112	[<50-749]
D10	50	[<50-631]

EFV concentrations decline after stopping EFV treatment (B)



EFV half-lives



SHORT-TERM VIRAL RESPONSE AFTER TREATMENT RESUMPTION

- After 8 weeks of HAART resumption following the considered interruption phase, plasma HIV1-RNA decreased to < 400 cp/ml in 19/21 pts.

DISCUSSION - CONCLUSION

- EFV half-life was highly variable among patients without influence on the short-term viral response after treatment resumption.
- Data suggest that closer and individualized drug monitoring of patients undergoing EFV treatment interruptions should be recommended.
- Virologic impact, including resistance remains to be deeply investigated.

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