12° CONGRESSO NAZIONALE
Italian Conference on AIDS and Antiviral Research

Reach out for including all

12-16 ottobre 2020
DIGITAL EDITION

Promosso da SIMIT Società Italiana di Malattie Infettive e Tropicali

P118

POSTER 4 YOU ICAR 2020

Reduced Bone catabolism and inflammation in patients switching to TAF-containing cART

E.S. Cannizzo[1], A Cozzi-Lepri[2], F Ceccherini S[3], R Scutari[3], C Alteri[4], A Tavelli[i5], D Bernacchia[6], E Merlini[1], A Castagna[7], A Antinori[8], A d' Arminio Monforte[1], G Marchetti[1]
on behalf of Icona and TAF-Icona Study Group

[1]Clinic of Infectious Diseases, Dept Health Sciences, University of Milan, ASST Santi Paolo e Carlo, Milan, Italy; [23] Dept of Experimental Medicine, University of Rome Tor Vergata, Rome, Italy; [4] Dept of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; 5Icona Foundation, Milan, Italy; 6 Infectious Diseases Unit, ASST FBF-Sacco, DIBIC "L. Sacco", University of Milan, Milan, Italy 7 Division of Infectious Diseases, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy; 8 HIV/AIDS Clinical Unit, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy

Introduction

- By reducing tenofovir plasma levels, tenofovir alafenamide (TAF) preserve bone mineral density (BMD).
- Changes in bone composition appear to be multi-factorial and can be affected by HIV reservoir, probably through the effects of immune dysregulation associated with a persistent low-grade inflammatory state.
- The impact of switch to TAF-containing regimens on osteo-immunity, inflammation and HIV-DNA is poorly investigated.

Aim

- To investigate changes in bone turnover, inflammatory markers and HIV –DNA in patients switching from TDF to TAF.

Methods

- We enrolled cART-treated HIV+ patients within Icona (HIV-RNA<50 cp/ml) switching from TDF- to TAF regiments.
- Samples were available pre-switch (T0) and 12 months post-switch (T1).
- Lab analyses:
  a) sCD14, C Reactive Protein (CRP), IL-6 and vascular cell adhesion molecule 1 (VCAM-1) (Luminex)
  b) C-terminal telopeptide-1 (CTX-1), Procollagen type I N-terminal Propeptide (P1NP) (Elisa),
  c) osteoclast precursors (OCP:CD14+CD16+CD51/61+), osteoblast precursors (OCB:CD15-OC+AP+), CD8+CD38+HLA-DR+ (Flow Cytometry)
  d) HIV-DNA (LTR5' ddPCR assay, normalized by cps/106 CD4+).

Pearson correlation and univariable and linear regression models using the markers variation over T0-T1 as outcome were used. Variable selection for inclusion in multivariable models was performed using a best subset approach with manual addition of known confounders.

Results

MAIN CHARACTERISTICS OF PATIENTS BY CD38+ LEVELS AT T0

We enrolled 146 pts: median (IQR) CD4 and age at switch were 672/mm3 (475, 879) and 48 years (40-55). All patients maintained virological suppression along all the 12 months

Characteristics	CD8+CD38+ HLA-DR+ <median	CD8+CD38+ HLA-DR+ >median	p-value*	Total
	N= 73	N= 73		N= 146
Gender, n(%)			1.000	
Female	13 (17.8%)	13 (17.8%)		26 (17.8%)
Mode of HIV Transmission, n(%)			0.734	
PWID	8 (11.0%)	8 (11.0%)		16 (11.0%)
MSM	37 (50.7%)	41 (56.2%)		78 (53.4%)
Heterosexual contacts	25 (34.2%)	23 (31.5%)		48 (32.9%)
Other/Unknown	3 (4.1%)	1 (1.4%)		4 (2.7%)
Nationality, n(%)			0.645	
Not Italian	10 (13.7%)	12 (16.4%)		22 (15.1%)
AIDS diagnosis, n(%)			0.337	
Yes	12 (16.4%)	8 (11.0%)		20 (13.7%)
HBsAg, n(%)			0.468	
Positive	3 (4.5%)	5 (7.5%)		8 (6.0%)
HCVAb, n(%)			0.606	
Positive	9 (12.7%)	11 (15.7%)		20 (14.2%)
Hepatitis co-infection*, n(%)			0.524	
Yes	12 (16.4%)	15 (20.5%)		27 (18.5%)
Calendar year of baseline*			0.444	
Median (IQR)	2017 (2017, 2018)	2017 (2017, 2017)		2017 (2017, 2017)
Age, years			0.863	
Median (IQR)	48 (40, 55)	49 (40, 55)		48 (40, 55)
CD4 count, cells/mmc			0.357	
Median (IQR)	685 (476, 891)	628 (466, 846)		672 (475, 879)
CD4 count nadir, cells/mmc			0.661	
Median (IQR)	255 (154, 350)	262 (63, 379)		261 (121, 369)

Results

UNADJUSTED MEAN VARIATION OF INFLAMMATION, BONE TURN OVER MARKERS AND HIV-DNA OVER T0-T1

In the unadjusted model, at T1 we observed a reduction in activation (-1.8 p<0.01), inflammatory markers (sCD14: -0.5 p<.01, IL-6:-0.8 p<.01),VCAM-1: -0.1 p<.01, with no changes in HIV-DNA (+12.5, p=0.85). Among bone markers, only CTX-1 showed a non-significant decreasing trend (-4.9 p=0.06), with no differences in OBP, OCP, P1NP

Biomarkers	N	T0 (at switch) Mean1	SD1	T1 (12 months after switch) Mean2	SD2	Change T0-T1 Difference	p-value
CD8+CD38+ HLA-DR+ (%)	146	9.6	10.7	7.7	9.4	-1.8	**<.01**
sCD14 (ug/ml)	148	2.0	0.7	1.6	0.6	-0.5	**<.01**
hsCRP (ug/ml)	148	3.4	4.1	3.1	3.1	-0.4	0.26
CTX-1 (ng/ml)	48	10.2	25.1	5.3	9.2	-4.9	**0.06**
DNA, per CD4 count	106	639.6	790.8	652.1	938.4	12.5	0.85
DNA, per PBMC	106	130.1	142.5	135.1	164.1	5.0	0.67
IL-6 (pg/ml)	148	2.9	2.3	2.2	2.3	-0.8	**<.01**
OBP (%)	147	5.4	4.2	4.7	3.8	-0.7	0.16
OCP (%)	147	0.8	0.3	0.8	1.3	-0.0	0.71
P1NP (pg/ml)	48	689.6	638.4	758.1	726.4	68.6	0.35
VCAM-1 (ug/ml)	148	1.2	0.6	1.1	0.6	-0.1	**<.01**

sCD14: soluble CD14; hsCRP: high sensitive C reactive protein; CTX-1: C terminal telopeptide-1; IL-6 : interleukine-6 ; OBP: osteoblast precursors ; OCP: Osteoclast precursors; P1NP: Type I procollagen N-terminal propeptide ; VCAM-1 : Vascular cell adhesion protein 1

Results

TESTIMATED MEAN CHANGE IN OSTEOCLAST PRECURSOR S (OCP) ASSOCIATED WITH FACTORS MEASURED AT T0

Having shown a trend for reduced resorption marker CTX-1, we performed a multivariable model to identify the factors associated with change in osteoclastogenesis. While this model showed no association between bone resorption and inflammation, we found a positive association between OCP change and T0 CD8+, independent of potential confounders, including CD38+ (0.10 increase in OCP per 100 CD8+/mm3 higher p=.004)

Mean variation in OCP over T0-T1				
Characteristics	Unadjusted (95% CI)	p-value*	Adjusted (95% CI)	p-value*
IL-6 at T0				
per log10 higher	0.26 (-0.46, 0.98)	0.482	-0.18 (-0.98, 0.63)	0.665
hsCRP at T0				
per log10 higher	0.40 (-0.01, 0.82)	0.061	0.33 (-0.13, 0.79)	0.156
CD8+CD38+ HLA-DR+, cells/mm3				
per 100 higher	1.20 (-0.88, 3.28)	0.260	1.45 (-0.67, 3.56)	0.183
CD8 count, cells/mm3				
per 100 higher	0.09 (0.03, 0.15)	0.006	0.10 (0.03, 0.18)	**0.004**
CD4 count cells/mm3				
per 100 higher	0.03 (-0.05, 0.10)	0.504	0.00 (-0.08, 0.09)	0.974
Anchor drug in TAF regimen				
RPV vs. EVG	0.26 (-0.25, 0.77)	0.327	0.46 (-0.08, 1.00)	0.094
Other vs. EVG	0.43 (-0.12, 0.98)	0.131	0.56 (-0.01, 1.13)	0.056

Linear multivariable regression model .The best subset procedure indicated that a 5 parameters model would have the highest adjusted R-square and be the best model for inference (according to the Hocking criterion). CD8+CD38+ HLA-DR+was added manually to the best 5 parameter model as it was regarded to be a key confounder

Conclusion

- In virologically suppressed HIV+ pts switching from TDF to TAF regimens, we describe an early decrease in pro-inflammatory markers and free osteoclast-derived collagen (CTX-1) suggesting a containment in bone resorption.
- This finding, together with the independent association between reduced post-switch osteoclast progenitors and high pre-switch CD8+, known osteoclastogenesis inhibitor in murines, might indicate a mechanistic pathway behind the greater bone safety of TAF.

Funding

ICONA Foundation is supported by unrestricted grants from Gilead Sciences, Janssen, MSD, Thera technologies and ViiV Healthcare; This study is supported by a grant from Gilead International

ICONA Study Group

BOARD OF DIRECTORS: A d'Arminio Monforte (President), A Antinori (Vice-President), M Andreoni, A Castagna, F Castelli, R Cauda, G Di Perri, M Galli, R Iardino, G Ippolito, A Lazzarin, GC Marchetti, G Rezza, F von Schloesser, P Viale.

SCIENTIFIC SECRETARY: A d'Arminio Monforte, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, E Girardi, A Gori, S Lo Caputo, F Maggiolo, C Mussini, M Puoti, CF Perno.

STEERING COMMITTEE: A Antinori, F Bai, A Bandera, S Bonora, M Borderi, A Calcagno, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, S Cicalini, A Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A Di Biagio, R Gagliardini, E Girardi, N Gianotti, A Gori, G Guaraldi, G Lapadula, M Lichtner, A Lai, S Lo Caputo, G Madeddu, F Maggiolo, G Marchetti, E Merlini, C Mussini, S Nozza, CF Perno, S Piconi, C Pinnetti, M Puoti, E Quiros Roldan, R Rossotti, S Rusconi, MM Santoro, A Saracino, L Sarmati, V Spagnuolo, V Svicher, L Taramasso.

STATISTICAL AND MONITORING TEAM: A Cozzi-Lepri, I Fanti, P Lorenzini, A Rodano', M Macchia, A Tavelli.

COMMUNITY ADVISORY BOARD: A Bove, A Camposeragna, M Errico, M Manfredini, A Perziano, V Calvino.

BIOLOGICAL BANK INMI: F Carletti, S Carrara, A Di Caro, S Graziano, F Petroni, G Prota, S Truffa.

PARTICIPATING PHYSICIANS AND CENTERS
Italy A Giacometti, A Costantini, V Barocci (Ancona); G Angarano, L Monno, E Milano (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, V Donati, G Verucchi (Bologna); F Castelnuovo, C Minardi, E Quiros Roldan (Brescia); B Menzaghi, C Abeli (Busto Arsizio); L Chessa, F Pes (Cagliarti); B Cacopardo, B Celesia (Catania); J Vecchiet, K Falasca (Chieti); A Pan, S Lorenzotti (Cremona); L Sighinolfi, D Segala (Ferrara); P Blanc, F Vichi (Firenze); G Cassola, M Bassetti, A Alessandrini, N Bobbio, G Mazzarello (Genova); M Lichtner, L Fondaco, (Latina); P Bonfanti, C Molteni (Lecco); A Chiodera, P Milini (Macerata); G Nunnari, G Pellicanò (Messina); A d'Arminio Monforte, M Galli, A Lazzarin, G Rizzardini, M Puoti, A Castagna, ES Cannizzo, MC Moioli, R Piolini, D Bernacchia, A Poli, C Tincati, (Milano); C Mussini, C Puzzolante (Modena); C Migliorino, G Lapadula (Monza); V Sangiovanni, G Borgia, V Esposito, G Di Flumeri, I Gentile, V Rizzo (Napoli); AM Cattelan, S Marinello (Padova); A Cascio, M Trizzino (Palermo); D Francisci, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); C Lazzaretti, R Corsini (Reggio Emilia); M Andreoni, A Antinori, R Cauda, A Cristaudo, V Vullo, R Acinapura, S Lamonica, M Capozzi, A Mondi, A Cingolani, M Rivano Capparuccia, G Iaiani, A Latini, G Onnelli, MM Plazzi, G De Girolamo, A Vergori (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, A De Vito(Sassari); B Rossetti, F Montagnani (Siena); A Franco, R Fontana Del Vecchio (Siracusa); C Di Giuli (Terni); P Caramello, G Di Perri, S Bonora, GC Orofino, M Sciandra (Torino); A Londero (Udine); V Manfrin, G Battagin (Vicenza); G Starnini, A Ialungo (Viterbo).