Hepatitis C Elimination in Indian Country

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NPAIHB
Indian Leadership for Indian Health

NW Tribal Epidemiology Center

Hepatitis C: An Overview

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Introduction

An estimated 3 million to 4 million persons in the United States are chronically infected with HCV, and approximately half are unaware of their status. These individuals may ultimately progress to advanced liver disease and/or hepatocellular cancer (HCC). However, those outcomes can be prevented by treatment, which is rapidly improving and offers the potential of a cure to more patients than has been previously possible.

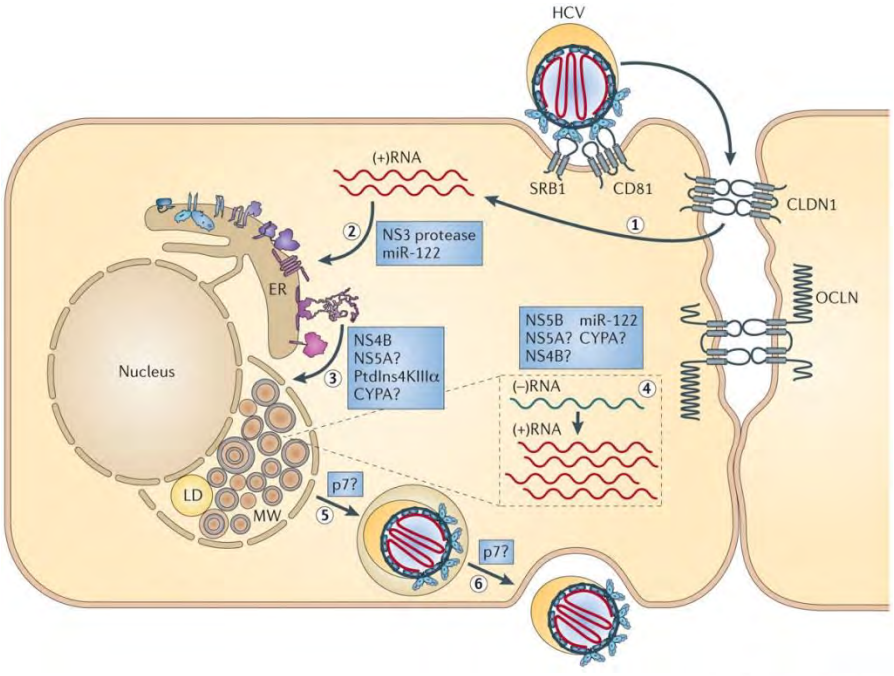
HCV causes more deaths than all reportable infectious diseases combined, including HIV/AIDS, and its impact on public health in Indian Country is considerable. This letter will outline the HCV burden, progression of disease, and medical options to reduce HCV related mortality.

The Cause

HCV is in the flaviviridae family of viruses. Exposure causes acute infection, which can be characterized by mild to severe illness, but is usually asymptomatic. In approximately 75%–85% of persons, HCV persists as a chronic infection, placing infected persons at risk for liver cirrhosis, HCC, and extrahepatic complications that develop over the decades following onset of infection (*CDC, 2012*).

Replication and Lifecycle

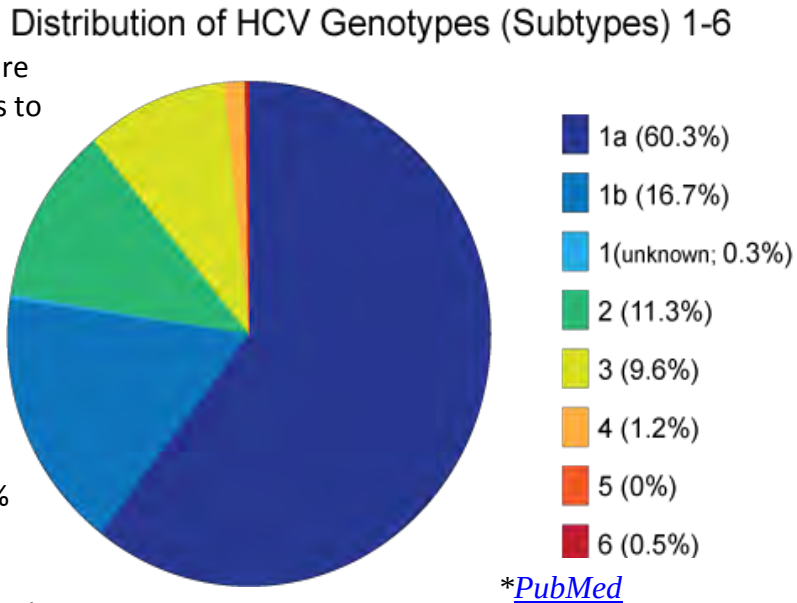
Following initial binding of the hepatitis C virus particle to scavenger receptor class B member 1 (SRB1) and CD81, the particle engages in further interactions with the tight junction proteins claudin 1 (CLDN1) and occludin (OCLN) and finally enters cells by receptor-mediated endocytosis (step 1). The viral RNA genome is



released into the cytoplasm and translated at the rough ER, giving rise to a polyprotein that is cleaved into mature proteins (step 2). Viral proteins, in conjunction with host cell factors, induce the formation of a membranous compartment (designated the membranous web (MW)) composed of single-, double- and multi-membraned vesicles as well as lipid droplets (LDs) (step 3). RNA replication occurs at an unspecified site within the membranous web and proceeds via a negative-sense copy ((–)RNA) that serves as a template for the production of excess amounts of positive-sense progeny RNAs ((+)RNA) (step 4). Assembly of HCV particles probably initiates in close proximity to the ER and lipid droplets, where core protein and viral RNA accumulate. The viral envelope is acquired by budding through the ER membrane in a process that is linked to lipoprotein synthesis (step 5). HCV particles are thought to be released via the constitutive secretory pathway (step 6). Viral and host cell factors that are targeted by inhibitors discussed in this Review are indicated in boxes. The steps of the replication cycle that are promoted by these factors are indicated. CYPA, cyclophilin A; PtdIns4KIIIα, phosphatidylinositol 4-kinase IIIα. (Bartenschlager, Lohmann & Penin, 2013)

Genotypes

An important variable for all patients with chronic HCV is the "genotype" of HCV with which they are infected. This is the strain of the virus to which they were exposed when they were infected, often many years prior to their evaluation, and it is determined by a simple blood test. Genotypes of HCV are genetically distinct groups of the virus that have arisen during its evolution. Approximately 75% of Americans with HCV have genotype 1 of the virus (subtypes 1a or 1b), and 20-25% have genotypes 2 or 3, with small numbers of patients infected with genotypes 4, 5, or 6. Most patients with HCV are found to have only one principal genotype, rather than multiple genotypes.



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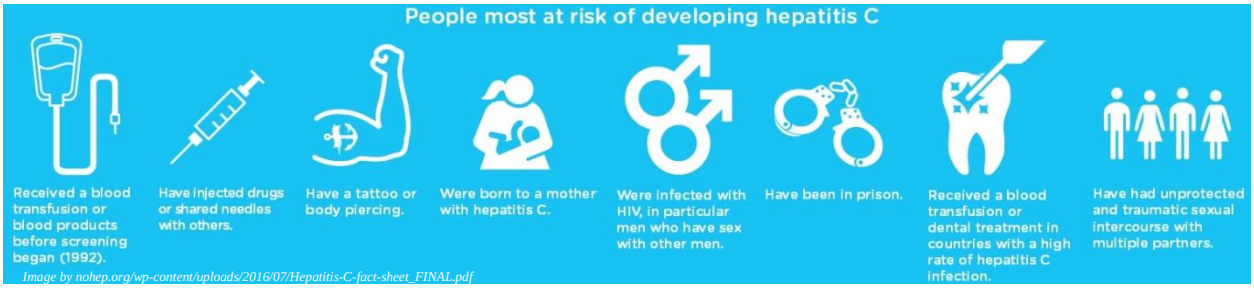
Epidemiology and Transmission

Because HCV is a bloodborne infection, risks for HCV transmission are primarily associated with exposures to contaminated blood or blood products. The highest prevalence of antibody to HCV (anti-HCV) was documented among persons with substantial or repeated direct percutaneous exposures, such as persons who inject drugs (PWID), those who received blood from infected donors, and persons with hemophilia (60%–90%); moderate rates were found among those with repeated direct or unapparent percutaneous exposures involving smaller amounts of blood, such as hemodialysis patients (10%–30%). Persons with unapparent percutaneous or mucosal exposures, including those with high-risk sexual behaviors, sexual and household

contacts of persons with chronic HCV infection (1%–10%), and persons with sporadic percutaneous exposures (e.g., health-care workers [1%–2%]), had lower rates.

The Birth Cohort 1945-1965 are estimated to have 75% of the HCV disease burden, with differing interpretations of exposures via injecting drug use and medical exposures. Factors for the subsequent decline in HCV infections may include safer injecting practice among PWID, infection saturation among PWID, stronger universal precautions in medical settings, and blood donor screening.



The overall prevalence of anti-HCV in the general population of the United States is estimated at 1.5%, or 3.9 million persons (95% confidence interval [CI] = 1.3–1.7; 3.4–4.4 million persons). These data underestimate the actual national prevalence because these surveys do not include samples of incarcerated or homeless persons, populations known to have high prevalence of HCV infection.

The distribution of HCV in Indian Country has mirrored national data. However, disease burden may be very community specific, with data from the Indian Health Service (IHS) indicating seroprevalence ranging from 2% to 12% among persons born 1945-1965. Veteran Affairs (VA) reports 8% of 1945-1965 birth cohort native veterans are anti-HCV positive.

NW AI/AN Epidemiology

Recently, both Oregon and Washington have compiled epidemiologic data on the impact of hepatitis C in their states. The Oregon report entitled "Viral Hepatitis in Oregon" (available at: https://public.health.oregon.gov/DiseasesConditions/HIVSTDViralHepatitis/AdultViralHepatitis/Documents/Viral_Hepatitis_Epi_Profile.pdf) was released in May, 2015; the Washington report, entitled "Viral Hepatitis C in Washington State" (available at: http://www.doh.wa.gov/Portals/1/Documents/Pubs/420-159-HCVEpiProfile.pdf), was released in June, 2016. The data in these two reports has not been corrected for misclassification of AI/AN race, so the disparities described are likely even greater than the current data demonstrates.

- Oregon:
    - Morbidity: Approximately 25 new cases of acute HCV infection are reported annually in Oregon and has been stable during the period 2009—2013. The actual number of cases that go unreported is much higher, as high as 332 new cases each year. AI/AN have the highest rate of acute HCV infection in OR

compared to other races/ethnicities (2.1 cases/100,000 persons compared to 0.6/100,000 for non-Hispanic Whites. Chronic HCV cases number approximately 5,087 annually. The highest rate is again found in AI/AN (127.7/100,000), more than twice the rate of non-Hispanic Whites (57.5/100,000).

- HCV-related hospitalizations numbered 3,917 from 2008—2012 with an average cost of $26,961 per admission. Admissions for treatment of liver cancer, chiefly, hepatocellular carcinoma (HCC) were the most expensive component of these costs averaging $52,345 per admission. HCC was the most common malignant outcome associated with HCV infection with 763 cases report from 1996—2012. In 2012, 47% of all HCC cases were attributed to chronic HCV infection. Again, AI/AN have the highest rates of HCC (4.1/100,000) compared to non-Hispanic Whites (3.1/100,000).

- Mortality: HCV-related mortality in Oregon was higher in 2011 than in the US as a whole 8.7 vs. 4.8 deaths per 100,000 persons. From 2009—2013, Oregon HCV-related deaths mirrored national figures in that most were male (71%) and in the baby-boomer age range, 45—64 (80%). AI/AN in Oregon have the highest rate of HCV-related mortality (17.4 deaths/100,000 persons, almost twice the rate for non-Hispanic Whites (8.9/100,000).

- Washington:
  - Morbidity: The number of acute HCV cases reported in Washington State has risen steadily since 2010. In the latest reporting year (2014), 83 cases of acute HCV were reported for an annual incidence of 1.2/100,000 persons. This represents the tip of the ice-berg – CDC estimates that only 7% of cases are reported so the true number of new Hepatitis C infections could be as high as 1,154. During the period from 2010—2014, AI/AN were over-represented accounting for 6.1% of acute HCV infections, while only making up 1% of the State population in 2014.

  - Chronic HCV infections have remained fairly stable over time in Washington State with 5,967 cases in 2014 (85.6/100,000). The majority of chronic HCV cases have unknown race/ethnicity information (82.8%). AI/AN account for 1.3% of chronic HCV cases where race/ethnicity is identified.

  - During the period 2010—2014, hospitalization rates for HCV infection have nearly doubled from approximately 87/100,000 in 2010 to 160/100,000 in 2014 whereas hospitalizations for hepatitis B and HIV infections have remained stable at around 20/100,000 and 30/100,000, respectively. Nearly all hospitalizations for HCV–related conditions were for emergency or urgent conditions and just under one-third of individuals hospitalized for HCV-related conditions experienced readmission. AI/ANs account for 4% of HCV-related hospitalizations. The age-adjusted rate of hospitalization for AI/ANs was nearly three times the

rate for the non-Hispanic White population of approximately 6/100,000. From 2010—2013, diagnosis of liver and intra-hepatic bile duct cancer was also three times higher for AI/ANs (22.34/100,000) than for non-Hispanic Whites (7.27/100,000). AI/ANs account for approximately 3% of all liver and intra-hepatic bile duct cancers in Washington and 2% liver transplants.

- Mortality: The number of HCV-related deaths in Washington increased for the period from 2000—2014 from 262 (4.4/100,000) to 645 (7.2/100,000). During this period, the age-adjusted mortality rate for AI/ANs has grown faster than for any other race or ethnicity. For the period from 2010—2014, the AI/AN Mortality rate of approximately 17/100,000 persons was approximately three times that of non-Hispanic Whites. AI/AN deaths accounted for about 4% of HCV-related deaths in Washington.

- Screening: Testing at State-funded screening sites showed an overall positivity of 28.8% for 4,876 screening tests performed, ranging from 0% to 65.7% across a variety of testing locations.

Clinical Presentation and Course of Hepatitis C

The natural history of HCV infection remains incompletely understood, in part due to differing research methods used to determine disease course across studies. There also seems to be variability in natural history between infected groups. For example, the risk of progression to cirrhosis after an estimated 20 years of HCV infection was approximately 22% in studies of patients from liver clinics, as compared with 4% in patients from cohort studies of transfusion of infected blood products.(Freeman, et. al, 2001) In general, HCV infection is characterized by the following:

- Frequent asymptomatic acute infection
- Persistent infection following acute infection in 60-85% of those infected
- Persistently elevated or fluctuating ALT elevations*
- *Serum alanine aminotransferase (ALT) levels are elevated in approximately 60-70% of patients with chronic infection, indicating intrahepatic inflammation, but these levels are highly variable and may fluctuate over time. The remaining 30-40% of patients have persistently normal ALT values, with positive anti-HCV and HCV RNA results
- Generally slow, but variable, disease progression

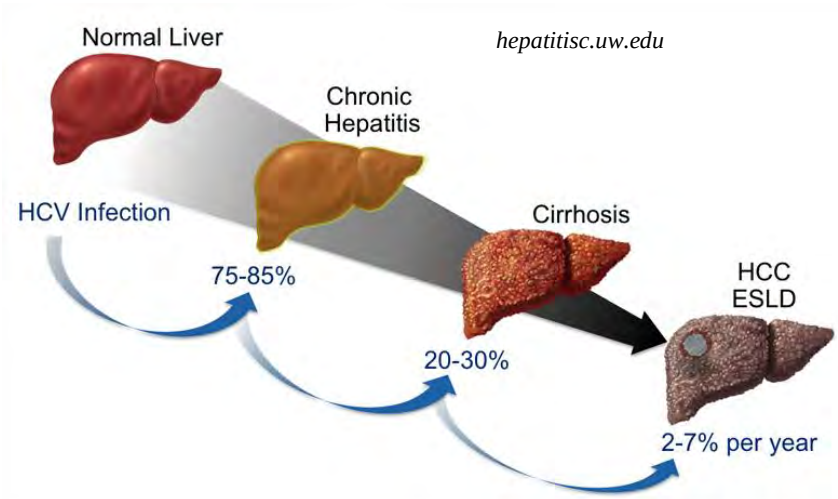
The average time from HCV exposure to seroconversion (detectability of anti-HCV antibody) is between 5 and 12 weeks. HCV RNA is detectable within 1-2 weeks after exposure. Tests for anti-HCV antibodies (serologic tests), include enzyme-linked immunoassay (ELISA) and recombinant immunoblot assay (RIBA). Tests for HCV itself (virologic tests), include qualitative and quantitative polymerase chain reaction (qPCR) and branched DNA (bDNA) assay.

Disease outside the liver due to HCV can be seen in some patients. Such HCV-associated conditions include:

- diabetes mellitus

- rheumatoid arthritis
- keratoconjuctivitis sicca
- mixed cryoglobulinemia
- membranoproliferative glomerulonephritis
- nephrotic syndrome
- porphyria cutanea tarda

Although over a third of all HCV patients likely have detectable cryoglobulins, few develop clinical features of cryoglobulinemia.



According to study data compiled by the VA, median time for progression to cirrhosis was 30 years. Among males over 40 years old who consumed more than 50 grams of alcohol per day, the mean time for progression to cirrhosis was 13 years. In contrast, among HCV-positive women less than 40 years old who consumed no alcohol, the mean time to cirrhosis was 42 years. Because of the variability in rates of progression, it has been suggested that there may be 3 outcome groups: rapid, intermediate, and slow fibrosers. Rapid fibrosers may progress to cirrhosis in 10-15 years, while slow fibrosers may not progress to cirrhosis despite many years of infection. It is hypothesized that more severe liver injury among alcohol users is due to alcohol-induced enhancement of viral replication or increased susceptibility of cells to viral injury.

Another factor that has become accepted as a contributor to fibrosis is fat within the liver (steatosis), which is felt to be either a marker of or a contributor to oxidative stress in the liver. Steatosis is linked to obesity and type 2 diabetes mellitus, so control of these factors has also become accepted as having a role in limiting fibrosis in patients with HCV.

Of concern is the presence of hepatic fibrosis that may progress to the development of cirrhosis. It is estimated that 20-30% of patients with chronic HCV infection will develop cirrhosis over the course of 20-30 years, but that the majority will never progress to this stage. Cirrhosis is associated with portal hypertension and can also lead to the following complications:

- Ascites
- Encephalopathy
- Variceal bleeding

- Coagulopathy
- Spontaneous bacterial peritonitis
- Hepatocellular carcinoma (HCC)

Once patients have experienced one of these "decompensating events," their survival is impaired.

Identification of HCV Status

The following recommendations for HCV testing are intended to augment the *Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease* issued by CDC in 1998 (CDC, 1998). In addition to testing adults of all ages at risk for HCV infection, CDC recommends that:

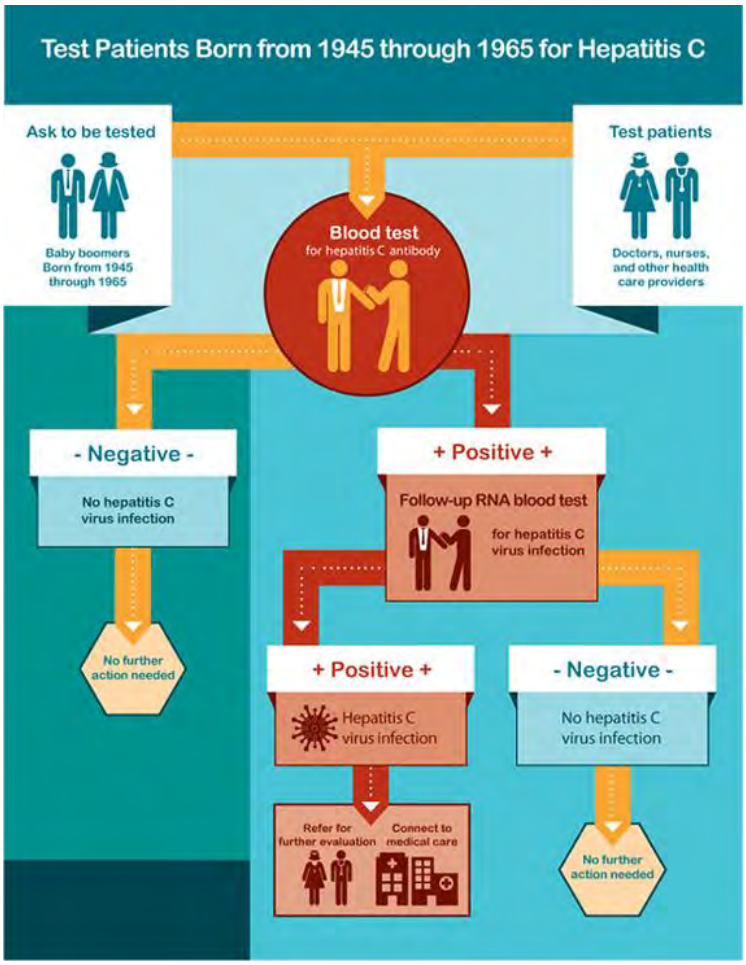
- Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk (Strong Recommendation, Moderate Quality of Evidence), and
- All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions (Strong Recommendation, Moderate Quality of Evidence).

HCV testing of persons in the 1945–1965 birth cohort is consistent with established general public health screening criteria as evidenced by the following factors: 1) HCV infection is a substantial health problem that affects a large number of persons, causes negative health outcomes, and can be diagnosed before symptoms appear; 2) testing for HCV infection is readily available, minimally invasive, and reliable; 3) benefits include limiting disease progression and facilitating early access to treatments that can save significant life years; and 4) testing is cost effective. Such testing would help identify unrecognized infections, limit transmission, and help HCV-infected persons receive beneficial care and treatment before onset of severe HCV-related disease.

Hepatitis C Antibody Testing

Laboratory testing methods for HCV included in these recommendations were established by CDC's *Guidelines for Laboratory Testing and Result Reporting of Antibody to Hepatitis C Virus* in 2003. No new methods are introduced in these recommendations. HCV testing should be initiated with an FDA-approved test for antibody to HCV (anti-HCV). These assays are highly sensitive and specific. An HCV point-of-care assay that can provide results in <1 hour is available for clinical use. An immunocompetent person without risks for HCV infection who tests anti-HCV negative is not HCV-infected and no further testing for HCV is necessary. Additional testing might be needed for persons who have ongoing or recent risks for HCV exposure (e.g., injection-drug use) and persons who are severely immunocompromised (e.g., certain patients with HIV/AIDS or those on hemodialysis).

A person whose anti-HCV test is reactive should be considered to either 1) have current HCV infection or 2) have had HCV infection in the past that has subsequently resolved (i.e., cleared). To identify persons with active HCV infection, persons who initially test anti-HCV positive should be tested by an HCV nucleic acid test (NAT).



Hepatitis C Nucleic Acid Testing : An FDA-approved HCV NAT (also referred to as an "HCV RNA test") should be used to identify active HCV infection among persons who have tested anti-HCV positive; FDA-approved tests include both quantitative HCV NATs (for HCV viral load) and qualitative NATs (for presence or absence of viremia). Persons who test anti-HCV positive or have indeterminate antibody test results who are also positive by HCV NAT should be considered to have active HCV infection; these persons need referral for further medical evaluation and care. A person who is anti-HCV positive but who tests negative by HCV NAT should be considered to not have active HCV infection.

Other HCV-Related Testing Issues: Quantitative NATs assess the level of viremia in the bloodstream expressed as HCV viral load. Although viral load is a critical marker for the effectiveness of treatment, it is not a reliable indicator of stage of disease. Similarly, liver enzyme tests (i.e., alanine aminotransferase [ALT]) reflect the level of liver inflammation at the time of the test, but are not correlated consistently with the stage of liver disease. ALT levels are subject to fluctuations associated with many factors other than infection, including BMI and use of alcohol or medication.

<u>Evaluation of HCV positive patients</u>

Patients need to be assessed for other co-morbidities that can affect the progression of disease and treatment such as diabetes mellitus, alcohol intake, HIV, and hepatitis A/B vaccination status. Foremost, stage of liver disease and liver function are critical to patient prognosis and course of action. Liver staging is generally done via biomarkers and METAVIR scoring rather than liver biopsies.

Prior to treatment, additional labs include the following checklist:

Hepatitis C Treatment Checklists

Prior to Treatment

Labs

Immediately prior:	___ Pregnancy test (if applicable)	Miscellaneous:
	___ Uric Acid (with ribavirin)	___ Hepatitis A (If vaccine status is unknown, draw HAV total)
Within 1 month:	___ CBC with differential	___ Hepatitis B (If vaccine status is unknown, draw HBsAg & HBsAb)
	___ CMP [1]	___ PHQ-9 baseline
	___ PT/INR	___ AUDIT-C
	___ HCV RNA	___ Counsel about pregnancy prevention
Within 3 months:	___ Genotype confirmation	___ Review & sign Treatment Agreement
	___ HBV DNA (if HBV cAb or sAg +)	
Within 6 months:	___ AFP	
	___ TSH	
	___ A1C or Fasting Glucose	
	___ Vitamin D 25OH (treat if deficient)	
Within 1 year:	___ HIV screening	
	___ NS5A RAV (genotype 3 only)	
Once:	___ IL-28b (if considering 8 weeks)	

Evaluation of Child-Pugh Classification of Cirrhosis

This metric assesses the severity of cirrhosis. The calculator is available at http://www.qxmd.com/calculate/child-pugh-score and a management strategy table is available here: http://www.hepatitis.va.gov/provider/guidelines/2009cirrhosis.asp#t-1

Evaluation of Hepatic Fibrosis and Cirrhosis

The fibrosis is graded on a 5-point scale from 0 to 4.

Fibrosis score:

F0 = no fibrosis
F1 = portal fibrosis without septa
F2 = portal fibrosis with few septa
F3 = numerous septa without cirrhosis
F4 = cirrhosis

These can be calculated using routine laboratory results via APRI and Fib4 scoring methods, which utilize liver enzymes, platelet counts, and age to calculate METAVIR. For ease of use, METAVIR clinical calculators are available here:

- http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
- http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

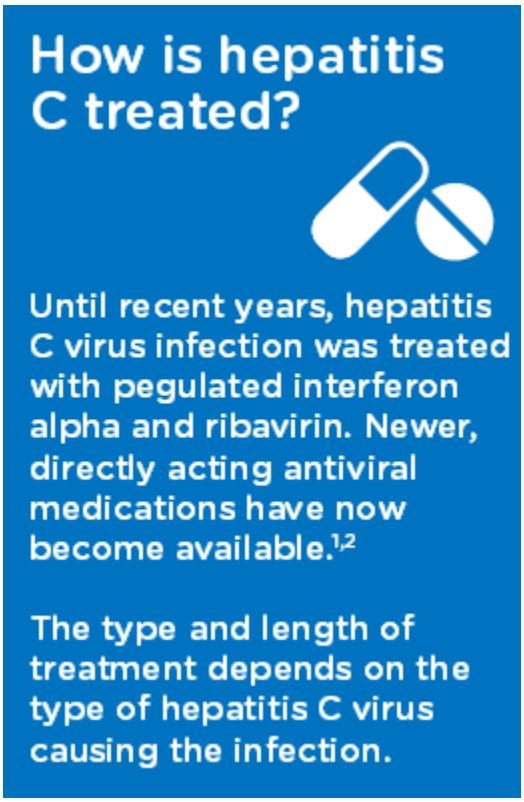
These calculations can be incorporated into HCV patient panels to enable sites to auto-calculate METAVIR scores and prioritize patients for treatment.

Transient elastography (FibroScan) is a new, non-invasive, rapid, and reproducible method allowing evaluation of liver fibrosis by measurement of liver stiffness. It is has higher accuracy for measuring liver stiffness that can be translated into a METAVIR score, particularly at the higher end of the METAVIR scale.

If cirrhosis is detected, hepatocellular surveillance is necessary, with an ultrasound every 6 months, with follow up imaging via phased CT if indicated.

Other management considerations of cirrhosis and portal hypertension often associated with cirrhosis can be found here: http://www.hepatitis.va.gov/provider/guidelines/2009cirrhosis.asp

Treatment of Hepatitis C



New treatments for HCV are shorter (usually 12 weeks), and have a sustained virological clearance (SVR, or clinical cure) of over 90%. These treatments are well tolerated, with few side effects. Although specialist input is generally required to finalize the treatment plan based on genotype and other factors, several IHS, Tribal and Urban (I/T/U) sites are successfully treating HCV with a primary care physician or clinical pharmacist as lead for non-complicated HCV patients. Specialist input is generally received via local collaborations or telehealth/telemedicine options freely available to all I/T/U sites.

These new drugs, direct acting antivirals, have enabled interferon-free regimens. The primary drugs for Genotypes 1 through Genotype 3, are

- Harvoni (Ledipasvir/Sofosbuvir)
- Daklinza (Daclatasvir) + Sovaldi (Sofosbuvir)
- Eplcusa (Sofosbuvir+Velpatasvir)

Additional drugs such as Ribavirin or Zepatier (Elbasvir/Grazoprevir) and others may be indicated, as per consultation with a specialist and AASLD guidelines at HCVguidelines.org

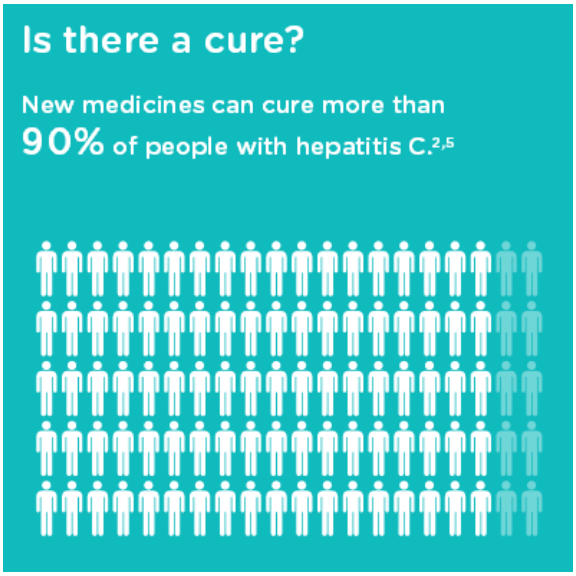
Although the main barrier to treatment has been cost, private and public insurance companies are beginning to cover the two to three month oral regimen for nearly every patient with chronic HCV. This can include patients who are actively injecting drugs and/or using alcohol. In order to provide free or low-cost medicines to those who qualify, patient assistance programs have been created by the pharmaceutical industry. In addition to these services some pharmaceutical companies will work with patients to see if the prescription for their drug is covered by the patient's insurance company or other drug plans. These services can be

accessed on the web or by calling the pharmaceutical company. For a list of programs, please visit:

- http://hepc.liverfoundation.org/resources/what-if-i-need-financial-assistance-to-pay-for-treatment/
- http://hcvadvocate.org/hepatitis/factsheets_pdf/Patient_Assistance.pdf

Rationale for Treatment of HCV

Treatment for HCV as soon as possible reduces the damage associated with viremia. Ongoing studies are showing that patients cured of HCV have a significantly lower risk of developing liver failure, cirrhosis, or liver cancer. There is emerging evidence that SVR can result in regression of cirrhosis/fibrosis, and increase life expectancy to the equivalent of non-cirrhotic patients.



Who to treat

The new treatments have few side effects or contraindications. Clinically, only pregnant women and children are not yet approved for treatment. Drug use, depression, and other factors, while important to address, their role in treatment is mainly for purposes of adherence rather than clinical response. Even late stage (decompensated cirrhosis) patients can be treated successfully and have a meaningful impact of life expectancy. Only patients who have a life expectancy less than one year due to a non-liver related condition are not advised to initiate HCV treatment. Some state Medicaid and other third party programs have clinical (stage 3 or 4) or sobriety requirements that are based on limited resources/cost rather than AASLD clinical guidelines.

Proposed NPAIHB Project to Eradicate HCV among NW AI/AN population

A sample policy for I/T/U facilities to provide a range of HCV services at the primary care level has been made available, and can be found online at http://www.npaihb.org/wp-content/uploads/2016/12/HCV-Guidelines-FINAL-12202016-1.docx. Consider adapting this template as needed to reflect your local conditions and priorities.

References

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IHS, Tribal and Urban Indian Healthcare HCV Guidelines

The Indian Health Service created a sample policy template for HCV screening, follow up and treatment. The following is a template, and as such it is not comprehensive and does not mandate any clinical activities. It does provide a sample policy for I/T/U facilities to provide a range of HCV services at the primary care level, and should be adapted as needed to reflect local conditions and priorities. An HCV policy can be instrumental for clinical staff to understand HCV patient needs, clinical algorithms, and best practices. For further questions or support, contact Dr. Jonathan Iralu, Chief Clinical Consultant, Infectious Disease, jonathan.iralu@ihs.

GUIDELINES FOR SCREENING, MANAGEMENT AND PRE-TREATMENT WORK-UP FOR HEPATITIS C VIRUS (HCV) WITHIN IHS, TRIBAL AND URBAN INDIAN HEALTHCARE FACILITIES

This template is a sample policy for HCV screening, follow up, and treatment. This is a template, and as such it is not comprehensive and does not mandate any clinical activities. It does provide a sample policy for I/T/U facilities to provide a range of HCV services at the primary care level, and should be adapted as needed to reflect local conditions and priorities. An HCV policy can be instrumental for clinical staff to understand HCV patient needs, clinical algorithms, and best practices. American Indians/Alaska Natives have the highest rate of mortality from HCV all I/T/U facilities are encouraged to provide early detection and linkage to care. For further questions or support, contact Dr. Jonathan Iralu, Chief Clinical Consultant, Infectious Disease, jonathan.iralu@ihs.gov

PURPOSE

To expand screening, management and pre-treatment care for HCV infection.

BACKGROUND

In the United States, an estimated 3 million persons are chronically infected with HCV. [1] Compared to other racial and ethnic groups, AI/ANs experience a higher rate of acute HCV incidence and one that has increased more quickly. [2] Compared to whites, AI/ANs experience a three-fold higher death rate from chronic liver disease—one of the multiple complications of chronic HCV infection. [3]

Certain practices pertaining to the screening, treatment, and management of HCV can prolong the length and quality of life of chronically infected patients. The American Association for the Study of Liver Diseases, the U.S. Preventive Services Task Force, and the Centers for Disease Control and Prevention endorse the below practices, as will IHS henceforth.

Among those with HCV in the U.S., 50% do not realize they are infected.[4] To identify HCV-infected patients, IHS clinicians should screen high-risk patients and all patients born from 1945 to 1965 for the presence of HCV antibodies. Patients born 1945-1965 accounts for the majority of HCV infections due to various causes including medical exposures or having injected drugs during in the 1950s-1980s.[5] Clinicians should confirm patients testing positive for HCV antibodies for HCV infection. After confirming HCV infection, clinicians should continue with a a pre-treatment checklist and in consultation with a specialist when needed, start patients on appropriate treatment regimens and continuously monitor patients' progress until they reach a cure.

A number of individuals in the IHS patient population have been diagnosed with HCV, but have never been linked to treatment. Over a 30-year period, an estimated 85% of patients with acute

HCV infection will go on to develop chronic HCV infection, 34% of patients will go on to develop cirrhosis, and 9% of patients will go on to develop hepatocellular carcinoma. Currently, effective treatments for HCV can reduce HCV viral loads to virtually non-detectable levels without the need for pegylated interferon, a medication associated with a longer duration of treatment and more severe side effects than other treatments. To prevent progression to cirrhosis, hepatocellular carcinoma, and liver failure, clinicians should stage HCV-infected patients, prioritizing patients with advanced liver fibrosis stages to receive immediate treatment. Clinicians should monitor patients with early liver fibrosis stages and also start these patients on treatment as it becomes available.

DEFINITIONS

Hepatitis C Virus (HCV): International Classification of Disease (ICD)-9: 070.41, 070.44, 070.51, 070.54, 070.70 through 070.71; ICD-10: B17.10, B17.11, B18.2, B19.20, B19.21 and HCV screening as Correct Procedural Terminology (CPT) 86803, or as per local Logical Observation Identifiers Names and Codes (LOINC) or laboratory taxonomies for hepatitis antibody testing.

Sustained Virologic Response (SVR): Hepatitis C virus remains undetectable in blood following completion of treatment. SVR is the goal of HCV treatment. SVR, the surrogate marker for HCV cure after completion of therapy is defined as undetectable HCV RNA using a highly sensitive assay 12 weeks following the end of treatment.

High-Risk Patient: A patient not currently diagnosed with HCV, but who has participated in certain behaviors, possesses certain medical conditions, and/or falls into certain categories that increase his or her risk of HCV infection. [6] The following patients should be routinely screened for HCV infection:

- Vietnam Veterans serving between 1964 and 1975
- HIV-positive individuals
- Patients who have ever injected illicit drugs, including those who injected drugs just once or a few times many years ago
- Patients with certain medical conditions, such as those with hemophilia with receipt of clotting factor concentrates before 1987, those with a current or history of long-term hemodialysis, and those with persistently abnormal alanine aminotransferase levels
- Patients who received a transfusion or organ transplant before July 1992 or received blood from a donor who later tested HCV-positive
- Patients with recognized exposure, for example, health care workers exposed after needle sticks, sharps or mucosal exposures to HCV-positive blood, and children born to HCV-positive mothers at 18 months of age or older

RESOURCES

National guidelines support the following recommendations. Each recommendation is referenced to an online resource.

HCV SCREENING

Screen for HCV-infected patients

1. Clinicians should screen the following categories of patients for HCV antibodies:
    a. Patients born from 1945 to 1965 (one-time screening), which national data has shown constitutes 75% of reported cases [5]. Additional age ranges may be included in this screening where local data suggests an elevated HCV burden may exist.
    b. Patients determined as high-risk (routine screening unless otherwise noted):
        i. Vietnam Veterans serving between 1964 and 1975
        ii. HIV-positive individuals (at least annual screening for HIV-positive men who have sex with men)
        iii. Patients who have ever injected illicit drugs, including those who injected drugs just once or a few times many years ago (at least annual screening for current injection drug users)
        iv. Patients with certain medical conditions, such as those with hemophilia with receipt of clotting factor concentrates before 1987, those with a current or history of long-term hemodialysis, and those with persistently abnormal alanine aminotransferase levels
        v. Patients who received a transfusion or organ transplant before July 1992 or received blood from a donor who later tested HCV-positive
        vi. Patients with recognized exposure, for example, health care workers exposed after needle sticks, sharps or mucosal exposures to HCV-positive blood, and children born to HCV-positive mothers

Test for HCV antibodies

1. Clinicians should screen for HCV in patients identified as belonging to the above categories using immunoassays, such as the OraQuick HCV Rapid Antibody Test (OraSure Technologies) or an FDA-approved, laboratory-conducted HCV antibody assay [7]. The best assay for this purpose is a HCV antibody test with reflex ribonucleic (RNA) confirmation.

Test for HCV RNA and determine viral load

1. Clinicians should perform Nucleic Acid Testing (NAT) for patients with reactive immunoassays (and for patients with non-reactive immunoassays if patients are immunocompromised or have been recently exposed to HCV).
2. Clinicians should consider a reactive immunoassay and a negative NAT result to signify a false positive serology or the patient having cleared infection. Clinicians should link patients with a positive NAT result to care; Clinicians should not repeat NAT for patients with a negative NAT result unless patients have been exposed to HCV within the past 6

months, patients present with clinical evidence of disease, or specimens have been mishandled or improperly stored.

3. Clinicians should determine a quantitative HCV RNA viral load to provide baseline markers to determine treatment progress.
4. Patients who are positive for HCV+ Ab but HCV RNA negative may have spontaneously cleared the virus. This occurs in an estimated 15%-25% of HCV exposed individuals. Such patients need no further follow up for HCV (except counseling on risk behaviors as appropriate) and will test positive for HCV Ab+ during their lifetimes. Consequently, any subsequent testing for HCV in this population subset should immediately include RNA testing.

Perform laboratory evaluation

Upon confirming chronic HCV infection, clinicians should perform the following set of additional laboratory tests (where tests are available):

1. General laboratory evaluation, including complete blood count, platelet count, thyroid function tests, and renal function tests
2. Tests to determine hepatic inflammation, such as alanine aminotransferase or aspartate aminotransferase
3. Tests to determine hepatobiliary disease, such as bilirubin and alkaline phosphatase
4. Tests to determine hepatic function, such as serum albumin and prothrombin time
5. Assays to detect significant co-infections, such as hepatitis A antibody, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, HIV antibody

Perform complete patient history and examination

Upon confirming chronic HCV infection, clinicians should perform complete patient medical histories and physical examinations. Clinicians should determine patients' risk factors for acquiring HCV infection, psychiatric history, significant comorbidities, co-infection with other viruses, stigmata of chronic liver disease, clinical manifestations attributable to HCV infection, history of prior treatment, and previous assessment of liver fibrosis. [8] Upon performing complete patient medical histories and physical examinations, clinicians should treat conditions that may delay HCV treatment and/or prevent patients from obtaining sustained virologic response.

Clinicians should also assess patients' alcohol histories to determine dependence that may delay treatment and/or prevent patients from achieving a sustained virologic response.

Psychiatric history

Whereas HCV treatments including interferon (a medication associated with neuropsychiatric side effects) are no longer necessary to develop a sustained virologic response, clinicians should still assess patients' past or current psychiatric issues during the initial visit. Psychiatric issues

are generally not contraindications for HCV treatment. Upon diagnosing psychiatric issues, clinicians should link patients to psychiatric treatment, as appropriate.

Significant comorbidities

Clinicians should determine secondary causes of liver disease, such as non-alcoholic fatty liver disease, alcoholic hepatitis, or autoimmune hepatitis. Clinicians should also advise obese patients to lose weight prior to beginning HCV treatment, and cessation of alcohol and tobacco use.

Co-infection with other viruses

Clinicians should screen HCV-infected patients for hepatitis A virus, hepatitis B virus, and human immunodeficiency virus (HIV). If patient is not immune to hepatitis A or B, consider vaccination.

Stigmata of chronic liver disease

Clinicians may consider the presence of the following physical signs and symptoms (in decreasing order of the likelihood ratio of cirrhosis) as indicators of cirrhosis: caput medusae/dilated abdominal wall vessels, loss of body/pubic hair, hepatic encephalopathy, gynecomastia, ascites, spider angiomata, palmar erythema, jaundice and scleral icterus, and liver stiffness.

Clinical manifestations

Clinicians should determine extrahepatic clinical manifestations of chronic HCV infection, such as arthralgias, neuropathy, nephropathy, glomerulonephritis, livedo reticularis, lichen planus, and cold agglutinin disease.

History of prior treatment

Clinicians should determine if patients have previously undergone HCV treatment. If patients have failed to obtain sustained virologic response with previous HCV treatment, clinicians should determine the following with regard to previous HCV treatment: medications, duration, timing, patient's degree of adherence, adverse effects, and when possible, viral kinetics and outcome.

Previous assessment of liver fibrosis

Clinicians should determine whether patients have previously had a liver biopsy. For patients who have had a liver biopsy, clinicians should record the date of the biopsy, the sample size, the fibrosis scoring system, and the fibrosis score. Clinicians should also note any previously performed non-invasive tests for determining liver fibrosis scores.

Stage HCV Liver Fibrosis

Although the gold standard to stage hepatic fibrosis is by performing a liver biopsy with histologic analysis, noninvasive testing with ultrasound transient elastography (FibroScan$_{TM}$) or blood test staging methods are widely used, acceptable, and more feasible. These methods include two of the following non-invasive tests for indirect markers of cirrhosis: Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4), and FibroSure.

When using non-invasive tests, if both tests determine the fibrosis score as F1, treatment is optional if patients have no contraindications; if both tests determine the fibrosis score as F2 or above, clinicians should begin patients on antiviral therapy if patient has no contraindications. If tests determine disparate results, clinicians should consider following up with a liver biopsy or FibroScan. [9]

Preventive care and counseling for chronic HCV patients

Before patients begin treatment, have a confirmed positive HCV RNA level, preferably quantitative in nature. A genotype test will also be needed to determine the recommended course of treatment. Clinicians should prioritize patients with advanced or compensated cirrhosis (F3 and F4 fibrosis scores, respectively), patients with severe or extrahepatic HCV, and liver transplant recipients to receive immediate treatment. [10-13]

Patients should also be vaccinated for Hepatitis A and B, if immunity is not detected.

While treatment may depend on a variety of factors, linkage to care for patients with chronic HCV infection should be as timely as possible. IHS sites should determine what is the best course of action for linkage to care that are the most feasible for their patients, based on the overall case load and acuity. Linkage to care can entail multiple options such as external referrals to specialists, or treatment within the facility with on-site (visiting specialist clinic) or remote specialist support (e.g. telehealth) for primary care clinician-led HCV treatment programs.

All HCV-confirmed patients should be counseled in regards to reducing the risk for spread of HCV infection, the risks for sexual partners, and the avoidance of hepatotoxic substances (OTC and prescription drugs, alcohol, and supplement use).

When appropriate, clinicians should counsel patients on weight loss and diet. Clinicians should advise patients about all restrictions and/or considerations before patients begin treatment. A pre-treatment checklist is in the appendix of this policy.

Approach to Monitoring After Receiving HCV Therapy:

The approach to monitoring patients following completion of a course of HCV therapy depends entirely on the patient's response to therapy. Three main scenarios exist: (a) the patient

achieved an SVR, (b) the patient completed therapy but did not achieve an SVR, or (c) the patient had an inadequate treatment course because of adherence problems, intolerance, or laboratory toxicity necessitating premature discontinuation of the treatment regimen.

Monitoring Patients who Achieved an SVR: Patients who have an undetectable HCV RNA at week 12 (or later) after completing HCV therapy are considered to have achieved an SVR. In a review by Welker of 44 studies involving more than 4,228 patients who achieved an SVR with an interferon-based regimen, 97% of patients maintained the SVR during the long-term follow-up period. Some experts will obtain an HCV RNA level 24 weeks after completing treatment in selected patients. In a more recent review by Manns, more than 99.2% of 1002 patients who achieved an SVR12 with interferon- or peginterferon-based therapy maintained undetectable HCV RNA levels for 5 years. Comparable data on the long-term durability of treatment response with all-oral DAA therapy is not yet available, but it is generally thought that SVR12 responses will represent sustained HCV clearance similar to that seen with interferon-based therapy. All patients who achieve an SVR should clearly understand they are not immune to HCV and can become reinfected with HCV. The AASLD/IDSA Guidance stratifies the follow-up for persons who achieve an SVR based on the degree of hepatic fibrosis and the risk of developing reinfection.

- Patients with without advanced fibrosis (Metavir stage F0-F2): These patients do not need special monitoring or follow-up specifically for HCV or liver care. This recommendation is based on data that show patients with SVR following HCV treatment generally do not have further progression of HCV-related liver fibrosis.
- Patients with Advanced Fibrosis (Metavir stage F3-F4): Although fibrosis may improve in these patients, they are considered to have persistent risk, albeit lower than before achieving an SVR, for developing hepatocellular carcinoma. Accordingly, these patients should have surveillance for hepatocellular carcinoma (HCC) with hepatic ultrasound every 6 months. In addition, patients with cirrhosis (F4 fibrosis) should have a baseline upper endoscopy to screen for varices, unless this has previously been done. Patients identified with varices should receive appropriate management and follow-up.
- Patients with Ongoing Risk of HCV Reinfection: Regardless of the degree of hepatic fibrosis, all patients with ongoing risk for acquiring HCV should have periodic assessment for HCV reinfection and counseling on prevention of reinfection. Obtaining HCV antibody does not provide useful information in these individuals with known prior HCV infection since they are highly likely to remain antibody positive. Thus, reassessment should consist of a quantitative HCV RNA level. In addition, for these patients, any flare in liver enzyme tests should prompt evaluation for reinfection with a quantitative HCV RNA level.
- Patients with Persistently Abnormal Liver Tests: Any patient that develops persistently elevated liver tests should undergo evaluation for possible other causes of liver disease, such as alcohol use, iron overload, or fatty liver disease.

Monitoring for Patients who do not Achieve SVR: The AASLD/IDSA guidance recommends the following for patients who did not achieve an SVR with HCV therapy.

- All Patients: For all patients who did not achieve an SVR, follow-up laboratory testing should occur every 6 to 12 months with a hepatic function panel, complete blood count, and international normalized ratio. In addition, these patients should have periodic reevaluation for retreatment, especially as new options become available. It is important these patients receive counseling for alcohol abstinence (or safe use) and avoidance of hepatotoxic medications.
- Patients with Advanced Fibrosis (Metavir Stage F3-F4): These patients should have surveillance for hepatocellular carcinoma with hepatic ultrasound every 6 months. In addition, patients with cirrhosis (F4 fibrosis) should have a baseline upper endoscopy to screen for varices, unless this has previously been done. Patients identified with varices should receive appropriate management and follow-up.

REPORTING

- Health providers in are required to report cases of chlamydia, gonorrhea, syphilis, genital herpes and chancroid to the local health department.
- STI reporting forms are available at: .

QUESTIONS AND RESOURCES

- This sample policy can be adapted for local use. These documents and accompanying information sheets can be found on the IHS HCV Program website: https://www.ihs.gov/Epi/index.cfm?module=epi_hepatitis_resources.

- Questions regarding HCV diagnosis, treatment, patient and partner follow-up, and reporting should be directed to the appropriate local tribal health department or to the respective state HCV program.

- HCV educational resources for providers and tribal health departments are available from the CDC [http://www.cdc.gov/hepatitis/hcv/patienteduhcv.htm] and the Northwest Portland Area Indian Health Board [http://www.npaihb.org/epicenter/project/prt_reports_publications_media_campaigns#HEP-C Brochure and Radio PSAs].

CONTACT INFORMATION FOR LOCAL HEALTH DEPARTMENT

<<insert address for reporting>>

<<insert phone number>>

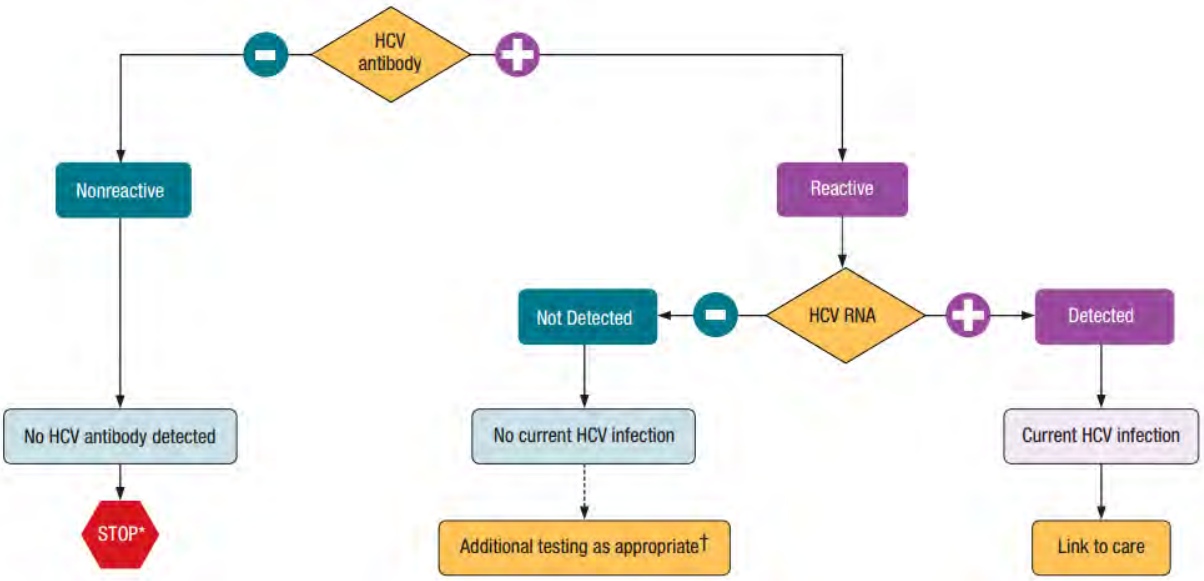
<<insert fax number>>

APPENDIX

(i) Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945-1965. MMWR 2012; Vol. 61 (RR-4)

(ii) Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease. MMWR 1998; Vol. 47 (RR-19)

(iii) Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection
http://www.cdc.gov/hepatitis/HCV/PDFs/hcv_flow.pdf



*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.

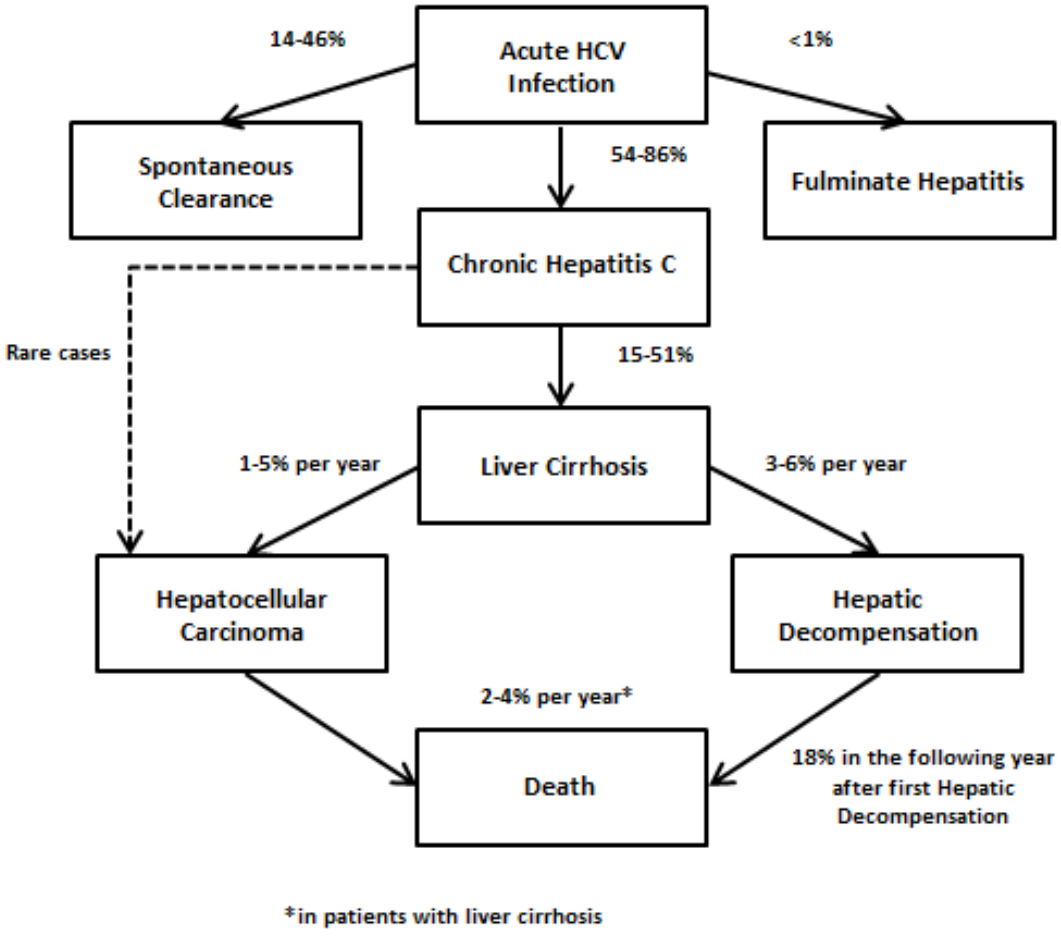
Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18).

(iv) Screening for Hepatitis C Virus Infection in Adults, American Association for the Study of Liver Disease http://www.hcvguidelines.org/

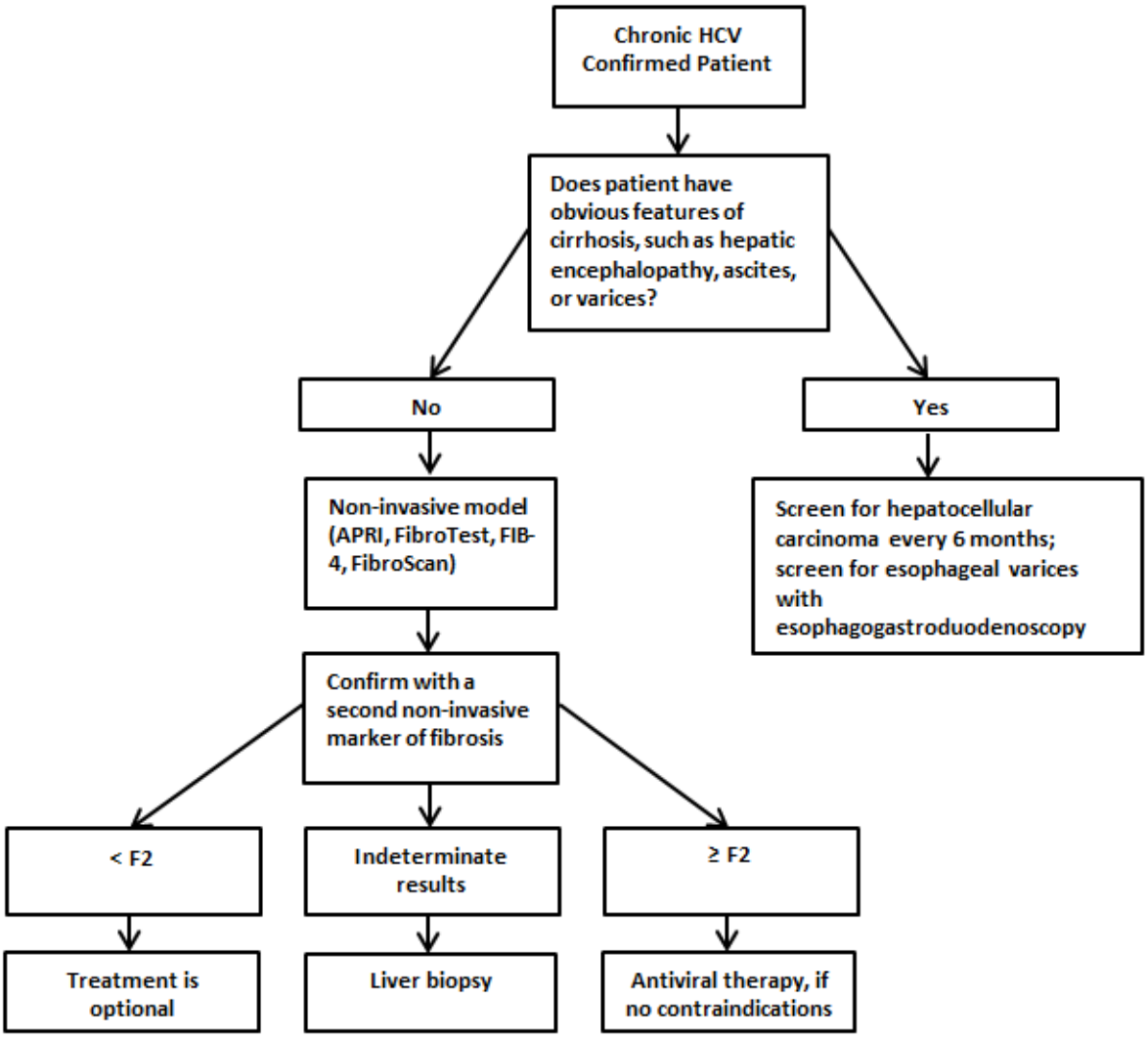
Population	Persons at high risk for infection and adults born between 1945 and 1965
Recommendation	Screen for hepatitis C virus (HCV) infection. Grade: B (The USPSTF recommends this service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial).
Risk Assessment	The most important risk factor for HCV infection is past or current injection drug use. Additional risk factors include receiving a blood transfusion before 1992, long-term hemodialysis, being born to an HCV-infected mother, incarceration, intranasal drug use, getting an unregulated tattoo, and other percutaneous exposures. Adults born between 1945 and 1965 are more likely to be diagnosed with HCV infection, either because they received a blood transfusion before the introduction of screening in 1992 or because they have a history of other risk factors for exposure decades earlier.
Screening Tests	Anti–HCV antibody testing followed by confirmatory polymerase chain reaction testing accurately identifies patients with chronic HCV infection. Various noninvasive tests with good diagnostic accuracy are possible alternatives to liver biopsy for diagnosing fibrosis or cirrhosis.
Screening Interval	Persons with continued risk for HCV infection (such as injection drug users) should be screened periodically. Evidence on how often screening should occur in these persons is lacking. Adults born between 1945 and 1965 and persons who are at risk because of potential exposure before universal blood screening need only be

	screened once.
Treatment	Antiviral treatment prevents long-term health complications of HCV infection (such as cirrhosis, liver failure, and hepatocellular carcinoma). The combination of pegylated interferon (α-2a or α-2b) and ribavirin is the standard treatment for HCV infection. In 2011, the U.S. Food and Drug Administration approved the protease inhibitors boceprevir and telaprevir for the treatment of HCV genotype 1 infection (the predominant genotype in the United States).
Balance of Benefits and Harms	On the basis of the accuracy of HCV antibody testing and the availability of effective interventions for persons with HCV infection, the USPSTF concludes that there is a moderate net benefit to screening in populations at high risk for infection. The USPSTF concludes that there is also a moderate net benefit to 1-time screening in all adults in the United States born between 1945 and 1965.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on screening for hepatitis B virus infection in adolescents, adults, and pregnant women. These recommendations are available at http://www.uspreventiveservicestaskforce.org/.

(v) Natural History of Hepatitis C Viral Infection [13]



(vi) Evaluation of Fibrosis in Patients with Chronic HCV [9]



(vii) When and in Whom to Initiate HCV Therapy: Factors Associated with Accelerated Fibrosis Progression [10]

Host	Viral
Non-Modifiable	Genotype 3
Fibrosis stage	Co-infection with hepatitis B virus (HBV)
Inflammation grade	Co-infection with human immunodeficiency virus (HIV)
Older age at time of infection	
Male sex	
Organ transplant	
Modifiable	
Alcohol consumption	
Obesity	
Nonalcoholic fatty liver disease	
Insulin resistance	

(viii) **Hepatitis C Pre-Treatment Checklist:**

- **Labs:**

Immediately prior: □ Pregnancy test □ Uric Acid (with ribavirin)

Within 1 month: □ Complete Blood Count with differential

□ Comprehensive Metabolic Panel (If GFR <30, do not start treatment; consult Liver Disease Specialist)

□ PT/INR □ HCV RNA

Within 3 months: □ Genotype confirmation

Within 6 months: □ AFP □ TSH □ A1C or Fasting Glucose

□ Vitamin D 25OH

Within 1 year: □ HIV screening

- **Screen & Review:** AUDIT-C __PHQ-9 ___Drug & Alcohol Screen (at discretion of provider)

- **Vaccine Status/Screening:** Hepatitis A & B vaccinations are recommended for all persons with HCV

□ Hepatitis A (If vaccine status is unknown, check hep A total IgG)

□ Hepatitis B (If vaccine status is unknown, check HBsAg & HBsAb) Other vaccines as appropriate:

□ Flu (annually) □ Pneumococcal-13 (≥ age 65 or high risk/immunosuppressed)

□ Pneumococcal-23 (≥ age 50 AN/AI living in Alaska or high risk)

□ Td (once every 10 years) OR Tdap (once) □ Zoster (≥ age 60)

- **Pre-Treatment Clinical Evaluation:**

□ Medical history including liver disease history and past hepatitis C treatment

□ Hypertension/Diabetes controlled □ Counsel about smoking cessation

□ Counsel about pregnancy prevention (see Treatment Agreement)

□ Review all medications; check for drug interactions with treatment meds

□ Physical Exam □ Hepatitis C Treatment Agreement reviewed and signed

□ ECG (If treatment includes ribavirin or peginterferon, over age 65 or h/o cardiac disease)

If treatment includes peginterferon complete the following:

□ Mental Health Evaluation if h/o depression or other psychiatric condition

□ Stress Test (h/o cardiac disease, prior to peginterferon or ribavirin)

□ Dilated retinal/ophthalmology exam (peginterferon candidates only who have HTN, HLD,

DM, or h/o retinal disease or blindness)

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Project ECHO® Hepatitis C Clinical Guidelines

The following document *is frequently edited* to reflect current updates in treatment guidelines for hepatitis C. Please contact one of Project ECHO's HCV team member listed on the website echo.unm.edu to access the latest version of the document via web link. *The link will connect you to the most recently updated version.*

Project ECHO®

Hepatitis C Clinical Guidelines

This document is frequently edited to reflect current updates in treatment guidelines for hepatitis C. Please access the document using the web link provided by Project ECHO staff and faculty. The link will connect you to the most recently updated version. If you do not have access to the link, please contact one of Project ECHO's HCV team member listed on the website echo.unm.edu. In order to minimize the need for tracking paper versions, we advise against the printing of this document.

This document was last updated on:

February 2, 2018

(All revisions highlighted in yellow)

(Click on logo above to go the Project ECHO® website)

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H. ECHO® HCV Clinic Administrative Documents
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- b. HCV Initial Presentation Form
- c. HCV Follow-up Presentation Form

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SCREENING FOR HCV INFECTION

Rationale for HCV Screening

In the United States, approximately 2.7-to 5 million patients are infected with chronic HCV infection (Edlin, 2011). Effective therapy is available for HCV and cure is achieved in a substantial proportion of patients who undergo therapy. Cure of HCV significantly reduces the patient's risk of developing cirrhosis, liver failure, liver transplant or hepatocellular cancer. HCV is a systemic disease linked to lymphoma, kidney disease and diabetes as well as a number of other conditions. Treatment with cure reduces all-cause mortality.

Recommendation for HCV Screening

Please see the following screening tools:

A.

- Screening Tool Generic Color
- Screening Tool Generic B&W
- Screening Tool Patient ID Color
- Screening Tool Patient ID B&W

Because most patients with chronic HCV do not have specific clinical symptoms related to their HCV infection, relying on clinical symptoms for screening is not recommended. Risk factors for infection include:

- Injection drug use
- Receipt of blood transfusion, blood products, or an organ transplant before 1992
- Chronic hemodialysis
- Shared personal care items, such as razors or toothbrushes, with a person who has hepatitis C
- Non-professional tattoo or body piercing
- Accidental needle stick injury
- Sex with an HCV-infected person
- Multiple sex partners or history of a sexually transmitted disease
- Mother with hepatitis C

B.

In addition, per recent CDC recommendations and approval via United States Preventative Services Task Force, all persons born between 1945 and 1965 should have a one-time screening for HCV (Moyer, 2013). The rationale for testing all persons born during that birth cohort include a high rate of positivity among that group with estimates suggesting 75% of all HCV-positive adults were born between 1945-1965. Additional reasons for the recommendation include the impact of testing of reducing morbidity and mortality related to HCV infections, an overall lack of awareness of the HCV epidemic, and the advances in treatment (Centers for Disease Control and Prevention, 2012).

Initial HCV Screening with Antibody Testing

C.

The HCV enzyme immunoassay (EIA) is the recommended initial screening test for HCV infection. Newer FDA-approved third generation EIA HCV antibody tests have a sensitivity and specificity greater than 99%. The EIA test determines whether the person has ever been infected with HCV, but it does not establish whether the patient has chronic (ongoing) infection or resolved infection.

Confirmation of Positive Antibody Tests with Quantitative HCV RNA

Patients who have a positive HCV EIA should undergo quantitative HCV RNA testing to determine whether they have active or resolved HCV infection. Quantitative HCV RNA tests (e.g., COBAS® TaqMan® HCV Test) are highly sensitive (10-50 IU/mL) for the detection of viremia. The HCV RNA level does not predict liver disease progression and should not be serially monitored to assess prognosis in persons not undergoing HCV treatment. See CDC "Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection."

Acute HCV

Among patients who develop acute HCV infection, approximately 20% will have spontaneous resolution of the HCV; the spontaneous resolution is often evident within 12 weeks after infection, but some patients have a more delayed clearance. Patients with acute HCV should have the HCV RNA repeated in ≥12 weeks to determine if spontaneous clearance occurred or if the patient has established a chronic HCV infection.

D. Routine Evaluation and Follow-Up of Persons with Chronic HCV Infection

Baseline Studies in Persons with Established Chronic HCV

Patients identified with chronic HCV infection (HCV RNA positive) should have the following baseline laboratory studies:

- Complete blood cell count with differential
- INR (international normalized ratio)
- Comprehensive metabolic panel including serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, and serum albumin
- HCV Genotype and subtype
- Quantitative HCV RNA
- Hepatitis A serology (total or IgG)
- Hepatitis B serology (HBsAg, anti-HBs, anti-HBc)
- HIV Antibody
- Alpha-fetal protein (AFP)
- Abdominal ultrasound with measurement of spleen size

All patients with chronic HCV should be evaluated for severity of liver disease and degree of inflammation. The following laboratory abnormalities may be found in patients with cirrhosis: neutropenia, thrombocytopenia (<150,000 platelets/mL), prolonged INR, reversal of AST to ALT ratio, elevated bilirubin, low albumin. Elevated creatinine may be found in patients with HCV associated renal disease. APRI and FIB4 scores are the best noninvasive and free tests with substantial accuracy.

A.

HCV Genotype

All patients with chronic HCV should undergo HCV genotype (GT) testing. There are six major HCV genotypes. In the United States, approximately 75% of persons infected with HCV have GT 1; among African-Americans infected with HCV, the prevalence of GT 1 is approximately 90% (Jacobson, et al., 2007). For patients considering HCV treatment, GT and GT subtyping should be obtained because it provides valuable prognostic information with respect to treatment response.

B.

C.

Quantitative HCV RNA

The quantitative HCV RNA level provides prognostic information related to treatment response, but does not correlate with the degree of liver inflammation or fibrosis.

HIV and Hepatitis A and B Virus Serologies

Because HIV and HCV infections share common routes of transmission, patients with HCV should be screened for HIV. All HCV-infected persons should be screened for immunity with HAV antibody (total or IgG) unless there is documentation of hepatitis A vaccination, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc) (irrespective of vaccination).

More information on hepatitis B serologic testing can be found at www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf (Center for Disease Control and Prevention, 2005)

Table 1: Interpretation of Hepatitis B serologies

Tests	Results	Interpretation
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible to HBV
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive or Negative	Previous exposure to HBV.These patients are not immune or "protected" and frequently have subclinical infection and are at risk for reactivation with immunosuppression. There is no role to vaccinate (or boost) these patients.
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to previous HBV vaccine exposure
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acute HBV infection
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronic HBV infection

Screening for Other Causes of Liver Disease

In some patients, other causes of liver disease may be considered including:

- Wilson Disease
- Hemochromatosis
- Autoimmune Hepatitis
- NASH

For more information regarding the diagnosis and management of these conditions, see the following AASLD practice guidelines: http://www.aasld.org/practiceguidelines/Pages/default.aspx

Vaccinations

Patients with chronic HCV should avoid becoming newly infected with either HAV or HBV. All patients without immunity should be vaccinated. Additionally, all patients with chronic liver disease, including ongoing alcoholism, should receive the pneumococcal vaccine (Center for Disease Control and Prevention, 2010).

Staging of Liver Disease

Staging of liver disease is important to determine intensity of liver inflammation and degree of fibrosis. Historically, liver biopsy was the gold standard however, alternative non-invasive tests are increasingly used.

The patient should be considered to have advanced fibrosis or cirrhosis if any of the following laboratory, radiographic or clinical findings are present (Lin, et al., 2011) (Sterling RK, 2006) (Fibrosure reference: Lab-Corp RTP):

- Presence or history of ascites or esophageal varices
- Platelet count < 150,000/mm^3
- APRI ≥ 1.0*
- FIB-4 ≥ 3.25*
- Fibrosure ≥ 0.72
- Imaging with evidence of cirrhosis (nodular contour of liver or evidence of portal hypertension)
- Liver biopsy with F3 or F4 fibrosis
- Transient elastography consistent with advanced fibrosis/cirrhosis

*Please find clinical calculators at the University of Washington: Hepatitis C Online webpage.

Monitoring for Hepatocellular Carcinoma

Patients with chronic HCV infection and advanced fibrosis/cirrhosis have an increased risk of developing hepatocellular carcinoma (HCC). The incidence of HCC is estimated to be 2% to 8% per year. These individuals should have surveillance for HCC with hepatic ultrasound every 6 months (Bruix J, 2005). Any suspicious lesions may require additional evaluation with a multi-phase contrast abdominal computed tomographic (CT) scan or a magnetic resonance imaging (MRI) study. Due to limited accuracy, alpha-fetoprotein (AFP) is considered an inadequate test for diagnosis in the surveillance for HCC and is not recommended alone without ultrasound. Routine surveillance every 6 months with ultrasound and AFP has been shown to reduce HCC related mortality by 37% (Zhang BH, 2004). Routine surveillance for HCC in persons with chronic HCV but without F3/ F4 cirrhosis is not recommended. Although rare, patients with cirrhosis who are cured of HCV infection may still develop HCC and should continue to have routine surveillance indefinitely. Surveillance in patients with stage 3 fibrosis is optional and not yet part of guidelines. Screening should be continued indefinitely. If high quality ultrasound is not available, biomarkers for HCC should be considered. The two FDA cleared biomarkers, AFPL3% and DCP can increase the accuracy of the risk prediction for HCC and modify the surveillance planning such as changing to MRI or CT for imaging instead of US if the biomarker values are elevated or more importantly, if they are rising (Gish, 2014).

Evaluation for Cirrhosis-Related Complications

In addition to monitoring for HCC, patients with cirrhosis should undergo evaluation for and management of any cirrhosis-related complications. Specifically, history and physical examination should evaluate the patient for edema, muscle wasting, encephalopathy and/or ascites. Patients with cirrhosis should undergo endoscopy to evaluate for the presence of esophageal varices to determine the need for banding and prophylaxis with a nonselective beta blocker (such as nadolol or propranolol) with a robust balance of risk and benefit of these drugs.

For detailed and additional information see the following AASLD guidelines: Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis

Indications for Referral to Hepatologist and for Liver Transplantation

Patients with cirrhosis should periodically have assessment of their liver status with a validated prognostic model, such as the Model for End-Stage Liver Disease (MELD) score which includes the patient's serum creatinine, total bilirubin and INR and can be calculated using online resources such as UW's Online Calculators located at: University of Washington: Hepatitis C Online webpage. The model can predict mortality risk and serves as an indicator for liver transplantation referral. Patients with a score of 15 or higher should be considered for evaluation for liver transplant. (American Association for the Study of Liver Disease, 2014)

Assessment and Management of Alcohol and Substance Use

All patients with chronic HCV should be counseled regarding their alcohol and drug use, including marijuana, tobacco, and prescription medication abuse. Alcohol use can accelerate the progression of liver disease, diminish the response to therapy and exacerbate the risks of therapy. Marijuana use has been shown to increase fibrotic changes. Cigarette smoking potentiates liver damage, increases the risk for HCC, and increases the risk of infection during therapy. Importantly, patients should not be excluded for treatment of HCV based on a past history of alcohol or drugs.

Evaluating and Modifying Obesity

Obesity is associated with the development of nonalcoholic fatty liver disease and hepatic steatosis, which can accelerate the progression of HCV-related liver disease. In addition, obesity-associated insulin resistance may diminish the response to HCV therapy. Overweight (defined as a BMI of ≥25 kg/m^2) and obese (BMI ≥30 kg/m^2) patients should receive counseling on weight reduction and referral to a weight reduction program if available. Nonalcoholic steatohepatitis (NASH) combined with HCV further increases the risk for HCC.

Ongoing Management of Patients Not on HCV Therapy

Patients with chronic untreated HCV or those who have failed HCV treatment should be followed regularly for their liver disease. Recent AASLD guidelines recommend yearly liver enzymes and liver function tests, CBC with platelets,INR, and re-evaluation for treatment. Patients should limit their intake of acetaminophen to less than 2 grams/day, abstain from alcohol and marijuana use, and maintain a normal body mass index (<25 kg/m^2).

Patients with cirrhosis should avoid non-steroidal anti-inflammatory drugs (NSAIDs) (Murray KF, 2005). Surveillance for HCC with imaging and AFP should be continued every 6 months in patients with cirrhosis.

Coffee and tea may be liver protective. Statins are safe for liver patients and may also have protective effect and decrease the risk of HCC (Bravi, Bosetti, Tavani, Gallus, & La Vecchia, 2013). Liver patients are often vitamin D deficient and supplementation is advised if vitamin D levels are low.

Overview of Monitoring

Table 2: Evaluation and Monitoring of Person with Chronic HCV Infection

Baseline	Every Six Months	Annually
• Complete blood cell count with differential • INR (international normalized ratio) • Serum creatinine • Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, and serum albumin • HCV Genotype and subtype • Quantitative HCV RNA • Hepatitis A serology (total or IgG) • Hepatitis B serology (HBsAg, anti-HBs, anti-HBc) • HIV Antibody • Alpha-fetal protein (AFP) • Vitamin D 25-OH • Abdominal ultrasound with spleen size • Endoscopy (in patients with cirrhosis)	• Abdominal ultrasound (in patients with cirrhosis) • AFP (in patients with cirrhosis)	• Complete blood cell count with differential • INR (international normalized ratio) • Serum creatinine • Liver enzyme tests to include: alanine aminotransferase (ALT) aspartate aminotransferase (AST) • Liver function tests to include: total and direct bilirubin and serum albumin

Patient Education

There are many myths and misconceptions about HCV in the general population. It is important to work with your patients so that they understand the assessment, treatment, potential complications and risks related to their disease. In addition, it is important to educate patients about preventing HCV transmission or becoming reinfected. While working with your patients remember the importance of providing education according to their cultural needs and health literacy levels.

Please use the following attachments as tools for patient education:

a. HCV Basics
b. Treatment Information for Patients
c. Educational Resources for Hepatitis C

Patients with Established HCV Infection: Evaluation for Therapy

Goals and Rationale for HCV Treatment

A. The goal of HCV treatment is viral eradication. Successful treatment of HCV decreases all-cause mortality and can result in decreased risk of developing cirrhosis, end-stage liver disease, and HCC. The benefits of therapy also include reduction in progression of fibrosis and extra-hepatic complications related to HCV (including but not limited to cryoglobulinemia, renal dysfunction, lymphoma, diabetes mellitus, neuropathy, arthralgias and skin manifestations including porphyria cutanea tarda). Additionally, viral eradication eliminates the risk of transmission of HCV to others (van der Meer AJ, 2012).

B. Treatment is recommended for patients with chronic HCV infection.

Treatment Terminology

Treatment naïve (TN): a patient who has not previously undergone HCV therapy

Treatment experienced (TE): a patient who has previously undergone HCV therapy

- *Treatment experience should clarify if prior treatment was with peg-interferon/ribavirin (PR) or direct-acting antivirals (DAAs such as boceprevir, simeprevir, sofosbuvir, etc)*

C. ***Sustained virologic response (SVR),*** or virologic cure, is the goal of therapy. Patients who achieve SVR have a very high likelihood of achieving a long-term cure of HCV (Murray KF, 2005). The currently accepted definition of SVR is an undetectable HCV viral load at least 12 weeks after the end of HCV therapy (SVR12) (American Association for the Study of Liver Diseases, 2015).

Relapser: patient who achieves an undetectable viral load during treatment or at the end of treatment but who has a detectable viral load after treatment is completed.

D. ## *Baseline Factors Predicting Response*

The relevance of risk factors is markedly diminished with newer therapies; however, in clinical trials the rate of SVR is lower in patients with cirrhosis, in particular with more advanced cirrhosis such as decompensated cirrhosis. Another factor which can predict reduced SVR is prior treatment failure, specifically prior DAA treatment failure.

HCV Resistance Testing

The advent of direct acting antivirals marked a new therapeutic challenge for HCV management. HCV is well known to mutate during replication, developing resistance associated substitutions (RASs) which may affect treatment

response. Overall, there are limited clinical data to recommend baseline RAS testing in treatment naïve patients with the following exceptions:

Elbasvir/grazoprevir for patients with HCV GT 1a: pre-treatment RAS testing required. In clinical trials, patients had markedly reduced SVR at 58% with some baseline RASs as compared to 99% SVR if no baseline RASs were present (Zeuzem et al, 2015). The presence of RASs warrants a longer treatment course and concomitant ribavirin when using elbasvir/grazoprevir in patients with HCV GT 1a. In this setting, elbasvir/grazoprevir is an alternative therapy for GT 1a.

Sofosbuvir/velpatasvir for patients with HCV GT3 who are treatment experienced and/or have cirrhosis. The presence of baseline NS5A RAS reduced SVR to 88% as compared to 97% in patients without baseline substitutions. Specifically the Y93H RAS is of concern because of the observation that in patients with the Y93H RAS, the SVR was 84%. As a result, current guidance indicates that if the Y93H RAS is identified, either ribavirin should be added to the regimen or an alternative therapy chosen. Similarly, when using daclatasvir plus sofosbuvir in this patient population, pre-treatment RAS testing is recommended.

A HCV Resistance Testing Cheat sheet is available by clicking here.

Risk of HBV Re-activation

E. All HCV DAAs include a boxed warning for HBV reactivation, with recommendations to evaluate patients for potential coinfection of HCV and HBV before initiating DAA therapy. The guidance stems from an FDA warning after 24 cases of HBV reactivation were identified in HBV-HCV–coinfected patients treated with DAAs (FDA 2016). The reported cases included two deaths and one liver transplant. As a result, all patients evaluated for HCV DAA therapy should be evaluated for coinfection with HBV with HBV surface antigen (HBsAg), HBV core antibody (anti-HBc), and HBV surface antibody (anti-HBs).

F. *Mental Health Assessment*

Mental health screening prior to initiating HCV therapy is recommended for multiple reasons. Patients infected with HCV have increased rates of depression (Weinstein AA, 2011) (Lee, Jamal, Regenstein, & Perrillo, 1997). In addition, active and untreated mental health issues can interfere with adherence to HCV treatment. A baseline evaluation can be helpful in identifying pre-existing issues and also as a barometer if psychiatric issues develop during HCV therapy. We recommend the use of the Patient Health Questionnaire (PHQ-9), a standardized depression screening tool, before and during HCV treatment. Family and social support issues should be explored to prepare the patient for the challenges of treatment and improve patient adherence to therapy. Treatment of depression will likely enhance care and is associated with improved adherence.

Please find the attachments below to assist in a baseline evaluation:

G.

- PHQ-9 in English
- PHQ-9 in Spanish
- PHQ-9 Scoring Guidelines
- PHQ-9 JGIM Article: Validity of a Brief Depression Severity Measure

Substance Abuse Assessment

Patients should be evaluated for alcohol, illicit drug use, prescription drug abuse, and marijuana use prior to initiating HCV therapy. The use of a standardized assessment tool such as AUDIT (The Alcohol Use Disorders Identification Test) is optional. Patients with extensive substance abuse histories may require formal rehabilitation programs prior to initiating treatment. However, active injection drug use is not a contraindication to HCV treatment (AASLD, 2017).[1] The decision to treat persons who inject drugs (PWIDs) should be undertaken with consideration of risk of reinfection and with provision of harm reduction education. Alcohol abstinence is required

and willingness to abstain from alcohol should be verified prior to initiation of therapy. Patients should abstain from the daily use of marijuana.

To learn more about AUDIT, please visit:
http://apps.who.int/iris/bitstream/10665/67205/1/WHO_MSD_MSB_01.6a.pdf

H. *Assessment of Medical Comorbidities*

All medical comorbid conditions should be optimally managed prior to starting HCV therapy. Prior to starting therapy, a thorough medical history should be obtained.

If there is evidence of cirrhosis, obtain a baseline abdominal ultrasound for HCC surveillance and an EGD for evaluation of esophageal varices.

I. *Overcoming Barriers to Initiating Treatment*

Clinicians should formally address any barrier that exists that interferes with the patient's ability to undergo HCV treatment including treatment programs for alcohol and substance use and mental health counseling. Patients are often not willing to undergo HCV treatment due to misinformation or concern of possible side effects. It is important to educate the patient on the natural history of HCV infection and the benefits of treatment.

J. *Reevaluating for Treatment*

Patients who are either unwilling or unable to undergo HCV therapy should undergo reevaluation for HCV therapy on an annual basis. In addition, as new treatments become available, treatment decisions should be reconsidered.

K. *Adherence to Treatment*

Adherence to HCV treatment is critical for response. Predictors of poor adherence include the presence of psychological problems, complexity of treatment, and side effects of medication (Osterberg L., 2005). Additionally, adherence is markedly reduced with increased frequency of medication dosing. Known barriers to adherence include patient-provider communication including a patient's poor understanding of the disease state, the risks and benefits of treatment, and a lack of understanding of how to take the medication.

There are no reliable markers to predict optimal adherence. Higher socioeconomic status, degree of education, and a lack of substance use history do not predict optimal adherence. Instead, all patients should be evaluated for readiness to start therapy, provided with a thorough understanding of their disease state including anticipating side effects, the impact of non-adherence, and offered emotional and practical support to manage their medication. They should be provided with suggestions for improving the convenience of the regimen and given educational tools such as pictures, pill boxes, or calendars. Adherence is improved with a team approach- engage family, friends, and other healthcare workers such as nurses, pharmacists, and peer counselors. Adherence should be addressed at every clinic visit. Patients who have access to a health care team they trust are more likely to adhere to treatment.

INITIATING HCV THERAPY

Pretreatment Work

A.

1. Laboratory Needs:
    a. Baseline Laboratory Studies Prior to Starting Therapy: obtain the following labs within 60 days of starting treatment to establish the baseline (week 0):
        - CBC with differential
        - Chem 7
        - Liver enzymes: ALT, AST, alkaline phosphatase
        - Liver function tests: albumin, total and direct bilirubin, INR
        - Vitamin D 25-OH
        - Urine or serum pregnancy test for women of childbearing capacity (ribavirin only)
        - Alpha fetoprotein (if cirrhosis)
        - HIVRNA and CD4 count (if HIV infected)

    b. The following labs should be current within the past 12 months*:
        - HCV-RNA Quant

    *For non-cirrhotic, treatment naïve patients with genotype 1, an HCV-RNA ***within 6 months*** of starting therapy must be available for consideration of an 8 week course of treatment.

    c. Patients must have documentation of the following labs:
        - HCV GT and subtype
        - HBsAg, anti-HBs, anti-HBc (irrespective of vaccine history)
        - HAV Ab (unless documentation of vaccination)
        - HIV Ab
2. Pre-treatment Resistance Testing:
    a. All patients with HCV GT 1a when considering the use of elbasvir/grazoprevir should be tested for NS5A RAVs (including treatment naïve, treatment experienced, or with or without cirrhosis)
    b. All patients with HCV GT 3 who have cirrhosis and/or are treatment experienced should be tested for Y 93 when considering sofosbuvir/velpatasvir or sofosbuvir plus daclatasvir

B.

3. Vitamin D Replacement:
    a. For 25 OH Vitamin D level <20ng/ml give Vitamin D3 50,000 units PO every week for 8 weeks then 2,000 units daily for one month.
    b. For 25 OH Vitamin D level ≥20ng/ml but <40ng/ml give Vitamin D3 2,000 units PO every day.
    c. Repeat 25 OH Vitamin D level after 3 months.

Patient Education

Patients should be educated about all aspects of HCV treatment including potential duration of therapy, side effects, drug-drug interactions and medication adherence challenges.

Please find attachments below:

- HCV Basics
- Treatment Information for Patients
- Educational Resources for Hepatitis C

Treatment for Persons with Chronic HCV

There are multiple FDA approved regimens for chronic HCV. Currently, highly effective interferon free therapy for chronic HCV infection is available. See decision trees for recommended therapies. Insurance formularies may prefer a specific regimen listed on the decision trees.

C.

Current HCV Medication List

TABLE 3: CURRENT MEDICATIONS FOR THE TREATMENT OF HEPATITIS C CHRONIC INFECTION

Generic Name	Brand Name
Direct-acting Antivirals (DAAs)	
Elbasvir/ Grazoprevir	Zepatier®
Glecaprevir/Pibrentasvir	Mavyret®
Ledipasvir/Sofosbuvir	Harvoni®
Paritaprevir/ritonavir/Ombitasvir	Technivie®
Paritaprevir/ritonavir/Ombitasvir with Dasabuvir	Viekira Pak®
Sofosbuvir/ Velpatasvir	Epclusa®
Sofosbuvir/ Velpatasvir/Voxilaprevir	Vosevi®
Other HCV medications used in combination with DAAs	
Ribavirin	Ribasphere®, RibaPak®, Copegus®, Rebetol®
Single-Agent DAAs	
Daclatasvir	Daklinza®
Simeprevir	Olysio®
Sofosbuvir	Sovaldi®

Direct-Acting Antivirals

A. ***Elbasvir/Grazoprevir:***
The combination of elbasvir (NS3/4A protease inhibitor) and grazoprevir (NS5A inhibitor) is formulated in a single tablet as Zepatier taken once daily. In the US it is approved for use in GT 1 and 4 in patients without cirrhosis, with compensated cirrhosis, and in patients with renal insufficiency including hemodialysis. **For patients with GT 1a, pre-treatment resistance testing for NS5A RAVs is required to determine the optimal duration and need for concomitant ribavirin use.**

B. ***Glecaprevir/Pibrentasvir:***
The combination of glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor) is formulated in a single tablet as Mavyret and taken as 3 tablets once daily with food. It is approved for use in GT 1-6 in patients without cirrhosis, with compensated cirrhosis, and in patients with renal insufficiency including hemodialysis.

C. ***Ledipasvir/Sofosbuvir:***
The combination of ledipasvir (NS5A inhibitor) and sofosbuvir (NS5B polymerase inhibitor) is formulated in a single tablet (400 mg sofosbuvir/90 mg ledipasvir) taken once daily with activity in GT 1-6. In the US, ledipasvir is indicated for GT 1 and 4 and available as Harvoni.

D. ***Sofosbuvir/Velpatasvir:***
The combination of velpatasvir (NS5A inhibitor) and sofosbuvir (NS5B polymerase inhibitor) is formulated in a single tablet as Epclusa taken once daily with or without food. Epclusa has activity against GT 1-6 in patients without cirrhosis, with compensated cirrhosis and with patients who have decompensated cirrhosis. Velpatasvir requires an acidic environment for absorption so patients on acid suppressive therapy must be counseled on appropriate concomitant use of Epclusa and acid

suppressive medications. Proton pump inhibitors should not be used with Epclusa. It is approved for use in patients with all levels of liver disease, including decompensated cirrhosis.

E. ***Sofosbuvir/Velpatasvir/Voxilaprevir:***

The triple combination is available as a single tablet taken once daily with food. It is available as Vosevi and is indicated for use in patients with prior DAA failure. The treatment is used in patients without cirrhosis or in those with compensated cirrhosis. Due to the velpatasvir component, proton pump inhibitors should be avoided and acid suppressive therapy overall should be minimized when using Vosevi.

F. ***Paritaprevir/ritonavir/Ombitasvir and Dasabuvir:***

Viekira Pak contains the combination of ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibito), and ritonavir (CYP3A inhibitor) and dasabuvir (non-nucleoside NS5B palm polymerase inhibitor). The combination therapy is indicated for patients with GT 1. The dosage is 2 tablets of ombitasvir/paritaprevir/ritonavir once daily and one dasabuvir tablet twice daily with food. The fat or calorie content of the food is not important for absorption.

Technivie contains ombitasvir and paritaprevir boosted with ritonavir. The combination, without dasabuvir, is indicated for GT 4 infections. The dosage is 2 tablets once daily with food. The fat or calorie content of the food is not important for absorption.

G. ***Daclatasvir:***

Daclatasvir (NS5A inhibitor) is approved for GT 1 and 3 in combination with sofosbuvir (NS5B polymerase inhibitor). Daclatasvir is available as a 30 mg and 60 mg tablet taken once daily; the dose of daclatasvir depends on concomitant medications. For patients with GT 1a and cirrhosis, pre-treatment NS5A resistance testing is suggested. Daclatasvir may also be used for treatment of other genotypes as per the AASLD treatment guidelines and insurance formulary preference. Daclatasvir (Daklinza) is taken with or without food.

H. ***Simeprevir***

Simeprevir (protease inhibitor) is an oral medication given 150 mg once daily with food and is used for GT 1 infections as part of combination therapy. It is available as Olysio.

I. ***Sofosbuvir***

Sofosbuvir (polymerase inhibitor) has antiviral activity against GT 1, 2, 3, and 4. It is available as a 400mg oral tablet dosed once daily and must be combined with another agent for efficacy. It is available as Sovaldi.

F.

Additional Medications Used in the Treatment of Chronic Hepatitis C

A. ***Ribavirin:***

Ribavirin is an oral medication. It is dosed twice a day for a total daily dose based upon body weight:

- <75 kg 1000mg/daily
- ≥75 kg 1200mg/daily

Several products of ribavirin are available as 200 mg tablets including Copegus® and RibaTab®, and as a 200 mg capsule, Rebetol®. The Ribasphere® RibaPak® is a prepackaged 2-tablet dosing product available as an 800 mg, 1000 mg, or 1200 mg daily dose.

RECOMMENDATIONS FOR HCV TREATMENT BY GENOTYPE:

The following decisions trees are available for genotype 1, 2, 3 and 4:

- Decision Tree Links and Key

The following references are used for HCV Decision Trees:

(Kowdley K, 2014), (Ferenci, et al., 2014) (Afdhal, et al., 2014) (Bourliere, et al., 2014) (Wyles, et al., 2014) (Zeuzem, 2015) (Jacobson, et al., 2013) (American Association for the Study of Liver Disease, 2014) (Flamm, et al., 2014) (Foster, 2014) (Jacobson, et al., 2007) (Kowdley K, 2014) (MR Charlton, 2013)

SPECIAL POPULATIONS

HIV Coinfection

A. Patients with HIV-HCV coinfection should be treated according to HCV monoinfection recommendations. An 8 week treatment course is recommended for glecaprevir/pibrentasvir only. There are limited data regarding the use of the 8 week treatment course when using ledipasvir/sofosbuvir in HCV-HIV coinfection.

Patients Who Develop Recurrent HCV Infection Post Liver Transplantation

B. Glecaprevir/pibrentasvir is approved for 12 weeks for treatment naïve or treatment experienced non-cirrhotic patients with chronic HCV GT 1-6. In treatment naïve or treatment experienced patients with compensated or decompensated cirrhosis with chronic HCV GT 1, 4, 5, or 6, ledipasvir/sofosbuvir with weight-based ribavirin is preferred for 12 weeks. In treatment naïve or treatment experienced patients with compensated or decompensated cirrhosis with chronic HCV GT 2 or 3, daclastasvir (60 mg) plus sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks is also a recommended treatment. For decompensated patients, consider initial low dose of ribavirin (600 mg) and increase as tolerated.

Patients with Renal Insufficiency

C. Patients with renal insufficiency, including hemodialysis, may be treated with elbasvir/grazoprevir or glecaprevir/pibrentasvir. Sofosbuvir is not indicated in patients with renal insufficiency as defined by an estimated Glomerular Filtration Rate (GFR) <30 ml/min/1.73m (Moyer, 2013). Daclatasvir and paritaprevir/ritonavir/ombitasvir with or without dasabuvir can be used in patients with mild, moderate or severe renal insufficiency. Currently there are limited data on the use of sofosbuvir, ledipasvir, or paritaprevir/ritonavir/ombitasvir with or without dasabuvir in dialysis, therefore no recommendation can be made for this patient population.

D.

Acute HCV Infection

E. Approximately 25% of patients with acute HCV infection will have spontaneous resolution of the HCV; as a result is reasonable to defer HCV treatment for 24 weeks after the detection of HCV antibody and HCV RNA. Patients with acute HCV present a unique treatment opportunity since SVR rates are substantially higher with treatment of acute HCV than chronic HCV. There are currently no guidelines regarding the use of direct acting antivirals for acute HCV. For further information see the AASLD/IDSA guidelines on acute infection. http://www.hcvguidelines.org/node/93

Patients with Compensated Cirrhosis

Compensated cirrhosis, identified as patients with Child Turcotte Pugh (CTP) Class A cirrhosis, can be treated with any of the DAA regimens.

Patients with Decompensated Cirrhosis (treatment naïve and treatment experienced)

F. Decompensated cirrhosis, identified as patients with CTP class B or C, can be treated with ledipasvir/sofosbuvir, sofosbubir/velpatasvir, or daclatasvir plus sofosbuvir. Elbasvir/grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/velpatavir/voxilaprevir and paritaprevir/ritonavir/ombitasvir with or without dasabuvir should not be used in patients with CTP class B or C cirrhosis namely due to concerns for the protease inhibitor potentiating liver failure. In patients with decompensated cirrhosis, ledipasvir/sofosbuvir and ribavirin for 12 weeks resulted in an SVR of 86-87% which was statistically comparable ledipasvir/sofosbuvir for 24 weeks of therapy (SVR 89-90%) (Flamm, et al., 2014). Similarly, the SVR rates in decompensated patients treated with sofosbuvir/velpatasvir for 12 weeks was 83%, 86% if treated for 24 weeks, and 94% for a 12-week course of sofosbuvir/velpatasvir plus ribavirin (Curry, 2015).

COMMON SIDE EFFECTS

Most commonly seen side effects are listed in table that follows.

TABLE 4: COMMON SIDE EFFECTS

Side Effects of DAAs

Drug Therapy	Side Effects
Daclatasvir	Headache; fatigue; nausea; diarrhea
Elbasvir/Grazoprevir	Headache; nausea
Glecaprevir/Pibrentasvir	Headache, fatigue
Ledipasvir/Sofosbuvir	Headache; fatigue
Ombitasvir/Paritaprevir/ritonavir and Dasabuvir	Fatigue; nausea; pruritus and other skin reactions; insomnia; asthenia
Simeprevir	Rash, including photosensitivity; pruritus; nausea
Sofosbuvir	Headache; fatigue
Sofosbuvir/Velpatasvir	Headache; fatigue
Sofosbuvir/Velpatasvir/Voxilaprevir	Headache; fatigue; diarrhea

PEG-IFN	Ribavirin
Flu-like symptoms: fever, headache, myalgia Fatigue Depression Irritability Insomnia Nausea Vomiting Anorexia Cognitive dysfunction	Rash Fatigue Nausea Vomiting

COMMON LABORATORY ABNORMALITIES

Hemolytic anemia is an expected effect of ribavirin exposure and may cause elevations in indirect bilirubin as well as subclinical elevations in uric acid. Interferon is known to cause bone marrow suppression resulting in various laboratory abnormalities. Many HCV DAAs can inhibit bilirubin transporters infrequently resulting in serum bilirubin abnormalities. The most common laboratory abnormalities are listed in the table below:

TABLE 5: COMMON LABORATORY ABNORMALITIES WITH PEG-IFN, RIBAVIRIN, AND DIRECT-ACTING ANTIVIRALS

Drug Therapy	Laboratory Abnormalities
Daclatasvir	Transient, asymptomatic lipase elevations
Elbasvir/Grazoprevir	Elevated or increasing ALT
Glecaprevir/Pibrentasvir	*Most common abnormalities reflect those abnormalities associated with other therapeutic agents*
Ledipasvir/Sofosbuvir	*Most common abnormalities reflect those abnormalities associated with other therapeutic agents*
Ombitasvir/Paritaprevir/ritonavir and Dasabuvir	Elevated or increasing ALT Elevated or increasing bilirubin
Simeprevir	Transient elevations in bilirubin Subclinical elevations of alkaline phosphatase
Sofosbuvir	*Most common abnormalities reflect those abnormalities associated with other therapeutic agents*
Sofosbuvir/Velpatasvir	*Most common abnormalities reflect those abnormalities associated with other therapeutic agents*
Sofosbuvir/Velpatasvir/Voxilaprevir	*Most common abnormalities reflect those abnormalities associated with other therapeutic agents*

PEG-IFN	RIBAVIRIN
Neutropenia Thrombocytopenia Lymphopenia Anemia Autoimmune thyroiditis- hyper or hypothyroid Elevated or increasing liver enzymes or liver dysfunction	Anemia Increases in indirect bilirubin associated with anemia Subclinical elevations of uric acid

A.

4-Week HCV RNA Positivity

All patients on HCV therapy should have their 4-week HCV RNA checked. If the 4 week HCV RNA is quantifiable, the following changes to therapy are recommended:
If the patient is on an 8-week course of Harvoni and has quantifiable HCV RNA at treatment week 4, extend the treatment duration to 12 weeks.

If the patient is on a 12-week course of treatment and has quantifiable HCV RNA at treatment week 4, add ribavirin for the remainder of the treatment course.

If the patient is already on a treatment with ribavirin and has quantifiable HCV RNA at treatment week 4, consider maximizing the ribavirin dose if clinically tolerated.

DRUG-DRUG INTERACTIONS

Drug-Drug Interactions Resources

Because new information on drug-drug interactions is updated frequently, we recommend the use of the following website to check for HCV drug interactions prior to start of HCV treatment:

A. https://www.hep-druginteractions.org/

Additional Drug Information

a. Complementary and Alternative Medicine Therapies for HCV:

B. Complementary and alternative medicine (CAM) therapies are used by a substantial number of persons with chronic HCV infection, with some surveys estimating in excess of 20% of patients with chronic HCV using at least one CAM therapy. The most commonly used alternative medicine is Silybum marianum, commonly referred to as silymarin or milk thistle (this inhibits P-Glycoprotein). Other agents used include echinacea, St. John's wort, valerian, and ginkgo biloba. Milk thistle is a known drug interaction for simeprevir, expected to reduce the efficacy of simeprevir and should be avoided during HCV therapy. Similarly, St. John's wort should not be used during any HCV therapy as this herb has multiple known drug-drug interactions and is expected to decrease the therapeutic efficacy of many drugs including sofosbuvir, simeprevir, daclatasvir, and elbasvir/grazoprevir by stimulating the P-glycoprotein. Thus, clinicians should ask patients about their use of "natural medications", including herbal products, vitamins, and supplements.

Although CAM therapies are frequently used, there are no data to support their use for patients with chronic HCV infection. In addition, alternative medications have the potential to interfere or interact with traditional therapies used to treat HCV. The use of St. John's wort is contraindicated with sofosbuvir and simeprevir. At present, the use of complementary medications is not recommended for patients with HCV. Moreover, some herbal products can pose additional risks to patients with cirrhosis because of effects on platelets and clotting ability.

CAM Recommendations:

- Patients who are candidates for hepatitis C therapy should stop all herbal supplements while on therapy.
- Patients who have cirrhosis who want to take herbal supplements should be counseled on the potential complications of using herbals. All herbal supplements in patients with cirrhosis should be evaluated for potential increased risk of bleeding.

b. Baking soda for acid suppression:

Some patients will use home remedies for acid suppressive therapy including baking soda. Because baking soda can reduce gastric pH it can potentially cause a drug interaction for therapies requiring an acidic environment for absorption such as ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir. Patients often do not readily recognize baking soda as a medication, thus it is important to ask specifically if patients are using baking soda.

c. Drugs to Avoid in Patients with Liver Disease:

- Antidepressants: Many antidepressants are extensively metabolized by the liver and can accumulate due to impaired metabolic activity. In general, antidepressants should be started at a lower dose and titrated up for effect. Duloxetine should not ordinarily be used due to reported cases of fatal hepatic failure.
- Benzodiazepines: The use of benzodiazepines should be evaluated in all patients due to concerns for abuse and the risk of over-sedation. Although all benzodiazepines are metabolized by the liver, lorazepam, oxazepam, and temazepam are metabolized through a pathway typically preserved even in patients with cirrhosis and have no dosage adjustment recommended in patients with liver disease. Alprazolam has altered metabolism in liver disease and can accumulate despite its short action of activity; therefore it should be used with caution. Chlordiazepoxide, clonazepam, and diazepam are all long-acting benzodiazepines known to accumulate in patients with liver disease and should be avoided in chronic use.
- OTC Pain Management: Acetaminophen and NSAIDs: Acetaminophen may be used in cirrhotic patients with a maximum use of 2 grams daily for no longer than 14 days at a time. Acetaminophen induced hepatotoxicity is a well-known cause of hepatic failure and often occurs due to unintentional overdosage. Moreover, even among healthy patients LFTs can increase to 3x the upper limit of normal at a dose of 4 grams daily for 14 days with complete resolution when acetaminophen is stopped (Watkins PB, 2006). (Patients should be counseled on the prevalence of acetaminophen in many OTC products and limit use. Patients with on-going pain management issues should be considered for alternative pain treatment. NSAIDs including aspirin, ibuprofen, naproxen, and others should be avoided in patients with cirrhosis due to an increased risk of bleed, potential for renal toxicity, and impaired response to diuretic therapy (Boyer, Zia, & Reynolds, 1979) (Zipser RD, 1979) (Wong F, 1979).
- Statins: Although statins are rarely associated with elevations in liver enzymes (<3%), there are currently no data to suggest statins should be avoided in patients with liver disease, including patients with HCV. No difference in AST/ALT elevations has been found among HCV seropositive or HCV seronegative patients. Additionally, patients with compensated cirrhosis are not known to experience an increase in statin related hepatotoxicity (Tandra S, 2009).[2] There are no known drug-drug interactions with sofosbuvir and statins. Concomitant use of ledipasvir with rosuvastatin increases the concentrations of rosuvastatin which is associated with an increased risk of myopathy including rhabdomyolysis. Coadministration of ledipasvir and rosuvastatin is not recommended. Gemfibrozil cannot be used with ombitasvir/paritaprevir/ritonavir and dasabuvir due to risk of QT prolongation. Lovastatin and simvastatin can cause myopathy and rhabdomyolyis and are contraindicated with ombitasvir/paritaprevir/ritonavir and dasabuvir. Rosuvastatin may be used at a maximum dose of 10 mg per day and pravastatin may be used at a max dose of 40 mg per day. Statins may be used with simeprevir but require lower dosages and monitoring for safety; increased levels of statins pose a risk for rhabdomylolysis. Statins are expected to increase with concomitant daclatasvir use. Consider holding statin therapy during HCV therapy. Pravastatin has the lowest risk of DDI and side effects. Both pravastatin and pitavastatin may be used with elbasvir/grazoprevir; all other statins should be used at the lowest possible dose or consider holding while on HCV therapy. Statins in patients with cirrhosis may have a marked effect on HCC prevention.
- Phosphodiesterase Inhibitors (sildenafil, tadalafil, vardenafil): The use of these agents for erectile dysfunction should be started at the lowest effective dose in patients with cirrhosis and titrated to effect. Individual drug-drug interactions vary.

How To Obtain Treatment Medications

Patient assistance programs exist for all currently available HCV medications. Please find the patient assistance program attachment below:

- Patient Assistance Programs

Monitoring of Patients Who Receive HCV Therapy

Planned Laboratory Studies and Visits during Therapy

Please find Project ECHO® flowsheets to help guide the treatment for your patient:

a. Treatment Flowsheets

A.

Pregnancy and Birth Control

Ribavirin can cause birth defects and fetal death. Pregnant women and men whose female partners are pregnant or considering pregnancy are not candidates for therapy. Patients must practice 2 forms of birth

B. control during treatment and for 6 months after. Simeprevir does not affect ethinyl estradiol/norethindrone concentrations. For sofosbuvir-based therapies, recommendations state that 2 forms of non-hormonal contraception should be used and that female patients should have a negative pregnancy test prior to initiating therapy and monthly thereafter. There are data indicating no loss of hormonal contraceptive efficacy when combined with either sofosbuvir or sofosbuvir/ledipasvir (German P, 2014).

Ethinyl estradiol containing products including oral contraceptives are a contraindication for the use of glecaprevir/pibrentasvir and ombitasvir/paritaprevir/ritonavir and dasabuvir due to observed ALT elevations. Female patients who are prescribed glecaprevir/pibrentasvir or ombitasvir/paritaprevir/ritonavir and dasabuvir who require 2 forms of contraception may use progestin only products and non-hormonal products such as condoms.

C.

Management of Anemia

a. Anemia in HCV treatment is predominantly due to ribavirin's accumulation within the red blood cell (RBC) and subsequent oxidative membrane damage causing hemolysis. Hemoglobin declines of approximately 1 gram per week of ribavirin exposure may occur in the first 4 weeks of treatment. Further declines are unlikely.

For patients experiencing anemia, the initial recommendation is for ribavirin dose reduction.

Recommendations:

1. The decision to reduce ribavirin should be based on individual patient characteristics and response of the hemoglobin level to ribavirin. Variables that affect this decision are baseline hemoglobin, renal function, and slope of the hemoglobin decline during the first 2-4 weeks of treatment, age, medical comorbidities, altitude, and presence or absence of cirrhosis.
2. Consider reducing ribavirin in patients who experience ≥25 % decline in hemoglobin within a 4-week period.
3. Do not dose reduce the direct acting antivirals (sofosbuvir, sofosbuvir/ledipasvir, simeprevir, ombitasvir/paritaprevir/ritonavir, dasabuvir, daclatasvir, elbasvir/grazoprevir, or sofosbuvir/velpatasvir) to manage anemia.
4. For Hgb <10 g/dl repeat CBC, contact ECHO® HCV specialist or present to HCV Clinic within 72 hours. If <8.5 g/dl hold RBV and contact ECHO® HCV specialist immediately.

Treatment Stopping Rules

a. Therapy is not response-guided. There are no stopping rules for treatment.

Patient Safety Summary

a. In order to ensure increased patient safety during treatment, closer monitoring is required for some patients. Treating sites are responsible for reviewing all laboratory results. If treatment results in any of the following conditions the patient will likely require more frequent monitoring:

D.

- Decline in Hgb more than 1 g/dL per week
- Hgb to <11 g/dL

E.

POST TREATMENT

Patients with undetectable HCV RNA at the end-of-treatment (EOT) should have an HCV RNA done 12 weeks after completing therapy. Long-term follow-up studies indicate that SVR represents durable eradication (cure) of HCV infection. If HCV RNA is detected following an end of treatment response, consider genotyping if there is any risk of reinfection. Routine testing of HCV RNA once SVR is demonstrated is not indicated.

GUIDELINES FOR PRESENTATION TO ECHO® CLINIC

How to Connect to an ECHO® Clinic

A. Connecting to an ECHO® Clinic is easy. Most Hubs provide connection options through phone and video. Video connection is always the preferred modality as it enhances the participant's opportunity to learn. Many participants can easily access the ECHO® clinic through a webcam, smart phone or tablet (with front and back cameras). Each Project ECHO Hub has different ECHO® Clinic hours on different days of the week. Please see the contact sheet on the following page to reach out to the Hub of interest for specific details.

Reasons to Present a Patient:

B. In general, the following are reasons to present a case. Each ECHO Hub may have additional reasons for patient case presentation.

1. Initial presentation for work up for treatment.
2. Patient previously presented with recommendations for further work-up.
3. Patients on treatment should be presented for the following reasons:
    - Report any on-treatment quantifiable HCV RNA
    - For assistance in managing any side effects or laboratory abnormalities
    - When a patient is taking ribavirin and:
        - Hemoglobin < 11 g/dl, has dropped ≥ 4 g from starting value, or has dropped ≥ 2 g since last lab draw

C.

How to Present a Patient

Each Project ECHO HCV Collaborative Hub site has a different process and forms for case presentation. To determine your hub's process, please contact your site with the information on the following page.

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Project ECHO Materials

Project ECHO provides myriad materials for the screening, management, and treatment of Hepatitis C, including the following:

- Initial presentation forms for pre-treatment evaluation
- HCV Treatment Decision Trees
- Treatment Flow Sheets
- HBV Reactivation
  - FDA Statement
  - Algorithm

Hepatitis C Initial Presentation

Presentation Date: ____/____/_____ Site: _____ Clinician: _____

PLEASE NOTE that case consultations do not create or otherwise establish a provider-patient relationship between any clinician and any patient whose case is being presented in this clinical setting. ***Always use Patient ID# when presenting a patient in clinic. Sharing patient name, initials or other identifying information violates HIPAA privacy laws.***

Screening Encounter Date: ____/____/_____ *(required)*

General Information/Demographics

Patient ECHO ID:		**Age:**	
Gender:	☐ Male ☐ Female		
Ethnicity – Hispanic or Latino:	☐ Yes ☐ No		
Race:	☐ American Indian, Alaska Native ☐ Asian ☐ Black, African American ☐ Native Hawaiian, Pacific Islander ☐ White		
Insurance:	☐ None ☐ Medicare ☐ Medicaid, MCO: _____ ☐ Commercial Health Insurance: _____ ☐ Other: _____		

Suspected Route of HCV Transmission (Check all that apply)

Suspected Route of Transmission	Yes	Description
Current or past injection drug use	☐	If yes, Injection Drug Use in the last 12 months? ☐ Yes ☐ No
Recipient of clotting factor concentrates made before 1987	☐	
Blood transfusion or solid organ transplant before July 1992	☐	
Needlestick injury in healthcare setting	☐	
Birth to an HCV-infected mother	☐	
Sex with an HCV infected person	☐	
Sharing contaminated personal items, such as razors or tooth brushes with an HCV infected person	☐	
Non-professional tattoo	☐	
Unknown	☐	

Medical Diagnoses (Check all that apply)

Liver Related History (select all that apply)	Yes	Description/Comments
HCV	☐	Year of diagnosis: _____
Cirrhosis	☐	Any evidence of decompensation? ☐ Ascites ☐ Hepatic encephalopathy ☐ Variceal bleed
Previous HCV Treatment	☐	Year: _____ Drug Regimen: Select Regimen Duration of treatment in weeks: _____
Liver Biopsy	☐	Year: _____ Results: _____
Hepatocellular Carcinoma	☐	Year of diagnosis: _____

Medical Diagnoses (select all that apply)	**Yes**	**Description/Comments**
Asthma	☐	
Auto Immune Disease	☐	Type of disease: _____
Brain Injury	☐	
Cancer	☐	Year: _____ Type of Cancer: _____
Chronic Pain	☐	
COPD	☐	
Coronary Artery Disease	☐	
Cryoglobulinemia	☐	
Diabetes Mellitus	☐	
Hepatitis B, chronic	☐	
HIV	☐	
Hypertension	☐	
Peripheral Neuropathy	☐	
Renal Insufficiency	☐	
Seizure Disorder	☐	
Solid Organ Transplant	☐	Year of transplant: _____ Organ transplanted: _____

Hepatitis Vaccinations and Labs

Vaccination/Labs		**Description/Comments**
Is patient immune to hepatitis A?		REMINDER: Patients with hepatitis C need to be vaccinated for both hepatitis A and B.
Hepatitis B surface antigen (HBsAg)		
Hepatitis B surface antibody (anti-HBs)		
Hepatitis B core antibody (anti-HBc)		

Psychiatric Diagnosis

Psychiatric Diagnosis	Yes	Description
Depression	☐	
Anxiety	☐	If yes, is patient on medication for anxiety? ☐Yes ☐No
Mania/Hypomania	☐	If yes, is patient on medication for Mania/Hypomania? ☐Yes ☐No

Survey Scores

PHQ-9 Score:		Date of survey: ____/____/_____

Substance Use History

Substance Use History	Yes	No	Description/Comments
Does patient currently drink alcohol?	☐	☐	If no, has the patient ever had a drinking problem? ☐Yes ☐No Date of last drink: ____/____/_____
Does patient currently use drugs other than alcohol?	☐	☐	If yes, check all that apply: ☐ Opiates ☐ Stimulants (cocaine, amphetamine, etc.) ☐ Benzodiazepines ☐ Marijuana
Does patient smoke cigarettes?	☐	☐	

Current Medications: (Please include dosage)

Medication Name	Dosage	Frequency

Medication Name	Dosage	Frequency

Current Method of Birth Control:

Medication Name	Dosage	Frequency

Body Mass Index

Height:		☐Centimeters	☐Inches
Weight:		☐Kilograms	☐Pounds
BMI:			

Laboratory

Basic Laboratories			
Date of Lab Draw:	/ /		
WBC		INR	
ANC		Albumin	
HGB		ALT	
HCT		AST	
Platelets		Alk Phos	
Creatinine		T. Bili	
GFR		Direct Bili	
Glucose		Total Prot	
Protime			

Other Essential Results	Date	Result
Fe	/ /	
TIBC	/ /	
TSAT	/ /	
Ferritin	/ /	
Vitamin D 25-OH	/ /	
AFP	/ /	
HIV Ab	/ /	
HCV Genotype	/ /	
HCV Viral Load	/ /	
Other:	/ /	

	Result	Fibrosis Score
APRI =		
FIB-4 =		
Fibrosure =		
Fibrotest =		
Fibroscan =		
MELD =		
Child-Pugh=		

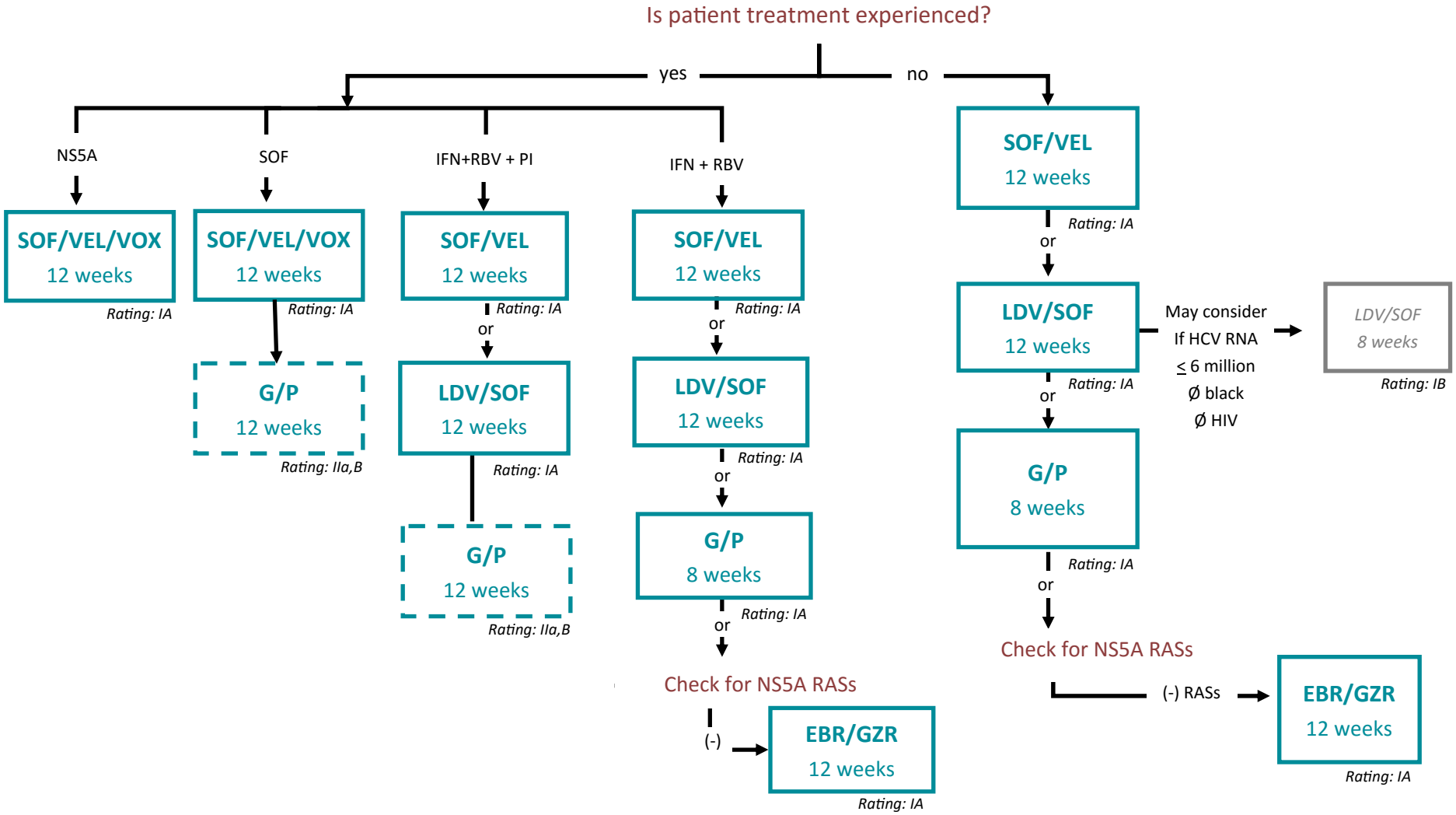
For Clinical Calculators (APRI, FIB-4, MELD, etc.), visit:
hepatitisc.uw.edu/page/clinical-calculators/meld

Metavir Score	Biopsy	Fibroscan	Elastography (ARFI/PSWE)	Fibrosure	APRI	FIB-4
F4	F4	≥ 12.5 kPa		≥ 0.75	≥ 1.0	>3.25
F3	F3	9.6 - 12.4 kPa	2.01-2.33 m/s	0.58-0.74		
F2	F2	7.1 – 9.5 kPA	1.38-2.0 m/s	0.49-0.57	≥ 0.7 < 1.0	<1.45
F1	F1	≤ 7.0 kPa	≤ 1.37	0.23-0.48	< 0.7	
F0	F0			≤ 0.22		

Please list any imaging or transient elastography results (e.g. Ultrasound, fibroscan, etc.):

Version: 12/11/2017

Hepatitis C : Genotype 1a Non-Cirrhotic Treatment Regimen



Direct Acting Antivirals (DAAs):

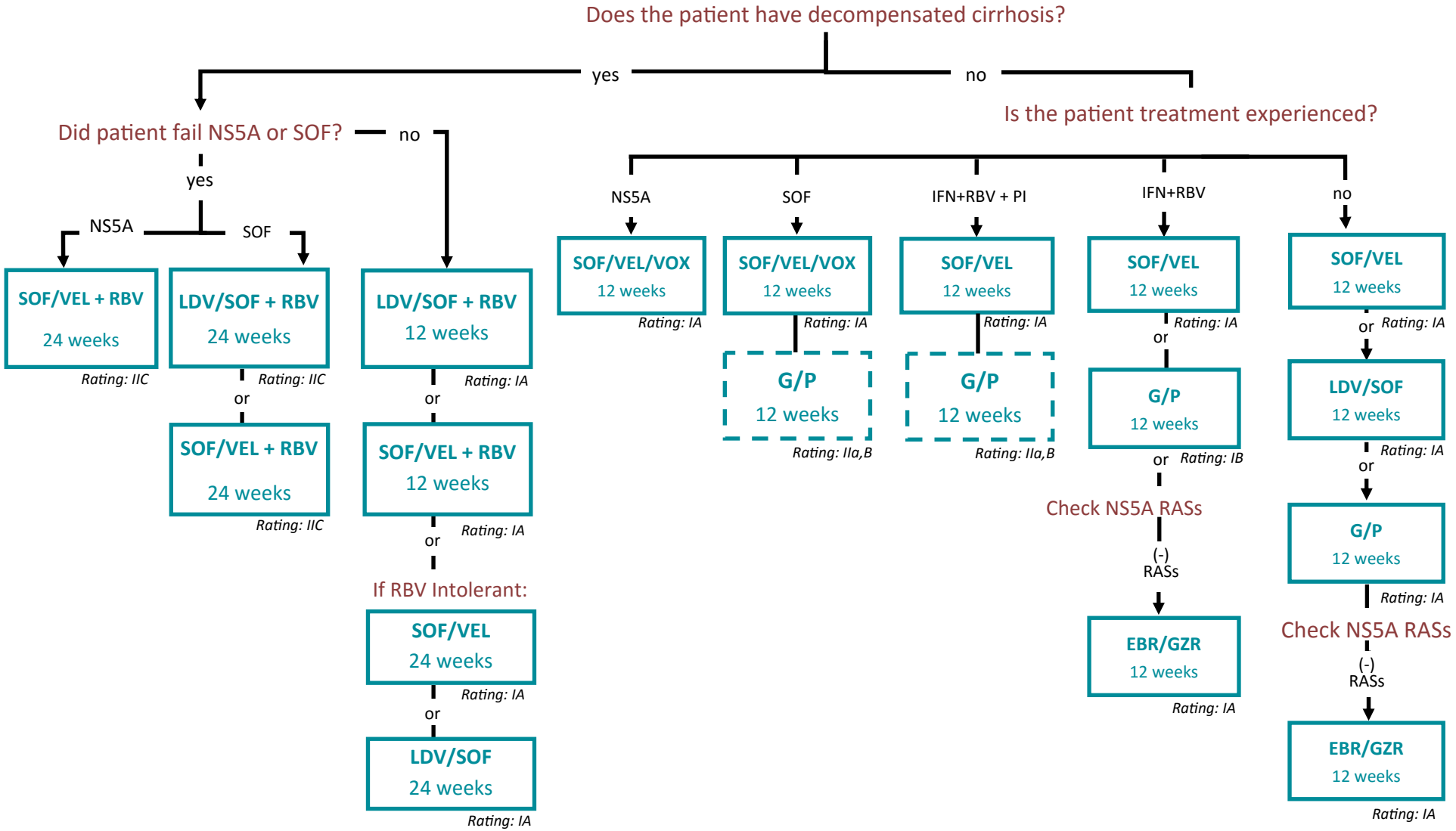
EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

**Rating for Level of Recommendation*

These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

Version: 12/11/2017

Hepatitis C : Genotype 1a Cirrhotic Treatment Regimen



*Rating for Level of Recommendation

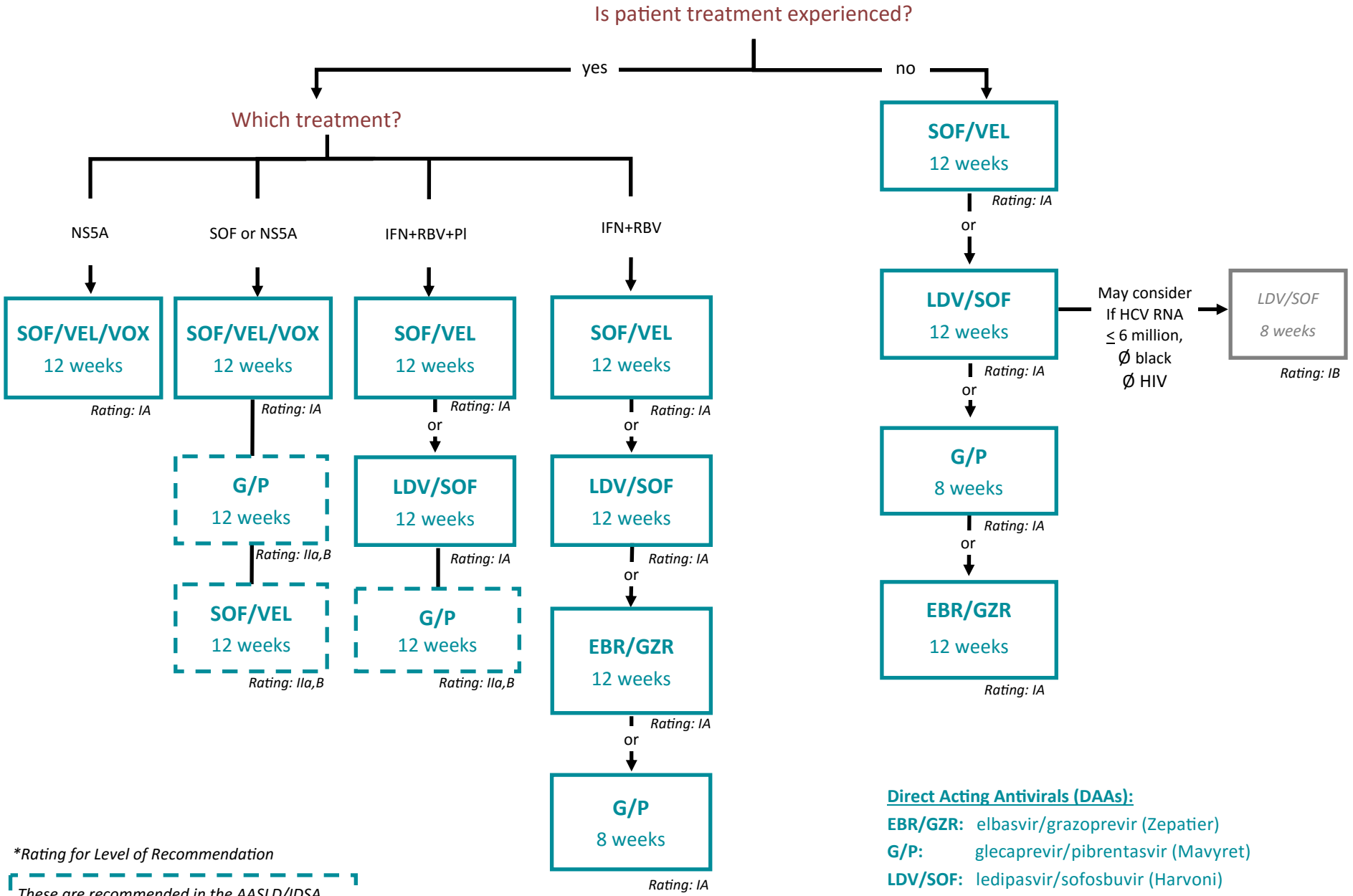
These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

Direct Acting Antivirals (DAAs):

EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

Version: 12/11/2017

Hepatitis C : Genotype 1b Non-Cirrhotic Treatment Regimen



*Rating for Level of Recommendation

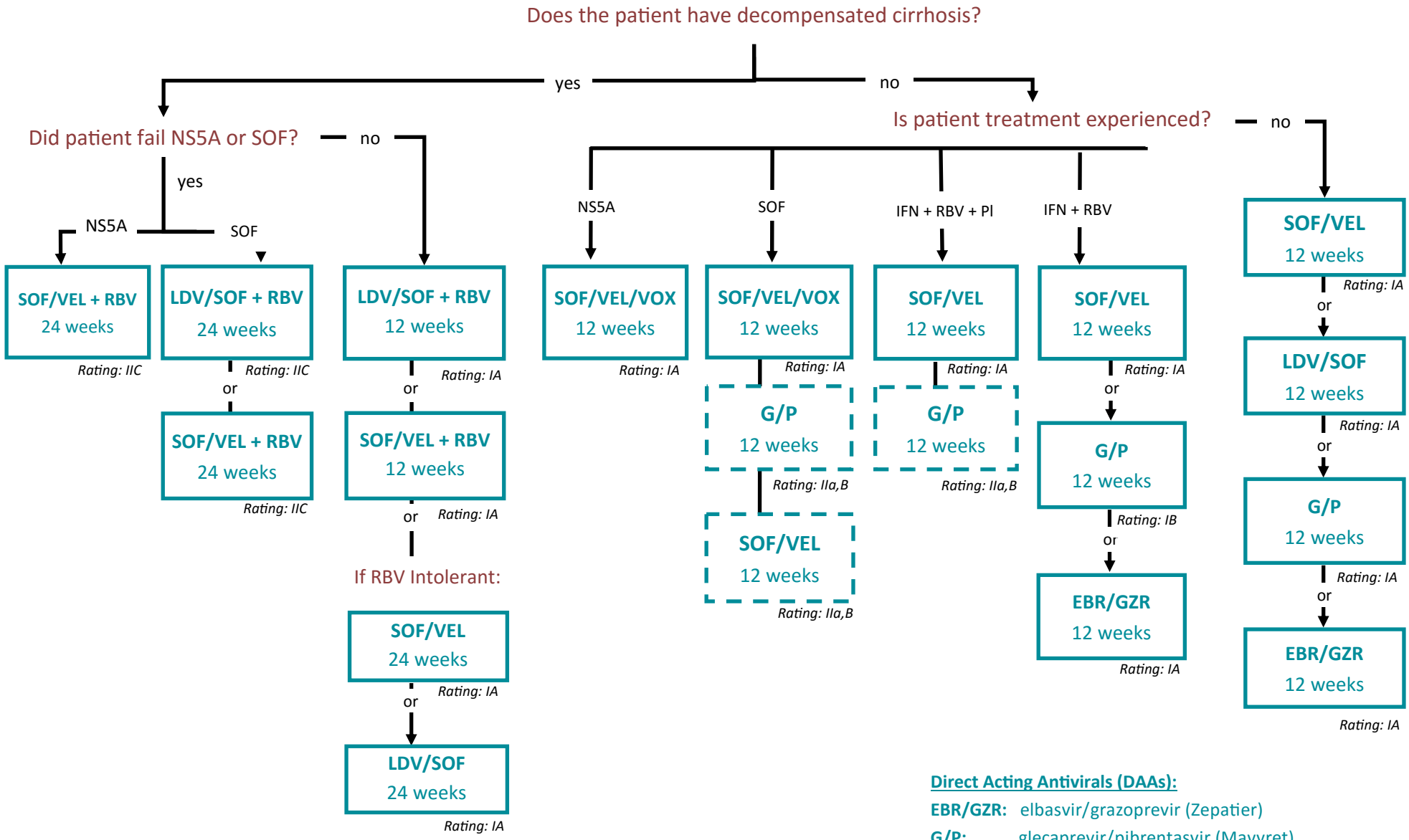
These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

Direct Acting Antivirals (DAAs):

EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

Version: 12/11/2017

Hepatitis C : Genotype 1b Cirrhotic Treatment Regimen



*Rating for Level of Recommendation

These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

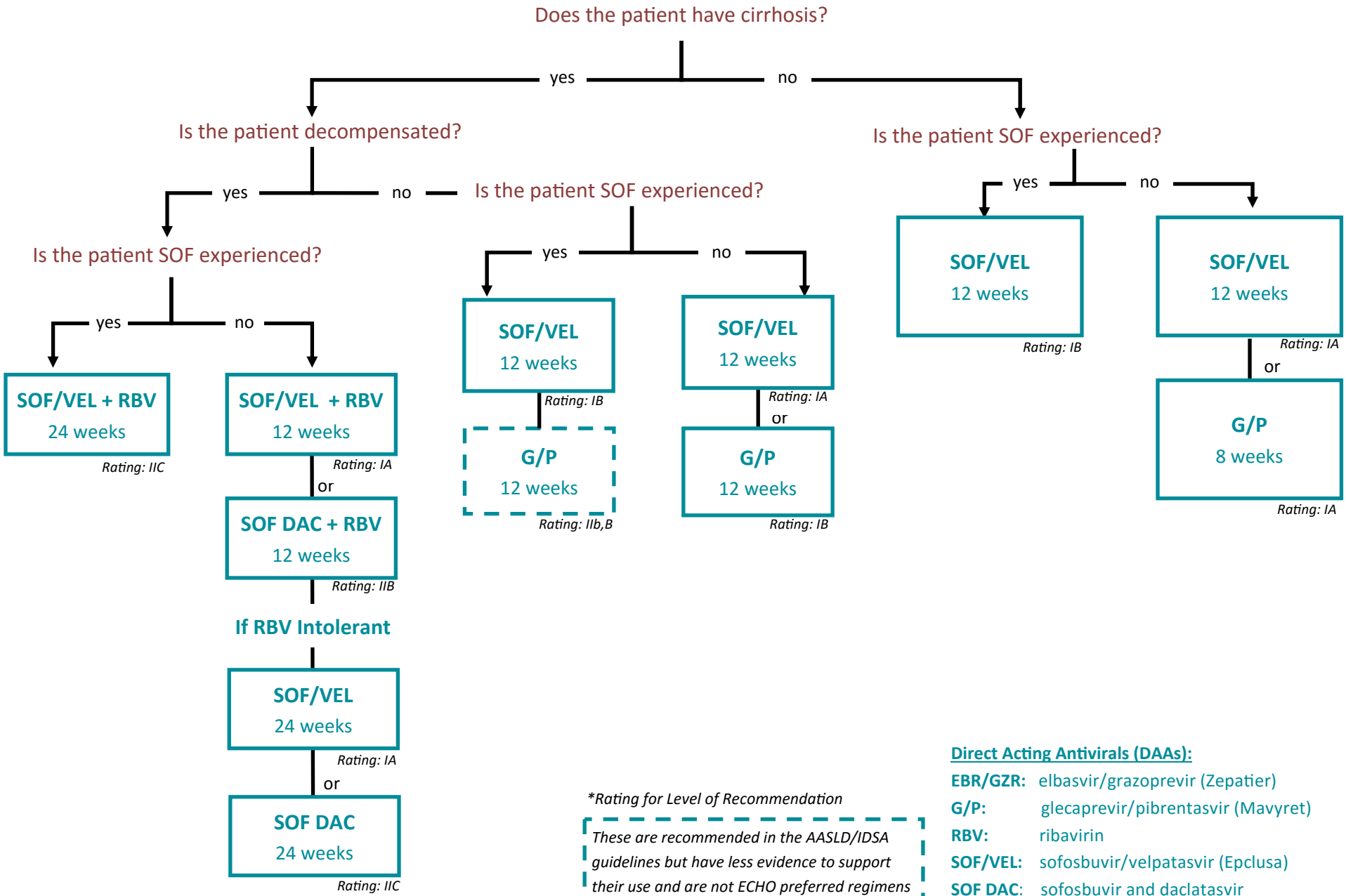
Direct Acting Antivirals (DAAs):

EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
RBV: ribavirin
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

Version: 12/11/2017

Hepatitis C Genotype 2 Treatment Regimen Decision Tree

Genotype 2 Patients



*Rating for Level of Recommendation

These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

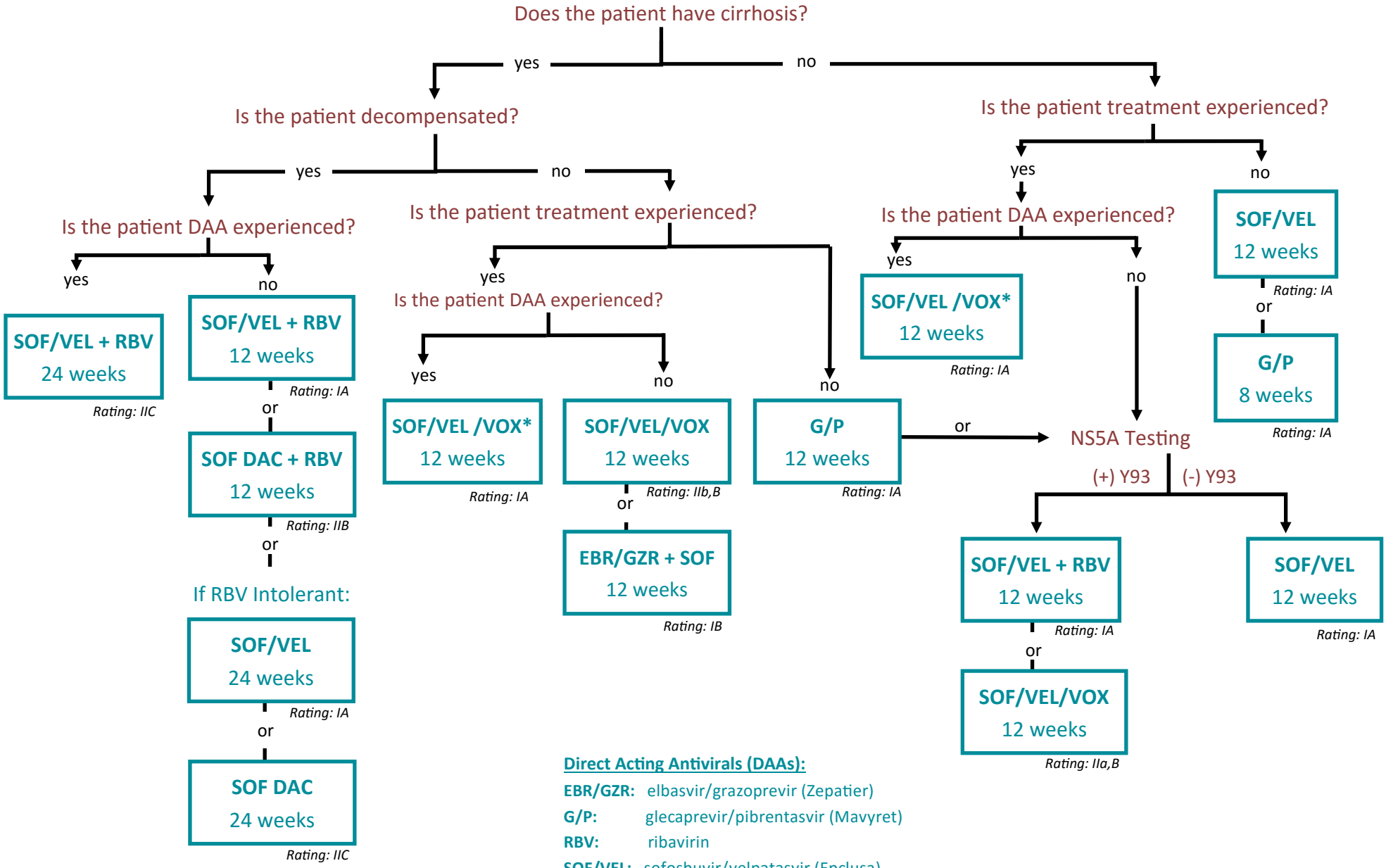
Direct Acting Antivirals (DAAs):

EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
RBV: ribavirin
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF DAC: sofosbuvir and daclatasvir

Version: 12/11/2017

Hepatitis C Genotypes 3 Treatment Regimen Decision Tree

Genotype 3 Patients



Direct Acting Antivirals (DAAs):

EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
RBV: ribavirin
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)**SOF DAC**: sofosbuvir and daclatasvir

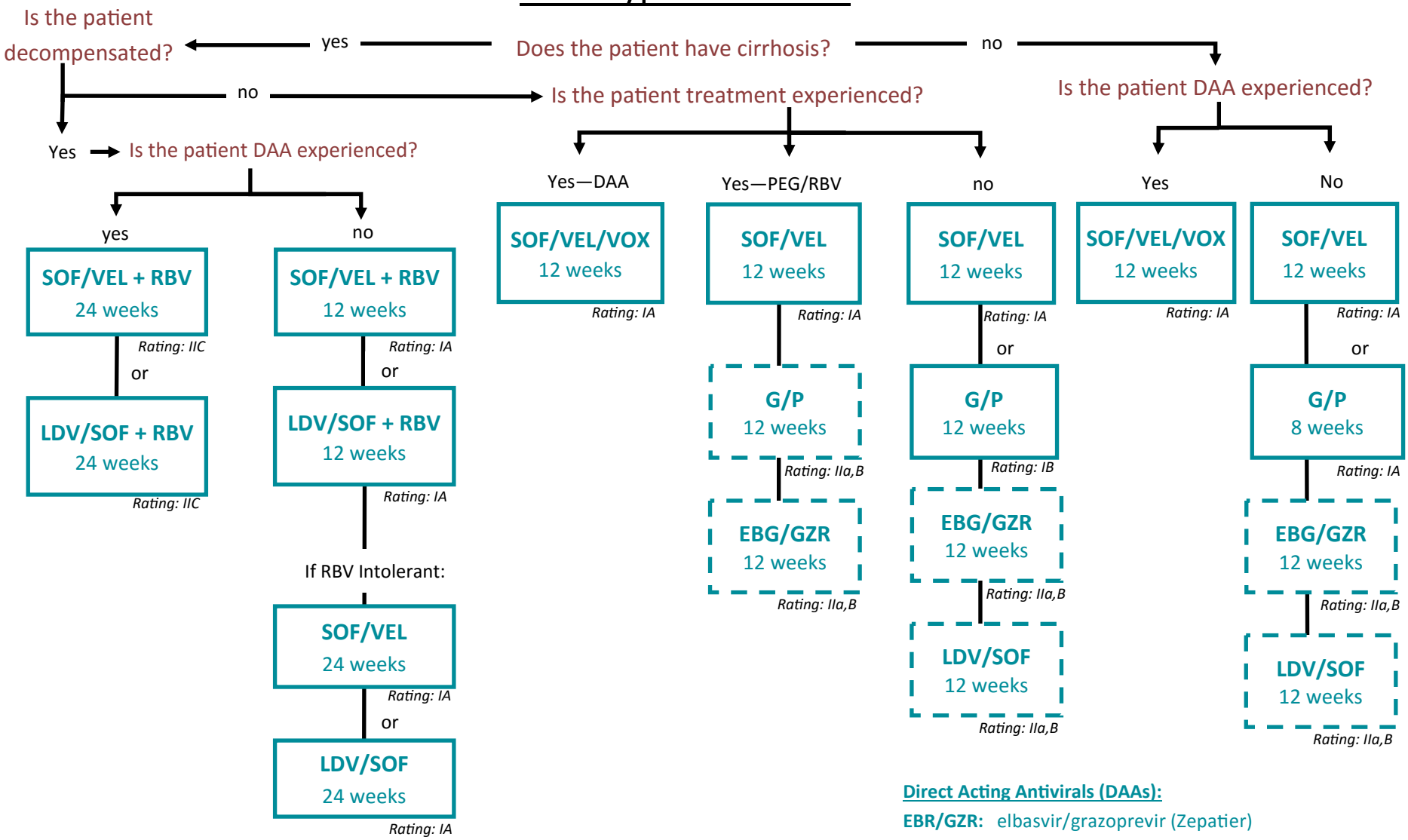
**Rating for Level of Recommendation*

*IF NS5A-experienced, add weight based RBV

Version: 12/4/2017

Hepatitis C Genotypes 4 Treatment Regimen Decision Tree

Genotype 4 Patients



*Rating for Level of Recommendation

These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

Direct Acting Antivirals (DAAs):

EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
RBV: ribavirin
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

Hepatitis C Treatment Flowsheets

Revised on 01/31/2018

Treatment Flowsheets

Please click the following links to access hepatitis C treatment flowsheets:

8 week course of treatment

12 week course of treatment

16 week course of treatment

24 week course of treatment

12 week course of treatment plus ribavirin

24 week course of treatment plus ribavirin

Project ECHO®

for 8 weeks

Hepatitis C Minimum Visit/ Labs Flow Sheet

Week of Treatment	Screening	Wk 0 Start of Tx	Wk 2	Wk 4	Wk 8 End of Tx	Wk 20
Dates	**N/A**	**01/01/18**	**01/15/18**	**01/29/18**	**02/26/18**	**05/21/18**
Visit		**x**	**x**	**x**	**x**	**x**
HCV RNA	**x**			**x** **If HCVRNA is quantifiable, present to ECHO; re-check at week 6**	**x**	**x**
CBC w/ Diff	**x**			**x**	**x**	**x**
Chem 7	**x**			**x**	**x**	**x**
LFTs/HFP	**x**			**x**	**x**	**x**
HBsAg **HBs Ab** **HBc Ab***	**x**					

Key Points to Remember:

1) Week 0 Visit is the day of the first dose of medication.

2) Lab draws are done the end of the treatment week.

3) HBc Ab should be total or IgG.

Patient Name:	**Date of Birth:**	**Patient ID:**	**Genotype:**

REV: 11/20/17 SLS

for 12 weeks

Hepatitis C Minimum Visit/ Labs Flow Sheet

Week of Treatment	Screening	Wk 0 Start of Tx	Wk 2	Wk 4	Wk 8	Wk 12 End of Tx	Wk 24
Dates	N/A	01/01/18	01/15/18	01/29/18	02/26/18	03/26/18	06/18/18
Visit		x	x	x	x	x	x
HCV RNA	x			x If HCVRNA is quantifiable, present to ECHO; re-check at week 6		x	x
CBC w/ Diff	x			x	x	x	x
Chem 7	x			x	x	x	x
LFTs/HFP	x			x	x	x	x
HBsAg HBs Ab HBc Ab*	x						

Key Points to Remember:

1) Week 0 Visit is the day of the first dose of medication.
2) Lab draws are done the end of the treatment week.
3) HBc Ab should be total or IgG.

Patient Name:	Date of Birth:	Patient ID:	Genotype:

REV: 11/20/17 SLS

for 16 weeks

Hepatitis C Minimum Visit/ Labs Flow Sheet

Week of Treatment	Screening	Wk 0 Start of Tx	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16 End of Tx	Wk 28
Dates	**N/A**	**01/01/18**	**01/15/18**	**01/29/18**	**02/26/18**	**03/26/18**	**04/23/18**	**07/16/18**
Visit		**X**	**X**	**X**	**X**	**X**	**X**	**X**
HCV RNA	**X**			**X** **If HCVRNA is quantifiable, present to ECHO; re-check at week 6**			**X**	**X**
CBC w/ Diff	**X**			**X**	**X**	**X**	**X**	**X**
Chem 7	**X**			**X**	**X**	**X**	**X**	**X**
LFTs/HFP	**X**			**X**	**X**	**X**	**X**	**X**
HBsAg HBs Ab HBc Ab*	**X**							

Key Points to Remember:

1) Week 0 Visit is the day of the first dose of medication.
2) Lab draws are done the end of the treatment week.
3) HBc Ab should be total IgG.

Patient Name:	**Date of Birth:**	**Patient ID:**	**Genotype:**

REV: 11/20/17 SLS

for 24 wks

Hepatitis C Minimum Visit/ Labs Flow Sheet

Week of Treatment	Screening	Wk 0 Start of Tx	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 End of Tx	Wk 36
Dates	N/A	01/01/18	01/15/18	01/29/18	02/26/18	03/26/18	04/23/18	05/21/18	06/18/18	09/10/18
Visit		x	x	x	x	x	x	x	x	x
HCV RNA	x			x If HCVRNA is quantifiable, present to ECHO; re-check at week 6					x	x
CBC w/ Diff	x			x	x	x	x	x	x	x
Chem 7	x			x	x	x	x	x	x	x
LFTs/HFP	x			x	x	x	x	x	x	x
HBsAg HBs Ab HBc Ab*	x									

Key Points to Remember:

1) Week 0 Visit is the day of the first dose of medication.
2) Lab draws are done the end of the treatment week.
3) HBc Ab should be total or IgG.

Patient Name:	Date of Birth:	Patient ID:	Genotype:

REV: 11/20/17 SLS

+ Ribavirin x 12 weeks

Hepatitis C Minimum Visit/ Labs Flow Sheet

Week of Treatment	Screening	Wk 0 Start of Tx	Wk 2	Wk 4	Wk 8	Wk 12 End of Tx	Wk 24
Dates	**N/A**	**01/01/18**	**01/15/18**	**01/29/18**	**02/26/18**	**03/26/18**	**06/18/18**
Visit		**X**	**X**	**X**	**X**	**X**	**X**
HCV RNA	**X**			**X** **If HCVRNA is quantifable, present to ECHO; re-check at week 6**		**X**	**X**
CBC w/ Diff	**X**		**X**	**X**	**X**	**X**	**X**
Chem 7	**X**			**X**	**X**	**X**	**X**
LFTs/HFP	**X**			**X**	**X**	**X**	**X**
Pregnancy	**X**	**X**		**X**	**X**	**X**	
HBsAg HBs Ab HBc Ab*	**X**						

Key Points to Remember:

1) Week 0 Visit is the day of the first dose of medication.
2) Lab draws are done the end of the treatment week.
3) HBc Ab should be total or IgG.

Key Points to Remember:	**Date of Birth:**	**Patient ID:**	**Genotype:**

REV: 11/21/17 SLS

+ Ribavirin for 24 weeks

Hepatitis C Minimum Visit/ Labs Flow Sheet

Week of Treatment	Screening	Wk 0 Start of Tx	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 End of Tx	Wk 36
Dates	**N/A**	**01/01/18**	**01/15/18**	**01/29/18**	**02/26/18**	**03/26/18**	**04/23/18**	**05/21/18**	**06/18/18**	**09/10/18**
Visit		X	X	X	X	X	X	X	X	X
HCV RNA	X			X If HCVRNA is quantifiable, present to ECHO; re-check at week 6					X	X
CBC w/ Diff	X		X	X	X	X	X	X	X	X
Chem 7	X			X	X	X	X	X	X	X
LFTs/HFP	X			X	X	X	X	X	X	X
Pregnancy	X	X		X	X	X	X	X		
HBsAg HBs Ab HBc Ab*	X									

Key Points to Remember:

1) Week 0 Visit is the day of the first dose of medication.
2) Lab draws are done the end of the treatment week.
3) HBc Ab should be total or IgG.

Key Points to Remember:	**Date of Birth:**	**Patient ID:**	**Genotype:**

REV: 11/20/17 SLS

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

Safety Announcement

[10-04-2016] The U.S. Food and Drug Administration (FDA) is warning about the risk of hepatitis B virus (HBV) becoming an active infection again in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death.

As a result, we are requiring a *Boxed Warning*, our most prominent warning, about the risk of HBV reactivation to be added to the drug labels of these DAAs directing health care professionals to screen and monitor for HBV in all patients receiving DAA treatment. This warning will also be included in the patient information leaflet or Medication Guides for these medicines.

Direct-acting antiviral medicines are used to treat chronic hepatitis C virus (HCV) infection, an infection that can last a lifetime. These medicines reduce the amount of HCV in the body by preventing HCV from multiplying, and in most cases, they cure HCV. Without treatment, HCV can lead to serious liver problems including cirrhosis, liver cancer, and death (see List of Direct-Acting Antivirals).

Health care professionals should screen all patients for evidence of current or prior HBV infection before starting treatment with DAAs, and monitor patients using blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up. It is currently unknown why the reactivation occurs.

Patients should tell your health care professional if you have a history of hepatitis B infection or other liver problems before being treated for hepatitis C. Do not stop taking your DAA medicine without first talking to your health care professional. Stopping treatment early could result in your virus becoming less responsive to certain hepatitis C medicines. Read the patient information leaflet or Medication Guide that comes with each new prescription because the information may have changed. Contact your health care professional immediately if you develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver problems.

We identified 24 cases of HBV reactivation reported to FDA[1] and from the published literature in HCV/HBV co-infected patients treated with DAAs during the 31 months from November 22, 2013 to July 18, 2016.[2-7] This number includes only cases submitted to FDA, so there are likely additional cases about which we are unaware. Of the cases reported, two patients died and one

required a liver transplant. HBV reactivation was not reported as an adverse event in the clinical trials submitted for the DAA approvals because patients with HBV co-infection were excluded from the trials. The trials excluded these patients in order to specifically evaluate the safety of DAAs, including their effects on the liver, in patients infected with only HCV and without the presence of another virus which affects the liver (see Data Summary).

We urge health care professionals and patients to report side effects involving DAAs and other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

List of Direct-Acting Antivirals (DAAs)*

Brand name	Active ingredient(s)	Drug Manufacturer
Daklinza	daclatasvir	Bristol-Myers Squibb
Epclusa	sofosbuvir and velpatasvir	Gilead Sciences
Harvoni	ledipasvir and sofosbuvir	Gilead Sciences
Olysio	simeprevir	Janssen
Sovaldi	sofosbuvir	Gilead Sciences
Technivie	ombitasvir and paritaprevir and ritonavir	Abbvie
Viekira Pak	dasabuvir and ombitasvir and paritaprevir and ritonavir	Abbvie
Viekira Pak XR	dasabuvir and ombitasvir and paritaprevir and ritonavir	Abbvie
Zepatier	elbasvir and grazoprevir	Merck Sharp Dohme

* DAA regimens not requiring use in combination with interferon. The DAA medicines, Victrelis (boceprevir) and Incivek (telaprevir), are not included in the list as they are used in combination with interferon and are no longer available in the United States.

Facts about Direct-Acting Antivirals (DAAs)

- Direct-acting antivirals (DAAs) are a class of prescription medicines that are FDA-approved to treat adults with hepatitis C virus (HCV) infection. These medicines are available as single-ingredient products and also in combination with other HCV medicines (see List of Direct-Acting Antivirals).
- DAAs reduce the amount of HCV in the body by preventing the virus from multiplying and, in most cases, cure HCV.
- Before starting DAA treatment, patients should tell their health care professionals if they:
    - Have current hepatitis B infection or have had hepatitis B infection in the past
    - Have liver problems other than HCV infection, such as cirrhosis
    - Have human immunodeficiency virus (HIV) infection
- Common side effects of DAAs depend on the specific medicines but can include tiredness, headache, and nausea.

Additional Information for Patients and Caregivers

- If you have had hepatitis B or are a carrier of hepatitis B virus (HBV), taking certain medicines called direct-acting antivirals (DAAs) to treat hepatitis C virus (HCV) infection could cause the HBV to become an active infection again. HBV reactivation may cause serious liver problems, including liver failure and death.
- Before taking DAA treatment, tell your health care professional if you have a history of hepatitis B infection or other liver problems.
- If you have had HBV, your health care professional should monitor you with blood tests to see if HBV infection becomes active while you are taking DAAs and for months after you stop taking DAAs.
- Talk to your health care professional if you have any questions or concerns about your HCV treatment.
- Contact your health care professional immediately if you develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver problems.
- Carefully read the patient information leaflet or Medication Guide that comes with your DAA drug prescriptions.
- Report any side effects from DAAs or other medicines to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Hepatitis B virus (HBV) reactivation has occurred in patients co-infected with hepatitis C virus (HCV) while undergoing treatment with DAAs for HCV infection. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. This risk has been observed with DAAs used without interferon to treat HCV infection.
- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of hepatitis B surface antigen (HBsAg) in a person who was previously HBsAg negative and hepatitis B core antibody (anti-HBc) positive. Reactivation of HBV replication is often followed by hepatitis, i.e., an increase in transaminase levels and, in severe cases, an increase in bilirubin levels, hepatic failure, and death.
- The mechanism through which HBV reactivation occurs is currently unknown.
- Cases of HBV reactivation have been reported in HCV patients treated with DAAs who are hepatitis B surface antigen (HBsAg) positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive), and were not receiving HBV antiviral treatment.
- To decrease the risk of HBV reactivation in patients co-infected with HBV and HCV, health care professionals should:
    - Screen all patients for evidence of current or prior HBV infection before initiating treatment with DAAs by measuring HBsAg and anti-HBc. In patients with serologic evidence of HBV infection, measure baseline HBV DNA prior to DAA treatment.

    - Monitor patients who show evidence of current or prior HBV infection for clinical and laboratory signs (i.e., HBsAg, HBV DNA, serum aminotransferase levels, bilirubin) of hepatitis flare or HBV reactivation during DAA treatment and post-treatment follow-up.
    - Consult a physician with expertise in managing hepatitis B regarding the monitoring and consideration for HBV antiviral treatment in HCV/HBV co-infected patients.
- Counsel patients to contact a health care professional immediately if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver injury.
- Encourage patients to read the patient information leaflet or Medication Guide that comes with their DAA prescriptions.
- Report adverse events involving DAAs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

A search of the FDA Adverse Event Reporting System (FAERS) database and the medical literature for cases reported and literature published between November 22, 2013, and July 18, 2016, identified 24 cases with confirmed reactivation of hepatitis B virus (HBV) infection who were receiving treatment with direct-acting antivirals (DAAs) for the treatment of HCV.[1-7] HBV reactivation usually occurred within 4-8 weeks, 52 days on average, of starting HCV treatment. Three of the patients decompensated, two of which died and one required hepatic transplantation.

The mechanism through which HBV reactivation occurs with DAAs is currently unknown. These medicines are not known to cause immunosuppression, but HBV reactivation may result from a complex interplay of host immunologic responses in the setting of infection with two hepatitis viruses. HBV reactivation was not reported as an adverse event during the clinical trials supporting the applications for the DAA approvals because HBV co-infection was one of the exclusion criteria. Patients with HBV co-infection were excluded in the initial phase 3 trials to allow a characterization of drug safety, including potential liver adverse reactions, in the presence of one hepatitis virus before conducting a more complicated safety evaluation of the drugs in patients infected with two hepatitis viruses.

Twelve of the 24 cases eventually received antiviral treatment active against HBV, either tenofovir or entecavir. Six cases did not report whether the patients received HBV treatment. The remaining six patients did not receive HBV treatment, and the reports did not contain sufficient information to assess why HBV treatment was not initiated. Treatment for HBV was reported to have been delayed in at least five of the 12 cases, and one patient died. Possible delays in HBV treatment occurred in at least three other cases, and one of these patients required a hepatic transplantation. With HBV treatment, most patients had improvement in HBV DNA, and in other signs and symptoms such as elevated transaminases, and malaise or fatigue.

In eight of the 24 cases, when transaminases started to rise, an adverse drug reaction caused by DAA hepatotoxicity was the initial diagnosis, and the medicines were discontinued. As the condition of patients deteriorated or failed to improve, HBV reactivation was considered among

the likely diagnoses. Thus, a common sequence of events was initiation of DAA-based HCV treatment, rapid drop of HCV RNA to undetectable levels within 1-2 weeks after normalization of transaminase levels (if they were elevated), followed by a rise in HBV DNA with or without increase in transaminases between weeks 4-8.

The patients who developed HBV reactivation were heterogeneous in terms of HCV genotype. These patients were also heterogeneous in terms of baseline HBV disease, fitting into three general categories of patients: those with detectable HBV viral load (n=7), those with positive HBsAg and undetectable HBV viral load (n=4), and those with negative HBsAg and undetectable HBV viral load (n=3). For the remaining 10 patients, HBsAg status was either not known or baseline HBV could not be interpreted.

References

1. The Food and Drug Administration Adverse Event Reporting System (FAERS).
2. Balagopal A, Thio CL. Editorial commentary: another call to cure hepatitis B. Clin Infect Dis 2015;61:1307-9.
3. Collins JM, Raphael KL, Terry C, Cartwright EJ, Pillai A, Anania FA,et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. Clin Infect Dis 2015;61:1304-6.
4. De Monte A, Courjon J, Anty R, Cua E, Naqvi A, Mondain V, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: Reactivation of hepatitis B virus coinfection as a further challenge. J Clin Virol 2016;78:27-30.
5. Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. J Med Case Rep 2015;9:164.
6. Kimura H, Ohkawa K, Sakakibara M, Imanaka K, Matsunaga T, et al. Sustained hepatitis C virus RNA clearance accompanied by elevation of hepatitis B virus DNA after short-term peginterferon-α, ribavirin and simeprevir therapy in chronic hepatitis patient having dual infection with hepatitis B and C viruses. Kanzo 2015;56:422-27.
7. Wang C, Ji D, Chen J, Shao Q, Li B, Liu J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. Clin Gastroenterol Hepatol. 2016 Jul 5. pii: S1542-3565(16)30370-6. doi: 10.1016/j.cgh.2016.06.023. [Epub ahead of print].

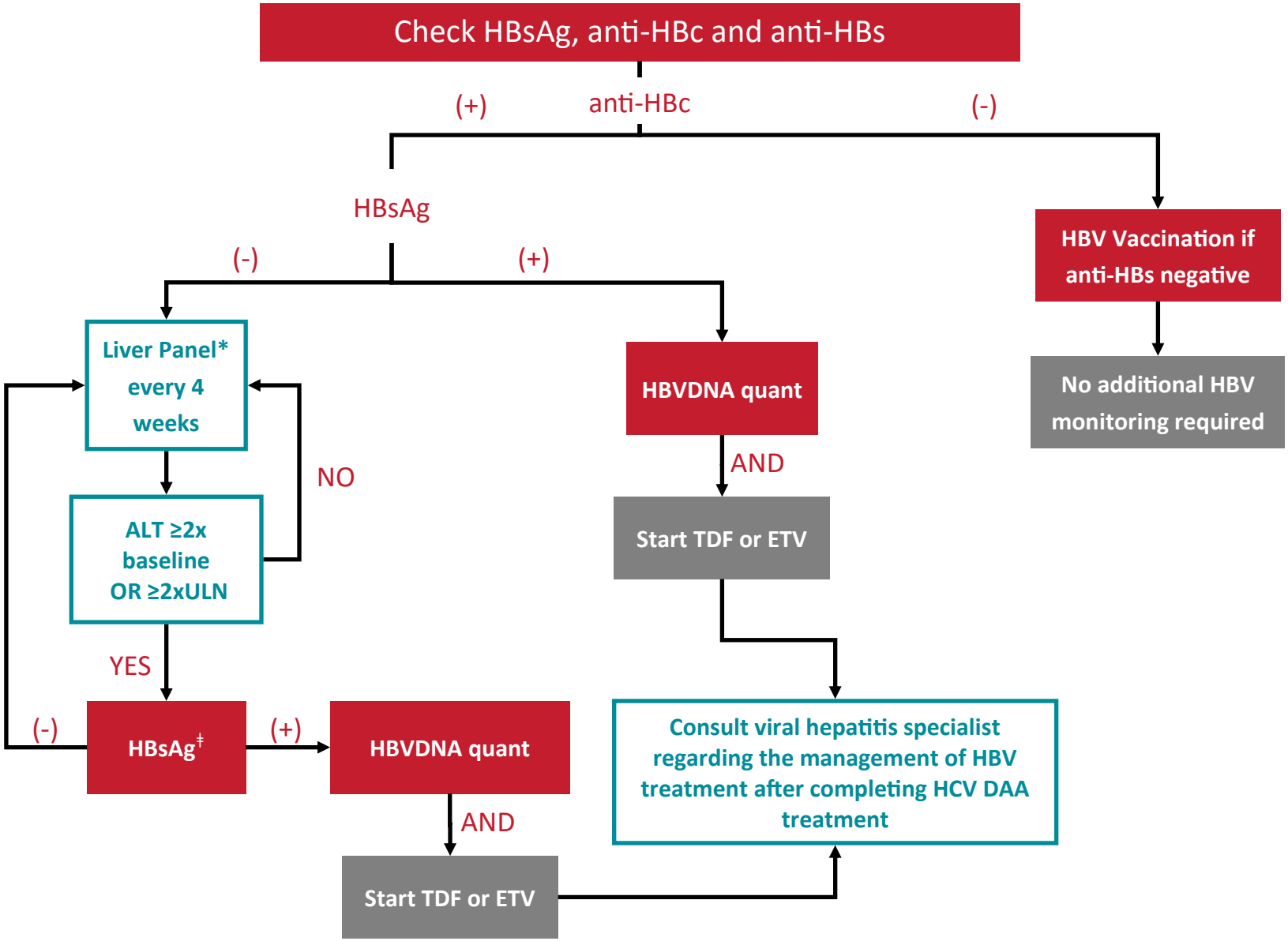
Related Information

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines

Version: 11/1/2016

Project ECHO HBV Monitoring for Patients on HCV Treatment



* Liver panel every 4 weeks while on HCV treatment and at 12 weeks post-treatment.

‡ HBsAg can be drawn at the same as HBVDNA for convenience or can ask for HBsAg with reflex HBVDNA.

Cost and Access to Direct-Acting Antiviral Agents

New drug regimens have made early detection and treatment of HCV critical, although the main barriers to treatment have been cost and complex prior-authorization processes. The new medications have been among the most expensive in history, although private and public insurance companies are beginning to cover the two to three month oral regimen and help cure this chronic disease. Fortunately in many states, including Washington, Medicaid will approve payment for nearly every patient with chronic HCV; this includes patients who are actively injecting drugs and/or using alcohol. Other private insurance companies will also cover the new medications, and patient assistance programs now provide free medication for eligible patients.

On January 6, the Indian Health Service issued a Dear Tribal Leader Letter to announce that the IHS recently signed an Interagency Agreement with the U.S. Department of Veterans Affairs (VA) authorizing the IHS to use the VA Veterans Health Administration's Consolidated Mail Outpatient Pharmacy (CMOP). With this development, Tribes and Tribal organizations with Indian Self-Determination and Education Assistance Act (ISDEAA) agreements will now be able to access the CMOP through the National Supply Service Center (NSSC).

Drug / Package Size	CMOP Product ID	IHS, Tribal and VA Price
Harvoni (28 tablets)	L0635	$5,750.00
Viekira Pak (28 dose cards)	V0260	$5,695.16
Zepatier (28 tablets)	E0673	$5,695.15
For additional drug costs and any questions related to access or eligibility for CMOP at your HIS or Tribal pharmacy, please directly contact CAPT Todd Warren, IHS National CMOP Coordinator, by telephone at (605) 390-2371 or by e-mail at todd.warren@ihs.gov		

Cost and Access to Direct-Acting Antiviral Agents

This is a PDF version of the following document:
Module 4: Evaluation and Preparation for Hepatitis C Treatment
Lesson 3: Cost and Access to Direct-Acting Antiviral Agents

You can always find the most up to date version of this document at https://www.hepatitisc.uw.edu/go/evaluation-treatment/cost-access-medications/core-concept/all.

Background

Since 2014, the United States Food and Drug Administration (FDA) approval of a new generation of direct-acting antiviral (DAA) oral medications has revolutionized the landscape for hepatitis C virus (HCV) treatment. Therapy with DAAs has been markedly more effective than older therapies, easier to tolerate, and highly effective, even in traditionally more difficult-to-treat patients, such as those with treatment experience, cirrhosis, or HIV coinfection. Enthusiasm for these therapies, however, has been tempered by the high price of these medications and the challenges patients and clinicians face with respect to drug access. For medical providers, the process of obtaining insurance approval for new HCV treatment regimens can be daunting, complicated, and time-consuming. In addition, even when drug approval occurs, it may occur only after a substantial delay, potentially resulting in loss to follow-up. The purpose of this core concept is to describe some of the financial barriers to obtaining medication, to review some cost-effectiveness data on these therapies, and to provide practical guidance on how medical providers can navigate the system to increase access to HCV treatment for their patients.

Price of Direct-Acting Antiviral Agents

List "Sticker" Price

The price of the drug typically discussed in the public arena is the wholesale acquisition cost, which is the published list or "sticker" price of the medication set by the pharmaceutical company. The DAA medications are among of the most expensive oral medications in history, with daily wholesale acquisition prices ranging from $650 to $1125 (Figure 1). The wholesale acquisition costs are substantially higher than the estimated production costs for the medications (Figure 2).[1] For example, the wholesale acquisition cost of a 12-week course of sofosbuvir is $84,000 and the estimated production cost is $68 to 136. The ultimate "price for cure" of a recommended HCV treatment course depends on the HCV genotype, liver disease severity, and the combination of medications used (Figure 3). For example, the cost of recommended therapy for a treatment-naive patient with genotype 1a ranges from $54,600 to $150,000. This is further increased when patients require a longer (24-week) duration of therapy, as can occur in patients with decompensated cirrhosis.

Actual Medication Cost

The actual cost paid for the medications, however, may be significantly less than the wholesale acquisition cost, due to contracts, rebates, and discounts negotiated between payers and pharmaceutical companies.[2] Although the wholesale acquisition cost is general public knowledge, information on the actual cost paid is not available to the public. Negotiations for pricing can vary considerably and depend in large part of the nature of the payer.[2] In many settings, these negotiations are often conducted on behalf of insurance plans by pharmacy benefit management (PBM), a third-party generally for-profit intermediary in the pharmacy supply chain, which can greatly influence the actual drug cost and potential reimbursement rates. When insurance companies are allied with specific PBMs, the agreements may facilitate medication access by lowering drug cost but often do so in exchange for exclusivity (restrictions that dictate which medication can be prescribed) and thereby may reduce choice for the medical provider and patient. These negotiations of drug pricing between pharmaceutical companies and payers or PBMs are for all intents and purposes confidential business dealings and can obscure the price transparency that is otherwise part of a truly free market.[3] Even with such negotiated discounts, the cost of these drugs can prohibit widespread access. One study that examined the published discount prices of sofosbuvir and ledipasvir-sofosbuvir in countries where such data were available suggested that paying for widespread treatment in national health systems would still consume large proportions of their entire pharmaceutical budget.[4] The exorbitant pricing of these DAAs has garnered considerable public scrutiny and outcry from the press and medical community.[5] Despite these objections, there has been little change to the pricing of these regimens.

Cost-Effectiveness of Direct-Acting Antiviral Agents

Definitions Related to Cost-Effectiveness Analysis

A cost-effectiveness analysis is a formal method to compare the costs and clinical outcomes associated with one intervention with another “standard” comparator and can be used to help set funding priorities. The unit used for this comparison is the incremental cost-effectiveness ratio (ICER), which is a statistic used to summarize the effectiveness of a health care intervention; the ICER is a ratio defined as the difference between the cost of two possible interventions divided by the difference in health effects of the two interventions (Figure 4). The most common application of ICER related to hepatitis C therapy is a cost-effectiveness analysis and the ICER is typically measured as cost per quality-adjusted life years (QALY) gained between two strategies. For example, a typical hepatitis C treatment ICER uses the costs of different therapies as the intervention comparison (cost of new therapy minus the old therapy) divided by the QALY comparison (QALY with new therapy minus QALY of old therapy) (Figure 5). The ICER is then determined as the cost in dollars per quality of life year (QALY) gained. Once the ICER is calculated, it is examined against a benchmark, generally $50,000 to $100,000 per QALY gained, which is considered in the United States to be our society’s “willingness to pay” threshold, although this value is clearly debatable.[6]

Issues to Consider with Cost-Effectiveness Studies

There are some caveats to consider in cost-effectiveness analyses. First, these statistical models are based on multiple assumptions regarding treatment strategies and the natural history of disease (largely based on prior literature) that should be noted carefully before interpreting results. Second, the cost-effectiveness analysis assumes the main objective is to maximize net health benefits for a target population under constrained resources, a primary goal that may not be shared by clinicians who are more focused on the welfare of the individual patients they serve. Third, these analyses comprise only one of many criteria, including political, societal, and ethical priorities, that need consideration when making decisions related to resource allocation. This last consideration is important when considering HCV therapy with DAAs. Most published cost-effectiveness analysis studies have reported that new treatments for hepatitis C appear to be cost-effective compared with older comparators, but note that the benefit to society (and payers) would not occur until at least 10 years after the initial treatment.[7] It is clear that while HCV DAAs may be cost-effective, the projected cost of widespread medication coverage of all HCV-infected patients in the United States would exceed $300 billion and is neither affordable nor feasible.[8,9]

Cost-Effectiveness Studies with DAAs

Several cost-effectiveness studies have been published on the DAAs, with summary points listed below. Notably, many of these studies did not include the potential treatment benefits accrued with reduction of non-liver-related morbidity and mortality, or the prevention of secondary HCV infection, which may confer significant downstream cost savings.

- Several cost-effectiveness analysis studies have examined ledipasvir-sofosbuvir in genotype 1 infection and most demonstrated this combination was cost-effective in selected groups compared with older standard of care (some version of interferon-based therapy), with most ICERs in the “willing to pay” range of less than $100,000 per QALY gained (Figure 6).[10]
- In the cost-effectiveness analyses performed by Chhatwal and Najafzadeh, in addition to the cost of the drug, patient age, and severity of fibrosis had substantial influence on the ICERs. In the ledipasvir-sofosbuvir analysis, there was a lower ICER observed in treatment-naive patients with cirrhosis compared to those without cirrhosis.[9] In contrast, treatment-experienced patients with genotype 1 infection and cirrhosis had a higher ICER than those without cirrhosis, mainly due to the greater cost of the ledipasvir-sofosbuvir treatment course for treatment-experienced patients with cirrhosis (24 weeks used in the analysis) versus the

12-week course for treatment-experienced patients without cirrhosis (Figure 7).[9]

- Studies by Linas and Najafzadeh concluded that genotype 2 or 3 is notably less cost-effective to treat than genotype 1 with sofosbuvir-based therapy in treatment-naïve non-cirrhotic patients.[11,12] This is not surprising when one considers that a reasonable majority of non-cirrhotic patients with genotype 2 or 3 infection can be cured with less expensive peginterferon-based therapy.

Process to Acquire HCV Treatment Medications

Insurance and Medicaid Approval

Because of the very high cost of new HCV regimens, many insurance companies and Medicaid programs require a prior authorization in order for the patient to receive the medications.[13,14] To date, insurance carriers do not have a uniform policy as to who qualifies for hepatitis C treatment, which adds complexity and challenges for patients and providers seeking DAA coverage. In addition, each state has its own Medicaid policies related to HCV therapy, and there is no uniform national policy as to who qualifies for the treatment under Medicaid. Many payers have adopted guidelines that involve rationing treatment to patients with advanced liver fibrosis (Metavir F3 or F4 fibrosis) or those patients deemed to have higher medical priority bases on a variety of clinical features (Figure 8). Clinicians who care for Medicaid patients with hepatitis C should attempt to find state-specific policies on prior authorization for hepatitis C treatment by contacting their state Medicaid board.The National Viral Hepatitis Roundtable and Harvard Center for Health Law and Policy Innovation have provided national summary of state Medicaid policies on HCV drug access in November 2016.[15]

Requirements to Acquire DAAs for Patients

Insurance companies and Medicaid programs often have multiple requirements that must be met before DAAs are authorized. These restrictive criteria may dictate who can prescribe DAAs and what clinical documentation and laboratory testing are necessary. They may stipulate the type of methods and criteria used for fibrosis staging. After the prescription for medication has been submitted, the patient should be counseled that it may take months before they receive a decision from their insurance company. The following list outlines some of the potential requirements that providers may encounter and note these vary by insurance and state:

- **Provider Experience**: Some policies stipulate that only certain medical providers that have adequate expertise in treating hepatic C can prescribe DAAs. Typically, hepatologists, gastroenterologists, and infectious diseases specialists have been granted permission to prescribe DAAs without any further requirements. General medical providers may need documentation of consultation support by experts, such as through the Extension for Community Health Outcome (ECHO) programs.[16,17]
- **Fibrosis Staging**: In most circumstances, insurers will require proof of fibrosis staging. Degree of fibrosis can be established by (a) liver biopsy OR (b) a combination of non-invasive measures, including AST-to-platelet ratio index (APRI), FibroSURE, and transient elastography.
- **Baseline Laboratory Studies**: Most insurance plans will require a thorough evaluation with laboratory studies prior to receiving approval for medications to treat HCV. Typical required baseline laboratory studies are listed below. In addition, except for the HCV genotype, a window of time may be required for these laboratory studies to be accepted as pretreatment studies.
    - HCV Genotype
    - HCV RNA
    - Complete blood count (CBC)
    - Serum creatinine and calculated glomerular filtration rate
    - Prothrombin Time (PT)/International Normalized Ratio (INR)
    - Hepatic function panel: albumin, total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase
- **Clinic Note Documentation**: Some or all of the following patient-specific information may be required in order to qualify for treatment coverage:
    - Alcohol sobriety for at least 6 months
    - CAGE or AUDIT-C alcohol use survey if the patient is not 100% abstinent to alcohol
    - No injection drug use for at least 6 months

- Drug or alcohol screening tests
- Pregnancy status if female of child-bearing age
- Evaluation of psychosocial readiness for treatment
- Justification of choice of regimen and duration of treatment
- Documentation of hepatitis A and B status

Medicaid Guidance

Effective November 5, 2015, the Centers for Medicare and Medicaid Services (CMS) released a guidance document (Assuring Medicaid Beneficiaries Access to Hepatitis C Drugs) for states with regard to access restrictions on DAA treatments for hepatitis C in state Medicaid programs. In this guidance, they note that although states have the discretion to establish limitations on coverage—for example, through preferred drug lists and use of prior authorization—these practices must ensure access to clinically appropriate treatment. Further, this CMS document states that limiting access to treatment to individuals with a fibrosis score of F3 or F4, requiring a period of abstinence from drug and alcohol use, or significantly limiting the types of providers able to prescribe hepatitis C drugs are examples of unreasonable restrictions on access to treatment. It remains to be seen whether this CMS guidance document will change Medicaid restrictions.

Insurance Denials

The insurance companies may block treatment with an outright denial, or they may deny a specific medication selection or duration of therapy. If the insurance company denies a medication for the patient, the medical provider should resubmit the application for the medication, with a specific appeal letter qualifying the request as a reapplication. Given the complexity of this process, assistance from a pharmacist or pharmacy technician, or someone experienced with the process, can prove crucial to ensure a streamlined process for the patient medication approval. In general, if a patient’s medication request is rejected twice they can apply for a patient assistance program with the pharmaceutical manufacturer, if that pharmaceutical has an active patient assistance program and the patient’s financial circumstances meet the program’s requirements.

Pharmaceutical Patient Assistance Programs

If an insurance company denies a patient’s HCV medication prescription twice, providers should consider contacting the pharmaceutical company Patient Assistance Programs. Unfortunately, not all medications have pharmaceutical company Patient Assistance Programs. Of note, the Gilead Support Path Program for ledipasvir-sofosbuvir and sofosbuvir now provides free medication only for eligible uninsured patients. In general, for most of the other patient assistance programs, patients are considered for Patient Assistance if their application has been rejected by their insurance company twice, the application resubmitted to their insurance company and rejected a second time (must be within 60 days), and patients have an income less than $100,000 per year. Patients should be counseled that the pharmaceutical company assistance program will likely require tax information, social security benefits, and other documents that reflect a patient’s income. The following is a list of active hepatitis C treatment pharmaceutical sponsored patient assistance programs for patients living in the United States.

Patient Advocacy Groups

Several groups have emerged that can act as advocates for patients struggling to deal with the diagnosis, symptoms and complications from Hepatitis C as well as act as advocates and resources for patients struggling through the insurance approval and drug assistance process. Such groups include:

- **Patient Advocate Foundation:** The Patient Advocate Foundation's Hepatitis C CareLine is a hotline (800-532-5274) for both patients and medical providers and this service non-profit organization that provides assistance, including case management services, to patients diagnosed with hepatitis C. The Hepatitis C CareLine has case managers that will assist patients in efforts to try and access new medications to treat hepatitis C.
- **HCV Advocate**: The HCV Advocate is a nonprofit organization founded in 1997 geared to providing education, support, and services to patients with HCV infection and coinfection with HCV and HIV, including medical providers. The website includes Educational material about HCV appropriate for patients, Information about HCV and disability services, Information about the Hepatitis C Support Project (HCSP), Updates on clinical trials for HCV treatments, and Current news updates on HCV news and HCV treatment.

Summary Points

- New DAAs have been highly effective in treating chronic HCV infection, but the extremely high cost of these medications has served as a major barrier to more widespread treatment access.
- The wholesale acquisition cost for the newer DAAs ranges from $417 to $1125 per day. The actual price paid for the medication may be significantly lower because of contracts, rebates, and discounts.
- Most new regimens for hepatitis C treatment have been shown to be cost-effective, but given the large numbers of persons infected with hepatitis C in the United States, universal treatment is neither feasible nor affordable at the current prices of these medications.
- The process of acquiring prior authorization approval for DAAs for patients with hepatitis C can be confusing and time-consuming, particularly with respect to staying up to date with the restrictions and requirements of various insurance plans.
- Many insurance and state Medicaid programs are only approving DAAs for hepatitis C treatment for patients with F3 or F4 fibrosis.

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[PubMed Abstract] -

Figures

Figure 1 Wholesale Acquisition Cost of Direct Acting Antiviral Agents

Wholesale Acquisition Cost (WAC) of Direct Acting Antiviral Agents used to Treat HCV			
Medication	**Trade Name**	**Manufacturer**	**WAC for 1 Day**
Daclatasvir	*Daklinza*	Bristol-Myers Squibb	$750
Elbasvir-Grazoprevir	*Zepatier*	Merck & Co., Inc.	$650
Ledipasvir-Sofosbuvir	*Harvoni*	Gilead Sciences	$1125
Glecaprevir-Pibrentasvir	*Mavyret*	AbbVie	$417
Ombitasvir-Paritaprevir-Ritonavir	*Technivie*	AbbVie	$912
Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir	*Viekira Pak*	AbbVie	$992
Simeprevir	*Olysio*	Janssen	$790
Sofosbuvir	*Sovaldi*	Gilead Sciences	$1000
Sofosbuvir-Velpatasvir	*Epclusa*	Gilead Sciences	$890
Sofosbuvir-Velpatasvir-Voxilaprevir	*Vosevi*	Gilead Sciences	$890

Figure 2 Wholesale Acquisition Cost versus Estimated Production Cost for DAAs and 12-Week Treatment Course

Source: Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. Clin Infect Dis. 2014;58:928-36.

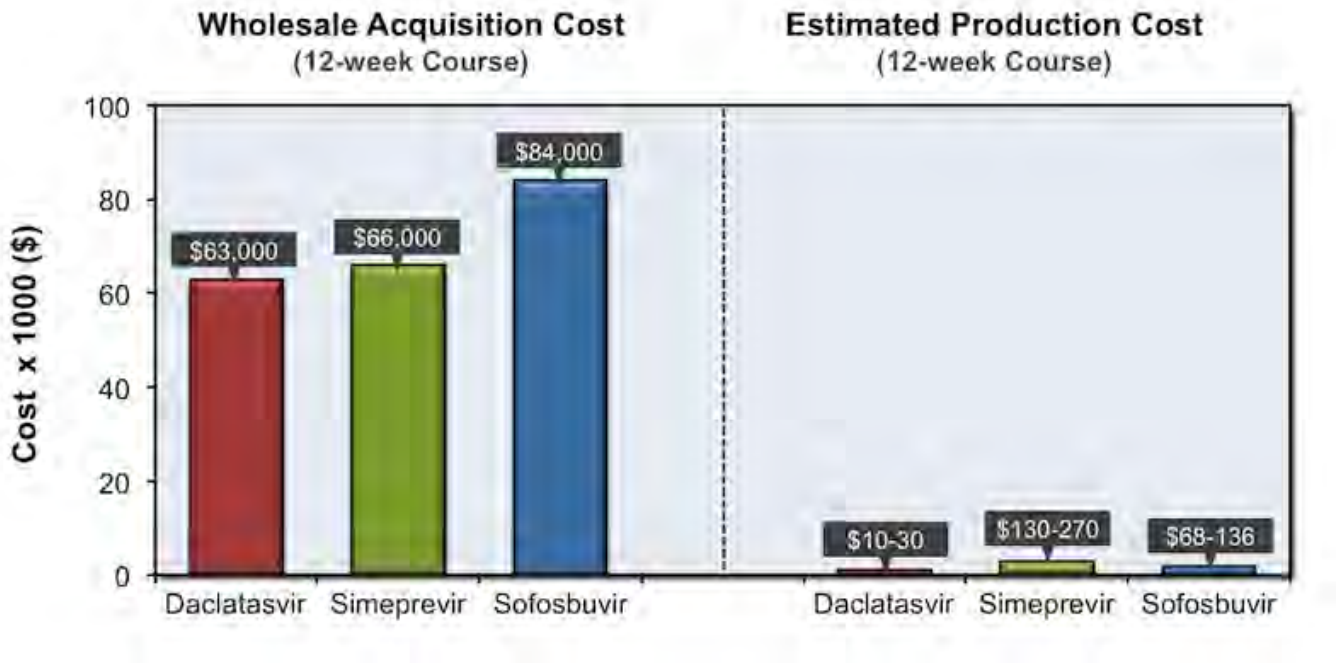

Figure 3 (Image Series) - Wholesale Acquisition Cost (WAC) for Treatment of HCV Genotypes 1 to 6 (Image Series) - Figure 3 (Image Series) - Wholesale Acquisition Cost (WAC) for Treatment of HCV Genotypes 1 to 6
Image 3A: Genotype 1a

Estimated Cost* for Initial Recommend Treatment of Genotype 1a HCV	
Regimen and Duration of Therapy^	**Cost of Regimen***
Elbasvir-Grazoprevir for 12 weeks	$54,600
Elbasvir-Grazoprevir for 16 weeks	$72,800
Ledipasvir-Sofosbuvir for 12 weeks	$94,500
Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + Ribavirin for 12 weeks	$83,819
Sofosbuvir + Simeprevir for 12 weeks	$150,000
Sofosbuvir-Velpatasvir for 12 weeks	$74,760
Sofosbuvir + Daclatasvir x 12 weeks	$147,000

^Regimen and Duration of therapy for Initial treatment of patients with Genotype 1a without cirrhosis
*Cost of regimen estimated based on Wholesale Acquisition Cost (WAC)

Figure 3 (Image Series) - Wholesale Acquisition Cost (WAC) for Treatment of HCV Genotypes 1 to 6
Image 3B: WAC_GT1b

Estimated Cost* for Initial Recommend Treatment of Genotype 1b HCV	
Regimen and Duration of Therapy^	**Cost of Regimen***
Elbasvir-Grazoprevir for 12 weeks	$54,600
Ledipasvir-Sofosbuvir for 12 weeks	$94,500
Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir for 12 weeks	$83,319
Sofosbuvir + Simeprevir for 12 weeks	$150,000
Sofosbuvir-Velpatasvir for 12 weeks	$74,760
Sofosbuvir + Daclatasvir x 12 weeks	$147,000

^Regimen and Duration of therapy for Initial treatment of patients with Genotype 1b without cirrhosis
*Cost of regimen estimated based on Wholesale Acquisition Cost (WAC)

Figure 3 (Image Series) - Wholesale Acquisition Cost (WAC) for Treatment of HCV Genotypes 1 to 6
Image 3C: Genotype 2

Estimated Cost of Regimens for Treatment HCV GT 2 HCV	
Regimen and Duration of Therapy	**Cost of Regimen***
GT 2 HCV without Cirrhosis	
Sofosbuvir-Velpatasvir x 12 weeks	$74,760
Daclatasvir + Sofosbuvir x 12 weeks	$147,000
GT 2 HCV with Compensated Cirrhosis	
Sofosbuvir-Velpatasvir x 12 weeks	$74,760
Daclatasvir + Sofosbuvir x 16 weeks	$196,000
Daclatasvir + Sofosbuvir x 24 weeks	$294,000
*Cost estimates based on Wholesale Acquisition Cost (WAC)	

Figure 3 (Image Series) - Wholesale Acquisition Cost (WAC) for Treatment of HCV Genotypes 1 to 6
Image 3D: Genotype 3

Estimated Cost of Regimens for Treatment HCV GT 3 HCV	
Regimen and Duration of Therapy	**Cost of Regimen***
GT 3 HCV without Cirrhosis	
Daclatasvir + Sofosbuvir x 12 weeks	$147,000
Sofosbuvir-Velpatasvir x 12 weeks	$74,760
GT 3 HCV with Compensated Cirrhosis	
Sofosbuvir-Velpatasvir x 12 weeks +/- Ribavirin	$74,760
Daclatasvir + Sofosbuvir x 24 weeks +/- Ribavirin	$294,000
*Cost estimates based on Wholesale Acquisition Cost (WAC)	

Figure 3 (Image Series) - Wholesale Acquisition Cost (WAC) for Treatment of HCV Genotypes 1 to 6
Image 3E: Genotype 4

Estimated Medication Cost* for Treatment of Genotype 4 Chronic HCV	
Regimen and Duration	**Cost of Regimen***
Ombitasvir-Paritaprevir-Ritonavir + Ribavirin x 12 weeks	$77,000
Sofosbuvir-Velpatasvir x 12 weeks	$74,760
Elbasvir-Grazoprevir x 12 weeks	$54,600
Ledipasvir-Sofosbuvir x 12 weeks	$94,500

^Regimen and Duration of therapy for Initial treatment of patients with Genotype 4 without cirrhosis and with compensated cirrhosis
*Cost of regimen estimated based on Wholesale Acquisition Cost (WAC)

Figure 3 (Image Series) - Wholesale Acquisition Cost (WAC) for Treatment of HCV Genotypes 1 to 6
Image 3F: Genotypes 5 or 6

Estimated Medication Cost* for Treatment of Genotype 5 and 6 Chronic HCV	
Regimen and Duration	**Cost of Regimen***
Sofosbuvir-Velpatasvir x 12 weeks	$74,760
Ledipasvir-Sofosbuvir x 12 weeks	$94,500
*Cost estimates based on Wholesale Acquisition Cost (WAC)	

Figure 4 General Principle of Incremental Cost-Effectiveness Ratio (ICER)

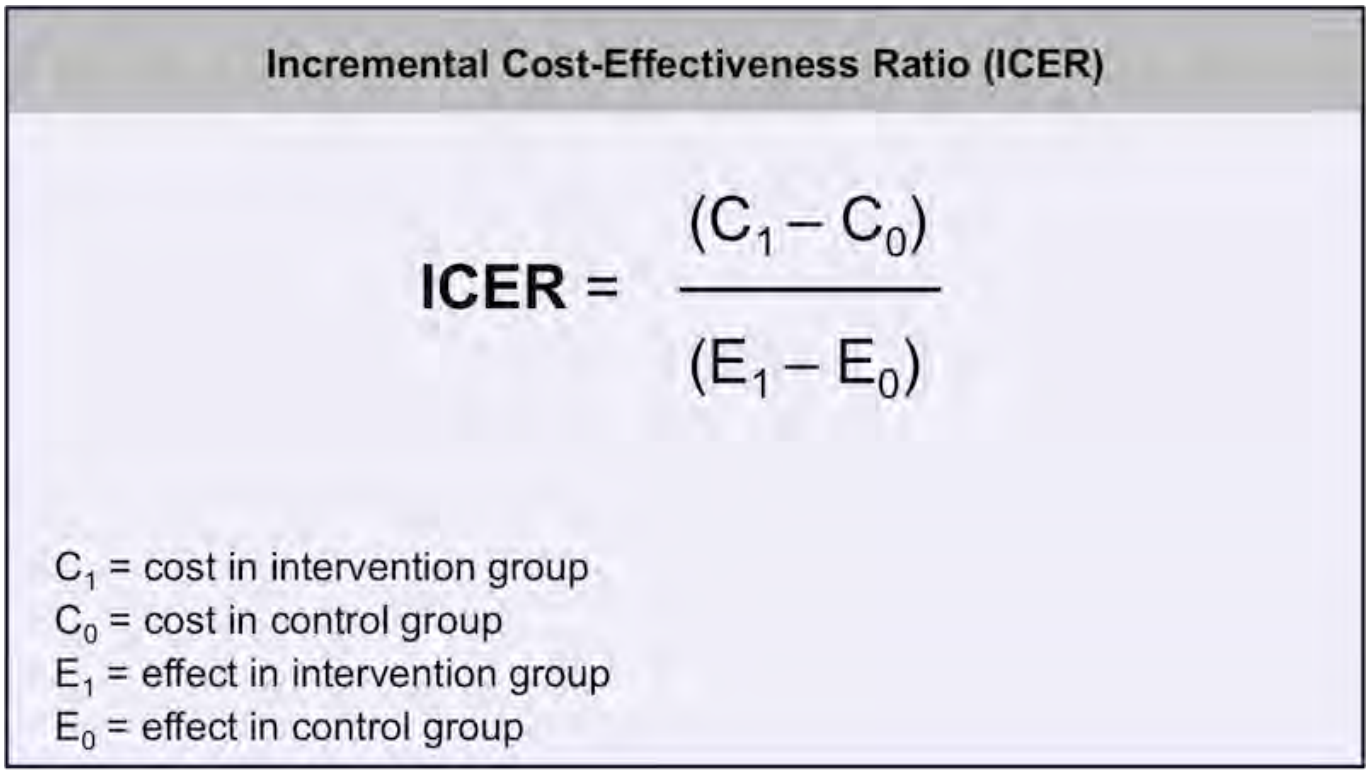

Figure 5 Incremental Cost-Effectiveness Ratio (ICER) with Hepatitis C Treatments

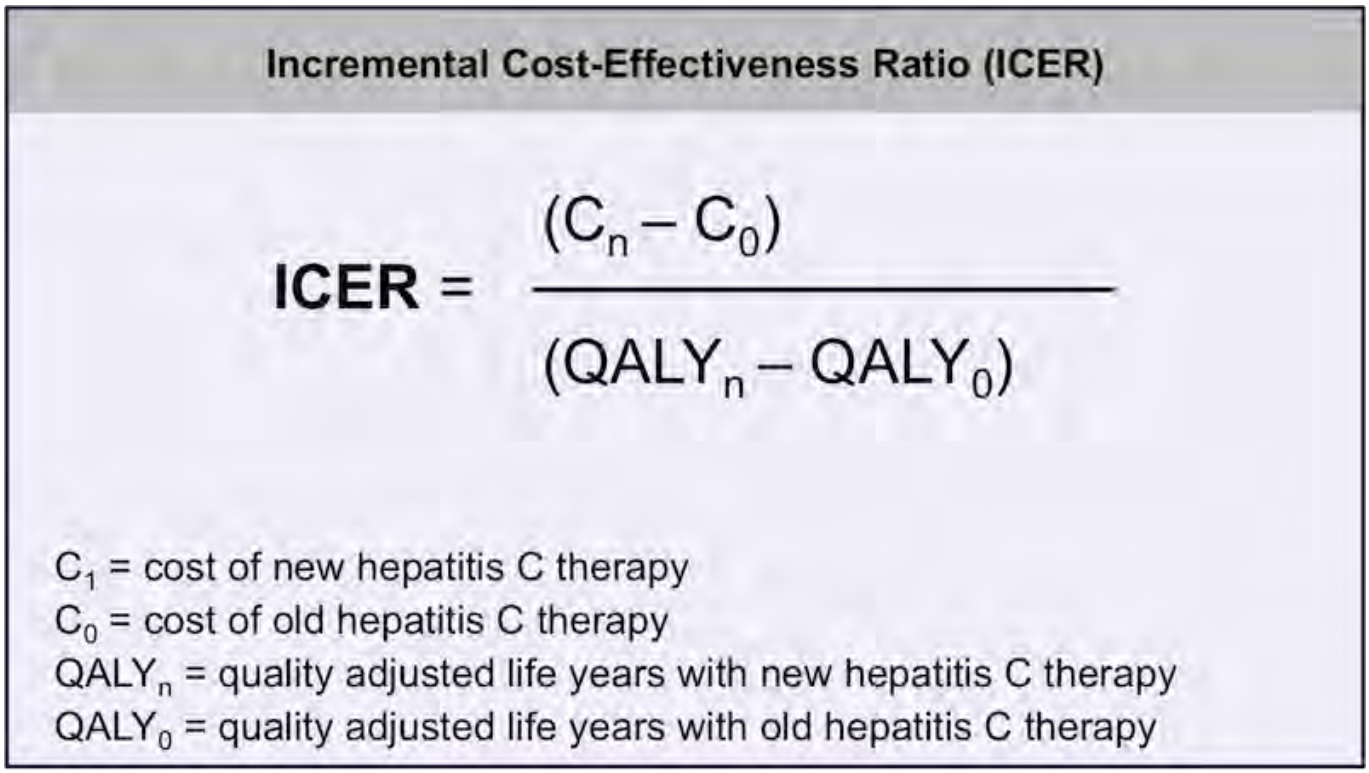

Figure 6 Cost Effectiveness Analysis Studies Involving Ledipasvir-Sofosbuvir

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Wholesale Acquisition Cost (WAC) of Direct Acting Antiviral Agents used to Treat HCV

Author	Target Population	Intervention versus Standard of Care	Incremental Cost-Effectiveness Ratio (ICER)
Chhatwal	Treatment-naïve and Treatment-experienced GT 1-4	For GT1: **LDV-SOF** versus PR + TPV or BOC	Naïve non-cirrhotics: $31,452 Naïve cirrhotics: $9,703 Experienced non-cirrhotics: $35,853 Experienced cirrhotics: $79,238
Younossi	Treatment-naïve and Treatment-experienced GT 1	**LDV-SOF** versus [no treatment, SOF + PR, SMV + PR, SOF + SMV, SOF + RBV, or PR + BOC]	LDV-SOF cost-saving (less costly and more effective) compared with older comparators with ICERs ~$29,000 versus PR + SOF under variety of scenarios
Najafzadeh	Treatment-naïve GT 1, 2, or 3	For GT1: **SOF + RBV**, **LDV-SOF**, **SOF + DCV** versus PR + SOF versus PR + BOC	LDV-SOF was cost-saving for GT1 when compared to PR + BOC with an estimated ICER of $14,432

Abbreviations: GT = genotype; LDV-SOF = ledipasvir-sofosbuvir; PR = peginterferon plus ribavirin; BOC = boceprevir; SOF = sofosbuvir; SMV = simeprevir; RBV = ribavirin; DCV = daclatasvir

Figure 7 Cost Effectiveness Analysis of Genotype 1 with Ledipasvir-Sofosbuvir

The numbers shown on the bar graph represent the incremental cost-effectiveness ratio (ICER) in dollars per quality of life year (QALY) for treatment-naive and treatment experienced patients with genotype 1 chronic HCV, including those with and without cirrhosis.

Source: Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med. 2015;162:397-406.

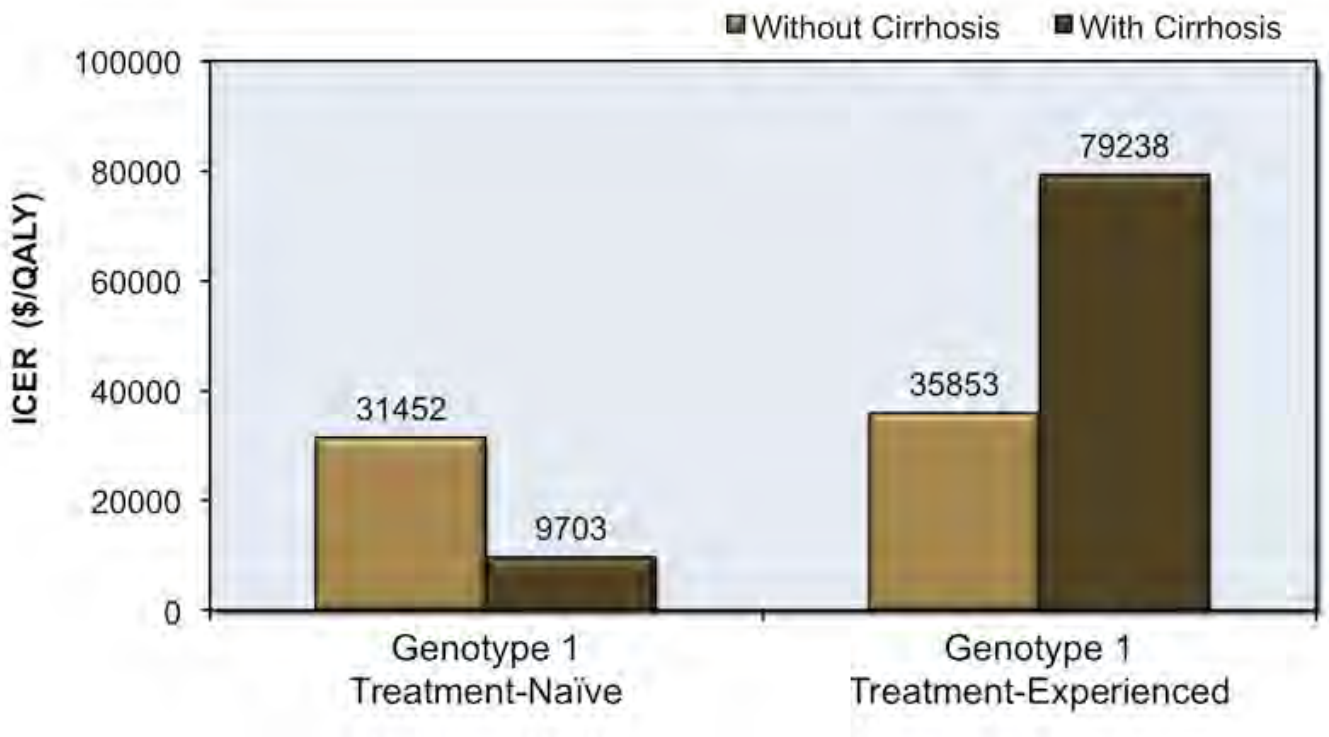
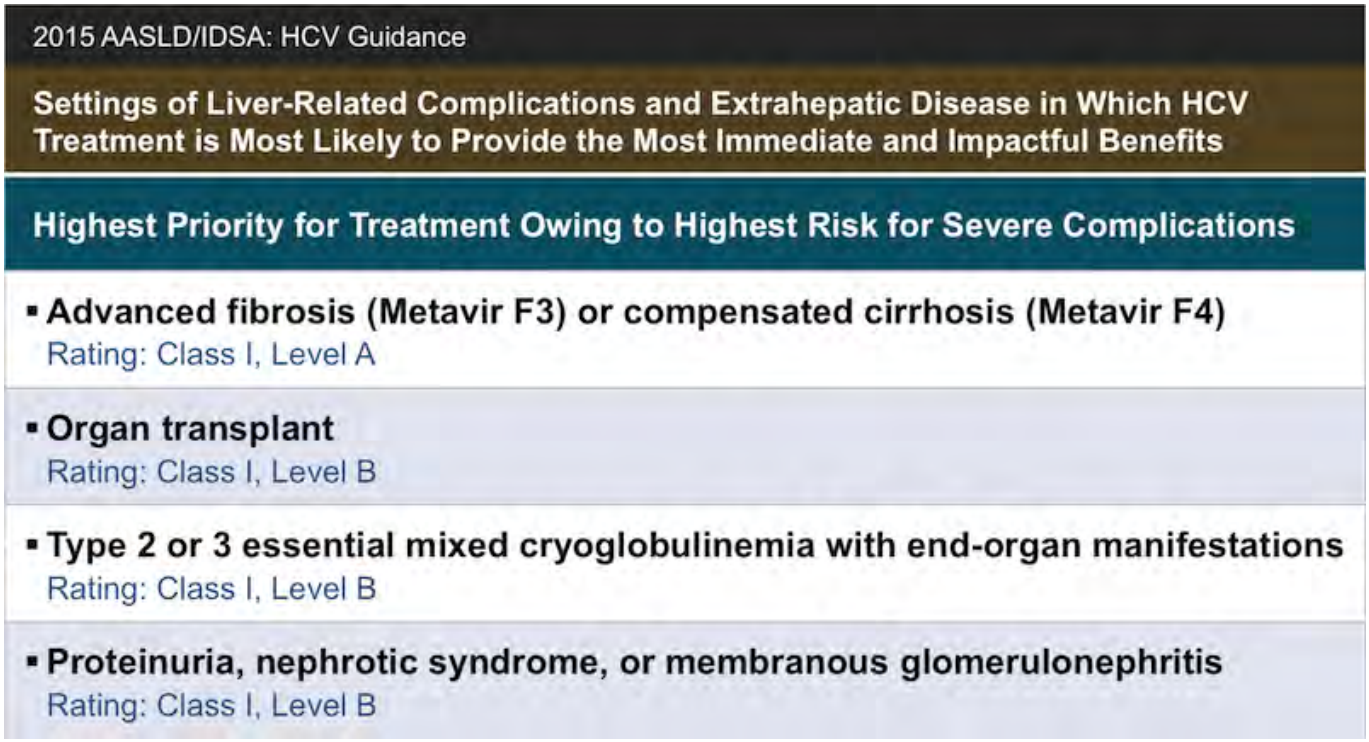


Figure 8 Highest Priority for Initiating HCV Treatment Based on Highest Risk for Severe Complications

Source: American Association for the Study of Liver Disease, the Infectious Diseases Society of America. When and whom to initiate HCV therapy. Recommendations for testing, management, and treating hepatitis C.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Indian Health Service
Rockville, MD 20857

JAN 0 6 2017

Dear Tribal Leader:

I am pleased to announce that the Indian Health Service (IHS) recently signed an Interagency Agreement with the U.S. Department of Veterans Affairs (VA) authorizing the IHS to use the VA Veterans Health Administration's Consolidated Mail Outpatient Pharmacy (CMOP).

With this development, Tribes and Tribal organizations with Indian Self-Determination and Education Assistance Act (ISDEAA) agreements will now be able to access the CMOP through the National Supply Service Center (NSSC). I want to thank Tribal Leaders and Federal staff at HHS and the VA for their work and collaboration that resulted in this agreement. This has been a priority for Tribes and the IHS for the past several years.

The CMOP is a sophisticated mail order pharmacy program that uses seven highly automated facilities to efficiently and safely fill prescriptions for VA beneficiaries. The CMOP utilizes common shipping carriers to deliver filled prescriptions directly to patient homes across the United States. In fiscal year (FY) 2016, approximately 119 million prescriptions were processed by the CMOP, which accounted for approximately 80 percent of all prescriptions dispensed by the VA. The CMOP's focus on quality management, patient safety, customer satisfaction, environmental safety, and infection control was recognized in 2016 by J.D. Powers and Associates U.S. National Pharmacy Study as being "Among the Best" for the eighth consecutive year. For more information about the CMOP and to see a video explaining the CMOP please go to: http://www.pbm.va.gov/PBM/CMOP/VA_Mail_Order_Pharmacy.asp.

The IHS began testing CMOP to mail prescriptions to American Indian and Alaskan Native patients in 2010. Since that time, approximately 60 IHS pharmacies have implemented CMOP, leading to the successful delivery of over 2 million prescriptions to IHS patients. The IHS is on track to complete implementation of CMOP in all federally operated IHS pharmacies by the end of FY 2017. Implementation of CMOP at IHS pharmacies has contributed to greater access to care, decreased patient wait times, expanded clinical pharmacy services and programs, and improved the overall pharmacy-patient experience.

To access the CMOP, Tribal pharmacies must use the IHS Resource and Patient Management System (RPMS), meet minimum technical requirements, and agree to the terms, conditions, and responsibilities set forth by CMOP. The IHS, through the NSSC, will act as a payment conduit for orders placed by Tribes and Tribal organizations, in accordance with buyback authority in the ISDEAA [25 U.S.C. § 5388] and in fiscal year appropriation acts. See, e.g., Consolidated Appropriations Act of 2014, Pub. L. 113-76, 128 Stat. 5 (2014).

Tribes and Tribal organizations will also be required to sign a customer agreement with the IHS NSSC, be responsible for the cost of the drugs purchased and any applicable CMOP fee, and be subject to the same program management and payment intermediary fees required for access to the Pharmaceutical Prime Vendor (PPV) program.

For you reference, I have enclosed a copy of the Interagency Agreement. If you have any questions related to access or eligibility for CMOP at your Tribal pharmacy, please directly contact CAPT Todd Warren, IHS National CMOP Coordinator, by telephone at (605) 390-2371 or by e-mail at todd.warren@ihs.gov.

Thank you for your partnership and collaboration. I look forward to full implementation of this Interagency Agreement.

Sincerely,

/Mary Smith/

Mary Smith
Principal Deputy Director

Enclosure: Interagency Agreement between Department of Veterans Affairs Veterans Health Administration Consolidated Mail Outpatient Pharmacy and Department of Health and Human Services Indian Health Service for The Use of the Veterans Health Administration's Consolidated Mail Outpatient Pharmacy System by the Indian Health Service

INTERAGENCY AGREEMENT[1]
between
DEPARTMENT OF VETERANS AFFAIRS
VETERANS HEALTH ADMINISTRATION
CONSOLIDATED MAIL OUTPATIENT PHARMACY
and
DEPARTMENT OF HEALTH AND HUMAN SERVICES
INDIAN HEALTH SERVICE
for
THE USE OF THE VETERANS HEALTH ADMINISTRATION'S CONSOLIDATED MAIL OUTPATIENT PHARMACY SYSTEM BY THE INDIAN HEALTH SERVICE

I. PURPOSE

This agreement will provide a centralized prescription filling center for Indian Health Service (IHS) and tribal health facilities through Department of Veterans Affairs (VA), Veterans Health Administration's (VHA) Consolidated Mail Outpatient Pharmacy system (CMOP).

The IHS and VHA (collectively, the parties) are entering into this agreement for their mutual benefit with Tribal health programs as third-party beneficiaries. Title I tribes have buyback authority through the Consolidated Appropriations Act of 2014, Pub. L. No. 113-76, 128 Stat. 5 (2014) and subsequent Appropriation Acts, to the extent such Acts continue to authorize the IHS to provide goods and services to Tribes and Tribal Organizations on a reimbursable basis. Likewise, Title V tribes have buyback authority through 25 U.S.C. § 458aaa-7. The IHS, through the National Supply Service Center, will act as a payment conduit for orders placed by Tribal health facilities.

An IHS or Tribal pharmacist will process, reconcile and electronically release non-urgent, chronic medication orders to the VHA CMOP for dispensing and shipping. The participating facility will have the ability to follow and track these medications through the dispensing process via an Internet Website. The technical aspects of this process will be based on those already utilized between the VHA CMOP and individual VHA medical facilities.

II. AUTHORITY

A. The Economy Act of 1932, 31 U.S.C. § 1535, as amended, and as prescribed by Federal Acquisition Regulation (FAR) Subpart 17.5. The requesting organization, the IHS, has considered the requirements of FAR 17.502 and 17.503(a) and (b) and has provided a determination and findings (D and F) pursuant thereto.

B. 38 U.S.C. § 8126. Limitation on prices of drugs procured by the Department of Veterans Affairs and certain other Federal agencies.

[1] Per agreement of the parties, this document sets forth the general terms and conditions of the IAA and will be used in lieu of FMS form 7600A.

C. The Snyder Act, 25 U.S.C. § 13.

III. IDENTIFICATION NUMBER

For purposes of Indian Health Service (IHS) internal administrative needs, this Agreement will carry the following identification number 2-OD-17-0008.

IV. RELATED AGREEMENT

A. Memorandum of Understanding between the VHA and the IHS, dated June 24, 2003.

B. Memorandum of Agreement between the VHA and the IHS on Health Information Technology Sharing, dated September 24, 2008.

C. Supplemental Project Agreement to the Memorandum of Agreement (MOA) between the VHA and the IHS on Health Information Technology Sharing: Use of the Veteran's Health Administration Consolidated Mail Outpatient Pharmacy System by the Indian Health Service.

D. Interconnection Security Agreement between the VA and the Department of Health and Human Services (DHHS), dated September 22, 2008.

E. VA Prime Vendor Contract V797P-12-D-0001, dated May 10, 2012.

V. SUPERSESSION

This Agreement supersedes the previous Interagency Agreement regarding the use of the VHA's CMOP system by the Indian Health Service, dated March 19, 2010.

VI. SCOPE

A. This agreement facilitates the use of the VHA CMOP by those IHS Areas and tribal health programs, which sign agreements with CMOP.

B. The CMOP will dispense medication orders received from the participating facilities to the requesting facility or directly to the patient in accordance with the terms of this agreement. VHA will provide program support, including training and contract management.

VII. PERIOD OF AGREEMENT

This agreement becomes effective upon the last signature of the parties for a period of one calendar year. This agreement will be automatically extended for additional one-year periods on its anniversary date unless either party gives the other 60-calendar-day written notice of intent to modify or terminate this agreement.

VIII. FINDINGS

A. The use of this interagency agreement is in the best interest of the Government.

B. The services cannot be obtained by the IHS as conveniently or economically by contracting directly with a private source.

C. The services do not require additional contract action by the VHA. Medication dispensed via this agreement will be appropriately acquired under existing VA pharmaceutical supply contracts, which include the IHS as an eligible ordering activity. However, the VA is specifically authorized by the General Services Administration to negotiate and manage Federal Supply Schedule (FSS) contracts for pharmaceuticals on behalf of other Federal agencies, including the IHS.

IX. GENERAL PROVISIONS

A. The intent of this agreement is to cost-effectively expand clinical and support capabilities of the participating facilities through use of VHA CMOP resources and by combining participating facilities prescription needs with VHA's. Improved efficiencies will be gained through more efficient and effective use of staff, reduction in medication error costs, and reduction in medication error litigation.

B. Nothing in this agreement shall be construed to shift the ultimate responsibility of any patient care from the ordering facility, its physicians, and its other healthcare professionals. It is further understood the agreement shall not impair the priority access of the VA or the IHS beneficiaries to health care provided through their respective program; the quantity or range of quality of health care services provided to the beneficiaries by the respective health care programs; or the eligibility of beneficiaries to receive health care through their respective programs. The terms of the agreement shall not in any way alter or affect congressional mandates imposed on the parties as governed by applicable law, regulation or policy. Moreover, the intent of this agreement is to expand the ability of each party to better and more efficiently meet its obligations to its respective beneficiaries.

C. The VHA and the IHS will comply with all applicable Federal laws and regulations regarding the confidentiality of health information. Medical records of the IHS patients are Federal records and are subject to some or all of the following laws: the Privacy Act of 1974, 5 U.S.C. § 552a; Privacy Act Regulations, 45 C.F.R. Part 5b; the Freedom of Information Act, 5 U.S.C. § 552; the Drug Abuse Prevention, Treatment, and Rehabilitation Act, 42 U.S.C.§ 290dd-2; Confidentiality of Alcohol and Drug Abuse Patients Records, 42 C.F.R. Part 2; the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment and Rehabilitation Act, 42 U.S.C. § 4541; the Administrative Simplification

requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), 45 C.F.R. Parts 160 and 164. All requests for release of information shall be in writing. All requirements of HIPAA will be met before there is any sharing of identifiable patient information.

D. The participating facilities and CMOP agree to sign agreements detailing specific operational issues that will be adhered to by each party. These agreements will be similar as those signed by the VHA Medical Centers serviced by CMOP.

E. The IHS, through the National Supply Service Center, will act as a payment conduit for orders placed by tribal health programs.

F. Nothing contained herein shall be construed to obligate the IHS or the VHA to any expenditure or obligation of funds in excess of, or in advance of, appropriations in accordance with the Anti-Deficiency Act, 31 U .S.C. § 1341.

G. Requests for amendments to this agreement will be directed to the agreement administration staff listed on Attachment A. All other communications shall be limited to the appropriate points of contact, also listed on Attachment A.

H. The IHS and VHA agree to take immediate action to resolve issues and disagreements that arise in accomplishing work under this agreement in accordance with FAR 17.504(c). In the event that disagreements arise that cannot be resolved by the signatories, then the parties will submit such disagreements to their respective legal representatives for resolution under mutually acceptable procedures, which may include third-party alternative dispute resolution procedures.

X. RESPONSIBILITIES

A. VHA will:

1. Receive and dispense the participating facility's medication orders sent electronically from the IHS national pharmacy software located at the IHS facility in accordance with Federal law (including data storage) and recognized national pharmacy standards (e.g., United States Pharmacopeia, American Pharmaceutical Association, American Society of Health Systems Pharmacists, etc.). Drug availability will be in accordance with the commonly used CMOP product list as indicated in the VA's National Drug File (NDF) and is subject to the ten (10) or more prescription minimum monthly usage before a product will be stocked.
2. Ship completed prescription orders directly to the participating facility or directly to the patient as pre-approved by the facility point of contact listed in Attachment A to the IHS Area's Interagency Agreement with CMOP.
3. Maintain the standards set by The Joint Commission at CMOP facilities servicing the participating facilities.

4. Ensure all added medication orders can be dispensed assuming medication Ð stock is available and all technical aspects are sufficiently operable. Ð
5. Maintain a goal of passing medication orders to the parcel delivery service within two days after filling of the order. Transit time to the participating facility or to the individual patient is dependent on the method of delivery selected. CMOP will collaborate with the participating facility on the selection of delivery method. Maintain the same timeliness standards for the provision of the participating facility's medications as for the provision of the VA's medications.
6. Package and deliver medications in accordance with CMOP's normal Ð operating and quality procedures, to include back orders, substitutions, and Ð lost medications. Ð
7. Ensure maximum efficiency and order tracking through coordination of Ð efforts between the participating facility and CMOP. Ð
8. Provide VA website account access to the participating facility for Ð prescription tracking purposes. Ð
9. Collaborate with the IHS concerning the functional requirements of the Ð interface between the IHS national pharmacy software and the CMOP Ð prescription processing system. Ð
10. Maintain a working relationship with the IHS and its pharmacy software vendor regarding closed loop tracking of prescriptions through the use of bar code technology and future radio frequency identification device tracking.
11. Route all requests for modification to the IHS Point of Contact (POC) as designated in Attachment A.
12. Invoice the drug cost at the same rate charged to VHA customers.
13. Provide thirty (30) days advance notification to the participating facilities for any cost/price change for administrative costs.
14. Provide support services for reconciliation of billing discrepancies.
15. Provide and maintain current POC and Agreement Administration (AA) staff information, Attachment A.
16. Provide monthly itemized electronic statements via e-mail to each facility's Chief Pharmacist and Finance Officer on the fifth calendar day of the month. Invoices shall detail the actual medication costs, applicable administrative fees, delivery costs for the orders placed by the facility, including supporting documentation for verification of accurate billing. Payment will be made via the Interagency Payment and Collection (IPAC) system and initiated by CMOP just prior to the end of the month with the electronic statements going out on the first work day of the month.
17. Drug costs incurred will be in accordance with the lowest applicable cost/pricing schedules that each participating facility is eligible for through the VA Prime Vendor Program including National Contract Drug pricing. Non-drug costs charged to the participating facility will match what is being charged to the VA Medical Centers serviced by the CMOP for current fiscal year.
18. The Intra-Governmental Payment and Collection (IPAC) system collection will be initiated by the servicing VHA CMOP.

19. The CMOP contracting office will maintain complete records of all IHS Area and tribal health program agreements and will monitor and report on each facility annually.
20. Conduct training for directors of the participating pharmacies concerning VHA CMOP operations.
21. Provide a quality control program which utilizes medication error prevention data in its control measures.
22. Package all medications to reduce the possibility of breakage, pilferage, and environment contamination, including freezing of liquid medications. Refrigerated or frozen items will receive special handling. Mailed packages will not be identified as containing pharmaceuticals.
23. Track package delivery status and work with carriers to resolve delivery delays to the extent possible.
24. Mask the description of the contents of cased products dispensed to patients to protect their privacy.
25. Generic pharmaceutical products will be dispensed by VHA CMOP unless only brand name product is available or there is a special exception approved by VHA's Pharmacy Benefit Management Strategic Health Care Group.
26. Maintain appropriate inventory levels to minimize out-of-stock situations and associated cancel-backs.

B. The IHS will:

1. Conduct the initial medication and/or supply use assessment by a licensed pharmacist on all prescriptions transmitted to CMOP that includes:
   a. appropriateness of the drug, dose, frequency, and route of administration;
   b. therapeutic duplications;
   c. real or potential allergies or sensitivities;
   d. real or potential interactions between the prescriptions and other medications, food, and laboratory values;
   e. review of current or potential impact as evidenced by laboratory values;
   f. other contraindications;
   g. variation from organizational criteria for use;
   h. checking for potential errors with look-alike/sound-alike drug pairs; and
   i. other relevant medication-related issues or concerns.
2. Transfer accurate medication ordering data via the IHS prescription software, a system compatible with the CMOP processing system.
3. Provide medication consultation to the patient.
4. Maintain a working relationship with CMOP to reconcile problems with the medication ordering process, order discrepancies, shipping, and payments.
5. Provide and maintain current POC information (Attachment A).
6. Route all requests for modification to this agreement to the agreement administration staff designated in Attachment A.
7. Provide dates as needed for cross-training and coordination among the IHS Area and facility staff including IHS Chief Executive Officers, Administrative Officers, Financial Officers, Area Chief and Assistant Chief Pharmacists, and facilities pharmacists.

8. Ensure "As Needed" orders, titrating orders, taper orders and range orders provide detailed patient instructions with defined dose and interval parameters.
9. Ensure that orders for supply items such as diabetic supplies, enteral nutrition and associated supplies, wound care supplies, incontinence appliances and supplies or ostomy supplies are ordered, measured, and fitted for the patient by a qualified prescriber, if applicable, prior to transmission to CMOP for processing and mailing to the patient.

XI. LIMITATIONS

CMOP will not accept standing orders, hold orders, automatic stop orders, resume orders, orders for compounded drugs or drug mixtures not commercially available or investigational medications.

XII. BILLING AND PAYMENT

A. The IHS facilities will pay CMOP for the costs associated with the filling of prescriptions. Payment will be made immediately upon receipt of the bill through the IPAC method initiated by CMOP. Adjustments to the bill will be coordinated between the IHS and CMOP with any adjustments being applied to the following month's bill. Prior to sending any prescriptions to be filled, each participating facility will submit the following billing information to the servicing CMOP: Agency Location code, Vendor Code and accounting string along with a POC name, phone number and e-mail address. A bill submitted to the participating facility for payment is not subject to audit or certification in advance of payment but may be retroactively adjusted to reflect actual costs.

B. Purchased and Referred Care funds may be used to purchase services under this agreement.

XIII. AMENDMENT

This agreement may be revised or amended only in writing with the signature approval of the parties to the agreement. Either party may modify or amend this agreement, or any part of its specific provisions, with signatory concurrence of the other party.

XIV. INTERPRETATION

A. If the VA and the IHS are unable to agree about a material aspect of this agreement, the parties agree to engage in an effort to reach mutual agreement in the proper interpretation of this agreement, including amendment of the agreement, as necessary, by escalating the dispute within their respective organizations.

B. If a dispute related to funding remains unresolved for more than ninety (90) calendar days after the parties have engaged in an escalation of the dispute, the parties agree to refer the matter to their respective Agency Chief Financial Officers with a recommendation that the parties submit the dispute to the CFO Council Intragovernmental Dispute Resolution Committee for review in accordance with Section VII of Attachment 1 to the Treasury Financial Manual, Volume 1, Bulletin No. 2007-03, Intragovernmental Transactions, Subject: Intragovernmental Business Rules, or subsequent guidance.

XV. TERMINATION

In the event of a cancellation or termination of this agreement, VHA shall not be liable for the IHS' share of any resulting costs unless the VA caused the termination by negligence or violation of any Federal rule, regulation, or statute. Any financial liability resulting from the actions of the IHS' facility in regard to the drugs and/or pharmacy services provided under this agreement shall be the responsibility of the IHS facility.

Accepted:	**Accepted:**
Department of Veterans Affairs, Veterans Health Administration	**Indian Health Service**
By: /Kenneth L. Siehr/	**By:** /Mary Smith/
Date: 12/15/2016	**Date:** 12/12/2016

ATTACHMENT A

Primary Points of Contact (PPC) and Agreement Administration Staff (AA)

Department of Veterans Affairs

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Hepatocellular Carcinoma Surveillance

The recent American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) hepatitis C guidance recommends surveillance for HCC in persons with chronic HCV infection who have advanced fibrosis or cirrhosis (Metavir stage F3 or F4). The recommended surveillance test is hepatic ultrasound and the recommended surveillance interval is every 6 months. The AASLD/IDSA guidance recommends that HCC surveillance in HCV- infected patients with advanced fibrosis or cirrhosis should continue after patients receive therapy for HCV, even if they achieve an SVR. The AASLD/IDSA guidelines do not recommend using AFP as a surveillance test; evolving data have shown that AFP has poor sensitivity and specificity as a surveillance tool for HCC.

Surveillance for Hepatocellular Carcinoma

This is a PDF version of the following document:
Module 2: Evaluation, Staging, and Monitoring of Chronic Hepatitis C
Lesson 6: Surveillance for Hepatocellular Carcinoma

You can always find the most up to date version of this document at https://www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/surveillance-hepatocellular-carcinoma/core-concept/all.

Significance of HCC and Rationale for Surveillance

Impact of Hepatocellular Cancer: Worldwide, hepatocellular carcinoma (HCC) is the sixth most common malignancy (Figure 1) and the third most common cause of cancer-related death (Figure 2). In the United States, HCC is the fastest growing cause of cancer-related death. The incidence of HCC in the United States has increased in recent years (Figure 3), largely attributable to a significant rise in hepatitis C-related HCC. In the United States, it is estimated that in 2013 there will be 30,640 new cases diagnosed and 21,670 deaths due to hepatitis C-related HCC.

Risk Factors: Cirrhosis from any cause is the primary risk factor for HCC: approximately 80% of cases of HCC occur in individuals with cirrhosis and the risk of developing HCC increases with fibrosis stage. Chronic HCV and chronic hepatitis B virus (HBV) infection are the most common risk factors for HCC. In the United States, approximately 50 to 60% of persons with HCC are infected with hepatitis C. Patients with chronic hepatitis C and cirrhosis have a 2 to 5% annual risk and a 7% to 14% risk over 5 years of developing HCC. The risk of developing HCC among persons infected with HCV increases with substantial alcohol intake—the risk increases in a linear fashion with daily alcohol intake greater than 60 g (approximately 6 cans of beer, shots of liquor, or glasses of wine). The overall incidence rate of HCC is approximately three times higher in males than females (Figure 4). Any patient with cirrhosis can develop HCC, including patients with cirrhosis from non-viral causes, such as alcoholic cirrhosis, autoimmune hepatitis, non-alcoholic fatty liver disease, hemochromatosis, glycogen storage disease, Wilson's disease, alpha-1-antitrypsin deficiency, and porphyria cutanea tarda.

Prognosis: The overall prognosis for patients diagnosed with HCC in the United States is poor, with an estimated median survival of 4.3 to 20 months and a 5-year survival of 10 to 15%. In general, patients who have HCC detected after the onset of symptoms have an extremely poor prognosis, with an overall 5-year survival of 0 to 10%. Symptoms may include abdominal pain, anorexia, early satiety, weight loss, obstructive jaundice, fever, watery diarrhea, and bone pain (from metastases). A select group of patients with good performance status who have HCC diagnosed at an early stage have a predicted survival longer than 5 years, but unfortunately most patients with HCC have advanced stages of cancer at the time of diagnosis.

Rationale for HCC Surveillance: The rationale for conducting HCC surveillance is that regular screening of at-risk asymptomatic patients may detect tumors at an early stage when potentially curative treatment can be offered.

Evidence for the Benefit of HCC Surveillance in HCV-Infected Patients

Definition of Screening and Surveillance: By definition, screening a patient for HCC means that the patient has no symptoms and the clinician does not have a reason to suspect the patient has HCC. With screening, the patient is asymptomatic but undergoes testing in order to detect HCC early and before the development of symptoms. Surveillance is the process of serial application of the screening test to detect the presence of HCC before it becomes clinically suspected or evident.

Evidence Supporting Surveillance in Patients with Chronic Hepatitis: A single prospective randomized controlled trial exists that assessed the impact of HCC surveillance on HCC-related mortality. This study enrolled 18,816 individuals aged 35 to 59 with HBV infection or a history of chronic hepatitis in urban Shanghai, China and the investigators compared patients who underwent HCC surveillance with those who did not undergo HCC surveillance. Overall, approximately two-thirds of the patients enrolled had documented positive HBsAg. The screening group (n = 9,373) was offered every 6-month surveillance with abdominal ultrasound and alpha fetoprotein (AFP) and the control group received no surveillance (n = 9,443). The screening group had only a 58% compliance with screening, but had their HCC diagnosed at an earlier stage (Figure 5) and had a reduction in HCC-related mortality when compared with the control group (Figure 6). Since most of the patients in this study had chronic hepatitis B, it is not the ideal study to support screening in patients with hepatitis C, but it is the largest prospective study of HCC screening in any population and provides evidence for screening in the hepatitis B population.

Absence of Data for HCC Surveillance in HCV-Infected Patients: There has been significant controversy about whether the findings of the trial conducted in China that predominantly involved HBV-infected patients can be extrapolated to patients with hepatitis C infection, and if so, whether it is strong enough evidence to be the basis for recommending that screening be performed in HCV patients in the United States. To date, no prospective randomized controlled trials of HCC screening in HCV-infected patients living in the United States have been published. There have been a number of small observational studies of varying quality done in mixed populations, but these studies did not separate HCV-infected patients from HBV-infected patients.

Indications for HCC Surveillance in Patients with Hepatitis C

Indication for HCC Surveillance: For patients with chronic hepatitis C infection, expert guidelines recommend performing HCC surveillance in any patient with chronic hepatitis C who has developed advanced fibrosis or cirrhosis (Metavir stage 3 or 4). Surveillance for HCC is not recommended for HCV-infected patients who do not have advanced fibrosis or cirrhosis. There are no clear-cut recommendations for patients with unknown stage of liver fibrosis. In this situation, some experts have suggested use of non-invasive markers to identify patients with probable advanced fibrosis or cirrhosis. Although the risk of HCV-related HCC decreases substantially in patients with cirrhosis who obtain a sustained virologic response with therapy for hepatitis C, the risk of HCC is not eliminated, even if they have documented improvement in cirrhosis.

Recommended Surveillance Interval for Screening: The interval time for surveillance is based on tumor doubling time, which generally is considered to occur in 6 to 12 months. Expert guidelines recommend using a surveillance interval of 6 months.

Indications for HCC Surveillance if Coinfected with Chronic Hepatitis B: Recommendations for HCC surveillance for patients with chronic hepatitis B are more aggressive than with hepatitis C. In general, hepatitis B is a much more oncogenic virus than hepatitis C, rates of HCC in hepatitis B patients are higher than hepatitis C patients, and HCC occurs in some patients with hepatitis B who do not have cirrhosis. For HCV-infected patients who are coinfected with hepatitis B, the HCC surveillance recommendations issued by the American Association for the Study of Liver Disease (AASLD) for chronic hepatitis B should be followed. For patients with hepatitis B infection, any of the following are considered indications for HCC screening:

- Asian males 40 years of age or older
- Asian females 50 years of age or older
- Patients with cirrhosis
- Family history of HCC
- Africans older than 20 years of age

Implementation of HCC Screening: Given the large population with chronic hepatitis C infection in the United States, several potential barriers exist for effective HCC screening in patients with chronic hepatitis C infection, including lack of clinician awareness of HCC screening recommendations, difficulty in identifying the correct patient population for screening, and cost of surveillance. Since current guidelines for patients with chronic hepatitis C recommend HCC screening only for those with cirrhosis or advanced fibrosis, clinicians must first accurately identify which patients meet these criteria. Determining whether the patient has cirrhosis is a complex process and also requires education and training. One study of the implementation of HCC screening in the VA system found that between 1998 and 2005, 126,670 patients with hepatitis C infection were identified and 10.1% of these patients had cirrhosis; among the patients with cirrhosis (with at least 2 years of follow-up), routine HCC surveillance occurred in 12.0%, inconsistent surveillance in 58.5%, and no surveillance in 29.5%.

Surveillance Testing Methods

Biomarker Serologic Tests

- **Alpha Fetoprotein (AFP):** Alpha fetoprotein (AFP) is the most widely used biomarker for HCC surveillance, but this test has a sensitivity of only 47 to 64% and a specificity of 82 to 95% for detecting HCC among HCV-infected patients. The poor sensitivity primarily results from the lack of uniform secretion of AFP by HCC tumors and the less than optimal specificity occurs because AFP is often elevated above the upper limit of normal in patients with advanced liver disease but without HCC. For example, a study that examined patients over a period of 13 to 14 years found that approximately 90% of AFP elevations were not associated with cancer. Instead, most cases involved a transiently elevated AFP level; for patients followed over this period, approximately 15% had an elevated AFP level at some point. Some experts have suggested that AFP can be useful for the diagnosis of HCC if the level is extremely elevated, but very few patients have extremely elevated AFP levels at screening. As outlined, for multiple reasons, AFP is no longer recommended as a routine surveillance test. If there is uncertainty about an imaging study and a biopsy cannot be performed, then AFP might provide useful additional information.
- **Des-gamma-Carboxy Prothrombin (DCP):** Des-gamma-carboxy prothrombin (DCP) has been used widely in Japan for HCC diagnosis and surveillance. The protein DCP is an abnormal prothrombin molecule generated as a result of an acquired defect in the posttranslational carboxylation of the prothrombin precursor in malignant cells; this prothrombin defect in malignant cells is similar to the deficit in vitamin K deficiency and DCP is also known as the Protein Induced by Vitamin K Absence (PIVKA). Experience with DCP in western countries, particularly the United States, remains limited. In a large study involving HCV-infected patients with cirrhosis, investigators examined DCP, AFP, and the combination of DCP and AFP, but none of these strategies showed adequate sensitivity to justify the use of DCP as a routine surveillance test. In contrast, DCP may have some utility as a marker of advanced HCC.

Radiographic Imaging

- **Hepatic Ultrasound:** Hepatic ultrasound is reported to have a sensitivity of 65 to 80% and specificity 87 to 94% for detecting HCC. The clinician's order for the hepatic ultrasound should designate the purpose of screening for HCC and the test should focus on examination of the right upper quadrant region, including evaluation of the liver for any evidence of a hepatic mass. The interpretation of ultrasound is operator-dependent and can be difficult in persons who are obese or have underlying cirrhosis, particularly those with nodular cirrhosis.
- **Computed Tomographic Abdominal Scan:** No current evidence exists for routine use of computed tomographic (CT) abdominal scanning as a routine surveillance test for HCC. In contrast, for patients who have a liver nodule greater than 1 cm detected on ultrasound, many experts recommend using a 4-phase (unenhanced, arterial, venous, and delayed) dynamic contrast CT scan of the liver as a secondary test for diagnosis. During the arterial phase, HCC lesions enhance more intensely than the surrounding liver, but the opposite is observed during the venous and washout phases (where HCC lesions have little enhancement). The characteristic finding with HCC is presence of arterial hypervascularity (uptake) in the lesion followed by venous or delayed phase washout. The role of 4-phase CT scan in the diagnosis of HCC is particularly important since many experts rely on CT or magnetic resonance imaging (MRI) findings to establish the diagnosis, without the need for liver biopsy, if characteristic radiographic findings for HCC are present.
- **Liver Magnetic Resonance imaging (MRI):** Similar to recommendations for abdominal CT scanning, no current evidence exists that supports a recommendation to use hepatic MRI as a routine surveillance test. For patients who have a nodule greater than 1 cm detected on ultrasound, a dynamic contrast-enhanced MRI is often recommended as a secondary test. This should be distinguished from the use of MRI as a screening test since current guidelines

do not recommend MRI as a screening test.

Recommendations from Professional Organizations for HCC Surveillance

American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA): The recent AASLD/IDSA hepatitis C guidance recommends surveillance for HCC in persons with chronic HCV infection who have advanced fibrosis or cirrhosis (Metavir stage F3 or F4). The recommended surveillance test is hepatic ultrasound and the recommended surveillance interval is every 6 months. The AASLD/IDSA guidance recommends that HCC surveillance in HCV-infected patients with advanced fibrosis or cirrhosis should continue after patients receive therapy for HCV, even if they achieve an SVR. The AASLD/IDSA guidelines do not recommend using AFP as a surveillance test; evolving data have shown that AFP has poor sensitivity and specificity as a surveillance tool for HCC. In an earlier document, the AASLD provided an algorithm for investigating a liver nodule if found on hepatic ultrasound (Figure 7).

Institute of Medicine: In January 2010, the Institute of Medicine issued a report on Hepatitis and Liver Cancer, calling for increased attention to the problem of liver cancer as a potential consequence of chronic viral hepatitis and need for increased awareness, screening, and appropriate surveillance to be performed.

National Cancer Institute (at the National Institutes of Health): The National Cancer Institute states that based on fair evidence, screening for HCC would not result in a decrease in mortality from hepatocellular cancer. Further they state that screening for HCC could result in rare but serious side effects that could occur with needle aspiration cytology.

Summary Points

- Cirrhosis is the most important risk factor for developing HCC in patients with chronic hepatitis C infection. Less commonly, HCC will occur in patients who have advanced fibrosis but without cirrhosis.
- Previously, HCC was a rare malignancy in the United States, but now is the fastest growing cause of cancer-related death; the rise in the incidence of HCC is attributed to the high prevalence of HCV and aging of the chronically HCV-infected population.
- Patients who develop HCC have a poor prognosis with an estimated median survival duration of 4.3 to 20 months after diagnosis.
- Potentially curative therapies for early stage HCC include hepatic resection or liver transplantation. The primary goal of HCC surveillance is to detect disease in an early stage and therefore increase the likelihood of potentially curative therapy.
- The AASLD practice guidelines recommend surveillance for HCC using abdominal ultrasound every 6 months for all HCV-infected patients who have advanced fibrosis or cirrhosis (Metavir stage F3 or F4). These recommendations are based on retrospective data and one prospective trial that primarily involved persons with chronic hepatitis B infection.
- In patients with advanced fibrosis or cirrhosis, successful treatment of HCV lowers the risk of developing HCC, but this risk is not eliminated. Accordingly, surveillance for HCC in patients with advanced fibrosis or cirrhosis should continue even after they achieve an SVR.
- Prior practice guidelines recommended using AFP in addition to ultrasound for HCC screening, but data showing low specificity and sensitivity of AFP has led to the AASLD recommendation to ultrasound alone.

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Figures

Figure 1 2008 Global Cancer Incidence

This graphic shows the global incidence of the most common cancers in in 2008. Overall, an estimated 12.7 million new cancers occurred globally in the year 2008. Approximately 750,000 persons had a diagnosis of HCC in 2008.

Source: International Agency for Research on Cancer. World Cancer Fact Sheet. August, 2010.

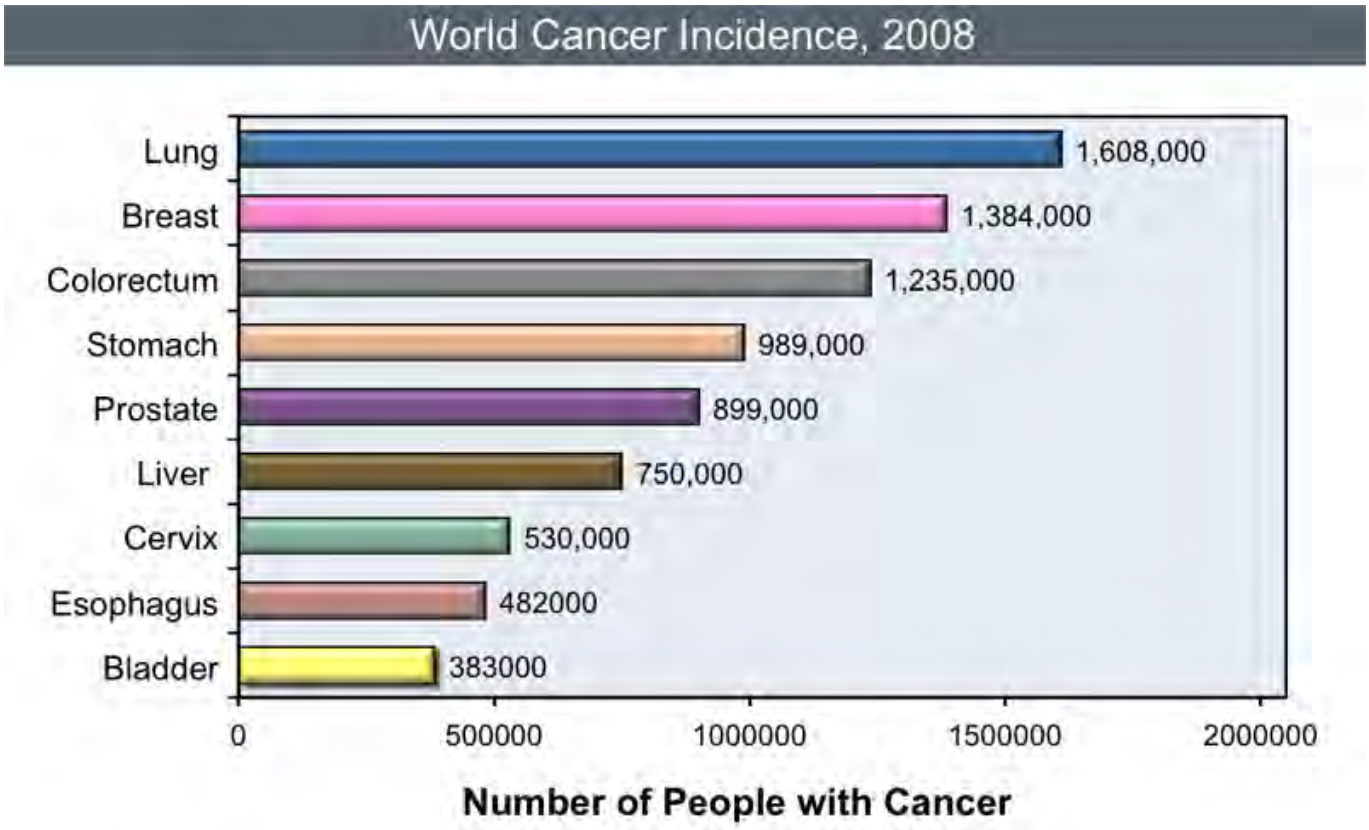


Figure 2 2008 Global Cancer Deaths

This graphic shows the number of global cancer deaths, by type of cancer in 2008. Approximately 700,000 persons died of HCC in 2008.

Source: World Health Organization. January 2013.

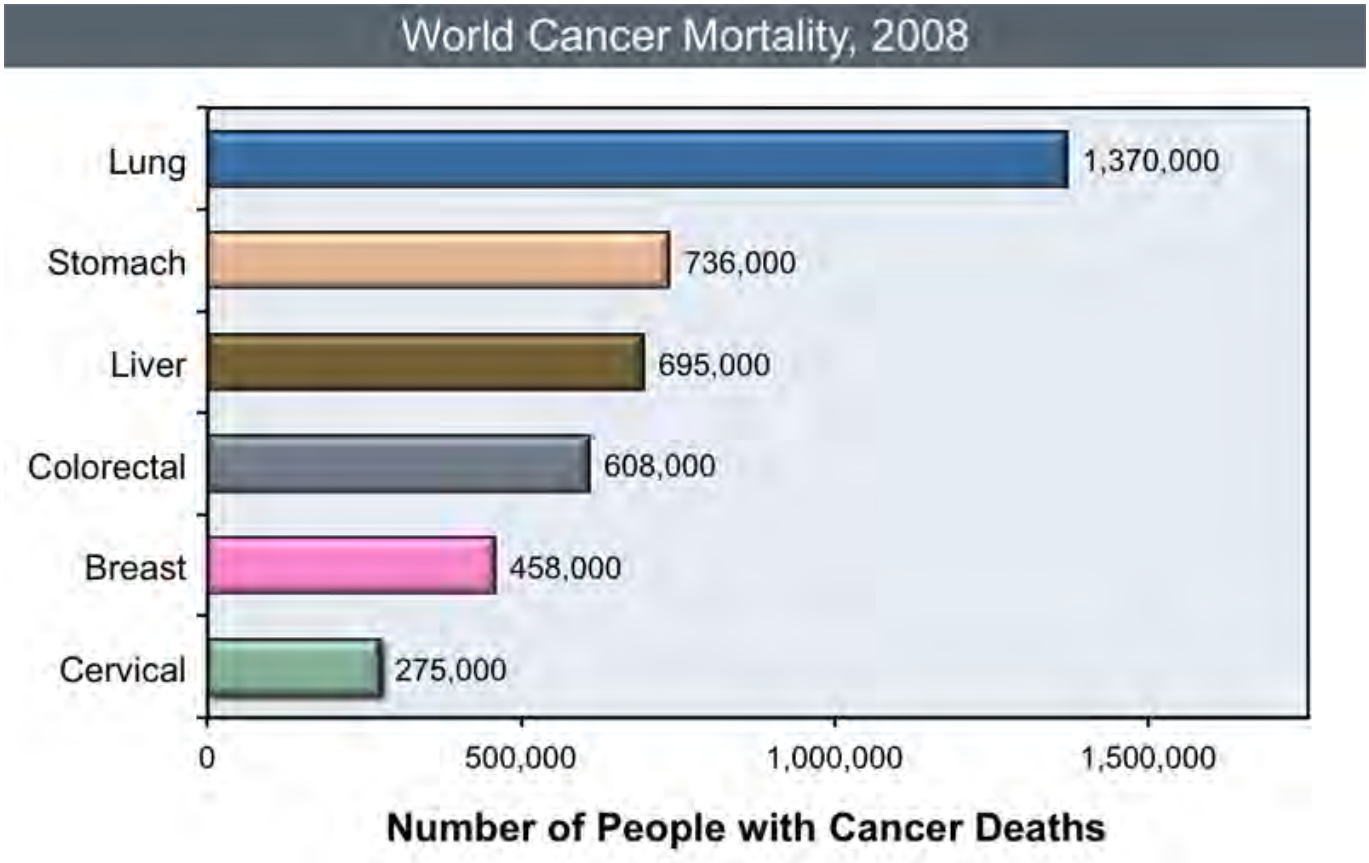


Figure 3 Age-Adjusted Rates of HCC in United States, 1992-2005

From 1992-2005, the age-adjusted rates of HCC have steadily increased, primarily due to increases in hepatitis C-related HCC.

Source: Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol. 2009;27:1485-91.

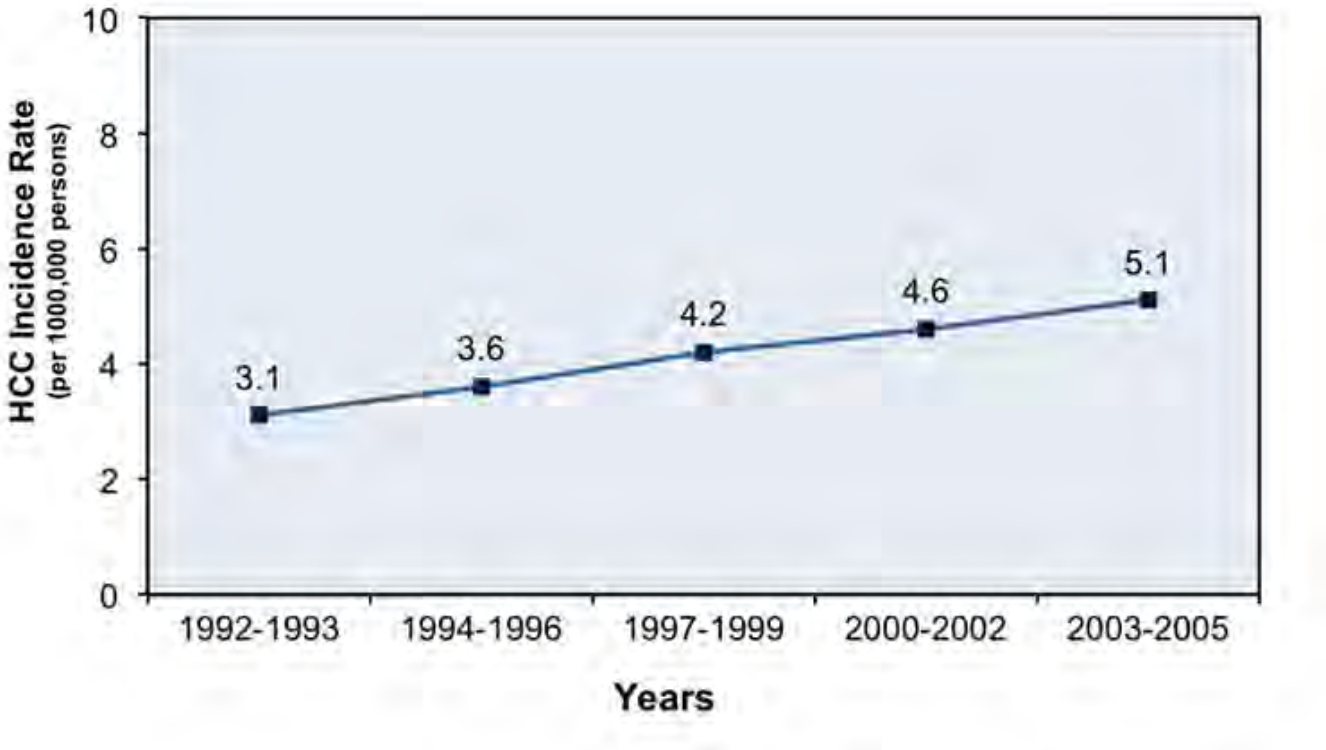


Figure 4 Incidence Rates of HCC in United States, by Sex, 2001-2006

These data show the annual HCC incidence rates (per 100,000 persons) based on year of diagnosis. The incidence rates in males (green line) was approximately 3 times that in females (purple line).

Source: Centers for Disease Control and Prevention (CDC). Hepatocellular carcinoma - United States, 2001-2006. MMWR Morb Mortal Wkly Rep. 2010;59:517-20.

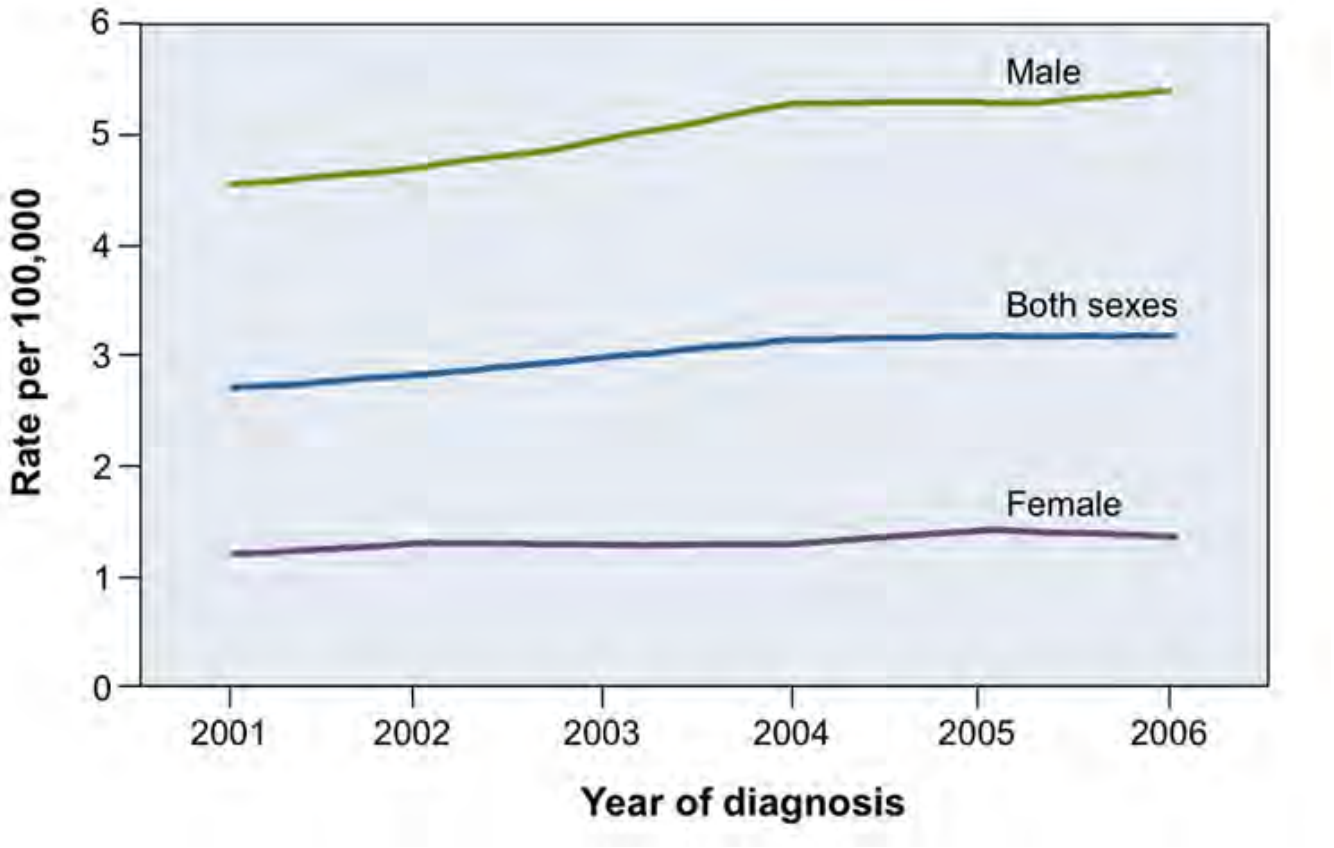


Figure 5 Impact of Screening on Stage of HCC at Time of Diagnosis

In a trial performed in Shanghai, China, more than 18,000 persons with chronic viral hepatitis (most of who had chronic hepatitis B), were randomized to screening for HCC or no screening (control). As shown, individuals who received screening were more likely to have their HCC diagnosed at an earlier stage (Stage 1) than those who did not have screening.

Source: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417-22.

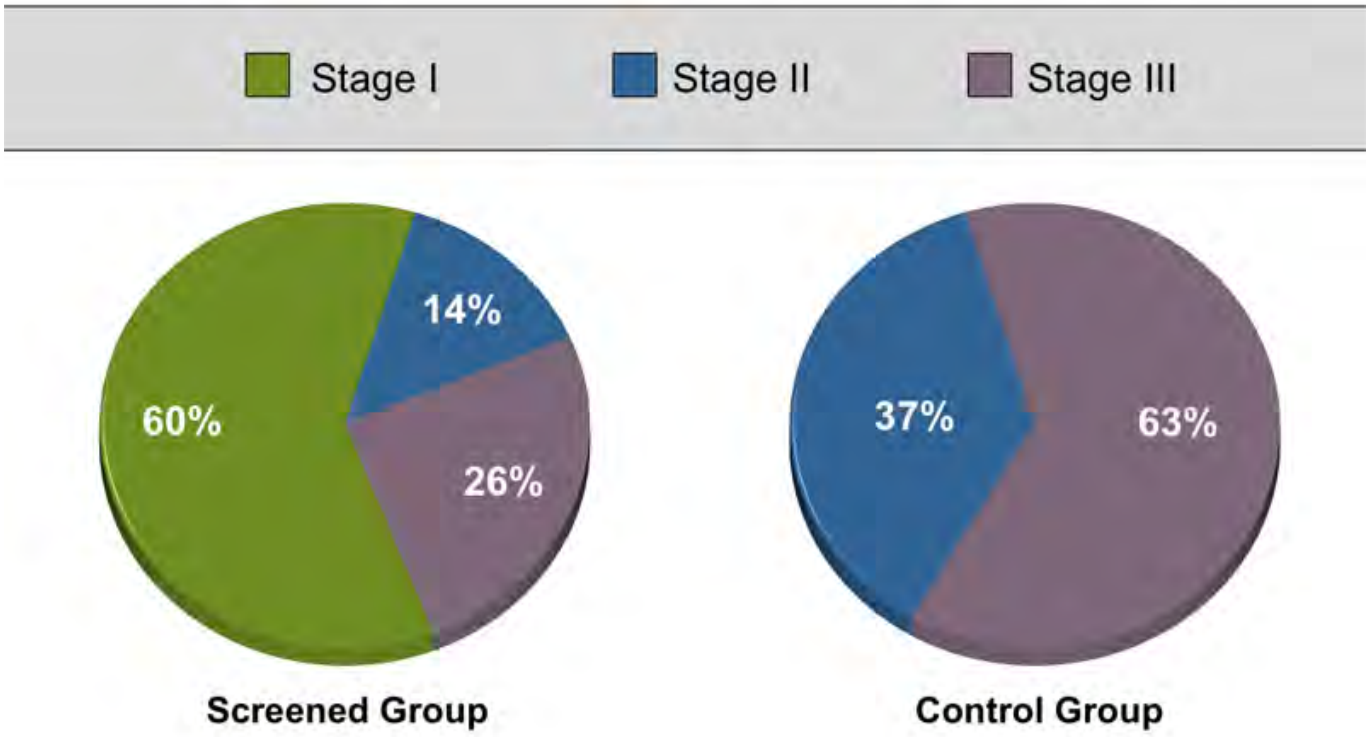


Figure 6 Impact of Screening on Survival after Diagnosis of HCC

In this trial, patients with chronic viral hepatitis who underwent screening for HCC had improved survival after the diagnosis of HCC when compared with the control group that did not receive screening for HCC.

Source: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417-22.

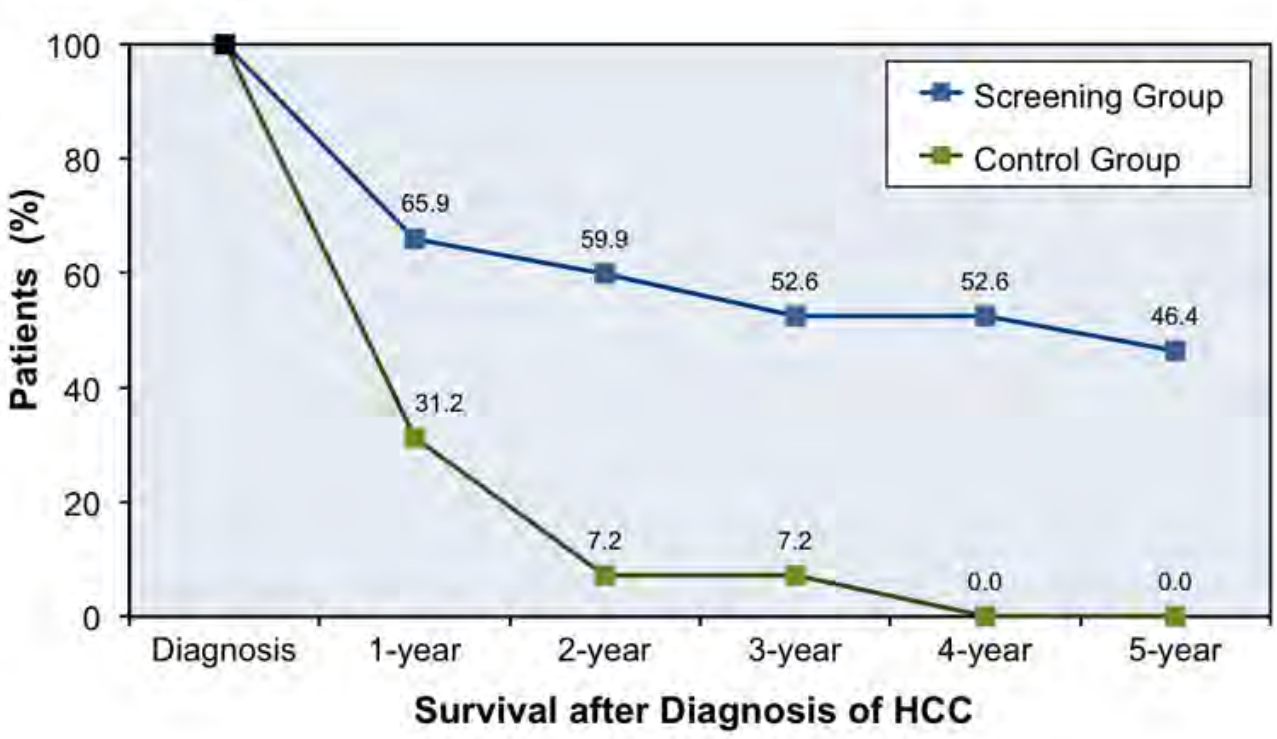
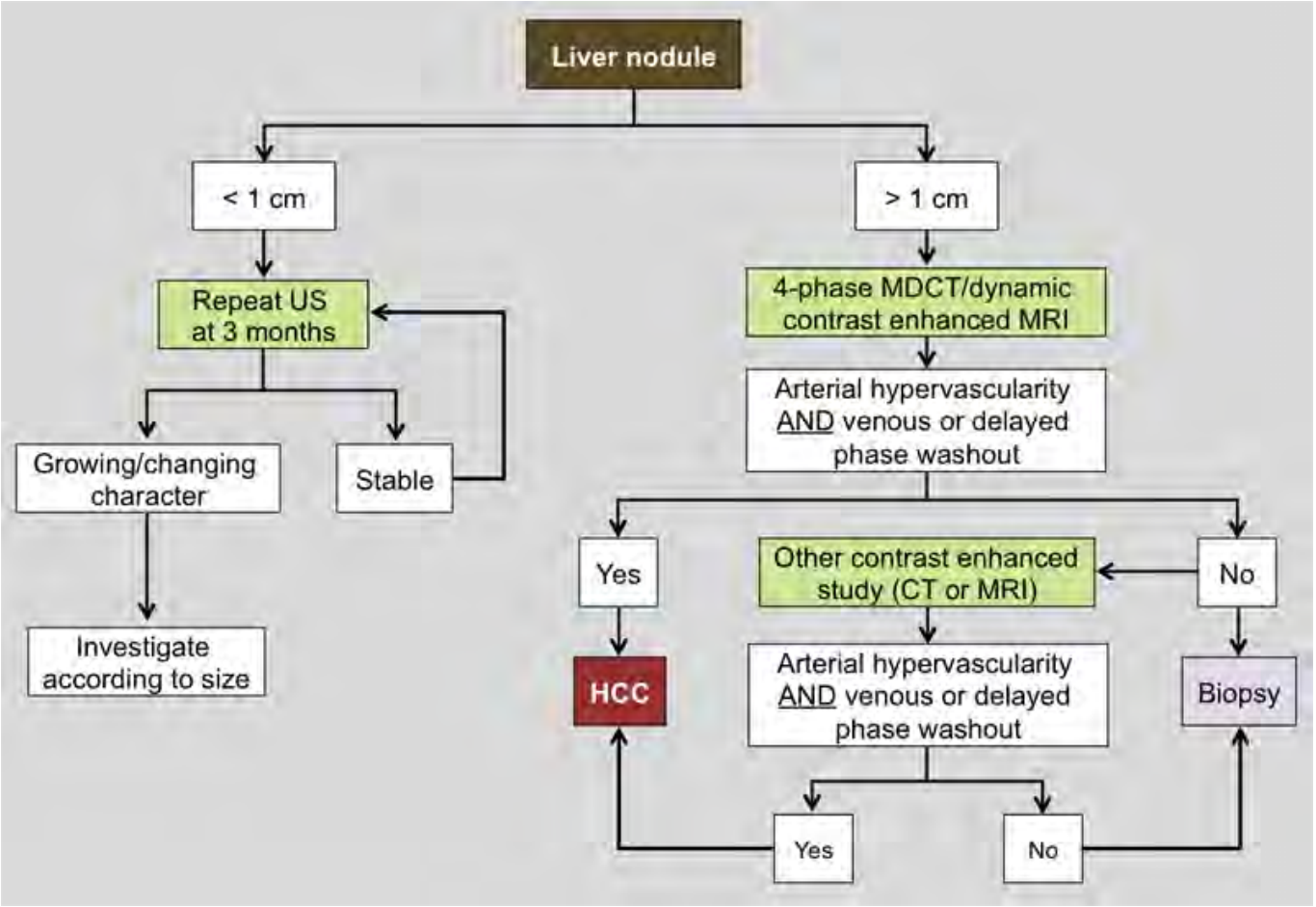


Figure 7 AASLD Diagnostic Algorithm for Suspected HCC Identified on Ultrasound

Abbreviations: CT = computed tomography; MDCT = multidetector CT; MRI = magnetic resonance imaging; US = ultrasound

Source: Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53:1020-2.



NPAIHB
Indian Leadership for Indian Health

NW Tribal Epidemiology Center

Hepatitis C Screening tool

American Indians/Alaska Natives have the highest rate of mortality from HCV and all I/T/U facilities are encouraged to provide early detection and linkage to care. The following is an easy-to-use screening tool that you can integrate into your clinic to encourage all adults get screened for HCV, at least once.

Hepatitis C Screening Tool: A Risk Factor Questionnaire

First Name	MI	Last Name
Date	**DOB**	**Medical Record #**

Ask the patient, the following questions:

	Yes	No	Don't Know	Notes/Comments
1. Are you age 20-69?				
2. Have you lived with someone who has hepatitis?				
3. Have you had a blood transfusion prior to 1992?				
4. Do you have tattoos or body art?				
5. Have you ever been in prison or jail?				
6. Have you ever injected drugs or used intranasal drugs?				

If the patient answered "Yes" or "Don't Know" to any of the above questions, they may be at risk for Hepatitis C. Please offer the patient to be tested for Hepatitis C.

Hepatitis C Reporting

The Viral Hepatitis Case Report form should be filled out for persons identified with either acute hepatitis C infection or past/present hepatitis C. Cases of hepatitis C should be reported to a health department, which in turn submits reporting data to the CDC via the Nationally Notifiable Diseases Surveillance System (NNDSS). Please find the Viral Hepatitis Case Report form on the following page.

VIRAL HEPATITIS CASE REPORT

The following questions should be asked for every case of viral hepatitis

Form Approved OMB No. 0920-0728 Exp. Date 01/31/2019

Prefix: (Mr. Mrs. Miss Ms. etc) _____ Last: _____ First: _____ Middle: _____

Preferred Name (nickname): _____ Maiden: _____

Address: Street: _____

City: _____ Phone: (_ _ _) _ _ _ – _ _ _ _ Zip Code: _ _ _ _ _ – _ _ _ _

SSN # (optional) _ _ _ – _ _ _ – _ _ _ _

Only data from lower portion of form will be transmitted to CDC

State: _____ County: _____ Date of Public Health Report M M / D D / Y Y Y Y

Case ID: _____

Legacy Case ID: _____

DEMOGRAPHIC INFORMATION

RACE: (check all that apply)

❑ Amer Indian or Alaska Native ❑ Black or African American ❑ White

❑ Asian ❑ Native Hawaiian or Pacific Islander ❑ Other Race, specify _____

ETHNICITY:

Hispanic ❑

Non-hispanic ❑

Other/Unknown ❑

SEX: Male ❑ Female ❑ Unk ❑

PLACE OF BIRTH: ❑ USA ❑ Other: _____

DATE OF BIRTH: M M / D D / Y Y Y Y

AGE: _ _ _ (years) (00 = <1yr , 999 = Unk)

CLINICAL & DIAGNOSTIC DATA

REASON FOR TESTING: (check all that apply)

❑ Year of birth (1945-1965)

❑ Screening of asymptomatic patient with reported risk factors

❑ Screening of asymptomatic patient with no risk factors (e.g., patient requested)

❑ Follow-up testing for previous marker of viral hepatitis

❑ Symptoms of acute hepatitis

❑ Blood/organ donor screening

❑ Evaluation of elevated liver enzymes

❑ Other: specify: _____

❑ Prenatal screening

❑ Unknown

CLINICAL DATA:

	Yes	No	Unk
Diagnosis date: M M / D D / Y Y Y Y			
Is patient symptomatic?	❑	❑	❑
if yes, onset date: M M / D D / Y Y Y Y			
At diagnosis, was the patient			
• Jaundiced?	❑	❑	❑
• Hospitalized for hepatitis?	❑	❑	❑
Was the patient pregnant?	❑	❑	❑
Due date: M M / D D / Y Y Y Y			
Did the patient die from hepatitis?	❑	❑	❑
• Date of death: M M / D D / Y Y Y Y			
Was the patient aware they had viral hepatitis prior to lab testing?	❑	❑	❑
Does the patient have a provider of care for hepatitis?	❑	❑	❑
Does the patient have diabetes?	❑	❑	❑
Diabetes diagnosis date: M M / D D / Y Y Y Y			

DIAGNOSTIC TESTS: (CHECK ALL THAT APPLY)

	Pos	Neg	Unk
• Total antibody to hepatitis A virus [total anti-HAV]	❑	❑	❑
• IgM antibody to hepatitis A virus [IgM anti-HAV]	❑	❑	❑
• Hepatitis B surface antigen [HBsAg]	❑	❑	❑
• Total antibody to hepatitis B core antigen [total anti-HBc]	❑	❑	❑
• Hepatitis B "e" antigen [HBeAg]	❑	❑	❑
• IgM antibody to hepatitis B core antigen [IgM anti-HBc]	❑	❑	❑
• Nucleic Acid Testing for hepatitis B [Hep B NAT]	❑	❑	❑
• Antibody to hepatitis C virus [anti-HCV]	❑	❑	❑
– anti-HCV signal to cut-off ratio _____			
• Supplemental anti-HCV assay [e.g., RIBA]	❑	❑	❑
• Antibody to hepatitis D virus [anti-HDV]	❑	❑	❑
• Antibody to hepatitis E virus [IgM anti-HEV]	❑	❑	❑

LIVER ENZYME LEVELS AT TIME OF DIAGNOSIS

• ALT [SGPT] Result _____ Upper limit normal _____

• Date of ALT result M M / D D / Y Y Y Y

• AST [SGOT] Result _____ Upper limit normal _____

• Date of AST result M M / D D / Y Y Y Y

If this case has a diagnosis of hepatitis A that has not been serologically confirmed, is there an epidemiologic link between this patient and a laboratory-confirmed hepatitis A case?	Yes	No	Unk
	❑	❑	❑

DIAGNOSIS: (check all that apply)

❑ Acute hepatitis A ❑ Acute hepatitis C ❑ Chronic HBV infection ❑ Perinatal HBV infection

❑ Acute hepatitis B ❑ Acute hepatitis E ❑ HCV infection (Past or Present)

Patient History — Acute Hepatitis A

Case ID: _____

During the **2-6 weeks** prior to onset of symptoms-	Yes	No	Unk
Was the patient a contact of a person with confirmed or suspected hepatitis A virus infection?	❑	❑	❑
If yes, was the contact (check one)			
• household member (non-sexual)	❑	❑	❑
• sex partner	❑	❑	❑
• child cared for by this patient	❑	❑	❑
• babysitter of this patient	❑	❑	❑
• playmate	❑	❑	❑
• other _____			
Was the patient			
• a child or employee in a day care center, nursery, or preschool?	❑	❑	❑
• a household contact of a child or employee in a day care center, nursery or preschool?	❑	❑	❑
If yes for either of these, was there an identified hepatitis A case in the child care facility?	❑	❑	❑

What is the sexual preference of the patient?

❑ Heterosexual ❑ Homosexual ❑ Bisexual ❑ Unknown

Please ask both of the following questions regardless of the patient's gender.

In the **2–6 weeks** before symptom onset how many	0	1	2–5	>5	Unk
male sex partners did the patient have?	❑	❑	❑	❑	❑
female sex partners did the patient have?	❑	❑	❑	❑	❑

In the **2–6 weeks** before symptom onset	Yes	No	Unk
Did the patient inject drugs not prescribed by a doctor?	❑	❑	❑
Did the patient use street drugs but not inject?	❑	❑	❑
Did the patient **travel or live** outside of the U.S.A. or Canada?	❑	❑	❑

If yes, where? 1) _____ 2) _____

(Country) 3) _____

What was the principle reason for travel? ❑ Business ❑ New Immigrant ❑ Other

❑ Tourism ❑ Visiting relatives/friends ❑ Adoption ❑ Unknown

In the **3 months** prior to symptom onset did anyone in the patient's household travel outside of the U.S.A. or Canada?	❑	❑	❑
Is the patient suspected as being part of a common-source outbreak?	❑	❑	❑
If yes, was the outbreak			
Foodborne — associated with an infected food handler	❑	❑	❑
Foodborne — **NOT** associated with an infected food handler	❑	❑	❑
Specify food item _____			
Waterborne	❑	❑	❑
Source not identified	❑	❑	❑
Was the patient employed as a food handler during the **TWO WEEKS** prior to onset of symptoms or while ill?	❑	❑	❑

VACCINATION HISTORY

	Yes	No	Unk	
• Has the patient ever received the hepatitis A vaccine?	❑	❑	❑	
	1	**>2**		
If yes, how many doses?	❑	❑		• In what year was the last dose received? Y Y Y Y (year)
	Yes	**No**	**Unk**	
• Has the patient ever received immune globulin?	❑	❑	❑	• If yes, when was the last dose received? M M / Y Y Y Y (mo/year)

Patient History — Acute Hepatitis B

Case ID: _____

	Yes	No	Unk
During the **6 weeks – 6 months** prior to onset of symptoms was the patient a contact of a person with confirmed or suspected acute or chronic hepatitis B virus infection?	❑	❑	❑
If yes, type of contact			
Sexual	❑	❑	❑
Household (non-sexual)	❑	❑	❑
Other: _____			

During the **6 weeks – 6 months** prior to onset of symptoms	Yes	No	Unk
Did the patient:			
• undergo hemodialysis?	❑	❑	❑
• have an accidental stick or puncture with a needle or other object contaminated with blood?	❑	❑	❑
• receive blood or blood products [transfusion]	❑	❑	❑
If yes, when? M M / D D / Y Y Y Y			
• receive any IV infusions and/or injections in the outpatient setting	❑	❑	❑
• have other exposure to someone else's blood	❑	❑	❑
specify: _____			
During the **6 weeks – 6 months** prior to onset of symptoms			
• Was the patient employed in a medical or dental field involving direct contact with human blood?	❑	❑	❑
If yes, frequency of direct blood contact?			
❑ Frequent (several times weekly) ❑ Infrequent			
• Was the patient employed as a public safety worker (fire fighter, law enforcement or correctional officer) having direct contact with human blood?	❑	❑	❑
If yes, frequency of direct blood contact?			
❑ Frequent (several times weekly) ❑ Infrequent			
• Did the patient receive a tattoo?	❑	❑	❑
Where was the tattooing performed? (select all that apply)			
❑ commercial parlor/shop			
❑ correctional facility ❑ other _____			

	Yes	No	Unk
Did the patient ever receive hepatitis B vaccine?	❑	❑	❑
	1	**2**	**3+**
If yes, how many shots?	❑	❑	❑
• In what year was the last shot received? __ __ __ __			
Was the patient tested for antibody to HBsAg (anti-HBs) within 1-2 months after the last dose	❑	❑	❑
• If yes, was the serum anti-HBs ≥ 10mIU/ml? (answer 'yes' if the laboratory result was reported as 'positive' or 'reactive')	❑	❑	❑

What is the sexual preference of the patient?

❑ Heterosexual ❑ Homosexual

❑ Bisexual ❑ Unknown

Ask both of the following questions regardless of the patient's gender.

In the **6 months** before symptom onset, how many	0	1	2–5	>5	Unk
• male sex partners did the patient have?	❑	❑	❑	❑	❑
• female sex partners did the patient have?	❑	❑	❑	❑	❑

Was the patient **EVER** treated for a sexually-transmitted disease?	Yes	No	Unk
	❑	❑	❑
• If yes, in what year was the most recent treatment? Y Y Y Y			

During the **6 weeks – 6 months** prior to onset of symptoms	Yes	No	Unk
• inject drugs not prescribed by a doctor?	❑	❑	❑
• use street drugs but not inject?	❑	❑	❑
• Did the patient have any part of their body pierced (other than ear)?	❑	❑	❑
Where was the piercing performed? (select all that apply)			
❑ commercial parlor/shop			
❑ correctional facility ❑ other _____			
• Did the patient have dental work or oral surgery?	❑	❑	❑
• Did the patient have surgery ? (other than oral surgery)	❑	❑	❑
Was the patient: (check all that apply)			
• hospitalized?	❑	❑	❑
• a resident of a long term care facility?	❑	❑	❑
• incarcerated for longer than 24 hours	❑	❑	❑
if yes, what type of facility (check all that apply)			
prison	❑	❑	❑
jail	❑	❑	❑
juvenile facility	❑	❑	❑

	Yes	No	Unk
During his/her lifetime, was the patient **EVER** incarcerated for longer than 6 months?	❑	❑	❑
• If yes, what year was the most recent incarceration? Y Y Y Y			
for how long? M M M (mos)			
Did patient have a negative HBsAg test within 6 months prior to positive test?	❑	❑	❑
Verified test date: M M / D D / Y Y Y Y			
Was the patient tested for hepatitis D?	❑	❑	❑
Did patient have a co-infection with hepatitis D?	❑	❑	❑

Perinatal Hepatitis B Virus Infection

Case ID: _____

RACE OF MOTHER:

❑ Amer Ind or Alaska Native ❑ Black or African American ❑ White ❑ Unknown

❑ Asian ❑ Native Hawaiian or Pacific Islander

❑ Other Race, specify: _____

ETHNICITY OF MOTHER:

Hispanic..... ❑

Non-hispanic ..... ❑

Other/Unknown..... ❑

	Yes	No	Unk	
Was **Mother** born outside of United States?.....	❑	❑	❑	If yes, what country? _____
Was the **Mother** confirmed HBsAg positive prior to or at time of delivery?..	❑	❑	❑	
• If no, was the mother confirmed HBsAg positive after delivery?	❑	❑	❑	
Date of earliest HBsAg positive test result.....	M M / D D / Y Y Y Y			

	0	1	2	3+
How many doses of hepatitis B vaccine did the child receive ?.....	❑	❑	❑	❑
• When?				
• Dose 1 M M / D D / Y Y Y Y				
• Dose 2 M M / D D / Y Y Y Y				
• Dose 3 M M / D D / Y Y Y Y				

	Yes	No	Unk
Did the child receive hepatitis B immune globulin (HBIG)?.....	❑	❑	❑
• If yes, on what date did the child receive HBIG?	M M / D D / Y Y Y Y		

Patient History — Acute Hepatitis C

Case ID: _____

	Yes	No	Unk
During the **2 weeks – 6 months** prior to onset of symptoms was the patient a contact of a person with confirmed or suspected acute or chronic hepatitis C virus infection?	❑	❑	❑
If yes, type of contact			
Sexual	❑	❑	❑
Household (non-sexual)	❑	❑	❑
Other: _____	❑	❑	❑

	Yes	No	Unk
During the **2 weeks – 6 months** prior to onset of symptoms **Did the patient:**			
• undergo hemodialysis?	❑	❑	❑
• have an accidental stick or puncture with a needle or other object contaminated with blood?	❑	❑	❑
• receive blood or blood products [transfusion]	❑	❑	❑
If yes, when?			
• receive any IV infusions and/or injections in the outpatient setting	❑	❑	❑
• have other exposure to someone else's blood	❑	❑	❑
specify: _____			
During the **2 weeks – 6 months** prior to onset of symptoms			
• Was the patient employed in a medical or dental field involving direct contact with human blood ?	❑	❑	❑
If yes, frequency of direct blood contact?			
❑ Frequent (several times weekly) ❑ Infrequent			
• Was the patient employed as a public safety worker (fire fighter, law enforcement or correctional officer) having direct contact with human blood?	❑	❑	❑
If yes, frequency of direct blood contact?			
❑ Frequent (several times weekly) ❑ Infrequent			
• Did the patient receive a tattoo?	❑	❑	❑
Where was the tattooing performed? (select all that apply)			
❑ commercial parlor/shop			
❑ correctional facility ❑ other _____			

What is the sexual preference of the patient?

❑ Heterosexual ❑ Homosexual

❑ Bisexual ❑ Unknown

Ask both of the following questions regardless of the patient's gender.

In the **6 months** before symptom onset, how many	0	1	2–5	>5	Unk
• male sex partners did the patient have?	❑	❑	❑	❑	❑
• female sex partners did the patient have?	❑	❑	❑	❑	❑

	Yes	No	Unk
Was the patient EVER treated for a sexually-transmitted disease?	❑	❑	❑
• If yes, in what year was the most recent treatment? Y Y Y Y			
During the **2 weeks – 6 months** prior to onset of symptoms			
• inject drugs not prescribed by a doctor?	❑	❑	❑
• use street drugs but not inject?	❑	❑	❑
Did the patient have a negative HCV antibody test within 6 months to a positive test?	❑	❑	❑
Vertified test date M M / D D / Y Y Y Y			
During the **2 weeks – 6 months** prior to onset of symptoms			
• Did the patient have any part of their body pierced (other than ear)?	❑	❑	❑
Where was the piercing performed? (select all that apply)			
☐ commercial parlor/shop			
☐ correctional facility			
☐ other _____			
• Did the patient have dental work or oral surgery?	❑	❑	❑
• Did the patient have surgery ? (other than oral surgery)	❑	❑	❑
Was the patient – (check all that apply)			
• hospitalized?	❑	❑	❑
• a resident of a long term care facility?	❑	❑	❑
• incarcerated for longer than 24 hours	❑	❑	❑
If yes, what type of facility (check all that apply)			
prison	❑	❑	❑
jail	❑	❑	❑
juvenile facility	❑	❑	❑

	Yes	No	Unk
During his/her lifetime, was the patient **EVER** incarcerated for longer than 6 months?	❑	❑	❑
• If yes, what year was the most recent incarceration? Y Y Y Y			
for how long? M M M (mos)			
Has the patient recieved medication for the type of hepatitis being reported?	❑	❑	❑

Patient History — Chronic Hepatitis B Infection

Case ID: _____

The following questions are provided as a guide for the investigation of lifetime risk factors for HBV infection. Routine collection of risk factor information for persons who test HBV positive is not required. However, collection of risk factor information for such persons may provide useful information for the development and evaluation of programs to identify and counsel HBV-infected persons.

	Yes	No	Unk
Did the patient receive clotting factor concentrates produced prior to 1987?	❑	❑	❑
Was the patient ever on long-term hemodialysis?	❑	❑	❑
Has the patient ever injected drugs not prescribed by a doctor even if only once or a few times?	❑	❑	❑
How many sex partners has the patient had (approximate lifetime)? _____			
Was the patient ever incarcerated?	❑	❑	❑
Was the patient ever treated for a sexually transmitted disease?	❑	❑	❑
Was the patient ever a contact of a person who had hepatitis?	❑	❑	❑
If yes, type of contact			
• Sexual	❑	❑	❑
• Household [Non-sexual]	❑	❑	❑
• Other	❑	❑	❑

	Yes	No	Unk
Was the patient ever employed in a medical or dental field involving direct contact with human blood?	❑	❑	❑
What is the birth country of the mother ? _____			
Has the patient recieved medication for the type of hepatitis being reported?	❑	❑	❑

Patient History — Hepatitis C Infection (past or present)

Case ID: _____

The following questions are provided as a guide for the investigation of lifetime risk factors for HCV infection. Routine collection of risk factor information for persons who test HCV positive is not required. However, collection of risk factor information for such persons may provide useful information for the development and evaluation of programs to identify and counsel HCV-infected persons.

	Yes	No	Unk
Did the patient receive a blood transfusion prior to 1992?	❑	❑	❑
Did the patient receive an organ transplant prior to 1992?	❑	❑	❑
Did the patient receive clotting factor concentrates produced prior to 1987?	❑	❑	❑
Was the patient ever on long-term hemodialysis?	❑	❑	❑
Has the patient ever injected drugs not prescribed by a doctor even if only once or a few times?	❑	❑	❑
How many sex partners has the patient had (approximate lifetime)? _____			
Was the patient ever incarcerated?	❑	❑	❑
Was the patient ever treated for a sexually transmitted disease?	❑	❑	❑
Was the patient ever a contact of a person who had hepatitis?	❑	❑	❑
If yes, type of contact			
• Sexual	❑	❑	❑
• Household [Non-sexual]	❑	❑	❑
• Other	❑	❑	❑

	Yes	No	Unk
Was the patient ever employed in a medical or dental field involving direct contact with human blood?	❑	❑	❑
Has the patient recieved medication for the type of hepatitis being reported?	❑	❑	❑

Media Materials

Please find an overview of AI/AN patient education materials and handouts in the following pages. If you are interested in additional resources or receiving the latest education materials, text HCV to 97779.

“Hep C is MY RESPONSIBILITY because...

...as a primary care provider, working on both prevention and treatment, I feel it is my duty to link our people to the services and treatment they need.”

Shannon Walker

Inupiaq, Family Practitioner, ARNP FNP-C

American Indians and **Alaska Natives**
have the highest **hepatitis C** mortality rate of any race or ethnicity.

It’s time to raise awareness. Encourage your patients to get tested and treated for hepatitis C.

Together, we can eliminate Hep C.

NPAIHB
Indian Leadership for Indian Health

This mask, from the exhibit “Aggravated Organisms,” was carved by Drew Michael and painted by Elizabeth Ellis to represent hepatitis C. The 10 human-sized wooden masks in the exhibit explored how different diseases can overtake human cells. The exhibit traveled through Alaska and the Seattle area, ending with the masks being burned in a traditional ceremony.

“Hep C is MY RESPONSIBILITY because...

...I am the only one who can impact my own health, and my health is a reflection of the world as I know it.”

Harriette Chacka
Makah

American Indians and **Alaska Natives**
have the highest **hepatitis C** mortality rate of any race or ethnicity.

It’s time to take care of ourselves and the ones we love.

Get tested. If you have hepatitis C, get treated.
Together, we can eliminate Hep C.

NPAIHB
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“Hep C is MY RESPONSIBILITY because...

...as a nurse, mother, and steward of this earth it is my responsibility to help make this world a healthier place for future generations.”

Jacquie Gilles

Registered Nurse

American Indians and **Alaska Natives** have the highest **hepatitis C** mortality rate of any race or ethnicity.

It’s time to raise awareness. Encourage your patients to get tested and treated for hepatitis C.

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Why is Hepatitis C everybody's responsibility?

"We are responsible for each other and ourselves."

– Kodiak Alutiiq Cultural Value

According to the Centers for Disease Control and Prevention American Indian and Alaska Native people have the highest mortality rate from hepatitis C (HCV) of any race or ethnicity. Hepatitis C is treatable in our communities, by our own providers.

The Hep C Mask

This mask, from the exhibit "Aggravated Organisms," was carved by Drew Michael (Yupik/Inupiaq) and painted by Elizabeth Ellis (Alutiiq/Sugpiaq) to represent hepatitis C. This mask traveled through Alaska and the Seattle area to spread awareness before being burned in a traditional ceremony.

The Northwest Portland Area Indian Health Board aims to raise awareness of the hepatitis C mask, the story of its modern creation, and its message of the importance of hepatitis C testing and treatment.

Learn more

Join the Health Board's teleECHO clinic focusing on the management & treatment of patients with hepatitis C. The 1-hour-long clinic includes an opportunity to present cases, receive recommendations from a specialist, engage in a didactic session, and become part of a learning community.

For more information:

- Text **HCV** to **97779**, or
- Visit **www.npaihb.org/hcv**

NPAIHB
Indian Leadership for Indian Health

Hepatitis C:

Everybody's Responsibility

Hepatitis C can be cured and our IHS, tribal, and urban Indian primary care clinics have the capacity to provide this cure

NPAIHB
Indian Leadership for Indian Health

Hepatitis C facts

1. It is estimated that as many as 120,000 AI/ANs are currently infected with the hepatitis C virus, of which the vast majority have not been treated.
2. Baby boomers, people born from 1945 through 1965, are five times more likely to have hepatitis C.
3. New outbreaks of hepatitis C in the United States among young adults, in predominantly suburban and rural areas, have emerged and may be fueling an increase in hepatitis C.
4. Early detection of the hepatitis C virus through routine and targeted screening is critical to the success of treating the virus with new drug regimens.
5. By treating at the primary care level, we can begin to eradicate this disease.
6. Curing a patient of hepatitis C greatly reduces their risk of developing liver cancer and liver failure.

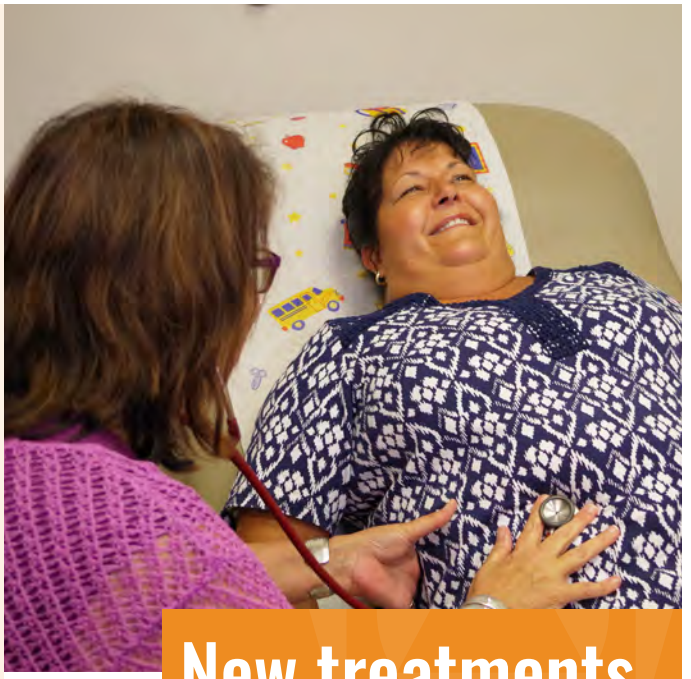
Be ready to talk to your patients about hepatitis C

Many IHS, tribal, and urban Indian (I/T/U) clinics have already initiated hepatitis C screening and treatment resulting in patients cured and earning greatly deserved gratitude from the communities they serve.

Patient talking points

- Hepatitis C is a disease that is spread through contact with the blood or body fluids of a person infected with the hepatitis C virus.
- Most people with hepatitis C do not know they are infected.
- The CDC recommends that all baby boomers, people born from 1945 through 1965, are screened for hepatitis C at least once.
- The development of new oral medications, with generally mild side effects, may provide a cure for hepatitis C infection.
- Our I/T/U primary care clinics have the capacity to provide this cure.

We're proving that hepatitis C is treatable in our communities, by our own providers.



New treatments

Hepatitis C has historically been difficult to treat, with highly toxic drug regimens and low efficacy (cure) rates. In recent years, however, medical options have vastly improved: current treatments have almost no side effects, are oral-only, and have cure rates of over 90%.

Curing a patient of chronic hepatitis C greatly reduces the risk of liver cancer and liver failure. These new drug regimens have made early detection and treatment of hepatitis C critical.

To learn about current FDA approved drug regimens visit hepatitisc.uw.edu

Are you screening for Hep C?

It's estimated as many as 120,000 American Indians and Alaska Natives (AI/ANs) are living with the Hepatitis C Virus.

AI/ANs have the highest Hepatitis C mortality rate of any race or ethnicity.

Encourage your patients to get tested and treated for Hepatitis C.

Together, we can eliminate Hepatitis C.

NPAIHB
Indian Leadership for Indian Health

www.npaihb.org/hcv

Hepatitis C:

Why Baby Boomers should get tested

People born from 1945-1965 are 5 times more likely to have Hepatitis C.

75% of people with Hepatitis C were born from 1945-1965.

Hepatitis C can cause liver damage, liver failure, and even death.

Successful treatment can eliminate Hepatitis C from the body.

Learn more:

cdc.gov/knowmorehepatitis

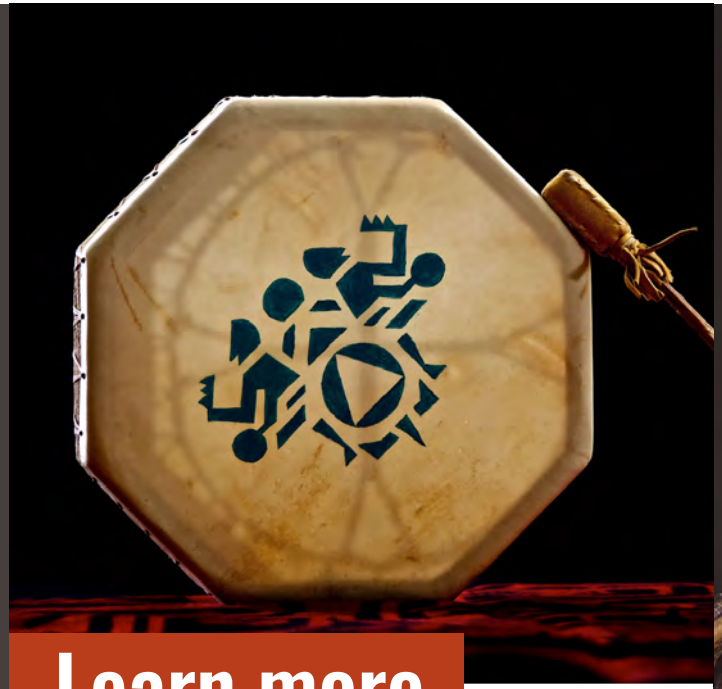
The Hep C Mask

This mask, from the exhibit "Aggravated Organisms," was carved by Drew Michael and painted by Elizabeth Ellis to represent Hepatitis C. It traveled through Alaska and the Seattle area to spread awareness before being burned in a traditional ceremony. The mask has now been made into a lapel pin. To request your Hep C pin, text MASK to 97779.

The Hepatitis C Mask

This mask, from the exhibit "Aggravated Organisms," was carved by Drew Michael (Yupik/Inupiaq) and painted by Elizabeth Ellis (Alutiiq/Sugpiaq) to represent hepatitis C. This mask and 9 more representing other diseases explore how our bodies' cells are sometimes overtaken by disease. The masks traveled through Alaska and the Seattle area to spread awareness before being burned in a traditional ceremony.

The Northwest Portland Area Indian Health Board aims to raise awareness of the hepatitis C mask, the story of its modern creation, and its message of the importance of hepatitis C testing and treatment.



Learn more

It's time to make a decision to get actively involved, raise awareness, and care for ourselves and the ones we love.

Text CURE to 97779

NPAIHB
Indian Leadership for Indian Health

www.npaihb.org/hcv

Hepatitis C:
Everybody's Responsibility

IHS, tribal, and urban Indian clinics can cure you of hepatitis C

"Getting treated makes you someone strong enough to get in and get help to wipe out this disease."

-Deb Myers (Makah), cured of hepatitis C

NPAIHB
Indian Leadership for Indian Health

Get tested

We are responsible for each other and ourselves.

- Up to 75% of people with hepatitis C do not know they have it.
- Many people live with hepatitis C for decades with no symptoms.
- Baby boomers born from 1945-1965 are 5 times more likely to have hepatitis C.
- Hepatitis C can cause liver damage, liver failure, and even death.

Get treated

New treatments have very few side effects.

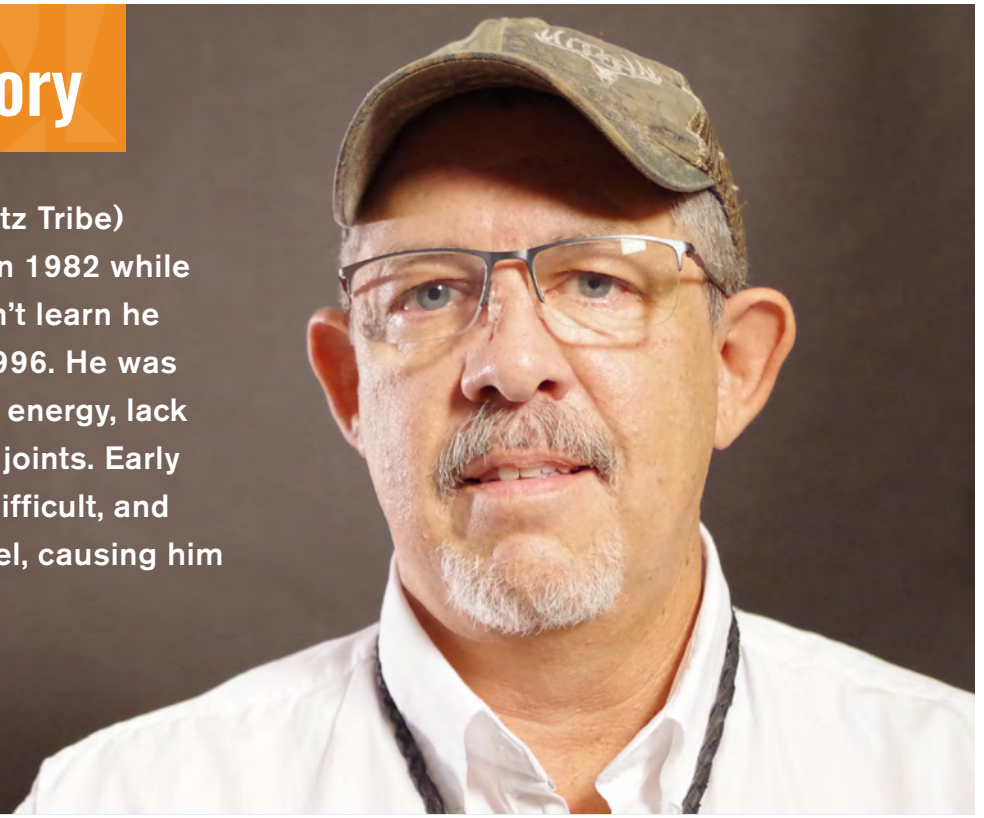
Treatment can be completed in as little as 8 weeks with 1 pill a day.

IHS or your tribal or urban Indian health center can help you find coverage for treatment.

Advocate for your health

- Help your doctor understand you're ready to put hepatitis C behind you.
- Express yourself and be clear–let your doctor know that you're ready to find a cure.
- Remember you are your best advocate. If your doctor doesn't provide treatment, ask to be referred to someone who does treat.

Michael's Story



Michael Buckner (Cowlitz Tribe) contracted hepatitis C in 1982 while getting tattoos, but didn't learn he had the disease until 1996. He was suffering from a loss of energy, lack of motivation, and achy joints. Early treatments were long, difficult, and unsuccessful for Michael, causing him to get discouraged.

"The long-term effects of having Hep C all these years have cost me greatly," **he said.**

But recently, Michael was offered a new treatment–one that took just 12 weeks to cure him of Hep C.

"There were no side effects, and I'm happy to say I don't have hepatitis C anymore. I'm more active, have more energy, am less achy, and feel more positive."

Michael urges others to get tested and treated, too.

"It's not going to go away unless you do something about it."

Get tested for Hepatitis C

We are responsible for each other and ourselves.

- Up to 75% of people with Hepatitis C do not know they have it.
- Many people live with Hepatitis C for decades with no symptoms.
- Baby boomers born from 1945-1965 are 5 times more likely to have Hep C.
- Hepatitis C can cause liver damage, liver failure, and even death.
- Successful treatment can eliminate Hepatitis C from the body.

NPAIHB
Indian Leadership for Indian Health

www.npaihb.org/hcv

If you have Hep C, GET TREATED

New treatments have fewer side effects.

Treatment can be completed in as little as 8 weeks with 1 pill a day.

Advocate for your health

- Help your doctor understand you're ready to put Hepatitis C behind you.
- Express yourself and be clear–let your doctor know that you're ready to find a cure.
- Remember you are your best advocate. If your doctor doesn't provide treatment, ask to be referred to someone who does treat.

To learn more about Hepatitis C, text CURE to 97779

The Hep C Mask

This mask, from the exhibit "Aggravated Organisms," was carved by Drew Michael and painted by Elizabeth Ellis to represent hepatitis C. It traveled through Alaska and the Seattle area to spread awareness before being burned in a traditional ceremony.

Hepatitis C Antibody Test results

When getting tested for Hepatitis C, be sure to ask when and how test results will be given to you. The test results usually take anywhere from 20 minutes to a few weeks to come back.

What do the results mean?

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 see if a person is currently infected with Hepatitis C. It is important that you ask for this follow-up test.

For more information

Talk to a health professional at your local clinic! Or visit www.cdc.gov/knowmorehepatitis

Northwest Portland Area Indian Health Board
2121 SW Broadway, Suite 300
Portland, Oregon 97201
www.npaihb.org

HEPATITIS C

TEST, TREAT, CURE

Why should you get tested for Hepatitis C?

Most people with Hepatitis C do not have any symptoms and do not know they are infected. Chronic Hepatitis C is a serious disease that can result in long-term health problems, including liver damage, liver failure, liver cancer, or even death. Hepatitis C can be in your body for many years with no symptoms.

- Baby boomers (born between 1945-1965) are five times more likely to have Hepatitis C.
- 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.

It is estimated that 2.7-3.9 million people in the United States have chronic hepatitis C

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

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

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

What should you know about Hepatitis C?

Hepatitis C (HCV for short) 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 get rid of the virus, but most people who get infected develop a 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. The good news: Hepatitis C is a preventable and curable disease.

People with Hepatitis C:

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

How would you know if you have Hepatitis C?

The only way to know if someone has Hepatitis C is to get tested. Doctors use a blood test to find out if a person has ever been infected with Hepatitis C.

Hepatitis C Antibody Test results

When getting tested for Hepatitis C, be sure to ask when and how test results will be given to you. The test results usually take anywhere from a few days to a few weeks to come back.

What do the results mean?

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 see if a person is currently infected with Hepatitis C. It is important that you ask for this follow-up test.

For more information

Talk to a health professional at your local clinic! Or visit www.cdc.gov/knowmorehepatitis

Northwest Portland Area Indian Health Board
2121 SW Broadway, Suite 300
Portland, Oregon 97201
www.npaihb.org

HEPATITIS C

WHY BABY BOOMERS SHOULD GET TESTED

Why should baby boomers get tested for Hepatitis C?

While anyone can get Hepatitis C, more than 75% of adults infected are baby boomers, people born from 1945 through 1965. Hepatitis C can be in your body for many years with no symptoms. Most people with Hepatitis C do not know they are infected.

- Baby boomers are five times more likely to have Hepatitis C.
- 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.

It is recommended that anyone born from 1945 through 1965 get tested for Hepatitis C.

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

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

Hepatitis C is mostly spread through contact with blood from an infected person. Many baby boomers could have been infected from contaminated blood and blood products before widespread screening of the blood supply began in 1992. Others may have become infected from injecting drugs, even if only once in the past. Still, many baby boomers with Hepatitis C 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 get rid of the virus, but most people who get infected develop a 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 usually be successfully treated with medications

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 to find out if a person has ever been infected with Hepatitis C.

AI/AN Hepatitis C Media Materials Currently Available

Title	Target Audience	Type	Intended Behavior	File
Hep C Brochure	Patient	Print: Brochure	Testing	http://www.npaihb.org/wpfb-file/hep-c-brochure-pdf/
Female Radio Ad	Patient	Audio: PSA	Testing	http://www.npaihb.org/wpfb-file/hepc30sradioad-female-mp3/
Male Radio Ad	Patient	Audio: PSA	Testing	http://www.npaihb.org/wpfb-file/hepc30sradioad-male-mp3/
Great Plains-	Patient	Print: Flyer	Testing	https://drive.google.com/file/d/0B0wS0xLTKfP9al96ZUpvMEd0b0U/view?usp=sharing
Great Plains-Video Doc	Patient	Video	Access Care/tx	https://drive.google.com/open?id=0B7iltWnLO8ZYMjBmcGhUalNxVlU
Great Plains-Hep C	Patient	2 Videos-15sec	Access Care/tx	https://drive.google.com/open?id=0B7iltWnLO8ZYREpaSW8ycDNKREk https://drive.google.com/open?id=0B7iltWnLO8ZYMnlIMzQ5X1preTg
Great Plains-IVDU/Addiction	Patient	Video-15sec	Access Care/tx	https://drive.google.com/open?id=0B7iltWnLO8ZYS1hqUGNfSzlVNDg
Great Plains-Rx/Addiction	Patient	Video-15sec	Access Care/tx	https://drive.google.com/open?id=0

				B7iltWnLO8ZYcEZSSXhHNk1mdzA
Great Plains-Hep C	Patient	Audio: PSA	Testing	https://drive.google.com/open?id=0B7iltWnLO8ZYbkFiOUxVN3luOU0
Great Plains-IV Drugs/Addiction	Patient-	Audio: PSA	Access Care	https://drive.google.com/open?id=0B7iltWnLO8ZYcDFNdjNnUlRrNEU
Great Plains-Rx Drugs/Addiction	Patient-Rx/Addiction	Audio: PSA	Access Care	https://drive.google.com/open?id=0B7iltWnLO8ZYdkdGc0d1QkpteVU
Great Plains-Hep C	Patient	Print: Flyer	Testing	https://drive.google.com/open?id=0B7iltWnLO8ZYYTlhZ21kbUFQRUk

Monitoring Drug Interactions

Because new information on drug-drug interactions is updated frequently, we recommend the use of the following website to check for HCV drug interactions prior to start of HCV treatment:

http://www.hep-druginteractions.org/

NPAIHB
Indian Leadership for Indian Health

NW Tribal Epidemiology Center

Technical Assistance and Support

New treatment options for Hepatitis C, along with an aging baby boomer cohort, have prioritized the need to panel patients to assist in determining local care management options. As part of collaboration with the Indian Health Service, the Northwest Portland Area Indian Health Board is assisting with the paneling and preliminary staging of Hepatitis C patients for sites. With IHS ITAC and VPN access, we have been reviewing and staging Hepatitis C patients for I/T/U clinics.

What the process would look like:

1. We will remotely access iCare and build a panel of your patients diagnosed with Hepatitis C.
2. We will review all charts in iCare for the most important information to stage patients (Liver Labs, Genotype, VL) and input those numbers into an excel spreadsheet to stage the patients for fibrosis using the APRI and FIB4 calculators.
3. We will share those data back with you so that your clinic can review and determine the best way forward to treat those patients (either in-house or referral).
4. We are also happy to provide TA at this point to explore systematic treatment options that other IHS area clinics have used.

If you have any questions or concerns, or are interested in learning more, please contact Jessica Leston (jleston@npaihb.org) or David Stephens (dstephens@npaihb.org)

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