PE2/43

Effect of simplification to INSTI-based dual therapy on residual inflammation and viral reservoir

E. Merlini[1], A. Cozzi-Lepri[2], C. Alteri[3], R. Scutari[4], A. Cingolani[5], F. Bai[1], F. Petroni[6], S. Lo Caputo[7], A. Antinori[8], C.F. Perno[3], A. d'Arminio Monforte[1], G. Marchetti*[1]

[1]Clinic of Infectious Diseases, Dept Health Sciences, University of Milan, ASST Santi Paolo e Carlo, Milan, Italy; [2]Institute for Global Health, University College of London, London, UK; [3]Department of Oncology and Hemato-Oncology University of Milan; [4]Department of Experimental Medicine, University of Rome "Tor Vergata"; [5]Institute of Clinical Infectious Diseases, Catholic University of Sacred Heart, Rome, Italy; [6] National Institute for Infectious Diseases 'L. Spallanzani' IRCCS, Rome, Italy; [7]Department of Infectious Diseases, University of Bari 'Aldo Moro', Bari, Italy; [8] HIV/AIDS Unit, National Institute for Infectious Diseases 'L. Spallanzani' IRCCS, Rome, Italy

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BACKGROUND

- Dual cART therapy has set up a new paradigm in HIV treatment that is now appointed by guidelines
- A concern endures whether or not dual regimens might loosen the control over residual inflammation, possibly affecting immune recovery

AIM

- to describe the trend in markers of inflammation, monocyte activation and HIV-DNA over 1 year of observation after a switch to INSTI-based dual therapy with VL≤50 copies/mL

STUDY DESIGN AND METHODS

STUDY POPULATION

- cART-treated HIV+ patients (HIV-RNA<50cp/mL) of Icona cohort
- Switched from triple combinations to an INSTI-containing 2DR for any cause
- On a stable triple cART for >= 12 months prior to the switch
- Availability of plasma samples at switch (T0) and 12±6 months post-switch (T1).

LAB ANALYSES

- Circulating sCD14, C Reactive Protein (CRP), IL-6 (Luminex); HIV-DNA (ddPCR).

STATISTICAL ANALYSES

- Paired T-test
- Non- parametric Spearman correlation

RESULTS

Table 1 – Characteristics of the study population

Characteristics	Total	RAL-based	DTG-based	p-value*
	N= 50	N= 17	N= 33	
Gender Female, n(%)	17 (34.0%)	5 (29.4%)	12 (36.4%)	0.627
Age, years, Median (IQR)	49 (42, 59)	51 (43, 62)	48 (40, 57)	0.170
Nationality Not Italian, n(%)	3 (6.0%)	2 (11.8%)	1 (3.0%)	0.164
Mode of HIV Transmission, n(%)				0.091
IDU	3 (6.0%)	3 (17.6%)	0 (0.0%)	
Homosexual contacts	20 (40.0%)	6 (35.3%)	14 (42.4%)	
Heterosexual contacts	25 (50.0%)	7 (41.2%)	18 (54.5%)	
Other/Unknown	2 (4.0%)	1 (5.9%)	1 (3.0%)	
AIDS diagnosis, yes n(%)	3 (6.0%)	2 (11.8%)	1 (3.0%)	0.223
HCVAb, n(%)				0.197
Negative	42 (84.0%)	13 (76.5%)	29 (87.9%)	
Positive	4 (8.0%)	3 (17.6%)	1 (3.0%)	
Not tested	4 (8.0%)	1 (5.9%)	3 (9.1%)	
CD4 count, cells/mmc, Median (IQR)	732 (568, 920)	673 (378, 920)	750 (595, 854)	0.152
CD4 count nadir, cells/mmc, Median (IQR)	293 (166, 420)	252 (118, 339)	318 (182, 486)	0.115
CD8 count, cells/mmc, Median (IQR)	724 (537, 1049)	950 (575, 1133)	699 (537, 854)	0.331
Viral load, copies/mL, Median (IQR)	15.00 (1.00, 37.00)	36.00 (9.00, 40.00)	8.00 (1.00, 36.00)	0.130
CD4 nadir, <=200 cells/mmc, n(%)	15 (30.0%)	6 (35.3%)	9 (27.3%)	0.562
Calendar year of baseline, Median (IQR)**	2015 (2014, 2016)	2014 (2013, 2014)	2016 (2015, 2016)	<.001
Follow-up time, months, Median (IQR)	15 (12, 18)	13 (12, 17)	15 (12, 18)	0.321
Time from first cART, years, Median (IQR)	4 (2, 10)	4 (3, 10)	4 (2, 9)	0.321
Antivirals in previous regimen, n(%)				0.100
PI/r-based	13 (26.0%)	1 (6.0%)	12 (36.0%)	
NNRTI-based	19 (38.0%)	11 (65.0%)	8 (24.0%)	
INSTI-based	18 (36.0%)	5 (29.0%)	13 (40.0%)	

*Chi-square or Mann-Whitney test as appropriate

RESULTS

- 50 patients were enrolled, 17/50 (34%) switching to raltegravir (RAL)-; 33/50 (66%) to dolutegravir(DTG) -containing 2DR (table 1).
- Upon switch to 2DR, CD4 modestly increased (p=0.038, Table 2), sCD14 significantly decreased (p<.00001, Table 2), while no changes in CD8, CD4/CD8 ratio, HIV-RNA and HIV-DNA, and other pro-inflammatory markers were observed (Table 2).
- The changes in sCD14 were more relevant in patients switching to DTG- vs RAL-containing 2DR (p interaction p=.014, Table 3).
- No correlations between inflammatory markers and viro-immunologic parameters were found.

Table 2 – Changes in viro-immunologic and pro-inflammatory biomarkers following dual therapy switch

	Viro-immunological markers					Pro-inflammatory markers		
	CD4, n	CD8, n	Ratio CD4/CD8	HIV-RNA, cp/ml	HIV-DNA, cp/10^6CD4	IL-6, pg/ml	CRP, ug/ml	sCD14, ug/ml
T0	762.9 (656.3, 869.5)	863.5 (722.8, 1004)	1.03 (0.88, 1.18)	20.28 (14.87, 25.69)	2.44 (2.23, 2.65)	1.65 (1.16, 2.13)	1.73 (1.21, 2.26)	1.25 (1.12, 1.38)
T1	823.1 (716.4, 929.9)	1082 (703.1, 1461)	1.06 (0.91, 1.22)	18.60 (13.38, 23.82)	2.43 (2.17, 2.68)	1.99 (1.15, 2.83)	1.58 (1.09, 2.07)	1.05 (0.94, 1.15)
Variation	60.20 (3.41, 117.0)	218.7 (-161, 598.3)	0.03 (-0.05, 0.12)	-1.68 (-8.23, 4.87)	-0.02 (-0.17, 0.12)	0.35 (-0.59, 1.28)	-0.15 (-0.56, 0.25)	-0.20 (-0.30, -0.10)
p-value*	**0.038**	0.253	0.416	0.609	0.764	0.463	0.454	**<.001**

*paired t test. Data are presented as mean (95% CI)

Table 3 – Changes in viro-immunologic and pro-inflammatory biomarkers following dual therapy switch, according to previous exposure to INSTI-containing regimen and to RAL or DTG in current dual therapy

	Viro-immunological markers					Pro-inflammatory markers		
	CD4, n	CD8, n	Ratio CD4/CD8	HIV-RNA, cp/ml	HIV-DNA, cp/10^6CD4	IL-6, pg/ml	CRP, ug/ml	sCD14, ug/ml
INSTI-free previous regimen								
T0	727.8 (576.7, 879.0)	791.9 (638.7, 945.1)	1.06 (0.84, 1.28)	19.66 (13.58, 25.73)	2.42 (2.17, 2.68)	1.64 (1.12, 2.17)	1.77 (1.19, 2.36)	1.26 (1.09, 1.44)
T1	775.3 (629.3, 921.4)	933.6 (546.3, 1321)	1.10 (0.88, 1.32)	18.78 (12.57, 24.99)	2.47 (2.22, 2.73)	2.06 (0.87, 3.25)	1.71 (1.13, 2.29)	1.04 (0.89, 1.19)
Variation	47.50 (-18.5, 113.5)	141.7 (-244, 527.8)	0.04 (-0.07, 0.15)	-0.88 (-6.51, 4.76)	-0.02 (-0.22, 0.18)	0.42 (-0.77, 1.61)	-0.06 (-0.57, 0.45)	-0.22 (-0.36, -0.09)
INSTI in previous regimen								
T0	825.3 (685.7, 964.8)	990.7 (696.3, 1285)	0.97 (0.78, 1.17)	21.39 (9.99, 32.79)	2.48 (2.00, 2.97)	1.65 (0.59, 2.71)	1.65 (0.53, 2.78)	1.23 (1.02, 1.43)
T1	908.1 (754.3, 1062)	1346 (498.3, 2194)	1.00 (0.78, 1.22)	18.28 (7.93, 28.63)	2.32 (1.61, 3.04)	1.87 (0.74, 2.99)	1.34 (0.39, 2.30)	1.06 (0.92, 1.21)
Variation	82.78 (-31.9, 197.4)	355.5 (-509, 1220)	0.02 (-0.12, 0.16)	-3.11 (-19.5, 13.25)	-0.02 (-0.22, 0.18)	0.21 (-1.48, 1.91)	-0.31 (-1.05, 0.42)	-0.16 (-0.31, -0.01)
Interaction p-value	0.642	0.917	0.801	0.006	0.612	0.151	0.857	0.690
RAL in 2DR								
T0	687.4 (466.6, 908.1)	883.1 (688.3, 1078)	0.89 (0.61, 1.16)	26.71 (18.49, 34.92)	2.67 (2.32, 3.03)	1.06 (0.67, 1.45)	2.22 (1.29, 3.15)	1.28 (1.06, 1.50)
T1	790.8 (551.9, 1030)	899.6 (688.7, 1111)	0.96 (0.70, 1.22)	16.18 (7.64, 24.71)	2.71 (2.35, 3.07)	1.80 (1.33, 2.27)	2.12 (1.14, 3.09)	1.12 (0.87, 1.36)
Variation	103.4 (28.31, 178.5)	16.59 (-53.1, 86.28)	0.07 (-0.06, 0.20)	-10.5 (-19.4, -1.63)	0.04 (-0.33, 0.40)	0.74 (0.14, 1.34)	-0.10 (-1.02, 0.81)	-0.16 (-0.32, -0.01)
DTG in 2DR								
T0	801.8 (679.7, 924.0)	853.4 (658.1, 1049)	1.10 (0.91, 1.29)	16.97 (9.93, 24.01)	2.34 (2.07, 2.61)	1.95 (1.25, 2.65)	1.48 (0.82, 2.13)	1.24 (1.07, 1.41)
T1	839.8 (723.7, 955.9)	1176 (603.0, 1749)	1.11 (0.91, 1.32)	19.85 (12.98, 26.72)	2.29 (1.96, 2.63)	2.09 (0.82, 3.36)	1.30 (0.74, 1.86)	1.01 (0.90, 1.13)
Variation	37.94 (-40.5, 116.4)	322.8 (-259, 904.3)	0.01 (-0.10, 0.12)	2.88 (-5.81, 11.57)	-0.05 (-0.21, 0.11)	0.14 (-1.27, 1.56)	-0.18 (-0.62, 0.26)	-0.22 (-0.36, -0.09)
Interaction p-value	0.196	0.776	0.873	0.625	0.287	0.949	0.725	0.014

*paired t test. Data are presented as mean (95% CI)

CONCLUSIONS

- In our cohort of successfully-treated HIV+ patients, switching to INSTI-based 2DR appeared to reduce sCD14 coupled to a slight CD4 rise in the face of stable HIV reservoirs.
- Our data suggest no disturbance to immune balance, rather a possible amelioration of the immune and inflammatory profile, during the first year of dual INSTI-based regimens, that will need to be confirmed in larger cohorts.

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Contact Information

Giulia Marchetti, MD, PhD, Associate Professor

giulia.marchetti@unimi.it