

Supplementary File 1: Phases of CHB disease

Chronic hepatitis B (CHB) infection is divided into four disease phases that are closely associated with age but are not necessarily sequential (Supplementary Figure S1): hepatitis B envelope antigen (HBeAg)-positive chronic infection (also known as immune tolerant [IT]), HBeAg-positive chronic hepatitis (also known as immune active [IA]), HBeAg-negative chronic infection (also known as immune control [IC], immune clearance, or immune inactive), and HBeAg-negative chronic hepatitis (also known as immune escape).¹ Some patients will not fall into any of these disease phases and are described as belonging to the 'grey zone',² which includes adult HBeAg-positive patients with normal alanine aminotransferase (ALT) but high or decreasing HBV DNA levels and adult HBeAg-negative patients with normal ALT but increasing HBV DNA levels.

Supplementary File 2: Search strategy for clinical review

PubMed searches were performed for HBV and adverse liver outcomes, HBV integration, and HBV treatment and cost (Supplementary Figure S2).

PubMed search terms:

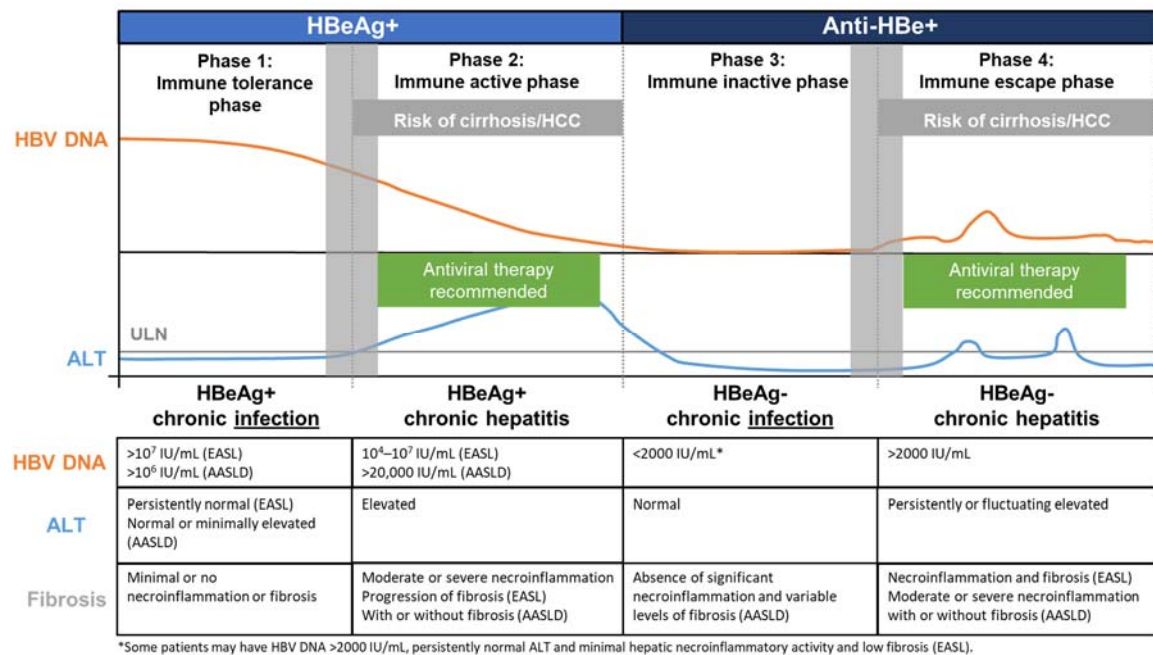
- HBV and adverse liver outcomes: "hepatitis B AND risk AND predict OR inform AND liver cirrhosis OR liver fibrosis OR hepatocellular carcinoma OR liver neoplasms OR disease progression AND clinical OR cohort OR registry OR study OR trial OR prospective OR retrospective"
- HBV integration: "hepatitis B virus OR HBV AND integration OR translocation AND hepatocellular carcinoma OR liver cancer OR liver neoplasms" and "hepatitis B virus OR HBV AND hepatocellular carcinoma OR liver cancer OR liver neoplasms AND molecular mechanisms"
- HBV treatment and cost: "hepatitis B AND chronic AND treatment and cost"

Inclusion criteria: articles of any type published up to 10 June 2021 were included.

Abstracts from three major international liver congresses (The International Liver Congress, The Liver Meeting and The Conference of the Asian Pacific Association for the Study of the Liver [APASL]) from 2019–2021 were also searched using the term ‘HBV’. Abstracts were manually reviewed and search results graded according to evidence and analysis type, strength of conclusions, and relevance to search objective. All authors reviewed results of the literature search and provided feedback as to which publications to omit and additional articles to include that had not been identified in the literature search.

For completeness, a full list of relevant literature – including additional papers suggested by authors during review of the selected literature – is provided in Supplementary File 2.

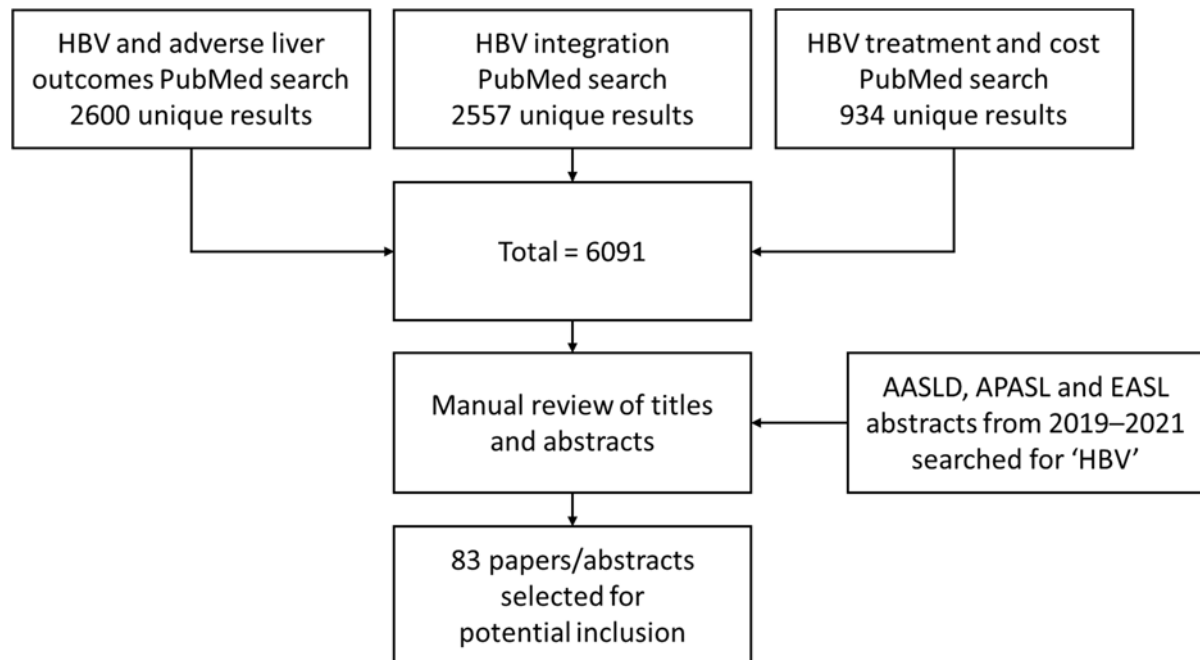
Supplementary Figure S1. CHB disease phases



The upper panel summarizes the changes in HBeAg status and HBV DNA and ALT levels associated with the four CHB disease phases. The lower panel includes the definitions of these phases according to EASL and AASLD guidelines.^{1,3} Patients in the HBeAg-positive chronic infection/immune-tolerant disease phase are HBeAg positive, with high HBV DNA levels and normal or minimally elevated ALT. These patients are considered to have minimal or no necroinflammation or fibrosis and are typically ineligible for antiviral treatment. Patients in the HBeAg-positive chronic hepatitis/immune-active disease phase are HBeAg positive, with decreasing HBV DNA levels and elevated ALT. These patients have evidence of liver damage, are considered at risk of cirrhosis and/or HCC, and are therefore eligible for antiviral treatment. Patients in the HBeAg-negative chronic infection/immune-control phase are HBeAg negative, with low HBV DNA levels and normal ALT. These patients are considered to have no significant necroinflammation, may have variable levels of fibrosis and are typically ineligible for antiviral treatment. Patients in the HBeAg-negative chronic hepatitis/immune-escape disease phase are HBeAg negative, with HBV DNA above 2000 IU/mL and persistently or fluctuating elevated ALT. These patients have evidence of liver damage, are considered at risk of cirrhosis and/or HCC, and are therefore eligible for antiviral treatment. AASLD, American Association for the Study of

Liver Diseases; ALT, alanine aminotransferase; CHB, chronic hepatitis B; EASL, European Association for the Study of the Liver; HBe, hepatitis B e; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ULN, upper limit of normal. (Figure adapted with permission from ©NICE 2013 Hepatitis B (chronic): diagnosis and management clinical guidelines. Available from <https://www.nice.org.uk/guidance/cg165>. All rights reserved. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this publication.)

Supplementary Figure S2. Flow diagram of literature search for clinical review



This flow diagram summarizes the literature search performed as part of this clinical review. Three PubMed searches were performed for HBV and adverse liver outcomes, HBV integration, and HBV treatment and cost. Articles of any type published up to 10 June 2021 were included, leading to a total of 6091 papers. Abstracts from three major international liver congresses (The International Liver Congress, The Liver Meeting, and The Conference of the Asian Pacific Association for the Study of the Liver [APASL]) from 2019–2021 were also searched using the term 'HBV'. All abstracts were manually reviewed and search results graded according to evidence and analysis type, strength of conclusions, and relevance to search objective. Eighty-three papers and congress abstracts were selected for potential inclusion in this clinical review, but only those directly relevant to the topic were cited due to space constraints. AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus.

Supplementary Table S1. Risk of liver damage in CHB patients with normal or minimally elevated ALT levels

Author and year	Study type	Patient population	Key finding
HBeAg-positive IT disease phase			
Lai 2007 ⁴	Retrospective review	CHB patients with persistently normal ALT, ALT 1–1.5x ULN*, and ALT >1.5x ULN* (N=192)	<ul style="list-style-type: none"> • 18% of patients with persistently normal ALT had stage 2+ fibrosis and 34% had grade 2 or 3 inflammation
Kumar 2008 ⁵	Prospective study	Asymptomatic CHB patients with persistently normal ALT or persistently or intermittently elevated ALT [†] (N=1387)	<ul style="list-style-type: none"> • Fibrosis stage ≥2 was present in 40% (HBeAg positive) and 13% (HBeAg negative) of CHB patients with persistently normal ALT
Wong 2008 ⁶	Prospective study	Treatment-naïve HBeAg-negative CHB patients stratified into five groups according to ALT level (N=1197)	<ul style="list-style-type: none"> • Patients with ALT levels >0.5–1x ULN[‡] had significantly increased risk of possible and probable cirrhosis compared with patients with ALT levels ≤0.5x ULN (p<0.001)[‡]
Zhang 2021 ⁷	Meta-analysis	19 studies in treatment-naïve CHB patients with normal ALT* (N=2771)	<ul style="list-style-type: none"> • Approximately 1/3 patients showed significant histological changes and 3% had cirrhosis

*ULN defined as 40 U/L. [†]Persistently normal defined as ≤40 IU/L, persistently or intermittently elevated defined as >40 IU/L. [‡]ULN defined as 58 IU/L. ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B envelope antigen; IT, immune tolerant; ULN, upper limit of normal.

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Supplementary File 2: Additional literature

Studies evaluating HCC risk in CHB patients with no antiviral treatment

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