

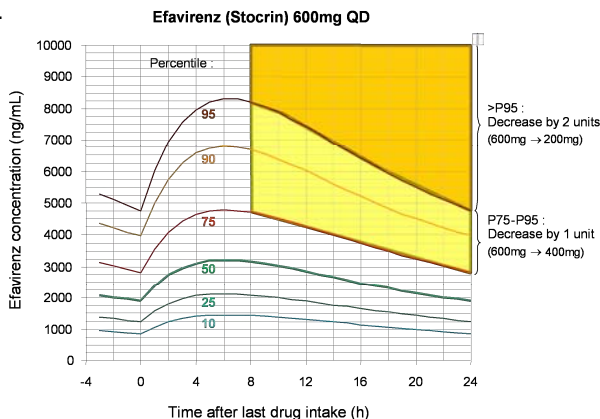
Therapeutic drug monitoring (TDM) enables efavirenz dose reduction in virologically-controlled patients

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Introduction

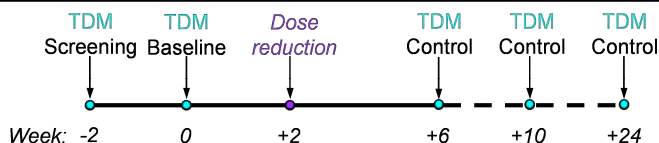
- Excessive antiretroviral drug concentrations increase the risk of toxicity. Therapeutic drug monitoring (TDM) may identify and correct excessively high concentrations, and thus minimize risk of toxicity.
- Treatment guidelines only recommend using TDM to help optimize antiretroviral therapy in selected patients, and there are no clear recommendations to guide the clinician who decides to adjust drug dosages.
- Prospective studies have suggested a relationship between EFV plasma concentrations and neuropsychiatric symptoms. Moreover, EFV is metabolized mainly by CYP2B6 and its concentration is associated with the CYP2B6 genetic polymorphism.
- Besides the benefit in terms of toxicity, dose reduction can also have a large impact on individual treatment cost.
- We tested a **simplified Bayesian algorithm** to guide efavirenz dosage adjustment in patients having EFV trough concentration above percentile 75 (P75) under 600 mg QD, with documented virological efficacy.



Methods

- This prospective 6-months open-label multicenter study included consecutive consenting participants with EFV concentration above P75 and undetectable HIV-RNA (< 40 copies/mL).
- EFV plasma concentrations were performed by liquid chromatography coupled with tandem MS (LC-MS/MS).
- Patient adherence to EFV was assessed electronically by Medication Event Monitoring System (MEMS®) and was defined as the percentage of days with correct dosing.
- Primary endpoint was the number of patients with plasma concentrations reaching the therapeutic targets (1'000-4'000 ng/mL) after at least one cycle of dose reduction, at 3 and 6 months.

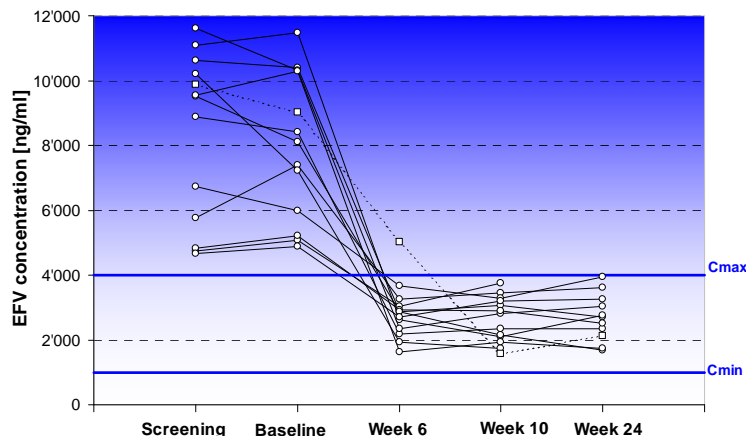
Study design



Results

- 15 participants, out of 74 patients screened (20%), were candidate for dosage adjustment at baseline: 53% male, median weight 67.5 kg [IQR 58-76], median CD4 count 479 cells/mm³ [374-567].
- Median baseline EFV concentration was 8'409 ng/mL [6'610-10'370], 33% between P75 and P95, qualifying to a 400 mg EFV dose, and 67% above P95, qualifying for a 200 mg EFV dose.
- Eleven patients have by now completed the study, reaching EFV plasma concentrations between 1'000 and 4'000 ng/mL at 6 months (median 2'707 ng/mL [2'237-3'141]).

Patients with EFV dose reduction



- TDM:** after dose reduction, EFV drug concentrations remained above the lower threshold of 1'000 ng/mL recommended by FDA for all patients.

For one patient, dose reduction was erroneously done at 400 mg QD instead of 200 mg QD at first cycle (protocol violation), and needed a second cycle of dose reduction to reach the recommended therapeutic interval of 1'000 - 4'000 ng/mL (*squares with dotted line on the graph*).

- Virological outcome:** all patients except one remained with undetectable HIV-RNA at 3 and 6 months.

One patient had a blip at week 24 (54 copies), resuppressed at the subsequent monitoring without treatment change.

- Adherence:** mean patient adherence to EFV was 98% (±2.0%) for all patients included in a cycle of dosage adjustment.

Conclusions

- TDM-guided efavirenz dose reduction was successful and safe over a 24-week period.
- A single cycle of dose reduction according to a Bayesian model led EFV plasma concentrations into the recommended therapeutic interval of 1'000 to 4'000 ng/mL, without compromising virological suppression.
- Besides potentially reducing side effects, this strategy is likely to produce substantial economies.