

# Persistent Risk for Hepatocellular carcinoma in patients on antiviral treatment: A Need for HBV cure

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During the past 20 years, with the advent of highly effective antiviral drugs for Hepatitis B virus (HBV), we have witnessed successful viral suppression as well as the delay and prevention of progressive liver disease leading to cirrhosis and hepatocellular carcinoma (HCC).

In the past, reduced incidence of HCC with antiviral treatment has been well documented with lamivudine, entecavir and tenofovir [1-4]

Furthermore, prevention of recurrent HCC was observed by numerous investigators including ours following initial tumor ablation when patients received combined antiviral treatment [5-10].

Nonetheless, as reported previously, we are observing a persistent risk for HCC in patients who have maintained successful suppression of viral replication with undetectable serum HBV DNA and normal liver function, even in patients who have been on anti-HBV therapy for greater than 18 years [11]. The duration of anti-HBV treatment for these patients ranged from 9.3 to 18.4 years (highlighted). Patients remained with undetectable serum HBV DNA for 6.7-12.4 years (highlighted) before developing their first HCC. The result of the observation is shown in table 1 [11].

In addition, among patients who are on antiviral therapy and post first tumor ablation, some of them continue developing new HC or recurrent HCC several years (5-10 years) after the first HCC (personal communication). In most cases, however, continued antiviral therapy and additional tumor ablation has been successful and patients remain well on continued antiviral treatment.

These persistent risks for new and recurrent HCC among patients with successful control of HBV are attributed to the incomplete control of HBV, namely due to the presence of cccDNA in the host's hepatocytes.

While we are able to achieve a functional cure, a complete cure that is able to eliminate the cccDNA has not yet been possible. Therefore, even though HBV is not actively replicating, cccDNA remains in the nucleus of the hepatocytes and continues hepatocarcinogenic process including HBV and host DNA integration.

While we are grateful for the current management of HBV associated HCC, there is a desperate need for the drugs that can eradicate the virus.

Due to the complexity of HBV replication, it has not been easy. However, there are several potential strategies, some of which are already in clinical trials. Preventing the virus from entering the new hepatocytes is considered one of the important steps. Recently the entry receptor was discovered to be sodium taurocholate co-transporting

polypeptide (NTCP) [12,13]. And the entry inhibitors that target the NTCP receptor can prevent de novo infection of hepatocytes by the HBV. One of the entry inhibitor is called Myrcludex-B which is a myristoylated PreS1 peptide. Currently the Myrcludex-B is in phase II clinical trial [14]. Prevention of the replication of new HBV DNA from the pregenomic RNA has been successful with currently available nucleos(t)ide analogues. Enhancing the host innate immunity has been tried with small molecule agonists of toll-like receptors (TLR) and currently in clinical trials with TLR-7 and TLR-9. A therapeutic vaccine engineered to activate an HBV-specific T cell immune response is in early stage of the clinical trial. Also, direct-acting antivirals to target HBV has been in early stage of clinical trial. Little is known how

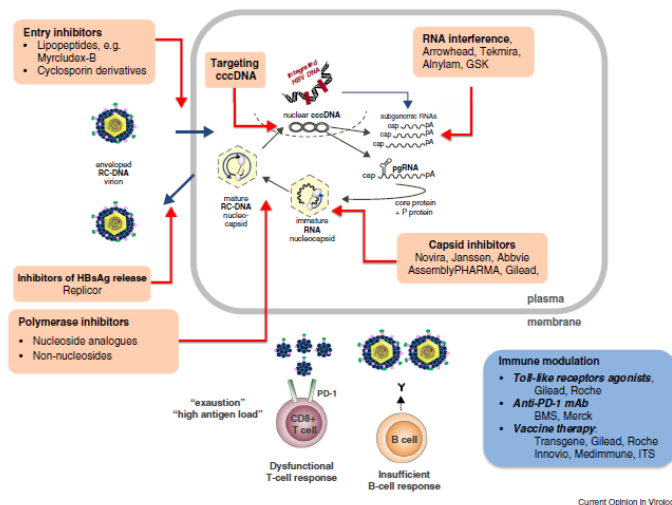


Figure 1. The landscape of HBV cure efforts.

All steps of the HBV replication cycle (virus entry, cccDNA formation, chromatinization and transcription, viral mRNAs, envelope protein secretion, core protein and the capsid, pol enzymatic activities), the intrahepatic innate immune responses and the deficient adaptive HBV specific B and T cell responses are currently being explored as potential new therapeutic targets (Lavrero et al. [15]).

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**Table 1.** Development of HCC in patients with cirrhosis on long-term antiviral therapy [11]\*

Pt #	Treatment Start	Anti-HBV treatment	HCC Diagnosis	Years on anti-HBV therapy at HCC diagnosis	Years with undetectable HBV DNA before HCC diagnosis	Size (cm) and site of HCC	HBV DNA at HCC diagnosis	Sex and Age (yr) at HCC Dx	Status
1	May 1998	LAM+TDF	February 2008	9.8	6.7	1.8x0.9 Lt	UD	76 F	alive
2	February 2004	TDF	June 2013	9.3	7.7	2.5 Lt	UD	57 M	dead
3	February 1996	TDF	July 2013	17.4	9.7	1.6x1.4 Rt	UD	73 M	alive
4	May 1996	LAM+TDF	October 2014	18.4	10.4	3.4 Rt	UD	74 M	alive
5	February 2000	TDF	April 2015	15.2	12.4	3.4x3.4 Rt	UD	62 M	alive

HCC: Hepatocellular Carcinoma, HBV: Hepatitis B Virus, 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 years): Average years with undetectable HBV DNA: median 9.7 years (6.7-12.4 years).

\*From *Minerva Gastroenterol Dietol* 2017; 63: 74-76. [11].

cccDNA is formed and regulated. Knowledge of this process would be crucial in the effort of HBV cure. Also direct targeting cccDNA is highly desired and it is hoped to become available in the near future

Recent update of the development of potential HBV cure drugs was recently presented by Levrero et al. [15] and Block et al. [16].

The lucidly illustrated “the landscape of HBV cure efforts” by Levrero et al. is shown below [16]. The chart clearly reveals the potential treatment strategies in the future (Figure 1).

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