2013 Update: Chronic Hepatitis B and C

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Gilead Sciences

Updated Treatment Guidelines for Chronic Hepatitis B


2 Lok A, McMahon, B. Hepatology 2009; 50:1-36
3 Liaw YF, et al. Hepatol Inter 2012; 6:531-561

Gilead Sciences, Inc.
Medical Affairs
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Summary of Treatment Criteria for CHB

<table>
<thead>
<tr>
<th>Guideline</th>
<th>HBsAg+</th>
<th>HBsAg-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA IU/mL</td>
<td>ALT UL</td>
</tr>
<tr>
<td>EASL 2012</td>
<td>≥2,000</td>
<td>And/or &gt;ULN and (+) biopsy</td>
</tr>
<tr>
<td>AASLD 2009</td>
<td>≥20,000</td>
<td>≥2x ULN or (+) biopsy</td>
</tr>
<tr>
<td>APASL 2012</td>
<td>≥20,000</td>
<td>Varies</td>
</tr>
<tr>
<td>US Algorithm 2008</td>
<td>≥20,000</td>
<td>≥ULN or (+) biopsy</td>
</tr>
<tr>
<td>AATA 2011</td>
<td>≥2,000</td>
<td>&gt;ULN</td>
</tr>
</tbody>
</table>

* Liver biopsy Stages 1-3, Grade 1-3; and/or Risk Impact Score ≥3

2 Lok A, McMahon, B. Hepatology 2009; 50:1-36
3 Liaw YF, et al. Hepatol Inter 2012; 6:531-561
FDA Approved Therapies for CHB

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Date Approved for Hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleosides/Nucleotides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>VIREAD®</td>
<td>Gilead Sciences</td>
<td>2008</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>TYZEKA®</td>
<td>Idenix and Novartis</td>
<td>2006</td>
</tr>
<tr>
<td>Entecavir</td>
<td>BARAACLIDE®</td>
<td>Bristol-Myers Squibb</td>
<td>2005</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>HEPEREX®</td>
<td>Gilead Sciences</td>
<td>2002</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>EPIVR-HBV®</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
</tr>
</tbody>
</table>

Interferons

<table>
<thead>
<tr>
<th>Peginterferon alfa-2a</th>
<th>PEGASYN®</th>
<th>Roche Laboratories</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa-2b, recombinant</td>
<td>INTRON® A</td>
<td>Schering Corporation</td>
<td>1992</td>
</tr>
</tbody>
</table>

Summary of Preferred CHB Therapies

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>HBsAg or HBsAg+ Without Cirrhosis</th>
<th>Compensated Cirrhosis</th>
<th>Decompensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASL 2012</td>
<td>TDF, ETV, or Peg-IFN</td>
<td>TDF or ETV</td>
<td>TDF or ETV</td>
</tr>
<tr>
<td>AASLD 2009</td>
<td>TDF, ETV, or Peg-IFN</td>
<td>TDF or ETV</td>
<td>LAM (or LdT) + ADV, TDF, or ETV</td>
</tr>
<tr>
<td>APASL 2012</td>
<td>TDF, ETV, or IFN-based therapy</td>
<td>TDF or ETV</td>
<td>TDF or ETV</td>
</tr>
<tr>
<td>US Algorithm 2008</td>
<td>TDF, ETV, or Peg-IFN</td>
<td>Peg-IFN may be used in well-compensated cirrhosis</td>
<td>TDF+LAM or TDF+ETV</td>
</tr>
<tr>
<td>AATA 2011</td>
<td>TDF or ETV</td>
<td>TDF or ETV</td>
<td>TDF or ETV</td>
</tr>
</tbody>
</table>

2009 AASLD Practice Guidelines – an Update to those published in 2007

HBV Screening

- Expanded to include:
  - US born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (> 8%)
  - Patients needing immunosuppressive therapy

Disease Monitoring

- Suggested to lower the upper limits of normal range ALT to 19 IU/L for females and 30 IU/L for males

Therapeutics

- Recommended tenofovir disoproxil fumarate (TDF) as a first line therapy
- Do not recommend entecavir (ETV) in HBV/HIV co-infected patients. ETV is not optimal in patients with lamivudine (LAM) resistance

HBV Screening Recommendations

- Individuals born in high (HBsAg prevalence >8%) and intermediate (HBsAg 2%-7%) areas of HBsAg prevalence
- Person who have ever injected drugs

- Household and sexual contacts of HBsAg+ persons
- Men who have sex with men

- Persons with multiple sexual partners or history of sexually transmitted diseases
- Inmates of correctional facilities

- Individuals with chronically elevated ALT or AST
- Individuals infected with HCV or HIV

- Patients undergoing renal dialysis
- All pregnant women
### Diagnostic criteria

#### Chronic hepatitis B
- HBsAg+ for > 6 months
- Serum HBV DNA > 20,000 IU/ml, lower values 2,000-20,000 IU/ml are often seen in HBeAg- CHB
- Persistent or intermittent elevation in ALT/AST levels
- Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

#### Inactive HBsAg carrier state
- HBsAg + for > 6 months
- HBeAg , anti-HBe
- Serum HBV DNA < 2,000 IU/ml
- Persistently normal ALT/AST levels
- Liver biopsy confirms absence of significant hepatitis

#### Resolved hepatitis B
- Previous known history of acute or chronic hepatitis B or the presence of anti-HBc+ ± anti-HBs+
- HBsAg-negative
- Undetectable serum HBV DNA
- Normal ALT levels

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### Goal of CHB Therapy

**The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease.**

**The ultimate goal is to prevent cirrhosis, hepatic failure, and HCC.**

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### Initial Evaluation of Patients with Chronic Hepatitis B

- Perform history and physical examination
- Obtain family history of liver disease, HCC
- Laboratory tests to assess liver disease—complete blood counts with platelets, hepatic panel and prothrombin time
- Tests for HBV replication—HBeAg/anti-HBe, HBV DNA
- Tests to rule out viral coinfections—anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV in those at risk
- Tests to screen for HCC—AFP at baseline and, in high risk patients, ultrasound
- Consider liver biopsy to grade and stage liver disease - for patients who meet criteria for chronic hepatitis

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### HBeAg-Positive CHB Management

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>&gt;20,000 IU/ml ≤ 2xULN</td>
<td>Low efficacy with current treatment. Observe; consider treatment when ALT becomes elevated. Consider biopsy in persons &gt; 40 years, ALT persistently high normal 2x ULN, or with family history of HCC. Consider treatment if HBV DNA &gt; 20,000 IU/mL and biopsy shows moderate/severe inflammation or significant fibrosis.</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>&gt;20,000 IU/ml &gt; 2xULN</td>
<td>Observe for 3-6 months and treat if no spontaneous HBeAg loss. Consider liver biopsy prior to treatment if compensated. Immediate treatment if icteric or clinical decompensation. IFN/PegIFNα, LAM, ADV, ETV, TDF or LdT may be used as initial therapy.**</td>
<td></td>
</tr>
</tbody>
</table>

**End-point of treatment – Seroconversion from HBeAg to anti-HBe. Duration of therapy:**
- PegIFNα: 48 weeks
- LAM/ADV/ETV/LdT/TDF: minimum 1 year, continue for at least 6 months after HBeAg seroconversion
- IFN non-responders / contraindications to TDF/ETV

**LAM and LdT not preferred due to high rate of drug resistance. ADV not preferred due to weak antiviral activity and high risk of resistance after 1st year.**

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**ALT ULN: 30 U/L for males, 19 U/L for females**

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Lok A.S.F. and McMahon B.J. Hepatology 2009; vol. 50 (3): 1-36
HBeAg-Negative CHB Management

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>≥ 20,000 IU/ml</td>
<td>&gt; 2xULN</td>
<td>IFN-α/peg IFN-α, LAM, ADV, ETV, TDF or LdT may be used as initial therapy. **</td>
</tr>
<tr>
<td></td>
<td>≥ 2,000 IU/ml</td>
<td>1 to ≥ 2xULN</td>
<td>Consider liver biopsy and treat if liver biopsy shows moderate/severe necroinflammation or significant fibrosis.</td>
</tr>
<tr>
<td></td>
<td>≤ 2,000 IU/ml</td>
<td>≤ ULN</td>
<td>Observe, treat if HBV DNA or ALT becomes higher.</td>
</tr>
</tbody>
</table>

**LAM and LdT not preferred due to high rate of drug resistance. ADV not preferred due to weak antiviral activity and high risk of resistance after 1st year.

CHB Management of Cirrhotic Patients

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>e/+/e- detectable</td>
<td>Compensated: HBV DNA &gt; 2,000 IU/mL—Treat. LAM/ADV/ETV/LdT/TDF may be used as initial therapy. **</td>
<td></td>
</tr>
<tr>
<td>e/+/e- undetectable</td>
<td>Compensated: Observe. Decompensated: Refer for liver transplant.</td>
<td></td>
</tr>
</tbody>
</table>

**LAM and LdT not preferred due to high rate of drug resistance; ADV not preferred due to weak antiviral activity and high risk of resistance after 1st year.

Manifestations of Antiviral Resistance

HCC screening

HBV carriers at high risk for HCC should be screened with ultrasound examination every 6-12 months.

High risk populations include:
- Asian men over 40 years
- Asian women over 50 years of age
- Persons with cirrhosis
- Persons with a family history of HCC
- Africans over 20 years of age
- Any carrier over 40 years with persistent or intermittent ALT elevation and/or high HBV DNA level >2,000 IU/mL
Screening and Pre-emptive Therapy Before Immunosuppressive Therapy or Chemotherapy

HBsAg and anti-HBc testing should be performed in patients who are at high risk of HBV infection prior to initiation of chemotherapy or immunosuppressive therapy.

Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy.

 Patients with baseline HBV DNA<2,000 IU/mL level should continue treatment for 6 months after completion of chemotherapy or immunosuppressive therapy.

 Patients with high baseline HBV DNA (>2,000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients.

 Lamivudine or telbivudine can be used if the anticipated duration of treatment is short (<12 months) and baseline serum HBV DNA is not detectable.

 Tenofovir or entecavir is preferred if longer duration of treatment is anticipated.

 IFN-α should be avoided in view of the bone marrow suppressive effect.

Management of Chronic Hepatitis B in Asian Americans

Myron J Tong, Calvin Q Pan, Hie-Won Hann, Kris V Kowdley, Steven-Huy B Han, Albert D Min, Truong-Sinh Leduc

Natural History Study of CHB Patients in the US

- Patients with CHB were enrolled in a study from January 1989 to March 1998, N=369
- Baseline laboratory tests: HBeAg, albumin, ALT, platelets, HBV DNA
- HCC surveillance (AFP and abdominal ultrasound) every 6 months for a mean of 84 months

Percent of patients who developed serious liver-related complications but did not qualify for treatment according to:

- AASLD (2009): 1.5% (1/67)
- EASL (2009): 31% (21/67)
- APASL (2008): 40% (25/67)
- 21% (14/67)

Natural History Study of CHB Patients in the US: Patients Who Developed Serious Liver-Related Complications may Be Excluded from Treatment by Current Guidelines/Algorithms

Percent of patients who would not qualify for treatment with additional criteria:

- Albumin ≤3.5 g/dL or platelets ≤130,000 mm³
- BCP and precore mutant

Percent of patients who would not qualify for treatment with additional criteria:

- APASL (2008): 1.5% (1/67)
- AASLD (2009): 1.5% (1/67)
- US Treatment Algorithm (2006): 0%
- EASL (2009): 0%


### Step 2, Evaluate Patients Diagnosed with CHB: Recommendations from the Asian American Treatment Algorithm

**Order HBeAg, HBV DNA, and ALT tests for all patients with CHB**

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Tolerant</td>
<td>+</td>
<td>&gt;2000 IU/mL</td>
<td>≤ULN</td>
<td>Monitor</td>
</tr>
<tr>
<td>Chronic Hepatitis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+</td>
<td>&gt;2000 IU/mL</td>
<td>&gt;ULN</td>
<td>Treat with TDF or ETV</td>
</tr>
<tr>
<td>Chronic Hepatitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>&gt;2000 IU/mL</td>
<td>&gt;ULN</td>
<td>Treat with TDF or ETV</td>
</tr>
<tr>
<td>Chronic Hepatitis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td>≤2000 IU/mL</td>
<td>≤ULN</td>
<td>Assess gray zone considerations</td>
</tr>
<tr>
<td>Chronic Hepatitis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td>Detectable</td>
<td>NA</td>
<td>Treat with TDF or ETV</td>
</tr>
<tr>
<td>Cirrhosis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+/-</td>
<td>NA</td>
<td>NA</td>
<td>Assess gray zone considerations</td>
</tr>
<tr>
<td>Cirrhosis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+/-</td>
<td>Undetectable</td>
<td>NA</td>
<td>Monitor</td>
</tr>
<tr>
<td>Decompensated Cirrhosis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+/-</td>
<td>NA</td>
<td>NA</td>
<td>Treat with TDF or ETV</td>
</tr>
</tbody>
</table>

<sup>a</sup> Or liver biopsy stage 1-3 and/or grade 1-3; <sup>b</sup> ALT normal range is based on local laboratory reference range; <sup>c</sup> Patients with signs and symptoms suggestive of advanced liver disease or indicative of cirrhosis should be evaluated by a specialist. These patients frequently require ongoing evaluation and management of liver-related complications.


### Step 3, Evaluate Patients in Gray Zone: Recommendations from the Asian American Treatment Algorithm

**Conduct liver biopsy if possible. If not, calculate Risk Impact Score**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Impact Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥40</td>
<td>1</td>
</tr>
<tr>
<td>Male sex</td>
<td>1</td>
</tr>
<tr>
<td>ALT: male ≥30 U/L or female ≥19 U/L</td>
<td>1</td>
</tr>
<tr>
<td>BCP mutation</td>
<td>2</td>
</tr>
<tr>
<td>HCC in first-degree relative</td>
<td>3</td>
</tr>
<tr>
<td>Albumin ≤3.5 g/dL or Platelet ≤130,000 mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3</td>
</tr>
</tbody>
</table>

**Total Score**

- ≥3: Treat
- <3: Monitor

*This scoring system is based on expert opinion and warrants further clinical experience and validation.*

*When to Stop Treatment in Asian American Patients: Recommendations from the Asian American Treatment Algorithm*

- **HBeAg+**
  - Treat until seroconversion to anti-HBe
  - Continue with consolidation therapy for 1-2 years
  - After stopping therapy, monitor for relapse
  - Seroreversion to HBeAg positivity
  - Reappearance of HBV DNA
  - ALT elevation

- **HBeAg-**
  - Continue antiviral treatment for life
  - If HBeAg becomes negative, then treatment may be stopped
  - Monitor closely for relapse

- **Cirrhosis**
  - Continue antiviral treatment for life

**HCC Surveillance in Asian Americans with CHB: Recommendations from the Asian American Treatment Algorithm**

<table>
<thead>
<tr>
<th>Surveillance Tests</th>
<th>Surveillance Interval</th>
<th>Surveillance Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP, Abdominal ultrasound</td>
<td>Every 6 months</td>
<td>High-risk patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCC in blood relatives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low- to moderate-risk patients&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Inactive carriers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Immune-tolerant patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- HBsAg+ males &lt;40 years, females &lt;50 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Patients with HBsAg loss</td>
</tr>
</tbody>
</table>

<sup>a</sup> If clinically active chronic hepatitis, cirrhosis, or other risk factors for HCC are present in these patients.
Hepatitis C Virus
Disease State Update

Global Prevalence of Chronic HCV Infection

- About 2% of world population estimated to have chronic HCV
- Egypt, Pakistan, and China have high rates of chronic HCV infection due to lack of standard precautions
- In the U.S. 3.2 million people, with estimates as high as 7 million, have chronic HCV, and ~12,000 die each year

The US Prevalence of Hepatitis C Infection Is Likely Underestimated

- The CDC estimates US prevalence to be 2.7-3.9 million (1%-1.5%)\cite{1,2}
- Based on NHANES data, which excludes homeless and incarcerated populations\cite{3}
- HCV infection prevalence may be as high as ~7 million with inclusion of populations omitted or underrepresented by NHANES\cite{3}

\*Homeless, incarcerated, veterans, active military duty, healthcare workers, nursing home residents, and patients on chronic hemodialysis or with hemophilia who received transfusions before 1992.

\*Miller et al. estimate about 18 million overall prevalence; In another study, Guerra et al estimated ~ 12.1 million 15-59 year olds are infected.

Distribution of HCV Genotypes in the US

Genotype 1 accounts for 78%
Genotype 2 accounts for 13%
Genotype 3 accounts for 1%
Genotype 4 accounts for 6%

Active HCV Infection is Associated With Higher All-Cause Mortality

REVEAL study: a prospective community-based cohort study in Taiwan designed to study the natural history and long-term disease burden of chronic hepatitis C
Risk of all causes mortality, hepatic diseases and extrahepatic diseases, significantly higher in anti-HCV seropositives with detectable HCV RNA vs anti-HCV seropositives with undetectable HCV RNA (P<0.001)

Mortality From Viral Hepatitis in the US (1999-2007)

Analysis of US multiple-cause mortality data from the National Center for Health Statistics
- Death certificate data in all US states and District of Columbia
- Approximately 21.8 million decedents
- Change in age-adjusted mortality rates (per 100,000 person-years)
  - HCV: increased 0.18 (P=0.002)
  - HIV: decreased 0.21 (P<0.001)
  - HBV: decreased 0.02 (P=0.25)

To Achieve Similar Mortality Decreases in HCV as Seen With HIV Requires New Policy Initiatives to Detect and Link HCV Patients to Care and Treatment

Estimated Peak Incidence: 25-31 years ago

It has been estimated that the number of people who have been infected for > 20 years could quadruple between 1990 and 2015.
Projected Incidence of HCV-Related Liver Cancer and Death Also Expected to Peak in Coming Decades

DCC=decompensated cirrhosis; HCC=hepatocellular carcinoma


HCV Is Leading Cause of Liver Transplants in the US

1. Available at: www.ustransplant.org/annual_reports/current/chapter_iv_forprint.pdf

Between 1995 and 2010, 41% of the 126,862 new primary registrants for liver transplants carried a diagnosis of HCV infection.

HCV Transmission & Diagnosis

*Other possible routes:*
- Tattoo/body piercing or needle-stick injuries
- Hemodialysis
- Sexual contact
- Maternal-fetal transmission

No risk factor identified in 10% of HCV cases
40% of HCV-infected persons unaware of their risk


Prevalence of Hepatitis C Infection in Certain Higher-Risk US Populations

- HCV infection is also more prevalent in men, HIV-positive persons, and individuals of Hispanic or African American heritage.


*In patients who received clotting factor concentrates before 1987.

IDU = injection drug use.

1998 CDC Risk-Based HCV Screening Recommendations

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood organs before July 1992
- Have ever been on hemodialysis
- Have evidence of liver disease (elevated ALT)
- Were born to HCV infected mothers
- Have HIV infection
- Received a needle stick injury or mucosal exposure to HCV-positive blood (health care, emergency medical and public safety workers)


The US Prevalence of Hepatitis C Infection Is Highest in the 1945-1965 Birth Cohort

- Based on CDC estimates, 77% of individuals infected with HCV (~2.06 million) were born between 1945 and 1965.


2012 CDC Recommendations for Birth Cohort (1945–1965) Screening

- Recommendation 1
  - Adults born from 1945 to 1965 should receive one-time testing for HCV without prior ascertainment of HCV risk
  - Grade: strong recommendation
  - Evidence: moderate-quality

- Recommendation 2
  - 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 as indicated
  - Grade: strong recommendation
  - Evidence: moderate-quality

2013 Updated USPSTF HCV Screening Recommendations

- In June 2013, the USPSTF issued its final recommendations regarding HCV screening:
  - Those at high risk for HCV infection
  - Those born from 1945 to 1965 (one-time screening of “Baby Boomers”, regardless of risk)
- For this update, the USPSTF reviewed the indirect chain of evidence showing benefits of screening through
  - Improvements in SVR with current treatments
  - Reductions in all-cause and liver-related mortality, and HCC associated with SVR
- A Grade B recommendation by the USPSTF means:
  - There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial
- The Affordable Care Act:
  - Requires nongrandfathered private health plans to cover clinical preventive services given an A or B Grade by USPSTF without cost sharing
  - Provides incentives for Medicaid programs to cover these services

The USPSTF=United States Preventive Services Task Force.


2013 Updated USPSTF HCV Screening Recommendations

Risk Assessment:*

- Those at high risk:
  - Most important risk factor 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 (“Baby Boomers”)

*Grade B recommendation for persons at high risk for infection and adults born between 1945 and 1965.


HCV Diagnostic Algorithm Based on Serologic Testing

- If patient lacks pre-existing antibodies to HAV or HBV
- HAV=hepatitis A virus, HBV=hepatitis B virus
- *HCV RNA testing should be performed in Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection

<table>
<thead>
<tr>
<th>Anti-HCV Antibody</th>
<th>HCV RNA</th>
<th>HCV Genotype</th>
<th>Consider Liver Biopsy</th>
<th>Vaccinate for HAV / HBV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>Positive</td>
<td></td>
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<tr>
<td>Negative</td>
<td>Negative</td>
<td></td>
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</tr>
</tbody>
</table>

No Further Testing

No Active Disease

HCV Pathophysiology and Disease Progression

*If patient lacks pre-existing antibodies to HAV or HBV

+HCV=hepatitis C virus, HAV=hepatitis A virus, HBV=hepatitis B virus

*HCV RNA testing should be performed in Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection

Acute vs. Chronic HCV

- **Acute HCV**
  - Detectable HCV RNA < 6 months
  - 15%-25% clear without treatment
  - 75%-85% develop chronic HCV

- **Chronic HCV**
  - Detectable HCV RNA ≥ 6 months
  - 5%-20% develop cirrhosis

Survival Probability in HCV Patients With Cirrhosis

Survival Probability

Patients (%)

0 20 40 60 80 100

0 12 24 36 48 60 72 84 96 108 120

Months

Patients at Risk

384 376 342 288 236 165 126 79 52 39 25

Extrahepatic Manifestations of HCV

- Mixed cryoglobulinemia (≤50%)
- Sjögren (sicca) syndrome (10%)
- Lymphoproliferative disorders (≤6%)
- Porphyria cutanea tarda (<5%)
- Neuropathy
- Membranoproliferative glomerulonephritis (10%-20%)
- Cryoglobulinemic vasculitis (<10% of cryoglobulinemia cases)

HCV Treatment Goals

- Corneal ulcers (Mooren ulcers)
- Thyroid disease
- Lichen planus
- Pulmonary fibrosis
- Type 2 diabetes
- Systemic vasculitis
- Pulmonary hypertension
- Arthritis, myalgias, inflammatory polyarthritides
- Autoimmune thrombocytopenia

Unlike HIV and HBV, HCV Can Be Cured

Achieving of a sustained virologic response (SVR) following completion of treatment is indicative of a cure.

4. Varies in regimen and duration based on genotype and other virus/disease factors.

The Goal of HCV Treatment Is Sustained Virologic Response (SVR)

- Defined as undetectable HCV RNA by PCR assay at a specific time point after antiviral therapy completion. Traditionally 24 weeks although studies have shown assessment of serum HCV RNA 12 weeks after the end of treatment using a highly sensitive assay may be as relevant as after 24 weeks to predict SVR.
- Patients with cirrhosis who achieved an SVR should continue to be monitored at 6- or 12-month intervals for the development of HCC.

Current HCV treatment recommendations available from AASLD, NIH, EASL, and APASL.

Sustained Virologic Response Is Associated With a Reduction in All-Cause Mortality

An international, multicenter, long-term follow-up study from 5 tertiary care hospitals in Europe and Canada of 530 advanced fibrosis/cirrhotic HCV patients treated with IFN-based regimen between 1990-2003. Sustained Virologic Response Is Associated With a Reduction in Liver-Related Mortality and HCC

Liver-Related Mortality or Liver Transplantation

Proportion of patients who achieved SVR: 36% (n=192). Thirteen patients with SVR and 100 patients without SVR died, with a 10-year cumulative all-cause mortality rate of 8.9% (95% CI 3.2%–14.6%) with SVR and 28.0% (95% CI 22.1%–32.4%) without SVR.


Hepatocellular Carcinoma

Treatment-Related Barriers Exclude Most HCV Patients From a Treatment Option

<table>
<thead>
<tr>
<th>Psychiatric/Medical Ineligibility</th>
<th>Intolerant to Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major uncontrolled depressive illness¹</td>
<td>Treatment discontinuation rates due to side effects range from 14% to 21%² -⁴</td>
</tr>
<tr>
<td>Significant CV disease¹</td>
<td></td>
</tr>
<tr>
<td>Untreated thyroid disease¹</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disorder¹</td>
<td></td>
</tr>
</tbody>
</table>

CV = cardiovascular


A Small Proportion of HCV Patients Are Currently Being Treated

<table>
<thead>
<tr>
<th>Number of Patients (Millions)</th>
<th>Prevalence</th>
<th>Diagnosed</th>
<th>Treated in 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2 M</td>
<td>2.9 M</td>
<td>1.6 M</td>
<td>842 K</td>
</tr>
<tr>
<td>United States</td>
<td>EU Core 5</td>
<td></td>
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</tr>
</tbody>
</table>

Treated – Synovate chart audits 2011

Summary

- Approximately 3.2 million persons in the US have chronic HCV infection¹
  - If left untreated, HCV infection can lead to advanced liver disease
    - Patients often asymptomatic in early stages of HCV infection²
    - There is an increasing burden of liver disease in aging baby boomers due to manifestations of HCV infection acquired 20-30 years ago²
  - Screening is easy and reliable² -⁴
    - CDC and USPSTF recommend screening all baby boomers in addition to those with other specific risk factors
  - HCV infection is curable (SVR=virologic cure)⁵
    - SVR reduces the risk of mortality and of developing advanced liver disease⁶,⁷
    - Patients with cirrhosis who achieved an SVR should continue to be monitored at 6- or 12-month intervals for the development of HCC⁸

*Outcomes based on 2-drug therapy with PegIFN and RBV.


Questions?