Review of the WHO Guidelines for the Screening, Care and Treatment of Persons with HCV

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This program is supported by educational grants from: AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck
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Educational Objectives

• Review data on the global prevalence of HCV
• Describe the natural history of HCV
• Identify the detrimental effects of untreated, chronic HCV to emphasize the need for diagnosis and treatment
• Define “cure” in HCV and discuss treatment advances in this disease
• Examine the WHO Guidelines for the screening, care and treatment of persons with HCV
• Discuss the global implications of the WHO guidelines
Introduction

- Hepatitis C virus infection (HCV) globally affects more than 185 million persons, of whom:
  - One third are predicted to develop liver cirrhosis or hepatocellular carcinoma (HCC)
  - 350,000 die annually
- HCV is a unique viral infection because it can be cured by treatment
  - Cure rates are steadily improving to > 90% as newer medications become available
- Despite high prevalence and availability of effective treatments, many patients remain undiagnosed or do not have access to treatment
- The World Health Organization (WHO) produced their first guidelines dealing with HCV in April 2014, which consist of 9 key recommendations
  - Complement existing guidance on the prevention of transmission of blood borne viruses, including HCV

Chronic HCV is a Major Global Concern
HCV Prevalence Varies Substantially Around the World

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence (%)</th>
<th>Estimated number of people infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
<td>1.4</td>
<td>&gt;2.4 million</td>
</tr>
<tr>
<td>Central Asia</td>
<td>3.8</td>
<td>&gt;2.9 million</td>
</tr>
<tr>
<td>East Asia</td>
<td>3.7</td>
<td>&gt;50 million</td>
</tr>
<tr>
<td>South Asia</td>
<td>3.4</td>
<td>&gt;50 million</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>2.0</td>
<td>&gt;11 million</td>
</tr>
<tr>
<td>Australia</td>
<td>2.7</td>
<td>&gt;0.6 million</td>
</tr>
<tr>
<td>Caribbean</td>
<td>2.1</td>
<td>&gt;0.7 million</td>
</tr>
<tr>
<td>Central Europe</td>
<td>2.4</td>
<td>&gt;2.9 million</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>2.9</td>
<td>&gt;6.2 million</td>
</tr>
<tr>
<td>Western Europe</td>
<td>2.4</td>
<td>&gt;10 million</td>
</tr>
</tbody>
</table>

HCV Prevalence Varies Substantially Around the World (Cont’d)

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence (%)</th>
<th>Estimated number of people infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andean Latin America</td>
<td>2.0</td>
<td>&gt;1.0 million</td>
</tr>
<tr>
<td>Central Latin America</td>
<td>1.6</td>
<td>&gt;3.4 million</td>
</tr>
<tr>
<td>Southern Latin America</td>
<td>1.6</td>
<td>&gt;0.9 million</td>
</tr>
<tr>
<td>Tropical Latin America</td>
<td>1.2</td>
<td>&gt;2.3 million</td>
</tr>
<tr>
<td>North Africa/Middle East</td>
<td>3.6</td>
<td>&gt;15 million</td>
</tr>
<tr>
<td>North America</td>
<td>1.3</td>
<td>&gt;4.4 million</td>
</tr>
<tr>
<td>Oceania</td>
<td>2.6</td>
<td>&gt;0.2 million</td>
</tr>
<tr>
<td>Central sub-Saharan Africa</td>
<td>2.3</td>
<td>&gt;1.9 million</td>
</tr>
<tr>
<td>East sub-Saharan Africa</td>
<td>2.0</td>
<td>&gt;6.1 million</td>
</tr>
<tr>
<td>South sub-Saharan Africa</td>
<td>2.1</td>
<td>&gt;1.4 million</td>
</tr>
<tr>
<td>West sub-Saharan Africa</td>
<td>2.8</td>
<td>&gt;8.4 million</td>
</tr>
</tbody>
</table>

In the US Alone, HCV is Nearly 4 Times as Prevalent as HIV and HBV

Prevalence of Chronic Viral Infections

Upper lightly shaded = Undiagnosed
Lower solid = Diagnosed

2.7 to 3.9 Million
75% Unaware of Infection

1.1 Million
21% Unaware of Infection

~800,000 to 1.4 Million
65% Unaware of Infection

HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.
However, Most Patients in the US with Chronic HCV Are Unaware that They Are Infected

- ~3,300,000 individuals are infected
- Only 825,000 are aware of their infection
- 2,475,000 are unaware of their infection

Global Distribution and Prevalence of Global Distribution of HCV Genotypes

HCV causes both acute and chronic infections. Acute infection is usually clinically silent and spontaneously clears within 6 months of infection in 15-45% of untreated patients. The remaining 55-85% of patients are considered to have chronic HCV which, if left untreated, leads to grave consequences.

**Natural History of HCV**

- Acute HCV infection
- Chronic infection 55-85%
  - Mild fibrosis
  - Moderate to severe fibrosis
  - Cirrhosis 15-30%
- Decompensated Cirrhosis
  - Hepatocellular carcinoma (2-4% per year in cirrhosis)
- Extrahepatic disease

Complications Due to HCV-Related Cirrhosis Expected to Rise Over the Next 10 Years*

Projected Number of Cases of Decompensated Cirrhosis and Hepatocellular Carcinoma Due to HCV

*Based on US epidemiology data
By 2007, Deaths From HCV Surpassed Those From HIV*

Change in Mortality Rates From 1999 to 2007

*Based on US mortality data
HCV is a *Curable* Disease
HCV Can Now Be *Cured* in Most Patients

- Unlike HIV and HBV infection, HCV infection is a *curable* disease
- What does *cure* mean?
  - Sustained virological response (SVR) is defined as undetectable HCV RNA 3 or 6 months after the end of treatment
  - SVR12 is almost invariably durable
- Over the past two decades, the success of treatment for HCV infection as measured by SVR has steadily increased
- Newer agents are demonstrating SVR rates > 90%

Highly Efficacious Treatments Are Not Enough!  
Higher Rates of Screening, Diagnosis and Treatment Are Necessary

<table>
<thead>
<tr>
<th>All HCV patients</th>
<th>PEG-IFN/RBV</th>
<th>95% SVR</th>
<th>95% SVR and higher rates of diagnosis/treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis and treatment</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Cure</td>
<td>20%</td>
<td>20%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>19%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Slide courtesy of Prof. Michael Manns
WHO Guidelines for Screening, Care and Treatment of Patients with HCV
The WHO Guidelines

• Intended for those working in low- and middle-income countries to:
  – Aid in the development of programs for the screening, care and treatment of persons with HCV infection
  – Guide in the management of patients infected with HCV

• Recommendations are divided into 3 categories:
  – Screening
  – Care
  – Treatment

WHO Guidelines: Recommendations on Screening for HCV Infection
Screening to Identify Persons with HCV Infection

- Many patients across the globe have limited access to HCV testing
- Often, a diagnosis of HCV is made with “symptomatic testing”, or testing once symptoms of cirrhosis or hepatocellular carcinoma are present
- HCV-induced liver damage is often advanced at this stage and therapy may be contraindicated; infection needs to be identified earlier
- **Recommendation:** Offer HCV serology testing to individuals with high HCV seroprevalence or with a history of HCV risk exposure/behavior

Populations with High HCV Prevalence or History of HCV Risk Exposure/Behavior

- Persons who have received medical or dental interventions in health-care settings where infection control practices are substandard
- Persons who have received blood transfusions prior to the time when serological testing of blood donors for HCV was initiated or in countries where serological testing of blood donations for HCV is not routinely performed
- Persons who inject drugs (PWID)
- Persons who have had tattoos, body piercing or scarification procedures done where infection control practices are substandard
- Children born to mothers infected with HCV
- Persons with HIV infection
- Persons who have used intranasal drugs
- Prisoners and previously incarcerated persons

When to Confirm a Diagnosis of Chronic HCV Infection

• ~15–45% of HCV infected persons spontaneously clear the infection\(^1,2\) and are anti-HCV positive but no longer infected with HCV\(^3\)
• Measurement of HCV RNA determines is virus is present
• HCV RNA results are:\(^3-6\)
  • Needed to distinguish persons with chronic HCV infection from those who have cleared the infection
  • Important prior to commencing and during treatment to assess treatment response

When to Confirm a Diagnosis of Chronic HCV Infection (Cont’ d)

• *Suggestion: Measure HCV RNA following a positive HCV serological test*
  – This is a conditional recommendation based on very low quality of evidence
  – Persons coinfected with both HIV and HCV may have false-negative HCV serological test results

WHO Guidelines: Recommendations on Care of People Infected with HCV
Screening for Alcohol Use and Counselling to Reduce Alcohol Intake

- A considerable amount of time can progress from HCV diagnosis to development of fibrosis and cirrhosis\(^1\)
  - Alcohol consumption can accelerate this progression\(^2\)
- “Heavy” intake of alcohol (between 210 and 560 g/week) doubles the risk of cirrhosis; even moderate alcohol consumption can be detrimental\(^3\)
- Globally, alcohol use in HCV patients varies; even in countries where alcohol intake is low alcohol reduction advice may have an impact\(^2\)

**Recommendation:**
- Perform an alcohol intake assessment in all HCV patients (WHO ASSIST)
- Offer behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake\(^2\)

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The elements of the WHO ASSIST package, designed for use in primary care settings, are described in 3 manuals:

1. A screening manual that contains a questionnaire; results determine the “risk score” for patient categorization:
   - Lower risk: no treatment needed
   - Moderate risk: brief intervention
   - High risk: referral to a specialist for assessment and treatment

2. An intervention manual that assists health-care workers in conducting a simple, brief intervention for patients at risk

3. The self-help guide for the patient to use to help change substance-use behavior.
Assessing the Degree of Liver Fibrosis and Cirrhosis

• Assessing the degree of fibrosis provides insight into likelihood of cure vs. serious treatment side effects\(^1\)
• Liver biopsy, followed by use of the METAVIR scoring system, are the gold standard to assess the degree of fibrosis\(^1\)

<table>
<thead>
<tr>
<th>METAVIR stage</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>No Fibrosis</td>
<td>Portal fibrosis without septa</td>
<td>Portal fibrosis with septa</td>
<td>Numerous septa without cirrhosis</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

• Liver biopsies in low income countries are infrequent due to high cost, invasiveness, the need for expert interpretation, etc.\(^1\)

• Newer techniques are available and based on ultrasound technology; transient elastography (performed with Fibroscan) is the most widely evaluated

Assessing the Degree of Liver Fibrosis and Cirrhosis (Cont'd)

• Blood tests are noninvasive and should be available in all clinics treating HCV patients to provide levels of ALT and AST and platelet counts

• These levels can be used to calculate APRI (diagnoses significant fibrosis and cirrhosis) and FIB4 scores (diagnoses significant fibrosis (> F2))

\[
\text{APRI} = \frac{\text{AST (IU/L)} / \text{AST_ULN (IU/L)} \times 100}{\text{platelet count (10}^9/\text{L})}
\]

\[
\text{FIB4} = \text{age (yr)} \times \text{AST(IU/L)} / \text{platelet count (10}^9/\text{L}) \times \left[\text{ALT(IU/L)}^{1/2}\right]
\]

• **Suggestion:** In resource-limited settings, APRI or FIB4 should be used for the assessment of hepatic fibrosis
  – Assumes liver biopsy is not an option
  – Fibroscan, which is more accurate than APRI and FIB4, may be preferable in settings with access to equipment and where cost is not a barrier

ALT = alanine aminotransferase, AST = aspartate aminotransferase, APRI = aminotransferase/platelet ratio index

WHO Guidelines:
Recommendations on Treatment
Achieving SVR Reduced the Risk of All-Cause Mortality in a Retrospective VA Study

- **Genotype 1** (n=12,166)
  - SVR rate: 35%
  - Cumulative Mortality (%)

- **Genotype 2** (n=2904)
  - SVR rate: 72%
  - Cumulative Mortality (%)

- **Genotype 3** (n=1794)
  - SVR rate: 62%
  - Cumulative Mortality (%)

Cumulative Mortality (%)

- **Non-SVR**
  - P<.0001

- **SVR**

More Second Generation DAAs Available: Less Need for PEG + RBV and Cure Rates Approach 100%

**Average SVR Rates from Clinical Trials**

- **Standard Interferon**
  - 1991: 6%
  - 1998: 16%
- **Ribavirin**
  - 1998: 34%
- **Peginterferon**
  - 2001: 42%
  - 2011: 55%
  - Peg-IFN/RBV 12m: 70%
  - Peg-IFN/RBV/2nd Generation DAA: 90%
  - Peg-IFN/RBV/3rd Generation DAA: 99%

Adapted from US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.
Principles of All Oral Regimens for HCV

• Combine drugs from different classes
  – Target multiple targets to increase efficacy
  – Decrease risk of viral resistance

• If done properly
  – Near universal efficacy
  – Shortened duration of therapy
  – Adverse events have minimal impact on patient’s quality of life
Assessing for HCV Treatment

• Substantial morbidity and mortality occurs with untreated HCV infection
• In addition, over the last two decades the success of treatment, as measured by SVR, has steadily increased
• The benefits outweigh the harms, especially with the new DAAs, with shorter durations of therapy and better safety profiles
• **Recommendation:** All adults and children with chronic HCV infection, including people who inject drugs (PWID), should be assessed for antiviral treatment

Assessing for HCV Treatment with PegIFN and RBV

• All genotypes of HCV respond to RBV and either standard IFN or PegIFN
• PegIFN is the accepted standard of care in high-income countries due to convenience and higher SVR rates
• However, IFN continues to be used in some low- and middle-income countries because it is much less expensive
• There is high-quality evidence that PegIFN and RBV are more effective than IFN and RBV.

• Recommendation: PegIFN/RBV combination is recommended for the treatment of chronic HCV infection rather than standard IFN/RBV

Assessing for HCV Treatment with Telaprevir or Boceprevir (1st Generation DAAs)

- The protease inhibitors boceprevir and telaprevir, used in combination with PegIFN and RBV, substantially increased SVR rates in persons with genotype 1 HCV infection.
- Use of these agents is costly, limited to genotype 1 patients and increases the likelihood of adverse events.
- However, data suggests that the benefit of increased SVR outweighed the increased risk of side effects.
- **Suggestion:** Triple therapy (treatment with telaprevir or boceprevir, given in combination with PegIFN and RBV) is suggested for genotype 1 HCV rather than dual therapy (PegIFN and RBV alone).

Treatment with Simeprevir (2nd Generation DAA)

• Simeprevir is a second generation protease inhibitor
• The benefits of simeprevir were considerable in view of the shorter duration of therapy, the much higher SVR, and the low rate of side-effects
• The Q80K mutation reduces the efficacy of simeprevir so patients must be tested for the presence of this mutation prior to treatment
• **Recommendation**: Simeprevir, given in combination with PegIFN and RBV, is recommended for persons with HCV genotype 1b infection and for persons with HCV genotype 1a infection without the Q80K polymorphism rather than PegIFN and RBV alone

Treatment with Sofosbuvir (2nd Generation DAA)

- Sofosbuvir is an HCV viral polymerase nucleotide inhibitor
- The efficacy of sofosbuvir either with RBV alone or RBV and PegIFN in genotypes 1, 2, 3 and 4 resulted in much higher SVR rates and a low rate of sofosbuvir-associated adverse events
- **Recommendation**: Sofosbuvir, given in combination with RBV with or without PegIFN (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than PegIFN and RBV alone (or no treatment for persons who cannot tolerate interferon).

Considering the Therapeutic Landscape Across the Globe

• The availability of IFN-free regimens has resulted in
  – Substantially improved efficacy and safety
  – Shorter duration of therapy

• Across the globe, however, resources are limited:
  – In lower-income countries, treatments access can be limited; implementation may be prioritized based on the highest risk of morbidity and mortality
  – In some low- and middle-income countries, standard IFN continues to be used because it is much less expensive

• The WHO guidelines take into account these inconsistencies across the globe

Clinical Considerations for the Specialist

• Genotype
• Genetic testing to detect polymorphisms that affect response to treatment
• Contraindications to treatment
• Monitoring for adverse events, treatment response and toxicity
• Special populations (e.g. patients who inject drugs, coinfection)

A Typical Patient Treatment Pathway

HCV antibody screening
Screen for other blood borne viruses

RNA test positive
Harm reduction
Address alcohol use
Consider OST
Vaccinate for HBV
Provide sterile injecting equipment
Peer intervention

Stage disease
Clinical examination exclude decompensation for IFN-containing regimens
APRI, FIB4 or TE

RNA test negative
Harm reduction
Address alcohol use
Consider OST
Vaccinate for HBV
Provide sterile injecting equipment
Peer intervention
Consider retesting (RNA)

If cirrhotic
Screen for varices
Screen for HCC
Consider transplantation

Assess for treatment
Consider co-morbidities, depression, pregnancy and potential drug-drug interactions
Genotype virus

Select regimens

Monitor for efficacy and toxicity

The growing prevalence of HCV is a global concern. If left undetected and untreated, HCV can progress to irreversible clinical consequences. Fortunately, with proper detection and treatment with newer agents more than 90% of patients can be cured. Implementation of the new WHO guidelines for HCV can assist in the:

- Screening: identifying patients with HCV and confirming the diagnosis
- Care: Assessing the degree of liver damage and reducing progression
- Treatment: Choosing the best treatment based on what drugs are regionally available

Global availability of options for screening, care and treatment vary; the guidelines have carefully taken this into account.

Additional Guidelines Are Available

• [www.hcvguidelines.org](http://www.hcvguidelines.org) (AASLD/IDSA guidance document) (most up to date)
• EASL guidelines (*Journal of Hepatology* 2015 vol. 63, 199-236)