HIV in the United States: 2015 Update

HIV Testing and Treatment

HCV Testing and New Treatments

Latent Tuberculosis

Questions
HIV Update
• Which one of the following is the new CDC recommended screening test for diagnosing HIV infection?

A. HIV Western blot
B. HIV RNA
C. 4th generation HIV antigen-antibody test
D. Modified HIV Western blot
HIV Testing: The Next Generation
<table>
<thead>
<tr>
<th>Generations of HIV EIA Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First</strong></td>
</tr>
<tr>
<td>Uses crude viral lysate</td>
</tr>
<tr>
<td><strong>Second</strong></td>
</tr>
<tr>
<td>Uses recombinant HIV antigens or peptides</td>
</tr>
<tr>
<td><strong>Third</strong></td>
</tr>
<tr>
<td>Detects IgM and IgG in “Sandwich” EIA</td>
</tr>
<tr>
<td><strong>Fourth</strong></td>
</tr>
<tr>
<td>Detects HIV antibodies and p24 antigen</td>
</tr>
</tbody>
</table>
Fourth Generation HIV Antigen-Antibody Assays

HIV p24 Antigen

HIV Antibodies
HIV and P24 Antigen

Capsid (p24 antigen)
Fourth-Generation HIV Antigen-Antibody Immunoassay

HIV p24 Capture Antibody

HIV-1 & HIV-2 Recombinant Proteins
Fourth-Generation HIV Antigen-Antibody Immunoassay

- p24 antigen
- anti-HIV IgG & IgM
- HIV p24 Capture Antibody
- HIV-1 & HIV-2 Recombinant Proteins
Fourth-Generation HIV Antigen-Antibody Immunoassay

HIV p24 Capture Antibody

HIV-1 & HIV-2 Recombinant Proteins

p24 antigen

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Fourth-Generation HIV Antigen-Antibody Immunoassay

- **p24 antigen**
- **anti-HIV IgG & IgM**
- **HIV-1 & HIV-2 Recombinant Proteins**
- **HIV p24 Capture Antibody**
### 4th Generation HIV Ag/Ab Combination Assays

<table>
<thead>
<tr>
<th>4th Generation FDA-Approved Tests</th>
<th>FDA Approval</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architect HIV Ag/Ab Combo</td>
<td>2010</td>
<td>Abbott Laboratories</td>
</tr>
<tr>
<td>GS HIV Combo Ag/Ab</td>
<td>2011</td>
<td>BioRad Laboratories</td>
</tr>
<tr>
<td>Alere Determine HIV 1/2 Ag/Ab Combo (Point of Care Test)</td>
<td>2013</td>
<td>Alere</td>
</tr>
</tbody>
</table>

- Combo assays detect HIV-1 p24 antigen and antibodies to HIV-1 and HIV-2
- Assays do not distinguish between HIV-1 antibody or HIV-2 antibody
- Only the Determine HIV 1/2 Ag/Ab Combo distinguishes p24 from HIV antibody
- Reduces “window” by about 10-15 days
- Detects approximately 60-80% of persons with acute HIV
Rapid Point-of-Care HIV Test
Alere Determine Rapid 4th-Generation HIV Ag/Ab Combo

- Detects HIV-1 and HIV-2 antibodies, and HIV-1 p24 Antigen
- Differentiates +Ag and/or +Ab
- Point of Care Test
- Results in 20 minutes
- Testing with
  - Fingerstick whole blood
  - Venous whole blood
  - Serum and plasma

Source: AlereHIV.com
Laboratory Diagnosis of Early HIV Infection

Timing of HIV RNA, HIV p24 antigen, and HIV Antibody
Early HIV Infection and Test Reactivity

Positive Test Days following HIV Acquisition

- HIV RNA
- 4th Gen
- EIA (3rd Gen)
- EIA (Rapid)
- WB
Antiretroviral Therapy
Strongly Recommend (AI)
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

ABSTRACT

BACKGROUND
Data from randomized trials are lacking on the benefits and risks of initiating antiretroviral therapy in patients with asymptomatic human immunodeficiency virus (HIV) infection who have a CD4+ count of more than 350 cells per cubic millimeter.

Conclusion: “The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells per cubic millimeter provided net benefits over starting such therapy in patients after the CD4+ count had declined to 350 cells per cubic millimeter.”
### Preferred Regimens for ARV-Naïve Patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI-Based</td>
<td>Darunavir + Ritonavir + Tenofovir-Emtricitabine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raltegravir + Tenofovir-Emtricitabine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elvitegravir-Cobicistat-Tenofovir-Emtricitabine</td>
<td></td>
</tr>
<tr>
<td>INSTI-Based</td>
<td>Dolutegravir-Abacavir-Lamivudine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dolutegravir + Tenofovir-Emtricitabine</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** 2015 HHS Antiretroviral Therapy Guidelines. AIDS Info (www.aidsinfo.nih.gov)
Initial Antiretroviral Therapy

1996

Breakfast

Lunch

Dinner

2015
## Antiretroviral Therapy: Single Tablet Regimens (STR)

<table>
<thead>
<tr>
<th>Combination</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir-Emtricitabine-Efavirenz</td>
<td>Atripla</td>
</tr>
<tr>
<td>Tenofovir-Emtricitabine-Rilpivirine</td>
<td>Complera</td>
</tr>
<tr>
<td>Tenofovir-Emtricitabine-Elvitegravir-Cobicistat</td>
<td>Stribild</td>
</tr>
<tr>
<td>Abacavir-Lamivudine-Dolutegravir</td>
<td>Triumeq</td>
</tr>
</tbody>
</table>

Photographs: Andrew Karpenko and Northwest AIDS Education and Training Center.
Hepatitis C Update
Recommended Risk-Based Routine HCV Testing

- **Based on Risk Behaviors:**
  - Injection-drug use (current or past)
  - Intranasal illicit drug use
- **Based on Risk Exposures:**
  - Long-term hemodialysis (ever)
  - Getting tattoo in unregulated setting
  - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood
  - Children born to HCV-infected women
  - Prior receipt of transfusions or organ transplants
  - Person ever incarcerated
- **Based on Risk Behaviors:**
  - HIV infection
  - Unexplained chronic liver disease and chronic hepatitis, including increased ALT
  - Solid organ donors (deceased and living)

Source: (1) CDC and Prevention; (2) AASLD/IDSA Hepatitis C Guidance.
Hepatitis C Testing Methods

- **Screening: Hepatitis C Antibody Testing**
  - Highly sensitive and specific
  - Reactive test indicates current or resolved infection

- **Supplemental: Nucleic Acid Testing**
  - Quantitative and qualitative HCV RNA tests used
  - Positive test indicates active infection
Recommended Testing Sequence for Identifying Current HCV Infection

1. **HCV Antibody**
   - **Nonreactive**
     - **No HCV antibody detected**
     - STOP*
   - **Reactive**
     - **HCV RNA**
       - **Not Detected**
         - **No current HCV infection**
         - Additional testing as appropriate*
       - **Detected**
         - **Current HCV infection**
         - Link to care

Hepatitis C: Progression of Disease

- Normal Liver
- Chronic Hepatitis
- Cirrhosis
- 20-25 years
- 25-30 years
- HCC
- ESLD
- Death

HCV Infection

Time
• In 2015, what is the realistic expectation for achieving SVR (cure) for hepatitis C with state-of-the-art treatment?

A. 60%
B. 75%
C. 85%
D. 95%
Hepatitis C Proteins

<table>
<thead>
<tr>
<th>Structural Proteins</th>
<th>Nonstructural (NS) Proteins</th>
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<tbody>
<tr>
<td>C</td>
<td>NS2</td>
</tr>
<tr>
<td>E1</td>
<td>NS3</td>
</tr>
<tr>
<td>E2</td>
<td>NS4A</td>
</tr>
<tr>
<td>p7</td>
<td>NS4B</td>
</tr>
<tr>
<td></td>
<td>NS5A</td>
</tr>
<tr>
<td></td>
<td>NS5B</td>
</tr>
</tbody>
</table>

- Cysteine Protease
- Serine Protease
- RNA Helicase
- Serine Protease Cofactors
- Membranous Web Induction
- RNA binding and assembly recognition complex
- RNA-Dependent RNA Polymerase

Vioparin
Categories of Direct Acting Antiviral Agents

Hepatitis C Direct Acting Antiviral Agent (DAA) Categories

- **NS3/4A Protease Inhibitor**
  - NS3: Serine Protease
  - NS4A: Serine Protease Cofactors

- **NS5A Inhibitor**
  - NS5A: RNA binding and assembly recognition complex

- **NS5B Polymerase Inhibitor**
  - NS5B: RNA-Dependent RNA Polymerase
New HCV Direct Acting Agents (DAAs)

**Protease Inhibitors**
- Simeprevir
- Paritaprevir/RTV

**NS5A Inhibitors**
- Daclatasvir
- Ledipasvir
- Ombitasvir

**NS5B Inhibitors**
- Sofosbuvir
- Dasabuvir

**Polymerase Inhibitors**
- Ombitasvir
<table>
<thead>
<tr>
<th>Direct-Acting Antiviral Agents (DAAs)</th>
<th>Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>Daklinza</td>
</tr>
<tr>
<td>Ledipasvir-Sofosbuvir</td>
<td>Harvoni</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir</td>
<td>Technivie</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir</td>
<td>Viekira Pak</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Olysio</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Solvaldi</td>
</tr>
</tbody>
</table>

*Source for Images: Hepatitis C Online*
## Hepatitis C
### Costs of New DAA Medications: 12 Week Course

<table>
<thead>
<tr>
<th>Drug (Generic Name)</th>
<th>Trade Name</th>
<th>Cost for 12 Weeks</th>
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</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>Daklinza</td>
<td>$63,000</td>
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<tr>
<td>Ledipasvir-Sofosbuvir</td>
<td>Harvoni</td>
<td>$94,500</td>
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<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir</td>
<td>Technivie</td>
<td>$76,650</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir</td>
<td>Viekira Pak</td>
<td>$83,300</td>
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<tr>
<td>Simeprevir</td>
<td>Olysio</td>
<td>$66,400</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi</td>
<td>$84,000</td>
</tr>
</tbody>
</table>
Comparative Treatment Goals with Antiviral Therapy

HIV
(latent reservoir)

- Proviral DNA
- Host DNA
- Host Cell

Lifelong suppression of viral replication

HCV
(no latent reservoir)

- HCV RNA
- Host DNA
- Host Cell

Definitive Viral Clearance

Sustained Virologic Response (SVR12) = Undetectable HCV RNA 12 Weeks Post Treatment
Background of the Hepatitis C Guidance

New direct-acting oral agents capable of curing hepatitis C virus (HCV) infection have been approved for use in the United States. The initial direct-acting agents were approved in 2011, and many more oral drugs are expected to be approved in the next few years. As new information is presented at scientific conferences and published in peer-reviewed journals, health care practitioners have expressed a need for a credible source of unbiased guidance on how best to treat their patients with HCV infection. To provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.

New sections will be added, and the recommendations will be updated on a regular basis as new information becomes available. An ongoing summary of “recent changes” will also be available for readers who want to be directed to updates and changes.
Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1 ION-1 Study: Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT-1 Naive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 214</td>
<td>LDV-SOF</td>
<td></td>
<td>SVR12</td>
<td></td>
</tr>
<tr>
<td>n = 217</td>
<td>LDV-SOF + RBV</td>
<td></td>
<td>SVR12</td>
<td></td>
</tr>
<tr>
<td>GT-1 Naive</td>
<td></td>
<td></td>
<td></td>
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<td>n = 217</td>
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<td>n = 217</td>
<td>LDV-SOF + RBV</td>
<td></td>
<td>SVR12</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Dosing**
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Abbreviations**: LDV = ledipasvir; SOF = sofosbuvir; RBV = ribavirin

Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
ION-1 Study: Results

ION-1: SVR 12 by Treatment Duration and Regimen

Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-Naïve HCV GT 1
ION-1 Study: Results

ION-1: SVR12 by Treatment Regimen and Liver Disease

Note: subgroup results do not include patients who withdrew consent or were lost to follow-up

Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + Ribavirin GT 1 and Compensated Cirrhosis: TURQUOISE-II Study

TURQUOISE II: SVR12

HCV Treatment: Key Concepts

- Very high SVR rates with new therapies
- Excellent SVR rates regardless of cirrhosis, race
- Excellent SVR rates in treatment experienced
- Genotype 3 is most difficult to treat
- All oral therapies becoming standard of care
- Cost of new therapies is huge barrier
University of Washington: Hepatitis C Online

Slide Lectures
State-of-the-Art
Expert Faculty
Mini-Lectures

About Hepatitis C Online
Hepatitis C Online is a free educational website from the University of Washington. The site is a comprehensive resource that addresses the diagnosis, monitoring, and management of hepatitis C virus infection.

What's New
The AASLD and the IDSA, in collaboration with the IAS-USA, have developed new recommendations for HCV management.

Take the Free Online Course
Browse or create an account and track your progress as you work through the course. After registering, you can obtain free CME or CNE credit.

Contributors
Site Overview

AASLD/IDSA/IAS-USA HCV Guidance

Funded by a grant from the Centers for Disease Control and Prevention
University of Washington
UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
IAS-USA

Hepatitis C Online: www.hepatitisc.uw.edu
Latent Tuberculosis
Tuberculin Skin Testing

Inject 0.1 ml of 5 tuberculin units of liquid tuberculin between the layers of the skin (intradermally), on the forearm.

Measure induration, not erythema.

Source: CDC and Prevention.
Tuberculin Skin Testing

- Widely used and inexpensive
- Poor specificity in persons who received BCG
- Poor sensitivity in immunocompromised patients
- Cross-reactivity with non-tuberculous mycobacteria
- Major drawback of requiring return visit at 48-72 hours

Interferon Gamma Release Assays (IGRAs)

- Two widely used tests:
  - QuantiFERON-TB Gold in Tube Assay
  - TSPOT.TB assay

- Measures in vitro responses of T-cells to *M. tuberculosis* antigens

- Higher specificity for *M. tuberculosis* than TST

- Test not impacted by prior BCG

- Problems with false-positives

- More costly than TST

### Groups with High Priority for Treatment of Latent Tuberculosis

**Positive IGRA or TST ≥ 5 mm**
- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on CXR consistent with old TB
- Organ transplant recipients
- Persons who are immunosuppressed for other reasons

**Positive IGRA or TST ≥ 10 mm**
- Recent immigrants (< 5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology lab personnel
- Children under 4 years of age, or children and adolescents exposed to adults in high-risk categories

*Persons with no known risk factors for TB may be considered for treatment of LTBI if they have either a positive IGRA result or if their reaction to the TST is 15 mm or larger.

+ Taking the equivalent of >15 mg/day of prednisone for ≥ 1 month, taking TNF-α antagonists

\(^{*}\)Correctional facilities, nursing homes, homeless shelters, hospitals, and other HC facilities
# First-Line Options for Treatment of Latent Tuberculosis*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>300 mg PO daily &lt;br&gt;or &lt;br&gt;900 mg PO twice weekly (DOT)</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td><strong>Once weekly DOT Dosing</strong>&lt;br&gt;&lt;br&gt;<strong>Isoniazid</strong>: 15 mg/kg round up to the nearest 50 or 100 mg; 900 mg maximum&lt;br&gt;&lt;br&gt;<strong>Rifapentine</strong>:&lt;br&gt;10.0–14.0 kg 300 mg&lt;br&gt;14.1–25.0 kg 450 mg&lt;br&gt;25.1–32.0 kg 600 mg&lt;br&gt;32.1–49.9 kg 750 mg&lt;br&gt;≥50.0 kg 900 mg maximum</td>
</tr>
</tbody>
</table>

Isoniazid available as 100 mg and 300 mg tablet; Rifapentine available as 150 mg tablets
Rifampin for isoniazid-intolerant or resistant

*Source: Centers for Disease Control and Prevention*
Treatment of Latent Tuberculosis
3 Months of INH + Rifapentine versus 9 Months of INH

Questions