ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Treatment of Chronic Hepatitis B in Ontario

Pharmacoepidemiology Unit: Censored Final Report

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Note
Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Summary

Overall National and Provincial Trends in Chronic Hepatitis B Medication Use

Utilization and costs of drugs used for the treatment of chronic hepatitis B have been increasing in Canada over the last 5 years. From the last quarter (Q4) of 2009 to the third quarter (Q3) of 2014, the number of prescriptions dispensed for hepatitis B medications in Canada increased by 34.6% (from 22,608 to 30,426 prescriptions dispensed) and costs have increased by 58.6% (from $11.9 million to $18.8 million). In Q3 2014, just over half (55.4%) of chronic hepatitis B medications dispensed in Canada were paid for by public drug programs, compared to 31.4% through private insurers, 13.0% through cash payment, and less than 1% through Noninsured Health Benefits (NIHB). Between Q4 2009 and Q3 2014, tenofovir was the most commonly prescribed chronic hepatitis B medication in Canada, which is also used for treatment of HIV infection, followed by lamivudine (62.6% and 21.3% of prescriptions dispensed in Q3 2014, respectively). Over the study period, prescriptions dispensed for tenofovir and entecavir have increased, while prescriptions for other chronic hepatitis B medications have decreased or remained stable.

The rate of provincially funded prescriptions dispensed for chronic hepatitis B medications was higher than the rate of non-provincially funded prescriptions dispensed, across all provinces. By Q3 2014, Ontario had the third highest rate of provincially funded chronic hepatitis B medication use (192 prescriptions dispensed per 100,000 eligible population compared to the national average of 172 prescriptions dispensed per 100,000 eligible population), behind British Columbia and Alberta. Ontario had the second highest (behind British Columbia) rate of non-provincially funded medication use (47 prescriptions dispensed per 100,000 population compared to the national average of 39 prescriptions dispensed per 100,000 population) in Q3 2014. The highest rates of prescriptions dispensed for chronic hepatitis B medications were noted in Alberta, British Columbia, Ontario and Quebec. This is likely due to the presence of larger urban centres and greater proportions of of immigrants in these provinces, as chronic hepatitis B is more prevalent among immigrants in Canada.[1;2]

Cross-Provincial Comparisons of Chronic Hepatitis B Medication Use among Public Drug Plan Beneficiaries

In 2013, Ontario had the second highest (behind Alberta) rate of publically funded chronic hepatitis B medication use (113 users per 100,000 eligible population), not including Quebec or Newfoundland and Labrador (due to unavailable data). Tenofovir, which is used for the treatment of chronic hepatitis B and HIV, had the highest rate of publically funded use across all provinces, except in British Columbia where lamivudine had the highest rate of use. The rate of publically funded chronic hepatitis B medication use was higher among younger adults (aged 18 to 65) compared to older adults (aged 66 and older) across all provinces in Canada in 2013 (120 and 52 users per 100,000 eligible population, respectively). The rate of use among younger adults was highest in Alberta while the rate of use among older adults was highest in British Columbia. Ontario had the second highest rate of use among younger adults (179 users per 100,000 eligible population) and among older adults (55 users per 100,000 eligible population).

Chronic Hepatitis B Medication Use in Ontario

Similar to national trends, between Q4 2009 and Q3 2014 prescriptions for chronic hepatitis B medications in Ontario increased by 34% (from 9,433 prescriptions dispensed to 12,665 prescriptions dispensed) and costs have increased by 72% (from $5.4 million to $9.3 million). By Q3 2014, almost half (49%; $4.6 million) of chronic hepatitis B medications dispensed in Ontario were paid for by the Ontario Public Drug Program, followed by private insurers (37%; $3.7 million), cash payment (14%; $1.0 million) and NIHB (<1%; $10,522).

Characteristics of Chronic Hepatitis B Medication Users in Ontario

There were 3,559 patients in Ontario who were treated with provincially funded chronic hepatitis B medications between January 2012 and December 2013. Tenofovir was the most commonly used drug (71.6%), followed by lamivudine (18.0%), standard interferon (5.3%), entecavir (3.0%), combination therapy (1.8%) and adefovir (<1%). We excluded tenofovir users who were using the medication exclusively for HIV. Patients were on average 56 years of age, male (65.2%), and lived in urban areas (98.2%). Approximately half of patients treated for chronic hepatitis B were born outside of Canada (ranging from 40.6% to 53.9% depending on drug), except for users of standard interferon (5.9%) and adefovir (10-20%), who were generally born in Canada. Gastroenterologists prescribed the majority (50-70%) of all prescriptions, except for standard interferon which was predominantly prescribed by medical oncologists (68.6%), likely reflecting its use for other indications.

Patterns of Chronic Hepatitis B Medication Use and Discontinuation among New Users in Ontario

Between 2003 and 2012, we identified 3,062 younger adults and 883 older adults who initiated a publically funded chronic hepatitis B medication in Ontario. The time to discontinuation of any hepatitis B treatment varied by the therapy initiated, in both younger ($p<0.0001$) and older adults ($p<0.0001$). Among both younger and older adults, patients who initiated an interferon therapy discontinued hepatitis B treatment sooner compared to those who initiated an oral antiviral therapy. These findings reflect the shorter duration of therapy approved for interferons (24-48 weeks) compared to antiviral therapies which have lifetime duration of use. After two years, less than 5% of interferon users were still on therapy, while 60-70% of younger adults and 70-80% of older adults were still on oral antiviral therapy. Among individuals initiating tenofovir, lamivudine and entecavir (the three most commonly prescribed oral hepatitis B medications), there was no difference in duration of therapy among older adults ($p=0.33$), however lamivudine users had a lower rate of adherence compared to entecavir and tenofovir users among younger adults ($p<0.0001$). We also performed a sensitivity analysis to examine the time to discontinuation of the initial hepatitis B medication. This analysis revealed that 10-20% of users initiating lamivudine switched to another hepatitis B therapy within two years, whereas less than 5% of users initiating a non-lamivudine hepatitis B therapy switched to another hepatitis B therapy.

Among all patients initiating an oral antiviral chronic hepatitis B medication, there was no difference in the duration of oral antiviral treatment between users born in Canada compared to users born outside of Canada, among both younger ($p=0.11$) and older ($p=0.65$) adult users.

Table of Contents

Acknowledgments 6
Introduction 7
Data Sources 7
IMS Geographic Prescription Monitor (GPM[12]) 7
Canadian Institute for Health Information NPDUIS 7
Administrative Databases in Ontario 8
Ontario Drug Benefit Database 8
HIV Database 8
Citizenship & Immigration Canada Database 8
Other Health Administrative Databases 8
Methods 9
National and Provincial Trends in Chronic Hepatitis B Medication Use 9
Cross-Provincial Comparisons of Provincially-Funded Chronic Hepatitis B Medication Use 9
Characteristics of Provincially-Funded Chronic Hepatitis B Medication Users in Ontario 10
Adherence among New Users of Chronic Hepatitis B Medications in Ontario 10
Exhibits and Findings 11
National Trends in Utilization of Chronic Hepatitis B Medications 11
Population-Adjusted Rates of Chronic Hepatitis B Medication Utilization, by Funding Type 14
Population-Adjusted Rates of Chronic Hepatitis B Medication Utilization, Among Public Plan Beneficiaries 18
Trends in Provincially-Funded Chronic Hepatitis B Medications in Ontario 21
Characteristics of Provincially-Funded Chronic Hepatitis B Medication Users in Ontario, Between 2012 and 2013 24
Patterns of Chronic Hepatitis B Medication Use and Discontinuation 28
Key Findings 30
Cyclic Trends 32
Health Equity 32
Limitations 32

Data Availability 32
Generalizability 34
Adherence 34
Overall Conclusion 34
Appendix A: Public Plan Listings for Chronic Hepatitis B Medications in Canada, by Province 35
Appendix B: Public Plan Listings and Summary of Requirements for Chronic Hepatitis B Treatment in Ontario 36
Reference List ..... **Error! Bookmark not defined.**

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Introduction

In Canada, there are currently seven medications that are used in the treatment of chronic hepatitis B. These medications can be divided into injectable interferon therapies (standard interferon (interferon alfa-2b) and pegylated interferon (pegylated interferon 2a)), and oral antiviral (nucleos/tides) therapies (lamivudine, tenofovir, entecavir, adefovir dipivoxil and telbivudine). Generic versions of these medications are only available for lamivudine, adefovir and entecavir. These medications differ in their public plan listings on provincial formularies across Canada. Detailed information on public plan listings is provided in Appendix A and Appendix B.

The objectives of this report are to describe national and provincial trends in the use of medications used to treat chronic hepatitis B and to identify patterns of use among new users with provincial drug coverage. Specifically, this report aims to:

1. Present national utilization trends of medications used to treat chronic hepatitis B across Canada, including cross-provincial comparisons of population-adjusted rates of use, by drug dispensed and by payer (public drug programs, private insurers, cash payment and Non-insured Health Benefits (NIHB).
2. Present cross-provincial comparisons of medications used to treat chronic hepatitis B funded through public drug programs across Canada using population-adjusted rates of use.
3. Examine trends in use of medications used to treat chronic hepatitis B funded through the Ontario Public Drug Program.
4. Describe characteristics of people with chronic hepatitis B who receive provincially funded treatment in Ontario.
5. Describe the course and length of chronic hepatitis B therapy among new users with chronic hepatitis B in Ontario.

Data Sources

IMS Geographic Prescription Monitor (GPM[12])

IMS Geographic Prescription Monitor (GPM[12]) is a premium source of sales intelligence on retail prescription activity in Canada. Data is obtained from a representative sample of 65% of all Canadian pharmacies and is projected monthly by province or customized geography. Projections incorporate the number of pharmacies in a given area, the distance between IMS-captured and uncaptured pharmacies, and the size of the pharmacies. Projections are representative of provincial and national sales volumes. Data available through IMS Geographic Prescription Monitor (GPM[12]) includes prescription volumes and units (e.g. tablets, patches) dispensed, and are stratified by payer type (e.g. public drug plan, private drug plan, cash, Non-Insured Health Benefits). Data from IMS Geographic Prescription Monitor (GPM[12]) is available from the fourth quarter of 2009 to the third quarter of 2014.

Canadian Institute for Health Information NPDUIS

The National Prescription Drug Utilization Information System (NPDUIS) was developed by the Canadian

Institute for Health Information (CIHI) to provide pan-Canadian information on public drug programs. NPDUIS data can be used to obtain estimates of populations eligible for provincial drug coverage in Alberta, British Columbia, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island. Data from NPDUIS is available from calendar year 2000 to 2013.

Administrative Databases in Ontario

These datasets were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

Ontario Drug Benefit Database

The Ontario Drug Benefit (ODB) database contains individual-level claims data for all prescription drugs dispensed to Ontario residents eligible for public drug funding. Eligibility criteria include unemployment, disability, high prescription drug costs relative to net household income, receipt of home care services, residence in a long-term care facility, or age 65 years or older. This database is of high quality, with an error rate of <1% and can be linked to other health administrative databases to obtain patient demographic information.[3] We analyzed data from the ODB between January 2000 and December 2013.

HIV Database

The Ontario HIV Database is a validated database containing all Ontario HIV positive patients in Ontario since fiscal year 1992. The database was created using physician claims from the Ontario Health Insurance Plan (OHIP) claims database. The case definition for HIV uses 3 or more physician claims with an HIV diagnosis over a 3 year period ascertain prevalence, and yielded a sensitivity of 96.2% (95% confidence interval [CI] 95.2-97.9%) and specificity of 99.6% (95% CI 99.1-99.8%) when compared to chart data.[4] We used data from the HIV database between January 2003 and December 2013 to define HIV co-infections.

Citizenship & Immigration Canada Database

The Citizenship and Immigration Canada (CIC) database contains information the Permanent Resident Database of all persons becoming permanent residents from 1985. This data was obtained from the Institute for Clinical Evaluative Sciences (ICES). The data contains permanent residents' demographic information such as country of citizenship and birth, level of education, mother tongue, and landing date. A limitation of this data is that immigrants who reside in Ontario but originally landed in another province will not be captured. We used data from the CIC database between January 2003 and December 2013 to define patients treated with hepatitis B drugs that were born outside of Canada and became permanent residents.

Other Health Administrative Databases.

We used data from the Ontario Registered Persons Database (RPDB), Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and National Ambulatory Care Reporting System (CIHI-NACRS), Ontario Health Insurance Plan (OHIP) and the ICES Physician Database (IPDB) to obtain patient vital statistics, describe health care utilization and other patient comorbidities and characteristics.

Methods

All analyses using administrative databases in Ontario available through the Institute for Clinical Evaluative Sciences were approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

National and Provincial Trends in Chronic Hepatitis B Medication Use

We used data from IMS Geographic Prescription Monitor (GPM[12]) to examine overall trends in the prescribing volumes of medications used to treat chronic hepatitis B, at both national and provincial levels. We examined the number of prescriptions dispensed for hepatitis B medications between October 1 2009 and September 30 2014. Analyses were stratified by payer, drug and province. Provincially funded prescriptions were those paid for through public drug programs; non-provincially-funded prescriptions were those paid for through private insurance plans, cash payments, or Non-Insured Health Benefits (NIHB). All cross-provincial analyses compared population-adjusted rates.

Population Adjustment

Provincial population estimates were obtained from Statistics Canada for each year from 2009 to 2013 and used to standardize overall utilization rates (per 100,000 population) of chronic hepatitis B medications dispensed across the different provinces. Population counts for 2014 were estimated using linear extrapolation. Because all individuals (both those eligible for public drug programs and non-beneficiaries) might pay for chronic hepatitis B medications out of pocket, measures of non-provincially funded utilization were adjusted using overall provincial population estimates from Statistics Canada.

For measures examining provincially funded utilization of chronic hepatitis B medications, we used the number of individuals eligible for provincial drug coverage in each year from 2009 to 2014 to standardize utilization rates (per 100,000 eligible population). In the case of provinces where we had individual-level data available through NPDUIS and ODB (i.e. Alberta, British Columbia, Manitoba, Saskatchewan, Ontario, New Brunswick, Nova Scotia and Prince Edward Island), we defined the number of eligible beneficiaries in each year as any individual who had at least one publically funded drug claim over the time period. In the case of Quebec, and Newfoundland and Labrador, we obtained estimates of eligible populations from the annual reports of each public drug program. For all provinces, eligible population counts for the most recent years (2013 and 2014) were estimated using linear extrapolation where data was not available.

Cross-Provincial Comparisons of Provincially-Funded Chronic Hepatitis B Medication Use

We used claims data from NPDUIS and ODB to examine trends in the number and rate of provincially funded users of chronic hepatitis B medications at the provincial level. We examined the number of users and rate of users in 2013. Analyses were stratified by province, drug and age (18-65, 66+). Provincially funded prescriptions were those paid for through public drug programs. All cross-provincial analyses compared population-adjusted rates (described above). Data was only available for Alberta, British Columbia, Manitoba, Saskatchewan, Ontario, New Brunswick, Nova Scotia and Prince Edward

Island.

Characteristics of Provincially-Funded Chronic Hepatitis B Medication Users in Ontario

We used claims data from ODB to perform additional analyses of utilization of chronic hepatitis B medications among users aged 18 and older in Ontario, stratifying by age (aged 18 to 65 vs. aged 66 and older), over a 2-year period between January 2012 and December 2013. These analyses examined demographic and clinical characteristics of individuals who were prescribed a hepatitis B medication in Ontario.

Adherence among New Users of Chronic Hepatitis B Medications in Ontario

We established a cohort of individuals who were new users of chronic hepatitis B medications between January 1, 2003 and December 31, 2012, to examine the duration of therapy in Ontario. A new user was defined as having no prescription for a chronic hepatitis B medication in the past 180 days. We followed each individual forward from the time of their first prescription until they discontinued any hepatitis B drug therapy, died, had 2 years of follow-up or reached the end of the study period (December 31, 2013). Discontinuation of hepatitis B treatment was defined on the basis of no subsequent prescription for a chronic hepatitis B medication within a grace period equal to 50% of the previous prescription duration, which is consistent with previously published studies[5-7]. Discontinuation date was defined as date of last prescription plus the day supply of the last prescription. We stratified this analysis by the chronic hepatitis B medication initiated. We presented the findings separately for users aged 18 to 65 and those aged 66 and older. We also performed a sensitivity analysis to examine the duration of therapy for the *initial* chronic hepatitis B medication prescribed among new users. We followed each individual forward from the time of their first prescription until they discontinued their initial drug, died, had 2 years of follow-up or reached the end of the study period (December 31, 2013) using the same methods described. We also stratified the analysis by whether the individual was born in Canada, among oral antiviral therapy users only. This analysis was limited to oral antiviral therapy users in order to make the groups comparable, since interferon therapy has a shorter course of therapy (up to 48 weeks) compared to oral antiviral therapies (lifetime use).

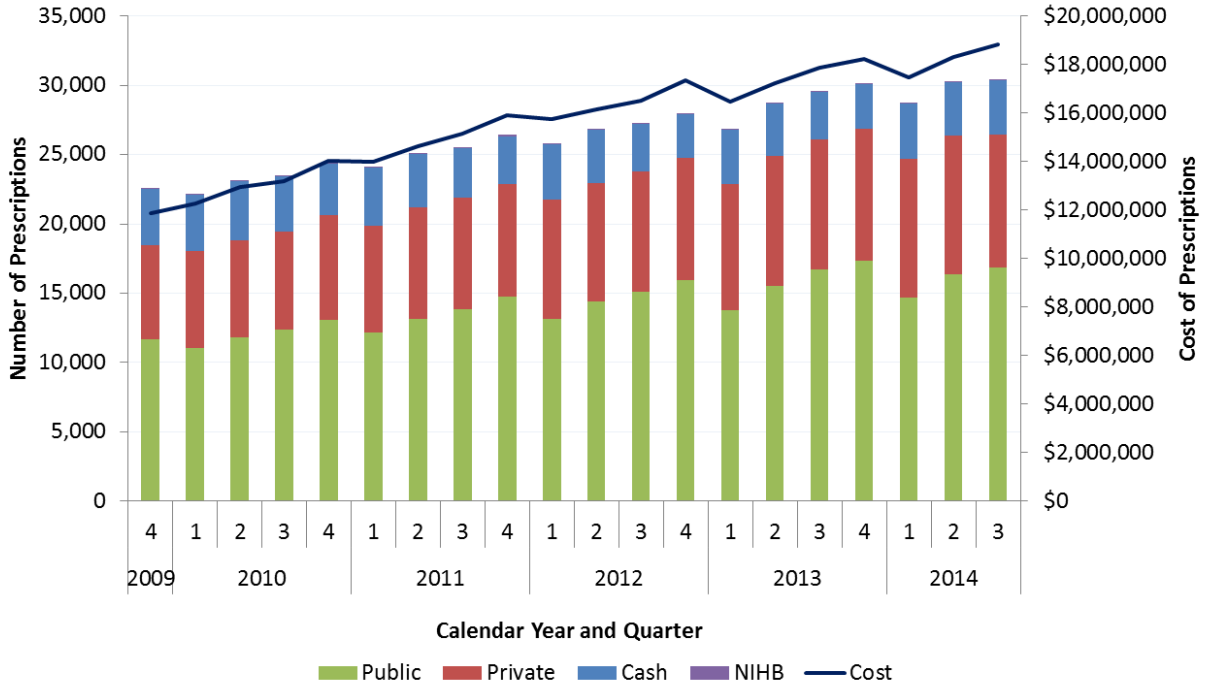
Exhibits and Findings

National Trends in Utilization of Chronic Hepatitis B Medications

Methodological Note:

Tenofovir that we included in these analyses is indicated for use among individuals with chronic hepatitis B or individuals with HIV. Also, standard interferon may be used to treat specific non-hepatitis B related malignancies. Data presented at the National level and in Provincial comparisons was unable to isolate use of these medications to patients with a diagnosis of chronic hepatitis B. Therefore, there will be an overestimation of prescriptions dispensed and costs for tenofovir and standard interferon in the treatment of chronic hepatitis B.

Exhibit 1: Total utilization and cost of chronic hepatitis B medications dispensed in Canada, by payer and quarter

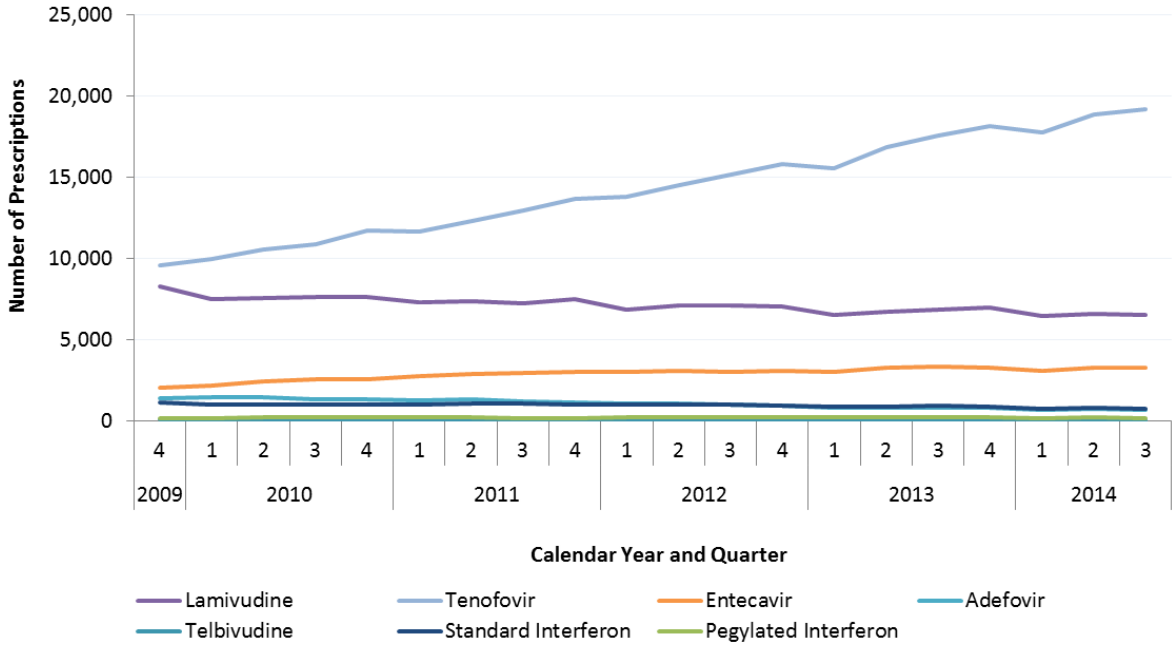


Utilization and costs of chronic hepatitis B medications in Canada have increased by 35% and 59% over the study period, respectively. During the third quarter of 2014, 55% of chronic hepatitis B medications dispensed in Canada were paid for by provincially-funded drug coverage programs.

Summary of Findings for Exhibit 1

1. The number of prescriptions dispensed for chronic hepatitis B medications in Canada has increased by 34.6% over the past 5 years, from 22,608 prescriptions dispensed in Q4 2009 to 30,426 prescriptions dispensed in Q3 2014.
2. By the end of the study period, a total of approximately $18.8 million was spent on all chronic hepatitis B medications nationally, an increase of approximately 58.6% from Q4 2009 ($11.9 million).
3. The majority of prescriptions dispensed in Canada for chronic hepatitis B medications were paid for by public drug coverage programs, which has increased by 44.8% from 11,640 prescriptions dispensed (Q4 2009) to 16,853 prescriptions dispensed (Q3 2014) Overall, costs for publically funded chronic hepatitis B medications have increased nearly 2-fold from $5.1 million (Q4 2009) to $9.9 million (Q3 2014).
4. The distribution of payers for chronic hepatitis B medications dispensed in Canada during Q3 2014 was 55.4% public (16,853 prescriptions), 31.4% private (9,562 prescriptions), 13.0% cash (3,954 prescriptions), and 0.2% NIHB (57 prescriptions). This accounted for $9.9 million in public drug costs, $6.7 million in private insurance costs, $2.0 million in cash payments, and $21,353 in NIHB costs.

Exhibit 2: Total utilization of chronic hepatitis B medications dispensed in Canada, by drug and quarter



Tenofovir is the most commonly prescribed chronic hepatitis B medication in Canada, followed by lamivudine. However, tenofovir use has continued to rise as lamivudine use has decreased over time.

Summary of Findings for Exhibit 2

1. Among all chronic hepatitis B medications dispensed in Q3 2014 (30,606 prescriptions), almost two-thirds (62.6%; 19,172 prescriptions) were for tenofovir, followed by lamivudine (21.3%; 6,532 prescriptions), entecavir (10.7%; 3,273 prescriptions), standard interferon (2.5%; 774 prescriptions), adefovir (2.2%; 660 prescriptions), pegylated interferon (0.6%; 171 prescriptions) and telbivudine (0.1%; 24 prescriptions).
2. Between Q4 2009 and Q3 3014, the number of prescriptions dispensed for tenofovir and entecavir have increased (99.4% and 57.9%, respectively), while prescriptions dispensed for telbivudine, adefovir, standard interferon and lamivudine have decreased (79.8%, 53.6%, 33.3% and 21.0%, respectively). The number of prescriptions dispensed for pegylated interferon has remained relatively stable over time.

Population-Adjusted Rates of Chronic Hepatitis B Medication Utilization, by Funding Type

Methodological Note:
Non-provincially funded utilization represents use outside of provincial drug plans. This includes prescriptions paid by:

- Private drug insurance
- Cash
- Non-Insured Health Benefits

Public plan listings for chronic hepatitis B medications vary across the provinces. Detailed information on public plan listings is provided in Appendix A and Appendix B.

Exhibit 3: Population-adjusted utilization of provincially funded chronic hepatitis B medications in Canada, by province and quarter

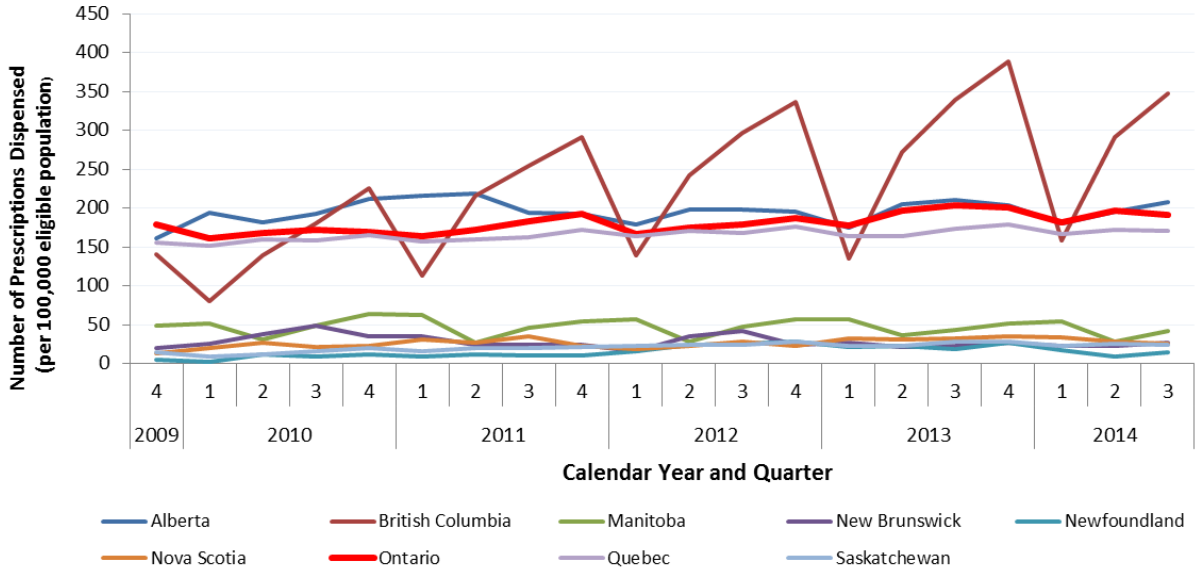
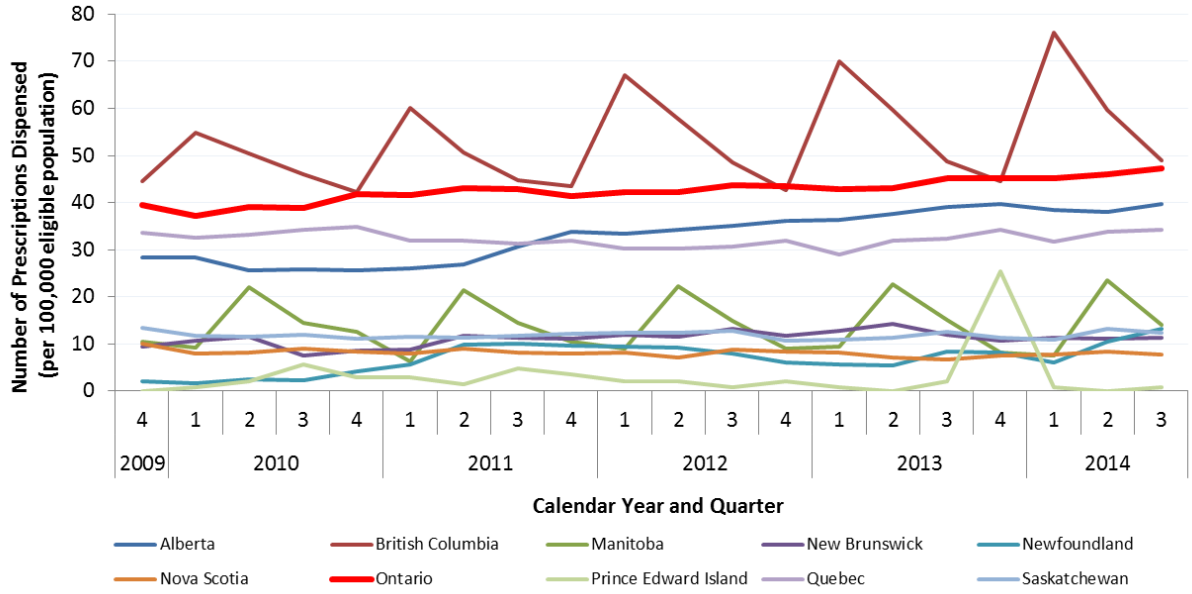


Exhibit 4: Population-adjusted utilization of non-provincially funded chronic hepatitis B medications in Canada, by province and quarter



The rate of provincially funded prescriptions dispensed for medications used to treat chronic hepatitis B was much higher compared to the rate of non-provincially funded prescriptions dispensed. Ontario has the third highest utilization of provincially-funded and the second highest utilization of non-provincially funded chronic hepatitis B medications in Canada.

Summary of Findings for Exhibit 3 and Exhibit 4

1. There was a wide variation in the number of prescriptions dispensed for provincially funded hepatitis B products between provinces in Canada (range in Q3 2014: 14 [Newfoundland] to 347 [British Columbia] prescriptions dispensed per 100,000 eligible population).
2. Cross-provincial variations were also noted amongst non-provincially funded hepatitis B products (range in Q3 2014: 0.68 [Prince Edward Island] to 49 [British Columbia] prescriptions per 100,000 population).
3. In Q3 2014, Ontario had the third highest rate of provincially-funded hepatitis B product use (192 prescriptions per 100,000 eligible population compared to the national average of 172 prescriptions per 100,000 eligible population), and the second highest rate of non-provincially funded product use (47 prescriptions per 100,000 population compared to the national average of 39 prescriptions per 100,000 population).
4. Overall, a higher number of prescriptions for provincially-funded hepatitis B products were noted in British Columbia, Alberta, Ontario and Quebec (Q3 2014: 347, 207, 191 and 171 prescriptions per 100,000 eligible population, respectively). Similarly, these provinces also exhibited the highest number of prescriptions for non-provincially funded products (Q3 2014: 49, 40, 47 and 34 prescriptions per 100,000 population, respectively). This is likely due to these provinces having a higher prevalence of immigrants, who generally have a higher prevalence of chronic hepatitis B in Canada.

Exhibit 5: Population-adjusted utilization of provincially funded chronic hepatitis B medications in Canada in 2013, by province and drug

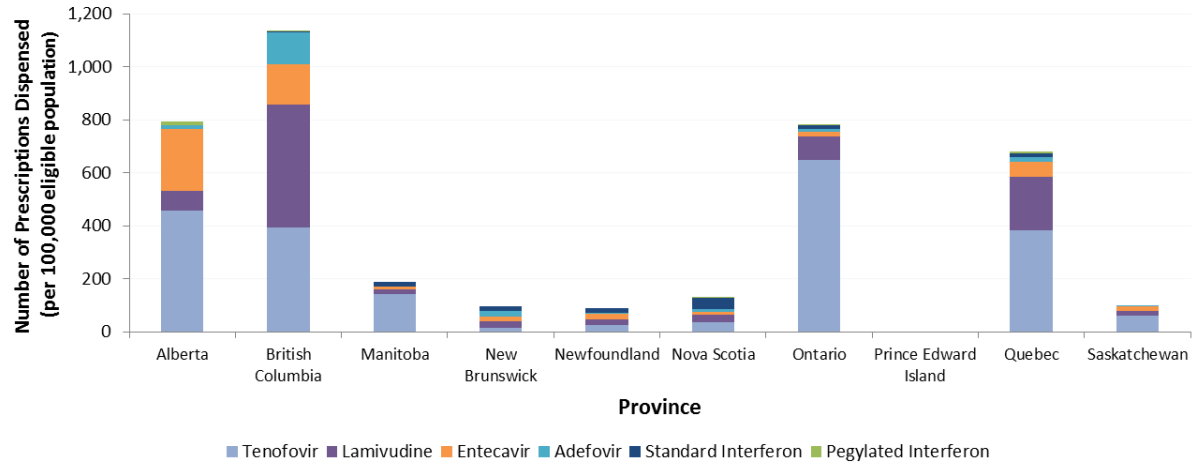
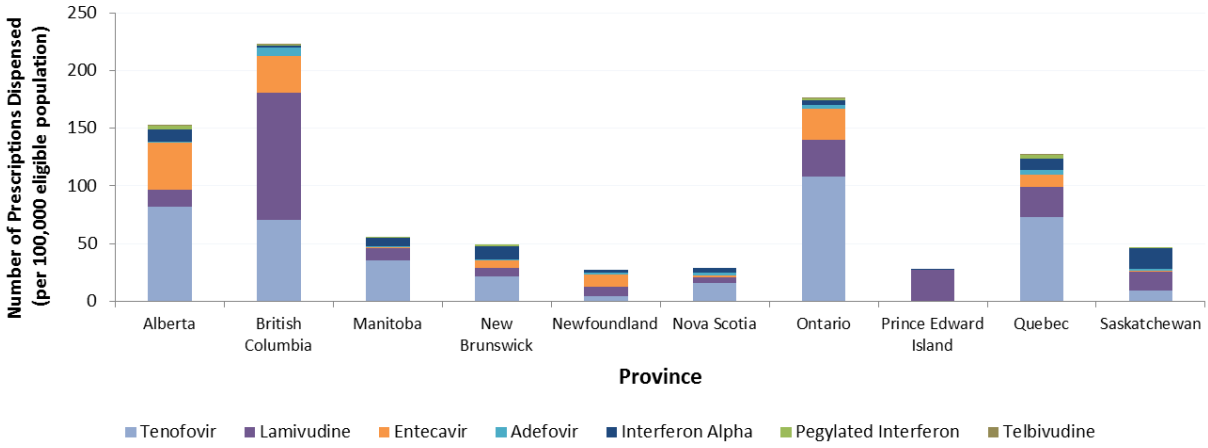


Exhibit 6: Population-adjusted utilization of non-provincially funded chronic hepatitis B medications in Canada in 2013, by province and drug



The type of hepatitis B therapy dispensed varied considerably across provinces in 2013, with tenofovir being most commonly prescribed in most provinces, the exceptions being British Columbia, Newfoundland and Labrador, PEI, and Saskatchewan.

Summary of Findings for Exhibit 5 and Exhibit 6

1. In 2013, the most common provincially funded chronic hepatitis B medication dispensed was tenofovir in Alberta, Manitoba, Newfoundland, Ontario, Quebec and Saskatchewan (457, 141 26, 648, 381, 60 prescriptions dispensed per 100,000 eligible population, respectively). Conversely, lamivudine was most commonly dispensed in British Columbia and New Brunswick (463 and 23 prescriptions dispensed per 100,000 eligible population) and standard interferon was most commonly dispensed in Nova Scotia (41.9 per 100,000 eligible population).
2. In 2013, tenofovir was the most commonly dispensed non-provincially funded chronic hepatitis B medication in Alberta, Manitoba, New Brunswick, Nova Scotia, Ontario and Quebec (82, 35, 21, 16, 108, 73 prescriptions dispensed per 100,000 population, respectively). In British Columbia and PEI, lamivudine was the most commonly dispensed non-provincially funded chronic hepatitis B medication (111 and 28 prescriptions dispensed per 100,000 population, respectively), compared to entecavir in Newfoundland (118 prescriptions dispensed per 100,000 population) and standard interferon in Saskatchewan (18 prescriptions dispensed per 100,000 population).
3. In PEI, lamivudine and standard interferon were the only non-provincially funded chronic hepatitis B medications dispensed, and there were no provincially funded prescriptions dispensed, in 2013.
4. Telbivudine had the lowest rate of non-provincially funded prescriptions dispensed across all provinces in Canada in 2013. There were no provincially funded prescriptions dispensed for telbivudine in any provinces since it is not a benefit on any provincial drug formulary.

Population-Adjusted Rates of Chronic Hepatitis B Medication Utilization, Among Public Plan Beneficiaries

Methodological Note:
The following analyses are conducted using public drug beneficiary data collected by the Canadian Institute for Health Information and ICES. Data for Nova Scotia and New Brunswick have been grouped together due to small cell sizes. Further, no data was available for Quebec and Newfoundland & Labrador. There were no provincially funded prescriptions dispensed for chronic hepatitis B medications in PEI during the study period, therefore no data is reported for PEI.

Exhibit 7: Population-adjusted utilization of provincially funded chronic hepatitis B medications in Canada in 2013, by province and drug

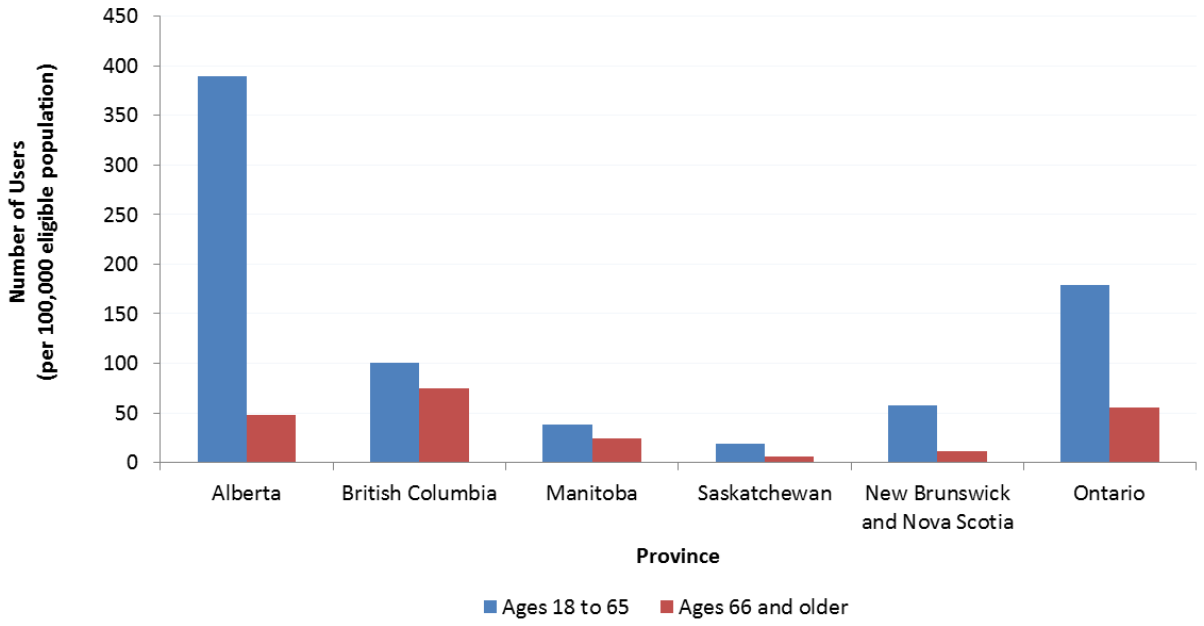
Province	Number of Users	Rate of Users (per 100,000 eligible population)						
		Overall	Drug					
			Lamivudine	Tenofovir	Adefovir	Entecavir	Standard Interferon	Pegylated Interferon
Alberta	697	134.6	14.1	72.2	2.1	49.6	0.0	2.9
British Columbia	2,323	93.9	56.0	33.8	9.0	7.7	*	*
Manitoba	236	35.2	4.8	26.9	0.7	2.1	1.8	*
Saskatchewan	87	15.3	5.4	8.6	1.1	1.8	0.0	0.0
New Brunswick and Nova Scotia	67	24.1	6.5	11.2	2.2	2.2	4.0	*
Ontario	3,749	113.2	17.3	92.6	1.6	2.8	3.0	*

The overall number and rate of provincially funded chronic hepatitis B medication users varied across provinces and drugs in Canada in 2013. The overall rate of use was highest in Alberta and Ontario.

Summary of Findings for Exhibit 7

1. In 2013, the number of provincially funded chronic hepatitis B medication users was highest in Ontario and British Columbia (3,749 and 2,323 users, respectively), while the rate of provincially funded chronic hepatitis B medication use was highest in Alberta and Ontario (135 and 113 users per 100,000 eligible population, respectively).
2. The lowest number of provincially funded chronic hepatitis B medication use was observed in New Brunswick and Nova Scotia, while the lowest rate of use was observed in Saskatchewan.
3. In 2013, tenofovir had the highest rate of use across all provinces, except in British Columbia where lamivudine had the highest rate of use.
4. Alberta had a much higher rate of entecavir use compared to the other provinces (50 users per 100,000 eligible population vs. less than 10 users per 100,000 eligible in the other provinces). British Columbia had a much higher rate of adefovir use (9 users per 100,000 eligible population vs. less than 3 users per 100,000 eligible in the other provinces) and lamivudine use (56 users per 100,000 eligible population vs. less than 20 users per 100,000 eligible in the other provinces)
5. The rate of standard interferon and pegylated interferon use were lowest in all provinces, with less than 5 users per 100,000 eligible population for all provinces across Canada.

Exhibit 8: Population-adjusted utilization of provincially funded chronic hepatitis B medications in Canada in 2013, by province and age



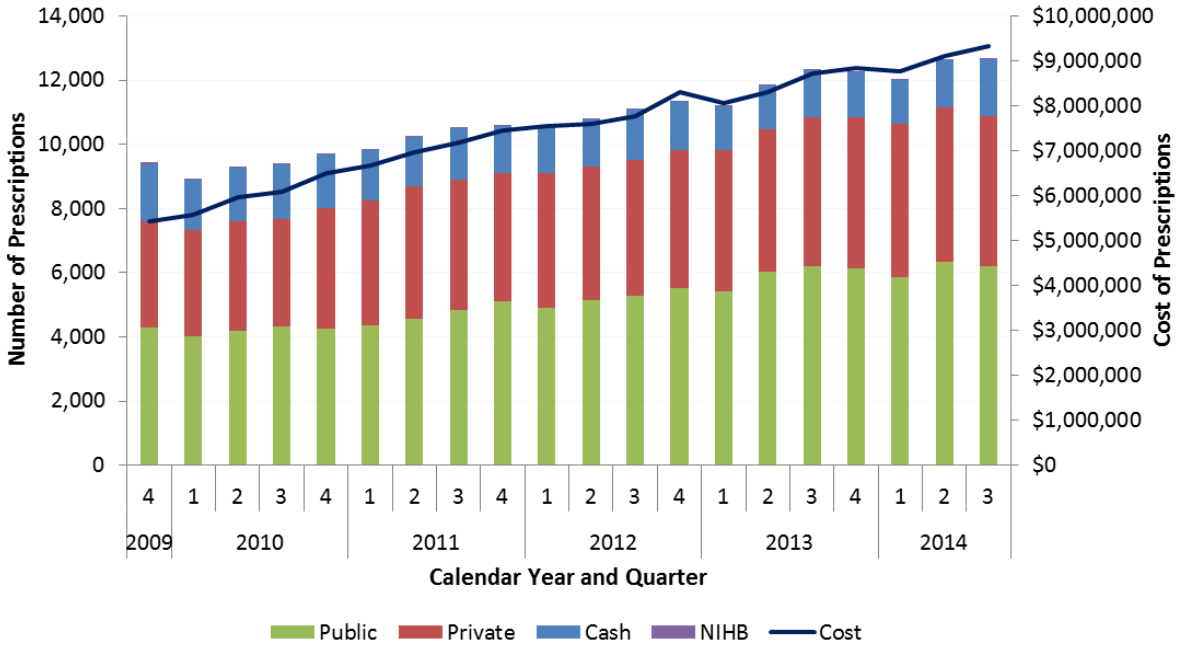
The rate of provincially funded chronic hepatitis B medication use was higher among those aged 18 to 65 compared to those aged 66 and older, and also varied across provinces in Canada in 2013.

Summary of Findings for Exhibit 8

1. The rate of provincially-funded chronic hepatitis B medication use was higher among younger adults (aged 18 to 65) compared to older adults (aged 66 and older) across all provinces in Canada in 2013 (120 and 52 users per 100,000 eligible population, respectively).
2. The rate of hepatitis B medication use was highest in Alberta (390 users per 100,000 eligible population) among younger adults and highest in British Columbia (75 users per 100,000 eligible population) among older adults.
3. The rate of hepatitis B medication use was lowest in Saskatchewan among both younger and older adults (19 and 6 users per 100,000 eligible population, respectively).
4. In Ontario, the rate of hepatitis B medication use was second highest among both younger and older adults (179 and 55 users per 100,000 eligible population).

Trends in Provincially-Funded Chronic Hepatitis B Medications in Ontario

Exhibit 9: Total utilization and cost of chronic hepatitis B medications in Ontario, by coverage and quarter



Utilization and costs of chronic hepatitis B medications in Ontario have increased by 34% and 72% over the study period, respectively. During the third quarter of 2014, almost half (49%) of chronic hepatitis B medications dispensed in Canada were paid for by provincially-funded drug coverage programs.

Exhibit 10: Distribution of the prescriptions dispensed for chronic hepatitis B medications in Ontario in 2013, by coverage

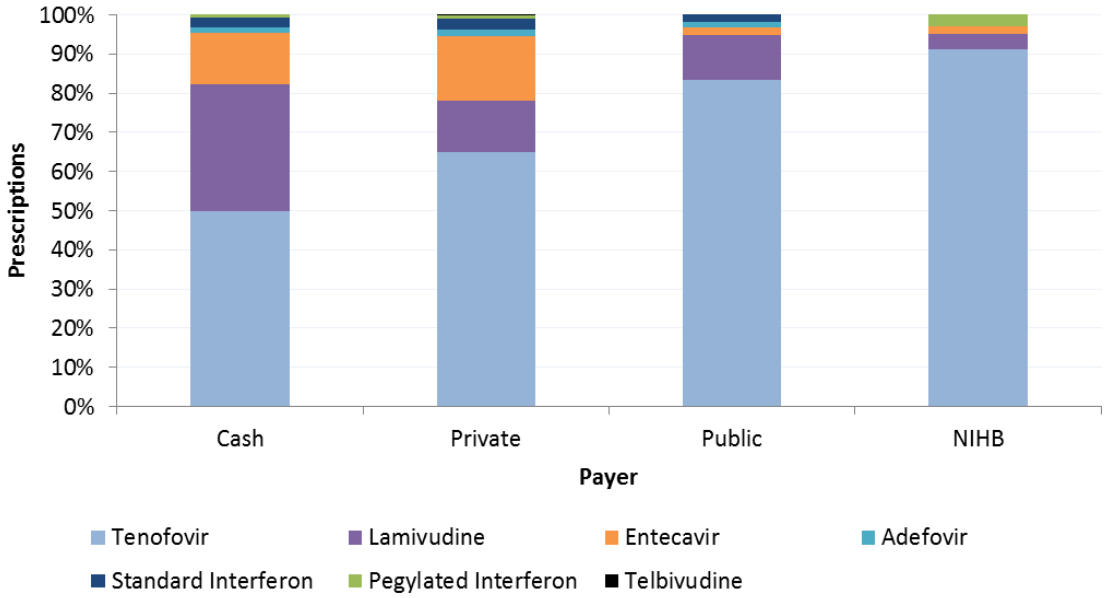
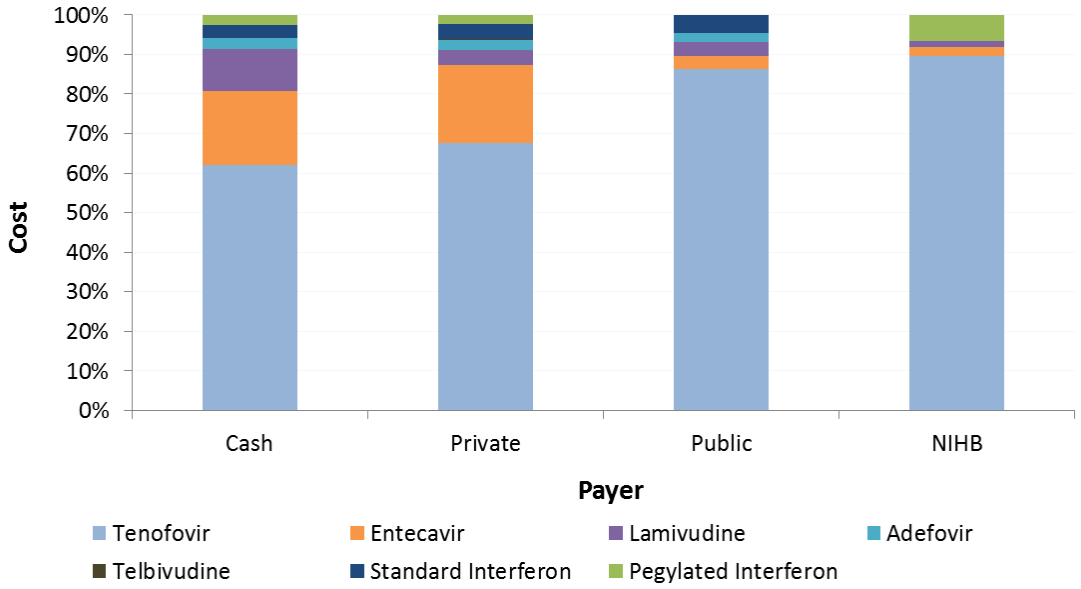


Exhibit 11: Distribution of the costs for chronic hepatitis B medications dispensed in Ontario in 2013, by coverage



Tenofovir comprises the majority of prescriptions and costs for chronic hepatitis B medications across all payers in Ontario. This is likely due to the cross indication for HIV infection. Entecavir spending is much higher among cash and private payers, and pegylated interferon costs are higher in NIHB compared to other payment methods.

Summary of Findings for Exhibit 10 and Exhibit 11

1. Similar to national trends, utilization of chronic hepatitis B medications has increased 34% over the study period in Ontario, from 9,433 prescriptions dispensed in Q4 2009 to 12,665 prescriptions dispensed in Q3 2014. Costs for chronic hepatitis B medications have increased by 72% over the study period in Ontario, from $5.4 million in Q4 2009 to $9.3 million in Q4 2014.
2. By the third quarter of 2014, almost half (49%; 6,186 prescriptions) of chronic hepatitis B medications dispensed in Ontario were paid for by public payers, followed by private (37%; 4,701 prescriptions), cash (14%; 1,761 prescriptions) and NIHB (<1%) payers. This accounted for $4.6 million public, $3.7 million private, $1.0 million cash and $10,522 NIHB costs.
3. There was a variation in the distribution of prescriptions and costs of chronic hepatitis B medications among payers in Ontario in 2013.
    a. Tenofovir was the most commonly dispensed medication covered by public payers (83.3%), private payers (64.8%), cash payments (49.8%) and NIHB (91.2%). Similarly, the majority (86%) of public payer costs were for tenofovir compared to 68% of drug costs paid in cash and 62% of private payer costs.
    b. Prescriptions dispensed for lamivudine was higher among cash payers than among private and public payers (32.5%, 13.3% and 11.4% of all prescriptions dispensed, respectively). Similarly, costs for lamivudine were higher among cash payers than among private and public payers (11%, 4% and 4% of all costs, respectively). This is likely due to a shift to a lower-costing option for patients having to pay out of pocket for treatment.
    c. Entecavir use was much higher in private and cash payers when compared to public payers (16.4%, 12.9% and 2% of all prescriptions dispensed, respectively). Costs for entecavir use represented a higher proportion among cash and private payers when compared to public payers (19%, 20% and 3% of all costs, respectively).
    d. Telbivudine was only dispensed and paid for by private payers.

Characteristics of Provincially-Funded Chronic Hepatitis B Medication Users in Ontario, Between 2012 and 2013

Methodological Note:
For the following analyses in Ontario, we excluded tenofovir users if they did not have a chronic hepatitis B diagnosis in the past 10 years, did not use another chronic hepatitis B medication in the past 10 years or were prescribed an overlapping HIV medication. This was done to remove individuals who may have been using tenofovir for HIV therapy.

Standard interferon may be used to treat specific non-hepatitis B related malignancies. No exclusions were made to restrict to hepatitis B patients for this medication.

Combination therapy is defined as an individual using two hepatitis B medications prescribed on the same day.

Exhibit 12: Baseline characteristics of provincially-funded chronic hepatitis B medication users in Ontario, by drug, calendar year 2012 to 2013

Characteristics	Drug						
	Overall	Combination Therapy	Standard Interferon	Lamivudine	Adefovir	Entecavir	Tenofovir
Number of users	N=3,559	N=64	N=188	N=639	N=15	N=106	N=2,547
Number of new users	624 (17.5%)	≤5	65 (34.6%)	135 (21.1%)	≤5	12 (11.3%)	409 (16.1%)
Age							
Mean (SD)	55.7 (14.6)	61.5 (10.9)	58.2 (14.6)	60.0 (13.2)	61.1 (11.3)	59.6 (12.5)	54.1 (14.8)
18-39	553 (15.5%)	≤5	26 (13.8%)	49 (7.7%)	≤5	≤5	471 (18.5%)
40-65	2,072 (58.2%)	37 (57.8%)	94 (50.0%)	364 (57.0%)	9 (60.0%)	64 (60.4%)	1,504 (59.0%)
66+	934 (26.2%)	26-30	68 (36.2%)	226 (35.4%)	≤5	36-40	572 (22.5%)
Number of Males	2,320 (65.2%)	48 (75.0%)	114 (60.6%)	436 (68.2%)	13 (86.7%)	68 (64.2%)	1,641 (64.4%)
Urban Residence	3,494 (98.2%)	64 (100.0%)	148 (78.7%)	634 (99.2%)	15 (100.0%)	106 (100.0%)	2,527 (99.2%)
Long-Term Care Residence	15 (0.4%)	0 (0.0%)	0 (0.0%)	≤5	0 (0.0%)	≤5	8 (0.3%)
Income Quintile							
1	803 (22.6%)	16-20	30 (16.0%)	161 (25.2%)	≤5	27 (25.5%)	567 (22.3%)
2	936 (26.3%)	6-10	28 (14.9%)	167 (26.1%)	≤5	24 (22.6%)	704 (27.6%)
3	724 (20.3%)	14 (21.9%)	43 (22.9%)	130 (20.3%)	≤5	20-25	513 (20.1%)
4	602 (16.9%)	21 (32.8%)	42 (22.3%)	99 (15.5%)	6 (40.0%)	21 (19.8%)	413 (16.2%)
5	481 (13.5%)	≤5	44 (23.4%)	81 (12.7%)	0 (0.0%)	10-15	339 (13.3%)
Born outside of Canada	1,773 (49.8%)	26 (40.6%)	10-15	317 (49.6%)	≤5	43 (40.6%)	1,373 (53.9%)
Prescriber of initial prescription							
Gastroenterology	1,790 (50.3%)	45 (70.3%)	0 (0.0%)	352 (55.1%)	10 (66.7%)	62 (58.5%)	1,321 (51.9%)
Infectious Disease	216 (6.1%)	0 (0.0%)	0 (0.0%)	8 (1.3%)	0 (0.0%)	7 (6.6%)	201 (7.9%)
Internal Medicine	299 (8.4%)	≤5	≤5	59 (9.2%)	≤5	15 (14.2%)	215 (8.4%)
Medical Oncology	157 (4.4%)	0 (0.0%)	129 (68.6%)	15 (2.3%)	0 (0.0%)	0 (0.0%)	13 (0.5%)
Hematology	40 (1.1%)	0 (0.0%)	23 (12.2%)	11 (1.7%)	0 (0.0%)	0 (0.0%)	6 (0.2%)
GP	490 (13.8%)	≤5	18 (9.6%)	51 (8.0%)	≤5	10 (9.4%)	408 (16.0%)
Unknown	511 (14.4%)	13 (20.3%)	10-15	121 (18.9%)	≤5	11 (10.4%)	353 (13.9%)

Characteristics	Drug						
	Overall	Combination Therapy	Standard Interferon	Lamivudine	Adefovir	Entecavir	Tenofovir
One of more hospitalizations in the last year	459 (12.9%)	≤5	90 (47.9%)	109 (17.1%)	0 (0.0%)	16-20	237 (9.3%)
Emergency room visits within the last year	762 (21.4%)	10-15	97 (51.6%)	154 (24.1%)	≤5	31 (29.2%)	468 (18.4%)
Physician office visits within the last year - Median (IQR)	10.0 (6-15)	9.0 (6-12.5)	21.0 (16-30)	11.0 (7-17)	8.0 (5-19)	11.0 (7-16)	9.0 (6-14)
Co-morbidities							
Mild Liver Disease	220 (28.9%)	10-15	≤5	73 (40.8%)	0 (0.0%)	13 (48.1%)	123 (28.3%)
Primary Cancer	223 (29.3%)	≤5	30 (28.3%)	69 (38.5%)	≤5	≤5	113 (26.0%)
Moderate or Severe Liver Disease	88 (11.6%)	≤5	0 (0.0%)	22 (12.3%)	≤5	6 (22.2%)	57 (13.1%)
Metastatic Cancer	91 (12.0%)	≤5	59 (55.7%)	10-15	0 (0.0%)	0 (0.0%)	16 (3.7%)
Charlson Morbidity Index							
No hospitalization	2,798 (78.6%)	50-55	82 (43.6%)	460 (72.0%)	10-13	79 (74.5%)	2,112 (82.9%)
0	186 (5.2%)	0 (0.0%)	10-15	29 (4.5%)	0 (0.0%)	≤5	139 (5.5%)
1	87 (2.4%)	≤5	≤5	21 (3.3%)	0 (0.0%)	≤5	57 (2.2%)
2	135 (3.8%)	≤5	25 (13.3%)	38 (5.9%)	0 (0.0%)	≤5	69 (2.7%)
3+	353 (9.9%)	5-10	67 (35.6%)	91 (14.2%)	≤5	16 (15.1%)	170 (6.7%)
Number of different medications used in the past year	5.4 (6.2)	8.2 (5.6)	6.7 (6.7)	7.4 (6.4)	9.4 (7.3)	6.9 (6.1)	4.7 (5.9)
Coinfections at cohort entry							
HIV	54 (1.5%)	0 (0.0%)	≤5	0 (0.0%)	0 (0.0%)	≤5	49 (1.9%)
Hepatitis C	181 (5.1%)	13 (20.3%)	0 (0.0%)	46 (7.2%)	≤5	≤5	116 (4.6%)
Unspecified Hepatitis	126 (3.5%)	≤5	0 (0.0%)	28 (4.4%)	0 (0.0%)	≤5	89 (3.5%)

**In accordance with the ICES privacy policy, in cases where the number of total users is less than 6, this number has been suppressed to ensure confidentiality. In cases where there is only one record being suppressed, another record has been suppressed (by providing a range in values) as well in order to avoid residual disclosure issues.*

There were 3,559 patients in Ontario who were treated with provincially-funded chronic hepatitis B medications between 2012 and 2013. Tenofovir was the most commonly used treatment. Chronic hepatitis B treated patients in Ontario were on average 56 years of age, mostly male, and lived in urban areas.

Summary of Findings for Exhibit 12

1. There were 3,559 patients in Ontario who were treated with provincially-funded chronic hepatitis B medications between 2012 and 2013. Tenofovir was the most common treatment, used by 2,547 (71.6%) patients. Chronic hepatitis B treated patients in Ontario were on average 56 years of age, mostly male (65.2%), and lived in urban areas (98.2%). Only a quarter of patients were over the age of 66 (26.2%; N=934).
2. Among all users, 624 (17.5%) were found to be new users of therapy. Tenofovir was the most commonly newly initiated treatment (65.5%; N=409) followed by lamivudine (21.6%; N=135).
3. Half of all patients treated for chronic hepatitis B in Ontario were born outside of Canada (49.8%). This was true for all treatments (ranging from 41% to 54%), except for standard interferon and adefovir users.
4. Gastroenterologists prescribed the majority (50.3%) of prescriptions for all medications, except for standard interferon which was predominantly prescribed by medical oncologists (69%). No prescriptions for standard interferon were prescribed by gastroenterologists or infectious disease physicians.
5. Standard interferons are likely being prescribed commonly by medical oncologists due to the alternate indications of this medication to treat specific non-hepatitis B related malignancies. Standard interferon users had much higher rates of hospitalization (48%), ED visits (52%), and cases for primary cancer (28%) and metastatic cancer (56%).
6. A small proportion of chronic hepatitis B treated patients had co-infections with HIV (1.5%) or Hepatitis C (5.1%). This was true across all drug groups except for combination therapy users among whom 20% had a co-infection with Hepatitis C.

NOTE: Pegylated interferon users are not included in Exhibit 17 due to small cell sizes. There were only 6 users captured between 2012 and 2013.

Patterns of Chronic Hepatitis B Medication Use and Discontinuation

Exhibit 13: Time to discontinuation of provincially-funded chronic hepatitis B medications among new users with more than 1 prescription in Ontario, by age and drug, January 2003 – December 2012

Age Group	Drug	Number of New Users	Percent Adherent[‡] After 1 Year	Percent Adherent[‡] After 2 Years	Median Time to Discontinuation	Log-Rank Test
18-65	**Overall**	**3,062**	**50-60%**	**40-50%**	**13-15 months**	
	Standard interferon	594	0-10%	0-10%	3-6 months	p<0.0001
	Pegylated interferon	185	0-10%	0-10%	3-6 months	
	Lamivudine	1,010	60-70%	40-50%	20-23 months	
	Adefovir	14	90-100%	80-90%	Did not reach	
	Entecavir	69	70-80%	60-70%	Did not reach	
	Telbivudine	0	NA	NA	NA	
	Tenofovir	1,190	70-80%	60-70%	Did not reach	
66+	**Overall**	**883**	**50-60%**	**40-50%**	**13-15 months**	
	Standard interferon	276	0-10%	0-10%	3-6 months	p<0.0001
	Pegylated interferon	10-15	0-10%	0-10%	3-6 months	
	Lamivudine	341	70-80%	60-70%	Did not reach	
	Adefovir	≤5	90-100%	90-100%	Did not reach	
	Entecavir	2	70-80%	60-70%	Did not reach	
	Telbivudine	0	NA	NA	NA	
	Tenofovir	225	80-90%	60-70%	Did not reach	

[‡]*Based on Kaplan Meier estimates*

**Not Available due to lack of follow-up time*

In accordance with the ICES privacy policy, in cases where the number of total users is less than 6, this number has been suppressed to ensure confidentiality. In cases where there is only one record being suppressed, another record has been suppressed (by providing ranges) as well in order to avoid residual disclosure issues.

The duration of provincially funded chronic hepatitis B treatment varied by the medication initiated in both the younger and older adults, and most notably between patients initiating interferons compared to oral antiviral therapies.

Summary of Findings for Exhibit 13

1. Between 2003 and 2012, 3,062 younger adults (aged 18-65) and 883 older adults (aged 66+) initiated provincially funded chronic hepatitis B medications in Ontario. The time to discontinuation of chronic hepatitis B treatment varied by the therapy initiated in both the younger and older adults ($p<0.0001$), and most notably between patients initiating interferons vs. antiviral therapies. These findings reflect the shorter duration of therapy that has been approved for interferons (168-336 days), compared to oral antiviral therapies which can have a lifetime duration of therapy.
2. Older adults initiating standard and pegylated interferon therapies were more likely to remain on any chronic hepatitis B medication after one year (5-10%, respectively) compared to the younger adults initiating these therapies (0-5%, respectively). After two years, less than 5% of users were still on therapy among both age groups.
3. Chronic hepatitis B therapy adherence was highest among both younger and older adults initiating adefovir (90-100% adherent after one year, respectively), despite having few users. The proportion of younger adults continuing an oral chronic hepatitis B treatment for more than one year was lowest among those initiating lamivudine (60-70%). The proportion of older adults continuing chronic hepatitis B treatment for more than one year was very similar among those initiating lamivudine, entecavir, and tenofovir (between 70-80%). More than half of both younger and older adults initiating adefovir, entecatvir, and tenofovir were still on a chronic hepatitis B treatment after two years.
4. In a subset analysis among individuals initiating tenofovir, lamivudine and entecavir (the three most commonly prescribed orals hepatitis B medications), there was no difference in duration of therapy among older adults ($p=0.33$), however lamivudine users had a lower rate of adherence compared to entecavir and tenofovir users among younger adults ($p<0.0001$). When comparing younger to older individuals, older adults were more adherent to therapy (entecavir, tenofovir and lamivudine) compared to younger users ($p<0.0001$).
5. In a sensitivity analysis examining the time to discontinuation of the chronic hepatitis B drug initiated (data not shown), 10-20% of users initiating lamivudine switched to another chronic hepatitis B drug within two years, whereas less than 5% of users initiating a non-lamivudine chronic hepatitis B drug switched to another chronic hepatitis B drug.

Key Findings

Overall National and Provincial Trends in Hepatitis B medication Use

Utilization and costs of drugs used for the treatment of chronic hepatitis B have increased by 34.6% over the past 5 years in Canada, with 30,426 prescriptions dispensed in the third quarter of 2014, which amounted to $18.8 million dollars in national expenditures. The majority (55.4%) of medications dispensed during Q3 2014 were paid for by provincially-funded drug coverage programs, compared to 31.4% through private insurers, 13% through cash payments, and less than 1% through Noninsured Health Benefits (NIHB). Tenofovir was the most commonly dispensed chronic hepatitis B medication in Canada, followed by lamivudine (62.6% and 21.3% of prescriptions dispensed in Q3 2014, respectively). Notably, prescriptions dispensed for tenofovir have been increasing in Canada; however this may be due to individuals using tenofovir for the treatment of HIV since we were unable to restrict this analysis to prescriptions specifically for hepatitis B. Prescriptions for entecavir have increased slightly over the past 5 years in Canada, while prescriptions for other hepatitis B products have decreased or remained stable.

The rate of provincially funded prescriptions dispensed for chronic hepatitis B medications was much higher than the rate of non-provincially funded prescriptions dispensed. By Q3 2014, Ontario had the third highest rate of provincially funded chronic hepatitis B medication use (192 prescriptions dispensed per 100,000 eligible population compared to the national average of 172 prescriptions dispensed per 100,000 eligible population), behind British Columbia and Alberta. Ontario had the second highest rate (behind British Columbia) of non-provincially funded medication use (47 prescriptions dispensed per 100,000 population compared to the national average of 39 prescriptions dispensed per 100,000 population) in Q3 2014. The highest rates of prescriptions dispensed for chronic hepatitis B medications were noted in Alberta, British Columbia, and Ontario and Quebec. This is likely due to the presence of larger urban centres and greater proportions of immigrants in these provinces, as chronic hepatitis B is more prevalent among immigrants in Canada.[1;2]

Cross-Provincial Comparisons of Chronic Hepatitis B Medication Use among Public Drug Plan Beneficiaries

In 2013, the rate of publically funded hepatitis B medication users was highest in Alberta followed by Ontario (144 users and 113 users per 100,000 eligible population, respectively). Tenofovir had the highest rate of publically funded users across all provinces, except in British Columbia where lamivudine had the highest rate of users. The higher rate of lamivudine use in British Columbia is expected since the criteria for tenofovir use are more restrictive in comparison to other provinces. The rate of publically funded hepatitis B medication users was higher among younger adults (aged 18 to 65) compared to older adults (aged 66 and older) across all provinces in Canada, in 2013. This rate of users was highest in Alberta among younger adults and highest in British Columbia among older adults. This rate was second

highest in Ontario among younger adults (179 users per 100,000 eligible population) and among older adults (55 users per 100,000 eligible population).

Chronic Hepatitis B Medication Use in Ontario

Similar to national trends, between Q4 2009 and Q3 2014 prescriptions and costs of chronic hepatitis B medications in Ontario have increased by 34% and 72%, respectively. During Q3 2014, 12,665 prescriptions were dispensed amounting to $9.3 million total expenditures. Almost half (49%; $4.6 million) of chronic hepatitis B medications dispensed in Ontario were paid for by provincially-funded drug coverage programs, followed by private insurance (37%; $3.7 million), cash payments (14%; $1.0 million) and NIHB (<1%; $10,522), in Q3 2014.

Characteristics of Hepatitis B medication Users in Ontario

There were 3,559 patients in Ontario who were treated with provincially funded hepatitis B medications between 2012 and 2013. Tenofovir was the most commonly used treatment (71.6%). Patients were on average 56 years of age, mostly male (65.2%), and lived in urban areas (98.2%). Half of patients treated for chronic hepatitis B were born outside of Canada (ranging from 40.6% to 53.9%), except for standard interferon (5.9%) and adefovir (10-20%) users. Gastroenterologists prescribed the majority (50-70%) of all prescriptions, except for standard interferon which was predominantly prescribed by medical oncologists (68.6%). The large majority of standard interferon prescribed by medical oncologists, likely reflects its use for other indications.

Patterns of Hepatitis B medication Use and Discontinuation in Ontario

Between 2003 and 2012, there were 3,062 younger adults and 883 older adults who initiated a publically funded chronic hepatitis B medication in Ontario. The duration of hepatitis B treatment varied greatly by the therapy initiated in both the younger ($p<0.0001$) and older adults ($p<0.0001$). In particular, patients who initiated an interferon discontinued treatment sooner compared to those who initiated an oral antiviral therapy. These findings reflect the shorter duration of therapy approved for interferons (24-48 weeks) compared to oral antiviral therapies which have a lifetime duration of use. Less than 5% of interferon users were still on therapy after two years, while 60-70% of younger adults and 70-80% of older adults were still on oral antiviral therapy after two years. Among individuals initiating tenofovir, lamivudine and entecavir (the three most commonly prescribed oral hepatitis B medications), there was no difference in duration of therapy among older adults ($p=0.33$), however lamivudine users had worse adherence compared to entecavir and tenofovir users among younger adults ($p<0.0001$). Older adults were also more adherent to oral therapy (entecavir, tenofovir and lamivudine) compared to younger users ($p<0.0001$). We also performed a sensitivity analysis to examine the time to discontinuation of the hepatitis B medication initiated. This analysis revealed that 10-20% of users initiating lamivudine switched to another hepatitis B therapy within two years, whereas less than 5% of users initiating a non-lamivudine hepatitis B therapy switched to another hepatitis B therapy over

this time.

Among all patients initiating an oral antiviral chronic hepatitis B medication, there was no difference in the duration of oral antiviral treatment between users born in Canada compared to users born outside of Canada, among both younger (p=0.11) and older (p=0.65) adult users.

Cyclic Trends

We observed a major cyclic trend in rates of provincially-funded use of chronic hepatitis B medications in British Columbia, with rates being lowest in the first quarter of the year and highest at the end of the year. A similar trend exists in Manitoba, with rates being highest in the first quarter of the year. British Columbia and Manitoba have more expanded public drug coverage among the younger population through their PharmaCare programs, and therefore it is likely that this phenomenon is being driven by patterns of deductible payments and associated stockpiling of drugs near the end of the coverage period (calendar year [January – December] in British Columbia, and fiscal year [April – March] in Manitoba). Rates of non-provincially-funded chronic hepatitis B medications use exhibited opposite trends in British Columbia and Manitoba. In British Columbia, the rate of non-provincially-funded chronic hepatitis B medications use was lowest in the last quarter of the year and highest at the beginning of the year. In Manitoba, rates were lowest in the first quarter of the year and highest in the second quarter.

Health Equity

Stratified analyses suggest that there is not a major equity issue in access to these medications by age or sex. Overall, chronic hepatitis B medication utilization was slightly higher among younger adults and among males, which is expected in this population. We compared therapy duration among individuals born in Canada and those born outside Canada, and found no apparent differences. Given the restricted listing of these products on the Ontario public drug formulary along with the high cost of these medications, access and affordability may be a barrier to some patients, however Ontario was found to have the highest rates of use in Canada.

Limitations

Data Availability

Several limitations to availability of data warrant discussion:

1. No data is available for the Territories, and therefore all analyses are restricted to inter-provincial comparisons.
2. IMS Geographic Prescription Monitor (GPM[12]) does not collect patient-level data, and therefore information on privately funded prescriptions is only available at the prescription and unit (e.g. tablet) level.

3. There is no data available for publically paid prescriptions in Quebec and Newfoundland & Labrador from NPDUIS. Therefore, we will be unable to make comparisons between Ontario rates and rates of use in these provinces.
4. Data on the number of individuals eligible for public drug coverage was estimated based on prescription trends (where available) and public annual reports. Therefore, these may slightly underestimate the true size of the public beneficiary population; however, this does reflect the number of active beneficiaries (e.g. those filling at least one prescription over a given year) each year.
5. Tenofovir is indicated for use among individuals with a diagnosis of chronic hepatitis B or HIV. Also, standard interferon may be used to treat specific non-hepatitis B related malignancies. We were unable to limit the use of these medications to individuals with a diagnosis of chronic hepatitis B at the National level and in cross-provincial comparisons due to unavailable patient characteristics available from IMS Geographic Prescription Monitor (GPM[12]) or NPDUIS. Therefore, prescriptions dispensed, costs and number of users for tenofovir and standard interferon medications are not limited to individuals with chronic hepatitis B.
6. For the Ontario specific analysis on user characteristics and adherence patterns, we excluded tenofovir users if they did not have a chronic hepatitis B diagnosis in the past 10 years, did not use another chronic hepatitis B medication in the past 10 years or were prescribed an overlapping HIV medication. This was done to remove individuals who may have been using tenofovir for HIV therapy. However, we may have excluded tenofovir users who truly had a diagnosis of chronic hepatitis B that was not captured in the administrative databases.
7. For the Ontario specific analysis on user characteristics and adherence patterns, standard interferon may be used to treat specific non-hepatitis B related malignancies. No exclusions were made to try to restrict this population to those specifically being treated for hepatitis B. Based on prescriber specialty, it appears that approximately two-thirds of individuals initiating interferon are being treated for malignancies (i.e. therapy is initiated by medical oncologist).
8. New users of chronic hepatitis B medications in Ontario were defined as having no past prescription for a chronic hepatitis B drug in the past 180 days, regardless of whether they had been eligible for drug coverage for at least 6 months. This is a less restrictive method that allows us to include new immigrants in Ontario who are starting these medications. However, we may be including patients who are not truly new users – for example, those who used Hepatitis B meds prior to the start of their ODB coverage. Therefore, the statistics for new users should be interpreted as new users of these medications in ODB, not necessarily completely treatment naïve.
9. Among users younger than 66 in the patterns of use analysis, if a patient appears to discontinue treatment, we do not know if they truly discontinued treatment or if they lost eligibility for public drug coverage. However, given the high costs of chronic hepatitis B medications, it is unlikely they would lose eligibility for drug coverage.
10. The record from the CIC database date from 1985, so those that immigrated before 1985 may

not be categorized as born outside of Canada. Further, immigrants who reside in Ontario but originally landed in another province will not be captured as an immigrant.

Generalizability

1. All analyses using IMS Geographic Prescription Monitor (GPM[12]) data reflect medication use among the entire population.
2. All analyses among public drug beneficiaries using NPDUIS and ODB data were restricted to those aged 18 and older, and therefore are only generalizable to this population.

Adherence

All data used in these analyses are based on dispensing patterns, and therefore we do not know whether subjects actually took the medications. This is particularly questionable among the population of individuals who were dispensed only one prescription for a chronic hepatitis B medication. It is possible that they never tried the medication, or tried it and did not finish their initial course of therapy. For this reason, we restricted our adherence measures to users who were dispensed more than one prescription.

Overall Conclusion

Utilization and costs of chronic hepatitis B medications are increasing both nationally and in Ontario. Tenofovir is the most commonly used chronic hepatitis B medication, however this may be in part due to use of this drug among patients with HIV. Variation in utilization across provinces reflects the variation in the reimbursement policies and populations. Overall, adherence to hepatitis B therapy is good, with over two-thirds of patients using oral antiviral therapies staying on therapy for more than two years. We also found no difference in adherence between the three most common oral agents (tenofovir, lamivudine, entecavir) among older individuals; however adherence to lamivudine was significantly worse than tenofovir and entecavir among younger individuals. Older adults were also significantly more adherent to oral therapy (entecavir, tenofovir and lamivudine) compared to younger users.

Appendix A: Public Plan Listings for Chronic Hepatitis B Medications in Canada, by Province

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

NAB=not a benefit
RES=restricted listing with specified criteria (e.g., special authorization, exception drug status)
FB=full benefit

Appendix B: Public Plan Listings and Summary of Requirements for Chronic Hepatitis B Treatment in Ontario

Generic name	Ontario Listing	Summary of Requirements

Interferon Alfa-2B	EAP	• Patients less than 50 years of age AND
		  ○ No cirrhosis AND
		  ○ High ALT and HBV

Pegylated interferon 2a	Not Listed	

Adefovir	EAP	• Proven lamivudine resistance OR virologic breakthrough
		  ○ Both with Stage 3 Liver Fibrosis or greater OR
		  ○ Evidence of Cirrhosis

Entecavir	EAP	• Treatment Naïve patients with high viral load AND
		  ○ Both with Stage 4 Liver Fibrosis or greater OR
		  ○ Evidence of Cirrhosis
		• Proven lamivudine failure
		  ○ Evidence of Cirrhosis
		• Proven lamivudine failure AND adefovir failure
		  ○ Evidence of Cirrhosis
		• Proven lamivudine resistance AND cirrhosis
		  ○ Adefovir Failure OR Contraindication to adefovir

Lamivudine	EAP	• FIRST LINE
		• Treatment Niave patients
		  ○ >40 years of age
		  ▪ Consistently High ALT levels
		  ▪ Both with Stage 3 Liver Fibrosis or greater OR
		  ▪ Evidence of Cirrhosis
		  ○ <40 years of age
		  ▪ Both with Stage 3 Liver Fibrosis or greater OR
		  ▪ Evidence of Cirrhosis
		• Treatment Naive patients (any age) who is receiving an organ transplant/immunosupressed
		  ○ Detectable Viral Load AND
		  ○ Consistently High ALT levels
		• Treatment Naive patients (any age) who is receiving chemotherapy
		  ○ Note: Length of Chemotherapy + 6 months
		• Note: Can be used in combination with adefovir. See above.

Generic name	Ontario Listing	Summary of Requirements
Tenofovir	EAP	• Treatment Naïve patients with high viral load AND ○ Both with Stage 4 Liver Fibrosis or greater OR ○ Evidence of Cirrhosis • Lamivudine Failure/resistence/breakthrough ○ Evidence of inadequate response AND ○ Both with Stage 3 Liver Fibrosis or greater OR ○ Evidence of Cirrhosis
Telbivudine	Not Listed	

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

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