GESA
Gastroenterological Society of Australia

Australian consensus recommendations for the management of hepatitis B infection

ashm

ASID

Australian Indigenous Doctors' Association

Australian College of Rural & Remote Medicine
WORLD LEADERS IN RURAL PRACTICE

ACMAV

AUSTRALASIAN HEPATOLOGY ASSOCIATION

LIVER FOUNDATION

hepatitis australia

RACP
Specialists. Together
EDUCATE ADVOCATE INNOVATE

ISBN 978-0-6488453-9-3

First published March 2022.

Disclaimer

The recommendations in this consensus statement represent the best available evidence at the time of compilation and are intended to be used as a guide only. The compilers of these recommendations shall not be liable for any loss, direct, indirect or consequential, on whatsoever account for any omission or negligent misstatement contained herein, or by reason of, arising from or in relation to any such user, by any other person, company or body relying or acting upon or purporting to rely or act upon any matter contained therein or arising thereout.

Suggested citation

Hepatitis B Consensus Statement Working Group. Australian consensus recommendations for the management of hepatitis B infection. Melbourne: Gastroenterological Society of Australia, 2022.

Contact

Gastroenterological Society of Australia
Level 1, 517 Flinders Lane
Melbourne VIC 3000
Australia
Phone: 1300 766 176
Website: www.gesa.org.au
Email: gesa@gesa.org.au

Contents

List of Figures

List of Tables

Abstract

Introduction

The prevalence of hepatitis B virus (HBV) infection in Australia is nearly 1%. In certain well-defined groups, the prevalence is far greater, yet an estimated 27% of people living with hepatitis B remain undiagnosed. Appropriate screening improves detection, increases opportunity for treatment and ultimately reduces the significant morbidity and mortality associated with the development of liver fibrosis and hepatocellular carcinoma (HCC).

Main recommendations

This statement highlights important aspects of hepatitis B management in Australia through 32 recommendations covering six areas: (1) prevalence, transmission and high-risk populations; (2) natural history of hepatitis B; (3) diagnosis and monitoring; (4) antiviral treatment; (5) complications; and (6) special groups (pregnant women and people with immunosuppression, viral coinfection or renal impairment). There have been recent changes in nomenclature and understanding of HBV's natural history, as well as a newly defined upper limit of normal for the results of liver tests that determine disease phase classification and threshold for antiviral treatment. As the main burden of hepatitis B in Australia is within migrant and Indigenous communities, early identification and management of people living with hepatitis B is essential to prevent adverse outcomes, including liver cancer and cirrhosis.

Change in management as a result of this statement

The recommendations in this consensus statement aim to raise awareness of the management of hepatitis B in Australia. The timely identification of people living with hepatitis B and, where appropriate, commencement of antiviral therapy can prevent development of cirrhosis and HCC, mother-to-child transmission and hepatitis B reactivation in immunocompromised individuals. Recognising patient and viral factors that predispose to the development of cirrhosis and HCC will enable clinicians to risk-stratify patients and appropriately implement surveillance strategies to prevent these complications of hepatitis B.

1 Introduction

1.1 Scope and purpose

This consensus statement was developed to provide a list of contemporary recommendations for health professionals involved in the care of adult patients living with hepatitis B. It is applicable to all clinicians involved in the management of people with hepatitis B, including specialist and general physicians, general practitioners, nurses, health coordinators, hospital administrators and policy makers. This is an extensive audience, and the resultant document is comprehensive, with the intention from the outset to require ongoing revisions as developments inevitably occur in this area. It covers epidemiology, natural history, diagnosis and monitoring, treatment and complications, as well as specific subgroups, such as people with coinfection, immunosuppressed individuals with hepatitis B reactivation, people undergoing liver transplantation, those with renal impairment and pregnant women, especially with regard to preventing vertical transmission.

One of the primary objectives is to provide a consensus statement to inform clinical decisions and to set a standard of care, with particular reference to the Australian health care setting, thus providing a local context for management recommendations. The expected benefits of this consensus statement include a standardised approach to the management of hepatitis B across varied health care settings in Australia. At a community level, the benefits of producing locally relevant guidance are ultimately to improve the health care, experience and outcomes of people living with hepatitis B infection.

1.2 Organisational structure

A chair and co-chair were selected from among Executive members of the Liver Faculty of the Gastroenterological Society of Australia (GESA), the Australasian Society for Infectious Diseases (ASID) and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). A guideline steering committee, comprising leading experts in the management of hepatitis B in Australia, provided governance structure. The proposed consensus statement was divided into six sections, with section chairs responsible for each working group. An expert advisory group for each section was tasked with reviewing the relevant section and ensuring scientific quality. A consumer oversight group — comprising individual representatives from high-prevalence groups, such as Aboriginal and Torres Strait Islander peoples and the Asian population, as well as people living with hepatitis B — reviewed the document and provided consumer feedback (see section 1.3).

More than 60 individuals contributed to this document. Patient advocacy and community groups were consulted and invited to working groups to provide advice from a patient and community perspective. Suggestions were then relayed through the working group chairs to the steering committee. A complete list of contributors, with their roles, disciplines and institutions, is provided in the Acknowledgements.

1.3 Notes on terminology

The consumer oversight group reviewed the draft of this document to ensure that due consideration is given to cultural groups who have a high prevalence of people living with hepatitis B; that the language used in reference to people living with hepatitis B is appropriate and sensitive; that the information provided in the consensus statement is balanced, fair and free from prejudice and bias; and that the information is complete, without significant omissions.

Rather than describing people with primary reference to the hepatitis B virus (HBV) (e.g. *HBV-infected people*), the preferred language is to refer to *people living with hepatitis B*. It was considered acceptable to refer to individuals as *patients* when discussing people living with hepatitis B who are engaged in health care.

With reference to Aboriginal and Torres Strait Islander peoples, these people are hereafter sometimes respectfully referred to as *Indigenous Australians*.

With reference to natural history and hepatitis B phases, we have endeavoured to embrace the latest terminology suggested by the European Association for the Study of the Liver (EASL) guidelines.[1] However, for clarity, especially for those readers familiar with the previous terminology, both terms have often been included where terms have changed. The terms *inactive carrier* and *healthy carrier* have not been used, as the former implies that the disease is inactive and the latter that the individual is healthy and therefore does not require active management and monitoring.

With reference to risk factors for acquisition of hepatitis B, the focus is on types of high-risk behaviour rather than particular community groups at risk.

With regard to immigration of people living with hepatitis B, the consumer oversight group considered the delicate balance between identifying people from high-prevalence countries who require screening and avoiding the implication that hepatitis B is an "imported disease", resulting in stigmatisation of an already vulnerable group. To raise awareness of the issues faced by immigrants to Australia, a summary of requirements for hepatitis B testing and the implications of a positive test result has been included (see section 6.3).

When discussing treatment with antiviral drugs, the terms *compliance* and *non-compliance* have been avoided, as they imply both a level of coercion or control by the health care provider and passivity of the health care recipient. The more positive term *adherence* (and *non-adherence*) is preferred, as this implies proactive behaviour. Alternatives are simply to describe the behaviour (e.g. *patients who stop taking their medication* or *patients who are disengaged with care*).

1.4 Declaration of funding

Unconditional grant funding was provided to GESA for completion of this consensus statement. Details of GESA's funding sources are available on the website (www.gesa.org.au). Sponsoring organisations are listed in the Acknowledgements.

In addition, ASHM provided an unrestricted contribution to direct project expenses, to assist in completion of the consensus statement.

1.5 Editorial independence

The impetus to produce this consensus statement arose from the Liver Faculty membership of GESA. The Liver Faculty Executive voted unanimously to proceed and elected members of the steering committee from among the Liver Faculty Executive and representatives from the Infectious Diseases craft group (Professor Gail Matthews from ASHM and Professor Benjamin Cowie from ASID). The Executive approached Associate Professor John Lubel (GESA) and Professor Gail Matthews (ASID, ASHM) to lead the development of this consensus statement. The steering committee oversaw and endorsed the draft document. Funding was from unrestricted grants provided by GESA and ASHM, with editorial independence maintained throughout manuscript development. Consensus was ensured by use of the modified Delphi process, discussed in section 2.2.

1.6 Competing interests

All participants were required to submit a form detailing their conflicts of interest and were encouraged to disclose any potential personal or family-related competing interests. These are listed in the Author disclosures.

1.7 Disclaimer

The recommendations outlined in this document are not to be read or interpreted in isolation. The accompanying text and technical remarks provide important background information and context for each recommendation. Similarly, many of the recommendations complement each other and can be open to misinterpretation if taken in isolation.

The authors have at all times endeavoured to produce a contemporary document. However, as new approaches to screening and novel therapies are developed, this document will inevitably become outdated and require periodic revisions.

1.8 Endorsements

This consensus statement has been endorsed by the following organisations:

- Gastroenterological Society of Australia (GESA)
- Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)
- Australasian Society for Infectious Diseases (ASID)
- Australian Indigenous Doctors' Association (AIDA)
- Australian College of Rural and Remote Medicine (ACRRM)
- Australian Chinese Medical Association of Victoria (ACMAV)
- Australasian Hepatology Association (AHA)
- Liver Foundation
- Hepatitis Australia
- Royal Australasian College of Physicians (RACP)

1.9 What's new?

Although GESA has previously produced guidance on the management of hepatitis B, these documents are now more than a decade old and lack the rigour of development that contemporary guidelines demand. Since their publication, there have been significant changes in our understanding of the screening strategy, natural history and treatment of hepatitis B. This consensus statement summarises the current management of hepatitis B in Australia.

2 Methodology

2.1 Grading of evidence and strength of recommendation

The recommendations in this consensus statement have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[2,3] For each recommendation, the quality of the evidence has been classified as one of four levels — high (A), moderate (B), low (C) or very low (D) — and the strength of recommendation as either strong (1) or weak (2) (Table 1).

This consensus statement was developed in accordance with the principles outlined by the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument. This tool assesses the methodological rigour and transparency with which guidelines are developed and was first published in 2003.[4] The original AGREE instrument was refined in 2010, with the current AGREE II instrument being the preferred tool.[5]

2.2 Methodology for reaching consensus

Consensus was determined by employing the modified Delphi approach.[6-8] This method was chosen as it allows for expert interaction, and there is evidence to support use of the modified technique over the original Delphi method.[9] It particularly suited the period during the COVID-19 pandemic in Australia, as the first two rounds of interaction could be conducted without the need for face-to-face meetings. A final round of discussion allowed further clarification and debate of contentious issues in a face-to-face meeting that was held in Melbourne, Victoria, but included interstate participants via videoconference if they were unable or unwilling to travel.

The manuscript generation and editorial process involved the following steps:

1. the steering committee generated clinically relevant questions;
2. working groups of members with relevant expertise were formed and asked to prepare a comprehensive appraisal of the medical literature on each topic and to address the questions raised, using the GRADE system to determine quality of evidence and strength of recommendations;

Table 1. Quality of evidence and strength of recommendations

Evidence quality	Definition	Grade
High	We are very confident that the true effect lies close to that of the estimate of the effect.	A
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	B
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	C
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	D
Recommendation	**Notes**	**Grade**
Strong	Recommendation is made with strong certainty. Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes and cost.	1
Weak	There is variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or higher resource consumption.	2

3. working group chairs and the steering committee reviewed the recommendations and returned draft manuscripts to the working group members for further clarification or comment;
4. expert advisory groups for each section reviewed the recommendations and manuscript, verified scientific accuracy and identified deficiencies;
5. a consumer oversight group reviewed all sections of the manuscript and provided feedback and advice to the working group chairs; and
6. working group chairs reviewed all comments from the expert advisory group and consumer oversight group and returned secondary drafts to the steering committee for final comments and editing.

Recommendations were reviewed using the modified Delphi method, with an initial two-round online questionnaire asking all document contributors (when the topic was in their field of expertise) for:

- their level of agreement with each recommendation using a five-point Likert scale (see below);[10] and
- any additional comments on the recommendation.

A total of 68 experts and consumer representatives, including people with lived experience of hepatitis B, were invited to participate in the modified Delphi process, with 66 respondents (97%) to the first-round questionnaire. In the second-round questionnaire, 66 participants (100% of first-round participants) were given access to the median, mode and interquartile range (IQR) of the group score, their own individual previous score and any comments made by other participants and were asked to repeat their individual evaluation of the recommendation statements.

A five-point Likert scale (strongly disagree, disagree, neutral, agree, strongly agree) was used to determine level of agreement or disagreement. A decision rule with a supermajority of >80% (summative *agree* and *strongly agree* responses) was used as the determinant for consensus, as previously described.[9,11,12] A response period of 10 business days was given for each questionnaire round. All recommendations were then reviewed at the hybrid (face-to-face and online) workshop held on 14 May 2021 in Melbourne. There were 38 attendees at the venue and 19 online participants. Voting was conducted using a de-identified electronic voting system. Focused discussions were directed to recommendations that had not reached >90% consensus after the first two rounds. It was agreed through a voting process (using an 80% majority rule) that one recommendation (Recommendation 7) required rewording and was to be submitted to a third and final online questionnaire. None of the recommendations were voted to be excluded. The third-round questionnaire was sent to all participants, with 65 (98.5%) responding. This modified recommendation fulfilled the decision rule to be included. A table summarising the results of all modified Delphi rounds is provided in the Supplementary data.

3 Summary of recommendations

The final recommendations are listed in Table 2. However, readers should refer to the relevant sections of this document for additional information and not interpret the recommendations in isolation.

Table 2. Recommendations of the hepatitis B consensus statement

No.	Consensus recommendation	GRADE classification*	Level of agreement, *n*† (%)‡	Section
1	At a minimum, all population groups with elevated (≥2%) CHB prevalence, a high risk of transmission and/or an increased risk of adverse outcomes from HBV infection (Table 4) should be offered testing to determine their HBV status.	C1	66 (98.5%)	4.4.1
2	All individuals with CHB should have a culturally and language-appropriate discussion regarding the management of CHB (using an accredited interpreter when necessary).	C1	66 (98.5%)	4.4.2
3	The ULN for serum ALT should be considered 19 IU/L in females and 30 IU/L in males.	C1	63 (95.2%)	5.2.2
4	Evaluation of people with CHB infection should include repeated assessments (e.g. HBV serology, ALT, HBV DNA level) to determine phase of disease and requirement for antiviral treatment.	A1	65 (100%)	6.6.1
5	Non-invasive assessment of liver fibrosis should be performed in all people with CHB as part of initial assessment.	A1	63 (98.4%)	6.6.2
6	Liver biopsy should only be considered when it influences management (e.g. uncertainty regarding the staging of fibrosis or coexistent pathologies).	A1	60 (96.7%)	6.6.2.4
7	The treatment of people with HBeAg-positive chronic infection characterised by persistently normal ALT is not routinely recommended. Antiviral therapy may be considered in certain circumstances (Table 13).	B1	65 (94.9%)	7.5.1.1
8	In people with HBeAg-positive chronic hepatitis, antiviral therapy is indicated when HBV DNA is >20,000 IU/mL and ALT is persistently elevated or there is evidence of fibrosis.	A1	62 (98.4%)	7.5.1.2
9	In people with HBeAg-negative chronic hepatitis, antiviral therapy is indicated when HBV DNA is >2000 IU/mL and ALT is persistently elevated or there is evidence of fibrosis.	A1	63 (98.4%)	7.5.2.2
10	All people with cirrhosis and any detectable HBV DNA, regardless of ALT levels, should be treated with antiviral therapy.	A1	62 (100%)	7.5.3
11	Where oral antiviral therapy is indicated, a potent NA with a high barrier to resistance (entecavir, tenofovir) should be used.	A1	62 (100%)	7.6
12	Interferon-based treatment regimens are contraindicated in decompensated cirrhosis.	B1	59 (98.3%)	7.6
13	All people being treated with antiviral therapy should undergo periodic review, including ALT, serum HBV DNA and, for tenofovir, renal function (eGFR) and serum phosphate.	A1	64 (100%)	7.9

No.	Consensus recommendation	GRADE classification*	Level of agreement, *n*† (%)‡	Section
14	Cessation of oral antiviral therapy may be considered in people without cirrhosis following HBeAg seroconversion or sustained HBsAg loss after a period of treatment consolidation. However, regular monitoring must be undertaken after treatment cessation, preferably in consultation with a clinician experienced in treating hepatitis B.	B2	60 (90.0%)	7.10.1
15	HCC surveillance should be offered to all people with cirrhosis, as well as non-cirrhotic individuals at increased risk of HCC (Table 17).	C1	64 (98.4%)	8.1.1.1
16	Liver ultrasound should be performed every 6 months in people with CHB infection who require HCC surveillance.	B1	62 (98.4%)	8.1.1.1
17	HCC surveillance should continue in the event of observed HBsAg loss in individuals assessed as having a high baseline risk for HCC (Table 17).	C1	63 (88.9%)	8.1.1.1
18	People with acute or acute-on-chronic liver failure from hepatitis B should be managed in consultation with a liver transplant unit.	C1	60 (96.7%)	8.2.2
19	People with extrahepatic manifestations of CHB infection should receive antiviral treatment.	C1	58 (96.6%)	8.3
20	Metabolic comorbidities, including obesity, diabetes mellitus, hypertension and dyslipidaemia, should be screened for and optimally managed in people with CHB.	C1	62 (95.2%)	8.5.1
21	All pregnant women should be tested for HBsAg during antenatal screening. HBsAg-positive women should undergo evaluation of phase of HBV infection (ALT, HBeAg, HBV DNA) and for presence of clinical liver disease.	A1	65 (100%)	9.1
22	Pregnant women with high viral load (>200,000 or 5.3 $\log_{10}$ IU/mL) should be offered tenofovir from the 28th week of pregnancy to reduce the risk of perinatal transmission of hepatitis B.	A1	61 (100%)	9.1
23	Infants born to HBsAg-positive mothers should receive HBIG and hepatitis B vaccination as soon as possible after birth (optimally within 4 hours). Infants should receive routine HBV vaccination at 2, 4 and 6 months of age.	A1	63 (98.4%)	9.1
24	Children born to HBsAg-positive women should be tested for HBsAg and anti-HBs 3 months after the last vaccine dose to determine vaccine response and to exclude MTCT.	A1	62 (91.9%)	9.1
25	HBsAg-positive people receiving cancer chemotherapy or moderate- or high-risk immunosuppression for non-malignant conditions (Table 20) should be treated with entecavir or tenofovir.	B1	63 (96.8%)	9.2
26	HBsAg-negative/anti-HBc-positive people who are being treated with agents associated with high risk of HBV reactivation (Table 19) should be treated with entecavir or tenofovir.	B1	61 (98.4%)	9.2
27	HBsAg-positive people receiving low-risk immunosuppression for non-malignant conditions (Table 20) should be monitored for hepatitis B reactivation with 3-monthly ALT and 6-monthly HBV DNA testing.	B1	62 (87.1%)	9.2

No.	Consensus recommendation	GRADE classification*	Level of agreement, *n*† (%)‡	Section
28	Testing for HCV, HIV and HDV should be performed in all HBsAg-positive people at initial assessment and periodically if there is ongoing risk of infection.	B1	63 (88.9%)	9.3
29	HBsAg-positive people receiving DAA therapy for hepatitis C are at high risk of hepatitis B reactivation. People with cirrhosis or who otherwise meet the criteria for treatment for hepatitis B should be treated with entecavir or tenofovir.	C1	60 (93.3%)	9.3.1
30	HBsAg-negative, anti-HBc-positive people receiving DAA therapy are at very low risk of HBV reactivation and do not need monitoring for hepatitis B reactivation in this setting.	B1	60 (93.3%)	9.3.1
31	Treatment of HBV–HIV coinfection should be with HBV-active antiretroviral therapy, including tenofovir, regardless of HBV disease phase.	B1	47 (100%)	9.3.3
32	Entecavir (with dose adjustment) or TAF is the preferred antiviral therapy in HBsAg-positive people with established renal impairment.	B1	60 (98.3%)	9.4

ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; CHB = chronic hepatitis B; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HBeAg = hepatitis B e-antigen; HBIG = hepatitis B immunoglobulin; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis delta virus; MTCT = mother-to-child transmission; NA = nucleos(t)ide analogue; TAF = tenofovir alafenamide; ULN = upper limit of normal.

* GRADE quality of evidence classification: A = high; B = moderate; C = low; D = very low. Strength of recommendation: 1 = strong; 2 = weak.

† Number of experts who participated in the final modified Delphi process vote for this recommendation.

‡ Percentage of expert advisors who either agreed or strongly agreed (based on five-point Likert scale, comprising strongly disagree, disagree, neutral, agree and strongly agree) in the final modified Delphi round for each recommendation.

4 Prevalence, transmission and high-risk populations

Chronic hepatitis B (CHB) affects more than 250 million people worldwide,[13-15] most of whom were infected at birth or in early childhood.[16] Untreated CHB leads to advanced liver disease in up to a quarter of those affected and causes an estimated 800,000 deaths annually due to cirrhosis and hepatocellular carcinoma (HCC).[16,17] In addition to its associated mortality, CHB has considerable personal and social impact on affected individuals, families and communities.[18]

In Australia, it is estimated there were 222,599 people living with CHB in 2020, representing 0.9% of the population.[19] Vaccination has greatly reduced incident infections and CHB prevalence in younger people since its introduction in the 1980s,[15,20-22] but there remains a substantial adult population with CHB who were born before this era.

HBV is transmitted through blood and other body fluids. Globally, the most common routes of transmission are vertically from mother to child during birth, horizontally between children and family members, through sexual contact, through non-sterile medical procedures and blood transfusions and by sharing of drug-injecting equipment.[23] In Australia, the most common routes of transmission for newly acquired infection are injecting drug use and sexual contact.[24,25] The risk of chronic infection is greatest in those exposed to HBV early in life, while exposure in adulthood leads to self-limiting acute infection in most cases (>95%).[26,27] As a result, most people living with chronic infection acquired HBV at birth or in early childhood, emphasising the importance of screening based on country of birth.

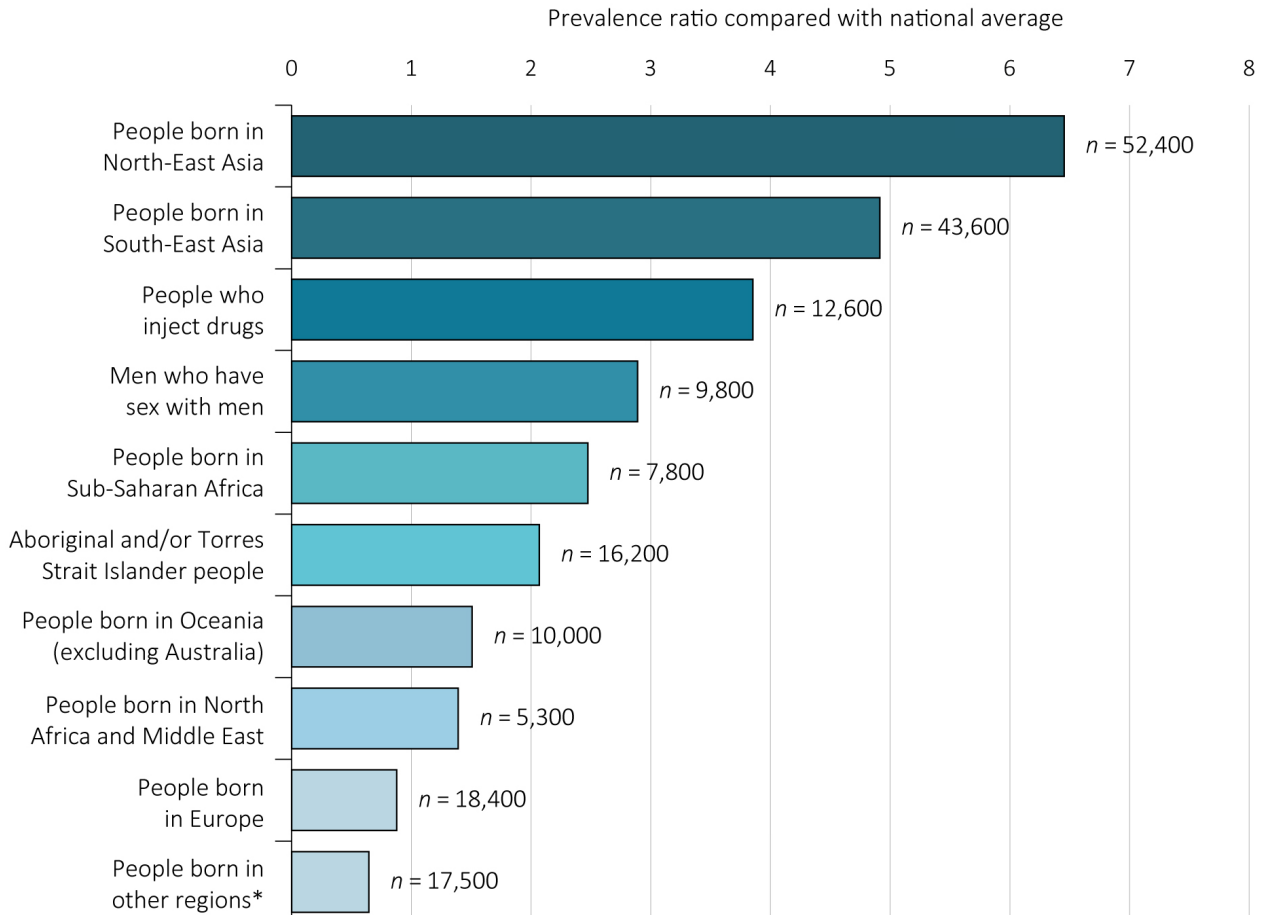
The populations at higher risk of CHB in Australia reflect these factors, with most affected people having been born overseas in regions of higher prevalence (Figure 1). Nearly half (46%) of all people living with CHB in Australia were born in the Asia-Pacific region, with the most common countries of origin being China, Vietnam and the Philippines.[28] Aboriginal and Torres Strait Islander people have also historically had a higher prevalence; they make up 3.3% of the total Australian population but represent about 7% of all people living with CHB in Australia.[28] Prevalence in Aboriginal and Torres Strait Islander people is highest in those who live in the most remote regions of the country.[28,29] CHB prevalence in Australia is highest in areas where these identified high-risk populations mostly reside, such as the Northern Territory, south-western Sydney and north-western Melbourne. In some of these regions, the prevalence of CHB reaches levels up to three times the national average (Figure 2).[28] The distribution of CHB prevalence is reflected in a similar regional pattern of liver cancer incidence.[28,30] People who inject drugs (PWID) and men who have sex with men (MSM) are also at greater risk of CHB in Australia, with a prevalence three to four times higher than that in the general population; they make up 5.6% and 4.3%, respectively, of the population affected by CHB (Figure 1).[28]

4.1 Vaccination and trends

Hepatitis B vaccination was first made available in Australia in the 1980s and was recommended for higher-risk groups, including Aboriginal and Torres Strait Islander people and infants born to mothers from high-prevalence regions. Universal vaccination was implemented in 1990 in the Northern Territory and in 2000 for all infants nationally.[31] In combination with adolescent catch-up programs, this has significantly reduced the incidence of newly acquired infection, particularly in young adults.[21] However, as vaccination cannot reduce prevalence in those already infected at birth or in early childhood, the number of people living with CHB in Australia has not declined during this period.[32] With increasing global coverage of hepatitis B vaccination, modelling estimates suggest the prevalence of CHB in Australia is expected to decline from 2028 onwards.[32] Within the Aboriginal and Torres Strait Islander population, prevalence has already begun to decline, and in many regions the CHB prevalence among those born in the vaccination era is now the same as in the non-Indigenous population.[20,29,33,34]

Globally, hepatitis B vaccination coverage has improved in recent years, but completion of the full three-dose schedule is still suboptimal, at 83% of

Figure 1. Prevalence ratio and total number of people living with chronic hepatitis B infection in Australia, by population subgroup, 2018



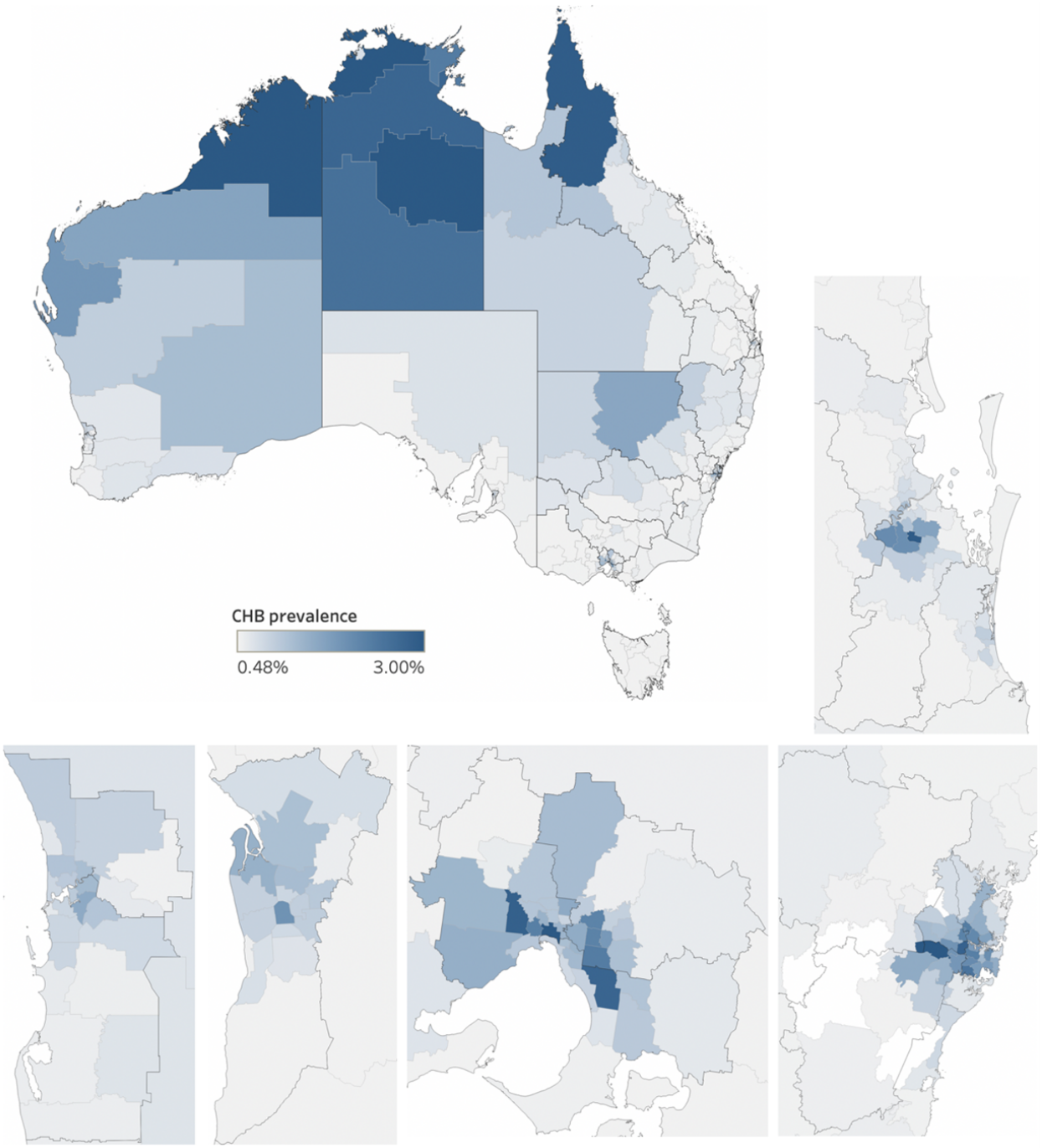
Data source: Chronic hepatitis B prevalence estimates based on mathematical modelling incorporating population-specific prevalence and population data.[28] Bars represent prevalence ratios and labels indicate number of people living with chronic hepatitis B infection.
* Includes people born in the Americas, Southern and Central Asia and those without a region of birth reported in the Census.

infants worldwide.[35] Birth-dose vaccination coverage, which is important in preventing vertical transmission, is even lower, sitting at 39% in 2016.[15] Vaccination uptake is high in the World Health Organization (WHO) Western Pacific Region (90%), which includes Australia and many countries from which migrants to Australia originate.[15] The impact of hepatitis B vaccination on CHB prevalence in many of these countries has been profound; most notably in China, where an estimated 28 million cases of CHB have been prevented through vaccination.[36] These shifts will continue to have flow-on effects for CHB prevalence in Australia if high vaccination rates are maintained and hepatitis B population prevalence continues to fall in key migrant source countries.

4.2 Treatment uptake and progress toward achieving WHO elimination targets

Australia has committed to both national and global strategic goals in relation to hepatitis B, aiming to improve diagnosis, treatment and care and therefore to reduce attributable mortality. At a global level, this includes commitments to eliminate hepatitis B as a public health threat by reducing incidence by 90% and mortality by 65% by 2030, through the achievement of targets of 90% for diagnosis and 80% for treatment uptake among those eligible for treatment.[37] At a national level, Australia is well short of reaching its strategic targets. Although there have been small improvements in the proportions of patients diagnosed and receiving care and antiviral therapy, these figures remain well below the target levels

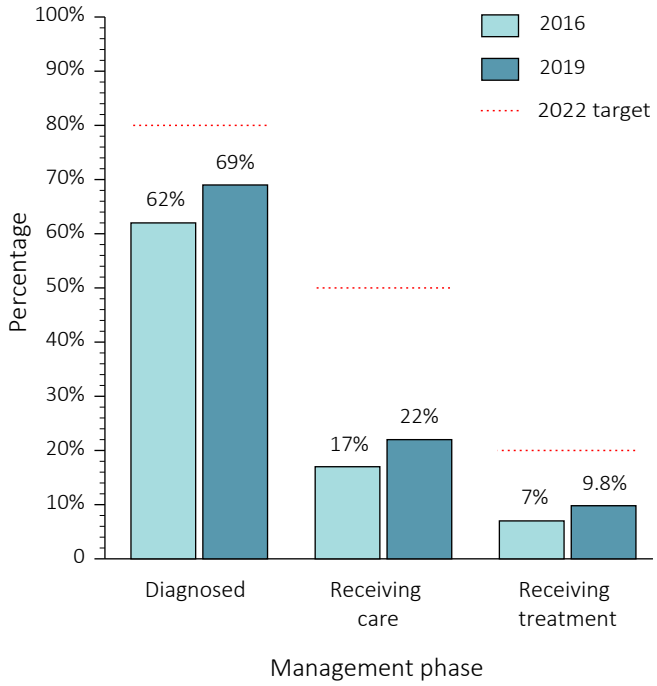
Figure 2. Prevalence of chronic hepatitis B infection in Australia, by statistical area, 2018



Data source: Chronic hepatitis B (CHB) prevalence estimates based on mathematical modelling incorporating population-specific prevalence and population data.[28] Prevalence of CHB by statistical area (level 3) using a heat map. Panels at the bottom show, from left to right, metropolitan maps for Perth, Adelaide, Melbourne and Sydney. The upper right map shows Brisbane.

(Figure 3).[19,38,39] Estimates for 2020 suggest that 73% of people living with CHB in Australia were diagnosed (target, 80%), 22.6% were receiving care (target, 50%) and only 10.7% of all those with CHB were receiving treatment (target, 20%).[19] With more than 1700 preventable deaths anticipated as a consequence, at the current rate of progress, Australia is projected to reach the National Hepatitis B Strategy targets in 2045 for the proportion in care and in 2046 for the proportion receiving treatment.[32] The 20% treatment target is based on natural history studies that estimate the proportion of people living with CHB who are

Figure 3. Cascade of care for chronic hepatitis B in Australia



Data sources: Chronic hepatitis B prevalence estimates based on mathematical modelling incorporating population-specific prevalence and population data.[28] Treatment and care data from Department of Human Services Medicare statistics. These are compared with 2022 national targets (red dashed lines).[28,38,39]

eligible for treatment in accordance with national[32,40] and international guidelines.[1,41] This estimate is influenced by demographic and clinical factors, and local modelling estimates suggest that up to 30% of Australians living with CHB are eligible for treatment under current Pharmaceutical Benefits Scheme (PBS) subsidy criteria.[32,42]

4.3 Hepatitis B-related advanced liver disease and mortality

In Australia, data from 1990 to 2002 showed that people living with CHB infection had a 12-fold higher risk of liver-related mortality and a 28-fold higher risk of liver cancer-related mortality than people without CHB.[43] Updated data for these risk estimates are not available, but it is expected they will have declined since highly effective antiviral therapy became available in Australia in 2005. The global burden of hepatitis B-related liver cirrhosis and liver cancer predominantly affects the Asia-Pacific region and Sub-Saharan Africa,[44] and the burden of HBV-related liver disease in Australia is disproportionately borne by migrants from these regions.[45,46] Aboriginal and Torres Strait Islander people are also at higher risk of HBV-related liver cirrhosis and liver cancer than non-Indigenous Australians.[47-49] This is thought to be partly due to the strong predominance of the subgenotype C4 infection, which carries a greater risk of liver fibrosis progression and liver carcinogenesis,[50] as well as the impacts of geographic remoteness and more limited access to health care services.[51]

Modelling has estimated that, in 2017, there were 12,000 people living with cirrhosis attributable to hepatitis B in Australia and 452 hepatitis B-related deaths, representing a reduction from the estimated peak of 575 deaths in 2007.[32] These findings have been supported by a linkage analysis of real-world hospital admissions data in New South Wales between 1993 and 2012, which identified a decline in age-standardised mortality attributable to hepatitis B, particularly from decompensated cirrhosis, likely reflecting the impact of treatment.[45] This study only captured patients with more advanced disease requiring hospitalisation and may therefore have underestimated the incidence of hepatitis B-related liver cirrhosis in the community.

In Australia between 1985 and 2017, 9% of liver transplants overall were attributable to hepatitis B-related liver disease, and 22% of liver transplants performed for HCC were attributable to hepatitis B. Relative to other causes of liver disease, the requirement for liver transplantation for hepatitis B-related liver disease is declining, likely reflecting the reduction in incidence of end-stage liver disease due to hepatitis B. The relative proportion of transplants performed for hepatitis B-related liver failure reduced from 6% during 1985–1999 to 2% during 2010–2017, while transplants for hepatitis B-related HCC also declined slightly (from 30% in 1985–1999 to 26% in 2009–2017) (unpublished data, Australian and New Zealand Liver Transplant Registry Database).[52]

The model-derived estimate of the number of deaths from HBV-related HCC in Australia in 2017 is 333, down from the estimated peak of 413 in 2007.[32] Despite this decline, HCC continues to be a significant cause of mortality for people with CHB infection. In a prospective population-based study in Victoria in

2012–2013, 22% of 272 identified incident cases of HCC were attributable to CHB, which was the third most common aetiology after hepatitis C and alcohol-related liver disease.[53,54] The NSW linkage studies have shown that 28% of all deaths in people with diagnosed CHB were liver-related, including 16% attributable to HCC.[45,55] A significant proportion of these deaths may have been preventable, given there was evidence of late diagnosis of CHB in up to a third of cases.[56]

Aboriginal and Torres Strait Islander Australians have a higher risk of HCC and HCC-related mortality than non-Indigenous Australians, and CHB is the most common aetiology in this population.[47] Data from retrospective analyses of the Northern Territory and South Australian cancer registries suggest the age-adjusted incidence of HCC is between four and six times higher in Indigenous Australians.[47,57,58]

4.4 Screening for hepatitis B virus infection

Several criteria for population-based disease screening have been specified,[59,60] and the evidence supporting the impact of early detection and treatment of CHB clearly justifies a recommendation for screening people at higher risk (Table 3).[61,62]

4.4.1 Cost-effectiveness of screening

Australian-specific evidence for cost-effectiveness of HBV screening strategies is limited. However, local modelling work has indicated that a comprehensive program of improved management, appropriate treatment and HCC surveillance among people with CHB is cost-effective compared with the current practice of limited treatment uptake or with HCC surveillance alone.[74] Improving the level of diagnosis and uptake of care for CHB has also been shown to be a cost-effective strategy,[68,75] but there has not yet been assessment of the impact of population-based testing based on prevalence.

However, there is considerable international evidence, from health systems similar to Australia's, that screening people for CHB is cost-effective. Studies in the United States, Canada and the Netherlands have found that screening of migrants from high-prevalence regions is cost-effective,[70-72,76-78] and one study specifically indicated that screening and referral would be as cost-beneficial as universal vaccination.[79] High levels of cost-effectiveness have also been shown for screening in other high-prevalence populations, including PWID and MSM.[76] The threshold for CHB prevalence at which screening becomes cost-effective varies across studies, with evidence from Canada showing decreased cost-effectiveness at a prevalence lower than 2%,[77] while other studies from Canada,

Table 3. Screening criteria and supporting evidence for chronic hepatitis B

Criterion	Evidence
Clinical importance based on prevalence, natural history and burden	• High-risk populations for CHB in Australia have a prevalence above 2% (see Table 4) • 15%–25% of people with CHB develop end-stage liver disease because of infection[16]
Available, valid, reliable and acceptable test	• Accredited hepatitis B testing is highly valid and reliable[63] • Hepatitis B testing is rebated by the Medicare Benefits Schedule[64]*
Available and accessible treatment with benefits when disease detected early	• Hepatitis B treatment is shown to reduce HCC incidence and liver-related mortality[65-67] • Treatment is subsidised by the Pharmaceutical Benefits Scheme[42]*
Evidence of impact of early diagnosis on reducing transmission, morbidity and mortality	• Early diagnosis allows access to treatment benefits (see above) • Modelled evidence shows improved diagnosis and treatment will reduce mortality[32,68] • Diagnosis allows vaccination of susceptible contacts to reduce transmission
Feasibility and cost-effectiveness of screening	• International data from settings with low hepatitis B prevalence indicate acceptable cost-effectiveness compared with established Australian thresholds[69-72]

CHB = chronic hepatitis B; HCC = hepatocellular carcinoma.
* For those patients eligible for Medicare; up to 10% of people living with CHB do not meet this criterion.[73]

Table 4. Groups that should be screened for hepatitis B in Australia

Group for screening*	Justification
Populations with higher prevalence of CHB	**Estimated prevalence of CHB**
People who inject drugs	3.8%[81]
Men who have sex with men	2.8%
Aboriginal and Torres Strait Islander people†	2%–8%[32,34,82,83]
People living with chronic hepatitis C	5%–7%[40,45,84]
People who have ever been incarcerated	2%–3%[85,86]
People born overseas in regions with ≥2% CHB prevalence[13,87-89]	**Estimated prevalence of CHB**
People born in North-East Asia	6.2%
People born in South-East Asia	4.8%
People born in the Pacific Islands†	2.9%
People born in North Africa	2.7%
People born in Central Asia	2.2%
People born in Southern Europe	2.3%
People born in Eastern Europe	2.0%
People born in Sub-Saharan Africa	2.4%
Populations with higher risk of onward transmission and/or adverse outcomes	**Reason**
Pregnant women	Additional prevention measures for women with CHB further reduces transmission risk[90,91]
People receiving immunosuppressive therapy	Risk of CHB exacerbation and death without prophylaxis[92,93]
Health care workers‡	High risk of transmission (if performing exposure-prone procedures);[94] treatment may be required to reduce viral load[95]
People with other chronic liver diseases (e.g. metabolic-associated fatty liver disease)	Risk of liver disease flare in people with comorbid disease[96]
People undergoing renal dialysis§	Higher transmission risk and more severe disease progression[97]
People living with HIV§	Higher susceptibility to CHB and more severe disease progression[98]
Household and sexual contacts of people with CHB	Significant risk of transmission through household[99] and sexual contact[100]
Children born to mothers with CHB	Significant risk of transmission in infants born to mothers with high viral load, even with vaccination[91]
People with multiple sexual partners	Risk of sexual transmission[100,101]

CHB = chronic hepatitis B. * Grade of recommendation for all these groups is strong. † Māori and other Indigenous peoples are also at higher risk of CHB and should be offered screening. ‡ All health care workers should be offered hepatitis B testing, while respecting their rights of privacy and legal protection in the workplace. § These people are also likely to have a higher prevalence of CHB.

the US and the Netherlands showed screening was cost-effective at a prevalence threshold of <0.5%.[69,71,72] This is below the average CHB prevalence in the general Australian population,[28] indicating that a broad approach to inclusion criteria for screening is justified. Although each health system is unique, and cost-effectiveness findings are not always applicable across countries, these various findings strongly suggest that, in the Australian context, screening of people at greater risk of CHB (prevalence ≥2%, as in Table 4) is likely to be cost-effective.

An estimated 27% of all people living with hepatitis B are undiagnosed, and late diagnosis remains common.[19,56] Disease progression occurs over time, and diagnosis may not be made until late-stage liver disease is evident. Opportunistic screening should be expanded to prevent adverse outcomes, such as cirrhosis and HCC,[32,38] given that early detection

and treatment reduce morbidity and mortality risks.[65,67,80] Screening is also recommended for people with increased risk of transmission (e.g. pregnant women) or severe disease (e.g. those undergoing immunosuppressive therapy), given the availability of highly effective prevention strategies.

Technical remarks

1. There is strong epidemiological evidence of the burden of disease attributable to undiagnosed CHB infection and the benefits of treatment.
2. There is limited quality clinical evidence assessing the outcomes of testing strategies to support CHB screening recommendations.
3. Cost-effectiveness data from similar settings to Australia support the application of a 2% CHB prevalence threshold for screening.
4. Estimates of CHB prevalence in population groups are based on local seroprevalence studies, where available, supplemented with international data.
5. Cost-effectiveness studies in the Australian context and ongoing assessment of changing CHB prevalence are required to further inform screening recommendations.

Recommendation 1

At a minimum, all population groups with elevated (≥2%) CHB prevalence, a high risk of transmission and/or an increased risk of adverse outcomes from HBV infection (Table 4) should be offered testing to determine their HBV status. (Evidence quality: Low; Grade of recommendation: Strong)

4.4.2 Pre-test consent and counselling

Before testing for CHB is carried out, it is important that appropriate consent is obtained and pre-test counselling is performed. As most people living with CHB come from culturally and linguistically diverse communities, it is essential that discussions are held before testing and after diagnosis, with the assistance of an accredited interpreter when necessary. Family members should not serve as convenient translators, as individual confidentiality and impartiality are important aspects of information transfer to people living with hepatitis B.

Recommendation 2

All individuals with CHB should have a culturally and language-appropriate discussion regarding the management of CHB (using an accredited interpreter when necessary). (Evidence quality: Low; Grade of recommendation: Strong)

5 Natural history of hepatitis B

It is important to be aware of the definitions of various infection states, ranging from acute to chronic infection, as well as the state of natural immunity and occult infection. These definitions are summarised in Table 5.

5.1 Acute hepatitis B infection

5.1.1 Definition of acute hepatitis B infection

Acute HBV infection is clinically defined as the acquisition of new hepatitis B infection in a previously uninfected individual, with persistence of hepatitis B surface antigen (HBsAg) for less than 6 months. Beyond this time, the HBV infection is defined as chronic. The period of acute infection is characterised by detectable levels of HBsAg, hepatitis B core antibody (anti-HBc) immunoglobulin M (IgM) and HBV DNA.[102]

5.1.2 Outcomes of acute hepatitis B infection

The clinical course of acute HBV infection can be variable and is dependent on the complex interplay between viral replication and the individual's innate and adaptive immune system response to the virus.[103,104] Viral clearance involves an adaptive T-cell reaction that induces both cytolytic-dependent and -independent antiviral effects exerted by antiviral cytokines, as well as the induction of B cells to produce neutralising antibodies aimed at diminishing the virus. People who achieve serological recovery from acute HBV infection are thought to have a strong T-cell response to several epitopes in different regions of the HBV genome, whereas those who become chronically infected exhibit a weaker response.[105,106] A robust and aggressive immune response can result in fulminant HBV infection, which occurs in about 1% of acute HBV cases and can be catastrophic. This is accompanied by marked elevations in liver transaminase levels, elevated bilirubin levels, prolongation of the international normalised ratio (INR) and the development of hepatic encephalopathy. Survival of patients with acute liver failure is only about 25% without liver transplantation.[107] Acute liver failure is more likely to occur in older patients and those with chronic hepatitis C virus (HCV) or hepatitis D virus (HDV) coinfection.[108]

Clearance rates and progression to CHB infection are highly dependent on genetic variations in viral proteins, host immunological factors and the age at which HBV is acquired. Most individuals infected with HBV will transition through a series of clinical events. The first event is the incubation period, which ranges from 1 to 6 months, during which time the person

Table 5. Definitions of hepatitis B stages

Acute hepatitis B infection is defined as the presence of HBsAg and anti-HBc IgM in blood that persists for less than 6 months. These serological findings may be accompanied by physical signs of an acute illness, from mild to severe disease, or people may be asymptomatic with changes in transaminase levels.
Chronic hepatitis B infection is defined as persistence of infection (presence of HBsAg in blood) for longer than 6 months (persistence of infection can be presumed based on history and likely source of infection).
Occult hepatitis B infection is defined as negative HBsAg and either positive or negative anti-HBc, with HBV DNA detectable in blood or liver tissue.
Immune through past infection (cleared or natural immunity) is defined as positive anti-HBc and anti-HBs. However, HBV DNA may persist in hepatocytes, and reactivation can occur with severe immunosuppression (see section 9.2).
Newly acquired hepatitis B infection is a surveillance definition for HBV that has been acquired in the past 24 months, where previous serological test results have been negative, or where anti-HBc IgM is positive, indicating recent infection.[102]

anti-HBc = hepatitis B core antibody (total, includes IgM and IgG); anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgG = immunoglobulin G; IgM = immunoglobulin M.

is asymptomatic. This is followed by the prodrome, which may be associated with a serum sickness-like syndrome or symptoms of nausea, jaundice and right upper quadrant discomfort. The third event is referred to as the icteric phase, which may last from 1 to 3 months.[109] The final phase is resolution, with loss of HBsAg, appearance of hepatitis B surface antibody (anti-HBs) and long-term immunity to HBV. The rate at which a patient develops protective anti-HBs is directly proportional to the severity of the acute infection and the development of jaundice but inversely related to patient age.

5.1.2.1 Impact of age on outcome of acute hepatitis B infection

About 90% of children with perinatally acquired HBV infection will remain hepatitis B e-antigen (HBeAg)-positive at the age of 15–20 years. HBeAg positivity decreases with increasing age, so that less than 10% of adults older than 40 years remain HBeAg-positive.[110] Characteristically, the histological injury is mild,[111,112] despite high viraemia, because of immune tolerance, which is probably a result of clonal deletion of T cells against HBV in the fetus induced by in utero exposure to HBeAg.[113] These children are often asymptomatic. Fulminant hepatitis is rare but can be seen, particularly in infants born to mothers with HBeAg-negative CHB infection.[112] Studies following cohorts of children infected in infancy or early childhood show that rates of spontaneous HBeAg seroconversion increase with age, with annual rates less than 2% in children under 3 years of age and increasing to 8% in puberty and early adulthood.[114,115]

Children over the age of 5 years who acquire HBV infection may display symptoms, including fatigue, myalgias, arthralgias and abdominal pain. These symptoms typically last only 1–5 days before resolving spontaneously.[116] Infections that have been acquired through parenteral transmission are more likely to clear, with disappearance of HBeAg and HBV DNA in the first two decades of life.[117] However, a significant proportion of these children will still progress to CHB infection. A long-term follow-up of cases acquired in childhood in Italy showed that 15% of patients cleared HBsAg, most (95%) had inactive HBV infection and 2% developed HCC over a 20-year period.[118] Sex and HBV genotype may also influence spontaneous HBeAg seroconversion. In boys, HBeAg seroconversion rates are higher in those who achieve puberty at an earlier age and may be associated with increasing testosterone levels. In girls, higher rates of HBV clearance and earlier spontaneous HBeAg seroconversion are seen in those who reach menarche before the age of 11.5 years.[119] HBeAg seroconversion rates are lower in those with HBV genotype C compared with genotype B.[120]

Cirrhosis is uncommon during childhood. In a Taiwanese cohort study, cirrhosis (confirmed by liver biopsy) developed in 5% of HBsAg-positive children.[121] HCC has been described in both Asian and European children with perinatal infection.[122-124] HCC in children occurs mainly in those older than 6 years, with a male predominance.[122-124] Most childhood cases of HCC (80%) are hepatitis B e antibody (anti-HBe)-positive and accompanied by cirrhosis. HCC has been described in children who have undergone early HBeAg seroconversion or rapid progression to cirrhosis.[123,124] This suggests that severe necroinflammation may occur during the process of HBeAg seroconversion, leading to cirrhosis, which is a risk factor for HCC. Cirrhosis, although infrequent, has also been observed in European paediatric populations. Cirrhosis was present in 3%–4% of patients at baseline in cohort studies of Italian and Spanish children with CHB infection.[118,125,126]

Most guidelines state that acute HBV infection acquired in adulthood is self-limiting in more than 95% of immunocompetent patients. However, recent studies have implied a more variable course and that it may take up to 12 months to clear HBsAg. In a Japanese study, genotypes A and C were associated with a longer time to clear HBsAg. Higher HBV DNA and HBsAg levels early in the course of infection also correlated with likelihood of chronicity.[127] Clinical manifestations of acute HBV infection in adults include anorexia, nausea, jaundice and right upper quadrant discomfort. The symptoms and jaundice generally disappear after 1–3 months, but some patients have prolonged fatigue even after normalisation of serum aminotransferase concentrations. More than 95% of these people will resolve the acute infection and develop anti-HBs.[102]

5.2 Chronic hepatitis B infection

5.2.1 Definition of chronic hepatitis B

The persistence of HBsAg in a person's blood beyond 6 months after acute HBV infection is indicative of CHB infection. This is discussed in greater detail in section 6.2.

5.2.2 Definition of normal serum alanine aminotransferase level

Defining the upper limit of normal (ULN) for serum alanine aminotransferase (ALT) level is important in the management of hepatitis B, as ALT is used to define natural history stage and determines eligibility for, and response to, treatment. Pathology services in Australia do not have standardised ULN cut-offs for ALT level and have historically calculated the ULN from the ALT distribution in a "healthy" population. An inherent problem with such an approach is the failure to recognise individuals with undiagnosed liver disease, such as metabolic (dysfunction)-associated fatty liver disease (MAFLD) and alcohol-related liver disease.

Published hepatitis B guidelines differ in their definition of the ULN for ALT level. In the 2017 EASL guidelines, the "traditional" ULN for ALT is considered "approximately" 40 IU/L.[1] In the 2016 American Association for the Study of Liver Diseases (AASLD) guidelines, the ULN was defined as 30 IU/L for men and 19 IU/L for women,[128] based on a retrospective cohort study of healthy blood donors in Italy.[129] In the updated 2018 AASLD guidance, the ULN for ALT for the purposes of guiding hepatitis B management was refined to 35 IU/L for men and 25 IU/L for women,[41] based on studies in European, North American and Asian populations that placed the normal ULN in the range of 29–33 IU/L for men and 19–25 IU/L for women.[129-131] In the Asian Pacific Association for the Study of the Liver (APASL) 2016 guidelines, the magnitude of elevation of ALT was compared with laboratory reference levels, and a suggested "conventional" ULN of 40 IU/L was chosen.[132]

Relevant to this discussion is a large prospective study in Korea, which examined mortality from liver disease in 142,055 people (94,533 men and 47,522 women) aged 35–59 years, with an 8-year follow-up.[133] According to area under the receiver operator curve (AUROC) analysis, the best cut-off for prediction of liver disease in men was an ALT level >30 IU/L.

The available evidence would support the use of an ALT ULN level of 19 IU/L in women and 30 IU/L in men, as there is a definite increase in liver-related mortality in people with ALT levels above these thresholds. However, interpretation of the ALT level must be taken in the context of factors known to increase it, including elevated body mass index (BMI), reduced physical activity, increasing age, alcohol consumption and certain medications.

Recommendation 3

The ULN for serum ALT should be considered 19 IU/L in females and 30 IU/L in males. (Evidence quality: Low; Grade of recommendation: Strong)

5.2.3 Phases of chronic hepatitis B infection

The natural history of CHB infection varies considerably, owing to the complex and dynamic interplay of host, viral and environmental factors that alters patient outcomes.[134-143] The two major determinants of whether acute HBV infection progresses to CHB are age and immune competence at the time of HBV acquisition. The host immune response is also a critical determinant of the natural history of CHB. Furthermore, the host immune response to HBV is responsible for the liver injury that ultimately leads to fibrosis and cirrhosis, rather than being a direct cytopathic effect of the virus on hepatocytes.[144,145]

Our understanding of the natural history of CHB has changed considerably over the past six decades, since the identification in the early 1960s of the HBsAg protein, originally called the "Australian antigen".[146] CHB is increasingly recognised to have phases that reflect the dynamic interplay of the virus and the host immune response. The four major phases are:

- I: immune tolerant;
- II: immune clearance;
- III: immune control; and
- IV: immune escape.

These phases are undergoing nomenclature changes to more aptly reflect the level of HBV replication and degree of host immune response to the replicating virus, so they are now divided by HBeAg status (positive or negative) and absence or presence of hepatitis (Figure 4). Importantly, these phases are of variable duration, and not all patients transition through each phase in sequential order or at all (because the phase is either entirely missed or occurs very rapidly). Patients may also revert to earlier phases throughout the course of their CHB infection.

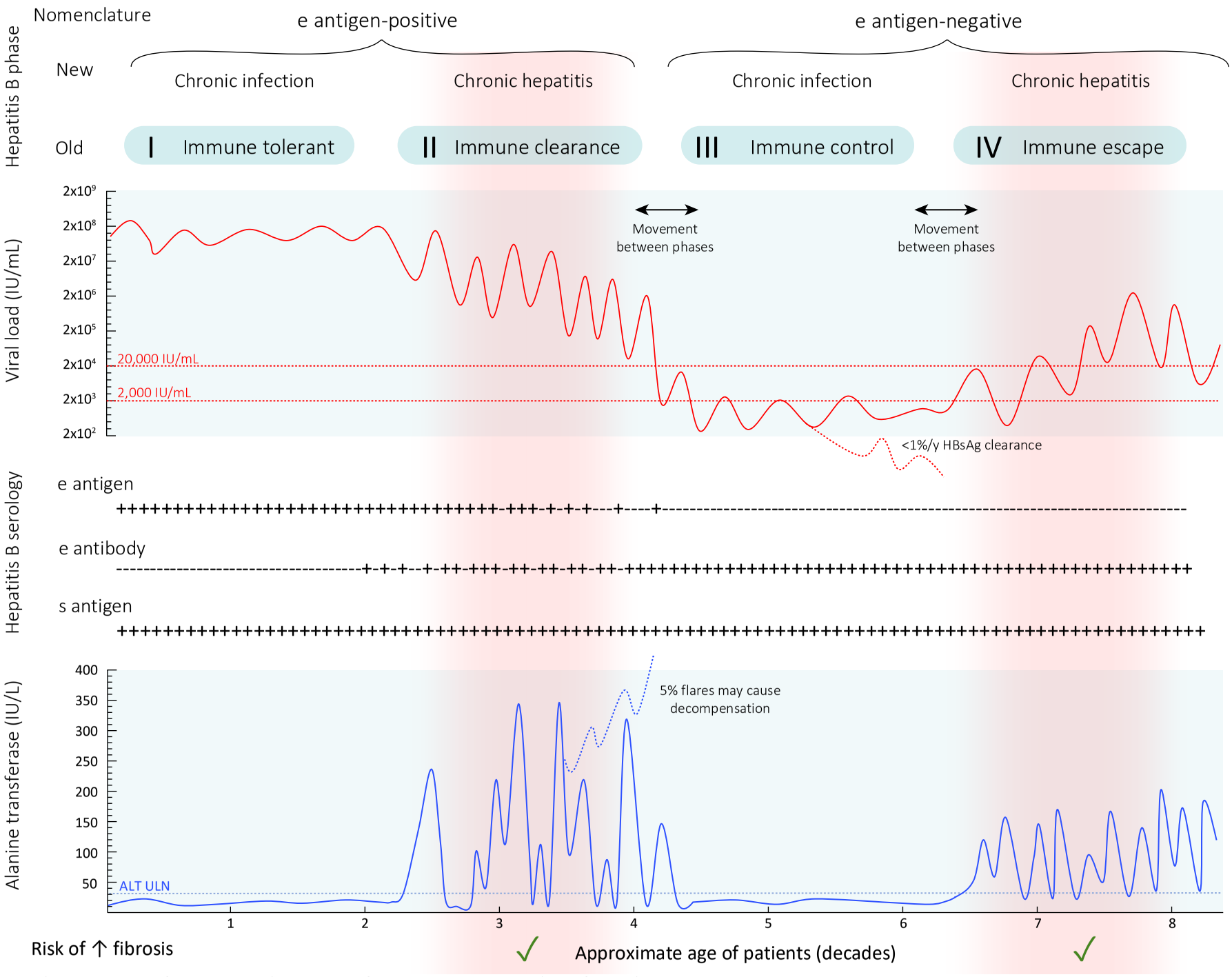
Phase V represents occult infection, defined by a negative HBsAg but detectable HBV DNA level. Occult hepatitis B is rare in Australia. Phase VI represents resolution or clearance, either spontaneous or treatment-induced, characterised by HBsAg loss with or without seroconversion and accompanied by undetectable HBV DNA levels.

These phases provide prognostic information for the likelihood of fibrosis progression and assist in determining need for treatment and frequency of monitoring. In addition, despite careful characterisation with HBeAg, HBV DNA and ALT levels, some patients fall into indeterminate grey areas between phases. Therefore, personalised assessment and management are required, taking into consideration other factors that may influence a patient's long-term outcomes.

Technical remarks

1. CHB is a dynamic disease, and individuals can transition through defined phases in variable ways.
2. Evaluation of patients requires knowledge of their HBeAg status, degree of necroinflammation (ALT level), and level of viraemia (HBV DNA level), which are important predictors of long-term outcomes and hence determine the need for treatment and management.

Figure 4. Natural history of chronic hepatitis B infection



ALT = alanine aminotransferase; HBsAg = hepatitis B surface antigen; ULN = upper limit of normal.

5.2.3.1 Phase I: immune tolerant (HBeAg-positive chronic infection)

The first phase of CHB, the immune tolerant phase, is increasingly referred to as the "HBeAg-positive chronic infection" phase. It is characterised by extremely high serum HBV DNA levels (≥20,000 IU/mL, but often many magnitudes greater; e.g. >10^{6-7} IU/mL) without evidence of necroinflammation, with normal or minimally elevated serum ALT levels (less than the laboratory ULN) and absent or minimal fibrosis and inflammation on liver biopsy.[147,148] In addition, HBsAg levels, if measured, are extremely high in this phase, demonstrating high levels of transcriptional activity of HBV covalently closed circular DNA (cccDNA; the template for transcription) in the liver.[149,150]

Phase I is most often seen, and is most prolonged, in patients with perinatally acquired CHB lasting anywhere between one and four decades, but rarely longer.[151-153] This variation in duration of the immune tolerant phase may be due in part to host–viral interactions. Spontaneous HBeAg seroconversion is rare in this phase (5%–10% per year).[154,155] In one large study from the US, HBV genotype was associated with time to HBeAg seroclearance; the median age at which 50% of patients cleared HBeAg was significantly lower in patients with HBV genotypes A, B, D and F than in those with HBV genotype C infection (<20 years vs 47.8 years).[151] Furthermore, patients with HBV genotypes C and F were more likely to serorevert back to HBeAg-positive CHB after HBeAg loss.[151] Other studies also showed variable ages at time of transition to phase II, ranging from 15 to 35 years in most, with 90% undergoing HBeAg loss by the age of 40 years in Asian cohorts; HBeAg loss was rare below the age of 3 years (<2%).[114,154,156] In childhood- or adult-acquired CHB, the immune tolerant phase is usually short or absent.[134,157]

Geography has also been linked with HBeAg clearance. European, Mediterranean and African patients with CHB demonstrate high annual rates of HBeAg loss, compared with South-East Asian patients.[157] However, detailed regional and country-specific prevalence rates of HBeAg seroprevalence are lacking.

Most studies report a favourable prognosis in patients with immune tolerant CHB, with low rates of cirrhosis and HCC over 5–10 years.[158-162] However, there are increasing reports of poorer outcomes, including higher rates of progression to significant fibrosis, cirrhosis and HCC and higher liver-related mortality, in immune tolerant patients with ALT levels below treatment initiation cut-offs (<1–2 × ULN) or above the new definitions of normal ALT levels (see section 5.2.2) but still below the laboratory reference ULN,[133,158] and in those for whom HBeAg seroconversion occurs after the age of 30 years.[163] These data highlight that people with immune tolerant CHB and persistently normal ALT levels have superior outcomes compared with those with borderline or fluctuating ALT levels. Age at HBeAg seroconversion is clearly also important in determining long-term outcomes.

5.2.3.2 Phase II: immune clearance (HBeAg-positive chronic hepatitis)

Loss of immune tolerance leads to phase II of CHB, immune clearance, which is also now referred to as the "HBeAg-positive chronic hepatitis" phase. It usually occurs during early adulthood. This phase is characterised by the development of liver necroinflammation and carries a risk of subsequent liver fibrosis. Patients in this phase remain HBeAg-positive, with reducing titres, and their HBV DNA levels remain high, although these are often variable and lower than those observed in phase I. ALT levels are

Technical remarks

1. The term "immune tolerant" CHB has increasingly been challenged, as immunological profiles from patients with CHB in the immune tolerant phase do not show true immunological tolerance. Rather, HBV-specific T-cell and B-cell responses are detectable during the immune tolerant phase of CHB, but they are weak, with functionally impaired effector responses.[164-166]
2. Higher than expected amounts of HBV integration and clonal hepatocyte expansion have been observed in patients with immune tolerant CHB, contradicting the idea that immune tolerant patients do not have evidence of markers associated with disease progression and that an immune response is not initiated.[164,167,168]
3. These changes in our understanding of this phase of CHB have led to changes in the nomenclature.

above the recommended normal levels and laboratory ULN, and liver histology shows necroinflammation mediated by the host immune response with varying degrees of fibrosis.

The precise mechanism for this loss of immune tolerance is unclear, but the activation of previously inadequate host immune responses is thought to be critical. Annual rates of loss of immune tolerance are reported to be 10%–15%,[169] and it occurs more rapidly in patients with childhood or adult acquisition of CHB infection.

The outcome is variable: some patients experience mild hepatitis, while others have large HBV flares, with or without liver failure. However, most patients remain asymptomatic, highlighting the importance of regular monitoring of these people. Most patients (up to 90%) undergo spontaneous HBeAg seroclearance or seroconversion and enter phase III of CHB. The 5- and 10-year cumulative incidence of HBeAg seroconversion from diagnosis of CHB is 50% and 70%, respectively.[117,170-172] Annual HBeAg seroclearance rates range from 3% to 17%.[114,154,163,173] A small proportion of individuals will also achieve HBsAg seroclearance, with or without seroconversion, following HBeAg seroclearance (1%–2% per year).[174] In the remaining patients, HBV replication continues, with concurrent elevations in ALT level, and these patients require antiviral therapy. In addition to being associated with fibrosis progression and cirrhosis, the immune clearance phase may be associated with clinical hepatic decompensation (in up to 5% of patients in some case series), and the duration and severity of this phase correlate with subsequent risk of cirrhosis and HCC.[175,176]

5.2.3.3 Phase III: immune control (HBeAg-negative chronic infection)

HBeAg seroconversion is a key event in the natural history of CHB and heralds phase III, or immune control. This phase is associated with a marked reduction in HBV replication and resolution of chronic hepatitis. As it is characterised by low HBV DNA levels (<2000 IU/mL) and normal ALT levels, it is increasingly known as the "HBeAg-negative chronic infection" phase. In addition to normalisation of ALT levels, this phase is associated with biochemical and histological improvement.[177-179] Some patients may have HBV DNA fluctuations between 2000 and 20,000 IU/mL, but progression of liver fibrosis is rare if the ALT level is persistently normal. Although HBeAg seroconversion is durable in most patients, HBeAg seroreversion to a HBeAg-positive state has been observed in a small proportion (7.8% over 3 years).[180]

HBsAg levels are lower in patients in phase III than in HBeAg-positive patients.[149,150] Rates of HBsAg loss in patients with phase III CHB remain low, at 1%–2% per year.[174] HBsAg loss is more likely to occur in patients with HBsAg levels ≤100 IU/mL,[181,182] particularly in those with very low levels (positive predictive value, 44%, 54% and 67% at 1 year in patients with HBsAg levels <100, <50 and <10 IU/mL, respectively).[182]

5.2.3.4 Phase IV: immune escape (HBeAg-negative chronic hepatitis)

Phase IV of CHB is the immune escape phase, characterised by the absence of HBeAg, presence of anti-HBe and loss of immune control, with high levels of HBV DNA (>2000 IU/mL) and ALT levels above the ULN. Owing to the necroinflammation that occurs in this phase, it is also now known as the "HBeAg-negative chronic hepatitis" phase. People with HBeAg-negative chronic hepatitis are usually older than those with HBeAg-positive chronic hepatitis and are more likely to have cirrhosis at the time of their first presentation.[183,184] The precise mechanism that culminates in immune escape has not been fully characterised. It is thought to be due to changes in host immune responses and changes in the viral pool from immune pressure, with many individuals harbouring HBV variants with mutations in the basal core promoter and/or the precore promoter regions.[185,186]

Transition to this phase from phase III occurs in up to a third of patients,[163,179,187] but the incremental transition from phase II to phase IV diminishes the length of time spent in the HBeAg-negative infection phase. Cumulative incidence of transition is 10.2% at 5 years and 17.4% at 10 years (7.4% incremental incidence over the subsequent 5 years) and plateaus at 19.3% at 15 years (1.9% incremental incidence) and 20.2% at 20 years (0.9% incremental incidence).[174] As fluctuating or persistently elevated ALT levels lead to progressive liver necroinflammation and fibrosis, antiviral therapy is recommended in this phase. In patients who

developed spontaneous HBeAg seroconversion and transitioned to HBeAg-negative CHB (phase III and phase IV), the 10-year risk of cirrhosis and HCC was found to be 10% and 2.5%, respectively, due to the liver fibrosis accrued during the immune elimination phase, plus the direct oncogenic effect of the virus.[163] The age at which HBeAg seroconversion occurs further influences this risk, with patients who achieved spontaneous HBeAg seroconversion after the age of 40 years having higher rates of HBeAg-negative chronic hepatitis (67%) and cirrhosis (43%) than those who underwent HBeAg seroconversion at or before 30 years of age (31% and 3.7%, respectively).[163] Furthermore, time to progression to HBeAg-negative hepatitis is shorter in patients who achieve HBeAg seroconversion later in life.

5.2.3.5 Phase V: occult hepatitis B infection

Phase V, or occult hepatitis B infection (OBI), is an additional CHB phase. It is characterised by a lack of HBsAg, positive anti-HBc with or without anti-HBs, low-level HBV replication (HBV DNA level usually <200 IU/mL) and normal ALT levels. This is different to resolved or past HBV infection, as patients have evidence of active HBV replication. OBI was first described after the development of highly sensitive HBV DNA polymerase chain reaction (PCR) assays, which allowed detection of HBV DNA in serum and/or liver tissues in HBsAg-negative patients with isolated anti-HBc, with or without anti-HBs.

The true global prevalence of OBI is not known, but reported prevalences have varied widely, from 1% to as high as 26.8% in Egyptian haemodialysis patients.[188,189] Estimates of the prevalence of OBI vary between countries and are influenced by the background prevalence of CHB in each population.[190] Seronegative OBI is less common, with reported estimates of 1%–20% of all OBI cases. OBI is rare in Australia, with an estimated 5.5 cases per 100,000 blood donors identified in a look-back study by the Australian Red Cross Blood Service.[191]

The molecular mechanisms are thought to be due to mutations in the "a" determinant of the HBsAg, the preS1 or preS2 domains of the HBsAg, or due to splicing variants, resulting in a failure of HBsAg binding to the commercially available assays and therefore not registering as a positive result.[190] These mutations are thought to occur after decades of CHB infection, but the true natural history, risk factors and factors associated with disease progression are not known. Patients with cirrhosis or significant fibrosis before the development of OBI should be managed similarly to other patients with CHB infection. These patients also remain at high risk of HBV reactivation in the context of immunosuppression and should be managed in a similar manner to HBsAg-positive patients undergoing immunosuppression. For more information about clinical situations in which OBI should be considered, see section 6.4.2.

5.2.3.6 Phase VI: "resolved" ("past") hepatitis B infection

The final phase of CHB infection is "past" or "resolved" HBV infection, which occurs after spontaneous HBsAg seroclearance, or "functional cure". Although rare, HBsAg loss is an important milestone in CHB infection and signifies profound suppression of HBV replication. It is accompanied by a greater than 60% reduction in HCC risk and significantly reduces other liver-related complications.[192,193] It is characterised by isolated anti-HBc, with or without anti-HBs; but, in contrast to OBI, HBV DNA is not detectable. Spontaneous HBsAg seroclearance is a rare event in the natural history of perinatally acquired CHB, occurring at an annual rate of 1%–2%[174] and particularly in individuals with HBsAg levels <100 IU/mL.[182]

Loss of HBsAg confers a favourable outcome if it occurs before the development of cirrhosis, with lower rates of HCC seen than in individuals who remain HBsAg-positive with low HBV DNA replication (incidence of HCC, 36.8 vs 195.7 per 100,000 person-years of follow-up in patients with HBsAg loss vs HBsAg-positive patients).[194] However, the risk of HCC remains in people with advanced fibrosis or cirrhosis before HBsAg loss. Furthermore, more recent data suggest that patients who achieve HBsAg loss when aged over 50 years remain at higher risk of HCC than patients who achieve HBsAg loss at or before 50 years of age (adjusted hazard ratio, 4.31; 95% CI, 1.72–10.84; $P = 0.002$), for both treatment-induced and spontaneous HBsAg loss.[195] Therefore, patients who achieve HBsAg loss after the age of 50 years should continue to undergo HCC surveillance.

Although spontaneous or treatment-induced functional cure is the best endpoint of CHB infection and the closest outcome to cure, it should be recognised that viral HBV DNA remains in the liver, in the form of integrated HBV DNA in the host genome and as cccDNA. The significance of the cccDNA is that it remains as a template for HBV transcription despite functional cure, and HBV reactivation can therefore occur in the setting of immunosuppression (see section 5.2.4.1).[196-198]

5.2.4 Other clinical scenarios in the natural history of chronic hepatitis B

5.2.4.1 Hepatitis B virus reactivation

Those with CHB or resolved HBV infection may be at risk of HBV reactivation. HBV reactivation is associated with immunosuppressive and biological-modifier therapies and can result in fulminant hepatitis, hepatic decompensation and death.[199] Risk of HBV reactivation varies according to whether HBV infection is current or past and the type of immunosuppressive regimen used (see section 9.2). Oral HBV antiviral therapy can prevent reactivation when used appropriately, and an Australian consensus statement recommends that all patients undergoing therapy for haematological malignancy or solid tumours be tested for hepatitis B infection.[93] With increasing use of potent immunomodulatory medications for non-malignant conditions, the criteria for HBV screening before starting therapy have broadened significantly and are discussed in detail in section 9.2. Despite published Australian guidelines,[93,198] high rates of suboptimal screening continue to be reported,[200] indicating a need for ongoing education and dissemination of information to all craft groups prescribing immunosuppressive therapies.

HBV reactivation has also been reported in patients with HBV–HCV coinfection who undergo treatment for HCV with direct-acting antiviral (DAA) therapies, with potentially fatal outcomes.[201-204] This was an unexpected finding and is thought to be due to the resolution or restoration of dysfunctional immune responses that occurs after HCV antigen removal with successful DAA therapy, which allows for increased HBV replication. In a study of 79 patients with HBV–HCV coinfection who received DAAs for their HCV, HBV reactivation was observed in 38% (12-month cumulative incidence, 40.4%) and was associated with a higher baseline HBsAg titre and the presence of cirrhosis at baseline.[204] HBV prophylaxis is now recommended for patients with HBV–HCV coinfection and cirrhosis who undergo DAA therapy for HCV.

5.2.4.2 Raised ALT level with normal or low HBV DNA level

Raised ALT levels with HBV DNA levels <20,000 IU/mL in HBeAg-positive patients and <2000 IU/mL in HBeAg-negative patients can be seen among those patients who are likely to lose HBeAg, as HBV exacerbation with a peak ALT level more than 5 × ULN is associated with a 46.5% chance of HBeAg seroconversion within 3 months.[205] Although uncommon, HBV DNA levels <0.5 pg/mL (28,600 IU/mL) have been observed in 4% of those with an exacerbation (flare) of CHB, with most having high HBV DNA levels (>300,000 IU/mL).[206] In addition, other concurrent factors unrelated to CHB may be contributing to a raised ALT level; other causes for raised ALT levels should therefore be excluded, particularly in patients with very low HBV DNA levels.

5.2.4.3 HBeAg-negative with persistently normal ALT level and HBV DNA level >2000 IU/mL

A systematic review of liver biopsy data published between 2000 and 2010 found that histologically significant liver disease was rare in HBeAg-negative patients with a persistently normal ALT level and HBV DNA level ≤20,000 IU/mL, and such patients required continued follow-up but not liver biopsy or immediate treatment.[207] The analysis included 451 patients, with two studies in which participants were European. However, Korean data from an historical cohort study (2000–2013) of 5414 patients reported a high risk of clinical events, including HCC, death and liver transplantation, in patients with untreated HBeAg-negative CHB infection, no significant ALT elevation and HBV DNA levels ≥2000 IU/mL.[208] Therefore, in these patients, other factors that may predict disease severity and poor outcomes need to be taken into consideration.

5.2.5 Incidence of disease progression in chronic hepatitis B

5.2.5.1 Cirrhosis and hepatic decompensation

In a large systematic review, cirrhosis incidence rates varied by region and phase of CHB infection.[209] For patients in phase III (immune control, HBeAg-negative chronic infection), cirrhosis incidence rates were 0.01 and 0.07 per 100 person-years in European and East Asian patients, respectively. For patients with HBeAg-positive CHB, cirrhosis incidence rates were 3.8 and 1.6 per 100 person-years in European and East Asian patients, respectively, corresponding to 5-year cumulative incidences of cirrhosis of 17% and 8%. Cirrhosis risk was significantly lower in East Asian than European patients (incidence rate ratio, 0.17; 95% CI, 0.05–0.56; $P < 0.003$) after adjusting for age and sex. Cirrhosis risk was higher for HBeAg-negative than HBeAg-positive patients and, among HBeAg-negative patients, was again higher in those from European countries compared with East Asian countries: cirrhosis incidence rates were 9.7 and 2.8 per 100 person-years in European and East Asian patients, respectively, with corresponding 5-year cumulative cirrhosis incidences of 38% and 13%. In patients with established early-stage cirrhosis, the 5-year cumulative risk of hepatic decompensation was 15%, and incidence rates were 3–4 per 100 person-years. Mean age of patients when they developed hepatic decompensation ranged from 55 to 60 years.

5.2.5.2 Hepatocellular carcinoma

The risk of developing HCC varies according to HBV phase, global region and presence of underlying cirrhosis. The annual incidence of HCC is estimated to be about 1% in people living with CHB infection in the absence of cirrhosis, and 2%–3% in those with cirrhosis.[210] In a large systematic review, the incidence rate ratio was higher in East Asian patients compared with those from Europe or North America (2.3; 95% CI, 1.3–4.1; $P = 0.003$).[209] For patients from East Asia, the HCC incidence rate per 100 person-years was 0.2 in HBeAg-negative patients in phase III, 0.6 in patients with CHB without cirrhosis and 3.7 in patients with compensated cirrhosis. Corresponding 5-year cumulative HCC incidence rates were 1%, 3% and 17%, respectively. HCC rates were lower in patients from Europe and the US: incidence rates per 100 person-years were 0.02 in patients with HBeAg-negative phase III CHB, 0.3 in patients with CHB without cirrhosis and 2.2 in patients with compensated cirrhosis. These corresponded with 5-year cumulative HCC incidence rates of 0.1%, 1% and 10%, respectively. Mean age at time of HCC diagnosis was 59 years in Asian patients and 63 years in European patients.

5.2.5.3 Liver-related mortality

In a large systematic review, liver-related mortality per 100 person-years ranged from 0.03 in patients with inactive CHB infection to 0.01 in patients with CHB without cirrhosis, and 2.9 and 3.3 in patients with CHB and compensated cirrhosis from Asia and Europe, respectively. Corresponding 5-year rates of liver-related mortality were 14% in Asian patients and 15% in European patients.[209] Incidence of liver-related mortality did not significantly vary by geographic location, with an incidence rate ratio of 0.8 (95% CI, 0.6–1.3), despite adjustment for age and sex. Mortality rates increased dramatically in patients with decompensated cirrhosis, with 5-year mortality rates ranging from 70% to 85%.

5.2.6 Factors associated with disease progression in chronic hepatitis B

The progression to cirrhosis, end-stage liver disease and HCC is variable and affected by host factors (particularly the host immune response), viral factors and environmental factors. Rates have therefore varied significantly across different populations around the world. Several risk calculators have been developed to predict future risk of HCC (see section 8.1.1.1). These include the REACH-B (Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B) score for Asian patients with CHB,[211,212] and the PAGE-B (Platelets, Age and Gender) score, which has superior performance in European patients with CHB.[212-214] However, these risk scores are not universally applied in clinical practice and do not take into consideration the multitude of complex factors that interact to alter disease progression.

There is currently no risk calculator that can help determine when patients will transition through the different phases of HBV infection or predict which patients are likely to develop more rapidly progressive disease. Development of risk calculators that can be

used for patients across different geographic regions and with different ages of acquisition, HBV genotypes, genetic backgrounds and ethnicities would augment the management of HBV.

5.2.6.1 HBV DNA levels

Given the differential risks of cirrhosis and HCC that are observed according to HBeAg status, which in turn determines HBV replication levels, the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV (REVEAL-HBV) study evaluated the impact of HBV DNA levels on subsequent risks of disease progression.[139,140,155,215] This large prospective community-based study in Taiwan, which included more than 3500 patients aged 30–65 years, showed that increasing HBV DNA levels were associated with increasing risk of HCC. The incidence of HCC ranged from 108 per 100,000 person-years in patients with low levels of HBV DNA (<300 copies/mL) to 1152 per 100,000 person-years in patients with very high HBV DNA levels (>10^6 copies/mL), with intermediate risk of HCC seen in patients with moderate HBV DNA levels.[139] This risk of HCC across a biological gradient of HBV DNA levels persisted after adjustment for other potential confounders, including age, sex, alcohol consumption, HBeAg status, ALT levels and cirrhosis at study entry (although most patients included in this study were HBeAg-negative). Subsequent studies of this cohort also showed that baseline HBV DNA levels were predictive of subsequent risk of cirrhosis.[140,216] Cox proportional hazard ratios adjusting for other variables showed that HBV DNA level was the strongest predictor of disease progression to cirrhosis (2.5 [95% CI, 1.6–3.8]; 5.6 [95% CI, 3.7–8.5]; and 6.5 [95% CI, 4.1–10.2] for patients with HBV DNA levels of 10^4–10^5 copies/mL, 10^5–10^6 copies/mL, and >10^6 copies/mL, respectively). Furthermore, HBV DNA level was shown to be a predictor of HCC-related, liver-related and all-cause mortality.[217]

However, the generalisability of these data to all HBeAg-positive patients is limited, as the REVEAL-HBV study population mainly consisted of patients with HBeAg-negative CHB (85%) from Taiwan, where genotypes B and C are predominant. Many studies evaluating medium-term outcomes in HBeAg-positive patients in phase I have shown that, despite high levels of HBV DNA, rates of significant fibrosis, cirrhosis and HCC are very low, thus supporting the current management approach for this group.[158,167,169,218,219] In contrast, HBeAg-positive patients who have transitioned to phase II have increased rates of disease progression, which is thought to be related to the cytopathic host immune response rather than the HBV DNA levels themselves.[117,170-172] Controversially, several recent studies have reported higher than expected rates of cirrhosis and HCC in people with phase I CHB infection.[220,221] However, this likely reflects differences in definitions of immune tolerance with respect to HBV DNA and ALT levels and may highlight a differential risk of HCC in phase I patients who are about to transition, or are in the process of transitioning, to phase II.

5.2.6.2 ALT levels

There is good evidence that elevated ALT levels are associated with increased mortality. In the National Health and Nutrition Examination Survey (NHANES) III in North America, which followed 14,950 adults with 12-year mortality data, an elevated ALT level, using the ULN criteria of 19 IU/L in women and 30 IU/L in men, conferred a hazard ratio of 8.2 (95% CI, 2.1–31.9) for liver-related mortality.[222] In a subgroup of these patients considered at low risk of liver disease (by virtue of exclusion of hepatitis B and C, low alcohol consumption, no evidence of diabetes and normal BMI and waist circumference), the median ALT level was 21 IU/L (IQR, 17–27) in men and 17 IU/L (IQR, 14–21) in women.[131]

5.2.6.3 Cirrhosis-specific factors

Cirrhosis develops in 2.1%–6.0% of people with CHB infection annually.[176,223,224] The rate of cirrhosis development depends on HBeAg status, with annual rates of 2.4% in HBeAg-positive people and 1.3% in HBeAg-negative/anti-HBe-positive people.[176] There is also wide geographical variation in rates of progression to advanced liver disease. Progression to cirrhosis is reportedly slower in patients with HBV genotype B than genotype C infection.[224] In Western European populations with CHB not treated with antiviral therapy, the estimated 5-year rate of progression to cirrhosis is 12% to 20%, while the estimated rate of progression from compensated cirrhosis to hepatic decompensation is 20% to 23%.[209] Studies from Asia and the US have shown that the lifetime risk of liver-related death is estimated to be 15%–40%, with the risk higher in men and in people over the

age of 50 years.[225,226] The risk of disease progression appears to be greatest in people who stay in the immune clearance phase,[158] who have delayed HBeAg seroconversion,[227] or who have had reactivation of HBV replication after HBeAg seroconversion.[172,179,228]

The severity of fibrosis stage at presentation correlates with risk of cirrhosis, which is fourfold higher for patients with stage F3 fibrosis than those with stage F1 or F2.[229,230] Repeated severe acute exacerbations with failure to suppress HBV replication have been shown to predict higher rates of cirrhosis.[159,176] A Korean study examining long-term outcomes reported that the probabilities of developing cirrhosis, decompensation and HCC were significantly higher in patients whose ALT levels were persistently elevated, with or without flares but without normalisation, than in patients whose ALT levels flared with normalisation or were persistently normal.[229] In patients with compensated HBV-related cirrhosis, baseline biochemical characteristics indicative of longer duration of liver disease, such as albumin and bilirubin levels and platelet count, are also significant predictors of liver decompensation, HCC occurrence and liver-related mortality.[231] The large-scale REVEAL-HBV study of a prospective cohort in Taiwan showed that, during a mean follow-up of 11 years, elevated serum HBV DNA level (≥10,000 copies/mL) was an independent risk predictor of disease progression to cirrhosis and HCC.[140,232]

5.2.6.4 Age of acquisition and duration of infection

Age of HBV acquisition is a host factor that affects the progression of CHB to cirrhosis and its complications. In a large systematic review, several studies identified that Asian patients aged ≥40 years had a higher risk of cirrhosis and HCC than those aged <40 years.[139,229,233,234] Similarly, Western studies have shown significantly increased incidences of cirrhosis and HCC with increasing age of study populations.[235-237] Therefore, older age appears to be an important determinant of progression to cirrhosis and HCC, probably because it is a surrogate marker of longer duration of HBV infection and liver disease.

5.2.6.5 Alcohol

Alcohol consumption in people with HBV infection may contribute to the development of end-stage liver disease. Alcohol misuse not only causes rapid progression of liver disease in people living with HBV but also reduces HBV clearance.[238,239] Although the mechanism by which alcohol promotes the progression of HBV-associated liver disease is not completely understood, potential mechanisms include suppression of the immune response, disruption to endoplasmic reticulum and Golgi apparatus function, and oxidative stress, thereby allowing increased HBV replication.[238,240]

In Taiwan, a regression analysis of the REVEAL-HBV study showed that habitual alcohol consumption was significantly associated with the development of HCC. The adjusted hazard ratio for HCC was 1.6 (95% CI, 1.1–2.4) for "habitual" alcohol consumption, defined as drinking alcohol on 4 or more days a week for a year or more.[139] In contrast, as a predictor of progression to cirrhosis, HBV DNA level was the strongest factor after adjusting for HBeAg status and serum ALT level (relative risk, 10.6; 95% CI, 5.7–19.6), while habitual alcohol consumption was not associated with the risk of cirrhosis (relative risk, 0.8; 95% CI, 0.6–1.2).[140]

Light to moderate alcohol consumption has been associated with, at best, a modest 1.5-fold increased risk of disease progression in patients with HBV infection, although this effect has not been observed in smaller studies.[240] However, heavy alcohol consumption is associated with significantly accelerated progression of liver disease, HCC and death. A French study reported that deaths related to HBV infection occurred at an earlier age in patients with a history of excessive alcohol consumption.[241] An Italian case–control study to investigate the dose–effect relationship between alcohol consumption and HCC found a steady linear increase in the odds ratio of HCC with increasing alcohol intake >60 g/day in both men and women.[242] In addition, there was an additive effect between alcohol consumption and CHB infection for risk of HCC, with an odds ratio of 2.13 in HBsAg-positive people drinking >60 g/day, compared with HBsAg-positive non-drinkers or those drinking ≤60 g/day of alcohol. Similarly, multivariate analysis of a prospective cohort study in Japan, which followed 610 consecutive HBsAg-positive patients for a median observation period of 4.1 years, found that cumulative alcohol consumption of ≥500 kg per person during the observation period was independently associated with HCC (relative risk, 8.37; 95% CI, 2.70–25.93;

P = 0.0002).[230] A prospective study following 2000 HBsAg-positive patients for 20 years found that lifetime alcohol consumption of >60 g/day was associated with a sixfold increase in the risk of death from cirrhosis and HCC.[243]

The metabolic syndrome, fatty liver and obesity, which are often associated with excessive alcohol consumption, also significantly contribute to liver-related morbidity in patients with HBV.[244,245] The AASLD guidelines state that more than seven standard drinks of alcohol per week for women and more than 14 drinks per week for men are associated with increased risk of cirrhosis and HCC.[41]

5.2.6.6 Carcinogens

5.2.6.6.1 Aflatoxin

Aflatoxins, produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, are the most potent naturally occurring human hepatocarcinogens. These fungi commonly infect ubiquitous crops, such as maize and peanuts, thereby exposing about 4.5 billion people to potential harm.[246] Additionally, when animals intended for dairy production consume aflatoxin-contaminated feed, a metabolite, aflatoxin M_1, is excreted in their milk.[247] Exposure is highest in tropical and subtropical regions, where the affected foods are dietary staples and often kept in suboptimal storage conditions.[246,247]

An increasing body of evidence suggests that aflatoxin exposure synergises with CHB infection to increase HCC risk in populations with both risk factors.[248,249] A specific arginine-to-serine mutation at codon 249 (249^{ser}) in the p53 gene has been detected in HCC tumours and as circulating cell-free DNA in patients with HBV- and aflatoxin-related cirrhosis.[250] In a case–control study that enrolled controls, patients with cirrhosis and patients with HCC from The Gambia, the 249^{ser} mutation was detected in 39.8% of patients with HCC, 15.3% of those with cirrhosis and only 3.5% of controls. Furthermore, a multiplicative effect of HBV and the 249^{ser} mutation was observed, with the odds ratio for HCC being 10.0 for HBV alone (95% CI, 5.16–19.6), 13.2 for the 249^{ser} mutation alone (95% CI, 4.99–35.0) and 399 if both were present (95% CI, 48.6–3270).[250]

5.2.6.6.2 Tobacco

Tobacco smoke contains various carcinogens, of which 11 are classified as significant human carcinogens.[256] A meta-analysis has provided epidemiological evidence of a positive association between current tobacco smoking and risk of HCC (pooled odds ratio, 1.55; 95% CI, 1.46–1.65), suggesting a causal role of smoking in HCC development.[257] Furthermore, CHB is a major cause of HCC and accounts for more than 54% of its incidence.[258] Long-term inflammation and oncogenic events caused by HBV — including transactivation of proto-oncogenes, inactivation of tumour suppressor genes, impairment of DNA repair mechanisms, enhanced expression of growth factors and deregulation of cell cycle — lead to cirrhosis and development of HCC,[259] which will also affect the

Technical remarks

1. The potential mechanism of chronic liver injury, regenerative hyperplasia and development of liver cancer involves the presence of aflatoxin-induced DNA mutations.[251] Inflammation and oxidative stress associated with chronic active hepatitis and aflatoxin exposure may also directly result in DNA damage and mutations.[252] Alternatively, HBV infection could predispose hepatocytes to the carcinogenic action of aflatoxins.
2. HBV may also alter the hepatic expression of aflatoxin-metabolising enzymes and affect the extent to which aflatoxins bind to DNA, as seen in some HBV animal models.[253]
3. Aflatoxin-induced DNA damage could increase viral DNA integration into the host genome and is thought to be immunosuppressive in animals. This may affect susceptibility to chronic viral infection in exposed individuals.
4. Aflatoxin could alter the pathogenicity of the hepatitis virus, perhaps affecting susceptibility to infection or viral replication.[254]
5. In some parts of the world, such as Taiwan, aflatoxin exposure is decreasing and, combined with increasing rates of HBV immunisation, HCC rates are falling. In other parts of the developing world, there is little evidence that aflatoxin exposure is decreasing. With climate change, aflatoxin contamination in food crops may be exacerbated due to conditions favouring proliferation of *Aspergillus* species.[255]

metabolic process of tobacco-related carcinogens. Therefore, it is possible that CHB and tobacco smoking may play a role both independently and jointly in liver carcinogenesis. Other research has found that cigarette smoking, heavy alcohol consumption and HBsAg positivity were independently associated with increased risk of mortality from HCC but did not interact synergistically.[260]

In a large population-based cohort study of men living with hepatitis B, smoking was associated, in a dose-dependent manner, with increased risk of HCC.[261] Various aspects of cigarette smoking were evaluated, with evidence found to support a mediating effect from increasing viraemia and ALT levels and a reduced natural killer cell fraction. Therefore, smoking potentially causes alterations in antiviral immunity and enhances viral replication, thereby proceeding to CHB and more advanced hepatic disease states. The number of years since quitting smoking was also found to be inversely associated with elevation in ALT levels, and the extent of the risk reduction for an ALT level ≥2 × ULN was substantial after quitting for ≥10 years. Thus, smoking may exacerbate the clinical course of CHB infection, whereas abstinence from smoking may lead to a normalisation of liver enzymes and should be encouraged in the management of these patients.

5.2.6.7 Sex

Male sex has been identified as an independent risk factor for cirrhosis.[140,234] The molecular mechanisms by which sex affects fibrosis progression remain unknown. The antifibrogenic effect of oestrogen, possibly through the inhibition of stellate cells, has been proposed as a mechanism.[262] Overall, the risk of HCC in chronic HBV carriers is several times higher in men than women.[139,229] In an Italian study of HBsAg-positive patients, the overall sex ratio (male to female) was 2.6. The sex ratio linearly increased with increasing severity of liver disease, from 1.3 in patients with a normal ALT level to 2.8 in those with CHB, 3.6 in those with liver cirrhosis and 6.8 in those with HCC.[263] In addition, immune clearance of HBV antigens was achieved faster in women than in men, as well as the control and delay of progression in HBV-induced liver diseases. HBV may well be responsive to sex hormone, which may explain the disparity of CHB-related end-stage liver diseases between the sexes and could provide new insights into future therapeutic development.[264]

5.2.6.8 Family history of hepatocellular carcinoma

Previous studies have reported familial aggregation of HCC, and extensive meta-analyses have suggested that family history of HCC increases the risk of HCC in patients with viral hepatitis.[265-267] However, the interaction between family history of HCC and presence of HBsAg, HBV DNA levels and presence or absence of HBeAg has not been fully elucidated.

An analysis of the Taiwanese REVEAL-HBV cohort showed the combined and synergistic effects of family history of HCC and HBsAg on HCC risk, with the highest risk among those who had both a family history of HCC and HBsAg positivity, in both unadjusted (hazard ratio, 28.33; 95% CI, 18.40–43.62; $P < 0.001$) and multivariate-adjusted (hazard ratio, 32.33; 95% CI, 20.78–50.30; $P < 0.01$) analyses.[268] Cumulative risks of HCC were 0.62% in HBsAg-negative patients without a family history of HCC, 0.65% in HBsAg-negative patients with a family history of HCC, 7.5% in HBsAg-positive patients without a family history of HCC, and 15.8% in HBsAg-positive patients with a history of HCC. When multivariate-adjusted analyses were stratified by family history of HCC, HBsAg status, HBeAg status and HBV DNA levels, the risk of HCC synergistically increased in a dose-dependent manner, with the highest risk seen in HBsAg- and HBeAg-positive individuals with a family history of HCC (hazard ratio, 174.61; 95% CI, 92.2–330.8; $P < 0.01$). During a median follow-up of 16.9 years, this corresponded to a cumulative risk of HCC of 40%.

An evaluation of an Italian cohort showed that participants with a positive family history of liver cancer had a two- to threefold increase in their HCC risk.[267] Further, the combination of family history of liver cancer and hepatitis B/C serum markers led to a more than 70-fold elevated risk of HCC, compared with participants with neither. Therefore, the routine use of family history of HCC, together with HBV serology status and HBV DNA levels, can further improve HCC risk stratification of people with hepatitis B.

5.2.6.9 Coinfection with hepatitis C or D or HIV

Coinfection is comprehensively discussed in section 9.3. Most early studies observed more severe liver

disease and a higher incidence of cirrhosis and HCC over long-term follow-up in patients with HBV–HCV coinfection; this has been supported by later studies, although not always consistently.[269-275] A recent meta-analysis estimated that individuals with HBV–HDV coinfection were more likely to develop cirrhosis and HCC within 5 and 10 years, respectively.[276] Liver-related mortality is higher in patients with HBV–HIV coinfection than in patients with either of HBV or HIV mono-infection.[277,278]

5.2.6.10 HBV genotype

HBV is divided into 10 genotypes (A to J, based on sequence divergence of >8%) and is further subdivided into subgenotypes (based on sequence divergence of 4%–8%).[142] The use of genotype to guide clinical care is far less established for HBV than it is for HCV, and genotyping of HBV is primarily done by research rather than clinical laboratories. However, evidence supporting the importance of HBV genotype for the natural history of CHB infection, with regard to progression of disease, risk of HCC and response to treatment, continues to emerge.[279,280]

5.2.6.11 HBeAg seroconversion

Spontaneous and treatment-induced HBeAg seroconversion is associated with improved outcomes, including low HBV DNA levels, reduced ALT levels, low risk of liver disease progression and a reduced risk of HCC.[288,289] However, a small proportion (less than 5%)[179,205] of people with spontaneous HBeAg seroconversion will subsequently regain HBeAg (HBeAg seroreversion), restoring the risk of poorer outcomes. Treatment-induced HBeAg seroconversion is much less stable than spontaneous HBeAg seroconversion.[290,291]

5.2.6.12 HBsAg seroclearance

HBsAg clearance is associated with similar long-term outcomes as seen in those with naturally resolved HBV infection.[292] Age at HBsAg clearance is an important factor, with HBsAg seroclearance before 50 years of age being associated with lower risk of significant fibrosis, HCC and end-stage liver disease.[155,293] However, the rate of both spontaneous and treatment-induced HBsAg clearance is low, at about 1%.[193,294]

Technical remarks

1. Genotype C HBV, which predominates in South-East Asia, has been associated with a higher risk of progression to cirrhosis, a longer duration of HBeAg positivity and a higher incidence of HCC, compared with genotype B.[151,281]
2. Some genotypes, such as B5 (previously classified as B6), which is prevalent in Alaskan natives, have been suggested to have a more benign course.[172,282]
3. Specific mutations in the precore basal core promoter region — including the negative regulatory element and the pre-S/S regions of the HBV genome — confer a substantially higher risk of progression to cirrhosis and HCC.[283,284]
4. There is no evidence to support any significant difference in response to nucleos(t)ide antiviral therapy on the basis of genotype; however, genotypes C and D are less responsive than genotypes A and B to treatment with interferon.[279,285]
5. Subgenotype C4 is an exclusive HBV genotype that has only ever been identified in the Indigenous population of Australia's Northern Territory.[286] It is not known how widely dispersed this genotype is among Aboriginal and Torres Strait Islander people in the rest of Australia.
6. HBV subgenotype C4 has molecular characteristics previously associated with more rapid progression to cirrhosis and an increased risk of HCC.[50] Clinical and epidemiological data from the Northern Territory suggest that this genotype does translate into a high incidence of HCC and increased progression to cirrhosis.[47,287] However, it is unclear what the relative contribution of HBV genotype is to this observed severe phenotype, compared with host factors such as comorbidities.

6 Diagnosis and monitoring

The diagnosis of acute or chronic HBV infection requires the correct ordering and interpretation of serological tests. The National Hepatitis B Testing Policy recommends that testing for people at risk of CHB infection should include three qualitative serological tests — HBsAg, anti-HBc and anti-HBs — to determine infection, exposure and immunity, respectively, with addition of anti-HBc IgM testing if acute or recent infection is suspected (Table 6).[295] A detailed history, including country of birth, overseas travel history, vaccination and exposure risks, and a physical examination are important to distinguish between possible recent, acute or chronic infection and to guide the addition of anti-HBc IgM testing.[40]

Qualitative serological tests have established thresholds (in IU/mL) and are usually reported as positive (detected) or negative (not detected), although some laboratories will report a quantitative result for anti-HBs, with a level ≥10 IU/mL indicating immunity through either past exposure or vaccination. When HBsAg is detected on initial screening, laboratories conduct further testing with an HBsAg neutralisation assay to confirm the diagnosis.[295] Serological testing for HBV in Australian laboratories uses immunoassay techniques that detect HBsAg with a sensitivity level of 0.05 IU/mL. A positive result usually represents HBV infection. False positive or transiently positive HBsAg results can be seen after HBV vaccination. No point-of-care HBsAg test has been approved by the Therapeutic Goods Administration for the diagnosis of hepatitis B, although such tests are recommended by the WHO and widely used in the Asia-Pacific region.[15]

6.1 Diagnosing acute hepatitis B

Acute HBV infection is defined serologically as the presence of HBsAg and anti-HBc IgM (Table 7), with or without symptoms, that persists for less than 6 months. Although acute HBV infection is most often asymptomatic, infection may result in a clinical syndrome 30–180 days (average, 75 days) after exposure.[296] The clinical presentation is influenced by cell-mediated immunity, so that most infections that occur at birth, in infancy and in early childhood usually have mild or minimal symptoms.[116] There are a range of symptomatic presentations in older children, adolescents and adults, from mild illness with fatigue through to fulminant hepatitis and death (estimated to occur in <1% of cases).[116] Aspartate aminotransferase (AST) and ALT levels are typically elevated to more than 10 times the ULN. Severe disease is associated with pre-existing liver disease, HCV infection, HBV genotype D and superinfection with HDV.

For people with current or recent clinical symptoms suggestive of acute hepatitis (e.g. fever, headache, malaise, loss of appetite, nausea, vomiting, diarrhoea, upper abdominal pain and jaundice with raised transaminase levels), hepatitis B serology (HBsAg, anti-HBs and anti-HBc, including anti-HBc IgM) forms part of the initial assessment.[295] Testing for other non-infectious and infectious causes of acute hepatitis (i.e. hepatitis A, C, D or E; Epstein–Barr virus; cytomegalovirus; syphilis; or bacterial infections) should also be done, depending on the risk exposure. HBeAg positivity and higher viral replication are seen in people with acute hepatitis, making it potentially

Table 6. Tests, standard nomenclature and interpretation for diagnosis of hepatitis B

Test	Nomenclature	Interpretation of positive test result*
Hepatitis B surface antigen	HBsAg	Current infection
Hepatitis B core antibody	anti-HBc	Past exposure (if HBsAg-negative)
Hepatitis B surface antibody	anti-HBs	Immunity to hepatitis B
Hepatitis B core antibody IgM	anti-HBc IgM	Acute or recent infection (and flare)

* In patients with positive anti-HBc and negative HBsAg serological test results, the presence of HBV DNA may persist (occult hepatitis B).

Table 7. Interpretation of hepatitis B serology

Serology	Interpretation of test result
HBsAg positive Anti-HBc positive Anti-HBs negative	Chronic hepatitis B infection
HBsAg positive Anti-HBc positive Anti-HBs negative Anti-HBc IgM positive	Acute hepatitis B infection
HBsAg negative Anti-HBc positive Anti-HBs positive	Immune through past infection (natural immunity) or "cleared" hepatitis B
HBsAg negative Anti-HBc negative Anti-HBs positive	Immune through vaccination
HBsAg negative Anti-HBc positive Anti-HBs* negative	Isolated core antibody positive is most commonly resolved infection with low anti-HBs titre (other possibilities: resolving acute hepatitis B, false positive result or occult hepatitis B)
HBsAg negative Anti-HBc negative Anti-HBs negative	Susceptible to hepatitis B infection

anti-HBc = hepatitis B core antibody (total, includes IgM and IgG); anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; IgG = immunoglobulin G; IgM = immunoglobulin M.
* In occult hepatitis B infection, anti-HBs may or may not be present.

more infectious. After resolution of the infection, anti-HBe may persist in serum for many years.[296]

There is no specific treatment for acute hepatitis B, other than supportive care; however, in fulminant cases, including in those with an INR >1.5, antiviral therapy is used.[297] Everyone diagnosed with acute HBV infection requires follow-up, including repeat serological testing at 6 months to determine if HBsAg is persisting and leading to CHB infection.[295] Progression from acute HBV infection to CHB is much more common in infants (85%–90%) than in adults (<5%).[111]

6.2 Diagnosing chronic hepatitis B

The diagnosis of CHB requires persistence of HBsAg for longer than 6 months.[298] The serological pattern of CHB is HBsAg-positive, anti-HBc-positive and anti-HBs-negative (Table 7). In the absence of a clear history or serology indicating recent acute infection, patients presenting for the first time with a positive HBsAg test result can be diagnosed with CHB infection without waiting to repeat the serology after 6 months.[295] Most people in Australia who are HBsAg-positive were born overseas,[28] and a positive HBsAg result in this context should also be interpreted as a diagnosis of chronic infection, without waiting to repeat the serology after 6 months and delaying initial management.[295]

Diagnosis should be followed up by appropriate counselling, in accordance with the National Hepatitis B Testing Policy.[295] Conveying a new diagnosis to the affected person should occur in private, without other family members present, using an accredited interpreter if required and employing the "teach-back" method (asking the person to explain to the clinician what they understand has been discussed) to assist the person to increase their knowledge and understanding.[299] The impact of a new diagnosis can be devastating, resulting in poor mental health, discrimination (in the workplace, home and community) and self-stigmatisation, including self-exclusion from normal family activities and intimacy with loved ones.[18,300,301] People newly diagnosed with CHB should be adequately informed and given

necessary support by their health care practitioner and offered referral to consumer organisations (https://www.hepatitisaustralia.com/local-hepatitis-organisations) and, if needed, organisations specialising in support for multicultural communities. Health care workers diagnosed with CHB, especially those who perform exposure-prone procedures, need consideration of a safe work environment for them and their patients and should be under the care of a specialist who understands the legislation.[95] All newly diagnosed people should be offered a follow-up appointment to discuss the diagnosis, arrange further tests and receive advice about lifestyle modifications to promote liver health, including safe drinking, smoking cessation and healthy weight goals.[295]

6.3 Immigration and hepatitis B testing

Applicants for permanent visas to remain in Australia are required to undergo criteria-based hepatitis B testing as part of their immigration medical examination. Historically, applicants with CHB infection would not meet the health requirements for a permanent visa, as their antiviral treatment would exceed the $40,000 threshold for projected lifetime health care utilisation costs.[302] However, this threshold was changed on 1 July 2019 to a projected 10-year health services and treatment cost of $49,000.[302,303] With this change, people with CHB who are treated with entecavir fulfil the health requirements for permanent visa approval. The cost of tenofovir treatment is also likely to drop below this threshold in the near future.

Despite this change, the association between hepatitis B status and visa application approval has increased the stigma of hepatitis B testing among migrants in Australia and disincentivised testing uptake.[304-306] From an ethical perspective, many health professionals advocate for the removal of the antiviral treatment cost-related health requirement for permanent visa applicants living with hepatitis B.

6.4 Interpretation of hepatitis B serology

Serology should be interpreted (Table 7) with consideration of the person's history and context.

Some laboratories may report a quantitative result for an anti-HBs test. In a vaccinated person, an anti-HBs antibody level <10 IU/mL could be due to incomplete vaccination, non-response to vaccination or waning immunity. If there is a previous documented result ≥10 IU/mL and the level has dropped below 10 IU/mL, further vaccine boosting is not required, as an anamnestic response will be protective if exposure occurs. Routine testing after vaccination is not advised, except in circumstances where confirmation of immunity is required (e.g. after exposure, for health care workers or people on dialysis or living with HIV).[307] An anamnestic response to a booster dose of vaccine can be measured 6–8 weeks after the booster dose is administered. In 7914 Taiwanese adolescents who received a complete vaccination course as infants, testing 15 years after the primary course showed that 25% had anti-HBs levels <10 IU/mL.[308] After a single booster dose, 94% of those with values of 1–9.9 IU/mL and 60% of those with values <1 IU/mL responded, achieving anti-HBs levels >10 IU/mL.

Quantitative HBsAg (qHBsAg) testing is used in the research context and is not yet part of routine clinical practice.[309] In HBeAg-positive patients, qHBsAg predicts HBeAg clearance, while in HBeAg-negative patients, it predicts spontaneous clearance of HBsAg.[310] qHBsAg is associated with HCC risk. It also has an established role in guiding individualised therapy for patients receiving interferon and is likely to become increasingly important in the decision to stop antiviral therapy in HBeAg-negative individuals, as well as in guiding new curative treatments.[309,311]

6.4.1 Isolated hepatitis B core antibody

The serological pattern of isolated positive anti-HBc is common in people from intermediate- to high-prevalence populations, and the prevalence increases with age.[312] Most people with this serological pattern will have cleared hepatitis B infection, with an anti-HBs titre that has dropped below the positive or detectable threshold (i.e. <10 IU/mL). They remain immune and are likely to have a good anamnestic antibody response if challenged by infection or vaccinated unnecessarily.[313,314] The serological pattern of isolated positive anti-HBc can also be caused by a false positive result (rare), resolving acute infection (i.e. before anti-HBs becomes positive) or OBI. HBV DNA testing is not recommended unless there is a clinical suspicion or

risk of occult infection. There is no Medicare rebate for HBV DNA testing if HBsAg is negative.[64]

6.4.2 Occult hepatitis B infection

OBI is defined as the persistence of HBV DNA in serum or hepatocytes of a person with a negative HBsAg test result, using currently available assays.[315] Detection of HBV DNA in liver tissue is considered the gold standard for diagnosis, but measurement in serum is more commonly used. Where HBV DNA testing is not available, isolated positive anti-HBc is considered a potential marker of OBI.[315] OBI can either be seropositive (positive for anti-HBc and/or anti-HBs) or seronegative (negative for anti-HBc and anti-HBs).[315] In any person who has cleared HBsAg, HBV DNA persists in the liver as episomal free cccDNA and/or as HBV DNA integrated into the host genome. Viral replication is usually suppressed by the immune system to produce undetectable HBV DNA levels in the serum, but, in those with OBI, low levels of viraemia (<200 IU/mL) may fluctuate over time from undetectable levels.

OBI is more common in people who are coinfected with other blood-borne viruses and those who are at higher risk of exposure to such viruses (e.g. people with coinfection with HCV or HIV, those who inject drugs or those on dialysis).[315] OBI is also diagnosed in people with cirrhosis of unknown cause, after either biopsy or transplantation, when liver tissue is tested for HBV DNA.[315]

As OBI can lead to transmission of HBV infection to blood or organ transplant recipients, and people with OBI are at risk of fatal disease flares or reactivation in the setting of potent immunosuppression, identifying this cohort remains important. Therefore, people with persistently abnormal liver function test results who are HBsAg-negative and anti-HBc-positive and have additional risk of liver disease or adverse consequences of infection (e.g. reactivation with high-dose immunosuppressive therapy) should be referred to a hepatitis specialist for consideration of testing for OBI.

The role of OBI in the development of HCC and cirrhosis is debated.[315]

6.5 Post-test counselling of patients with newly diagnosed hepatitis B

The goal of the initial management of people diagnosed with hepatitis B is to mitigate the impact on their social, psychological and physical wellbeing. Everyone living with CHB requires an initial assessment, support to understand the implications of the diagnosis and an ongoing plan for monitoring.[298] Initial management should include the provision of adequate and ongoing counselling and support after the diagnosis.

Counselling given to people newly diagnosed with hepatitis B should include information about the diagnosis and natural history, treatment options, the importance of regular monitoring and how to prevent transmission to others. There should be an emphasis on positive health messages, including self-care and the availability of protection afforded by vaccination for both family members and close contacts, as well as how to implement standard precautions regarding sharing of personal grooming equipment, safe sexual practices and blood safety.[295] Information about obligations of disclosure (rights and responsibilities) should be discussed, and appropriate support provided.

Management of a person newly diagnosed with hepatitis B should extend, with the person's consent, to the counselling and testing of family members and close household and sexual contacts, and vaccination of these people if they are susceptible.[295] Hepatitis B is a notifiable condition in most jurisdictions, and laboratories and health care practitioners are required to notify the relevant health department. Where possible, the person should be informed about this notification, its purpose and what, if any, action the health department is likely to take. This is especially important for people applying for or currently living in Australia on visas, who may need further advice and specialist referral, as a diagnosis of hepatitis B can have a negative impact on their visa application or status.[302]

Recent Australian Health Practitioner Regulation Agency changes require health care workers who perform exposure-prone procedures to be regularly tested for blood-borne viruses, including HBV.[95] Diagnosis of a health care worker requires skilled

advice about options for treatment and practice and may involve public health unit investigation.

6.6 Assessment of patients with newly diagnosed hepatitis B

The initial assessment of a person with hepatitis B includes a comprehensive medical history, including a history of liver cancer in the family; a thorough physical examination for evidence of liver dysfunction, cirrhosis and portal hypertension; and further investigations to determine disease activity and treatment eligibility.[1,41,132,316]

People newly diagnosed with hepatitis B should therefore be assessed to determine:

- the phase of infection and disease activity;
- the presence of cirrhosis or significant fibrosis;
- the presence of coinfection (HIV, HDV and HCV);
- immunity to hepatitis A (hepatitis A antibody [anti-HAV] immunoglobulin G [IgG]);
- comorbidities (e.g. alcohol use, smoking, overweight, diabetes, MAFLD or other causes of chronic liver disease); and
- the need for ongoing monitoring and HCC surveillance (noting any family history of HCC).

6.6.1 Assessment of phase and disease activity

Assessment of the phase of infection is necessary to indicate whether the person has active disease and is therefore eligible for antiviral treatment. For those who are not eligible for treatment, the phase of infection will determine the required interval for regular review and monitoring. Levels of HBV DNA, HBeAg, anti-HBe and ALT are used to establish phase (see section 5).[1,41,128,298] Although higher levels are reported as normal in some laboratories, an ALT level ≥19 IU/L in women and ≥30 IU/L in men should be considered elevated (see section 5.2.2).[40]

A single ALT level, whether normal or elevated, should be interpreted with caution, and follow-up testing should be arranged over a 3–6-month period (sequential ALT tests or liver function tests ordered 3–6 months apart). A review of the person's historical ALT test results before their diagnosis, if available, may also indicate a history of persistently raised ALT levels over a long period and inform treatment decisions. Patients may transition in and out of phases, and, even within a phase, viral loads and ALT levels may fluctuate. The rationale for repeated assessments is to more accurately determine the natural history of hepatitis B in the individual and thus inform the clinician of the need for antiviral therapy or ongoing monitoring.

Recommendation 4

Evaluation of people with CHB infection should include repeated assessments (e.g. HBV serology, ALT, HBV DNA level) to determine phase of disease and requirement for antiviral treatment. (Evidence quality: High; Grade of recommendation: Strong)

6.6.2 Assessment of hepatic fibrosis

Treatment is recommended for anyone with CHB, cirrhosis and a detectable viral load (see section 7). These people should also undergo 6-monthly HCC surveillance with alpha-fetoprotein (AFP) testing and ultrasound because of a significantly increased risk of liver cancer. Assessing whether significant fibrosis or cirrhosis is present is therefore a crucial part of the initial assessment.[1,41,132,316] In Australia, the requirement for a liver biopsy before starting antiviral therapy was removed in 2011, increasing access to treatment. A range of non-invasive tests to measure fibrosis, including serum panels and imaging modalities, have since been evaluated (Table 8). Liver biopsy continues to have a diagnostic role in hepatitis B if there are concerns about other underlying liver abnormalities.

6.6.2.1 Transient elastography and other imaging techniques

Liver stiffness can be measured by various techniques: transient elastography (TE), acoustic radiation force impulse (ARFI) elastography, shear wave elastography (SWE) using modified ultrasound probes and magnetic resonance elastography (MRE).

TE, using a dedicated FibroScan® (Echosens, Paris) machine, is most widely used in Australia, although access is limited in regional areas. It is fast, simple, safe, well tolerated and has been extensively

Table 8. Diagnostic accuracy of non-invasive fibrosis tests in patients with chronic hepatitis B virus infection

Test	≥F2 fibrosis				Cirrhosis			
	Cut-off	AUROC	Sensitivity (%)	Specificity (%)	Cut-off	AUROC	Sensitivity (%)	Specificity (%)
Indirect markers								
FIB-4 Index (high cut-off)	3.25		16.2	73.6				
FIB-4 Index (low cut-off)	1.45–1.62	0.78	65	77	2.9–3.6	0.96	42	96
APRI (low cut-off)	0.5	0.79	84	41	1.5	0.75	54	78
APRI (high cut-off)	1.5		49	84	2		28	87
Direct markers								
Hyaluronic acid	113–203	0.73	63–80	78–94				
Hepascore	0.32	0.75	74	69	0.55	0.86	84	82
FibroTest	0.38	0.77	65	78	0.52	0.84	76	77
Imaging-based techniques								
TE	5.8–8.8	0.88	80	82	9.0–16.9	0.96	83	87
ARFI	1.63	0.76			2	0.82		
SWE	8.1	0.99			10.8	0.95		
MRE	2.8	0.98	94	97	4.09	0.96	91	86

APRI = aspartate aminotransferase to platelet ratio index; ARFI = acoustic radiation force impulse; AUROC = area under the receiver operator curve; FIB-4 = Fibrosis-4; MRE = magnetic resonance elastography; SWE = shear wave elastography; TE = transient elastography.

evaluated for hepatitis B and other forms of chronic liver disease. TE is now recommended in most Australian and international treatment guidelines.[1,41,132,316] Liver stiffness is indicated by a numeric value between 2.5 and 75 kPa. TE is an easily performed, rapid bedside test, with an immediate read-out for clinical use. Limitations of TE include confounding effects of inflammatory activity, body habitus and steatosis on liver stiffness values.[317] TE has reduced accuracy in lower stages of fibrosis, similar to blood-based biomarkers. Obtaining consistent TE readings depends on an experienced operator, variably defined as someone who has completed 100–500 examinations.[318,319] A standardised protocol should be used: the patient should have fasted for at least 2 hours before being placed in the supine position, with the right arm in full abduction, and the reading taken in the midaxillary line with the probe tip placed in the 9th to 11th intercostal space.[320] TE readings can be affected by a range of variables and need to be interpreted in context. In particular, ALT level should be noted at the time of TE examination, as hepatitis flares can increase TE readings, independent of liver fibrosis.[321]

ARFI elastography uses radiation-forced impulses to measure liver stiffness while using B-mode ultrasonography. In contrast to TE, which has a fixed region of interest at a fixed insertion depth, ARFI elastography has a flexible region of interest at variable depths, which enables measurement in patients with ascites and obesity. A recent study

Technical remarks

1. Typical requirements for valid TE readings include a minimum of 10 readings, success rate of measurements ≥60% and an IQR to median ratio of ≤0.30.[316]
2. TE readings are continuous and overlap with fibrosis stages, so arbitrary "cut-offs" determine sensitivity and specificity. In people with CHB, TE performs best to exclude cirrhosis, with negative predictive values typically 95%–100%.[316]
3. An XL probe is recommended for patients with BMI >30 kg/m^2 or if the skin-to-capsule distance is >25 mm.[320]

showed that advanced fibrosis is a predictor of non-discordance between biopsy and ARFI. Similar to other studies, optimum cut-off values decreased in patients with normal ALT levels.[229,322]

SWE is a novel real-time two-dimensional elastography technique, which allows a quantitative estimate of liver stiffness in kilopascals during routine liver ultrasound. Further, overlapping elastography with regular B-mode ultrasonography allows precise choice of the region of interest, unlike TE. Two-dimensional SWE has also been shown to discriminate between advanced fibrosis (≥F3) and F4 fibrosis better than the Fibrosis-4 (FIB-4) Index and AST to platelet ratio index (APRI).[323]

MRE, a modified contrast technique developed to characterise the elasticity of tissues, is a non-invasive, reproducible, advanced diagnostic technique for staging hepatic fibrosis.[324] In contrast to TE, MRE does not correlate with necroinflammatory scores or necroinflammation seen on biopsy, and its technical success rate is reported as 92.5%.[317] MRE using three-dimensional spin-echo echo planar imaging is a novel approach associated with a 2.2% failure rate and high diagnostic accuracy.[325] Other magnetic resonance-based imaging techniques to assess fibrosis, including diffusion-weighted imaging, dynamic contrast-enhanced imaging and multiparametric imaging, are in development and await further validation.[317]

Recommendation 5

Non-invasive assessment of liver fibrosis should be performed in all people with CHB as part of initial assessment. (Evidence quality: High; Grade of recommendation: Strong)

6.6.2.2 Serum biomarkers

There are several indirect and direct non-invasive markers for predicting severity of fibrosis in patients with HBV infection. Multiple studies using a combination of these parameters have yielded useful non-invasive scores for fibrosis. Direct biomarkers that mirror the extracellular matrix turnover can be used to assess dynamic changes in liver fibrogenesis,[326] for staging fibrosis but also theoretically for monitoring progression or regression. These markers have been studied individually and in panel combinations.

The APRI (https://www.mdcalc.com/ast-platelet-ratio-index-apri) uses standard pathology test results, is easy to use and has been recommended by the WHO as a non-invasive test of fibrosis, especially in lower- and middle-income countries.[298] The person's AST level (in IU/L) as a fraction of the normal AST level is divided by platelet count (× 10^9/L) and multiplied by 100 to produce a ratio. The APRI is well validated in multiethnic cohorts and in countries with high and low HBV prevalence.

The FIB-4 Index was initially derived from a cohort of patients with HCV–HIV coinfection[327] and subsequently validated in people living with hepatitis B.[328] FIB-4 is calculated using a combination of readily available blood test results and age, using the formula: (age [years] × AST [IU/L]) ÷ (platelets [10^9/L] × √ALT [U/L]). In a validation cohort of 668 people with hepatitis B, FIB-4 had an AUROC for cirrhosis of 0.926 (95% CI, 0.906–0.945) and was superior to APRI (0.729; 95% CI, 0.690–0.767; $P < 0.001$). Similarly, the AUROC for severe fibrosis outperformed that for APRI (0.910; 95% CI, 0.888–0.933 vs 0.702; 95% CI, 0.664–0.737; $P < 0.001$).[328] The authors concluded that, using FIB-4, cirrhosis could be correctly diagnosed in 70.5% of people. In another study using data from two Phase III trials, FIB-4 correlated with increasing fibrosis ($P < 0.001$); however, there was considerable overlap in the calculated scores for each stage in fibrosis (according to the Ishak system).[329] Most patients (173/195) with advanced fibrosis (Ishak score, 4–6) had FIB-4 scores below the cut-off value suggested in the original study.[327] A systematic review and meta-analysis evaluating both APRI and FIB-4 concluded that both scores were only moderately sensitive and accurate for identifying hepatitis B-related fibrosis.[330] In the summary data of 22 studies, including 6455 patients, the mean area under the summary receiver operating characteristic curve (AUSROC) for detecting significant fibrosis with FIB-4 was only 0.76 (range, 0.69–0.87). Similarly, the mean AUSROC of FIB-4 for detecting cirrhosis was 0.78 (range, 0.71–0.93).[330]

Hepascore is a patented test that comprises age, sex and levels of hyaluronic acid, bilirubin, gamma-glutamyl transferase (GGT) and alpha-2-macroglobulin. It is an automated panel test that requires a single analyser and serum sample. A meta-analysis of the use of Hepascore in chronic liver disease included

21 studies, with 588 patients with HBV.[331] Combining HBV studies, the mean adjusted AUROC was 0.83 for significant fibrosis, 0.91 for advanced fibrosis and 0.92 for cirrhosis.

The Enhanced Liver Fibrosis (ELF) panel combines hyaluronic acid, tissue inhibitor of metalloproteinase 1 and aminoterminal propeptide of type III procollagen. In a study of 182 patients with HBV, when using the ELF test to identify severe fibrosis at cut-offs of 9.08 and 9.94, 60% of patients would have correctly avoided liver biopsy, and 16% incorrectly.[332] The AUROC values for any fibrosis and cirrhosis were 0.77 and 0.83, respectively. An Asian study of 170 patients with HBV published the same year showed that the ELF test had an AUROC of 0.81 for predicting liver-related events, which was higher than liver stiffness measured by TE and histological fibrosis grade.[323]

Although not yet available in Australia, FibroTest is a patented test that combines five serum biochemical parameters (alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, L-glutamyl transpeptidase and bilirubin). It is useful in ruling out CHB-related cirrhosis but has suboptimal accuracy in diagnosing significant fibrosis and cirrhosis.[333]

Some tests have associated costs that limit their use in Australia. Nevertheless, where TE is unavailable, serum-based fibrosis tests should be used. APRI is most often recommended, as it is well validated, inexpensive and based on standard pathology test results. Whichever non-invasive fibrosis test is used, the results should not be relied on in isolation but should be interpreted in the context of other clinical parameters that may influence the result (e.g. ALT level, BMI, hepatic congestion, cholestasis).

6.6.2.3 Combination use of non-invasive tests

To increase the diagnostic accuracy of non-invasive tests, combined models using two or more tests have been tried. A dual approach combining either APRI or FIB-4 Index with liver stiffness measurement by FibroScan resulted in less than 4% of patients requiring a biopsy to confirm cirrhosis.[334] A stepwise application of TE with APRI or FIB-4 Index in patients with HBV and ALT levels <5 × ULN found an increase in positive predictive value for cirrhosis, from 0.677 to 0.808 and 0.724, respectively. A remarkable 76% of biopsies to confirm cirrhosis were avoided with this approach.[335] A novel combination model called the LAW (liver stiffness, APRI, woman) index has been used in a training and validation cohort of 492 patients with HBV. The LAW index was a better predictor of necroinflammatory activity ≥A3 or fibrosis grade ≥F2 than the APRI or TE alone in both groups (AUROC, 0.862–0.870).[336]

6.6.2.4 Liver biopsy

In patients with HBV infection, liver biopsy is seen as the gold standard for assessing the degree of liver injury, including both inflammatory activity and fibrosis stage. Due to its invasive nature and potential complications, it is reserved for clinical situations where its results are anticipated to change management, such as when non-invasive investigations do not define the nature and severity of the HBV-related liver disease or in patients with comorbidities. In HBV infection, there is a varying degree of predominantly lymphocytic portal inflammation with interface hepatitis and spotty lobular inflammation in the liver. Inflammation is minimal in the HBeAg-positive and -negative infection phases but is pronounced in the HBeAg-positive chronic hepatitis phase. Liver biopsy can indicate bridging necrosis and confluent necrosis.[147] The Knodell, Ishak and METAVIR histological systems are used to assess disease activity and treatment response.[1,41] Additionally, a liver biopsy may be used to confirm HCC or identify the coexistence of other causes of liver injury.

Despite its continued use, liver biopsy is far from an ideal standard. Its high cost, invasiveness, risk of complications and need for expert histological interpretation, as well as significant interobserver and sampling variability, limit its use in clinical practice.[317] For this reason, liver biopsy is usually reserved for investigating persistent liver enzyme abnormalities only after other treatment is initiated, including dietary advice for patients with non-alcoholic steatohepatitis; reduction in alcohol intake if relevant and antiviral therapy for CHB, if indicated.[337] Liver biopsy should only be performed by a trained operator who is able to provide an adequate specimen, and a histopathologist trained in hepatology should be available to report on the specimen.

Recommendation 6

Liver biopsy should only be considered when it influences management (e.g. uncertainty regarding the staging of fibrosis or coexistent pathologies). (Evidence quality: High; Grade of recommendation: Strong)

6.6.3 Assessment of coinfection

Coinfection with HIV, HDV or HCV can increase liver injury and the risk of HCC. As management, particularly treatment recommendations, is different in people with coinfection, everyone with CHB infection should be tested for hepatitis D (anti-HDV), hepatitis C (anti-HCV) and HIV antibodies.

People living with CHB should also be tested for hepatitis A virus (HAV) immunity (anti-HAV IgG) and offered vaccination if susceptible, as coinfection with HAV can precipitate a progression in liver disease, decompensation or fulminant hepatitis.

6.6.4 Assessment of comorbidities

Comorbidities, such as alcohol use, diabetes and MAFLD, can increase liver injury and the risk of HCC. A detailed history and assessment of risk factors and appropriate screening according to preventive health guidelines should be conducted. This should include a detailed family history, including cancer history; personal history of alcohol consumption and smoking; and an examination, including measurement of blood pressure and BMI. Consideration should be given to screening for diabetes.[338]

6.7 Monitoring and surveillance

6.7.1 Monitoring when not receiving antiviral therapy

Everyone with CHB infection who is not receiving treatment requires monitoring.[1,41,61] The aim of monitoring is to identify a change in clinical status — a rise in either ALT or HBV DNA level — which may indicate progression to active disease or cirrhosis (requiring initiation of antiviral therapy in either case) or early detection of HCC. People undergoing monitoring who are not receiving treatment are usually in the immune control or immune tolerant phase of disease and should have no evidence of cirrhosis on initial assessment. As with all chronic diseases, retaining people in care over their lifespan is challenging because of a range of patient, health care worker, health service, community, economic and logistical factors. This is particularly the case if people living with hepatitis B are not receiving treatment and the benefits of ongoing monitoring have not been adequately explained in a way that resonates with them.

Regular monitoring of people not receiving treatment is recommended to comprise at least an annual check of HBV DNA level and 6-monthly liver function tests, with or without 6-monthly ultrasound and AFP testing for HCC surveillance.[339] The evidence base for monitoring is limited and based on cohort studies looking at rates of progression of liver disease.[298] The current intervals of assessment are based on an understanding of the time taken to develop significant liver injury. In the Australian context, the intervals are constrained by the Medicare benefits assigned to testing, particularly for HBV DNA testing, which is restricted to a yearly testing rebate for people not receiving treatment.[64]

Ideally, testing should be opportunistic and flexible, particularly in remote and rural settings and in populations such as Aboriginal and Torres Strait Islander people, who may have limited access to culturally appropriate health care.

6.7.2 Frequency of fibrosis assessment when not receiving antiviral therapy

Fibrosis assessment for people living with CHB infection and not receiving treatment is recommended to occur at regular intervals. After initial assessment at baseline, international recommendations advise annual assessment of fibrosis, by calculation of APRI score or an alternative method.[298,300,340] Consideration should be given to repeating a fibrosis assessment for people who have re-engaged in care after being lost to follow-up or having missed routine 6-monthly liver function tests or annual HBV DNA tests.

Without being too prescriptive, it seems reasonable for people with CHB who are HBeAg-negative and have an HBV DNA level <2000 IU/mL (who are not receiving treatment) to undergo assessment of fibrosis at 2-yearly intervals with TE, or APRI if TE is not available. In people with CHB who are HBeAg-positive,

or HBeAg-negative with an HBV DNA level greater than 2000 IU/mL, assessment of fibrosis should occur more frequently (yearly). Those from either group who miss routine follow-up should be reassessed once re-engaged with care.

6.7.3 Assessment of HCC risk and need for surveillance

As discussed in detail in section 8.1.1, an important aspect of monitoring patients living with hepatitis B is assessing their risk of developing HCC and, where indicated, entering those at increased risk into an HCC surveillance program. In essence, HCC surveillance comprises 6-monthly ultrasound, with or without AFP testing, and is required for all patients with cirrhosis and other populations with an annual HCC incidence greater than 0.2%.

Despite clear guidelines regarding who should undergo HCC surveillance, rates remain low, with optimal participation estimated to be 1.7%–25% in Australia and overseas.[340-343] Many factors contribute to low participation rates, including:

- health system factors;
- low enrolment in care for CHB;[344]
- clinicians not ordering tests for those in care;[342]
- upfront and hidden costs related to attending medical appointments;
- logistical challenges, including access for people in rural and remote areas; and
- lack of culturally appropriate information that outlines the benefits and risks of HCC surveillance in a way that resonates with people with CHB and empowers them to make good choices.[340,345-347]

Several tools are available for clinicians to identify individuals at increased risk of HCC (see section 8.1.1.1). They combine history, clinical findings, laboratory test results and liver stiffness measurements to estimate risk and are often population- or region-specific. These tools have not been validated in the context of HCC risk in Australia, where there is a more diverse population affected by CHB,[348] but they may be relevant to individual patients.[214,349,350]

HCC can also develop in patients without cirrhosis after HBsAg seroconversion. Independent predictors include being male or aged 50 years or older or having pre-existing cirrhosis at the time of seroconversion. In a retrospective cohort study of people with HBsAg seroconversion attending a Korean tertiary centre, the annual incidence of HCC was 2.85% and 0.29% in people with and without cirrhosis, respectively.[351] In the non-cirrhotic group, the annual incidence of HCC was greater in men than women (0.4% vs 0%), with a hazard ratio of 8.96 (95% CI, 1.17–68.80; $P = 0.04$) for development of HCC in men.[351]

7 Treatment

7.1 Goals of treatment

The primary goals of treatment are to improve both quality of life and survival of people with HBV infection, in addition to achieving a reduction in HBV transmission. These goals can be achieved through sustained HBV suppression, which reduces the risk of liver disease progression, the risk of HCC development and HBV infectivity.

Achieving these goals must take both viral and patient factors into account, including an appreciation of the natural history of the disease (see section 5) and a comprehensive patient assessment (see section 6.5). Despite its potential benefits, treatment uptake in Australia remains well below national targets, with modelling suggesting less than 10% of all people with CHB infection receive antiviral treatment, well short of the WHO treatment target of 20% for Australia (see section 4.2).[28,38]

7.2 Treatment endpoints

Various definitions of HBV cure have been proposed.[352,353] Virological cure is defined as eradication of HBV from the blood and liver. Although this is the ultimate goal of HBV therapies, it is unachievable because of the persistence of HBV cccDNA within the nucleus of hepatocytes after hepatocyte infection. The cccDNA can persist in the hepatocyte despite long-term viral suppression, even in the presence of HBsAg loss and the development of anti-HBs. The persistence of cccDNA allows for HBV reactivation under immunosuppressive states. However, *functional cure* of HBV is achievable after long-term treatment in a small proportion of patients: 3%–7% of those treated with peginterferon and 1%–12% of those treated with nucleos(t)ide analogue (NA) therapy.[354-359] It is defined as a sustained loss of HBsAg with or without development of anti-HBs, in conjunction with an undetectable serum HBV DNA level.

Pharmacotherapy is not recommended for all patients with CHB infection because a virological cure is not yet possible, and a functional cure is achieved in only a minority of patients. Although pharmacotherapy is generally safe, and virological suppression can be reliably achieved with NA therapy, long-term treatment is required with NAs and can be associated with side effects and complications. Peginterferon is used infrequently but provides another treatment option for selected patients who are interested in a finite duration of therapy and are willing to accept the side effect profile. All approved treatment strategies aim to suppress HBV replication, to reduce hepatic inflammation and prevent progressive liver injury. The current suggested endpoint of antiviral treatment is HBsAg seroclearance, which has good off-treatment durability and is associated with improved disease outcomes.

Therefore, therapy should generally be directed towards patients at risk of developing complications of CHB infection, including those with evidence of hepatic fibrosis or at higher risk of developing HCC. However, additional factors to be considered when determining when and how to commence therapy for HBV infection include:

- patient preference;
- risk of transmission, such as in health care workers or patients with high-risk behaviour for transmission (see Table 4);
- pregnancy and family planning;
- extrahepatic manifestations of HBV; and
- other relevant patient comorbidities or coinfections.

7.3 Overview of antiviral agents for chronic hepatitis B

Available treatments for HBV infection are shown in Table 9. Oral NAs with a high barrier to resistance — namely, entecavir, tenofovir disoproxil and tenofovir alafenamide (TAF) — are the recommended first-line treatments for people with CHB infection (Table 10). Peginterferon may also be considered in selected patients (Table 10). In 2018, most people who received

Table 9. Antiviral therapies for hepatitis B virus infection

Drug	Dosage (adults) and route of administration	Duration of treatment	Pregnancy category		Potential important side effects
			FDA	TGA	
PBS-listed drugs					
Entecavir	0.5 mg daily, or 1 mg daily,* oral	Indefinite	C	B3	Rare: • Lactic acidosis (patients with decompensated cirrhosis only)
Tenofovir disoproxil (TD)	TD fumarate 300 mg, or TD maleate 300 mg, or TD phosphate 291 mg daily, oral	Indefinite	B	B3	Uncommon: • Nephropathy • Reduced bone mineral density Rare: • Fanconi syndrome • Lactic acidosis†
Peginterferon alfa-2a	180 µg weekly, subcutaneous injection	48 weeks	C	B3	Common: • Influenza-like symptoms • Fatigue • Mood disturbance • Cytopenia Uncommon: • Autoimmune disorders (most often thyroid dysfunction)
Drugs that are recommended but not PBS-listed					
Tenofovir alafenamide‡	25 mg daily, oral	Indefinite	na	na	Rare: • Lactic acidosis†
Drugs that are not recommended					
Lamivudine	100 mg daily, oral	Indefinite	C	B3	Rare: • Pancreatitis • Lactic acidosis†
Adefovir	10 mg daily, oral	Indefinite	C	B3	Uncommon: • Acute renal failure Rare: • Fanconi syndrome • Lactic acidosis†

FDA = US Food and Drug Administration; na = not applicable; PBS = Pharmaceutical Benefits Scheme; TGA = Therapeutic Goods Administration.
* The dosage of entecavir should be increased to 1 mg daily for people with chronic hepatitis B who have decompensated cirrhosis and/or are lamivudine-experienced. Tenofovir is preferred for people who are lamivudine-experienced.
† All nucleos(t)ide analogues carry a warning in their product information about lactic acidosis and severe hepatomegaly, but these adverse events were observed among people with HIV receiving older nucleoside analogues (e.g. stavudine and didanosine) and have not occurred among people with chronic hepatitis B infection in clinical trials.
‡ Tenofovir alafenamide was recommended for PBS listing by the Pharmaceutical Benefits Advisory Committee in March 2017 but, at time of writing, is not yet available through the PBS for hepatitis B mono-infection.

treatment for CHB infection through the PBS were prescribed first-line monotherapy with either entecavir (58.2%) or tenofovir disoproxil (35.1%). A small proportion of people were prescribed lamivudine (5.4%), and only 0.4% received peginterferon.[28,87]

7.4 Agents recommended for first-line use in Australia

7.4.1 Nucleos(t)ide analogues

The three preferred oral agents are the nucleoside analogue entecavir and the nucleotide analogues tenofovir disoproxil and TAF, although the latter is not yet available on the PBS for HBV mono-infection.[360]

Table 10. Comparison of treatment strategies for chronic hepatitis B infection

	Peginterferon	Nucleos(t)ide analogue*
Aim of treatment strategy	Induction of long-term immune control with finite treatment	Control of hepatitis and prevention of disease progression by inhibiting viral replication
Viral suppression	Variable	High
Tolerability	Low	High
Drug administration	Weekly subcutaneous injection	Daily oral
Treatment duration	Finite (maximum 48 weeks)	Indefinite
Risk of viral resistance	No	None to minimal†
Contraindications	Yes (including decompensated liver disease and comorbidities)	No (drug selection and dose adjustment may be required)‡
Long-term safety concerns	Rare (persistence of neuropsychiatric and autoimmune adverse events)	Possible for tenofovir only (renal and bone disease)
Effect on HBeAg loss	Moderate (dependent on baseline characteristics)	Low to moderate (increases with duration of therapy)
Effect on HBsAg loss	Uncommon (dependent on baseline characteristics)	Very rare (HBeAg-positive > HBeAg-negative)

HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen.
* Entecavir, tenofovir alafenamide (TAF) or tenofovir disoproxil.
† No in vivo resistance to tenofovir or TAF has been detected to date.
‡ Dose adjustments in patients with an estimated glomerular filtration rate <50 mL/min/1.73 m^2 are required for all nucleos(t)ide analogues, except TAF (no dose recommendation for TAF in patients with creatinine clearance <15 mL/min who are not receiving haemodialysis).

The main advantages of treatment with a potent NA are predictable long-term high antiviral efficacy (achieving undetectable serum HBV DNA levels) and a favourable safety and tolerability profile. These agents can be safely used by almost all patients with HBV infection, and they are the only options for people with decompensated liver disease, extrahepatic manifestations or acute hepatitis B or who have had a liver transplantation. NAs are also the only option for preventing HBV reactivation (e.g. in people receiving immunosuppression). In conjunction with hepatitis B immunoglobulin (HBIG) and HBV vaccination, they form an important part of the strategy for preventing vertical HBV transmission from mothers with a high viral load to their infants (see section 9.1).

In randomised clinical trials comparing entecavir, tenofovir disoproxil and TAF, there was no significant difference in HBV DNA suppression (>90%), HBeAg seroconversion (12%–34%) or HBsAg loss (<1%).[360-364] Long-term viral suppression by tenofovir disoproxil or entecavir can result in histological improvement (including regression of cirrhosis) and reduction in the incidence of cirrhosis, decompensated liver disease, liver transplantation and HCC.[365-369] A sustained off-treatment response is uncommon, and long-term therapy should be anticipated, particularly among people with HBeAg-negative infection.

The choice of NA should consider patient factors, including liver disease stage, pregnancy or family planning, prior NA exposure and comorbidities (Table 11). Although it is clear that treatment with NAs reduces risk of HCC among people with HBV infection, the data are conflicting as to whether one agent (tenofovir or entecavir) is superior to the other in lowering this risk.[370-373] A recent systematic review and meta-analysis suggests that the HCC

Table 11. Considerations in selection of recommended nucleos(t)ide analogue

Factor to be considered	Entecavir	Tenofovir disoproxil*
Prior exposure to nucleoside analogues†	✗	✓
At risk of or with confirmed bone disease‡	✓	✗
At risk of or with confirmed renal disease§	✓¶	✗
Pregnancy	✗	✓
Decompensated cirrhosis	✓	✓

* There are three formulations of tenofovir disoproxil (TD): TD fumarate (300 mg), TD maleate (300 mg) and TD phosphate (291 mg). Tenofovir alafenamide, a preparation used in HIV antiviral therapy, is not yet available on the Pharmaceutical Benefits Scheme for hepatitis B virus monotherapy.
† For patients with prior adefovir monotherapy, entecavir is the drug of choice.
‡ This may include chronic steroid use (or other medications that affect bone density), history of fragility fracture or osteoporosis.
§ This may include an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, albuminuria (30 mg albumin/24 h or moderate dipstick proteinuria), low phosphate level (<2.5 mg/dL) or haemodialysis.
¶ Entecavir dose needs to be adjusted if eGFR is <50 mL/min/1.73 m^2.

risk reduction is likely to be equivalent for both drugs, providing reassurance that either tenofovir or entecavir is appropriate therapy for achieving HCC risk reduction.[374]

7.4.1.1 Entecavir

Entecavir, a purine-derived nucleoside analogue, has potent antiviral activity (Table 12), excellent tolerability and a very low risk of drug resistance in people who are NA-naive; entecavir resistance may be seen in about 1% of patients at 5 years.[375] However, due to the high rates of entecavir resistance that have been observed in up to 50% of lamivudine-refractory patients after 5 years of treatment,[375] entecavir is not the preferred agent for people with lamivudine-resistant HBV infection. Few side effects are reported with its use, with the most common being fatigue (<10%) and headache (<10%). The recommended dose of entecavir is 0.5 mg daily for people who are treatment-naive or 1 mg daily for patients with lamivudine resistance or hepatic decompensation. It should be taken on an empty stomach, 2 hours before or after a meal. Entecavir requires dose adjustment in certain circumstances, including renal impairment and decompensated liver disease.

7.4.1.2 Tenofovir

In Australia, the three formulations of tenofovir disoproxil (and their daily doses) are tenofovir disoproxil fumarate (TDF; 300 mg), tenofovir disoproxil maleate (300 mg) and tenofovir disoproxil phosphate (291 mg). There is no evidence of differences in efficacy or side effects between these preparations, and studies have shown them to be bioequivalent.[376]

TDF, an acyclic adenine nucleotide, can be used as first-line therapy in people who are treatment-naive, who have had prior exposure to HBV treatment or who have developed drug resistance to other NAs. Although generally very safe, long-term administration of TDF may be associated with acute kidney injury, chronic renal disease, proximal tubular dysfunction and decreased bone mineral density; there have also been case reports of Fanconi syndrome among people with HBV mono-infection.[377,378] In general, development of renal dysfunction has been uncommon (<2%) among participants in clinical trials and observational cohort studies, particularly in those who are treatment-naive.[365,378,379] However, results of individual studies may be conflicting.[378] In a meta-analysis of 1300 people with CHB infection, there was no statistically significant difference between entecavir and tenofovir with regard to renal safety profile (including serum creatinine level, estimated glomerular filtration rate [eGFR], and serum phosphate level), but the duration of observation in the included studies was short (median, 18 months).[369] On-treatment monitoring of serum creatinine level, eGFR and serum phosphate level is recommended to detect and avoid progressive renal injury.

TAF, a prodrug of tenofovir with lower peripheral blood concentrations, appears to be as effective for virological suppression as tenofovir disoproxil and may be associated with less renal and bone toxicity (using sensitive biomarkers of renal function and bone turnover).[361,362] However, long-term safety data for TAF are unavailable. TAF is used in HIV antiviral therapy and is not yet available on the PBS for HBV monotherapy. The recommended daily dose of TAF is 25 mg.

Table 12. Comparison of viral and biochemical responses for tenofovir and entecavir

Time point	Response type	HBeAg status	Tenofovir	References	Entecavir	References
48 weeks	Virological response*	Negative	93.2%	Marcellin et al[380]	90.2%	Lai et al[381]
		Positive	76.1%		94.9%	Chang et al[382]
	Biochemical response†	Negative	76.3%		77.8%	Lai et al[381]
		Positive	68.0%		68.4%	Chang et al [382]
240 weeks	Virological response	Negative	89.6%	Liang et al[383]	95.0%	Lee et al[384]
		Positive	84.5%		93.6%	Chang et al[357]
	Biochemical response	Negative	87.5%		87.5%‡	Lee et al[384]
		Positive	80.4%		76.9%	Chang et al[357]

ALT = alanine aminotransferase; HBeAg = hepatitis B e-antigen.
* Virological response defined as plasma hepatitis B virus DNA level <69 IU/mL.
† Biochemical response defined as ALT level <34 IU/L in women and <43 IU/L in men, when baseline level was above this.
‡ Only 96-week ALT normalisation data presented.

7.4.1.3 Other nucleos(t)ide analogues

Lamivudine, adefovir and telbivudine are no longer recommended as first-line therapies in Australia or by the WHO, but they may still be prescribed. For people using these antiviral agents, which have a lower barrier to the development of drug resistance, a rising ALT or HBV DNA level may indicate resistance (or non-adherence). Confirmed drug resistance should prompt a change of antiviral therapy, with preference for tenofovir disoproxil, given the potential for resistance to entecavir in patients with previous lamivudine exposure (see section 7.11).

7.4.2 Peginterferon

Subcutaneous injection of peginterferon alfa for 48 weeks remains a treatment option for people with CHB infection, although in practice this therapy is rarely employed.[28] The exact mechanism by which interferon has an antiviral effect is not clear, but it is believed to have both direct antiviral (degradation of cccDNA and viral messenger RNA and inhibition of viral DNA) and host immunomodulatory (boosting host immune response against infected hepatocytes and facilitating viral clearance) effects.[385] The rationale for its use is induction of long-term immunological control with treatment of finite duration; up to 30% of people with HBeAg-positive CHB infection will achieve HBeAg seroconversion up to 6 months after the end of treatment, and a small proportion achieve HBsAg loss or seroconversion.[354-356] Overall, the response rates for interferon are modest, highly variable and associated with an unfavourable safety and tolerability profile. Contraindications (including decompensated liver disease, pregnancy and comorbidities) and side effects (including influenza-like symptoms, fatigue, bone marrow suppression, thyroid dysfunction and autoimmunity, and neuropsychiatric disturbance) limit its use.[354-356]

Assessment of pre-treatment patient characteristics (including disease activity, HBV genotype, liver disease stage, HBV DNA level and HBeAg status) can help select those who are more likely to respond to interferon therapy. Baseline predictors of response include genotype A infection, lower HBV DNA level (<20,000,000 IU/mL) and higher ALT level (>2 × ULN).[354-356] In general, HBeAg-positive individuals are more likely to respond to treatment than those who are HBeAg-negative. To limit toxicity and avoid treatment futility, on-treatment predictors and the application of stopping rules at 12 or 24 weeks are useful additional tools to individualise the treatment strategy. Lack of suppression of HBV DNA by 6 months is usually indicative of non-response, and treatment may then be discontinued. Peginterferon should only be considered for patients who do not wish to receive long-term treatment and those who are more likely to

have a favourable response (i.e. people with HBeAg-positive CHB infection, HBV genotype A, lower HBV DNA level and elevated ALT level).

7.5 When and why to start antiviral therapy

When determining eligibility and appropriateness for hepatitis B treatment, it is necessary to first characterise the phase of infection and the severity of hepatic fibrosis (see section 6.5). As discussed in section 5, people with HBV infection may transition in and out of phases, and a period of re-evaluation and repeated assessment may be warranted before therapy is initiated (see Recommendation 4).

The indications for treatment are based on three parameters: serum HBV DNA level, serum ALT level and liver disease stage (assessed by non-invasive methods or liver biopsy). In people without cirrhosis, HBeAg-negative and HBeAg-positive phases of CHB infection have different thresholds for starting therapy, whereas everyone with CHB and cirrhosis should be treated with antiviral therapy (generally NAs). The endpoint of treatment is suppression of viral replication, with seroconversion from HBeAg to anti-HBe; HBeAg seroconversion is associated with a durable response in 50%–90% of people.

Other factors that influence the decision to start treatment include the individual's age, health status, risk of HBV transmission, family history of HCC (see section 8.1.1.1) or cirrhosis, and extrahepatic manifestations.[1]

The aim of treatment is to prevent disease progression or the development of HCC. Response to treatment is monitored by measurement of HBV DNA levels, with the aim of full suppression of viral replication. HBV DNA has been shown to be the strongest predictive marker for disease progression and outcomes, including progressive liver fibrosis and the risk of HCC.[1]

7.5.1 HBeAg-positive chronic hepatitis B (phases I and II)

7.5.1.1 Phase I: immune tolerant (HBeAg-positive chronic infection)

The first phase of CHB (HBeAg-positive chronic infection or immune tolerant) is characterised by HBeAg positivity and high levels of HBV DNA (often >1 million IU/mL), without elevation of serum ALT levels. As discussed in section 5.2.2, the definition of elevated ALT level varies across international guidelines,[1,41,128,132] but in this consensus statement, the ULN is considered to be 19 IU/L for women and 30 IU/L for men. As the immune tolerant phase is generally associated with low rates of liver fibrosis progression and HCC development,[158,386] we support the international guideline recommendations against routine use of antiviral therapy for patients in this phase of infection, based on cost of therapy and lack of proven benefit in reducing HCC occurrence.[1,128,132]

Older age, male sex and low platelet count are independent predictors of clinical events in the immune tolerant phase.[221] This suggests there may be a subgroup of patients who could benefit from HBV therapy (Table 13), although, on careful evaluation, many of these patients have evidence of raised ALT levels or risk factors for occult liver fibrosis and cofactors such as alcohol use, coinfection and MAFLD. This highlights the importance of careful evaluation and reassessment of adults in the immune tolerant phase.[387] Another potential reason to treat patients in this phase is viral suppression, to reduce the risk of transmission. This is particularly relevant for patients with high-risk behaviour for HBV transmission and for health care workers with CHB infection. Confirmed and persistent viral suppression to HBV DNA levels <200 IU/mL is required for health care workers who perform exposure-prone procedures, as per national guidelines.[95]

Recommendation 7

The treatment of people with HBeAg-positive chronic infection characterised by persistently normal ALT is not routinely recommended. Antiviral therapy may be considered in certain circumstances (Table 13). (Evidence quality: Moderate; Grade of Recommendation: Strong)

Table 13. Circumstances in which antiviral therapy may be considered for people with HBeAg-positive chronic infection*

Increased risk of HCC development (e.g. first-degree family history of HCC)
Age >35 years
Coinfection (e.g. HBV with HDV or HCV)
Prevention of HBV transmission to others (e.g. health care workers)
Extrahepatic manifestations of HBV (see Recommendation 19)
Concurrent liver disease (e.g. MAFLD, alcohol-related liver disease)

HBeAg = hepatitis B e-antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis delta virus; MAFLD = metabolic (dysfunction)-associated fatty liver disease.
* Not all the circumstances listed (for consideration under Recommendation 7) are reimbursed under the Pharmaceutical Benefit Scheme. Recommendation 7 does not include people with cirrhosis (covered in Recommendation 10) and other settings in which antiviral therapy is strongly recommended.

Technical remarks

1. As commonly used risk-based algorithms have not targeted the immune tolerant population, quantification of the risk of HCC or liver disease progression in this population is difficult.[139,214,388-390]
2. A common strategy is to start antiviral therapy in patients in the immune tolerant phase when they are over the age of 30–40 years and therefore exhibit "delayed" HBeAg seroconversion and have a higher risk of cirrhosis development.[163,227,391]
3. Patients who have evidence of significant hepatic fibrosis or a family history of HCC should also be considered for antiviral therapy, although whether a significant family history of HCC relates to age, biological relationship or number of affected relatives remains to be determined.[392]
4. In the Australian context, the current PBS listing for NAs is limited to patients with cirrhosis or evidence of liver injury, shown either by confirmed elevated serum ALT level or liver biopsy.

7.5.1.2 Phase II: immune clearance (HBeAg-positive chronic hepatitis)

In the second phase of CHB (HBeAg-positive chronic hepatitis or immune clearance), there is intermittent or persistent elevation in serum ALT level, which puts the individual at risk of developing progressive fibrosis and eventually cirrhosis. For this reason, patients who persistently fulfil eligibility criteria are considered appropriate for antiviral therapy. Many patients will have no symptoms, despite occasional significant elevations in ALT level ("flares"), reaffirming the importance of periodic review and reassessment for treatment eligibility.

For people with HBeAg-positive chronic hepatitis, the PBS-listed treatment options are entecavir, tenofovir disoproxil and peginterferon. Selecting an antiviral regimen requires consideration of both host and viral factors. In considering HBV treatment initiation and choice of agent, the patient's age, comorbidities, risk of HBV transmission, family history of HCC or cirrhosis, and extrahepatic manifestations should be considered.

For most people, treatment with entecavir or tenofovir disoproxil is optimal because of their high efficacy, excellent safety profile and ease of administration.[361-364] For NA therapy, treatment cessation can be considered 12 months after HBeAg seroconversion, with subsequent monitoring for viral relapse. A systematic review showed pooled durable rates of virological remission at 12 and 24 months after NA discontinuation of 63% and 53%, respectively, in patients with HBeAg-positive CHB infection.[393] As relapse is common, NA treatment duration is often indefinite.

Treatment with peginterferon requires careful patient selection. For people considering this treatment, pre-treatment predictors of response include low HBV DNA levels, high serum ALT levels (>2 × ULN), HBV genotype (A > B > C > D) and high activity scores on liver biopsy.[354-356] Substantial on-treatment declines in quantitative HBsAg level and HBV DNA level (at Week 12 and Week 24) can aid with predicting which individuals are more likely to undergo HBeAg seroconversion and, conversely, can identify patients for whom continuation of therapy is futile. Measurement of quantitative HBsAg is becoming increasingly available in Australian laboratories.[311]

Treatment with peginterferon is for a maximum of 48 weeks.

Recommendation 8

In people with HBeAg-positive chronic hepatitis, antiviral therapy is indicated when HBV DNA is >20,000 IU/mL and ALT is persistently elevated or there is evidence of fibrosis. (Evidence quality: High; Grade of recommendation: Strong)

Technical remarks

1. Due to the varying methods of fibrosis assessment that are available in Australia, the level of fibrosis necessary to consider initiating treatment has not been specifically defined. Clinician judgement should be used.

7.5.2 HBeAg-negative chronic hepatitis (phases III and IV)

Patients with HBeAg-negative chronic infection should undergo regular monitoring of ALT and HBV DNA levels to detect the 10%–20% who will develop more active disease and meet criteria for treatment in the longer term. Patients should also be evaluated for severity of liver fibrosis or presence of cirrhosis and undergo appropriate HCC surveillance, according to the Australian HCC consensus statement.[339]

7.5.2.1 Phase III: immune control (HBeAg-negative chronic infection)

In the third phase of CHB (HBeAg-negative chronic infection or immune control), viral loads fall below 2000 IU/mL and the ALT level remains within the normal range. Consequently, progression of liver disease is uncommon. Patients in this phase are not generally eligible for antiviral therapy but need to undergo regular evaluation to determine movement into phase IV (or back into phase II).

7.5.2.2 Phase IV: immune escape (HBeAg-negative chronic hepatitis)

The fourth phase of CHB (HBeAg-negative chronic hepatitis or immune escape) is characterised by HBeAg negativity, raised levels of HBV DNA (>2000 IU/mL) and ALT, and at least moderate liver necroinflammation or fibrosis. This phase is associated with progression to cirrhosis and HCC. Treatment is recommended for patients in the immune escape phase.

Recommendation 9

In people with HBeAg-negative chronic hepatitis, antiviral therapy is indicated when HBV DNA is >2000 IU/mL and ALT is persistently elevated or there is evidence of fibrosis. (Evidence quality: High; Grade of recommendation: Strong)

7.5.3 Hepatitis B and cirrhosis

People living with hepatitis B infection who are identified as having cirrhosis are at risk of hepatic decompensation and at significantly increased risk of developing HCC. Treatment with antiviral therapy reduces the risk of liver disease progression or HCC and should be offered to all individuals with cirrhosis.

Recommendation 10

All people with cirrhosis and any detectable HBV DNA, regardless of ALT levels, should be treated with antiviral therapy. (Evidence quality: High; Grade of recommendation: Strong)

7.6 Choice of antiviral therapy

For most people, treatment with a potent NA, such as entecavir or tenofovir disoproxil, is optimal because of their high efficacy, excellent safety profile and ease of administration.[361-364] Resistance to tenofovir has not been reported in vivo, and resistance to entecavir is infrequently encountered. Both these drugs therefore offer a high barrier to formation of resistance.

As HBsAg loss is rare in patients with HBeAg-negative CHB, NA therapy is usually given long term.[1] Patients with HBeAg-negative infection can safely stop taking NAs if they achieve HBsAg loss. Although NA discontinuation is more established in patients with HBeAg-positive infection, there is evidence that NAs can be discontinued in HBeAg-negative patients, provided they have had prolonged viral suppression with NA therapy.[393] The probability of durable off-NA virological remission in patients with HBeAg-negative CHB is related to the duration of on-therapy virological remission and is significantly higher in patients who remained in virological remission under NAs

for >24 months, compared with ≤24 months.[393] A systematic review of the discontinuation of NA therapy in patients with CHB indicated that the pooled durable rates of virological remission at 12 and 24 months after NA discontinuation in HBeAg-negative patients were only 44% and 31%, respectively.[393,394] Furthermore, there is potential for severe HBV reactivation after cessation of NA therapy, characterised by ALT levels >5–10 × ULN, associated with the development of jaundice or hepatic decompensation. For this reason, close follow-up of patients is required after cessation of NA therapy, and we do not recommend NA therapy be discontinued in patients with cirrhosis.

Recommendation 11

Where oral antiviral therapy is indicated, a potent NA with a high barrier to resistance (entecavir, tenofovir) should be used. (Evidence quality: High; Grade of recommendation: Strong)

For treatment-naive patients aged over 60 years with bone or renal disease, treatment with entecavir is preferable.[1] Treatment with peginterferon is rarely used in this group because of the high risk of relapse and significant side effects.[355] Treatment with peginterferon is for a maximum of 48 weeks and is contraindicated in patients with hepatic decompensation.

Recommendation 12

Interferon-based treatment regimens are contraindicated in decompensated cirrhosis. (Evidence quality: Moderate; Grade of recommendation: Strong)

7.7 Preparing people for hepatitis B therapy

Given the complicated and dynamic natural history of hepatitis B, together with multiple therapeutic options and the likely long duration of NA therapy, it is imperative that people living with hepatitis B are given appropriate counselling on the therapy options, duration of therapy and likely short- and long-term adverse effects. Clearly communicating these aspects of therapy will strengthen the clinician–patient relationship and assist in the patient's understanding and adherence to proposed therapies.

7.7.1 Cultural considerations in treatment

Different cultural understandings and low levels of health literacy regarding CHB have been identified in Aboriginal and Torres Strait Islander people from several communities around Australia.[395,396] Other Australian populations for whom English is not a first language also have knowledge gaps and misconceptions about CHB.[397-399] In a study among migrants and refugees living with CHB in Melbourne, 90% of people did not understand the associated risk of cancer and had common misconceptions about HBV transmission, including believing that it is transmitted by mosquitoes and through sharing food.[399]

Most individuals are asymptomatic when starting antiviral medications for CHB infection and, once started, antiviral medication is generally continued long term, with the potential for resistance if there is suboptimal adherence. Using available language-appropriate resources and approaches in a culturally safe way has been shown to improve adherence to long-term medication.[400] Culturally appropriate approaches may include, but are not limited to, being mindful of sex and gender, family relationships, stigma, blame and shame.

7.7.2 Aboriginal and Torres Strait Islander Australians

Aboriginal and Torres Strait Islander Australians are disproportionately affected by CHB and its consequences.[38] Liver disease is the third most significant contributor to the gap in life expectancy between Aboriginal and Torres Strait Islander Australians and non-Indigenous Australians,[401] and liver cancer is six times more common in this population.[47] Importantly, there is no evidence that medication adherence among Aboriginal and Torres Strait Islander people is lower than that among the general population.[402] Adherence is determined not only by patient factors, but also by health provider relationships, sociocultural issues and the health system.

7.8 Primary care and tertiary care: when to refer

Patients with serious complications from hepatitis B infection should be referred for tertiary care. These include patients with hepatic decompensation, cirrhosis, HBV reactivation during immunosuppression or suspected HCC on screening. Other situations requiring referral include hepatitis B infection in pregnancy, coinfection with HCV or HIV and whenever the primary care practitioner is uncertain about hepatitis B management.

PBS regulations restrict prescribing for HBV antiviral therapy under the Section 100 (S100) Highly Specialised Drugs program. GPs and nurse practitioners can prescribe antiviral therapy in the community if they have completed an S100 training program.

Only a minority of GPs have received additional training in hepatitis B management, yet most hepatitis B monitoring in Australia (as determined by viral load testing) is performed by these clinicians; nearly 60% of disease monitoring is conducted in the primary care setting.[28] This consensus statement and other practical resources[40] aim to assist GPs to monitor HBV disease progression and appropriately refer patients to tertiary care.

The cascade of care for hepatitis B in Australia shows that only a small proportion of patients are adequately investigated and treated.[21] In response, the National Hepatitis B Strategy has called for increasing diagnosis and management of patients in primary care.[38] Primary care doctors and nurses can receive education in hepatitis B management through training organisations such as ASHM. ASHM administers the S100 training program for GPs, which requires completion of a course and passing a post-course assessment before allowing GPs to prescribe antiviral medications in the community, with continuing medical education then required to maintain accreditation as a prescriber.[403]

An important part of training is being able to know when to refer patients for specialist care.[404] Recommendations in this document centre on the standard primary care specialist pathway model. Using shared care and integrative care models, such as Project Echo,[405] may allow primary care providers to manage more complex patients in primary care with close specialist support.

7.9 On-treatment monitoring

All patients receiving antiviral therapy require monitoring. This includes periodic evaluation of their response to treatment, as well as monitoring for adverse effects.

A suggested schedule for monitoring during treatment with potent NAs is shown in Table 14.[1] Monitoring of renal function should include at least eGFR and fasting serum phosphate level. In the presence of renal impairment, NA dose, interval or medication may need to be modified. After 1 year of antiviral therapy with NAs, more than 90% of patients will have fully supressed HBV DNA. Failure to supress viral levels may suggest suboptimal adherence or (in the case of entecavir) development of resistant mutations, necessitating further review appointments.[392]

Table 14. Monitoring during nucleos(t)ide analogue treatment*

Baseline	First year	Second and subsequent years
Full blood count	6-monthly	6-monthly
Liver function tests	3-monthly	6-monthly
eGFR, serum phosphate	3-monthly	6-monthly
HBV DNA	3-monthly	6-monthly
HBsAg	Annually	Annually
HCC surveillance	6-monthly	6-monthly

* Based on European Association for the Study of the Liver guidelines.[1]
eGFR = estimated glomerular filtration rate; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma.

Recommendation 13

All people being treated with antiviral therapy should undergo periodic review, including ALT, serum HBV DNA and, for tenofovir, renal function (eGFR) and serum phosphate. (Evidence quality: High; Grade of recommendation: Strong)

7.9.1 Assessment of treatment response

Defining response to NA antiviral therapy is important in both clinical practice and clinical studies. The following definitions have been proposed:

- Non-response or primary antiviral therapy failure: failure to achieve more than 1 $\log_{10}$ decrease from baseline within 3 months of starting therapy;
- Suboptimal response: considered to be between 1 $\log_{10}$ and 2–3 $\log_{10}$ decrease from baseline within 3 months of starting therapy; and
- Secondary antiviral therapy failure: a rebound of 1 $\log_{10}$ or greater from nadir in those with an initial antiviral response.[406]

Although primary and secondary failure may be due to poor adherence to therapy, other factors, such as issues of drug absorption and bioavailability and selection of HBV resistant mutants, must be considered.

7.10 Cessation of pharmacotherapy

A key indication for antiviral therapy in patients with HBV infection is to lower the long-term risk of hepatic fibrosis progression and HCC. Therefore, most patients continue NA treatment long term.[1,128] However, there are accepted scenarios in which medication can be stopped. In general, accepted outcome measures in these situations include HBV viral suppression, loss of HBeAg and HBsAg, normalisation of liver function and resolution of liver injury.[1,128]

7.10.1 Stopping nucleos(t)ide analogues

As the aim of CHB treatment is viral suppression, long-term treatment is necessary for most individuals. However, recent studies have explored finite NA treatment in a subset of carefully selected patients, highlighting that treatment with NAs can be stopped in certain situations, with monitoring.[407-410]

Stopping NA treatment first needs careful consideration of the risks, including relapse, decompensation, liver cancer and death. NA treatment should **not** be ceased in patients with cirrhosis, during concurrent hepatitis C treatment or in patients with HCC.[407-410] After cessation of NA therapy, patients need more frequent monitoring for flares and decompensation. Further assessment should also include the burden of adherence, cost, risk of drug resistance and patient preference.

Discontinuation can be considered in the following situations:[1,128,393]

- HBsAg loss (with or without HBsAg seroconversion);
- in HBeAg-positive patients, after at least 12 months of HBeAg loss; and
- in HBeAg-negative patients with longstanding (≥2 years) undetectable HBV DNA levels, who are not cirrhotic and who will comply with virological monitoring after cessation.[1,393]

This last point is controversial, with some international guidelines considering this to be a high-risk group in whom cessation is not recommended.[1,128] However, evidence would favour considering cessation in selected low-risk individuals, with frequent monitoring. Low risk in this setting is poorly defined but would include an assessment of the patient's willingness to undergo more frequent monitoring, whether there is concurrent liver injury or significant fibrosis and the individual's age. We strongly advise against treatment discontinuation in people with cirrhosis.

Recommendation 14

Cessation of oral antiviral therapy may be considered in people without cirrhosis following HBeAg seroconversion or sustained HBsAg loss after a period of treatment consolidation. However, regular monitoring must be undertaken after treatment cessation, preferably in consultation with a clinician experienced in treating hepatitis B. (Evidence quality: Moderate; Grade of recommendation: Strong)

7.10.2 Stopping peginterferon monotherapy

Peginterferon is infrequently used in the treatment of CHB infection, but in certain instances it may be administered as part of personalised treatment plans (almost always in HBeAg-positive patients).[132,411,412] The optimal use of peginterferon is governed by the principles of patient selection (baseline-guided therapy) and adjustment of treatment based on response (response-guided therapy).

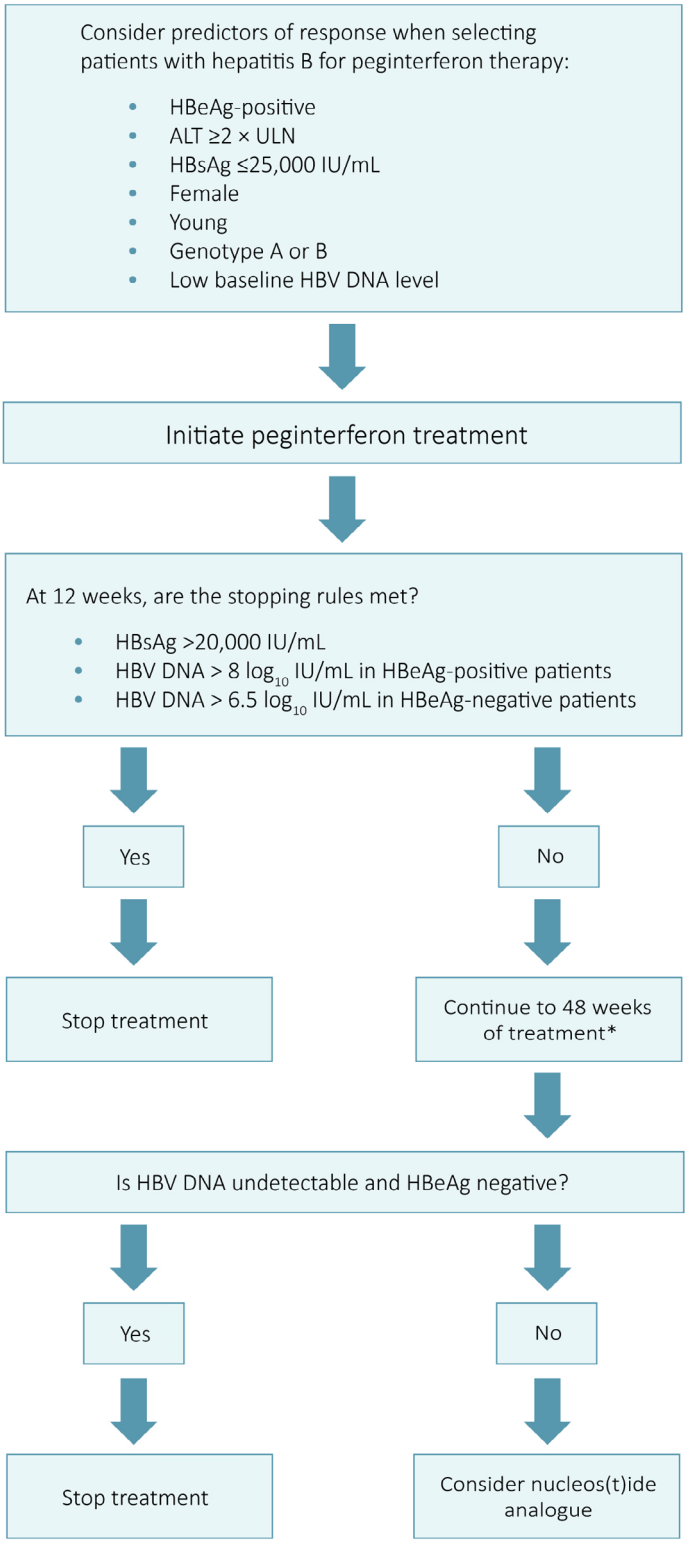
Using response-guided therapy, the assessment of treatment response should be done at 12 weeks, not at 48 weeks.[411,413] Guidelines for HBeAg-positive patients have suggested that response-guided therapy be undertaken at 24 weeks, with an HBsAg level >20,000 IU/mL and a decrease in HBV DNA level less than 2 log IU/mL being used as stopping rules.[411] However, subsequent meta-analysis of eight studies involving 1423 patients (765 HBeAg-positive, 658 HBeAg-negative) showed similar performance of HBsAg and HBV DNA cut-offs at 12 and 24 weeks.[414] Markers of therapeutic response include seroconversion (HBeAg and HBsAg) and decline in HBV DNA and HBsAg levels.[411,412] During treatment, it is recommended that liver function and full blood count are assessed monthly, serum HBV DNA level every 3 months, HBeAg status at 6 and 12 months, and HBsAg quantitation at 12 weeks, 24 weeks and at end of treatment.[415] Data for more than 48 weeks of interferon treatment are sparse, and most trials recommend up to 48 weeks of therapy. Longer durations are only rarely used for selected patients on a case-by-case basis.[132,411,412]

Patient baseline characteristics associated with a higher chance of achieving a sustained response to peginterferon therapy and underpinning baseline-guided therapy for HBeAg-positive patients include a low baseline HBV DNA level (<20,000 IU/mL, with a prediction of HBeAg seroconversion at 1 year; odds ratio, 10.45; $P = 0.025$[412]) and high ALT level (≥2 × ULN, with HBeAg seroconversion occurring in 44.8% vs 18.5% of patients with ALT level <2 × ULN[416]).[417] Furthermore, HBeAg-positive patients with a baseline HBsAg level ≤25,000 IU/mL have been shown to achieve higher rates of HBeAg clearance and seroconversion (35% vs 16.3%, $P < 0.001$).[411,418] Additional factors associated with improved response to peginterferon therapy include female sex, younger age[132,411] and genotype, with patients with genotype A or B responding better than those with genotype C or D in HBeAg-positive disease.[411,417]

The application of response-guided therapy is driven by treatment stopping rules (Figure 5). At 12 weeks, the stopping rules are:

- HBsAg level >20,000 IU/mL;
- HBV DNA level >8 $\log_{10}$ IU/mL in HBeAg-positive patients; and

Figure 5. Algorithm for stopping rules when using peginterferon for hepatitis B



ALT = alanine aminotransferase; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; ULN = upper limit of normal.
* At 24 weeks, predictors to continue treatment to 48 weeks include HBsAg level <20,000 IU/mL in HBeAg-positive patients; or >1 log IU/mL drop in HBsAg level in HBeAg-negative patients; or drop in HBV DNA level of >2 log IU/mL.

- HBV DNA level >6.5 $\log_{10}$ IU/mL in HBeAg-negative patients.

At 24 weeks, predictors to continue treatment to 48 weeks include:

- HBsAg level <20,000 IU/mL in HBeAg-positive patients; or
- >1 log IU/mL drop in HBsAg level in HBeAg-negative patients; or
- drop in HBV DNA level of >2 log IU/mL.

7.11 Antiviral drug resistance

Drug resistance, defined by the development of viral strains with mutations in viral sequence, can occur with NA therapy[1] but not with interferon treatment. Preventing resistance with NA therapy is achieved by using a first-line agent with a high barrier to resistance (entecavir or tenofovir). Variable adherence to therapy is a strong risk factor for the development of resistance to agents with a low barrier to resistance.[1] Use of antivirals with a low barrier to resistance is no longer recommended due to the development of multidrug-resistant strains with poor suppression of HBV viral replication. Once drug resistance is confirmed, management changes should be instigated promptly.

7.11.1 Prior treatment exposure

NAs can select for viral strains with HBV mutations in the DNA polymerase in a predictable and class-dependent manner.[419] Drugs with a high barrier to resistance require multiple viral mutations to confer resistance; in contrast, viral resistance can develop with a single mutation when antivirals with a low barrier to resistance are used (Table 15). In practice, tenofovir offers the highest barrier to resistance, with no reported phenotypic resistance caused by genotypic resistance.[420,421]

7.11.2 Resistance testing

Monitoring of HBV DNA levels during therapy should occur every 3–6 months until HBV DNA is undetectable, then every 6–12 months to detect persistent viraemia or viral breakthrough.[419] Persistent viraemia is defined as detectable HBV DNA 48 weeks after starting treatment.[1,419] However, with drugs that have a high barrier to resistance, such as tenofovir and entecavir, persistent viraemia is defined as detectable HBV DNA at 96 weeks of treatment. Viral breakthrough is defined as a rise in HBV DNA level of >1 $\log_{10}$ IU/mL compared with the nadir during therapy, or an HBV DNA level >100 IU/mL in a person with previous levels of <10 IU/mL.

The most frequent cause of persistent viraemia or viral breakthrough is non-adherence to medication; however, in the absence of another explanation, viral resistance must be considered. As resistance testing

Table 15. Polymorphisms that have been associated with resistance to nucleos(t)ide analogues

	Hepatitis B variant							
Nucleos(t)ide analogue	**Wild-type**	**M204V**	**M204I**	**L180M + M204V**	**A181T/V**	**N236T**	**L180M + M204V/I ± I169T ± V173L ± M250V**	**L180M + M204V/I ± T184G ± S202I/G**
Lamivudine	S	R	R	R	I	S	R	R
Telbivudine	S	S	R	R	I	S	R	R
Entecavir	S	I	I	I	S	S	R	R
Adefovir	S	I	I	I	R	R	S	S
TD/TAF	S	S	S	S	I	I	S	S

I = intermediate; R = resistant; S = susceptible; TAF = tenofovir alafenamide; TD = tenofovir disoproxil. Source: Zoulim and Locarnini.[422,423]

is not routinely available, patients using antiviral agents with a low barrier to resistance should be switched to a drug with a high barrier to resistance, such as tenofovir or entecavir (unless they have prior lamivudine exposure).

7.11.3 Treatment choices in drug resistance

NA resistance is uncommon when using entecavir or tenofovir disoproxil as a first-line agent, and a detectable viral load instead usually reflects non-adherence to therapy. NA treatment resistance was more common in the past, when antivirals with a low barrier to resistance were started.[424] Two strategies are available to deal with resistance:[1,424] the "switch strategy", in which resistance is treated by substituting a drug with a higher barrier to resistance; and the "add strategy", in which a second agent is combined with the initial treatment regimen to cover the resistance that has emerged (Table 16). In Australia, the switch strategy is preferred, but the add strategy has been used in specialised settings, such as in patients undergoing liver transplantation.[425] Under PBS restrictions, combination therapy is not permitted, with the exception of lamivudine–TDF, which can be prescribed for patients with resistance to lamivudine. Monitoring is recommended when there is a change of therapy, as outlined in section 7.9, with the addition that assessment of HBV DNA is undertaken at 1 month.[1,419]

Table 16. Strategies for dealing with drug resistance with nucleos(t)ide analogue therapy

Antiviral resistance	Switch strategy (preferred)	Add strategy*	References
Lamivudine	Switch to tenofovir disoproxil	Add tenofovir disoproxil	419,426-428
Telbivudine	Switch to tenofovir disoproxil	Add tenofovir disoproxil	429,430
Adefovir	Switch to entecavir	Add entecavir	419,426-428
Entecavir	Switch to tenofovir disoproxil	Add tenofovir disoproxil	431
Multidrug	Switch to tenofovir disoproxil	Add tenofovir disoproxil	432-434

* Under the Pharmaceutical Benefits Scheme (PBS), patients may receive tenofovir disoproxil in combination with lamivudine but not with other PBS-subsidised antihepadnaviral therapy.

8 Complications

For most people living with CHB infection, the major potential complications are the development of HCC and the progression of liver fibrosis, leading to cirrhosis and the development of portal hypertension, with its associated sequelae. Other complications include acute decompensation in patients with established cirrhosis and acute liver failure, as a consequence of either acute HBV infection or HBV reactivation of chronic infection and extrahepatic manifestations.

8.1 Hepatocellular carcinoma

People with CHB infection have a lifetime risk of HCC that is 10- to 25-fold higher than those without infection.[209] Furthermore, it is estimated that more than 50% of HCC cases globally are attributable to HBV.[435] The annual HCC incidence per 100 person-years in East Asia is 0.2 in people with HBeAg-negative chronic infection, 0.6 in non-cirrhotic people with HBeAg-negative or HBeAg-positive chronic hepatitis and 3.7 in patients with compensated cirrhosis. In Europe and the US, the annual incidence rates per 100 person-years in these groups are 0.02, 0.3 and 2.2, respectively.[209]

The development of HCC is dependent on a combination of viral, host and environmental factors.[436] Men have a two- to fourfold higher risk than women.[435] A first-degree family history of HCC confers a twofold increase in risk, which is synergistic at each stage of HBV infection.[268] Other patient factors that increase HCC risk include advancing age, cigarette smoking, alcohol consumption, obesity and diabetes.[437] Viral factors that increase risk of HCC include high HBV DNA levels, positive HBeAg status, high HBsAg levels, genotype C, HBV mutations and viral coinfection (HDV, HCV or HIV).[139,436,438-440]

8.1.1 Surveillance for hepatocellular carcinoma

HCC surveillance with 6-monthly ultrasound, with or without AFP testing, is recommended for people with CHB infection and an increased risk of HCC. This matter is extensively discussed in the 2020 Australian consensus statement on HCC management.[339] The purpose of HCC surveillance is to detect tumours early, when curative treatment — including liver resection, transplantation and locoregional therapies (radiofrequency or microwave ablation) — can be offered, to improve overall survival and quality of life.

As HCC surveillance requires significant resources and commitment from both health care providers and patients, it is necessary to appropriately select patients at higher risk who may benefit. For people with CHB infection, surveillance has been shown to be cost-effective in populations with an annual HCC incidence as low as 0.2%.[441,442] As the population with CHB and cirrhosis has an annual incidence (2%–7%) that exceeds the 0.2% cost-effectiveness threshold, everyone in this group should be offered HCC surveillance. However, for people with more advanced cirrhosis (Child–Pugh class C) or who are over 70 years of age, surveillance may offer no survival benefit.[339] In this setting, individual factors, such as life expectancy and the patient's health care wishes, should guide the need for HCC surveillance.[339]

For people living with CHB infection who do not have cirrhosis, the annual incidence of HCC is influenced by age, sex, genotype, comorbidities and family history.[443] The Australian consensus statement on HCC includes recommendations for groups of people with CHB in whom surveillance should be performed, with variable strength of evidence for each group.[339] Its recommendations use a broad definition of region of origin (which might have different interpretations) as a proxy for genotype, do not account for the effect of antiviral treatment in reducing risk and are based on studies in specific populations, where environmental factors may also contribute to risk of HCC development.[128,444,445]

Overall, HCC surveillance is considered cost-effective in patients with HBV when the annual HCC incidence is 0.2% or more for patients without cirrhosis, and 1.5% for patients with cirrhosis.[442]

8.1.1.1 Who should undergo surveillance?

The Australian consensus statement on HCC management recommends HCC surveillance in all

Technical remarks

1. As cost-effectiveness thresholds are based on modelling studies pre-dating current antiviral regimens,[446] there are limited data on the benefit of HCC surveillance in people receiving suppressive HBV treatment.
2. Liver ultrasound has a sensitivity ranging from 58% to 89% and specificity greater than 90% for HCC surveillance.[447] In practice, ultrasound sensitivity may be reduced by patient factors (e.g. obesity) or operator-dependent variability.
3. Serum AFP testing in combination with ultrasound appears to improve the sensitivity of HCC surveillance compared with ultrasound alone, but an effect on survival is yet to be shown.[53,448,449]
4. The ideal surveillance interval is 6 months, based on median tumour doubling time. Annual surveillance decreases sensitivity to 50% and leads to reduced survival.[450,451] Shortened surveillance intervals of 3 months do not improve HCC detection.[452]

patient with cirrhosis, as well as people with CHB infection without cirrhosis who are at high risk of HCC (Table 17).[339]

Table 17. Populations with chronic hepatitis B in whom surveillance for HCC should be performed

Population
• People with cirrhosis
• People *without* cirrhosis:
▸ Asian men older than 40 years
▸ Asian women older than 50 years
▸ Sub-Saharan Africans older than 20 years*
▸ Aboriginal and Torres Strait Islander people older than 50 years†
▸ With coinfection with hepatitis delta virus
▸ With family history of HCC (first-degree relative)
▸ Observed HBsAg loss with prior indications for HCC surveillance
• Other high-risk groups in whom surveillance can be considered:
▸ People from other racial groups, according to risk scores (e.g. PAGE-B)
▸ Māori and Pacific Islander men older than 40 years and women older than 50 years*

HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; PAGE-B = HCC predictive score based on age, sex and platelet count.[214]
* Reliable data not available, but HCC incidence is likely to be increased.
† Based on Northern Territory linkage data.[47]
Modified with permission from the Hepatocellular Carcinoma Consensus Statement Steering Committee, *Australian recommendations for the management of hepatocellular carcinoma: a consensus statement.*[339]

In CHB infection, several other host, viral and environmental risk factors for HCC development have been identified. Importantly, these contributions may be dynamic in nature (e.g. increasing viral loads in immune escape phase or fibrosis progression due to non-HBV causes, despite viral suppression), such that the annual HCC incidence risk threshold may be reached at a later stage of the disease's natural history. Thus, for patients who do not initially meet HCC surveillance criteria, ongoing monitoring for risk factor accumulation is warranted.

Several risk stratification scores have been developed to predict HCC risk for individual patients (Table 18).[214,350,390,453-455] The predictors of increased risk in these scores include age and sex (common across all scores), with variance in the included laboratory test results (ALT, albumin, bilirubin, viral load, HBeAg status, platelet count and presence of cirrhosis or liver elastography).

There are not yet any validation studies in the Australian context for these scores. The characteristics of the conception cohorts used to formulate the scores should also be noted when considering their applicability to the Australian setting. Most cohorts consisted of Asian, mostly non-cirrhotic patients, and most infections were from vertical or early-childhood horizontal transmission. They differed in their treatment settings (community vs hospital-based patients), as well as by HBV treatment status. In contrast to most of the scores, the PAGE-B cohort consisted of 1815 European patients receiving HBV viral suppression, among whom HCC risk was associated with age greater than 50 years, male sex and low platelet count. Recently, the aMAP (age, male sex, albumin–bilirubin and platelet count) score was

derived in an Asian cohort with HBV infection and validated in several populations, including both Asian and European patients with HBV and patients with cirrhosis and HCV infection or non-viral cirrhosis. In the validation cohorts, the negative predictive value for HCC development was over 99%.

Using risk stratification scores, people with CHB infection and without cirrhosis may be considered for HCC surveillance if they exceed the cost-effectiveness threshold. The choice of score for clinical use should be based on which derivation population best represents the intended surveillance population.

Although the risk of HCC is attenuated by effective viral suppression with HBV antiviral treatment, it is not eliminated.[211] In treated patients, the annual incidence of HCC ranges from 0.01% to 1.4% in patients without cirrhosis and from 0.9% to 5.4% in patients with cirrhosis.[211] Consequently, patients receiving long-term viral suppression should remain under surveillance or commence surveillance when their risk factor profile approaches the thresholds and categories indicated above.

Similarly, the risk of HCC is ongoing for patients who have achieved HBsAg clearance.[194,456] It is thought that infection from birth or childhood, with prolonged duration of immune tolerance, leads to viral integration of the host genome and hence continued risk of HCC development despite HBsAg clearance. However, HCC risk appears to be persistent mostly in those with cirrhosis, who are older or who have coinfection with HCV or HDV. The risk in people without cirrhosis is less clear.[351,457]

Recommendation 15

HCC surveillance should be offered to all people with cirrhosis, as well as non-cirrhotic individuals at increased risk of HCC (Table 17). (Evidence quality: Low; Grade of recommendation: Strong)

Recommendation 16

Liver ultrasound should be performed every 6 months in people with CHB infection who require HCC surveillance. (Evidence quality: Moderate; Grade of recommendation: Strong)

Recommendation 17

HCC surveillance should continue in the event of observed HBsAg loss in individuals assessed as having a high baseline risk for HCC (Table 17). (Evidence quality: Low; Grade of recommendation: Strong)

Technical remarks

1. Data for providing a firm recommendation on the risk of HCC in Indigenous people with HBV infection are lacking. Broadly, the incidence of HCC is higher in Indigenous than non-Indigenous people, by about sixfold, and HBV is the leading cause of HCC in Indigenous people.[47]
2. Available evidence, although not high-level, consistently suggests that Indigenous Australians are at increased risk of liver cancer, as well as poorer outcomes.[458]

Table 18. Hepatocellular carcinoma risk stratification scores

	REACH-B[390]	PAGE-B[214]	GAG-HCC[453]	CU-HCC[350]	LSM-HCC[454]	aMAP[455]
Origin of study cohorts	Taiwan, Hong Kong and South Korea	Europe (10 centres)	Hong Kong	Hong Kong	Hong Kong	Global; patients with/without HBV and with/without cirrhosis
Antiviral treatment	Untreated	Treated	Untreated	Untreated	Untreated	Treated
Age	0 points: <35 years 1 point: 35–39 years 2 points: 40–44 years 3 points: 45–49 years 4 points: 50–54 years 5 points: 55–59 years 6 points: 60–65 years	0 points: 16–29 years 2 points: 30–39 years 4 points: 40–49 years 6 points: 50–59 years 8 points: 60–69 years 10 points: >70 years	1 point per year	0 points: ≤50 years 3 points: >50 years	0 points: ≤50 years 10 points: >50 years	Included in risk formula
Sex	0 points: female 6 points: male	0 points: female 6 points: male	0 points: female 16 points: male	—	—	Included in risk formula
Albumin	—	—	—	0 points: >35 g/L 20 points: ≤35 g/L	0 points: >35 g/L 1 point: ≤35 g/L	Included in risk formula
Bilirubin	—	—	—	0 points: ≤18 µmol/L 1.5 points: >18 µmol/L	—	Included in risk formula
ALT	0 points: <15 IU/L 1 point: 15–44 IU/L 2 points: ≥45 IU/L	—	—	—	—	—
HBeAg	0 points: HBeAg-negative 2 points: HBeAg-positive	—	—	—	—	—
HBV DNA	0 points: <4 log copies/mL 3 points: 4 to <5 log copies/mL 5 points: 5 to <6 log copies/mL 4 points: >6 log copies/mL	—	3 points per log copies/mL	0 points: ≤4 log copies/mL 1 point: 4–6 log copies/mL 4 points: >6 log copies/mL	0 points: ≤200,000 IU/mL 5 points: >200,000 IU/mL	—
Platelets	—	0 points: ≥200,000/mm^3 6 points: 100,000–199,999/mm^3 9 points: <100,000/mm^3	—	—	—	Included in risk formula
Liver stiffness measurement	—	—	—	—	0 points: ≤8.0 kPa 8 points: 8.1–12.0 kPa 14 points: >12.0 kPa	—
Cirrhosis	—	—	0 points: no cirrhosis 30 points: cirrhosis	0 points: no cirrhosis 15 points: cirrhosis	—	—
HBV core promoter mutation	—	—	0 points: absent 19 points: present	—	—	—
Score risk groups	17-point risk scale (Low: ≤9)	Low: ≤9 Intermediate: 10–17 High: ≥18	Low: <101 High: ≥101	Low: <5 Intermediate: 5–19 High: ≥20	Low: 0–10 High: 11–30	Low: <50 High: ≥60
Score performance*	AUC: 0.783–0.796 Low-risk NPV: 99.2%	Low-risk NPV: 100% Low-risk sensitivity: 100%	Low-risk NPV: 98.3% Low-risk sensitivity: 84.1%	Low-risk NPV: 97.3% Low-risk sensitivity: 82.2%	Low-risk NPV: 99.7% Low-risk sensitivity: 92.3%	Low-risk NPV: 99.3%–100% Low-risk sensitivity: 85.7%–100%

ALT = alanine aminotransferase; aMAP = Age, Male, Albumin–bilirubin and Platelets; AUC = area under the receiver operating characteristic curve; CU-HCC = Chinese University-HCC; GAG-HCC = Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-HCC; HBeAg = hepatitis B e-antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; LSM-HCC = Liver Stiffness Measurement-HCC; NPV = negative predictive value; PAGE-B = Platelets, Age and Gender; REACH-B = Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B.

* Outcome for all scores was 5-year incidence of HCC. NPVs are influenced by disease prevalence, whereas sensitivity (true positive rate) is not.

8.1.1.2 Surveillance rates in Australia

HCC surveillance programs in Australia are cost-effective and improve overall survival.[54,459,460] However, HBV-specific data on HCC surveillance uptake and adherence are limited. In a Melbourne-based prospective cohort of 272 patients newly diagnosed with HCC, people with hepatitis B and without cirrhosis were most likely to have not participated in surveillance; however, this subgroup comprised only 21 participants. Of the total cohort, 89% had an indication for HCC surveillance, but only 40% participated.[54] In the general practice setting, an audit of 80 people with CHB infection found that the participation rate for surveillance was 75%, but adherence was suboptimal or poor in two-thirds of the cohort.[340]

Strategies to improve surveillance uptake and adherence have been studied in the Australian setting. A study involving a hospital cohort in Adelaide showed that improved clinician and patient education, together with system redesign, increased adherence from 46% of people undertaking screening within 6 months at baseline to 92% at 3 years after the intervention. At baseline, none of the participants had engaged in screening for 2 consecutive years, and this increased to 64% after the intervention. Health system redesign included creation of a nursing role dedicated to the task, establishment of a screening database with a patient recall function and patient contact in the event of non-attendance.[342] A specialist nurse-led HCC surveillance model in Perth showed acceptable adherence of 71% for liver ultrasound performed within 7 months.[461]

Technical remarks

1. Most published data regarding HCC surveillance adherence and uptake are from international health systems and may not be generalisable to the Australian context.
2. Potential barriers to HCC surveillance or adherence specific to the Australian setting include access to care in remote or regional areas, levels of health literacy and associated stigma in vulnerable populations, including Aboriginal or Torres Strait Islander communities and migrants.[399,462,463]

8.1.2 Management of hepatocellular carcinoma

The management of HCC should occur in multidisciplinary teams that include hepatologists, diagnostic and interventional radiologists, medical and radiation oncologists, hepatobiliary surgeons, palliative care physicians and specialist nurses. As patients with HBV-related HCC often present without coexisting complications of cirrhosis, they may be more suitable for treatment regimens with curative intent, which include surgical resection, percutaneous ablation and liver transplantation. For recommendations on the management of HCC, refer to the Australian consensus statement on HCC management.[339]

8.2 Advanced liver disease

The spectrum of advanced liver disease from HBV infection ranges from cirrhosis, with or without complications of portal hypertension (e.g. gastro-oesophageal varices, ascites, hepatic encephalopathy and splenomegaly), to the uncommon scenario of acute liver failure. In people with untreated CHB infection, between 12% and 20% will progress to cirrhosis over 5 years.[209] As discussed in section 7.5.3, all patients with cirrhosis and any detectable HBV DNA should be treated indefinitely with HBV antiviral therapy. In contrast to cirrhosis, the development of acute liver failure is rare, affecting between 0.1% and 0.5% of people with HBV infection.[464]

8.2.1 Decompensated cirrhosis

Decompensated cirrhosis is characterised by the presence of ascites, hepatic encephalopathy, variceal bleeding or non-obstructive jaundice. In people with established, untreated HBV-related cirrhosis, the risk of decompensation is 20% over 5 years.[209] The prognosis of decompensated cirrhosis in the absence of treatment is poor, with 68%–71% survival at 1 year, reducing to 14%–35% at 5 years.[465] After antiviral treatment, 1-year transplant-free survival increases to over 90%.[369,466] Therefore, patients with an episode of decompensation should be treated with potent NAs, such as entecavir or tenofovir, and referral for liver transplantation should be considered.

The benefit of liver transplantation is generally seen once the Model for End-Stage Liver Disease (MELD) score is 15 or greater.[467] NAs should be commenced

and continued for life in patients with decompensated cirrhosis, regardless of HBV viral load. The goal of treatment is to suppress viral replication, improve liver function, reduce the risk of mortality and potentially avoid the need for liver transplantation. About 35% of patients can be removed from the liver transplant waiting list after starting NAs.[468] Alternatively, if liver transplantation is required in the setting of progressive liver dysfunction, NAs reduce the risk of reinfection of the graft.

Patients with decompensated cirrhosis who are taking NAs should be monitored for the risk of lactic acidosis, particularly if their MELD score is >20 or if there is existing renal impairment.[469] Renal impairment is common in patients with decompensated cirrhosis, and NA dose adjustment may be required. Interferon-based regimens are contraindicated in patients with decompensated cirrhosis. HCC surveillance and routine management of portal hypertension and other complications of decompensated cirrhosis should continue for these patients,[470] unless advance care directives are being considered or are already in place.

Acute decompensation can also occur from severe acute reactivation of CHB infection in the setting of immunosuppression, viral mutation or antiviral treatment cessation, or spontaneously. NA therapy should be started to control such disease flares; however, a small proportion of patients may continue to deteriorate, despite a reduction in HBV viral load. Factors associated with poor outcomes in this group include an elevated serum bilirubin level (>120 µmol/L), elevated serum creatinine level (>200 µmol/L) and detectable HBV DNA.[471] Acute decompensation due to HBV reactivation is a medical emergency and should be managed in consultation with a liver transplant unit. Patients whose condition does not improve with NA therapy should be urgently considered for liver transplantation.

Technical remarks

1. The uncommon presentation of severe reactivation of CHB infection resulting in acute decompensated cirrhosis has been classified as acute-on-chronic liver failure in recent studies.[472-474] However, there is a lack of international consensus on the precise definition of acute-on-chronic liver failure, and the disease course in HBV infection may vary compared with other aetiologies.[475]
2. Regardless of the nomenclature used, a failure to resolve clinical decompensation in patients taking NAs should prompt referral for liver transplantation.

8.2.2 Acute liver failure

Acute (fulminant) liver failure is a medical emergency that is characterised by the rapid onset of jaundice, encephalopathy and coagulopathy (INR >1.5) in the absence of pre-existing cirrhosis.[476,477] These patients require urgent consultation with a liver transplant unit. Acute liver failure may occur from acute HBV infection or from reactivation in the context of immunosuppression, viral mutation or non-adherence to treatment, or spontaneously.

Acute liver failure caused by acute HBV infection can be diagnosed by the presence of anti-HBc IgM. The viral load is characteristically low in this setting, with hepatic injury predominantly due to the immune response to the virus. In contrast, acute liver failure caused by reactivation of CHB infection is usually characterised by a high viral load (>5 $\log_{10}$ IU/mL) and undetectable or very low levels of anti-HBc IgM.

The prognosis of acute liver failure due to HBV infection is poor without liver transplantation. Outcomes are marginally worse in patients who have had reactivation of CHB infection than in those with acute HBV infection.[478]

The incidence of HBV-induced acute liver failure is estimated to be up to 0.5% of HBV infections.[464] Data are scant in Australia, with one study reporting that HBV accounted for 12% of acute liver failure presentations to the Victorian Liver Transplant Unit over 15 years, with associated transplant-free survival of 35%.[479] Moreover, HBV accounts for 23% of liver transplants performed for acute liver failure in Australia and New Zealand.[480]

HBV-associated acute liver failure (in patients with an INR >1.5) should be treated with NAs. Although the benefit of antiviral therapy is less conclusive than it is for treating decompensated cirrhosis, given the frequent requirement for liver transplantation in patients with acute liver failure, minimising the potential for HBV reinfection of the liver graft is warranted.[481,482]

Recommendation 18

People with acute or acute-on-chronic liver failure from hepatitis B should be managed in consultation with a liver transplant unit. (Evidence quality: Low; Grade of recommendation: Strong)

8.3 Extrahepatic manifestations of hepatitis B

Extrahepatic manifestations of hepatitis B are uncommon but may occur in both acute and chronic infection. They should be regarded as an indication for antiviral treatment.

A serum sickness syndrome, characterised by skin rash, fever, myalgias and arthralgias, may affect up to 10%–20% of people with acute infection. This syndrome is thought to be caused by immune complexes involving HBsAg and usually precedes and resolves with the onset of jaundice.[483]

Extrahepatic manifestations of chronic infection include glomerulonephritis, polyarteritis nodosa, aplastic anaemia, Guillain–Barré syndrome, polyarthritis, skin rashes and cryoglobulinaemia.[484] The incidence of these manifestations is highly variable. Glomerulonephritis associated with HBV infection occurs predominantly in children and is most often caused by membranous nephropathy, although membranoproliferative glomerulonephritis and IgA nephropathy also occur. Remission often accompanies HBeAg seroconversion, with an unclear role for antiviral therapy.[485] HBV-related polyarteritis nodosa symptoms are the same as those in non-HBV-related forms of the disease, with antiviral therapy often conferring clinical benefit.[486] Skin manifestations include bullous pemphigoid, lichen planus and Gianotti–Crosti syndrome.[484]

Recommendation 19

People with extrahepatic manifestations of CHB infection should receive antiviral treatment. (Evidence quality: Low; Grade of recommendation: Strong)

8.4 Preventing fibrosis progression

Concurrent infection with HCV, HDV and/or HIV exacerbates liver fibrosis progression. People with CHB infection should be tested for viral coinfection and offered treatment as appropriate (see section 9.3).

Several non-viral factors have been shown to influence progression of liver disease in people with CHB infection. Heavy alcohol consumption is associated with increased liver inflammation and risk of cirrhosis and HCC.[230,487-489] In particular, a history of heavy drinking (>60 g/day) has been reported to increase the risk of progression to cirrhosis by sixfold compared with abstinence or minimal alcohol intake.[243] Furthermore, the risk of HCC was shown to be higher in people with HBsAg-positive infection consuming >80 g/day of alcohol, compared with those with HBsAg-positive infection who did not drink or drank <80 g/day.[490]

Cigarette smoking has been associated with advanced fibrosis in untreated male patients with CHB infection in a dose–response manner (odds ratio, 1.32 and 1.51 for 0–10 pack-years and ≥10 pack-years, respectively, compared with those who never smoked).[491] In addition, smoking ≥10 pack-years (odds ratio, 0.29) and alcohol consumption of ≥20 g/day (odds ratio, 0.19) both reduce the likelihood of fibrosis regression after initiation of antiviral therapy, compared with those who never smoked and non-drinkers, respectively.

The metabolic syndrome, or its components of central obesity, impaired glucose metabolism, hypertension, elevated triglyceride levels and reduced high-density lipoprotein cholesterol level, predicts risk of fibrosis progression independent of viral activity.[244,492,493] There appears to be an additive effect of individual metabolic syndrome components, as the odds of having cirrhosis increase incrementally from 1.4 to 5.5 in the presence of one to five components of metabolic syndrome.[492]

Epidemiological studies suggest a protective effect of coffee against liver fibrosis and HCC in a dose–response manner among people with chronic liver disease, including those with CHB infection.[494,495] However, studies specifically of populations with CHB infection were unable to confirm these benefits after adjustment for viral characteristics.[496,497] Although silymarin (extract of milk thistle) has shown promise

as a hepatoprotective and antiviral agent in hepatitis C infection,[498] two systematic reviews have found no significant effect on liver histology, complications or mortality in patients with liver disease, including those with CHB.[499,500] Curcumin has exhibited antiviral, antifibrotic and anticancer properties in preclinical HBV models, but clinical studies are lacking.[501-503] Thus, evidence supporting the role of non-prescription and other proposed antifibrotic agents in preventing or impeding fibrosis progression in people with CHB infection is limited.

Technical remarks

1. Although alcohol consumption, smoking and metabolic syndrome have been shown to be associated with more advanced fibrosis and HCC in people with CHB infection, evidence of the benefit of their elimination on delaying fibrosis progression is limited.
2. The definition of heavy drinking varies, with several studies choosing >60–80 g/day of alcohol (equivalent of six to eight standard drinks) as the definition of heavy alcohol consumption.
3. Most studies diagnosed liver fibrosis and cirrhosis using clinical and non-invasive assessments (e.g. liver stiffness measurement by TE), with liver histology used in a minority of cases.

8.5 Management of comorbidities

8.5.1 Obesity, diabetes and the metabolic syndrome

Abdominal obesity is a known risk factor for the development of HCC, MAFLD, insulin resistance, the metabolic syndrome and type 2 diabetes.[504] It has been shown to significantly exacerbate liver fibrosis and worsen disease outcomes in people living with CHB.[505] Furthermore, obesity has been shown to diminish treatment responses in people with CHB infection, with lower rates of fibrosis regression seen during long-term NA therapy.[506]

The impact of hepatic steatosis on the progression of CHB disease is less clear. Steatosis has been associated with advanced fibrosis, as measured by TE, in patients with CHB infection — both those receiving treatment and those who were treatment-naive.[507] However, murine models suggest hepatic steatosis inhibits HBV viral replication.[508] This is consistent with a clinical study from Hong Kong, which found that increasing steatosis was associated with lower HBV DNA levels.[509]

Patients with CHB infection should receive regular screening for components of the metabolic syndrome, including measuring blood pressure, BMI and fasting lipid levels and screening for diabetes. The presence of type 2 diabetes accelerates disease progression and cirrhosis development in people with CHB infection.[510] Patients with CHB and obesity and/or metabolic syndrome should receive structured programs aimed at making lifestyle changes, with a goal of weight loss. Even modest weight loss has been shown to reduce liver fat and improve hepatic insulin resistance.[511,512] Lifestyle changes should include dietary modification and habitual physical exercise incorporating aerobic and resistance training. Dietary modification should include energy restrictions and exclusion of MAFLD-promoting foods, such as processed foods and those containing high amounts of fructose.[477]

Recommendation 20

Metabolic comorbidities, including obesity, diabetes mellitus, hypertension and dyslipidaemia, should be screened for and optimally managed in people with CHB. (Evidence quality: Low; Grade of recommendation: Strong)

8.5.2 Alcohol

The evidence for light to moderate alcohol consumption affecting disease progression in people with CHB infection is less clear than that for heavy consumption (see section 8.4). The recommended maximum alcohol intake in healthy men and women is 10 standard drinks a week,[513] but there is no international consensus on what defines light, moderate or heavy alcohol consumption. Furthermore, there are no data regarding the threshold at which no liver damage occurs from alcohol consumption in people with CHB infection. Studies have shown a modest increase in the relative risk of HCC (varying from 1.13 to 1.6) in people with CHB infection who habitually consume moderate amounts of alcohol.[155,260] People with HBV-related cirrhosis should remain abstinent from alcohol.

9 Specific subpopulations

9.1 Pregnant and lactating women

Hepatitis B has little impact on maternal health or pregnancy outcomes unless there is significant underlying liver disease, such as cirrhosis. HBV infection during pregnancy is associated with a greater risk of gestational diabetes.[514,515] Hepatitis flares are uncommon during pregnancy and, although common postpartum, are usually mild and self-limiting.[516,517] Postpartum monitoring with liver function tests is recommended.

Without infant immunoprophylaxis (HBIG and vaccine), MTCT often occurs, leading to chronic infection in the infant — this is an incurable lifelong problem with serious clinical sequelae.[27] Immunoprophylaxis is highly effective, except in the setting of a high maternal viral load (i.e. HBV DNA >200,000 or 5.3 $\log_{10}$ IU/mL), when MTCT can still occur in up to 10% of vaccinated infants.[518-520] Assessment of maternal HBV DNA levels early in the second trimester (before Week 28) and commencement of antiviral therapy at 28–30 weeks' gestation are recommended by guidelines.[1,41]

Tenofovir, which has a well-established safety profile (especially in pregnancy), high potency and low rates of resistance, is the preferred antiviral therapy for women of childbearing potential. Tenofovir is available for 6 months via streamlined authority on the PBS specifically for this indication. Women taking entecavir or interferon at the time of conception should switch to tenofovir. Although the optimal time to cease tenofovir is not established, usual practice is to stop treatment between 6 and 12 weeks postpartum. Caesarean section is not required to prevent MTCT.[521] Prenatal testing (chorionic villus sampling and amniocentesis) in mothers with high viral loads carries a significant risk of MTCT and should be avoided if alternatives are possible.[522]

As described in detail in recommendations from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, infants should receive HBIG, preferably within 12 hours and certainly within 48 hours of birth, in addition to receiving a birth dose of HBV vaccine within 24 hours.[523] In addition to receiving subsequent HBV vaccine doses at 2, 4 and 6 months of age, it is recommended that infants born preterm (before 32 weeks) or with low birthweight (<2000 g) receive a further HBV vaccine dose at 12 months.

Breastfeeding is not a risk for MTCT of hepatitis B, and breastfeeding vaccinated infants is recommended. The mother can continue breastfeeding even if she is taking tenofovir, which appears in low quantities in breast milk and in a form that cannot be readily absorbed.

Previous guidelines have suggested that all infants of mothers with hepatitis B infection be tested at about 9 months of age. A recent study showed that MTCT did not occur from mothers without a high viral load.[91] An effective vaccine response was seen in 99.4% of infants born to such mothers. Although testing can reasonably be performed in all babies from HBsAg-positive mothers, testing of infants from mothers with high viral loads should be prioritised.

Recommendation 21

All pregnant women should be tested for HBsAg during antenatal screening. HBsAg-positive women should undergo evaluation of phase of HBV infection (ALT, HBeAg, HBV DNA) and for presence of clinical liver disease. (Evidence quality: High; Grade of recommendation: Strong)

Recommendation 22

Pregnant women with high viral load (>200,000 or 5.3 $\log_{10}$ IU/mL) should be offered tenofovir from the 28th week of pregnancy to reduce the risk of perinatal transmission of hepatitis B. (Evidence quality: High; Grade of recommendation: Strong)

Recommendation 23

Infants born to HBsAg-positive mothers should receive HBIG and hepatitis B vaccination as soon as possible after birth (optimally within 4 hours). Infants should receive routine HBV vaccination at 2, 4 and 6 months of age. (Evidence quality: High; Grade of recommendation: Strong)

Recommendation 24

Children born to HBsAg-positive women should be tested for HBsAg and anti-HBs 3 months after the last vaccine dose to determine vaccine response and to exclude MTCT. (Evidence quality: High; Grade of recommendation: Strong)

9.2 Immunosuppression

Immunosuppressive drugs allow unimpeded HBV replication. Cessation or periodic administration (e.g. cycles of cancer chemotherapy) of immunosuppressive therapy may result in immune reconstitution and a vigorous immune response to HBV. Recommendations regarding the treatment of hepatitis B in the setting of immunosuppression for haematological and solid-organ malignancies (summarised in this section and in Recommendation 25 as "cancer chemotherapy") have been published in an Australian consensus statement.[93]

Reactivation of hepatitis B is defined as a greater than 10-fold increase in HBV DNA level from baseline or HBsAg seroreversion in someone with evidence of past HBV infection (i.e. anti-HBc positivity, with or without anti-HBs).[198,524] Although limited data suggest the presence of anti-HBs may reduce the risk of reactivation in anti-HBc-positive patients receiving lymphoma treatment,[525] anti-HBs status should not be used to determine the need for NA prophylaxis.[524]

All HBsAg-positive patients receiving immunosuppressive cancer chemotherapy require prophylactic antiviral therapy.[93] Patients with past HBV exposure require evaluation for risk of reactivation (Table 19).

The use of potent immunosuppressive therapies, once restricted to oncology, is now widespread in nearly all fields of medicine, including (but not limited to) rheumatology, dermatology, neurology and gastroenterology (Table 20).

Immunosuppression conferring a high risk of HBV reactivation includes B-cell reducing therapies (e.g. anti-CD19/20) for non-malignant conditions, such as rituximab and ocrelizumab for treating Wegener's granulomatosis and multiple sclerosis, respectively. Alemtuzumab (for multiple sclerosis) depletes both T and B cells via CD52 inhibition and therefore confers a high risk. People receiving haematopoietic stem cell transplantation are also considered at high risk of HBV reactivation.[93]

Immunosuppression conferring a lower but unquantifiable risk includes tumour necrosis factor alpha inhibitors (e.g. etanercept, adalimumab, certolizumab, golimumab and infliximab), other

Table 19. Risk of HBV reactivation with cancer chemotherapy in HBsAg-negative/anti-HBc-positive people (past HBV exposure)

High-risk cancer chemotherapy (>10% risk of HBV reactivation)
Haematopoietic stem cell transplantation
B-cell depleting/B-cell active agents (e.g. anti-CD20, anti-CD38)*
Acute leukaemia and high-grade lymphoma therapy†
Lower-risk cancer chemotherapy (<1% risk of HBV reactivation)
All others not included in the high-risk category

Anti-HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.
* Such as rituximab, obinutuzumab, ocrelizumab, ofatumumab, daratumumab and ibrutinib.
† There is a lower level of evidence for risk of HBV reactivation in acute leukaemia and high-grade lymphoma therapy.
Source: Hepatitis B Management During Cancer Therapy Consensus Statement Group 2019, *Hepatitis B management during immunosuppression for haematological and solid-organ malignancies: an Australian consensus statement 2019*.[93]

Table 20. Risk of HBV reactivation with immunosuppression for non-malignant conditions

High-risk immunosuppression (>10% risk of HBV reactivation)
B-cell depleting agents*
High-dose corticosteroids (>20 mg per day) for >4 weeks
Moderate-risk immunosuppression (1%–10% risk of HBV reactivation)
Tumour necrosis factor alpha inhibitors†
Oher cytokine inhibitors and integrin inhibitors‡
Low-dose corticosteroids (<10 mg per day) for >4 weeks
Low-risk immunosuppression (<1% risk of HBV reactivation)
Immunomodulators (e.g. thiopurines, methotrexate and calcineurin antagonists)
Moderate–high-dose corticosteroids (>10 mg per day) for <1 week

HBV = hepatitis B virus.
* Such as rituximab, ocrelizumab and ofatumumab.
† Such as etanercept, adalimumab, certolizumab and infliximab.
‡ Such as abatacept, ustekinumab, natalizumab and vedolizumab.
Note: this is not an exhaustive list, as new agents are introduced frequently.

cytokine or integrin inhibitors (e.g. abatacept, ustekinumab, natalizumab and vedolizumab) and tyrosine kinase inhibitors (e.g. imatinib and nilotinib). Immunomodulators, including thiopurines, methotrexate and calcineurin inhibitors, also cause moderate immunosuppression through various mechanisms.[526]

High-dose corticosteroids (>20 mg daily for >4 weeks) can lead to HBV reactivation, via activation of the HBV glucocorticoid responsive element and suppression of T-cell function.[526] Prophylactic NA therapy is recommended to prevent reactivation in HBsAg-positive patients receiving immunosuppression with corticosteroids alone or in combination with other agents.[41] However, HBsAg seroreversion occurs rarely among HBsAg-negative patients during immunosuppression that does not contain B-cell depleting therapy (e.g. anti-CD19/20), and NA prophylaxis is not recommended for these patients.

Patients with OBI (HBsAg-negative and detectable HBV DNA) receiving high-risk immunosuppression should be managed in a similar manner to people who are HBsAg-positive.

Recommendation 25

HBsAg-positive people receiving cancer chemotherapy or moderate- or high-risk immunosuppression for non-malignant conditions (Table 20) should be treated with entecavir or tenofovir. (Evidence quality: High; Grade of recommendation: Strong)

Recommendation 26

HBsAg-negative/anti-HBc-positive people who are being treated with agents associated with high risk of HBV reactivation (Table 19) should be treated with entecavir or tenofovir. (Evidence quality: Moderate; Grade of recommendation: Strong)

Recommendation 27

HBsAg-positive people receiving low-risk immunosuppression for non-malignant conditions (Table 20) should be monitored for hepatitis B reactivation with 3-monthly ALT and 6-monthly HBV DNA testing. (Evidence quality: Moderate; Grade of recommendation: Strong)

Technical remarks

1. NA treatment should be continued for at least 12 months after cessation of non-B-cell depleting immunosuppression and for at least 18–24 months after cessation of B-cell depleting agents.[93] EASL guidelines suggest continuing for 18 months after cessation of rituximab.[1]
2. It should be noted that entecavir and tenofovir are not currently listed on the PBS for the indication of prophylactic antiviral therapy in circumstances of significant immunosuppression.
3. Patients should be monitored for a further 12 months after cessation of NA treatment, with 3-monthly testing of ALT, HBsAg and HBV DNA levels.[1,93] Monitoring HBV DNA levels more frequently than annually is not currently supported by the Medicare Benefits Schedule.
4. All clinicians prescribing immunosuppressive therapy should be aware of the risk of HBV reactivation and implement appropriate screening strategies to identify individuals at risk.
5. Regardless of the underlying condition, all patients receiving highly immunosuppressive therapies should be screened for HBV, as the consequences of reactivation can be fatal.

9.3 Coinfection with HCV, HDV or HIV

Recommendation 28

Testing for HCV, HIV and HDV should be performed in all HBsAg-positive people at initial assessment and periodically if there is ongoing risk of infection. (Evidence quality: Moderate; Grade of recommendation: Strong)

9.3.1 HBV–HCV coinfection

About 6% of people diagnosed with HBV infection in Australia are coinfected with HCV.[43] Liver disease is accelerated in people living with HBV–HCV dual infection.[527] Since the advent of DAA therapy for HCV, adverse outcomes, including death, have been attributed to HBV reactivation.[528] As a result, the US Food and Drug Administration required a boxed warning to be included on DAA labelling and in patient information, indicating that testing for HBV and monitoring for HBV relapse are required among people receiving DAAs for HCV.[529]

Clinically significant HBV reactivation is extremely rare in HBsAg-negative, anti-HBc-positive people, and they do not require HBV therapy.[530] However, HBsAg and HBV DNA levels should be retested after therapy if the ALT level remains elevated.

Recommendation 29

HBsAg-positive people receiving DAA therapy for hepatitis C are at high risk of hepatitis B reactivation. People with cirrhosis or who otherwise meet the criteria for treatment for hepatitis B should be treated with entecavir or tenofovir. (Evidence quality: Low; Grade of recommendation: Strong)

Recommendation 30

HBsAg-negative, anti-HBc-positive people receiving DAA therapy are at very low risk of HBV reactivation and do not need monitoring for hepatitis B reactivation in this setting. (Evidence quality: Moderate; Grade of recommendation: Strong)

Technical remarks

1. Cases of HBV reactivation leading to adverse outcomes, including death, have also been reported in studies from Asia.[531]
2. The recommendations given here are consistent with the Australian HCV management consensus statement and the EASL, AASLD and APASL guidelines.[1,128,132,532]
3. In people without cirrhosis and with detectable HBV DNA below the criteria for treatment (<2000 IU/mL), concomitant HBV treatment and DAA therapy could also be considered.

9.3.2 HBV–HDV coinfection

HDV is a small RNA virus, reliant on HBsAg for replication, which affects about 5%–10% of people with CHB infection.[533,534] Australian data showed seroprevalences of 4.1% among 4407 individuals tested in Queensland between 1997 and 2016 and 4.8% among 2314 Victorians tested from 2000 to 2009.[535,536] HDV is commonly transmitted among MSM and PWID.[534] Regions with high HDV endemicity include Africa (West Africa and Horn of Africa), Asia (Central and Northern Asia), Pacific Islands, Middle East, Eastern Europe and South America (Amazonian Basin).[533] In Australia, among people who were born overseas, those with HBV–HDV coinfection were most

often born in Sudan, Pakistan or Vietnam.[537] Testing for HDV should be performed in anyone who is positive for HBsAg. Testing should initially be for anti-HDV antibody, and infection is then confirmed with PCR testing for HDV RNA if the antibody test is positive.

Peginterferon is the only available drug with proven antiviral efficacy against chronic HDV infection.[538] Suppression of HDV RNA occurs in up to 50% of people during 48 weeks of peginterferon therapy.[539] However, HDV viraemia can fluctuate during treatment and may not predict post-treatment response, with relapse occurring in up to 50% of people after on-treatment HDV suppression.[539,540] Virological response may be higher with therapy extended to 96 weeks.[541] However, conclusive data are lacking.

NAs alone are ineffective against HDV and do not increase the efficacy of peginterferon when used in combination. However, NAs have been shown to decrease HBsAg titres when combined with peginterferon,[539] and they may be useful in suppressing residual HBV replication, particularly in patients with decompensated liver disease, for whom peginterferon is contraindicated. Retreatment with peginterferon could be considered, although supportive data are lacking.

Bulevirtide is a novel drug that has activity against both HDV and HBV via inhibition of the sodium taurocholate co-transporting polypeptide receptor. It has completed Phase III trials in people with chronic HDV infection. Although not yet approved in Australia, it has recently been approved by both the US Food and Drug Administration and European Medicines Agency for the treatment of hepatitis D.

Technical remarks

1. Loss of HBsAg occurs in up to 10% of people treated with peginterferon and indicates long-term cure of chronic HDV infection.[539]
2. Late relapse may occur at any time after treatment, and long-term follow-up is recommended while HBsAg remains positive.[539]

9.3.3 HBV–HIV coinfection

About 27,500 Australians are living with HIV infection, of whom about 5% are coinfected with HBV.[21,542] The natural history of HBV is modified by HIV coinfection: HBV DNA levels, rates of HBeAg persistence, development of CHB infection and liver disease-related mortality are all higher than those in HBV mono-infection.[543,544] Without treatment, progression of fibrosis is more rapid and development of cirrhosis more common,[545] although the risk of liver disease is significantly reduced in people receiving long-term suppression with tenofovir-based antiretroviral therapy.[546,547] Therefore, early treatment of both HIV and HBV is recommended to prevent liver disease related to CHB infection.[1,41,132,298,548,549]

TAF is widely available in Australia for treating people living with HIV. It is associated with reduced rates of renal disease and osteopenia and is preferred over tenofovir in people with HBV–HIV coinfection.[550] Safety data regarding use of TAF during pregnancy are available, and TAF is now recommended as a preferred NA option for treatment of HIV in pregnancy.[551] Tenofovir is also an appropriate option.

The risk of HCC among people with HBV–HIV coinfection is unclear. A trend towards increased HCC risk in people with HIV was reported among people with HBV in NSW from 2000 to 2014.[552] HCC remains a leading cause of liver-related death among people with HIV infection, and HIV may be associated with decreased survival from HCC.[553] Therefore, people with HBV–HIV coinfection are offered 6-monthly liver ultrasounds and entry into an HCC surveillance program.

Recommendation 31

Treatment of HBV–HIV coinfection should be with HBV-active antiretroviral therapy, including tenofovir, regardless of HBV disease phase. (Evidence quality: Moderate; Grade of recommendation: Strong)

Technical remarks

1. Entecavir is also a potent inhibitor of HBV replication. However, it has weak anti-HIV activity and can lead to HIV resistance. It should only be used in combination with effective antiretroviral therapy against HIV.
2. Safety data for TAF in people with prior tenofovir-related renal disease or severe chronic kidney disease (eGFR, <30 mL/min/1.73 m^2) are lacking, although TAF may be used in people with an eGFR of 30–70 mL/min/1.73 m^2.[554]
3. One study suggests a low risk of HCC in people without cirrhosis and with early introduction (at age <46 years) of tenofovir.[555]
4. If pre-exposure prophylaxis is used in someone who has HBV and is at risk of infection with HIV, it should be used continuously, rather than on-demand, to achieve HBV suppression and avoid drug-resistant HBV.

9.4 Renal impairment

Renal impairment may occur in people with HBV infection as an extrahepatic manifestation, as a complication of NA therapy or as a complication of decompensated cirrhosis, such as hepatorenal syndrome. HBV status should be determined in patients receiving dialysis or renal transplantation, to reduce both transmission and relapse of undiagnosed HBV infection. As NA treatment is long term, and often lifelong, monitoring for renal complications in an ageing population is particularly important.

9.4.1 Renal monitoring

Renal adverse events, including nephrotoxicity with reduced glomerular filtration rate (GFR), hypophosphataemia, Fanconi syndrome, reduced bone mineral density and lactic acidosis, have been reported, predominantly due to tenofovir and adefovir, and to a lesser degree entecavir.[378,556,557] Pre-treatment and on-treatment renal monitoring should be performed to identify those who are at risk and may require alterations in their management. Entecavir or TAF, if available, are the treatments of choice for people at high risk of developing renal disease because of underlying diabetes, decompensated cirrhosis, pre-existent proteinuria or glomerulonephritis, nephrotoxic drug exposure or transplantation.

Although tenofovir primarily undergoes renal excretion and is associated with an increased risk of renal tubular damage in patients with HBV–HIV coinfection,[558] the risk remains low in patients with HBV mono-infection[365] and is similar to the risk seen with long-term entecavir.[559] TAF is associated with less renal toxicity than tenofovir disoproxil,[560] but it is only available in Australia for the treatment of HIV–HBV coinfection. Nevertheless, TAF may be considered for patients with renal disease related to previous tenofovir disoproxil exposure.

TAF is a prodrug of tenofovir that has greater plasma stability than TDF, resulting in increased delivery of the active metabolite tenofovir diphosphate to hepatocytes, as well as lower dosages being required.[561] Compared with 300 mg of TDF, circulating levels of tenofovir are 90% lower with a 25 mg daily dose of TAF, resulting in lower exposure to the potentially nephrotoxic tenofovir.[562] In two Phase III studies, analysis at 96 weeks showed that patients treated with TAF had similar levels of viral suppression as those treated with TDF; however, those treated with TAF had a significantly smaller median change in GFR (–1.2 vs –4.8 mL/min; $P < 0.001$) than those treated with TDF.[361,362,563] In a study of 490 virally supressed patients, switching from TDF to TAF had no effect on viral suppression rates, but a significant difference in creatinine clearance reduction was seen (–0.94 mL/min in TAF-treated patients compared with 2.74 mL/min in those who kept taking TDF for a further 48 weeks).[564]

All patients with HBV infection should undergo baseline assessment of renal function, and renal function should be monitored during NA therapy. All patients treated with tenofovir should have serum creatinine and phosphate levels monitored every 3 months in the first year and every 6 months thereafter. A similar approach should be used for patients who are at risk of renal disease or who develop an eGFR <60 mL/min/1.73 m^2 or phosphate levels <0.65 mmol/L (<2 mg/dL). If patients develop renal and bone complications while receiving treatment with tenofovir, a switch to TAF (if available) or entecavir should be considered. Any patient with renal

impairment requiring treatment for HBV should be managed by a specialist with experience in this setting.

Recommendation 32

Entecavir (with dose adjustment) or TAF is the preferred antiviral therapy in HBsAg-positive people with established renal impairment. (Evidence quality: Moderate; Grade of recommendation: Strong)

9.4.1.1 Patients receiving dialysis

HBsAg-positive rates in patients receiving dialysis are reportedly 1% in the US and 1.3%–14.6% in Asian patients.[565] In Australia's Northern Territory, 8.9% of patients receiving haemodialysis had HBsAg positivity, with 42.7% having evidence of previous HBV exposure.[566] This is similar to the population prevalence in a comparable cohort.[34] As nosocomial transmission of HBV may occur in dialysis units, all patients should be screened for HBV infection, and seronegative patients should be vaccinated. Response rates to HBV vaccine are poor in patients receiving dialysis, so double the usual vaccine dose should be given, with further courses of vaccination given if patients fail to develop protective levels of anti-HBs.[567,568]

All HBsAg-positive patients receiving dialysis should be monitored. Those who require treatment should receive NA therapy. Treatment with entecavir or TAF is recommended, with dose adjustments required for patients with an eGFR <50 mL/min/1.73 m^2 for entecavir and <15 mL/min/1.73 m^2 for TAF.[361,362,569] Adefovir and tenofovir are nephrotoxic and should be avoided in patients receiving dialysis who have residual renal function.[425] Peginterferon is safe in patients receiving dialysis, although it is poorly tolerated and its efficacy is unproven.[570]

9.4.1.2 Renal transplantation

HBV infection of kidney donors or recipients is associated with negative outcomes.[569] All potential transplant donors and recipients should be tested for HBsAg, anti-HBs and anti-HBc. Those with decompensated cirrhosis or portal hypertension should be considered for combined kidney and liver transplantation.[41] For HBsAg-positive recipients, NA therapy should commence at the time of transplantation and continue long term.[571] Entecavir is the preferred treatment option because of its low resistance rates and high tolerability in renal patients. If available, TAF should be used in preference to TDF because of its long-term safety in renal patients.[361,362] The role of NA prophylaxis for transplant recipients who are positive for anti-HBc but negative for HBsAg is unclear. Most guidelines recommend monitoring for re-emergence of HBsAg and treating with NAs, regardless of ALT level, for these rare events.[1,572] However, routine prophylaxis is not usually recommended. NA prophylaxis could be considered in transplant recipients receiving T-cell depleting therapy and those who are negative for anti-HBs.[572]

Among recipients from an anti-HBc-positive donor, a long-term HBV seroconversion rate of 2.3% has been shown.[573] To reduce the risk of HBV transmission and reactivation, renal transplant recipients should be vaccinated before transplantation, and, in the setting of high and prolonged immunosuppression, NA prophylaxis for 12 months should be considered.[572,574] All patients require close monitoring for reactivation, with 6-monthly HBsAg monitoring and NA treatment administered if HBsAg is detected.

Technical remarks

1. Surveillance with urinary glucose and protein testing should also be performed in patients at high risk of renal disease.[575]
2. Screening for HBV infection should be performed regardless of the intended mode of dialysis, and patients without HBV immunity should be vaccinated.
3. Vaccination with enhanced regimens, including double-dose or intradermal vaccination, should be considered if standard vaccination is unsuccessful.[576]
4. NA dose should be adjusted according to creatinine clearance based on eGFR.
5. Renal transplant recipients with HBsAg positivity and low HBV DNA levels should still receive NA prophylaxis.

9.5 Liver transplantation

The proportion of transplants performed for the primary indication of HBV infection in Australia and New Zealand fell from 9% in 1995–1999 to 4% in 2015–2017. However, HBV is a secondary diagnosis in up to 17% of transplants,[52] presumably due to the development of HCC in patients with cirrhosis receiving long-term treatment with antivirals.

In the 1980s and 1990s, HBV infection was considered a contraindication to liver transplantation because of unacceptably high recurrence rates (up to 65%) often leading to early graft loss.[577] With the availability of HBIG, the rate of reinfection fell to 29% in patients who were HBV DNA-negative at the time of transplantation, but HBIG was largely ineffective in patients with high viral loads.[578] Using the combination of HBIG and lamivudine, HBV recurrence fell to less than 5%, with resulting improvements in survival.[579,580] Once HBV DNA suppression could be achieved with lamivudine in most patients, the need for long-term HBIG (which was costly and inconvenient for patients) was questioned. A 2003 study showed that patients who were negative for HBV DNA at the time of liver transplantation had no HBV recurrence after a short course (1 month) of HBIG, in addition to long-term lamivudine.[581]

Now that highly potent NAs are available, the requirement for HBIG has been further explored, with protocols showing that HBIG can be withdrawn at 24 weeks, or even only a few days, after transplantation, or that no HBIG need be given at all, with minimal risk of HBV recurrence in selected patients deemed at low risk (HBV DNA-negative at time of transplantation).[582-584] Conversely, for patients who are expected to be non-compliant or patients with a higher risk of HBV recurrence, such as those who receive a transplant for HCC, HDV or HIV coinfection, long-term HBIG prophylaxis can be considered, in addition to entecavir or tenofovir.

In an era of donor organ shortage, the use of grafts from anti-HBc-positive but HBsAg-negative donors offers an opportunity to increase the number of available grafts. Due to a high rate of de novo infection (15%–48%, depending on the recipient's anti-HBc and anti-HBs status), the use of long-term prophylaxis is mandatory.[585] In patients receiving NA prophylaxis, the de novo infection rate has been reported as zero.[586]

The presence of anti-HBc in recipients of anti-HBs- and anti-HBc-negative grafts appears to carry negligible risk. These patients do not warrant prophylaxis, although monitoring of serum ALT and HBV DNA levels during periods of intense immunosuppression or therapy with DAAs for HCV infection may be warranted.[587-589]

Technical remarks

1. In patients undergoing liver transplantation, the use of TAF in combination with calcineurin inhibitors is attractive, given the improved renal safety of TAF over tenofovir. To date, only a small observational study has been performed in liver transplant patients, showing a small reduction in serum creatinine levels. No recommendation can be made on the use of TAF in this setting.[590]

10 Conclusion

Through a collaborative approach, these recommendations provide a framework for management of hepatitis B in Australia. Ultimately, this document aims to educate and empower all health care workers involved in managing people with hepatitis B infection and, in so doing, to improve the care delivered to people living with this virus.

Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
AGREE	Appraisal of Guidelines for Research & Evaluation
Anti-HAV	hepatitis A antibody
Anti-HBc	hepatitis B core antibody
Anti-HBe	hepatitis B e antibody
Anti-HBs	hepatitis B surface antibody
APASL	Asian Pacific Association for the Study of the Liver
APRI	aspartate aminotransferase to platelet ratio index
ARFI	acoustic radiation force impulse
ALT	alanine aminotransferase
ASHM	Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
ASID	Australasian Society for Infectious Diseases
AST	aspartate aminotransferase
AUROC	area under the receiver operator curve
BMI	body mass index
cccDNA	covalently closed circular DNA
CHB	chronic hepatitis B
DAA	direct-acting antiviral
DNA	deoxyribonucleic acid
EASL	European Association for the Study of the Liver
eGFR	estimated glomerular filtration rate
ELF	Enhanced Liver Fibrosis
FIB-4	Fibrosis-4
GESA	Gastroenterological Society of Australia
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBeAg	hepatitis B e-antigen

HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D (delta) virus
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalised ratio
IQR	interquartile range
MAFLD	metabolic (dysfunction)-associated fatty liver disease
MELD	Model for End-Stage Liver Disease
MRE	magnetic resonance elastography
MSM	men who have sex with men
MTCT	mother-to-child transmission
NA	nucleos(t)ide analogue
OBI	occult hepatitis B infection
PBS	Pharmaceutical Benefits Scheme
PCR	polymerase chain reaction
PWID	people who inject drugs
qHBsAg	quantitative hepatitis B surface antigen
SWE	shear wave elastography
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TE	transient elastography
ULN	upper limit of normal
WHO	World Health Organization

Acknowledgements

Funding

We gratefully acknowledge the sponsors for this project:

- Bayer
- Medtronic Australasia
- Sirtex Medical
- Eisai
- Novartis
- Gilead Sciences

We confirm that the sponsors have not had, nor sought, involvement in the selection of the project, design, conduct, analysis or outcomes, or articulation of the results. Sponsors have not been involved with the project committee directly, although they may have been involved through normal operations with project participants — see the Author disclosures.

Participation

Name	State	Organisation	Role
Prof Leon Adams	WA	GESA	Natural history EAG
Prof Golo Ahlenstiel	NSW	GESA	Diagnosis and monitoring EAG
Dr Nicole Allard	Vic	VIDRL	Diagnosis and monitoring WG Chair
Dr Tanya Applegate	NSW	Kirby Institute	Diagnosis and monitoring WG
Dr Jennifer Audsley	Vic	GESA	Natural history WG
Dr David Baker	NSW	GESA	Treatment WG
Dr Robert Batey	NSW	GESA	Diagnosis and monitoring WG
A/Prof Sally Bell	Vic	Monash Health	Diagnosis and monitoring EAG
Dr Scott Bowden	Vic	VIDRL	Diagnosis and monitoring EAG
Prof Wendy Cheng	WA	Royal Perth Hospital	Treatment EAG
Dr Paul Clark	Qld	GESA	Complications WG
Prof Benjamin Cowie	Vic	ASID/ASHM	Steering committee
A/Prof Jane Davies	NT	GESA	Treatment WG
Prof Joshua Davis	NSW	GESA	Natural history WG
A/Prof Anouk Dev	Vic	Monash Health	Natural history WG
Mr John Didlick	NSW	Hepatitis Australia	Consumer oversight group

Name	State	Organisation	Role
Prof Gregory Dore	NSW	GESA	Epidemiology EAG
A/Prof Mark Douglas	NSW	GESA	Diagnosis and monitoring WG
A/Prof Joe Doyle	Vic	Burnet Institute	Special groups WG
Dr Samuel Elliott	SA	GESA	Natural history WG
Prof Jacob George	NSW	Westmead Hospital	Complications EAG
A/Prof Michelle Giles	Vic	Alfred Health	Special groups EAG
Dr Behzad Hajarizadeh	NSW	Kirby Institute	Epidemiology WG
Prof Margaret Hellard	Vic	Burnet Institute	Diagnosis and monitoring EAG
Dr Jacinta Holmes	Vic	St Vincent's Hospital Melbourne	Natural history WG Chair
Dr Thai Hong	Vic	AVHPA-V	Complications WG
Dr Kelly Hosking	NT	GESA	Epidemiology EAG
A/Prof Jessica Howell	Vic	St Vincent's Hospital Melbourne	Epidemiology WG
Dr David Iser	Vic	St Vincent's Hospital Melbourne	Special groups WG Chair
A/Prof William Kemp	Vic	Alfred Health	Treatment WG Chair
Dr Sushena Krishnaswamy	Vic	ASID and Monash Health	Epidemiology EAG
A/Prof Alice Lee	NSW	GESA	Diagnosis and monitoring EAG
Dr Christopher Leung	Vic	Australian Chinese Medical Association of Victoria and Chinese Health Promotion Coalition	Consumer oversight group
A/Prof Miriam Levy	NSW	GESA	Special groups WG
Dr Ken Liu	NSW	Royal Prince Alfred Hospital	Complications WG
A/Prof John Lubel	Vic	GESA – Liver Faculty	Co-Chair
Prof Michaela Lucas	WA	GESA	Special groups EAG
Ms Jennifer MacLachlan	Vic	VIDRL	Epidemiology WG Chair
Dr Avik Majumdar	NSW	Royal Prince Alfred Hospital	Complications WG Chair
Ms Mei Mak	Vic	Hepatitis Victoria (patient representative)	Treatment WG
Dr Marianne Martinello	NSW	Kirby Institute	Complications EAG
Prof Gail Matthews	NSW	ASID, ASHM and Kirby Institute	Co-Chair
Prof Geoffrey McCaughan	NSW	Royal Prince Alfred Hospital	Complications EAG
Ms Joanne Mitchell	Vic	Alfred Health	Project Officer

Name	State	Organisation	Role
Prof James O'Beirne	Qld	Sunshine Coast University Hospital	Special groups WG
A/Prof Christopher Pearce	Vic	Australian College of Rural and Remote Medicine	Consumer oversight group
Dr Matthew Penn	Vic	GESA	Complications WG
A/Prof Stephen Pianko	Vic	Monash Health	Treatment EAG
Dr Dilip Ratnam	Vic	Monash Health	Treatment EAG
Prof Peter Revill	Vic	VIDRL	Natural history EAG
Dr Jacqui Richmond	Vic	Burnet Institute	Epidemiology WG
Prof Stuart Roberts	Vic	Alfred Health	Treatment EAG
Prof Joe Sasadeusz	Vic	Melbourne Health	Special groups EAG
Prof Nick Shackel	NSW	GESA	Treatment WG
Prof William Sievert	Vic	Monash Health	Natural history EAG
Prof Monica Slavin	Vic	Royal Melbourne Hospital	Special groups EAG
Dr Briohny Smith	WA	Sir Charles Gairdner Hospital	Special groups WG
Ms Sally Spruce	NSW	AHA (Chair)	Consumer oversight group
Dr Michael Stormon	NSW	GESA	Special groups EAG
A/Prof Simone Strasser	NSW	Royal Prince Alfred Hospital	Steering committee
Dr Caroline Tallis	Qld	GESA	Complications EAG
Prof Alex Thompson	Vic	GESA – Liver Faculty and Board	Steering committee
A/Prof Edmund Tse	SA	Royal Adelaide Hospital	Treatment EAG
Dr Thomas Tu	NSW	Westmead Institute for Medical Research	Consumer oversight group
Prof Kumar Visvanathan	Vic	GESA	Diagnosis and monitoring WG
Dr Michael Wallace	WA	GESA	Epidemiology EAG
Prof James Ward	Qld	University of Queensland Poche Centre for Indigenous Health	Consumer oversight group
A/Prof Amany Zekry	NSW	GESA	Natural history EAG

AHA = Australasian Hepatology Association; ASHM = Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine; ASID = Australasian Society for Infectious Diseases; AVHPA-V = Australian Vietnamese Health Professionals Association of Victoria; EAG = expert advisory group; GESA = Gastroenterological Society of Australia; VIDRL = Victorian Infectious Diseases Reference Laboratory; WG = working group.

Author disclosures

Leon Adams has been a member of the Metavention Advisory Board since 2019 and was a member of the Pfizer Advisory Board in July 2018. He is a holder of Australian and US patents for Hepascore.

David Baker is a member of the Gilead and AbbVie advisory boards and has received grants for overseas travel or conference expenses from Gilead and AbbVie.

Sally Bell received speaker fees from the New Zealand Society of Gastroenterology Annual Scientific Meeting 2021.

Paul Clark is a member of the Board of the Australian Liver Foundation and has received grants for overseas travel or conference expenses from Gilead, AbbVie and Bristol Myers Squibb.

Jane Davies holds Board membership or another office and has performed paid employment or contracting work with ASHM.

Joshua Davis was the President of ASID from 2018 to 2020.

John Didlick is a member of the ASHM National Hepatitis B and Hepatitis C Testing Policy Expert Reference Committees, the Kirby Institute Annual Surveillance Report Reference Group and the Kirby HBV and HCV Cascades Working Groups. He has performed paid employment for Hepatitis Australia and has received significant hospitality from the National Prisons Hepatitis Network.

Greg Dore is a member of the Hepatitis C Advisory Board. He is a member of the Board, has performed paid employment or contracting work and has received international conference travel support and research grants from Gilead Sciences, AbbVie and Merck Sharp & Dohme. He has supported PBS listing of all major DAA regimens, including in public statements and the media.

Joe Doyle holds Board membership or another office for ASID and has performed paid employment or contracting work and received significant hospitality from Gilead Sciences, AbbVie and Merck.

Samuel Elliott holds Board membership or another office for ASHM and the Royal Australian College of General Practitioners and has performed paid employment or contracting work and received significant hospitality from Gilead.

Jacob George holds Board membership or another office and has performed paid employment or contracting work with Bristol Myers Squibb, Gilead, Eisai, Bayer, Pfizer, AbbVie and Merck Sharp & Dohme. Members of his immediate family hold Board memberships or other offices; have performed paid employment or contracting work with Bayer, Novartis, Pfizer, Sanofi, Genzyme and Shire Actelion; and have received grants for overseas travel or conference expenses from Genzyme, Bayer and Actelion.

Jacinta Holmes is a member of the CSL Advisory Board and has received speaker fees from Gilead and AbbVie.

Jessica Howell is the recipient of a Gilead Fellowship research grant.

David Iser is a member of the ASHM Board of Directors and has received speaker fees from AbbVie, Gilead and Merck Sharp & Dohme.

William Kemp is a member of the advisory board of Gilead, Bayer and Merck Sharp & Dohme and has received speaker fees from Bayer and AbbVie.

Michaela Lucas holds shares in and has received significant hospitality from CSL.

Jennifer MacLachlan held Board membership with Hepatitis Victoria during 2015–2020 and has performed paid employment or contracting work with Royal Melbourne Hospital, the Department of Health and Human Services and North Western Melbourne Primary Health Network. She has received research grants from the Australian Government Department of Health, the Victorian Cancer Agency, the Royal Melbourne Hospital Foundation and the Ramsay Foundation.

Avik Majumdar is a member of the advisory board of Gilead and Novartis, has received speaker fees from Gilead and Eisai and is the recipient of a Gilead Fellowship research grant.

Gail Matthews holds Board membership or another office with ASHM and has received research grants from Gilead and AbbVie.

Matthew Penn has performed paid employment or contracting work with ASHM and the Victorian HIV and Hepatitis Integrated Training and Learning program.

Stephen Pianko holds Board membership with GESA and has performed paid employment or contracting work for and received significant hospitality from AbbVie and Gilead.

Peter Revill has received funding from Gilead for a research grant.

Jacqui Richmond holds Board membership or another office with AbbVie and has performed paid employment or contracting work for AbbVie and Gilead.

Stuart Roberts holds Board membership or another office with CSL, Eisai and AstraZeneca and has performed paid employment or contracting work for Eisai and AstraZeneca.

Joe Sasadeusz holds Board membership or another office with, has performed paid employment or contracting work for and has received significant hospitality from Gilead.

Nick Shackel has been an advisory board member and speaker for Roche, Bristol Myers Squibb, Gilead, Bayer, Astellas and Novartis.

Briohny Smith has performed paid employment or contracting work with Gilead and Norgine.

Sally Spruce is President of the Australasian Hepatology Association (unpaid position).

Simone Strasser is a member of the Board of the Australian Liver Foundation and an Associate Editor for *Transplantation*. She has received honoraria for participation on advisory boards and/or speaker fees from Bayer, Eisai, AbbVie, Gilead, Bristol Myers Squibb, Merck Sharp & Dohme, Norgine, Astellas, Novartis, WL Gore, Ipsen, Pfizer, AstraZeneca, Roche, Chiesi, Dr Falk Pharma and Guerbet Australia.

Caroline Tallis is a member of the Gilead Hepatitis C Advisory Board.

Alex Thompson has received funding from the National Health and Medical Research Council (MRFF Practitioner Fellowship 1142976); has received honoraria for participation on advisory boards and/or speaker fees from AbbVie, Gilead Sciences, Roche Diagnostics, Bristol Myers Squibb, Merck, Immunocore, Janssen, Assembly Biosciences, Arbutus Biopharma, Vir Biotechnology, Eisai, Ipsen and Bayer; and has received research or grant support from Gilead Sciences, Merck, Bristol Myers Squibb, AbbVie and Roche Diagnostics.

Thomas Tu has performed paid employment or contracting work with Gilead and received significant funding from ACH[2] project grants and the National Health and Medical Research Council.

Michael Wallace has received grants for overseas travel or conference expenses from Bayer (ILCA Conference).

Amany Zekry is a member of the Bayer Advisory Board.

All other authors declare no conflicts of interest.

References

1. European Association for the Study of the Liver. EASL 2017 Clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67: 370-398.
2. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013; 66: 719-725.
3. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64: 401-406.
4. Agree Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003; 12: 18-23.
5. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. J Clin Epidemiol 2010; 63: 1308-1311.
6. Gustafson DH, Shukla RK, Delbecq A, Walster GW. A comparative study of differences in subjective likelihood estimates made by individuals, interacting groups, Delphi groups, and nominal groups. Organ Behav Hum Perform 1973; 9: 280-291.
7. Snape D, Kirkham J, Preston J, et al. Exploring areas of consensus and conflict around values underpinning public involvement in health and social care research: a modified Delphi study. BMJ Open 2014; 4: e004217.
8. Eubank BH, Mohtadi NG, Lafave MR, et al. Using the modified Delphi method to establish clinical consensus for the diagnosis and treatment of patients with rotator cuff pathology. BMC Med Res Methodol 2016; 16: 56.
9. Morgan PJ, Lam-McCulloch J, Herold-McIlroy J, Tarshis J. Simulation performance checklist generation using the Delphi technique. Can J Anaesth 2007; 54: 992-997.
10. Becker M, Jaschinski T, Eikermann M, et al. A systematic decision-making process on the need for updating clinical practice guidelines proved to be feasible in a pilot study. J Clin Epidemiol 2018; 96: 101-109.
11. Cheung JJ, Chen EW, Darani R, et al. The creation of an objective assessment tool for ultrasound-guided regional anesthesia using the Delphi method. Reg Anesth Pain Med 2012; 37: 329-333.
12. Maertens H, Aggarwal R, Macdonald S, et al. Transatlantic multispecialty consensus on fundamental endovascular skills: results of a Delphi consensus study. Eur J Vasc Endovasc Surg 2016; 51: 141-149.
13. Schweitzer A, Horn J, Mikolayczyk R, Ott J. Worldwide prevalence of chronic hepatitis B virus infection: estimations based on a systematic review of data published between 1965 and 2013. Lancet 2015; 386: 1546-1555.
14. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018; 3: 383-403.
15. World Health Organization. Global hepatitis report, 2017. Geneva: WHO, 2017.
16. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004; 11: 97-107.
17. Global Burden of Disease Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1736-1788.
18. Tu T, Block JM, Wang S, et al. The lived experience of chronic hepatitis B: a broader view of its impacts and why we need a cure. Viruses 2020; 12: 515.
19. MacLachlan JH, Stewart S, Cowie BC. Viral Hepatitis Mapping Project: National Report 2020. Sydney: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, 2021. https://ashm.org.au/programs/Viral-Hepatitis-Mapping-Project/ (accessed 28 Jan 2022).
20. Liu B, Guthridge S, Li SQ, et al. The end of the Australia antigen? An ecological study of the impact of universal newborn hepatitis B vaccination two decades on. Vaccine 2012; 30: 7309-7314.
21. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2018. Sydney: The Kirby Institute, University of New South Wales, 2018. https://kirby.unsw.edu.au/report/hiv-viral-hepatitis-and-sexually-transmissible-infections-australia-annual-surveillance (accessed 15 Nov 2021).
22. Global Burden of Disease Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1151-1210.
23. World Health Organisation. Hepatitis B [fact sheet]. Geneva: WHO, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b (accessed 15 Nov 2021).
24. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2012. Sydney: The Kirby Institute, University of New South Wales, 2012.
25. NNDSS Annual Report Working Group. Australia's notifiable disease status, 2015: annual report of the National Notifiable

Diseases Surveillance System. Commun Dis Intell (2018) 2019; 43.

26. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009; 50: 661-662.

27. Edmunds WJ, Medley GF, Nokes DJ, et al. The influence of age on the development of the hepatitis B carrier state. Proc Biol Sci 1993; 253: 197-201.

28. MacLachlan JH, Smith C, Towell V, Cowie BC. Viral Hepatitis Mapping Project: National Report 2018–19. Sydney: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, 2020. https://ashm.org.au/programs/Viral-Hepatitis-Mapping-Project/ (accessed 15 Nov 2021).

29. Graham S, MacLachlan JH, Gunaratnam P, Cowie BC. Chronic hepatitis B prevalence in Australian Aboriginal and Torres Strait Islander people before and after implementing a universal vaccination program: a systematic review and meta-analysis. Sexual Health 2019; 16: 201-211.

30. Australian Cancer Atlas. Brisbane: Cancer Council Queensland, Queensland University of Technology, Cooperative Research Centre for Spatial Information, 2018. https://atlas.cancer.org.au/ (accessed 15 Nov 2021).

31. National Centre for Immunisation Research and Surveillance. Significant events in hepatitis B vaccination practice in Australia. Sydney: NCIRS, 2019. http://ncirs.org.au/sites/default/files/2019-07/Hepatitis-B-history-July%202019.pdf (accessed 15 Nov 2021).

32. McCulloch K, Romero N, MacLachlan J, et al. Modeling progress toward elimination of hepatitis B in Australia. Hepatology 2020; 71: 1170-1181.

33. Graham S, Guy RJ, Cowie B, et al. Chronic hepatitis B prevalence among Aboriginal and Torres Strait Islander Australians since universal vaccination: a systematic review and meta-analysis. BMC Infect Dis 2013; 13: 403.

34. Davies J, Li SQ, Tong SY, et al. Establishing contemporary trends in hepatitis B sero-epidemiology in an Indigenous population. PLoS One 2017; 12: e0184082.

35. World Health Organization. Hepatitis B (HepB3): Immunization coverage estimates by WHO region. Geneva: WHO, 2021. http://apps.who.int/gho/data/view.main.81300?lang=en (accessed 15 Nov 2021).

36. Cui F, Shen L, Li L, et al. Prevention of chronic hepatitis B after 3 decades of escalating vaccination policy, China. Emerg Infect Dis 2017; 23: 765-772.

37. World Health Organization. Global health sector strategy on viral hepatitis, 2016–2021. Towards ending viral hepatitis. Geneva: WHO, 2016. https://apps.who.int/iris/handle/10665/246177 (accessed 1 Sep 2017).

38. Australian Government Department of Health. Third National Hepatitis B Strategy 2018–2022. Canberra: Commonwealth of Australia, 2018. http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-bbvs-1/$File/Hep-B-Third-Nat-Strategy-2018-22.pdf (accessed 15 Nov 2021).

39. Romero N, McCulloch K, Allard N, et al. National surveillance for hepatitis B indicators. Measuring the progress towards the targets of the National Hepatitis B Strategy: annual report 2019. Melbourne: WHO Collaborating Centre for Viral Hepatitis, Doherty Institute, 2020. https://www.doherty.edu.au/uploads/content_doc/National_Surveillance_for_Hepatitis_B_Indicators_2019_final.pdf (accessed 15 Nov 2021).

40. Allard NL, Matthews G (ed). B Positive. All you wanted to know about hepatitis B: a guide for primary care providers. Sydney: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, 2018. http://hepatitisb.org.au/ (accessed 15 Nov 2021).

41. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67: 1560-1599.

42. Australian Government Department of Health. Pharmaceutical Benefits Scheme: Schedule of pharmaceutical benefits. Canberra: Commonwealth of Australia, 2021. http://www.pbs.gov.au/info/browse/publications (accessed 15 Nov 2021).

43. Amin J, Dore GJ, O'Connell DL, et al. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. J Hepatol 2006; 45: 197-203.

44. Global Burden of Disease Liver Cancer Collaboration. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol 2017; 3: 1683-1691.

45. Alavi M, Grebely J, Hajarizadeh B, et al. Mortality trends among people with hepatitis B and C: a population-based linkage study, 1993–2012. BMC Infect Dis 2018; 18: 215.

46. Clark PJ, Stuart KA, Leggett BA, et al. Remoteness, race and social disadvantage: disparities in hepatocellular carcinoma incidence and survival in Queensland, Australia. Liver Int 2015; 35: 2584-2594.

47. Parker C, Tong SY, Dempsey K, et al. Hepatocellular carcinoma in Australia's Northern Territory: high incidence and poor outcome. Med J Aust 2014; 201: 470-474.

48. Li M, Roder D, McDermott R. Diabetes and smoking as predictors of cancer in Indigenous adults from rural and remote communities of North Queensland – a 15-year follow up study. Int J Cancer 2018; 143: 1054-1061.

49. Powell EE, Skoien R, Rahman T, et al. Increasing hospitalization rates for cirrhosis: overrepresentation of disadvantaged Australians. EClinicalMedicine 2019; 11: 44-53.

50. Littlejohn M, Davies J, Yuen L, et al. Molecular virology of hepatitis B virus, sub-genotype C4 in northern Australian Indigenous populations. J Med Virol 2014; 86: 695-706.

51. Howell J, Pedrana A, Cowie BC, et al. Aiming for the elimination of viral hepatitis in Australia, New Zealand, and the Pacific Islands and Territories: where are we now and barriers to meeting World Health Organization targets by 2030. J Gastroenterol Hepatol 2019; 34: 40-48.

52. Lynch SV, Balderson GA (ed). ANZLT Registry report 2017. Brisbane: Australia and New Zealand Liver Transplant Registry, 2017. https://www.anzlitr.org/wp-content/uploads/Reports/29thReport.pdf (accessed 15 Nov 2021).

53. Hong TP, Gow P, Fink M, et al. Novel population-based study finding higher than reported hepatocellular carcinoma incidence suggests an updated approach is needed. Hepatology 2016; 63: 1205-1212.

54. Hong TP, Gow PJ, Fink M, et al. Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study. Med J Aust 2018; 209: 348-354.

55. Alavi M, Law MG, Grebely J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: a population-based study. J Hepatol 2016; 65: 879-887.

56. Samji H, Yu A, Kuo M, et al. Late hepatitis B and C diagnosis in relation to disease decompensation and hepatocellular carcinoma development. J Hepatol 2017; 67: 909-917.

57. Banham D, Roder D, Keefe D, et al. Disparities in cancer stage at diagnosis and survival of Aboriginal and non-Aboriginal South Australians. Cancer Epidemiol 2017; 48: 131-139.

58. Condon JR, Zhang X, Dempsey K, et al. Trends in cancer incidence and survival for Indigenous and non-Indigenous people in the Northern Territory. Med J Aust 2016; 205: 454-458.

59. Grimes DA, Schulz KF. Uses and abuses of screening tests. Lancet 2002; 359: 881-884.

60. Wilson J, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization, 1968.

61. World Health Organization. Guidelines on hepatitis B and C testing. Geneva: WHO, 2017. https://www.who.int/publications/i/item/9789241549981 (accessed 15 Nov 2021).

62. Abara WE, Qaseem A, Schillie S, et al. Hepatitis B vaccination, screening, and linkage to care: best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2017; 167: 794-804.

63. Amini A, Varsaneux O, Kelly H, et al. Diagnostic accuracy of tests to detect hepatitis B surface antigen: a systematic review of the literature and meta-analysis. BMC Infect Dis 2017; 17 Suppl 1: 698.

64. Australian Government Department of Health. MBS Online: Medicare Benefits Schedule. Canberra: Commonwealth of Australia, 2020. http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/downloads (accessed 3 Mar 2020).

65. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013; 58: 98-107.

66. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol 2010; 53: 348-356.

67. Tada T, Kumada T, Toyoda H, et al. Long-term prognosis of patients with hepatitis B infection: causes of death and utility of nucleos(t)ide analogue therapy. J Gastroenterol 2015; 50: 795-804.

68. Xiao Y, Howell J, van Gemert C, et al. Enhancing the hepatitis B care cascade in Australia: a cost-effectiveness model. J Viral Hepat 2020; 27: 526-536.

69. Eckman MH, Kaiser TE, Sherman KE. The cost-effectiveness of screening for chronic hepatitis B infection in the United States. Clin Infect Dis 2011; 52: 1294-1306.

70. Hutton DW, Tan D, So SK, Brandeau ML. Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B. Ann Intern Med 2007; 147: 460-469.

71. Wong WW, Woo G, Jenny Heathcote E, Krahn M. Cost effectiveness of screening immigrants for hepatitis B. Liver Int 2011; 31: 1179-1190.

72. Suijkerbuijk AWM, van Hoek AJ, Koopsen J, et al. Cost-effectiveness of screening for chronic hepatitis B and C among migrant populations in a low endemic country. PLoS One 2018; 13: e0207037.

73. MacLachlan JH, Cowie BC. Bridging the access gap: Medicare ineligibility in people living with chronic hepatitis B. Intern Med J 2018; 49: 122-125.

74. Robotin MC, Kansil M, Howard K, et al. Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening. J Hepatol 2009; 50: 990-998.

75. Butler JR, Korda RJ, Watson KJ, Watson AR. The impact of chronic hepatitis B in Australia: projecting mortality, morbidity and economic impact. Canberra: Australian Centre for Economic Research on Health, 2009.

76. Chahal HS, Peters MG, Harris AM, et al. Cost-effectiveness of hepatitis B virus infection screening and treatment or vaccination in 6 high-risk populations in the United States. Open Forum Infect Dis 2019; 6: ofy353.

77. Rossi C, Schwartzman K, Oxlade O, et al. Hepatitis B screening and vaccination strategies for newly arrived adult Canadian immigrants and refugees: a cost-effectiveness analysis. PLoS One 2013; 8: e78548.

78. Veldhuijzen IK, Toy M, Hahne SJ, et al. Screening and early treatment of migrants for chronic hepatitis B virus infection is cost-effective. Gastroenterology 2010; 138: 522-530.

79. Jazwa A, Coleman MS, Gazmararian J, et al. Cost-benefit comparison of two proposed overseas programs for reducing

chronic hepatitis B infection among refugees: is screening essential? Vaccine 2015; 33: 1393-1399.

80. Kumada T, Toyoda H, Tada T, et al. Effect of nucleos(t)ide analogue therapy on hepatocarcinogenesis in chronic hepatitis B patients: a propensity score analysis. J Hepatol 2013; 58: 427-433.

81. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health 2017; 5: e1192-e1207.

82. Deng L, Reekie J, Ward JS, et al. Trends in the prevalence of hepatitis B infection among women giving birth in New South Wales. Med J Aust 2017; 206: 301-305.

83. Reekie J, Kaldor JM, Mak DB, et al. Long-term impact of childhood hepatitis B vaccination programs on prevalence among Aboriginal and non-Aboriginal women giving birth in Western Australia. Vaccine 2018; 36: 3296-3300.

84. Gidding HF, Dore GJ, Amin J, Law MG. Trends in all cause and viral liver disease-related hospitalizations in people with hepatitis B or C: a population-based linkage study. BMC Public Health 2011; 11: 52.

85. Reekie JM, Levy MH, Richards AH, et al. Trends in HIV, hepatitis B and hepatitis C prevalence among Australian prisoners – 2004, 2007, 2010. Med J Aust 2014; 200: 277-280.

86. Butler T, Simpson M. National prison entrants' blood-borne virus survey report 2004, 2007, 2010, 2013 and 2016. Sydney: Kirby Institute, UNSW Sydney, 2017. https://kirby.unsw.edu.au/sites/default/files/kirby/report/JHP_National-Prison-Entrants-Report-2004-2007-2010-2013-2016.pdf (accessed 15 Nov 2021).

87. MacLachlan J, Allard N, Carville K, et al. Mapping progress in chronic hepatitis B: geographic variation in prevalence, diagnosis, monitoring and treatment, 2013–15. Aust N Z J Public Health 2018; 42: 62-68.

88. He WQ, Duong MC, Gidding H, et al. Trends in chronic hepatitis B prevalence in Australian women by country of birth, 2000 to 2016. J Viral Hepat 2020; 27: 74-80.

89. Reekie J, Gidding HF, Kaldor JM, Liu B. Country of birth and other factors associated with hepatitis B prevalence in a population with high levels of immigration. J Gastroenterol Hepatol 2013; 28: 1539-1544.

90. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med 2016; 374: 2324-2334.

91. Thilakanathan C, Wark G, Maley M, et al. Mother-to-child transmission of hepatitis B: examining viral cut-offs, maternal HBsAg serology and infant testing. Liver Int 2018; 38: 1212-1219.

92. Leung C, Tsoi E, Burns G, Sievert W. An argument for the universal prophylaxis of hepatitis B infection in patients receiving rituximab: a 7-year institutional experience of hepatitis screening. Oncologist 2011; 16: 579-584.

93. Hepatitis B Management During Cancer Therapy Consensus Statement Group. Hepatitis B management during immunosuppression for haematological and solid-organ malignancies: an Australian consensus statement 2019. Melbourne: Hepatitis B Management During Cancer Therapy Consensus Statement Group, 2019. https://www.asid.net.au/documents/item/1741 (accessed 26 Aug 2021).

94. Werner BG, Grady GF. Accidental hepatitis-B-surface-antigen-positive inoculations: use of e antigen to estimate infectivity. Ann Intern Med 1982; 97: 367-369.

95. Communicable Diseases Network of Australia. Australian national guidelines for the management of healthcare workers living with blood borne viruses and healthcare workers who perform exposure prone procedures at risk of exposure to blood borne viruses. Canberra: Australian Government Department of Health, 2018. https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-cdna-bloodborne.htm (accessed 5 May 2020).

96. Shiffman ML. Approach to the patient with chronic hepatitis B and decompensated cirrhosis. Liver Int 2020; 40 Suppl 1: 22-26.

97. Edey M, Barraclough K, Johnson DW. Review article: Hepatitis B and dialysis. Nephrology (Carlton) 2010; 15: 137-145.

98. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. Hepatology 2009; 49 (5 Suppl): S138-S145.

99. Bernier RH, Sampliner R, Gerety R, et al. Hepatitis B infection in households of chronic carriers of hepatitis B surface antigen: factors associated with prevalence of infection. Am J Epidemiol 1982; 116: 199-211.

100. Alter MJ, Coleman PJ, Alexander WJ, et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. JAMA 1989; 262: 1201-1205.

101. Sira J, Brown M, Ambegaokar S, et al. The necessity of education and hepatitis B vaccination for young people: a study of high risk behaviour for blood borne viruses in the United Kingdom. J Child Health Care 2019; 23: 437-445.

102. Shiffman ML. Management of acute hepatitis B virus infection. Curr Hepatol Rep 2020; 19 Suppl 2: 276-284.

103. Bertoletti A, Ferrari C. Innate and adaptive immune responses in chronic hepatitis B virus infections: towards restoration of immune control of viral infection. Gut 2012; 61: 1754-1764.

104. Dandri M, Locarnini S. New insight in the pathobiology of hepatitis B virus infection. Gut 2012; 61 Suppl 1: i6-i17.

105. Yang PL, Althage A, Chung J, et al. Immune effectors required for hepatitis B virus clearance. Proc Natl Acad Sci U S A 2010; 107: 798-802.

106. Boni C, Fisicaro P, Valdatta C, et al. Characterization of hepatitis B virus (HBV)-specific T-cell dysfunction in chronic HBV infection. J Virol 2007; 81: 4215-4225.

107. Lee WM. Etiologies of acute liver failure. Semin Liver Dis 2008; 28: 142-152.

108. Shukla NB, Poles MA. Hepatitis B virus infection: co-infection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus. Clin Liver Dis 2004; 8: 445-460, viii.

109. Krugman S. Incubation period of type B hepatitis. N Engl J Med 1979; 300: 625.

110. Chu CM, Sheen IS, Lin SM, Liaw YF. Sex difference in chronic hepatitis B virus infection: studies of serum HBeAg and alanine aminotransferase levels in 10,431 asymptomatic Chinese HBsAg carriers. Clin Infect Dis 1993; 16: 709-713.

111. Beasley RP, Hwang LY, Lin CC, et al. Incidence of hepatitis B virus infections in preschool children in Taiwan. J Infect Dis 1982; 146: 198-204.

112. Yuki N, Nagaoka T, Yamashiro M, et al. Long-term histologic and virologic outcomes of acute self-limited hepatitis B. Hepatology 2003; 37: 1172-1179.

113. Milich DR, Jones JE, Hughes JL, et al. Is a function of the secreted hepatitis B e antigen to induce immunologic tolerance in utero? Proc Natl Acad Sci U S A 1990; 87: 6599-6603.

114. Chang MH, Sung JL, Lee CY, et al. Factors affecting clearance of hepatitis B e antigen in hepatitis B surface antigen carrier children. J Pediatr 1989; 115: 385-390.

115. Liaw YF, Chu CM, Lin DY, et al. Age-specific prevalence and significance of hepatitis B e antigen and antibody in chronic hepatitis B virus infection in Taiwan: a comparison among asymptomatic carriers, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. J Med Virol 1984; 13: 385-391.

116. McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985; 151: 599-603.

117. Bortolotti F, Cadrobbi P, Crivellaro C, et al. Long-term outcome of chronic type B hepatitis in patients who acquire hepatitis B virus infection in childhood. Gastroenterology 1990; 99: 805-810.

118. Bortolotti F, Guido M, Bartolacci S, et al. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. Hepatology 2006; 43: 556-562.

119. Wu JF, Tsai WY, Tung YC, et al. Effect of menarche onset on the clinical course in females with chronic hepatitis B virus infection. J Pediatr 2014; 165: 534-538.

120. Lin CL, Kao JH. Natural history of acute and chronic hepatitis B: the role of HBV genotypes and mutants. Best Pract Res Clin Gastroenterol 2017; 31: 249-255.

121. Chang MH, Hsu HY, Hsu HC, et al. The significance of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis B e antigen before 3 years of age. Hepatology 1995; 22: 1387-1392.

122. Chang MH. Hepatitis B virus infection. Semin Fetal Neonatal Med 2007; 12: 160-167.

123. Wen WH, Chang MH, Hsu HY, et al. The development of hepatocellular carcinoma among prospectively followed children with chronic hepatitis B virus infection. J Pediatr 2004; 144: 397-399.

124. Giacchino R, Navone C, Facco F, et al. HBV-DNA-related hepatocellular carcinoma occurring in childhood. Report of three cases. Dig Dis Sci 1991; 36: 1143-1146.

125. Ruiz-Moreno M, Otero M, Millan A, et al. Clinical and histological outcome after hepatitis B e antigen to antibody seroconversion in children with chronic hepatitis B. Hepatology 1999; 29: 572-575.

126. Bortolotti F, Guido M, Cadrobbi P, et al. Spontaneous regression of hepatitis B virus-associated cirrhosis developed in childhood. Dig Liver Dis 2005; 37: 964-967.

127. Yotsuyanagi H, Ito K, Yamada N, et al. High levels of hepatitis B virus after the onset of disease lead to chronic infection in patients with acute hepatitis B. Clin Infect Dis 2013; 57: 935-942.

128. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016; 63: 261-283.

129. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002; 137: 1-10.

130. Lee JK, Shim JH, Lee HC, et al. Estimation of the healthy upper limits for serum alanine aminotransferase in Asian populations with normal liver histology. Hepatology 2010; 51: 1577-1583.

131. Ruhl CE, Everhart JE. Upper limits of normal for alanine aminotransferase activity in the United States population. Hepatology 2012; 55: 447-454.

132. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016; 10: 1-98.

133. Kim HC, Nam CM, Jee SH, et al. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ 2004; 328: 983.

134. Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 2006; 43 (2 Suppl 1): S173-S181.

135. Chu CM, Liaw YF. Genotype C hepatitis B virus infection is associated with a higher risk of reactivation of hepatitis B and progression to cirrhosis than genotype B: a longitudinal study of hepatitis B e antigen-positive patients with normal aminotransferase levels at baseline. J Hepatol 2005; 43: 411-417.

136. Thakur V, Guptan RC, Kazim SN, et al. Profile, spectrum and significance of HBV genotypes in chronic liver disease patients in the Indian subcontinent. J Gastroenterol Hepatol 2002; 17: 165-170.

137. Kao JH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology 2000; 118: 554-559.

138. Kao JH. Role of viral factors in the natural course and therapy of chronic hepatitis B. Hepatol Int 2007; 1: 415-430.

139. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006; 295: 65-73.

140. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006; 130: 678-686.

141. McMahon BJ. Epidemiology and natural history of hepatitis B. Semin Liver Dis 2005; 25 Suppl 1: 3-8.

142. McMahon BJ. The influence of hepatitis B virus genotype and subgenotype on the natural history of chronic hepatitis B. Hepatol Int 2009; 3: 334-342.

143. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009; 49 (5 Suppl): S45-S55.

144. Tan A, Koh S, Bertoletti A. Immune response in hepatitis B virus infection. Cold Spring Harb Perspect Med 2015; 5: a021428.

145. Bengsch B, Chang KM. Evolution in our understanding of hepatitis B virus virology and immunology. Clin Liver Dis 2016; 20: 629-644.

146. Blumberg BS, Alter HJ, Visnich S. A “new” antigen in leukemia sera. JAMA 1965; 191: 541-546.

147. Mani H, Kleiner DE. Liver biopsy findings in chronic hepatitis B. Hepatology 2009; 49 (5 Suppl): S61-S71.

148. Chang MH, Hwang LY, Hsu HC, et al. Prospective study of asymptomatic HBsAg carrier children infected in the perinatal period: clinical and liver histologic studies. Hepatology 1988; 8: 374-377.

149. Nguyen T, Thompson AJ, Bowden S, et al. Hepatitis B surface antigen levels during the natural history of chronic hepatitis B: a perspective on Asia. J Hepatol 2010; 52: 508-513.

150. Thompson AJ, Nguyen T, Iser D, et al. Serum hepatitis B surface antigen and hepatitis B e antigen titers: disease phase influences correlation with viral load and intrahepatic hepatitis B virus markers. Hepatology 2010; 51: 1933-1944.

151. Livingston SE, Simonetti JP, Bulkow LR, et al. Clearance of hepatitis B e antigen in patients with chronic hepatitis B and genotypes A, B, C, D, and F. Gastroenterology 2007; 133: 1452-1457.

152. Lok AS, Lai CL. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. Hepatology 1988; 8: 1130-1133.

153. Lok AS. Natural history and control of perinatally acquired hepatitis B virus infection. Dig Dis 1992; 10: 46-52.

154. Chu CM. Natural history of chronic hepatitis B virus infection in adults with emphasis on the occurrence of cirrhosis and hepatocellular carcinoma. J Gastroenterol Hepatol 2000; 15 Suppl: E25-E30.

155. Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. J Gastroenterol Hepatol 2011; 26: 628-638.

156. Yang HC, Shih YF, Liu CJ. Viral factors affecting the clinical outcomes of chronic hepatitis B. J Infect Dis 2017; 216 Suppl 8: S757-S764.

157. Hadziyannis SJ. Natural history of chronic hepatitis B in Euro-Mediterranean and African countries. J Hepatol 2011; 55: 183-191.

158. Hui CK, Leung N, Yuen ST, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. Hepatology 2007; 46: 395-401.

159. Chu CM, Hung SJ, Lin J, et al. Natural history of hepatitis B e antigen to antibody seroconversion in patients with normal serum aminotransferase levels. Am J Med 2004; 116: 829-834.

160. Manno M, Camma C, Schepis F, et al. Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. Gastroenterology 2004; 127: 756-763.

161. Zacharakis GH, Koskinas J, Kotsiou S, et al. Natural history of chronic HBV infection: a cohort study with up to 12 years follow-up in North Greece (part of the Interreg I-II/EC-project). J Med Virol 2005; 77: 173-179.

162. Wong GL, Chan HL, Yu Z, et al. Liver fibrosis progression in chronic hepatitis B patients positive for hepatitis B e antigen: a prospective cohort study with paired transient elastography examination. J Gastroenterol Hepatol 2013; 28: 1762-1769.

163. Chen YC, Chu CM, Liaw YF. Age-specific prognosis following spontaneous hepatitis B e antigen seroconversion in chronic hepatitis B. Hepatology 2010; 51: 435-444.

164. Kennedy PTF, Sandalova E, Jo J, et al. Preserved T-cell function in children and young adults with immune-tolerant chronic hepatitis B. Gastroenterology 2012; 143: 637-645.

165. Sukriti S, Pati NT, Bose S, et al. Impaired antigen processing and presentation machinery is associated with immunotolerant state in chronic hepatitis B virus infection. J Clin Immunol 2010; 30: 419-425.

166. Vanwolleghem T, Hou J, van Oord G, et al. Re-evaluation of hepatitis B virus clinical phases by systems biology identifies unappreciated roles for the innate immune response and B cells. Hepatology 2015; 62: 87-100.

167. Bertoletti A, Kennedy PT. The immune tolerant phase of chronic HBV infection: new perspectives on an old concept. Cell Mol Immunol 2015; 12: 258-263.

168. Milich DR. The concept of immune tolerance in chronic hepatitis B virus infection is alive and well. Gastroenterology 2016; 151: 801-804.

169. Andreani T, Serfaty L, Mohand D, et al. Chronic hepatitis B virus carriers in the immunotolerant phase of infection: histologic findings and outcome. Clin Gastroenterol Hepatol 2007; 5: 636-641.

170. Fattovich G, Rugge M, Brollo L, et al. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. Hepatology 1986; 6: 167-172.

171. Yuen MF, Hui CK, Cheng CC, et al. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. Hepatology 2001; 34: 139-145.

172. McMahon BJ, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. Ann Intern Med 2001; 135: 759-768.

173. Yang HC, Shih YF, Liu CJ. Viral factors affecting the clinical outcomes of chronic hepatitis B. J Infect Dis 2017; 216 Suppl 8: S757-S764.

174. Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. Hepatology 2007; 45: 1187-1192.

175. Yuen MF, Lai CL. Natural history of chronic hepatitis B virus infection. J Gastroenterol Hepatol 2000; 15 Suppl: E20-E24.

176. Liaw YF, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Hepatology 1988; 8: 493-496.

177. Realdi G, Alberti A, Rugge M, et al. Seroconversion from hepatitis B e antigen to anti-HBe in chronic hepatitis B virus infection. Gastroenterology 1980; 79: 195-199.

178. Hoofnagle JH, Dusheiko GM, Seeff LB, et al. Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. Ann Intern Med 1981; 94: 744-748.

179. Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology 2002; 35: 1522-1527.

180. Lok AS, Lai CL, Wu PC, et al. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. Gastroenterology 1987; 92: 1839-1843.

181. Chan HL, Wong GL, Tse CH, et al. Viral determinants of hepatitis B surface antigen seroclearance in hepatitis B e antigen-negative chronic hepatitis B patients. J Infect Dis 2011; 204: 408-414.

182. Chen YC, Jeng WJ, Chu CM, Liaw YF. Decreasing levels of HBsAg predict HBsAg seroclearance in patients with inactive chronic hepatitis B virus infection. Clin Gastroenterol Hepatol 2012; 10: 297-302.

183. Hadziyannis SJ, Papatheodoridis GV. Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. Semin Liver Dis 2006; 26: 130-141.

184. Zarski JP, Marcellin P, Leroy V, et al. Characteristics of patients with chronic hepatitis B in France: predominant frequency of HBe antigen negative cases. J Hepatol 2006; 45: 355-360.

185. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology 2001; 34: 617-624.

186. Funk ML, Rosenberg DM, Lok AS. World-wide epidemiology of HBeAg-negative chronic hepatitis B and associated precore and core promoter variants. J Viral Hepat 2002; 9: 52-61.

187. Chu CM, Liaw YF. Spontaneous relapse of hepatitis in inactive HBsAg carriers. Hepatol Int 2007; 1: 311-315.

188. Torbenson M, Thomas DL. Occult hepatitis B. Lancet Infect Dis 2002; 2: 479-486.

189. Abu El Makarem MA, Abdel Hamid M, Abdel Aleem A, et al. Prevalence of occult hepatitis B virus infection in hemodialysis patients from egypt with or without hepatitis C virus infection. Hepat Mon 2012; 12: 253-258.

190. Makvandi M. Update on occult hepatitis B virus infection. World J Gastroenterol 2016; 22: 8720-8734.

191. Kiely P, Margaritis AR, Seed CR, et al. Hepatitis B virus nucleic acid amplification testing of Australian blood donors highlights the complexity of confirming occult hepatitis B virus infection. Transfusion 2014; 54: 2084-2091.

192. Liu F, Wang XW, Chen L, et al. Systematic review with meta-analysis: development of hepatocellular carcinoma in chronic hepatitis B patients with hepatitis B surface antigen seroclearance. Aliment Pharmacol Ther 2016; 43: 1253-1261.

193. Zhou K, Contag C, Whitaker E, Terrault N. Spontaneous loss of surface antigen among adults living with chronic hepatitis B virus infection: a systematic review and pooled meta-analyses. Lancet Gastroenterol Hepatol 2019; 4: 227-238.

194. Yip TC, Chan HL, Wong VW, et al. Impact of age and gender on risk of hepatocellular carcinoma after hepatitis B surface antigen seroclearance. J Hepatol 2017; 67: 902-908.

195. Simonetti J, Bulkow L, McMahon BJ, et al. Clearance of hepatitis B surface antigen and risk of hepatocellular carcinoma in a cohort chronically infected with hepatitis B virus. Hepatology 2010; 51: 1531-1537.

196. Yeo W, Chan PK, Zhong S, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol 2000; 62: 299-307.

197. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009; 27: 605-611.

198. Lubel JS, Angus PW. Hepatitis B reactivation in patients receiving cytotoxic chemotherapy: diagnosis and management. J Gastroenterol Hepatol 2010; 25: 864-871.

199. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. Gastroenterology 2017; 152: 1297-1309.

200. Hall SAL, Shaikh A, Teh K, et al. Hepatitis B screening before rituximab therapy: a multicentre South Australian study of adherence. Intern Med J 2018; 48: 936-943.

201. Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis. Hepatology 2017; 66: 13-26.

202. De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. J Clin Virol 2016; 78: 27-30.

203. Holmes JA, Yu ML, Chung RT. Hepatitis B reactivation during or after direct acting antiviral therapy – implication for susceptible individuals. Expert Opin Drug Saf 2017; 16: 651-672.

204. Yeh ML, Huang CF, Huang CI, et al. Hepatitis B-related outcomes following direct-acting antiviral therapy in Taiwanese patients with chronic HBV/HCV co-infection. J Hepatol 2020; 73: 62-71.

205. Yuen MF, Yuan HJ, Hui CK, et al. A large population study of spontaneous HBeAg seroconversion and acute exacerbation of chronic hepatitis B infection: implications for antiviral therapy. Gut 2003; 52: 416-419.

206. Kumar M, Jain S, Sharma BC, Sarin SK. Differentiating acute hepatitis B from the first episode of symptomatic exacerbation of chronic hepatitis B. Dig Dis Sci 2006; 51: 594-599.

207. Papatheodoridis GV, Manolakopoulos S, Liaw YF, Lok A. Follow-up and indications for liver biopsy in HBeAg-negative chronic hepatitis B virus infection with persistently normal ALT: a systematic review. J Hepatol 2012; 57: 196-202.

208. Choi GH, Kim GA, Choi J, et al. 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: 215-226.

209. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008; 48: 335-352.

210. Raffetti E, Fattovich G, Donato F. Incidence of hepatocellular carcinoma in untreated subjects with chronic hepatitis B: a systematic review and meta-analysis. Liver Int 2016; 36: 1239-1251.

211. Papatheodoridis GV, Chan HL, Hansen BE, et al. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol 2015; 62: 956-967.

212. Voulgaris T, Papatheodoridi M, Lampertico P, Papatheodoridis GV. Clinical utility of hepatocellular carcinoma risk scores in chronic hepatitis B. Liver Int 2020; 40: 484-495.

213. Brouwer WP, van der Meer AJP, Boonstra A, et al. Prediction of long-term clinical outcome in a diverse chronic hepatitis B population: role of the PAGE-B score. J Viral Hepat 2017; 24: 1023-1031.

214. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016; 64: 800-806.

215. Chen CJ, Yang HI, Iloeje UH, REVEAL-HBV Study Group. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology 2009; 49 (5 Suppl): S72-S84.

216. Chen CJ, Iloeje UH, Yang HI. Long-term outcomes in hepatitis B: the REVEAL-HBV study. Clin Liver Dis 2007; 11: 797-816, viii.

217. Iloeje UH, Yang HI, Jen CL, et al. Risk and predictors of mortality associated with chronic hepatitis B infection. Clin Gastroenterol Hepatol 2007; 5: 921-931.

218. Carey I, D'Antiga L, Bansal S, et al. Immune and viral profile from tolerance to hepatitis B surface antigen clearance: a longitudinal study of vertically hepatitis B virus-infected children on combined therapy. J Virol 2011; 85: 2416-2428.

219. Lee HA, Lee HW, Kim IH, et al. Extremely low risk of hepatocellular carcinoma development in patients with chronic hepatitis B in immune-tolerant phase. Aliment Pharmacol Ther 2020; 52: 196-204.

220. Kim GA, Han S, Choi GH, et al. 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: 1169-1179.

221. Kim GA, Lim YS, Han S, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. Gut 2018; 67: 945-952.

222. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. Gastroenterology 2009; 136: 477-485.e11.

223. Fattovich G, Brollo L, Giustina G, et al. Natural history and prognostic factors for chronic hepatitis type B. Gut 1991; 32: 294-298.

224. Sumi H, Yokosuka O, Seki N, et al. Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease. Hepatology 2003; 37: 19-26.

225. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. Lancet 1981; 2: 1129-1133.

226. Dickinson JA, Wun YT, Wong SL. Modelling death rates for carriers of hepatitis B. Epidemiol Infect 2002; 128: 83-92.

227. Chu CM, Liaw YF. Chronic hepatitis B virus infection acquired in childhood: special emphasis on prognostic and therapeutic implication of delayed HBeAg seroconversion. J Viral Hepat 2007; 14: 147-152.

228. Chu CM, Liaw YF. Predictive factors for reactivation of hepatitis B following hepatitis B e antigen seroconversion in chronic hepatitis B. Gastroenterology 2007; 133: 1458-1465.

229. Park BK, Park YN, Ahn SH, et al. Long-term outcome of chronic hepatitis B based on histological grade and stage. J Gastroenterol Hepatol 2007; 22: 383-388.

230. Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol 1998; 28: 930-938.

231. Fattovich G, Pantalena M, Zagni I, et al. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. Am J Gastroenterol 2002; 97: 2886-2895.

232. Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. Gastroenterology 2012; 142: 1140-1149.e3.

233. Yu MW, Hsu FC, Sheen IS, et al. Prospective study of hepatocellular carcinoma and liver cirrhosis in asymptomatic chronic hepatitis B virus carriers. Am J Epidemiol 1997; 145: 1039-1047.

234. Huo T, Wu JC, Hwang SJ, et al. Factors predictive of liver cirrhosis in patients with chronic hepatitis B: a multivariate analysis in a longitudinal study. Eur J Gastroenterol Hepatol 2000; 12: 687-693.

235. Brunetto MR, Oliveri F, Coco B, et al. Outcome of anti-HBe positive chronic hepatitis B in alpha-interferon treated and untreated patients: a long term cohort study. J Hepatol 2002; 36: 263-270.

236. Fattovich G, Olivari N, Pasino M, et al. Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years. Gut 2008; 57: 84-90.

237. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004; 127 (5 Suppl 1): S35-S50.

238. Ganesan M, Eikenberry A, Poluektova LY, et al. Role of alcohol in pathogenesis of hepatitis B virus infection. World J Gastroenterol 2020; 26: 883-903.

239. Larkin J, Clayton MM, Liu J, Feitelson MA. Chronic ethanol consumption stimulates hepatitis B virus gene expression and replication in transgenic mice. Hepatology 2001; 34: 792-797.

240. Iida-Ueno A, Enomoto M, Tamori A, Kawada N. Hepatitis B virus infection and alcohol consumption. World J Gastroenterol 2017; 23: 2651-2659.

241. Marcellin P, Pequignot F, Delarocque-Astagneau E, et al. Mortality related to chronic hepatitis B and chronic hepatitis C in France: evidence for the role of HIV coinfection and alcohol consumption. J Hepatol 2008; 48: 200-207.

242. Donato F, Tagger A, Gelatti U, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 2002; 155: 323-331.

243. Ribes J, Cleries R, Rubio A, et al. Cofactors associated with liver disease mortality in an HBsAg-positive Mediterranean cohort: 20 years of follow-up. Int J Cancer 2006; 119: 687-694.

244. Wong GL, Chan HL, Yu Z, et al. Coincidental metabolic syndrome increases the risk of liver fibrosis progression in patients with chronic hepatitis B—a prospective cohort study with paired transient elastography examinations. Aliment Pharmacol Ther 2014; 39: 883-893.

245. Chan AW, Wong GL, Chan HY, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol 2017; 32: 667-676.

246. Williams JH, Phillips TD, Jolly PE, et al. Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences, and interventions. Am J Clin Nutr 2004; 80: 1106-1122.

247. Strosnider H, Azziz-Baumgartner E, Banziger M, et al. Workgroup report: public health strategies for reducing aflatoxin exposure in developing countries. Environ Health Perspect 2006; 114: 1898-1903.

248. Ross RK, Yuan JM, Yu MC, et al. Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. Lancet 1992; 339: 943-946.

249. Omer RE, Kuijsten A, Kadaru AM, et al. Population-attributable risk of dietary aflatoxins and hepatitis B virus infection with respect to hepatocellular carcinoma. Nutr Cancer 2004; 48: 15-21.

250. Kirk GD, Lesi OA, Mendy M, et al. 249^{ser} TP53 mutation in plasma DNA, hepatitis B viral infection, and risk of hepatocellular carcinoma. Oncogene 2005; 24: 5858-5867.

251. Chen CJ, Wang LY, Lu SN, et al. Elevated aflatoxin exposure and increased risk of hepatocellular carcinoma. Hepatology 1996; 24: 38-42.

252. Cai P, Zheng H, She J, et al. Molecular mechanism of aflatoxin-induced hepatocellular carcinoma derived from a bioinformatics analysis. Toxins (Basel) 2020; 12: 203.

253. Cullen JM, Brown DL, Kissling GE, et al. Aflatoxin B1 and/or hepatitis B virus induced tumor spectrum in a genetically engineered hepatitis B virus expression and Trp53 haploinsufficient mouse model system for hepatocarcinogenesis. Toxicol Pathol 2009; 37: 333-342.

254. Banerjee R, Caruccio L, Zhang YJ, et al. Effects of carcinogen-induced transcription factors on the activation of hepatitis B

virus expression in human hepatoblastoma HepG2 cells and its implication on hepatocellular carcinomas. Hepatology 2000; 32: 367-374.

255. Wild CP, Gong YY. Mycotoxins and human disease: a largely ignored global health issue. Carcinogenesis 2010; 31: 71-82.

256. IARC Working Group. IARC monographs on the evaluation of carcinogenic risks to humans: Volume 83 Tobacco smoke and involuntary smoking. Lyon: International Agency for Research on Cancer, 2004.

257. Abdel-Rahman O, Helbling D, Schob O, et al. Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma: an updated systematic review of 81 epidemiological studies. J Evid Based Med 2017; 10: 245-254.

258. Marrero JA, Fontana RJ, Fu S, et al. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol 2005; 42: 218-224.

259. Anthony PP. Hepatocellular carcinoma: an overview. Histopathology 2001; 39: 109-118.

260. Jee SH, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. J Natl Cancer Inst 2004; 96: 1851-1856.

261. Wang YH, Chuang YH, Wu CF, et al. Smoking and hepatitis B virus-related hepatocellular carcinoma risk: the mediating roles of viral load and alanine aminotransferase. Hepatology 2019; 69: 1412-1425.

262. Shimizu I. Impact of oestrogens on the progression of liver disease. Liver Int 2003; 23: 63-69.

263. Stroffolini T, Esvan R, Biliotti E, et al. Gender differences in chronic HBsAg carriers in Italy: evidence for the independent role of male sex in severity of liver disease. J Med Virol 2015; 87: 1899-1903.

264. Wang SH, Chen PJ, Yeh SH. Gender disparity in chronic hepatitis B: mechanisms of sex hormones. J Gastroenterol Hepatol 2015; 30: 1237-1245.

265. Yu MW, Chang HC, Liaw YF, et al. Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. J Natl Cancer Inst 2000; 92: 1159-1164.

266. Lok AS, Lai CL. Factors determining the development of hepatocellular carcinoma in hepatitis B surface antigen carriers. A comparison between families with clusters and solitary cases. Cancer 1988; 61: 1287-1291.

267. Turati F, Edefonti V, Talamini R, et al. Family history of liver cancer and hepatocellular carcinoma. Hepatology 2012; 55: 1416-1425.

268. Loomba R, Liu J, Yang HI, et al. Synergistic effects of family history of hepatocellular carcinoma and hepatitis B virus infection on risk for incident hepatocellular carcinoma. Clin Gastroenterol Hepatol 2013; 11: 1636-1645.e1-3.

269. Crespo J, Lozano JL, de la Cruz F, et al. Prevalence and significance of hepatitis C viremia in chronic active hepatitis B. Am J Gastroenterol 1994; 89: 1147-1151.

270. Fattovich G, Tagger A, Brollo L, et al. Hepatitis C virus infection in chronic hepatitis B virus carriers. J Infect Dis 1991; 163: 400-402.

271. Fong TL, Di Bisceglie AM, Waggoner JG, et al. The significance of antibody to hepatitis C virus in patients with chronic hepatitis B. Hepatology 1991; 14: 64-67.

272. Liaw YF, Chen YC, Sheen IS, et al. Impact of acute hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. Gastroenterology 2004; 126: 1024-1029.

273. Marot A, Belaid A, Orlent H, et al. Characteristics of patients with hepatitis B virus and hepatitis C virus dual infection in a Western European country: comparison with monoinfected patients. Clin Res Hepatol Gastroenterol 2017; 41: 656-663.

274. Mavilia MG, Wu GY. HBV–HCV coinfection: viral interactions, management, and viral reactivation. J Clin Transl Hepatol 2018; 6: 296-305.

275. Villari D, Pernice M, Spinella S, et al. Chronic hepatitis in patients with active hepatitis B virus and hepatitis C virus combined infections: a histological study. Am J Gastroenterol 1995; 90: 955-958.

276. Miao Z, Zhang S, Ou X, et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis delta virus infection. J Infect Dis 2020; 221: 1677-1687.

277. Singh KP, Crane M, Audsley J, et al. HIV-hepatitis B virus coinfection: epidemiology, pathogenesis, and treatment. AIDS 2017; 31: 2035-2052.

278. Thio CL, Seaberg EC, Skolasky Jr R, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002; 360: 1921-1926.

279. Liu CJ, Kao JH, Chen DS. Therapeutic implications of hepatitis B virus genotypes. Liver Int 2005; 25: 1097-1107.

280. Cao GW. Clinical relevance and public health significance of hepatitis B virus genomic variations. World J Gastroenterol 2009; 15: 5761-5769.

281. Yang HI, Yeh SH, Chen PJ, et al. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. J Natl Cancer Inst 2008; 100: 1134-1143.

282. McMahon BJ, Alberts SR, Wainwright RB, et al. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. Arch Intern Med 1990; 150: 1051-1054.

283. Chu CM, Lin CC, Lin SM, et al. Viral load, genotypes, and mutants in hepatitis B virus-related hepatocellular carcinoma: special emphasis on patients with early hepatocellular carcinoma. Dig Dis Sci 2012; 57: 232-238.

284. Watanabe K, Takahashi T, Takahashi S, et al. Comparative study of genotype B and C hepatitis B virus-induced chronic hepatitis in relation to the basic core promoter and precore mutations. J Gastroenterol Hepatol 2005; 20: 441-449.

285. Liu CJ, Kao JH. Genetic variability of hepatitis B virus and response to antiviral therapy. Antivir Ther 2008; 13: 613-624.

286. Davies J, Littlejohn M, Locarnini SA, et al. Molecular epidemiology of hepatitis B in the Indigenous people of northern Australia. J Gastroenterol Hepatol 2013; 28: 1234-1241.

287. Davies J, Smith EL, Littlejohn M, et al. Towards genotype-specific care for chronic hepatitis B: the first 6 years follow up from the CHARM cohort study. Open Forum Infect Dis 2019; 6: ofz469.

288. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-1273.e1.

289. Likhitsup A, Lok AS. Understanding the natural history of hepatitis B virus infection and the new definitions of cure and the endpoints of clinical trials. Clin Liver Dis 2019; 23: 401-416.

290. Chen CH, Lu SN, Lee CM, et al. Patients with interferon-induced HBeAg seroconversion have a higher risk of HBV reactivation and HBeAg seroreversion. Hepatol Int 2014; 8: 365-374.

291. Xing T, Xu H, Cao L, Ye M. HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients receiving long-term nucleos(t)ide analog treatment: a systematic review and network meta-analysis. PLoS One 2017; 12: e0169444.

292. Block TM, Gish R, Guo H, et al. Chronic hepatitis B: what should be the goal for new therapies? Antiviral Res 2013; 98: 27-34.

293. Yuen MF, Wong DK, Fung J, et al. HBsAg seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. Gastroenterology 2008; 135: 1192-1199.

294. Yeo YH, Ho HJ, Yang HI, et al. Factors associated with rates of HBsAg seroclearance in adults with chronic HBV infection: a systematic review and meta-analysis. Gastroenterology 2019; 156: 635-646.e9.

295. Hepatitis B Virus (HBV) Testing Policy Expert Reference Committee. National hepatitis B testing policy. Sydney: Australasian Society for HIV Medicine, Viral Hepatitis and Sexual Health Medicine, 2021. http://testingportal.ashm.org.au/national-hbv-testing-policy/ (accessed 17 Nov 2021).

296. Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009; 373: 582-592.

297. Mantzoukis K, Rodriguez-Peralvarez M, Buzzetti E, et al. Pharmacological interventions for acute hepatitis B infection: an attempted network meta-analysis. Cochrane Database Syst Rev 2017; (3): CD011645.

298. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: WHO, 2015. https://www.who.int/publications/i/item/9789241549059 (accessed 1 Sep 2017).

299. Tran S, Bennett G, Richmond J, et al. 'Teach-back' is a simple communication tool that improves disease knowledge in people with chronic hepatitis B – a pilot randomized controlled study. BMC Public Health 2019; 19: 1355.

300. Richmond J, Smith E, Wallace J, et al. Hepatitis B testing and diagnosis experiences of patients and primary care professionals in Australia. Aust Fam Physician 2017; 46: 513-519.

301. Allard N, Emery J, Cowie B, Furler J. Knowing and telling: how African-Australians living with chronic hepatitis B understand hepatocellular carcinoma risk and surveillance. Aust J Prim Health 2018; 24: 141-148.

302. Riches L, Cowie B, Nanver Z, Thomas L. Hepatitis B and immigration. Sydney: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, 2020. https://www.ashm.org.au/resources/HBV-Resources-list/hepatitis-b-and-immigration/ (accessed 28 Apr 2020).

303. Australian Government Department of Home Affairs. Meeting our health requirement. Canberra: Australian Government, 2021. https://immi.homeaffairs.gov.au/help-support/meeting-our-requirements/health (accessed 4 Feb 2021).

304. Wallace J, McNally S, Richmond J. National hepatitis B needs assessment. Melbourne: Australian Research Centre in Sex, Health and Society, La Trobe University, 2007.

305. Wallace J, McNally S, Richmond J, et al. Challenges to the effective delivery of health care to people with chronic hepatitis B in Australia. Sex Health 2012; 9: 131-137.

306. Smith-Palmer J, Cerri K, Sbarigia U, et al. Impact of stigma on people living with chronic hepatitis B. Patient Relat Outcome Meas 2020; 11: 95-107.

307. Australian Technical Advisory Group on Immunisation (ATAGI). Australian immunisation handbook. Canberra: Australian Government Department of Health, 2018. https://immunisationhandbook.health.gov.au/ (accessed 17 Nov 2021).

308. Wu TW, Lin HH, Wang LY. Chronic hepatitis B infection in adolescents who received primary infantile vaccination. Hepatology 2013; 57: 37-45.

309. Liaw YF. Clinical utility of HBV surface antigen quantification in HBV e antigen-negative chronic HBV infection. Nat Rev Gastroenterol Hepatol 2019; 16: 631-641.

310. Matthews GV, Ali RJ, Avihingsanon A, et al. Quantitative HBsAg and HBeAg predict hepatitis B seroconversion after initiation of HAART in HIV-HBV coinfected individuals. PLoS One 2013; 8: e61297.

311. Cornberg M, Wong VW, Locarnini S, et al. The role of quantitative hepatitis B surface antigen revisited. J Hepatol 2017; 66: 398-411.

312. Hyun CS, Lee S, Ventura WR. The prevalence and significance of isolated hepatitis B core antibody (anti-HBc) in endemic population. BMC Res Notes 2019; 12: 251.

313. Ural O, Findik D. The response of isolated anti-HBc positive subjects to recombinant hepatitis B vaccine. J Infect 2001; 43: 187-190.

314. McMahon BJ, Parkinson AJ, Helminiak C, et al. Response to hepatitis B vaccine of persons positive for antibody to hepatitis B core antigen. Gastroenterology 1992; 103: 590-594.

315. Raimondo G, Locarnini S, Pollicino T, et al. Update of the statements on biology and clinical impact of occult hepatitis B virus infection. J Hepatol 2019; 71: 397-408.

316. Kemp W, Levy M, Weltman M, et al. Australian Liver Association (ALA) expert consensus recommendations for the use of transient elastography in chronic viral hepatitis. J Gastroenterol Hepatol 2015; 30: 453-462.

317. Parikh P, Ryan JD, Tsochatzis EA. Fibrosis assessment in patients with chronic hepatitis B virus (HBV) infection. Ann Transl Med 2017; 5: 40.

318. Boursier J, Konate A, Guilluy M, et al. Learning curve and interobserver reproducibility evaluation of liver stiffness measurement by transient elastography. Eur J Gastroenterol Hepatol 2008; 20: 693-701.

319. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 2019; 156: 1264-1281.e4.

320. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015; 63: 237-264.

321. Chan HL, Wong GL, Choi PC, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009; 16: 36-44.

322. Zhang D, Chen M, Wang R, et al. Comparison of acoustic radiation force impulse imaging and transient elastography for non-invasive assessment of liver fibrosis in patients with chronic hepatitis B. Ultrasound Med Biol 2015; 41: 7-14.

323. Kim YW, Kwon JH, Jang JW, et al. Diagnostic usefulness of real-time elastography for liver fibrosis in chronic viral hepatitis B and C. Gastroenterol Res Pract 2014; 2014: 210407.

324. Lee JE, Lee JM, Lee KB, et al. Noninvasive assessment of hepatic fibrosis in patients with chronic hepatitis B viral infection using magnetic resonance elastography. Korean J Radiol 2014; 15: 210-217.

325. Shi Y, Xia F, Li QJ, et al. Magnetic resonance elastography for the evaluation of liver fibrosis in chronic hepatitis B and C by using both gradient-recalled echo and spin-echo echo planar imaging: a prospective study. Am J Gastroenterol 2016; 111: 823-833.

326. Valva P, Rios DA, De Matteo E, Preciado MV. Chronic hepatitis C virus infection: serum biomarkers in predicting liver damage. World J Gastroenterol 2016; 22: 1367-1381.

327. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006; 43: 1317-1325.

328. Kim BK, Kim DY, Park JY, et al. Validation of FIB-4 and comparison with other simple noninvasive indices for predicting liver fibrosis and cirrhosis in hepatitis B virus-infected patients. Liver Int 2010; 30: 546-553.

329. Kim WR, Berg T, Asselah T, et al. Evaluation of APRI and FIB-4 scoring systems for non-invasive assessment of hepatic fibrosis in chronic hepatitis B patients. J Hepatol 2016; 64: 773-780.

330. Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology 2015; 61: 292-302.

331. Huang Y, Adams LA, Joseph J, et al. The ability of Hepascore to predict liver fibrosis in chronic liver disease: a meta-analysis. Liver Int 2017; 37: 121-131.

332. Trembling PM, Lampertico P, Parkes J, et al. Performance of Enhanced Liver Fibrosis test and comparison with transient elastography in the identification of liver fibrosis in patients with chronic hepatitis B infection. J Viral Hepat 2014; 21: 430-438.

333. Salkic NN, Jovanovic P, Hauser G, Brcic M. FibroTest/Fibrosure for significant liver fibrosis and cirrhosis in chronic hepatitis B: a meta-analysis. Am J Gastroenterol 2014; 109: 796-809.

334. Li Y, Cai Q, Zhang Y, et al. Development of algorithms based on serum markers and transient elastography for detecting significant fibrosis and cirrhosis in chronic hepatitis B patients: significant reduction in liver biopsy. Hepatol Res 2016; 46: 1367-1379.

335. Liang XE, Zhong C, Huang L, et al. Optimization of hepatitis B cirrhosis detection by stepwise application of transient elastography and routine biomarkers. J Gastroenterol Hepatol 2017; 32: 459-465.

336. Lee JM, Seo YS, Kim TH, et al. The LAW index as an accurate indicator of the initiation of antiviral treatment in patients with chronic hepatitis B. J Gastroenterol Hepatol 2017; 32: 208-214.

337. Trepo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet 2014; 384: 2053-2063.

338. Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. Melbourne: RACGP, 2016. https://www.racgp.org.au/download/Documents/Guidelines/Redbook9/17048-Red-Book-9th-Edition.pdf (accessed 17 Nov 2021).

339. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. Melbourne: Gastroenterological Society of Australia, 2020. https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/ (accessed 17 Nov 2021).

340. Allard N, Cabrie T, Wheeler E, et al. The challenge of liver cancer surveillance in general practice: Do recall and reminder systems hold the answer? Aust Fam Physician 2017; 46: 859-864.

341. Singal AG, Yopp A, Skinner CS, et al. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. J Gen Intern Med 2012; 27: 861-867.

342. Kennedy NA, Rodgers A, Altus R, et al. Optimisation of hepatocellular carcinoma surveillance in patients with viral hepatitis: a quality improvement study. Intern Med J 2013; 43: 772-777.

343. Goldberg DS, Valderrama A, Kamalakar R, et al. Hepatocellular carcinoma surveillance rates in commercially insured patients with noncirrhotic chronic hepatitis B. J Viral Hepat 2015; 22: 727-736.

344. Allard NL, MacLachlan JH, Cowie BC. The cascade of care for Australians living with chronic hepatitis B: measuring access to diagnosis, management and treatment. Aust N Z J Public Health 2015; 39: 255-259.

345. Singal AG, Li X, Tiro J, et al. Racial, social, and clinical determinants of hepatocellular carcinoma surveillance. Am J Med 2015; 128: 90.e1-7.

346. Goebel M, Singal AG, Nodora J, et al. How can we boost colorectal and hepatocellular cancer screening among underserved populations? Curr Gastroenterol Rep 2015; 17: 22.

347. Farvardin S, Patel J, Khambaty M, et al. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. Hepatology 2017; 65: 875-884.

348. Allard N, Dev A, Dwyer J, et al. Factors associated with poor adherence to antiviral treatment for hepatitis B. J Viral Hepat 2017; 24: 53-58.

349. Yang HI, Sherman M, Su J, et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Clin Oncol 2010; 28: 2437-2444.

350. Wong VW, Chan SL, Mo F, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. J Clin Oncol 2010; 28: 1660-1665.

351. Kim GA, Lee HC, Kim MJ, et al. Incidence of hepatocellular carcinoma after HBsAg seroclearance in chronic hepatitis B patients: a need for surveillance. J Hepatol 2015; 62: 1092-1099.

352. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic hepatitis B infection: a review. JAMA 2018; 319: 1802-1813.

353. Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. J Hepatol 2017; 67: 847-861.

354. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352: 2682-2695.

355. Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004; 351: 1206-1217.

356. Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet 2005; 365: 123-129.

357. Chang TT, Lai CL, Kew Yoon S, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. Hepatology 2010; 51: 422-430.

358. Wong RJ, Nguyen MT, Trinh HN, et al. Hepatitis B surface antigen loss and sustained viral suppression in Asian chronic hepatitis B patients: a community-based real-world study. J Viral Hepat 2017; 24: 1089-1097.

359. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci 2015; 60: 1457-1464.

360. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? J Virus Erad 2018; 4: 72-79.

361. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1: 185-195.

362. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1: 196-206.

363. Sriprayoon T, Mahidol C, Ungtrakul T, et al. Efficacy and safety of entecavir versus tenofovir treatment in chronic hepatitis B patients: a randomized controlled trial. Hepatol Res 2017; 47: E161-E168.

364. Koike K, Suyama K, Ito H, et al. Randomized prospective study showing the non-inferiority of tenofovir to entecavir

in treatment-naive chronic hepatitis B patients. Hepatol Res 2018; 48: 59-68.

365. Marcellin P, Gane E, Buti M, 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: 468-475.

366. Wong GL, Chan HL, Mak CW, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. Hepatology 2013; 58: 1537-1547.

367. Wu CY, Lin JT, Ho HJ, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. Gastroenterology 2014; 147: 143-151.e5.

368. Liu K, Choi J, Le A, et al. Tenofovir disoproxil fumarate reduces hepatocellular carcinoma, decompensation and death in chronic hepatitis B patients with cirrhosis. Aliment Pharmacol Ther 2019; 50: 1037-1048.

369. Lok AS, McMahon BJ, Brown Jr RS, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. Hepatology 2016; 63: 284-306.

370. Li M, Lv T, Wu S, et al. Tenofovir versus entecavir in lowering the risk of hepatocellular carcinoma development in patients with chronic hepatitis B: a critical systematic review and meta-analysis. Hepatol Int 2020; 14: 105-114.

371. Yip TC, Wong VW, Chan HL, et al. Tenofovir is associated with lower risk of hepatocellular carcinoma than entecavir in patients with chronic HBV infection in China. Gastroenterology 2020; 158: 215-225.e6.

372. Choi J, Kim HJ, Lee J, et al. Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: a Korean nationwide cohort study. JAMA Oncol 2019; 5: 30-36.

373. Hsu YC, Wong GL, Chen CH, et al. Tenofovir versus entecavir for hepatocellular carcinoma prevention in an international consortium of chronic hepatitis B. Am J Gastroenterol 2020; 115: 271-280.

374. Tseng CH, Hsu YC, Chen TH, et al. Hepatocellular carcinoma incidence with tenofovir versus entecavir in chronic hepatitis B: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020; 5: 1039-1052.

375. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. Hepatology 2009; 49: 1503-1514.

376. Lee S, Kim E, Moon SJ, et al. Comparative pharmacokinetics between tenofovir disoproxil phosphate and tenofovir disoproxil fumarate in healthy subjects. Transl Clin Pharmacol 2021; 29: 45-52.

377. Gracey DM, Snelling P, McKenzie P, Strasser SI. Tenofovir-associated Fanconi syndrome in patients with chronic hepatitis B monoinfection. Antivir Ther 2013; 18: 945-948.

378. Lampertico P, Chan HL, Janssen HL, et al. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. Aliment Pharmacol Ther 2016; 44: 16-34.

379. Wong GL, Tse YK, Wong VW, et al. Long-term safety of oral nucleos(t)ide analogs for patients with chronic hepatitis B: a cohort study of 53,500 subjects. Hepatology 2015; 62: 684-693.

380. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008; 359: 2442-2455.

381. Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006; 354: 1011-1020.

382. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006; 354: 1001-1010.

383. Liang X, Gao Z, Xie Q, et al. Long-term efficacy and safety of tenofovir disoproxil fumarate in Chinese patients with chronic hepatitis B: 5-year results. Hepatol Int 2019; 13: 260-269.

384. Lee KS, Kweon YO, Um SH, et al. Efficacy and safety of entecavir versus lamivudine over 5 years of treatment: a randomized controlled trial in Korean patients with hepatitis B e antigen-negative chronic hepatitis B. Clin Mol Hepatol 2017; 23: 331-339.

385. Chen YC, Liaw YF. Pharmacotherapeutic options for hepatitis B. Expert Opin Pharmacother 2016; 17: 355-367.

386. Wong GL, Wong VW, Choi PC, et al. Clinical factors associated with liver stiffness in hepatitis B e antigen-positive chronic hepatitis B patients. Clin Gastroenterol Hepatol 2009; 7: 227-233.

387. Zhou K, Terrault N. Immune tolerant HBV and HCC: time to revise our tolerance levels for therapy? AME Med J 2018; 3: 27.

388. Sharma SA, Kowgier M, Hansen BE, et al. Toronto HCC risk index: a validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. J Hepatol 2017; 68: 92-99.

389. Riveiro-Barciela M, Tabernero D, Calleja JL, et al. Effectiveness and safety of entecavir or tenofovir in a Spanish cohort of chronic hepatitis B patients: validation of the Page-B score to predict hepatocellular carcinoma. Dig Dis Sci 2017; 62: 784-793.

390. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011; 12: 568-574.

391. Chu CM, Liaw YF. Prognosis of immune-tolerant phase chronic hepatitis B. Gut 2018; 67: 988.

392. Suk-Fong Lok A. Hepatitis B treatment: what we know now and what remains to be researched. Hepatol Commun 2019; 3: 8-19.

393. Papatheodoridis G, Vlachogiannakos I, Cholongitas E, et al. Discontinuation of oral antivirals in chronic hepatitis B: a systematic review. Hepatology 2016; 63: 1481-1492.

394. Papatheodoridi M, Papatheodoridis G. Can we stop nucleoside analogues before HBsAg loss? J Viral Hepat 2019; 26: 936-941.

395. Wallace J, Pitts M, McNally S, et al. A situational analysis of chronic hepatitis B in the Torres Strait: we nab them and then we let them go, just like fish. Melbourne: La Trobe University, 2011.

396. Davies J, Bukulatjpi S, Sharma S, et al. "Only your blood can tell the story" – a qualitative research study using semi-structured interviews to explore the hepatitis B related knowledge, perceptions and experiences of remote dwelling Indigenous Australians and their health care providers in northern Australia. BMC Public Health 2014; 14: 1233.

397. Hajarizadeh B, Wallace J, Richmond J, et al. Hepatitis B knowledge and associated factors among people with chronic hepatitis B. Aust N Z J Public Health 2015; 39: 563-568.

398. Wallace J, McNally S, Richmond J, et al. Managing chronic hepatitis B: a qualitative study exploring the perspectives of people living with chronic hepatitis B in Australia. BMC Res Notes 2011; 4: 45.

399. Dahl TF, Cowie BC, Biggs BA, et al. Health literacy in patients with chronic hepatitis B attending a tertiary hospital in Melbourne: a questionnaire based survey. BMC Infect Dis 2014; 14: 537.

400. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization, 2003. https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf (accessed 17 Nov 2021).

401. Australian Institute of Health and Welfare. Contribution of chronic disease to the gap in adult mortality between Aboriginal and Torres Strait Islander and other Australians. Canberra: AIHW, 2011. https://www.aihw.gov.au/reports/indigenous-australians/contribution-of-chronic-disease-to-the-gap-in-mort/ (accessed 17 Nov 2021).

402. de Dassel JL, Ralph AP, Cass A. A systematic review of adherence in Indigenous Australians: an opportunity to improve chronic condition management. BMC Health Serv Res 2017; 17: 845.

403. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine. Hepatitis B s100 Prescriber Program: a guide for general practitioners, other community-based medical practitioners and nurse practitioners. Sydney: ASHM, 2020. https://www.ashm.org.au/HBV/prescriber-programs/ (accessed 17 Nov 2021).

404. Iser D, Lawler J. Clinical assessment of patients with hepatitis B virus infection. In: Allard N, Matthews G, eds. B Positive. All you wanted to know about hepatitis B: a guide for primary care providers. Sydney: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, 2018.

405. Mohsen W, Chan P, Whelan M. Hepatitis C treatment for difficult to access populations: can telementoring (as distinct from telemedicine) help? Intern Med J 2019; 49: 351-357.

406. Pawlotsky JM, Dusheiko G, Hatzakis A, et al. Virologic monitoring of hepatitis B virus therapy in clinical trials and practice: recommendations for a standardized approach. Gastroenterology 2008; 134: 405-415.

407. Chien RN, Kao JH, Peng CY, et al. Taiwan consensus statement on the management of chronic hepatitis B. J Formos Med Assoc 2019; 118: 7-38.

408. van Bommel F, Berg T. Stopping long-term treatment with nucleos(t)ide analogues is a favourable option for selected patients with HBeAg-negative chronic hepatitis B. Liver Int 2018; 38 Suppl 1: 90-96.

409. Moreno-Cubero E, Del Arco RTS, Pena-Asensio J, et al. Is it possible to stop nucleos(t)ide analogue treatment in chronic hepatitis B patients? World J Gastroenterol 2018; 24: 1825-1838.

410. Idilman R. The summarized of EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Turk J Gastroenterol 2017; 28: 412-416.

411. Zhang W, Zhang D, Dou X, et al. Consensus on pegylated interferon alpha in treatment of chronic hepatitis B. J Clin Transl Hepatol 2018; 6: 1-10.

412. Wang YC, Yang SS, Su CW, et al. Predictors of response to pegylated interferon in chronic hepatitis B: a real-world hospital-based analysis. Sci Rep 2016; 6: 29605.

413. Peng H, Wei F, Liu JY, et al. Response-guided therapy of regimens based on PEG-interferon for chronic hepatitis B using on-treatment hepatitis B surface antigen quantification: a meta-analysis. Hepatol Int 2015; 9: 543-557.

414. Pavlovic V, Yang L, Chan HL, et al. Peginterferon alfa-2a (40 kD) stopping rules in chronic hepatitis B: a systematic review and meta-analysis of individual participant data. Antivir Ther 2019; 24: 133-140.

415. Boccaccio V, Russo ML, Carbone M, Bruno S. Treatment discontinuation with peg-interferon: what to consider. Expert Rev Clin Pharmacol 2015; 8: 761-768.

416. Liaw YF, Jia JD, Chan HL, et al. Shorter durations and lower doses of peginterferon alfa-2a are associated with inferior hepatitis B e antigen seroconversion rates in hepatitis B virus genotypes B or C. Hepatology 2011; 54: 1591-1599.

417. Buster EH, Hansen BE, Lau GK, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. Gastroenterology 2009; 137: 2002-2009.

418. Lampertico P, Messinger D, Cornberg M, et al. A genotype-specific baseline score predicts post-treatment response to peginterferon alfa-2a in hepatitis B e antigen-negative chronic hepatitis B. Ann Gastroenterol 2018; 31: 712-721.

419. Lim YS. Management of antiviral resistance in chronic hepatitis B. Gut Liver 2017; 11: 189-195.

420. Dupouey J, Gerolami R, Solas C, Colson P. Hepatitis B virus variant with the a194t substitution within reverse transcriptase before and under adefovir and tenofovir therapy. Clin Res Hepatol Gastroenterol 2012; 36: e26-e28.

421. Dos Santos M, Pacheco SR, Stocker A, et al. Mutations associated with drug resistance and prevalence of vaccine escape mutations in patients with chronic hepatitis B infection. J Med Virol 2017; 89: 1811-1816.

422. Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. Gastroenterology 2009; 137: 1593-1608.e1-2.

423. Zoulim F, Locarnini S. Management of treatment failure in chronic hepatitis B. J Hepatol 2012; 56 Suppl 1: S112-S122.

424. Tacke F, Kroy DC. Treatment for hepatitis B in patients with drug resistance. Ann Transl Med 2016; 4: 334.

425. Schiff ER, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. Hepatology 2003; 38: 1419-1427.

426. Zoulim F, Locarnini S. Optimal management of chronic hepatitis B patients with treatment failure and antiviral drug resistance. Liver Int 2013; 33 Suppl 1: 116-124.

427. Tana MM, Ghany MG. Hepatitis B virus treatment: management of antiviral drug resistance. Clin Liver Dis (Hoboken) 2013; 2: 24-28.

428. Bang KB, Kim HJ. Management of antiviral drug resistance in chronic hepatitis B. World J Gastroenterol 2014; 20: 11641-11649.

429. Zhang Y, Lian JQ, Li Y, et al. Telbivudine plus adefovir therapy for chronic hepatitis B patients with virological breakthrough or genotypic resistance to telbivudine. Eur J Gastroenterol Hepatol 2013; 25: 814-819.

430. Poordad F, Chee GM. Viral resistance in hepatitis B: prevalence and management. Curr Gastroenterol Rep 2010; 12: 62-69.

431. Ismail AM, Sharma OP, Kumar MS, et al. Virological response and antiviral resistance mutations in chronic hepatitis B subjects experiencing entecavir therapy: an Indian subcontinent perspective. Antiviral Res 2013; 98: 209-216.

432. Zhang Q, Han T, Nie CY, et al. Tenofovir rescue regimen following prior suboptimal response to entecavir and adefovir combination therapy in chronic hepatitis B patients exposed to multiple treatment failures. J Med Virol 2015; 87: 1013-1021.

433. Qian F, Zou W, Qin J, Li D. Naturally occurring genotypic drug-resistant mutations of HBV in Huzhou, China: a single-center study. Infect Drug Resist 2017; 10: 507-509.

434. Grossi G, Loglio A, Facchetti F, et al. Tenofovir alafenamide as a rescue therapy in a patient with HBV-cirrhosis with a history of Fanconi syndrome and multidrug resistance. J Hepatol 2017; 68: 195-198.

435. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557-2576.

436. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. J Hepatol 2016; 64 (1 Suppl): S84-S101.

437. Wong VW, Janssen HL. Can we use HCC risk scores to individualize surveillance in chronic hepatitis B infection? J Hepatol 2015; 63: 722-732.

438. Chan HL, Hui AY, Wong ML, et al. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. Gut 2004; 53: 1494-1498.

439. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002; 347: 168-174.

440. Fattovich G, Giustina G, Christensen E, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. Gut 2000; 46: 420-426.

441. European Association for the Study of the Liver. EASL Clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236.

442. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.

443. Omata M, Cheng AL, Kokudo N, et al. Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017; 11: 317-370.

444. Kew MC, Marcus R, Geddes EW. Some characteristics of Mozambican Shangaans with primary hepatocellular cancer. S Afr Med J 1977; 51: 306-309.

445. Kramvis A, Kew MC. Relationship of genotypes of hepatitis B virus to mutations, disease progression and response to antiviral therapy. J Viral Hepat 2005; 12: 456-464.

446. Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236.

447. Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. J Hepatol 2003; 39: 1076-1084.

448. Tzartzeva K, Obi J, Rich NE, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018; 154: 1706-1718.e1.

449. Wong GL, Chan HL, Tse YK, et al. On-treatment alpha-fetoprotein is a specific tumor marker for hepatocellular carcinoma in patients with chronic hepatitis B receiving entecavir. Hepatology 2014; 59: 986-995.

450. Singal A, Volk ML, Waljee A, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in

patients with cirrhosis. Aliment Pharmacol Ther 2009; 30: 37-47.

451. Han KH, Kim DY, Park JY, et al. Survival of hepatocellular carcinoma patients may be improved in surveillance interval not more than 6 months compared with more than 6 months: a 15-year prospective study. J Clin Gastroenterol 2013; 47: 538-544.

452. Trinchet JC, Chaffaut C, Bourcier V, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology 2011; 54: 1987-1997.

453. Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol 2009; 50: 80-88.

454. Wong GL, Chan HL, Wong CK, et al. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. J Hepatol 2014; 60: 339-345.

455. Fan R, Papatheodoridis G, Sun J, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol 2020; 73: 1368-1378.

456. Chen YC, Sheen IS, Chu CM, Liaw YF. Prognosis following spontaneous HBsAg seroclearance in chronic hepatitis B patients with or without concurrent infection. Gastroenterology 2002; 123: 1084-1089.

457. Yip TC, Wong GL, Chan HL, et al. HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. J Hepatol 2019; 70: 361-370.

458. Australian Institute of Health and Welfare. Australia's health 2018. Canberra: AIHW, 2018. https://www.aihw.gov.au/reports/australias-health/australias-health-2018/ (accessed 19 Nov 2021).

459. Chinnaratha MA, Campbell K, Mathias R, et al. Improved survival of hepatocellular carcinoma patients diagnosed with a dedicated screening programme–a propensity score adjusted analysis. J Gastrointest Cancer 2019; 50: 888-893.

460. Qian MY, Yuwei JR, Angus P, et al. Efficacy and cost of a hepatocellular carcinoma screening program at an Australian teaching hospital. J Gastroenterol Hepatol 2010; 25: 951-956.

461. Nazareth S, Leembruggen N, Tuma R, et al. Nurse-led hepatocellular carcinoma surveillance clinic provides an effective method of monitoring patients with cirrhosis. Int J Nurs Pract 2016; 22 Suppl 2: 3-11.

462. Preston-Thomas A, Fagan P, Nakata Y, Anderson E. Chronic hepatitis B––care delivery and patient knowledge in the Torres Strait region of Australia. Aust Fam Physician 2013; 42: 225-231.

463. Guirgis M, Nusair F, Bu YM, et al. Barriers faced by migrants in accessing healthcare for viral hepatitis infection. Intern Med J 2012; 42: 491-496.

464. Wright TL, Mamish D, Combs C, et al. Hepatitis B virus and apparent fulminant non-A, non-B hepatitis. Lancet 1992; 339: 952-955.

465. Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. J Hepatol 2012; 57: 442-450.

466. Singal AK, Fontana RJ. Meta-analysis: oral anti-viral agents in adults with decompensated hepatitis B virus cirrhosis. Aliment Pharmacol Ther 2012; 35: 674-689.

467. Merion RM, Schaubel DE, Dykstra DM, et al. The survival benefit of liver transplantation. Am J Transplant 2005; 5: 307-313.

468. Jang JW, Choi JY, Kim YS, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. Hepatology 2015; 61: 1809-1820.

469. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology 2009; 50: 2001-2006.

470. European Association for the Study of the Liver. EASL Clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018; 69: 406-460.

471. Fontana RJ, Hann HW, Perrillo RP, et al. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. Gastroenterology 2002; 123: 719-727.

472. Garg H, Sarin SK, Kumar M, et al. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. Hepatology 2011; 53: 774-780.

473. Zhao RH, Shi Y, Zhao H, et al. Acute-on-chronic liver failure in chronic hepatitis B: an update. Expert Rev Gastroenterol Hepatol 2018; 12: 341-350.

474. Seto WK, Lai CL, Yuen MF. Acute-on-chronic liver failure in chronic hepatitis B. J Gastroenterol Hepatol 2012; 27: 662-669.

475. Bernal W, Jalan R, Quaglia A, et al. Acute-on-chronic liver failure. Lancet 2015; 386: 1576-1587.

476. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology 2012; 55: 965-967.

477. European Association for the Study of the Liver. EASL Clinical practical guidelines on the management of acute (fulminant) liver failure. J Hepatol 2017; 66: 1047-1081.

478. Dao DY, Hynan LS, Yuan HJ, et al. Two distinct subtypes of hepatitis B virus-related acute liver failure are separable by quantitative serum immunoglobulin M anti-hepatitis B core antibody and hepatitis B virus DNA levels. Hepatology 2012; 55: 676-684.

479. Hey P, Hanrahan TP, Sinclair M, et al. Epidemiology and outcomes of acute liver failure in Australia. World J Hepatol 2019; 11: 586-595.

480. Fink M, Byrne M (ed). ANZLITR 30th annual report. Melbourne: Australia & New Zealand Liver and Intestinal Transplant Registry, 2020. https://www.anzlitr.org/wp-content/uploads/Reports/30thReport.pdf (accessed 5 May 2020).

481. Dao DY, Seremba E, Ajmera V, et al. Use of nucleoside (tide) analogues in patients with hepatitis B-related acute liver failure. Dig Dis Sci 2012; 57: 1349-1357.

482. Miyake Y, Iwasaki Y, Takaki A, et al. Lamivudine treatment improves the prognosis of fulminant hepatitis B. Intern Med 2008; 47: 1293-1299.

483. Hollinger FB, Lau DT. Hepatitis B: the pathway to recovery through treatment. Gastroenterol Clin North Am 2006; 35: 425-461, x.

484. Kappus MR, Sterling RK. Extrahepatic manifestations of acute hepatitis B virus infection. Gastroenterol Hepatol (N Y) 2013; 9: 123-126.

485. Lai KN, Lai FM, Chan KW, et al. The clinico-pathologic features of hepatitis B virus-associated glomerulonephritis. Q J Med 1987; 63: 323-333.

486. Guillevin L, Lhote F, Cohen P, et al. Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients. Medicine (Baltimore) 1995; 74: 238-253.

487. Villa E, Rubbiani L, Barchi T, et al. Susceptibility of chronic symptomless HBsAg carriers to ethanol-induced hepatic damage. Lancet 1982; 2: 1243-1244.

488. Chevillotte G, Durbec JP, Gerolami A, et al. Interaction between hepatitis B virus and alcohol consumption in liver cirrhosis. An epidemiologic study. Gastroenterology 1982; 85: 141-145.

489. Lin CW, Lin CC, Mo LR, et al. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol 2013; 58: 730-735.

490. Donato F, Tagger A, Chiesa R, et al. Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: a case-control study in Italy. Hepatology 1997; 26: 579-584.

491. Xiong M, Li J, Yang S, et al. Impacts of cigarette smoking on liver fibrosis and its regression under therapy in male patients with chronic hepatitis B. Liver Int 2019; 39: 1428-1436.

492. Wong GL, Wong VW, Choi PC, et al. Metabolic syndrome increases the risk of liver cirrhosis in chronic hepatitis B. Gut 2009; 58: 111-117.

493. Yu MW, Lin CL, Liu CJ, et al. Influence of metabolic risk factors on risk of hepatocellular carcinoma and liver-related death in men with chronic hepatitis B: a large cohort study. Gastroenterology 2017; 153: 1006-1017.e5.

494. Corrao G, Zambon A, Bagnardi V, et al. Coffee, caffeine, and the risk of liver cirrhosis. Ann Epidemiol 2001; 11: 458-465.

495. Setiawan VW, Wilkens LR, Lu SC, et al. Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. Gastroenterology 2015; 148: 118-125.

496. Jang ES, Jeong SH, Lee SH, et al. The effect of coffee consumption on the development of hepatocellular carcinoma in hepatitis B virus endemic area. Liver Int 2013; 33: 1092-1099.

497. Ong A, Wong VW, Wong GL, Chan HL. The effect of caffeine and alcohol consumption on liver fibrosis – a study of 1045 Asian hepatitis B patients using transient elastography. Liver Int 2011; 31: 1047-1053.

498. Polyak SJ, Ferenci P, Pawlotsky JM. Hepatoprotective and antiviral functions of silymarin components in hepatitis C virus infection. Hepatology 2013; 57: 1262-1271.

499. Jacobs BP, Dennehy C, Ramirez G, et al. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. Am J Med 2002; 113: 506-515.

500. Rambaldi A, Jacobs BP, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. Cochrane Database Syst Rev 2007; (4): CD003620.

501. Bruck R, Ashkenazi M, Weiss S, et al. Prevention of liver cirrhosis in rats by curcumin. Liver Int 2007; 27: 373-383.

502. Rechtman MM, Har-Noy O, Bar-Yishay I, et al. Curcumin inhibits hepatitis B virus via down-regulation of the metabolic coactivator PGC-1alpha. FEBS Lett 2010; 584: 2485-2490.

503. Teng CF, Yu CH, Chang HY, et al. Chemopreventive effect of phytosomal curcumin on hepatitis B virus-related hepatocellular carcinoma in a transgenic mouse model. Sci Rep 2019; 9: 10338.

504. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL–EASD–EASO Clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64: 1388-1402.

505. Yu MW, Shih WL, Lin CL, et al. Body-mass index and progression of hepatitis B: a population-based cohort study in men. J Clin Oncol 2008; 26: 5576-5582.

506. Seto WK, Fung J, Cheung KS, et al. Body-mass index is associated with fibrosis regression during long-term nucleoside analogue therapy in chronic hepatitis B. Aliment Pharmacol Ther 2016; 44: 1071-1079.

507. Sun J, Li Y, Sun X, et al. Association between abdominal obesity and liver steatosis and fibrosis among patients with chronic hepatitis B measured by Fibroscan. Exp Ther Med 2019; 18: 1891-1898.

508. Hu D, Wang H, Wang H, et al. Non-alcoholic hepatic steatosis attenuates hepatitis B virus replication in an HBV-

immunocompetent mouse model. Hepatol Int 2018; 12: 438-446.

509. Hui RWH, Seto WK, Cheung KS, et al. Inverse relationship between hepatic steatosis and hepatitis B viremia: Results of a large case-control study. J Viral Hepat 2018; 25: 97-104.

510. Huang YW, Wang TC, Lin SC, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis B patients with newly diagnosed diabetes: a nationwide cohort study. Clin Infect Dis 2013; 57: 1695-1702.

511. Petersen KF, Dufour S, Befroy D, et al. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes 2005; 54: 603-608.

512. Wong VW, Chan RS, Wong GL, et al. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. J Hepatol 2013; 59: 536-542.

513. National Health and Medical Research Council, Australian Research Council, Universities Australia. Australian guidelines to reduce health risks from drinking alcohol. Canberra: Commonwealth of Australia, 2020. https://www.nhmrc.gov.au/health-advice/alcohol (accessed 19 Nov 2021).

514. Tan J, Mao X, Zhang G, et al. Hepatitis B surface antigen positivity during pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. J Viral Hepat 2018; 25: 1372-1383.

515. Giles ML, Davey MA, Wallace EM. Chronic hepatitis B infection and the risk of gestational diabetes: a cross-sectional study. BJOG 2020; 127: 1147-1152.

516. Nguyen V, Tan PK, Greenup AJ, et al. Anti-viral therapy for prevention of perinatal HBV transmission: extending therapy beyond birth does not protect against post-partum flare. Aliment Pharmacol Ther 2014; 39: 1225-1234.

517. Bzowej NH, Tran TT, Li R, et al. Total alanine aminotransferase (ALT) flares in pregnant North American women with chronic hepatitis B infection: results from a prospective observational study. Am J Gastroenterol 2019; 114: 1283-1291.

518. Zou H, Chen Y, Duan Z, et al. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat 2012; 19: e18-e25.

519. Wen WH, Chang MH, Zhao LL, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol 2013; 59: 24-30.

520. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust 2009; 190: 489-492.

521. Yang M, Qin Q, Fang Q, et al. Cesarean section to prevent mother-to-child transmission of hepatitis B virus in China: a meta-analysis. BMC Pregnancy Childbirth 2017; 17: 303.

522. Yi W, Pan CQ, Hao J, et al. Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers. J Hepatol 2014; 60: 523-529.

523. Troung A, Walker S, Women's Health Committee. Management of hepatitis B in pregnancy. Melbourne: Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2019.

524. Reddy KR, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015; 148: 215-219.

525. Seto WK, Chan TS, Hwang YY, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol 2014; 32: 3736-3743.

526. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2014; 8: 443-468.

527. Bini EJ, Perumalswami PV. Hepatitis B virus infection among American patients with chronic hepatitis C virus infection: prevalence, racial/ethnic differences, and viral interactions. Hepatology 2010; 51: 759-766.

528. Bersoff-Matcha SJ, Cao K, Jason M, et al. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus: a review of cases reported to the U.S. Food and Drug Administration Adverse Event Reporting System. Ann Intern Med 2017; 166: 792-798.

529. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. Silver Spring, Md: FDA, 2016. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-risk-hepatitis-b-reactivating-some-patients-treated (accessed 19 Nov 2021).

530. Sulkowski MS, Chuang WL, Kao JH, et al. No evidence of reactivation of hepatitis B virus among patients treated with ledipasvir-sofosbuvir for hepatitis C virus infection. Clin Infect Dis 2016; 63: 1202-1204.

531. Kanda T, Lau GKK, Wei L, et al. APASL HCV guidelines of virus-eradicated patients by DAA on how to monitor HCC occurrence and HBV reactivation. Hepatol Int 2019; 13: 649-661.

532. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (June 2020). Melbourne: Gastroenterological Society of Australia, 2020. https://www.gesa.org.au/public/13/files/Education%20%26%20Resources/Clinical%20Practice%20Resources/Hep%20C/hepatitis%20C%20virus%20infection%20a%20consensus%20statement%20June%202020!.pdf (accessed 19 Nov 2021).

533. World Health Organization. Hepatitis D [fact sheet]. Geneva: WHO, 2021. https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-d (accessed 19 Nov 2021).

534. Chen HY, Shen DT, Ji DZ, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. Gut 2019; 68: 512-521.

535. Coghill S, McNamara J, Woods M, Hajkowicz K. Epidemiology and clinical outcomes of hepatitis delta (D) virus infection in Queensland, Australia. Int J Infect Dis 2018; 74: 123-127.

536. Shadur B, MacLachlan J, Cowie B. Hepatitis D virus in Victoria 2000–2009. Intern Med J 2013; 43: 1081-1087.

537. Jackson K, MacLachlan J, Cowie B, et al. Epidemiology and phylogenetic analysis of hepatitis D virus infection in Australia. Intern Med J 2018; 48: 1308-1317.

538. Triantos C, Kalafateli M, Nikolopoulou V, Burroughs A. Meta-analysis: antiviral treatment for hepatitis D. Aliment Pharmacol Ther 2012; 35: 663-673.

539. Heidrich B, Yurdaydin C, Kabacam G, et al. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. Hepatology 2014; 60: 87-97.

540. Wranke A, Serrano BC, Heidrich B, et al. Antiviral treatment and liver-related complications in hepatitis delta. Hepatology 2017; 65: 414-425.

541. Wedemeyer H, Yurdaydin C, Ernst S, et al. O4 Prolonged therapy of hepatitis delta for 96 weeks with pegylated-interferon-α-2A plus tenofovir or placebo does not prevent HDVRNA relapse after treatment: the HIDIT-2 Study [abstract]. J Hepatol 2014; 60 (1 Suppl): S2-S3.

542. Lincoln D, Petoumenos K, Dore GJ, Australian HIV Observational Database. HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. HIV Med 2003; 4: 241-249.

543. Colin JF, Cazals-Hatem D, Loriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology 1999; 29: 1306-1310.

544. Thio CL, Seaberg EC, Skolasky Jr R, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicentre Cohort Study (MACS). Lancet 2002; 360: 1921-1926.

545. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med 2006; 166: 1632-1641.

546. Price H, Dunn D, Pillay D, et al. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. PLoS One 2013; 8: e68152.

547. Tuma P, Medrano J, Resino S, et al. Incidence of liver cirrhosis in HIV-infected patients with chronic hepatitis B or C in the era of highly active antiretroviral therapy. Antivir Ther 2010; 15: 881-886.

548. Piroth L, Pol S, Lacombe K, et al. Management and treatment of chronic hepatitis B virus infection in HIV positive and negative patients: the EPIB 2008 study. J Hepatol 2010; 53: 1006-1012.

549. Rockstroh JK, Bhagani S, Benhamou Y, et al. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. HIV Med 2008; 9: 82-88.

550. Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis 2016; 16: 43-52.

551. Office of AIDS Research, National Institutes of Health. Recommendations for the use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. Rockville, Md: NIH, 2021. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines (accessed 29 Jan 2022).

552. Waziry R, Grebely J, Amin J, et al. Trends in hepatocellular carcinoma among people with HBV or HCV notification in Australia (2000–2014). J Hepatol 2016; 65: 1086-1093.

553. Pinato DJ, Allara E, Chen TY, et al. Influence of HIV infection on the natural history of hepatocellular carcinoma: results from a global multicohort study. J Clin Oncol 2019; 37: 296-304.

554. Post FA, Tebas P, Clarke A, et al. Brief report: switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected adults with renal impairment: 96-week results from a single-arm, multicenter, open-label Phase 3 study. J Acquir Immune Defic Syndr 2017; 74: 180-184.

555. Wandeler G, Mauron E, Atkinson A, et al. Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: relevance for screening strategies. J Hepatol 2019; 71: 274-280.

556. Han Y, Zeng A, Liao H, et al. The efficacy and safety comparison between tenofovir and entecavir in treatment of chronic hepatitis B and HBV related cirrhosis: a systematic review and meta-analysis. Int Immunopharmacol 2017; 42: 168-175.

557. Maggi P, Montinaro V, Leone A, et al. Bone and kidney toxicity induced by nucleotide analogues in patients affected by HBV-related chronic hepatitis: a longitudinal study. J Antimicrob Chemother 2015; 70: 1150-1154.

558. Pradat P, Le Pogam MA, Okon JB, et al. Evolution of glomerular filtration rate in HIV-infected, HIV-HBV-coinfected and HBV-infected patients receiving tenofovir disoproxil fumarate. J Viral Hepat 2013; 20: 650-657.

559. Lok AS, Trinh H, Carosi G, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naive patients with chronic hepatitis B. Gastroenterology 2012; 143: 619-628.e1.

560. Arribas JR, Thompson M, Sax PE, et al. Brief report: randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: Week 144 results. J Acquir Immune Defic Syndr 2017; 75: 211-218.

561. Murakami E, Wang T, Park Y, et al. Implications of efficient hepatic delivery by tenofovir alafenamide (GS-7340) for hepatitis B virus therapy. Antimicrob Agents Chemother 2015; 59: 3563-3569.

562. Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. J Hepatol 2015; 62: 533-540.

563. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018; 68: 672-681.

564. Lampertico P, Buti M, Fung S, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol 2020; 5: 441-453.

565. Finelli L, Miller JT, Tokars JI, et al. National surveillance of dialysis-associated diseases in the United States, 2002. Semin Dial 2005; 18: 52-61.

566. Davies J, Jabbar Z, Gagan F, Baird RW. Blood-borne viruses in the haemodialysis-dependent population attending Top End Northern Territory facilities 2000–2009. Nephrology (Carlton) 2012; 17: 501-507.

567. Fabrizi F, Martin P, Messa P. Novel perspectives on the hepatitis B virus vaccine in the chronic kidney disease population. Int J Artif Organs 2015; 38: 625-631.

568. Fehr T, Ambuhl PM. Chronic hepatitis virus infections in patients on renal replacement therapy. Nephrol Dial Transplant 2004; 19: 1049-1053.

569. Yap DY, Chan TM. Evolution of hepatitis B management in kidney transplantation. World J Gastroenterol 2014; 20: 468-474.

570. Campistol JM, Esforzado N, Martinez J, et al. Efficacy and tolerance of interferon-alpha(2b) in the treatment of chronic hepatitis C virus infection in haemodialysis patients. Pre- and post-renal transplantation assessment. Nephrol Dial Transplant 1999; 14: 2704-2709.

571. Yap DY, Tang CS, Yung S, et al. Long-term outcome of renal transplant recipients with chronic hepatitis B infection-impact of antiviral treatments. Transplantation 2010; 90: 325-330.

572. Sasadeusz J, Grigg A, Hughes PD, et al. Screening and prophylaxis to prevent hepatitis B reactivation: transplant recipients. Clin Liver Dis 2019; 23: 493-509.

573. Mahboobi N, Tabatabaei SV, Blum HE, Alavian SM. Renal grafts from anti-hepatitis B core-positive donors: a quantitative review of the literature. Transpl Infect Dis 2012; 14: 445-451.

574. Ouseph R, Eng M, Ravindra K, et al. Review of the use of hepatitis B core antibody-positive kidney donors. Transplant Rev (Orlando) 2010; 24: 167-171.

575. Bonjoch A, Echeverria P, Perez-Alvarez N, et al. High rate of reversibility of renal damage in a cohort of HIV-infected patients receiving tenofovir-containing antiretroviral therapy. Antiviral Res 2012; 96: 65-69.

576. Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA 2011; 305: 1432-1440.

577. O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. J Hepatol 1992; 14: 104-111.

578. Samuel D, Bismuth A, Mathieu D, et al. Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. Lancet 1991; 337: 813-815.

579. Marzano A, Salizzoni M, Debernardi-Venon W, et al. Prevention of hepatitis B virus recurrence after liver transplantation in cirrhotic patients treated with lamivudine and passive immunoprophylaxis. J Hepatol 2001; 34: 903-910.

580. Al-Hamoudi W, Elsiesy H, Bendahmash A, et al. Liver transplantation for hepatitis B virus: decreasing indication and changing trends. World J Gastroenterol 2015; 21: 8140-8147.

581. Buti M, Mas A, Prieto M, et al. A randomized study comparing lamivudine monotherapy after a short course of hepatitis B immune globulin (HBIg) and lamivudine with long-term lamivudine plus HBIg in the prevention of hepatitis B virus recurrence after liver transplantation. J Hepatol 2003; 38: 811-817.

582. Teperman LW, Poordad F, Bzowej N, et al. Randomized trial of emtricitabine/tenofovir disoproxil fumarate after hepatitis B immunoglobulin withdrawal after liver transplantation. Liver Transpl 2013; 19: 594-601.

583. Radhakrishnan K, Chi A, Quan DJ, et al. Short course of postoperative hepatitis B immunoglobulin plus antivirals prevents reinfection of liver transplant recipients. Transplantation 2017; 101: 2079-2082.

584. Fung J, Wong T, Chok K, et al. Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: results up to 8 years. Hepatology 2017; 66: 1036-1044.

585. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. J Hepatol 2010; 52: 272-279.

586. Wong TC, Fung JY, Cui TY, et al. Liver transplantation using hepatitis B core positive grafts with antiviral monotherapy prophylaxis. J Hepatol 2019; 70: 1114-1122.

587. Maguire D, Heaton ND, Smith HM. Failure of reactivation of hepatitis B after liver transplantation in hepatitis B surface antigen-negative, core antibody-positive recipients. Transplantation 2002; 73: 481-482.

588. Nugroho A, Lee KW, Kim H, et al. De novo hepatitis B virus infection after liver transplantation in hepatitis B core-positive recipients using hepatitis B core-negative grafts. Transplant Proc 2019; 51: 842-844.

589. Tucci A, Rizza S, Cocchis D, et al. Early and late hepatitis B reactivation after IFN- or DAA-based therapy of recurrent hepatitis C in anti-HBc-positive liver transplant recipients. Transplantation 2018; 102: e354-e355.

590. Sripongpun P, Mannalithara A, Kwo PY, Kim WR. Potential benefits of switching liver transplant recipients to tenofovir alafenamide prophylaxis. Clin Gastroenterol Hepatol 2020; 18: 747-749.

Supplementary data

List of clinical questions

Natural history

i. What is the significance of raised ALT in the setting of undetectable HBV DNA?

ii. What is the accepted normal ALT in terms of treatment threshold for HBV?

iii. Should patients with CHB be monitored for HBsAg clearance? How often does it occur? What is the significance (in <50- and >50-year-olds)?

iv. What is the distribution of phases of CHB by age group and region of birth?

v. What is the definition of / prevalence of / significance of occult HBV infection?

vi. What is the evidence for difference in natural history associated with mutations? Include specifically reference to subgenotype C4 in Indigenous people.

Epidemiology

i. What is the effect of vaccination on the incidence and seroprevalence of HBV in Australia? Include both domestic and overseas vaccination.

ii. How will the epidemiology of HBV change in Australia over the coming decades — related to both domestic and international vaccination (effect on migrants from main source countries)?

iii. What are the differences between HBeAg-negative and HBeAg-positive disease? Why do we differentiate patients in this way?

iv. Are there regional differences in Australian prevalence?

v. What is the vaccination uptake in Indigenous Australians?

vi. What proportions of patients are currently eligible for treatment in Australia? How do we set appropriate and achievable national targets?

vii. Is Australia on track to meet the WHO 2030 elimination targets for CHB?

viii. What is the burden of CHB-associated cirrhosis in Australia?

ix. What is the burden of HBV-associated HCC in Australia?

Diagnosis and monitoring

i. When is liver biopsy indicated in CHB?

ii. How does TE perform in fibrosis staging for CHB?

iii. How reliable is positive surface antigen serology in defining CHB?

iv. How should patients be assessed and monitored for fibrosis? — TE, SWE, non-invasive serum markers in primary care, etc.

Treatment

i. When should a detectable HBV DNA during treatment be acted upon?

ii. Is there any rationale of superiority in NA selection, and how do you choose between current therapy options? Including coverage of differential HCC risk — Korea, Hong Kong, US, Australian data.

iii. What is the cumulative toxicity rate in patients on long-term NA therapy?

iv. Should patients on TDF be having urinary phosphate and bone monitoring?

v. What scheduled blood test monitoring is minimally necessary in patients on NA therapy?

vi. What is the role of TAF?

vii. When should treatment be stopped in HBeAg-negative patients, or patients with viral suppression in general?

viii. Should treatment be stopped in patients with HbsAg loss and cirrhosis?

ix. Do patients in immune tolerance warrant treatment? Ever? Sometimes?

x. What is the role of quantitative HBsAg in monitoring?

xi. What is the market share of entecavir and tenofovir in Australia?

xii. Which patients should be considered for interferon therapy?

xiii. Should persons with compensated cirrhosis and low levels of viraemia be treated with antiviral agents?

xiv. When should treatment be started in HBeAg-negative patients?

xv. When should patients aged under 30 be started on NA treatment?

xvi. What are the treatment considerations in patients with features of non-alcoholic fatty liver disease?

Complications

i. Does anything (other than NAs/interferon) delay fibrosis development?

ii. What is the role of coffee? Exercise? Curcumin? Milk thistle?

iii. What are the management considerations for comorbidities — alcohol, obesity?

iv. What groups of non-cirrhotic patients should be screened for HCC?

v. What is the optimal screening recommendation for patients with CHB?

vi. When should we start surveillance for HCC in Indigenous patients with HBV?

vii. When should we start surveillance for HCC in white people of European ancestry with HBV? Or should we never unless they have cirrhosis, first-degree-relative family history?

viii. What proportion of people requiring HCC surveillance with CHB in Australia are receiving it?

ix. What is the impact of HCC surveillance on mortality — new evidence?

x. What are strategies to improve HCC surveillance uptake?

Special groups

Perinatal transmission

i. When and how should HBV-positive women be assessed/monitored in pregnancy?

ii. Should pregnant women who are HBsAg-positive with high viral load receive antiviral treatment in the third trimester to prevent perinatal transmission of HBV? And what is the threshold?

iii. When should treatment be stopped postpartum?

iv. Is tenofovir really safe in pregnancy? Is entecavir really harmful? Should entecavir be switched if a woman becomes pregnant while taking entecavir?

v. Can women breastfeed while taking tenofovir?

vi. Should all children of HBV-positive mothers be tested for HBV? When and with what?

vii. How should HBV-positive children be followed?

viii. Should children with HBeAg-positive CHB be treated with antiviral therapy to decrease liver-related complications?

Coinfection – HDV, HCV, HIV

i. Is HDV worth treating? What are the real-world Australian data for success with interferon? Which patients are the best candidates for treatment?

ii. HBV–HCV coinfection — which patients being treated for HCV also need HBV antiviral therapy initiated?

iii. HBV–HIV coinfection — what NAs should be selected/avoided?

Immunosuppression (other than for haematological malignancies)

i. When should I screen people for HBV when planning immunosuppression?

ii. How do I manage people with HBV, or past infection with HBV, who are planned for immunosuppression?

iii. A brief summary should be included, covering most immunosuppression situations.

Transplantation

i. How often are HBV patients transplanted in Australia currently?

ii. Do we want to include post-transplant prophylaxis?

Renal impairment

i. How common is, and what is the pattern of, kidney injury in HBV, and with NAs?

ii. What monitoring is required for phosphate wasting and glycosuria?

iii. Do elderly patients need to be monitored more closely than younger patients?

Legal and miscellaneous issues

i. What are the issues for access to treatment for non-Medicare card holders — students etc?

ii. What are the changes in immigration and refugee testing for HBV in the past few years? How does a finding of HBsAg affect application for permanent residency and citizenship?

Results of modified Delphi rounds

	mDelphi 1								mDelphi 2								
Recommendation	*n*	Mode	Mean	Median	25%	75%	IQR	Agreement	*n*	Mode	Mean	Median	25%	75%	IQR	Agreement	% Swing D1–D2*
1	64	5	4.8	5	5	5	0	95.3	66	5	4.9	5	5	5	0	98.5	3.2
2	66	5	4.8	5	4.75	5	0.25	100.0	66	5	4.8	5	5	5	0	98.5	–1.5
3	61	4	4.3	4	4	5	1	86.9	63	4	4.3	4	4	5	1	95.2	8.4
4	63	5	4.9	5	5	5	0	100.0	65	5	4.9	5	5	5	0	100.0	0.0
5	63	5	4.8	5	5	5	0	96.8	63	5	4.8	5	5	5	0	98.4	1.6
6	59	5	4.4	4	4	5	1	96.6	60	4	4.4	4	4	5	1	96.7	0.1
7	61	4	4.0	4	3.5	5	1.5	75.4	61	4	3.9	4	4	4	0	77.0	1.6
7 mDelphi 3									65	5	4.5	5	4	5	1	94.9	
8	61	5	4.7	5	5	5	0	95.1	62	5	4.8	5	5	5	0	98.4	3.3
9	62	5	4.8	5	5	5	0	98.4	63	5	4.9	5	5	5	0	98.4	0.0
10	63	5	4.8	5	5	5	0	98.4	62	5	4.9	5	5	5	0	100.0	1.6
11	62	5	5.0	5	5	5	0	100.0	62	5	5.0	5	5	5	0	100.0	0.0
12	57	5	4.8	5	5	5	0	98.2	59	5	4.9	5	5	5	0	98.3	0.1
13	63	5	4.8	5	5	5	0	96.8	64	5	4.9	5	5	5	0	100.0	3.2
14	60	5	4.5	5	4	5	1	93.3	60	5	4.4	4	4	5	1	90.0	–3.3
15	64	5	4.7	5	5	5	0	96.9	64	5	4.8	5	5	5	0	98.4	1.6
16	64	5	4.8	5	5	5	0	98.4	62	5	4.8	5	5	5	0	98.4	–0.1
17	60	4	4.4	4	4	5	1	93.3	63	4	4.3	4	4	5	1	88.9	–4.4
18	58	5	4.6	5	4	5	1	94.8	60	5	4.5	5	4	5	1	96.7	1.8
19	58	5	4.5	5	4	5	1	98.3	58	5	4.5	5	4	5	1	96.6	–1.7
20	61	5	4.6	5	4	5	1	93.4	62	5	4.6	5	4	5	1	95.2	1.7
21	64	5	4.9	5	5	5	0	100.0	65	5	5.0	5	5	5	0	100.0	0.0
22	60	5	4.8	5	5	5	0	100.0	61	5	4.9	5	5	5	0	100.0	0.0
23	64	5	4.9	5	5	5	0	100.0	63	5	4.8	5	5	5	0	98.4	–1.6
24	62	5	4.7	5	4	5	1	96.8	62	5	4.5	5	4	5	1	91.9	–4.8
25	61	5	4.8	5	5	5	0	98.4	63	5	4.7	5	5	5	0	96.8	–1.5
26	60	5	4.7	5	4.25	5	0.75	95.0	61	5	4.7	5	4	5	1	98.4	3.4
27	61	4	4.0	4	4	5	1	82.0	62	4	4.1	4	4	5	1	87.1	5.1
28	63	5	4.4	5	4	5	1	84.1	63	5	4.3	4	4	5	1	88.9	4.8
29	58	5	4.4	5	4	5	1	89.7	60	4	4.4	4	4	5	1	93.3	3.7
30	60	4	4.3	4	4	5	1	93.3	60	4	4.3	4	4	5	1	93.3	0.0
31	47	5	4.6	5	4	5	1	97.9	47	5	4.6	5	4	5	1	100.0	2.1
32	59	5	4.6	5	4	5	1	96.6	60	5	4.6	5	4	5	1	98.3	1.7

IQR = interquartile range; mDelphi = modified Delphi; ***n*** = number of participants voting.
* % Swing D1–D2 = percentage swing between modified Delphi 1 and modified Delphi 2 rounds.