12° CONGRESSO NAZIONALE

ICAR

Italian **C**onference on
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Reach out for including all

12-16 ottobre 2020

DIGITAL EDITION

Promosso da

SIMIT Società Italiana di Malattie Infettive e Tropicali

e da

INMI, Istituto Nazionale per le Malattie Infettive
ISS, Istituto Superiore di Sanità
AMCLI, Associazione Microbiologi Clinici Italiani
SIICA, Società Italiana di Immunologia, Immunologia Clinica e Allergologia
SIMaST, Società Interdisciplinare per lo Studio delle Malattie Sessualmente Trasmissibili
SITA, Società italiana per la Terapia Antinfettiva
SIV-ISV, Società Italiana di Virologia - Italian Society for Virology
ANLAIDS, Associazione Nazionale per la lotta all'AIDS
ARCIGAY, Associazione LGBT Italiana
ASA Onlus, Associazione Solidarietà AIDS Onlus
EpaC Onlus, Associazione EpaC Onlus
LILA, Lega Italiana per la lotta contro l'AIDS
MARIO MIELI, Circolo di Cultura Omosessuale
NADIR, Associazione Nadir Onlus
NPS Italia Onlus, Network Persone Sieropositive
PLUS, Persone LGBT Sieropositive onlus

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Residual Inflammation and CD4/CD8 Recovery After Switching to Dual Therapy

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Authors declare that there are no conflicts of interest

Background

- Recently, switching to dual/monotherapy has been demonstrated to be associate with a stabilization of CD4/CD8 ratio, due to an increase in CD8+ T-cells

Mussini et al. BMC Medicine (2018) 16:79

- A lower CD4/CD8 ratio can be interpreted as a measure of dysregulation of a patient's immune system and has been associated with a higher risk of AIDS and non-AIDS events

Mussini et al. Lancet (2015) Mar;2(3):e98-106

- Persistently lower CD4/CD8 ratio has been associated with increased innate and adaptive immune activation and immune senescence phenotype in HIV-infected patients

Serrano-Villar et al. PLoS Pathog. 2014;10:e1004078

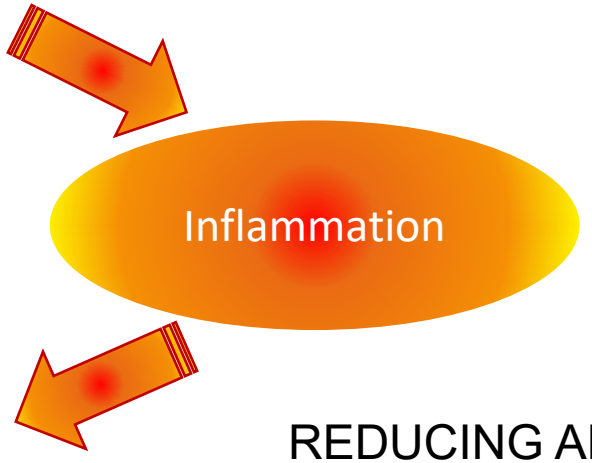
Hypothesis

Switch to dual therapy

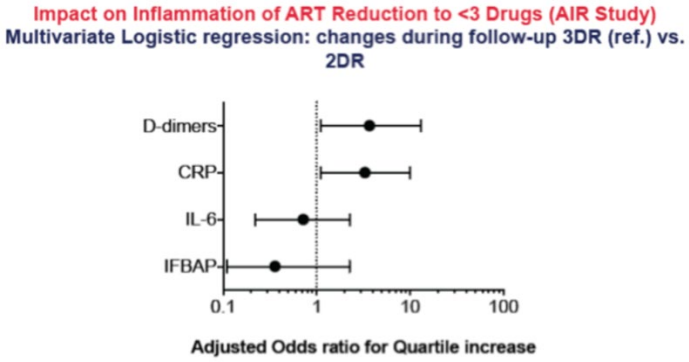
↑ CD8 → stabilization CD4/CD8 ratio

↑risk of clinical progression

↑ immune activation/inflammation



REDUCING ART TO LESS THAN 3-ARV REGIMEN LINKED TO INCREASED SYSTEMIC INFLAMMATION



Serrano-Villar S, et al. AIDS 2020 #OAB0304

Primary Objective

To investigate whether inflammatory markers at 2-6 months from switch might be associated with changes in CD4/CD8 ratio 12 months post switch

Secondary Objective

To investigate whether inflammatory biomarkers at 2-6 months post switch might predict the reduction of CD4/CD8ratio to below 0.45, in patients with CD4/CD8 ratio≥0.45 at switch

Methods

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STUDY POPULATION

- 3-drugs cART regimen from ART-naïve,
- switching to dual therapy or different triple therapy after HIV-RNA suppression
- maintenance of switch regimen for at least 12 months (T12)
- 1 stored plasma sample between 2-6 months from switch

LAB ANALYSES

- Circulating sCD14, C Reactive Protein (CRP), IL-6 (Luminex)

STATISTICAL ANALYSES

- Multivariable linear regression
- Poisson regression

Characteristics of the study population

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	All study population	Triple	Dual	p
Patients characteristics	N=407	N=376	N=31	
Male gender, n(%)	336 (82.6%)	313 (83.2%)	23 (74.2%)	0.202
Age, median (IQR)	42 (35-49)	41 (35-49)	45 (37-52)	0.293
Mode of HIV transmission, n(%)				
heterosexual	155 (38.1%)	145 (38.6%)	10 (32.3%)	0.837
IDU	31 (7.6%)	29 (7.7%)	2 (6.5%)	
MSM	204 (50.1%)	186 (49.5%)	18 (58.1%)	
Other/unknown	17 (4.2%)	16 (4.3%)	1 (3.2)	
migrants, n(%)	65 (16.0%)	59 (15.7%)	6 (19.4%)	0.593
previous aids event, n(%)	51 (12.3%)	47 (12.5%)	4 (12.9%)	0.948
years of infection, median (IQR)	3.3 (1.7-6.5)	3.3 (1.6-6.3)	4.0 (1.9-6.8)	0.331
HCV Ab, n(%)				
negative	361 (88.7%)	332 (88.3%)	29 (93.6%)	0.515
positive	32 (7.9%)	30 (8.0%)	2 (6.5%)	
unknown	14 (3.4%)	14 (3.7%)	0	
CD4 before cART start, median (IQR)	326 (189-466)	325 (180-475)	359 (243-432)	0.793
<200	106 (26.7%)	101 (27.5%)	5 (17.2%)	0.232
CD4 at switch, median (IQR)	592 (410-797)	592 (408-796)	556 (476-820)	0.584
0-200	27 (6.6%)	27 (7.2%)	0.0	0.304
201-500	123 (30.2%)	113 (30.0%)	10 (32.3%)	
501+	257 (63.1%)	236 (62.8%)	21 (67.7%)	
CD8 at switch, median (IQR)	841 (616-1195)	835 (613-1184)	977 (646-1233)	0.325
Months of HIVRNA<=50 before switch	24 (11-41)	24 (12-41)	19 (12-36)	0.869
Delta ratio (12m-BL)	0.08 (-0.0005; 0.18)	0.09 (0.002; 0.20)	0.04 (-0.02; 0.12)	0.031

	All study population	Triple	Dual	p
Patients characteristics	N=407	N=376	N=31	
Triple therapy				
2NRTI+NNRTI		134 (35.6%)		
2NRTI+bPI		89 (23.7%)		
2NRTI+INSTI		148 (39.4%)		
other		5 (1.3%)		
Dual therapy				
3tc+atv/c			1 (3.2%)	
3tc+drv/r			10 (32.2%)	
3tc+atv/r			5 (16.1%)	
3tc+atv			4 (12.9%)	
3tc+dgv			6 (19.4%)	
etv+ral			2 (6.4%)	
etv+drv/r			1 (3.2%)	
lpv+mvc			1 (3.2%)	
drv/r+ral			1 (3.2%)	
Previous cART regimen				
2NRTI+NNRTI	133 (32.7%)	128 (34.0%)	5 (16.1%)	0.026
2NRTI+bPI	185 (45.4%)	164 (43.6%)	21 (67.7%)	
2NRTI+INSTI	85 (20.9%)	81 (21.5%)	4 (12.9%)	
other	3 (1.0%)	3 (0.9%)	1 (3.2%)	

Patients switching to dual therapy featured higher plasma IL-6 and CRP early after switch vs patients switching to triple therapy

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MARKERS	All study population		Triple	Dual	p
CRP, ug/mL median (IQR)	1.5 (0.6-5.1)		1.4 (0.6-4.8)	3.5 (0.8-9.7)	**0.061**
mean (SD)	3.5 (4.4)		3.5 (4.3)	5.4 (5.4)	
sCD14, ug/mL median (IQR)	1.5 (1.2-1.9)		1.5 (1.2-1.9)	1.5 (1.3-2)	0.308
mean (SD)	1.6 (0.62)		1.6 (0.6)	1.8 (0.8)	
IL6, pg/mL median (IQR)	1.7 (1.1-2.9)		1.6 (1.1-2.7)	2.0 (1.5-3.5)	**0.039**
mean (SD)	2.3 (2.0)		2.2 (1.8)	3.2 (3.0)	
Months between switch and sample, median (IQR)	3.6 (2.0-5.0)		3.5 (2.0-5.0)	4 (2.7-5.0)	0.370

The multivariable linear regression showed a modest association between CRP early after switch and T12 CD4/CD8 ratio in DT

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1a. Linear Regression Model in all patients (n=407)

	UNIVARIATE				MULTIVARIATE*			
	Beta	95% CI		P	Beta	95% CI		P
CRP per 10 ug/mL	0.188	0.120	0.257	<0.001	0.023	-0.011	0.057	0.183
sCD14 per 10 ug/mL	0.145	0.022	0.268	0.021	0.047	-0.073	0.167	0.441
IL6, per 10 pg/mL	0.092	0.030	0.154	0.004	0.033	-0.009	0.074	0.123
CRP per 1 log ug/mL	0.085	0.173	0.002	0.056	-0.088	-0.181	0.006	0.066
sCD14 per 1 log ug/mL	-0.20	-0.52	0.11	0.195	-0.22	-0.54	0.10	0.176
IL6 per 1 log pg/mL	0.073	0.238	0.092	0.372	-0.115	-0.280	0.051	0.165
CRP >=1.5 (median) vs <1.5	0.074	0.196	0.047	0.221	-0.118	-0.258	0.023	0.096
sCD14 >=1.5 (median) vs <1.5	-0.02	-0.13	0.10	0.743	-0.02	-0.14	0.09	0.661
IL6 >=1.7 (median) vs <1.7	-0.029	-0.154	0.096	0.639	-0.062	-0.196	0.071	0.346

*adjusted for ethnicity, CD4 and CD8 at the switch, years of HIV-RNA suppression, type of cART

1b. Linear Regression Model in patients switching to triple therapy (n=376)

	UNIVARIATE				MULTIVARIATE*			
	Beta	95% CI		P	Beta	95% CI		P
CRP per 10 ug/mL	0.006	0.055	0.044	0.820	0.003	-0.001	0.006	0.137
sCD14 per 10 ug/mL	-0.02	-0.37	0.34	0.918	0.10	-0.24	0.44	0.573
IL6, per 10 pg/mL	-0.024	-0.093	0.045	0.494	-0.007	-0.117	0.102	0.894
CRP per 1 log ug/mL	0.005	0.031	0.042	0.771	0.014	-0.020	0.048	0.426
sCD14 per 1 log ug/mL	-0.01	-0.12	0.09	0.805	0.01	-0.09	0.11	0.835
IL6 per 1 log pg/mL	0.020	0.091	0.052	0.587	-0.011	-0.079	0.056	0.743
CRP >=1.5 (median) vs <1.5	-0.015	-0.058	0.028	0.486	-0.010	-0.051	0.031	0.627
sCD14 >=1.5 (median) vs <1.5	-0.02	-0.06	0.03	0.453	0.00	-0.04	0.04	0.892
IL6 >=1.7 (median) vs <1.7	-0.027	-0.070	0.016	0.220	-0.023	-0.064	0.018	0.267

*adjusted for ethnicity, CD4 and CD8 at the switch, years of HIV-RNA suppression

1c. Linear Regression Model in patients switching to dual therapy (n=31)

	UNIVARIATE				MULTIVARIATE*			
	Beta	95% CI		P	Beta	95% CI		P
CRP per 10 ug/mL	0.321	0.002	0.001	0.006	0.159	-0.023	-0.069	0.023
sCD14 per 10 ug/mL	0.525	0.06	-0.29	0.33	0.922	-0.11	-0.43	0.22
IL6, per 10 pg/mL	0.341	-0.031	-0.13	0.07	0.532	-0.050	-0.15	0.05
CRP per 1 log ug/mL	0.748	0.005	-0.03	0.04	0.772	-0.006	-0.04	0.03
sCD14 per 1 log ug/mL	0.546	0.00	-0.10	0.09	0.954	-0.03	-0.213	0.07
IL6, per 1 log pg/mL	0.839	-0.02	-0.08	0.804	0.508	-0.03	-0.10	0.03
CRP >=1.5 (median) vs <1.5	0.264	-0.02	-0.05	0.02	0.429	-0.02	-0.06	0.02
sCD14 >=1.5 (median) vs <1.5	0.380	0.00	-0.04	0.04	0.979	-0.02	-0.06	0.02
IL6 >=1.7 (median) vs <1.7	0.118	-0.02	-0.06	0.01	0.213	-0.03	-0.07	0.01

*adjusted for ethnicity, CD4 and CD8 at the switch, years of HIV-RNA suppression, type of cART

Modest association between high level of IL-6 and the CD4/CD8 descent to <0.45

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Poisson Regression Model in patients with CD4/CD8≥0.45 at switch

	UNIVARIATE				MULTIVARIATE*			
	IRR	95% CI		P	IRR	95% CI		P
CRP per 10 ug/mL	0.92	0.77	1.10	0.370	0.90	0.74	1.09	0.272
sCD14 per 10 ug/mL	0.62	0.23	1.72	0.363	0.48	0.18	1.29	0.147
IL6, per 10 pg/mL	1.062	0.84	1.35	0.622	1.040	0.79	1.37	0.784
CRP per 1 log ug/mL	0.687	0.25	1.91	0.472	0.465	0.14	1.52	0.206
sCD14 per 1 log ug/mL	0.38	0.03	5.34	0.473	0.16	0.01	2.07	0.159
IL6 per 1 log pg/mL	4.08	0.65	25.40	0.132	3.97	0.52	30.42	0.185
CRP >=1.5 (median) vs <1.5	0.99	0.29	3.41	0.983	1.07	0.30	3.76	0.914
sCD14 >=1.5 (median) vs <1.5	0.72	0.21	2.49	0.607	0.73	0.19	2.72	0.637
IL6 >=1.7 (median) vs <1.7	4.64	0.99	21.85	0.052	4.01	0.84	19.23	0.082

*adjusted for HCV, nadir CD4, CD4 at the switch

Conclusions

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- In our cohort of cART-treated HIV+ patients, switching to dual therapy seemed to disturb 12-month CD4/CD8 stability, possibly associated with higher CRP.

- High circulating IL-6 early after switch, irrespective of dual or triple therapy, seemed to exert a modest independent effect on the reduction of 12-month CD4/CD8 to below 0.45.

Despite a modest association between dual therapy and inflammation, 75% (23) of patients were on PI-based dual therapy and only the 25% (8) were on INSTI-based dual therapy.

Larger cohort studies with longer follow-up and new regimen INSTI-based dual therapy are needed to better elucidate the potential role of residual inflammation

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