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Soluble activation and inflammation markers in HIV dual therapy in the setting of virologic suppression: Trilobithe Study

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Introduction

The introduction of combination antiretroviral therapy (cART) has produced an important decrease in the mortality and morbidity of HIV-1-infected patients. However, toxicity-related cART has been shown to be an important issue for the long-term evolution of the patients. Dual antiretroviral strategies are being evaluated as an alternative treatment for the HIV-infected population with increasing age and comorbidities. Although several studies suggest adequate efficacy with less adverse events, concern exists about the possibility of a lower antiretroviral action than triple therapy, resulting in higher residual viremia, systemic inflammatory activity, and immune activation.

To ascertain this issue, we evaluated the plasma levels of activation, inflammation, Th1/Th2 response and blood coagulation in supressed HIV-1 patients after 24 and 48 weeks of switching to dual therapy.

Patients

This **tri**ple- **lo**wered to **bi**- **the**rapy study (**Trilobithe**) is a non-comparative pilot study**,** using random sampling method, conducted with HIV patients who met the criteria of suppressive HIV infection during at least one year under triple therapy, or at 24 and 48 weeks of maintenance of suppression after switching to dual therapy due to toxicity or simplification:

1. Patients on triple therapy (Baseline, N=31)
2. Patients after 24 weeks under dual therapy (N=15)
3. Patients after 48 weeks under dual therapy (N=42)

The main dual therapies included dolutegravir (DTG)+rilpivirine (RPV, 77%), lamivudine+ritonavir/darunavir (r/DRV, 14%), r/DRV+RPV (7%) and r/DRV+raltegravir (2%).

Methods

Demographic and immune virological parameters such as nadir CD4 T cell count, CD4 and CD8 T cell counts and percentage, CD4/CD8 ratio, anti-HCV antibodies, HCV RNA load, HIV-1 RNA loads, were analysed. Plasma samples were used to quantitate the following: IL6, IP10, hs-CRP, sCD14, sCD163, using R&D ELISA Quantikine; D-dimer using ELISA Invitrogen; and IFNγ, TNFα and IL4 using R&D Luminex HS assay. The study was approved by our IRB (EC 139/18).

Results

Table 1: Characteristics of the patients

	Patients on triple therapy	Patients after 24 weeks of dual therapy	Patients after 48 weeks of dual therapy	Anova P
N	31	15	42	
Age (years)	51 [46-54]	53 [50-62]	51 [48-57]	0.057
Gender (male)	25, 80.6%	10, 66.7%	30, 71.4%	0.564
Route of transmission (n, %)				
IDU	13, 41.9%	7, 46.7%	16, 38.1%	0.873
MSM	10, 32.3%	3, 20%	14, 33.3%	0.654
Heterosexual	8, 25.8%	5, 33.3%	12, 28.6%	0.864
Time of HIV diagnosis (months)	249 [167-278]	286 [183-322]	264 [143-324]	0.689
Time on ART (months)	217 [135-251]	174 [101-270]	217 [102-264]	0.939
Time on previous therapy (months)	58 [35-89]	54 [26-70]	70 [32-102]	0.434
Number of previous regimens	5 [2-9]	5 [2-8]	4.5 [2-8]	0.486
AIDS (n, %)	6, 25%	4, 26.7%	13, 31%	0.501
Plasma HIV RNA cenit (log copies/mL)	4.85 [4.60-5.30]	4.75 [4.55-5.48]	4.80 [4.10-5.10]	0.252
HCV infection				
Antibodies anti-HCV positive	16, 51.6%	9, 60%	16, 38.1%	0.312
Plasma HCV RNA positive	16, 51.6%	9, 60%	16, 38.1%	0.312
Nadir CD4 count (cells/mm^3)	219 [109-284]	240 [84-301]	221 [91-292]	0.891
CD4 T-cell count (cells/mm^3)	601 [455-913]	584 [515-911]	649 [471-825]	0.895
CD8 T-cell count (cells/mm^3)	846 [555-1138]	664 [548-1109]	783 [640-1143]	0.839
CD4/CD8 ratio	0.69 [0.45-0.88]	0.91 [0.55-1.15]	0.79 [0.62-1.04]	0.766
CD4 T-cell percentage	26.9 [23.1-33.1]	28.2 [22.3-35.7]	29.0 [22.8-36.1]	0.874
CD8 T-cell percentage	41.5 [31.7-49.2]	30.9 [27.2-46.8]	35.9 [29.9-47.1]	0.595

No differences in baseline, demographic or immunovirologic factors between the different three groups were found, although patients under the dual regimens had better immunological situation. although with no statistical significance,

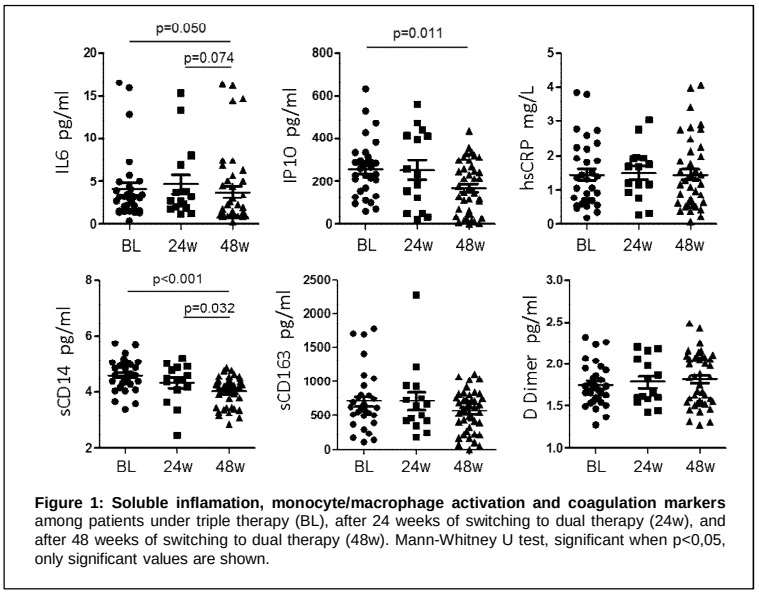

Figure 1: Soluble inflamation, monocyte/macrophage activation and coagulation markers among patients under triple therapy (BL), after 24 weeks of switching to dual therapy (24w), and after 48 weeks of switching to dual therapy (48w). Mann-Whitney U test, significant when p<0,05, only significant values are shown.

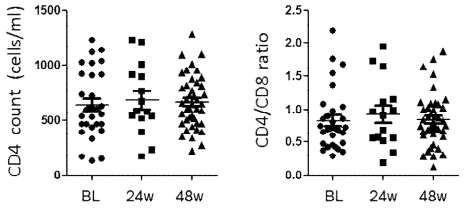

Figure 2: CD4 count and CD4/CD8 ratio. Mann-Whitney U test, significant when p<0,05, only significant values are shown.

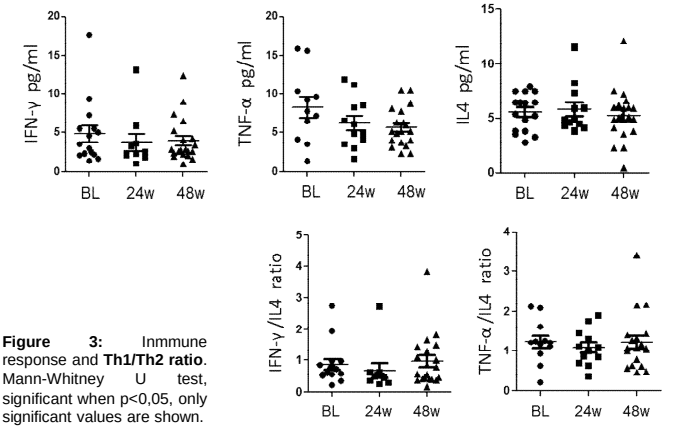

Figure 3: Inmmune response and **Th1/Th2 ratio**. Mann-Whitney U test, significant when p<0,05, only significant values are shown.

Discussion

In this pilot study, patients receiving different dual strategies, and with similar baseline characteristics to those receiving triple therapy, showed no deterioration of soluble markers of inflammation, activation or immune response, at least after one year of dual therapy. Moreover, significant lower levels of IL6 and sCD14 levels were found in patients on dual therapy. Hence, dual therapy might be a useful strategy for the management of patients with increasing age and comorbidities.