Extending treatment eligibility for chronic hepatitis B virus infection

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STANDFIRST

Progress towards hepatitis B virus (HBV) elimination targets remains slow, despite efforts to support enhanced prevention, diagnosis and treatment. On the basis of insights from interventions against HIV, we argue for the wider use of antiviral therapy for HBV, highlighting the potential public health benefits in preventing liver disease and reducing transmission.

MAIN TEXT

Ambitious targets set by the United Nations Sustainable Development Goals aim to reduce global hepatitis B virus (HBV) incidence by 90% and mortality by 65% by 2030 [1]. However, deaths from chronic HBV infection (CHB) are increasing, with a rising incidence of hepatocellular carcinoma (HCC) of particular concern in Africa and the Western Pacific (Suppl Fig 1) [1]. Guidelines for treatment with nucleos(t)ide analogue (NA) agents (Suppl Table 1) can be impractical to implement, and result in only a minority of the CHB population being offered treatment. In this Comment, we consider the rationale for modifying eligibility criteria for NA therapy.

CHB is assessed according to sex and age, using laboratory markers, including HBV viral load, viral antigens (HBsAg and HBeAg) and liver enzymes, together with imaging using ultrasonography and/or elastography, and biopsy data when available (Suppl Table 1). Current thresholds for therapy are based on a traditional system that considers different ‘phases’ of infection (Suppl Fig 2), based on the assumption that minimal liver damage occurs when biomarkers are below defined thresholds.

NA therapy aims to reduce inflammation and fibrosis and to limit the risk of chronic liver disease, including HCC. However, even HBV infection phenotyped as ‘minimally active’ retains a risk of chronic hepatocyte injury, and progressive liver disease can occur, with viral genomic integration events early in life that can drive HCC [2] (Suppl Table 2). Treatment can therefore be of benefit even in those with normal liver enzyme levels and low-level viraemia, especially if introduced early and mediating complete viral suppression [3]. Thus, expanded treatment for CHB could be considered a primary prevention approach to protect against liver disease.

In children and adolescents, guidelines typically recommend a conservative approach to HBV treatment (Suppl Table 1), assuming an ‘immunotolerant’ profile (Suppl Fig 2). However, emerging evidence suggests that treating HBV infection early might mediate faster viraemic control, with benefits that potentially include limiting symptoms, reducing the tissue reservoir,

increasing clearance and reducing transmission risk [4]. All of these benefits are comparable to those harnessed by NA therapy for HIV, but more studies to evaluate the effect of NA use in acute and paediatric infection are needed.

On the basis of existing guidelines, 1:3 to 1:4 individuals with CHB in Europe, North America and East Africa are considered NA treatment-eligible and fewer than 1:5 in West Africa (Suppl Fig 1). It is striking that in some of the world's highest endemicity regions, such small proportions of the CHB population meet treatment criteria. Extending treatment eligibility could tackle the large population reservoir in such regions.

Existing systems for classification of liver disease can be misleading, as CHB phenotypes can be indeterminate, there is a lack of data representing diverse populations and co-morbidities, and the progression of pathology is not necessarily linear (Suppl Fig 2). Algorithms prioritize treatment only for older adults (Suppl Table 1) and are a blunt tool for inferring end-organ damage (Suppl Table 2) while assessment at intervals can miss clinically significant episodes of hepatic inflammation, and relevant monitoring is not widely accessible or affordable [5].

Although the HBV vaccine is necessary for elimination, it is unlikely to be sufficient. Modelling data demonstrate long timeframes to achieve targets, owing to the substantial established population reservoir of infection, poor administration of birth dose vaccine, gaps in coverage, insecure cold chains, and inadequate or waning antibody titres [6]. However, diagnosis and treatment, if deployed widely, can 'switch off' HBV transmission, with evidence from a mathematical model demonstrating an effect as potent as routine vaccination [6].

Preventive interventions are based on the assumption that transmission is most likely to occur from highly viraemic carriers, but this is often difficult to confirm, and in 2019 the minimum infectious dose was revised down from 100 to 16 viral copies (equivalent to 3 IU) [7]. Therapy is already recommended for healthcare workers with viral load as low as 200 IU/ml, setting a precedent for NA therapy to prevent transmission (Suppl Table 1). Biological parallels between HIV and HBV suggest that the HIV field might inform approaches for HBV, including population evidence that undetectable HIV viraemia is untransmissable, such that treatment provides benefits for the population as well as for the individual [8].

Prevention of mother-to-child transmission interventions require clinical and laboratory infrastructure and can be challenging to deliver, especially in low and middle-income countries. The current viral load threshold for antenatal tenofovir disoproxil fumarate (TDF) therapy is high, and treatment is not routinely initiated until the third trimester, such that vertical transmission can still occur even when guidelines are followed (Suppl Table 1). Standardizing antenatal HBV interventions, with relaxed and simplified criteria supporting broader and earlier access to therapy, could offer clinical and resource benefits for prevention of mother-to-child transmission, as for HIV.

Drug intolerance, adverse effects, toxicity and resistance are potential risks of relaxing treatment guidelines. However, TDF-induced nephrotoxicity and loss of bone mineral density have primarily been documented in HIV cohorts and in the setting of pre-existing co-morbidity (Suppl Table 2); further studies are required in HBV monoinfection. A meta-analysis incorporating data from thousands of pregnancies did not identify any association between NA therapy for HBV and adverse outcomes [9]. Expanded exposure to therapy might lead to an increase in drug resistance in both HIV and HBV, although the genetic barrier to resistance to first-line agents in HBV is high [10].

Drug toxicity can be mitigated by simple laboratory monitoring and by altering therapy through dose reduction, or switching TDF to tenofovir alafenamide (TAF) or entecavir (Suppl Table 2). Although TAF is not available in many settings to date, this is expected to change as it becomes incorporated into fixed-dose HIV combination therapy. Mitigation for resistance requires concurrent screening for both HBV and HIV, scrutiny for cases of treatment failure, and potential consideration of a role for dual therapy in selected cases.

TDF is generally affordable and accessible, and the costs of drug deployment can be offset against disability-adjusted life years (Suppl Table 2). Where the disease burden is high in young adults, economic benefits can become apparent within modest timeframes, particularly where HBV interventions can capitalize on existing infrastructure. Ethical considerations include the psychosocial implications of long-term treatment, stigma associated with both infection and treatment, improved inclusivity of participants for trials, trade-offs between risks and benefits of new agents, ambiguity around correlates of cure, and the long duration of follow-up needed to determine outcomes.

Simplification of algorithms could remove or diminish barriers to treatment, by reducing the number, complexity and cost of investigations that are mandated, limiting the burden of undetected tissue damage, and switching off transmission. The simplest and most inclusive recommendation would be to offer NA treatment to all with confirmed CHB (defined as testing persistently positive for HBsAg over ≥6 months). However, careful risk–benefit assessments are needed, with interventions tailored to local needs and resources (Suppl Fig 3). Although there are urgent long-term needs for wider access to diagnosis, new biomarkers and curative therapy, striking gains could be made in the meantime through our existing therapeutic armamentarium, drawing on safe, effective, affordable and widely available NA agents.

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Competing interests

The authors declare no competing interests.

Box 1: Summary of action points for expanding NA therapy for CHB.

1. Reduce the cost and complexity of clinical, laboratory and imaging tests that are required to stratify individuals for HBV treatment.
In this way, we can reduce demands on resources, clinical and laboratory infrastructure, and personnel.

2. Simplify recommendations for PMTCT, including universal screening and more widespread treatment of antenatal women.
Simplified algorithms are required that allow TDF prescribing, independent of laboratory facilities and follow-up clinical visits (e.g. antenatal therapy could be based on point of care testing for HBsAg).

3. Improve protocols for HBV testing and treatment alongside other public health initiatives.
HBV interventions can be linked with programmes for HIV, HCV and syphilis, and/or with other healthcare interventions targeting specific risk groups (e.g. maternal and child health, services for sex workers).

4. Develop biomarkers that are sensitive and specific for disease progression, and evaluate their performance in different settings.
New biomarkers, including fibrosis scores (± HBV sequencing data) will allow therapy to be better targeted to the groups at highest risk of long term liver disease, including HCC.

5. Enhance data collection to provide better understanding of HBV epidemiology, transmission, pathophysiology, and health economics in diverse population settings.
Region-specific data are urgently needed in order to refine guidelines that support wide access to therapy, while avoiding unnecessary risks and costs. Deployment of interventions may vary according to local characteristics of disease (e.g. population prevalence of infection, incidence of HCC, rate of vertical transmission).

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Extending treatment eligibility for chronic hepatitis B virus infection: Supplementary Material

Suppl Table 1: Summary of international HBV treatment guidelines: criteria for starting NA therapy. Treatment guidelines for the initiation and monitoring of therapy are published by the American Association for the Study of Liver Disease (AASLD)[1], the European Association for the Study of the Liver (EASL)[2] and the Asia-Pacific Association for the Study of the Liver (APASL)[3]. No specific guidelines exist for Africa (although there are some country-specific guidelines)[4], and there is concern that the biomarker thresholds have not been adequately validated and access to the required tests remains poor across sub-Saharan Africa.[5] Additional treatment considerations, such as co-infection with hepatitis D virus, are covered elsewhere.[6]

Criteria for starting treatment	**AASLD guidelines (North America)[1]**		**EASL guidelines (Europe)[2]**		**APASL guidelines (Asia/South Pacific)[3]**	
HBeAg status[a]	HBeAg positive	HBeAg negative	HBeAg positive	HBeAg negative	HBeAg positive	HBeAg negative
HBV DNA VL (IU/ml)	>20,000	>2,000	>20,000	>2,000	>20,000	>2,000
ALT[b]	≥2xULN	≥2xULN	≥2xULN	≥ULN	≥2xULN	≥2xULN
Elasto-graphy[c]	Use to check for signs of fibrosis if ALT >ULN but <2xULN	Use to check for signs of fibrosis if ALT >ULN but <2xULN	Can be used for estimation of the extent of fibrosis	Indications of at least moderate liver necro-inflammation or fibrosis	Use to check for signs of fibrosis if ALT >ULN but <2xULN	Use to check for signs of fibrosis if ALT >ULN but <2xULN
Age criteria in adults	If ALT raised and >40yrs	If ALT raised and >40yrs	If high HBV DNA levels and >30yrs (even if ALT <ULN)	No specific guidance	If ALT raised and >35yrs	If ALT raised and >35yrs
Frequency of laboratory assessment	Frequency of laboratory follow-up between 3-12 monthly depending on ALT.		Frequency of laboratory follow-up between 6-24 monthly depending on HBsAg levels.		Frequency of laboratory follow-up between 3-12 monthly depending on HBeAg status, HBV DNA and ALT.	

(Table continued from previous page)

Criteria for starting treatment	AASLD guidelines (North America)[1]	EASL guidelines (Europe)[2]	APASL guidelines (Asia/South Pacific)[3]
Children	Treatment suggested if ALT elevation >1.3 ULN for ≥6 months (although normal reference ranges for children not well established). Treatment not recommended for elevated HBV DNA VL if ALT normal. ETV can be used in children aged ≥2 years and TDF ≥12 years.	Treatment should be considered with caution as CHB is typically asymptomatic, and 'most children do not meet standard treatment indications'. Evaluation should include consideration of comorbidity. ETV, TDF, TAF can be considered. Alternative guidelines are referenced [7].	Treatment indicated for cirrhosis, severe reactivation, and by algorithm incorporating HBeAg, HBV DNA VL, ALT, liver biopsy for histology, family history of HCC, and co-existing liver disease. 3TC in children aged ≥ 3 years, TDF ≥12 years and ETV ≥16 years.
Pregnancy	All women meeting the HBV treatment criteria should remain on treatment. Treat pregnant women with HBV DNA >200,000 IU/mL with TDF (suggested at weeks 28-32 and for 3 months after delivery).	All women meeting the HBV treatment criteria should remain on treatment. Treat pregnant women with HBV DNA >200,000 IU/ml or HBsAg >4 $\log_{10}$ IU/ml, starting TDF at weeks 24–28, and continue for 12 weeks after delivery.	Consider therapy for all pregnant women. Focus is on treatment for highest risk group with HBV DNA >6–7 $\log_{10}$ IU/ml: treat from 28-32 weeks with TDF or telbivudine, until delivery.
Healthcare workers (HCW)[d]	Treat those with HBV DNA >1000 IU/ml; seek expert advice and counselling.	Treat those with HBV DNA ≥200 IU/ml to reduce levels of HBV DNA, ideally to undetectable.	Treat those with HBV DNA >1000 IU/ml; seek expert advice and counselling.
Cirrhosis	Decompensated cirrhosis: treat irrespective of other factors. Consider for transplant.	Compensated or decompensated cirrhosis: treat irrespective of other factors.	Decompensated cirrhosis: treat irrespective of other factors. Compensated cirrhosis: treat if VL >2,000 IU/ml[e]

[a] Treatment criteria for HBV therapy typically differ depending on HBeAg status

[b] Upper limits of normal (ULN) for ALT in healthy adults vary from 29-35 U/L for males and 19-25 U/L for females. Abnormality should be persistent (defined by monitoring over time) to meet treatment eligibility criteria.

[c] Recommended thresholds for elastography in patients with CHB are (a) 9 kPa with normal ALT and liver stiffness or (b) 12kPa with raised ALT but <5xULN and liver stiffness [2].

[d] Treatment for HCWs also depends on whether the work carried out includes exposure-prone procedures (EPP).

[e] Updated consensus Asian guidelines for the treatment of CHB in Resource-Limited Settings (published Nov 2019) now recommend treatment for compensated cirrhosis, regardless of other biomarkers, including viral load.[8]

Suppl Table 2: Consideration of diverse factors in the risk/benefit analysis of relaxing criteria for HBV therapy

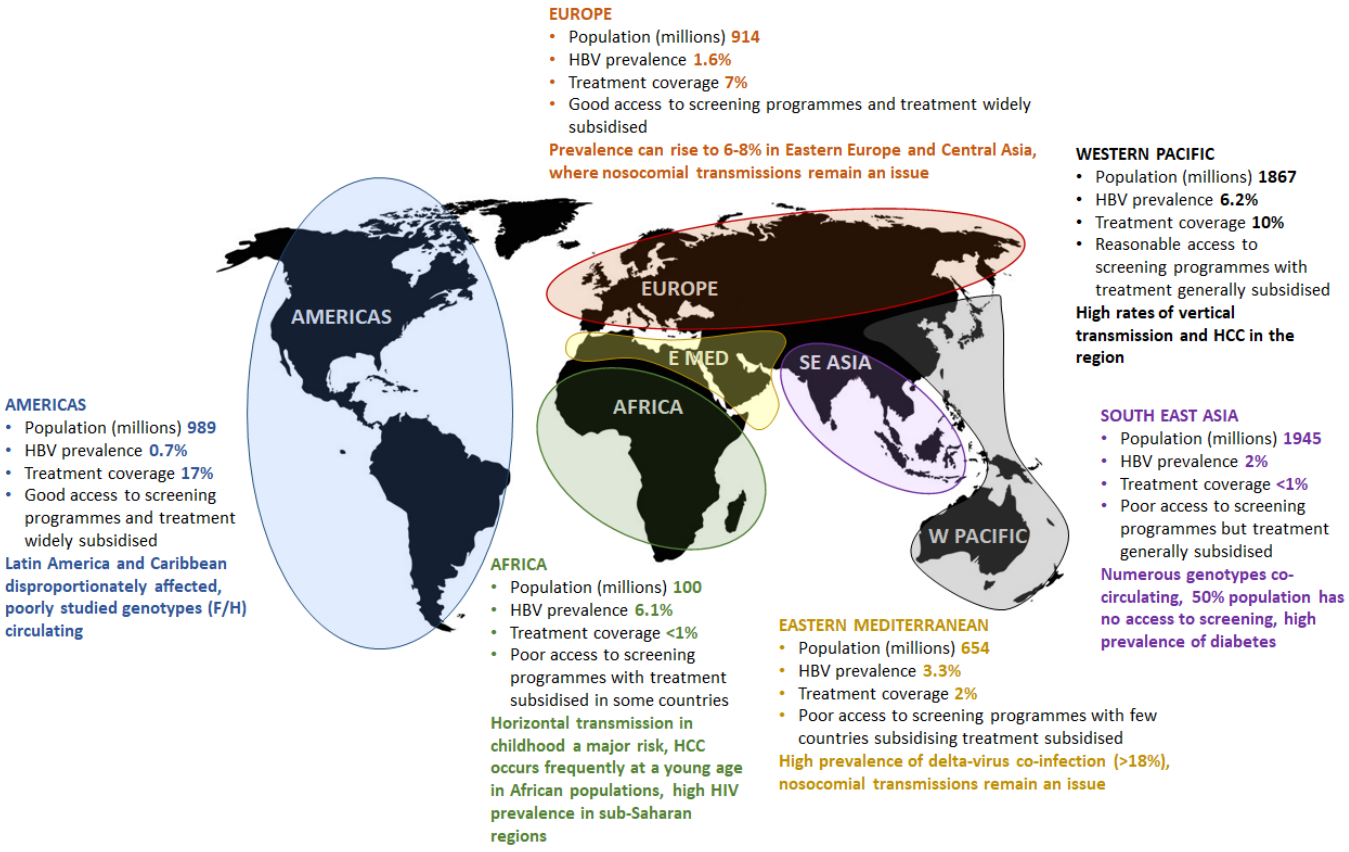
	Factors in support of extending HBV treatment	Factors against extending HBV treatment
Burden of individual disease arising from CHB	• Treatment reduces long term risk of liver disease, even in HBeAg-negative individuals without evidence of high viral load or liver inflammation[9–15]. • Cirrhosis and HCC can occur even without evidence of inflammatory liver disease; cancer may result from genomic integration early in life[9,16–18]. • Primary prevention strategy is well accepted for other conditions (e.g. modification of cardiovascular risk). • Treatment of children and adolescents may reduce the hepatic reservoir and increase chance of clearance[19–21]. • Early treatment initiation in HIV-HBV coinfection is associated with favourable outcomes[22,23].	• High proportion of individuals with CHB do not progress to long-term liver disease. • Large numbers are needed to treat in order to reduce incident cases of liver disease. • Despite high viral loads in children, there is no evidence of progressive liver disease in the majority of cases of paediatric infection.
Data availability and stratification	• Treating a wider pool of those with HBV infection offers a simplified low-cost approach in settings where high resolution data on infection phenotypes are limited. • Reliable stratification into distinct risk groups can be challenging[24], particularly for LMIC settings[25,27,28] • Novel biomarkers may provide improved stratification[26], but are not widely available. • Laboratory-based fibrosis scores lack precision[27,29]. • Simplified WHO guidelines for LMICs remain imperfect, with a chance that individuals at risk of liver disease do not meet treatment criteria[28,30,31].	• Limited data for many settings provide a poor evidence foundation for planning widespread treatment.
Economic and infra-structure considerations	• Cost of TDF is low[32]. • Cost of drugs and infrastructure is offset by savings made as a result of a reduced burden of liver disease. • Costs can be offset through shared infrastructure (e.g. HIV clinical care)[33]. • Treating more of the population with HBV infection removes barriers imposed by complex and costly algorithms for assessment, including in pregnancy[34,35].	• Prolonged duration of provision of therapy and clinical follow-up. • Care provision incurs costs of therapy, laboratory monitoring, personnel, clinical facilities. • TDF monotherapy is not universally available. • ETV is frequently unaffordable. • Access to diagnosis and treatment varies by region, and may be difficult for certain vulnerable groups, especially if the costs are borne by the individual and their family.

Impact on transmission, including PMTCT	• Treating all cases of CHB can supplement vaccination as an approach for interrupting transmission, including both vertical and horizontal routes.[36] • Early therapy in pregnancy makes an impact on viral suppression[37] broader and earlier access to antenatal TDF, could improve PMTCT in programmes that mirror HIV interventions[14,34,37]. TDF ART regimens in pregnancy have a better risk profile than other drug combinations[38]. • Transmission can occur at low VL[39, 40, 41], and from dried blood [42] so intervention should not only be focussed on groups with high VL. • Vaccination provides incomplete protection for a variety of reasons (delayed first dose, incomplete coverage, inadequate antibody titres)[33,36,43,44,45]	• Large numbers needed to treat in order to reduce cases of transmission. • The majority of transmission events are thought to arise from individuals with high VL.
Side-effects or toxicity	• Tenofovir is safe and well tolerated in the majority of individuals. • Alternative regimens or dose reduction can be offered in cases of toxicity [46]. • Evidence for renal toxicity in HBV monoinfection is limited and mainly arises from HIV studies [47]; kidney disease may in fact be reduced by robust HBV treatment. • Monitoring for renal toxicity is cheap and accessible in most settings. • TDF is safe in pregnancy and breast-feeding [48]; TDF regimen associated with a lower risk of adverse birth outcomes than other ART drug combinations [38].	• Potential risks of TDF therapy; gastrointestinal disturbance, less frequent anaemia or neutropaenia, rash, arthralgia, myalgia[49]; risk of hepatic flare if treatment is stopped[50]. TDF-induced nephrotoxicity (though primarily documented in HIV[47], and/or pre-existing chronic kidney disease[49,51,52]). • Laboratory infrastructure and costs are necessary for monitoring patients on therapy. • Justification of potential intolerance, side-effects or toxicity is difficult among individuals who have very low risk of disease or transmission.
Drug resistance	• The genetic barrier to tenofovir resistance is high, and resistance is not widely recognised to be a clinical concern. • Dual therapy (TDF/3TC) has been shown to be effective and can be easily and cheaply employed for individuals with drug-resistant virus.	• Data are emerging to suggest possible tenofovir resistance [53,54]. • Compliance is difficult to assure, and may be more complicated in individuals with low risk, asymptomatic infection, leading to an enhanced risk of selecting drug resistant variants.
Ethical and psychosocial considerations	• Safe, effective drugs should be made accessible to all those with infection, reducing personal risks and limiting the risk of spread. • Enhancing provision of treatment provides an opportunity to provide advocacy,	• Younger patients may not be willing to start therapies that are planned for long-term; healthy individuals may 'perceive themselves as sick' [56,57]. • Deploying more widespread

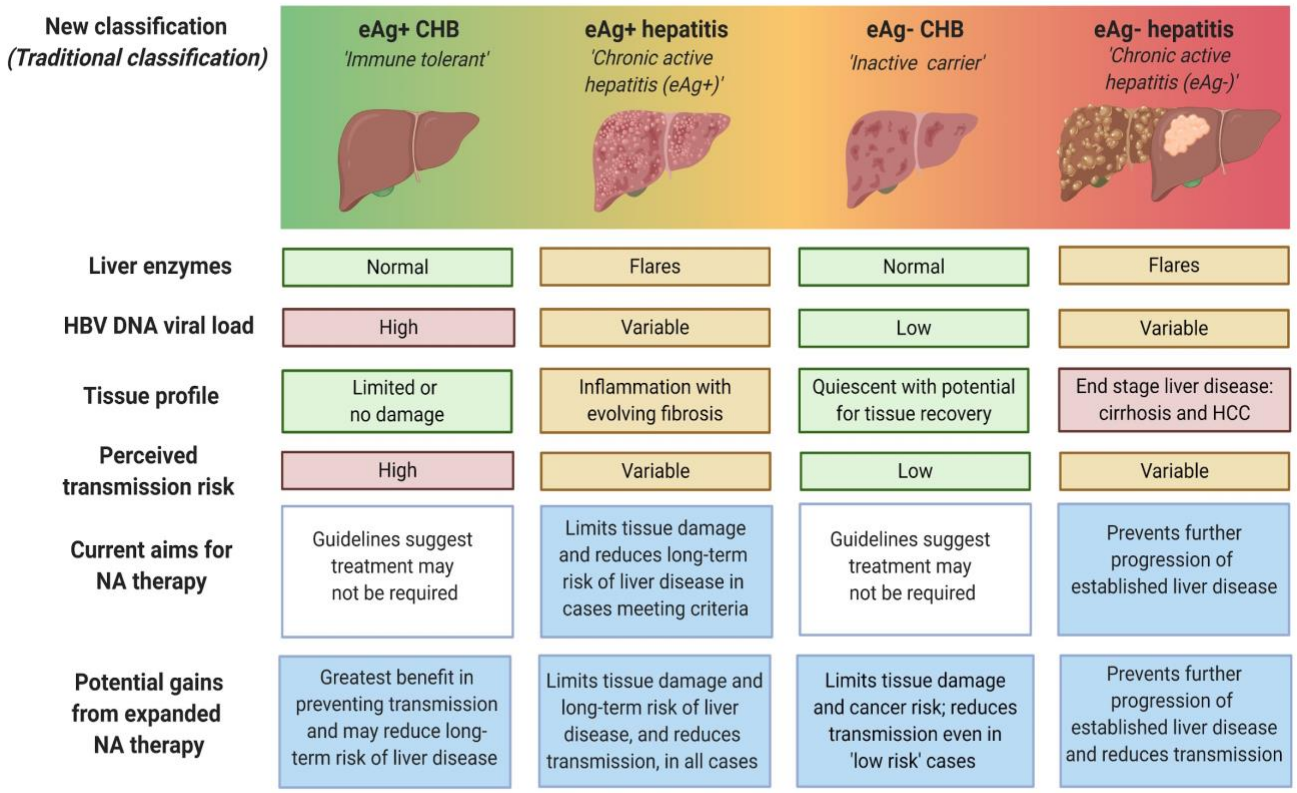
	education and information, thus reducing stigma. ● Mental health can be improved when active treatment is provided. ● HBV can be considered a neglected tropical disease; urgent advocacy and better treatment are required for vulnerable populations in high burden countries [55].	treatment on public health grounds can be difficult to justify for individuals. ● Daily pill burden may be a barrier. ● If HBV treatment is scaled up, other healthcare provision may suffer. ● Therapy can lead to stigma [55]. ● Compliance may be poor, especially if treatment is started in younger and/or asymptomatic individuals. ● Awareness is frequently poor [58].
Contribution to global HBV elimination targets	● 'Test and treat' strategies may be the fastest route to achieving elimination targets, when implemented alongside vaccination programmes. ● If the current *status quo* is maintained, elimination targets will not be met by the 2030 international target [36].	● Incidence is already reducing in many areas, due to vaccination. . ● There is no legislation or incentivisation associated with elimination targets. ● Existing drugs mediate viral suppression in most but not all cases, and do not bring about cure; a priority should be new cure interventions[59].

3TC - lamivudine; ART - antiretroviral therapy; CHB - chronic hepatitis B virus infection; ETV - entecavir; HCC - hepatocellular carcinoma; LMIC - low/middle income country; PMTCT - prevention of mother to child transmission; TDF - tenofovir disoproxil fumarate; VL - viral load

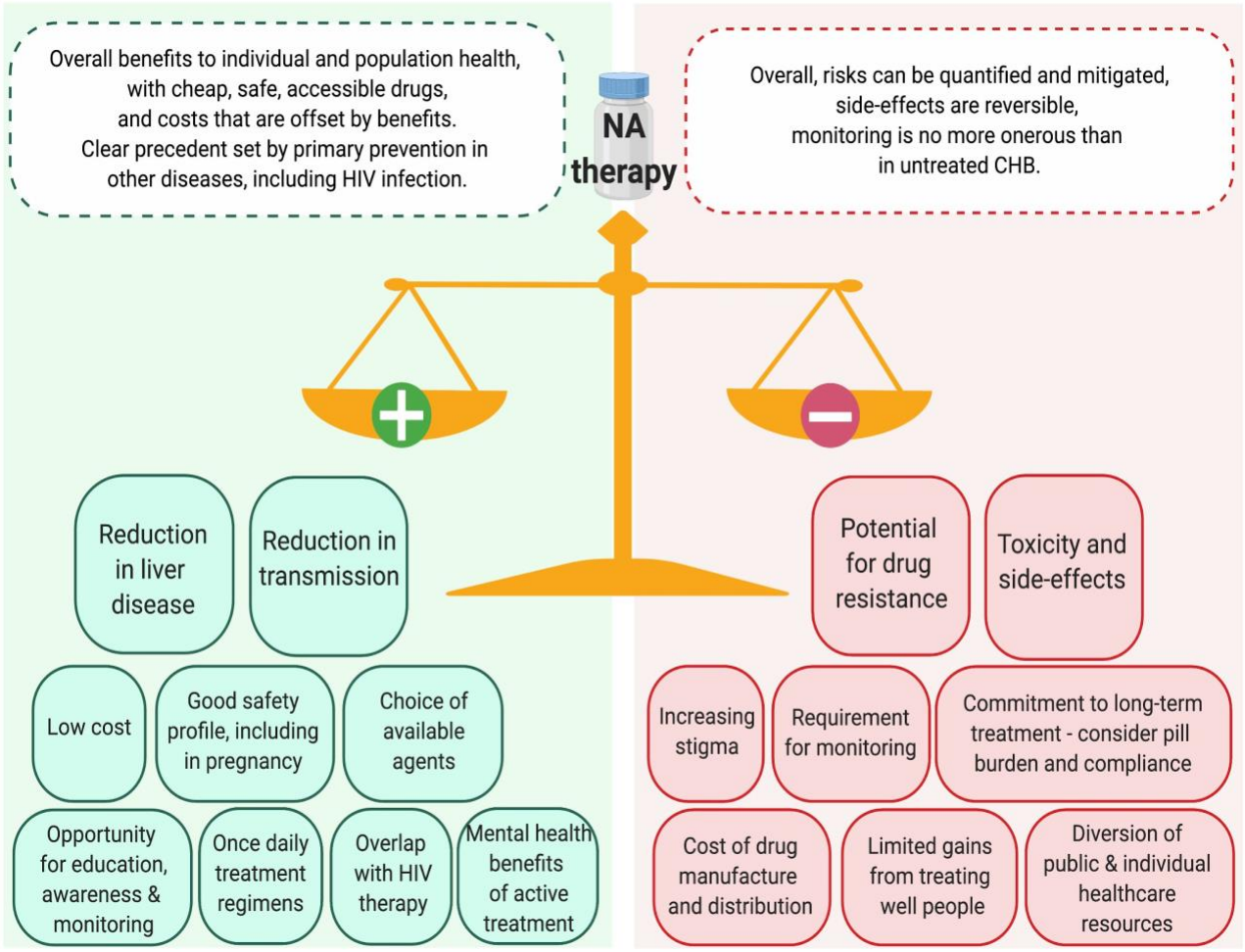
Suppl Fig 1: Global prevalence of HBV, treatment coverage and access to screening programmes. Data summarised from the Lancet Gastroenterology & Hepatology Commission[60], with WHO regions represented. Serological evidence suggests that approximately a third of the world's population has been exposed to HBV[36]. Detailed regional prevalence data, estimating the proportion of patients meeting WHO treatment eligibility criteria, and identifying specific regional challenges, are required in order to invest and allocate resources for screening and testing effectively. Current estimates from patients reviewed in hospital suggests 25-34% individuals diagnosed with CHB in Europe, North America and East Africa are eligible for treatment[61–64]. In West Africa, smaller proportions of CHB cohorts meet criteria for therapy (4-18%)[65,66].



Suppl Fig 2: Spectrum of chronic HBV infection, highlighting groups in whom therapy is currently advocated, and a wider pool who could potentially benefit from expanded treatment. Classification is controversial, and there is a lack of clear biological understanding surrounding the detailed mechanistic host/viral interactions characterising each phase, although broad patterns determined by biomarkers are well recognised. We here present updated classifications in bold,[2] with previous/traditional classifications given underneath in italics. Figure created using BioRender.com.



Suppl Fig 3: Considerations associated with broadening HBV treatment. Points in favour of expanding therapy are shown in green, and risks and challenges in red. Figure created using BioRender.com.



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