****

**Effects of tenofovir disoproxil fumarate on intrahepatic viral burden and liver immune microenvironment in patients with chronic hepatitis B**

**Pan D, Soulette C, Aggarwal A, *et al.* Effects of tenofovir disoproxil fumarate on intrahepatic viral burden and liver immune microenvironment in patients with chronic hepatitis B. *Gut* 2025; 74: 628–638. doi: 10.1136/gutjnl-2024-332526.**

In this randomised double-blind trial, treatment naïve patients were allocated to receive tenofovir disoproxil fumarate (TDF) or placebo for 3 years. Important patient characteristics were absence of decompensation or hepatocellular carcinoma (HCC), HBV (hepatitis B virus) viraemia above 2000 IU/mL and serum ALT (alanine transaminase) 1-2x upper limit of normal (ULN), irrespective of HBeAg (hepatitis B e-antigen) status. Core liver biopsies were collected at baseline and year 3. Within this study population, based on current European Association for the Study of the Liver (EASL) guidelines, none of the participants would have been eligible for nucleos(t)ide analogues (NAs).

Utilising state of the art gene technologies, Pan et al., were able to analyse the effects of TDF on intrahepatic viral antigen burden and the liver immune microenvironment. Immune related genes such as PDCD1 (Programmed cell death protein 1, encoding PD-1), CXCL10 (C-X-C Motif Chemokine Ligand 10), CXCL11 (C-X-C Motif Chemokine Ligand 11), and regulatory T cells such as FOXP3 (forkhead box P3), CTLA4 (Cytotoxic T-lymphocyte associated protein 4) were also found to be significantly downregulated in the TDF cohort. There was reduction in densities of cytotoxic CD8+ (cluster of differentiation 8) T cells in proximity to HBV core + (cccDNA +cells (covalently closed circular DNA)), but not HBsAg+ (hepatitis B surface antigen positive) (HBV-integrated). Importantly, HBV core+ cells were significantly reduced in patients treated with TDF; however, by contrast, there was no reduction in HBsAg+ hepatocytes. Significantly, the total burden of HBV DNA integration in hepatocytes was reduced by TDF treatment.

Pan *et al.,* conclude that NA therapy reduces intrahepatic viral DNA burden and transforms the liver immune microenvironment. Their study has invited further questions regarding the role of differential cytotoxic T cells and potential for new HBV cure strategies.