# Anti-HBV/HCV Therapy as Secondary Hepatocellular Carcinoma Prevention

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Contributor: Saleh Alqahtani

Chronic infections with either hepatitis B or C virus (HBV or HCV) are among the most common risk factors for developing hepatocellular carcinoma (HCC). The hepatocarcinogenic potential of these viruses is mediated through a wide range of mechanisms, including the induction of chronic inflammation and oxidative stress and the deregulation of cellular pathways by viral proteins. Given the tumorigenic potential of HBV/HCV, it is no surprise that obtaining sustained viral suppression or eradication proves to be effective in preventing HCC.

HCC HBC HCV hepatocellular carcinoma prevention

## 1. Introduction

Primary liver cancer ranks as the sixth most common cancer globally and the third leading cause of cancer-related death [1]. Hepatocellular carcinoma (HCC) is by far the most dominant histological subtype of liver cancer, accounting for about four-fifths of all cases [2]. Globally, the incidence of HCC is increasing, with GLOBOCAN predicting an increase from 841,000 cases in 2018 to 1.4 million cases in 2040. In parallel, it also predicts increased mortality, from 780,000 deaths in 2018 to 1.3 million in 2040 [3]. Infections with hepatitis B (HBV) or C virus (HCV) represent the most significant risk factors for the development of HCC, followed by heavy alcohol consumption. Epidemiological data from 50 countries indicate that at least 60% of all HCC cases are attributable to either HBV or HCV [4]. Although virus-related HCC is prevalent worldwide, there are notable geographical variations in the proportion of patients with HCC associated with HCV versus those with HBV. Reflecting the incidence and distribution of these two hepatitis viruses, HBV-induced HCC is more common in countries with a low to middle human development index. In contrast, HCV is responsible for most virus-related HCC cases in regions with a higher developmental index [5].

## 2. Anti-HBV Therapy as Secondary HCC Prevention

An initiative to increase HBV awareness and treatment was commenced by the WHO and other health agencies in 2016, with the aim of eliminating viral hepatitis by 2030 [6]. High-impact interventions were planned, followed by studies that modeled the hepatitis epidemiology and covered aspects such as increasing sanitation, newborn mass vaccination against HBV, screening, and linkage to care of the infected populations. In patients with an untreated HBV infection, the incidence of HCC increases with the increase in the serum HBV DNA level. The advised first-line regimen for chronic hepatitis B is INF-α and tenofovir (TDF) and entecavir (ETV), which reduces hepatic

inflammation via viral suppression [7]. Randomized controlled trials and meta-analyses have demonstrated that administering IFN for a finite duration reduces the risk of HCC in treated compared to untreated patients [8][9][10][11]. In most patients, the continued administration of either NA has caused attenuation, but unfortunately not the eradication, of the HCC risk. The persistence of the HCC risk results from NA failing to eradicate cccDNA and the integrated sequences of the HBV DNA. This leads to the limited rates of serum HBsAg clearance in NA-treated patients, whereas the persistence of residual HCC risk has been recognized even in patients who do not show serum HBsAg following anti-viral therapy, specifically in those patients with HBsAg seroclearance occurring after 50 years of age [7]. As per a joint report of the American and European Societies of the Study of the Liver, the pragmatic goal of NA therapy is to achieve a functional HBV cure, defined as permanent HBsAg clearance with or without HBsAg seroconversion after treatment completion [12]. In real-world practice, however, durable suppression of serum HBV DNA coexisting with detectable HBsAg is the expected outcome of most patients treated with NA [13][14][15].

Several large-scale epidemiological studies identify high levels of HBV DNA in the serum as a critical risk factor for HCC development in chronic HBV cases [16][17]. The REVEAL-HBV study, which followed more than 3600 HBsAg carriers for an average of 11 years, revealed an independent dose-dependent relationship between a serum HBV DNA level above 2000 IU/mL and HCC development [18]. Other HBV-related factors associated with an increased risk for HCC include specific variations in the HBV DNA sequence, the HBV genotype, mutations in the basal core promoter, and levels of quantitative HBsAg [19][20][21]. Given the close relationship between these viral characteristics and the risk for HCC, HBV replication is a logical target for preventing HCC in this setting.

The first evidence for preventing HCC with anti-viral therapy in patients with chronic HBV comes from studies with older NAs, such as lamivudine and adefovir. Liaw et al. reported that lamivudine (with a mean treatment duration of 3 years) significantly reduced the HCC risk compared to a placebo (HCC incidence 3.9% vs. 7.4%; hazard ratio (HR): 0.49; $p = 0.047$) [22]. A meta-analysis, including more than 6800 patients, reported similar 4-year HCC rates in lamivudine-treated and control patients [23]. However, these first-generation NAs are no longer used, mainly due to suboptimal virological responses associated with HBV resistance, which is referred to as a low genetic resistance barrier. Currently, the treatment guidelines for HBV unanimously recommend the use of ETV or TDF [7][24]. These agents are well-tolerated and have a much higher genetic resistance barrier. Their long-term use induces sustained virological suppression in the vast majority of patients (>95%), along with histological improvements and regression of fibrosis and cirrhosis [25][26]. Furthermore, cohort and population studies carried out all across the world demonstrate that long-term use (>5 years) of either ETV or TDF prevents the development of HCC in the majority of patients [13][27][28][29]. A cohort study from Hong Kong including 1225 chronic HBV patients who were treated with ETV between 2002 and 2015 compared the HCC incidence among ETV-treated patients to the expected HCC incidence calculated with well-established HCC risk scores for a patient with chronic HBV [28]. The reduction in HCC risk achieved with ETV was significant starting from year six of treatment with a standardized incidence ratio of 0.68 (95% CI: 0.535–0.866). Notably, the HCC-preventing effect of ETV was seen in both cirrhotic and non-cirrhotic patients [28].

## 3. Anti-HCV Therapy for the Prevention of HCC

Like HBV, active HCV infection is central to the hepatocarcinogenic process. Thus, viral elimination is the goal for the secondary prevention of HCC. In this respect, studies from the IFN era convincingly demonstrated that an SVR following IFN-based therapy reduced the risk for HCC to 0.5–1% per year (vs. 2–8% per year in untreated chronic HCV patients with cirrhosis) [30][31]. Unfortunately, an SVR to IFN-based therapy was only achieved in half of the patients. Furthermore, IFN toxicity limits its use in patients with cirrhosis.

During the last decade, IFN-free DAA drugs have revolutionized the HCV treatment landscape. An SVR is obtained with these agents in >95% of patients, and most show improvements in liver fibrosis and liver function and a reduction in portal hypertension [32]. Moreover, these agents have an excellent safety profile and minimum adverse effects and can be used in patients with decompensated liver disease. Achieving SVR is proven to be beneficial at all stages of fibrosis, including in patients with decompensated cirrhosis; however, the elimination of risk in HCC in patients with decompensated cirrhosis cannot be achieved; therefore, surveillance for HCC is extremely important for patients with advanced fibrosis or cirrhosis after achieving SVR. [33]. Bruno et al. discuss the ‘point of no return’, since disturbances to the liver architecture in decompensated cirrhosis tend to have a poor prognosis that leads to the development of HCC [34]. Box 1 provides the summary of treatment options for viral hepatitis that are under consideration or development aimed towards HCC prevention.

**Box 1.** Summary of viral hepatitis treatment options under current consideration or development aimed towards HCC prevention.

- Current international treatment guidelines recommend ETV or TDF as equal first-line treatment options for chronic HBV.
- Pegylated-IFN-α-based therapies in selected patients may cure HBV infection; however, it can be associated with significant severe side effects.
- Novel agents under investigation include those that block HBV entry into hepatocytes, target cccDNA using CRISPR technology or epigenetic silencing, promote the degradation of viral RNA with RNA interference molecules, or disrupt the production and secretion of viral proteins.
- Recent advances in understanding HBV–host interactions highlight how exploiting host-targeting may lead to a viral cure strategy.

## 4. Conclusions

Chronic infections with HBV or HCV are the dominant causes of HCC globally. The growing body of evidence on the direct and indirect hepatocarcinogenic effects of these viruses underscores the importance of viral eradication

as a secondary prevention measure for HCC. Over the last years, a long list of retrospective and prospective studies has convincingly demonstrated the HCC-preventive effects of anti-viral therapy. As far as HBV-related carcinogenesis is concerned, there is overwhelming evidence for the positive impact of the pharmacological suppression of HBV on the risk of HCC. However, even patients who achieve cure following anti-HBV or anti-HCV therapy can still have a persistent residual HCC risk. In this respect, the implementation of dedicated HCC surveillance programs for those patients with the highest HCC risk remains essential. Research continues to be invested in developing novel anti-HBV or anti-HCV therapeutic modalities that could eliminate the HCC risk and develop a predictive model of HCC risk and the best surveillance strategies.

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