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INVITED REVIEW

The economic argument for hepatitis B treatment simplification and expansion

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Abstract

One component of decisions regarding hepatitis B virus (HBV) treatment simplification and expansion is the economic perspective. Literature was reviewed for studies which provide estimates for the economic impact of simplifying and expanding treatment eligibility. Eight published studies and four unpublished studies were included and all but one subset of one study found that expanding treatment criteria would result in programs that would be at minimum cost-effective and most often highly cost-effective.

KEYWORDS
disease burden, economic impact, eligibility, HBV, treatment

1 | INTRODUCTION

As we enter our eighth year on the path towards viral hepatitis elimination as a public health threat, with only six more years to go, it is imperative that we applaud the progress that has been made while simultaneously examining shortcomings. In 2022, it was estimated that there were 258 million people living with HBV, 3.2% of the global population.[1] The number of individuals diagnosed with HBV has increased to 14% in 2022. However, this is still far from the 60% target by 2025 and 90% diagnosed by 2030.[2] The largest gains towards WHO elimination targets continue to be observed in prevention, with 85% of infants globally receiving full coverage of HBV vaccine, and the global prevalence among children aged 5 years and younger being 0.7%.[1]

Levels of treatment have remained stubbornly low, with only an estimated 8% of the eligible and less than 3% of total HBV-infected population being on treatment in 2022. These low treatment rates can also be observed by their impact, or lack thereof, with multiple publications showing that HBV liver-related deaths continue to increase globally.[1,3,4] There is clearly something fundamentally wrong with the way HBV elimination is being executed.

Of the approximately 258 million people living with HBV, less than 5% (11.2 million) live in the high-income countries.[1] While these high-income countries contribute little to the global burden, they are instrumental in setting the guidelines. There are a plethora of liver societies that put out their own treatment guidelines but the majority of countries globally utilize either The American Association of Liver Disease (AASLD) or the European Association for the Study of Liver (EASL) treatment guidelines.[5,6] These associations base their guidelines on strong empirical data, with the hepatologist centred aim to identify those most at risk of progressing to late-stage liver disease and treating them and only them. Infectious disease and public health perspectives are considered but the current guidelines focus on HBV as a liver disease rather than an infection or a cancer-causing virus. A notable exception is China who developed their own guidelines that cover 31% of all HBV infections globally. Their new guidelines define treatment eligibility as HBsAg and PCR positivity with no viral load or liver function test requirements.[7]

We know from our experiences with hepatitis C virus, that it is imperative that primary care practitioners (PCPs) are able to diagnose and treat people living with viral hepatitis. The current HBV guidelines are quite cumbersome for PCPs, particularly those working with marginalized communities, including immigrants,

Abbreviations: AASLD, American Association of Liver Disease;; ALT, alanine transaminase; DALY, disability-adjusted life year; EASL, European Association for the Study of Liver; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCP, primary care practitioner; PCR, polymerase chain reaction; QALY, quality adjusted life year; RT, rapid test; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

where a large portion of people living with HBV live in Western countries.[8–13] The wait and see approach that is recommended for the majority of HBV-infected individuals may lead to people not taking the risk of the virus as seriously as they should. The bi-annual or quarterly testing for those currently deemed treatment ineligible is a high burden on both individuals as well as the health care system. While these are problems that patients and providers face globally, in many low-income settings providers do not have ready access to the diagnostics necessary to follow the AASLD, EASL or WHO guidelines.[14]

One method that has been proposed to increase treatment uptake and to allow a more equitable access to HBV treatment, is to simplify treatment guidelines. This approach aims to be PCP friendly, and to increase access in countries where there is limited access to laboratory tests. While treatment simplification can save costs by reducing or eliminating some diagnostics, the expansion of treatment will result in higher treatment costs and it is necessary to quantify these trade-offs economically particularly in light of expanded treatment resulting in reduced costs as some cases of late-stage liver disease will be averted. This study aims to examine the recent literature on treatment simplification and expansion from the economic perspectives to better guide decision-making in the future.

There are different factors that motivate individuals, institutions and governments in altering guidelines. For some it may be the pure numbers (risks, progression, reduced risk, etc.), for others it is the number of lives saved and personal stories, and for others it is the economic considerations. In this study we hope to contribute evidence for the economic factor. However, even if all of these evidence are present, without political will, it is unlikely that there will be major changes to guidelines nor a true commitment to viral hepatitis elimination.

2 | HIGH-INCOME COUNTRIES

In the United Kingdom a study was conducted to examine the economic impact of using various non-invasive tests to initiate treatment, with an additional scenario examining the impact of treating everyone with no staging diagnostics.[15] The cost-effectiveness threshold was defined as £30,000. For HBeAg- individuals it was found that treating all individuals regardless of fibrosis stage would be cost-effective, costing £28,137 per Quality Adjusted Life Year (QALY) gained. While treating all HBeAg+ individuals regardless of fibrosis scoring resulted in higher QALY gains, it was also outside of the defined cost-effectiveness threshold, costing an estimated £39,474 per QALY gained.

In the Republic of Korea a study examined the impact of starting treatment in the immune tolerant phase as opposed to waiting for individuals to become immune active.[16] This study found that starting treatment in the immune tolerant phase would be cost-saving. A separate study examined the impact of expanding the current treatment guidelines to removing all ALT restrictions and treating 70% of the infected population with an HBV viral load ≥2000 IU/mL. This intervention would have the largest impact on disease burden, reducing the number of liver-related deaths by 33% and would be highly cost-effective.

A study from France examined the impact of expanding treatment eligibility compared to the status quo in three separate scenarios.[17] While all scenarios were found to be highly cost effective, the scenario that modelled the impact of treating all people living with HBV would result in the most effective strategy in terms of life years and QALYs.

An analysis from Saudi Arabia found that treating all individuals, as opposed to meeting the WHO targets by 2030 under the current guidelines, would save almost double the number of lives.[18] However, this strategy needed to be combined with a 50% decrease in the treatment cost to result in the scenario being highly cost effective, with current prices resulting in a cost-effective scenario. Similarly, a study from the United States found that treating everyone living with HBV would only be cost effective under the current treatment costs but could become highly cost-effective if the annual cost of treatment was decreased to $2000 and would become cost-saving if the treatment cost dropped to $750 per year.[19]

3 | LOW- AND MIDDLE-INCOME COUNTRIES

A recent study from China modelled 135 variations on expanded treatment strategies and compared them to base.[20] Increasing the treatment rate to 80% after expanding eligibility to everyone who is HBsAg+ was found to reduce the largest number of liver-related complications and save the highest number of lives. Thus, while the scenario was estimated to cost the most, it would also result in the most QALYs gained.

In Uzbekistan a real-world study found that treating and testing everyone who was HBsAg+ was not only more cost-effective than the base, but that it also resulted in patients seeking care earlier in their disease and with fewer patients being lost to follow-up.[21]

China and Uzbekistan have both adopted what are essentially treat all guidelines, with China requiring detectable HBV DNA where available and individuals to be 30 years or older (as informed by their robust childhood vaccination program).[7]

4 | PREVIOUSLY UNPUBLISHED ANALYSES

The Polaris Observatory, housed within The Center for Disease Analysis Foundation has conducted cost-effectiveness analyses for the elimination of HBV at the national population level in 23 countries. Only four of these, South Korea, Saudi Arabia, the United States of America and Uzbekistan have been previously published.[18,19,21,22] The results of four previously unpublished analyses that examined

TABLE 1 Unpublished economic impact analyses.

Country	Treatment strategies	Key results
Brazil	• Base scenario • National strategy plan ○ Expand treatment eligibility to all individuals with a viral load ≥2000 IU/mL to meet 90% diagnosed and 80% treated targets by 2030	• Expanding treatment eligibility and meeting the WHO targets was found to be highly cost-effective
Colombia	• Base scenario • WHO 2030—Meet 90% diagnosed and 80% treated targets by 2030 • WHO 2030 TDF—Meet the aforementioned targets and purchase generic TDF from the revolving fund • WHO 2030 Simplified and TDF—Building on the previous scenario but reducing the number of tests for treatment initiation and follow-up ○ Treatment initiation • 4 viral loads to 1 • 1 HBeAg to 0 ○ Treatment follow-up • 2 viral loads to 1 • 1 HBeAg to 0 ○ Ineligible for treatment follow-up • 2 viral loads to 1 • 1 HBeAg to 0 • 1 HBsAg to 0 • WHO 2030 RT, simplified and TDF—Building on the previous scenario but using a rapid test for initial screening at the population level	• All scenarios were found to be cost-effective • Only the WHO 2030 RT, simplified and TDF scenario was found to be highly cost-effective
Ethiopia	• Base scenario • WHO Elimination—meet 90% diagnosed and 80% treated targets by 2030, expand treatment eligibility to all individuals with a viral load ≥2000 IU/mL • Test and Treat All—Meet the WHO 2030 targets and treat everyone who is HBsAg+ ○ Removing all viral load test requirements	• The impact on the disease burden of the WHO Elimination (≥2000 IU/mL) and Test & Treat All were similar and both were found to be highly cost-effective • The cost per DALY averted for Test and Treat All was almost half that of WHO Elimination ($550 vs. $930)
Kazakhstan	• Base scenario • WHO Elimination—meet 90% diagnosed and 80% treated targets by 2030 ○ Simplified diagnostics compared to base ○ Market prices for treatment, HBsAg and PCR testing implemented • Test and Treat All—Meet the WHO 2030 targets and treat everyone who is HBsAg+ ○ Builds on WHO Elimination but removes all viral load test requirements	• Both scenarios were found to be highly cost-effective • The cost per DALY averted for Test and Treat All was almost half that of WHO Elimination (239,400 KZT vs. 122,700 KZT)

the impact of simplified or expanded treatment eligibility have been included in the current work (Table 1). All country analyses are run at the national population level, and the base scenario, to which all other scenarios are compared to assumes no change in current treatment, diagnosis or eligibility into the future.

In Brazil expanding the treatment eligibility to anyone with a viral load ≥2000 IU/mL, and then meeting the WHO targets would be highly cost-effective. In Colombia, multiple scenarios were run to examine the incremental impacts of reducing the cost of treatment (moving to generic TDF), simplifying initial and follow-up diagnostics and finally in using a rapid test for the initial HBV screening. The only scenario that was found to be highly cost-effective was the one that utilized rapid tests, generic pricing and greatly reduced the number of initial and annual tests (Table 1).

In countries as distinct as Ethiopia and Kazakhstan it was found that meeting the WHO targets would be highly cost-effective for both countries. However, if a treat all approach was taken, the cost per DALY averted would be almost halved (Table 1).

5 | DISCUSSION

The economic arguments for simplifying and expanding HBV treatment are quite consistent and clear, despite the often-large increase in the number of individuals treated, the savings from averting late-stage liver disease and in some cases simplifying diagnostic paradigms result in these scenarios being consistently cost-effective with most being highly cost-effective and even cost-saving. These findings are consistent in countries with various regions, income groups and disease burdens and even across different modelling approaches.

One limitation of the current study is that most countries have low treatment rates, and that of course expanding treatment drastically is better than the status quo of doing very little. However, the Republic of Korea has an estimated 57% of their eligible infected population on treatment and even in that high treatment and high-income setting there are large benefits observed from expanding their eligibility criteria.[1]

High-income countries have started moving towards treading individuals with a viral load >2000 IU/mL and an ALT greater than the upper limit of normal. It is only a matter of time before the liver associations follow suit.[1] As previously mentioned, these countries have relatively smaller burdens and the impact of hepatitis B on their health systems is small enough that they have the luxury to slowly expand treatment eligibility. It should be a harbinger to the world that China, the country in which almost one-third of all people living with HBV reside in, has decided to drastically expand treatment guidelines to treat everyone with a detectable viral load, based on the study that found this approach to be cost-effective.

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CONFLICT OF INTEREST STATEMENT

Devin Razavi-Shearer is an employee of the Center for Disease Analysis Foundation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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