



# Incidence and severity of neuropsychiatric adverse events of efavirenz given as a stepped dosage over 2 weeks versus the usual dosage.

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**Background:** Efavirenz (EFV) is a first line antiretroviral drug but the incidence of neuropsychiatric side effects (NPSEs), reported in  $\geq 50\%$  of patients initiating EFV, may limit its use in a significant proportion of them. Given the chronology of NPSEs and that EFV induces its own metabolism with lower plasma drug levels after 7-10 days on treatment, we postulated a relation between EFV plasma levels and the incidence of NPSEs and that a **stepped dosage over 2 weeks could decrease the incidence and intensity of NPSEs without reducing its virological and immunological efficacy.**

## Objectives:

- To compare the incidence and severity of NPSEs of EFV given as a stepped dosage over 2 weeks versus the usual dosage.
- To evaluate the virological and immunological efficacy with both dosage

## Material and Methods:

Randomized, double blind, multicentric clinical trial in which a stepped dosage (arm A) was compared with the usual administration (arm B).

Inclusion criteria:

- HIV-infected patients  $\geq 18$  years of age who were scheduled to initiate therapy with EFV + 2 NRTIs.
- A negative urine pregnancy test and an acceptable method of contraception for women of childbearing potential.
- Written informed consent.

Exclusion criteria:

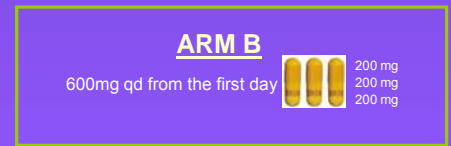
- Pregnancy
- Illegal drug, methadone use and new psychiatric drugs within the previous 4 weeks
- Major psychiatric disease antecedents, hepatic insufficiency and drugs which pharmacokinetic interactions with EFV.

Neuropsychiatric side effects (NPSEs) were assessed using 2 questionnaires:

- A Likert-type scale specifically designed
- A validated sleep disorder questionnaire

- Incidence and intensity of dizziness.
- Incidence and intensity of hangover.
- Hallucinations.
- Confusion and disorientation.
- Concentration problems.
- Character disorder.
- Anxiety.
- Depression.
- Level of satisfaction with the sleep.
- Insomnia.
- Drowsiness.
- Nightmares.

Efficacy was assessed by plasma HIV-RNA (cop/mL) and CD4 counts at 0, 1, 2, 4, 12 and 24 weeks

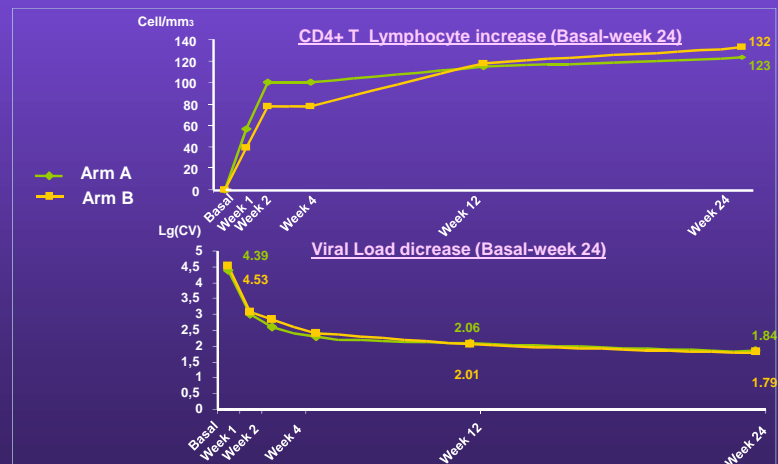
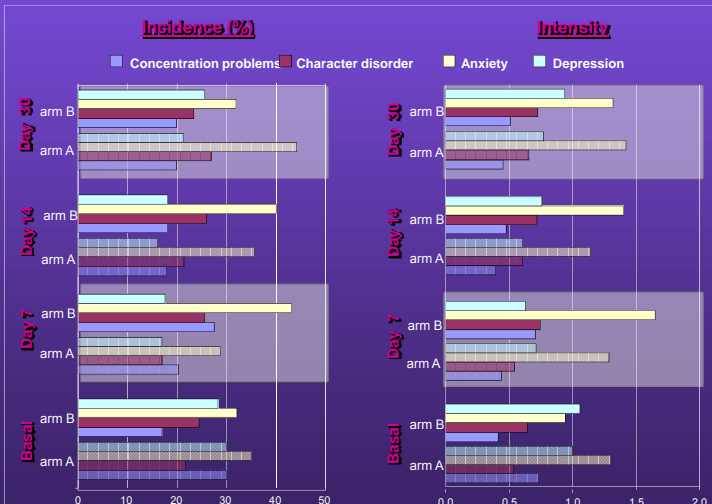
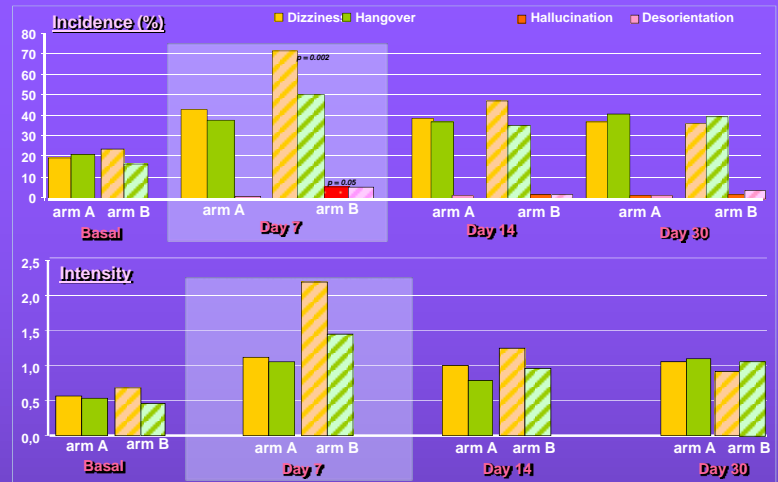


600mg qd from 14 day forward in both arms

**Results:** 115 patients was enrolled in the study (arm A: 60, arm B: 54). The baseline characteristics were similar in both groups, (Table.1). Before the number of discontinuations was 8 of 60 patients (13.3%) in arm A, 14 of 54 patients (25.9%). At day 7, dizziness was referred by 44.1% and 72.5% of patients in arm A and arm B respectively ( $p=0.003$ ), hangover was 39% in arm A and 51% in arm B. The intensity of NPSEs significantly lower in arm A than arm B. Hallucination incidence was 0% in arm A and 5.9% in arm B ( $p=0.005$ ). No difference in sleep disorder were observed between both groups, and the virological and immunological evolution were similar.

Table.1: Baseline demographic characteristic

	ARM A, n=60	ARM B, n=54
age, median years (rango)	39 (30-40)	40 (34-45)
weight, median kg (rango)	68,8 (60,2-75,3)	65,4 (57,9-76,1)
Male, sex, n° (%)	47 (78,3%)	44 (81,5%)
RNA-VIH, median cop/ml	55687 (7630-179000)	52555 (7237-232787)
CD4+ cell count, median cells/mm.	263 (162-343)	210 (111-315)
HIV transmission category, n° (%)		
ADVP	11 (18,6%)	11 (20,4%)
Homosexual	29 (49,2%)	25 (46,3%)
Heterosexual	15 (25,4%)	15 (27,8%)
Other	4 (6,8)	3 (5,6%)
Naive Patients, n° (%)	30 (60%)	28 (63,6)
NRTIs associate, n° (%)		
TDF + FTC	37 (74%)	31 (70,5%)



**Conclusions:** An stepped dosage of EFV over first 2 weeks of treatment is an alternative to reduce the incidence and intensity of neuropsychiatric side effects related to EFV without reducing its virological and immunological efficacy.