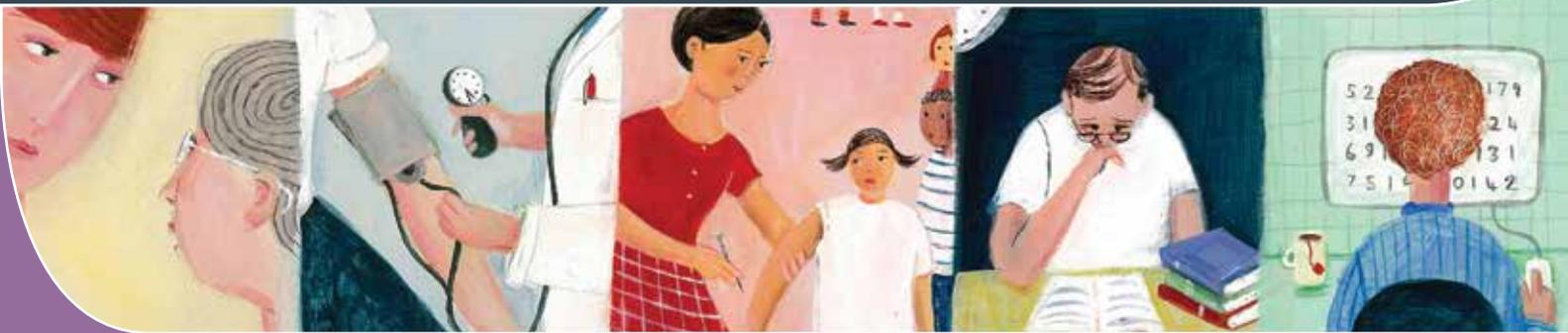


# check

Independent learning program for GPs



Unit 492 March 2013

## Chronic viral hepatitis



# check

Independent learning program for GPs



## Chronic viral hepatitis

Unit 492 March 2013

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### Medical Editors

Catherine Dodgshun  
Trisha Boetto  
Jill Pope

### Supervising Editor

Sharon Lapkin

### Editor

Rosemary Moore

### Production Coordinator

Beverley Gutierrez

### Senior Graphic Designer

Jason Farrugia

### Graphic Designer

Beverly Jongue

### Authors

David Baker  
Annie Fraser  
Robert Batey

### Contributors

Monica Robotin  
Benjamin Cowie  
Cathy Pell  
Vanessa Towell

### Reviewer

Eric Khong

### Author of QI&CPD activity

Catherine Dodgshun

The five domains of general practice  Communication skills and the patient-doctor relationship

 Applied professional knowledge and skills  Population health and the context of general practice

 Professional and ethical role  Organisational and legal dimensions



RACGP

This unit of *check* explores the topic of chronic viral hepatitis. It focuses mainly on diagnosis and management of hepatitis B and C given their propensity for chronicity. The importance of recognising individuals at risk cannot be over-emphasised given the morbidity that is often associated with these viruses.

The authors of and contributors to this unit bring a wealth of clinical, research and teaching experience.

**The authors of and contributors to this unit are:**

David Baker MBChB, DCH, Dip Med (Sexual Health), an associate at East Sydney Doctors, a clinical advisor at the Australasian Society for HIV Medicine (ASHM) and a senior lecturer at the University of Notre Dame, Sydney. He works in a large general practice that cares for more than 1500 patients with hepatitis C and a similar number with HIV infection. Dr Baker is involved in research of primary care models that support people who inject drugs to receive comprehensive care in the general practice setting including opiate substitution and antiviral therapy for HIV and HCV.

Robert Batey AM, BSc(Med), MBBS, MD, MRACP, FRACP, MRCP(UK), FRCP(UK), FACHAM(RACP), a hepatologist and addiction medicine physician and the clinical director of the Viral Hepatitis Program at ASHM. He is a professorial fellow, Flinders University, Alice Springs Hospital and conjoint professor of medicine at Newcastle University. His research interests over 40 years include iron metabolism, pathogenesis of alcohol-related liver disease and viral hepatitis management strategies.

Annie Fraser BSc(Hons) Nursing Studies, City University, London, clinical nurse educator with the 'B positive program' at Cancer Council NSW. She is a member of the British Association for Studies of the Liver Nurses Forum, the Australasian Hepatology Association and ASHM.

Monica Robotin MBBS, FRACS, MBA, M Appl Epid, M Int Health, has a combined a clinical career in surgery with public health and epidemiology. Over the last 12 years, her work has focused on research and research translation in blood borne viruses. She is the medical director of Cancer Council New South Wales, as well as a senior lecturer at the School of Public Health at The University of Sydney. She is the chief investigator of the B Positive Program. Her research work is focused on economic modeling, intervention-based research and qualitative research seeking to improve practitioner and community awareness and education about hepatitis B.

Benjamin Cowie MBBS, PhD, Grad Dip Clin Epi, FRACP, an infectious diseases physician with the Victorian Infectious Diseases Service at the Royal Melbourne Hospital, and an epidemiologist at the Victorian Infectious Diseases Reference Laboratory. He has been appointed to the Hepatitis B Expert Resource Panel of the Western Pacific Regional Office of the World Health Organization, and is chair of the Viral Hepatitis Special Interest Group of the Australasian Society for Infectious Diseases. He is also an honorary senior lecturer in the Department of Medicine at The University of Melbourne.

Cathy Pell MBBS (Hons), MM (Sex Hlth), FACHSHM, a sexual health physician and GP at the Taylor Square Clinic, Darlinghurst, NSW, and a clinical advisor at ASHM.

Vanessa Towell BA, a program manager for the National Policy and Education Division of ASHM, where she has been responsible for ASHM's hepatitis B program. Vanessa was the project coordinator and on the writing team for the new National Hepatitis B Testing Policy. Vanessa is a member of the Coalition to Eradicate Viral Hepatitis in the Asia Pacific.

Sonja Hill BSc, a senior project officer at ASHM working primarily on the hepatitis C education and prescriber program. Her interests include the development of resources and online modules in the area of hepatitis C.

**The learning objectives of this unit are to:**

- develop increased confidence in the diagnosis of hepatitis B and C, including a knowledge of potential presentations, priority populations for testing, what investigations to request and an awareness of the importance of informed consent and accurate interpretation of hepatitis serology
- develop increased confidence in requesting appropriate investigations in patients who present with abnormal liver function tests (LFT) or whose preliminary serological tests for hepatitis B or C virus are positive
- advise patients with chronic hepatitis B or active hepatitis C on lifestyle issues to prevent deterioration of liver function, and advise patients on prevention of transmission
- understand the indications for referral to a specialist 'liver clinic' in patients infected with hepatitis B or hepatitis C virus, and list the factors that affect when to treat with therapy
- describe the standard of care for neonates born to mothers with chronic hepatitis B
- understand the importance of managing a patient in their wider sociocultural context and in light of their other medical problems.

This issue concludes my role as medical editor. I would like to thank the publications team, *gplearning*, and all the authors and reviewers of *check* and extend a warm welcome to the new medical editors, Dr Trisha Boetto and Dr Jill Pope.

Kind regards,



Catherine Dodgshun MBBS, DRANZCOG, FRACGP  
Medical Editor, *check* Program

**GUIDE TO ABBREVIATIONS AND ACRONYMS IN THIS UNIT OF CHECK**

Ab	antibody	BMI	body mass index	HCV	hepatitis C virus
AFP	alpha-fetoprotein	BP	blood pressure	HCV PCR	hepatitis C virus polymerase chain reaction
ALP	alkaline phosphatase	COPD	chronic obstructive pulmonary disease	HDV	hepatitis D virus
ALT	alanine transaminase	CRP	C-reactive protein	HIV	human immunodeficiency virus
anti-HBc	hepatitis B core antibody	ESR	erythrocyte sedimentation rate	IgG	immunoglobulin G
anti-HBe	antibody to the e antigen of hepatitis B	FBE	full blood examination	INR	international normalised ratio
anti-HBs	hepatitis B surface antibody	GGT	gamma-glutamyl transferase	LFT	liver function test
anti-HCV	hepatitis C antibody	HAV	hepatitis A virus	MSU	midstream urine
APTT	activated partial thromboplastin time	HBeAg	hepatitis B e antigen	NAFLD	non-alcoholic fatty liver disease
AST	aspartate transaminase	HBsAg	hepatitis B surface antigen	PBS	Pharmaceutical Benefits Scheme
BGL	blood glucose level	HBV	hepatitis B virus	UEC	urea, electrolytes, creatinine
		HCC	hepatocellular carcinoma		

**CASE 1**

**JACK'S PARTNER THINKS HE DRINKS TOO MUCH**

Jack, aged 42 years, is new to your practice. He tells you that his partner has sent him to see you, as she thinks he drinks too much. Jack says he likes 'to party' on the weekend when he drinks more than 10 standard drinks (100 g) of alcohol on both Friday and Saturday nights. Otherwise he says he has always been well. On specific questioning, he also reports occasional intravenous use of 'ice' (amphetamines).

Jack reports that he has been well recently and hasn't had any abdominal pain. He has a history of obesity, but has no other relevant past history. He takes no regular medications and has not been prescribed or taken any over-the-counter medications for some time. He has no relevant family history.

On examination Jack is overweight, with a body mass index (BMI) of 31 kg/m<sup>2</sup> and central abdominal obesity with a waist circumference of 102 cm. Jack's blood pressure is 133/86 mmHg. Abdominal examination reveals no hepatomegaly and he has no peripheral stigmata of chronic liver disease.

**Table 1. Jack's LFT results**

	Result	Normal reference interval
Bilirubin	17 µmol/L	3–20 µmol/L
Alkaline phosphatase (ALP)	52 U/L	30–110 U/L
Gamma-glutamyl transferase (GGT)	125 U/L	10–50 U/L
Alanine transaminase (ALT)	168 U/L	5–40 U/L
Aspartate transaminase (AST)	173 U/L	5–40 U/L
Total protein	76 g/L	64–79 g/L
Albumin	38 g/L	35–48 g/L

**FURTHER INFORMATION**

After obtaining informed consent for the appropriate tests, you request blood tests. The results of Jack's LFTs are shown in *Table 1*.

The results of Jack's hepatitis B and C serology are:

- hepatitis B surface antigen (HBsAg) negative
- hepatitis B surface antibody (anti-HBs) 56 mIU/mL
- hepatitis C antibody (anti-HCV) positive

Jack's human immunodeficiency antibody (HIV Ab) is negative. His fasting blood glucose level (BGL) is elevated and there is evidence of dyslipidaemia with hypertriglyceridaemia.

Jack returns to discuss the results, having booked a long consultation at your suggestion.

**QUESTION 1** 

What investigations would you request for Jack?

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**QUESTION 2** 

How would you interpret and explain Jack's results to him?

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**QUESTION 3** 

What are possible causes for Jack's abnormal LFTs? What is/are the most likely cause/s?

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**QUESTION 4** 

What further investigations would you request to determine the cause of Jack's abnormal LFTs?

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**FURTHER INFORMATION**

Hepatitis C virus ribonucleic acid by polymerase chain reaction test (HCV PCR) is negative. Fasting iron studies are normal. Upper abdominal ultrasound reveals changes consistent with fatty liver disease and no evidence of focal pathology.

You determine that Jack has fatty liver disease with alcoholic liver disease.

**QUESTION 5**  

What further management and follow-up would you suggest?

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**CASE 1 ANSWERS**

**ANSWER 1**

Investigations should include:

- Full blood examination (FBE) as Jack's alcohol intake may be associated with FBE abnormalities
- urea, electrolytes, creatinine (UEC)
- LFTs as Jack's alcohol intake and obesity place him at risk of fatty liver disease, and his drug use places him at risk of hepatitis B and C
- fasting lipids, as Jack's alcohol intake may be associated with hypertriglyceridaemia. In addition, obesity may be associated with dyslipidaemia as part of the metabolic syndrome
- fasting BGL, as obesity may be associated with an elevated fasting BGL as part of the metabolic syndrome
- hepatitis A IgG - to identify whether Jack has immunity and assess the need for hepatitis A immunisation<sup>1</sup>
- HBsAg, anti-HBs and hepatitis B core antibody (anti-HBc)<sup>1</sup>
- anti-HCV<sup>1</sup>
- human immunodeficiency virus antibody (HIV Ab).<sup>1</sup>

Informed consent should be obtained before testing for hepatitis B, C and HIV. This consent should include an assessment of risk, discussion about the reason for the test, the meaning of a positive or negative test result, the window period and ways to prevent infection or reduce the risk of transmission. It should also involve discussion about confidentiality, the availability of treatment, assessment of social supports and arrangement of follow-up to discuss the results.

Sexual health screening should also be performed depending on Jack's sexual history.

**ANSWER 2**

Jack may require a long appointment to explain his results. You should inform him that:

- he has been infected with hepatitis C, but that further investigation is needed to determine if the infection is active or has cleared. About 25% of people will clear hepatitis C virus (HCV) spontaneously.<sup>2</sup>
- he is immune to hepatitis B
- his HIV Ab test is negative, but that it can take up to 3 months following exposure for a positive result to occur, so retesting is necessary
- his LFTs are abnormal and further investigation is necessary to determine the cause
- he has a metabolic disturbance that can predispose him to conditions such as diabetes. Note that Jack has central obesity (defined as waist circumference  $\geq 94$  cm) in combination with raised BP (defined as systolic BP  $\geq 130$  mmHg or diastolic BP  $\geq 85$  mmHg), raised fasting BGL ( $\geq 5.6$  mmol/L) and hypertriglyceridaemia (TG  $\geq 1.7$  mmol/L) consistent with metabolic syndrome.

This consultation also provides an opportunity to discuss Jack's injecting drug use and alcohol use.

**ANSWER 3**

There are a number of possible causes for Jack’s abnormal LFTs. Table 2 summarises the causes of abnormal LFTs,<sup>3</sup> which can be divided into causes of cholestasis or hepatocellular damage. Jack’s pattern of abnormal LFTs is consistent with hepatocellular damage. The most likely cause of Jack’s abnormal LFTs is a combination of obesity-related fatty liver disease and alcoholic liver disease. Hepatitis C might also be causing Jack’s abnormal LFTs. Further investigation is necessary. Jack’s LFTs also reveal an isolated elevation of GGT, which could be consistent with recent consumption of excessive alcohol.

Table 2. Classification of LFT abnormalities		
Pattern	Laboratory features	Common causes
Cholestasis	ALP >200 U/L ALP more than three times ALT	<ul style="list-style-type: none"> <li>Biliary obstruction</li> <li>Pregnancy (needs further assessment)</li> <li>Drugs (e.g. erythromycin, oestrogen)</li> <li>Infiltration (e.g. malignancy)</li> </ul>
Hepatocellular damage	ALT >200 U/L ALT >three times ALP	<ul style="list-style-type: none"> <li>Infection (e.g. hepatitis B, C, A; Epstein–Barr virus; cytomegalovirus)</li> <li>Alcohol (AST often &gt;twice ALT)</li> <li>Fatty liver disease</li> <li>Drugs (e.g. paracetamol)</li> <li>Metal overload (e.g. hereditary haemochromatosis, copper overload)</li> <li>Hypoxia (lactate dehydrogenase usually &gt;1.5 times AST)</li> <li>Autoimmune conditions</li> </ul>

Reproduced with permission from Coates, P. Liver function tests. Aust Fam Physician 2011 Mar;40(3).<sup>3</sup>

**ANSWER 4**

HCV PCR should be requested to determine if HCV is active or cleared. Fasting iron studies should be requested to help exclude haemochromatosis. Abdominal ultrasound may be helpful in showing signs of fatty liver disease or other pathology. An oral glucose tolerance test also may be indicated.

Other investigations for rarer diseases (such as an autoimmune screen and test for copper overload) should be performed where appropriate.

**ANSWER 5**

Issues that require further management or follow-up in Jack are listed below.

- Jack’s problem drinking and injecting drug use. With respects to Jack’s problem drinking, he may benefit from brief intervention in general practice or referral for more in-depth counselling.<sup>4</sup> Figure 1 outlines an approach to the management of problem drinking in general practice.<sup>4</sup> His drug use should also be addressed. In the longer term, Jack will need regular review of his alcohol and drug intake.
- Jack’s HCV status. The fact that HCV PCR is negative is highly likely to mean that HCV has cleared. However, HCV PCR should be repeated in

6 months to confirm HCV clearance. Explain to Jack that previous HCV infection does not provide any protection against future infections of a different genotype (strain) and Jack should have ongoing monitoring if he continues to be at risk from injecting drug use.

- Discussion regarding prevention of transmission and testing of others.
- Vaccination with hepatitis A vaccine if not immune.
- Repeat HIV Ab testing in 3 months.
- Jack’s risk for other health problems as part of the metabolic syndrome, including diabetes.<sup>5</sup> It is important to inform Jack about the importance of a healthy diet, regular exercise and maintaining an ideal weight, and to support him in his efforts.
- Jack will need regular review to monitor his weight, LFTs, BGL and serum lipids.

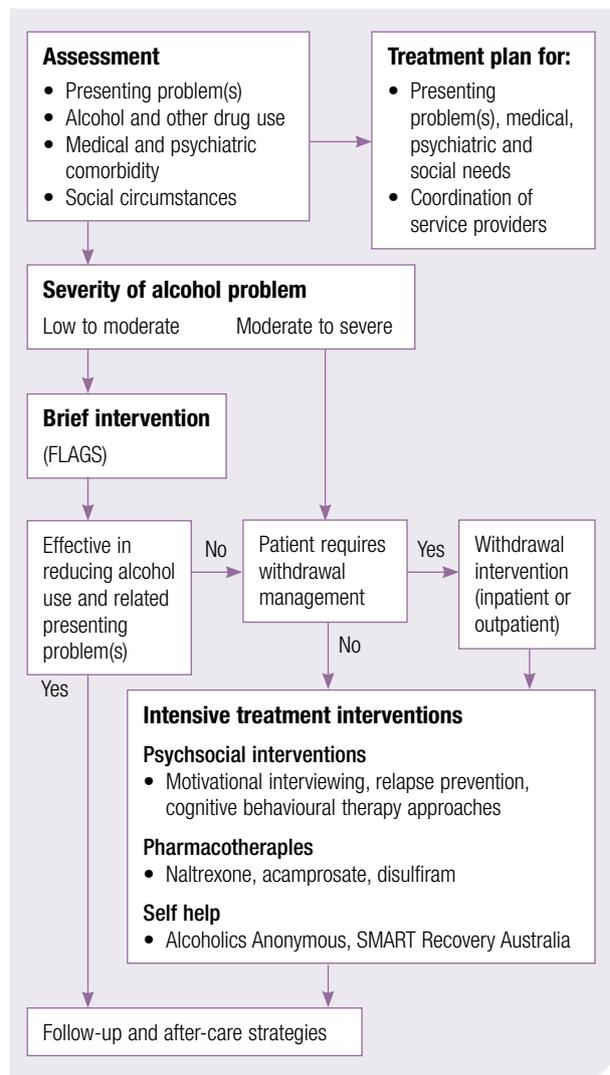


Figure 1. An approach to managing problem drinking in general practice. Key: FLAGS is an acronym for feedback, listening, advice, goals and strategies. Reproduced with permission from Demirkol A, Conigrave K, Haber P. Problem drinking management in general practice. Aust Fam Physician 2011 Aug;40(8):576–82.<sup>4</sup>

**CASE 2**

**MICHELLE HAS TESTED POSITIVE TO HEPATITIS C IN THE PAST AND IS THINKING ABOUT HAVING A BABY**

Michelle, aged 35 years, has been attending your practice for the past 5 years on an occasional basis. She used heroin in her early 20s, but stopped using after a year of methadone treatment. She previously tested positive for HCV, but wasn't interested in treatment at that time because she had heard that 'interferon can make you crazy'. In the past few years Michelle says she has 'turned her life around' – she is working full-time and is in a stable relationship. Currently, she and her partner are using condoms for contraception. Michelle is thinking about having a child, but is worried about passing on hepatitis C to her partner or baby.

Michelle has no gastrointestinal symptoms, has no other past history and takes no medications. On examination, her BP is 121/76 mmHg, her abdominal examination reveals no hepatomegaly and she has no peripheral stigmata of chronic liver disease.

**QUESTION 1**  

What investigations would you request to assess Michelle in relation to her history of hepatitis C?

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**FURTHER INFORMATION**

You request HCV PCR and LFTs. Michelle's HCV PCR is positive. The results of her LFTs are shown in *Table 3*.

Table 3. Michelle's LFT results		
	Result	Normal reference interval
Bilirubin	15 µmol/L	3–20 µmol/L
ALP	72 U/L	30–110 U/L
GGT	43 U/L	10–50 U/L
ALT	224 U/L	5–40 U/L
AST	256 U/L	5–40 U/L
Total protein	73 g/L	64–79 g/L
Albumin	42 g/L	35–48 g/L

**QUESTION 2**   

What advice would you give Michelle about transmission of HCV to her partner or potential unborn child?

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**QUESTION 3**  

Michelle asks about the timing of hepatitis C treatment. She wonders if she should try to have a baby now, or have hepatitis C treatment first and then try to conceive. What advice would you give Michelle in relation to the timing of hepatitis C treatment?

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**QUESTION 4** 

Are there any other investigations that you could request prior to referral to a 'liver clinic'?

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**FURTHER INFORMATION**

Michelle has genotype 3 hepatitis C with a viral load of 300 000 IU/mL.



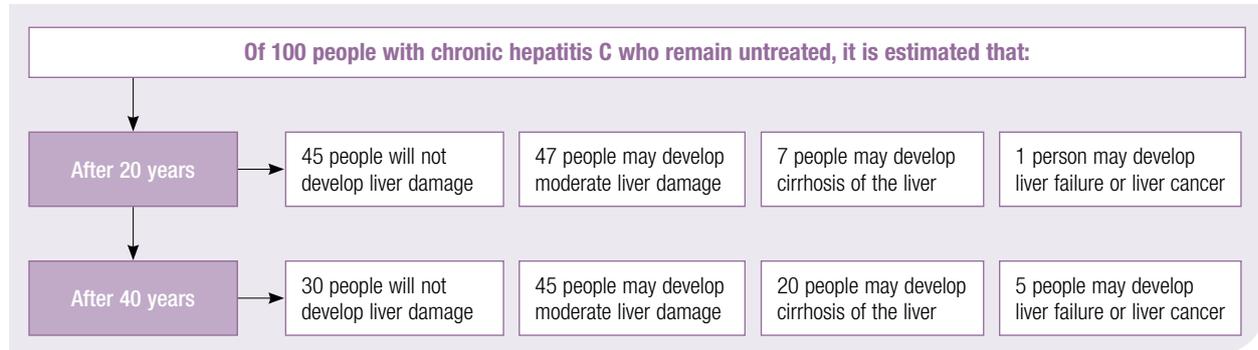


Figure 2. Outcomes for chronic hepatitis C. This figure shows the different potential outcomes for untreated chronic hepatitis C. It does not show the outcome for individual people. Factors such as alcohol intake, age when hepatitis C was acquired, and current level of inflammation may all influence a person's individual outcome. Adapted with permission from Dore G. Hepatitis NSW. 2HepCQuestions. Sydney, NSW: Hepatitis NSW, 2012:9.<sup>7</sup>

antiviral therapy (12–18 months in total), as one component of current treatment – ribavirin – is a teratogen. Alternatively, she may decide it is best to try to start a family now, given her age, and accept the small risk of HCV transmission to her baby. It is important to inform Michelle of the possible outcomes for chronic hepatitis C (see Figure 2).<sup>7</sup>

**ANSWER 4**

Prior to treatment, the HCV genotype and the HCV quantitative PCR (also called the viral load) should be determined.

There are six HCV genotypes, with the three more common types in Australia being 1, 2 and 3.<sup>2</sup> HCV genotype is the most predictive factor associated with the effectiveness of antiviral treatment.<sup>2</sup> HCV genotype testing is funded by Medicare for those patients considering hepatitis C treatment.

**ANSWER 5**

Michelle has genotype 3, with a HCV viral load <400 000 IU/mL, so she has a good chance of clearing HCV with 24 weeks of pegylated interferon/ribavirin therapy. She should be referred to a specialist clinic. At the clinic, her degree of liver fibrosis is likely to be assessed with a non-invasive test called a FibroScan®. If she has early liver disease, she could reasonably wait for improved treatment to become available in the next 4–5 years.<sup>8</sup> If she has more advanced liver fibrosis, or if she wants to clear HCV, she could have standard pegylated interferon/ribavirin treatment now. If fibrosis is advanced, she will require 48 weeks of treatment. This may influence her decision.

**ANSWER 6**

There are multiple potential side effects from, as well as contraindications to, the use of interferon/ribavirin.<sup>6</sup> Table 5 outlines the side effects and contraindications of interferon/ribavirin therapy.<sup>9</sup> Patients require careful assessment prior to treatment, as well as considerable support and monitoring throughout their treatment. This support is provided by multidisciplinary teams, which increasingly involves GPs. Good social/family support networks can also help patients manage side effects. Newer therapies, currently in clinical trials, promise to be more effective and safer to use.

**ANSWER 7**

Various patient resources are available, such as *Pregnancy, birth and beyond: a resource for women about hepatitis C*, which is available online from the Hepatitis Resource Centre's website (see Resources). For peer support, Michelle can be referred to the Hepatitis Australia National Information line (see Resources).

**Table 5. Current therapy for hepatitis C: adverse effects and contraindications**

Interferon		
Common adverse effects	Rare adverse effects	Contraindications
<ul style="list-style-type: none"> <li>• Malaise, fatigue, low-grade fever</li> <li>• Diarrhoea, anorexia, weight loss</li> <li>• Irritability, forgetfulness</li> <li>• Depression, anxiety</li> <li>• Insomnia</li> <li>• Neutropenia</li> <li>• Thrombocytopenia</li> <li>• Thyroid dysfunction</li> <li>• Decreased sexual libido</li> <li>• Injection-site erythema</li> <li>• Hair thinning/loss</li> <li>• Worsening of psoriasis</li> </ul>	<ul style="list-style-type: none"> <li>• Interstitial lung disease</li> <li>• Cardiomyopathy</li> <li>• Retinopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Decompensated liver disease</li> <li>• Severe depression, psychosis</li> <li>• Uncontrolled diabetes</li> <li>• Cardiac failure</li> <li>• Autoimmune disease</li> <li>• Organ transplantation (other than liver)</li> <li>• Pregnancy/breastfeeding</li> </ul>
Ribavirin		
Common adverse effects		Contraindications
<ul style="list-style-type: none"> <li>• Rash/pruritus</li> <li>• Upper respiratory tract congestion</li> <li>• Haemolytic anaemia (dose dependent)</li> <li>• Teratogenicity</li> </ul>		<ul style="list-style-type: none"> <li>• Renal failure</li> <li>• Pregnancy/breastfeeding</li> <li>• Inability/unwillingness to use adequate contraception</li> </ul>

Reproduced with permission from Dore G, Temple-Smith M, Lloyd A. Hepatitis C: an expanding perspective. Melbourne: IP Communications 2009.<sup>13</sup>

**CASE 3**

**MUSTAFA PRESENTS WITH FATIGUE**

Mustafa, aged 58 years, has been attending your practice for the past few years. He was born in Egypt and migrated to Australia when he was 24 years of age with his wife and children. He manages an import business and works about 40 hours a week. Mustafa presents today requesting a 'blood test' as he has been very tired over the past 6 months. He describes feeling physically 'worn out' and has to 'push himself' through the day before collapsing at home exhausted on the couch. On further questioning, he describes vague upper abdominal discomfort and some nausea after meals. Symptom review reveals no other symptoms and he says his mood is normal, he sleeps well from 11 pm to 7am on most nights, eats a balanced diet and his weight has been stable.

Mustafa has a history of schistosomiasis, for which he was treated in Egypt many years ago. He rarely drinks alcohol.

On examination, Mustafa is overweight with a BMI of 27 kg/m<sup>2</sup>. He has a few spider naevi and you can just feel a firm liver edge below the costal margin. There is no splenomegaly. The rest of his physical examination is normal.

**QUESTION 1**  

What investigations would you request?

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**FURTHER INFORMATION**

You request blood tests. Mustafa's FBE reveals an anaemia with a haemoglobin of 112 g/L (normal 130–180 g/L) and reduced platelet count of 110 000 × 10<sup>9</sup>/L (normal 150–400 × 10<sup>9</sup>/L). His fasting BGL is 6.5 mmol/L (normal 3.8–6.0 mmol/L); the results of Mustafa's LFTs are shown in *Table 6*.

**Table 6. Mustafa's LFT results**

	Result	Normal reference interval
Bilirubin	20 µmol/L	3–20 µmol/L
ALP	56 U/L	30–110 U/L
GGT	88 U/L	10–50 U/L
ALT	180 U/L	5–40 U/L
AST	232 U/L	5–40 U/L
Total protein	62 g/L	64–79 g/L
Albumin	28 g/L	35–48 g/L

**QUESTION 2** 

What further investigations you would request?

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**FURTHER INFORMATION**

You request further blood tests including HBV and HCV serology, iron studies and an oral glucose tolerance test. HBsAg, anti-HBs and anti-HBc are not detected. Anti-HCV is detected and further testing reveals that HCV PCR is positive. An oral glucose tolerance test shows impaired fasting glucose and normal 1-hour and 2-hour readings.

Abdominal ultrasound shows probable cirrhosis.

**QUESTION 3** 

What is the likely diagnosis?

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**QUESTION 4** 

Are there any other investigations that you could perform prior to referral to a 'liver clinic'?

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**FURTHER INFORMATION**

Mustafa has genotype 4 HCV, with a viral load of 850 000 IU/mL. His alpha fetoprotein (AFP) is 5 µg/L (normal <20 µg/L).

**QUESTION 5**  

What information would you give Mustafa about treatment with interferon/ribavirin?

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**QUESTION 6**  

What would management and follow-up of Mustafa's condition involve?

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**QUESTION 7** 

What symptoms and signs might Mustafa have if his liver disease decompensated? What would you do then?

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**CASE 3 ANSWERS**

**ANSWER 1**

Investigations for lethargy could include:

- FBE
- iron studies
- UEC
- LFTs
- fasting BGL
- thyroid stimulating hormone and, if abnormal, the laboratory will usually perform free thyroxine and free triiodothyronine
- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

**ANSWER 2**

As Mustafa has signs suggestive of cirrhosis, investigations should include:

- hepatitis A IgG – to identify whether Mustafa has immunity and assess the need for hepatitis A immunisation
- HBsAg, anti-HBs and anti-HBc – as hepatitis B can cause cirrhosis
- anti-HCV – as hepatitis C can cause cirrhosis
- INR – to assess synthetic function of the liver
- fasting iron studies to check for haemochromatosis.<sup>1</sup>

Informed consent for these investigations should be obtained.

Note that Egypt has a high prevalence of hepatitis C, thought to be due to poor infection control standards during the past practise of parenteral therapy for schistosomiasis.<sup>10</sup>

A positive hepatitis C antibody test should be followed by an HCV PCR test to confirm active infection. Given the initial examination and results suggest cirrhosis, Mustafa should be referred for an abdominal ultrasound.

Given Mustafa's raised fasting BGL, an oral glucose tolerance test should be requested.

**ANSWER 3**

Mustafa is likely to have chronic active HCV infection that has progressed to cirrhosis. Cirrhosis occurs as a consequence of chronic liver disease, but is actually a pathological diagnosis that describes fibrosis and nodular regeneration in the liver.

**ANSWER 4**

It would be reasonable to check HCV genotype and HCV quantitative PCR. Genotype 4 hepatitis C is common in Egypt, but less common in Australia. In general, genotype 4 is less responsive to treatment than types 2 or 3, but more responsive than genotype 1.

AFP (and abdominal ultrasound) could also be requested to screen for hepatocellular carcinoma (HCC).

**ANSWER 5**

Cirrhosis without complications is termed 'compensated'.<sup>11</sup> Cirrhosis associated with complications (such as ascites, coagulopathy, variceal bleeding, hepatorenal syndrome or hepatic encephalopathy) is termed 'decompensated'. Treatment with interferon/ribavirin is a treatment option if Mustafa's cirrhosis is compensated. However, in general, decompensated cirrhosis cannot be treated with interferon/ribavirin.<sup>12</sup>

Table 7 reveals a list of some of the markers of cirrhosis.<sup>2</sup>

**Table 7. Markers of cirrhosis include:**

- Increased INR and prolonged activated partial thromboplastin time (APTT)
- Hypoalbuminaemia
- Thrombocytopenia
- AST/ALT ratio >1

Reproduced with permission from the Australian Society for HIV medicine. General practitioners and hepatitis C. Darlinghurst, NSW: ASHM, 2012.<sup>2</sup>

**ANSWER 6**

Mustafa should be referred to a gastroenterologist for assessment, which should also include a discussion about interferon/ribavirin and an upper gastrointestinal endoscopy to exclude oesophageal varices, as well as his long-term management. He will need regular and lifelong follow-up as he has cirrhosis.

Important lifestyle issues should be discussed with Mustafa, including minimising alcohol use and avoiding hepatotoxic medication. HCV infection and cirrhosis are associated with insulin resistance, so weight management is important. Prevention of transmission of HCV should also be discussed.

Mustafa should be monitored for deteriorating liver function and for the development of hepatocellular carcinoma. Screening involves abdominal ultrasound and AFP levels every 6 months.<sup>13</sup> Mustafa's abnormal fasting BGL also needs monitoring, especially during HCV treatment, as interferon may lead to a worsening of glycaemic control.

**ANSWER 7**

Decompensated cirrhosis may present with jaundice or complications such as ascites, coagulopathy, variceal bleeding, hepatorenal syndrome or hepatic encephalopathy.<sup>13</sup> It may be associated with hypoalbuminaemia or a prolonged INR.

Patients with decompensated cirrhosis should be referred to a specialist centre for liver transplant assessment.



**FURTHER INFORMATION**

You request further tests, and the results show that Cheng is HBeAg negative, anti-HBe positive and his serum hepatitis B virus deoxyribonucleic acid (HBV DNA) level (also called the HBV DNA viral load) is  $1.65 \times 10^4$  IU/mL.

**QUESTION 4**  

What phase of chronic hepatitis B is Cheng currently in?

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**QUESTION 5**  

Given Cheng's diagnosis of chronic hepatitis B and family history of liver cancer, what tests would you request to screen for HCC? How frequently would you perform surveillance for HCC?

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**QUESTION 6** 

When would you refer Cheng to a specialist for treatment?

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**QUESTION 7**    

Given that Cheng has chronic hepatitis B, what would you advise Cheng's family?

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**CASE 4 ANSWERS**

**ANSWER 1**

Cheng has clinical manifestations (spider naevi, palmar erythema, splenomegaly and 'easy bruising') of cirrhosis. His cirrhosis appears to be compensated, as there is no evidence of jaundice or complications such as ascites, variceal bleeding, hepatorenal syndrome or hepatic encephalopathy. This would need to be confirmed with further investigations and imaging.

The differential diagnosis includes causes of chronic liver disease such as infection with hepatitis B or C, malignancy, alcoholic liver disease, fatty liver disease, autoimmune disease or conditions such as haemochromatosis. Given Cheng's country of origin, absence of alcohol intake and normal BMI, hepatitis B is the most likely cause of his chronic liver disease.

**ANSWER 2**

Cheng is in one of the priority populations for chronic hepatitis B testing. In order to confirm whether Cheng has chronic HBV infection, exclude other causes of chronic liver disease, ascertain his hepatic function and check for complications, blood tests should include:

- HBsAg, anti-HBs and anti-HBc
- anti-HCV
- LFTs
- FBE
- INR
- UEC
- fasting BGL
- fasting iron studies
- AFP.

An abdominal ultrasound should be requested to confirm the likely presence of cirrhosis and help exclude malignancy.

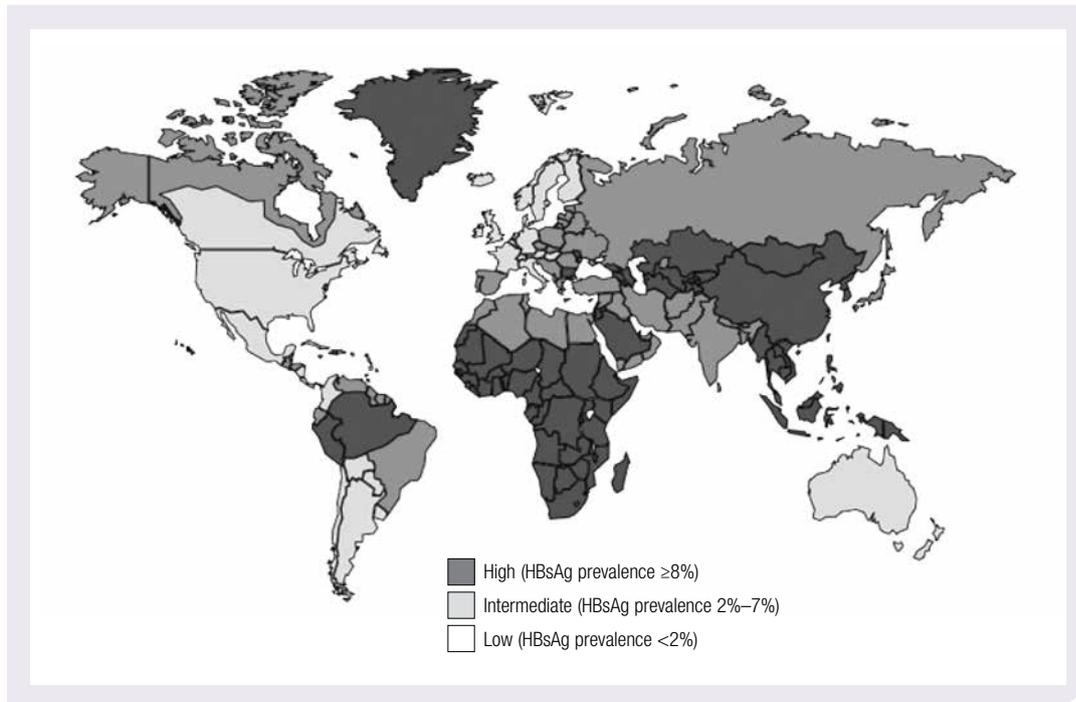


Figure 3. Geographic distribution of hepatitis B.

Reproduced with permission from Centres for Disease Control and Prevention. Geographical distribution of hepatitis B. Atlanta, Georgia: United States Department of Health and Human Services, Centres for Disease Control and Prevention, 2013. Available at [www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/viral-hepatitis-figure3.html](http://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/viral-hepatitis-figure3.html) [accessed 13 February 2013].

### FEEDBACK

The priority populations for chronic hepatitis B testing include:

- being born in Asia, Africa, the Middle East, Pacific Islands, Eastern and Southern Europe
- Aboriginal and Torres Strait Islander peoples
- men who have sex with men
- people who inject drugs
- sex workers
- household contacts of individuals diagnosed with chronic hepatitis B.<sup>14,15</sup>

Figure 3 shows the geographic distribution of hepatitis B virus infection.<sup>16</sup>

HBV is one of the world's most common infectious diseases. In 2008, the World Health Organization estimated that 2 billion people had been infected with HBV globally and 350–400 million were living with chronic hepatitis B worldwide.<sup>14</sup> People with chronic hepatitis B experience a high burden of chronic disease and premature death.<sup>17</sup> In countries where hepatitis B infection is endemic, most HBV is acquired at birth or in early childhood and leads to chronic infection. This explains the high proportion of people living with chronic hepatitis B being migrants from high prevalence countries. All patients with chronic hepatitis B require regular monitoring and consideration of treatment.

### ANSWER 3

Cheng's AST/ALT ratio is consistent with established cirrhosis. His platelet count is low, which can occur in cirrhosis. Hepatosplenomegaly was evident on examination, which is also consistent with cirrhosis.

Further investigations for HBV to clarify the phase of his chronic hepatitis B include HBeAg and serum HBV DNA level.

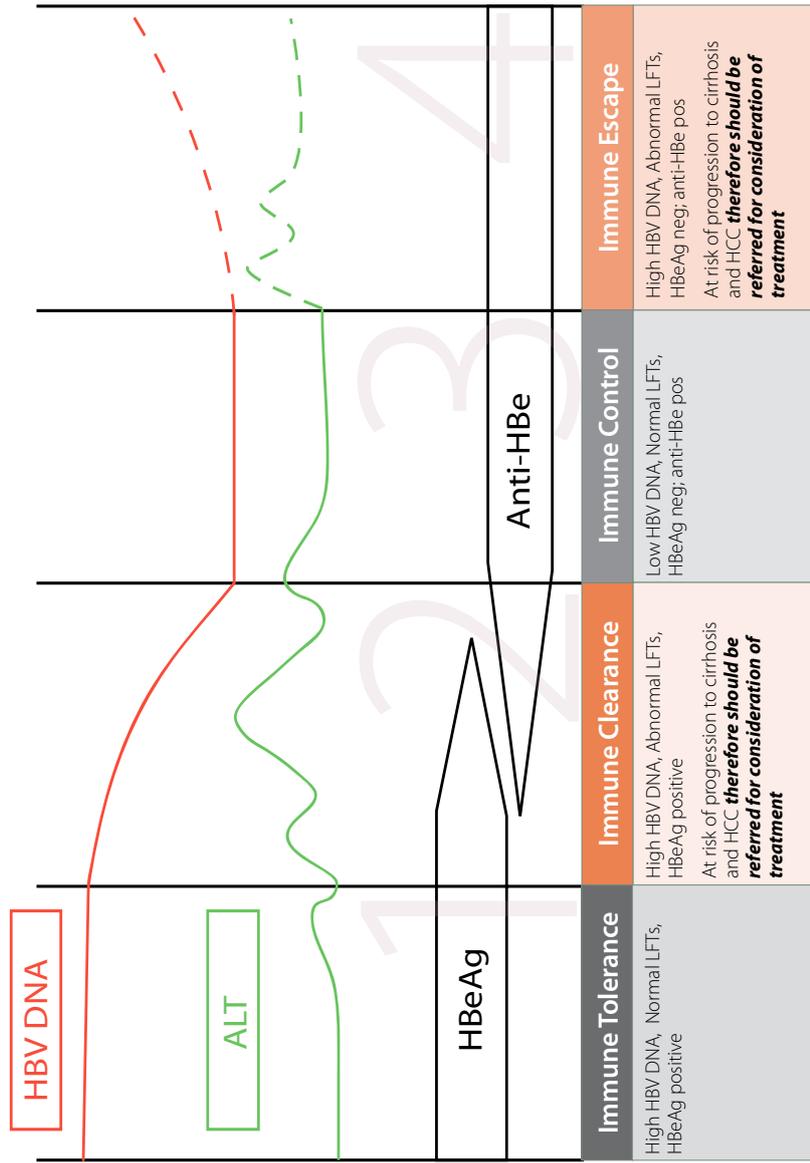
### ANSWER 4

Given Cheng's serology, he is in phase IV, also called the 'Immune escape phase'. He has abnormal LFTs, an elevation of his serum HBV DNA level, he is HBeAg negative and anti-HBe positive. He remains infectious and HBV transmission to close household contacts via blood or body fluids is a high possibility. Even though Cheng is HBeAg negative, his HBV DNA is raised, and this in addition to the open sores on his hands would make him somewhat infectious to household contacts. Cheng will need to be advised regarding the risks to his household contacts and work colleagues given the sores on his hands. However, he should be advised that HBV is not spread through kissing, hugging or sharing of food.

Refer to Figure 4 for a diagrammatic representation of the natural history and phases of chronic hepatitis B.<sup>18</sup> Refer to Figure 5 for a summary of interpretation of hepatitis B serology.<sup>19</sup>

# Decision Making in HBV

## Natural History of Chronic HBV The 4 Phases and Relevance to Treatment Decisions











For more information see: *B Positive – All you wanted to know about Hepatitis B: a guide for primary care providers*. Additional copies and electronic version available at: <http://www.ashm.org.au/publications>  
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 Produced April 2010  
 Funded by the Australian Government, Department of Health and Ageing.

Figure 4. Australasian Society for HIV Medicine. Decision making in HBV. Natural history of chronic HBV. The 4 phases and relevance to treatment decisions. Reproduced with permission from [www.ashm.org.au/images/publications/patientfactheets/hbv/decision\\_making\\_hbv.pdf](http://www.ashm.org.au/images/publications/patientfactheets/hbv/decision_making_hbv.pdf) [accessed 30 December 2012].

# Decision Making in HBV

## Evaluating your HBV Laboratory Diagnosis

Tests (Grouped)	Result	Interpretation
HBsAg	negative	susceptible
anti-HBc	negative	
anti-HBs	negative	
HBsAg	negative	resolved HBV infection
anti-HBc	positive	
anti-HBs	positive	vaccinated
HBsAg	negative	
anti-HBc	negative	
anti-HBs	positive	acute HBV infection* (high titre)
HBsAg	positive	
anti-HBc	positive	
IgM anti-HBc *	positive	
anti-HBs	negative	
anti-HBs	negative	chronic HBV infection*
HBsAg	positive	
anti-HBc	positive	
IgM anti-HBc *	negative	
anti-HBs	negative	
HBsAg	negative	various possibilities including: distant resolved infection, recovering from acute HBV, false positive, occult HBV
anti-HBc	positive	
anti-HBs	negative	

\*Anti-HBc IgM can sometimes be detected during a flare of chronic HBV infection  
 Mast 2006

If HBsAg positive	If normal ALT, low level or undetectable HBV DNA level	If active disease (abnormal ALT, detectable HBV DNA level greater than 2,000 IU/ml, 10,000 copies/ml), or evidence of chronic liver disease)	HCC Surveillance is recommended in these HBsAg pos groups:
<p>It is essential to assess the stage of disease by determining:</p> <ul style="list-style-type: none"> <li>Hepatitis B e antigen status (HBeAg and anti-HBe)</li> <li>HBV DNA level</li> <li>LFT, FBC, INR and alpha foetoprotein (AFP)</li> <li>Physical examination</li> <li>Liver ultrasound</li> </ul> <p>In addition:</p> <ul style="list-style-type: none"> <li>Discuss transmission and prevention of other BDVs, test if risk factors present</li> <li>Screen household contacts and sexual partners for HBsAg &amp; anti-HBs &amp; anti-HBe, then vaccinate if not immune, or if not already infected. Vaccination is recommended for all high risk groups, and is provided free in many cases. Contact your Health Department immunisation or Public Health programs for details.</li> </ul>	<p>Monitor patient as stated in previous column on at least an annual basis.</p> <p>Refer patient if concerned (eg suspicion of immunosuppressed or advanced liver disease).</p>	<p>Refer for assessment and/or consideration of antiviral therapy</p> <ul style="list-style-type: none"> <li>Consider hepatocellular carcinoma (HCC) surveillance (6 monthly ultrasound &amp; AFP)</li> </ul>	<ul style="list-style-type: none"> <li>Asian men &gt; 40</li> <li>Asian women &gt; 50</li> <li>Africans &gt; 20</li> <li>Patients with cirrhosis</li> <li>HCC family history</li> </ul>

For more information see: **B Positive** – All you wanted to know about Hepatitis B: a guide for primary care providers. Additional copies and electronic version available at: <http://www.ashm.org.au/publications>

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Figure 5. Australasian Society for HIV Medicine. Decision making in HBV. Evaluating your HBV: laboratory diagnosis. Reproduced with permission from [www.ashm.org.au/images/publications/patientfactsheets/hbv/decision\\_making\\_hbv.pdf](http://www.ashm.org.au/images/publications/patientfactsheets/hbv/decision_making_hbv.pdf). [accessed 30 December 2012].<sup>19</sup>

**ANSWER 5**

Cheng should be monitored because he is an Asian man aged  $\geq 40$  years irrespective of having a family history of liver cancer.

It is recommended that all patients living with chronic hepatitis B be monitored with regular LFTs and serum HBV DNA level testing.<sup>20</sup>

The following patients should undergo surveillance for HCC with 6-monthly AFP and liver ultrasound:

- Asian men aged  $\geq 40$  years
- Asian women aged  $\geq 50$  years
- Africans aged  $\geq 20$  years
- people with cirrhosis (see *Case 3*)
- those with a family history of liver cancer (HCC).<sup>20</sup>

**FEEDBACK**

HCC is an important cancer to screen for. The following facts relate to HCC:

- HCC is the fifth most common cancer in the world and third leading cause of cancer-related death.<sup>21</sup>
- China alone accounts for  $>50\%$  of newly diagnosed HCC.<sup>22</sup>
- Unlike HCV, HBV-associated HCC may occur in the absence of cirrhosis, although the incidence is higher in people living with cirrhosis.
- Up to one in four adults who become chronically infected with hepatitis B during childhood die from liver cancer or cirrhosis caused by the chronic infection.<sup>23</sup>
- Aboriginal and Torres Strait Islander peoples are also disproportionately affected.

**ANSWER 6**

Cheng's serum HBV DNA level exceeds 2000 IU/mL and his ALT is elevated  $>1-2$  times the upper limit of normal so he should be referred to a specialist for consideration for treatment. However, due to the evidence of his cirrhosis, he is eligible for treatment at any detectable serum HBV DNA level and irrespective of his ALT result.<sup>15,24</sup>

Since November 2011, the mandatory requirement for liver biopsy to access HBV treatment funded by the Pharmaceutical Benefits Scheme (PBS) has been removed. If required, the patient with chronic hepatitis B can undergo a FibroScan<sup>®</sup> to assess the extent of his liver fibrosis prior to consideration of treatment.<sup>14,15</sup>

**ANSWER 7**

Cheng is likely to have been infected with hepatitis B for many years – probably since birth or early childhood. His wife and children should be tested for hepatitis B and, if negative, given vaccination (which is funded for household and sexual contacts of people living with chronic hepatitis B in many jurisdictions) as soon as practicable. It is imperative that if any of Cheng's family have been infected with HBV they should be monitored and referred for treatment as required.

Cheng should also be advised to contact his family in China to urge them to be tested, vaccinated and treated, if appropriate.

**CASE 5**

**SHANE RETURNS FROM ASIA UNWELL**

Shane, aged 21 years, is an Australian-born single man, employed in a local electronics store as a salesman. He has recently returned from a trip through Asia where he had heterosexual contact with several partners. He says that only some of these encounters involved using condoms. He ate at many roadside stalls, but did not develop any gastrointestinal symptoms while on holiday. He says that he planned his trip quickly and did not receive any vaccinations before travelling.

Shane lives at home with his parents and two younger siblings, who are all well.

He says he has tried ecstasy tablets, amphetamines (by injection) with clean equipment and heroin on one occasion using clean equipment. He drinks 8–10 standard drinks (80–100 g) of alcohol at parties every 2–3 weeks. Shane takes no medications and has no other relevant past medical history or family history.

Shane presents feeling very unwell, with joint aches and pains but no swelling. In the last 12 hours, he has had anorexia, nausea and some vomiting and pain in his right upper quadrant.

On examination Shane looks unwell and is jaundiced. His weight is 70 kg with a BMI of 21 kg/m<sup>2</sup>. He is afebrile and his other vital signs are within normal limits.

Abdominal examination reveals tenderness in the right upper quadrant and hepatomegaly with a span of 15 cm. He also has a tippable spleen. There are no masses and ascites is not present. He has no peripheral stigmata of chronic liver disease. His peripheral joints are tender, but are not swollen and there is no overlying erythema. The rest of his physical examination is normal and there are no track marks.

**QUESTION 1** 

What is your differential diagnosis?

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**QUESTION 2**   

What investigations would you request to confirm the diagnosis? What problem might you encounter with Medicare funding in requesting these tests?

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**FURTHER INFORMATION**

You obtain informed consent and request various tests in Shane. Shane's LFT results are shown in *Table 9*. His hepatitis serology reveals:

- HBsAg positive
- anti-HBc positive
- anti-HBs negative
- anti-HCV negative
- hepatitis A antibody (HAV Ab) negative.

**Table 9. Shane's LFT results**

	Result	Normal reference interval
Bilirubin	80 µmol/L	3–20 µmol/L
ALP	130 U/L	30–110 U/L
GGT	120 U/L	10–50 U/L
ALT	6508 U/L	5–40 U/L
AST	3014 U/L	5–40 U/L
Total protein	77 g/L	64–79 g/L
Albumin	38 g/L	35–48 g/L

Shane's human immunodeficiency antibody test (HIV Ab) test is negative.

Shane's FBE reveals an elevated white cell count and his haemoglobin and platelet count are within normal limits. His INR and UEC are within normal limits.

**QUESTION 3**  

Given Shane's preliminary test results, what investigations would you request next?

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**FURTHER INFORMATION**

You request further tests. HBeAg is positive, anti-HBe is negative and hepatitis D virus antibody (HDV Ab) is negative. His serum HBV DNA level is  $6.2 \times 10^9$  IU/L.

**QUESTION 4** 

What is your clinical diagnosis?

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**QUESTION 5**   

What management would you advise for Shane?

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**QUESTION 6**  

How is hepatitis B transmitted and what is the likely source in Shane's case? Who of Shane's contacts need to be contacted and managed in this situation?

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**QUESTION 7** 

Is HCV excluded by the negative HCV result?

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**QUESTION 8** 

What is the prognosis for Shane?

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## CASE 5 ANSWERS

**ANSWER 1**

Given Shane's history of travel, his drug use, clinical presentation and unremarkable family history, the most likely diagnosis is acute viral hepatitis. Hepatitis A, B, C, D and E are all possibilities. Other possible causes of Shane's hepatitis are cytomegalovirus or Epstein–Barr virus, but rarely are these quite so acute in their presentation.

While hepatitis A virus (HAV) has become much less common in Australia over the past 30 years, the occasional outbreak does still occur when food supply is contaminated with sewage. It should always be considered in an adult presenting with acute hepatitis, especially if they have been overseas and have not been vaccinated against HAV. Note that in children, acute infection with each of the hepatitis viruses is associated with milder liver disease than is the case with adults.

Drug-induced liver injury and alcohol-related liver inflammation do not usually cause such systemic symptoms and are therefore less likely diagnoses in Shane.

**ANSWER 2**

It is important to determine the presence or absence of hepatitis, define the cause of that hepatitis and assess the impact of this on Shane's liver. LFTs, FBE, INR and UEC are all appropriate.

For some time now it has not been possible to request a full viral hepatitis screen and receive Medicare rebates on an initial screen for viral hepatitis. If all of the serology for HBV is requested (HBsAg, anti-HBc, anti-HBs), the laboratory may not perform HAV and HCV serology or, if these tests were performed, the patient might receive an account for the latter two. For more detailed information on Medicare funding of hepatitis B tests see *Resources*.

In a situation like Shane's, where the patient is experiencing an acute illness, it may be most practical to request HBsAg, HAV antibody and HCV antibody on the first round of investigations, and once the nature of the infection has been determined, further serology or viral studies can then be requested.

**ANSWER 3**

The results are consistent with active hepatitis B, which may be acute and the cause of the current symptoms, or it could be chronic and the current symptoms may reflect a flare of chronic hepatitis B. HDV super-infection is excluded by the negative HDV Ab test. It is important to check for HDV co- or super-infection in Shane, as co-infection with any other virus (HCV, HDV, HIV) does alter the clinical course of a viral hepatitis and it may complicate management strategies. It is still possible that Shane has acquired HCV on top of a chronic hepatitis B virus (HBV) infection. Further information is required.

**ANSWER 4**

The most likely diagnosis is acute hepatitis B infection and in this situation, a serum HBV DNA level is not going to alter management. In adults, acute hepatitis B will result in viral clearance from serum in 95% of cases in a period of 2–6 months.<sup>14</sup> The acute hepatitis reflects an active immune response to the infection and it would be expected that in 6 months, the patient is likely to have normal LFTs and hepatitis serology that reveals:

- HBsAg negative
- anti-HBc positive
- anti-HBs positive
- anti-HeAg negative
- anti-HBe positive.

While seroconversion means that an individual is unlikely to transmit HBV at this stage it must be remembered that the HBV is never completely eradicated from the liver. In older age or if the patient is immune suppressed, the disease may flare again.

**ANSWER 5**

Currently, while Shane is acutely unwell, management consists of:

- advising him that active treatment of his HBV is not required at present as he has a very high likelihood of clearing the virus himself
- advising him that his liver should settle back to its normal function in the next 2–3 months
- encouraging him to communicate with his sexual contacts to advise them of the need to be tested to confirm their HBV status, if they have not been fully vaccinated previously.

**ANSWER 6**

In adults, sexual transmission is the most likely means of acquiring HBV infection. In children, mother-to-child transmission (also known as vertical transmission) or transmission from a peer (also known as horizontal transmission) are the common means of acquisition.

**ANSWER 7**

Shane should be advised that it would be wise to repeat HIV and HCV Ab testing in 3 months as HCV has not been excluded because of the 'window period' for seroconversion. Testing for HCV Ab would also be very helpful if Shane did clear HBV, but his LFTs failed to normalise. In that case HCV infection would be a possible explanation for his persisting abnormal LFTs. Shane should be advised on the appropriate means to prevent transmission in the meantime.

**ANSWER 8**

At this stage Shane's prognosis should be regarded as good, with the hope that he will recover fully, become immune to HBV and have normal liver function for life.

He should be provided with information about alcohol and drug use and will need regular monitoring in that regard.

**CASE 6**

**HAZEL HAS ABNORMAL LFTs**

Hazel, aged 45 years, is a married Indigenous Australian living in Tennant Creek. She has three children aged 20, 18 and 14 years. She presents to see you today for the results of tests that you requested recently in the setting of her diabetes and renewal of her simvastatin prescription for hyperlipidaemia. You note that her medical record states that she is a 'healthy HBV carrier'.

On specific questioning, Hazel says that she has been well lately, with no symptoms such as abdominal pain, vomiting or change in weight.

Hazel has a history of type 2 diabetes, for which she takes metformin. She also has hyperlipidaemia and obesity. On examination her BMI is 30 kg/m<sup>2</sup> and her BP is 125/85 mmHg.

The results of Hazel's LFTs are shown in *Table 10*.

Table 10. Hazel's LFT results		
	Result	Normal reference interval
Bilirubin	15 µmol/L	3–20 µmol/L
ALP	130 U/L	30–110 U/L
GGT	253 U/L	10–50 U/L
ALT	234 U/L	5–40 U/L
AST	120 U/L	5–40 U/L
Total protein	77 g/L	64–79 g/L
Albumin	37 g/L	35–48 g/L

Other results reveal the following:

- Hazel's FBE is within normal limits
- her UEC reveal electrolytes that are within normal limits
- her creatinine is 90 µmol/L (normal 60–110 µmol/L)
- her estimated glomerular filtration rate is 79 mL/min/1.73m<sup>2</sup> (normal >90 mL/min/1.73 m<sup>2</sup>)
- her HbA1c is 9.5% (normal <6.0%), which is essentially unchanged from her last HbA1c performed 6 months ago
- Hazel's serum lipid studies are within normal limits.

**QUESTION 1** 

What does the term 'healthy carrier' of hepatitis B really mean?

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**QUESTION 2** 

What factors in Hazel's history could be contributing to her abnormal LFTs? What further information do you need?

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**FURTHER INFORMATION**

Hazel consumes up to 15 standard drinks (150 g) of alcohol in a drinking session at least once a week. She says she would like to stop, but feels pressured by her family and peers. She is concerned by the abnormal LFTs and asks you for help.

You request hepatitis serology, the results of which reveal that she is:

- HBsAg positive
- anti-HBc positive
- anti-HBs negative.

**QUESTION 3** 

What possibilities now exist to explain Hazel's abnormal LFTs? What further investigations might you request in order to plan further management?

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**FURTHER INFORMATION**

You request further tests and they reveal that Hazel is HBeAg negative, anti-HBe positive and HCV Ab negative. Her serum HBV DNA level is  $4 \times 10^5$  IU/mL. Her AFP is 7 µg/L (normal <20 µg/L).

Abdominal ultrasound suggests fatty liver and indicates there is no evidence of chronic liver disease, cirrhosis or portal hypertension.

You conclude that Hazel has active hepatitis B infection.

**QUESTION 4** 

What phase of HBV infection is Hazel currently in? Is HBV the only liver problem she is facing?

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**QUESTION 5** 

Does Hazel need treatment for her HBV infection? What does treatment achieve?

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**QUESTION 6** 

Outline your management plan for Hazel and her relevant contacts.

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**CASE 6 ANSWERS**

**ANSWER 1**

Hazel's medical record states that she is a 'healthy carrier' of HBV. There is no such thing as a 'healthy carrier'. It is imperative to reassess all chronic HBV-infected patients on a regular basis, as the phase of the disease changes over time. The term 'health carrier' was coined 30 years ago, before the natural history of the disease was well defined. It referred to patients with serological evidence of HBV infection (i.e. HBsAg positivity) but normal LFTs. It then became applied to those who were HBsAg positive and anti-HBe positive with normal LFTs. It is now very well recognised that both of these states are not stable endpoints and patients may progress to active liver disease again.<sup>2</sup>

**ANSWER 2**

Hazel has abnormal LFTs consistent with a mixed hepatic-cholestatic picture. Possibilities include:

- non-alcoholic fatty liver disease (NAFLD)
- alcohol
- medication
- biliary disease
- HCC
- liver metastases.

Hazel's abnormal liver tests may be the result of various factors, either alone or in concert. Hazel is overweight and this, in its own right, can cause NAFLD. She also has diabetes, which is not well controlled. Diabetes can cause NAFLD in the presence or absence of overt obesity. However, further information, including an alcohol history, is required before making a diagnosis of NAFLD. It is most confidently diagnosed in those who abstain from alcohol. Diagnosis of NAFLD in those who are drinking at recommended 'safe' levels is perilous, as some patients appear to be more sensitive to the toxic effects of alcohol than others<sup>1</sup> and alcohol histories are notoriously unreliable. Medication could also be causing Hazel's abnormal LFTs.

The raised ALP and GGT raise the possibility of some obstructive component to her liver condition and also the less likely presence of a lesion within the liver (such as an HCC or liver metastases).

Further information such as an alcohol history and hepatitis serology, AFP and abdominal ultrasound are required.

**ANSWER 3**

The tests do not provide a definitive diagnosis and possibilities include:

- active HBV in either the immune clearance or immune escape phase
- fatty liver, which is contributed to by alcohol, diabetes and/or obesity
- biliary disease, HCC or liver metastases.

Further investigations that should be requested include HBeAg and

anti-HBe, serum HBV DNA level, as well as AFP. Hazel should also be referred for an abdominal ultrasound. Refer to *Table 11* for a list of tests that should be performed in hepatitis B positive individuals.<sup>25</sup>

**Table 11. Investigations to perform in hepatitis B**

Test	Reason why the result is important
HBeAg/anti-HBe serology	Quantify replication, identify phase of infection, identify who to treat and assess prognosis
HBV DNA viral load	
HAV, HCV, HDV and HIV serology	Identify co-infection and assess the need for vaccination for HAV
LFTs	Assess inflammatory activity and synthetic function
FBE	Identify thrombocytopenia, which could suggest cirrhosis
INR and APTT	Help establish synthetic function
AFP	Screen for hepatocellular carcinoma
Abdominal ultrasound including portal venous doppler	Assess for the presence of cirrhosis, portal hypertension and hepatocellular carcinoma
All these investigations are rebatable by Medicare for a patient diagnosed with hepatitis B, although there are restrictions on how often HBV DNA viral load can be performed.	
Hepatitis B Program, Epidemiology Unit, Victorian Infectious Diseases Reference Laboratory (2011). New HBV Diagnosis – What now? Reproduced with permission from www.hepbhelp.org.au [accessed 30 December 2012]. <sup>25</sup>	

#### ANSWER 4

Hazel has chronic HBV infection in the immune escape phase with a high HBV DNA viral load (see *Figure 4*). This is likely to be contributing to her abnormal LFTs. She should be considered for HBV treatment, in addition to receiving a management plan for her diabetes, obesity and alcohol intake. It would be helpful to involve an Aboriginal health worker and utilise a multidisciplinary approach. A GP management plan and team care arrangement could be useful in this situation.

In a patient who is HBV positive, the risk of HCV infection needs to be considered. In Australians who have no history of injecting drug use, prevalence of HCV is higher in Indigenous Australians.<sup>26</sup> In general, screening for HCV, HDV and HIV is recommended in HBV infected people as co-infection has a significant impact on their management. To download a Hepatitis B GP Management Plan template see *Resources*.

Hazel also has fatty liver. Reduction in alcohol intake, weight loss and control of diabetes are important. The cause of the cholestatic picture of her abnormal LFTs remains unclear.

People with HBV have an increased risk of HCC. Screening for HCC is indicated for many patients, even in the presence of normal LFTs. The risk for HCC only becomes clinically relevant after a number of years of HBV infection and the Gastroenterological Society of Australia

guidelines recommend the appropriate starting age and frequency of screening for populations with chronic HBV infection.<sup>15</sup> In Hazel's case, the absence of cirrhosis and the lack of any family history of HCC place her in a low-risk group and screening is recommended from 50 years of age, with 6-monthly AFP and abdominal ultrasound.

#### ANSWER 5

Treatment options should be discussed with Hazel and she should be advised of the need to be referred to a specialist unit to discuss treatment further.

Managing her other medical and social issues is imperative if treatment is to be effective in the long-term.

Active treatment of HBV with antiviral agents such as entecavir and tenofovir has been shown to decrease the risk of:

- disease progression
- HCC development
- HBV transmission to other family and personal contacts.

The fact that treatment is not available in Hazel's local town should not stop discussion of referral and treatment, as many services now offer shared care protocols and telemedicine connections to allow treatment without the need for extensive travel.

#### ANSWER 6

A management plan for Hazel could include:

- addressing alcohol intake – Hazel should be referred to an Aboriginal Health Service for support to reduce alcohol intake and empowerment to be able to avoid alcohol, as her liver disease requires her preferably to abstain in order to avoid progression to cirrhosis. The issue of HBV plus alcohol is important as the two factors together speed the progress of disease complications. Consider pharmacotherapy for alcohol use disorder, but be aware that this is often not acceptable to patients
- attending to her diabetes – check her adherence to metformin (and monitor her renal function), consider adding gliclazide, and if this combination does not control her diabetes adequately, consider other oral agents or insulin therapy
- assessing her further for renal disease
- addressing Hazel's weight issue, and supporting her with an appropriate diet and exercise plan
- discussing referral to a liver or infectious diseases specialist for advice on treatment for her HBV. It is likely that entecavir or tenofovir would be recommended for her HBV infection, and treatment is usually taken life-long. Adherence to treatment is important
- checking the HBV status of her children and partner (test for HBsAg, anti-HBs and anti-HBc) to assess whether they are susceptible, immune or chronically infected. A number of issues are relevant to consider here including whether Hazel's children were vaccinated, and whether vaccination courses were completed. If testing shows that they are susceptible, they should be vaccinated.

**CASE 7**

**KIM-LY IS PREGNANT**

Kim-Ly, aged 30 years, is new to your practice and presents for her first antenatal visit with her husband. She recently migrated to Australia from rural Vietnam with her husband and two of her siblings. Kim-Ly has one child aged 2 years and she is now 12 weeks pregnant by certain dates. Kim-Ly's parents are still in Vietnam, as are three of her siblings. She has one sister and one brother in Australia, living in different cities.

You seek the services of a telephone interpreter with her consent and obtain further history. With her first child, Kim-Ly says she had a normal vaginal delivery at term with no antenatal or postnatal complications. Kim-Ly takes no medications and is not aware of any past medical problems. She has never smoked and does not drink alcohol.

Examination reveals a healthy woman with a BMI of 21 kg/m<sup>2</sup>, BP of 103/56 mmHg with a uterus consistent with dates, no hepatomegaly, no peripheral stigmata of chronic liver disease and normal cardiovascular, respiratory and thyroid examinations.

**QUESTION 1**   

What are some of the issues that need to be considered in Kim-Ly's management?

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**QUESTION 2**   

What investigations would you request?

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**FURTHER INFORMATION**

You obtain informed consent and request blood tests consistent with the antenatal screening recommendations of your local tertiary hospital, but also with an awareness of the conditions Kim-Ly is at greater risk of than the Australian population in general.

Her FBE reveals a haemoglobin of 105 g/L (normal 115–165 g/L) with a mean corpuscular volume of 70 fL (normal 80–100 fL), normal white cell count and platelet count.

Kim-Ly's iron studies are consistent with iron deficiency and her DNA analysis for thalassemia is negative. You ascertain that her iron deficiency is likely to be related to her low intake of dietary iron in the setting of the increased demands of pregnancy. You suggest increasing her intake of iron and commencing iron supplements.

Her hepatitis serology reveals:

- HBsAg positive
- anti-HBs negative
- anti-HBc positive.

Her LFTs are within normal limits, her blood group is A positive, she is protected against rubella and has negative syphilis serology. Her vitamin D level is within the normal range and a midstream urine (MSU) for microscopy and culture is negative.

Given the above results, you request further tests and the results of further hepatitis serology are as follows:

- HCV Ab negative
- HAV total Ab positive; HAV IgM negative
- HBe Ag positive
- anti-HBe negative.

**QUESTION 3**   

How would you interpret Kim-Ly's hepatitis B serology? How would you manage Kim-Ly?

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**QUESTION 4** 

What is the most likely source of Kim-Ly's HBV infection?

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**FURTHER INFORMATION**

When you explain to Kim-Ly that she has HBV infection, she appears very anxious and asks if she might have HIV as well. You are unsure why she is concerned about HIV.

**QUESTION 5** 

What is the most appropriate way to approach and address Kim-Ly's concern about HIV?

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**FURTHER INFORMATION**

With interpreter assistance, you assess that:

- Kim-Ly is very anxious about the effect of HBV on her pregnancy
- she requests treatment for her HBV
- she has had no recent risk exposure for HIV
- her family in Vietnam has not been tested for HBV
- her sister in Melbourne has HBV
- her brother is immune to HBV, having been vaccinated

You explain to Kim-Ly about the importance of testing and vaccination for HBV and advise that her family members consult their doctors. You obtain informed consent and request an HIV test.

**FURTHER INFORMATION**

You refer Kim-Ly to a specialist antenatal clinic with a link to a specialist HBV treatment service. They measure her serum HBV DNA level and it is  $6 \times 10^8$  IU/L. They determine that antiviral treatment is not indicated at this stage of pregnancy.

**QUESTION 6** 

What is the effect of pregnancy on HBV infection? What is the standard approach to preventing HBV spread from mother to child at delivery?

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**CASE 7 ANSWERS**

**ANSWER 1**

The following issues need to be considered in Kim-Ly's management:

- effective communication, the use of an interpreter and the effect of culture on health and the patient–doctor interaction, with the need for the doctor to be sensitive and culturally safe
- general health and health in this pregnancy to date
- vaccination history – especially against rubella, pertussis and influenza, and past history of chickenpox
- family history of Kim-Ly and her husband – including of diabetes, multiple births, chromosomal conditions or genetic conditions such as thalassaemia
- social supports and connectedness
- provision of advice regarding the effects of medications, the importance of a healthy diet and exercise, and prevention of infections such as listeriosis and toxoplasmosis
- supplementation with folic acid and iodine, and consideration of supplementation with vitamin D, calcium and iron if deficiency exists
- investigations that should be requested as part of antenatal screening including blood tests
- investigations that should be offered as part of screening for Down syndrome
- discussion about the models of antenatal care.

In particular, two conditions that could have a significant impact on the pregnancy need to be considered in an individual with Kim-Ly's ethnicity. They are thalassaemia and HBV.

Kim-Ly is from a high prevalence country for HBV (>8%)<sup>27</sup> and she is pregnant. HBV is more prevalent than HCV and HIV in Vietnam. HIV has an estimated prevalence of 0.4%, but there are provinces throughout Vietnam with a higher prevalence.<sup>28</sup> HCV is mainly found if injecting drug use has been part of the patient's life. It would be important to gently make enquiries about injecting use, but probably not at the initial appointment, if this is the first time you have met the patient.

### ANSWER 2

Suggested screening tests (depending on the guidelines of your local tertiary hospital) include: FBE, blood group and antibodies, HBsAg, rubella IgG and syphilis serology, vitamin D level and MSU for microscopy and culture. Given that Kim-Ly is from a country with a high prevalence of HBV, it would be reasonable to request HBsAg, anti-HBs and anti-HBc and LFTs. HIV may also form part of the recommended screening guidelines, and informed consent for testing is essential.

Screening for Down syndrome should be discussed and offered.

### ANSWER 3

Kim-Ly is infected with HBV (she most likely has chronic HBV) and is immune to HAV.

LFTs do change significantly in pregnancy and most obviously in the third trimester. The increase in blood volume leads to a fall in albumin levels, placental production of ALP increases and oestrogens cause a fall in GGT levels. The altered immune status of pregnancy results in less liver inflammation in active viral hepatitis in many patients, but for some with HBV, the opposite occurs and the disease flares during pregnancy.

Kim-Ly's hepatitis B is in the immune tolerance phase (see *Figure 4*), in that she is eAg positive and has normal LFTs. Treatment for her HBV infection is not indicated in the immune tolerance phase but it would be important to:

- ensure she is referred to a specialist antenatal clinic with a link to a specialist HBV treatment service. They will measure her serum HBV DNA level, as she may warrant treatment in the third trimester to minimise transmission of HBV to her baby at delivery.<sup>29</sup> If her HBV viral load is >10<sup>7</sup> IU/mL, antiviral therapy needs to be considered. This treatment is in addition to the standard of administration of HBV vaccine and hepatitis B immunoglobulin (HBIg) to the baby at delivery.
- advise Kim-Ly that during and particularly following pregnancy HBV may flare and thus it is important to monitor her liver tests 3 monthly during and for 6 months after the pregnancy
- explain that there is a need to test Kim-Ly's relevant contacts, and offer vaccination to those who are at risk of HBV through current lack of immunity.

This information needs to be discussed with Kim-Ly in the presence of an interpreter to ensure she understands the complexity of this infection and its implication both on her life and that of her baby.<sup>30</sup> Contact the Australian Government's Department of Immigration and Citizenship's Translating and Interpreting Service to engage the services of a telephone interpreter (see *Resources*).

### ANSWER 4

In high prevalence countries, the most common means of transmission of HBV infection is from mother to child around the time of birth. This makes it important to try to determine her mother's HBV status and that of her siblings. Refer to the ASHM testing portal (see *Resources*) for more information.

Kim-Ly is in the immune tolerance phase of the disease and this further supports the fact that she has been infected from childhood, as adult exposure to the disease leads to viral clearance from the serum in >95% of cases.<sup>14</sup> Finding HBV in any of her siblings increases the likelihood of her mother being the source of her infection. This must be conveyed in a way that does not lay blame on the mother and instead heightens the need for correct management of this pregnancy to prevent the transmission of HBV to Kim-Ly's baby.

### ANSWER 5

It is important to recognise that while many patients will nod assent to their understanding of complex medical issues, there is often a reluctance to acknowledge that they do not understand what is being said.<sup>31</sup> This often applies to people whose first language is not English, be they Australian-born, Aboriginal or Torres Strait Islander peoples or people recently arrived from other countries. Every effort should be made to use interpreter services (either telephone or face-to-face) to facilitate a meaningful discussion.

When testing for blood-borne viruses (HIV, HCV, HBV), informed consent should be obtained. Informed consent for testing means that the person being tested agrees to be tested on the basis of understanding the testing procedures, and the reasons for testing and is able to assess the personal implications of testing. Obtaining informed consent may take more than one consultation. The importance of using an interpreter in this process cannot be over-emphasised. It would be imperative to obtain the results of HIV testing and explain those to Kim-Ly before she sees the specialist.

### ANSWER 6

Pregnancy may be associated with both a reduction of HBV activity and occasional flares of activity. Rarely, a patient may experience a severe flare of activity that can be life threatening. After delivery, disease activity can again change, so it is critical that LFTs are monitored 3 monthly through pregnancy and in the early post-partum period.

As indicated in *Answer 3*, standard care to prevent HBV transmission from mother to child is to:

- administer HBV vaccine as soon as possible (preferably within 24 hours) after delivery to all babies born to mothers who are HBsAg positive.<sup>14</sup> Universal vaccination programs mean this is now offered to all children in many countries.
- Give HBIg to the baby (in a different injection site to HBV vaccine) when the mother is HBeAg positive, to minimise risk of transmission.<sup>14</sup>

Note that mode of delivery has no effect on mother-to-child transmission when prophylaxis is given.

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### RESOURCES FOR DOCTORS

- ASHM (Australasian Society for HIV Medicine) is an Australasian organisation supporting the HIV, viral hepatitis and sexual health workforce. Its website is [www.ashm.org.au](http://www.ashm.org.au) and it provides information on HIV and hepatitis as well as training courses and online modules for doctors. Resources available on its website include:
  - decision making in HBV
  - decision making in HCV
  - hepatitis B and primary care providers
  - general practitioners and hepatitis C
  - nurses and hepatitis C
  - HIV, viral hepatitis and STIs: a guide for primary care
  - B Positive: all you wanted to know about hepatitis B – a guide for primary care
  - co-infection: HIV & viral hepatitis – a guide for clinical management
  - hepatitis C: clinical management in opiate pharmacotherapy settings
  - HIV and viral hepatitis C: policy, discrimination, legal and ethical issues
  - hepatitis B GP management plan template – available at [www.ashm.org.images.au/hbv/hbv\\_gmp.rtf](http://www.ashm.org.images.au/hbv/hbv_gmp.rtf) [accessed 14 February 2013].
- National hepatitis C and hepatitis B testing policies as well as information on requesting, interpreting and conveying the results of hepatitis B and C serology are available at [www.testingportal.ashm.org.au](http://www.testingportal.ashm.org.au) [accessed 14 February 2013].
- HepBHelp is an independent website that aims to assist GPs in the further investigation and management of patients diagnosed with chronic hepatitis B infection. It also provides information on access to the nearest hepatitis B clinic. It is available at [www.hepbhelp.org.au](http://www.hepbhelp.org.au) [accessed 14 February 2013].
- The Gastroenterology Society of Australia provides recommendations on the management of chronic hepatitis B in its publication *Australia and New Zealand chronic hepatitis B recommendations*. It is available at [www.gesa.org.au/files/editor\\_upload/File/Professional/Chronic%20Hep%20B%20Summary%20Algorithm.pdf](http://www.gesa.org.au/files/editor_upload/File/Professional/Chronic%20Hep%20B%20Summary%20Algorithm.pdf) [accessed 14 February 2013].
- The Australian Government's Department of Immigration and Citizenship's Translating and Interpreting Service provides access to telephone interpreters via 1300 131 450 (doctors priority line). Further information and registration forms for medical practitioners are available at [www.immi.gov.au/living-in-australia/help-with-english/help\\_with\\_translating/](http://www.immi.gov.au/living-in-australia/help-with-english/help_with_translating/) [accessed 14 February 2013].
- Information on the delivery of sexual health services with respect and culturally appropriate communication is available in *Cultural respect and communication guide. A resource to assist sexual*

*health service delivery to Aboriginal communities*. It is available at [www.tvgpn.org.au/Welcome\\_files/Programs/ATSI\\_Health/Sexual\\_Health\\_guide.pdf](http://www.tvgpn.org.au/Welcome_files/Programs/ATSI_Health/Sexual_Health_guide.pdf) [accessed 14 February 2013].

- The *Australian Immunisation Handbook* provides information on immunisation for hepatitis B and C and is available at [www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-hepatitisb](http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-hepatitisb) [accessed 14 February 2013].
- The Medicare Benefits Schedule provides information on Medicare funding of blood tests and is available at [www.mbsonline.gov.au/](http://www.mbsonline.gov.au/) [accessed 14 February 2013].
- *AUDIT: The alcohol use disorders identification test. Guidelines for use in primary health care* by Babor TF, De la Fuente JR, Saunders J, Babor M (1989), is published by the World Health Organization
- The CAGE questionnaire is an acronym based on four questions used to screen for alcohol abuse. It is available in the *Journal of the American Medical Association*. 252(14);1905–1907, 1984.

### RESOURCES FOR PATIENTS

- ASHM is available at [www.ashm.org.au](http://www.ashm.org.au) and provides hepatitis B fact sheets in a range of languages for people with newly diagnosed hepatitis B. It also provides access to the DVD *C me, hear me. Hepatitis C in our own words*.
- The Australian Capital Territory Hepatitis Resource Centre provides fact sheets and access to a range of publications containing information on hepatitis B and C for patients and is available at [www.hepatitisresourcecentre.com.au/resource.html](http://www.hepatitisresourcecentre.com.au/resource.html) [accessed 14 February 2013].
- Hepatitis Australia provides information for patients on hepatitis B and C. Its website is available at [www.hepatitisaustralia.com](http://www.hepatitisaustralia.com). It also services a national hepatitis helpline, which are available by telephoning 1300 437 222.
- The Gastroenterological Society of Australia is available at [www.gesa.org.au](http://www.gesa.org.au) and provides information for patients on a range of gastroenterological conditions including fatty liver disease.

### Chronic viral hepatitis

In order to qualify for 6 Category 2 points for the QI&CPD activity associated with this unit:

- read and complete the unit of *check* in hard copy or online at the *gplearning* website at [www.gplearning.com.au](http://www.gplearning.com.au), and
- log onto the *gplearning* website at [www.gplearning.com.au](http://www.gplearning.com.au) and answer the following 10 multiple choice questions (MCQs) online, and
- complete the online evaluation.

If you are not an RACGP member, please contact the *gplearning* helpdesk on 1800 284 789 to register in the first instance. You will be provided with a username and password that will enable you access to the test.

The expected time to complete this activity is 3 hours.

Do not send answers to the MCQs into the *check* office. This activity can only be completed online at [www.gplearning.com.au](http://www.gplearning.com.au)

If you have any queries or technical issues accessing the test online, please contact the *gplearning* helpdesk on 1800 284 789.

**FOR A FULL LIST OF ABBREVIATIONS AND ACRONYMS USED IN THESE QUESTIONS PLEASE GO TO PAGE 3. FOR EACH QUESTION BELOW SELECT ONE OPTION ONLY.**

#### QUESTION 1

Mahali, aged 64 years, presents to you with symptoms and signs of cirrhosis. You request blood tests, which reveal that he has a hepatitic picture of abnormal LFTs, is HBsAg positive, HBeAg negative, anti-HBe positive and has a high HBV DNA level. Which of the following phases of HBV is Mahali most likely to be currently in?

- Immune tolerance phase
- Immune activation phase
- Immune clearance phase
- Immune control phase
- Immune escape phase.

#### QUESTION 2

Which of the following describes the most appropriate situation with respect to access to treatment for Mahali?

- He is not currently eligible for treatment and should be monitored with 6-monthly LFTs and annual HBV DNA.
- An ALT of twice the upper limit of normal is required for him to be eligible for PBS-funded HBV treatment.
- He requires a liver biopsy to be eligible for PBS-funded HBV treatment.
- He requires a CT scan confirming the clinical diagnosis of cirrhosis to be eligible for PBS-funded treatment.
- He is currently eligible for PBS-funded HBV treatment.

#### QUESTION 3

Tai, aged 53 years, was born in Thailand and has chronic hepatitis B. He does not have cirrhosis and has no family history of HCC. Which of the following best describes the monitoring Tai should undergo to screen for HCC?

- Three-monthly AFP and abdominal ultrasound
- Six-monthly AFP and abdominal ultrasound
- Six-monthly AFP and annual abdominal ultrasound
- Annual AFP and annual abdominal ultrasound
- AFP annually and abdominal ultrasound every 2 years.

#### QUESTION 4

Kartia, aged 28 years, is 38 weeks pregnant and is HBsAg positive, HBeAg positive with normal LFTs and a high HBV DNA. Which of the following best describes the standard of care that is recommended at delivery for Kartia's baby to prevent transmission of HBV?

- HBIG alone
- HBV vaccination alone
- HBIG and HBV vaccination
- HBIG, HBV vaccination and antiviral therapy for baby
- HBIG, HBV vaccination, antiviral therapy for baby and avoidance of breastfeeding.

#### QUESTION 5

Swahali, aged 45 years, presents to you for the first time and says that she has chronic hepatitis B. She would like to know more about infection with HBV. Which of the following is true of HBV or patients infected with chronic hepatitis B?

- Most HBV is acquired at birth or in early childhood in countries with a low prevalence of HBV.
- In countries where HBV is endemic, most HBV leads to infection that spontaneously clears.
- Regions with a high prevalence of HBV include the United Kingdom and Northern Europe.
- All patients with chronic hepatitis B require regular monitoring.
- Patients in all phases of hepatitis B infection require antiviral treatment.

#### QUESTION 6

Matthew, aged 32 years, presented to you with acute hepatitis B 6 months ago. His LFTs are now normal and his serology reveals that he is HBsAg negative, anti-HBc positive, anti-HBs positive, anti-HBe negative and anti-HBe positive. On the basis of these results, you could inform him that:

- he has eradicated HBV from the liver
- he is currently highly infectious
- he should be considered for treatment
- the disease could flare in the future if he were immune suppressed
- he needs no further follow-up at any stage.

**QUESTION 7**

Aiden, aged 35 years, is new to your practice and presents with abdominal pain and nausea. In the course of investigation you discover a hepatitic picture of abnormal LFTs. Subsequent hepatitis serology reveals that he is HBsAg negative, anti-HBc negative and anti-HBs positive. This serology is most consistent with:

- A. resolved HBV infection
- B. 'healthy carrier' status
- C. vaccination
- D. a false positive
- E. low grade chronic HBV infection.

**QUESTION 8**

You are giving a presentation on HCV to colleagues in your practice. Which of the following is true of HCV?

- A. It is commonly transmitted via sexual means.
- B. Mother-to-child transmission occurs in about 5% of pregnancies on average.
- C. About 75% of people infected with HCV will clear the infection spontaneously.
- D. The presence of anti-HCV on serological testing is consistent with clearance of the infection.
- E. A negative antibody test reliably excludes exposure to the infection.

**QUESTION 9**

Kalem, aged 38 years, has risk factors for acquiring HCV. You request blood tests and note that his results include that he is anti-HCV positive and HBsAg negative and has abnormal LFTs. Which of the following tests would be most appropriate to confirm that he has active infection with HCV?

- A. HCV antigen
- B. HCV RNA by PCR
- C. HCV DNA by PCR
- D. Abdominal ultrasound
- E. FibroScan®.

**QUESTION 10**

Which of the following factors best predicts the effectiveness of antiviral treatment for HCV?

- A. Age
- B. Gender
- C. Duration of infection
- D. HCV genotype
- E. Viral load.



