P 162

Liver enzyme variation after switching to Emtricitabine/Tenofovir Alafenamide/Bictegravir is associated with Glucose increase in a real-life cohort.

N. Squillace1, E. Ricci2, P. Maggi3, B. Menzaghi4, G.V. De Socio5, G. Orofino6, B.M. Celesia7, A. Bandera8, E. Salomoni 9, A. Di Biagio10, L. Taramasso10, S. Piconi11, E.Sarchi12, L.Valsecchi13, G.F. Pellicanò14, G. Cenderello15 and P. BonfantiP1, ***for the CISAI Study Group***

1.Infectious Diseases Unit ASST-MONZA, San Gerardo Hospital-University of Milano-Bicocca, Monza; 2.Fondazione ASIA Onlus, Buccinasco (MI), Italy; 3.Infectious Diseases Unit, AORN Sant'Anna e San Sebastiano, Caserta, Italy; 4.Unit of Infectious Diseases, ASST della Valle Olona – Busto Arsizio (VA); 5.Unit of Infectious Diseases, Santa Maria Hospital, Perugia; 6.Division I of Infectious and Tropical Diseases, ASL Città di Torino; 7.Unit of Infectious Diseases, Garibaldi Hospital, Catania; 8.Infectious Disease Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; 9.SOC 1 USLCENTRO FIRENZE, Unit of Infectious Diseases, Santa Maria Annunziata Hospital, Florence; 10. Infectious Diseases, San Martino Hospital Genoa, University of Genoa, Genoa; 11.Unit of Infectious Diseases, A. Manzoni Hospital, Lecco; 12.Infectious Diseases Unit, S.Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; 13.1st Department of Infectious Diseases, ASST Fatebenefratelli Sacco, Milan, Italy; 14.Infectious Diseases, G. Martino Hospital -University of Messina, Messina; 15.Infectious Diseases Department, Sanremo Hospital, Sanremo, Italy

Introduction

- Switching from TDF to TAF was associated with ALT reduction both in HBV and HIV infected people (1-2).
- However no pathogenic mechanism was found in people living with HIV (PLWH) without viral hepatitis and long-term ALT variations on TAF treatment are unknown.
- Few data are available about risk of impaired glucose tolerance and INSTI treatment.
- An association between Insulin Resistance and ALT increase was demonstrated (3).
- Our aim was to investigate the role of emtricitabine/tenofovir alafenamide/bictegravir (FTC/TAF/BIC) regimen on metabolic and hepatic safety in a real-life setting.

Methods

- Consecutive PLWH enrolled in SCOLTA project switching to or initiating their first antiretroviral treatment (ART) with FTC/TAF/BIC were included.
- T0 and T1 were defined as results at baseline and 6-month follow-up respectively. PLWH with HBV co-infection were excluded. ALT variations were evaluated both in Naïve and Experienced patients and were correlated to metabolic parameters.
- AST/creatinine (ac)Non Alcoholic Steato-Hepatitis (NASH) score (4) was calculated.
- Triglycerides/High Density Lipoprotein-Cholesterol (TGL/HDL) ratio was used to as a marker of Insulin Resistance.

Table 1. Patients'characteristics

Variables at enrollment	N or mean or median	% or SD or IQR
Age, years	48.0	SD 12.1
Sex M	399	74.0%
Caucasian	474	87.9%
Risk factor for HIV acquisition		
Sexual	353	65.5%
IDU	70	13.0%
Other/ND	116	21.5%
BMI Kg/m²	25.4	SD 4.7
Weight, Kg	74.8	SD 15.0
HCV coinfection	88	18.7%
Naive	87	16.1%
Detectable HIVRNA in 452 experienced patients	84	18.4%
Previous ART		
FTC/TAF/elvitegravir/cobicistat	159	39.4%
FTC/TAF/dolutegravir	66	14.6%
Other DTG-based	35	7.7%
Any other TAF-including	88	19.5%
TDF-including	22	4.9%
Other	33	7.3%
Unknown	49	10.8%
Detectable HIVRNA (452 exp. pts)	83	18.4%
CD4 (87 naive pts), cells/mm3	308	IQR 112-533
CD4 (324 exp. pts), cells/mm3	600	IQR 436-828
Total cholesterol, mg/dL	190	SD 44
HDL-cholesterol, mg/dL	53	SD 19
LDL-cholesterol, mg/dL	109	SD 38
Triglycerides, mg/dL	112	IQR 84-165
Blood glucose (494 non-diabetic pts), mg/dL	93	SD 17
Blood glucose (28 diabetic pts), mg/dL	166	SD 68
AST, UI/dL	22	IQR 18-27
ALT, UI/dL	22	IQR 16-31

Legend to table 1: SD, Standard Deviation; IQR, Inter Quartile Range; CI, Confidence Interval; M, Male; LDL-C, Low Density Lipoprotein-Cholesterol; HDL-C, High Density Lipoprotein; TGL, Tryglicerides; BG, Blood Glucose; eGFR, estimated Glomerular Filtration Rate; IU, International Unit; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; IDU, Intravenous Drug User; HCV, Hepatitis C Virus.

Results

Out of 770 enrolled PLWH, 539 had at least one follow-up visit and were included in the analysis (see **Table 1** for patients'characteristics) . Mean age was 48 yo (±12.1), 74% were male, 16.1% were naïve to antiretrovirals, Mean BMI was 25.4 (±4.7). Most experienced PLWH (39.4%) were previously on FTC/TAF/elvitegravir/cobicistat and had an undetectable HIV-RNA <40 copies/mL (82.6%) with a median CD4 cell count of 600 cell/micrL (IQR 436-828). Age was significantly different in experienced vs naïve PLWH (49.2 ± 11.7 vs 41.5± 12.1 yo respectively , p<0.001). At T1 (see **Table 2**), in patients naïve at baseline, total cholesterol (TC), LDL-Cholesterol (LDL-c) HDL-cholesterol (HDL-c) and TGL showed a significant increase, while ALT and acNASH decreased significantly. Experienced PLWH showed a significant reduction of TC and TGL and an increase in Glucose in nondiabetic PLWH. ALT and acNASH increased. No differences were found between abnormal ALT at baseline and at follow-up.

In experienced PLWH, at baseline, a correlation was found between ALT and TGL (Spearman rho=0.26, p<0.0001), ALT and TGL/HDL-c ratio (rho=0.23, p<0.0001), and glucose (rho=0.13, p=0.01). At follow up the correlation was confirmed: ALT and TGL (r=0.21, p<0.0001), ALT and TGL/HDL-c ratio (r=0.17, p=0.003) and ALT and glucose (rho=0.11, p=0.049). Change from baseline correlated in the case of ALT and glucose in nondiabetic experienced patients (rho=0.14, p=0.02, see **Figure 1**)

Weight increased in naïve patients (+1.4 kg [95% CI 0.4, 2.2] Kg, p=0.04) but not in experienced ones.

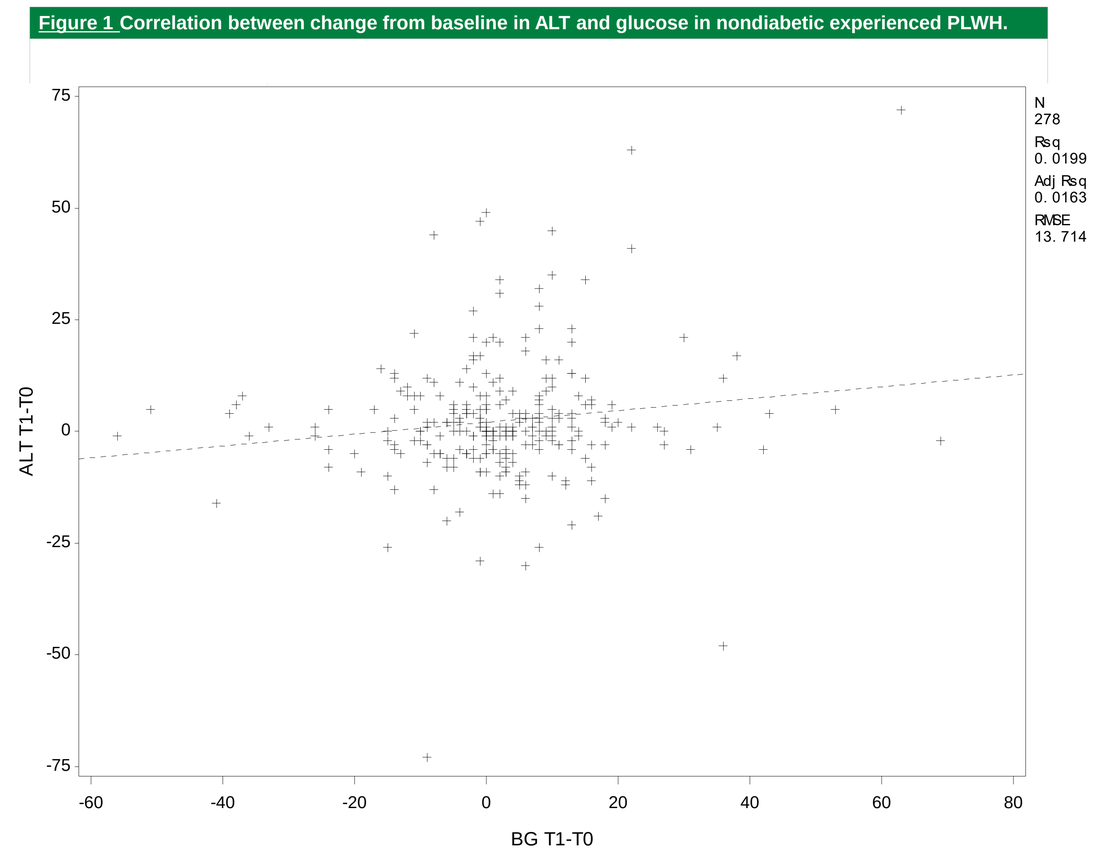
eGFR reduced significantly both in experienced and naïve subjects.

Table 2. Change from baseline by naive status

	Experienced			Naive			P*
	T0 Mean SD or median (IQR) or N (%)	T1 Mean SD or median (IQR) or N (%)	T1-T0 Mean (95% CI)	T0 Mean SD or median (IQR) or N (%)	T1 Mean SD or median (IQR) or N (%)	T1-T0 Mean (95% CI)	
Weight	75.6 ± 15.2	76.0 ± 13.8	0.3 (-0.2, 0.8)	69.9 ± 12.5	71.9 ± 12.3	**1.4 (0.4, 2.2)**	**0.04**
Total Cholesterol	194 ± 42	188 ± 40	**-5.4 (-8.6, -2.2)**	171 ± 46	183 ± 38	**15.0 (7.3, 22.6)**	**<0.0001**
LDL-C	111 ± 38	108 ± 35	-2.5 (-5.5, 0.4)	99 ± 38	108 ± 31	**9.8 (3.4, 16.2)**	**0.001**
HDL-C	54 ± 19	55 ± 18	0.1 (-1.0, 1.3)	48 ± 19	52 ± 17	**4.8 (1.9, 7.8)**	**0.002**
TGL	115 (85-170)	104 (76-153)	**-13.1 (-20.4, -5.8)**	97.5 (77-149)	99 (77-131)	0 (-13.5, 13.5)	0.09
BG in non-diabetic BG in diabetic	93 ± 17 165 ± 72	96 ± 21 168 ± 70	**2.2 (0.5, 4.0)** 2.3 (-30.2, 34.9)	89 ± 13 170 ± 26	89 ± 12 173 ± 72	0.4 (-2.6, 0.4) 32 (-108, 171)	0.29 0.53
eGFR	86.3 ± 21.9	83.5 ± 20.5	-2.5 (-2.9, -1.1)	105.1 ± 29.4	89.9 ± 23.7	**-15.3 (-19.9, -10.8)**	**<0.0001**
AST	22 (18-27)	23 (18-28)	-0.6 (-3.4, 2.1)	25 (19-31)	22 (19-27)	-3.8 (-7.8, 0.3)	**0.22**
ALT	22 (16-31)	23 (16-34)	**2.4 (0.8, 4.0)**	23 (17-31)	19 (14-26)	**-5.8 (-11.0, -0.7)**	**0.0002**
acNASH <4.15 4.15-7.73 ≥7.74	(N=311) 272 (87.5%) 33 (10.6%) 6 (1.9%)	(n=272) 242 (89.0%) 23 (8.5%) 7 (2.6%)	-0.22 (-0.70, 0.25)	(N=77) 52 (67.5%) 21 (27.3%) 4 (5.2%)	(N=70) 62 (88.6%) 7 (10.0%) 1 (1.4%)	**-0.95 (-1.55, -0.35)§§**	0.059

Legend to table 2: *T1-T0 comparison by naïve status; **Bold and red font**: p<0.05 for change from baseline; SD, Standard Deviation; IQR, Inter Quartile Range; CI, Confidence Interval; M, Male; LDL-C, Low Density Lipoprotein-Cholesterol; HDL-C, High Density Lipoprotein; TGL, Tryglicerides; BG, Blood Glucose; eGFR, estimated Glomerular Filtration Rate; IU, International Unit; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; acNASH, ast/creatinine Non Alcoholic Steato-Hepatitis score.

Figure 1 Correlation between change from baseline in ALT and glucose in nondiabetic experienced PLWH.



Discussion and Conclusion

- As expected we found ad increase in lipids after initiation of FTC/TAF/BIC in naïve PLWH. A reduction in ALT and acNASH was demonstrated in naïve PLWH suggesting a beneficial effect of on a possible HIV-induced steato-hepatitis.
- A significant weight increase was confirmed in naïve PLWH.
- In experienced PLWH an amelioration of lipid profile was observed (most patients with a previous therapy including Cobicistat). No significant weight gain was observed (6 months follow-up).
- A statistically significant increase in ALT and glucose was observed in experienced PLWH even if with ALT predominantly in the normal ranges and with no new diagnosis of diabetes. A correlation was found between a marker of Insulin Resistance (TGL/HDL) and ALT increase confirmed by a correlation between glucose and ALT increase. acNASH also increased suggesting a possible fat accumulation in the liver.
- In experienced PLWH (with a significant higher weight vs naïve) switching to FTC/TAF/BIC an increase in Insulin Resistance might drive the increase in ALT due to development of steato-hepatitis; in naïve PLWH resolution of viral damages due to the reduction of viral load may be predominant with no effect on Insulin Resistance.

Reference

1. Kovari H, Surial B, Tarr PE, et al. Changes in alanine aminotransferase levels after switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) in HIV-positive people without viral hepatitis in the Swiss HIV Cohort Study. *HIV Med*. 2021;22(7):623-628.
2. Agarwal K, Brunetto M, Seto WK, et al. 96weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68(4):672–681.
3. Arjmand B, Ebrahimi Fana S, Ghasemi E, et al. Metabolic signatures of insulin resistance in non-diabetic individuals. *BMC Endocr Disord*. 2022;22(1):212.
4. Wu XX, Zheng KI, Boursier J, et al. acNASH index to diagnose nonalcoholic steatohepatitis: a prospective derivation and global validation study. EClinicalMedicine. 2021;41:101145

Contacts: nicolasquillace74@gmail.com