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Effectiveness and rate of discontinuation of lead-in dosing of efavirenz-containing regimens in HIV-infected antiretroviral-naive patients in Taiwan

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Introduction

1. Combination antiretroviral therapy containing efavirenz plus tenofovir and lamivudine or emtricitabine remain the preferred ART regimens that are recommended by many international guidelines.
2. CNS or neuropsychiatric disturbances have been reported in 25%-70% of the patients receiving efavirenz-containing regimens.
3. These symptoms usually arise within the first few days of treatment and may lead to early discontinuation of efavirenz.
4. In the randomized clinical trial by Gutierrez-Valencia A et al, stepwise dose escalation of efavirenz over 2 weeks (200 mg in the first 6 days and 400 mg in day 7 to day 13, followed by 600 mg daily subsequently) reduces the incidence and intensity of efavirenz-related neuropsychiatric adverse events (NPAEs) while maintaining its efficacy.
5. The purpose of this prospective observational study is to determine the effectiveness and rate of discontinuation of efavirenz in HIV-infected antiretroviral-naive patients who started regimens containing efavirenz at a half dose within the first week of treatment in Taiwan.

Patients and Methods

1. Study period: 1 June, 2012 to 28 February , 2015.
2. Study subjects: at the National Taiwan University Hospital (NTUH) in Taiwan, where HIV care, including cART and monitoring of CD4 count and plasma HIV RNA load, is provided free-of-charge.
3. The strategy of starting efavirenz at a half dose was adopted with an attempt to reduce the short-term neuropsychiatric adverse effects and related early discontinuations among our patients. The decision to start full-dose or half-dose efavirenz was made at the discretion of treating physicians after counseling for initiation of cART was conducted by physicians and case managers.

Data collection

1. Two groups of patients were defined: patient starting efavirenz at a half dose as lead-in dosing within the first 7 to 8 days, followed by full dose thereafter (half-dose group) and patients starting efavirenz at a full dose (600 mg) (full-dose group).
2. HIV-1 RNA loads and CD4 cell counts at baseline and weeks 4, 12, 24.
3. The serologies for hepatitis B and C virus (HBV and HCV, respectively) were also recorded at baseline.
4. The primary endpoint of the study was the proportion of subjects who had to stop efavirenz-containing regimens; and the secondary end points included the proportion of patients achieving HIV-1 RNA <50 copies/ mL at weeks 4, and weeks 20 to 24; and changes of CD4 count from baseline to week 4, and weeks 20-24.
5. A subgroup of patients were invited to participate in therapeutic drug monitoring of plasma efavirenz concentrations 12 hours after the previous dosing at least 4 weeks after starting efavirenz.

Laboratory investigations

1. Hepatitis B surface antigen (HBsAg), anti-HBs antibody, and hepatitis B core antibody (anti-HBc antibody); and antibodies to hepatitis C virus.
2. CD4 cell count was determined by flow cytometry, and plasma HIV RNA load by Roche real-time PCR (limit of detection, 20 copies/mL)
3. High molecular weight genomic DNA was extracted from PBMC using the Wizard® Genomic DNA purification kit (Promega, WI, USA). Polymerase-chain-reaction restriction fragment-length polymorphism (PCR-RFLP) was performed to determine the SNPs of *CYP2B6* G516T.

Results

1. During the 26-month study period, 404 patient started efavirenz-containing cART: 224 (55.5%) in the half-dose group and 180 (44.5%) in the full-dose group (Table 1).

2. After initiation of efavirenz-containing regimens, 147 patients (36.4%) stopped efavirenz-containing regimens after an average interval of 77 days. The reasons of efavirenz discontinued shown in figure 1.

3. During the study period, 124 patients (94 half-dose group and 30 in the full-dose) paticipated in TDM of plasma efavirenz concentration 12 hours after previous dose (C_{12}) (Table 1).

1. The virological and immunological responses were re-assessed in 287 patients at week 16 after excluding those who discontinued efavirenz before 20 weeks of therapy (Figure 2).

Conclusions

1. Starting efavirenz at half a dose within the first week followed by full dose subsequently in antiretroviral-naive HIV-infected Taiwanese patients could reduce the discontinuation rate.

2. Initiating lead-in dosing of efavrienz within the first week does not compromise the virological and immunological response when compared to the initiation of full dose upfront.

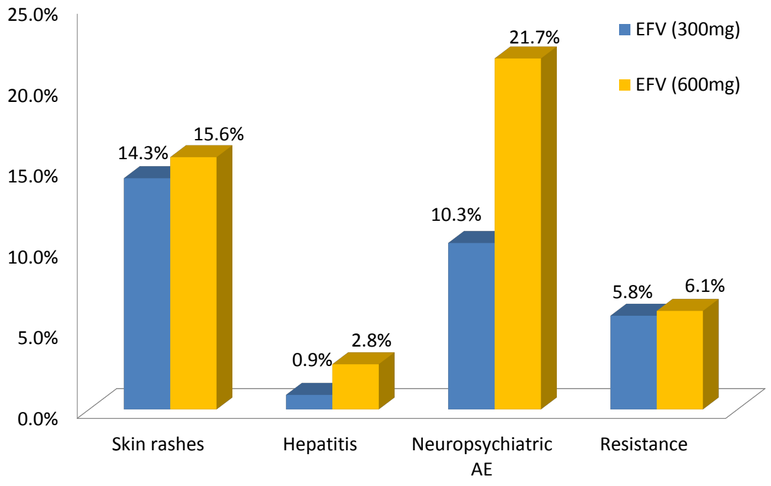

Figure 1. The reasons of stopping efavirenz

Table 1. Comparisons of HIV-infected patients who started lead-in dosing of EFV versus those who started full-dose EFV upfront

Variable	EFV 300 mg	EFV 600 mg	All patients	p value
Case number, n	224 (55.5)	180 (44.6)	404 (100.0)	-
Age, mean (SD), years	32.4 (9.0)	34.4 (9.8)	33.4 (9.5)	0.04
Male sex, n (%)	220 (98.2)	177 (98.3)	397 (98.3)	0.93
MSM (homo/bisexual)	216 (96.4)	168 (93.3)	384 (95.1)	0.15
HBsAg-positive (386)	24 (11.0)	25 (14.9)	49 (12.7)	0.26
Anti-HCV-positive (388)	5 (2.3)	10 (5.9)	15 (3.9)	0.07
CD4 count at baseline, mean (SD), cells/mm^3	317 (192)	241 (186)	283 (193)	<.0001
PVL at baseline, mean (SD), log$_{10}$ copies/ml	4.9 (0.7)	5.0 (0.7)	4.9 (0.7)	0.41
Baseline GOT, mean (SD) ,N= 272	45 (99)	55 (103)	49 (100)	0.39
Baseline GPT, mean (SD),N=273	38 (58)	57 (109)	46 (85)	0.08
Backbone, n (%)				
Combivir	53 (23.7)	91 (50.6)	144 (35.6)	<.0001
Kivexa	7 (3.1)	9 (5.0)	16 (3.9)	0.34
TDF/3TC or Truvada	164 (73.2)	80 (44.4)	244 (60.4)	<.0001
Skin rashes, n (%)	34 (15.2)	33 (18.3)	67 (16.6)	0.39
Time to skin rashes, mean (SD), day	11 (2.2)	10 (6.8)	11 (4.9)	0.86
Patients undergoing TDM, n	94	30	124	
Interval between cART initiation and TDM, day, mean (SD)	186.6 (158.2)	288.6 (216.7)	211.2 (178.6)	0.02
Plasma concentrations level, mg/L, mean (SD)	2.7 (1.38)	2.0 (0.55)	2.5 (1.26)	0.0003
CD4 increase from baseline to week 16, mean (SD)	166 (146)	170 (142)	168 (144.)	0.82
PVL decrease at week 16 log$_{10}$, n= 144, 101	3.24 (0.76)	3.15 (1.03)	3.20 (0.88)	0.46

Figure 2. Virological response of efavirenz at week 16 (ITT analysis)