HEPATITIS C UPDATE

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Philadelphia FIGHT Community Health Centers
Outline

- Overview and Epidemiology of HCV
- Management of HCV exposure
- Acute HCV Management
- Chronic HCV Management
- Challenges with HCV access to care
Natural History of HCV Infection

- Acute HCV
  - 75-85% chance of chronic HCV
  - 15-25% chance of spontaneous resolution

- Chronic HCV
  - Hepatic Inflammation
  - Hepatic Fibrosis
    - 20% in 20 yrs
  - Cirrhosis
    - 2 - 4% per yr
    - 2 - 5% per yr
      - Hepatocellular Carcinoma
      - Hepatic Decompensation

Alcohol, HIV, and hepatitis B may accelerate fibrosis.

www.CDC.gov

Extrahepatic manifestations associated with HCV

**Hematologic**
- Mixed cryoglobulinemia
- Aplastic anemia
- Thrombocytopenia
- Non Hodgkin’s b-cell lymphoma

**Dermatologic**
- Porphyria cutanea tarda
- Lichen planus
- Cutaneous necrotizing vasculitis

**Renal**
- Glomerulonephritis
- Nephrotic syndrome

**Neuropsychiatric**
- Depression

**Ocular**
- Corneal Ulcer
- Uveitis

**Vascular**
- Necrotizing Vasculitis
- Polyarteritis Nodosa

**Neuromuscular**
- Weakness/ myalgia
- Peripheral neuropathy
- Arthritis/Arthralgias

**Autoimmune Phenomena**
- CREST syndrome
Sources of Infection for Persons with Newly Diagnosed HCV

- IDU 60%
- Transfusion prior to 1992 10%
- Sexual 15%
- Unknown 10%
- Other 5%

CDC, National Hepatitis C prevention strategy 2001.
Seroprevalence of HCV: 170M to 200M worldwide

Epidemiology of HCV in the US

- Most common blood-borne infection in the US
  - 3.2 million to 5.2 million persons chronically infected
  - Birth cohort 1945-1965: 3.27% antibody positive
    - Non-Hispanic blacks: 6.31%
    - Non-Hispanic whites: 2.92%
    - Mexican American/other: 2.78%
- 50% to 75% of individuals chronically infected with HCV are unaware of their infection

References:
Chak E. *Liver Internat.* 2011, 2:1090-1101
Smith BD. AASLD poster #394, 2011
Armstrong GL. *Annals of Int Med*, 2006 144; 705-714
Treatment cascade for people with chronic HCV infection

- Chronic HCV-Infected*: 100%
- Diagnosed and Aware†: 50%
- Access to Outpatient Care‡: 43%
- HCV RNA Confirmed§: 27%
- Underwent Liver Biopsy‖: 17%
- Prescribed HCV Treatment‖: 16%
- Achieved SVR**: 9%

Sexual Transmission of HCV

- HCV RNA in semen / vaginal secretions
- Risk of HCV transmission by sexual contact in monoinfected:
  - Long-term monogamous partnerships: 0.6%/year
  - Multiple partners / at-risk for STIs: 1.8%/year
- HIV coinfection ↑ rate of sexual transmission
  - Increase in the incidence of HCV reported in HIV-positive MSM
    - Swiss cohort: 18-fold increase in incidence rates from 1998 to 2011
  - Behavioral factors and viral factors

Terrault N. Hepatology 2002;36:S99-105
Bradshaw D. Curr Opin Inf Dis 2013; 26(1):66-72
Biobehavioral Factors & Increased HCV Transmission in HIV+ MSM

- Increased ART Efficacy
  - Increased life expectancy, energy
  - Increased duration sexual activity

- Changes in Sexual Behavior
  - Therapeutic optimism
  - Beliefs that ART decreases infectiousness
  - Decrease condom use
  - Serosorting*

- Increased STDs
  - Inflammation
  - Mucosal abrasion
  - Bleeding (?)

- Increased Traumatic Practices
  - Unprotected anal intercourse
  - Group sex
  - Fisting
  - Abrasion
  - Bleeding (?)

- Increased Substance Use
  - Mucosal drug use

*Engaging in unprotected sex with individuals who have the same HIV serostatus
CDC Recommendations for HCV testing

- Birth Cohort based screening
  - All individuals born between 1945 and 1965 should be tested at least once for HCV
  - All individuals outside of this cohort with a HCV risk factor should be screened
  - Cost-effective
  - 1-time cohort screening would identify about 86% of undiagnosed cases, compared with 21% with risk-based screening

- US Preventive Services Task Force: Grade B recommendation

CDC. MMWR 2012;61(No. RR-4).
http://www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm
Recommended testing sequence for identifying 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

*STOP: Proceed to next patient.
†Additional testing as appropriate based on clinical judgment.
The role of Occupational Healthcare Providers

- Implementation of screening programs
  - Birth cohort and risk based screening
  - EMR modification
- Awareness/Education programs
- Destigmatization

- The National Viral Hepatitis Roundtable is a resource
  - www.nvhr.org
Health-care workers who have substantial HCV viral replication (≥10^4 genome equivalents/mL) be restricted from performing procedures that are prone to exposure and that all health-care workers with confirmed chronic HCV infection should be treated.

The achievement of an SVR in such individuals will not only eliminate the risk of HCV transmission to patients but also decrease circumstantial loss of experienced clinicians.

The role of Occupational Healthcare Providers

- Development of comprehensive treatment programs
- Work with HCV treaters within the institution
  - Hepatology, GI, Infectious Diseases
- Mentorship programs to become independent treaters
  - ECHO model
Managing HCV Exposure

- Baseline HCV antibody and RNA testing should be done within 48 hours of the exposure.
- If baseline testing is negative, repeat testing is recommended.
  - At a minimum, repeat testing should be done 4 months to 6 months later.
  - When earlier identification of infection or reinfection is desired, HCV RNA and ALT testing every 4 weeks to 6 weeks for 6 months is recommended.
Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure

- **HCV antibody (Ab) negative, HCV RNA negative**
  - **No HCV infection**
  - Repeat testing for 6 months to assess for new infection
    - Test HCV RNA and HCV Ab
      - **HCV RNA positive or seroconversion**
        - **Acute HCV infection**
      - **HCV RNA negative or seroconversion**
        - **No HCV infection**
        - Counsel on risk reduction
        - Annual testing for high-risk patients

- **HCV Ab positive, HCV RNA negative**
  - **Prior resolved infection**
  - Repeat testing to assess for outcome of acute infection
    - Monitor HCV RNA and alanine aminotransferase (ALT) for at least 12 weeks
      - **Spontaneous clearance**
      - **HCV RNA negative x 2, 12 weeks apart**
        - **No HCV infection**
        - **HCV RNA positive at 6 months**
          - **Chronic HCV infection**
            - See initial treatment of chronic HCV infection

- **HCV Ab negative, HCV RNA positive**
  - **Acute infection already present**
  - Repeat testing to assess for outcome of acute infection

- **HCV Ab positive, HCV RNA positive**
  - **Prior chronic infection**

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Exposure 48 hours // 12 weeks 24 weeks

Baseline testing within 48 hours of exposure
### Interpretation for Diagnosis of Acute HCV Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV antibody</strong></td>
<td>• May be negative in the first 6 weeks after exposure</td>
</tr>
<tr>
<td></td>
<td>• May be delayed or absent when the individual is immunosuppressed</td>
</tr>
<tr>
<td></td>
<td>• Presence alone does not distinguish between acute and chronic infection</td>
</tr>
<tr>
<td></td>
<td>• Low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result</td>
</tr>
<tr>
<td><strong>HCV RNA</strong></td>
<td>• Viral fluctuations greater than $1 \log_{10} 10^{10}$ IU/mL may indicate acute HCV infection</td>
</tr>
<tr>
<td></td>
<td>• May be transiently negative during acute HCV infection</td>
</tr>
<tr>
<td></td>
<td>• Alone does not distinguish between acute and chronic infection</td>
</tr>
<tr>
<td><strong>Alanine aminotransferase (ALT)</strong></td>
<td>• Fluctuating peaks during acute HCV infection suggest acute infection</td>
</tr>
<tr>
<td></td>
<td>• May be normal during acute HCV infection</td>
</tr>
<tr>
<td></td>
<td>• May be elevated due to other liver insults such as alcohol consumption</td>
</tr>
</tbody>
</table>
Acute Infection with No Discrete Exposure

- Acute infection should be suspected if there is a new rise in the ALT level without an alternate cause.
- Acute infection should also be suspected when there are low (especially <104 IU/mL) or fluctuating (>1 log10 IU/mL) HCV RNA values.
- A low signal-to-cutoff ratio of HCV antibody along with detectable HCV RNA may also be suggestive of the early weeks of acute primary infection.
- Patients suspected of having acute HCV infection should also have a laboratory evaluation to exclude other or coexisting causes of acute hepatitis and should be tested for HIV.
- **Preexposure or postexposure prophylaxis with antiviral therapy is Not Recommended.**
  Rating: Class III, Level C

www.hcvguidelines.org

Medical Management & Monitoring in Acute HCV Infection

- Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (e.g., every 4 weeks to 8 weeks) for 6 months to 12 months is also recommended to determine spontaneous clearance of HCV infection versus persistence of infection.
  Rating: Class I, Level B

- Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (e.g., acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.
  Rating: Class I, Level C

- Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.
  Rating: Class I, Level B

www.hcvguidelines.org
Managing Chronic infection: 2° Prevention, Counseling our patients

- Limit acetaminophen < 2 grams/day
- Avoid ingestion of raw seafood
  - Vibrio vulnificus & Vibrio parahaemolyticus infection
- Maintain BMI < 25 kg/m²
- Avoid iron supplements, unless documented deficiency
- Immunizations/management of HBV coinfection
- Formal reevaluation yearly for consideration of HCV treatment
  - repeat fibrosis staging at 2-4 year intervals
- Abstain from alcohol use

Pre-treatment evaluation

- Factors that may need to be addressed prior to treatment initiation
  - Substance Use, HIV testing, psychiatric history, pregnancy screen, cardiac, pulmonary or renal disease

- HIV Assessment if Co-Infected
  - OIs past or present, malignancy, CD4, HIV VL, ART & adherence

- Liver Disease Assessment
  - CBC, INR, CMP
  - Evidence of HBV infection (HBsAg) and/ or HBV and HAV immunity
  - Quantitative HCV RNA
  - HCV genotype, subtype
  - Treatment history, outcome
  - Disease staging

Staging HCV Liver Fibrosis

- Important part of chronic HCV work-up

- Identify cirrhosis:
  - Strongly consider antiviral therapy
  - ↑ hepatocellular carcinoma risk: need to screen
  - Monitor for hepatic decompensation
  - Consider liver transplant evaluation

- Determine cirrhosis by:
  - Liver biopsy
  - Non-invasive tests
Options for Liver Fibrosis Assessment

Liver Biopsy

Serum Biomarkers

FibroScan
Staging of Liver Disease: Liver Biopsy

**Gold standard**

- Invasive
- Morbidity (3/1,000)
- Mortality (1/10,000)
- Observer variability
- Sampling error and costly
Monitoring for HCC

- Advanced fibrosis and cirrhosis
  - Hepatic ultrasound +/- AFP every 6 months
    - Suspicious mass lesion requires more specific testing with a multi-phase contrast CT or MRI
    - AFP alone is inadequate screening test for HCC

- Routine screening for HCC without advanced fibrosis is not recommended

The cirrhotic patient

- Evaluate for encephalopathy & ascites
  - If ascites refer to hepatologist
    - Diagnostic paracentesis
    - Evaluation for liver transplant
- Endoscopy to evaluate for the presence of esophageal varices
  - Need for prophylaxis with a non-selective beta blocker

Initiating HCV Treatment

- Adherence counseling and medication teaching
- Assess for drug-drug interactions
- In Co-Infected patients
  - All ART drug switches should be done in collaboration with the HIV practitioner
  - ART-naive patients with CD4 > 500 cells/mm$^3$
    - Some clinicians may choose to defer ART until HCV treatment is completed
  - HIV patients with lower CD4 counts (eg, <200 cells/mm$^3$)
    - ART should be initiated expeditiously
  - HCV therapy may be delayed until the patient is stable on HIV treatment

SVR (Cure) Associated with Decreased All-Cause Mortality

530 patients with advanced fibrosis, treated with interferon-based therapy, and followed for 8.4 (IQR 6.4-1.4) years

Van der Meer et al. JAMA 2012; 308:2584
Evolving HCV Treatment


SVR RATE (%)

IFN 6 m IFN 12 m IFN/RBV 6 m IFN/RBV 12 m PEG 12 m PEG/RBV 12 m BOC/TVR New DAAs

Adapted from Strader DB. Clin Liver Disease 2012, 1:1; 6-11.
Direct Acting Agents

[Diagram showing the lifecycle of Hepatitis C Virus, highlighting various steps and inhibitors.]
DAA: Direct Acting Antivirals

**Protease**
- **NS3 /4A Inhibitors**
  - High potency
  - Limited genotypic coverage
  - Low barrier to resistance

**Polymerase**
- **NS5B Nucleos(t)ide Inhibitors (NI)**
  - Intermediate potency
  - Pan genotypic coverage
  - High barrier to resistance

- **NS5B Non Nucleoside Inhibitors (NNI)**
  - Intermediate potency
  - Limited genotypic coverage
  - Low barrier to resistance

- **NS5A Inhibitors**
  - High potency
  - Multi-genotypic coverage
  - Intermediate barrier to resistance
Mnemonic to remember DAAs

- Look at end of the drug’s name
  - **PRE**vir = **PR**otEase inhibitor
    - Telaprevir, boceprevir, simeprevir
  - **U**vir = **nU**cleotide or non-**nU**cleotide polymerase inhibitor
    - Sofosbuvir, dasabuvir
  - **Asv**ir = **NS5A** inhibitor
    - Ledipasvir, ombitasvir, daclatasvir
Factors Associated with Treatment and Cure

- **HCV Genotype**
  - 1, 2, 3, 4, 5, 6
  - Subtype: 1a, 1b

- **Stage of liver fibrosis**
  - Cirrhosis versus no cirrhosis
  - Metavir score F0-F4

- **HCV treatment status**
  - Naïve versus treatment experienced
    - Relapse, partial responder, null responder

- **Special populations**
  - Transplant, chronic kidney dis, age >70, children
# AASLD/ IDSA: Recommended HCV regimens for treatment-naïve patients (GT 1)

<table>
<thead>
<tr>
<th>Duration of Therapy (weeks)</th>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Cirrhosis</td>
<td>With Cirrhosis*</td>
</tr>
</tbody>
</table>
| Elbasvir 50mg+ Grazoprevir 100mg qd± RBV | 12**  
16+ RBV | 12**  
16+RBV | 12 | 12 |
| Daclatasvir 60mg + sofosbuvir 400mg qd | 12 | 24  
(± RBV‡) | 12 | 24  
(± RBV‡) |
| Ledipasvir/sofosbuvir (90/400 mg qd) | 12† | 12 | 12† | 12 |
| Sofosbuvir 400 mg + simeprevir 150 mg qd± RBV‡ | 12 | 24 | 12 | 24 |
| Sofosbuvir 400mg + Velpatasvir 100mg qd | 12 | 12 | 12 | 12 |
| Ombitasvir/paritaprevir/r (25/150/100 mg qd) + dasabuvir 250 mg bid ± RBV | 12  
(with RBV) | 24§  
(with RBV) | 12  
(no RBV) | 12  
(no RBV) |

Weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]).

*Compensated cirrhosis.

**No NS5a RAVS detected, no RBV needed.

† 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-therapy HCV RNA <6 million IU/mL. Shortening treatment to less than 12 weeks should be done with caution and performed at the discretion of the practitioner.

‡ Role of RBV is unclear, awaiting results from larger phase 3 studies for clarification.

§12 weeks may be considered for some patients based on prior treatment history.

AASLD/IDSA: Recommended HCV regimens for treatment-naïve patients*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype 2</strong></td>
<td>Sofosbuvir + Velpatasvir for 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir + Sofosbuvir for 12 weeks (16-24wks for compensated cirrhosis)</td>
</tr>
<tr>
<td><strong>Genotype 3</strong></td>
<td>Sofosbuvir + Velpatasvir for 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir + Sofosbuvir for 12 weeks (24 wks +/- RBV for compensated cirrhosis)</td>
</tr>
<tr>
<td><strong>Genotype 4</strong></td>
<td>Ledipasvir/sofosbuvir for 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + Velpatasvir for 12 weeks</td>
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<tr>
<td></td>
<td>Ombitasvir/paritaprevir/r + RBV for 12 weeks</td>
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<tr>
<td></td>
<td>Elbasvir/ Grazoprevir for 12 weeks</td>
</tr>
<tr>
<td><strong>Genotype 5 &amp; 6</strong></td>
<td>Ledipasvir/Sofosbuvir for 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + Velpatasvir for 12 weeks</td>
</tr>
</tbody>
</table>

Weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]).

*In patients without cirrhosis and compensated cirrhosis.

ION 4 Trial

- Ledipasvir/Sofosbuvir in HCV genotype 1 or 4 in co-infected patients
- Open-label
- HCV treatment-naïve or experienced
- 20% with compensated cirrhosis
- Platelets >50K/mm3
- Hemoglobin >10 mg/dL
- Creatinine clearance >60 mL/min
- On ART:
  - HIV RNA <50 copies/mL
  - CD4 >100 cells/mm3
ION-4 Trial

No impact on SVR12 rate: gender, HCV genotype, baseline HCV RNA, IL28B genotype, cirrhosis, prior HCV treatment, ART regimens, and baseline CD4 count.

Lower SVR12 rate observed among black patients (90%).

ION-4: Additional Outcomes

- Virologic failure (n=12)
  - Breakthroughs (n=2)
  - Relapse (n=10, all black)
  - Post-treatment NS5A RAVs (n=10)
  - No NS5B S282T at baseline or time of failure

- No HIV RNA rebound and CD4 counts remained stable

- Generally safe and well tolerated
  - No discontinuations due to adverse events
  - Creatinine $\geq 0.4$ mg/dL (n=4; 1%)
    - Completed treatment and no ART change (n=2)
    - Tenofovir DF dose reduction (n=1) and discontinuation (n=1)

TURQUOISE-I Trial

- **ABT-450/r/Ombitasvir + Dasabuvir + RBV (n=31)**
- **ABT-450/r/Ombitasvir + Dasabuvir + RBV (n=32)**

- Ombitasvir/Paritaprevir/r + Dasabuvir + RBV in HCV Genotype 1 with **HIV Co-Infection**
- Open-label
- HCV RNA >10,000 IU/mL
- HCV treatment-naïve or PR experienced
- Child-Pugh A cirrhosis allowed
- Stable HIV disease
- ART restricted to regimens based on Atazanavir (44%)

TURQUOISE-I Trial

- Virologic failure (n=2)
  - Both were GT1a, prior PR null responders, and cirrhotic
  - RAVs in ≥2 targets at time of failure

- HIV RNA breakthroughs (n=5/63)

- Safety
  - No serious adverse events
  - RBV dose reduction (n=6, all w/ SVR)
  - Most common adverse events
    - Fatigue, insomnia, nausea, headache

- Indirect hyperbilirubinemia most common abnormality (17/63; 15/17 were receiving atazanavir-based ART)

ALLY-2 Trial

- Daclatasvir + Sofosbuvir in HCV/HIV Coinfection, Open-label
- Genotype 1-4
- Treatment-naïve and experienced
- Cirrhosis allowed
- HIV status
  - ART: HIV RNA <50 copies/mL & CD4 >100 cells/mm³
  - No ART: CD4 >350 cells/mm³

Wyles D, et al. 22nd CROI. Seattle, 2015. Abstract 151LB.
ALLY-2 Trial

12-week regimen: no impact of race, baseline HCV RNA, cirrhosis, baseline NS5A RAVs, or ART regimens on SVR12. Genotype 4 results not shown (n=3).

Wyles D, et al. 22nd CROI. Seattle, 2015. Abstract 151LB.
# Allowed ARVs in Ally-2

<table>
<thead>
<tr>
<th></th>
<th>ALLY-2</th>
<th>ION-4</th>
<th>TURQUOISE-1*</th>
</tr>
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<tbody>
<tr>
<td>Atazanavir/r</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>+</td>
<td></td>
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<tr>
<td>Efavirenz</td>
<td>+</td>
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<tr>
<td>Nevirapine</td>
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<tr>
<td>Rilpivirine</td>
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<td>Dolutegravir</td>
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<tr>
<td>Raltegravir</td>
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<td>Enfuvirtide</td>
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<tr>
<td>Maraviroc</td>
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<tr>
<td>Zidovudine</td>
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<td>Lamivudine</td>
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<tr>
<td>Abacavir</td>
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<tr>
<td>Tenofovir</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Emtricitabine</td>
<td>+</td>
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</tr>
</tbody>
</table>

- **ION-4**
  - Ledipasvir/Sofosbuvir
  - 12 weeks
  - GT1 or 4
  - Naïve or Experienced

- **Turquoise-1**
  - Obitasvir + paritaprevir/r + dasabuvir + RBV
  - 12 or 24 weeks
  - GT1
  - Naïve or Experienced

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*TURQUOISE 1b will evaluate darunavir/r*
## Summary GT1 Monoinfection: Ledipasvir/Sofosbuvir +/- RBV

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>Duration</th>
<th>SVR 12 Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-1* (n= 865)</td>
<td>GT-1 Treatment-naïve (16% with cirrhosis)</td>
<td>LDV/SOF</td>
<td>12 weeks</td>
<td>99% (211/214)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>12 weeks</td>
<td>97% (211/217)</td>
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<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>24 weeks</td>
<td>98% (212/217)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>24 weeks</td>
<td>99% (215/217)</td>
</tr>
<tr>
<td>ION-2+ (n= 440)</td>
<td>GT-1 Treatment-experienced (20% with cirrhosis)</td>
<td>LDV/SOF</td>
<td>12 weeks</td>
<td>94% (102/109)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>12 weeks</td>
<td>96% (107/111)</td>
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<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>24 weeks</td>
<td>99% (108/109)</td>
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<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>24 weeks</td>
<td>99% (110/111)</td>
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<tr>
<td>ION-3^ (n= 647)</td>
<td>GT-1 Treatment-naïve (0% with cirrhosis)</td>
<td>LDV/SOF</td>
<td>8 weeks</td>
<td>94% (202/215)</td>
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<tr>
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<td></td>
<td>LDV/SOF + RBV</td>
<td>8 weeks</td>
<td>93% (201/216)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>12 weeks</td>
<td>95% (206/216)</td>
</tr>
</tbody>
</table>

Summary GT1 Monoinfection: Paritaprevir/r/Ombitasvir, Dasabuvir ± RBV

<table>
<thead>
<tr>
<th>Study (duration)</th>
<th>Patients</th>
<th>Treatment Regimen</th>
<th>SVR₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEARL-II (12 weeks)</td>
<td>GT1b treatment-experienced</td>
<td>AbbVie regimen + RBV (n = 88)</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AbbVie regimen only (n = 91)</td>
<td>100%</td>
</tr>
<tr>
<td>PEARL-III (12 weeks)</td>
<td>GT1b treatment-naïve</td>
<td>AbbVie regimen + RBV (n = 210)</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AbbVie regimen only (n = 209)</td>
<td>99%</td>
</tr>
<tr>
<td>PEARL-IV (12 weeks)</td>
<td>GT1a treatment-naïve</td>
<td>AbbVie regimen + RBV (n = 100)</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AbbVie regimen only (n = 205)</td>
<td>90%</td>
</tr>
<tr>
<td>TURQUOISE-II (12 and 24 weeks)</td>
<td>GT1 treatment-naïve and treatment-experienced with compensated cirrhosis</td>
<td>AbbVie regimen + RBV, 12 weeks (n = 208)</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AbbVie regimen + RBV, 24 weeks (n = 172)</td>
<td>96%</td>
</tr>
<tr>
<td>SAPPHIRE-I (12 weeks)</td>
<td>GT1 treatment-naïve</td>
<td>AbbVie regimen + RBV (n = 473)</td>
<td>96%</td>
</tr>
<tr>
<td>SAPPHIRE-II (12 weeks)</td>
<td>GT1 treatment-experienced</td>
<td>AbbVie regimen + RBV (n = 297)</td>
<td>96%</td>
</tr>
</tbody>
</table>

AbbVie regimen consists of ABT-450/ritonavir (150 mg/100 mg) coformulated with Ombitasvir (ABT-267) (25 mg), dosed once daily, and Dasabuvir (ABT-333) (250 mg), dosed twice daily. RBV weight-based dosing, twice daily. Abbreviation: GT, genotype.
**C-EDGE TN: Study Design**

- **n = 316**
  - Grazoprevir (GZR) 100 mg + Elbasvir (EBR) 50 mg

- **n = 105**
  - Placebo

**Follow-Up**
- FUW12
- FUW16
- FUW12
- FUW8
- FUW4
- D1
- TW12
- TW8
- TW4
- D1

- **Phase 3, randomized, placebo-controlled trial, HCV monoinfected**
- **GZR/EBR fixed-dose combination tablet given once daily, without ribavirin, for 12 weeks**
- **After a 4-week follow-up period, placebo recipients were unblinded and received open-label GZR/EBR**
- **Stratification by cirrhosis and HCV geno/subtype**

## C-EDGE TN: Results

### SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>GT1a</th>
<th>GT1b</th>
<th>GT4</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR12 (%)</strong></td>
<td>95 ±1</td>
<td>92 ±1</td>
<td>99 ±1</td>
<td>100 ±1</td>
<td>80 ±1</td>
</tr>
<tr>
<td><strong>Non-Virologic Failure</strong></td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Breakthrough</strong></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

ASTRAL-1, Pangenotypic Regimen

- SOF/VEL x 12 weeks, GT 1-6
- Patients with (19%) and without cirrhosis
- 32% treatment experienced

Feld JJ. et al. AASLD Nov 2015
Treatment experienced patients

- SOF/VEL + GS-9857 x 12 weeks, GT 1-6
- 79% had prior DAA exposure
- N=128

Lawitz E. et al. EASL 2016
Liver Fibrosis Regression After Anti-HCV Therapy in HIV/HCV-Coinfected Patients

- Prospective, observational cohort in Madrid
  - HIV/HCV receiving PR since 2004
  - Baseline liver biopsy or transient elastography
  - Fibrosis regression: ≥1 point reduction in fibrosis METAVIR score

- Median follow-up: 6.8 years

- Primary endpoints
  - Death from any cause
  - Liver-related death

### Overall Baseline Characteristics

<table>
<thead>
<tr>
<th>Patients (n=133)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median age (years)</td>
<td>43.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 (cells/mm³)</td>
<td>440</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HCV genotype 1/2/3/4 (%)</td>
<td>59/2/26/17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median HCV RNA (log₁₀ IU/mL)</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AFP (ng/mL)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histology activity index</td>
<td>5.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver stiffness score</td>
<td>22.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Achieved SVR (%)</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

PR: pegIFN + RBV.
Liver Fibrosis Regression After Anti-HCV Therapy in HIV/HCV-Coinfected Patients

- Factors associated with outcomes (hazard ratios)
  - All-cause death
    - Fibrosis regression: 0.36 ($P<0.01$)
  - Liver-related death
    - Fibrosis regression: 0.15 ($P<0.01$)
  - Liver-related complications
    - Fibrosis regression: 0.09 ($P<0.01$)
    - Achieving SVR: 0.24 ($P=0.01$)

Fibrosis Regression According to SVR Status

- Achieved SVR (n=42)
  - 55% Fibrosis regression
  - 45% No fibrosis regression

- No SVR (n=91)
  - 15% Fibrosis regression
  - 85% No fibrosis regression

Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.

Rating: Class I, Level A
Current Challenges in HCV Care

- Restrictive criteria for drug approval for many payers
  - Documented history of abstinence from alcohol and drugs for at least 6 months prior to treatment
    - For a recipient with a history of substance dependence need a blood alcohol level and UDS to document abstinence
  - Metavir fibrosis score of F3 or F4
  - HIV may not be a mitigating factor
- Arduous prior authorization process for providers
- Significant improvement seen in PA Medicaid

Two Tiered Healthcare

Figure Legend
- Absolute denial of DAA prescription
- Denial of DAA prescription preceding fill

- Overall: 29.7%, 16.2%
- US Medicaid: 70.8%, 46.3%
- US Medicare: 18.0%, 5.0%
- Commercial Insurance: 18.7%, 10.2%

V. LoRe. AASLD 2015, LB-5.
Current Challenges in HCV Care

- Approximately 8 hrs of staff time per patient
- 1 to 4 months to go through the process
When insurance will not cover drugs, what are the options?

- Wait for new drugs to be approved
  - No guarantee that those will be covered/ patient will qualify
- Wait until patient qualifies
  - Sobriety
  - Worsening fibrosis
- Take legal action
- Apply to patient assistance programs to obtain free drug
  - There is only one company that does this currently
  - Financial information to qualify
  - Proof that patient does not qualify for insurance
  - Challenging to navigate
# Changes to State Medicaid Rx Restrictions

<table>
<thead>
<tr>
<th>2014</th>
<th>2015/ 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>- F3/F4</td>
<td>- F2 for HCV Mono infected patients</td>
</tr>
<tr>
<td>- No exception for HIV patients</td>
<td>- F0 for HIV/HCV Coinfection or anyone with extrahepatic manifestation</td>
</tr>
<tr>
<td>- No drugs or alcohol for 6 months</td>
<td>- No sobriety requirement</td>
</tr>
<tr>
<td>- Specialist Physician</td>
<td>- Experienced provider</td>
</tr>
</tbody>
</table>
Welcome to the NVHR Hepatitis C Resources Page

NVHR’s program aims to increase the number of people born 1945-1965 (baby boomers) and other communities at risk tested for hepatitis C. This page has information for providers, patients, and organizations and highlights the work of our community partners.
Thank you!