00599

ADIPOCYTE DIFFERENTIATION AND ANTIRETROVIRAL DRUGS: AN IN VITRO MODEL

M. A. Carleo[1], A. Perna [2], P. Rosario[1], S. Mascolo[1], A. Lucariello[3], G. Palmiero[1], V. Rizzo[1], A. M. Rossomando[1], A. Baldi[4], A. De Luca [5], P. Maggi [6], **V. Esposito[1]**

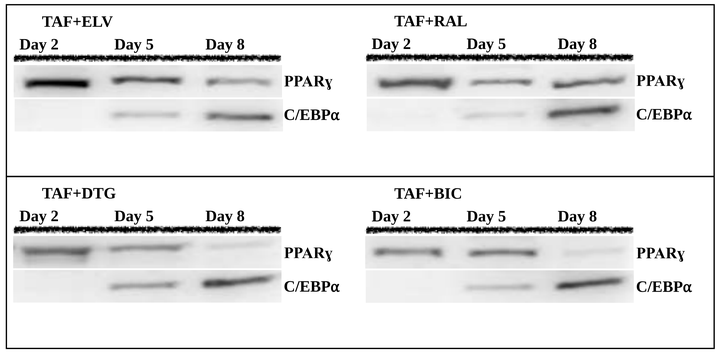
[1]Infectious Diseases and Gender Medicine Unit "D. Cotugno" Hospital – AO dei Colli, Naples Italy, [2]Department of Medicine and Health Sciences "Vincenzo Tiberio", University of Molise, Campobasso, Italy, [3]Department of Sport Sciences and Wellness, University of Naples "Parthenope", Naples, Italy, [4]Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, Università degli Studi della Campania "L. Vanvitelli", Caserta, Italy, [5]Department of Mental and Physical Health and Preventive Medicine, Section of Human Anatomy, University of Campania "Luigi Vanvitelli", Naples, Italy, [6]University of Campania "Luigi Vanvitelli", Caserta Italy.

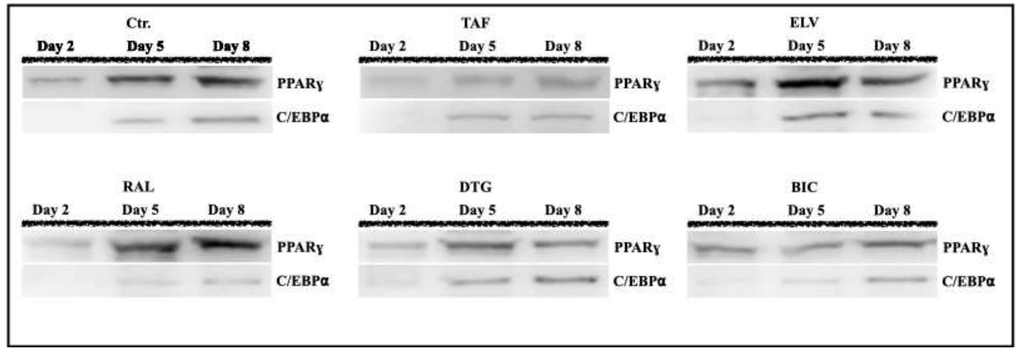
BACKGROUND

The Integrase Strand Transfer Inhibitors (INSTI) class of drugs is characterized by a good tolerability profile and a relatively high genetic barrier to HIV drug resistance. However, several studies reported greater weight gain among persons receiving INSTI-based regimens for initial therapy as compared to protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens. These studies could be affected by several potential biases, because of the large number of metabolic comorbidities affecting these patients together to high risk of pharmacological interactions. Since adipocyte differentiation recognizes an important regulatory checkpoint by two families of transcription factors, the CCAAT/enhancer-binding proteins (C/EBPs) and the peroxisome proliferator-activated receptors (PPARs), the evaluation of the expression of adipocyte differentiation markers, such as PPAR-γ and C/EBP-α, is routinely used to evaluate fat tissue differentiation and it has been already assessed to investigate adipocyte differentiation in studies on HIV infected patients.

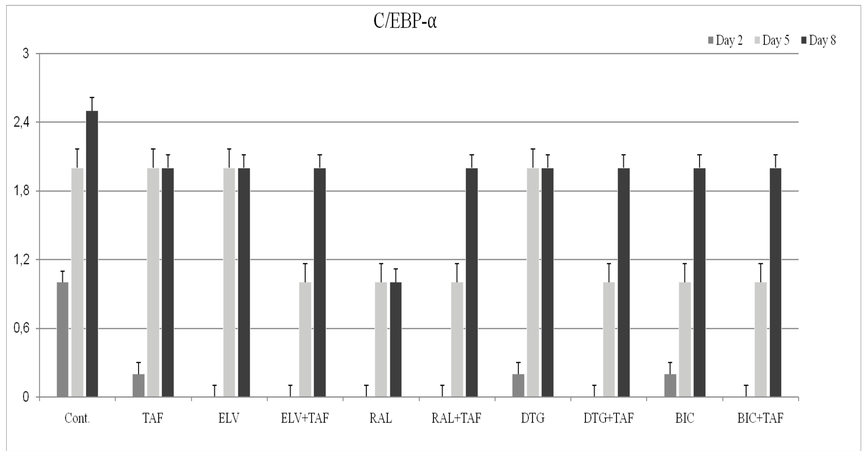
METHODS

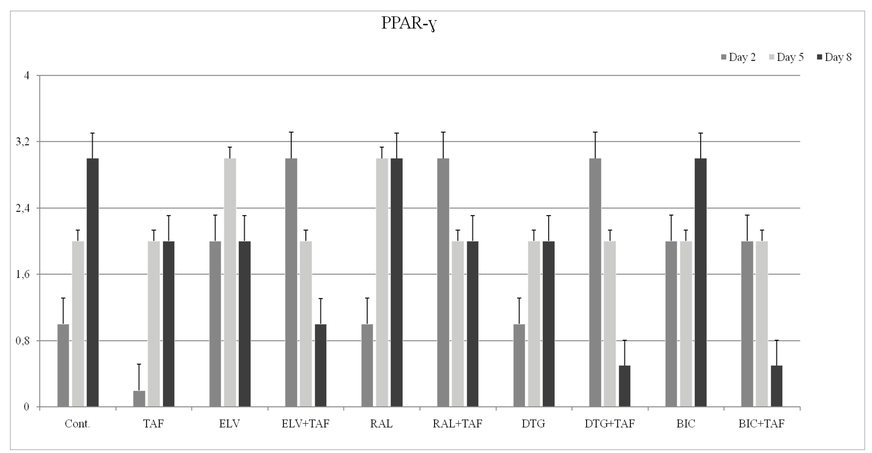
We used the 3T3-L1 cells *in vitro* model of adipogenesis to investigate the effects on adipocyte differentiation of the newer NRTI, tenofovir alafenamide fumarate (TAF), alone or in combination with the four INSTIs, raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG) and bictegravir (BIC). The effects of the drugs on cell viability were determined by the MTT assay (data not shown). Expression levels of PPARɣ and C/EBPα, and the intracellular lipid accumulation by Red Oil staining, were used to monitor adipocyte differentiation. Imagej software was used to relatively quantify proteins expression levels from western blot analysis.

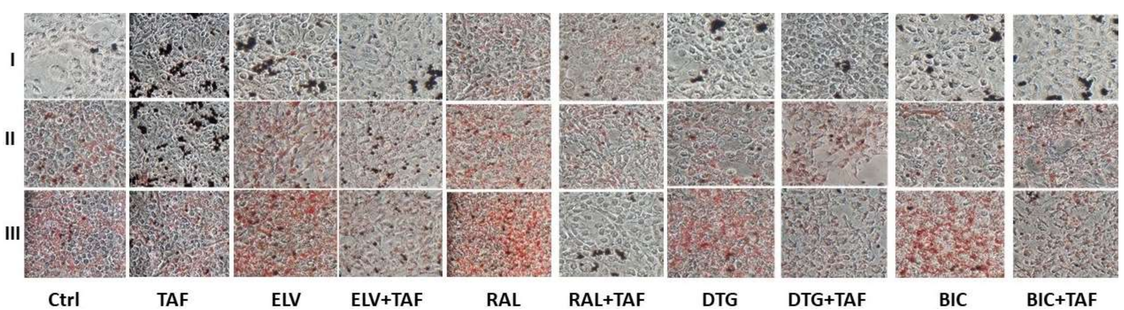




Western Blot analysis showing different PPAR-γ and C/EBP-α expression levels according to different anti-HIV drugs







3T3L1 Red oil staining according to different steps of adipocyte differentiation and different antiretroviral drugs.

RESULTS

Compared to the control, RAL, EVG, DTG and BIC were all able to increase adipogenesis, being RAL and ELV somehow more efficient, while TAF slightly inhibited adipogenesis. When used in combination with the other INSTIs, TAF was able to reduce the adipogenic effects of all the four drugs. This effect was more evident when TAF was used in combination with DTG and BIC.

Author Contact Information: Vincenzo Esposito, Infectious Diseases and Gender Medicine Unit "D. Cotugno" Hospital – AO dei Colli, Via G. Quaglieriello, 54 80131 Naples Italy. E-mail: vincenzoesposito@ospedalideicolli.it

CONCLUSIONS

Several clinical data suggest that therapy with INSTIs could determine weight gain, especially if associated with TAF. Our results confirm that INSTIs could increase adipogenesis, while, on the other hand, in our 3T3L1 cells *in vitro* model of adipogenesis, TAF shows an inhibitory effect, being able to effectively contrast the increased adipogenesis caused by other INSTIs, in particular DTG and BIC. Taken together, these evidences are suggestive for an antagonistic effect of different antiretroviral drugs routinely used in therapeutic association on adipocyte differentiation. In the light of our observations we hypothesize that clinical data showing an additive effect of INSTIs and TAF on weight gain could be affected by biases due to the multifactorial nature of the weight gain phenomenon.