

Treatments for Chronic Hepatitis B

Environmental Scan and Local/Historical Context

September 28th, 2015

Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

In Canada, seven treatments for chronic hepatitis B (CHB) (adefovir, entecavir, lamivudine, telbivudine, tenofovir, interferon alfa-2B, and pegylated interferon 2a) are available. Adefovir, entecavir and lamivudine are available as generic products.

In Ontario, treatments for CHB (with the exception of telbivudine and pegylated interferon) are available through the Exceptional Access Program (EAP). In Canada, many of the older products (in particular lamivudine) that are available generically are restricted but have preferred listing via a special authorization program in most jurisdictions. Telbivudine is not listed in any jurisdiction across Canada.

Across international jurisdictions, a variation in coverage of CHB treatments was found. In the United States, many of the reimbursement formularies limited access to more expensive treatments (those without generic options) and had preferential listings for less costly options as first-line treatments. Variation in the recommendation and use of interferon was found across all jurisdictions and plans.

Part B: Guidelines for the treatment of CHB

Five guidelines were reviewed including the Canadian Association for the Study of the Liver (CASL), NICE (National Institute for Health and Care Excellence), American Association for the Study of Liver Disease (AASLD), European Association for the Study of the Liver (EASL), and Asian-Pacific Consensus guidelines. These guidelines/consensus statements generally aligned and recommended that tenofovir or entecavir be used as first-line treatment for treatment-naïve patients. The greatest variation in recommendation was found in the NICE guidelines which recommended pegylated interferon as first-line therapy when possible. All guidelines recommend tenofovir and only one guideline recommended adefovir plus lamivudine as first-line treatment for lamivudine-failed patients.

Part C: Impact of different drug reimbursement schemes CHB treatments

There is a lack of literature investigating various reimbursement schemes for treatments of CHB. Only two studies were found and they both explored the impact of coverage compared to no coverage on clinical outcomes and adherence to policy.

Part D: Summary of Selected Topics

CHB Treatment Resistance: Treatments currently approved for CHB are often required as long-term treatment to maintain the viral suppression. Over prolonged periods of treatments drug resistance to some of the medications may occur. Drug resistance decreases the susceptibility of a virus to the inhibitory effect of a drug and impacts the efficacy of the treatment. Prevalence of resistance varies across treatments, with the highest level of resistance found with lamivudine (70-80% within 5 years) and lowest with tenofovir (0%).^{1, 21, 2} Several guidelines have included management recommendations of patients with documented hepatitis B resistance.

CHB Treatment in Pregnant Patients: Information on treatment recommendations for pregnant patients is noted as a place for possible changes to the current Exceptional Access Program criteria for CHB treatments. Guidelines suggest that tenofovir, telbivudine or lamivudine be used during pregnancy in order to prevent perinatal HBV transmission in women with high viral loads or in women with significant fibrosis or cirrhosis. Tenofovir and telbivudine are the only class B pregnancy drugs of all hepatitis B treatments.

Age Recommendations for CHB treatment: In Ontario, the Exceptional Access Program provides age-related requirements for reimbursement of hepatitis B treatments. Current criteria require more severe clinical prognosis for those below the age of 40. There is little consistent evidence to suggest a specific cut-off, although there is evidence to support age as a clinically important factor.

Health Canada warnings and advisories: Health Canada issued an information release in 2007 regarding drug resistance in HIV co-infected patients treated with entecavir. Health Canada issued an advisory in 2008 regarding increased risk of peripheral neuropathy associated with the use of telbivudine.

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Introduction

Hepatitis B is an infectious illness caused by the hepatitis B virus and affects the liver of infected individuals.^{3, 4} Outcomes of poor disease control can lead to serious cirrhosis and hepatocellular carcinoma.^{3, 4} There are currently 7 possible treatments available in Canada: standard interferon, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, and tenofovir.

Chronic hepatitis B (CHB) is a global public health concern with an estimated 360 million people infected worldwide.³⁻⁶ Prevalence of CHB varies greatly by region, with the highest rates found in sub-Saharan Africa and east Asia.³⁻⁶ In Canada, it is estimated that close to 600,000 people are chronically infected with CHB. CHB is largely considered a disease of immigrants with an estimated 6% prevalence, compared to 1% in Canadian born individuals.^{5, 7} Rates are also higher in aboriginal individuals with an estimated prevalence of 4%.^{5, 7} CHB can be a serious and life-threatening infection if untreated with patients progressing to end-stage liver disease and developing hepatocellular carcinoma.^{3, 7, 8} It is estimated that the rate of liver failure is 20-25% and rate of hepatocellular carcinoma is around 5% for patients with CHB.^{3, 7-9} In Ontario, CHB was ranked the fourth most common cause of death among infectious diseases, with an estimated 346 deaths per year.¹⁰

The goal of any CHB treatment is to prevent or reverse liver disease progression and minimize risk of development of hepatocellular carcinoma, decrease risk of transmission, and improve quality of life.^{11, 12} CHB treatments are categorized into two groups of treatments: oral nucleos(t)ides and interferons. Oral nucleos(t)ides include adefovir, entecavir, telbivudine, tenofovir, and lamivudine. There are two available interferons: standard interferon and pegylated interferon. In general, oral nucleos(t)ides are often a lifelong and continuous treatment. Interferons are used as a finite treatment regimen (usually over 48) but in a proportion of (25-40%) patients seroconversion is achieved and will minimize the need for prolonged chronic treatment.^{11, 12} Selection of treatment is complex and takes into account many factors including but not limited to: serum alanine aminotransferase (ALT), markers of liver damage, viral levels, age, and past-treatment.^{11, 12}

The objectives of this report are:

- **Part A:** To summarize coverage of treatments for CHB through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- **Part B:** To summarize the guidelines for the treatment of CHB
- **Part C:** To review the evidence relating to the impact of different drug reimbursement schemes for chronic hepatitis B treatments on patient access and/or utilization and costs

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability and costs of chronic hepatitis B treatments in Canada

In Canada, there are currently 7 possible treatments available in Canada: standard interferon, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. These drugs are available as oral tablets or as oral solutions, and as injectables (for subcutaneous administration) for the interferon based regimens. Exhibit 1 outlines the dosage forms and costs (based on wholesale costs) for treatments. Only 3 of the 7 agents have an available generic option.

Exhibit 1: Treatments for Hepatitis B available in Canada

Drug Name	Brand name	Manufacturer	Availability	Dosage form	Generic available	Monthly cost*	Date available
Entecavir	Baraclude	Bristol-Myers Squibb	0.5 and 1 mg 0.05 mg/ml	Oral Tablet and Solution	Yes	Generic- \$495.00 Brand - \$696.30	June 2006
Lamivudine	Heptovir	Glaxosmithkline	100 mg 5 mg/ml	Oral Tablet and Solution	Yes	Generic- \$105.95 Brand- \$149.04	December 1998
Adefovir	Hepsera	Gilead Sciences	10 mg	Oral Tablet	Yes	Generic- \$613.00 Brand - \$770.23	April 2006
Telbivudine	Sebivo	Novartis	600 mg	Oral Tablet	No	\$580.63	December 2006
Tenofovir	Viread	Gilead Sciences	300 mg	Oral Tablet	No	\$594.01	March 2004
Interferon alfa-2b	Intron A	Merck	10, 18, 25, 30, 60 million IU/ml in powder, ready-to- use solution, and multi-dose pen	Injection Solutions	No	\$1,593.00	March 1997
Pegylated interferon 2a	Pegasys	Hoffman-La Roche	180 mcg/0.5 and 1 ml in pre- filled syringes and vials	Injection Solutions	No	\$1,670.48	May 2004

*Based on costs obtained from McKesson (Accessed: March 27, 2015). Based on a 30 day supply at the lowest recommended dose

Summary

- Treatment of chronic hepatitis B is available in oral formulations (tablets and solution) and injectable solutions.
- Oral therapies range in cost from \$149.50 to \$613.00 per month. Interferon costs were both around \$1,600 per month. Only 3 of the 7 agents have a generic available.

Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. No review was completed for lamivudine, interferon alfa-2b, and pegylated interferon 2a, as these products were available prior to 2003. For the newer agents that were reviewed by the CDR, a summary of recommendations is found in Exhibit 2. Note that we only looked at indications for medications related to CHB; non-CHB indications were not reviewed.

Exhibit 2: Summary of Common Drug Review recommendations for chronic hepatitis B treatments

Product	Review #1 with recommendation	Review #2	Recommended Use
Adefovir	Hepsera (2006) Hepatitis B Do Not List	Hepsera (2007) Hepatitis B List with Criteria	Used in combination with lamivudine in patients who fail lamivudine.
Entecavir	Baraclude (2007) Hepatitis B List with Criteria	N/A	Recommended for patients with cirrhosis only.
Telbivudine	Sebvio (2006) Hepatitis B Do Not List	N/A	N/A
Tenofovir	Viread (2009) Hepatitis B List with Criteria	N/A	Recommended for patients with cirrhosis only.

Product listing in Ontario

All hepatitis B treatments (except telbivudine and pegylated interferon) are funded by the Ontario Public Drug Programs through the Exceptional Access Program. A summary of the listing criteria for each drug can be found in Exhibit 3.

Exhibit 3: Summary of Exceptional Access Program requirements for chronic hepatitis B treatment

Product	EAP Criteria – Completed Annually (except post-liver transplant)
Adefovir	<ul style="list-style-type: none"> - <i>Proven lamivudine resistance OR virologic breakthrough</i> <ul style="list-style-type: none"> ○ <i>Both with Stage 3 Liver Fibrosis or greater OR</i> ○ <i>Evidence of Cirrhosis</i>
Entecavir	<ul style="list-style-type: none"> - <i>Treatment Naïve patients with high viral load AND</i> <ul style="list-style-type: none"> ○ <i>Both with Stage 4 Liver Fibrosis or greater OR</i> ○ <i>Evidence of Cirrhosis</i> - <i>Proven lamivudine failure</i> <ul style="list-style-type: none"> ○ <i>Evidence of Cirrhosis</i> - <i>Proven lamivudine failure AND adefovir failure</i> <ul style="list-style-type: none"> ○ <i>Evidence of Cirrhosis</i> - <i>Proven lamivudine resistance AND cirrhosis</i> <ul style="list-style-type: none"> ○ <i>Adefovir Failure OR Contraindication to Adefovir</i>
Lamivudine	<p><i>FIRST LINE</i></p> <ul style="list-style-type: none"> - <i>Treatment Naive patients</i> <ul style="list-style-type: none"> ○ <i>>40 years of age</i> <ul style="list-style-type: none"> ▪ <i>Consistently High ALT levels</i> ▪ <i>Both with Stage 3 Liver Fibrosis or greater OR</i> ▪ <i>Evidence of Cirrhosis</i> ○ <i><40 years of age</i> <ul style="list-style-type: none"> ▪ <i>Both with Stage 3 Liver Fibrosis or greater OR</i> ▪ <i>Evidence of Cirrhosis</i> - <i>Treatment Naive patients (any age) who are receiving an organ transplant/immunosuppressed</i> <ul style="list-style-type: none"> ○ <i>Detectable Viral Load AND</i> ○ <i>Consistently High ALT levels</i> - <i>Treatment Naive patients (any age) who are receiving chemotherapy</i> <ul style="list-style-type: none"> ○ <i>Note: Length of Chemotherapy + 6 months</i> <p><i>Note: Can be used in combination with Adefovir. See above.</i></p>
Tenofovir	<ul style="list-style-type: none"> - <i>Treatment Naïve patients with high viral load AND</i> <ul style="list-style-type: none"> ○ <i>Both with Stage 4 Liver Fibrosis or greater OR</i> ○ <i>Evidence of Cirrhosis</i> - <i>Lamivudine Failure/resistance/breakthrough</i> <ul style="list-style-type: none"> ○ <i>Evidence of inadequate response AND</i> ○ <i>Both with Stage 3 Liver Fibrosis or greater OR</i> ○ <i>Evidence of Cirrhosis</i>
Interferon alfa-2b	<ul style="list-style-type: none"> - <i>Patients less than 50 years of age AND</i> <ul style="list-style-type: none"> ○ <i>No cirrhosis AND</i> ○ <i>High ALT and HBV</i>

Summary

- In Ontario, chronic hepatitis B treatments (with the exception of telbivudine and pegylated interferon) are listed as EAP. Criteria for treatment are complex and based on clinical presentation
- Lamivudine is covered as the first-line treatment. Entecavir and tenofovir are limited to patients with more severe disease or those that fail lamivudine.
- Interferon is reserved for patients less than 50 years of age and pegylated interferon is not covered.

Public Plan Listings in Canada

Part 1: Listing Status

Exhibit 4: Public plan listings in Canada for Chronic Hepatitis B treatments

Drug	Trade name/generic	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB / NU / NW
Entecavir	Baraclude	RES											
Lamivudine	Heptovir	RES	RES	RES	FB	RES	FB	FB	RES	NAB	NAB	FB	FB
Adefovir	Hepsera	RES	NAB										
Telbivudine	Sebivo	NAB											
Tenofovir	Viread	RES	RES	RES	RES	RES	FB	RES	RES	FB	RES	RES	NAB
Interferon alfa-2b	Intron A	RES	NAB	RES	FB	RES	FB	FB	RES	NAB	RES	NAB	FB
Pegylated interferon 2a	Pegasys	NAB	RES	RES	NAB	NAB	FB	RES	RES	NAB	RES	NAB	NAB

NAB=not a benefit

RES=restricted listing with specified criteria (e.g., special authorization, exception drug status)

FB=full benefit

Part 2: Telephone Interview with Public Drug Program Representatives

A representative from each public drug program was invited to participate in a 30 minute telephone interview to gather further information about formulary listing of drugs used to treat chronic hepatitis B. Exhibit 4 summarizes the information obtained in the interviews.

Exhibit 5: Summary of interviews with representative from public drug program

Province	Listing	What was the basis for listing/change in listing?
British Columbia	Restricted (enforced)	Criteria reviewed in 2008/2009 Standard chronic hepatitis B form is required for approval of the medications Adefovir, entecavir, tenofovir, lamivudine, interferon alfa-2b require special authorization for coverage. No coverage for Pegasys, as no requests for this drug for treatment of chronic hepatitis B
Saskatchewan	Restricted (enforced)	Criteria reviewed in October 2010 (no changes made) Adefovir, entecavir and tenofovir: criteria based on CDEC recommendations. Intron and Pegasys require special authorization for coverage
Manitoba	Restricted (enforced), general listing (lamivudine, interferon alfa-2b)	Limited number of physicians prescribe treatment for chronic hepatitis B Adefovir, entecavir, tenofovir: criteria based on CDEC recommendations For tenofovir, requests have been made for use of this drug in patients without cirrhosis No coverage for Pegasys, as no requests for this drug for treatment of chronic hepatitis B
Nova Scotia	Restricted (enforced)	Criteria reviewed in 2007 Adefovir, entecavir, tenofovir: criteria based on CDEC recommendations Intron and Pegasys require special authorization for coverage
Prince Edward Island	Restricted, general listing (tenofovir)	Adefovir and entecavir added to formulary (restricted) in April 2014 Adefovir, entecavir: criteria based on CDEC recommendations Tenofovir: restrictions removed in March 2009 (at that time only covered for HIV-infected patients) No coverage for Pegasys, as no requests for this drug for treatment of chronic hepatitis B
New Brunswick	Restricted, general listing (lamivudine, interferon alfa-2b)	Adefovir, entecavir and tenofovir: criteria based on CDEC recommendations.
NIHB	Restricted, general listing (lamivudine, interferon alfa-2b)	Entecavir: criteria based on CDEC recommendations Tenofovir, adefovir and Pegylated interferon 2a are not listed on the NIHB formulary (no requests for these agents)
Yukon	Restricted, general listing (lamivudine)	Entecavir, tenofovir: approval on a case-by-case basis No coverage for Intron A or Pegasys, as no requests for these drugs for treatment of chronic hepatitis B

Restriction Criteria

In order for patients to be eligible for publically funded treatments for chronic hepatitis B, various jurisdictions use restriction criteria based on the CDEC recommendations.

Summary

- In most provinces, the majority of treatments are covered. Five provinces have lamivudine listed as a general benefit.
- Telbivudine is not covered in any province and pegylated interferon is only available in 6 of 12 jurisdictions.
- Quebec has the most treatments listed as general benefits with 4 of the 7 available. The most restrictive jurisdiction is PEI and NIHB with only 3 of the 7 available.

Selected International Jurisdictions

United States

As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list (“formulary”) has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider. Prior authorization is often based on failure of a first-line treatment or severity of disease.

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.¹³ Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval.¹⁴ In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix 3 for examples of copayments with tiered formulary systems). (Exhibit 5)

Exhibit 6: Listing of treatments for CHB for select plans in the United States

Drug Plan	Adefovir	Entecavir	Lamivudine	Telbivudine	Tenofovir	Interferon alfa-2b	PEG interferon-2b
AETNA Preferred List (3-Tier system) (www.aetna.com)	Tier 1	Tier 3	Tier 3	Tier 3 (Tier 1 G)	Tier 2	NC	Tier 2
Amerigroup Medication Formulary (Medicare markets in Florida, Louisiana, Maryland, Nevada, New Jersey and Washington) (www.Providers.amerigroup.com)	Tier 5 (Specialty)	Not-Listed	Tier 3 (Preferred brand)	Tier 5 (Specialty) – Prior Authorization	Tier 5 (Specialty)	Tier 5 (Specialty) – Prior Authorization	Tier 5 (Specialty) – Prior Authorization
Blue Cross Blue Shield of South Carolina Preferred Drug List (www.southcarolinablues.com)	Preferred	Preferred	Preferred	Non-Preferred	Preferred	Preferred	Preferred
Blue Cross Blue Shield of Texas Standard Preferred Drug List (2015) (www.bcbstx.com)	Preferred	Preferred	Preferred	NC	Preferred	NC	Prior Authorization
Illinois Medicaid Preferred Drug List* http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf	Non-preferred	Preferred	Non-Preferred	Non-Preferred	Non-preferred	NC	Non-Preferred
Kaiser Permanente 2015 Medicare Part D Comprehensive Formulary (5-tier system) (www.healthy.kaiserpermanente.org)	Tier 2	Tier 2	Tier 2	Tier 4	Tier 5	Tier 5	Tier 5
Oregon Fee-for-Service Enforceable Physical Health Preferred Drug List 2015 (http://www.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx)	Non-preferred	Non-preferred	Preferred	Non-preferred	Preferred	Non-preferred	Non-preferred
Texas Medicaid Preferred Drug List (http://www.txvendordrug.com/pdl/)	Preferred	Preferred	Preferred	Preferred	Preferred	Preferred	Preferred
WellCare Comprehensive Formulary (Medicare Advantage Plans) (covers New York, Connecticut, Florida, Georgia, Hawaii and others) (5-tier system) (https://www.wellcare.com/medicare_formulary/new_york)	Tier 5	Tier 1	Tier 4	Tier 5	Tier 5	Tier 5	Not Listed
Wellmark Prior authorization/Step therapy (http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx)	Tier 1	Tier 1	Tier 2	Tier 2	Tier 2	Not listed	Not Listed

Other Countries

Australia: In Australia, the Pharmaceutical Benefits Scheme (PBS) restricts some treatments for Chronic Hepatitis B to specific populations. The criteria are more relaxed than in Ontario allowing for greater access to newer agents.

Exhibit 7: Treatments of Chronic Hepatitis B (Australia)

Product	Criteria
Adefovir	<ol style="list-style-type: none"> 1. Patients without cirrhosis who have failed therapy and who satisfy all of the following criteria: (a) elevated ALT levels and (b) elevated HBV DNA 2. Patients with cirrhosis who has failed therapy and who has detectable HBV DNA.
Entecavir	<ol style="list-style-type: none"> 1. Patients without cirrhosis who have failed lamivudine and who satisfy all of the following criteria:(a) Elevated serum ALT levels and (b) elevated HBV DNA 2. Patients with cirrhosis who have failed lamivudine and who have detectable HBV DNA.
Lamivudine	<ol style="list-style-type: none"> 1. Patients without cirrhosis who satisfy all of the following criteria: (a) elevated HBV DNA and (b) evidence of liver injury 2. Patients with cirrhosis who have detectable HBV DNA.
Telbivudine	<ol style="list-style-type: none"> 1. Patients without cirrhosis who are treatment naive and satisfy all of the following criteria: (a) Elevated HBV DNA levels, (b) Evidence of chronic liver injury 2. Patients with chronic hepatitis B with cirrhosis who are treatment naive and who have detectable HBV DNA.
Tenofovir	<ol style="list-style-type: none"> 1. Patients must meet the following criteria: (a) Patient must not have cirrhosis, (b) treatment naive, (c) have elevated HBV DNA levels, and (d) have evidence of chronic liver injury
Interferon alfa-2b or Peginterferon 2B	<ol style="list-style-type: none"> 1. Patients without cirrhosis who satisfy all of the following criteria: (a) Elevated HBV DNA levels and (b) Evidence of chronic liver injury as determined 2. Patients with cirrhosis who have detectable HBV DNA.

*New Zealand*¹⁵: In New Zealand, the Pharmaceutical management Agency (PHARMAC) is the agency that decides which medicines, medical devices and related products are subsidized. Exhibit 7 outlines the funding hepatitis B treatments. Initial applications for treatment are limited to specialists (gastroenterologists or infectious disease) and some general practitioners.

Exhibit 8: Treatments of Hepatitis B in New Zealand

Product	Criteria
Adefovir	<ul style="list-style-type: none"> Lamivudine resistance based on raised ALT, high viral load, and detection of mutation. If patient is cirrhotic than must be used in combination with lamivudine. Monotherapy only approved for non-cirrhotic patients
Entecavir	<ul style="list-style-type: none"> Treatment naïve patients with high ALT or fibrosis stage 3 or cirrhosis Patients must not be coinfectd (Hep C or HIV or Hep D)
Lamivudine	<ul style="list-style-type: none"> Can be prescribed by many specialists Use is limited to transplant, immunosuppressed, and chemotherapy patients
Telbivudine	<ul style="list-style-type: none"> Not listed
Tenofovir	<ul style="list-style-type: none"> Patients must have failed/resistance to either lamivudine, adefovir or entecavir and must have high viral load or cirrhosis Used in pregnant patients
Interferon alfa-2b or PEGinterferon 2B	<ul style="list-style-type: none"> Limited to treatment naïve patients with the following: High ALT and HBeAg positive or fibrosis level 2, no co-infection

Summary

- In the United States, most drug plans (in particular Medicaid-based plans) cover only selected therapies (i.e., preferred). Most plans list adefovir or entecavir as the preferred treatment. In general, those medications available as generic are most often considered “preferred”.
- In Australia, the reimbursement recommendations are more aligned with international guidelines allowing for access to tenofovir as first-line for treatment-naïve patients
- In New Zealand reimbursement of hepatitis B drugs limits prescription of most treatments to specific specialists. Entecavir is first-line for treatment naïve patients. Tenofovir is available first-line to pregnant patients.

Part B: Guidelines for the treatment of Chronic Hepatitis B

Various consensus recommendations and guidelines are available for the management of patients with chronic hepatitis B. We concentrated our review of recommendations related to the first-line treatment recommendations of chronic hepatitis B. Further details on treatment initiation are available in Appendix 4.

Canadian Association for the Study of the Liver (CASL)- 2012⁷

The Canadian Association for the Study of the Liver updated the guidelines, in light of new data from randomized controlled trials and changes in other international guidelines. Their recommendations aim to give guidance for the treatment of patients with chronic hepatitis B in the Canadian context.

Recommendation: The guidelines recommend tenofovir or entecavir as the first-line treatment for treatment-naïve patients due to their low rates of resistance. They also recommend tenofovir as first-line therapy for lamivudine resistant patients. Pegylated-interferon remains a recommended first-line treatment for some patients.

NICE (National Institute for Health and Care Excellence): Diagnosis and management of chronic hepatitis B in children, young people and adults¹⁶

This guideline, which was initially developed in 2009 and updated in 2013, is based on the best available evidence for the treatment and care of patients with chronic hepatitis B. The major recommendations related to the use of treatments in patients with chronic hepatitis b are as follows:

Recommendation: For patients with hepatitis B and compensated liver disease offer a 48-week course of peginterferon as first-line. Tenofovir is recommended as a second-line treatment in those that do not seroconvert after peginterferon or unable to tolerate peginterferon. Entecavir was listed as a second line therapy for those unable to tolerate tenofovir.

American Association for the Study of Liver Disease (AASLD) – 2009¹⁷

This guideline, which was initially developed in 2007 and updated in 2009, is based on the best available evidence for the treatment and care of patients with chronic hepatitis B. The major recommendations related to the use of treatments in patients with chronic hepatitis b are as follows:

Recommendation: The AASLD guidelines recommend tenofovir or entecavir as the first-line treatment for treatment-naïve patients due to their low rates of resistance. They also recommend tenofovir as first-line therapy for lamivudine resistant patients. Interferon therapy remained a recommended a first-line treatment for patients without cirrhosis. Peginterferon was recommended over interferon.

EASL Clinical Practice Guidelines: Management of Chronic hepatitis B virus Infection¹¹

The European Association for the Study of the Liver guidelines for the management of hepatitis B were revised in 2009. Recommendations for the treatment of chronic hepatitis B were made.

Recommendation: The EASL guidelines also recommend tenofovir or entecavir as the first-line treatment for treatment-naïve patients due to their low rates of resistance and cited potency. They also recommend tenofovir as first-line therapy for lamivudine resistance patients. Interferon therapy remained a recommended first-line treatment for patients without cirrhosis. Peginterferon was recommended over interferon.

Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update¹⁸

The Asian-Pacific Association for the Study of the Liver guidelines for the management of chronic hepatitis B were revised in 2012 since their previous guidelines published in 2008. Recommendations for the treatment of chronic hepatitis B were made.

Recommendation: This guideline also recommends tenofovir or entecavir as the first-line treatment for treatment-naïve patients due to their low rates of resistance and cited potency. They do cite the need for pharmaco-economic studies for each country to help inform the decision of second-line therapy. They also recommend tenofovir or adding adefovir to lamivudine as first-line therapy for lamivudine resistant patients. Interferon therapy remained a recommended first-line treatment for patients without cirrhosis.

Summary

- There have been 5 major guidelines/consensus recommendations published for the treatment of CHB.
- Four of the 5 guidelines recommend tenofovir or entecavir as first-line for treatment naïve patients. Tenofovir is recommended as first-line for lamivudine-resistant patients in all guidelines.
- The greatest variation in recommendations was those of the NICE guidelines which recommended peginterferon as first-line therapy when possible.

Part C: Impact of different drug reimbursement schemes for CHB treatments

Methods

A literature search was conducted in PubMed using the terms: (Hepatitis B) AND (healthcare accessibility OR health policy OR reimbursement incentive OR national health programs OR cost sharing). Bibliographies of identified articles were scanned for additional relevant articles. We aimed to find studies that assessed the reimbursement or drug policy related to hepatitis B treatments.

Results

The original search yielded 374 studies, of which only 2 studies were identified for inclusion through the literature search.^{19, 20} These studies reviewed the clinical impact of initiation of programs for treatment of CHB in Taiwan and Pakistan. Neither program explored how variations in their drug coverage program impacted or changed outcomes. The study from Taiwan explored the impact of the introduction of a national drug program on the incidence of hepatocellular carcinoma. They concluded that there is a strong temporal relationship with the introduction of the program and the decrease in the incidence of hepatocellular carcinoma.¹⁹ Qureshi et al. explored the impact of national viral hepatitis treatment program in Pakistan. Less than 6% of the patients in the program had a diagnosis of CHB. They found little adherence to their inclusion guidelines (18.5%) and poor follow-up. These shortcomings were thought to be associated with limited resources for proper lab-testing to allow for proper selection and implementation of therapy.²⁰

Summary

- There is a lack of literature investigating various reimbursement schemes for chronic hepatitis B and their impact on clinical outcomes.

Part D: Summary of Selected Topics

CHB Treatment Resistance

The goals for treatment of patients with CHB are to prevent disease progression and prolong the survival of patients.²¹ Seven therapies have been approved for the treatment of CHB in Canada namely: interferon alfa, pegylated interferon alfa, and five nucleos(t)ide analogues. These nucleos(t)ide analogues are divided into three groups based on their structure:

- Nucleoside analogues:
 - L-nucleosides (lamivudine, telbivudine)
 - D-cyclopentanes (entecavir)
- Nucleotide analogues:
 - Alkyl phosphonates (adefovir, tenofovir)

The oral therapies currently approved only control the hepatitis B viral infection, but do not eradicate it.²² Therefore, most patients will require long-term treatment to maintain the HBV DNA suppression. However, resistance to the oral agents affects the long-term treatment with some of these agents. Antiviral drug resistance is defined as the decreased susceptibility of a virus to the inhibitory effect of a drug, resulting from a series of adaptive mutations under the selection pressure of antiviral treatment.¹ Clinically, antiviral resistance is suspected when serial HBV DNA testing shows increases in viral load of more than 10-fold compared with nadir.⁷ Lamivudine has a low genetic barrier to resistance, adefovir

and telbivudine have an intermediate barrier to resistance and entecavir and tenofovir have high genetic barrier to resistance.²³ In patients who are nucleos(t)ide-analogue naïve, lamivudine resistance occurs frequently and is reported in up to 80% of patients treated for five years. This compares to approximately 30% of patients treated with adefovir at five years for HBeAg-negative patients. Over a 6-year period, resistance to entecavir remains low (approximately 1-2%). Similarly, no tenofovir resistance was noted during the initial 3-year trials.²¹ (Table 1)

Exhibit 9: Cumulative annual incidence of resistance among patients who are nucleos(t)ide analogue naïve

Antiviral	Proportion of patients (%) who develop resistance
Lamivudine	1 year: 23-24% 3 years: 49-55% 5 years: 70-80%
Adefovir*	1 year: 0% 3 years: 11% 5 years: 29%
Telbivudine	1 year: 5% 3 years: no data
Entecavir	1 year: 0.2% 3 years: 1-2% 5 years: 1-2%
Tenofovir	1 year: 0% 3 years: 0% 5 years: 0%

*for HBeAg-negative patients

Multidrug resistance during treatment for CHB is defined by the occurrence of resistance to both nucleoside and nucleotide analogues.² Cross-resistance is present in drugs belonging to the same class (e.g., lamivudine and telbivudine), or in drugs belonging to difference classes (e.g., lamivudine and adefovir).² Approximately 51% of lamivudine-refractory patients develop entecavir resistance in 5 years. No tenofovir resistance has been detected among lamivudine-treated patients.^{21, 24} (Table 2)

Exhibit 10: Cross-resistance profiles of antiviral drugs in CHB

Classification	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
LAM + LdT resistance	R	R	I	S	S
ADV resistance	S	S	S	R	I
LAM + LdT + ADV resistance	R	R	S	R	I
ADV + TDF resistance	R	R	S	R	R
ETV resistance	R	R	R	S	S
TDF resistance	R	S	S	NA	R

LAM: lamivudine; LdT: telbivudine; ADV: adefovir; ETV: entecavir; TDF: tenofovir; S: sensitive; I:

intermediate; R: resistant; NA: not available

Risk factors for the development of resistance depend on the baseline characteristics of the patients, viral factors, drug properties and treatment regimens. For development of lamivudine resistance, male gender, older age, high body mass index, high alanine aminotransferase (ALT) level, high HBV-DNA concentration, high histological score and presence of core promoter mutations have been identified as risk factors.¹ Patients with undetectable HBV-DNA at week 24 of lamivudine treatment had a substantially lower rate of virologic breakthrough. In patients with non-response (<1 log₁₀ drop in HBV DNA at week 12) or a partial response (detectable HBV DNA at week 24) to lamivudine, treatment should be adapted to a more potent drug or the addition of a second drug.²⁵ Another important factor to consider when evaluating treatment failure is adherence to treatment. Retrospective studies have shown that problems in treatment adherence may lead to treatment failure, including partial virological response and viral breakthrough.²¹ It has been suggested that the use of potent drugs (such as tenofovir and entecavir) may minimize resistance rates in non-adherent patients.

There have been potential consequences of viral resistance cited, including acute exacerbations of the CHB (resulting in increases in ALT concentrations) and potentially more rapid progression to acute liver failure.^{2, 21} As well, drug resistance mutations have been detected in treatment-naïve patients, although the clinical relevance of this finding is uncertain.²¹ For patients who develop multidrug-resistant hepatitis B virus, there may be an increased cost of treatment as combination therapy may be needed for some patients.²⁶

Several guidelines have included management of patients with documented hepatitis B resistance. In general, entecavir is no longer recommended in lamivudine-experienced patients due to increased rate of resistance to entecavir over time. Guidelines suggest the addition of tenofovir, or if tenofovir not available, the addition of adefovir to lamivudine (Table 3)

Exhibit 12: Recommendations from guidelines for oral rescue therapy in CHB patients with antiviral drug resistance

Guideline	Lamivudine resistance	Adefovir resistance	Entecavir resistance
Canadian Association for the Study of the Liver (2012) ⁷	TDF	LAM, LDT, ETV	ADV, TDF
National Institute for Health and Care Excellence (2013) ¹⁶	TDF	No recommendations	None stated
European Association for the Study of the Liver (2012) ¹¹	TDF Add ADV if TDF not available	Nucleos(t)ide naïve: ETV, TDF Lamivudine resistance: TDF and add nucleoside analogue	TDF or TDF + emtricitabine

American Association for the Study of Liver Diseases (2009) ¹⁷	Add ADV or TDF Switch to TDF + emtricitabine	Add LAM Switch to TDF + emtricitabine Switch to or add ETV	Switch to TDF or TDF + emtricitabine
Asian-Pacific Association for the Study of the Liver (2012) ¹⁸	Add ADV Switch TDF	Add LAM, LDT, ETV Switch TDF	Add TDF or ADV

CHB Treatment in Pregnant Patients

It is recommended that tenofovir, telbivudine or lamivudine be used during pregnancy in order to prevent perinatal HBV transmission in women with high viral loads or in women with significant fibrosis or cirrhosis.

Before pregnancy: Women with HBV who have fibrosis or cirrhosis before pregnancy, should be treated with pegylated-interferon (PEG-IFN) therapy urgently. If a woman does not have either fibrosis or cirrhosis, she can wait until post-partum to receive treatment. If contraindications to PEG-IFN exist, the women can take tenofovir instead. It is recommended that women wait until the end of the PEG-IFN treatment before becoming pregnant, however, if a woman becomes pregnant during treatment, her treatment should be changed to a drug designated safe for pregnancy. PEG-IFN should be avoided during pregnancy due to its anti-proliferative effects.

During pregnancy: Drugs which are safe during pregnancy include tenofovir and telbivudine, which are designated as FDA category B drugs (i.e. animal studies have shown no risk for the fetus but there are inadequate well-controlled human studies), or lamivudine, which has evidence of safety during pregnancy, although it is a FDA category C drug (i.e. animal studies have shown some risk to the fetus and there are inadequate well-controlled human studies). If a woman does not have fibrosis or cirrhosis but has high viral loads ($> 10^6$ IU/mL) during pregnancy, she should be treated with telbivudine, tenofovir or lamivudine during the third trimester of pregnancy in order to reduce the risk of perinatal transmission of HBV to the newborn.

After pregnancy: Close monitoring of hepatic flares is required, especially if the woman is not being treated.

Exhibit 13: FDA Pregnancy Ratings for Hepatitis B Treatments

	Lamivudine	Adefovir	Entecavir	Tenofovir	Interferon alfa-2b	Pegylated Interferon 2a	Telbivudine
Rating	C	C	C	B	C	C	B

Exhibit 14: Environmental Scan of International Guideline recommendations for Hepatitis B Treatment during Pregnancy

Canadian Association for the Study of the Liver ⁷	National Institute for Health and Care Excellence ¹⁶	American Association for the Study of Liver Diseases ¹⁷	The European Association for the Study of the Liver ¹¹	The Asian Pacific Organization for the Study of the Liver ¹⁸
<p>Before pregnancy:</p> <ul style="list-style-type: none"> ○ Pegylated interferon used if no contraindications (if low viral load, high ALT, genotype A or B) ○ Must delay pregnancy until end of course <p>During pregnancy:</p> <ul style="list-style-type: none"> ○ If treatment happening before pregnancy and patient has not yet reached treatment goals, treatment must be continued until goals are met, but with telbivudine, tenofovir or lamivudine ○ Initiate treatment during second or third trimester of pregnancy if high viral load ($>2 \times 10^6$ IU/mL or $>7 \log_{10}$ copies/mL), possibility of complications (threatened miscarriage, preterm delivery), or birth of an infant with previous prophylaxis failure, in order reduce chances of transmission ○ Tenofovir recommended as first-line treatment, and telbivudine or lamivudine is an alternative if tenofovir is contraindicated <p>After pregnancy:</p> <ul style="list-style-type: none"> ○ If treatment not initiated, patient should be monitored during pregnancy and postpartum for flares 	<p>Before pregnancy:</p> <ul style="list-style-type: none"> ○ No recommendation <p>During pregnancy:</p> <ul style="list-style-type: none"> ○ Offer tenofovir to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby ○ Monitor quantitative HBV DNA 2 months after starting tenofovir and ALT monthly after the birth to detect postnatal HBV flares in the woman <p>After pregnancy:</p> <ul style="list-style-type: none"> ○ Stop tenofovir 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment 	<p>Before pregnancy:</p> <ul style="list-style-type: none"> ○ No recommendation <p>During pregnancy:</p> <ul style="list-style-type: none"> ○ Women with Hepatitis B who are pregnant should inform their providers so Hepatitis B immune globulin and hepatitis B vaccine can be administered to their newborn upon delivery <p>After pregnancy:</p> <ul style="list-style-type: none"> ○ No recommendations 	<p>Before pregnancy:</p> <ul style="list-style-type: none"> ○ Women without fibrosis/cirrhosis should delay therapy until postpartum ○ Women with fibrosis/cirrhosis should receive Pegylated interferon therapy, unless it is contraindicated or has failed, in which case tenofovir can be used ○ If patient becomes unexpectedly pregnant, therapy should be changed to tenofovir <p>During pregnancy:</p> <ul style="list-style-type: none"> ○ Lamivudine, telbivudine or tenofovir can be given during last trimester for women with high levels of viremia to reduce risk of transmission (in addition to HBIg and HBV vaccination) <p>After pregnancy:</p> <ul style="list-style-type: none"> ○ Close monitoring of hepatic flares is important 	<p>Before pregnancy:</p> <ul style="list-style-type: none"> ○ Interferon-based therapy is best before pregnancy ○ Patient must not get pregnant until the end of therapy <p>During pregnancy:</p> <ul style="list-style-type: none"> ○ For mothers with high viral load ($>2 \times 10^6$ IU/mL), use of lamivudine, telbivudine or tenofovir is appropriate to prevent transmission ○ Telbivudine should be used as first-line therapy, then tenofovir <p>After pregnancy:</p> <ul style="list-style-type: none"> ○ No recommendations

Age Recommendations for Hepatitis B Treatment

In Ontario, the Exceptional Access Program provides age-related guidelines surrounding hepatitis B treatment. First-line therapy for treatment-naïve patients is either lamivudine or interferon-alpha treatment. When these treatments fail, tenofovir, adefovir and/or entecavir can be offered. To initiate lamivudine treatment for patients who are **over 40 years of age**, an HBV DNA > 1,000IU/mL AND three separate ALT levels $\geq 1.3 \times$ ULN within the 6 month period prior to treatment OR liver biopsy showing metavir stage 3 fibrosis OR documented evidence of cirrhosis is required. For patients under the age of 40 with similar HBV DNA levels > 1,000IU/mL, a liver biopsy showing metavir stage 3 fibrosis or greater OR documented evidence of cirrhosis is required. Other age-related guidelines include treatment initiation of interferon-alpha for patients under 50 years of age only.

The studies cited by international guidelines all demonstrate that advanced age is a risk factor for liver deterioration, cirrhosis, hepatocellular carcinoma (HCC), and reactivation of hepatitis B. The exact age range at which severe deterioration occurs is suggested as 40 years of age but the evidence is inconclusive. A small number of studies have explored the impact of age on CHB outcomes.²⁷⁻³² One small study demonstrated that, of the 25 patients under the age of 40 with high viral load and normal ALT included, only three had significant fibrosis.²⁷ However, with advanced age, risk of fibrosis was found to increase.²⁷ Another often cited study showed that younger patients are more likely to undergo HbeAg seroconversion.²⁸ Of the 483 patients in this study, seroconversion occurred before age 30 in 218 patients, from 31-40 years in 199 patients, and after 40 years in 66 patients.²⁸ This illustrates that, in older patients, the HBV infection is unlikely to independently resolve itself, and that liver deterioration is more likely. Contradictory to these findings, a large study on PEG-IFN therapy in HBeAg+ patients demonstrates that older age is a predictor of better response.²⁹

Exhibit 13: Review of age-related recommendations for Hepatitis B treatment initiation

Guidelines	Canadian Association for the Study of the Liver ⁷	National Institute for Healthcare and Excellence ¹⁶	American Association for the Study of Liver Diseases ¹⁷	The European Association for the Study of the Liver ^{11, 11, 18}	The Asian Pacific Organization for the Study of the Liver ¹⁸
	<ul style="list-style-type: none"> One of the predictors of seroconversion is age younger than 40 Predictors of poor response to IFN treatment – older than 40 years Hepatitis B carriers who should undergo regular screening include Asian men > 40 years, Africans > 20 years, Asian women > 50 years 	<ul style="list-style-type: none"> In people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3), consider 6-monthly surveillance for HCC if the person is older than 40 years and has a family history of HCC and HBV DNA greater than or equal to 20,000 IU/ml. Do not offer surveillance for HCC in people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3) who have HBV DNA less than 20,000 IU/ml and are younger than 40 years Offer liver biopsy to adults with a transient elastography score less than 6 kPa if they are younger than 30 years and have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart. Offer liver biopsy to children (≤ 18 years) with HBV DNA > 2,000 IU/mL and ALT > ULN on 2 consecutive tests 3 months apart 	<ul style="list-style-type: none"> If ALT levels are between 1-2 ULN, recheck ALT for 1-3 months; consider liver biopsy if age 40, ALT borderline or mildly elevated on serial tests. Consider treatment if biopsy shows moderate/severe inflammation or significant fibrosis HBV infected patients with ALT values close to the ULN may have abnormal histology and can be at increased risk of mortality from liver disease especially those above age 40 Liver biopsy is usually not necessary in young patients (below 30) who are HBeAg+ and have persistently normal ALT 	<ul style="list-style-type: none"> Immunotolerant patients: HBeAg+ patients under 30 years of age with persistently normal ALT levels and a high HBV DNA level, without any evidence of liver disease and without a family history of HCC or cirrhosis, do not require immediate liver biopsy or therapy. Follow-up at least every 3–6 months is mandatory. Consider liver biopsy or even therapy in such patients over 30 years of age and/or with a family history of HCC or cirrhosis. 	<ul style="list-style-type: none"> HBeAg+ subjects older than 40 years with persistently 'high normal' ALT levels may have significant hepatic necroinflammation or fibrosis HBeAg- carriers with normal ALT have risk of cirrhosis, decompensation and HCC correlated with advanced age at entry

Health Canada Alerts and Warnings

- Health Canada issued information in 2007 regarding a case-report of possible drug resistance in a HIV co-infected individual.³³ Based on this information, manufacturers of entecavir issued a warning of using the medication in co-infected patients.
 - Health Canada issued an advisory in 2008 regarding increased risk of peripheral neuropathy associated with the use of telbivudine.³⁴ Based on this advisory, manufacturers of telbivudine included a warning of the risk in the product monographs.
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Discussion

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability in Canada

- In Canada, 7 treatments for CHB (entecavir, lamivudine, adefovir, telbivudine, tenofovir, interferon alfa-2B, and pegylated interferon 2a) are available.
- Adefovir, lamivudine, and entecavir are available as generic formulations.
- Across Canada, the majority of the medications are restricted in access.

Public Plan Listing in Ontario

- In Ontario, treatments for CHB are available through the Exceptional Access Program.
- Telbivudine and Peginterferon are not available through the Exceptional Access program.
- Lamivudine is covered as first-line treatment, with entecavir and tenofovir limited to patients with more severe disease or those who fail lamivudine.

Public Plan Listing in Canada

- In most provinces, the majority of treatments are covered in some form. Five provinces have lamivudine listed as a general benefit.
- Telbivudine is not covered in any jurisdiction and pegylated interferon is only available in 6 of 12 Canadian jurisdictions.
- Quebec has the most treatments as general benefits with 4 of the 7 available. The most restrictive jurisdiction is PEI and NIHB with only 3 of the 7 available.

Selected International Jurisdictions

- In the United States, most drug plans (in particular Medicaid-based plans) cover only a selected therapy (i.e., “preferred”). Most plans list adefovir or entecavir as the preferred treatment. In general, those medications available as generic are considered “preferred”.
- In Australia, the reimbursement recommendations are more aligned with international guidelines allowing for access to tenofovir as first-line for treatment-naïve patients
- In New Zealand reimbursement of CHB drugs limits prescription of most treatments to specific specialists. Entecavir is first-line for treatment naïve patients. Tenofovir is available as first-line therapy to pregnant patients.

Part B: Guidelines for the treatment of CHB

Part B: Guidelines for the treatment of CHB

- Five guidelines/consensus statements were reviewed including Canadian Association for the Study of the Liver (CASL), NICE (National Institute for Health and Care Excellence), American Association for the Study of Liver Disease (AASLD), EASL Clinical practice guidelines, and Asian-Pacific Consensus

guidelines.

- In general, most guidelines recommend tenofovir or entecavir as first-line for treatment naïve patients. Tenofovir is recommended as first-line for lamivudine-resistant patients.
- The greatest variation of recommendations was those of the NICE guidelines which recommended peginterferon as first-line therapy when possible.

Part C: Impact of different drug reimbursement schemes for treatments of CHB

- There is a lack of literature investigating various reimbursement schemes for CHB and their impact on clinical outcomes.
- Two studies were found that assessed the impact of offering treatments for CHB and generally showed positive impact on clinical outcomes.

Part D: Summary of Selected Topics

CHB Treatment Resistance

- Over prolonged periods of treatments drug resistance to some of the medications may occur.
- Prevalence of resistance varies across treatments, with the highest level of resistance found with lamivudine (70-80% within 5 years) and lowest with tenofovir (0%).^{1, 21, 2}
- Several guidelines have included management recommendations of patients with documented hepatitis B resistance.

CHB treatment in Pregnant Patients:

- Information on treatment recommendations for pregnant patients is noted as a place for possible changes to the current exceptional access program criteria for CHB treatments.
- Guidelines suggest that tenofovir, telbivudine or lamivudine be used during pregnancy in order to prevent perinatal HBV transmission in women with high viral loads or in women with significant fibrosis or cirrhosis.
- Tenofovir and telbivudine are the only class B pregnancy drugs of all hepatitis B treatments.

Age Recommendations for CHB treatment:

- Guidelines suggest the age of 40 as an important clinical factor when choosing to initiate treatment
- Current EAP criteria require more severe clinical prognosis for those below the age of 40.
- There is little consistent evidence to suggest a specific cut-off, although there is evidence to support age as a clinically important factor.

Health Canada warnings and advisories:

- Health Canada issued an information release in 2007 regarding drug resistance in HIV co-infected patients treated with entecavir.
- Health Canada issued an advisory in 2008 regarding increased risk of peripheral neuropathy associated with the use of telbivudine.

Health Equity

In Ontario, treatments for CHB are available through the Public Drug formulary through the Exceptional Access program. No health equity issues have specifically been identified for Ontario. However, some commentaries from around Canada caution to the possible inappropriate and under treatment of CHB among immigrant and aboriginal populations.¹²

Conclusion

In Canada, 7 treatments for CHB (entecavir, lamivudine, adefovir, telbivudine, tenofovir, interferon alfa-2B, and pegylated interferon 2a) are available. Most public drug plans in Canada require special authorization prior to funding treatments. Telbivudine is not listed in any jurisdiction across Canada.

In Ontario, all treatments for CHB are available through the Exceptional Access Program. The criteria for reimbursement in Ontario differ from most international clinical guidelines; in Ontario, lamivudine is considered first-line therapy whereas guidelines, including the Canadian guidelines, recommend either tenofovir or entecavir as first-line therapy. Many US plans have selected entecavir or adefovir as the first line agent. Little information is available on the impact of drug reimbursement options on clinical outcomes.

Appendix 1: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
British Columbia	http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp
Alberta	https://idbl.ab.bluecross.ca/
Saskatchewan	http://formulary.drugplan.health.gov.sk.ca/
Manitoba	http://web6.gov.mb.ca/eFormulary/
Ontario	https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
Quebec	http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
New Brunswick	http://www.gnb.ca/0212/nbpdpformulary-e.asp
Nova Scotia	http://novascotia.ca/dhw/pharmacare/formulary.asp
Prince Edward Island	http://healthpei.ca/formulary
Newfoundland	http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp
Yukon Territories	https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961:::~:
NIHB (Non-insured Health Benefits Program)	http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fournir/pharma-prod/med-list/index-eng.php

Appendix 2: Interview Questions

How long have you listed treatments for CHB on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list CHB treatments this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Why are certain CHB treatments NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?
Do you have any special restrictions regarding the use of CHB treatments?

Appendix 3: Tiered cost-sharing options

Prescription Drug Plan	Tier 1 (generic)	Tier 2 (preferred brand)	Tier 3 (non-preferred brand)	Tier 4 (specialty)
Plan A	\$5	\$28	\$55	25%
Plan B	\$2	\$20	\$40	N/A
Plan C	\$10	\$25	50%	25%
Plan D	\$4	\$17	75%	25%

Adapted from:

<http://www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/medicare/medicarepartd/medicare-part-d-formularies-and-drug-coverage>

Appendix 4: Environmental Scan of International Guidelines for Hepatitis B Treatment Initiation

Guidelines	Canadian Association for the Study of the Liver (2012)	National Institute for Health and Care Excellence (2013)	American Association for the Study of Liver Diseases (2009)	The European Association for the Study of the Liver (2009)	The Asian Pacific Organization for the Study of the Liver (2012)
Treatment Initiation for treatment naïve patients	<p>1. HBeAg+ AND HBV DNA <20,000 IU/mL AND >1 x ULN for 3-6 months</p> <p>OR</p> <p>2. HBeAg+ AND HBV DNA <2,000 IU/mL AND >1 x ULN for 3-6 months</p>	<p>1. Adults ≥ 30 years AND HBV DNA > 2,000 IU/mL AND ALT >ULN on 2 consecutive tests 3 months apart</p> <p>OR</p> <p>2. Adults < 30 years AND HBV DNA > 2,000 IU/mL AND ALT >ULN on 2 consecutive tests 3 months apart AND (necroinflammation OR fibrosis evidence OR elastography score > 6 kPa)</p> <p>OR</p> <p>3. Adults with transient elastography score ≥ 11 kPa</p> <p>OR</p> <p>4. Adults with HBV DNA > 20,000 IU/mL AND ALT > ULN on 2 consecutive tests AND 3 months apart</p> <p>OR</p> <p>5. Children with significant fibrosis AND ALT > ULN on 2 consecutive tests 3 months apart</p>	<p>1. HBeAg+ AND HBV DNA >20,000 IU/mL AND ALT ≤ ULN AND (biopsy shows moderate/severe inflammation OR significant fibrosis)</p> <p>OR</p> <p>2. HBeAg+ AND HBV DNA >20,000 IU/mL AND (ALT > 2 x ULN for 1-3 months OR icteric or clinical decompensation)</p> <p>OR</p> <p>3. HBeAg- AND HBV DNA >20,000 IU/mL AND ALT > 2x ULN</p> <ul style="list-style-type: none"> Treatment may be considered in patients with HBV DNA 2,000-20,000 IU/mL (especially for patients of older age and with cirrhosis) <p>OR</p> <p>4. HbeAg+/- AND cirrhosis AND HBV DNA >2,000 IU/mL, compensated</p> <p>OR</p> <p>5. HbeAg+/-, cirrhosis, HBV DNA levels detectable OR undetectable, decompensated</p>	<p>1. HBV DNA > 2,000 IU/mL AND (ALT > ULN OR ALT is normal) AND (moderate to severe active necroinflammation OR at least moderate fibrosis)</p> <p>OR</p> <p>2. HbeAg+/- AND ALT > 2 x ULN AND HBV DNA > 20,000 IU/mL</p> <p>OR</p> <p>3. Compensated cirrhosis AND detectable HBV DNA (even if ALT is normal)</p> <p>OR</p> <p>4. Decompensated cirrhosis AND detectable HBV DNA levels</p>	<p>1. HBeAg+ AND HBV DNA ≥ 20,000 IU/mL AND ALT 2-5 x ULN (if for 3-6 months or if concerns for hepatic decompensation)</p> <p>2. HBeAg+ AND HBV DNA ≥ 20,000 IU/mL AND ALT > 5 x ULN (if HBV DNA < 2 x 10⁵ IU/mL, can choose to observe if no concerns for hepatic decompensation)</p> <p>3. HBeAg+ AND HBV DNA ≥ 20,000 IU/mL AND ALT normal – 2 x ULN AND moderate or greater inflammation or fibrosis on biopsy</p> <p>4. HBeAg- AND HBV DNA ≥ 2,000 IU/mL AND ALT > 2 x ULN (if for 3-6 months or if concerns for hepatic decompensation)</p> <p>5. HBeAg- AND HBV DNA ≥ 20,000 IU/mL AND ALT normal – 2 x ULN AND ≥ 40 years AND moderate or greater inflammation or fibrosis</p>

Guidelines	Canadian Association for the Study of the Liver (2012)	National Institute for Health and Care Excellence (2013)	American Association for the Study of Liver Diseases (2009)	The European Association for the Study of the Liver (2009)	The Asian Pacific Organization for the Study of the Liver (2012)
Treatment Specifications	<ul style="list-style-type: none"> • Tenofovir or entecavir is first-line therapy for treatment-naïve HBV patients • For patients with compensated hepatitis B cirrhosis AND <ul style="list-style-type: none"> ○ HBV DNA $\geq 2,000$ IU/mL – treat with entecavir or tenofovir, consider combination ○ HBV DNA < 2000 IU/mL – consider entecavir or tenofovir or close observation • For HIV and HBV-infected patients, treat with tenofovir AND (emtricitabine OR lamivudine) with anti-HIV drug 	<ul style="list-style-type: none"> • In HBeAg+/- adults/children with compensated liver disease, offer PEG-IFN as first-line • In adults with decompensated liver disease, offer entecavir if no history of lamivudine resistance <ul style="list-style-type: none"> ○ Offer tenofovir if there is history of lamivudine resistance ○ Reduce dose of tenofovir in people with renal impairment • In adults with Hepatitis C co-infection, offer PEG-IFN and ribavirin • In adults with Hepatitis D co-infection and significant fibrosis, offer PEG-IFN 	<ul style="list-style-type: none"> • PEG-IFN, tenofovir and entecavir are preferred first-line treatments for naïve adults • IFN-α and lamivudine are preferred first-line treatments for naïve children • Patients with compensated cirrhosis should be treated with nucleotide analogue (NA) therapy (specifically tenofovir or entecavir) • Patients with decompensated cirrhosis should be given lamivudine or telbivudine initially in combination with adefovir or tenofovir • HIV-infected individuals who are not on highly active antiretroviral therapy (HAART) and will not be on HAART in the near future should be treated with PEG-IFN or adefovir • HIV-infected individuals that need therapies that target both HBV and HIV should receive lamivudine plus tenofovir or emtricitabine plus tenofovir • HIV-infected individuals that are already on effective HAART that does not target HBV should be treated with PEG-IFN or adefovir (or tenofovir in case of lamivudine resistance) 	<ul style="list-style-type: none"> • Tenofovir and entecavir recommended as first-line therapy • For patients who need treatment of finite duration in order to achieve sustained off-treatment response (HBeAg+/- patients with high chance of anti-HBe seroconversion – defined as ALT >3 times ULN and HBV DNA less than 2×10^6 IU/ml or $6.3 \log_{10}$ IU/ml at baseline), PEG-IFN should be used • NAs can be used for finite treatment as well for HBeAg+ patients who seroconvert to anti-HBe on treatment, but treatment duration is unpredictable • Long-term treatment with NAs (tenofovir and entecavir should be used as first-line monotherapies) is recommended for HBeAg+ patients who do not develop anti-HBe seroconversion and HBeAg- patients. This strategy is also recommended in patients with cirrhosis irrespective of HBeAg status or anti-HBe seroconversion on treatment • Tenofovir and entecavir are preferred for patients with 	<ul style="list-style-type: none"> • In highly viremic patients with ALT level >5 times x ULN, use entecavir, tenofovir, telbivudine or lamivudine (if there is concern about hepatic decompensation) <ul style="list-style-type: none"> ○ Use IFN-based therapy in patients with no concern about hepatic decompensation. • For HBeAg-positive patients with ALT level between 2 and 5 times ULN, either IFN-based therapy or an NA can be used • HIV-infected individuals should receive antiretrovirals with tenofovir and emtricitabine or lamivudine <ul style="list-style-type: none"> ○ If the CD4 count > 500 and ART is not needed, adefovir or PEG-IFN can be used • In patients with HCV or HDV co-infection, determine which virus is dominant and treat accordingly • In patients with current or impending hepatic decompensation, entecavir or tenofovir should be used <ul style="list-style-type: none"> ○ Telbivudine, lamivudine or adefovir can be used in NA-naïve patients

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				<p>cirrhosis (PEG-IFN must be avoided)</p> <ul style="list-style-type: none"> • In HIV-infected individuals, tenofovir combined with emtricitabine or lamivudine plus a third agent active against HIV should be used • In a small number of HIV-infected patients with CD4 count >500/ml, HBV can be treated before anti-HIV therapy is given – PEG-IFN, adefovir or telbivudine can be used • If undetectable HBV DNA is not reached at 12 months, HIV-targeting treatment should be given • In HDV-infected individuals, PEG-IFN should be given • In HCV-infected individuals, NAs should be given 	

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<p>Treatment failure</p>	<p>Primary nonresponse is defined as a $< \log_{10}$ reduction in HBV DNA at week 12 or resistance which is defined as $< 2 \log_{10}$ reduction in HBV DNA at 24 weeks of antiviral therapy.</p> <ul style="list-style-type: none"> If receiving lamivudine or adefovir, can switch to tenofovir or entecavir at 24 weeks (in absence of lamivudine resistance) <p><i>Resistance-</i></p> <ol style="list-style-type: none"> Lamivudine resistance <ul style="list-style-type: none"> Addition of adefovir to lamivudine after virological breakthrough* and before clinical breakthrough** OR Tenofovir monotherapy Adefovir resistance <ul style="list-style-type: none"> Switch to lamivudine OR telbivudine OR entecavir Can also switch to tenofovir if rtN236T genetic mutation is absent Entecavir resistance <ul style="list-style-type: none"> Switch to adefovir OR tenofovir Telbivudine resistance <ul style="list-style-type: none"> Switch to adefovir OR tenofovir* <p>Increase in viral</p>	<ul style="list-style-type: none"> In HBeAg+/- adults/children with compensated liver disease who don't undergo HBeAg seroconversion (HBeAg has been cleared, anti-HBe is present and HBV DNA is undetectable or less than 2000 IU/ml) or who relapse (revert to being HBeAg+ after seroconversion) after PEG-IFN treatment, offer tenofovir as second-line and entecavir as alternative second-line if tenofovir is contraindicated or not tolerated Consider stopping PEG-IFN halfway through treatment course if HBV DNA level has decreased by less than $2 \log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml, and offer second-line treatment If people taking tenofovir have detectable HBV DNA levels at 48 weeks, provide adherence support <ul style="list-style-type: none"> If HBV DNA remains detectable at 96 weeks, and there is no history of lamivudine resistance, consider adding lamivudine to tenofovir <p>In people with a history of</p>	<ul style="list-style-type: none"> Patients who failed to respond to prior IFN- (standard or pegylated) therapy may be retreated with NA's Patients who failed to achieve primary response as evidenced by $< 2 \log$ decrease in HBV DNA levels after at least 6 months of NA therapy should be switched to an alternative treatment or receive additional treatment <p><i>Resistance-</i></p> <p>Resistance is demonstrated through virologic breakthrough which is defined as a $1 \log_{10}$ (10- fold) increase in serum HBV DNA from nadir during treatment in a patient who had an initial virologic response.</p> <ol style="list-style-type: none"> Lamivudine-resistance <ul style="list-style-type: none"> Add adefovir OR tenofovir In HIV-infected individuals, stop lamivudine, switch to Truvada (emtricitabine and tenofovir) Adefovir-resistance <ul style="list-style-type: none"> Add lamivudine OR switch to/add entecavir In HIV-infected individuals, stop adefovir AND switch to Truvada Entecavir-resistance <ul style="list-style-type: none"> In HIV-infected individuals, switch to tenofovir OR Truvada Telbivudine-resistance 	<p>Primary non-response is defined as less than $1 \log_{10}$ IU/ml decrease in HBV DNA level from baseline at 3 months of therapy. Partial virological response is defined as a decrease in HBV DNA of more than $1 \log_{10}$ IU/ml but detectable HBV DNA after at least 6 months of therapy in compliant patients.</p> <ul style="list-style-type: none"> In case of primary non-response to adefovir, patients should switch to entecavir or tenofovir In patients receiving lamivudine OR telbivudine with a partial virological response at week 24, OR receiving adefovir with a partial virological response at week 48, change to entecavir or tenofovir <p><i>Resistance -</i></p> <p>Resistance or virological breakthrough is defined as a confirmed increase in HBV DNA level of more than $1 \log_{10}$ IU/ml compared to the nadir (lowest value) HBV DNA level on therapy; it may precede a biochemical breakthrough, characterized by an increase in ALT levels.</p> <ol style="list-style-type: none"> Lamivudine resistance: <ul style="list-style-type: none"> Switch to tenofovir (add adefovir if tenofovir is not available) Adefovir resistance: 	<p>Resistance is defined as viral breakthrough evident by more than $1 \log$ IU/mL increase of HBV DNA from the nadir.</p> <ol style="list-style-type: none"> Lamivudine resistance <ul style="list-style-type: none"> Add on adefovir OR switch to tenofovir Switch to entecavir can be done but is not preferred Adefovir resistance <ul style="list-style-type: none"> Add on lamivudine OR telbivudine OR entecavir OR switch to tenofovir Telbivudine resistance <ul style="list-style-type: none"> Add on adefovir OR switch to tenofovir Entecavir resistance <ul style="list-style-type: none"> Add on tenofovir OR adefovir <p>Switching to IFN-based therapy can also be done if patient has resistance to lamivudine or other NA's.</p>

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	<p>load of 1 log₁₀ IU/mL or greater above the nadir, measured on two consecutive samples one month apart, occurring after the first three months of therapy</p> <p>**A rise in alanine aminotransferase greater than the upper limits of normal during treatment associated with a rise in viral load of 1 log₁₀ IU/mL or greater. This may also be due to either genotypic resistance or non-adherence</p>	<p>lamivudine resistance, consider adding entecavir to tenofovir</p>	<ul style="list-style-type: none"> • Add adefovir OR tenofovir OR (stop telbivudine AND switch to Truvada) 	<ul style="list-style-type: none"> • If the patient was NA naive before adefovir, switch to entecavir OR tenofovir (entecavir is preferred in patients with high viremia) • If the patient has history of lamivudine resistance, switch to tenofovir and add a nucleoside analogue <p>3. Telbivudine resistance:</p> <ul style="list-style-type: none"> • Switch to OR add tenofovir (add adefovir if tenofovir is not available) <p>4. Entecavir resistance:</p> <ul style="list-style-type: none"> • Switch to OR add tenofovir (add adefovir if tenofovir is not available) 	

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