

## EDITORIAL

# Persistent Risk for HBV Associated Hepatocellular Carcinoma in spite of Sustained and Successful Viral Suppression: The Need for Drugs for HBV Cure

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As the years of antiviral treatment for chronic hepatitis B increase, we are witnessing persistence of the risk for hepatocellular carcinoma (HCC). Even with successful control of hepatitis B virus (HBV) replication over a decade (even over 12 years), there remains the risk for HCC in patients with chronic hepatitis B (CHB).

Currently, HCC is the second most common cancer death.<sup>1</sup> Worldwide, the majority of HCC is causatively associated with chronic HBV infection.<sup>2-5</sup> In 2006, with their landmark 12-year prospective study, Chen and his colleagues discovered that the high baseline HBV DNA level was closely associated with the high risk for the development of HCC.<sup>6</sup>

Treatment with nucleos(t)ide analogues (NAs), which began with lamivudine in 1998, has resulted in significant improvement in the survival of patients with CHB with the reduced incidence of HCC. These findings were observed with lamivudine,<sup>7,8</sup> entecavir<sup>9</sup> and tenofovir.<sup>10</sup>

Nonetheless, as the duration of antiviral treatment increases, there still remains the risk for HCC in spite of undetectable HBV DNA in serum for years as reported by different investigators<sup>11-15</sup> with the observation time of 4-5 years including ours.<sup>14</sup> As shown in the table 1, our experience shows the longest years of successful viral suppression before the development of HCC. The maximum treatment period before HCC was 18.7 years. The longest time of negative serum HBV DNA was 12.4 years as shown in the table below.<sup>14</sup>



## Open Access

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Table 1. Development of HCC in patients with cirrhosis on long-term antiviral therapy

Pt	Date startTx	Change in Child Class On Tx	Date HCC Dx	Size (cm) and site of HCC	Sex & Age (yr) at HCC Dx	Yrs on anti-HBV Tx at HCC Dx	HBVDNA at HCC Dx	Yrs with undetectable HBV DNA Before HCC Dx	Anti-HBV Tx	Status
3	5/1998	A→A	2/2008	1.8x0.9 Lt	76 F	9.8	UD	6.7	LAM+TDF	alive
6	2/2004	A→A	6/2013	2.5 Lt	57 M	9.3	UD	7.7	TDF	dead
7	2/1996	A→A	7/2013	1.6x1.4 Rt	73M	17.4	UD	9.7	TDF	alive
9	5/1996	A→A	10/2014	3.4 Rt	74M	18.4	UD	10.4	LAM +TDF	alive
10	2/2000	A→A	4/2015	3.4x3.4 Rt	62M	15.2	UD	12.4	TDF	alive

UD: undetectable, LAM: lamivudine, TDF: tenofovir disoproxil fumarate

Average years on antiviral therapy: Average 14 years with a median of 15.2 years (9.3-18.4 yrs)

Average years with undetectable HBV DNA: median 9.7 years (6.7-12.4)

This table is from Ref. 14 (Minerva Gastroenterol Dietol 2017;63:74-76)

Persistent risk for HCC is attributed to the inability of eradicating the HBV with the current treatment using NA's. The NA's are effective in suppressing the replication of HBV but do not eliminate the covalently closed circular DNA (cccDNA), the template for viral replication which is located inside the nucleus of the hepatocytes.

Hepatocarcinogenesis by HBV can be multifactorial and integration of HBV DNA into the host DNA is considered one of the most important mechanisms. This integration would lead to rearrangement of chromosomes, deregulation and instability of gene expression that leads to oncogenesis.<sup>16-18</sup>

In order to cure the HBV infection, several approaches may be needed; eradication of the cccDNA, inhibition of viral entry from the serum to the newly formed hepatocytes, T cell vaccine which targets specifically HBV DNA, enhancing the host immune activity including the innate immunity with toll-like receptor agonists and suppression of viral replication. Additional approach would be an inhibition of maturation of the pregenomic mRNA in the hepatocyte nucleus and block its export to hepatocyte cytoplasm. The process would cut down the generation of HBV core particle in the cytoplasm which would significantly reduce the production of cccDNA.

While the cure for hepatitis C virus infection has become possible with the direct-acting antivirals recently developed, cure for HBV is still far from achievement. Fortunately, multiple compounds with potential HBV cure are being identified by the scientists in the world and the massive effort for HBV eradication is in progress.<sup>19,20</sup> We look forward to achieving our long-awaited cure of HBV infection.

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