INCREASED TOTAL AND LDL CHOLESTEROL PLASMA LEVELS UPON DIRECT ANTIVIRAL AGENTS (DAAS) DRIVEN HCV ERADICATION

P245

G. Taliani[1], G. Marchetti[2], A. Cingolani[3], M. Lichtner[4], S. Cicalini[5], E. Quiros Roldan[6], M. Ursitti[7], E. Girardi[8], A. Antinori[5], M. Puoti[9], A. d'Arminio Monforte[2], A. Cozzi-Lepri on behalf of Icona and Hepalcona Foundation Study Group

1 Sapienza University of Rome, Department of Clinical Medicine, Rome, Italy; 2 ASST Santi Paolo e Carlo, University of Milan, Clinic of Infectious and Tropical Diseases, Milan, Italy; 3 Policlinic A. Gemelli, Catholic University of the Sacred Heart, Institute of Clinical Infectious Diseases Rome Italy; 4 SM Goretti Hospital, Sapienza University of Rome, Unit of Infectious Diseases, Latina, Italy; 5 INMI L. Spallanzani IRCCS, HIV/AIDS Unit, Rome, Italy; 6 ASST Spedali Civili, University of Brescia, Department of Clinical and Experimental Sciences, Brescia, Italy; 7 S. Maria Nuova IRCCS Hospital, Department of Infectious Diseases, Reggio Emilia, Italy; 8 INMI L. Spallanzani IRCCS, Department of Epidemiology, Rome, Italy; 9 ASST Grande Ospedale Metropolitano Niguarda, Division of Infectious Diseases, Milan, Italy; 10 University College London, Institute for Global Health, London, UK;

BACKGROUND

- HCV has complex interactions with human lipid metabolism leading to downregulation of cholesterol levels.
- Treatment with DAAs was proven to induce a sharp and significant increase in total and low-density lipoprotein cholesterol (LDL) persisting after the end of treatment (EOT).
- DAD study has demonstrated that longer usage of DRV and not ATV is associated to CV events independently of lipid levels[1].

AIMS

- The aim was to examine cholesterol changes in HIV-HCV co-infected patients after HCV clearance and according to DRV/r, ATV/r or RAL exposure during DAA.

STUDY DESIGN AND METHODS

- The analysis includes data of HIV/HCV co-infected patients in the Icona and HepaIcona cohorts for whom pairs of biomarkers were available.
- The first pair (T0,T1) includes the two most recent values in a window [-12;0] months of the date of DAA initiation. The second pair (T1,T2) uses the latest in the window [+4;+12] months from the date EOT.
- Mean values at each time-point were calculated as well the difference among pairs.
- Univariable paired t-test were conducted to test whether the variations were significantly different from zero.
- An ANCOVA analysis was used to test whether there was an effect of DRV/r, ATV/r and RAL use.

RESULTS

We included 468 patients on ART, who achieved SVR; 22% on DRV/r, 20% on ATV/r and 24% on RAL. Patients' characteristics: median age 52 (50-55) years; 26% female; median BMI 24 (21-26) kg/m2; median CD4 584 (357, 824) cells/mmc; HCV genotype 1a (36%), genotype 1b (11%), genotype 3a (18%) and genotype 4 (13%) (Table 1).

Pair analyses for all biomarkers are reported in Table2 (A and B). Total and LDL-cholesterol along with platelet count, which prior to DAA tended to be stable or decrease, significantly increased after HCV clearance whereas high-density lipoprotein (HDL) cholesterol remained unchanged. These changes, which occur in a short time-lapse, potentially contribute to an increase in CVD risk through shared or separate pathways (as shown by means of a Direct Acyclic Graph [DAG] Figure).

Table 1 – Main characteriticsof the study population

Characteristics	T0-T1	T1-T2	Both	Total
	N= 51	N= 167	N= 250	N= 468
Age, years, median (IQR)	53 (49, 55)	52 (50, 55)	52 (50, 55)	52 (50, 55)
Gender, Female, n(%)	14 (27.5%)	49 (30.2%)	57 (22.4%)	120 (25.6%)
LDL cholesterol, mg/dL, median (IQR)	81 (61, 105)	88 (65, 117)	90 (62, 115)	87 (62, 115)
HDL cholesterol, mg/dL, median (IQR)	41 (35, 51)	40 (34, 53)	40 (31, 50)	40 (32, 51)
Total cholesterol, mg/dL, median (IQR)	149 (124, 178)	156 (136, 184)	156 (129, 188)	156 (131, 185)
BMI, kg/m^3, median (IQR)	21 (19, 23)	24 (20, 27)	24 (21, 26)	24 (21, 26)
ALT, U/L, median (IQR)	58 (39, 90)	59 (35, 99)	70 (42, 110)	64 (39, 101)
AST, U/L, median (IQR)	56 (45, 75)	50 (34, 92)	62 (37, 99)	57 (37, 92)
Platelets, x10^3/mmc, median (IQR)	172 (125, 216)	147 (103, 198)	142 (93, 191)	148 (100, 197)
Gamma-GT, U/L, median (IQR)	83 (52, 153)	82 (44, 133)	88 (49, 165)	84 (49, 145)
Haemoglobin, g/dL, median (IQR)	15 (13, 15)	15 (14, 16)	15 (14, 16)	15 (14, 16)
Leukocytes, cells/mmc, median (IQR)	5955 (4800, 7600)	5660 (4520, 6900)	5400 (4180, 7200)	5645 (4400, 7200)
Neutrophils, cells/mmc,median (IQR)	3040 (2400, 4360)	2990 (2185, 3970)	2730 (1979, 3790)	2900 (2100, 3850)
Albumin, g/dL, median (IQR)	4.20 (3.70, 4.35)	4.13 (3.80, 4.40)	4.06 (3.70, 4.34)	4.10 (3.72, 4.38)
Creatinine, mg/dL, median (IQR)	0.80 (0.70, 0.97)	0.81 (0.70, 0.97)	0.83 (0.75, 1.00)	0.82 (0.72, 1.00)
INR, median (IQR)	1.05 (0.91, 1.11)	1.10 (1.01, 1.16)	1.00 (0.96, 1.13)	1.06 (0.98, 1.15)
Total Bilirubin, mg/dL, median (IQR)	0.64 (0.50, 1.04)	0.73 (0.50, 1.45)	0.80 (0.56, 1.30)	0.75 (0.50, 1.33)
Tryglicerides, mg/dL, median (IQR)	117 (82, 162)	106 (86, 165)	130 (90, 189)	121 (88, 173)
Blood glucose, mg/dL, median (IQR)	90 (82, 107)	90 (83, 104)	93 (82, 104)	92 (82, 104)
CD4 count, cells/mmc, median (IQR)	549 (418, 803)	598 (351, 838)	576 (354, 820)	584 (357, 824)
CD8 count, cells/mmc, median (IQR)	834 (593, 1037)	840 (581, 1171)	737 (514, 1129)	788 (546, 1125)
cd4/CD8, median (IQR)	0.72 (0.51, 0.97)	0.70 (0.48, 1.01)	0.74 (0.45, 1.07)	0.73 (0.46, 1.05)
HIV-RNA, log10 copies/mL, median (IQR)	20 (1, 39)	20 (1, 39)	19 (1, 39)	20 (1, 39)
Use of DRV/r, n(%)	16 (31.4%)	33 (20.4%)	54 (21.2%)	103 (22.0%)
Calendar year of DAA start, median (IQR)	2015 (2015, 2016)	2016 (2015, 2016)	2015 (2015, 2016)	2015 (2015, 2016)
Calendar year of EOT, median (IQR)	2016 (2015, 2016)	2016 (2015, 2016)	2016 (2015, 2016)	2016 (2015, 2016)

Figure – DAG for the model exploring the causal link between HCV-RNA eradication and risk of CVD

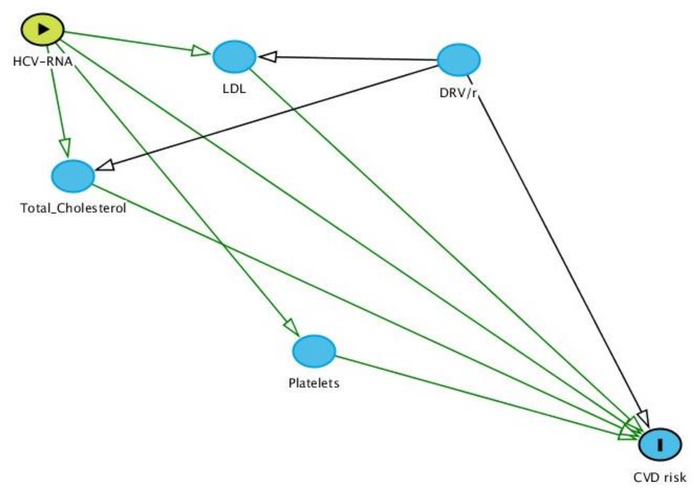

Table2 – Mean values and differences of biomarkers -matched pair analysis. (A) 2 most recent values in a 12 months window -before DAA initiation. (B) 2 latest values in the window [+4;+12] after EOT.

(A) T0-T1 (both pre-DAA)

Biomarker	N	Mean1	SD1	Mean2	SD2	Difference	p-value
LDL	138	90.9	36.9	88.1	34.3	-2.7	0.11
HDL	197	42.1	14.4	42.1	13.3	-0.1	0.90
T-Chol	306	158.5	43.0	157.0	40.8	-1.5	0.36
Triglycerides	304	147.9	90.9	142.2	84.8	-5.8	0.24
BMI	89	23.8	3.5	23.9	3.4	0.1	0.70
Albumin	141	4.0	0.6	4.2	2.0	0.1	0.42
Creatinine	422	1.1	4.3	1.3	5.9	0.2	0.59
WBC	426	5961	2292	6053	2382	92.8	0.25
Neutrophils	371	3200	1523	3268	1512	68.5	0.30
Platelets	432	158.8	78.7	154.8	72.2	-4.0	0.01
INR	79	1.08	0.16	1.36	2.36	0.28	0.29
Glucose	356	97.98	32.70	98.09	31.68	0.11	0.94
ALT	431	84.57	75.23	79.77	58.82	-4.81	0.07
AST	398	72.25	54.36	67.95	43.71	-4.30	0.04
GGT	290	132.7	141.0	123.1	120.6	-9.67	0.07
Haemoglobin	433	14.45	1.83	14.61	1.70	0.16	<.01
Bilirubin	409	1.06	1.08	1.05	1.06	-0.01	0.88
HIV-RNA (log10)	401	1.05	0.96	0.90	0.94	-0.15	<.01
CD4 count	470	684.4	841.3	722.8	1036	38.3	0.27
CD8 count	417	900.8	519.1	903.5	572.9	2.71	0.87
CD4/CD8 ratio	417	0.79	0.44	0.80	0.44	0.01	0.13

(B) T1-T2 (pre and post DAA)

Biomarker	N	Mean1	SD1	Mean2	SD2	Difference	p-value
LDL	157	88.7	34.5	109.4	32.1	20.7	<.01
HDL	258	44.4	16.4	45.6	14.1	1.2	0.12
T-Chol	417	158.7	40.4	180.3	42.7	21.6	<.01
Triglycerides	423	137.5	80.2	136.0	84.1	-1.5	0.72
BMI	169	23.9	3.7	24.2	3.8	0.2	0.05
Albumin	259	4.2	0.5	5.5	6.7	1.3	<.01
Creatinine	683	1.1	4.6	1.0	0.7	-0.2	0.34
WBC	693	5971	2252	9375	44059	3404	0.04
Neutrophils	603	3286	1845	5550	26886	2265	0.04
Platelets	704	153.0	69.7	166.6	72.3	13.5	<.01
INR	145	1.25	1.74	1.14	0.26	-0.11	0.44
Glucose	549	99.26	31.52	98.28	31.88	-0.98	0.32
ALT	695	79.92	60.14	27.81	20.92	-52.1	<.01
AST	653	69.53	48.60	29.03	16.87	-40.5	<.01
GGT	439	116.6	107.8	47.38	53.11	-69.2	<.01
Haemoglobin	702	14.61	1.66	14.62	1.70	0.01	0.81
Bilirubin	645	1.10	1.04	1.03	3.06	-0.07	0.59
HIV-RNA (log10)	638	0.88	0.92	0.75	0.92	-0.13	<.01
CD4 count	705	694.2	921.1	718.2	908.0	24.0	0.54
CD8 count	595	868.8	536.5	954.9	659.3	86.09	<.01
CD4/CD8 ratio	595	0.83	0.47	0.84	0.59	0.01	0.48

Moreover, in patients exposed to DRV/r a significant increase of total cholesterol was observed over T1-T2 compared to unexposed ones (Δ+10.5mg/dL; p=0.02); while a decrease was found for RAL treated patients (Δ-8.5mg/dL; p=0.04) and no evidence for a difference for ATV/r treated patients (Δ+0.05mg/dL; p=0.99).

CONCLUSIONS

- ***A complex and rapid change of risk factors for CVD risk seems to occur in HIV-HCV co-infected patients after HCV eradication with DAA, including increase of total and LDL-cholesterol and platelets.***
- ***The clinical impact of these short term changes in lipid profiles on the long term CVD risk still need to be evaluated, as well as the role of DRV/r which might contribute to the increase of total cholesterol.***
- ***It is increasingly important to assess individuals' risk profiles before starting HCV treatment***

Acknowledgments

ICONA Foundation 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, S Lo Caputo, C Mussini, M Puoti, CF Perno.*
STEERING COMMITTEE: *A Antinori, F Bai, C Balotta, A Bandera, S Bonora, M Borderi, A Calcagno, A Capetti, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, S Cicalini, A Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A De Luca, A Di Biagio, E Girardi, N Gianotti, A Gori, G Guaraldi, G Lapadula, M Lichtner, S Lo Caputo, G Madeddu, F Maggiolo, G Marchetti, L Monno, C Mussini, S Nozza, CF Perno, C Pinnetti, M Puoti, E Quiros Roldan, R Rossotti, S Rusconi, MM Santoro, A Saracino, L Sarmati.* ***STATISTICAL AND MONITORING TEAM:*** *A Cozzi-Lepri, I Fanti, L Galli, P Lorenzini, A Rodano', M Macchia, A Tavelli.* ***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, C Fabrizio (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); 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, C Viscoli, A Alessandrini, N Bobbio, G Mazzarello (Genova); M Lichtner, S Vita, (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, S Cannizzo, MC Moioli, R Piolini, AL Ridolfo, S Salpietro, C Tincati, (Milano); C Mussini, C Puzzolante (Modena); C Migliorino, G Lapadula (Monza); V Sangiovanni, G Borgia, V Esposito, F Di Martino, I Gentile, L Maddaloni (Napoli); AM Cattelan, S Marinello (Padova); A Cascio, C Colomba (Palermo); F Baldelli, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); G Magnani, MA Ursitti (Reggio Emilia); M Andreoni, A Antinori, R Cauda, A Cristaudo, V Vullo, R Acinapura, G Baldin, M Capozzi, A Mondi, A Cingolani, M Rivano Capparucia, G Iaiani, A Latini, R Gagliardini, MM Plazzi, S Savinelli, A Vergori (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, P Bagella (Sassari); A De Luca, B Rossetti (Siena); A Franco, R Fontana Del Vecchio (Siracusa); D Francisci, C Di Giuli (Terni); P Caramello, G Di Perri, S Bonora, GC Orofino, M Sciandra (Torino); M Bassetti, A Londero (Udine); G Pellizzer, V Manfrin (Vicenza); G Starnini, A Ialungo (Viterbo).*

Hepalcona Study Group

A Costantini (Ancona); L Monno, A Saracino, G Bruno (Bari); F Maggiolo, C Suardi (Bergamo); G Verucchi, L Badia (Bologna); F Castelnuovo, C Minardi (Brescia); B Menzaghi, C Abeli (Busto Arsizio); A Pan, S Lorenzotti (Cremona); L Sighinolfi, D Segala (Ferrara); P Blanc, V Vichi (Firenze); G Cassola, C Viscoli, A Alessandrini, N Bobbio, G Mazzarello (Genova); M Lichtner, R Marocco (Latina); P Bonfanti, C Molteni (Lecco); A Chiodera, M Maracci (Macerata); A d'Arminio Monforte, M Galli, A Lazzarin, M Puoti, A Castagna, F Bai, MC Moioli, L Milazzo, C Uberti-Foppa (Milano); C Mussini, C Puzzolante (Modena); C Migliorino, G Lapadula (Monza); V Esposito, G Borgia, A Maddaloni, I Gentile (Napoli); A Cascio, M Trizzino (Palermo); F Baldelli, C Pallotto (Perugia); G Parruti, F Sozio (Pescara); G Magnani, M Ursitti (Reggio Emilia); A Antinori, V Vullo, G Taliani, R Acinapura, A Vergori, A Mondi, MM Plazzi, P Zuccalà, M Rivano Capparucia (Roma); G Madeddu, P Bagella (Sassari); A De Luca, B Rossetti (Siena) P Caramello, GC Orofino (Torino).

References

Ryom L, Lundgren JD, El-Sadr W et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV. 2018 Jun 1; 5(6):e291–300.

Funding

ICONA Foundation is supported by unrestricted grants from BMS, Gilead Sciences, Janssen, MSD and ViiV Healthcare