DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington, DC 20420

IL 10-2014-18
Reply to: 10P3

December 30, 2014

UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

PREVENTION, DIAGNOSIS, AND TREATMENT OF HEPATITIS B VIRUS INFECTION (HBV)

1. PURPOSE: This Veterans Health Administration (VHA) Information Letter provides information to VHA clinicians on the background, prevention, screening, diagnosis, and treatment of chronic infection by hepatitis B virus (HBV) in Veterans. It does not address evaluation of health care workers with occupational exposure to HBV or look-back investigations of potential health care-associated exposures to HBV.

2. BACKGROUND:

a. Infection attributable to hepatitis B virus is a common, preventable cause of liver failure, cirrhosis and liver cancer. There are approximately 350 million individuals chronically infected with hepatitis B virus worldwide; and globally, HBV accounts for more than 600,000 deaths every year (see Attachment A). In the United States (U.S.), there are an estimated 800,000 to 1.4 million hepatitis B carriers (representing a prevalence of 0.3-0.5 percent), with up to two-thirds of these individuals unaware of their diagnosis. HBV is responsible for 2,000-4,000 deaths annually in the U.S., and there are an estimated 46,000 new HBV infections annually.

b. The prevalence of hepatitis B infection among U.S. Veterans is higher than in the general U.S. population (see Attachment B). Studies of selected subpopulations of Veterans have found a 31 percent prevalence of prior or current hepatitis B infection among homeless Veterans and Veterans admitted to a psychiatric hospital (see paragraphs 4c-d).

c. Hepatitis B is transmitted through percutaneous, sexual, and perinatal routes. Populations at increased risk of HBV infection include individuals born in geographic regions with a high (≥8 percent) or intermediate (2-7 percent) prevalence of HBV infection, household contacts and sex partners of persons with chronic HBV infection, men who have sex with men (MSM), injection drug users (IDUs), and individuals with human immunodeficiency virus (HIV) infection. Pregnant women are a population of concern because of the potential for preventable perinatal transmission to newborns. Hemodialysis patients and health care workers are other at-risk populations because of the potential for health care-associated exposure to HBV.

d. The incubation period for acute infection ranges from 2 to 3 months. Approximately 30-50 percent of individuals ≥5 years of age who are acutely infected have signs and symptoms of acute infection including fever, fatigue, anorexia, nausea, vomiting, abdominal pain, jaundice, and arthralgias. These symptoms can persist for several months.

e. The risk of developing chronic hepatitis B infection after acute infection depends on age and immune status. Adults with acute infection have a less than 5 percent chance of developing chronic infection. HIV-infected individuals are more likely to develop a chronic carrier state than those who are HIV uninfected.

f. Approximately 15 percent of individuals who become infected after childhood and 25 percent of those who become chronically infected during childhood die from cirrhosis or liver cancer.

g. Individuals with chronic hepatitis B, those in the inactive carrier state, and those with occult hepatitis B (detectable HBV DNA with negative hepatitis B surface antigen [HBsAg] and variable presence of hepatitis B core and surface antibodies) are at risk for flares or reactivation of hepatitis B in the setting of immunosuppression (see paragraphs 4a and 4e).

h. Most individuals who are exposed to HBV have predictable serologic responses, depending on the course of infection.

(1) Figures 1 and 2 (see Attachments A and B) show the time course of appearance of antibodies after infection with HBV. HBSAg is the first serologic marker to become positive after exposure, followed by hepatitis B e antigen (HBeAg), hepatitis B core antibody (HBcAb), hepatitis B e antibody (HBeAb), and hepatitis B surface antibody (HBsAb). HBV DNA (not pictured here) appears before any serologic marker.

(2) HBsAg can be detected as early as 1 week after exposure. In individuals who recover from acute HBV infection, HBsAg is eliminated from the blood; in individuals who develop chronic infection, HBsAg persists. HBcAb appears at the same time as symptoms or liver function test abnormalities, and persists for life regardless of whether HBV infection resolves or becomes chronic. IgM-class HBcAb is present during acute infection, and may be present during an exacerbation of chronic infection. Individuals who are immune as a result of vaccination will have a negative HBcAb result.

(3) HBsAb generally appears after recovery from acute infection, or after immunization. HBsAb does not appear in patients with chronic HBV infection.

(4) HBeAg appears during both acute and chronic infection, and tends to be cleared overtime. High levels of HBeAg are associated with high levels of viremia and greater risk of HBV transmission.

(5) Detectable hepatitis B DNA accompanied by negative HBsAg may indicate occult hepatitis B infection.

3. RECOMMENDATIONS:

a. **Screening.** The availability of highly effective vaccines against HBV allows prevention of HBV infection. Furthermore, for individuals who are chronically infected with HBV, treatment with highly potent antiviral agents allows secondary prevention of complications such as cirrhosis and liver cancer. Thus, identification of individuals who may benefit from either immunization or antiviral treatment is a key goal for clinicians caring for patients at risk of HBV infection. The VHA National Center for Health Promotion and Disease Prevention (see

paragraph 4h) recommends that individuals in the following high-risk groups be considered for hepatitis B screening:

(1) **Previously Unvaccinated and:**

(a) HIV infected;

(b) Hemodialysis patients;

(c) Patients with elevated ALT/AST of unknown etiology;

(d) Patients needing immunosuppressive therapy, including chemotherapy immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders (e.g., corticosteroids and biologic response modifiers);

(e) Injection drug users;

(f) Men who have sex with men;

(g) Household, needle-sharing, or sex contacts of persons known to be HBsAg positive;

(h) Donors of blood, plasma, organs, tissue, or semen;

(i) Individuals born to HBsAg positive mothers; or

(j) Individuals who are the source of blood or body fluids for exposures that might require post exposure prophylaxis.

(2) **Previously Vaccinated Individuals who Initiated Risky Behaviors Before Receiving the Hepatitis B Vaccination Series as Adolescents or Adults.**

(3) **Regardless of Vaccination Status:**

(a) Individuals born in regions of high and intermediate HBV endemicity (HBsAg prevalence ≥8 percent and 2-7 percent, respectively). This includes immigrants and children adopted from these regions.

(b) U.S.-born individuals not vaccinated as infants whose parents were born in regions with high hepatitis B endemicity (HBsAg prevalence ≥8 percent).

(4) **Pregnant Women.** The Department of Veterans Affairs (VA)/Department of Defense (DoD) Clinical Practice Guideline for Management of Pregnancy (see paragraph 4f) recommends routine screening for HBsAg in pregnant women at the initial prenatal visit, as do the U.S. Centers for Disease Control and Prevention (CDC) (see paragraph 4a). Repeat laboratory screening of pregnant women with identification of hepatitis risk factors during the pregnancy (e.g., health care worker, injection drug use, exposure to hepatitis, visit for evaluation or therapy for sexually transmitted infections, new tattoos, and blood transfusions) is recommended.

NOTE: *High- and intermediate-prevalence areas include: all countries in Asia, Africa, and the South Pacific Islands; the Middle East except Cyprus and Israel; Malta; Spain; the Arctic (indigenous populations of Alaska, Canada, and Greenland); Ecuador; Guyana; Suriname; Venezuela; the Amazon regions of Bolivia, Brazil, Colombia, and Peru; all countries in Eastern Europe except Hungary; Antigua and Barbuda; Dominica; Granada; Haiti; Jamaica; St. Kitts and Nevis; St. Lucia; Turks and Caicos; Guatemala; and Honduras.*

b. **Prevention.**

(1) **Primary Prevention.** VHA National Center for Health Promotion and Disease Prevention recommends hepatitis B immunization for previously unvaccinated adults who are at increased risk of contracting HBV infection (see paragraph 4j for at-risk individuals), and for any other adult who is seeking protection from HBV infection. A combined hepatitis A and hepatitis B vaccine (Twinrix®) may be given to individuals at risk of hepatitis A.

(a) Nonimmune pregnant women with hepatitis risk factors should be vaccinated against hepatitis B. Women at risk of HBV infection during pregnancy should be counseled regarding additional methods to prevent HBV infection (see paragraph 4f).

(b) Serologic testing for hepatitis B immunity is not necessary after routine vaccination. Serologic testing after immunization is recommended for healthcare workers and public safety workers at high risk of continued exposure, chronic hemodialysis patients, HIV-infected persons, immunocompromised persons, and the sex partners of HBsAg-positive persons.

(c) Veterans should be advised of strategies for minimizing the risk of acquiring hepatitis B, including the use of barrier methods during sexual activity, not sharing drug paraphernalia, and not sharing toothbrushes or razors.

(2) **Prevention of Transmission.**

(a) General. Patients who are HBsAg positive (i.e., acute or chronic HBV infection) should advise their sex contacts to be vaccinated; to use barrier precautions during sexual intercourse if the partner is not vaccinated or naturally immune; to avoid sharing toothbrushes, razors, and drug paraphernalia; to cover open wounds; and not to donate blood, sperm, or organs.

(b) Pregnant women. Pregnant women who are HBsAg positive should be counseled about the importance of initiating infant hepatitis B vaccination and treating the infant with hepatitis B immune globulin within 12 hours of delivery. Pregnant women with high hepatitis B viral loads should be counseled about the possibility of antiviral therapy in the last month of pregnancy (see paragraph 4f).

c. **Testing for Chronic Hepatitis B and Interpretation of Results.**

(1) With most individuals who have never been tested, have had incomplete testing or have risk factors (e.g., injection drug use) in the absence of immunity, the provider should test for HBsAg; testing for HBsAb or HBcAb also should be performed.

(2) For individuals at high risk of infection (see paragraph 3a above), HBsAg and HBcAb testing should be performed before initiation of immunosuppressive therapy (see paragraph 4h).

(3) Interpretations of different combinations of serologic results are shown in Table 1 (see Attachment C).

d. **Antiviral Treatment.**

(1) **Acute Hepatitis B.** In general, patients with acute hepatitis B should not be treated with antiviral therapy, as >95 percent of adults with acute hepatitis B will recover without developing chronic infection or other sequelae.

(2) **Chronic Hepatitis B.** Patients with chronic hepatitis B should be referred to an infectious disease specialist or hepatologist for assessment for hepatitis B treatment candidacy.

(3) **HIV Pre-exposure Prophylaxis in Patients with Chronic Hepatitis B.** Individuals with chronic hepatitis B who are interested in the use of emtricitabine/tenofovir for pre-exposure prophylaxia (PrEP) for HIV should be referred to a hepatologist or infectious disease specialist before initiation of PrEP.

(4) **HIV/HBV Coinfection.** All first-line therapies for hepatitis B also are active against HIV; monotherapy of HBV without addressing HIV treatment creates a high risk of HIV resistance mutations. Patients with HIV/HBV coinfection should be referred immediately to an infectious disease specialist.

(5) **Veterans Receiving Immunosuppression.** Prophylactic antiviral therapy may be provided to hepatitis B carriers at the onset of chemotherapy or immunosuppressive therapy (see paragraph 4a). Such patients should be managed in consultation with a hepatologist or infectious disease specialist.

e. **General Medical Care.** Veterans with chronic hepatitis B who are not immune to hepatitis A should receive hepatitis A vaccination (see paragraph 4i).

4. REFERENCES:

a. VA/DoD Clinical Practice Guideline for Management of Pregnancy, 2009. Available at http://www.healthquality.va.gov/guidelines/WH/up/ .

b. VHA Directive 2013-008, Infectious Disease Reporting. Available at http://vaww.va.gov/vhapublications/ViewPublication.asp?pub_ID=2909. ***NOTE:*** *This is an internal VA Web site not available to the public.*

c. VHA National Center for Health Promotion and Disease Prevention. Screening for Hepatitis B Guidance Statement. Available at http://vaww.prevention.va.gov/Screening_for_Hepatitis_B.asp. ***NOTE:*** *This is an internal VA Web site not available to the public.*

d. National Center for Health Promotion and Disease Prevention. Hepatitis A Immunization Guidance Statement. Available at http://vaww.prevention.va.gov/Hepatitis_A_Immunization.asp. ***NOTE:*** *This is an internal VA Web site not available to the public.*

e. VHA National Center for Health Promotion and Disease Prevention. Hepatitis B Immunization Guidance Statement. Available at http://vaww.prevention.va.gov/Hepatitis_B_Immunization.asp. ***NOTE:*** *This is an internal VA Web site not available to the public.*

f. Centers for Disease Control and Prevention. Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection. MMWR Recomm Rep. 2008 Sep 19; 57(RR-8):1-20.

g. Gelberg L, Robertson MJ, Leake B, et al. Hepatitis B among homeless and other impoverished US military veterans in residential care in Los Angeles. Public Health. 2001 Jul; 115(4):286-9.

h. Ioannou GN. Hepatitis B virus in the United States: infection, exposure, and immunity rates in a nationally representative survey. Ann Intern Med. 2011 Mar 1; 154 (5):319-28.

i. Raimondo G, Allain JP, Brunetto MR, et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. J Hepatol. 2008 Oct; 49(4):652-7.

j. Tabibian JH, Wirshing DA, Pierre JM, et al. Hepatitis B and C among veterans in a psychiatric ward. Dig Dis Sci. 2008 Jun; 53(6):1693-8.

5. INQUIRIES: Questions regarding this Information Letter may be directed to the Director, HIV, Hepatitis, and Public Health Pathogens Programs (HHPHP) at 202-461-1040 or by email at vhahhphp@va.gov.

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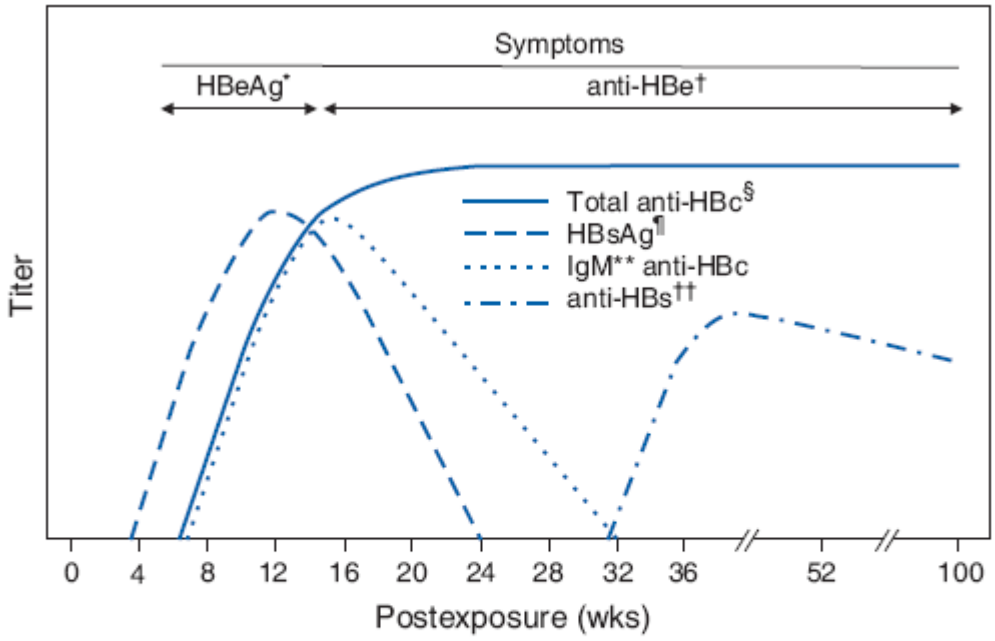
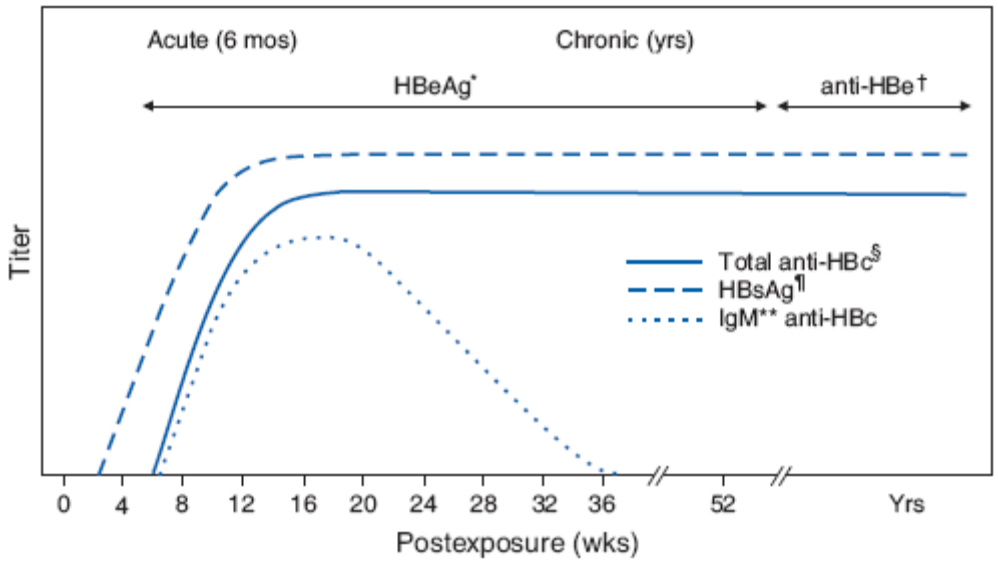
Figure 1: Typical serologic course of acute hepatitis B virus infection with recovery



* Hepatitis B e antigen.
† Antibody to HBeAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.
†† Antibody to HBsAg.

Figure 2: Typical serologic course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection



* Hepatitis B e antigen.
† Antibody to HBeAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.

Table 1. Interpretation of Laboratory Results for Hepatitis B Infection

HBsAg	HBsAb	HBcAb (Total)	HBcAb IgM	Interpretation	Subsequent Action
–	–	–	N/A*	Susceptible to HBV infection	Initiate immunization series as indicated by VHA Clinical Practice Guideline on Hepatitis B immunization: http://vaww.prevention.va.gov/Hepatitis_B_Immunization.asp
–	+	–	N/A	Immune owing to vaccination	No action needed
–	+	+	N/A	Immune owing to natural infection	No action needed
–	–	+	N/A	Four possibilities: 1. Resolved infection (most common) 2. False-positive HBcAb, thus susceptible 3. "Low-level" chronic infection 4. Resolving acute infection	Refer to hepatologist or infectious disease specialist if taking immunosuppressive medication or planning to start.
+	–	N/A	+	Acute infection	If clinically stable, check ALT, HBV DNA, and HBeAg. Recheck ALT in 1-2 months, and recheck HBsAg in 6 months to determine whether chronic hepatitis B has developed. Exposed contacts should be notified and advised to receive medical evaluation. If required under state law, report acute hepatitis B infection to State/Local Public Health authorities as per subparagraph 4i. If required under state law report chronic hepatitis B infection to State/Local Public Health authorities as per subparagraph 4i.

HBsAg	HBsAb	HBcAb (Total)	HBcAb IgM	Interpretation	Subsequent Action
+	−	+	−	Chronically infected	Order ALT, HBeAg, and HBV DNA tests. Discuss with hepatologist or infectious disease specialist for consideration of antiviral therapy. Implement hepatocellular cancer screening every 6-12 months in high-risk individuals: cirrhotics, family history of hepatocellular carcinoma, Asian men >40 years, Asian women >50 years, Africans >20 years, any carrier >40 years with intermittent or persistent ALT elevations or HBV DNA >2,000 IU/mL.

* N/A = not applicable