The Changing Landscape of Hepatitis C Testing and Therapy

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Hepatitis C Virus (HCV)

- Flaviviridae family
- Recent widespread human transmission
  - Transfusion services
  - ID drug use
- Chronic HCV Infection
  - 3.8 million U.S.
  - >130 million worldwide
- Most chronic infection undiagnosed
Discovery HCV

• Search for basis of non-A, non-B hepatitis
  – 85% of blood transfusion hepatitis
  – DNA or RNA virus?

• Purify nucleic acid from infected chimpanzee

• Copy and clone into bacteriophage λgt11

• Identify clones expressing viral proteins using antibodies from non-A, non-B patient

“It is not unrealistic to expect that other elusive agents may now be recognized using similar approaches”

Harvey Alter     Annals of Internal Medicine 1991
- Genome ssRNA
- Replicates in hepatocytes
- HCV genome does not integrate into host genome allowing spontaneous clearance and therapeutic cures

Viral load tests
Genotyping (low resolution)

5' UTR

Interferon sensitivity

Genotyping (high resolution)

pro-protein

Serine protease inhibitors
NS3/4A

RNA polymerase

Genotyping (high resolution)
HCV Genotypes 1-7

- Multiple Subtypes (a, b, c ...)
- Type 1 virus most common in the US and most challenging to treat
- Assays and therapies optimized to type 1 virus

![Pie chart showing the distribution of HCV genotypes](image-url)
Genotype and subtype used to inform:

- Selection of therapy
- Length/duration of therapy
- Likelihood of resistance mutations

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>SUBTYPE (total=84)</th>
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<tbody>
<tr>
<td>1</td>
<td>a, b, c, d, e, f, g, h, i, j, k, l, m (13)</td>
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<tr>
<td>2</td>
<td>a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r (18)</td>
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<tr>
<td>3</td>
<td>a, b, c, d, e, f, g, h, i, k (10)</td>
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<td>4</td>
<td>a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u (21)</td>
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<tr>
<td>5</td>
<td>a (1)</td>
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<tr>
<td>6</td>
<td>a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t (20)</td>
</tr>
<tr>
<td>7</td>
<td>a (1)</td>
</tr>
</tbody>
</table>

Confirmed subtypes Provisional subtypes

Provisional subtypes added since 2005

Comb et al. 2007; http://euhcvdb.ibcp.fr/euHCVdb
Natural History of Hepatitis C

- Acute Hepatitis C (rarely diagnosed)
- Chronic Hepatitis C
  - 85% chance of developing Chronic Hepatitis C
  - 20% chance of developing Cirrhosis
  - 1-5% chance of developing Liver cancer

- #1 cause of cirrhosis
- #1 cause of liver failure
- 10,000 death per year
- #1 cause for liver transplant in the US
The Changing Face of HCV in the US

Natural History of Chronic HCV Progression

• Chart review of 485 plasma donors infected in Austria during 1970s (mean follow-up: 31 yrs)

- First liver transplant: 18 yrs after infection
- First death: 28 yrs after infection

Risk Factors - HCV Transmission

Source: Centers for Disease Control and Prevention

- Injection Drug Users: 60%
- Sexual: 15%
- Health Care Workers Perinatal: 10%
- Transfusions & Organ Transplants before screening: 10%
- Non Identified Risks: 5%
HCV Prevention

- 1986 Indirect blood screening for HCV and HIV prevention measures
- Anti-HCV test licensed 1992
- Discovery of HCV 1989
- Needlestick Safety and Prevention Act 2001

22,000 new cases reported in 2012

Recent Increase in HCV Infection

- Between 2007 to 2012
  - 50% increase in case reporting
  - 200% increase in 17 states
- Risk factors
- ~70% persons who inject drugs
- Previous oral prescription narcotic use
- Equally male to female
- Young, ages 18-29 years
- Rural and suburban
- White

Transmission Among Persons Who Inject Drugs

- Transmission risks
  - Injection duration
  - Injection frequency
  - Equipment sharing
- HCV prevalence
  - 27 to 51%
- Incidence declined in response to HIV harm reduction (syringe access programs)

Other Modes HCV Transmission

• Accidental needle stick in healthcare setting
  – HCV risk is 1.3%, HIV risk is 0.3%
• 18 healthcare-associated outbreaks from 2008 to 2013
  – 223 cases involving over 90,550 at-risk persons notified
• Non-injecting drug use (e.g., intranasal cocaine use)
• Perinatal-infants born to HCV infected mothers
  – ~4% risk if mother infected with HCV
  – ~25% risk if mother co-infected with HCV and HIV
• Sexual transmission is rare
  – HIV infected MSM at highest risk
• Miscellaneous reported
  – Unregulated tattooing

Bending the HCV Outcomes Curve

- Estimated 45% to 85% of HCV persons with chronic HCV are unaware of infection
- Screening strategies have been based on risk*
  - Blood transfusion before 1992, IV drug exposure
  - Many in highest risk cohort do not identify themselves
- Recent treatments only ~ 50% effective, expensive
  - Many identified persons have elected to wait for better drugs which are now available (Combination DAAs)

In 2012 the CDC issued guidelines recommending a one-time anti-HCV antibody test for all baby boomers (those born during 1945 through 1965), although those at high risk should be tested regularly.

Other Screening Indications

• Persons who have injected drugs (once)
• Persons with conditions associated with HCV
  – HIV
• Elevated aminotransferase (ALT)
• Hemodialysis
• Transfusions/organ transplants prior to 1992
• Children of HCV infected mothers
• Exposed healthcare workers
• Sexual partners of HCV infected individuals *
Laboratory Testing for HCV Infection

• Serology - anti-HCV antibodies screening test (EIA or CIA)

RIBA

Virus Detection - HCV RNA
qualitative PCR or TMA
quantitative real-time PCR
HCV Immunoassay (IA)

HCV IA detects antibodies to 3 or more viral proteins
## Signal to Cutoff Ratios (S/Co)

<table>
<thead>
<tr>
<th>Screening Test Kit Name</th>
<th>Manufacturer</th>
<th>Assay Format</th>
<th>Signal-to-cut-off ratio predictive true positive</th>
<th>S/CO predicts HCV viremia</th>
<th>S/CO guide to choosing screening confirmation (RIBA vs PCR) testing algorithm now obsolete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortho HCV Version 3.0</td>
<td>Ortho</td>
<td>EIA</td>
<td>&gt; 3.8</td>
<td></td>
<td></td>
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<tr>
<td>ELISA Test System</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Abbott HCV EIA 2.0</td>
<td>Abbott</td>
<td>EIA</td>
<td>&gt; 3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VITROS Anti-HCV</td>
<td>Ortho</td>
<td>CIA</td>
<td>&gt; 8.0</td>
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<td></td>
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<tr>
<td>AxSYM Anti-HCV</td>
<td>Abbott</td>
<td>MEIA</td>
<td>&gt; 10.0</td>
<td></td>
<td></td>
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<tr>
<td>Architect Anti-HCV</td>
<td>Abbott</td>
<td>CMIA</td>
<td>&gt; 5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advia Centaur HCV</td>
<td>Siemens</td>
<td>CIA</td>
<td>&gt; 11.0</td>
<td></td>
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</tbody>
</table>
anti-HCV RIBA 3.0

Reagent manufacture discontinued 2013
HCV Algorithm (2013)

- HCV Ab
  - Reactive
    - HCV RNA
      - Detected
        - Current HCV Infection
      - Not Detected
        - No current HCV Infection
  - Nonreactive
    - STOP

STOP
<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Acute or chronic HCV depending on clinical context</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Past, resolved HCV infection; False Positive Screen</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Absence of HCV infection</td>
</tr>
</tbody>
</table>
HCV Molecular Confirmation Issues

• Confirm with “sensitive” HCV RNA test
  – COBAS AmpliPrep/ COBAS Taqman, quantitative (Roche)
  – RealTime HCV, quantitative (Abbott)
  – APTIMA HCV RNA, qualitative (Hologic) FDA approved for diagnosis HCV

• Both HCV Viral Load tests are very sensitive but none are FDA approved for diagnosis (still confirmation standard)

• Confirmation with quantitative assay is both process and cost efficient (baseline for therapeutic monitoring)
Issues for Timely Confirmatory Testing

• Time gap in Screening vs PCR confirmation
  – Patients at risk for follow up.

• Re-testing screening sample by PCR condoned by CDC, however, potential contamination risk?
  – Reflex PCR testing of 2\textsuperscript{nd} tube for sero-positives?
  – Pre-aliquoting samples prior to serologic and potential molecular testing?

• Unmet need: Rapid, unified screening/assay process (POC?)
Candidates for Therapy and Outcome Predictors

- >18 years
- Antibody & RNA *
- Liver bx (chronic hepatitis), not required
- Stage of disease appropriate
- No Rx contraindications

- VL < 400,000 I.U./ml
- Age
- Sex
- Race
- Weight
- Fibrosis
- Steatosis
- Insulin resistance
- Alcohol consumption
- All less predictive than IL28 (traditional interferon Rx)*
- New treatment options (DAAs) effective for previous difficult to treat patients
HCV Treatment:
Goal is Sustained Viral Response (SVR)

HCV RNA

“undetectable”

0  12  18

ETR
End Therapeutic Response

SVR
Sustained Viral Response
SVR = Improved Outcomes!

- SVR – virologic “cure”
  - Durable
  - Leads to improved histology
  - Leads to clinical benefits
    - Decreases decompensation
    - Decreases risk of hepatocellular carcinoma
    - Decreases mortality

Treatment of Chronic Hepatitis C (Pre-2011)

First HCV direct acting antiviral (DAA)
Protease Inhibitor (PI)

PI + PegIFN/RBV
(6-12 mos)[8-10]

PegIFN/ribavirin
(6-12 mos)[6,7]

50-60

PegIFN monotherapy
(6-12 mos)[5,6]

25-30

Interferon/ribavirin
(6-12 mos)[3,4]

38-43

Standard interferon
(12-18 mos)[2,3]

15-20

Standard interferon
(6 mos)[1]

8-12

1991

1995

1998

2001

2011

SVR (%)

HCV Therapies Continue to Evolve: *Unmet needs driving drug development*

The ideal treatment for HCV:

- Potent efficacy across all patient populations
- High barrier to resistance
- Tolerability profile/ Fewer side effects
- All oral / Easier Dosing
- GT1 efficacy/ Pan-genotypic activity
- Short treatment duration
- Simple stopping rules and treatment algorithm
- Low cost
- Optimal convenience

HCV Therapies Continue to Evolve: *Unmet needs driving drug development*
Direct Acting Antivirals (DAA)
Basis for New Therapies

Receptor binding and endocytosis

Fusion and uncoating

Transport and release

(+) RNA

Translation and polyprotein processing

RNA replication

Virion assembly

NS3/4 protease inhibitors

Membranous web

ER lumen

LD

NS5B polymerase inhibitors
Nucleoside/nucleotide Nonnucleoside

NS5A* inhibitors

*Role in HCV life cycle not well defined

# DAA Class Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protease inhibitors</th>
<th>Nucleos(t)ide Polymerase inhibitors</th>
<th>Nonnucleoside Polymerase inhibitors</th>
<th>NS5A inhibitors</th>
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<tbody>
<tr>
<td>Potency</td>
<td>High; Variable among HCV genotypes</td>
<td>Moderate-high; Consistent across genotype, subtype</td>
<td>Variable; Variable among HCV genotypes</td>
<td>High; multiple HCV genotypes</td>
</tr>
<tr>
<td>Barrier to Resistance</td>
<td>Low; 1a &lt; 1b</td>
<td>High; 1a = 1b</td>
<td>Very Low; 1a &lt; 1b</td>
<td>Low; 1a &lt; 1b</td>
</tr>
<tr>
<td>Drug Interaction Potential</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Rash, Anemia, ↑Bilirubin</td>
<td>Mitochondrial Nuc interactions (ART, RBV)</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Variable; QD to TID</td>
<td>QD</td>
<td>Variable; QD to TID</td>
<td>QD</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd gen PIs: better barrier, pangenotypic</td>
<td>Single target Active site</td>
<td>AllostERIC; Many targets</td>
<td>Multiple antiviral MOA</td>
</tr>
</tbody>
</table>

Paul Pockros 2013
New Therapies (Post-2011)

• Greatly increased likelihood of sustained viral response (SVR)
• Better Tolerated
• Shorter Treatment Regimens
• Simpler Treatment and Monitoring Algorithms
• More Drug Options
• Expensive
HCV Treatment: Tests for Selection and Guidance of Therapy

• Selection
  – Genotype and subtype
  – Stage of disease
  – Past treatment history

• Guidance
  – Genotype and subtype guided
    • how long to treat
  – Response guided
    • How long to treat/when to stop
Two Approaches to Guided Therapy

• Genotype Guided Therapy
  – Rx some genotypes shorter
    (GT2,3 interferon ribavirin therapy)
  – Rx other genotypes longer
    (GT1, 4, 5, 6 interferon ribavirin therapy)

• Response Guided Therapy
  – Rx based on rate VL decline
  – Treatment duration
  – Stopping rules
Response-Guided Therapy
“First Generation Direct Acting Antivirals”

# Recommended Regimens for Treatment-Naive GT1 HCV Pts

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Noncirrhotic Regimen</th>
<th>Duration, Wks</th>
<th>Compensated Cirrhotic Regimen</th>
<th>Duration, Wks</th>
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</thead>
<tbody>
<tr>
<td>GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12*</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>GT1a</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>24</td>
</tr>
<tr>
<td>GT1b</td>
<td>OMV/PTV/RTV + DSV</td>
<td>12</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1a</td>
<td>SMV + SOF ± RBV</td>
<td>12</td>
<td>SMV + SOF ± RBV</td>
<td>24</td>
</tr>
<tr>
<td>GT1b</td>
<td>SMV + SOF</td>
<td>12</td>
<td>SMV + SOF</td>
<td>24</td>
</tr>
</tbody>
</table>

*Shorter course can be considered in pts with pretreatment HCV RNA < 6 million IU/mL at provider’s discretion but should be done with caution.

**Relevant Medications**

- **DSV** dasabuvir
- **LDV** ledipasvir
- **OMV** ombitasvir
- **PTV** paritaprevir
- **RBV** ribavirin
- **RTV** ritonavir
- **SMV** simeprevir
- **SOF** sofosbuvir
- **RTV** ritonavir

From Sulkowski Clinical Care Options 2015
Genotype 1 HCV Ledipasvir (LDV) and Sofosbuvir (SOF)

HCV Current Recommendations, New All Oral Therapies:

Treatment Naïve patients: HCV genotype, duration important

<table>
<thead>
<tr>
<th>Genotype†</th>
<th>Week</th>
<th>Treatment Regimen</th>
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<tbody>
<tr>
<td>1, 4, 6</td>
<td>1, 2</td>
<td>LED+SOF</td>
</tr>
<tr>
<td>1</td>
<td>1, 2</td>
<td>PAR+[RTV/ OMB+DAS+/-RBV]*</td>
</tr>
<tr>
<td></td>
<td>2, 3</td>
<td>SOF/SPV +/-RBV**</td>
</tr>
<tr>
<td></td>
<td>1, 4</td>
<td>SOF +RBV</td>
</tr>
<tr>
<td>2, 3, 4</td>
<td>1, 2</td>
<td>SOF +RBV</td>
</tr>
<tr>
<td></td>
<td>3, 4</td>
<td>SOF +RBV+ PEG-INF</td>
</tr>
</tbody>
</table>

SOF=sofosbuvir; PAR=Paritaprevir; OMB = Ombitasvir; DAS = Dasabuvir; RTV = Ritonavir; SPV=Simeprevir; RBV=Ribavirin; gt = genotype PEG-INF = pegylated interferon

† Italics indicates alternative regimen recommendation * Genotype 1b: +RBV only if cirrhosis, 12 wks ** -RBV only for genotype 4

Note: For genotype 5, PEG-INF+RBV can be used as an alternative

Evolving Landscape of HCV
Updated 2014 AASLD Guidelines

Establish Starting Point
Determine treatment duration

Week 4 Retest Week 6 if not TND*

Identify adherence-
Treatment Failure only if viral loads goes up

Assess viral suppression in response to therapy

Detect Treatment Relapse

End of Treatment

Baseline

SVR 12
SVR 24 or more

*If quantitative HCV viral load has increased by greater than 10-fold (>1 log_{10} IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended.

HCV Genotyping Considerations

• Patients with HCV genotype 1a tend to have higher relapse rates than patients with HCV genotype 1b with certain regimens.
• Genotype 1a patients may receive more aggressive therapy
• Genotype 1 HCV infection that cannot be subtyped should be treated as genotype 1a infection

AASLD/IDSA HCV Guidance 05-29-15c
HCV Genotyping Methods

- LiPA (reverse hybridization line probe)
  - (5’UTR, Core)
- Nucleic Acid Sequencing (Sanger or NGS)
  - (5’UTR, Core, NS5)
- Primer specific PCR (Abbott TaqMan) FDA approved
  - (5’UTR, NS5)
- GenMark
  - (5’UTR, Core)
HCV Genotyping Test Issues

• Tests targeting only 5’ UTR do not reliably discriminate types 1a vs 1b or type 1 vs rare type 6 HCV

• Interrogation of core and NS5B associated with low percentage of no calls due to sequence variability of targets
HCV Genotyping for Drug Resistance

• **Resistance Associated Variation (RAVs)** arise due to selection (previous failed therapies)
• Spontaneous RAVs also present in untreated populations
• Mutations may confer fitness cost
• Barrier to resistance varies with drug class
• Evolving recommendations for resistance testing
HCV GT1a Infections with NS3 (protease) Q80K Polymorphism

• Efficacy of SMV/PEG/RBV substantially reduced*
• Sofosbuvir plus simeprevir**
  – 1a patients with Q80K mutation have lower rates of SVR
• Recommendations for testing for NS5A and other mutations are now emerging


**Lawitz E, Matusow G, DeJesus E et al EASL 2015;S264 AASLD/IDSA HCV Guidance 05-29-15
New Indications for RAV Testing

• NS5A mutations likely detected in setting of virologic breakthrough post DAA treatment
  – ledipasvir, ombitasvir, and daclatasvir
• NS5A inhibitor mutations likely stable and detectable as long as 2 years after treatment.
• NS3 region mutations may also occur (protease inhibitors)
  – Paritaprevir and simeprevir
• Treatment examples
  – ledipasvir/sofosbuvir
  – ombitasvir/paritaprevir/ritonavir/dasabuvir
  – Daclatasvir/sofosbuvir
• Indication for RAV testing: Treatment is urgent and previous treatment with NS5A/NS3 inhibitors has failed
• Test NS5A and NS3 regions
• Indications NS5B polymerase testing less clear
• Testing currently limited to a few specialty labs
• Field new and rapidly evolving
Evaluating the Cost Effectiveness of New Therapies

• In 2011, average wholesale acquisition costs of drugs alone were $32,000 to over $100,000
• Quality adjusted life years for those regimens considered reasonable
• New regimens are $100,000 to $175,000 in U.S.
• Incremental cost benefits have been demonstrated
• Evaluating cost effectiveness of new regimens also has to reflect the increased efficacy of the treatment (cost/cure)
• Will competition and or regulation bend the cost curve?

The HCV Revolution

• Viral discovery
• Advancing therapeutics
• Evolving laboratory technology
• Convergence on use of high quality molecular tests for detection and genotyping (VL considered)
• Broad population screening
• Education, screening, resource availability, team based management
• Economic models to bring affordable care for chronic HCV infection