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


1 Infectious Diseases Unit ASST MONZA, San Gerardo Hospital-University of Milano-Bicocca, Monza, 2 Foundation ASIA-Orbu, Buccinasco, (MI), Italy. 3 Infectious Diseases Unit, Azienda Sanitaria “Sant’Anna di San Sebastiani, Cava, Italy. 4 Unit of Infectious Diseases, ASST della Vede Dieme – Burin Anzaldo (VA); 5 Unit of Infectious Diseases, Santa Maria Hospital, Perugia. 6Division of Infectious Diseases, University of Modena, Italy. 7 Unit of Infectious Diseases, Gamberdi Hospital, Catania. 8 Infectious Diseases Unit, Fondazione IRCCS Cervello Ospedale Maggiore Policlinico, Milan, Italy. 9 Unit of Infectious Diseases, Santa Maria Annunziata Hospital, Florence. 10 Infectious Diseases, San Martino Hospital Genoa, University of Genova, Genova. 11 Unit of Infectious Diseases, A. Manzoni Hospital, Lecco. 12 Infectious Diseases Unit, S. Antonio e Biagio o Cesare Ampuolo Hospital, Alessandria, Italy. 13 1st Department of Infectious Diseases, ASST Fatebenefratelli Sacco, Milan, Italy. 14 Infectious Diseases, G. Martino Hospital – University of Messina. 15 13th 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 coinfection were excluded. ALT variations were evaluated both in Naïve and Experienced patients and were correlated to metabolic parameters.
- AST/creatinine (a/c) Non Alcoholic Steato-Hepatitis (NASH) score (4) was calculated.
- Triglycerides/High Density Lipoprotein-Cholesterol (TGL/HDL) ratio was used as a marker of Insulin Resistance.

Table 1. Patients’ characteristics

| Characteristic | n (%) | Reference
|----------------|-------|----------------|
| Age, years     | 55.0 (±4.2) | 0.0167
| Gender         | Male 50 (71.9%) | 0.0002
| Race           | White 52 (76.7%) | 0.0006
| BMI, kg/m²     | 27.2 (5.0) | 0.0003
| CD4, cells/μL | 568 (298 - 767) | 0.0105
| Viral load     | Undetectable 268 (56.6%) | 0.0140
| eGFR, ml/min/1.73 m² | 83.5 (77.0 - 90.7) | 0.0000
| TGL, mg/dL     | 144 (77 - 210) | 0.0000
| HDL, mg/dL     | 55 (33 - 74) | 0.0100
| TDF, days/year | 76 (61 - 104) | 0.0000
| INSTI          | 15 (22.7%) | 0.0000
| TAF             | 6 (8.8%) | 0.0000
| FTC/TAF/BIC     | 3 (4.4%) | 0.0000
| TAF/FTC/BIC     | 2 (2.9%) | 0.0000
| FTC/FTC/BIC     | 10 (14.3%) | 0.0000
| FTC                  | 10 (14.3%) | 0.0000
| TAF                  | 6 (8.8%) | 0.0000
| FTC                  | 10 (14.3%) | 0.0000
| BIC                  | 15 (22.7%) | 0.0000
| Any other NA-PI including | 8 (11.9%) | 0.0000
| NA-PI               | 15 (22.7%) | 0.0000
| INSTI               | 15 (22.7%) | 0.0000
| TAF                  | 6 (8.8%) | 0.0000
| FTC                  | 10 (14.3%) | 0.0000
| TAF                  | 6 (8.8%) | 0.0000
| TDF                  | 76 (112) | 0.0000
| FTC                  | 10 (14.3%) | 0.0000
| BIC                  | 15 (22.7%) | 0.0000
| FTC/TAF/BIC         | 3 (4.4%) | 0.0000
| FTC/FTC/BIC         | 2 (2.9%) | 0.0000
| FTC                  | 10 (14.3%) | 0.0000
| TAF                  | 6 (8.8%) | 0.0000
| TDF                  | 76 (112) | 0.0000

Table 2. Change from baseline by naïve status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T0 Mean (SD)</th>
<th>T1 Mean (SD)</th>
<th>T1 % change from T0</th>
<th>T1 Score (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGL/HDL</td>
<td>83.5 (77.0 - 90.7)</td>
<td>55 (33 - 74)</td>
<td>-35.8% (p&lt;0.0001)</td>
<td>-28.0 (7.3%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL</td>
<td>55 (33 - 74)</td>
<td>23 (17.3 - 30)</td>
<td>-58.1% (p&lt;0.0001)</td>
<td>-34.8 (10.4%)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

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 cells/microl (IQR: 436.8-826). 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, HDL-Cholesterol (HDL-c) and TGL showed a significant increase, while ALT and aNASH decreased significantly. Experienced PLWH showed a significant reduction of TC and TGL and an increase in Glucose in non diabetic PLWH. ALANASH 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<0.001), ALT and TGL/HDL-c ratio (rho=0.23, p=0.001), and glucose (rho=0.13, p=0.01). At follow up the correlation was confirmed: ALT and TGL (r=0.21, p=0.001), ALT and TGL/HDL-c ratio (r=0.17, p=0.003) and ALT and glucose (r=-0.11, p=0.049). Change from baseline in the case of ALT and glucose in nondiabetic experienced patients (n=14, p=0.02, see Figure 1)

Weight increased in naïve patients (Δ±1.4 kg [95% CI 0.2, 2.2] kg), p=0.04) but not in experienced ones. eGFR reduced significantly both in experienced and naïve patients.

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 aNASH was demonstrated in naïve PLWH suggesting a beneficial effect of 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. aNASH 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

Contacts: nicolasquillacorte74@gmail.com