

Once a day HAART regimen in treatment naive HIV-1 infected adults in Senegal

ANRS 12-04 / IMEA 011 study

R.LANDMAN¹, S.THIAM², M.VRAY³, A.CANESTRI¹, R.SCHIEMANN¹, C.DALBAN³, E. DELAPORTE⁴, S. MBOUP², PS. SOW², MA. FAYE NIANG², PM. GUEYE², G. PEYTAVIN¹, S. BADIANE², PM. GIRARD¹, JP. COULAUD¹, I. NDOYE² for the ANRS 12-04/IMEA 011 study group.

¹IMEA Hôpital Bichat Claude Bernard Paris France, ²PNLS Dakar Senegal, ³INSERM SC4 Paris, ⁴IRD Montpellier France.

Study design

Trial design
 Prospective, open label one arm study in which all patients received, monthly, the three following drugs at bedtime: didanosine tablets 200 mg for patients < 60 kg and 400 mg for patients > 60 kg, lamivudine 300 mg and efavirenz 600 mg.

Inclusion criteria
 CD4 : 50 to 350 cells/mm³, plasma HIV-RNA > 30 000 copies/ml , antiretroviral naive patients, informed consent signed.

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 Fann, 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 15 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, plasma HIV-1 RNA measurement, 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 15 months. CD4 cell counts, CD8 cell counts and Plasma HIV-1 RNA measurements were done at 0, 3, 6, 9, 12 and 15 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. As a second and more compliance assessment, pharmacological dosing of the three drugs was done after one and six months of treatment.

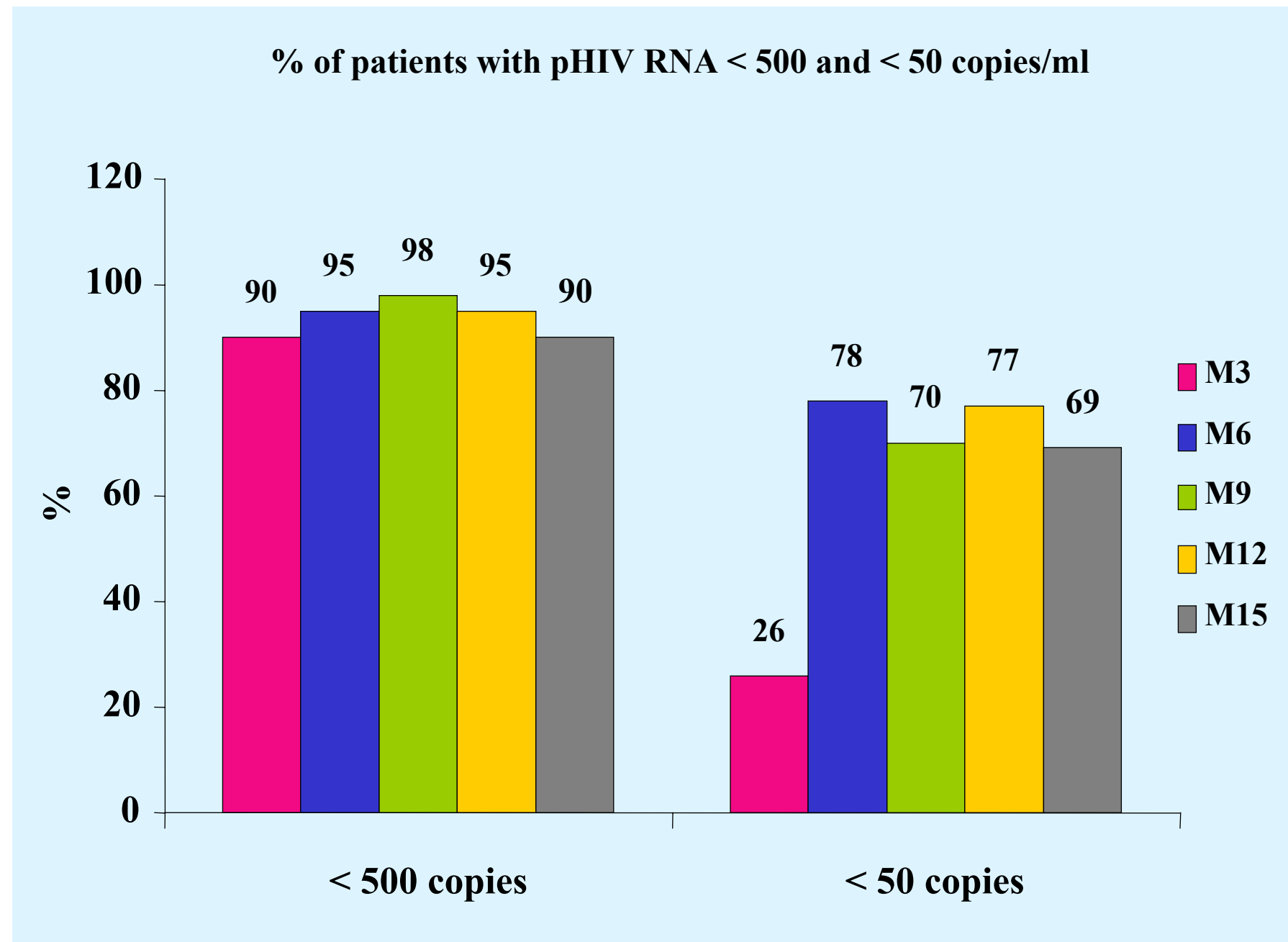
End-points and statistical analysis

- 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 15 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 the percentage of patients reaching the end-point of at least equal to 70% (lower limit of the 95% confidence interval).

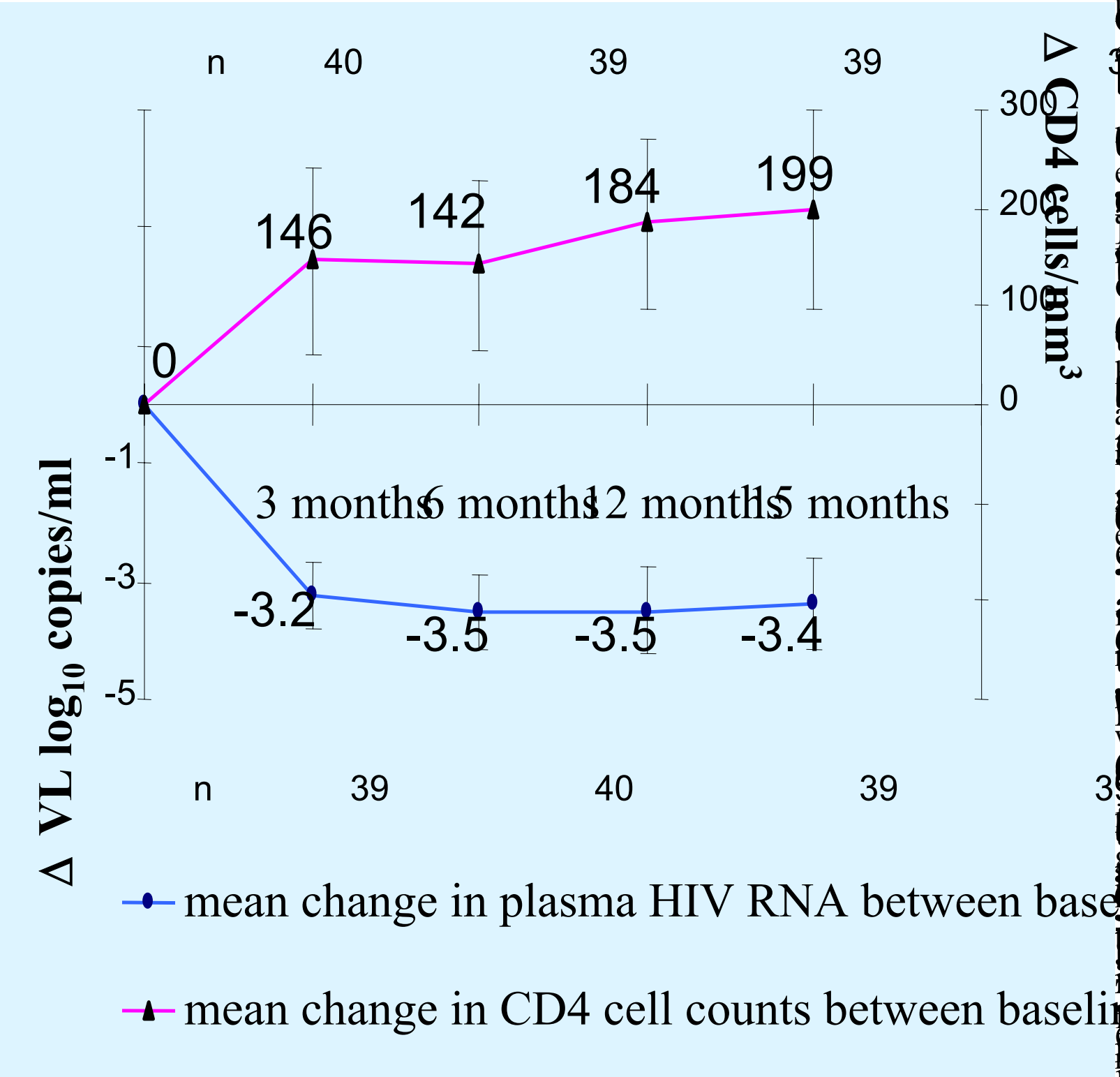
Baseline characteristics

Baseline characteristics	n=40
Mean Age (years) ± SD	37 ± 8
Sex ratio (F/M)	1
CDC groups	A : 6 (15%) B : 16 (40%) C : 18 (45%)
Weight ± SD (Kg) Range	59 ± 8 [43-77]
Karnofsky score (%)	100 : 32 (80%) 90 : 8 (20%)
Mean CD4 cells/mm ³ ± SD Range	164 ± 75 [48-347]
Mean plasma HIV RNA ± SD (Log10 copies/ml) Range	5.4 ± 0.4 [4.5-5.9]

Plasma HIV RNA



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



Plasma drug concentrations

Plasma drug concentrations showed a percentage of patients with adequate plasma concentrations of efavirenz (> 1.1 mg/l) of 95%, and 83% at 1 and 6 months, respectively. For lamivudine (adequate plasma concentrations 100-200 ng/ml) these percentages were 97% and 85% at 1 and 6 months, respectively. As expected plasma didanosine levels were below level of detection (< 10 ng/ml) 12 hours after intake for 95 and 93 % of the patients at M1 and M6 respectively.

Plasma concentrations mean ± SD (n=40)	ddI ng/ml	3TC ng/ml	Efavirenz mg/l
Month 1	11.5 ± 1.5	323 ± 210	3.7 ± 2.9
Month 6	11.5 ± 1.4	279 ± 210	3.4 ± 4.7

Compliance

Adherence to treatment, assessed by questionnaire, was generally good. Most of patients reported to take their tablets every day without exceptions (95%). Some patients reported to miss one or two pills per month. Only three patients interrupted their antiretroviral drug for more than three days. One patient definitively withdrew from the trial after 14 months because he left Senegal.