

TENOFOVIR INDUCED HEPATITIS

Hemant R. Gupta¹, Nishi Vishwanathan², Utina Kichu³, Minal A. Meshram⁴

¹Associate Professor and HOI, Department of Medicine, JJ Group of Hospitals and Grant Government Medical College, Mumbai, Maharashtra, India.

²Intern, Department of Medicine, JJ Group of Hospitals and Grant Government Medical College, Mumbai, Maharashtra, India.

³Chief Resident, Department of Medicine, JJ Group of Hospitals and Grant Government Medical College, Mumbai, Maharashtra, India.

⁴Chief Resident, Department of Medicine, JJ Group of Hospitals and Grant Government Medical College, Mumbai, Maharashtra, India.

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PRESENTATION OF CASE

A 23-year-old sero-positive male on TLE (Tenofovir, Lamivudine, Efavirenz) regimen for 8 months was admitted under medicine care with complaints of yellowish discolouration of eyes and skin, abdominal bloating, nausea and decreased appetite in the last 3 months.

The use of Highly Active Anti-Retroviral Therapy (HAART) for management of HIV seropositive patients has brought about radical enhancement in their lifespan and quality of life. Recognising the side effects and toxicity of long-term use of ART is crucial for their management. Tenofovir is a nucleotide analog reverse-transcriptase inhibitor (NtRTI) and cases of Tenofovir induced hepatitis are rare. However, a majority of NtRTIs can induce mitochondrial damage and therefore have potential for liver damage. Here, we report a rare case of tenofovir causing hepatitis in a patient with none of the recognisable risk factors who is seropositive.

DIFFERENTIAL DIAGNOSES

- Viral hepatitis including Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D and Hepatitis E.
- Autoimmune hepatitis.
- Alcoholic hepatitis.
- Medication induced Hepatitis (e.g. Tenofovir induced hepatitis).
- Leptospirosis.
- Liver abscess.

CLINICAL DIAGNOSIS

On general examination patient was conscious, orientated to time, place and person; pulse 84/min, blood pressure 110/70 mmHg in right upper arm in supine position, respiratory rate 18/min. Initially, the patient was treated as a case of jaundice under evaluation in a seropositive patient. There were no signs of liver cell failure. Systemic examination was unremarkable, except right upper quadrant tenderness.

PATHOLOGICAL DISCUSSION

Liver toxicity is one of the most relevant adverse effects of ART, owing to its frequency and the fact that it can lead to interruption of therapy, clinical hepatitis and death.⁽¹⁻³⁾

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Corresponding Author:

Nishi Vishwanathan,

A/18, Divine Light Soc., Andheri-Kurla Road,

Andheri East, Mumbai-400093, Maharashtra, India.

E-mail: nishiv1995@gmail.com

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It is well known that any antiretroviral drug can produce liver toxicity.

Tenofovir is an NtRTI. It selectively inhibits viral reverse transcriptase, a crucial enzyme in retroviruses such as Human Immunodeficiency Virus (HIV), while showing limited inhibition of DNA polymerase α , β and mitochondrial DNA polymerase γ which are human enzymes. The drug Tenofovir lacks an important hydroxyl group, which prevents the formation of a 5' to 3' phosphodiester linkage. This linkage is needed for elongation of the DNA chain. Once Tenofovir gets incorporated, it causes premature termination of DNA transcription. This prevents viral replication. Inhibition of mitochondrial DNA polymerase γ by NtRTI is hypothesised to cause hepatitis. Mitochondrial toxicity is an infrequent but a distinctive type of hepatotoxicity that may evolve to acute liver failure. Mitochondrial toxicity can lead to a variety of manifestations such as lactic acidosis, hepatitis, myopathy, nephrotoxicity, pancreatitis and peripheral neuropathy.^(3,4) The relative potential of inhibition of mitochondrial DNA polymerase gamma in cell cultures have been postulated as zalcitabine > didanosine > stavudine > lamivudine > zidovudine > abacavir.⁽⁴⁾ In vitro data support an additive or synergistic long-term mitochondrial toxicity with some NtRTI combinations. Hydroxyurea, used as coadjuvant treatment, seems to increase the toxic effect of some NtRTI due to the rise of intracellular levels of 50 triphosphates products. In all the reported cases, patients had some or the other underlying factor or some risk factor predisposing to mitochondrial toxicity. Pre-existing Hepatitis B or Hepatitis C infection tends to predispose towards hepatitis. In the case reported by Murphy et al the predisposing factor was pre-existing renal insufficiency, co-administration of Didanosine which has high affinity for mitochondrial DNA polymerase and use of diuretics.⁽⁵⁾ In another case reported by Hashim et al, there was underlying HCV infection, E. coli bacteraemia and hypotensive episodes.⁽⁶⁾ Contrary to this in the present case, none of the identifiable risk factors were present and patient's baseline investigations were all normal.

DISCUSSION OF MANAGEMENT

On general examination, vital parameters were normal and on systemic examination no significant abnormality was found. Investigations showed severe anaemia with haemoglobin 13.6 gm/dL. Total leucocyte count 12,000 cells/dL, platelet count of 497,000/dL. In liver function test, aspartate transaminase was 414 IU/L, alanine transaminase 296 IU/L and total bilirubin 5.7 mg/dL. In renal function test, serum urea was 18 mg/dL and serum creatinine 0.7 mg/dL. Serum sodium was 141 mEq/L and serum potassium was 3.6 mEq/L. Serum amylase was 125 IU/L and serum lipase was

136 IU/L. Patient was on ART regimen of TLE (Tenofovir, Lamivudine, Efavirenz) for 8 months.

CD4 count was 814. Viral markers were negative for all known causes of hepatitis including Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D and Hepatitis E. There were no signs of alcoholic or autoimmune hepatitis. Infections affecting the liver like Leptospirosis were also ruled out.

FINAL DIAGNOSIS

Diagnosis of Tenofovir induced hepatitis was made. Tenofovir was stopped immediately and the patient was kept under close observation. The liver function test showed a drastic improvement within next few days after stopping TLE regimen and supportive treatment. The three main considerations necessary for the management of transaminase elevation after the introduction of HAART (Highly Active Antiretroviral Therapy) are severity, clinical impact and aetiologic mechanisms. The presence of liver decompensation is one of the reasons to stop treatment. To conclude, though rare, Tenofovir can cause severe hepatitis in a patient with all normal parameters.⁽⁷⁾ Clinicians should keep these identified adverse effects in mind and look for the warning signs in patients on ART, especially when it comes to a TLE regimen containing Tenofovir.

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