VARIABLE ACCESS FOR ANTIVIRAL TREATMENT OF CHRONIC HEPATITIS B INFECTION IN CANADA: A DESCRIPTIVE STUDY

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Complete List of Authors:	Congly, Stephen; University of Calgary Cumming School of Medicine, Medicine Brahmania, Mayur; Western University,
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Abstract:	Background: Antiviral treatment for chronic hepatitis B (CHB) infection can be costly, which presents challenges for universal drug coverage for the estimated 600,000 people living with CHB in Canada. We appraised criteria for reimbursement of CHB antivirals in Canada. Methods: We reviewed the reimbursement criteria for lamivudine (LAM), adefovir (ADF), tenofovir (TDF), entecavir (ETV), telbivudine (TBV), pegylated or standard interferon (IFN), and emtricitabine/TDF in the 10 provinces and 3 territories as well as federal programs. Data was extracted from publically available formularies. The primary outcomes extracted were prescriber details, reimbursement regulations and published list price. Results: All public insurance programs limit access to antiviral treatment in patients with CHB based on viral characteristics, fibrosis or specialist approval. LAM use is only restricted by BC and Ontario. 43% of programs cover either ETV or TDF with no restriction while the remainder of programs cover these agents if patients have advanced fibrosis/cirrhosis. 64.3% of programs provide coverage of IFN although almost half of these programs only reimburse non-pegylated IFN which is not currently recommended for CHB treatment. Interpretation: This descriptive review of criteria for reimbursement of CHB antivirals in Canada showed substantial variability among provinces and territories

	along with reimbursement criteria not consistent with current practices in the management of CHB. The findings can inform health policy and support the development and adoption of a national CHB strategy to ensure equitable and timely access to treatment no matter where patients reside in Canada.

ORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational stud collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location manuscri where ite reported
bstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title First para Methods N/A
on					
d	2	Explain the scientific background and rationale for the investigation being reported	Yes	Introduction	Page 3
	3	State specific objectives, including any prespecified hypotheses	Yes	Introduction	Page 3
gn	4	Present key elements of study design early in the paper	Yes	Abstract and Methods	Page 4
	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	Methods	Page 4
s	6	*(a) Cohort study* - Give the	Yes	RECORD 6.1: The methods of study	Yes, unde

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	participan N/A N/A
	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Yes/feasibility	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Yes/feasil
es/ nt	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Feasibility study		
	9	Describe any efforts to address potential sources of bias	Feasibility study		

	10	Explain how the study size was arrived at	Feasibility study		
	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Yes, in results		
	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Yes, in methods and results		
		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	N/A N/A
		..		RECORD 12.3: State whether the	Personal

				study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	identified feedback
s	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	N/A
e data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Not available N/A N/A		
ata	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or	N/A		

		summary measures			
ts	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Feasibility study		
yses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A		
	18	Summarise key results with reference to study objectives	Yes, in box		
s	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes, in limitations section	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Yes, feasi study for designing study
on	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes, in interpretation section		

bility	21	Discuss the generalisability (external validity) of the study results	Yes		
rmation					
	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes		
ty of aw ng		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Yes, in ap

e: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD
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VARIABLE ACCESS FOR ANTIVIRAL TREATMENT OF CHRONIC HEPATITIS B INFECTION IN CANADA: A DESCRIPTIVE STUDY

Stephen E. Congly[1] MD, MSc, FRCPC and Mayur Brahmania[2] MD, MPH, FRCPC

[1]Department of Medicine, Division of Gastroenterology and Hepatology, Foothills Medical Center, University of Calgary, Calgary, AB, Canada & [2]Department of Medicine, Division of Gastroenterology and Multi Organ Transplant Unit, London Health Sciences Center, University of Western, London, ON, Canada

Contact Information:

Mayur Brahmania MD MPH FRCPC

Division of Gastroenterology and Multi Organ Transplant Unit

University of Western

Room A10-224

London Health Sciences Centre: University Hospital

London, Ontario, Canada

N6A 5A5

Telephone: 519-663-3946

Fax: 519-663-3876

ABSTRACT

Background: Antiviral treatment for chronic hepatitis B (CHB) infection can be costly, which presents challenges for universal drug coverage for the estimated 600,000 people living with CHB in Canada. We appraised criteria for reimbursement of CHB antivirals in Canada.

Methods: We reviewed the reimbursement criteria for lamivudine (LAM), adefovir (ADF), tenofovir (TDF), entecavir (ETV), telbivudine (TBV), pegylated or standard interferon (IFN), and emtricitabine/TDF in the 10 provinces and 3 territories as well as federal programs. Data was extracted from publically available formularies. The primary outcomes extracted were prescriber details, reimbursement regulations and published list price.

Results: All public insurance programs limit access to antiviral treatment in patients with CHB based on viral characteristics, fibrosis or specialist approval. LAM use is only restricted by BC and Ontario. 43% of programs cover either ETV or TDF with no restriction while the remainder of programs cover these agents if patients have advanced fibrosis/cirrhosis. 64.3% of programs provide coverage of IFN although almost half of these programs only reimburse non-pegylated IFN, which is not currently recommended for CHB treatment.

Interpretation: This descriptive review of criteria for reimbursement of CHB antivirals in Canada showed substantial variability among provinces and territories along with reimbursement criteria inconsistent with current practices in the management of CHB. The findings can inform health policy and support the development and adoption of a national CHB strategy to ensure equitable and timely access to treatment no matter where patients reside in Canada.

Key Words: Reimbursement, CHB, Insurance, Access

INTRODUCTION:

Chronic hepatitis B (CHB) is a global infection affecting over 250 million individuals with different prevalence depending on the geographic region (1). In Canada, up to 600,000 individuals are chronically infected, with 70% of CHB carriers being immigrants (2-5). It is estimated over a lifetime of CHB infection that 40% of patients will progress to cirrhosis, hepatocellular carcinoma (HCC), and/or liver-related mortality (6-9). The Ontario Burden of Infectious Disease Study recently found CHB ranked as the fourth most common cause of death (346/year) among all infectious diseases annually, but also fourth in years lost due to premature mortality, years equivalent of reduced functioning, and total health adjusted life years, ranking just behind hepatitis C, human papilloma virus (HPV), and *Streptococcus* pneumonia but noticeably ahead of HIV (6th), *Clostridium difficile* (9th), and tuberculosis (16th) (10).

The goal of treatment for CHB is to improve quality of life, prevent/reverse liver disease progression to liver cirrhosis and liver failure, and to minimize the risk of HCC. Major worldwide associations, including the Canadian Association for the Study of the Liver (CASL), American Association of the Study of Liver Disease (AASLD), the European Association for the Study of Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL) have developed treatment algorithms documenting effective timing of therapy to prevent the aforementioned complications (Table 1 and 2) (11-14).

Provincial regulations may limit the ability of physicians to deliver safe, effective, and tolerable antivirals due to cost or outdated policies. A Canadian study has shown the major barrier to adequate care for CHB remains the provincial restrictions on reimbursement with 64% of patients on treatment requiring reimbursement through public drug programs (15). As Canada remains a top destination for immigrants and despite implementation of a universal vaccination program, the CHB

population will continue to rise or at the very least stay constant due to immigration. Thus, the primary aim of the study was to appraise reimbursement criteria in Canada for all commercially approved therapies for CHB including lamivudine (LAM), adefovir (ADF), tenofovir (TDF), entecavir (ETV), telbivudine (TBV), pegylated or standard interferon (IFN), and emtricitabine/TDF.

METHODS:

Data sources

We collected reimbursement criteria for TDF, ETV, IFN, LAM, TBV, ADF, and emtricitabine/TDF for all provinces and territories in Canada as well as the federal programs of Correctional Services Canada (CSC), Veterans' Affairs and Non-Insured Health Benefits (NIHB) for First Nations and Inuit. Each provincial/territorial health ministry sets its own reimbursement criteria thus information was collected from jurisdiction websites. We extracted data from publicly available online reimbursement information (Appendix 1) as well as e-mailed provincial health authorities when required for further information. When information could not be retrieved or was not available (e.g., the therapy was not reimbursed), data were labelled "NA" (i.e., not available). Information was collected by both authors and cross-checked with inconsistencies being resolved through consensus.

Primary outcomes

Primary outcomes were based on: 1) minimum fibrosis stage required and 2) prescriber type restrictions. The data was organized into categories so that criteria could be compared across provinces/territories. We categorized fibrosis data as the minimum fibrosis stage required (categories: no restrictions, ≥ F2, ≥ F3 or F4 of the Meta-Analysis of Histologic Data in Viral Hepatitis scoring system or equivalent). Prescriber data were categorized as whether any provider

could prescribe the medication, if there was restriction by speciality (e.g. internal medicine, hepatologist, gastroenterologist or infectious diseases) or whether a provider with experience treating patients with CHB infection could prescribe treatment once designated prescriber status as defined by the jurisdiction was met.

Statistical Analysis

We used descriptive statistics to show the proportion of provinces/territories that restrict drug coverage by primary outcome.

RESULTS:

Prescriber Limitations for CHB Treatment

Prescriptions for CHB were restricted to specialists/designated prescribers in 5/14 (36%) programs. In Saskatchewan, Nova Scotia, and the Yukon, specialist recommendation/consultation was encouraged although who exactly was considered a specialist was not explicitly defined. In New Brunswick, permissible prescribers included hepatologists, gastroenterologists and infectious diseases specialists, while in Alberta all internal medicine specialists, which would encompass New Brunswick's categories, were authorized prescribers. For both Alberta and New Brunswick, practitioners with experience in CHB management could apply to become a designated prescriber.

Reimbursement Requirements for Drugs

Lamivudine

Lamivudine (LAM) is covered by all provincial and federal plans although there are significant differences between coverage requirements (Table 3). In Manitoba, Quebec, the Yukon, PEI, Newfoundland and Labrador and all three federal programs there is no restriction on access or

who can prescribe LAM for CHB. Notably, Newfoundland and Labrador restrict prescriptions to 30 days and use a 150 mg formulation, which is not the recommended dose, i.e., 100 mg. Alberta, New Brunswick, Nova Scotia and Saskatchewan restrict prescribers, as described above, although Saskatchewan only recommends consultation with a specialist. Ontario will cover patients with HBV DNA levels over 1000 IU/mL with elevated liver enzymes or evidence of fibrosis/cirrhosis. The most restrictive province is BC with specific requirements for HBV DNA levels and ALT levels in non-cirrhotics but covering all patients with cirrhosis.

Adefovir

The majority of public drug plans restrict or do not cover adefovir (ADF) with the least restrictions found in Alberta requiring only an authorized prescriber while CSC had no restrictions reported. Adefovir is not covered by Manitoba, Ontario, New Brunswick or Veterans Affairs. For many public plans (Saskatchewan, Quebec, New Brunswick, PEI, Yukon and NIHB), ADF would be covered in combination with LAM if there was LAM failure based on a DNA of >1 log above the nadir after three months of treatment provided noncompliance was not the reason for failure as per the Canadian Drug Expert Committee (CDEC). Saskatchewan and the Yukon require specialist input. BC also follows the CDEC recommendation but does not require LAM to be used with ADF. Quebec additionally covers patients with an increase in the HBV DNA by 1 log or proven resistance with a HBV DNA >20,000 IU/mL in patients with Child Pugh B/C cirrhosis, post liver transplant patients, patients co-infected with HIV but not on anti-retrovirals, patients with HBV DNA >20,000 IU/mL (HBeAg positive) or >2,000 IU/mL in HBeAg negative patients.

Telbivudine

None of the provincial drug programs nor any of the federal programs reimburse telbivudine.

Emtricitabine/Tenofovir

The minority of public programs cover emtricitabine/TDF for CHB treatment. Quebec, New Brunswick and the federal programs have no restrictions on coverage and Yukon covers it on a case-by-case recommendation. Saskatchewan, Manitoba, Ontario, PEI and Newfoundland and Labrador cover this drug for HIV infection only while it is not covered for any indication in BC, Alberta and Nova Scotia.

Tenofovir

There are currently two forms of tenofovir on the market: tenofovir disoproxil fumarate (TDF) which has recently become generic as well as tenofovir alafenamide fumarate (TAF). The latter was approved by Health Canada in June 2017. No public health plans in Canada reimburse TAF. Only a few provinces cover TDF with few or no restrictions; Alberta requires TDF be prescribed by an authorized prescriber while Quebec, PEI, New Brunswick, CSC and Veteran Affairs have no restrictions. Interestingly, CSC covers the 245 mg formulation of TDF, which is usually prescribed at 300mg. TDF is covered in the Yukon on a case-by-case evaluation with recommendation by a specialist. In Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Newfoundland and Labrador and the NIHB, TDF is covered for patients with cirrhosis and a DNA >2000 IU/mL matching the CDEC recommendation with Saskatchewan also suggesting specialist involvement. Manitoba additionally will cover TDF in patients with cirrhosis and resistance to LAM. Ontario covers TDF for patients with HBV DNA levels over 1000 IU/mL with elevated liver

enzymes or evidence of fibrosis/cirrhosis. Ontario will also cover TDF for patients who have failed other therapies, pregnant patients with DNA > 1,000,000 IU/mL and for chemoprophylaxis. BC has the most restrictive guidelines for TDF covering only non-cirrhotic patients with LAM resistance, ADF experienced with viremia and LAM resistance. For patients with cirrhosis, either a HBV DNA >200,000 IU/mL) or between 2000-200,000 IU/mL and ALT >3x ULN is required for coverage.

Entecavir

Entecavir (ETV) coverage requirements are similar to TDF in most provinces. Quebec, Manitoba and CSC cover ETV in adults with no restrictions while Alberta covers it at the request of an authorized prescriber. In Saskatchewan, most maritime provinces as well as the NIHB, the coverage criteria are identical to the CDEC guidelines of having cirrhosis and having a DNA >2000 IU/mL. Coverage in the Yukon is case by case by specialist request and is not covered by Veteran Affairs. BC and New Brunswick have identical coverage requirements for ETV as it does for TDF (see above). In Ontario, ETV is covered with HBV DNA levels over 1000 IU/mL with elevated liver enzymes or evidence of fibrosis/cirrhosis, intolerance to other HBV medications as well as for chemoprophylaxis.

Peginterferon Alfa-2a/2b

Interferon in any form is not covered for CHB treatment in the Yukon, Manitoba, Nova Scotia or PEI. Manitoba covers peginterferon alfa-2a for HCV while PEI covers both forms for HCV. Peginterferon alfa-2a is the preferred drug in Alberta (prescribed by an authorized prescriber), Quebec, New Brunswick, and in the NIHB. Quebec has no restrictions on peginterferon alfa-2a's use while New Brunswick covers HBeAg negative chronic hepatitis B patients with compensated liver

disease, liver inflammation and evidence of viral replication with demonstrated intolerance or failure to LAM therapy for 48 weeks with specialist requests. NIHB covers patients with a DNA >2000 IU/mL without cirrhosis and no limitation on HBeAg status on the request of a specialist. BC covers interferon alfa-2b in patients who are HBeAg positive with an ALT> 2x ULN for 24 weeks. Similarly, Ontario covers interferon alfa requiring F3 fibrosis or less on biopsy, age less than 50, DNA between 10,000-10,000,000 IU/mL and two ALT values of >2x ULN in the past 6 months. CSC is the most liberal for coverage allowing for both pegylated interferon alfa-1 and alfa-2 to be prescribed. In Saskatchewan, interferon alfa-2b is covered for up to 6 months, Newfoundland covers alfa 1a and 2b with identical criterion to New Brunswick while Veteran Affairs covers interferon alfa 2b.

INTERPRETATION:

We found substantial variability in criteria for reimbursement of CHB antivirals by jurisdiction in Canada. Currently, no provinces/territories limit reimbursement to only patients with advanced fibrosis, but 2/14 (14%) explicitly require elevated ALT levels. CDEC recommendations limiting ETV and TDF to patients who had cirrhosis were present in 6/14 (43%) of programs. Overall, 4/13 (31%) of jurisdictions had some form of explicit restriction of prescribers to specialists.

A number of the reimbursement requirements nationally are somewhat perplexing. It is unclear why interferon is approved for HBe antigen negative patients and not for HBe antigen positive patients in a number of provinces given the reasonable response rate in the HBe antigen positive population (12). In addition, restrictions such as fibrosis stage are neither cost-effective nor evidence-based. Although a “one-size-fits-all” strategy has drawbacks (e.g., the ability of

provinces/territories to respond to CHB burdens will vary), the development and adoption of a national CHB strategy in Canada akin to hepatitis C care in Australia could facilitate volume-based discounting, reduce provincial/territorial heterogeneity and direct treatment to at-risk populations. Further, equitable access could be broadened to eliminate the "postal code lottery" to enable the safe and effective treatment of CHB while controlling the burden of CHB care in Canada. Clinician knowledge of drug prices is variable (16) which may impact delivery of the highest value care, and so in addition to further education, prudent policy coverage decisions will also be critical to deliver cost-effective care.

When CDEC made its initial recommendations, TDF and ETV were approximately $18-22/day in which case restriction of a drug to patients with advanced fibrosis could theoretically make sense from a cost-effectiveness/budget impact standpoint. However, with generic TDF entering the market the difference between LAM and highly potent oral nucleos/tide analogues (i.e., TDF/ETV) is between $1-2/day (Table 4). Lamivudine is not a favoured drug given the high rate of resistance (70% in five years) and weaker viral suppression (17). The reduced efficacy of viral suppression may allow patients to develop progressive fibrosis in spite of being on treatment, which will increase the overall burden on the health care system economically. As such, the initial savings with using LAM as a drug will likely lead to additional costs downstream. It would be an important area of future investigation to repeat the previous economic analyses with more modern outcome data and costs as well as budget impact analyses to improve our use of resources and patient outcomes and hopefully standardize care nationally.

Based on the current list pricing of medications as well as the different populations these drugs would be considered in, we propose recommendations for reimbursement nationwide considering best practices and the cost of drugs in alignment with internationally recognized

guidelines (Table 5). We acknowledge the immediate budget impact may vary from jurisdiction to jurisdiction although our recommendations are designed to be cost-effective in the long-term and eliminate costly and less effective drugs from routine reimbursement.

Limitations:

There were several study limitations. Not all provinces/jurisdictions provided pricing information about the medications and there is the potential that the online criteria may be incomplete. Further, criteria may have been updated after the data were extracted although typically most formularies do not change significantly month to month. As well, this study cannot address implementation of criteria. Last, this study only examines publically available formularies as we were unable to retrieve online private health insurance criteria for comparison

Implications for practice:

This review of criteria for reimbursement of CHB antivirals in Canada showed considerable reimbursement heterogeneity due to a lack of government alliance and direction for the treatment of CHB. To achieve World Health Organization hepatitis elimination targets by 2030 increased identification and uptake of CHB therapy, especially by the immigrant population, is essential to reduce CHB incidence and contribute to viral elimination in Canada (18).

CONCLUSION:

The current criteria for reimbursement of antiviral medication to treat CHB in Canada shows substantial interjurisdictional heterogeneity with most provinces/territories having restrictions based on liver disease stage and allowing prescribing by specialists only. Given the significant variability to

access currently and marked drop in drug prices we advocate for improved access to medications nationally to improve patient outcomes and eliminate geographical disparity.

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Table 1: Treatment Recommendations by Various International Organizations: HBeAg-Positive.

	AASLD 2018 (USA)	EASL 2017 (Europe)	CASL 2012 (Canada)	APASL 2015 (Asia)
Treatment Definitely Recommended	1. ALT>2x ULN and HBV DNA >20,000	1. ALT >2xULN and HBV DNA >20,000 2. ALT >ULN and HBV DNA >2000 and/or Liver biopsy showing moderate to severe inflammation/fibrosis 3. Cirrhosis	1. ALT elevated for 3-6 months and HBV DNA >20,000	1. ALT >2x ULN And HBV DNA >20,000 2. Liver biopsy showing moderate to severe inflammation/ significant fibrosis 3. Compensated cirrhosis and HBV DNA >2000 4. Decompensated cirrhosis
Treatment Should be Considered	1. ALT>2xULN and HBV DNA 2000-20,000 2. ALT 1-2x ULN and HBV DNA >20,000 3. Age over 40 4. Evidence of moderate/severe inflammation/fibrosis	1. HBV DNA elevated and Age over 30 2. Family history of HCC or cirrhosis and extrahepatic manifestations	1. ALT >ULN for 3-6 months or liver biopsy showing moderate/severe inflammation/fibrosis and HBV DNA >20,000	Monitor all non-treated patients every 3 months. Biopsy recommended for treatment decisions if: a) noninvasive tests suggest evidence of significant fibrosis b) ALT is persistently elevated c) Age >35 years d) Family history of HCC or cirrhosis.
Monitor	1. ALT<ULN	1. ALT <ULN 2. HBV DNA <2000	1. ALT <ULN 2. HBV DNA <2000	

Preferred First Line Treatment (Alphabetical)	Entecavir Peg-IFN Tenofovir	Entecavir Peg-IFN Tenofovir	Entecavir Peg-IFN Tenofovir	Entecavir Peg-IFN Tenofovir

HBV DNA in IU/ml; ULN=Upper Limit Normal
AASLD ALT ULN in men 35, women 25. EASL/APASL ALT ULN 40, CASL ALT ULN undefined

Table 2: Treatment Recommendations by Various International Organizations: HBeAg-Negative.

	AASLD 2018 (USA)	EASL 2017 (Europe)	CASL 2012 (Canada)	APASL 2015 (Asia)
Treatment Definitely Recommended	1. ALT >2x ULN and HBV DNA >2000 2. Cirrhosis and HBV DNA >2000	1. HBV DNA >2000 and ALT>ULN and/or Liver biopsy showing moderate/severe inflammation/fibrosis 2. HBV DNA >20,000 and ALT >2x ULN 3. Cirrhosis	1. ALT elevated for 3-6 months and HBV DNA >2000	1. ALT >2x ULN and HBV DNA >2000 2. Liver biopsy showing moderate to severe inflammation/ significant fibrosis 3. Compensated cirrhosis and HBV DNA >2000 4. Decompensated cirrhosis
Treatment Should be Considered	1. ALT 1-2x ULN 2. HBV DNA >2000 3. Age over 40 4. Liver biopsy showing moderate/severe inflammation/fibrosis	1. HBV DNA elevated and Age over 30 2. Family history of HCC or cirrhosis and extrahepatic manifestations	1. ALT >ULN for 3-6 months or liver biopsy showing moderate/severe inflammation/fibrosis and HBV DNA>2000	Monitor all non-treated patients every 3 months. Biopsy recommended for treatment decisions if: a) noninvasive tests suggest evidence of significant fibrosis b) ALT is persistently elevated c) Age >35 years d) Family history of HCC or cirrhosis.
Monitor	1. ALT<ULN and HBV DNA <2000	1. HBV DNA <2000 2. ALT<ULN	1. ALT<ULN 2. HBV DNA <2000	
Preferred First Line Treatment (Alphabetical)	Entecavir PEG-IFN Tenofovir	Entecavir PEG-IFN Tenofovir	Entecavir PEG-IFN Tenofovir	Entecavir PEG-IFN Tenofovir

HBV DNA in IU/mL; ULN=Upper Limit Normal

AASLD ALT ULN in men 35, women 19. EASL/APASL ALT ULN 40, CASL ALT ULN undefined

Table 3: Criteria for Re-Imbursement of HBV Medications in Canada

Territory	Lamivudine	Adefovir	Entecavir	Tenofovir[1]	Interferon	Emtrictiabine/ Tenofovir
CDEC[2]	N/A[3]	Take with LAM for LAM failure	Cirrhosis with DNA >2000 IU/mL	Cirrhosis with DNA >2000 IU/mL	N/A	N/A
BC	ALT and viral load requirement OR cirrhosis	LAM resistance	Cirrhosis and viral load +/- ALT	Cirrhosis and viral load +/- ALT OR LAM resistance	alfa2b HBeAg + with ALT and viral load requirement	N/A
AB	No restriction for specialists	No restriction for specialists	No restriction for specialists	No restriction for specialists	PEG2a No restriction for specialists	N/A
SK	No restriction for specialists	As per CDEC with specialist consultation	As per CDEC with specialist consultation	As per CDEC with specialist consultation	alfa-2b 6 months with specialist consultation	N/A
MB	No restriction	N/A	No restriction	As per CDEC OR Cirrhosis with LAM resistance	N/A	N/A
ON	HBV DNA ≥1000 with ALT >ULN or fibrosis/cirrhosis	N/A	HBV DNA ≥1000 with ALT >ULN or fibrosis/cirrhosis	HBV DNA ≥1000 with ALT >ULN or fibrosis/cirrhosis	alfa2b F3 fibrosis or less, <50 with ALT and DNA requirements	N/A
PQ	No restriction	As per CDEC OR >CP A6 OR post LT with DNA requirement	No restriction	No restriction	PEG2a No restriction	No restriction
NB	No restriction for specialists	N/A	No restriction for specialists	No restriction for specialists	PEG2a HBeAg -, liver inflammation, failed LAM	No restriction

NS	No restriction with specialist request	As per CDEC	As per CDEC	As per CDEC	N/A	N/A
PEI	No restriction	As per CDEC	As per CDEC	No restriction	N/A	N/A
NL	No restriction	As per CDEC	As per CDEC	As per CDEC	alfa1a/2b HBeAg -, liver inflammation, failed LAM with specialist consultation	N/A
YK	No restriction	As per CDEC with specialist recommendation	Case by case with specialist recommendation	Case by case with specialist recommendation	N/A	Case by case with specialist recommendation
NIHB	No restriction	As per CDEC	As per CDEC	As per CDEC	PEG2a Non-cirrhotic with DNA requirements and specialist request	No restriction
Corrections Canada	No restriction	No restriction	No restriction	No restriction	PEG2a/2b No restrictions	No restriction
Veterans Affairs	No restriction	N/A	N/A	No restriction	N/A	No restriction

[1]TAF not listed by any program
[2]CDEC = Canadian Drug Expert Committee
[3] N/A: No recommendation or not listed
Telbivudine is not reimbursed by any Canadian public program

Table 4: Cost of CHB Treatment in Canada per dose

Drug	BC	AB	SK	MB	ON	PQ	NS	NL	YK
Lamivudine									
Originator Price	5.17	4.79	4.79	-	-	4.56	-	5.22	4.71
Generic Price	3.81	3.53	3.53	-	3.53	3.53	3.53	3.85	3.53
Adefovir									
Originator Price	26.28	23.84	24.34	-	-	23.22	-	26.53	24.34
Generic Price	20.28	18.25	18.25	-	20.44	18.25	20.44	22.28	-
Tenofovir									
Originator Price	-	18.49	18.77	25.51	19.55	17.29	-	21.34	18.77
Generic Price	5.28	4.89	4.89	4.89	4.89	4.89	4.89	5.33	4.89
Entecavir									
Originator Price	23.76	22.00	22.00	-	-	22	-	23.98	22.00
Generic Price	5.94	5.50	5.50	16.5	16.5	5.50	5.50	5.99	5.50
Emtricitabine/Tenofovir									
Originator Price	-	-	27.70	29.21	29.21	26.10	26.10	31.84	24.83
Generic Price	-	-	7.30	7.30	7.30	7.30	7.30	7.96	-
Interferon	alfa2b	PEG2a	alfa2b		alfa2b	PEG2a		alfa2b	
Originator Price	-	-	-	-	-	-	-	-	-
Generic Price	135.89	407.39	125.82	-	145.84	395.84	-	659.31	-

BC, ON and NS: Max Price Paid
PEI, NB, NIHB, Corrections Canada and Canadian Pensions Plan do not report cost
alfa2b cost reported as 10 MU dosing

Adefovir: Only Apo generic
Lam: Only Apo generic
TDF: Apo, Teva, Mylan, Auro

NL: Defined cost = list + 8.5%
BC: List price + 5-8%

Table 5: Recommendations for a Universal Drug Coverage Strategy

Tenofovir/Entecavir	Universal coverage who meet standard international criteria for treatment: HBeAg positive: DNA > 20,000 IU/mL and ALT >2 x ULN HBeAg negative: DNA >2000 IU/mL and ALT >2x ULN Cirrhosis/Advanced fibrosis Prophylaxis of maternal transmission with DNA >1 x 10^6 IU/mL Chemotherapy prophylaxis for patients at high risk of HBV reactivation
Lamivudine	Prophylaxis for patients at lower risk of HBV reactivation
Adefovir	Removal of Adefovir from routine coverage given its increased cost as compared to TDF and ETV along with lower efficacy.
PEG-Interferon	Consider use in HBeAg positive and negative patients

Appendix 1: Provincial Formulary Databases

Province	Website	Formulary Update
BC	https://pharmacareformularysearch.gov.bc.ca/faces/SearchResults.xhtml	27 Feb 2018
AB	https://idbl.ab.bluecross.ca/idbl/load.do	12 Mar 2018
SK	http://formulary.drugplan.ehealthsask.ca/	1 Mar 2018
MB	https://www.gov.mb.ca/health/mdbif/index.html	25 Jan 2018
ON	https://www.formulary.health.gov.on.ca/formulary/	28 Feb 2018
PQ	http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/liste_med/liste_med_2018_03_01_en.pdf	1 Mar 2018
NB	http://www2.gnb.ca/content/dam/gnb/Departments/h-s/pdf/en/NBDrugPlan/NewBrunswickDrugPlansFormulary.pdf	1 Mar 2018
NS	https://novascotia.ca/dhw/pharmacare/documents/formulary.pdf	1 Mar 2018
PEI	https://www.princeedwardisland.ca/sites/default/files/publications/pei_pharmacare_formulary.pdf	Feb 2018
NL	http://www.health.gov.nl.ca/health/prescription/newformulary.asp	1 Mar 2018
YK	http://www.hss.gov.yk.ca/drugformulary.php	13 Mar 2018
NIHB	https://www.canada.ca/content/dam/hc-sc/documents/services/publications/health-system-services/non-insured-health-benefits-drug-benefit-list/dbl-2018-eng.pdf	8 Mar 2018
VA	http://www.veterans.gc.ca/eng/services/health/treatment-benefits/poc/poc10/search	5 Mar 2018

*Accessed 13 March 2018