Australian and New Zealand

Chronic Hepatitis B (CHB) Recommendations

SUMMARY & ALGORITHM
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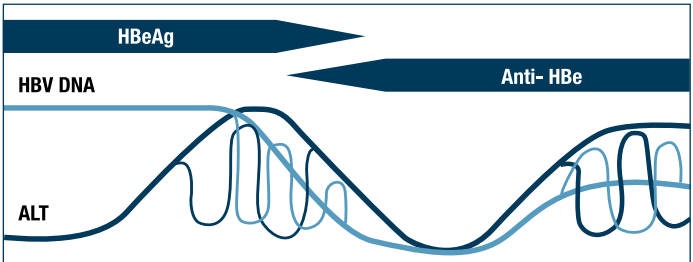
CHB Natural History & Disease Progression



	Phase I Immune Tolerance	Phase II Immune Clearance	Phase III Immune Control	Phase IV Immune Escape
HBsAg	>6 months	>6 months	>6 months	>6 months
HBeAg	+	+	-	-
Anti-HBe	-	Spontaneous seroconversion to anti-HBe may occur	+	+
ALT	Persistently normal	Persistently or intermittently elevated	Persistently normal	Persistently or intermittently elevated
HBV DNA	≥20,000 IU/mL	Persistently or intermittently ≥20,000 IU/mL	<2,000 IU/mL	Persistently or intermittently ≥2,000 IU/mL
Liver Histology	Normal or mild hepatitis	Moderate - severe hepatitis ↓ Cirrhosis →	Normal or mild hepatitis Inactive Cirrhosis ←	Moderate - severe hepatitis ↓ Cirrhosis

Natural History of CHB

- Hepatitis B is an immune-based disorder in which the extent of disease as well as the frequency and quality of virologic response are profoundly influenced by the depth of the host immunologic response.
- Progression to chronic infection varies from 90% among perinatally exposed (and unvaccinated) infants; 30% among children age under 5 years; and <5% for adults.
- Conservative figures estimate 91,500 -163,500 Australians and 67,000 New Zealanders have CHB infection. In Australia there are 6,000-8,000 new NNDSS* notifications annually.

* National Notifiable Disease Surveillance System.

References: 1 - 15. Complete recommendations and references at www.gesa.org.au

Screening of High Risk Groups

High-Risk Groups

Persons born in hyperendemic areas

Individuals born in areas of high[a] and intermediate prevalence rates[b] for HBV including immigrants and adopted children:[c,d]

- **Asia:** All countries (except Sri Lanka)
- **Africa:** All countries
- **South Pacific Islands:** All countries and territories
- **Middle East:** All countries (except Cyprus)
- **Western Europe:** Greece, Italy, Malta, Portugal, and Spain
- **Eastern Europe:** all countries (except Hungary)
- **The Arctic:** indigenous populations
- **South America:** Argentina, Bolivia, Brazil, Ecuador, Guyana, Suriname, Venezuela, and Amazon region of Colombia and Peru
- **Central America:** Belize, Guatemala, Honduras, and Panama
- **Caribbean:** Antigua and Barbuda, Dominica, Dominican Republic, Grenada, Haiti, Jamaica, Puerto Rico, St. Kitts and Nevis, St. Lucia, St. Vincent and Grenadines, Trinidad and Tobago, and Turks and Caico

Indigenous populations[d]

Injecting drug use[d]

Household contact with someone diagnosed with CHB[d]

HIV infection[d]

Inmates of correctional facilities[d]

Men who have sex with men[d]

Individuals with HCV or HIV[d]

Patients undergoing dialysis[d]

Patients undergoing chemo- or immuno-suppressive therapy

a HBsAg prevalence >8%
b HBsAg prevalence 2 to 7%
c If HBsAg-positive persons are found in the first generation, subsequent generations should be tested
d Those who are seronegative should receive hepatitis B vaccine

Diagnosis & Evaluation

Diagnosis of CHB

HBsAg + > 6 months

No clinical or laboratory evidence of acute hepatitis B

Initial Evaluation

History and physical examination

Laboratory testing:

- Liver function tests, full blood examination, INR
- HBeAg/anti-HBe, HBV DNA (quantitative viral load)
- Test for HBV genotype (if available)
- HCV antibody, hepatitis D virus antibody and antigen*, HIV antibody
- Total antibody to hepatitis A virus; vaccinate if no immunity
- Alfa-foetoprotein and abdominal ultrasound to screen for HCC**

Consider gastroscopy to look for oesophageal varices if clinical, laboratory or imaging evidence of cirrhosis

Liver biopsy is strongly recommended prior to initiating therapy

Factors Associated with Increased Rates of Cirrhosis and/or HCC

- Older age (longer duration of infection)
- Habitual alcohol consumption
- Co-infection with hepatitis C virus (HCV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV)
- Carcinogens such as aflatoxin and tobacco
- Male gender
- Family history of HCC
- History of reversion from anti-HBe to HBeAg
- Presence of cirrhosis
- HBV genotype C
- Core promoter mutation

* In selected patients from the Pacific Islands, Mediterranean, parts of South America and Africa.
**Biopsy may be particularly helpful in patients older than 35-40 years of age with normal ALT levels.

References: 20 - 21, 25. Complete recommendations and references at www.gesa.org.au

Approved Treatments

Approved Treatment Options 2009			Efficacy Data with Treatments HBeAg+*		
Drug Class	Chemical Classification	Name	Duration of Treatment	HBeAg Seroconversion Rate (%)	Patients with HBV DNA undetectability (at one year) (%)*
Nucleoside Analogues	Pyrimidine base	Lamivudine (LAM)	One year Three year	18 40	40-44
		Telbivudine (LdT)	One year Three year	22 33	60
	Purine base	Entecavir (ETV)	One year Three year	21 39	67
Nucleotide Analogues	Acyclic Phosphonate	Adefovir (ADV)	One year Three year	18 43	21
		Tenofovir (TDF)	One year Three year	21 NA	76
Cytokines	Pegylated interferon (pegIFN)		48 weeks	27	37

Advantages and Disadvantages of Treatments		
	pegIFN	**Nucleosides/Nucleotides**
Advantages	• Defined treatment duration. • No antiviral resistance. • Durability of HBeAg seroconversion.	• Easy to administer and monitor. • Safe in patients with cirrhosis/ decompensated liver disease. • Few, if any, side effects.
Disadvantages	• Subcutaneous administration. • Significant side effects. • Contraindicated in Child's B + C cirrhosis. • No more effective than placebo in patients with high HBV DNA and low ALT levels.	• Generally prolonged duration of therapy. • Antiviral resistance is common with some agents with prolonged therapy.

*Not head-to-head trials; different patient populations and trial designs. IFN and LAM: hybridisation assay; ADV, ETV, and PegIFN: PCR assay. References: 4, 22 - 24. Complete references at www.gesa.org.au

Treatment Goals & Objectives

Treatment Goal

Improve patient survival by preventing or delaying the development of complications of cirrhosis and hepatocellular carcinoma.

Treatment Objectives

HBV DNA suppression (< 2,000 IU/mL; preferably PCR undetectable < 50 IU/mL)	
ALT within normal limits	
Histological improvement	
HBsAg Clearance	Loss of HBsAg and seroconversion to anti-HBs is a complete response.
	It is durable in most cases.
	Loss of HBsAg is not common after therapy, occurring in: • 3-8% of patients receiving IFN therapy • <5% of patients receiving nucleoside/nucleotide analogue therapy.
HBeAg Clearance	Loss of HBeAg and seroconversion to anti-HBe is associated with decreased viral replication and improved liver histology.
	Seroreversion to detectable HBeAg following treatment reported in: • 10-30% of patients receiving IFN therapy • <60% of patients receiving nucleoside/nucleotide analogue therapy if therapy is stopped soon after HBeAg becomes undetectable.

 References: 4, 25 - 40. Complete recommendations and references at www.gesa.org.au

On & Off Treatment Monitoring

Suggested Evaluation for Patients who are NOT Treatment Candidates	
Immune Tolerance Phase	**Immune Control Phase**
If ALT levels <2 x ULN: HBeAg and liver function tests every 12 months. **If ALT levels increase >2 x ULN:** Increase monitoring frequency to every 3-6 months.	HBV DNA and liver function tests every 12 months.
Consider liver biopsy and treatment if ALT levels are persistently >2 x ULN and if HBeAg seroconversion does not occur within 6 months. For patients over age 40 years with ALT elevations 1-2 x ULN, consider biopsy and treatment.	If ALT levels increase, check serum HBV DNA and exclude other possible causes of ALT elevation. Consider liver biopsy and treatment if HBV DNA >2,000 IU/mL or ALT remains elevated and no other cause found and / or if liver biopsy shows significant fibrosis.
Consider HCC screening in high risk patients.	

Monitoring for Patients ON Nucleoside/Nucleotide Treatment	
Baseline	**Full blood examination (FBE):** Haemoglobin, leukocytes, platelet count **Liver function tests (LFT):** ALT, ALP, bilirubin, albumin **Virology:** HBsAg, HBeAg, anti-HBe, HBV DNA **Serum creatinine**
Post 1-month	LFT, HBV DNA
Post 3-month (and then every third month)	FBE, LFT, HBV DNA, HBeAg/ anti-HBe (for HBeAg-positive patients) Serum creatinine Analysis for possible resistance mutations if virological break through.
End of Treatment and 3, 6, 12 months after the end of treatment	FBE, LFT, HBsAg, HBeAg, anti-HBe, HBV DNA

Monitoring for Patients ON pegIFN Treatment	
Baseline	**Full blood examination (FBE):** Haemoglobin, leukocytes including neutrophil count, platelets **Liver function tests (LFT):** ALT, ALP, bilirubin, albumin **Virology:** HBsAg, HBeAg, anti-HBe, HBV DNA
Every month	FBE and LFT
Every three months	HBV DNA, HBeAg/anti-HBe (HBeAg-positive patients), Thyroid stimulating hormone
End of Treatment and 1,3, 6 months after the end of treatment	FBE and LFT
Every 3 - 6 months after end of treatment for 12 to 18 months	HBsAg, HBeAg, anti-HBe, HBV DNA

HBeAg-Positive

HBV DNA ≥ 20,000 IU/mL

Immune Tolerance

HBeAg (+) with high HBV DNA & normal ALT

Consider liver biopsy if age >40 yrs

Only treat if moderate/severe inflammation or fibrosis on biopsy

Immune Clearance

HBeAg (+) with high HBV DNA & elevated ALT (>2x ULN)§

Observe for 3-6 months for spontaneous seroconversion

Liver biopsy prior to treatment

TDF, ETV and pegIFN are appropriate†

Monitor virological response

Long term nucleoside/nucleotide (NA) treatment may be required

Continue NA therapy after HBeAg seroconversion for at least 6-12 months

Monitor for viral relapse post-therapy

† Please refer to PBS/Pharmac Schedule for reimbursed indication

§ The upper limit of normal for serum ALT concentrations is 30 IU/L for men and 19 IU/L for women.

Complete recommendations and references at www.gesa.org.au

HBeAg-Negative

HBV DNA < 2,000 IU/mL

Immune Control

HBeAg (-) with normal ALT

Observe

Consider therapy only in patients with significant inflammation or fibrosis on biopsy even if low level replication or the ALT is normal

HBV DNA ≥ 2,000 IU/mL

Immune Escape

HBeAg (-) with elevated ALT (1-2 x ULN)§

Review alternative causes of ALT elevation

Consider biopsy if clinical suspicion of significant liver disease

Treat if moderate/severe inflammation or fibrosis on biopsy

TDF, ETV or pegIFN preferred†

Monitor virological response

Continue treatment until HBsAg clearance is achieved

Immune Escape

HBeAg (-) with elevated ALT (>2 x ULN)§

Consider liver biopsy

Treat

TDF, ETV or pegIFN preferred†

Monitor virological response

Long-term nucleoside/ nucleotide (NA) treatment required

Continue treatment until HBsAg clearance is achieved

† Please refer to PBS/Pharmac Schedule for reimbursed indication
§ The upper limit of normal for serum ALT concentrations is 30 IU/L for men and 19 IU/L for women.
Complete recommendations and references at www.gesa.org.au

Compensated Disease

Screen for HCC with US and AFP examination every 6-12 months

Compensated Cirrhosis (HBeAg+ or HBeAg-)

HBV DNA < 2,000 IU/mL

Treat or observe

TDF, ETV or ADV preferred†

To avoid flares pegIFN should only be used with caution in early, well-compensated cirrhosis†

Long term treatment required

HBV DNA ≥ 2,000 IU/mL

Treat

TDF, ETV or ADV preferred†

To avoid flares pegIFN should only be used with caution in early, well-compensated cirrhosis†

Long term treatment required

† Please refer to PBS/Pharmac Schedule for reimbursed indication.

Decompensated Disease

Screen for HCC with US and AFP examination every 6-12 months

Decompensated Cirrhosis (HBeAg+ or HBeAg-)

Any detectable level of HBV DNA

Treat early

Combination with a
nucleotide (TDF / ADV) and a nucleoside (LAM / ETV)
or use a drug with a high barrier to resistance†

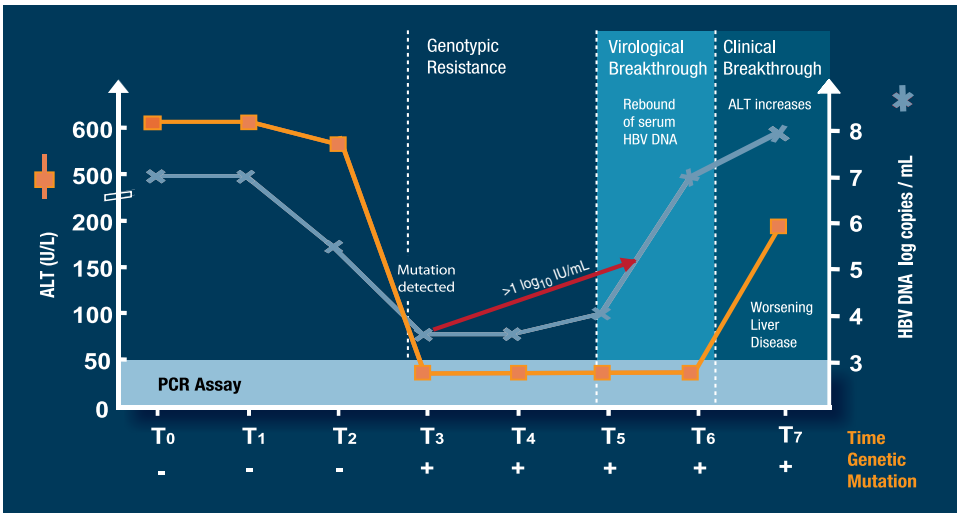
pegIFN is
contraindicated

Life-long treatment required

Consider / refer to transplant centre for
evaluation for OLT

Treatment Response

Cumulative Rates of Antiviral-Resistance Reported in Clinical Trials (%)#						
Treatment		Rates of genotypic resistance (%)				
		Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
Nucleosides	Lamivudine (LAM)	24	38	49	67	70
	Telbivudine (LdT)	3 - 4	8 - 21			
	Entecavir (ETV) (treatment naïve patients)	0	0.5	1.2	1.2	1.2
	Entecavir (ETV) (lamivudine resistant patients)	6	15	36	46	51
Nucleotides	Adefovir (ADV) (treatment naïve patients)	0	3	11	18	29
	Adefovir (ADV) (lamivudine resistant patients)	5	20	16		
	Adefovir + lamivudine combination (ADV + LAM) (lamivudine resistant patients)	0	0	0	0	
	Tenofovir (TDF) (Naïve and lamivudine resistant patients)	0	0			



Not head-to-head trials; different patient populations and trial designs.

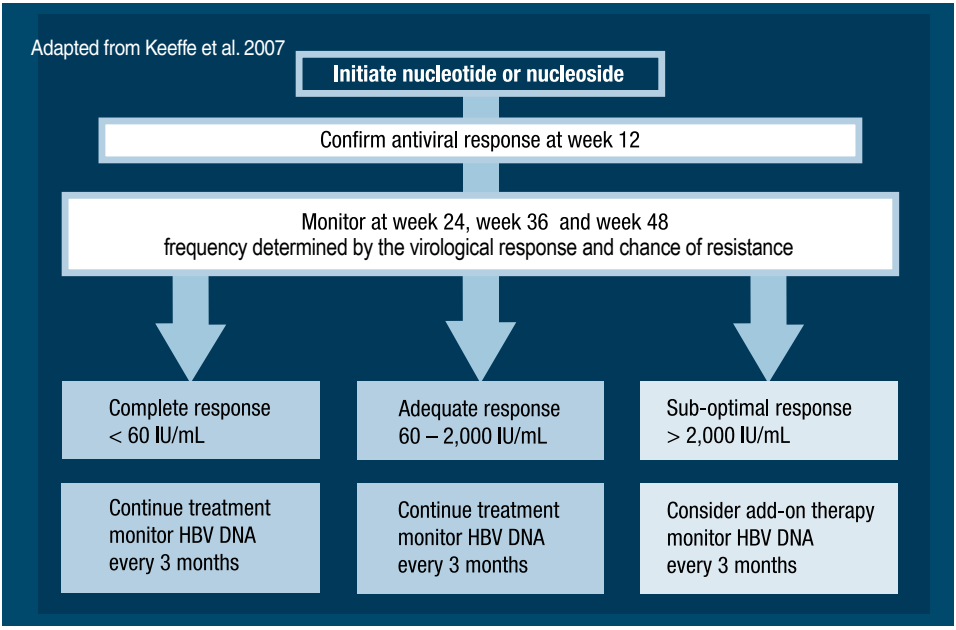
References: 41 - 59. Complete recommendations and references at www.gesa.org.au

Resistance Management

Sub-optimal Response & Resistance Prevention Strategies

A reasonable clinical goal is to develop an overall strategy that prevents the selection of resistance. Prevention of resistance requires the adoption of strategies that effectively control virus replication.

Maximise Antiviral Activity	• Select most effective regimen
Maximise Genetic Barriers to Resistance	• Avoid sequential monotherapy • Avoid treatment interruptions • Choose drugs requiring multiple resistance mutations (single therapy or a combination of drugs with different resistant profiles)
Increase Pharmacologic Barriers	• Ensure patient compliance • Add-on regimen: combination nucleotide (ADV, TDF) + nucleoside (LAM, ETV, LdT). • Modify treatment strategy early i.e. before viral load rebounds (HBV DNA ≥ 1 $\log_{10}$ IU/mL from the nadir)



References: 60 - 65. Complete recommendations and references at www.gesa.org.au

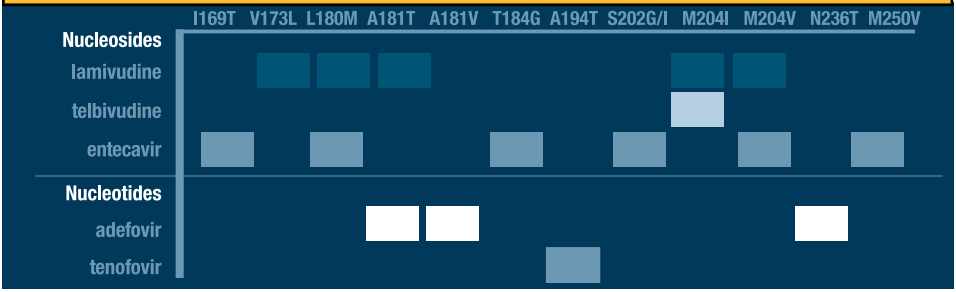
Cross Resistance & Combination Therapy

Cross Resistance

Nucleotides and nucleosides are structurally unique and they have different patterns of drug resistance.

Cross-resistance occurs when there is a decreased susceptibility to more than one antiviral drug conferred by the same amino acid substitution or combination of amino acid substitutions.

Drugs within the same structural family (e.g. two nucleosides) are more likely to exhibit cross-resistance. e.g. lamivudine-resistant mutants (rtM204V or rtM204I mutants) are resistant to other nucleoside analogues such as telbivudine while they remain susceptible to nucleotide analogues such as adefovir and tenofovir.



Tenofovir A194T mutation has been reported in two HIV/HBV co-infected patients following combination therapy with tenofovir and lamivudine. The clinical significance of this mutation is unknown.

Resistance Management Strategies to Specific Antivirals

Combining two antiviral agents which are not cross-resistant (i.e. nucleotide + nucleoside) may delay or prevent the occurrence of viral resistance without compromising tolerance in both (HBeAg±) naïve or resistant patients.

Lamivudine (LAM) Resistance	• Add adefovir or • Switch or add tenofovir
Adefovir (ADV) Resistance*	• Add lamivudine, telbivudine or entecavir or • Switch to tenofovir or tenofovir plus nucleoside agent or • Switch to entecavir (if no prior lamivudine resistance)
Entecavir (ETV) Resistance*	• Add adefovir or tenofovir • Switch to tenofovir
Multidrug Resistance#	• The optimal rescue therapy is not known but one option is to add tenofovir (if the patient is not on adefovir) in combination with a nucleoside analogue. • The most effective treatment of multi-drug resistant CHB is prevention through judicious use of antiviral therapy and avoidance of sequential antiviral monotherapies.

* Limited in vivo data, available data indicate that addition of rescue therapy is less likely to result in sequential drug resistance than switching to rescue therapy. # In vivo data lacking. References: 61, 66- 76.

Special Populations Co-Infections

HBV / HCV Co-Infection

No standard of care established for patients co-infected with HBV and HCV. Treatment recommendations on HBV/HCV co-infection cannot be made at this time. Assessment of the "dominant" virus may be helpful in determining a treatment strategy.

HCV dominant	pegIFN + ribavirin treatment in standard doses for 12 months is an option.
HBV dominant	pegIFN, with or without ADV or ETV is an option.
Decompensated cirrhosis	Referral to a transplant centre in appropriate patients. There is a possible beneficial role of viral co-infection in the immunosuppressed post-transplant population.
Triple infection HCV/HBV/HDV	pegIFN is a reasonable treatment option despite the lack of data to support use.
Triple infection HCV/HBV/HIV	Individual care plans should be coordinated with an HIV specialist and hepatologist.

HBV / HDV Co-Infection

Hepatitis delta virus (HDV) is an incomplete RNA virus that only infects patients with pre-existing HBV infection.

pegIFN treatment at standard doses for a minimum of 12 months is a promising option.

There is no evidence that ribavirin, acyclovir or LAM, alone or in combination with IFN-based therapy, enhances treatment outcomes.

HBV / HIV Co-Infection

Pre-HAART CHB treatment	In HBeAg-positive use ADV or PegIFN. In HBeAg-negative use ADV. Do not use LdT, ETV or agents with dual activity.
HAART & CHB treatment	HAART should include two dual-acting drugs (e.g. LAM, TDF, FTC, ETV). Combine a nucleoside and a nucleotide analogue to prevent resistance (i.e., TDF + LAM). If HAART is altered, the CHB component should be continued, or substituted with another agent. If the patient has achieved HBeAg seroconversion an adequate course of consolidation treatment must be undertaken prior to discontinuation of CHB treatment.
HAART only No CHB treatment	If HBV replication controlled dual-acting agents may not be required. Only add CHB treatment if HIV replication is controlled or there is evidence of liver disease.
LAM Resistance	A HAART regimen with maximum activity against both viruses is required. Maintain LAM, add TDF or ADV.
Cirrhosis	Combination CHB therapy (e.g., TDF + FTC or LAM) should be included in the HAART regimen. If no indication for anti-HIV therapy use ADV + ETV or LdT. Patients with decompensation should be treated and considered for liver transplantation.

Special Populations

Liver Transplant Patients

All patients awaiting transplantation should be immunised against HBV. Recipients with documented seroconversion following HBV immunisation and persistent protective levels of anti-HBs (>10 IU/mL) do not require antiviral prophylaxis. See complete guidelines for additional recommendations.

High-risk group (HBeAg-positive, with detectable HBV DNA)	Commence patients on antiviral therapy at the time of placement on the transplant waiting list (if not before). Initiate HBIG/LAM during the anhepatic phase or immediately post-operatively. In patients with YMDD mutations, combination of LAM and ADV, or the latter alone, is recommended.
Low-risk group (HBeAg-negative, HBV DNA negative)	Initiate low dose HBIG during the anhepatic phase. LAM and/or ADV (in presence of YMDD mutations) should be given on the day of the transplant. Both monthly low dose HBIG and antiviral treatment should be ongoing.
>12 months post transplantation	The switch to a combination of ADV/LAM provides effective prophylaxis against recurrence, equivalent to that provided by ongoing HBIG/LAM therapy. Combination ADV/LAM therapy is less expensive and is less burdensome to patients.

Chemotherapy / Immunosuppressive Therapy

Perform HBsAg screening in all persons, prior to initiation of chemo- or immunosuppressive therapy. Patients undergoing bone marrow or solid organ transplantation or immunosuppressive monoclonal antibody therapy (rituximab, infliximab) should be screened for HBV markers before treatment.

HBV naïve	Patients should be immunised against hepatitis B, as should haematopoietic stem cell donors.
HBsAg or HBV DNA positive	Prophylactic LAM can prevent, or ameliorate, the course of reactivation and increases the likelihood of completing chemotherapy without interruption. Use of TDF, ADV or ETV may be preferred especially in patients who require long-term therapy. If LAM resistance develops, add TDF or ADV. Avoid pegIFN due to bone marrow suppressive effect and the risk of exacerbating immune-mediated diseases.
HBsAg-negative, anti-HBc positive	Insufficient data to recommend prophylactic nucleoside/nucleotide treatment. Treat if evidence of HBV reactivation, without waiting for a rise in ALT. Consider vaccinating isolated anti-HBc-positive patients with an HBV vaccine. Antiviral prophylaxis may be more strongly indicated in those who remain with isolated anti-HBc than in those who develop an anti-HBs response.
HBsAg-negative, anti-HBc negative	Prophylaxis is not required.

References: 93 - 103. Complete recommendations and references at www.gesa.org.au

Pregnancy & Lactation

Pregnancy / Lactation	
All pregnant women should be screened for HBsAg, even if previously tested or vaccinated. No clear recommendations on treatment can be made at this time.	
On treatment	Women who become pregnant may continue antiviral treatment only if the potential benefit of treatment outweighs the risk to the foetus. Careful consideration should be given to discontinuing pegIFN (Category B3) and nucleoside analogue therapy (Category B3) unless treatment is absolutely indicated.
With high viral load	Limited evidence to suggest LAM, taken in the last month of pregnancy, may reduce high viral load and reduce, but not eliminate, the risk of child vaccination break-through. Routine use of antivirals in the third trimester is not supported by evidence.
Delivery	The mode of delivery does not appear to have a significant effect on vertical transmission.
Breast feeding	HBsAg-positive mothers are encouraged to breastfeed their babies. It is recommended that the baby breastfeeds after the administration of the HBIG. Avoid breastfeeding if nipples are cracked or bleeding.
Management of infants	All infants born to HBsAg positive women should receive hepatitis B vaccine and HBIG (0.5 mL) ≤12 hours of birth, administered at different injection sites.

Glossary of Acronyms

ADV adefovir dipivoxil
AIDS acquired immunodeficiency syndrome
ALT alanine aminotransferase
ART antiretroviral treatment
CHB chronic hepatitis B
CHC chronic hepatitis C
DNA deoxyribonucleic acid
ETV entecavir
FTC emtricitabine
HAART highly active antiretroviral therapy
HBcAg hepatitis B core antigen
HBeAg hepatitis B e antigen
HBIG hepatitis B immunoglobulin
HBsAg hepatitis B s (surface) antigen
HBV hepatitis B virus
HCC hepatocellular carcinoma
HCV hepatitis C virus
HDV hepatitis D virus
HIV human immunodeficiency virus
IDU injecting drug user
IFN standard interferon alfa (2a or 2b)
IT intention-to-treat
IU International Units
LAM lamivudine
LAM-R lamivudine resistance
LdT telbivudine
MIU million international units
ml millilitre
MU million units
NA nucleotide / nucleoside
PCR polymerase chain reaction
pegIFN pegylated interferon alfa (2a or 2b)
RCT randomised controlled trial
RNA ribonucleic acid
TDF tenofovir disoproxil fumarate
ULN upper limit of normal range

References

Complete recommendations and references at www.gesa.org.au

1. Hui C-K, Leung N, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immunetolerant phase. Hepatology 2007; 46(2):395-401.
2. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis 2003;23:47-58.
3. McMahon B. The natural history of chronic hepatitis B virus infection. Semin Liver Dis 2004;24 (Suppl 1):17-21.
4. Lok A, Heathcote E, Hoofnagle J. Management of hepatitis B: 2000-summary of a workshop. Gastroenterology 2001;120:1828-53.
5. de Franchis R, Hadengue A, et al. EASL International Consensus Conference on Hepatitis B. J Hepatol 2003;39 (Suppl 1):S3-S25.
6. Hoofnagle J, et al. Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. Ann Intern Med 1981;94:744-8.
7. Fattovich G, et al. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-Hbe in chronic hepatitis type B. Hepatology 1986;6:167-72.
8. Manno M, et al. Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. Gastroenterology 2004;127:756-63.
9. Lok A, Liang R, et al. Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy: report of a prospective study. Gastroenterology 1991;100:182-8.
10. Lok A, Lai C, et al. Spontaneous hepatitis e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. Gastroenterology 1987;92:1839-43.
11.Manesis E, Papatheodoridis G, Hadziyannis S. Serum HBV-DNA levels in inactive hepatitis B virus carriers. Gastroenterology 2002;122:2092-3.
12. Hsu Y-S, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology 2002;35:1522-7.
13. Brunetto M, et al. The outcome of anti-HBe positive chronic hepatitis B in alpha–interferon treated and untreated patients: a long term cohort study. J Hepatol 2002;36:263-70.
14. Hadziyannis S. Hepatitis B e antigen negative chronic hepatitis B: from clinical r ecognition to pathogenesis and treatment. Viral Hepatitis Reviews 1995;1:7-36.
15. Hadziyannis S, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology 2001;34(4 Pt 1):617-24.
16. Lok A, McMahon B. Chronic hepatitis B. Hepatology 2007;45(2):507-39.
17. Holden S, et al. Chronic HBV infection in SSWA HS; antenatal screening detects high rates of previously unrecognised cases. J Gastro Hepatol 2007;Abstract October.
18. Lin S, et al. Why should we routinely screen Asian American adults for hepatitis b: a cross sectional study of Asians in California. Hepatology 2007;46:1034-40.
19. Hutton D, et al. Cost Effectiveness of Screening and Vaccination Asian and Pacific Islander Adults for Hepatitis B. Ann Intern Med 2007;147(7):460-9.
20. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis 2003;23:47-58.
21. Yim H, Lok A. Natural History of Chronic Hepatitis B Virus Infection: What We Knew in 1981 and What We Know in 2005 Hepatology 2006;43:S173-S81.
22. Lai C, Gane E, et al. Telbivudine versus Lamivudine in Patients with Chronic Hepatitis B. N Engl J Med 2007;357(25):2576-88.
23. Marcellin P, et al. A Randomized, Double-Blind, Comparison of Tenofovir DF (TDF) versus Adefovir Dipivoxil (ADV) for the Treatment of HBeAg-Negative Chronic Hepatitis B (CHB): Study GS-US-174- 0102 In: AASLD. Boston MA; 2007.
24. Heathcote E, et al. A randomized, double-blind, comparison of tenofovir DF (TDF) versus adefovir dipivoxil (ADV) for the treatment of HBeAg-positive chronic hepatitis B (CHB). Hepatology 2007;46:S861A.
25. Iloeje U, Yang H, Su J, Jen C, You S, Chen C. Predicting Cirrhosis Risk Based on the Level of Circulating Hepatitis B Viral Load. Gastroenterology 2006;130(3):678-86.
26. Lai C. Therapeutic advances in chronic hepatitis B J Gastro Hepatol 2004;19:S5-S9.
27. Lok A, McMahon B. Chronic hepatitis B: update of recommendations. Hepatology 2004;39:857-61.
28. EASL. Consensus statement (long version). In: EASL International Consensus Conference on Hepatitis B; 2003 13-14 September 2002; Geneva, Switzerland: J Hepatol; 2003. S3-S25.
29. Liaw Y-F, et al. Asia Pacific consensus statement on the management of chronic hepatitis B: an update. J Gastro Hepatol 2003;18:239-45.
30. Lau G, et al. PEGinterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005;352:2682-95.
31. Marcellin P, 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(12):1206-17.

References

Complete recommendations and references at www.gesa.org.au

32. Janssen 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(9454):123-9.
33. Marcellin P, et al. Adefovir Dipivoxil for the Treatment of Hepatitis B e Antigen-Positive Chronic Hepatitis B. N Engl J Med 2003;348:808-16.
34. Hadziyannis S, et al. Long-Term Therapy with Adefovir Dipivoxil for HBeAg-Negative Chronic Hepatitis B. N Engl J Med 2005;352:2673-81.
35. Lai C, et al, for the BEHoLD AI463027 Study Group. Entecavir versus Lamivudine for Patients with HBeAg- Negative Chronic Hepatitis B. N Engl J Med 2006;354:1011-20.
36. Niederau C, et al. Longterm follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. N Engl J Med 1996;334:1422-7.
37. Lau D, et al. Long-term follow up of patients with chronic hepatitis B treated with interferon-alfa. Gastroenterology 1997;113:1660-7.
38. van Zonneveld M, et al. Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. Hepatology 2004;39:804-10.
39. Lok A, et al. Long-term follow-up of chronic hepatitis B patients treated with interferon alfa. Gastroenterology 1993;105:1833-8.
40. Song B, et al. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. Hepatology 2000;32:803-6.
41. Liaw Y, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-31.
42. Leung N, et al. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. Hepatology 2001;33:1527-32.
43. Locarnini S. Primary resistance, multidrug resistance, and cross-resistance pathways in HBV as a consequence of treatment failure. Hepatol Int 2008;2:147 - 51.
44. Zoulim F. Mechanism of viral persistence and resistance to nucleoside and nucleotide analogs in chronic hepatitis B virus infection. Antiviral Research 2004;64:1-15.
45. Bartholomeusz A, Locarnini S. Antiviral drug resistance: clinical consequences and molecular aspects. Semin Liver Dis 2006;26(2):162-70.
46. Lai C, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. Clin Infect Dis 2003;36:687-96.
47. Chang T, et al. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. J Gastroenterol Hepatol 2004;19(11):1276-82.
48. Lok A, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2003;125:1714-22.
49. Lai C, et al. Telbivudine versus Lamivudine in Patients with Chronic Hepatitis B. N Engl J Med 2007;357(25):2576-88.
50. Lai C, et al. Two-year results from the GLOBE trial in patients with hepatitis B: greater clinical and antiviral efficacy for telbivudine (LdT) vs. lamivudine. Hepatology 2006;44(Suppl.1):222A.
51. Tenney D, et al. Entecavir at Five Years Shows Long Long- Term Maintenance of High Genetic Barrier to Hepatitis B Virus Resistance In: Conference of the Asia-Pacific Association for the Study of the Liver (APAS L). Seoul, Korea; 2008.
52. Hadziyannis S, et al. Long-term Therapy With Adefovir Dipivoxil for HBeAg-Negative Chronic Hepatitis B for up to 5 Years Gastroenterology 2006;131(6):1743-51
53. Rapti I, Dimou E, Mitsoula P, Hadziyannis S. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAgnegative chronic hepatitis B. Hepatology 2007;45(2):307-13.
54. Lee Y, et al. Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. Hepatology 2006;43: 1385-91.
55. Lampertico P, et al. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. Gastroenterology 2007; 133:1445-51.
56. Heathcote E, et al. A randomized, double-blind, comparison of tenofovir DF (TDF) versus adefovir dipivoxil (ADV) for the treatment of HBeAg-positive chronic hepatitis B (CHB). Hepatology 2007;46:S861A.
57. Marcellin P, et al. A Randomized, Double-Blind, Comparison of Tenofovir DF (TDF) versus Adefovir Dipivoxil (ADV) for the Treatment of HBeAg-Negative Chronic Hepatitis B (CHB): Study GS-US-174-0102 In: AASLD. Boston MA; 2007.
58. Heathcote J, et al. A Randomized, Double-Blind, Comparison of Tenofovir DF (TDF) versus Adefovir Dipivoxil (ADV) for the Treatment of HBeAg Positive Chronic Hepatitis B (CHB): Study GS-US-174- 0103. In: AASLD. Boston MA; 2007.
59. Zoulim F, Buti M, Lok A. Antiviral-resistant hepatitis B virus: can we prevent this monster from

References

Complete recommendations and references at www.gesa.org.au

growing? J Viral Hepat 2007;14(Suppl 1):29-36.
60. Lok A, et al. Antiviral drug-resistant HBV: Standardization of nomenclature and assays and recommendations for management. Hepatology 2007;46(1):254-65.
61. Locarnini S, et al. Management of antiviral resistance in patients with chronic hepatitis B. Antivir Ther 2004;9:679-93.
62. Di Bisceglie A, et al. Telbivudine GLOBE trial: maximal early HBV suppression is predictive of optimal two-year efficacy in nucleoside-treated hepatitis B patients. Hepatology 2006;44:230A.
63. Hadziyannis S, et al. Long-term Therapy With Adefovir Dipivoxil for HBeAg-Negative Chronic Hepatitis B for up to 5 Years Gastroenterology 2006;131(6):1743-51
64. Keeffe E, et al. Report of an international workshop: Roadmap for management of patients receiving oral therapy for chronic hepatitis B. Clin Gastroenterol Hepatol 2007;5(8):890-7.
65.Richman D. The implications of drug resistance for strategies of combination antiviral chemotherapy. Antiviral Res 1996;29:31-3.
66. Lok A, et al. Antiviral drug-resistant HBV: Standardization of nomenclature and assays and recommendations for management. Hepatology 2007;46(1):254-65.
67. Seigneres B, et al. Inhibitory activity of dioxolane purine analogs on wild-type and lamivudine-resistant mutants of hepadnaviruses. Hepatology 2002;36(710–722).
68. Delaney W, et al. Intracellular metabolism and in vitro activity of tenofovir against hepatitis B virus. Antimicrob Agents Chemother 2006;50:2471-7.
69. Allen M, et al. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Hepatology 1998;27(6):1670-7.
70. Yang H, et al. Cross-resistance testing of next-generation nucleoside and nucleotide analogues against lamivudine-resistant HBV. Antivir Ther 2005;10:625-33.
71. Lampertico P, et al. Adefovir rapidly suppresses hepatitis B in HBeAg-negative patients developing genotypic resistance to lamivudine. Hepatology 2005;42(6):1414-9.
72. Rapti I, et al. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAgnegative chronic hepatitis B. Hepatology 2007;45(2):307-13.
73. Leemans W, et al. Selection of an entecavir-resistant mutant despite prolonged hepatitis B virus DNA suppression, in a chronic hepatitis B patient with preexistent lamivudine resistance: successful rescue therapy with tenofovir. . European J Gastro Hepatol 2008;28(8):773-7.
74. Yang H, et al. Cross-resistance testing of next-generation nucleoside and nucleotide analogues against lamivudine-resistant HBV. Antivir Ther 2005;10:625-33.
75. Chang T, et al. A dose ranging study of the efficacy and tolerability of entecavir in Lamivudine-refractory chronic hepatitis B patients. Gastroenterology 2005;129:1198-209.
76. van Bommel F, et al. Tenofovir for patients with lamivudine resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. Hepatology 2006;44:318–25.
77. Liaw Y. Role of hepatitis C virus in dual and triple hepatitis virus infection. Hepatology 1995;22:1101–8.
78. Dai C, et al. Influence of hepatitis C virus on the profiles of patients with chronic hepatitis B virus infection. J Gastro Hepatol 2001;16:636-40.
79. Jardi R, et al. Role of hepatitis B, C, and D viruses in dual and triple infection: influence of viral genotypes and hepatitis B precore and basal core promoter mutations on viral replicative interference. Hepatology 2001;34:404-10.
80. Liaw Y. Concurrent hepatitis B and C virus infection: Is hepatitis C virus stronger? J Gastro Hepatol 2001;16:597–8.
81. Liaw Y. Hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. J Gastroenterol 2002;37:65-8.
82. Hadziyannis S. Decreasing prevalence of hepatitis D virus infection. J Gastro Hepatol 1997;12:745–6.
83. Wu J, et al. Natural history of hepatitis D viral superinfection: significance of viremia detected by polymerase chain reaction. Gastroenterology 1995;108:796–802.
84. Niro G, et al. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. Hepatology 2006;44:713–20.
85. Farci P, et al. Treatment of chronic hepatitis D with interferon alfa-2a. N Engl J Med 1994;330:88–94.
86. Castelnau C, et al. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT -PCR for follow-up. Hepatology 2006;44(728–35).
87. Gunsar F, et al. Two-year interferon therapy with or without ribavirin in chronic delta hepatitis. Antivir Ther 2005;10:721-6.
88. Erhardt A, et al. Treatment of chronic hepatitis delta with pegylated interferon-alpha;2b. Liver Int 2006;26(7):805-10.

References

Complete recommendations and references at www.gesa.org.au

89. Alter M. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol 2006;44 (Suppl 1):S6 -9.
90. Iser D, Sasadeusz J. Current treatment of HIV/hepatitis B virus coinfection. J Gastro and Hepatol 2008;23(5):699-706.
91. Brook M, et al. BHIVA guidelines on HIV and chronic hepatitis: coinfection with HIV and hepatitis B virus infection (2005). HIV Med 2005;6:84-95.
92. Alberti A, et al. Short Statement of the first European Consensus Conference on the Treatment of Chronic Hepatitis B and C in HIV Co-infected Patients. J Hepatol 2005;42(5):615-24.
93. Todo S, et al. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. Hepatology 1991;13:13:619.
94. Gish R, McCashland T. Hepatitis B in liver transplant recipients. Liver Transpl 2006;12(11):S54-64.
95. No authors listed. Viral hepatitis guidelines in hemodialysis and transplantation. Am J Transplant 2004 4 (Suppl 10):72-82.
96. Angus PW, et al. A Randomized Study of Adefovir Dipoxil in Place of HBIG in Combination with Lamivudine As Post–Liver Transplantation Hepatitis B Prophylaxis. Hepatology 2008;48:1460-1466.
97. Lok A, et al. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991;100(1):182-8.
98. Levy P, et al. Clinical course of spontaneous reactivation of hepatitis B virus infection in patients with chronic hepatitis B. Hepatology 1990;12(3 Pt 1):570-4.
99. Yeo W, Johnson P. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology 2006;43(2):209-20.
100. Hui C, et al. Kinetics and risk of de novo hepatitis B infection in HBsAg–negative patients undergoing cytotoxic chemotherapy. Gastroenterology 2006;131:59–68.
101. Lau G, et al. Prophylactic lamivudine therapy for hepatitis B patients undergoing immunosuppressive therapy. Blood 2002;100(8):3054.
102. Yeo W, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer 2004;90(7):1306 -11.
103. Sookoian S. Effect of pregnancy on preexisting liver disease: Chronic viral hepatitis. Ann Hepatol 2006;5(3):190-7.

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