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## Rates and risk factors for hepatitis B reactivation in a cohort of persons in the inactive phase of chronic hepatitis B—Alaska, 2001–2010

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### Abstract

**Background**—A high prevalence of reactivation of hepatitis B has been documented among immunosuppressed individuals in the inactive phase of chronic hepatitis B; However, the proportion of and the risk factors for reactivation are largely unknown among non-immunosuppressed persons.

**Objectives**—Estimate the incidence rate of and risk factors for hepatitis B reactivation in a population-based cohort of persons in the inactive phase of chronic hepatitis B in Alaska.

**Study design**—A cohort of 414 Alaska Native Persons in the inactive phase of hepatitis B (HBV DNA < 2000 IU/mL and normal alanine aminotransferase (ALT) for 12 months) was followed-up for 10 years. Reactivation of hepatitis B was defined as HBV DNA ≥ 2000 IU/mL and ALT ≥ 40 IU/L. Cox-proportional hazards regression models were used to identify factors associated with reactivation.

**Results**—A total of 36 (9%) persons had reactivation during 2984 person-years of follow-up, with an annual incidence of 1.2%. Persons aged ≥ 50 years (1.8%) at study entry had the highest

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#### Competing interest

Alaska Native Tribal Health Consortium Liver Disease and Hepatitis Program received honoraria in 2011 from Gilead Sciences, but not for this study.

#### Ethical approval

The Institutional Review Boards of the Alaska Area and the Centers for Disease Control and Prevention approved the study protocol.

#### Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. Presented in part at ID Week 2012, A Joint Meeting of IDSA, SHEA, HIVMA, and PIDS, October 17–21, 2012, San Diego, CA, USA. Poster number 1018.

incidence rates of reactivation although incidence rates were not significantly different by age group. Risk factors for hepatitis B reactivation were male sex (Hazard Ratio (HR) = 2.41; 95% Confidence Interval (CI): 1.17–4.96), HBV DNA ≥ 1000 IU/mL at study entry (HR = 7.61; 95% CI: 2.81–20.6), and HBV genotype B (HR = 6.08; 95% CI: 1.32–28.0).

**Conclusions**—The incidence of hepatitis B reactivation was low during the 10 years of follow-up. However, given the higher risk of reactivation than their counterparts, males, and those with HBV DNA ≥ 1000 IU/mL need to be followed-up more frequently.

## Keywords

Hepatitis B; Reactivation of infection; Incidence; Risk factors

## 1. Background

Over 350 million persons worldwide and 730,000 persons in the United States have chronic hepatitis B virus (HBV) infection, a major cause of cirrhosis and liver cancer [1,2]. Almost 20 years ago, the Alaska Native population has had one of the highest rates of chronic hepatitis B, and chronic liver disease was associated with higher proportion of deaths among American Indian/Alaska Native people compared to other racial/ethnic groups in the United States [3,4].

Three phases of chronic HBV infection are recognized: the immune tolerant phase, the immune active phase, and the inactive phase [5]. Although a high prevalence of reactivation of HBV infection has been documented among immunosuppressed individuals in the inactive hepatitis B phase [6], reactivation also might occur among non-immunosuppressed individuals. However, the proportion of persons in the inactive phase of chronic hepatitis B who will reactivate and the risk factors for reactivation are largely unknown [6]. Cohort studies assessing the incidence of and risk factors for hepatitis B reactivation among persons in the inactive phase of chronic hepatitis B are limited in number and the majority of studies recruited inactive carriers from hospitals [7,8], or blood banks [9,10]. Studies including population-based cohorts are lacking. Hence, it is unclear how frequently follow-up visits and testing should be performed among persons in the inactive hepatitis B phase. Current American Association for the Study of Liver Disease (AASLD) practice guidelines suggest that persons in the inactive phase should be followed every 6–12 months [11].

## 2. Objectives

We conducted this study to determine the incidence of and identify factors associated with hepatitis B reactivation in a population-based cohort of Alaska Native persons in the inactive phase of chronic hepatitis B.

## 3. Study design

### 3.1. Study population

Detailed information about the Alaska Native cohort has been described previously [12,13]. In summary, a mass population screening program for hepatitis B conducted during 1983–1987 among 52,000 Alaska Native persons identified 1536 persons chronically infected with

hepatitis B. Of those, 1407 consented to participate in the cohort study and were contacted every 6 months for blood specimen collection. HBV DNA was tested at baseline and repeated whenever ALT levels were elevated and among persons with a family history of hepatocellular carcinoma (HCC) or who had one or more HBV DNA levels above 2000 IU/mL.

For this study, we examined persons who fulfilled the National Institutes of Health (NIH) criteria for the inactive HBV phase between the dates of 10/01/2001 and 12/31/2010. As of 10/1/2001, 1175 consented persons with chronic hepatitis B infection were still alive, and of those, a total of 414 met the study criteria for the inactive hepatitis B phase. The inactive HBV phase was defined as fulfilling the following three criteria on study entry: (1) most recent HBV DNA < 2000 IU/mL; (2) most recent hepatitis B e antigen (HBeAg) negative or antibody to hepatitis e antigen (anti-HBe) positive, and (3) alanine aminotransferase (ALT) <40 IU/L for at least 12 months. We excluded persons who were negative for HBsAg at study entry, and HBsAg-positive persons who were co-infected with hepatitis C or HIV. Reactivation of hepatitis B was defined as (1) HBV DNA ≥ 2000 IU/mL and (2) ALT ≥ 40 IU/L. The occurrence of these events did not have to be simultaneous; the time of reactivation was considered the time of fulfillment of both events.

Basic demographic (age, sex, and ethnicity) and clinical information (age at first positive HBsAg, body mass index (BMI), ALT, HBV genotype, and HBV DNA levels) was abstracted to identify risk factors for hepatitis B reactivation. Body mass index was classified as normal (<25 kg/m<sup>2</sup>), overweight (25 ≤ BMI < 30 kg/m<sup>2</sup>), and obese (BMI ≥ 30 kg/m<sup>2</sup>) [14].

The Institutional Review Boards of the Alaska Area and the Centers for Disease Control and Prevention approved the study protocol.

### 3.2. Laboratory testing

Enzyme-linked immunoassay (Abbott Laboratories, Irving, TX) was used to measure HBsAg, antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core (anti-HBc). The OneStep Hepatitis B 'e' Antigen Test Strip and the Maxi Test Anti-HBe Rapid Test were used to test for HBeAg, and anti-HBe, respectively, according to the manufacturer's instructions (IND Diagnostic Inc., Delta, British Columbia, Canada). We validated both tests using sera previously tested with the Abbott Laboratories enzyme-linked immunoassay kits, which are no longer commercially available.

Real-time quantitative polymerase chain reaction (PCR), with a lower limit of detection of 100 copies/mL (20 IU/mL) was used to determine HBV viral loads. Briefly, HBV DNA was extracted from stored serum specimens using the MagNA Pure Compact System and Total Nucleic Acid Extraction Kit I according to manufacturer's instructions (Roche Applied Science, Indianapolis, IN). Subsequently, a 118-bp fragment of the core gene was amplified, and HBV viral loads were determined by comparison to a set of HBV DNA standards amplified in parallel with the samples being tested [15]. HBV genotyping was performed by polymerase chain reaction as previously described [16].

### 3.3. Statistical analysis

Categorical data were reported as percentages while continuous variables were described using means and standard deviations. The annual incidence of hepatitis B reactivation was calculated using survival analysis by dividing the number of persons that had reactivation of their HBV infection by the total number of person-years of follow-up. We used Poisson regression to compare the incidence of reactivation across age groups, genotypes and categories of HBV DNA. Univariable Cox-proportional hazards regression was conducted to identify the variables associated with hepatitis B reactivation. Subsequently, we included those variables in the multivariable model to identify significant determinants of hepatitis B reactivation after controlling for all potential risk factors. Statistical analysis was conducted using STATA v. 10 and *P*-values <0.05 were considered statistically significant.

## 4. Results

The mean age of study participants at the time of entry into the study was  $40.1 \pm 14.3$  years; 43% were male. More than half were diagnosed with a positive HBsAg before the age of 20 years. The ALT levels were within normal range for all cohort members, and 13% had HBV DNA  $> 1000$  IU/mL at study entry (Table 1).

This cohort was followed up for an average of  $7.4 \pm 1.9$  years (median: 8.2 years; range: 1.3–9.2 years), had a median of 10 (range: 1–83) ALT measurements (96.1% had three or more ALT and 84.1% had 5 or more ALT), and a median of 2 (range: 1–19) HBV DNA levels during the study period. A total of 36 (9%) inactive carriers developed reactivation of their HBV infection after an average of  $5.8 \pm 2.0$  years (median: 6.7 years; range: 1.3–9.0 years) of follow-up. The first elevated median HBV DNA level among those who reactivated was 3701 IU/mL (range: 2040–65,933 IU/mL) and 25% of those who reactivated had HBV DNA  $> 10,000$  IU/mL on their first elevated HBV DNA. Peak median HBV DNA levels among those who reactivated was 4379 IU/mL (range: 2040–973,173 IU/mL) and 33% of those who reactivated had peak HBV DNA levels  $> 10,000$  IU/mL. Among the 36 carriers who reactivated their hepatitis B infection, 11 had a maximum ALT  $> 100$ , and 31 had at least one repeat HBV DNA level during the follow-up period. Of these, 19 (61%) had elevated HBV DNA on more than one occasion.

The annual incidence of reactivation of hepatitis B was 1.2% after 2984 person-years of follow-up (Table 2). The highest annual incidence rates of reactivation were found among inactive carriers who were  $> 50$  years old (1.8%) at study entry, however the incidence of reactivation was not statistically different across the various age groups ( $p = 0.06$ ). The proportion of persons who had reactivation of infection increased with study time in both genders. However, a larger proportion of males had reactivation earlier during the study period (within 2–4 years) compared to females who generally experienced reactivation 6 years after study entry (Fig. 1).

In the unadjusted analysis, persons aged 40–49 years at study entry had a lower risk for reactivation of infection than those aged 18–29 years (Table 3). Males were two times more at risk of reactivation than females. Ethnic group and age at first detection of a positive HBsAg were not significant determinants of reactivation. Almost one in four inactive

carriers of hepatitis B who had HBV DNA > 1000 IU/mL on study entry had reactivation, compared to only 4% of those with HBV DNA levels <29 IU/mL (Table 3). Furthermore, compared to inactive carriers having an HBV DNA < 1000 IU/mL at study entry, those with HBV DNA ≥ 1000 IU/mL had a significantly higher incidence of hepatitis B reactivation (32.5 per 1000 persons per year vs. 8.9 per 1000 persons per year,  $p < 0.01$ ). Persons with HBV genotype B had a significantly higher cumulative incidence of reactivation (22%) compared to those with other HBV genotypes (9%).

Cox proportional hazards regression analysis showed that the risk of reactivation of hepatitis B was independently associated with age at study entry since persons aged 30–49 years at study entry had significantly lower risk for reactivation than those aged 18–29 years. In addition, male sex (Hazard Ratio (HR) = 2.41; 95% confidence interval (CI): 1.17–4.96), HBV DNA ≥ 1000 IU/mL at study entry (HR = 7.61; 95% CI: 2.81–20.6), and HBV genotype B (HR = 6.08; 95% CI: 1.32–28.0) were also significantly associated with reactivation of hepatitis B (Table 4). Of the 414 persons in the inactive phase of hepatitis B, 19 (4.6%) were treated for hepatitis B after entry into the study; of the 19, seven (36.8%) had reactivation of hepatitis B infection. Three were treated prior to reactivation because of elevated AFP ( $n = 1$ ) or HCC ( $n = 2$ ), and four were treated after reactivation; of these four, three had consistent elevations in HBV DNA after treatment (two of them had cancer: gastric cancer, colon cancer); the remaining 12 patients who did not reactivate were treated because of a family history of HCC ( $n = 3$ ), undergoing chemotherapy for another cancer ( $n = 2$ ), HCC ( $n = 2$ ), undergoing immunosuppressive treatment for Crohn's disease ( $n = 2$ ), chronic AFP elevation ( $n = 1$ ), receiving immunosuppressive therapy for auto-immune hepatitis ( $n = 1$ ), and presence of cirrhosis ( $n = 1$ ).

Of the 378 persons who did not have reactivation of HBV infection, 136 (36.0%) experienced one or more ALT elevations with 30 (7.9%) persons having ALT ≥ 100 IU/L with no increase in HBV DNA ≥ 2000 IU/mL. In addition, 13 persons had an elevation of HBV DNA ≥ 2000 IU/mL (median: 3366 IU/mL, range: 2120–42,300 IU/mL) without ever having an ALT ≥ 40 IU/L. During 2001–2010, 26 (8.7%) inactive carriers of chronic hepatitis B seroconverted to a negative HBsAg for an annual rate of 8.7 sero-conversions per 1000 carriers and none had reactivation of hepatitis B during follow-up.

Of the 13 cohort members who had a liver biopsy during the study, two inactive carriers had minimal fibrosis (Ishak score = 1), and two other had mild fibrosis (Ishak score = 2), but none were diagnosed with cirrhosis. Four cohort members developed HCC within 2.7, 4.6, 6.2, and 7.6 years after study entry; however none met the criteria for reactivated hepatitis B infection and none had elevations in HBV DNA based on repeated testing. A total of 28 (6.8%) inactive carriers died during the study period with an annual mortality rate of 0.9%. One inactive carrier died from HCC, two from hepatic failure and one from liver failure secondary to cancer of the gallbladder.

## 5. Discussion

This study measured the incidence of and assessed risk factors for hepatitis B reactivation in a cohort of 414 persons in the inactive phase of chronic hepatitis B in Alaska who were

followed for an average of 7.4 years. The annual incidence of reactivation was 1.2% and a total of 9% experienced reactivation by the end of 2010. The prevalence and incidence of reactivation seem to vary by the duration of follow-up and the HBV DNA cut-off point considered for reactivation. Studies which followed persons in the inactive phase of chronic hepatitis B for less than 5 years, rarely reported occurrence of reactivation among inactive carriers although the majority had detectable low levels of HBV DNA [17,18]. Longitudinal studies with an average of 7–10 years of follow-up reported a cumulative incidence of reactivation ranging from 2.0% to 23.8% [7–9,19], and an annual incidence rate of reactivation ranging between 0.4% and 1.6% [9,19,20]. Some studies used an HBV DNA 2000 IU/mL ( $10^4$  copies/mL) to indicate reactivation of infection [9,19], while other studies defined reactivation of hepatitis B as HBV DNA  $\geq$  20,000 IU/mL ( $10^5$  copies/mL) [7,8] which would affect estimates of incidence rates.

In our study, males had a higher risk for and more importantly tended to experience reactivation of HBV infection sooner after entry into the study than females. Male sex has been previously reported as a risk factor for reactivation [7,9,21], which is consistent with increased risk of chronic HBV infection, liver cancer, and death among males compared to females with HBV infection [22].

The most important finding in this study was the high risk of reactivation in those with a baseline HBV DNA  $\geq$  1000 IU/mL, which occurred in one quarter of inactive carriers fitting this category. Inactive carriers with HBV DNA  $\geq$  1000 IU/mL had almost a fourfold higher incidence rate of reactivation than those with HBV DNA  $<$  1000 IU/mL. The AASLD chronic hepatitis B practice guidelines recommend following chronically infected patients every 3–12 months depending on disease activity [11]. Our finding suggests the need to follow-up inactive carriers with HBV DNA  $\geq$  1000 IU/mL more frequently than others.

While we found a higher risk for reactivation among inactive carriers with genotype B infection, only few inactive carriers in our cohort had genotype B ( $n = 9$ ) leading to a wide confidence interval. A higher likelihood of reactivation was reported among inactive carriers with genotype C infection compared to those with genotype B in Taiwan [21,23], while longitudinal studies in Europe included mainly homogeneous populations infected with genotype D. We had 23 inactive carriers with genotype C, therefore we can rule out that having a larger number of genotype C inactive carriers might have influenced the findings.

Although 9% of inactive carriers in our cohort experienced reactivation, very few developed advanced liver disease which is consistent with findings from several studies [7,8,10,19,20]. It is notable that none of the four inactive carriers who were diagnosed with HCC during the study had reactivation. However, these inactive carriers were treated as soon as HCC was diagnosed which might have been responsible for lowering their risk. Our findings reinforce the importance of regular surveillance for HCC among HBV infected persons who remain in the inactive phase.

This study has several limitations. Data on other risk factors that might potentially influence reactivation such as alcohol intake, smoking, diabetes status, and HBV precore and basal core mutations were unavailable. Moreover, biopsy results were lacking from a large

proportion of the study population because most of these individuals live in remote villages making it impossible to examine them on a regular basis. We could not calculate the incidence of reactivation by the age at HBV infection, as the exact time of infection was not available for the majority of inactive carriers; however a large prospective study conducted in this population showed that most persons who became chronically infected with HBV infection were exposed to HBV at a very young age [24].

Despite these limitations, the findings in this study are of significant benefit and might help identify persons in the inactive phase of chronic hepatitis B who need closer follow-up. Although the incidence of reactivation is low after almost 10 years of follow-up, males, and persons having HBV DNA  $\geq 1000$  IU/mL might need more frequent follow-up, compared to others in the inactive phase. In addition those who experience reactivation might need to be treated sooner after reactivation in order to avoid complications of HBV infection such as cirrhosis and liver cancer.

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## Abbreviations

<b>HBV</b>	hepatitis B virus
<b>ALT</b>	alanine aminotransferase
<b>DNA</b>	deoxyribonucleic acid
<b>HR</b>	Hazard Ratio
<b>CI</b>	confidence interval
<b>AASLD</b>	American Association for the Study of Liver Disease
<b>AFP</b>	alpha-fetoprotein
<b>AST</b>	aspartate aminotransferase
<b>HCC</b>	hepatocellular carcinoma
<b>NIH</b>	National Institutes of Health
<b>HBsAg</b>	hepatitis B surface antigen
<b>HBeAg</b>	hepatitis B e antigen
<b>anti-HBe</b>	antibody to hepatitis e antigen
<b>BMI</b>	body mass index
<b>anti-HBs</b>	antibody to hepatitis B surface antigen
<b>anti-HBc</b>	antibody to hepatitis B core
<b>PCR</b>	polymerase chain reaction



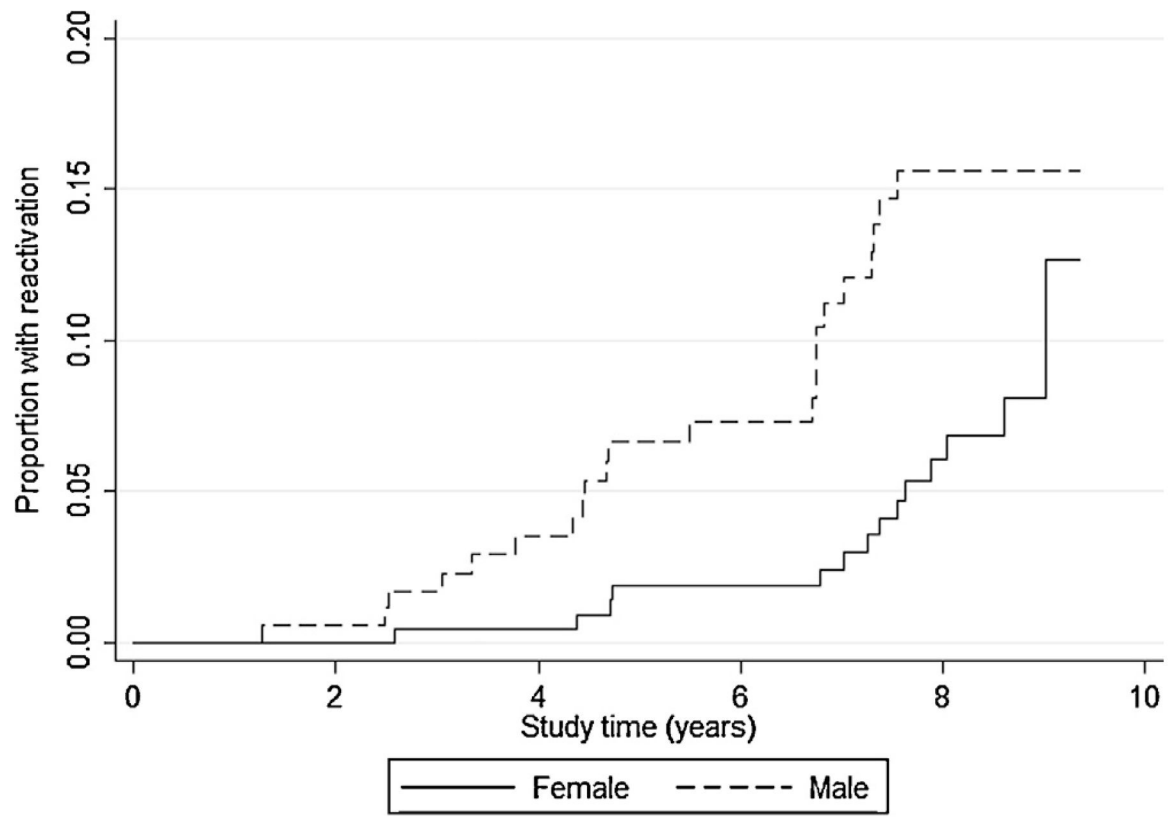
**SD** standard deviation

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**Fig 1.** Proportion of hepatitis B reactivation by sex during the study time.

**Table 1**

Demographic and clinical characteristics of the cohort of persons in the inactive phase of chronic hepatitis B – Alaska, 2001–2010.

	<i>n</i> ( <i>N</i> = 414)	%
Demographic characteristics		
Age at study entry (years)		
18–29	117	28.3
30–39	113	27.3
40–49	92	22.2
50+	92	22.2
Sex (males)	179	43.2
Ethnic group		
Alaska/American Indian	31	7.5
Aleut	30	7.2
Eskimo	353	85.3
Clinical characteristics		
Body mass index <sup>a</sup>		
Normal (<25)	114	27.5
Overweight (25–29)	106	25.6
Obese (≥ 30)	148	35.7
ALT at study entry (mean ± SD) (IU/L)	22.3 ± 7.4	
HBV DNA levels (IU/mL) at study entry		
<29	185	44.7
29–199	55	13.3
200–999	119	28.7
1000–1999	55	13.3
HBV genotype <sup>b</sup>		
A	57	13.8
B	9	2.2
C	23	5.6
D	209	50.5
F	71	17.1

ALT, alanine aminotransferase; SD, standard deviation; HBV, hepatitis B virus

<sup>a</sup> *n* = 368.

<sup>b</sup> *n* = 369.

**Table 2**

Reactivation of hepatitis B by age at study entry — Alaska, 2001–2010.

Age at study entry (years)	<i>n</i> /total	Percent reactivation (%)	Person-years of follow-up	Annual Incidence of reactivation (per 100 person-years)
18–29	13/117	11	832	1.6
30–39	8/113	7	815	1.0
40–49	3/92	3	678	0.4
50+	12/92	13	659	1.8
Total	36/414	9	2984	1.2

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**Table 3**

Hepatitis B reactivation by demographic and clinical characteristics.

	<u>Proportion of reactivation</u>		<u>Survival analysis</u>
	<i>n</i> /total	%	Unadjusted HR (95%CI)
Demographic characteristics			
Age at study entry (years)			
18–29	13/117	11%	1.00
30–39	8/113	7%	0.62 (0.36–1.50)
40–49	3/92	3%	0.28 (0.08–0.99)*
50+	12/92	13%	1.14 (0.52–2.49)
Sex			
Females	14/235	6%	1.00
Males	22/179	12%	2.33 (1.19–4.57)*
Ethnic group			
Alaska/American Indian	2/31	6%	0.72 (0.17–3.00)
Aleut	5/30	17%	2.25 (0.87–5.82)
Eskimo	29/353	8%	1.00
Clinical characteristics			
Age at first positive HBsAg (years)			
<10	15/137	11%	1.00
10–19	6/95	6%	0.56 (0.22–1.45)
20–29	3/78	4%	0.32 (0.09–1.12)
30–39	8/60	13%	1.12 (0.47–2.64)
40–49	1/23	4%	0.39 (0.05–2.94)
50+	3/21	14%	1.35 (0.39–4.68)
Body mass index			
Normal (<25)	12/114	11%	1.00
Overweight (25–29)	14/106	13%	1.30 (0.60–2.81)
Obese (≥30)	10/148	7%	0.61 (0.26–1.41)
HBV DNA levels) at study entry (IU/mL)			
<29	8/185	4%	1.00
29–199	5/55	9%	2.21 (0.72–6.75)
200–999	10/119	8%	2.05 (0.81–5.20)
1000–1999	13/55	24%	5.84 (2.42–14.1)***
HBV genotype			
A	5/57	9%	1.18 (0.36–3.86)
B	2/9	22%	6.76 (1.36–33.8)*
C	2/23	9%	1.14 (0.23–5.65)
D	18/209	9%	1.10 (0.44–2.79)
F	6/71	8%	1.00

HR, Hazard Ratio; CI, confidence interval; HBV, hepatitis B virus.

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 $p < 0.05$ .

\*\*\*  
 $p < 0.001$ .

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**Table 4**

Factors associated with hepatitis B reactivation, multivariate cox proportional hazard model — Alaska, 2001–2010.

Variable	Adjusted Hazard Ratio (95%CI)	P-Value
Age at study entry (years)		
18–29	1.00	
30–39	0.34 (0.12, 0.90)	0.03
40–49	0.20 (0.05, 0.70)	0.01
50+	0.77 (0.33, 1.77)	0.53
Sex		
Females	1.00	
Males	2.41 (1.17, 4.96)	0.01
HBV DNA levels at study entry (IU/mL)		
<29	1.00	
29–199	2.51 (0.75, 8.36)	0.13
200–999	2.28 (0.80, 6.46)	0.12
1000–1999	7.61 (2.81, 20.6)	<0.001
HBV genotype		
Non-B	1.00	
B	6.08 (1.32, 28.0)	0.02

HR, Hazard Ratio; CI, confidence interval; HBV, hepatitis B virus