

## First evaluation of d4T, ddI and EFV in antiretroviral naive patients in Senegal. ANRS 12-06/IMEA 012 study.

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### Study design

#### Trial design

Prospective, open label one arm study in which all patients received, monthly, the three following drugs twice a day: didanosine EC 250 mg or 400 mg if weight > 60 kg, stavudine 30 mg or 40 mg if weight > 60 kg and efavirenz 600 mg.

Two hospitals in Dakar, including 3 centres participated to the study (Service des Maladies Infectieuses and Centre de Traitement ambulatoire of the University Hospital in Fatick, Hôpital Principal).

#### Study procedures

Patients were seen and examined at screening, at the day of inclusion (day 0), at weeks 2, 4 and every month thereafter until 18 months. Screening evaluation included a medical history (including HIV-1 seropositivity status, CDC stage, concomitant medications, concomitant pathologies), measurement of weight and vital signs, assessment of Karnofsky Performance Scale, Hematological profile, blood chemistry profiles, urine pregnancy test, CD4 cell counts, CD8 cell counts, measurement of plasma HIV-1 RNA, hepatitis B and hepatitis C virus serologies.

Biological evaluation including hematology, liver enzymes, bilirubine and creatinine, glycaemia, triglycerides, cholesterol was done at week 0, 2, 4 and every 3 months thereafter until 18 months. CD4 cell counts, CD8 cell counts and Plasma HIV-1 RNA measurements were done at 0, 3, 6, 9, 12 and 18 months of treatment.

Concerning the patient's compliance, questionnaires were held every month. In addition, a profound psychosocial enquiry took place at baseline and after 6 months of treatment.

#### End-points and statistical analysis

The primary end-point was the percentage of patients with plasma HIV-1 RNA <500 copies/ml at 6 months. Secondary end-points were CD4 cell counts at 6 months, CD4 cell counts and plasma HIV-1 RNA at 12 and 18 months, severe adverse events, percentage of patients who discontinued the treatment and compliance.

Continuous variables were expressed either as the mean and standard deviation or as the median and range. Ninety-five percent confidence interval was provided for primary and secondary end-points.

Analysis was performed on an intent-to-treat basis.

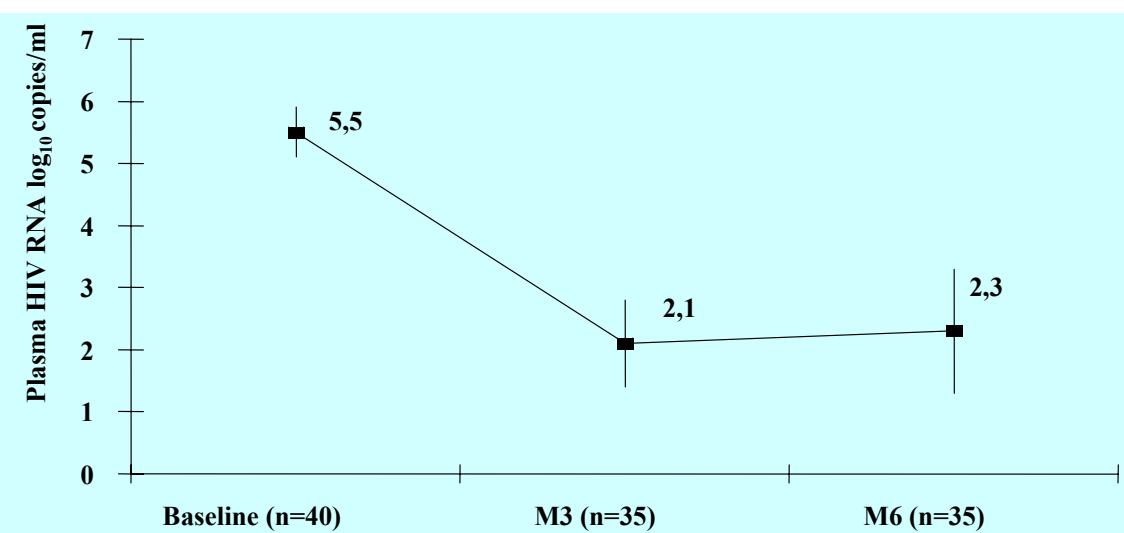
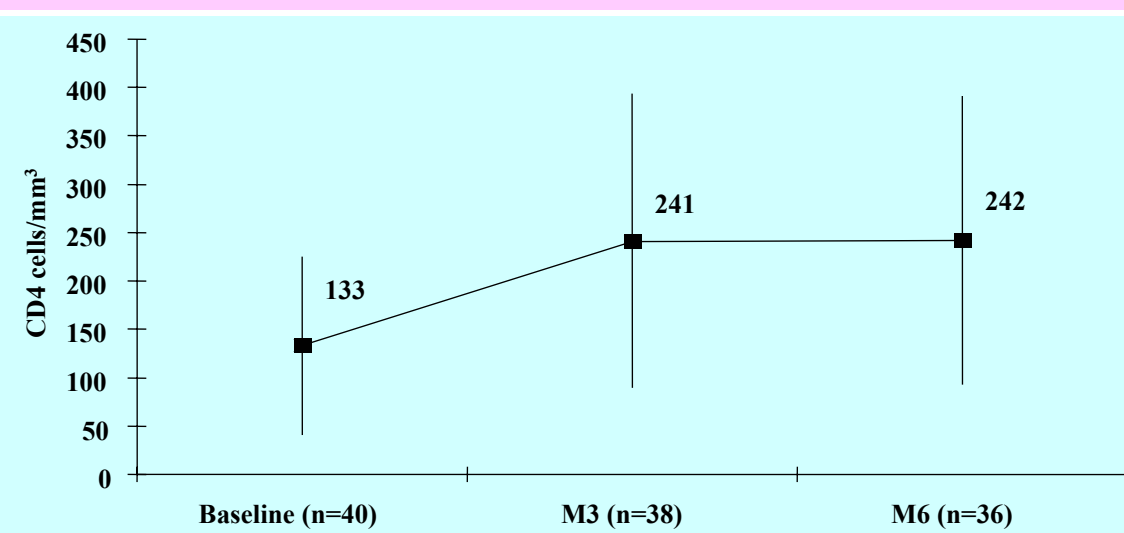
The sample size of 40 patients was chosen in order to permit the detection of a percentage of patients reaching the end-point of at least equal to 70% (lower limit of the 95% confidence interval).

#### Inclusion criteria

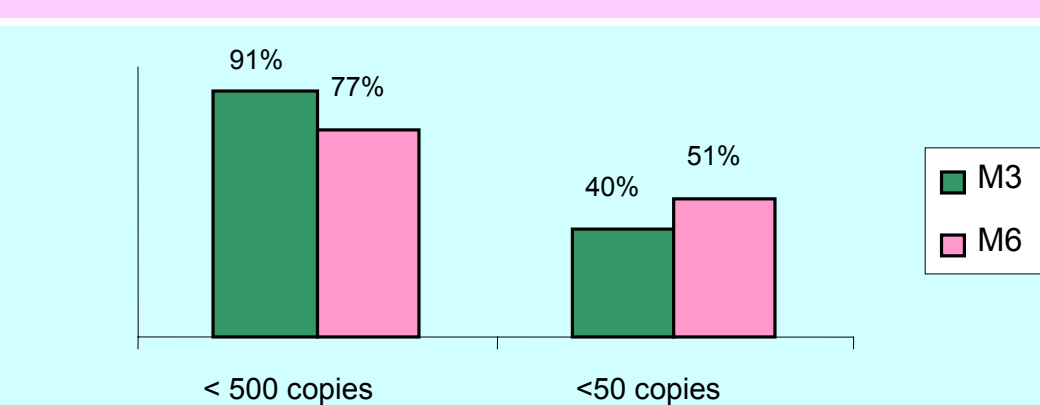
0 < CD4 < 350 cells/mm<sup>3</sup>, plasma HIV-RNA > 30 000 copies/ml, antiretroviral naive patients, informed consent signed.

Baseline characteristics	n=40
Mean Age (years) ± SD	36 ± 7
Sex ratio (F/M)	1.3
CDC groups	B : 19 (48%) C : 21 (52%)
Mean plasma HIV RNA ± SD (Log <sub>10</sub> copies/ml)	5.53 ± 0.40
Range	[4.60-5.88]
Mean CD4 cells/mm <sup>3</sup> ± SD	133 ± 92
Range	[1-346]
Percentage CD4<50 cells/mm <sup>3</sup>	23%

### Evolution from baseline of CD4 cell counts and plasma HIV RNA (mean ± SD)



### % of patients with pHIV RNA < 500 and < 50 copies/ml



### Evolution of weight from baseline

The mean change in weight from baseline to 3 and 6 months was respectively 3 ± 6.3 kg, 4.5 ± 7.3 kg, indicating an increase. At 3 months, 23 patients (62%) had an increased weight, 10 (27%) decreased and 4 (11%) had no change. At 6 months, 24 patients (75%) had an increased weight, 7 (22%) decreased and 1 (3%) had no change.

### Adverse events

#### Treatment-related adverse events

Four grade 1-2 neuropathy before M4 without drugs changing, two grade 3 at M3 with interruption of d4T and ddI and switching by AZT+3TC. Eleven patients experienced efavirenz-related CNS-symptoms at the beginning of the treatment (first month) with intermittent interruption in only one case.

#### Not treatment-related adverse events

Two grade 3 malariae  
One multifocal tuberculosis  
One aggravation of Kaposi Sarcoma at M3 treated by bleomycine.  
Four deaths secondary to :  
One reactivation of MAC associated at malaria at M2  
Two diarrhoea with septicemia at M4 and M6  
One encephalopathy with fever in an alcoholic non compliant patient

### Conclusions

#### Our first results indicate:

- Peripheral neuropathy could be a limitation factor for d4T and ddI association in this population.
- Despite the HAART regimen, 10% of death occurred particularly in patients with low CD4 cells at baseline (3/4 patients < 50 cells/mm<sup>3</sup>).
- Nevertheless our first results at six months show a similar rate of undetectable viral load and increase of CD4 cell counts as compared to other HAART regimen even in a symptomatic patients with low CD4 (23% of patients < 50 cells/mm<sup>3</sup>) and high viral load at baseline.

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