TITLE: Descriptive Study: Hepatitis B Testing and Linkage to Care in a Canadian Urban Tertiary Referral Centre

AUTHORS: Lau Keith CK[1,2] BHSc; Shaheen Abdel Aziz[1] MD; Aspinall Alexander A[1] MD; Ricento Tazuko[3]; Qureshi Kamran[3]; Congly Stephen E.[1] MD; Borman Meredith A[1] MD; Jayakumar Saumya[1] MD; Eksteen Bertus[1] MD; Lee Samuel S[1] MD; Stinton Laura[1] MD; Swain Mark G[1] MD; Burak Kelly W[1*] MD; and Coffin Carla S[1, 2*] MD

1. Calgary Liver Unit, Division of Gastroenterology and Hepatology, Department of Medicine, Cumming School of Medicine, University of Calgary, Alberta, Canada
2. Department of Microbiology, Immunology and Infectious Diseases, Cumming School of Medicine, University of Calgary, Alberta, Canada
3. Alberta Health Services, Calgary, Alberta, Canada

***CORRESPONDING AUTHORS:**

Kelly W. Burak and Carla S. Coffin

6D21, Teaching, Research and Wellness Building

3280 Hospital Drive N.W.

Calgary, Alberta, Canada, T2N 4Z6

Tel: (403) 592-5049 Fax: (403) 592-5090

Email: kwburak@ucalgary.ca ; cscoffin@ucalgary.ca

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Dr. Coffin has served as a speaker, advisory board member and/or has received research support from Bristol Myers Squibb, Glaxo Smith Kline, Gilead Sciences, Janssen and Merck.

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ABSTRACT

Background & Aims: Despite universal vaccination, chronic hepatitis B (CHB) in North America remains a public health concern due to immigration. In a 1-year period, we aimed to (1) characterize the number of individuals who tested positive for HBV surface antigen (HBsAg) within a large urban Canadian health care region (Calgary, Alberta) and (2) assess if recommended laboratory tests and specialist consultation were done for identified HBsAg+ individuals. **Methods**: Based on laboratory and Alberta Health Services (AHS) administrative data, we identified all adults (age > 18y) who tested HBsAg+ from January 1st - December 31st 2014 within the Calgary Zone of AHS. Demographic and relevant laboratory data was extracted within 6 months of a positive HBsAg test, and referral to hepatology (2011-2014) based on centralized clinic triage referral data. Non-parametric statistical methods were used for analyses. **Results**: We identified 1214 HBsAg+ individuals (48% female, median age 44y [IQR 36-55]). Overall, 52% completed HBV E antigen testing (13% positive) and 56% had viral load testing (median 2.8logIU/mL, IQR 2.1–3.8). 98% had alanine aminotransferase testing (median 23U/L, IQR 16-34) of which 10% had elevated levels, defined as ≥2x upper limit of normal (38U/L in female; 60U/L in male). Available clinic referral and follow-up data showed that 12% received anti-HBV and 32% were referred to a hepatologist. **Interpretations**: Many HBsAg+ individuals lack the recommended laboratory assessments. The results highlight the necessity of continual CHB public health screening efforts in Canada and adequate follow-up towards reaching the 2030 WHO viral hepatitis elimination goal.

Abstract word count: 250

Introduction

The hepatitis B virus (HBV) is a significant global pathogen with an estimated 240 million chronic HBV (CHB) carriers worldwide (1,2), especially in Asia and sub-Saharan Africa countries. Despite universal childhood vaccination in Canada since the mid -1990's, CHB still afflicts ~260,000 Canadians, especially in new Canadians who were born in HBV-endemic regions and living in larger urban centres [2].

CHB infection, as defined by positive hepatitis B surface antigen (HBsAg) for greater than 6 months duration, can lead to severe liver disease including cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (3). Current potent oral antiviral therapies (i.e., nucleos/tide analogs, NA) rarely lead to HBsAg clearance but are highly effective in suppressing HBV replication and preventing liver disease development (4,5). Ongoing monitoring of all CHB carriers is recommended to determine liver disease risk and need for antiviral therapy including laboratory assessments (i.e., alanine aminotransferase, ALT, HBV DNA levels or viral load, HBV E antigen, HBeAg, and HBV E Antibody, HBeAb) status (4) and ultrasound for HCC surveillance based on age and presence of other risk factors (i.e., family history of HCC, co-infection) (4–7).

HBV is a reportable disease to the Public Health Agency of Canada (PHAC), but due to the lack of standardized nationwide reporting practices, the prevalence and incidence of HBV in Canada is likely underestimated. (8). Recent PHAC data, excludes data from Ontario, a Canadian province with relatively high CHB prevalence (8). Further the PHAC report is inconsistent with data presented by the British Columbia Center of Disease Control (BCCDC) which reports a much higher incidence and prevalence of CHB in the province of BC (9). The World Health Organization (WHO) has advocated for targeted prevention and treatment strategies in an

ambitious initiative to eliminate viral hepatitis as a public health threat by 2030 (10). A key WHO service coverage target is to increase diagnosis of HBV and identify those needing treatment to 30% by 2020 and 90% by 2030. Overall, there is limited data regarding the epidemiology of HBV in Canada. Therefore, to increase understanding and appreciation of CHB disease burden in Canada, we utilized laboratory administrative data and clinical referral data to characterize individuals within a single large urban Canadian center who tested positive for HBsAg in 2014.

Patients and Methods:

Study Population

We conducted a retrospective cohort study that utilized administrative data from the Calgary Laboratory Services (CLS) and a provincial registry of individuals with publically insured health care coverage (i.e., Alberta health care) to identify adult patients that tested positive for HBsAg within the Calgary Zone of Alberta Health Services (AHS) between January 1 and December 31, 2014. Each individual record included in this database has a unique identifier (i.e., provincial health number or PHN) that is given to Alberta residents registered with the province of Alberta Health Care Insurance Plan (AHCIP), a universal plan that covers >99% of Alberta residents (11). Available demographic (i.e. sex and age) and laboratory information (i.e., ALT, HBV DNA, HBeAg, and HBeAb) on this cohort was extracted within six months of a positive HBsAg test. The study was done under an approved ethics protocol from the University of Calgary Conjoint Health Research Ethics Board (REB), according to the Declaration of Helsinki (Ethics ID REB14-0609).

Data Sources

Provincial registry and laboratory administrative data was cross-referenced with clinical referral data, including those who subsequently received antiviral treatment based on the Calgary Liver Unit, Division of Gastroenterology and Hepatology electronic referral and treatment database. The Calgary Liver Unit operates a centralized outpatient referral clinic for all viral hepatitis patients serving a casement area of 1.2 million in Southern Alberta. Details on the Calgary Liver Unit clinic referral structure, patient assessment and treatment database have been previously published (12–15). It is standard clinical practice for all new referrals with hepatitis B to undergo liver fibrosis assessment by transient elastography (i.e., TE or FibroScan®, Echosens, France). HBsAg and HBeAb serology was tested by immunoassay at the Alberta Provincial Laboratory (Abbott Architect, Mississauga ON, Canada) and HBV DNA levels in serum was determined by Taqman PCR assay with a lower limit of detection of 10 IU/mL (Abbott Diagnostics, Mississauga, ON, Canada).

Outcomes and Statistical Analysis:

We used Fisher Exact test or Chi Square test for categorical data and Kruskal Wallis or Student's t-test for continuous data, where appropriate. Continuous variables were summarized as median and interquartile range (IQR), while categorical variables were expressed as number and percentile. Clinically significant lab tests were defined as ALT two times the upper limit of normal (based on expert guidelines ALT 2xULN is ≥38 U/L in females and ≥60 U/L in males) and HBV DNA ≥3.3 logIU/mL (i.e., ≥2000 IU/mL) (4,5).

Results:

A total of 1214 individuals (48% female, median age 44 years [IQR 36-55]) tested positive for HBsAg within the Calgary zone between January 1 and December 31, 2014. Additionally, 24 individuals (2%) tested positive for hepatitis C virus antibody (anti-HCV), indicating previous or current hepatitis C infection. 19 of these individuals also received HCV RNA testing, all of whom were positive thus confirming HBV and HCV coinfection.

Of the 1214 HBsAg+ individuals, 1192 (98%) were tested for ALT, 682 (56%) were tested for HBV DNA, 630 (52%) were tested for HBeAg status, and 145 (12%) were tested for HBeAb serology (**Figure 1**). In the 1192 individuals with ALT testing, the median was 23 U/L (IQR 16-34). This includes the 117 (10%) individuals with clinically significant ALT elevation (i.e., 2x ULN, equivalent to ≥38 U/L in females and ≥60 U/L in males) (**Figure 1A**). HBV DNA testing identified 533 (78%) individuals with detectable viremia (median of 2.8 logIU/mL, IQR 2.1-3.8), of which 179 (26%) had a high level of HBV viremia, ≥3.3 logIU/mL (i.e., 2000 IU/mL) (**Figure 1B**). Out of those tested for HBeAg, 548 (87%) were found to be HBeAg negative (**Figure 1C**). In these 548 cases, 433 (79%) individuals had viral load testing with a median 2.5 logIU/mL (IQR 1.4–3.3) (**Figure 1C**). 111 (77%) with serology testing for HBeAb were identified as reactive for HBeAg (**Figure 1D**). Further, of the 1214 HBsAg+ individuals, only 125 (10.3%) received testing for the four laboratory assessments (ALT, HBV viral load, HBeAg, HBeAb) in the study criteria.

Although 117 cases were found to have clinically significant ALT, potentially needing consideration for antiviral therapy (i.e., ALT 2xULN), 49 (42%) did not have concomitant HBV DNA testing at least within the 1-year assessment period. Despite the incomplete laboratory testing in many individuals, 31 cases (21 [68%] male, median age 42 [IQR 33-55]) were found to

have both elevated ALT and HBV DNA levels thereby potentially meeting criteria for ongoing close follow-up and/or needing referral for consideration of hepatitis B antiviral therapy. However, cross-referencing these cases to the Calgary Liver Unit referral / treatment database showed that only 13 (42%) of the 31 individuals were subsequently treated for hepatitis B (**Figure 1E**).

Treatment and Clinical Referral Data

Comparison to clinical treatment data, revealed that 144 (12%) of the 1214 cases in our HBsAg+ cohort have received anti-HBV therapy. The most common antiviral therapy was Tenofovir (104 [72%]), followed by Entecavir (26 [18%]), Pegylated-Interferon (9 [6%]), Lamivudine (3 [2%]), Adefovir (1 [0.7%]), and Telbivudine (1 [0.7%]) (**Figure 2A**). At last follow-up, the median TE (ie., Fibroscan®) measurements in 121 (84% of 144 on treatment) individuals tested was 6.9 kPa (IQR 4.3–10.2) (**Figure 2B**).

Additionally, clinical referral data revealed that overall 390 (32%) of our total cohort has received specialist consultation with a hepatologist from 2011-2016. In the individuals who had seen a specialist, 389 (99.7%) have been tested for ALT (median 23.5, IQR 17-36), 286 (73.3%) had HBV DNA testing (median 2.4 logIU/ml, IQR 1.1-3.5), 273 (70%) had testing for HBeAg status and 60 (15.4%) had testing for HBeAb (**Table 1**). 84.6% (230/273) tested HBeAg negative, 14.4% (54/389) had clinically significant ALT elevation (2xULN) (**Table 1**). Overall 14 cases of the 390 individuals that have seen a hepatologist were identified as elevated ALT (2xULN) and high HBV DNA (≥3.3 logIU/mL or 2000 IU/ mL) and potentially eligible for antiviral therapy. Our further analysis using Calgary Liver Unit treatment data revealed that 7/ 14 cases have received anti-HBV treatment (**Table 1**).

In 824 cases that did not see a specialist, 98% had ALT testing (median ALT 22 U/L [IQR 16-33]). However, a significantly lower number of cases without specialist consultation had testing for HBV DNA (n = 396 [48.1%]; median 2.5 logIU/mL [IQR 1.5–3.4]), HBeAg (n = 357 [43.3%]; 231 [89%] negative), and HBeAb (n = 85 [10.3%]; 66 [77.7%] positive) (p <0.01, <0.01, and 0.01, respectively) in comparison to individuals with specialist consultation (**Table 1**). Further, only 6 (35%) of the 17 cases potentially eligible for anti-HBV therapy (ALT 2xULN and HBV ≥3.3 logIU/mL) have received antiviral treatment (**Table 1**).

Interpretations

Based on administrative data, our study found a large number (n=1214) of HBsAg positive cases in a single large urban Canadian centre (Calgary Health Zone) within the 2014 calendar year. In our cohort of HBsAg positive cases, we confirmed that a significant number of patients were not completely evaluated for possible liver disease risk with testing for ALT in 98%, HBV DNA in 56%, and HBeAg in 52%. It is worth noting that only 12% of HBsAg positive cases were HBeAg positive, but this data is not surprising given the older age of the cohort (median age 44y, IQR 36-55) who would have transitioned to either the so-called inactive carrier phase or later state HBeAg-negative/reactivation phase. Data is not available on the prevalence of BCP/pre-core mutations to confirm the latter. Moreover, 32% of our cohort were known to be seen by a hepatologist in our centre within a 5-year period (2011-2016). It is also noteworthy that 19 (1.6%) of our 1214 cases were found to be co-infected with hepatitis C (ie., positive for anti-HCV and HCV RNA), another major risk factor for chronic liver disease. Studies in a United States Veterans Cohort have shown that chronic hepatitis C carriers with documented HBV viremia were at significantly higher risk of cirrhosis (16).

The number of HBsAg positive individuals in our findings are comparable to that reported by the BCCDC for the province of British Columbia, Canada in 2014 (9) which has a population census of ~4.6 million. According to 2015 census data, approximately 300,000 including both Canadian born and foreign born individuals moved to the city of Calgary within the last 10 years (2005-2015) (17). Migration, namely immigration of individuals from HBV endemic areas, contributes to increased incidence in Canada and other Western countries (e.g., USA) as the prevalence of HBV in migrants reflect their country of origin (18). Our research findings are similar to a study on care delivery and outcomes among US Veterans with CHB in which a low prevalence of recommended laboratory testing (97% ALT, 44% HBV DNA and <50% HBeAg/anti-HBe) as well as liver imaging was done (19). Further, individuals with specialist care in both our cohort and the US Veterans with CHB were observed to have a higher frequency of HBV DNA (73% and 66%, respectively) and HBeAg (70% and 68%) testing (19). Our study is also compatible with data published from the hepatitis B research network, a prospective observational cohort of 1625 adult CHB carriers in 21 clinical centres in the United States and in Toronto, Canada in which 74% of the cohort were HBeAg negative, median age 42 years, and 50% male (20).

The current study is limited due to the use of retrospective administrative laboratory data some of which was not available prior to 2011. Thus, many of the individuals identified in 1-year period may not be newly diagnosed CHB carriers and it is unknown if some had specialist assessment and deemed not needing antiviral therapy or ongoing close follow-up. Nonetheless, we expect that a significant number of cases were newly diagnosed since repeat HBsAg testing is not usually necessary since spontaneous HBsAg loss is a rare event, reported to occur in <1% of CHB carriers (21–23). The findings reported in this current study are limited by the inability to

distinguish between acute and chronic HBV infection individuals. However, the number of acute HBV infections in Canada is expected to be minimal. For example, in 2014, only 14 individuals were identified as experiencing acute HBV infection in British Columbia (9). In fact, it is likely this study may underestimate the burden of HBsAg-positive cases. We excluded all cases that tested HBsAg positive who did not have an ordering physician based in the current health-care zone or if the patient was not registered within the current health region (i.e., Calgary Zone of Alberta Health Services). However, many cases could have recently moved within the province / or had specialist assessment as well as testing in a laboratory or health care facilities outside of the designated health care region. Nevertheless, the study suggests that there are significant gaps in care for CHB carriers.

We do not have current data on the number of cases who had ultrasound surveillance for HCC. However, this is an area of investigation by study co-authors (AA and KWB) utilizing an additional automated HCC screening database in partnership with a specialist radiology/ultrasound referral clinic in Calgary. Previous studies have demonstrated the medical and financial advantages of implementing HCV screening strategies in Canada (24,25). Similarly, future directions of our study will explore the cost-effectiveness of HBV screening and/or surveillance in Alberta and Canada. Future studies will also include a longer follow-up period capturing all available laboratory and provincial health administrative data from 2011. This data will be used for feedback to public health and primary care physicians regarding appropriate screening, testing and referral for chronic hepatitis B carriers.

Overall, a large majority (90%) of individuals in the study cohort lack testing of all laboratory assessments and most (68%) had no consultation with a specialist. These findings in combination with the reported treatment results suggest that the management of HBV in Canada,

a first-world nation, falls well below the ambitious standards of the WHO (10). In order to achieve the WHO goal of HBV elimination by 2030, further stringent preventative actions and disease surveillance is required not only in HBV endemic areas, but also in Canada and other first-world nations, many of whom similarly report poor diagnostic and disease management rates of CHB (26–30). In summary, the current study suggests that the burden of CHB is significant in a single urban centre in Canada, based on administrative data in an only 1-year period. Many identified individuals did not have recommended laboratory monitoring to identify liver disease risk and need for antiviral therapy. The study contributes to filling the knowledge gap in the epidemiology of CHB in Canada and highlights the need for a concerted public health effort for surveillance and treatment of chronic hepatitis B.

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Ethics ID REB14-0609

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Figure Legends

Figure 1. Flow chart of laboratory assessments of 1214 individuals who tested HBsAg positive in Calgary, Alberta in 2014.

A. 98% of the HBsAg+ cohort had ALT testing (median 23 U/L, IQR 16-34), of which 10% had elevated ALT levels (defined as ALT > 2X upper limit of normal, [≥38 U/L in females, ≥60 U/L in males]).

B. 56% of the HBsAg+ cohort had HBV DNA testing (median 2.8 logIU/mL, IQR 2.1–3.8), of which 26% had HBV DNA ≥3.3 log or 2000 IU/mL

C. 52% of the HBsAg+ cohort had HBeAg testing, 87% (n = 543) HBeAg negative. In 548 HBeAg negative cases, 79% (n = 433) had HBV DNA testing with median 2.4 logIU/mL (IQR 1.4–3.3).

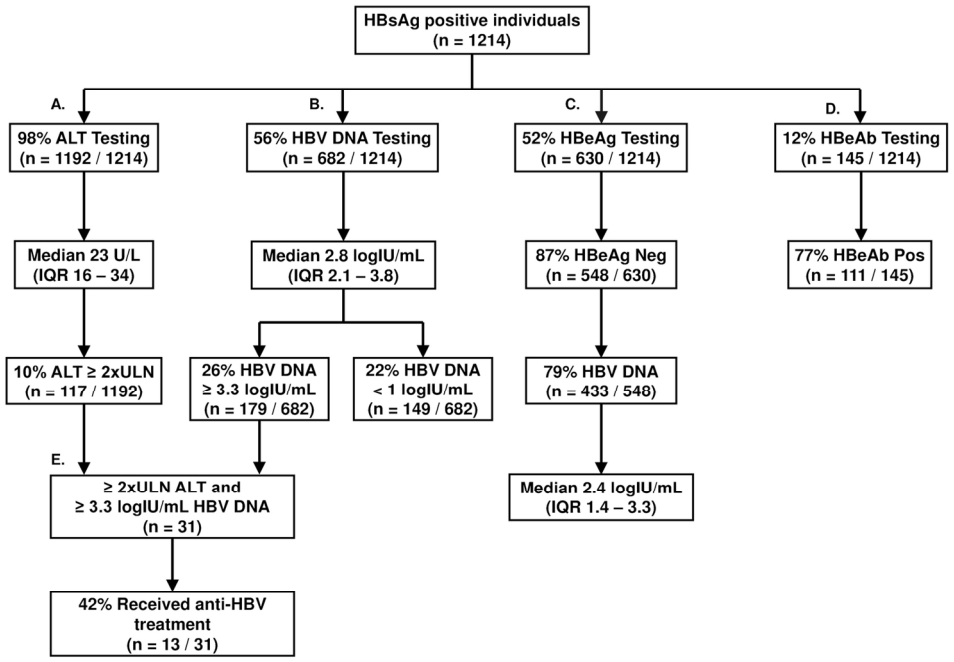
D. 12% of the HBsAg+ cohort had HBeAb testing; 111 were positive for HBeAb.

E. In the 31 potentially eligible for treatment (both elevated ALT and HBV viremia), 13 individuals have received anti-HBV treatment.

Figure 2. Summary of anti-HBV treatment and fibrosis assessment by transient elastography (Fibroscan®) at last follow-up. Overall 12% of the HBsAg+ cohort received anti-HBV therapy and 84% received assessment with TE (median 6.9 kPa, IQR 4.3-10.2).

Table 1. Comparison of laboratory assessments (ie., ALT, HBV DNA, HBeAg, and HBeAb testing) in individuals with (n = 390) and without (n = 824) specialist consultation. Individuals with specialist consultation have a higher frequency of receiving testing for HBV DNA (p value <0.01), HBeAg (p value <0.01), and HBeAb (p value 0.01) than those without specialist consultation.

Variable	Specialist consultation n = 390 (32.1%)	No specialist consultation n = 824 (67.9%)	P Value
ALT Testing (n [%])	389 (99.7%)	803 (97.5%)	0.01
Cases with testing:			
Median (IQR)	23.5 U/L (17-36)	22 U/L (16-33)	0.02
≥ 2xULN (n [%])	54 (14.4%)	63 (7.7%)	<0.01
HBV DNA Testing (n [%])	286 (73.3%)	396 (48.1%)	<0.01
Cases with testing:			
Median (IQR)	2.4 logIU/mL (1.1-3.5)	2.5 logIU/mL (1.5-3.4)	0.37
< 1 logIUmL (n [%])	79 (27.6%)	75 (18.9%)	<0.01
≥ 3.3 logIUmL (n [%])	77 (26.9%)	103 (26.0%)	0.79
HBeAg Testing (n [%])	273 (70.0%)	357 (43.3%)	<0.01
Cases with testing:			
Negative (n [%])	231 (84.6%)	317 (88.8%)	0.15
HBeAb Testing (n [%])	60 (15.4%)	85 (10.3%)	0.01
Cases with testing:			
Positive (n [%])	45 (75.0%)	66 (77.7%)	0.84
HBV DNA Testing if:			
ALT ≥ 2ULN (n [%])	37 (68.5%)	31 (49.2%)	0.04
Median (IQR)	2.8 logIU/mL (1.5-4.9)	4.1 logIU/ml (1.4-5.8)	0.48
< 1 logIUmL (n [%])	7 (18.9%)	6 (19.4%)	1.00
≥ 3.3 logIUmL (n [%])	14 (37.8%)	17 (54.8%)	0.22
Negative HBeAb (n [%])	186 (80.5%)	247 (77.9%)	0.52
Median (IQR)	2.5 logIU/mL (1.2-3.3)	2.5 logIU/mL (1.6-3.3)	0.30
< 1 logIUmL (n [%])	51 (27.4%)	39 (15.8%)	<0.01
≥ 3.3 logIUmL (n [%])	46 (24.7%)	60 (24.2%)	0.91
Anti-HBV therapy if: ALT ≥ 2xULN and HBV DNA ≥ 3.3 logIUmL (n, %)	7 (50.0%)	6 (35.3%)	0.48



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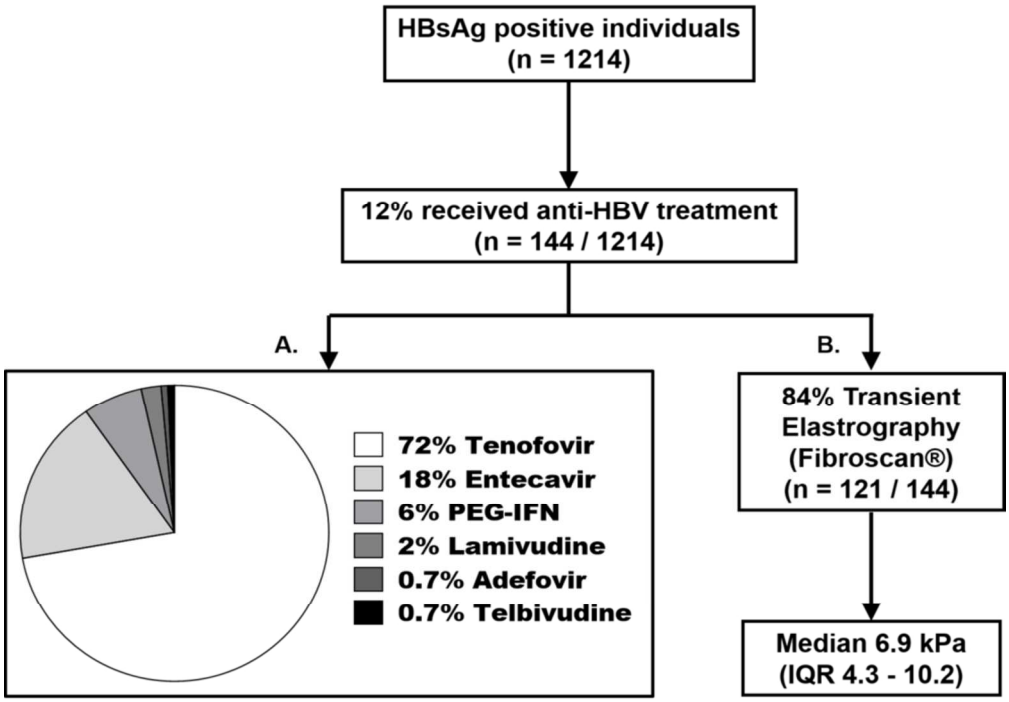

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