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# Impact of expanding hepatitis B treatment guidelines: A modelling and economic impact analysis

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## Summary

**Background:** Antiviral treatment in patients with chronic hepatitis B (CHB) may decrease the risk of hepatocellular carcinoma (HCC) and death. However, only 2.2% of CHB patients receive antiviral treatment globally. The complexity and strictness of the current clinical practice guidelines may limit expanding the treatment coverage for CHB.

**Aims:** We examined the impact of expanding treatment criteria on future disease burden in Korea, a hepatitis B virus (HBV) endemic country with high diagnostic rates (74.2%).

**Materials:** Dynamic country-level data were used to estimate the HCC incidence, overall mortality and economic impact of three incremental scenarios compared to the base case in Korea through 2035.

**Results:** In 2020, 1,409,000 CHB cases were estimated, with the majority born before 1995. All scenarios assumed treating 70% of eligible individuals. The first scenario removes viral load restrictions in cirrhotic patients, which would avert 13,000 cases of HCC and save 11,800 lives. The second scenario, lowering the alanine aminotransferase (ALT) level restriction to the upper limit of the normal in non-cirrhotic patients, would avert 26,700 cases of HCC and save 23,300 lives. The last scenario removes the restriction by ALT and HBeAg in treating non-cirrhotic individuals with a viral load of ≥2000 IU/ml, which would avert 43,300 cases of HCC and save 37,000 lives. All scenarios were highly cost-effective.

**Conclusions:** Simplifying and expanding treatment eligibility for CHB would save many lives and be highly cost-effective when combined with high diagnostic rates. These dynamic country-level data may provide new insights for their global application.

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## 1 | INTRODUCTION

Hepatitis B virus (HBV) chronically infects approximately 292 million individuals globally and is a leading cause of liver cirrhosis, hepatocellular carcinoma (HCC) and liver-related death.[1] Chronic infection with HBV (CHB) caused 820,000 deaths in 2019, surpassing the number of deaths caused by human immunodeficiency virus ($n$ = 690,000) or hepatitis C virus infection ($n$ = 290,000).[2]

The World Health Organisation (WHO) aims to eliminate HBV as a public health threat and has set goals to reduce the number of individuals dying of HBV infection by 65% by 2030.[3] Testing and treatment are the primary means of reducing HBV-related deaths in chronically infected individuals. Blood tests for the HBV surface antigen (HBsAg) have high sensitivity and specificity and have been developed for use at the point of care. Furthermore, the wide availability of effective antiviral treatments for CHB infection offers a great potential for significantly reducing HBV-related mortality and HCC incidence. Nonetheless, only 2.2% (6.6 million) of individuals with CHB infection received treatment in 2019, which is far from the target of the WHO (treating 80% of eligible patients by 2030).[3] According to the Polaris Observatory, not a single country is on track to achieve the HBV mortality goal of the WHO by 2030.[4]

A major challenge in expanding the treatment coverage for CHB infection is the complexity and strictness of the current clinical practice guidelines. Most current guidelines for CHB infection recommend initiating antiviral treatments after identifying hepatic necroinflammation through liver biopsy or elevated serum levels of both alanine aminotransferase (ALT) and HBV DNA as well as considering the patient's age, HBeAg status and presence of cirrhosis.[5–9] Accordingly, only few individuals with CHB infection (12%–25%) were identified to be eligible for antiviral treatment.[3]

The Republic of Korea is an HBV endemic country with a prevalence of approximately 4% among adults.[10] Korea has been at the forefront of HBV prevention measures, implementing national vaccine programmes in 1995.[11] Consequently, the generation born after 1995 will face a significantly lower burden of HBV as they age; however, there remains a substantial population born prior to the implementation of national vaccination who remain at risk of progression to cirrhosis, HCC and death. Korea has a national screening program for HBV, leading to a high diagnostic rate (74.2%).[12] The treatment guidelines and reimbursement criteria for CHB infection in Korea are similar to many other national and international guidelines. Accordingly, only approximately 18.6% (n = 262,000) of the total estimated individuals with CHB infection (n = 1,409,000) received antiviral treatment in 2019. However, many recent cohort studies have consistently suggested the promising impact of expanding treatment indications on reducing the incidence of HCC and overall mortality among those with CHB infection who are not currently eligible for treatment.[13–18]

Therefore, this study was designed to examine the impact of expanding treatment criteria on the future disease burden caused by HBV in Korea at the population level through modelling. Moreover, this study measured the cost-effectiveness of those possible treatment expansion scenarios. Although this is a country-specific study, estimating the trends in HCC incidence and overall mortality by expanding treatment criteria for CHB infection in Korea would offer new insights for its global application.

## 2 | MATERIALS AND METHODS

### 2.1 | PRoGReSs model

A fully dynamic transmission and Markov disease burden model was populated with historical, Korean-specific background population, mortality and epidemiological HBV data. The model tracked the distribution of HBsAg across sex, age (1-year age cohorts), year, disease stage (i.e., acute, chronic, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and death), and viral load (categorical). The PRoGReSs model has been previously described in detail.[1] Age- and sex-specific progression rates, including spontaneous clearance and fulminant infection, advanced individuals through the disease stages over time (Appendix S1). The disease progression rates for males were increased to consider the predominance of genotype C HBV and comorbidities and match sex-specific cancer registry data in Korea (Appendix S1). Horizontal and vertical transmission of disease was estimated considering historical and current prophylaxis measures. Korean-specific historical data inputs included HBsAg prevalence by age, HBeAg prevalence among pregnant women, and prophylaxis coverage rates by year, annual number of liver transplants, treatment and diagnostic rates (Table 1).

### 2.2 | Characteristics of the Korean HBV population

A literature review was conducted to gather all available epidemiological data. After this was complete, two meetings with a panel of local clinical and research experts were conducted to build consensus on the most accurate input data for the PRoGReSs model while also providing additional studies and data points. Korean-specific background data from the 2019 United Nation's Department of Economic and Social Affairs (Population Division) were used for population and mortality by sex and 1-year age cohort for every year from 1900 to 2035.[30] The most recent published prevalence estimate revealed an overall prevalence of 2.9% among all ages and approximately 4% among adults.[10] To estimate the age- and sex-specific prevalence, the results of the Korean National Health and Nutrition Examination Survey 2014–2018 were averaged.[19] For the age groups that were excluded from the survey (<10 years), the prevalence was calculated from the model using the historical prophylaxis measures, prevalence of HBsAg+ among pregnant women, and births by age of mother, while considering mother-to-child transmission, horizontal transmission and mortality. For older age cohorts (i.e., 75–79, 80–84 and 85+ years), HBV-related mortality and background mortality were used to estimate the decline in prevalence in these age groups. Using a published study, it was

**TABLE 1** Model inputs and assumptions

| Category | Item | Year | Value | Source |
|---|---|---|---|---|
| Disease burden model parameters | HBsAg+ prevalence rate | 2016 | 2.9% | [10] |
| | HBsAg+ prevalence—age and sex distribution | 2014–2018 | - | [19] |
| | HBeAg+ among HBsAg+ WoCBA | 2002 | 31.8% | [20] |
| | Viral load ≥20,000 IU/ml among HBeAg+ | 2002–2008 | 90% | [21] |
| | Viral load ≥20,000 IU/ml among HBeAg− | 2002–2008 | 13% | [21] |
| | Total diagnosed | 2020 | 1,125,400 | [12], Expert input |
| | Newly diagnosed | 2016 | 19,600 | Expert input |
| | Total treated | 2019 | 262,000 | Expert input |
| | Historical Treatment | 1993–2016 | - | [22], Expert input |
| | Annual liver transplants | 2019 | 1579 | [23] |
| | Liver transplants due to HBV | 2008–2011 | 75% | [24] |
| | Timely birth dose coverage (all births) | 2019 | 92% | [25] |
| | HepB3 dose coverage (all births) | 2019 | 98% | [25] |
| | HBIG coverage (infants born to HBsAg+) | 2018 | 100% | Expert input |
| | Antiviral treatment of eligible pregnant women | 2020 | 40% | Expert input |
| Economic modelling inputs | Disability weight—chronic HBV | | 0 | - |
| | Disability weight—compensated cirrhosis | | 0 | - |
| | Disability weight—decompensated cirrhosis | | 0.178 | [26] |
| | Disability weight—HCC | | 0.466 | [26] |
| | Disability weight—liver transplant | | 0.024 | [26] |
| | GNI per capita (US$) | 2019 | 33,790 | [27] |
| | HIRA Threshold (US$) | 2019 | 20,000 | [28] |
| | Discounting | | 4.5% | Insurance database |
| Screening and lab costs per test (US$) | HBsAg | 2017 | 2.41 | Insurance database |
| | HBeAg | 2017 | 3.48 | Insurance database |
| | Viral load testing | 2017 | 23.54 | Insurance database |
| | ALT testing | 2017 | 1.65 | Insurance database |
| | Fibroscan | 2017 | 71.95 | Insurance database |
| | Comprehensive blood panel | 2017 | 11.67 | Insurance database |
| | IgG anti-HAV | 2017 | 13.89 | Insurance database |
| | Anti-HCV | 2017 | 3.91 | Insurance database |
| | Ultrasound | 2017 | 126.77 | Insurance database |
| | AFP | 2017 | 4.10 | Insurance database |
| | Quantification HBsAg | 2017 | 10.98 | Insurance database |
| Treatment costs (US$) | Treatment (annual) | 2017 | 895 | Insurance database |

(Continues)

TABLE 1 (Continued)

| Category | Item | Year | Value | Source |
|---|---|---|---|---|
| Annual health state costs (US$) | Chronic HBV | 2017 | 1627 | 29 |
| | Compensated cirrhosis | 2017 | 3238 | 29 |
| | Decompensated cirrhosis | 2017 | 8372 | 29 |
| | Hepatocellular carcinoma | 2017 | 17,491 | 29 |
| | Liver transplant | 2017 | 109,172 | 29 |
| | Post-liver transplant | 2017 | 11,834 | 29 |

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; anti-HAV, hepatitis A virus antibody; anti-HCV, hepatitis C virus antibody; GNI, gross national income; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HepB3, three doses of hepatitis B vaccination administered; HIRA, Health Insurance Review and Assessment Service; WoCBA, women of childbearing age.

estimated that 31.8% of HBsAg+ pregnant women were HBeAg+.[20] High viral load in the general population, defined as ≥20,000 IU/ml, was assumed to be present in 90% of HBeAg+ individuals and 13% of HBeAg- individuals.[21]

## 2.3 | Historical prevention and care paradigm

The PRoGReSs model considered the impact of treatment and prevention on the transmission and disease burden over time.

Previously, it was estimated that 3% of pregnant women eligible for antiviral treatment, as a method of prophylaxis, were treated. This number was estimated to have increased to 40% by 2020, with coverage levels approaching 100% in university hospitals.

From 2002 to 2008, 74.2% of individuals over the age of 30 years enrolled in the cancer screening program at the National Cancer Centre were aware of their HBV status.[12] Based on expert input, because of the ageing population and robust screening programmes, this proportion has increased to 80% by 2020, representing 1.21 million infected individuals living in Korea including immigrants. To reach this 2020 estimate, it was assumed that 19,600 individuals with CHB were newly diagnosed annually. Historical treatment data were available from 1999 to 2013,[22] with expert input estimating that by 2020, 262,000 individuals with CHB were treated with antiviral drugs.

Current Korean guidelines and National Health Insurance Services recommend treating individuals with decompensated cirrhosis if HBV DNA is detectable; individuals with compensated cirrhosis if HBV DNA is ≥2000 IU/ml; and non-cirrhotic immune-active patients defined as ALT levels more than twice the upper limit of the normal range by a local laboratory (ULN; 40 IU/ml for males and females) or significant fibrosis or inflammation in addition to viral load requirements of ≥2000 IU/ml for HBeAg- individuals and ≥ 20,000 IU/ml for HBeAg+ individuals.[7] Based on the current eligibility, it was estimated that 25% of patients with CHB, excluding individuals who have progressed to cirrhosis or later, are currently eligible for treatment (Table 2).[17,31] Annual liver transplantation data were available from 2005 to 2019 from the Korean Network of Organ Sharing database. Based on HCC data, it was assumed that 75% of all transplants were due to HBV.[24]

## 2.4 | Scenario development and assessment

The PRoGReSs model was populated and calibrated to the aforementioned data inputs. Then, multiple scenarios were developed to examine the future impact of different treatment rates and eligibility requirements compared with the current treatment paradigm (Table 2). Furthermore, an economic analysis was performed to examine the cost-effectiveness of all scenarios.

- **Base Scenario**: This scenario was designed to measure the future impact of inaction on the disease burden and economy of maintaining the current eligibility requirements and treatment coverage. The estimated annual number of newly diagnosed patients ($n$ = 19,600) and the total number of treated patients ($n$ = 262,000) in 2020 were assumed to be maintained in the future.
- **Scenario No. 1 (Base scenario + Removing viral load restriction for the cirrhotics)**: This scenario expands the treatment criteria of current guidelines to remove viral load restriction for the treatment of the cirrhotic patients, and increasing the treatment coverage to 70% of the eligible individuals by 2030 (Figure 1).
- **Scenarios No. 2 (Scenario No. 1 + Lowering ALT restriction to ≥ ULN for the non-cirrhotic CHB)**: This scenario examines the impact of maintaining the current HBeAg status and viral load guidelines but lowering the ALT restriction from 2× ULN to ULN for the treatment and including Scenario No. 1. This scenario assumed that the eligibility of the CHB population would increase from 25% to 36% based on the aforementioned studies applied to the infected Korean population (Figure 1).
- **Scenario No. 3 (Scenario No. 2 + Removing ALT restriction and treating HBV DNA ≥ 2000 IU/ml)**: This scenario examines the impact of eliminating both the HBeAg status and ALT restrictions to treatment and instead treating 70% of those with a viral load ≥2000 IU/ml and including Scenario No. 2 (Figure 1). This scenario assumed that the eligibility of the CHB population would increase from 25% to 54% based on the aforementioned studies applied to the infected Korean population.

**TABLE 2** Scenario inputs and cost-effectiveness outcomes (2020–2035)

| Scenarios | Treatment eligibility | | Total no. of patients treated in 2030[b] | Cost effectiveness | | |
|---|---|---|---|---|---|---|
| | CHB population | Cirrhotic population | | DALYs averted | Incremental cumulative direct costs (US$) | ICER US$/DALY[a] |
| Base: Maintaining current eligibility requirements and treatment coverage | 25% | 88% | 262,000 | - | - | - |
| No. 1: Base scenario + Removing viral load restriction for the cirrhotics | 25% | 100% | 330,000 | 179,833 | 168 | 932 |
| No. 2: Scenario No. 1 +lowering ALT restriction to ≥ULN for non-cirrhotic CHB | 36% | 100% | 450,000 | 355,675 | 486 | 1367 |
| No. 3: Scenario No. 2 +removing ALT restriction and treating HBV DNA ≥2000 IU/mL | 54% | 100% | 676,000 | 559,994 | 1446 | 2583 |

Abbreviations: ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBV, hepatitis B virus; DALYs, disability-adjusted life years; ICER, incremental cost-effectiveness ratio; ULN, upper limit of normal.

[a]The willingness-to-pay threshold by the Korean government in 2019 was US$20,000/DALY.

[b]Scenarios Nos. 1–3 assumed to treat 70% of eligible individuals in each.

In all scenarios, it was assumed that treatment eligibility was between the ages of 15 and 85 years and that treatment efficacy was 90% by virological response. Owing to the high prophylaxis rates in Korea, the interventions analysed excluded an expansion of prevention efforts and instead assumed the continuation of current rates into the future.

### 2.5 | Uncertainty analysis

The uncertainty intervals (UIs) were calculated via a sensitivity analysis using Crystal Ball (release 11.1.2.3.500). β-PERT distributions were used for all uncertain inputs.[32] A Monte Carlo simulation estimated 95% UIs, with 100 simulations run per scenario. The UIs were calculated based on range inputs for prevalence, transmission, transition and mortality rates (Appendix S1).[1,33]

### 2.6 | Economic impact analysis

Cost data were collected using the same process as that for the epidemiological inputs for the model. Direct cost inputs were collected, including healthcare, screening, prophylaxis, diagnostics and treatment from the reimbursement price list from the National Health Insurance Service (NHIS) of the South Korean government and then weighted by the experts (Table 1). The model estimated the annual disability-adjusted life years (DALYs) for each scenario to estimate incremental cost-effectiveness ratios (ICERs). The current Korea Health Insurance Review and Assessment Service (HIRA) guidelines stipulate that those interventions with a cost per quality-adjusted life year gained under US dollars $20,000 are deemed cost-effective.[28]

## 3 | RESULTS

### 3.1 | Disease burden

The model estimated that in 2020, 1,409,000 (UI: 1,292,000–1,523,000) cases were HBsAg+, a prevalence rate of 2.75%. Due to the prophylaxis efforts and mortality, this number was expected to decrease to 1,210,000 (UI: 994,000–1,206,000), a prevalence rate of 2.37%, by 2030. Among the total infected population, the model estimated that 74% were 35–64 years of age. In 2020, approximately 1280 (UI: 720–2390) incident cases had decompensated cirrhosis, approximately 9500 (UI: 5460–11,740) incident cases had HCC, and approximately 10,000 (UI: 6530–11,890) had liver-related deaths. The prevalence of HBsAg-positivity was estimated to be less than 0.1% among infants and 0.1% among 5-year-old children in 2020.

Four scenarios were developed to examine the future impact of different treatment rates and eligibility requirements on disease burden caused by HBV in Korea between 2020 and 2035, as described in the Methods section (Table 2). The total estimated number of individuals on antiviral treatment incrementally increased from the Base Scenario to Scenario No. 3 (Table 2 and Figure 1). The future impact of the four scenarios at a country level between 2020 and 2035 was estimated using the PRoGReSs model, as follows (Table 2 and Figure 2).

- **Base Scenario**: If the current treatment and diagnostic rates were continued into the future, the estimated total number of treated patients was assumed to remain constant in the future ($n$ = 262,000). The prevalence of HBsAg positivity was projected to continue to decline in children and reach less than 0.1% in both infants and 5-year-old children by 2030. The total number

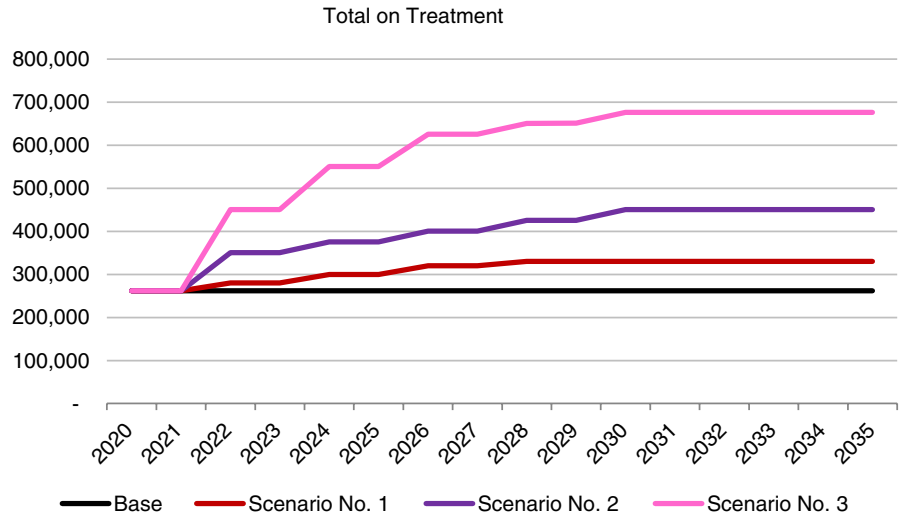


**FIGURE 1** Estimated number of individuals on treatment by scenarios in Korea (2020–2035). Base Scenario: Maintaining the current eligibility requirements and treatment coverage. The estimated total number of treated patients ($n$ = 262,000) in 2020 were assumed to be maintained in the future. Scenario No. 1: Expanding the treatment criteria of current guidelines to remove viral load restriction for the treatment of the cirrhotic patients. Treatment increases stepwise to a maximum of 330,000 individuals in 2030. Scenarios No. 2: Lowering the ALT restriction from 2 X ULN to ULN for the treatment and including Scenario No. 1. Treatment increases stepwise to a maximum of 450,000 individuals in 2030. Scenario No. 3: Eliminating both the HBeAg status and ALT restrictions to treatment and treating those with a viral load ≥2000 IU/ml and including Scenario No. 2. Treatment increases stepwise to a maximum of 676,000 individuals in 2030.

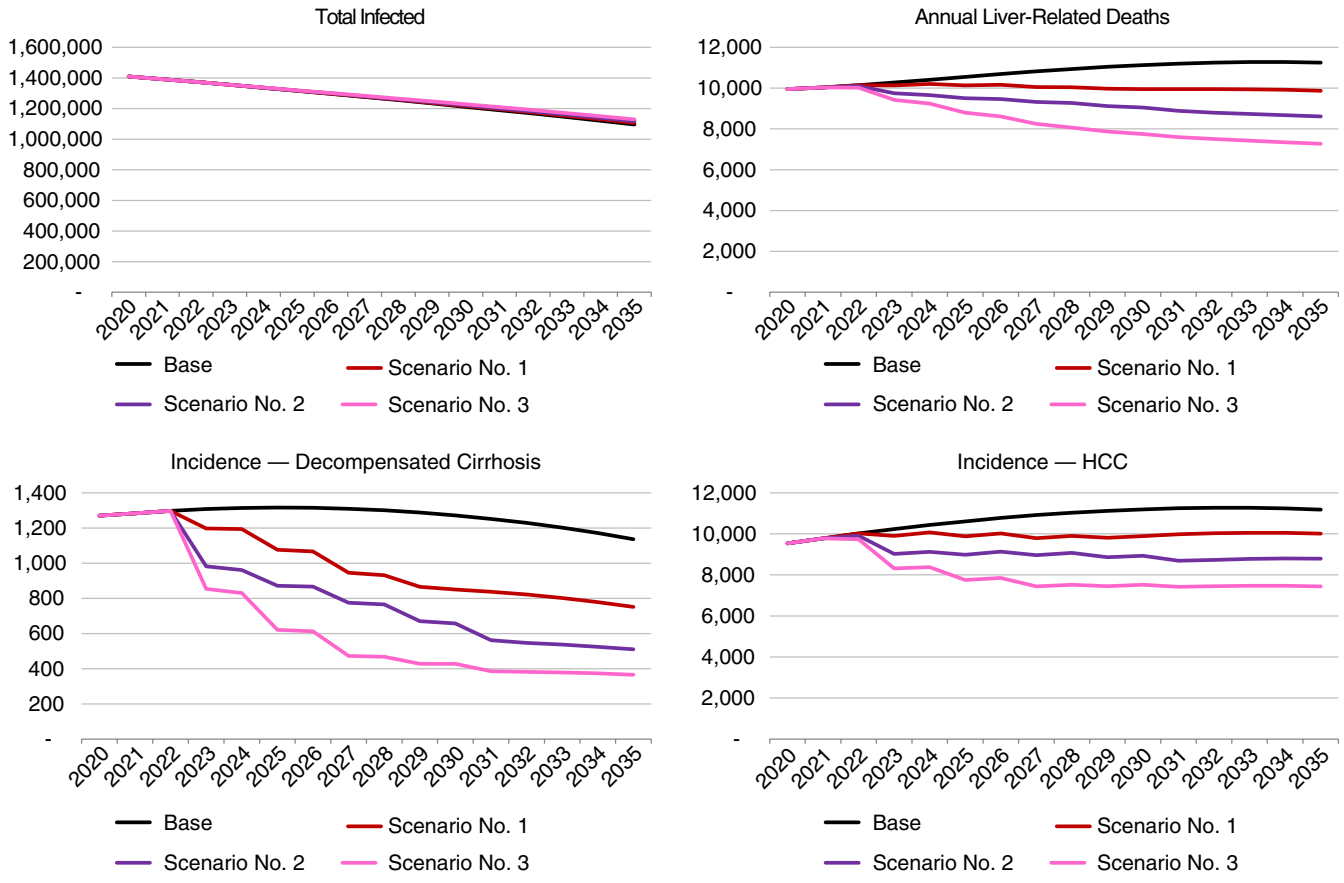


**FIGURE 2** Estimated disease burden of hepatitis B virus by scenarios in Korea (2020–2035).

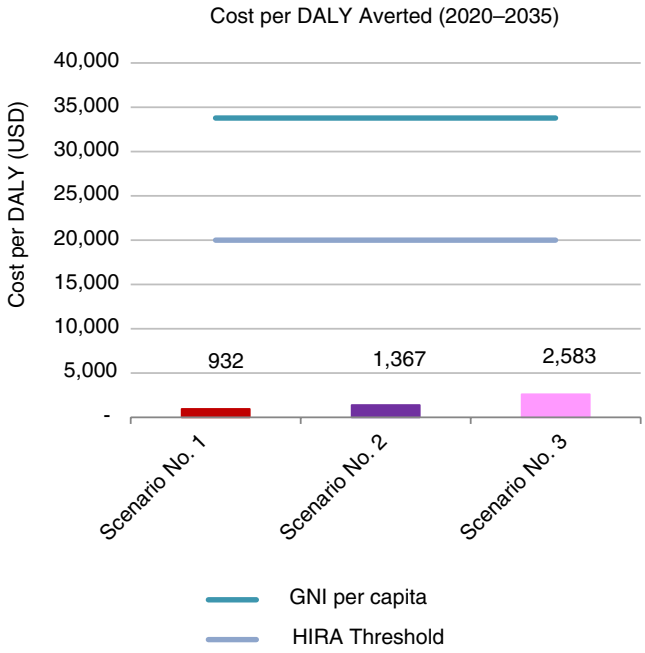


**FIGURE 3** Estimated cost per disability-adjusted life year averted by scenarios in Korea (2020–2035). DALY, disability-adjusted life years; GNI, gross national income; HIRA, Korea Health Insurance Review and Assessment Service. The willingness-to-pay threshold by the Korean government (Health Insurance Review and Assessment Service, HIRA) in 2019 was US$20,000/DALY.

of infections was projected to decline by 22% to 1,095,700 (UI: 898,000–1,206,000) by 2035. However, the incidence of decompensated cirrhosis was estimated to increase by 11%, HCC by 17% and liver-related deaths by 13%, as the infected population advances in disease state and age between 2020 and 2035.

- **Scenario No. 1 (Base scenario + Removing viral load restriction for the cirrhotics)**: This scenario assumed that 330,000 would be treated by 2028. Increasing and extending treatment slowed the advancement of the disease, resulting in a 34% reduction in the incidence of decompensated cirrhosis, 10% reduction in the incidence of HCC, and 12% reduction in liver-related deaths in 2035 compared to the Base Scenario. Consequently, the projected number of total infections by 2035 slightly increased as infected individuals live longer. Compared with the Base Scenario, this scenario averted 4300 (UI: 3200–6100) cases of decompensated cirrhosis and 13,000 (UI: 8800–14,400) cases of HCC and saved 11,800 (UI: 10,800–12,300) lives.
- **Scenarios No. 2 (Scenario No. 1 + Lowering ALT restriction to ≥ ULN for the non-cirrhotic CHB)**: With more relaxed treatment criteria, more patients could be treated over time, reaching a maximum of 450,000 by 2030. This scenario resulted in a 55% reduction in the incidence of decompensated cirrhosis, 21% reduction in the incidence of HCC, and 23% reduction in liver-related deaths in 2035 compared with the Base Scenario. Compared with the Base Scenario, this scenario averted 7200 (UI: 4700–12,100) cases of decompensated cirrhosis and 26,700 (UI: 17,000–30,500) cases of HCC and saved 23,300 (UI: 18,800–24,800) lives.
- **Scenario No. 3 (Scenario No. 2 + Removing ALT and HBeAg restriction, and treating HBV DNA ≥ 2000 IU/ml)**: By further relaxing the treatment criteria, the total number of individuals treated increased to 676,000 by 2030. Compared to the Base Scenario, this scenario resulted in a 68% reduction in the incidence of decompensated cirrhosis, 33% reduction in the incidence of HCC, and 35% reduction in liver-related deaths in 2035. This scenario averted 9800 (UI: 5900–18,700) cases of decompensated cirrhosis and 43,300 (UI: 26,000–51,600) cases of HCC and saved 37,000 (UI 28,200–42,300) lives compared to the Base Scenario.

### 3.2 | Economic burden

Compared with the base scenario, all scenarios (Scenario Nos. 1–3) were determined to be highly cost-effective through 2035, defined as the cost per DALY averted being far less than the Korean threshold for willingness-to-pay by HIRA guidelines (US$20,000 per DALY), from a healthcare system perspective considering direct cost only (Table 2 and Figure 3). While Scenario No. 1 was found to be the most cost-effective with an ICER of US$932, Scenario Nos. 2 and 3 were found to have ICERs of only US$1367 and US$2583, respectively, which were far below the Korean threshold for willingness-to-pay. Given the high cost-effectiveness from a healthcare system perspective considering direct cost only and the high number of death averted by Scenario Nos. 1–3, cost-effectiveness analysis from a societal perspective considering productivity loss by premature death was not conducted.

We further examined the impact of treating three different age groups in Scenario No. 3; those with age ≥ 15 years (base), ≥30 years, and ≥ 40 years. There were more early-stage outcomes averted in treating older population. Thus, the ICERs were $2583, $2256 and $1908 for treating those with age ≥ 15 years, ≥30 years, and ≥ 40 years, respectively, and all were far below the Korean threshold for willingness-to-pay.

## 4 | DISCUSSION

Testing and treatment are the two primary means of reducing HBV-related deaths in the patients who already have the infection. Although the availability of effective treatment for chronic hepatitis B infection offer great potential for eliminating CHB as public health threats, only 6.6 million (2.2% coverage) are receiving the treatment in 2019 globally.[2] A collective effort is needed to address gaps in the coverage of testing and treatment of hepatitis B. In these regards, Korea has a unique environment to estimate the impact of expanding treatment coverage for CHB, including the high prevalence of CHB among adults (4%), high diagnostic rate (74.2%) and the presence of strong local guidelines and reimbursement criteria for the antiviral treatment by nationwide compulsory health insurance system.

Despite the robust universal vaccination program and the prevention of mother-to-child transmission campaigns, a large population

was infected before these campaigns, who continue to be at risk of HBV-related morbidity and mortality. If the current treatment rates were continued through 2035, incident cases of HCC and liver-related deaths are expected to increase, with a slight decrease in the incident cases of decompensated cirrhosis. In contrast, all three scenarios of incremental treatment expansion resulted in reductions in HBV-related morbidity and mortality and were found to be highly cost-effective. From a healthcare system perspective, considering direct cost only, treatment expansion to 70% of eligible individuals and eliminating the viral load restrictions for individuals with cirrhosis (Scenario No. 1) would result in the most cost-effective scenario with an ICER of US $932 per DALY, but would only save approximately 11,800 lives. Meanwhile, the most aggressive scenario modelled (Scenario No. 3) would cost significantly more (US$2583 per DALY), but would save the lives of over three times as many people (37,000 deaths averted) and would be still highly cost-effective, incurring costs far below the willingness-to-pay threshold in Korea (US$20,000 per DALY).

In 2016, the World Health Assembly passed the Global Health Sector Strategy on Viral Hepatitis, which aims to eliminate HBV and HCV by 2030.[34] The targets include 90% global coverage of three-dose infant vaccination by 2020; timely birth-dose vaccination in 50% of infants by 2020 and in 90% by 2030; and prevalence in children aged 5 years of 1% by 2020 and 0·1% by 2030. The global prevention target for HBV has been met, as measured by the prevalence of hepatitis B surface antigen to 0.9% in 2019 among children younger than 5 years.[2] In this study, the prevalence of HBsAg-positivity in Korea was estimated to be even lower than the global estimate (0.1% among 5-year-old children in 2020).

WHO's prevention targets by 2030 included diagnosis of 90% of people infected with HBV and antiviral treatment of 80% of those diagnosed and eligible for treatment. However, access to diagnosis and treatment for HBV remains limited. In 2019, only 10% of individuals with CHB infection were diagnosed. Even among those diagnosed with CHB infection, only 22% received treatment.[2] Even in high-resource countries, substantial gaps exist between the evaluation and treatment of patients with CHB infection. For example, in the United States, only half of patients with CHB infection with private insurance received complete evaluation for treatment eligibility (measurement of ALT, HBV DNA and HBeAg). Among patients with an adequate evaluation to determine treatment eligibility, only 11.2% and 13.9% were eligible for treatment according to the AASLD and EASL guidelines, respectively.[35]

In a recent systematic review and meta-analysis, among 145,789 patients with CHB infection from 162 studies, a pooled estimate of treatment eligibility according to the WHO or any other guidelines was only 19% (95% CI, 18%–20%).[36] In this study, 18.6% ($n = 262,000$) of the total estimated individuals with CHB ($n = 1,409,000$) received antiviral treatment in 2019, suggesting that most treatment-eligible patients with CHB infection in Korea are actually being treated. Nonetheless, the crude incidence of HCC and mortality caused by HCC has not significantly decreased since 1999.[22] Furthermore, the proportions of patients who developed HCC outside treatment recommendations according to the APASL, AASLD and EASL criteria were as high as 64.0%, 46.0% and 33.5%, respectively.[13]

These data suggest that the complexity and strictness of current guidelines in defining treatment eligibility is a serious challenge in accomplishing the WHO's target to eliminate HBV by 2030. Although the expansion of treatment criteria in CHB patients is highly controversial,[37] many Korean studies have suggested that expanding treatment indications may significantly reduce the incidence of HCC and mortality among those with CHB infection not currently eligible for treatment.[13–18,38] In fact, the results of this study are consistent with those of the previous global modelling studies, which suggested that scaling up the coverage of treatment to 80% of eligible individuals with CHB infection is essential to achieve a target of a 65% reduction in mortality by HBV.[39]

While the risk of treatment-emergent adverse events is low, as the number of individuals treated increases, the absolute number of individuals experiencing treatment-emergent adverse events will also increase. While this is an important area to explore, it is beyond the scope of the current study and may have to be studied separately. In this particular study, we have focused on the difference in effectiveness between the treated group and the untreated group which represents a gain in terms of disease burden, but not the effectiveness for each treatment group. We have considered that ETV, TDF and TAF are the drugs currently recommended for the first-line antiviral treatment in patients with CHB because of their high antiviral potency and negligible risk of drug-resistance during long-term treatment. In fact, a recent study from Korea which used ETV, TDF and TAF in equal proportion, has demonstrated that expanding the treatment criteria to immune-tolerant patients with CHB infection showed extremely high cost-effectiveness with a negative ICER value (a 'dominant' strategy) by preventing premature deaths and productivity loss of economically active patients.[29] The results of the one-way sensitivity analyses indicated that the most influential parameters on the cost-effectiveness of the treatment in the immune tolerant-phase were those related to the risk of HCC (serum HBV DNA levels, platelet counts and age at treatment initiation) and the price of antiviral treatments. As the price of antiviral treatments decreases with the introduction of generic products of ETV and TDF in recent years,[40–42] earlier treatment initiation could be shown to be more cost-effective even after considering the risk of treatment-emergent adverse events, in the young patient groups currently considered to be not cost-effective. Moreover, given that the patients with high-level viremia are contagious, treating these patients would bring collective benefit to society through the reduction of transmission.

This study has several limitations. First, the PRoGReSs model is a population-based model at the national level. Thus, it will not specify any specific regions that may have higher or lower hepatitis B burdens and access to prophylaxis or treatment. Second, while the risk of treatment-emergent adverse events is low, as the number of individuals treated increases, the absolute number of individuals experiencing these events will also increase. Third, while it has been shown that long-term treatment can result in the regression of fibrosis, the model assumes that successful treatment would halt progression.[43] The exceptions to this assumption in the model are

the transition probabilities to HCC, which are reduced but not eliminated.[43–46] Thus, the model could be underestimating the impact of treatment. Fourth, cost-effectiveness analysis from a societal perspective considering productivity loss by premature death was not conducted. However, given the high cost-effectiveness from a healthcare system perspective considering direct cost only and the high number of death averted by Scenario Nos. 1–3, we expect that the cost-effectiveness could be further improved from a societal perspective, as shown by a recent study.[29] Lastly, the model does not consider any possible future advances in treatment options, which may or may not be available by 2035.

While the cost-effectiveness of the presented interventions would need to be conducted, particularly in countries with a low hepatitis B burden and high cost of diagnostics, the future reductions in HBV-related morbidity and mortality by percentage are expected to be similar globally. A recent publication from Korea[29] showed that the strategy of treating immune tolerant phase CHB would be cost-effective at about 20–50% level of the original products' price in the United States and the United Kingdom, where generic products are available at low prices. Although the antiviral treatment using original drugs in the immune tolerant phase may not be cost-effective in several countries, it needs to be considered that cost-effectiveness could be improved through a decrease in drug costs in the near future, and the cost of antiviral treatment should no longer be the main obstacle.

In conclusion, relaxing the current restrictions for antiviral treatment and subsequent increase in treatment coverage in patients with CHB, tens of thousands of Korean lives could be saved by 2035 in a highly cost-effective manner. The earlier treatment strategy is being increasingly supported by the accumulating data on the long-term efficacy and safety of anti-HBV drugs with high potency, high genetic barrier to resistance, and decreasing cost. Therefore, simplifying and expanding treatment eligibility for CHB would save many lives and be highly cost-effective when combined with high diagnostic rates. These dynamic country-level data may provide new insights for their global application.

## AUTHOR CONTRIBUTIONS

**Young-Suk Lim:** Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); resources (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Sang Hoon Ahn:** Data curation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Jae-Jun Shim:** Data curation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Homie Razavi:** Conceptualization (equal); funding acquisition (equal); project administration (equal); resources (equal); writing – original draft (equal); writing – review and editing (equal). **Devin Razavi-Shearer:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Dong Hyun Sinn:** Conceptualization (equal); data curation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal).

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## REFERENCES

1. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, Chen DS, van Damme P, Abbas Z, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3(6):383–403.
2. World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Geneva: World Health Organization; 2021.
3. World Health Organization. Interim guidance for country validation of viral hepatitis elimination. Geneva: World Health Organization; 2021.
4. Foundation C. Polaris Observatory - Maps - Elimination. 2021; https://cdafound.org/dashboard/polaris/maps.html. Accessed October 15, 2021.
5. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015.
6. European Association for the Study of the liver. Electronic address eee, European Association for the Study of the L. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370–98.
7. Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines for management of chronic hepatitis B. Clin Mol Hepatol. 2019;25(2):93–159.
8. Terrault NA, Lok ASF, McMahon BJ, Chang K-M, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatol. 2018;67(4):1560–99.
9. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HLY, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1–98.
10. Yim SY, Kim JH. The epidemiology of hepatitis B virus infection in Korea. Korean J Intern Med. 2019;34(5):945–53.
11. Cho EJ, Kim SE, Suk KT, An J, Jeong SW, Chung WJ, et al. Current status and strategies for hepatitis B control in Korea. Clin Mol Hepatol. 2017;23(3):205–11.
12. Shin A, Cho ER, Kim J, Sung J, Park KW, Lim MK, et al. Factors associated with awareness of infection status among chronic hepatitis B and C carriers in Korea. Cancer EpidemiolBiomarkers Prev. 2009;18(6):1894–8.

13. Sinn DH, Kim SE, Kim BK, Kim JH, Choi MS. The risk of hepatocellular carcinoma among chronic hepatitis B virus-infected patients outside current treatment criteria. J Viral Hepat. 2019;26(12):1465–72.
14. Kim GA, Lim YS, Han S, Choi J, Shim JH, Kim KM, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. Gut. 2018;67(5):945–52.
15. Kim GA, Han S, Choi GH, Choi J, Lim YS. Moderate levels of serum hepatitis B virus DNA are associated with the highest risk of hepatocellular carcinoma in chronic hepatitis B patients. Aliment Pharmacol Ther. 2020;51(11):1169–79.
16. Choi GH, Kim GA, Choi J, Han S, Lim YS. High risk of clinical events in untreated HBeAg-negative chronic hepatitis B patients with high viral load and no significant ALT elevation. Aliment Pharmacol Ther. 2019;50(2):215–26.
17. Shim JJ, Kim JW, Oh CH, Lee YR, Lee JS, Park SY, et al. Serum alanine aminotransferase level and liver-related mortality in patients with chronic hepatitis B: a large national cohort study. Liver Int. 2018;38(10):1751–9.
18. Lee HW, Kim SU, Park JY, Baatarkhuu O, Kim DY, Ahn SH, et al. Prognosis of untreated minimally active chronic hepatitis B patients in comparison with Virological responders by antivirals. Clin Transl Gastroenterol. 2019;10(6):e00036.
19. Prevention KCfDCa. Korean National Health and Nutrition Examination Survey 2014–2018. 2019.
20. Kang HS, Song BC, Ji CX, Kim SY, Kim SK. Serologic markers of hepatitis B virus in pregnant women in Jeju Island. Korean J Hepatol. 2004;10(3):191–6.
21. Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust. 2009;190(9):489–92.
22. Choi J, Han S, Kim N, Lim YS. Increasing burden of liver cancer despite extensive use of antiviral agents in a hepatitis B virus-endemic population. Hepatol. 2017;66(5):1454–63.
23. Sharing KNfO. 2019 Statistical yearbook of organ transplant.
24. Yoon JS, Lee HA, Park JY, Kim BH, Lee IJ, Chon YE, et al. Hepatocellular carcinoma in Korea between 2008 and 2011: an analysis of Korean Nationwide cancer registry. J Liver Cancer. 2020;20(1):41–52.
25. WHO/UNICEF. Reported official target population, number of doses administrered and official coverage. 2020; http://www.who.int/immunization/monitoring_surveillance/data/en/. Accessed 01 Nov 2020.
26. World Health Organization. The global burden of disease concept. Geneva: World Health Organization; 2015.
27. The World Bank. GNI per capita, Atlas method (current US$). 2017; https://data.worldbank.org/indicator/NY.GNP.PCAP.CD.
28. Lee E-K. Applicability to Asia of "New Age" Decision Making: The Korean Experience. HTAi Conference; 2016; Tokyo.
29. Kim HL, Kim GA, Park JA, Kang HR, Lee EK, Lim YS. Cost-effectiveness of antiviral treatment in adult patients with immune-tolerant phase chronic hepatitis B. Gut. 2021;70(11):2172–82.
30. World Population Prospects 2019, Online edition. United Nations, Department of Economic and Social Affairs, Population Division, https://population.un.org/wpp/. Accessed 2019-09-20.
31. Chen CJ, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatol. 2009;49(5 Suppl):S72–84.
32. Malcolm DG, Roseboom JH, Clark CE, Fazar W. Application of a technique for Research and Development program evaluation. Oper Res. 1959;7(5):646–69.
33. Li X, Mukandavire C, Cucunubá ZM, Echeverria Londono S, Abbas K, Clapham HE, et al. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study. Lancet. 2021;397(10272):398–408.
34. World Health Organization. Global Health sector strategies for viral hepatitis. Geneva: World Health Organization; 2016. p. 2016–21.
35. Ye Q, Kam LY, Yeo YH, Dang N, Huang DQ, Cheung R, et al. Substantial gaps in evaluation and treatment of patients with hepatitis B in the US. J Hepatol. 2022;76(1):63–74.
36. Tan M, Bhadoria AS, Cui F, Tan A, van Holten J, Easterbrook P, et al. Estimating the proportion of people with chronic hepatitis B virus infection eligible for hepatitis B antiviral treatment worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(2):106–19.
37. Lee HW, Kim SU, Baatarkhuu O, Park JY, Kim DY, Ahn SH, et al. Comparison between chronic hepatitis B patients with untreated immune-tolerant phase vs. those with virological response by antivirals. Sci Rep. 2019;9(1):2508.
38. Choi WM, Kim GA, Choi J, Han S, Lim YS. Increasing on-treatment hepatocellular carcinoma risk with decreasing baseline viral load in HBeAg-positive chronic hepatitis B. J Clin Invest. 2022;132(10):e154833.
39. Nayagam S, Thursz M, Sicuri E, Conteh L, Wiktor S, Low-Beer D, et al. Requirements for global elimination of hepatitis B: a modelling study. Lancet Infect Dis. 2016;16(12):1399–408.
40. IMS Institute for Healthcare Informatics. Price declines after branded medicines lose exclusivity in the U.S. January 2016. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-brandedmedicines-lose-exclusivity-in-the-us.pdf. Accessed May, 7 2019.
41. Vondeling GT, Cao Q, Postma MJ, Rozenbaum MH. The impact of patent expiry on drug prices: a systematic literature review. Appl Health Econ Health Policy. 2018;16(5):653–60.
42. Padula WV, Larson RA, Dusetzina SB, Apperley JF, Hehlmann R, Baccarani M, et al. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. J Natl Cancer Inst. 2016;108(7):djw003.
43. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet. 2013;381(9865):468–75.
44. Nguyen MH, Yang HI, Le A, et al. Reduced incidence of hepatocellular carcinoma in cirrhotic and noncirrhotic patients with chronic hepatitis B treated with tenofovir-a propensity score-matched study. J Infect Dis. 2019;219(1):10–8.
45. Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatol. 2017;66(5):1444–53.
46. Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci. 2015;60(5):1457–64.

## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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