Instructions on Completing the Modules

*The results of the assessments and evaluations are confidential, and the data is used to meet requirements of our federally funded grant.

Please make sure to turn in Pre-Test, Post-Test, and Module Evaluation.

- **Before** reading the module, and without looking at it, complete the Pre-Test. Record your answers on the examination form marked Pre-Test. *(Found at the start of the module.)* Keep the completed answer form to return at the completion of the module.

- Complete the module as outlined in the syllabus.

- **After** reading the module, please complete the Post-Test.
  - Record your answers on the examination form marked Post-Test. *(Found at the end of the module.)* Keep the completed answer form to return with the pre-test at the completion of the module.

  Complete the Module Evaluation. *(Found after the post-test.)* Keep the completed module evaluation form to return with the pre-test and post-test at the completion of the module.

- **To obtain credit for the module you must:**
  1. Complete [online](#) or return the MTGEC Participant Profile
  2. Return the Pre-Test, Post-Test, and Module Evaluation
  3. Obtain a score of 70% or better on the Post-Test
Pre-test: Viral Hepatitis Update
(Record responses on examination form)

1. The elevation of which one of the following laboratory tests is most closely associated with jaundice due to hepatitis?
   a. Alanine transferase
   b. Alkaline phosphatase
   c. Bilirubin
   d. Ammonia level

2. What drug therapy is used to treat ascites in the patient with advanced liver disease?
   a. Propranolol
   b. Combination spironolactone plus furosemide diuretic therapy
   c. Lactulose
   d. Octreotide

3. Which factor would most closely correlate with an outbreak of hepatitis A (HAV)?
   a. Poor sanitation in a developing country
   b. Homosexual activity
   c. Intravenous drug use
   d. Exposure to blood in a health care setting

4. Which statement is true regarding treatment of the patient who develops symptomatic acute HAV?
   a. They should be given a dose of immune serum globulin (ISG)
   b. Rest, good nutrition, and avoidance of alcohol is the best treatment
   c. They should be given a dose of ISG and started on the vaccine series
   d. They should be started on the vaccine series; there is no need for ISG

5. For all EXCEPT which one of the following persons is post-exposure prophylaxis against HAV recommended?
   a. A household member of an infected person
   b. A daycare worker in the center with an infected child
   c. A chef who works in the same food establishment with the infected person
   d. A coworker in the same office building where the infected person is employed
6. Which of the following statements about hepatitis B (HBV) is false?
   a. All persons who contract HBV have symptoms during the acute infection that allows easy recognition of the infection.
   b. If not treated, neonates & children compared to adults have a greater risk of developing chronic HBV.
   c. The HBV vaccine is recommended for all children.
   d. Hepatitis B immune globulin (HBIG) is used when an unvaccinated person is exposed to a person with chronic HBV.

7. Which laboratory marker is most closely associated with chronic HBV?
   a. Anti-HBs
   b. Anti-HBc
   c. HBsAg
   d. HBeAg

8. For which one of the following laboratory combinations is drug therapy versus observation recommended for chronic HBV?
   a. Positive HBeAg, HBV-DNA titer > 20,000 IU/ml, and ALT < 2x normal
   b. Negative HBeAg, HBV-DNA titer > 20,000 IU/ml, and ALT > 2x normal
   c. Negative HBeAg, HBV-DNA titer >2,000 IU/ml, and ALT 1-2x normal
   d. Negative HBeAg, HBV-DNA titer < 20,000 IU/ml, and ALT normal

9. Which of the following is the most likely adverse effect of interferon that occurs early in therapy (i.e. during the first few weeks)?
   a. flu-like symptoms
   b. depression
   c. neutropenia
   d. thyroid dysfunction

10. Viral resistance in chronic HBV is the greatest concern with which one of the following nucleoside(tide) analog antiviral agents?
    a. Lamivudine
    b. Adefovir
    c. Tenofovir
    d. Entecavir

11. What is the most common genotype for hepatitis C (HCV) in the United States?
    a. Genotype 1
    b. Genotype 2
    c. Genotype 3
    d. Genotype 4
12. All of the following persons would be considered at high risk for HCV EXCEPT?
   a. A 25 year old female who was an intravenous drug user up until 3 years ago.
   b. A 35 year old male who underwent a hip fracture repair with blood supplementation 2 years ago.
   c. A 60 year old male who underwent an open appendectomy in his teenage years.
   d. A 34 yo female who is positive for human immunodeficiency virus (HIV) as a result of indiscriminant sexual activity.

13. According to the CDC guidelines, which of the following populations should be screened for Hepatitis C?
   a. Individuals born between 1945-1965
   b. Individuals with sexual partners who are HCV-positive
   c. Individuals who work in any health care setting
   d. Intranasal drug users

14. Which statement is TRUE regarding HCV disease course?
   a. The majority of persons who contract acute HCV progress to symptomatic jaundice.
   b. The majority of persons who contract HCV will clear the virus after the acute infection.
   c. Of those persons who develop chronic HCV, 80% will progress to cirrhosis & advanced liver disease.
   d. Hepatic carcinoma (HCC) is associated with chronic HCV in some persons.

15. Once an individual tests positive for HCV-antibodies with the OraQuick device, which of the following tests are required to confirm a diagnosis of active HCV infection?
   a. HCV RNA test
   b. Alanine aminotransferase (ALT) test
   c. Repeat HCV-antibody test
   d. HCV antigen test

16. Patients will require follow-up testing if they have had a possible exposure to HCV in the past.
   a. 1 month
   b. 3 months
   c. 6 months
   d. 12 months
17. A patient with chronic HCV responds to treatment with an undetectable HCV-RNA level at the end of the treatment course; eight weeks after treatment, HCV-RNA is once again detectable. What pattern of response best characterizes the patient?
   a. A null responder
   b. A partial responder
   c. A response relapser
   d. A sustained virologic response patient

18. Which of the following regimens provide the best chance of a sustained virologic response (SVR) for HCV genotype 1?
   a. Interferon for 48 weeks
   b. Peginterferon plus ribavirin (RBV) for 24 weeks
   c. Peginterferon plus RBV plus telaprevir for 12 weeks
   d. Sofobuvir/ledipasvir for 12 weeks

19. Which of the following are side effects of daclatasir (Daklinza®) ?
   a. Headache
   b. Fatigue
   c. Diarrhea
   d. All of the above

20. Which statement is TRUE regarding use of the newer (since 2013) direct acting antivirals (DAAs) agents for the treatment of chronic HCV?
   a. All the new DAAs must be given multiple times during the day, and adherence is important.
   b. All of the new DAA regiment have fewer adverse effects compared to the regimen of peginterferon plus ribavirin.
   c. All of new DAAs have the advantage of no risk of HCV resistance to the given agent.
   d. All of the new DAAs have the advantage of posing very few drug interactions.
Module: Viral Hepatitis Update

PRE-TEST

Participant Information

1. Name: ________________________________________

2. Mailing address: ________________________________
   ______________________________________________
   ______________________________________________
   ______________________________________________
   ______________________________________________

3. Date exam completed __________________________

Questions: (Please circle one response per question)

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Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment
Page 6 of 89
MNA CE expiration date: 5/13/2018
VIRAL HEPATITIS UPDATE WITH A FOCUS ON HEPATITIS C:
EPIDEMIOLOGY, SCREENING, AND TREATMENT

Michael P Rivey, M.S. Pharm, BCPS, FASHP
Jessi Cahoon, Pharm.D.

University of Montana Skaggs School of Pharmacy

A 3-hour Screening Module from the
Montana Geriatric Workforce Enhancement Program

A Consortium of:
The University of Montana, Missoula
Mountain Pacific Health, Helena
RiverStone Health, Billings
St. Vincent Healthcare, Billings

Montana Geriatric Education Center website

May 2016

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MONTANA GERIATRIC EDUCATION CENTER
Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment

Disclosures

Montana Geriatric Workforce Enhancement Program Goals/Purpose
Improve health outcomes for older adults in rural Montana via increased knowledge of older adult care and treatment of health problems by health professionals.

Successful completion of this continuing education activity includes:
- Completion of the Pre-Test
- Reading of text
- Visiting websites as directed in module (if appropriate)
- Completion of the Post-Test with at least 70% accuracy
- Completion of the module evaluation

Contact Hours: 3, including 3 Rx Hours for Nurses

Montana Nurses Association (MNA)
The Montana Geriatric Education Center is an approved provider of continuing nursing education by the Montana Nurses Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation.
MNA Continuing Nursing Education Expiration Date: 5/13/2018

Conflicts of Interest
The planners and presenters of the CE activity have disclosed no relevant financial relationship with any commercial companies pertaining to this activity.

This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and human Services (HHS) under grant number U1QHP28733, Geriatric Workforce Enhancement Program (GWEP); the total award is $2,143,140 and supports the Montana GWEP 100%. This information or content and conclusions are those of the authors and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS or the U.S. Government.
Description of Module

Content:

In recent years, the incidence of Hepatitis C has increased dramatically, prompting changes in screening guidelines, with the most significant change being the recommendation that all people born between the dates of 1945 and 1965 be tested once. This module has been designed to provide the reader with a general overview of the three major forms of viral hepatitis that have major health care ramifications in the United States. Attention is given to risk factors, clinical presentations, laboratory testing, preventative strategies, updated guidelines for the screening of hepatitis C in older adults, and treatments for hepatitis A, B, and C. Secondly, the process for screening with the OraQuick® HCV Rapid AntibodyTest is delineated with the goal of providing a training document for health care professionals and health professions students, including those involved with the ImProving Health Among Rural Montanans (IPHARM) program.

Learning Objectives:

On completion of this module, the learner will be able to:

1. Discuss the impact of hepatitis A, B, and C in United States, including current trends in the diseases.

2. Describe methods to prevent hepatitis A and B through vaccination, including who should receive vaccination.

3. Discuss the importance of the hepatitis C genotype and how it impacts treatment.

4. Identify persons at risk for contracting chronic hepatitis C and the updated guidelines for screening.

5. Describe the process for screening for hepatitis C, including the identification of persons to be referred for follow-up by medical care providers.

6. Recognize current drug therapy used in the treatment of hepatitis C.
# Table of Contents

**Pre-test: Viral Hepatitis Update**.........................................................................................................................2

I. **Viral Hepatitis Overview** ..........................................................................................................................................12
   A. Types of viral hepatitis ..............................................................................................................................................12
   B. Clinical Presentation of Hepatitis ..............................................................................................................................13
      1. *Acute hepatitis* ........................................................................................................................................................13
      2. *Chronic hepatitis* ....................................................................................................................................................14
      3. *Manifestations of advanced liver disease* ..................................................................................................................15
   C. Hepatitis A ..................................................................................................................................................................16
      1. *Epidemiology and risk factors* ...............................................................................................................................16
      2. *Diagnosis and laboratory testing* ..........................................................................................................................18
      3. *Prevention of HAV* ..................................................................................................................................................18
      4. *Treatment of HAV exposure & infection* ................................................................................................................20
   D. Hepatitis B ..................................................................................................................................................................22
      1. *Epidemiology and risk factors* ...............................................................................................................................22
      2. *Diagnosis and laboratory testing* ..........................................................................................................................23
      3. *Prevention of HBV* ..................................................................................................................................................26
      4. *Treatment of HBV exposure* ...................................................................................................................................29
      5. *HBV Infection and treatment of chronic HBV* ......................................................................................................29

II. **Hepatitis C** ..............................................................................................................................................................34
   A. Epidemiology: societal impact .......................................................................................................................................34
      1. *Genotypes* ...............................................................................................................................................................35
      2. *Risk factors* ............................................................................................................................................................35
   B. Disease course ..............................................................................................................................................................36
      1. *Acute HCV* .............................................................................................................................................................36
      2. *Chronic HCV* ..........................................................................................................................................................36
   C. Laboratory testing ..........................................................................................................................................................37
   D. Prevention of HCV ........................................................................................................................................................38
   E. Screening for HCV ........................................................................................................................................................39
      1. *Screening recommendations: Who should be tested?* ...............................................................................................39
      2. *HCV Screening guidelines* ....................................................................................................................................39
3. Current public health campaigns promoting HCV testing ........................................ 42
4. IPHARM Screening test ................................................................................................. 43
5. Requirements for reporting HCV in Montana .......................................................... 50
6. Barriers to testing ........................................................................................................ 50
F. Treatment of HCV ....................................................................................................... 50
1. Drugs used in the treatment of chronic HCV (Tables 15 & 16) 35, 38 .................... 53
2. Current guidelines for the treatment of chronic HCV ............................................. 58
3. Summary & future challenges in the drug treatment of chronic HCV ..................... 60

III. Websites for HCV .................................................................................................... 62

IV. References ................................................................................................................. 63

Appendix A: IPHARM Patient Consent Form ..................................................................... 68
Appendix B: IPHARM Student HCV Screening Procedure Checklist ................................. 71
Appendix C: IPHARM OraQuick Test Kit Storage Temperature Log ............................... 75
Appendix D: IPHARM OraQuick HCV Control Kit Log ................................................... 76
Appendix E: CDC Hepatitis C General Information .......................................................... 77
Appendix F: Why Baby Boomers Should Be Tested ......................................................... 79
Appendix H: Post-test: Viral Hepatitis Update ............................................................... 83
APPENDIX I: Evaluation: Viral Hepatitis Update ............................................................ 88
I. Viral Hepatitis Overview

The changes that have occurred in the understanding and the treatment of viral hepatitis (referred to as hepatitis in this module unless otherwise noted) over the past 35 years have been dramatic and have resulted in major health care impact. A vaccine for hepatitis A (HAV), approved in the mid-1990s, was quickly incorporated into childhood vaccination schedules, targeting a major source group for spread of the infection. The introduction and widespread use of a vaccine for hepatitis B (HBV) in the early 1980s was followed by an 81% decrease in the disease incidence over the next 25 years. Previously known as a nonA, nonB form, hepatitis C (HCV) was isolated in 1988 and rapidly recognized as a major cause of chronic hepatitis. Most recently, new treatment options for patients with chronic HCV have resulted in a high probability of cure for what is the most common blood-borne infection in the United States (US).

There are many details and nuances regarding the approach to treatment of the types of hepatitis that are beyond the scope of this educational module. For example, special patient populations such as those co-infected with human immunodeficiency virus (HIV) along with the viral hepatitis have unique treatment considerations. The reader should appreciate that the purpose of this document is a general educational overview of the three major forms of viral hepatitis that are important in the US.

A. Types of viral hepatitis

There have been six major types of viral hepatitis identified to date including HAV, HBV, HCV, hepatitis D (HDV, delta), hepatitis E (HEV), and hepatitis G (HGV). The first 3 types are major health care issues in the US and will be discussed in this module. It is important to understand that each major type of viral hepatitis has several identified genotypes that possess different clinical implications, although knowledge in this area is incomplete.

The forms of hepatitis differ in the type of virus causing the infection, their inherent infectivity, the route of transmission for infection, and the potential for causing a chronic carrier state. Only HBV is a DNA virus while other forms of hepatitis are caused by RNA viruses. HAV and HEV are transmitted by fecal-oral contamination although genotypes of HEV have been transmitted from animal reservoirs (zoonotically). All other types of hepatitis are transmitted by infected blood or blood products. HAV infection causes only an acute infection, whereas the other forms of hepatitis have been associated with chronic infection.
There are unique characteristics associated with HDV, HEV, and HGV that result in less importance for these types of hepatitis in the US. HDV is a pathogen that only occurs only in the presence of HBV infection. As such, it can be considered an opportunistic infection in the patient with chronic HBV, although importantly, one that promotes more advanced liver disease. HEV was previously known as a primary cause of acute hepatitis occurring in developed countries, but now also is receiving attention as a cause of chronic infection in immunosuppressed individuals such as organ transplant recipients. HGV, also known as GB virus-C, is usually found as a co-infection with other forms of hepatitis, but carries little risk of advancing liver disease, suggesting it may not be an actual hepatitis virus.

B. Clinical Presentation of Hepatitis

1. Acute hepatitis

The most important aspect surrounding the acute presentation of each type of hepatitis is an appreciation that many patients with an acute infection will go unrecognized since they will either be asymptomatic or have prolonged mild symptoms characteristic of many viral illnesses, without developing jaundice. Moreover, the clinical presentation of a patient with acute hepatitis is similar for the various forms of hepatitis, characterized by an initial incubation period of viral replication and resultant shedding. The incubation phase is followed by a pre-icteric (pre-jaundice) or prodromal phase with typical viral infection symptoms of fatigue, malaise, nausea, and anorexia.

Patients then may or may not progress to worsening symptoms of nausea and vomiting, fever, diarrhea, and abdominal pain in the right upper quadrant. The icteric (jaundice) phase due to hepatocellular obstruction follows and is characterized by darkening of the urine (to brown), light-colored stools, yellowing of the sclera of the eyes, and pruritis. Laboratory tests indicative of liver function including the bilirubin, alanine (ALT) and aspartate (AST) transaminases, and alkaline phosphatase are almost always elevated during this phase. After the icteric phase, most patients enter the convalescent phase that lasts for several months. Fortunately, only rarely will a patient progress to fulminant hepatitis.

There are general differences for the typical durations of time in the acute disease phases for the types of hepatitis, but great variation is observed across patients (Table 1).
Table 1: Characteristics of the 3 major forms of hepatitis

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>15-50 days mean: 30 days</td>
<td>45-180 days mean: 80 days</td>
<td>15-160 days mean: 50 days</td>
</tr>
<tr>
<td>Type of virus</td>
<td>RNA</td>
<td>DNA (Dane particle)</td>
<td>RNA</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td>Fecal-oral</td>
<td>Blood</td>
<td>Blood</td>
</tr>
<tr>
<td>Onset of clinical illness</td>
<td>Sudden</td>
<td>Insidious</td>
<td>Insidious</td>
</tr>
<tr>
<td>Likelihood of symptomatic hepatitis at onset</td>
<td>&lt; 5% children 70-80% adults</td>
<td>15-30% (uncommon in neonates &amp; children)</td>
<td>5-10%</td>
</tr>
<tr>
<td>Development of jaundice</td>
<td>&lt;10% children 30 adults</td>
<td>30% children 5-10% adults</td>
<td>25% children 5-10% adults</td>
</tr>
<tr>
<td>Development of inactive carrier state</td>
<td>None</td>
<td>Up to 50% of chronic disease</td>
<td>&lt; 1% of chronic disease</td>
</tr>
<tr>
<td>Development of chronic Infection</td>
<td>None</td>
<td>80-90% neonates 25% children 2-7% overall</td>
<td>80-85%</td>
</tr>
<tr>
<td>Risk of hepatocellular carcinoma</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

2. Chronic hepatitis

After the acute infection, patients may not replace infection antigen markers (to be discussed with individual diseases) in their blood with antibody markers that confer protection against ongoing infection. If the antigen markers persist for greater than 6 months, the patient is considered to have developed chronic hepatitis. While there are many factors that affect the subsequent disease course, patients with chronic hepatitis suffer from recurrent disease exacerbations that can lead to cirrhosis and hepatocellular carcinoma (HCC).
Importantly, patients with chronic hepatitis serve as a reservoir for infecting other people. Infection is spread through risk behavior that will be discussed, although the source of infection for many patients goes unrecognized.

3. **Manifestations of advanced liver disease**

Chronic liver disease can progress to advanced liver disease characterized by cirrhosis and HCC. Chronic hepatitis and alcoholism are the two primary causes of cirrhosis in the US. The process can take place over 20-30 years and is typically characterized by the absence of symptoms or mild nonspecific symptoms such as fatigue. Obviously, this aspect limits the recognition of people who are chronic carriers of hepatitis.

As cirrhosis progresses, inflammatory and fibrotic changes occur within the liver, giving rise to the manifestations of advanced liver disease. Increased blood pressure within the portal vein (portal hypertension) contributes to the development of ascites and esophageal varices, as well as promoting splanchnic vascular dilation and shunting of blood “around” the liver that can result in spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome. Impaired hepatocyte function reduces protein synthesis that may cause coagulation abnormalities with an increased risk of bleeding (Table 2).

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Hallmark laboratory tests</th>
<th>Treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>Inc. serum bilirubin + urine urobilinogen + urine bilirubin</td>
<td>• Supportive’ good diet</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>None</td>
<td>• Nonselective beta blocker (isosorbide mononitrate may be added)</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>None</td>
<td>• Treatment of portal hypertension</td>
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<tr>
<td></td>
<td></td>
<td>• Endoscopic intervention: cauterization, ligation (EVL)</td>
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<td></td>
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<td>• Blood supplementation if needed for bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Octreotide or somatostatin if bleeding</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Inc. INR</td>
<td>• Vitamin K</td>
</tr>
<tr>
<td>Ascites</td>
<td>Dec. albumin</td>
<td>• Sodium restriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Diuretic therapy with a combination of spironolactone and furosemide</td>
</tr>
<tr>
<td>Hepatic encephalopathy (HE)</td>
<td>Inc. serum ammonia</td>
<td>• Protein restriction (initially)</td>
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<tr>
<td></td>
<td></td>
<td>• Lactulose</td>
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<td>• Rifaximin</td>
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Table 2: Manifestations of advanced liver disease

Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment
Page 15 of 89
MNA CE expiration date: 5/13/2018
<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Hallmark laboratory tests</th>
<th>Treatment(s)</th>
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<tbody>
<tr>
<td>Spontaneous bacterial peritonitis (SBP)</td>
<td>WBCs in peritoneal fluid</td>
<td>• Cefotaxime or other 3rd generation cephalosporin</td>
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<td></td>
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<td>• Ofloxacin as an oral option</td>
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<td>• Antibiotic prophylaxis after attack</td>
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<td>Hepatorenal syndrome</td>
<td>Inc. serum creatinine</td>
<td>• Stop diuretics</td>
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<td>• Intravenous albumin plus vasoactive drug</td>
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<td>(octreotide or midodrine)</td>
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</tbody>
</table>

Inc. = increased; Dec. = decreased; INR = International Normalized Ratio; WBC= white blood cell

The development of the manifestations of cirrhosis clearly is associated with poor patient outcomes, with death occurring in approximately half of patients who develop ascites within a 2 year period. Patients also may progress to liver failure, leaving liver transplantation as the only cure. Finally, patients with cirrhosis have an associated increased risk for HCC.

C. Hepatitis A

1. Epidemiology and risk factors
Hepatitis A (HAV), originally called infectious hepatitis, is unique among the forms of hepatitis in that it is associated only with an acute infection that may or may not result in symptoms. An exposed person develops antibodies and then is protected for life from reinfection; there is no carrier state for HAV. As noted, HAV transmission occurs by the fecal-oral route, either by person-to-person contact with an infected person or ingestion of HAV-containing water or food. As such, infections with HAV usually occur in clusters of people. As would be expected based on its close association with sanitation, HAV is endemic to most developing and poor countries, with persons in those countries having nearly universal exposure to the hepatitis.8, 9

Risk factors for contracting HAV in the US reflect exposure to an infected person via travel, group clustering, poor hygienic practices, and increased susceptibility to infection (Table 3).
Table 3: Risk factors for HAV

<table>
<thead>
<tr>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Exposure to contaminated food or water</td>
</tr>
<tr>
<td>• Travel to, or living in area with poor sanitation</td>
</tr>
<tr>
<td>• Sexual or household contacts of infected person</td>
</tr>
<tr>
<td>• International travel to, or work in, countries with endemic HAV without being immunized</td>
</tr>
<tr>
<td>• Attend or work in child care center</td>
</tr>
<tr>
<td>• Men who have sex with men</td>
</tr>
<tr>
<td>• Illicit drug use, especially by injection</td>
</tr>
<tr>
<td>• Positive for human immunodeficiency virus (HIV)</td>
</tr>
<tr>
<td>• Chronic liver disease</td>
</tr>
<tr>
<td>• Clotting-factor disorder, such as hemophilia</td>
</tr>
</tbody>
</table>


The incidence of acute HAV infections has declined in the US over the past 20 years in all patient age groups. The decline is primarily attributable to the introduction of a vaccine in the mid-1990s, followed by its inclusion in vaccination schedules and recommendations. A low of 1398 cases of HAV were reported to the Centers for Disease Control and Prevention (CDC) in 2011, a dramatic decrease from 4488 cases in 2005 and nearly 30,000 cases in 1995 (Figure 1).

Figure 1: Incidence of acute HAV infections reported to the CDC
2. Diagnosis and laboratory testing

The diagnosis of a HAV infection is based on clinical suspicion of exposure together with a laboratory test for immunoglobulin (Ig) M antibody to the virus, called anti-HAV. The test for the IgM antibody is used because it is detectable for 5-10 days prior to the onset of symptoms. While the shedding of the viral RNA precedes the development of anti-HAV, the viral load test is not used in clinical practice. Laboratory testing assesses total anti-HAV that includes both IgM and IgG anti-HAV. 

Because viral shedding precedes the antibody development and represents patients who are infective to others, decisions regarding HAV prevention are commonly made on the basis of possible exposure. However, testing for HAV immunity is justified to identify persons already protected from the hepatitis, especially in areas where HAV exposure is common.

3. Prevention of HAV

The development of a vaccine to protect against contracting HAV (pre-exposure prophylaxis) has had a major impact on the disease incidence in all age groups, but especially in children. The inclusion of the vaccine in the childhood immunization schedule was endorsed by the Advisory Committee on Immunization Practices (ACIP) for all children at age 1 year, as was “catch-up” for older children (Table 4). This was an important aspect in the overall prevention of acute HAV since children who contract the hepatitis are rarely symptomatic, and even if symptomatic, do not progress to the icteric stage. Children previously had been a major reservoir for propagation of HAV.

Changes to HAV vaccination recommendations in the past few years include guidelines for household and close contacts of internationally adopted children and updated travel recommendations. Specifically, travel guidelines allowed for the sole use of a single antigen vaccine for healthy patients, whereas the addition of immune serum globulin (ISG) to the vaccine is still recommended for older adults, immunocompromised patients, and those with chronic liver disease or other conditions if departure to the HAV endemic area is occurring within 2 weeks.
Table 4: ACIP pre-exposure recommendations for HAV vaccination.12

<table>
<thead>
<tr>
<th>Routine vaccination (Minimum age: 12 months):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initiate the 2-dose Hep A vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.</td>
</tr>
<tr>
<td>• Children who have received 1 dose of Hep A vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.</td>
</tr>
<tr>
<td>• For any person aged 2 years and older who has not already received the Hep A vaccine series, 2 doses of Hep A vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Catch-up vaccination:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The minimum interval between the two doses is 6 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special populations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Administer 2 doses of Hep A vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemcity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemcity. The first dose should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.</td>
</tr>
</tbody>
</table>

Three inactivated vaccine products are available for use in HAV, including one that combines HAV with HBV antigens (TwinRix®). There are differences in the inclusion of a preservative and how antigen content is expressed between the products (Table 5).11 All are considered to be greater than 95% effective and the active immunity from the vaccine appears to be life-long for HAV.15 Adverse effects are usually mild and typical for a vaccine including injection site reactions, pain of injection, malaise, and headache.
Table 5: HAV vaccine products

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age (years)</th>
<th>Antigen content</th>
<th>Preservative</th>
<th>Recommended dosage schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaqta®</td>
<td>1-18</td>
<td>25 units 50 units</td>
<td>No</td>
<td>2 doses at 0 and 6-18 months</td>
</tr>
<tr>
<td></td>
<td>19 and older</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Havrix®</td>
<td>1-18</td>
<td>720 ELISA units 1440 ELISA units</td>
<td>Yes</td>
<td>2 doses at 0 and 6-12 months</td>
</tr>
<tr>
<td></td>
<td>19 and older</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twinrix®</td>
<td>18 and older</td>
<td>720 ELISA units</td>
<td>Yes</td>
<td>3 doses at 0, 1, and 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 doses at 0, 7 days, 21-30 days, and 12 months (accelerated schedule)</td>
</tr>
</tbody>
</table>

4. Treatment of HAV exposure & infection

The treatment following exposure to HAV differs in 2 groups of people. The larger group includes persons who likely have been exposed to the disease but either did not contract HAV or are asymptomatic. Treatment of these persons is known as post-exposure prophylaxis and is recommended for household contacts, or those who have ingested food possibly handled by an infected person. The second group includes people who develop acute HAV disease.

Post-exposure prophylaxis can include immune serum globulin (ISG) and/or HAV vaccine. Use of the vaccine has the obvious advantage of conferring active and likely life-long immunity for the recipient, is easier to administer, and has greater patient acceptance. Whereas ISG previously was the standard agent used for post-exposure prophylaxis, HAV vaccine compared to ISG was determined to be equally efficacious in preventing acute hepatitis in healthy persons when given within 14 days of the exposure. However, a comparative study of the two options has not been conducted in patient groups who tend to have worse HAV outcomes, including older patients and those with chronic liver or other diseases.

Consequently, guidelines now advocate the use of ISG or single antigen HAV vaccine for post-exposure prophylaxis depending on patient characteristics. A dose of single antigen vaccine should be administered to all persons recently exposed to a person with HAV (Table 6). If the person is healthy and between ages 12 months and 40 years, the vaccine alone suffices for treatment; the vaccine series should be completed according to the schedule. On the other
hand, ISG at a intramuscular dose of 0.02 mL/kg is administered to patients younger than 12 months or greater than 40 years of age, those with underlying medical conditions noted in the previous section, and those who cannot receive the vaccine. Patients receiving ISG /should simultaneously receive the first dose of the vaccine series.\textsuperscript{14}

The use of either post-exposure prophylaxis option is at least 85% effective in avoiding symptomatic hepatitis in persons at risk if given within 2 weeks of exposure. Patrons of food establishments are generally not candidates for post-exposure prophylaxis since the 2-week period for efficacy has commonly been exceeded by the time the index case exhibits clinical hepatitis. School attendees, office workers, and hospital staff are also not recommended for post-exposure prophylaxis unless close contact with the HAV infected person is documented.\textsuperscript{14}

**Table 6: Post-exposure HAV prophylaxis after contact with HAV infected person\textsuperscript{14}**

<table>
<thead>
<tr>
<th>Person Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household members &amp; sexual contacts</td>
<td>May also include ongoing contact, e.g., babysitters</td>
</tr>
<tr>
<td>Person who has shared illicit drugs</td>
<td></td>
</tr>
<tr>
<td>Daycare children cohort and workers</td>
<td>• May affect those in only one classroom/area of daycare if center does not care for children in diapers</td>
</tr>
<tr>
<td></td>
<td>• Also given if cases occur in at least 2 households of daycare attendees</td>
</tr>
<tr>
<td>Families of child in daycare</td>
<td>Recommended if child in diapers and if cases occur in 3 households of daycare attendees</td>
</tr>
<tr>
<td>Food handlers at same establishment</td>
<td></td>
</tr>
</tbody>
</table>

Treatment of the person who develops acute HAV infection with clinical symptoms is supportive. There is no pharmacotherapy for acute HAV. Supportive therapy includes rest, good nutrition, the avoidance of alcohol and other hepatotoxic agents, and perhaps drug therapy for symptoms. For example, topical or systemic antihistamines may be used for troublesome pruritus due to jaundice.

The duration of an acute episode of HAV is variable but typically 6-8 weeks, followed by a period of convalescence for 1-2 months. Almost all patients recover without residual liver damage.
damage. Nevertheless, there is still a 0.2% risk of fulminant hepatitis and death from HAV, a risk that increases in patients over 40 years of age and in those with pre-existing liver disease.⁸

For more information on Hepatitis A see: Hepatitis A Questions and Answers for the Public and The World Health Organization’s Global Alert and Response: Hepatitis A.

D. Hepatitis B

1. Epidemiology and risk factors
Hepatitis B (HBV) was originally called serum hepatitis and has always been regarded as a highly virulent form of hepatitis; it is much more virulent than HIV or HCV. Transmission of HBV occurs primarily by exposure to infected blood, but also can occur by contact with body fluids like semen, vaginal fluid, and other exudates of infected persons.¹⁷ Illustrating the virulence of HBV, infection clusters have been associated with exposure to infected instrumentation in the health care setting.¹⁸ Infection with HBV can be spread either horizontally (family members in households) or vertically (mother to baby, the mode of transmission that propagates HBV in areas of high endemicity) (Table 7). The virus has at least 8 genotypes that vary with geographic location and perhaps with transmission mode. It is known that the genotype of HBV influences clinical outcome and response to therapy; fortunately, the US predominantly has genotype A that responds better to interferon-based therapy.¹⁹

Table 7: Risk factors for HBV infection¹,¹⁷

<table>
<thead>
<tr>
<th>Exposure to blood of an HBV infected person</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Injection-drug use</td>
</tr>
<tr>
<td>• Neonate delivered to HBV-positive mother</td>
</tr>
<tr>
<td>• Healthcare-related needle stick or other exposure to blood</td>
</tr>
<tr>
<td>• Institution or correctional facility work or residence</td>
</tr>
<tr>
<td>• Treatment with contaminated healthcare instrumentation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Horizontal contact with family members or close contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Body fluids but also via articles such as toothbrushes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sexual exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sex with person with confirmed HBV</td>
</tr>
<tr>
<td>• Men who have sex with men</td>
</tr>
<tr>
<td>• Heterosexual with multiple or casual partners</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ transplantation from infected donor</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Chronic dialysis</th>
</tr>
</thead>
</table>

Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment
Page 22 of 89
MNA CE expiration date: 5/13/2018
Like HAV, the incidence of HBV is low in the US compared to other areas in the world. The major route of HBV transmission in areas of low endemicity such as the US and Western Europe is by sexual contact.\(^9\)

Moreover, the incidence of HBV has significantly decreased since the introduction of the HBV vaccine. Inclusion of the vaccine in vaccination programs directed at risk groups, active screening for HBV during pregnancy, immunization of infants born to infected mothers, and the advent of universal precautions in healthcare settings factor in the dramatically decreased incidence. Nevertheless, HBV infection continues to have an incidence of approximately 1 case per 100,000 persons in the US, and about 1% of patients die from the hepatitis.\(^20\)

**Figure 2: Incidence of HBV by age group in USA, 2000-2013 \(^9\)**

![Incidence of HBV by age group in USA, 2000-2013](image)

2. **Diagnosis and laboratory testing**

The diagnosis of HBV is much more complicated than for HAV or HCV, in that it involves multiple serologic markers for assessing HBV in both acute and chronic disease. HBV is a DNA virus (Dane particle), giving rise to antigens and antibodies to surface and core components of the viral particle. The various serum markers are variably present during the disease stages. Antigens to HBV indicate active infection whereas antibody markers are typically associated with immunity, although they may disappear if a patient develops chronic infection. Clinical
suspicion and screening of high risk persons for HBV is important as a majority of patients with acute disease are asymptomatic. 

During acute HBV infection, the serum HBV surface antigen (HBsAg) first appears during the incubation phase, preceding the onset of symptoms or liver enzyme elevation. The HBsAg marker is the most abundant surface antigen and proves to be key to the disease course, since its disappearance with the detection of antibodies to the surface antigen (Anti-HBs) indicates clearing of the acute infection and life-long immunity (Figure 3). Antibody to HBV core antigen (Anti-HBc) rises as clinical disease progresses during the acute infection and has a role during a “core window” typically just before the recovery phase, when serum levels of HBsAg and Anti-HBs both may fall below detectable levels. There are both immunoglobulin M (IgM) and G (IgG) sources for Anti-HBc; the Anti-HBc IgM is used in the diagnosis of acute HBV. The core antigen (HBcAg) has no role in HBC diagnosis since it is an intracellular antigen only present in hepatocytes.

A HBV secretory protein antigen called HBeAg emerges after HBsAg during the acute infection and is replaced by an antibody (Anti-HBe) if the infection resolves. Viral HBV replication is assessed by HBV DNA production that is detectable and then resolves in fairly close association with the acute infection process.
Chronic HBV infection is defined as the persistence of serum HBsAg beyond 6 months. Persons with chronic HBV may or may not have HBeAg, but if present, levels are considered a marker of viral replication. \(^2\) HBV DNA correlates with disease activity in chronic disease and is used to predict prognosis, as well as make decisions regarding the need for liver biopsy and therapy initiation. Anti-HBc IgG is present in chronic HBV but only is used in epidemiologic research studies.

In summary, the use of viral antigens (HBsAg and HBeAg), antibodies (Anti-HBs, Anti-HBc, and Anti-HBe), and viral load (HBV-DNA) are incorporated into laboratory testing for acute and chronic HBV (Table 8).
Table 8: Serology in acute & chronic HBV

<table>
<thead>
<tr>
<th>State</th>
<th>HBsAg</th>
<th>HBeAg</th>
<th>Anti-HBs</th>
<th>Anti-HBc (IgM)</th>
<th>Anti-HBe</th>
<th>HBV-DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible to HBV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Immune from infection</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acute infection</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ to +++</td>
</tr>
</tbody>
</table>

3. Prevention of HBV

The introduction of a vaccine dramatically affected the impact of HBV hepatitis in the US by promoting more aggressive screening of high risk groups as well as immunization programs in all newborns and adolescents who have a greater risk of developing chronic infection. In addition to the high risk groups listed in Table 7 above, HBV screening is also recommended in persons born in areas of the world with a HBsAg prevalence of ≥ 2%, born to parents born in areas with a HBsAg prevalence ≥ 8%, pregnant women, persons infected with HIV, and those who will receive immunosuppressive therapy for a medical condition such as rheumatoid arthritis.²³⁻²⁵ Because HBV vertical transmission from mother to infant is known to occur in 70-90% of deliveries, passive immunization with hepatitis B immune globulin (HBIG) is combined with the vaccine at the time of birth for the neonates. Unfortunately, a 10-15% failure rate still occurs despite the combined approach.²⁶
# Table 9: ACIP recommendations for HBV vaccination

## Routine vaccination (minimum age: birth):

### At birth:

- Administer monovalent HepB vaccine to all newborns before hospital discharge.
- For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series at age 9 through 18 months (preferably at the next well-child visit).
- If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother’s HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

### Doses following the birth dose:

- The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
- Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the first dose. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks.
- Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

## Catch-up vaccination:

- Unvaccinated persons should complete a 3-dose series.
- Children aged 4 months through 6 years should receive doses at 0, 1 month, and 2 months
- Children aged 7 years through 18 years should receive doses at 0, 1, and 2 months
- A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
There are five HBV vaccine products including two single-antigen three combination products. The products and doses recommended vary according to the populations that they target for use (Table 10). All HBV vaccines should be given via the intramuscular route.

**Table 10: HBV vaccine products**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age groups</th>
<th>Content</th>
<th>Dose</th>
<th>Recommended dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Engerix-B®</strong></td>
<td>Birth through 19 yrs</td>
<td>20 mcg/ml</td>
<td>0.5 ml</td>
<td>3 doses at 0, 1, and 6 months</td>
</tr>
<tr>
<td></td>
<td>20 yrs and older</td>
<td></td>
<td>1.0 ml</td>
<td>3 doses at 0, 1, and 6 months</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis adults</td>
<td></td>
<td>2.0 ml</td>
<td>4 doses at 0, 1, 2, and 6 months</td>
</tr>
<tr>
<td><strong>Recombivax®</strong></td>
<td>Birth through 19 yrs</td>
<td>10 mcg/ml</td>
<td>0.5 ml</td>
<td>3 doses at 0, 1, and 6 months</td>
</tr>
<tr>
<td></td>
<td>11 through 15 yrs</td>
<td></td>
<td>0.5 ml</td>
<td>3 doses at 0, 1, and 6 months OR</td>
</tr>
<tr>
<td></td>
<td>20 yrs and older</td>
<td></td>
<td>1.0 ml</td>
<td>2 doses at 0 and 4-6 months</td>
</tr>
<tr>
<td></td>
<td>Predialysis/dialysis</td>
<td>40 mcg/ml (dialysis)</td>
<td>1.0 ml</td>
<td>3 doses at 0, 1, and 6 months</td>
</tr>
<tr>
<td><strong>Twinrix®</strong></td>
<td>18 yrs and older</td>
<td>20 mcg/ml + Hep A</td>
<td>1.0 ml</td>
<td>3 doses at 0, 1, and 6 months OR</td>
</tr>
<tr>
<td><strong>Comvax®</strong></td>
<td>6 wks through 6 yrs</td>
<td>10 mcg/ml + Hib</td>
<td>0.5 ml</td>
<td>3 doses at 2, 4, and 12-15 months of age</td>
</tr>
<tr>
<td><strong>Pediarix®</strong></td>
<td>6 wks through 6 yrs</td>
<td>20 mcg/ml + DTaP + IPV</td>
<td>0.5 ml</td>
<td>3 doses at 2, 4, and 6 months of age</td>
</tr>
</tbody>
</table>

Hep A = hepatitis A; Hib = haemophilus b conjugate; DTaP = diphtheria and tetanus toxoids and acellular pertussis absorbed; IPV = inactivated polio vaccine

Post-vaccination testing for immunity is recommended in certain groups to determine if additional interventions should be implemented. An Anti-HBs serum titer of 10 mIU/ml is representative of an immune response. However, it is known that approximately 10% of healthy persons will not respond to the standard vaccine series; the CDC recommends an additional vaccine dose with further testing or a second complete series of vaccine for those persons. Groups in whom post-vaccination testing should occur include infants born to HBsAg-positive mothers, healthcare workers at risk for continued exposure to HBV, sexual
partners of chronic HBV patients, and immunocompromised individuals such as HIV or dialysis patients. It is also known that the Anti-HBs level will fall below the level of “protection” after 10 years in over 20% of persons who initially respond. Fortunately, a vaccine booster dose is about 95% effective in reestablishing the immune response, suggesting an amnestic response in which the person’s immune system still recognizes HBV despite the low antibody level.

4. Treatment of HBV exposure
Post-exposure prophylaxis to persons exposed to possible HBV infection incorporates both HBIG and HBV vaccine. The recommended action taken depends on the HBV status of the source of exposure and the vaccination status of the exposed person. If the source person is known to be positive for HBsAg, then the exposed person, if unvaccinated, should receive both HBIG as well as start the vaccine series. If the exposed person was previously vaccinated, then they should receive a single booster of the vaccine. If the HBV antigen status of the source person is unknown, the exposed person, if unvaccinated, should start the vaccine series, while no treatment is recommended in the previously vaccinated exposed person.

Recent guidelines specifically focus on HBV post-exposure testing and treatment of healthcare workers. The guidelines incorporate the exposed healthcare worker’s vaccination history, the exposed worker’s post-exposure immune status based on serologic Anti-HBs testing, and the source person’s HBV status. As expected, post-exposure recommendations are more variable for this group. If the healthcare worker had a documented serologic response to the vaccine series, no post-exposure action is needed regardless of the source HBsAg status. If the healthcare worker had a documented serologic nonresponse to the vaccine, HBIG is given if the source person is either unknown or positive for HBsAg. If the healthcare worker received the vaccine series but serologic response was not determined, treatment is based on the source status and the result of post-exposure testing of the worker.

5. HBV Infection and treatment of chronic HBV
Approximately 2/3 of persons infected with HBV are asymptomatic or have only mild symptoms of the disease. The other 1/3 of infected patients present with acute hepatitis as described above; fortunately, fulminant hepatitis occurs in less than 1% of patients. As with HAV, the treatment of the patient with acute HBV is supportive.

All patients, regardless of the acute disease presentation, are at risk for the development of chronic HBV as defined by serologic testing. The risk for the development of chronic HBV is clearly age-related, occurring in an estimated 90-95% of infants, 25-30% of children, and 5% of adults who are infected. Once a person has developed chronic HBV, the clinical course is
variable with patients developing an inactive carrier state, having chronic hepatitis with recurring disease flares, or progressing to cirrhosis and possibly HCC (Figure 4).\textsuperscript{30} Moreover, there is evidence that reactivation of HBV can occur in any patient with a prior HBV infection, although it more likely to occur in the chronic HBV patient.\textsuperscript{31}

**Figure 4: HBV disease course** \textsuperscript{20}

Patients with chronic HBV, all whom are positive for HBsAg in serum, are divided into four subgroups of patients defined by serology. Patients who are positive for HBeAg form two subgroups including those who are considered “immune-tolerant” with normal ALT but elevated HBV-DNA levels in serum, and those who considered to have “active” disease with elevated ALT and HBV-DNA levels. As would be expected, patients in the immune-tolerant group have mild disease with a low risk of progression while those in the active group more commonly progress to cirrhosis at a rate of 2-3\% yearly.

Similarly, patients who are negative for HBeAg are subdivided into “inactive carrier” and “active” disease groups. Inactive carrier patients have positive anti-HBe, normal ALT, and undetectable or low HBV-DNA levels in serum, and typically have a benign disease course and
perhaps even remission. Patients in the active disease group also have a positive anti-HBe, but have elevated ALT and HBV-DNA levels and typically suffer a worse disease course. Factors that affect the disease course and risk of progression to cirrhosis and HCC have been delineated and include disease severity, disease flare frequency, alcohol use, smoking, the degree of HBV DNA elevation, coinfection with HIV, HCV, or HDV, and others.\textsuperscript{31,32}

The treatment of chronic HBV centers on two primary approaches, with the use of either an immunomodulating or antiviral agent. In consideration of the prolonged and sometimes insidious course of chronic HBV, not all patients are candidates for treatment. Because HBV resides intracellularly, treatment is not considered curative but rather of benefit due to suppression of viral replication and avoidance of consequent manifestations of cirrhosis and HCC. As such, factors including patient age, serologic subgroup, concurrent conditions or coinfections, HBV DNA viral load, and liver status as determined by ALT, symptoms, and histology determine whether treatment is indicated in a given patient (Table 10).\textsuperscript{11,33} The monitoring of ALT levels is recommended every 6 months to detect the patient who transitions from an inactive to active disease status.

### Table 10: Chronic HBV treatment recommendations \textsuperscript{11,33}

<table>
<thead>
<tr>
<th>HBeAg status</th>
<th>HBV-DNA titer</th>
<th>ALT</th>
<th>Treatment action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>&gt; 20,000 IU/ml</td>
<td>&gt; 2 x normal</td>
<td>Drug therapy</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt; 20,000 IU/ml</td>
<td>≤ 2 x normal</td>
<td>Observation</td>
</tr>
<tr>
<td>Negative</td>
<td>&gt; 20,000 IU/ml</td>
<td>&gt; 2 x normal</td>
<td>Drug therapy</td>
</tr>
<tr>
<td>Negative</td>
<td>&gt; 2,000 IU/ml</td>
<td>1-2x normal</td>
<td>Observation</td>
</tr>
<tr>
<td>Negative</td>
<td>&lt; 2,000 IU/ml</td>
<td>Normal</td>
<td>Observation</td>
</tr>
</tbody>
</table>

Immunomodulation therapy that enhances a person’s own immune defense against HBV involves the use of interferon-alfa, either with the conventional product (IFN) administered three times weekly or more commonly with the pegylated preparation (Peg-IFN) that has a longer half-life that allows for once weekly dosing. Antiviral therapy uses nucleoside and nucleotide analogs (Table 11). The choice between the two approaches is determined by comparative advantages of each approach. Recent guidelines by the American Association for
the Study of Liver Diseases (AASLD) for the treatment of chronic HBV were released in November 2015 and published in January 2016.\textsuperscript{33}

Table 11: Pharmacotherapy of chronic HBV \textsuperscript{1,33}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Typical duration of therapy</th>
<th>Adverse effects</th>
<th>HBV resistance</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-alfa</td>
<td>5 MU daily or 10 MU SC 3x weekly</td>
<td>6 months to 1 year</td>
<td>Early: flu-like symptoms, Late: psychiatric, bone marrow suppression, thyroid dysfunction, others</td>
<td>No</td>
<td>Early flu-like syndrome affects nearly all patients, but rarely requires discontinuation</td>
</tr>
<tr>
<td>Peg-interferon</td>
<td>180 mcg SC weekly</td>
<td>1 year</td>
<td>Same as conventional interferon</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lamivudine (Epivir-HBV\textsuperscript{*})</td>
<td>100 mg po daily</td>
<td>1-5 years</td>
<td>Mild: HA, fatigue, nausea, abdominal pain</td>
<td>Yes, increases each year</td>
<td>Greatest resistance seen</td>
</tr>
<tr>
<td>Adefovir (Hepsera\textsuperscript{*})</td>
<td>10 mg po daily</td>
<td>2-5 years</td>
<td>Minimal: renal toxicity at high doses</td>
<td>Yes, less if lamivudine combined</td>
<td>Renal toxicity is a concern, but less than with HIV dosage; monitor SCr</td>
</tr>
<tr>
<td>Entecavir (Baraclude\textsuperscript{*})</td>
<td>0.5 mg po daily</td>
<td>2-6 years</td>
<td>Similar to lamivudine</td>
<td>Yes, do not combine with lamivudine</td>
<td>1\textsuperscript{st} line.</td>
</tr>
<tr>
<td>Telbivudine (Tyzeka\textsuperscript{*})</td>
<td>600 mg po daily</td>
<td>2-5 years</td>
<td>Mild: some cases of myopathy &amp; elevated creatinine kinase</td>
<td>Yes, increases each year</td>
<td>Resistance development similar to lamivudine</td>
</tr>
<tr>
<td>Tenofovir (Viread\textsuperscript{*})</td>
<td>300 mg po daily</td>
<td>3-6 years</td>
<td>Mild: abdominal pain, diarrhea, HA, fatigue, elevated SCr</td>
<td>No, but less effective in resistant strains</td>
<td>1\textsuperscript{st} line. Similar to adefovir, but with much less renal toxicity</td>
</tr>
</tbody>
</table>

MU = million units; SC = subcutaneously; po = by mouth; HA = headache; HIV = human immunodeficiency virus; SCr = serum creatinine

Advantages associated with an IFN-based approach include a finite duration of therapy of typically 12 months, the absence of resistance to the drug, and a more reliable stable response in the 20-40\% of patients who respond.\textsuperscript{34} The normalization of ALT levels will occur in about 50-70\% of patients. Factors associated with a better response to IFN have been identified,
including high pretreatment ALT values, a lower baseline viral load, the HBV genotype, being non-Asian race, and the presence of significant inflammation seen on liver biopsy.\textsuperscript{11,33} Disadvantages of the choice of IFN-based therapy include the need for injectable therapy, a significant adverse effect profile, and a contraindication to use in patients with decompensated (active) cirrhosis. Patients receiving IFN-based therapy commonly have a hepatitis disease “flare” two or three months into therapy as the body’s immune system mounts a response to the HBV infection.\textsuperscript{1}

In contrast, antiviral agents are used until a response is attained, which may take years of treatment. A response is sometimes lost when the drug is discontinued. Seroconversion rates are approximately 5-20% after one year of therapy with the given antiviral agent, and increase with each year of continued therapy to result in rates similar to IFN-based therapy. Compared to IFN, these are oral drugs taken on a daily basis, have much more favorable adverse effect profiles, are less costly, and are thought safer for use in decompensated cirrhosis. A major concern regarding the nucleoside or nucleotide analogs is the development of HBV resistance; in the case of lamivudine, resistant mutants develop in 24% of patients after 1 year, increasing up to 80% after 5 years of therapy. It is recommended that patients who develop resistant mutants should be treated with combination antiviral therapy. In consideration of their low resistance and adverse effect profiles, entecavir and tenofovir are preferred first-line antivirals.\textsuperscript{32}

The recent AASLD guidelines provide useful recommendations regarding the use of HBV antivirals. In HBeAg-positive patients without cirrhosis, a “period of consolidation” of 12 months of continuing antiviral treatment is recommended after developing anti-HBe levels, normalization of ALT, and undetectable HBV-DNA. In the same situation in a patient who was HBeAg-positive but has cirrhosis, indefinite antiviral treatment should be considered. Indefinite antiviral therapy is also recommended in all patients who are HBeAg-negative. Finally, antiviral therapy is recommended for use in any chronic HBV patient with decompensated cirrhosis, regardless of HBeAg status, ALT, or HBV-DNA levels.\textsuperscript{33}

Empiric combinations of IFN plus an antiviral drug, or the use of two antiviral drugs, have not been found to enhance overall efficacy. Unlike in HCV, the addition of ribavirin to IFN-based therapy also does not improve response. While an advantage of lower, but not avoided resistance to the antiviral drug(s) can be achieved with combination therapy, increased drug costs and adverse effects also occur. At present, empiric combination therapy is recommended only for select groups of patients.\textsuperscript{33}

For more information, see the HBV Website.
II. Hepatitis C

Hepatitis C (HCV) infection may be the most important medical issue facing the US today. It is the most common blood-borne infection and has emerged as the primary disease resulting in advanced liver disease including HCC and the need for liver transplantation. Moreover, chronic disease commonly develops and the number of cases of chronic HCV has continued to rise since the identification in 1989 of the virus previously known as non-A, non-B hepatitis. However, HCV is considered curable.

Just as recognition of the prevalence and importance of chronic HCV has evolved, so has the therapeutic approach to a cure. The achievement of a sustained virologic response (SVR) indicative of a cure has improved to over 90% with current pharmacotherapy. Treatment advances have paralleled increased efforts to identify persons with chronic HCV through screening programs. However, the identification of persons with chronic HCV brings new challenges regarding the appropriate timing of treatment and the resultant healthcare costs of the drug therapy.

A. Epidemiology: societal impact

An estimated 3.2 million people in the US and over 180 million persons worldwide have known HCV. After the yearly incidence of new acute HCV cases reported to the CDC declined and then remained steady from 2002-2011, the number of reported cases dramatically increased in recent years (Figure 5). With a prolonged chronic disease course of 20-30 years, the total number of cases is increasing and HCV is estimated to now affect close to 2% of the US population. It is important to note that only an estimated 25-50% of existing HCV cases are diagnosed due to asymptomatic or mild acute disease presentation. Thus, the labeling of chronic HCV along with HBV as part of a “silent epidemic” seems justified. Adding to the challenge surrounding chronic HCV is the fact that in most settings, only about 20% of patients have received treatment directed at a cure.
1. Genotypes

The RNA virus HCV has six major genotypes that have subtypes; at least 90 subtypes have been identified. The genotype of HCV has been found to have a major influence on the response to treatment and while response rates are now above 90% for all HCV genotypes, recommended drug regimens are still genotype-specific. Genotypes 1a and 1b cause 75% of HCV infections in the US and traditionally had the lowest likelihood of treatment response/cure. Other HCV cases in the US are primarily caused by genotypes 2 and 3, accounting for about 20% of infections.  

2. Risk factors

The transmission of HCV occurs via contact with infected blood; risk factors for infection are similar to those seen in HBV in that “high-risk” behaviors are associated with the hepatitis. Injectable drug use is currently the most common risk factor in the US, resulting in an increased disease burden in young adults. Because of its recent discovery, risk factors for HCV include the receipt of clotting factors and blood transfusions before the early 1990s (Table 12). Nevertheless, it is important to note that approximately 40-45% of persons diagnosed with chronic HCV have no identifiable risk factor. The common absence of an identifiable risk factor, unprotected high-risk behaviors during young adult years, and possible exposure via the
blood supply understandably have contributed to an increased prevalence in the 1945-1965 birth cohort, the so-called “baby boomers.”

### Table 12: Risk factors for HCV

<table>
<thead>
<tr>
<th>Blood exposure by high-risk behaviors</th>
<th>Intravenous drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intrasanal use of illicit substance</td>
</tr>
<tr>
<td></td>
<td>Sexual indiscretion: multiple partners or men having sex with men</td>
</tr>
<tr>
<td></td>
<td>Tattooing, body piercing, or acupuncture with unsterilized instruments</td>
</tr>
<tr>
<td>Exposure by circumstance</td>
<td>Birth date between 1945-1965</td>
</tr>
<tr>
<td></td>
<td>Sexual transmission from HCV partner</td>
</tr>
<tr>
<td></td>
<td>Receipt of clotting factors before 1987</td>
</tr>
<tr>
<td></td>
<td>Receipt of blood transfusion before 1992</td>
</tr>
<tr>
<td></td>
<td>Healthcare needle-stick with contaminated needle or other occupational exposure</td>
</tr>
<tr>
<td></td>
<td>Perinatal transmission from HCV-infected mother</td>
</tr>
<tr>
<td></td>
<td>Organ transplantation</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Concurrent disease/condition risk</td>
<td>HIV infection</td>
</tr>
<tr>
<td></td>
<td>HBV infection</td>
</tr>
<tr>
<td></td>
<td>Chronic liver disease of unknown cause</td>
</tr>
</tbody>
</table>

### B. Disease course

1. **Acute HCV**

   Like other forms of hepatitis, the presentation of acute infection with HCV is often asymptomatic or characterized by mild symptoms such as fatigue, anorexia and nonspecific gastrointestinal symptoms such as nausea and diarrhea. Therefore, acute HCV often goes unrecognized. If symptomatic, the course for HCV is typical, with patients progressing through the prodomal, icteric, and convalescent phases. It is estimated that only 15-25% of persons contracting HCV will clear the acute infection laboratory markers that will be discussed.

2. **Chronic HCV**

   The great propensity for HCV to progress to the chronic disease state, affecting up to 85% of those infected, is certainly what has made it a priority medical issue. As with HBV, chronic HCV
is defined by the presence of a HCV RNA viral load that is detectable six months after the acute infection. Because persons who develop chronic disease often go unrecognized after an asymptomatic or mild acute disease attack, this accounts for the large pool of undiagnosed HCV patients.

As with HBV, persons with chronic HCV enter a disease course continuum that is slowly progressive over 10-30 years. It is estimated that approximately 20% will progress to cirrhosis, with 1-4% of those patients subsequently developing HCC each year.\(^5\)

**Figure 6: HCV disease course**\(^5,41\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV infection</td>
<td>100%</td>
</tr>
<tr>
<td>None or mild symptoms</td>
<td>70%</td>
</tr>
<tr>
<td>Acute symptomatic hepatitis</td>
<td>30%</td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
<td>rare</td>
</tr>
<tr>
<td>Chronic HCV</td>
<td>80-85%</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>80%</td>
</tr>
<tr>
<td>Eventual cirrhosis</td>
<td>20%</td>
</tr>
<tr>
<td>Hepatic carcinoma (HCC)</td>
<td>1-4%/year</td>
</tr>
<tr>
<td>5-50 years</td>
<td></td>
</tr>
</tbody>
</table>

**C. Laboratory testing**

The laboratory testing for HCV is simple in that it involves testing only for HCV antibodies in blood that, if positive, leads to determining the viral load (HCV RNA). Almost all persons...
exposed to HCV, whether they clear the acute infection or progress to chronic disease, will develop HCV antibodies (Anti-HCV). However, the appearance of Anti-HCV may not occur until weeks after contracting the infection and persons with acute HCV could be missed. In the 15-20% of patients who spontaneously clear the acute infection, the test for Anti-HCV will remain positive for life; thus additional HCV RNA testing is required to identify persons with chronic HCV.³⁷

Persons with a positive Anti-HCV test should be tested with a molecular assay to determine HCV RNA. In contrast to Anti-HCV, detectable HCV RNA levels are present early following exposure to HCV. Concurrently, ALT levels may rise that indicate hepatic injury and the impeding onset of symptomatic acute disease. As the acute phase of HCV subsides, the ALT levels decrease towards normal and HCV RNA levels either become undetectable indicating that the acute infection has been cleared, or will persist as the person enters the chronic disease phase. As noted, after at least 6 months of HCV RNA detection, the person is considered to have chronic HCV.¹¹

During the chronic disease process, HCV RNA and ALT levels will variably fluctuate as the underlying liver disease progresses. The chronic disease process may result in inflammation and resultant fibrosis of the liver that damages the normal tissue structure, possibly leading to cirrhosis.⁴² Scoring systems including the METAVIR score are commonly used to classify the severity of liver damage, based on biopsy results of the grade (inflammatory) and stage (fibrosis) of liver damage.⁴¹ If a patient develops cirrhosis, additional tests such as imaging techniques may be used to detect HCC. Although the determination of the optimal time to treat a person with chronic HCV is a current evolving issue, testing before treatment involves HCV RNA quantification, genotype determination, and liver biopsy, in addition to the ALT.

D. Prevention of HCV

Since HCV has at least 6 genotypes and over 90 subtypes, no vaccine is available for the prevention of the disease. There also is no pharmacotherapy available for post-exposure prophylaxis.

The promotion of a healthy lifestyle including; tobacco, cannabis, and alcohol avoidance; as well as a good diet and weight loss have been associated with slowing chronic HCV disease progression.⁴¹,⁴³,⁴⁴ Susceptible patients with chronic HCV should be vaccinated against HAV and HBV. Herbal products such as milk thistle (silymarin) have been promoted for use in patient with hepatitis, but there is no evidence that any of the products affect the progression of HCV.
Therefore, keys to the prevention of HCV lie in the education and avoidance of risk behaviors and the identification of the persons with chronic HCV who serve as a reservoir for spread of the disease. Screening is the most effective method to identify persons with chronic HCV.

E. Screening for HCV

1. Screening recommendations: Who should be tested?
In 2012, the CDC expanded the HCV screening recommendations to include a one-time screening for those born between 1945 and 1965.\textsuperscript{45} Estimates suggest this birth cohort accounts for 76.5% of those who will test positive for Anti-HCV, with an HCV prevalence rate five times higher than other age groups. Recent data indicate prevalence in this age cohort of 3.29%. The recommendation represented a marked adjustment from traditional HCV screening that focused on individuals with the highest risk of transmission. However, the addition of age-based screenings was justified, given that over half of HCV infections were not being identified with risk-based screenings and that the new screening model was determined to be similarly cost-effective.\textsuperscript{38}

Other more obvious groups included in HCV screening guidelines are individuals with clinical indications for testing including those with known HCV exposure and those with signs of liver inflammation. The 2012 CDC recommendations did not supersede previous guidelines but rather included the 1945-1965 birth cohort in addition to prior high-risk groups in whom screening was indicated.\textsuperscript{38,45}

2. HCV Screening guidelines
Screening guidelines for HCV have been provided by several organizations. Primary sources for guidelines include the CDC, the American Association for the Study of Liver Diseases (AASLD), the Infectious Disease Society of America (IDSA), the International Antiviral Society-USA (IAS-USA), and the US Preventative Services Task Force (USPSTF).\textsuperscript{38,41,45,46} The IAS-USA collaborated with the AASLD-IDSA in their publication of the 2015 HCV management guidelines.\textsuperscript{38} HCV guidelines with a more global perspective include those from the World Health Organization (WHO) and the European Association for the Study of the Liver (EASL). Most of the guideline organizations followed suit after the addition of the age-based screening recommendations by the CDC, and include a one-time screening for asymptomatic individuals born between 1945 and 1965.\textsuperscript{38,45,46}

Other guidelines have been developed by groups with more specialized readership including the American Academy of Family Physicians and the American College of Gastroenterology (ACG). The ACG HCV guidelines have not been updated since 2009.\textsuperscript{41}
There are discrepancies among existing guidelines regarding what constitutes high-risk behaviors and exposures (Table 13). Current CDC guidelines consider intranasal drug users and individuals who receive a tattoo from a non-certified facility to be “of uncertain need” for routine HCV testing, which differs from the AASLD-IDSA guidelines where screening is recommended.\(^\text{38,47}\) CDC guidelines also do not explicitly include solid organ donors; however, the 2013 US Public Health Service, released guidelines for solid organ transplant patients that included Hepatitis C screenings.\(^\text{45,47,48}\) WHO guidelines are the only ones that provide screening recommendations for sexual partners of HCV-infected individuals. WHO recognized heterosexual couple HCV transmission is “very low” and noted higher risk rests with HIV-infected men who have sex with men. WHO also accounted for variability of importance of risk factors depending on country.\(^\text{49}\)

Also, the screening frequency recommended for patients who continue to participate in high-risk behavior is variable across the organizations. The AASLD-IDSA guidelines define a one-year screening interval for intravenous drug users and HIV-infected males who have sex with males and periodic testing for all others with high exposure risk.\(^\text{38}\) In contrast, the USPSTF recommends that individuals who continue to participate in high-risk behavior should receive periodic testing but offer no definitive interval.\(^\text{46}\) Finally, the CDC recommends people who may have been exposed to HCV in the last six months be retested.\(^\text{45}\)
<table>
<thead>
<tr>
<th>Guideline Organization</th>
<th>CDC</th>
<th>USPSTF</th>
<th>AALSD/IDSA</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of publication</td>
<td>2012</td>
<td>2013</td>
<td>2015</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Birth Cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals born between 1945-1965</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>High Risk Behaviors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous drug users</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Intranasal drug users</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>High Risk Exposures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hemodialysis patients</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tattoo recipients at unregulated sites</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion recipients (prior to 1992)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Organ transplant recipients (prior to 1992)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotting factor concentrate recipients (prior to 1987)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Incarcerated individuals (previous or current)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Babies born to HCV-positive mothers</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Healthcare or public safety workers with known exposures</td>
<td>X</td>
<td>X*</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion recipients whose donors later tested positive for HCV</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid Organ Donors</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Individuals with signs of liver inflammation (elevated ALTs)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infected individuals</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Individuals with sexual partners who are HCV-infected</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*USPSTF suggests screening for “other percutaneous exposures” and mentions “health care workers” in the text
† WHO suggests screening for “blood or blood product” recipients and does not define “prior 1992” or “prior to 1987” time frames
3. Current public health campaigns promoting HCV testing

The CDC has developed a comprehensive, nationwide HCV awareness campaign called Know More Hepatitis and dedicated the month of May as Hepatitis Awareness Month. The campaign was started in 2012 in conjunction with the CDC recommendation to encourage persons born between 1945 and 1965 to be screened for HCV. The campaign uses public service announcements, advertisements, educational materials, social media and digital tools with the intended audience of patients and providers.\(^{50,51}\)

Regional public health efforts have also been developed including Rhode Island Defeats Hep C that are geared toward identifying and treating patients with the goal of eliminating HCV in the state. The campaign is focused on HCV awareness, testing with intention to treat, building a sustainable program, and progress evaluation.\(^{52}\) Another example is the Test, Listen, Cure (TLC) program located in Memphis, TN, covering the areas of western Tennessee, eastern Arkansas and northern Mississippi. The TLC campaign is a collaborative effort with hospitals, clinics and nonprofit groups to provide health education materials about HCV and to provide continuing education to at least 200 practitioners. Project materials were developed to be culturally sensitive to the largely African American population of these states in addition to being accessible to those with a lower literacy level and education background.\(^{53}\)

There also are several non-profit organizations working to educate and support individuals infected with HCV. The nationwide Hepatitis C Support Project was started in 1997 and provides information, advocacy, and support.\(^{54}\) Another organization called the Hepatitis C Association offers educational programs and support materials in addition to the Help4Hep helpline. The free helpline provides callers with information, support and referrals through one-on-one conversations with trained counselors.\(^{55}\)

In 2015, the nonprofit Chronic Liver Disease Foundation partnered with the retailer Walgreens and began offering free point-of-care HCV testing at select store locations in 12 US cities. The program began in August 2015 and is slated to end in January 2016. The selected sites offer testing and patient counseling; patients who test positive receive referrals to the Chronic Liver Disease Foundation’s Hepatology Centers of Expertise.\(^{56}\)

Locally in Missoula, the nonprofit group, Open Aid Alliance, offers free HCV and HIV testing to persons at high risk of transmission. Open Aid Alliance hosts promotional events in the community to spread awareness about the services they offer. At an HCV screening appointment, individuals receive testing, counseling, educational handouts and referrals for follow-up medical care.
4. IPHARM Screening test

The Anti-HCV test detects antibodies to HCV present in the blood as a result of contact with the virus. As previously discussed, antibodies are present in the body even if an HCV infection has resolved, and the test cannot distinguish between an active, chronic, or resolved HCV infection. If positive, a HCV RNA test that determines virus in the blood must be conducted to determine whether the subject has an active or chronic HCV infection. The CDC has published the recommendation to begin the HCV test sequence with rapid or laboratory Anti-HCV blood testing.\(^{57}\)

The OraQuick\textsuperscript{\textregistered} HCV Rapid Antibody Test is a single-use system that offers qualitative detection of HCV antibodies from blood samples obtained through venipuncture or fingerstick methods. The OraQuick\textsuperscript{\textregistered} HCV antibody test has Clinical Laboratory Improvement Amendments (CLIA) waived status and is FDA-approved.\(^{58}\) The CDC began recommending the OraQuick\textsuperscript{\textregistered} HCV antibody test in 2013 after data demonstrated the specificity (99.7\%) and sensitivity (98.9\%) of the point-of-care test was comparable to other FDA-approved laboratory Anti-HCV tests.\(^{57,59}\)

Despite its name, it is important to note that the OraQuick\textsuperscript{\textregistered} HCV antibody test cannot be completed with an oral swab sample like other OraQuick\textsuperscript{\textregistered} and OraSure\textsuperscript{\textregistered} products. OraSure\textsuperscript{\textregistered} has a salivary HCV test that is used in Europe but no saliva-based HCV tests have FDA approval in the US.\(^{60}\)

IPHARM has elected to use the OraQuick\textsuperscript{\textregistered} HCV Rapid Antibody Test because it is a FDA-approved Anti-HCV test that can be used in non-clinical settings.\(^{57,61}\) The blood specimen can be obtained by a fingerstick and has the test has a relatively short completion time of 20 to 40 minutes.\(^{61}\) There are several tests on the market.

- **Test description**

  The OraQuick\textsuperscript{\textregistered} HCV Rapid Antibody Test is available in kits of 25 or 100 count that include divided test packages, reusable test stands, specimen collection loops and a package insert. The test package will include one single-use testing device and a developer solution vial. Other supplies needed include a dual timer that can time 20 to 40 minutes, a biohazard waste container and materials for fingerstick blood collection.

  The OraQuick\textsuperscript{\textregistered} HCV Rapid Antibody Test Kit Controls, which is sold separately, ensures the test is working properly and that the test administrator can properly perform the test and interpret the results. The Kit Controls should be refrigerated with target temperature range of 36-46\(^\circ\)F. The Kit Controls procedure should be completed when:
1. New test administrator starts performing the test.
2. New shipment of test kits is received.
3. New test kit lot is opened.
4. Temperature of test kit storage falls outside of 36-86°F.
5. Temperature of testing area falls outside of 59-99°F.

The test packages should be stored unopened in the temperature range of 36-86°F and the test should be performed at temperatures between 59-99°F. If the test kits are stored under refrigeration, then the test package should be brought to operating temperature (59-99°F) before it is opened. The test stand should be set upright and placed on an even surface. The test package has two compartments, one that houses the test vial and the other for the test device. The developer solution vial should be taken out of the package and the cap removed, then the vial should be placed in one of the slots of the test stand. Do not open the test device compartment until the test administrator is ready to begin testing, in order to prevent contamination.

- Instructions for using an OraQuick® HCV Rapid Antibody Test: (OraQuick® Package Insert)

1. Collecting the specimen: Wear disposable gloves for the entire duration of the test. Clean the patient’s finger using an alcohol wipe and allow the finger to air dry. Use a sterile lancet to puncture the skin and hold the finger downward and apply gentle pressure beside the puncture. Use a gauze pad to wipe away the first drop and wait for another drop of blood to form. Using a new specimen collection loop, touch the rounded end of the loop to the blood drop until the loop is entirely filled with blood. If the loop is dropped or comes into contact with any surface it must be discarded in the biohazard container and a new loop will need to be used.

2. Mix the specimen in the testing solution: Insert the collection loop into the testing vial without touching the sides. Use the loop to stir the blood into the solution, then remove the loop from the solution and discard the loop in a biohazard container. The vial solution should appear pinkish, which indicates that the blood was mixed correctly into the solution. If the solution is not pink, then the test should be stopped and all used testing materials should be
discarded into a biohazard container. The test will need to be repeated with new materials.

3. Using the test device: Remove the testing device from its package compartment. An absorbent packet should be in the compartment with the testing device; if it is not present, then the testing device must be discarded and a new testing device will be required. Do not cover the two holes in the back of the device with labels or other materials and ensure that the flat pad is not touched. The test device should be inserted with the flat pad entering the vial first with the result window facing the test administrator. Allow the testing device to rest in the vial. The test device must be put into the vial within 60 minutes after the blood sample is mixed in the solution. Start the dual timer for 20 and 40 minutes and do not remove the device from the vial until the test is complete. The pink solution will flood the result window and then disappear as the test continues.

4. Reading the results: Wait for at least 20 minutes for the results to appear in the result window but do not wait for more than 40 minutes to read the results. Read the results using the C Zone (control) and T Zone (test).

   1. Nonreactive: A line appears in the C Zone but no line appears in the T Zone. No HCV antibodies were detected in the specimen.

   2. Reactive: Lines, no matter how faint, appear in the C and T Zones. HCV antibodies were detected in the specimen.

   3. Invalid: No line appears in C Zone or one partial line forms in either the C or T Zone. This means a problem occurred when the test was running due to the blood specimen or the test device and the test should be repeated with a new test package and a new blood sample. Contact OraSure Technologies Customer Service if the result is still invalid with repeated testing. An invalid result cannot be interpreted.

See appendix for step-by-step OraQuick® HCV Rapid Antibody Test instructions.  

Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment
Page 45 of 89
MNA CE expiration date: 5/13/2018
• Test interpretation (Table 14 and Figure 7)

1. If HCV-antibodies are absent, then the test will read nonreactive and the individual is assumed not to be infected with HCV and the testing sequence stops at that point.
   - It should be remembered that the appearance of anti-HCV will sometimes lag several weeks behind contracting acute HCV.
   - The AASLD-IDSA guidelines also recommend follow-up HCV RNA testing for immunocompromised patients and those exposed to HCV in the previous six months with negative anti-HCV tests.\(^{38}\)

2. If HCV-antibodies are present, then the test will read reactive and further testing is required. Any persons with a reactive Anti-HCV test should receive follow-up HCV RNA testing to determine if they have an active or chronic HCV infection.
   - Approximately 78% of individuals who test reactive for HCV-antibodies will also test positive for HCV RNA.\(^{46}\)
   - A reactive Anti-HCV test and negative HCV RNA test indicates that an individual either had a past HCV infection or had a false-positive Anti-HCV test.\(^{57}\)
   - Approximately 15-25% of HCV-infected individuals will seroconvert without treatment.\(^{45}\)
<table>
<thead>
<tr>
<th>Test Outcome</th>
<th>Interpretation</th>
<th>Further Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody nonreactive</td>
<td>No HCV antibody detected</td>
<td>Sample can be reported as nonreactive for HCV antibody. No further action required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If recent HCV exposure in person tested is suspected, test for HCV RNA.*</td>
</tr>
<tr>
<td>HCV antibody reactive</td>
<td>Presumptive HCV infection</td>
<td>A reactive result is consistent with current HCV infection, past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA detected</td>
<td>Current HCV infection</td>
<td>Provide person tested with appropriate counseling and link person tested to medical care and treatment.†</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA not detected</td>
<td>No current HCV infection</td>
<td>No further action required in most cases.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In certain situations§ follow up with HCV RNA testing and appropriate counseling.</td>
</tr>
</tbody>
</table>

* If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.

† It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.

§ If the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
FIGURE 7: Recommended testing sequence for identifying current HCV infection

* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
• Patient counseling during IPHARM screenings

Each patient will receive an informational sheet that explains what HCV is, how it is contracted, why the 1945-1965 birth cohort should be screened, the detrimental effects associated with chronic infection, and the risks and benefits of seeking treatment. Each patient will be given a consent form that explains what Anti-HCV testing entails and what information can be concluded from the results. Every patient will have an opportunity to opt out of testing and each patient who agrees to the test must sign the consent form before testing starts. After the test is completed, patients will be counseled about their reactive or nonreactive Anti-HCV test results.

If the patient tests nonreactive to HCV antibodies, then they will be informed that their test results show they are not infected with HCV, unless they have had a possible exposure in the past few weeks. Patients from the birth cohort will not need to be screened again, unless they have recently participated in high-risk behaviors or had a high-risk exposure.45

If the patient has a reactive test, then they will be counseled on the necessity for confirmatory HCV RNA testing at their earliest convenience to determine the presence of an active or chronic infection. In addition, counseling will be given regarding:45

1. The necessity of a medical evaluation to determine the presence of any liver damage, evaluate the need for HAV and HBV vaccinations, assess possible HIV, and discuss possible treatment options.

2. Limiting risk factors that have been identified for HCV disease progression including reducing alcohol intake, limiting acetaminophen (Tylenol®) use, and possibly weight management.

3. Preventing the transmission of HCV by ceasing blood/tissue/semen donations, and not sharing items that can result in blood contact (e.g., toothbrush, razors, nail clippers).

See appendix for full counseling checklist.

Regardless of the test result, each patient will be given information about how to reduce their risk of HCV transmission by avoiding high-risk exposures and behaviors. Patients also will receive educational handouts from the Hepatitis C Support Project and Open Aid Alliance.

• Videos of test instructions and counseling document

OraQuick® Instructional video
Counseling Guide for Public Health Settings
5. Requirements for reporting HCV in Montana
The Montana Health Department mandates that information about a positive HCV case must be reported to the regional Health Department within seven days after positive results are received by a local health officer. The case report should include the following information, if it is available: name, address, date of birth, gender, race, ethnicity, dates of disease onset, date disease was reported, whether the case is suspected or confirmed, name and address of physician, and name and contact information of the reporter. The identifying information is kept confidential by the Health Department but someone from the Department will contact every reported case as a control measure.

6. Barriers to testing
The sparsely distributed nature of healthcare facilities represents a barrier to healthcare access in rural Montana; including the availability of HCV testing and specialist care. Moreover, non-specialist medical providers may not be aware of new HCV screening recommendations, the prevalent nature of the infection, the availability of testing, or how to administer these tests. As of the first half of 2015, 14.4% of Montanans were uninsured, which is above the national average of 11.7%. Individuals who are underinsured or uninsured may choose not to get tested since they may not be able to afford the recommended treatments. Other individuals may be unwilling to be screened as they are unaware of their true risk of HCV, since exposure risks are associated with specific years and require the knowledge of the risk exposures. The fact that many chronic HCV patients are asymptomatic discourages them from participating in screening. The 1945-1965 birth cohorts may not want to be associated with, or participate in, screenings for a disease characterized by high-risk behaviors. Intravenous drug use continues to be the greatest risk factor for contracting HCV in the US, which can increase the stigma associated with being HCV-positive. Finally, some patients at high risk of HCV transmission such as illicit drug users have limited motivation for self-care that includes obtaining healthcare screenings.

F. Treatment of HCV
The treatment of acute HCV is supportive with a healthy diet and avoidance of previously delineated substances that may affect the development or progression of chronic HCV. Follow-up testing for the development of chronic disease is an important part of the treatment plan for a person exposed to or presenting with acute HCV.

Chronic HCV is the focus of drug treatment for the disease and it is clear that successful treatment has a dramatic effect in terms of health outcomes. Progression of liver fibrosis and cirrhosis, liver-related as well as all-cause mortality, hepatocellular carcinoma, the need for
liver transplantation, and extra-hepatic manifestations are decreased while patients’ health-related quality of life scores are increased in association with successful HCV treatment. Consequently, it is accepted that treatment and cure of chronic HCV represents clinical benefit in the vast majority of patients.

Any discussion regarding the treatment of HCV must start with definitions of the virologic outcomes that describe responses to treatment (Figure 8). A patient who is a null responder has failed to respond to treatment as defined by a meaningful reduction in the HCV RNA viral load in blood. A meaningful reduction in the HCV RNA viral load but failure at the end of treatment to achieve an undetectable viral load defines a partial responder. Patients with an undetectable viral load at the end of drug therapy treatment include those who relapse due to the reappearance of a detectable viral load within 12-24 weeks after treatment concludes, and those who achieve a sustained virologic response (SVR) that is considered a chronic HCV cure. An SVR was previously defined as an undetectable viral load 24 weeks after the end of treatment; with the new direct acting antivirals (DAAs), the time period to define SVR has been shortened to 12 weeks.

**Figure 8: Patterns of nonresponse to drug treatment of HCV**

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Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment
Page 51 of 89
MNA CE expiration date: 5/13/2018
The historically large number of null and partial responders to treatment as well as those who relapse after a course of treatment gives rise to categorization of patients into “treatment-naïve” and “treatment-experienced” groups. As might be expected, treatment-experienced patients have lower SVR rates with a second treatment. Trials of drug therapy for chronic HCV have always differentiated treatment response due to this important factor and present treatment guidelines are specific for the two groups.

The treatment of chronic HCV has dramatically evolved, especially for genotype 1 that is predominant in the US patient population. Early on, it was appreciated that treatment response was highly dependent on HCV genotype, with genotype 1 having much lower rates of SVR in response to treatment, compared to genotypes 2 & 3. Original chronic HCV treatment in the late 1980s used interferon (IFN) given for a 24 week period; IFN continued to be the basis of treatment until late 2013. However, it quickly became clear that IFN was less effective in treating chronic HCV compared to HBV. As a result, changes in how IFN-based therapy was used in terms of product formulation, duration of treatment, and combination therapy with the goal of improved treatment efficacy defined by a SVR occurred during the time period. Changes included increasing the weekly dose of IFN (around 1993), prolonging the treatment duration of IFN-based therapy to at least 48 weeks (around 1995), the addition of ribavirin to IFN therapy (around 1998), substituting the pegylated product to allow once weekly dosing (around 2002), and the development and addition of direct acting antivirals (around 2011). Each change resulted in improvement in the SVR rates, but genotype 1 response rates were always about half of those seen in patients with genotype 2 and 3 (Figure 9). The HCV genotype continues to influence drug regimen recommendations.\textsuperscript{1,38}
In mid-2011, telaprevir and boceprevir were approved as the first DAAs for chronic HCV; they were approved for use only in patients with genotype 1. Their inclusion in the combination regimen with PegIFN and RBV achieved an impressive increase in the SVR rate. However, the new oral agents also resulted in a greater number of adverse effects, sometimes severe, that raised concerns regarding patient adherence to the drug regimen. It had been previously shown that chronic HCV patients who were adherent to less than 80% of the cumulative doses of IFN and RBV had lower SVR rates.

Drugs used in the treatment of chronic HCV (Tables 15 & 16)

Interferon (IFN) and Pegylated Interferon (PegIFN): The interferon products used for treatment of chronic HCV are the same as those used for chronic HBV. They are injectable products given subcutaneously, at a dosage adjusted for renal impairment. Since the introduction of PegIFN that allows for once-weekly dosing, it has been used in all chronic HCV and most HBV treatment regimens. PegIFN in combination with ribavirin was the standard of treatment for all genotypes of HCV until 2011. The drug still appears in recommended treatment regimens for genotypes 2 and 3, but is no longer recommended for use in genotype 1. IFN products have the disadvantage of causing very common and sometimes serious adverse effects. The drug causes an early flu-like syndrome in nearly all patients who receive it. Moreover, the drug cannot be used in patients with significant depressive disorders or decompensated cirrhosis.
Ribavirin (RBV): The drug is a guanosine analog with antiviral effects that have not been fully delineated, but clearly provide additive SVR benefit when combined with PegIFN. The drug is given orally at a dose based on patient weight that was been shown to be a major factor in HCV response. The drug cannot be used alone, and when combined with PegIFN poses additional adverse effects, especially anemia. RBV is a proven teratogen.

Boceprevir and Telaprevir: These two agents were the first oral DAAs introduced in 2011, having benefit as inhibitors of the NS3/4A serine protease of the HCV viral particle. They were originally added to PegIFN plus RBV therapy since HCV resistance developed if the drugs were used alone. These drugs are no longer recommended for use in HCV and have been withdrawn from the market. Nevertheless, it is important to be aware of these drugs since some HCV treatment-experienced nonresponders have received these agents in the recent past. Disadvantages of these agents included a significant number of required daily doses, the need for administration with food, a large number of drug interactions, prevalent adverse effects, and cost.

Simeprevir (Olysio®): The agent was the first of the “second generation” DAAs, introduced in November 2013. It also is a NS3/4A serine protease inhibitor, but requires only once-daily oral dosing. While studied with PegIFN plus ribavirin, it is now recommended in regimens with sofosbuvir. A genetic variant characterized by a NS3 Q80K polymorphism promotes resistance, and genotype 1 treatment-experienced patients may be screened for the variant. The adverse effect profile is less than with other protease inhibitors and consists mainly of dermatological effects, including severe photosensitivity reactions that should be monitored. However, CYP450 3A drug interactions are a concern with simeprevir.

Sofosbuvir (Solvadi®): Approved in December 2013, sofosbuvir has possibly had the greatest impact of the DAAs since it marked the first use of all-oral drug regimens to treat chronic HCV. It is a nucleotide analog NS5B polymerase inhibitor that is available as a single drug or in a combination preparation with ledipasvir. In either case, it is given as a once-daily oral tablet. Sofosbuvir is well tolerated with adverse effects including headache and fatigue and it appears to pose little risk of HCV resistance (although it is not used alone). Its metabolism does not involve the CYP450 system resulting in fewer drug interactions, although it is a p-glycoprotein substrate. Sofosbuvir is primarily cleared through the urine and accumulates in renal impairment; the optimal dosage in the patients with a creatinine clearance less than 30 ml/min is unknown.

Ledipasvir-sofosbuvir (Harvoni®): Ledipasvir is an inhibitor of the HCV NSSA protein replication complex and is available only in the once-daily oral tablet combination with sofosbuvir. The drug product was approved in October 2014 and rapidly incorporated to treatment.
recommendations for chronic HCV. The dosing convenience is complimented by SVR rates consistently over 90% after 12 weeks of treatment in both treatment-naïve and treatment-experienced HCV genotype 1 patients. It also has the advantage of being effective in patients who were nonresponders to HCV regimens that included one of the “first-generation” protease inhibitors. Adverse effects are well tolerated and similar to those of sofosbuvir alone. Drug interactions include those of sofosbuvir but also importantly include gastric acid suppressants that decrease ledipasvir absorption.

**Viekira Pak®:** This combination drug therapy approved in December 2014 includes three drugs, ombitasvir, paritaprevir, and ritonavir, combined in one tablet that is packaged with two tablets of dasabuvir. Ombitasvir is a NS5A inhibitor, paritaprevir is a NS3/4A protease inhibitor whose concentration is “boosted” by the ritonavir, and dasabuvir is NS5B polymerase inhibitor. The combination is used only for genotype 1, recommended for use with or without RBV, and for 12 or 24 weeks depending on the presence of cirrhosis. While the dosing is slightly more complicated than other regimens, this also is an all-oral drug therapy. Adverse effects are well tolerated, but occur more often if combined with RBV. As might be expected, drug interactions are more common and affect both the CYP450 and p-glycoprotein systems.

**Daclatasir (Daklinza®):** The most recent drug approved in July 2015 for chronic HCV, daclatasir is a NS5A replication complex inhibitor. It was first approved in the US for treatment of genotype 3, but quickly was incorporated into recommended regimens for genotypes 1 and 2. The oral drug is given once-daily in combination with sofosbuvir, with or without RBV. The drug is well tolerated with adverse effects of headache, fatigue, nausea, and diarrhea. It is unique in having daily dose recommendations based on concomitant drugs that affect the CYP3A system. As with other HCV drugs that are CYP3A substrates, potential drug interactions must be assessed.
### Table 15: Drugs used in chronic HCV $^{1,11,35,38}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical dosage</th>
<th>Adverse effects</th>
<th>Financial assistance program</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN</td>
<td>180 mcg SC weekly (alfa-2a)</td>
<td><strong>Early:</strong> flu-like symptoms, injection site reactions</td>
<td><strong>Pegasys Access Solutions</strong>®</td>
</tr>
<tr>
<td></td>
<td>1.5 mcg/kg SC weekly (alfa-2b)</td>
<td><strong>Late:</strong> mood alterations, nausea, anorexia, insomnia, endocrine alterations, neutropenia, thrombocytopenia</td>
<td><strong>SP Cares Hep</strong>®</td>
</tr>
<tr>
<td>RBV</td>
<td>500 mg po twice daily ($\leq$75 kg)</td>
<td>Rash, pruritis, dry cough, hemolytic anemia, fatigue, GI complaints</td>
<td></td>
</tr>
<tr>
<td></td>
<td>600 mg po twice daily (&gt;75 kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>150 mg po daily with food</td>
<td>Rash, pruritis, photosensitivity, hyperbilirubinemia</td>
<td><strong>Olysio Support</strong>®</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>400 mg po daily</td>
<td>Fatigue, headache</td>
<td><strong>Support Path</strong>®</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>90 mg/400 mg po daily</td>
<td>Fatigue, headache</td>
<td><strong>Harvoni Support Path</strong>®</td>
</tr>
<tr>
<td>Viekira Pak®</td>
<td>Omb 25 mg/Par 150 mg/Rit 100mg – 2 tabs po in AM; Das 250mg po bid</td>
<td>Fatigue, nausea, pruritis, skin reactions, insomnia, asthenia</td>
<td><strong>Abbvie ProCeed</strong>®</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>60 mg po daily</td>
<td>Fatigue, headache, nausea, diarrhea</td>
<td><strong>PatientSupportConnect.com</strong>®</td>
</tr>
</tbody>
</table>

PegIFN = pegylated interferon; RBV = ribavirin; Omb = ombitasvir; Par = paritaprevir; Rit = ritonavir; Das = dasabuvir
### Table 16: Drug Interactions with Direct-Acting Antivirals & Selected Concomitant Medications

<table>
<thead>
<tr>
<th>Concomitant medications</th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Viekira Pak®</th>
<th>Daclatasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric acid suppressants</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Alfuzosin/tamsulosin</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV antiretrovirals&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Azole antifungals&lt;sup&gt;a, b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Buprenorphine/naloxone</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cisapride (not available in US)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol products</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>X (inhaled, intranasal)</td>
<td>X</td>
</tr>
<tr>
<td>Macrolide antimicrobials&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Milk thistle</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Other antiarrhythmics&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase type 5 inhibitors</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Rifamycin antimicrobials</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Salmeterol</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sedatives&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Statins&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment
Page 57 of 89
MNA CE expiration date: 5/13/2018
2. Current guidelines for the treatment of chronic HCV

The AASLD guidelines for the treatment of chronic HCV as reflected in this document are current as of January 15, 2016 (Tables 17 & 18). Guidelines for genotypes 4, 5, and 6 are not addressed in this module but do have AASLD treatment recommendations. Treatment-experienced patients are typically nonresponders to Peg-IFN plus RBV (included in Table 18) but also can be patients who have failed to respond to other regimens such as ones that included telaprevir or boceprevir or a newer DAA (For these regimens, the reader should consult current guidelines). It is important that the reader appreciates that HCV treatment guidelines are continuously and rapidly updated by the AASLD as new drugs become available. Because of the healthcare impact, research of new drugs for HCV is very active, as demonstrated by the recent approvals of many new DAA agents.

Table 17: Current AASLD guidelines for the treatment of chronic HCV genotype 1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment Group</th>
<th>Cirrhosis</th>
<th>AASLD recommended regimens</th>
<th>Treatment duration</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Naïve</td>
<td>No</td>
<td>1. daclatasvir + sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. ledipasvir/sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Viekira Pak + RBV</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. simeprevir + sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>Naïve</td>
<td>Yes</td>
<td>1. daclatasir + sofosbuvir</td>
<td>24 weeks</td>
<td>With or without RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. ledipasvir/sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Viekira Pak + RBV</td>
<td>24 weeks</td>
<td>With or without RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. simeprevir + sofosbuvir</td>
<td>24 weeks</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>experienced</td>
<td>No</td>
<td>1. daclatasir + sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. ledipasvir/sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Viekira Pak + RBV</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. simeprevir + sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>1a or 1b</td>
<td>Experienced</td>
<td>Yes</td>
<td>1. daclatasir + sofosbuvir</td>
<td>24 weeks</td>
<td>With or without RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. ledipasvir/sofosbuvir</td>
<td>24 weeks</td>
<td>Decrease to 12 weeks if</td>
</tr>
<tr>
<td>Genotype</td>
<td>Treatment Group</td>
<td>Cirrhosis</td>
<td>AASLD recommended regimens</td>
<td>Treatment duration</td>
<td>Comment(s)</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>-----------</td>
<td>---------------------------</td>
<td>--------------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Naïve</td>
<td>No</td>
<td>1. daclatasir + sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. ledipasvir/sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Viekira Pak</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. simeprevir + sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Naïve</td>
<td>Yes</td>
<td>1. daclatasir + sofosbuvir</td>
<td>24 weeks</td>
<td>With or without RBV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. ledipasvir/sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Viekira Pak + RBV</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. simeprevir + sofosbuvir</td>
<td>24 weeks</td>
<td>With or without RBV</td>
</tr>
</tbody>
</table>

- **a** Dose of daclatasir in any regimen may need to be adjusted based on concomitant drugs
- **b** Viekira Pak = paritapevir/ritonavir/ombitasvir plus dasabuvir
- **c** Experienced= nonresponder on prior PEG-IFN + RBV only (does not include other regimens)
- **d** Compensated cirrhosis, not active at time of treatment

RBV = ribavirin
### Table 18: Current AASLD guidelines for the treatment of chronic HCV genotypes 2 & 3

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment Group</th>
<th>Cirrhosis</th>
<th>AASLD recommended regimens</th>
<th>Treatment duration</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>naïve</td>
<td>No</td>
<td>1. daclatasir + sofosbuvir</td>
<td>12 weeks</td>
<td>Preferred if RBV intolerant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. sofosbuvir + RBV</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>naïve</td>
<td>Yes⁴</td>
<td>1. daclatasir + sofosbuvir</td>
<td>16 weeks</td>
<td>Preferred if RBV intolerant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. sofosbuvir + RBV</td>
<td>16 weeks</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>experienced</td>
<td>No⁶</td>
<td>1. sofosbuvir + RBV</td>
<td>16-24 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. sofosbuvir + RBV + PEG-IFN</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>naïve</td>
<td>No</td>
<td>1. daclatasir + sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. sofosbuvir + RBV + PEG-IFN</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>naïve</td>
<td>Yes</td>
<td>1. daclatasir + sofosbuvir</td>
<td>24 weeks</td>
<td>With or without RBV</td>
</tr>
<tr>
<td>3</td>
<td>experienced</td>
<td>No</td>
<td>1. daclatasir + sofosbuvir</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. sofosbuvir + RBV + PEG-IFN</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>experienced</td>
<td>Yes</td>
<td>1. daclatasir + sofosbuvir + RBV</td>
<td>24 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. sofosbuvir + RBV + PEG-IFN</td>
<td>12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

---

³⁸ Compensated cirrhosis, not active at time of treatment

³⁸ No current recommendations for patients with cirrhosis

PEG-IFN= pegylated interferon; RBV = ribavirin

---

### 3. Summary & future challenges in the drug treatment of chronic HCV

New drug therapy advances in the treatment of chronic HCV have been recent and rapid, and it can be expected that other effective drugs will be approved in the near future. As such, the AASLD guidelines should always be reviewed for the most recent guidelines that incorporate newly released drugs. The development of recent DAAs has clearly advanced HCV treatment by providing convenient oral drug therapy given for a much shorter duration of therapy, with dramatically increased efficacy as well as greatly improved adverse effect profiles. However, a
major clinically-relevant issue of drug interactions surrounds each new regimen (Table 16). And, the optimal approach to retreatment of failures with the new DAAs and the issue of HCV resistance to the new agents are current unresolved issues. Moreover, the cost of treatment represents a current barrier to universal use in all persons with chronic HCV.

There is no doubt that the greatest challenge surrounding the successful treatment of chronic HCV in the US is now the cost of therapy that in turn limits access to effective therapy. The cost of a course of therapy with the new DAAs is typically between $85,000 and $150,000. Data are available to suggest current HCV therapy is cost-effective in probably all patients, but also demonstrate the need for additional resources in the present system. Insurers have responded by limiting coverage of treatment to patients who meet certain criteria such as advanced fibrosis as defined by the METAVIR score, or by implementing expensive patient copays. Insurer approvals are mostly based on AASLD recommendations regarding which chronic HCV patient groups are “high” and “highest” priority for treatment, although the organization advocates treatment in all patients with chronic HCV unless they have a short life expectancy due to causes other than liver disease. Categorization of the highest priority treatment groups reflects that patients at greatest risk for liver complications from HCV are likely to receive more immediate drug therapy benefits (Table 19). Manufacturers of the new DAAs have patient assistance programs but the cost of therapy limits access even by most financially stable patients (Table 15). The manufacturers have come under recent government scrutiny to justify the expense of the new HCV drugs.

Table 19: Current AASLD recommendations for high and highest priority patient candidates for immediate chronic HCV treatment

<table>
<thead>
<tr>
<th>High Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>• METAVIR F2 (fibrosis) stage</td>
</tr>
<tr>
<td>• HIV or HBV coinfection</td>
</tr>
<tr>
<td>• Coexistent liver disease due to other cause (e.g., nonalcoholic steatohepatitis)</td>
</tr>
<tr>
<td>• Debilitating fatigue</td>
</tr>
<tr>
<td>• Insulin-resistant Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>• Porphyria cutanea tarda</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highest Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>• METAVIR F3 (advanced fibrosis) or F4 (compensated cirrhosis) stage</td>
</tr>
<tr>
<td>• Organ transplant recipients</td>
</tr>
<tr>
<td>• Type 2 or 3 cryoglobulinemia with end-organ manifestations (e.g., vasculitis)</td>
</tr>
<tr>
<td>• Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis</td>
</tr>
</tbody>
</table>
Current knowledge suggests widespread use of HCV screening programs such as IPHARM will result in the identification of a great number of asymptomatic or mildly symptomatic patients who do not yet have liver laboratory function abnormalities or significant inflammation/fibrosis. At present, universal and non-criteria based treatment of chronic HCV does not exist primarily due to the drug therapy cost issue. It has been recently projected that treating all patients with chronic HCV in the US would cost approximately $200 billion, which represents over 60% of the entire US spending on prescription drugs. Nevertheless, the effective treatment of chronic HCV in patients before they develop manifestations of liver disease is also certainly cost-effective when viewed over the lifespan of the patients. Moreover, the treatment of chronic HCV represents an important public health issue by lessening or removing the sources for new infections. The treatment of chronic HCV should be well understood by all healthcare practitioners who can assume a critical educational role, as it will undoubtedly be a great challenge for the US healthcare system in the next decade.

III. Websites for HCV

HCV Guidance: Recommendations for Testing, Managing and Treating Hepatitis C

Hep-drug interactions

CDC Viral Hepatitis-Hepatitis C Information

CDC Hepatitis C General Information

Hepatitis C: Why Should Baby Boomers Be Tested?

HCSP Fact Sheet: Testing Positive-Now What?
IV. References


Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment Page 63 of 89
MNA CE expiration date: 5/13/2018


Viral Hepatitis Update with a Focus on Hepatitis C: Epidemiology, Screening and Treatment
Page 65 of 89
MNA CE expiration date: 5/13/2018


What is Hepatitis C?

Hepatitis C is a viral infection that is spread by blood-to-blood contact. Over many years the virus can damage the liver and result in the loss of liver function or even liver cancer. A person infected with Hepatitis C will not usually have symptoms and may spread the virus to others without knowing they are infected. There are no vaccines for Hepatitis C, but there are medical treatments available to help prevent further damage to the liver and hopefully cure the infection.

Who should be screened for Hepatitis C?

The Centers for Disease Control and Prevention (CDC) and the U.S. Preventative Services Task Force (USPSTF) recommend that individuals born between 1945-1965 receive a one-time screening for Hepatitis C due to increased risk of infection in this age group. Persons who have engaged in behaviors associated with Hepatitis C exposure should also be screened regardless of their age.

What happens during a Hepatitis C screening?

Screening takes 20-40 minutes to complete and it will be done using a drop of blood obtained by a finger stick. The drop of blood will be inserted into a testing solution, and then a testing device will be inserted into the solution. The OraQuick® test will tell whether or not a person tests positive for Hepatitis C antibodies.

What does a positive result mean?

A positive result on this test does not diagnose you with Hepatitis C. A positive result can mean that you have been exposed to Hepatitis C at some point in your life and cleared the virus on your own, but it can also indicate that you have active disease. If you test positive, you should seek further testing from your healthcare provider to verify your Hepatitis C status and determine whether or not treatment is needed.

Yes, I want to be screened for Hepatitis C today

No, I do not want to be screened for Hepatitis C today
Hepatitis C Test Consent Form, Page 2

IPHARM will provide Hepatitis C screening to you today at your request and for the specific purpose of providing you with information that may relate to your health. An explanation of the results and how they may relate to your health will be provided by IPHARM personnel.

What will happen today and what happens to the result record?
IPHARM personnel will conduct the OraQuick® HCV Rapid Antibody Test you have requested, obtain the results, and explain the results to you. You will receive the original copy of the results for your records. If you test positive we are obligated to report these results to the Montana State Health Department in accordance with Montana State Law. The personal information that will be reported is your name, date of birth, address, telephone number and test results. An employee from the Montana State Health Department will contact you to discuss your positive results. IPHARM personnel will record your results for statistical purposes on a data sheet that does not include your name. The results will be used in IPHARM reports complied with all other test results. IPHARM will keep your agreement to be tested and results sheets confidential, separated, and secure. IPHARM further agrees to use personnel trained to provide the OraQuick® test and to follow general methods approved for this tests. IPHARM agrees to exercise due caution in those areas associated with the tests provided.

What do I agree to if I sign below?
By signing below, you indicate you have read and understand this form. You agree to receive testing from IPHARM for the OraQuick® test you have requested. You understand that your result will be kept confidential and that a positive result must be reported to the Montana State Health Department under rule 37.114.204. You agree that IPHARM has no responsibility to contact your health care provider. Finally, you agree to hold IPHARM personnel harmless for acts beyond their control or outside their responsibility in providing you these tests.

Do I need to give these results to my health care provider?
IPHARM strongly encourages you to take your results to your provider when you next schedule an appointment. In some cases, IPHARM may suggest you schedule an appointment with your provider soon. IPHARM reminds you that the OraQuick® screening test result, whether positive or negative, does not provide you or your provider with enough information to make a therapeutic decision about your health. However, the test result may indicate you should have further tests done and/or undertake changes in your life that could improve your health and protect the health of those around you.

Printed name of patient __________________________ Date __________________________

Patient signature __________________________ Signature of IPHARM personnel __________________________
CONTACT INFORMATION

Name (first, last): ____________________________________________

Date of Birth: ______________________________________________

Sex: MALE FEMALE

Race: Caucasian American or Alaskan Indian African American

Hispanic Asian/Pacific Islander Other

Mailing Address: ______________________________________________

City: __________________________ State: _______ Zip Code:_______

Email Address: _____________________________________________

Telephone Number: _________________________________________

Ok to leave a message? Yes No

SPECIMEN IDENTIFIER AND DATE HERE

Anti-HCV Positive: ________________ Anti-HCV Negative: ____________
Appendix B: IPHARM Student HCV Screening Procedure Checklist

Student HCV Screening Procedure Checklist

Step 1: HCV Screening Introduction

_____ Patient was informed about HCV infection and that IPHARM is now offering HCV screenings to its patients using a rapid HCV antibody test that takes 20 minutes.

_____ Patient was informed that the CDC recommends baby boomers (DOB: 1945-1965) be screened for HCV due to the increased prevalence of HCV in this population.

_____ Patient was informed about the benefits of knowing their HCV status (transmission, liver damage, treatment).

_____ Patient was informed the HCV antibody test uses a drop of blood, similar to the other tests offered and it tells whether or not they have HCV antibodies are present.

_____ Patient was informed that the presence of HCV antibodies indicates they were either previously infected with HCV or are currently infected with HCV and follow-up testing may be necessary depending on their results.

Step 2: Documentation

_____ Patient received HCV screening information and opt-out form.

_____ Patients, who do not want to be screened, were offered an HCV informational folder and no further action was taken.

_____ Patients, who want to be screened, received the informed consent document and demographic data sheet.

_____ Patient had the content of the informed consent document explained to them.

_____ Patients signed the informed consent and filled out the demographic data sheet to the best of their ability.

Step 3: Testing Procedure

_____ Check control test log and temperature test log to ensure control tests have been appropriately performed and testing can proceed.

_____ Set-up blood collection materials including biohazard container, gloves, alcohol wipes, gauze, and lancets.
Set-up work station with testing materials including buffer solution, testing device, test stand, and timer.

Follow the OraQuick® HCV: Rapid Antibody Test instructions:

Step 1: Collect blood sample with lancet using aseptic technique.

Step 1b: Mix blood sample in buffer solution.

Step 2: Insert testing device into buffer solution.

Step 3: Read test results between 20-40 minutes.

Refer to Step 4: Patient Counseling: Counsel ALL PATIENTS and complete those steps while waiting for test results.

Interpret Test Results by identifying the C Zone (Control Zone) and T Zone (Test Zone) and select one of the following:

Nonreactive: Line is present in the C Zone

Reactive: Lines, no matter how faint, are present in the C Zone and T Zone

Invalid: 1. A partial line(s) is present in the C Zone and/or T Zone
        2. No line is present in the C Zone
        3. A red background obscures the results.
        (If result is Invalid, then repeat Step 3: Testing Procedure)

Step 4: Patient Counseling

ALL PATIENTS

Patient was educated about HCV and the benefits of getting tested were reiterated.

Patient was educated about HCV transmission (blood-blood contact, high-risk behaviors and exposures, HCV lifespan outside of body, how it is not transmitted).

Patient was prepared to receive test results whether reactive or nonreactive.

Patient was invited to ask questions.

(Optional) If patient admits to one or more high-risk behaviors and exposures, then assess if these occurred less than six months ago.
NONREACTIVE

_____ Patient with a nonreactive test was informed HCV antibodies were not detected and they do not have HCV infection.

_____ Patient received nonreactive patient education folder and all content, if possible, was discussed with the patient including:

_____ Persons born between 1945-1965 only need to be screened once, if they have no other risk factors.

_____ HCV transmission prevention

_____ (Optional) If a patient is concerned about a high risk exposures or high risk behaviors in the previous six months, then inform them they will need to be retested in 12 weeks.

REACTIVE

_____ Patient with reactive tests was informed that HCV antibodies were detected, which means they either were previously infected with HCV or are currently infected with HCV.

_____ Patient was informed that 15-25% of people will clear HCV on their own, without treatment but the other 75-85% will test positive for HCV-RNA and be diagnosed with HCV infection.

_____ Patient was informed that they will require a follow-up, diagnostic test called HCV-RNA, which will detect if there is live virus in their blood.

_____ Patient was informed that HCV-RNA testing can be completed by most healthcare providers but further medical evaluation and assessment of treatment options may require a specialist like an infectious disease doctor or a gastroenterologist, which require referral by a primary healthcare provider.

_____ Patient received reactive patient education folder and all content, if possible, was discussed with the patient, including:

_____ Patient was informed most individuals with HCV do not know they are infected and most have no recollection of any high-risk exposures or behaviors.

_____ Patient was informed of how to prevent transmission (sex, blood-contact) to close contacts until they can get confirmatory testing.

_____ Patient was informed that most patients will be asymptomatic but possible symptoms were explained.
Patient was informed about the chronicity of HCV infection and that long-term infection can result in detrimental effects on the liver.

Patient was informed how to keep their liver healthy until they receive a follow-up medical evaluation about the current health status of their liver.

Patient was informed that current pharmaceutical treatment options result in up to a 90% cure rate with 12 week treatment courses and while they are expensive, many are covered by Medicaid and Medicare.

Patients must be informed that we are mandated to send their contact information to their local Health Department and that they will be contacted by a Health Department employee.

Patient was given follow-up outcome card *mailer* and asked to return it to IPHARM in 30 days.
Appendix C: IPHARM OraQuick Test Kit Storage Temperature Log

### IPHARM OraQuick Test Kit and Control Kit Storage Temperature Logs

<table>
<thead>
<tr>
<th>Date/Time</th>
<th>Temperature</th>
<th>Storage Location</th>
<th>Action Required?</th>
<th>Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date/Time</th>
<th>Temperature</th>
<th>Storage Location</th>
<th>Action Required?</th>
<th>Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### IPHARM OraQuick Desired Temperature Ranges

<table>
<thead>
<tr>
<th>Desired Temperature Range</th>
<th>Test Kit Storage</th>
<th>Control Kit Storage</th>
<th>Testing Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>36-86 °F</td>
<td>Refrigeration Optional</td>
<td>Refrigeration Necessary</td>
<td>Standard Room Temperature</td>
</tr>
<tr>
<td>36-46 °F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59-99 °F</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix D: IPHARM OraQuick HCV Control Kit Log

<table>
<thead>
<tr>
<th>Date</th>
<th>Site</th>
<th>Test Kit</th>
<th>Control Kit</th>
<th>Initial</th>
<th>Lot #</th>
<th>Exp Date</th>
<th>Closed</th>
<th>Open</th>
<th>Start Temp</th>
<th>temp</th>
<th>End Temp</th>
<th>temp</th>
<th>Result</th>
<th>Expected Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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- **Run Control Kit**
  - New operator
  - New test kit lot
  - Temperature of test kit storage is outside of 36-46°F

- **Result**
  - Yes (Y): Negative controls yield non-reactive test results.
  - No (N): Negative or positive control test results.

- **Expected Results**
  - OraQuick HCV Control Kit Log

- **Proper Storage**
  - Properly store OraQuick HCV Control Kit in a refrigerator at 36-46°F.

- **Expiration**
  - Store at room temperature or in a refrigerator at 36-46°F.
Appendix E: CDC Hepatitis C General Information

HEPATITIS C

General Information

What is hepatitis?
"Hepatitis" means inflammation of the liver. The liver is a vital organ that processes nutrients, filters the blood, and fights infections. When the liver is inflamed or damaged, its function can be affected.

Heavy alcohol use, toxins, some medications, and certain medical conditions can cause hepatitis. However, hepatitis is most often caused by a virus. In the United States, the most common types of viral hepatitis are Hepatitis A, Hepatitis B, and Hepatitis C.

How is Hepatitis C spread?
Hepatitis C is usually spread when blood from a person infected with the Hepatitis C virus enters the body of someone who is not infected. Today, most people become infected with Hepatitis C by sharing needles, syringes, or any other equipment to inject drugs. Before widespread screening of the blood supply in 1992, Hepatitis C was also spread through blood transfusions and organ transplants. While uncommon, poor infection control has resulted in outbreaks in healthcare settings.

While rare, sexual transmission of Hepatitis C is possible. Having a sexually transmitted disease or HIV, sex with multiple partners, or rough sex appears to increase a person’s risk for Hepatitis C. Hepatitis C can also be spread when getting tattoos and body piercings in unlicensed facilities, informal settings, or with non-sterile instruments. Also, approximately 6% of infants born to infected mothers will get Hepatitis C. Still, some people don’t know how or when they got infected.

Most people who get infected with the Hepatitis C virus develop a chronic, or lifelong, infection.

What is Hepatitis C?
Hepatitis C is an infection of the liver that results from the Hepatitis C virus. Acute Hepatitis C refers to the first several months after someone is infected. Acute infection can range in severity from a very mild illness with few or no symptoms to a serious condition requiring hospitalization. For reasons that are not known, about 20% of people are able to clear, or get rid of, the virus without treatment in the first 6 months.

Unfortunately, most people who get infected are not able to clear the Hepatitis C virus and develop a chronic, or lifelong, infection. Over time, chronic Hepatitis C can cause serious health problems including liver disease, liver failure, and even liver cancer.

What are the symptoms of Hepatitis C?
Many people with Hepatitis C do not have symptoms and do not know they are infected. If symptoms occur, they can include: fever, feeling tired, not wanting to eat, upset stomach, throwing up, dark urine, gray-colored stool, joint pain, and yellow skin and eyes.

When do symptoms occur?
If symptoms occur with acute infection, they can appear anytime from 2 weeks to 6 months after infection. If symptoms occur with chronic Hepatitis C, they can take decades to develop. When symptoms appear with chronic Hepatitis C, they often are a sign of advanced liver disease.

Continued on next page
How would you know if you have Hepatitis C?

The only way to know if you have Hepatitis C is to get tested. Doctors use a blood test, called a Hepatitis C Antibody Test, which looks for antibodies to the Hepatitis C virus. Antibodies are chemicals released into the bloodstream when someone gets infected. Antibodies remain in the bloodstream, even if the person clears the virus.

A positive or reactive Hepatitis C Antibody Test means that a person has been infected with the Hepatitis C virus at some point in time. However, a positive antibody test does not necessarily mean a person still has Hepatitis C. An additional test called a RNA test is needed to determine if a person is currently infected with Hepatitis C.

Can Hepatitis C be treated?

Yes. However, treatment depends on many different factors, so it is important to see a doctor experienced in treating Hepatitis C. New and improved treatments are available that can cure Hepatitis C for many people.

How can Hepatitis C be prevented?

Although there is currently no vaccine to prevent Hepatitis C, there are ways to reduce the risk of becoming infected with the Hepatitis C virus.

- Avoid sharing or reusing needles, syringes or any other equipment to prepare and inject drugs, steroids, hormones, or other substances.
- Do not use personal items that may have come into contact with an infected person’s blood, even in amounts too small to see, such as razors, nail clippers, toothbrushes, or glucose monitors.
- Do not get tattoos or body piercings from an unlicensed facility or in an informal setting.

For more information

Talk to your health professional, call your health department, or visit www.cdc.gov/hepatitis.
### Appendix F: Why Baby Boomers Should Be Tested

#### Why should baby boomers get tested for Hepatitis C?

While everyone can get Hepatitis C, more than 75% of adults infected are baby boomers. People born from 1945 through 1965. Most people with Hepatitis C don’t know they are infected.

- Baby boomers are five times more likely to have Hepatitis C.
- Liver disease, liver cancer, and deaths from Hepatitis C are on the rise.
- The longer people live with Hepatitis C, the more likely they are to develop serious, life-threatening liver disease.
- Getting tested can help people learn if they are infected and get them into lifesaving care and treatment.
- For many people, treatments are available that can cure Hepatitis C and prevent liver damage, cirrhosis, and even liver cancer.

#### Why do baby boomers have such high rates of Hepatitis C?

The reason that baby boomers have high rates of Hepatitis C is not completely understood. Most boomers are believed to have become infected in the 1970s and 1980s when rates of Hepatitis C were the highest. Since people with Hepatitis C can live for decades without symptoms, many baby boomers are unknowingly living with an infection they got many years ago.

Hepatitis C is primarily spread through contact with blood from an infected person. Many baby boomers could have gotten infected from contaminated blood and blood products before widespread screening of the blood supply in 1992 and universal precautions were adopted. Others may have become infected from injecting drugs even if only once in the past. Still, many baby boomers do not know how or when they were infected.

#### What should baby boomers know about Hepatitis C?

Hepatitis C is a serious liver disease that results from infection with the Hepatitis C virus. Some people who get infected with Hepatitis C are able to clear, or get rid of, the virus, but most people who get infected develop a chronic, or lifelong, infection. Over time, chronic Hepatitis C can cause serious health problems including liver damage, cirrhosis, liver cancer, and even death. In fact, Hepatitis C is a leading cause of liver cancer and the leading cause of liver transplants.

People with Hepatitis C:

- Often have no symptoms
- Can live with an infection for decades without feeling sick
- Can be successfully treated with medications

---

**CDC recommends that anyone born from 1945 through 1965 get tested for Hepatitis C.**

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**Continued on next page**
How would someone know they have Hepatitis C?

The only way to know if someone has Hepatitis C is to get tested. Doctors use a blood test, called a Hepatitis C Antibody Test, to find out if a person has ever been infected with Hepatitis C. The Hepatitis C Antibody Test looks for antibodies to the Hepatitis C virus. Antibodies are chemicals released into the bloodstream when someone gets infected.

Hepatitis C Antibody Test results

When getting tested for Hepatitis C, ask when and how test results will be shared. The test results can take anywhere from half an hour to several days or weeks to come back.

Non-reactive or a negative Hepatitis C Antibody Test

- A non-reactive, or negative, antibody test means that a person does not have Hepatitis C.
- However, if a person has been recently exposed to the Hepatitis C virus, he or she will need to be tested again.

Reactive or a positive Hepatitis C Antibody Test

- A reactive, or positive, antibody test means that Hepatitis C antibodies were found in the blood and a person has been infected with the Hepatitis C virus at some point in time.
- A reactive antibody test does not necessarily mean a person still has Hepatitis C.
- Once people have been infected, they will always have antibodies in their blood. This is true if even if they have cleared the Hepatitis C virus.
- A reactive antibody test requires an additional, follow-up test to determine if a person is currently infected with Hepatitis C.

For more information

Talk to a health professional, call the health department, or visit www.cdc.gov/knowmorehepatitis.
Appendix G: HCSP Fact Sheet: Testing Positive-Now What?

Testing Positive – Now What?

Foreword
Testing positive for antibodies to the hepatitis C virus (anti-HCV) may be scary, but now you have information that can improve your health and well-being. This fact sheet will explore what testing positive means, and what you can do about it. Don’t panic – the knowledge you now have will help you make healthier decisions for you and your liver. Information is the key to living well with hepatitis C.

Testing positive for antibodies doesn’t necessarily mean you have hep C
When you test positive for anti-HCV, it means that you have been infected with the hepatitis C virus (HCV). What the test doesn’t tell you is whether you currently have HCV. About 55–85% of people with anti-HCV still have the virus in their body six months after infection. This means that 15–45% people (about 1 in 4) have antibodies, but not the virus. In these people, their immune system was able to “clear,” or get rid of, HCV. If you test positive for anti-HCV, you need to get a confirmatory viral load test to see if you still have HCV. This test measures HCV RNA, or genetic material in the blood. If you have “cleared” or “resolved” the virus, this test will come back “undetectable.” If the test comes back “detectable,” then you are living with chronic (long-term) hepatitis C.

If you don’t know whether you still have HCV, live like you do
If you know you have antibodies to HCV, but have been unable to get the additional confirmation test, you are not alone. The viral load tests are expensive and hard to get without insurance. Since most people who have anti-HCV do have HCV, the best thing to do while you wait for the test is to live like you have hepatitis C, taking good care of yourself and protecting the health of your liver.

If you have hep C, you have time
Once you are confirmed as having hepatitis C, there will probably be many things running through your mind. Hepatitis C is a slow-moving disease, so most likely
HCSP FACT SHEET

Testing Positive – Now What?

You will have a lot of time to make decisions about your health. Take the time to learn about hepatitis C and make the right decisions for yourself. Don’t make any snap decisions in the moment. In fact, you shouldn’t make any important decisions right away – you may still be in shock. There may be some days when you feel balanced and ready to take steps towards a healthier life, and other days when you don’t want to deal with your hepatitis C – this is normal. Take the time to think about what is important for you now, and remember you will have time to make all the decisions you need to make.

Your body, your liver, and hepatitis C
Your liver is the largest internal organ and has over 500 important functions. Almost everything that we eat, drink, smoke, swallow, or absorb through the skin goes through the liver. Since hepatitis C affects the liver and can cause liver damage, you may want to think about what you put into your body so you can minimize the harm to your liver. The most harmful thing for your liver is alcohol, so it’s important to reduce your alcohol intake as much as you can. Eating a healthy, low-fat, low salt diet, drinking lots of water, and getting enough rest and moderate exercise will help your liver do its job.

Disclosure: telling others you have hepatitis C
You may be wondering how to tell others that you have tested positive for HCV. First, you don’t have to tell anyone until you are ready; however, it is important to tell your healthcare provider (who will keep it confidential) because having hepatitis C may influence the medications and tests you get. If you have only a positive antibody test result, you’ll have to decide if you want to disclose now or after your confirmation test. There are two main reasons to tell others: support for yourself and because you think they should get tested for hepatitis C. Think about whom you want to tell, why you want to tell them, how you will tell them, and when and where you will tell them. Make sure you have support by first telling someone who will be there for you.

Preventing transmission to others
While it is important to take care of yourself, you may also have questions about how to make sure you don’t transmit HCV to someone else. HCV is transmitted through direct blood contact – someone else has to get your blood directly into their blood through sharing a needle, a razor, nail clippers, a toothbrush, or anything that may have your blood on it. HCV has been found to survive outside the body for up to four days. Even when blood is present, there also has to be an opening for the blood to get into the other person’s body. It is also possible for HCV to be transmitted through sex or from a mother to her baby during pregnancy or birth, but this doesn’t happen very often. You cannot transmit HCV through hugging, kissing, sharing eating or drinking utensils, or sharing a bathroom.

Next steps: medical care for hepatitis C
In addition to getting your positive antibody test result confirmed, it is important to get additional testing and vaccinations once you know you have HCV. You need to be tested for, and, if needed, vaccinated against hepatitis A and hepatitis B if you have hepatitis C to avoid getting more than one type of hepatitis, which will be hard on your liver. Your doctor will do more tests to see how your liver is doing, and may do a biopsy (removal of a small liver tissue sample) to see if your liver is damaged. You may also want to find out what kind of HCV you have (called genotype) and how much HCV you have in your blood (called viral load). Getting all of these tests will give you and your doctor information so that you can make the best treatment decisions.

Deciding about treatment
There are treatments that may get rid of HCV, but they aren’t for everyone, and some people don’t need treatment. Treatments work better for some people than others. How well it works depends on how long you have been infected, how much your liver is damaged, and other factors. Also, HCV treatment is very expensive and interferon-based therapies can have significant side
Appendix H: Post-test: Viral Hepatitis Update  
(Record responses on examination form)

1. The elevation of which one of the following laboratory tests is most closely associated with jaundice due to hepatitis?  
   a. Alanine transferase  
   b. Alkaline phosphatase  
   c. Bilirubin  
   d. Ammonia level

2. What drug therapy is used to treat ascites in the patient with advanced liver disease?  
   a. Propranolol  
   b. Combination spironolactone plus furosemide diuretic therapy  
   c. Lactulose  
   d. Octreotide

3. Which factor would most closely correlate with an outbreak of hepatitis A (HAV)?  
   a. Poor sanitation in a developing country  
   b. Homosexual activity  
   c. Intravenous drug use  
   d. Exposure to blood in a health care setting

4. Which statement is true regarding treatment of the patient who develops symptomatic acute HAV?  
   a. They should be given a dose of immune serum globulin (ISG)  
   b. Rest, good nutrition, and avoidance of alcohol is the best treatment  
   c. They should be given a dose of ISG and started on the vaccine series  
   d. They should be started on the vaccine series; there is no need for ISG

5. For all EXCEPT which one of the following persons is post-exposure prophylaxis against HAV recommended?  
   a. A household member of an infected person  
   b. A daycare worker in the center with an infected child  
   c. A chef who works in the same food establishment with the infected person  
   d. A coworker in the same office building where the infected person is employed
6. Which of the following statements about hepatitis B (HBV) is false?
   a. All persons who contract HBV have symptoms during the acute infection that allows easy recognition of the infection.
   b. If not treated, neonates & children compared to adults have a greater risk of developing chronic HBV.
   c. The HBV vaccine is recommended for all children.
   d. Hepatitis B immune globulin (HBIG) is used when an unvaccinated person is exposed to a person with chronic HBV.

7. Which laboratory marker is most closely associated with chronic HBV?
   a. Anti-HBs
   b. Anti-HBc
   c. HBsAg
   d. HBeAg

8. For which one of the following laboratory combinations is drug therapy versus observation recommended for chronic HBV?
   a. Positive HBeAg, HBV-DNA titer > 20,000 IU/ml, and ALT < 2x normal
   b. Negative HBeAg, HBV-DNA titer > 20,000 IU/ml, and ALT > 2x normal
   c. Negative HBeAg, HBV-DNA titer >2,000 IU/ml, and ALT 1-2x normal
   d. Negative HBeAg, HBV-DNA titer < 20,000 IU/ml, and ALT normal

9. Which of the following is the most likely adverse effect of interferon that occurs early in therapy (i.e. during the first few weeks)?
   a. flu-like symptoms
   b. depression
   c. neutropenia
   d. thyroid dysfunction

10. Viral resistance in chronic HBV is the greatest concern with which one of the following nucleoside(tide) analog antiviral agents?
    a. Lamivudine
    b. Adefovir
    c. Tenofovir
    d. Entecavir

11. What is the most common genotype for hepatitis C (HCV) in the United States?
    a. Genotype 1
    b. Genotype 2
    c. Genotype 3
    d. Genotype 4
12. All of the following persons would be considered at high risk for HCV EXCEPT?
   a. A 25 year old female who was an intravenous drug user up until 3 years ago.
   b. A 35 year old male who underwent a hip fracture repair with blood supplementation 2 years ago.
   c. A 60 year old male who underwent an open appendectomy in his teenage years.
   d. A 34 yo female who is positive for human immunodeficiency virus (HIV) as a result of indiscriminant sexual activity.

13. According to the CDC guidelines, which of the following populations should be screened for Hepatitis C?
   a. Individuals born between 1945-1965
   b. Individuals with sexual partners who are HCV-positive
   c. Individuals who work in any health care setting
   d. Intranasal drug users

14. Which statement is TRUE regarding HCV disease course?
   a. The majority of persons who contract acute HCV progress to symptomatic jaundice.
   b. The majority of persons who contract HCV will clear the virus after the acute infection.
   c. Of those persons who develop chronic HCV, 80% will progress to cirrhosis & advanced liver disease.
   d. Hepatic carcinoma (HCC) is associated with chronic HCV in some persons.

15. Once an individual tests positive for HCV-antibodies with the OraQuick device, which of the following tests are required to confirm a diagnosis of active HCV infection?
   a. HCV RNA test
   b. Alanine aminotransferase (ALT) test
   c. Repeat HCV-antibody test
   d. HCV antigen test

16. Patients will require follow-up testing if they have had a possible exposure to HCV in the past.
   a. 1 month
   b. 3 months
   c. 6 months
   d. 12 months
17. A patient with chronic HCV responds to treatment with an undetectable HCV-RNA level at the end of the treatment course; eight weeks after treatment, HCV-RNA is once again detectable. What pattern of response best characterizes the patient?
   a. A null responder
   b. A partial responder
   c. A response relapser
   d. A sustained virologic response patient

18. Which of the following regimens provide the best chance of a sustained virologic response (SVR) for HCV genotype 1?
   a. Interferon for 48 weeks
   b. Peginterferon plus ribavirin (RBV) for 24 weeks
   c. Peginterferon plus RBV plus telaprevir for 12 weeks
   d. Sofobuvir/ledipasvir for 12 weeks

19. Which of the following are side effects of daclatasir (Daklinza®)?
   a. Headache
   b. Fatigue
   c. Diarrhea
   d. All of the above

20. Which statement is TRUE regarding use of the newer (since 2013) direct acting antivirals (DAAs) agents for the treatment of chronic HCV?
   a. All the new DAAs must be given multiple times during the day, and adherence is important.
   b. All of the new DAA regimen have fewer adverse effects compared to the regimen of peginterferon plus ribavirin.
   c. All of new DAAs have the advantage of no risk of HCV resistance to the given agent.
   d. All of the new DAAs have the advantage of posing very few drug interactions.
Module: Viral Hepatitis Update

POST-TEST

Participant Information

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3. Date exam completed _______________________

Questions: (Please circle one response per question)

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For credit, please return this completed page to:

MTGEC/IPHARM
Skaggs Building Room 318
University of Montana
32 Campus Drive
Missoula MT, 59812-1522
## APPENDIX I: Evaluation: Viral Hepatitis Update

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4. Reviewing the previous options, how do you plan to implement the information from this module to strengthen your practice, employment or personal goals? (check any that apply)

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6. The test questions were relevant to the module content.

7. Please provide suggestions to improve the online learning experience to meet your needs.

8. Please offer ideas or suggestions for new modules.

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