

# A COMPARISON OF SIX ANTIVIRAL REGIMENS IN DRUG-NAÏVE PATIENTS

GIULIANO RIZZARDINI<sup>1</sup>, DARIA TRABATTONI<sup>2</sup>, AMEDEO CAPETTI<sup>3</sup>, GUGLIELMO MIGLIORINO<sup>1</sup>, GIAN MARCO VIGEVANI<sup>3</sup>, MARIO CLERICI<sup>2</sup>

<sup>1</sup>H DI CIRCOLO, BUSTO ARSIZIO, ITALY; <sup>2</sup>UNIV MILANO, MILANO, ITALY; <sup>3</sup> H L SACCO, MILANO, ITALY.

## ABSTRACT

**Background:** Assessment of multiple Immunovirological parameters may be useful in determining optimal combinations of antiretrovirals.  
**Methods:** Seventy-six HIV-infected naive patients (66M/9F; 28IVDU; 15MSM, 33hetero) were enrolled in a study aiming at comparing different antiviral regimens (AZT/ddI/ABC; AZT/3TC/ABC; AZT/ddI/EFV; AZT/3TC/EFV; AZT/ddI/IDV/r and AZT/3TC/IDV/r). Median CD4 count and viremia at baseline were 217/mm<sup>3</sup> and 238,301 copies/ml, respectively. Quantitative (CD4 counts) and qualitative (PHA-stimulated 3H thymidine incorporation and cytokine production) immunologic parameters were measured at baseline and after 1 and 6 months of therapy.  
**Results:** All regimens resulted in increases in CD4 counts and suppression of HIV plasma viremia. Median CD4 count at 6 mos was significantly better in ABC-treated patients compared to all other groups, and was also significantly more solid in 3 vs. 4 drugs-treated patients (median CD4 count: 3 drugs= 373 CD4/mm<sup>3</sup>; 4 drugs= 246 CD4/mm<sup>3</sup>; p= 0.01). The best suppression of HIV viremia (all patients with >50 copies/ml) was observed in AZT/3TC/ABC patients. PHA-stimulated 3H thymidine incorporation as well as IFN $\gamma$  and IL2 production at 6 mos were significantly better in patients using four drugs (AZT/ddI/IDV/r and AZT/3TC/IDV/r) and, among the three drugs combinations, in AZT/3TC/EFV-treated individuals.  
**Conclusions:** These results suggest that ABC-containing regimens are associated with the highest CD4 counts and the strongest suppression of HIV plasma viremia, whereas boosterized PI-containing regimens have a more robust effect on functional immune parameters after 6 months from starting therapy in drug-naive patients.

## BACKGROUND

- ❖ The initiation of highly active antiretroviral therapy is associated with immunological improvements
- ❖ HAART results in a rapid first-phase increase in CD4 and CD8 T cell numbers that likely represents redistribution of lymphocytes from tissue sites. The second phase of this response is characterized by a slow increase in the number of naive CD4 and CD8 T cells and a reduction in the number of memory CD8 T cells. In addition, there is a reduction of immune activation detectable both at the cellular level (e.g., CD38, HLA-DR, and Ki67) and by plasma markers (e.g., soluble tumor necrosis factor receptor II).
- ❖ CD4 T cell proliferative responses to pathogens such as cytomegalovirus (CMV) and mycobacteria improve, but human immunodeficiency virus (HIV) specific responses are enhanced less predictably.
- ❖ It is not clear whether the class of antiretroviral drugs used determines the nature and extent of immune reconstitution; assessment of multiple immunologic parameters is useful in determining optimal combinations of antiretrovirals.

## AIM

Which is the best initial therapy in naive patients?

3 drugs vs 4 drugs  
 3TC vs ddI  
 EFV vs ABC  
 PI or No PI

## MATERIAL and METHODS

### STUDY DESIGN AND PATIENT SELECTION

- ❖ 76 patients enrolled in the study.
- ❖ All patients classified as “naive” (mostly “advanced naive”).
- ❖ Patients randomly divided into 6 groups that underwent different regimens.
- ❖ Clinical and immunovirologic analyses at baseline 1, and 6 months.

### SIX DIFFERENT THERAPEUTIC REGIMENS

A (n=13)	AZT + ddI + ABC
B (n=13)	AZT + 3TC + ABC
C (n=14)	AZT + ddI + EFV
D (n=8)	AZT + 3TC + EFV
E (n=11)	AZT + ddI + IDV/r
F (n=15)	AZT + 3TC + IDV/r

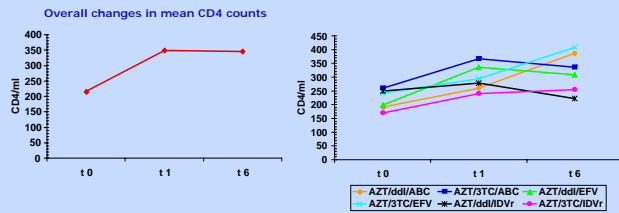
### CLINICAL AND IMMUNOVIROLOGIC CHARACTERIZATION OF PATIENTS AT BASELINE (median; range)

Group	CD4 counts	HIV plasma viremia
overall	217 (10-668)	238,301 (2,120 >500,000)
A	191 (100-330)	218,240 (10,600- >500,000)
B	280 (30-440)	203,494 (2,340- >500,000)
C	198 (10-507)	225,232 (35,500- >500,000)
D	243 (30-504)	387,846 (85,500 - >500,000)
E	249 (10-650)	221,120 (35,500 >500,000)
F	170 (7-668)	228,612 (13,541 >500,000)

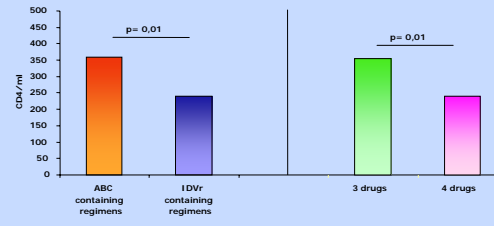
### IMMUNOLOGIC ANALYSES

- ❖ CD4 counts and HIV plasma viremia
- ❖ Mitogen and HIV antigens-stimulated IL-2, IL-10 and IFN $\gamma$  production by PBMC
- ❖ Mitogen and HIV antigens-stimulated proliferation of PBMC.

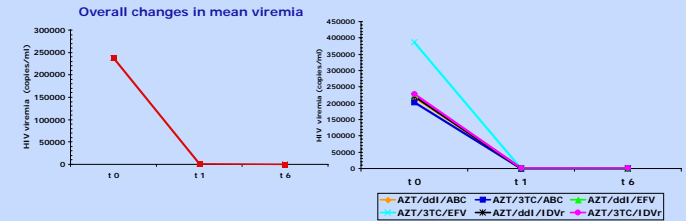
## RESULTS



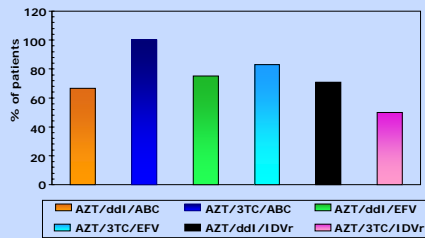
**Figure 1.** "Quantitative" immunovirologic parameters: CD4 counts. Overall changes in mean CD4 counts (left panel) and mean values observed in the six different groups of patients (right panel) are shown.



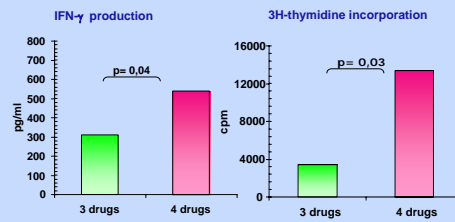
**Figure 2.** CD4 counts at mo 6. Comparisons between ABC- and IDVr-containing regimens (left panel) and between 3-drugs and 4-drugs regimens (right panel) are shown.



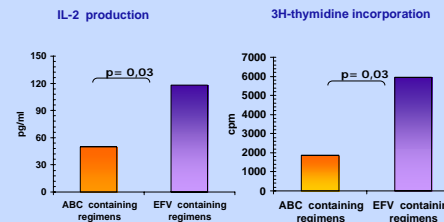
**Figure 3.** HIV plasma viremia. Overall changes in mean CD4 counts (left panel) and mean values observed in the six different groups of patients (right panel) are shown.



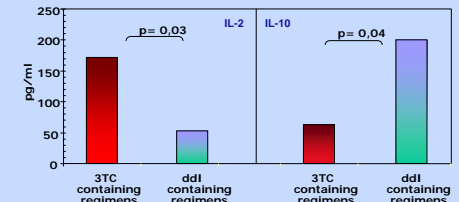
**Figure 4.** Percentage of patients with undetectable viremia (>50 copies/ml).



**Figure 5.** "Functional" immunologic parameters: cytokine production (left panel) and proliferation (right panel). Comparisons between 3-drugs and 4-drugs regimens.



**Figure 6.** "Functional" immunologic parameters: cytokine production (left panel) and proliferation (right panel). Comparisons between ABC- and EFV-containing regimens.



**Figure 7.** "Functional" immunologic parameters: cytokine production (IL-2, left panel and IL-10, right panel) at mo 6. Comparisons between 3TC- and ddI-containing regimens.

## CONCLUSIONS

### In naive patients

- ❖ AZT+3TC+ABC results in better suppression of HIV plasma viremia after 6 mos of therapy
- ❖ ABC-containing regimens are associated with the best CD4 counts after 6 mos of therapy
- ❖ 3 drugs result in a higher increase of CD4 T cells compared with associations with 4 drugs (PI/r)
- ❖ Four drugs result in a more robust production of IFN $\gamma$  and a better proliferative response compared to 3 drugs
- ❖ 3TC is associated with a higher production of IL-2 and a lower production of IL-10 compared to ddI
- ❖ EFV is associated with a higher production of IL-2 and better proliferative response compared to ABC

### In naive patients:

- ❖ ABC-containing regimens are associated with the best CD4 counts and the better suppression of HIV plasma viremia after 6 mos of therapy
- ❖ Amongst the three drugs combinations AZT + 3TC + EFV are associated with the strongest modulation of functional immune parameters