3TC-DTG Dual Therapy and Its Implications in Hepatic Steatosis in People Living With HIV

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Citation:

1. Abstract

1.1. Purpose: Hepatic disease is one of the major comorbidities in people living with HIV. We intended to define the incidence of NAFLD and to identify any factors which may be associated with such a condition.

1.2. Methods: We performed abdominal Ultra Sound (US) on people living with HIV at our clinical center. Detection and grading of hepatic steatosis were based on the assessment of liver echogenicity. The grade of hepatic fibrosis was evaluated via Fib-4. About the patients analyzed, we collected baseline characteristics as well as HIV clinical history and liver function tests at the time of visit. Those with a history of chronic hepatitis (viral or alcoholic) were excluded. We then compared parameters through non-parametric tests and linear regression, as appropriate.

1.3. Results: We analyzed 72 patients: 51 (71%) were males, with a median age of 48 years (IQR 41-55), a median time from HIV diagnosis of 10 years (IQR 4-18) and a median time on ARV of 8 years (IQR 4-14). Thirty patients (41.7%) presented a radiologic pattern of steatosis: 15 presented mild steatosis, 13 moderate and 2 severe steatoses. In our cohort, in a multivariate analysis, we found that the condition of steatosis was predicted by a previous baseline AIDS event (p=0.009) and a higher baseline GPT value (p=0.029); conversely, being on a dual regimen with 3TC+DTG (p=0.05) was inversely associated with hepatic steatosis, after adjusting for age, sex and HIV risk factor.

1.4. Conclusion: A dual regimen of DTG+3TC appears less likely to be associated with hepatic steatosis.

2. Introduction

Hepatic disease is one of the major comorbidities in people living with HIV (PLWH) [1]. Although most of the cases of liver disease are acknowledged to major-hepatotropic-viruses co-infection such as HBV and HCV, the Non-Alcoholic Fatty Liver Disease (NAFLD) is emerging as a common condition in this population [2]. NAFLD is the liver expression of the metabolic syndrome consisting of different liver conditions, ranging from simple steatosis to Non Alcoholic Steatohepatitis (NASH) [3].

Thus, over the years hepatic steatosis - especially when causing inflammation and hepatocellular damage - has been proven to be a potent contributor to develop or progress to liver fibrosis in both the general population as well as in HIV-monoinfected individuals.
With an overall prevalence of NAFLD in PLWH widening from 15% to 60%, NAFLD appears to represent the manifestation of the viral activity of HIV itself, lipodystrophy and chronic combination antiretroviral therapy (cART) [5-14]. Since both Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and protease inhibitors have shown an association with insulin resistance and mitochondrial toxicity, those exposed to long-term cART including these agents are more likely to develop NAFLD and its complications [15]. Although only liver biopsy has the power to discern between the various manifestation of liver disease, many non-invasive diagnostic techniques have been proposed over the years. As rapid progression to fibrosis and cirrhosis has been reported in PLWH, a better understanding of NAFLD in HIV-monoinfected people receiving cART appears to be vital for further prevention of HIV comorbidities [16-17]. Since US is a very helpful and accessible device to screen patients, with very low costs and no harm for the patient, we intended to define the incidence of NAFLD and to identify any factors which may be associated with such a condition. Non-Alcoholic Fatty Liver Disease is characterized by excessive hepatic fat accumulation and defined by the presence of steatosis in >5% of hepatocytes. NAFLD includes two pathologically distinct conditions with different prognoses: Non-Alcoholic Fatty Liver (NAFL) and Non-Alcoholic Steatohepatitis (NASH). NASH comprehends a wide spectrum of disease severity, including fibrosis, cirrhosis and Hepatocellular Carcinoma (HCC) [18].

The diagnosis of NAFLD requires the exclusion of both secondary causes such as hereditary disorders (e.g. Wilson diseases, hemochromatosis), steatogenic medications (e.g. amiodarone, methotrexate, tamoxifen, corticosteroids, valproate), viral hepatitis (especially genotype 3-hepatitis C virus (HCV)-related) or a daily alcohol consumption of 30 g for men and 20 g for women [19], although patients consuming moderate amounts of alcohol may be still predisposed to NAFLD if they have metabolic risk factors.

Liver biopsy is the gold standard for diagnosing NAFLD, but the procedure is invasive and not risk-free, and sampling errors may occur [18]. For these reasons, in recent years many noninvasive methods have been proposed for the diagnosis of hepatic steatosis. US is accurate in detecting moderate-severe steatosis (i.e. fat accumulation >30%) with a >80% sensitivity and >95% specificity, while in mild steatosis the reported sensitivity is <67% with a specificity <93% compared to liver biopsy [20].

### 4. Results

We analyzed 72 patients: 51 (71%) were males, with a median age of 48 years (IQR 41-55), a median time from HIV diagnosis of 10 years (IQR 4-18) and a median time on ARV of 8 years (IQR 4-14). Twenty-three patients (32%) had a previous AIDS event, median CD4+ cell nadir was 167 cell/mm3 (IQR 30-271) while median peak HIV-RNA value was 5.0 log10 copies/mL (IQR 4.2-5.7). Regarding ARV regimens, 45 patients (62.5%) were on a standard 3-drug regimen with 2 NRTIs (32 with an INI, 4 with bPI and 9 with NNRTI), 16 patients (22.2%) were on a dual regimen with 3TC+DTG, 9 (12.5%) with a 2DR with 3TC+bPI while 2 patients (2.8%) were on a 4+ drug regimen. Full patients’ characteristics are available in (Table 1).

### Table 1: Patients’ Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>51 (70.8)</td>
</tr>
<tr>
<td>Age (Years), median (IQR)</td>
<td>47.9 (41.4-55.0)</td>
</tr>
<tr>
<td>HIV risk factor, n (%):</td>
<td></td>
</tr>
<tr>
<td>- MSM</td>
<td>40 (55.6)</td>
</tr>
<tr>
<td>- Heterosexual</td>
<td>31 (43.1)</td>
</tr>
<tr>
<td>- IDU</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Years from HIV diagnosis, median (IQR)</td>
<td>10.2 (3.9-17.7)</td>
</tr>
<tr>
<td>Years on ARV, median (IQR)</td>
<td>8.0 (3.8-13.7)</td>
</tr>
<tr>
<td>Previous AIDS event, n (%)</td>
<td>23 (31.9)</td>
</tr>
<tr>
<td>Months of virologic suppression, median (IQR)</td>
<td>60.0 (26.3-111.9)</td>
</tr>
<tr>
<td>Peak HIV-RNA (log10 copies/mL), median (IQR)</td>
<td>5.01 (4.15-5.70)</td>
</tr>
<tr>
<td>Nadir CD4+ cell count (cell/mm3), median (IQR)</td>
<td>167 (30-271)</td>
</tr>
<tr>
<td>Previous virologic failure, n (%)</td>
<td>25 (34.7)</td>
</tr>
<tr>
<td>ARV regimen at baseline, n (%):</td>
<td></td>
</tr>
<tr>
<td>- 2NRTI + INI</td>
<td>32 (44.4)</td>
</tr>
<tr>
<td>- 2NRTI + NNRTI</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>- 2NRTI + PI</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>- 3TC+bPI</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>- 3TC+DTG</td>
<td>16 (22.2)</td>
</tr>
<tr>
<td>- Other</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Diagnosis of steatosis, n (%)</td>
<td>30 (41.7)</td>
</tr>
<tr>
<td>Right hepatic lobe diameter (cm), median (IQR)</td>
<td>14.8 (13.1-16.1)</td>
</tr>
<tr>
<td>Spleen diameter (cm), median (IQR)</td>
<td>10.5 (9.6-12.0)</td>
</tr>
<tr>
<td>Spleen surface (cm2), median (IQR)</td>
<td>36.5 (32.1-49.5)</td>
</tr>
</tbody>
</table>
At baseline, median hepatic right lobe diameter was 14.8 cm (IQR 13.1-16.1), median spleen diameter was 10.5 cm (IQR 9.6-12.0) while median spleen estimated surface was 36.5 cm² (IQR 32.1-49.5). Thirty patients (41.7%) presented a radiologic pattern of steatosis: 15 presented mild steatosis, 13 moderate and 2 severe steatoses.

In our cohort, in a multivariate analysis, we found that the condition of steatosis was predicted by a previous baseline AIDS event (aHR 13.1, 95%CI 1.9-90.0, p=0.009) and a higher baseline GPT value (aHR 1.05, 95% CI 1.01-1.10, p=0.029); conversely, being on a dual regimen with 3TC+DTG (aHR 0.03, 95% CI 0.01-1.08, p=0.05) was inversely associated with hepatic steatosis, after adjusting for age, sex and HIV risk factor.

A wider right hepatic lobe was associated with a higher baseline triglycerides value (per 10 mg/dL more, +0.07cm, 95% CI 0.02-0.12, p=0.012) while it was negatively predicted by a longer period of virologic suppression (per 10 months more, -0.14cm, 95% CI -0.24 - -0.04, p=0.008), after adjusting for time on DTG, sex, age, HIV risk factor, years on ARV and baseline CD4+ cell count.

Regarding spleen diameter, we found that a wider spleen diameter was predicted by an higher peak HIV-RNA (per 1 log10 copies/mL, +0.47 cm, 95%CI 0.04-0.90, p=0.033) while it was reversely associated with time of virologic suppression (per 10 months more, -0.14cm, 95% CI -0.24 - -0.04, p=0.008), after adjusting for time on DTG, sex, age, ARV regimen, previous AIDS event and CD4+ cell nadir. A spleen diameter over 12 cm was negatively predicted by being on a 2-drug regimen with 3TC+DTG (aHR 0.03, 95%CI 0.01-0.73, p=0.031) as well as being on a 2-drug regimen with 3TC+bPI (aHR 0.01, 95%CI 0.01-0.24, p=0.007), after adjusting for age, sex, previous AIDS event, HIV risk factor, peak HIV-RNA and baseline CD4+ cell count.

5. Discussion

In our cohort, Non Alcoholic Fatty Liver Disease is confirmed to be a very common condition in PLWH as 41.7% of our population showed this condition, rate in line with those described in other published works [21]. The implication of such a condition are to be considered of fundamental importance in the population of interest as it is an aging one nowadays. Beside those with chronic viral hepatitis coinfection, liver health is of rising interest in PLWH as they’re receiving chronic therapies lifelong. In this view, we were able to distinguish the three ultrasonographic patterns of hepatic steatosis and only half of the cases showed a mild steatosis (50%), while the other half was witnessed with moderate involvement in the majority of the cases (43%) with 7% of patients reaching a severe grade of steatosis. Among those with severe steatosis, all of them was receiving either 3 or 4 antiretroviral drugs, while among those with moderate steatosis only two were on a dual therapy with 3TC-DTG: one had a previous history of NNRTI discontinuation due to alteration in liver function tests and a previous prolonged antitubercular treatment, while the the other patient was simplified to the given dual therapy because of hypertriglyceridemia. In our cohort, patients on a 2-drug regimen with 3TC-DTG show a lower rate of hepatic steatosis compared with those on other ARV regimens. The good tolerability of this strategy has already been described, with various real-life studies highlighting the favorable effects on total cholesterol and triglycerides even in the short-term [22-24]. The class of Integrase Inhibitors has shown since its introduction an overall better tolerability compared with boosted-Pis and NNRTIs [25, 26] and this reflects also on mitochondrial toxicity and fasten lipids profile [27]. Most recent guidelines [28] have become aware of the importance of ARV regimens in preventing NAFLD and suggest the use of lipid-neutral ARV regimens in patients at risk of developing NAFLD.

As clinicians, we need to fully embrace the fundamental concept that our patients are not only People Living With HIV (PLWH), but are also People Ageing With HIV (PAWIH); thus, this new view denote the urge for a safer and cleaner therapeutic strategy to minimize the long-term side effects in the elderlies that are and will be living with HIV.

In conclusion, although Non Alcoholic Fatty Liver Disease remains a common finding in people ageing with HIV receiving antiretroviral therapy, our data suggests that a dual regimen of dolutegravir plus lamivudine appears less likely to be associated with such a condition, hinting a safer metabolic profile of this 2-drug regimen when compared to standard cART.

Due to the limited number of patients observed in this report, further data are needed to confirm this study.

6. Funding

This study was performed as part of our routine work.

7. Author Contribution Statement

DM and AC managed patients and wrote the manuscript; FT performed ultrasonography exams; GB, CP, AD, FL, SB collected data; DM, AB and SDG conceived the study. All authors revised the manuscript.

8. Ethics Statement

The study was conducted in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2008), created by the World Medical Association. All patients’ gave written consent to data collection.

References:


