Hepatitis C Virus Infection in Injection Drug Users

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Topics to Cover

- HCV epidemiology (focus on IDU)
- HCV natural history
- HCV screening and treatment (focus on IDU)
- Barriers to HCV care in IDU
- Models of care delivery that integrate HCV and substance use treatment
- Directions for future research
Historical Background: Hepatitis C Virus (HCV)

• RNA virus, 6 major genotypes
• “non-A, non-B hepatitis”
• First identified 1988
• Screening in blood products 1992
• No vaccine currently available
Prevalence of HCV in the US

- Based on population based survey (NHANES), anti-HCV prevalence in the U.S. is 1.6%
  - 4.1 million (CI, 3.4 million to 4.9 million) anti-HCV–positive persons nationwide
- Prevalence with chronic infection (viral load +) is 1.3%
  - 3.2 million (CI, 2.7 million to 3.9 million) with chronic HCV
- **Strongest risk factor for HCV is injection drug use**
  - OR for IDU=149 (95% CI: 45-494) v. transfusion prior to 1992
    OR=2.6 (95% CI: 0.9-7.3)
  - 48.4% of anti-HCV–positive persons reported a history of IDU
  - Among those reporting IDU, 83.3% had not used injection drugs for at least 1 year before the survey.

Prevalence of HCV among IDU in the U.S.

- Prevalence of anti-HCV among IDU in U.S. studies range 40-90%\textsuperscript{1,2}
- Prevalence estimate in US/Canada: 73% (LL-UL: 70-77)\textsuperscript{3}
  - HIV prevalence in IDU ~15%\textsuperscript{4}
- 1.5 million HCV-infected IDU in US (v. 10 million infected world-wide)\textsuperscript{3}

Global HCV Prevalence Among IDUs


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Incidence of Acute HCV Infection
United States, 1960-2001

CDC: unpublished data

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HCV Incidence Among IDU in the U.S.

• Incidence of HCV ~10-30 cases/100 person-years\textsuperscript{1,2}

• HCV incidence also declining in IDU, but not as dramatic as HIV\textsuperscript{3}

• Proportion of cases reporting IDU has increased\textsuperscript{4}
  – 31.8% cases 1982-1989
  – 33.5% cases 1990-1993
  – 45.6% cases 1994-2006

• IDU are the “core” of the HCV epidemic

HCV Incidence in the U.S. Among IDU

Figure 1. Incidence per 100 person-years of human immunodeficiency virus and hepatitis C virus infection by recruitment cohort in the AIDS Linked to the Intravenous Experience (ALIVE) cohort, 1988–2009.
Risk Factors for HCV in IDU

- Age
- Duration of IDU
  - Narrow window for intervention: 20-50% infected within first 2 years of IDU\(^1,2\)
- Severity of IDU
- Risky IDU behaviors

Factors that Facilitate HCV Transmission in IDU

• High concentration of virus in blood of chronic carriers
• High prevalence of disease in IDU
• Stability of virus in the environment
  – Persists as dried sample up to 1 week\(^1\)
  – Persists up to 60 days in syringes\(^2\)
• Sharing of injecting equipment
  – Swabs, cookers, syringes, filters, water\(^3\)

Percentage of Hepatitis C Virus RNA Detection on Used Injecting Equipment

Interventions to Prevent HCV Transmission in IDU

• Meta-analysis of behavioral and treatment interventions, including opioid agonist treatment (OAT) and needle and syringe programs (NSP)\(^1\)
  – 26 studies pooled
  – Combined interventions reduced risk of seroconversion by 75% (RR 0.25; 95% CI: 0.07-0.83)

• Meta-analysis of 6 UK studies of OAT and NSP\(^2\)
  – Full harm reduction (OAT plus NSP) reduced odds of seroconversion by 79% (OR=0.21; 95% CI: 0.08-0.52)

• *Data suggest that combined OAT and NSP programs are effective in decreasing HCV transmission in IDU*

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HCV Natural History: Hepatic Complications

- **Chronic hepatitis**
  - Occurs in approximately 80% of patients infected

- **Cirrhosis**
  - 5-25% develop cirrhosis over 20-30 years

- **Hepatocellular Cancer**
  - 1-3% of cirrhotic patients develop HCCa per year
  - Rarely occurs outside the setting of cirrhosis

HCV Natural History: Hepatic Fibrosis


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Slide Adapted from Roche Presentation: “Understanding Hepatitis C and Its Treatment”
Factors Associated with Progressive Fibrosis

- Alcohol
- Duration of infection
- Older age at infection
- Male
- Co-infection with HBV or HIV
- Being overweight/liver steatosis
- Smoking

HCV Morbidity and Mortality

• Chronic liver disease is 12th leading cause of death in U.S. in 2009\(^1\)
  – approx 1/2 is HCV-related
• Incidence of HCCA has tripled in the past 2 decades, primarily from HCV\(^2\)
• HCV is the #1 cause for liver transplants in the US\(^3\)
• HCV-related mortality projected to increase 2000-20\(^4\)


Figure. Annual age-adjusted mortality rates from hepatitis B and hepatitis C virus and HIV infections listed as causes of death in the United States between 1999 and 2007.

Because a decedent can have multiple causes of death, a record listing more than 1 type of infection was counted for each type of infection.

HCV Mortality

• Increased mortality observed for liver and non-liver causes
  – Study of 20,000+ blood donors, ½ HCV+ and ½ matched HCV-
  – Vital status from U.S. NDI, mean follow-up 7 years
  – Hazards ratios (HR) for death associated with HCV:
    • Liver: HR=45.99 (95% CI: 11.32-186.74)
    • CV: HR=2.21 (1.41-3.46)

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HCV Mortality

• Increased mortality observed for liver and non-liver causes
  – Study NHANES participants with linked mortality file (n=9378), median follow-up 14.8 years
  – Adjusted mortality rate ratio for HCV+ v. HCV-
    • Liver: RR=26.46 (95% CI: 8.00-87.48)
    • All-cause: RR=2.37 (1.28-4.38)

Non-Hepatic Complications of HCV

- Strongly associated
  - Mixed cryoglobulinemia
  - Sjögren (sicca) syndrome
  - Lymphoproliferative disorders
  - Porphyria cutanea tarda
  - Membranoproliferative glomerulonephritis
  - Neuropathy
  - Cryoglobulinemic (leukocytoclastic) vasculitis

- Possibly associated
  - Corneal ulcers (Mooren ulcers)
  - Thyroid disease
  - Lichen planus
  - Pulmonary fibrosis
  - Type 2 diabetes
  - Systemic vasculitis (polyarteritis nodosa, microscopic polyangiitis)
  - Arthralgias, myalgias, inflammatory polyarthritis
  - Autoimmune thrombocytopenia

- Manifestations associated with interferon therapy
  - Thyroiditis
  - Myelosuppression
  - Lichen planus
  - Myalgias
  - Retinopathy
  - Depression
  - Arthralgias

HCV Mortality in IDU

• Research suggests HCV is becoming a major cause of mortality in IDU
  – Cohort study of 2654 patients entering methadone treatment in Australia 1980-5
  – Linked to NDI death data up to 2008
  – Liver-related deaths increased over time, was most common cause last year of follow-up
    • 1/5 deaths (17%) from liver causes, hepatitis
    • Rate of death 17 from liver causes 17 x higher than general population

HCV Mortality in IDU

Figure 2  Trends across time in deaths per 1000 person-years (PY) for the most common underlying causes of death (participants with death causes recorded, n = 432); CI: confidence interval
The Evolution of HCV Therapy

Overall SVR* (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>24 Wks</th>
<th>48 Wks</th>
<th>48 Wks</th>
<th>48 Wks</th>
<th>Genotype 1 Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>IFN</td>
<td>6%</td>
<td>19%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001-2011</td>
<td>IFN + RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011-</td>
<td>PEG IFN + RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEG IFN + RBV + PI</td>
<td>54%-63%</td>
<td></td>
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</tr>
</tbody>
</table>

*SVR rates for all genotypes combined.


Slide Adapted from Roche Presentation: “Understanding Hepatitis C and Its Treatment”
Benefits of SVR

• Durable effect, <1% have relapse (“cure”)\(^1\)
• Reduces progression of liver disease and development of hepatocellular CA\(^2\)
• Ameliorates HCV-related extrahepatic manifestations
• Improves Quality of Life\(^3\)
• May be associated with mortality benefit\(^4\)

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Are Current Efforts for Screening and Treatment Adequate?

- National estimates: NHANES 2001-2008
  - 393 anti-HCV positive; 170 (43%) interviewed\(^1\)
  - Only 49.7% were aware of HCV status prior to notification
    - Awareness twice as likely if health insurance, five times as likely if had usual source of medical care

- Among IDU:
  - Single study street recruited 197 IDU, only 61% of HCV+ were aware infected\(^2\)

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\(^1\) Denniston, Monina, McQuillan, Jiles. *Hepatology*. E-pub 2011.
Risk Factor Based Screening

• *Persons who have injected drugs*
• Persons with high prevalence conditions:
  – HIV
  – Hemophilia
  – Hemodialysis
  – Elevated transaminases
• Recipients of blood or organs prior to 1992
• Children born to HCV-infected mothers
• Healthcare workers with a needle stick
• Current sexual partners of HCV-infected persons
Treatment Rates in IDU

• Studies suggest very low rates of HCV treatment are low among current/former IDU (1-16%)\textsuperscript{1-3}

• Guidelines state that IDU is not an absolute contraindication to treatment

• Numerous barriers to treatment exist for IDU

## Barriers to HCV Treatment in IDU

<table>
<thead>
<tr>
<th>Individual barriers</th>
<th>Provider barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low patient motivation</td>
<td>Perceived non-adherence</td>
</tr>
<tr>
<td>Unstable lifestyle</td>
<td>Perceived risk of re-infection</td>
</tr>
<tr>
<td>Mod-severe depression</td>
<td>Knowledge of HCV</td>
</tr>
<tr>
<td>Active drug use</td>
<td>Environmental barriers</td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>No health insurance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>No physician</td>
</tr>
<tr>
<td>No transportation</td>
</tr>
</tbody>
</table>

Integration of Care for Substance Abuse and HCV

• Linking services for substance use and medical care may reduce barriers to treatment

• Study by Litwin, et al.
  – Provided HCV treatment on-site in methadone clinics in the Bronx, NY
    • 73 patients treated
    • 55% achieved ETR, 45% achieved SVR


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Treatment Outcomes for Opioid Dependent Patients/IDU

- Recent systematic review of HCV treatment in IDU:
  - 10 studies of IDU that included non-IDU comparison
  - Median rate of SVR among IDUs was 54.3% (range, 18.1%-94.1%)
    - Comparable to responses (54%-63%) in clinical trials
  - Only one small study restricted to active IDU, not informative

Additional Reasons to Screen for HCV if Not a Treatment Candidate

• Modify behaviors
  – Transmission risk behaviors
    • Sharing equipment/syringes, sexual behaviors
  – Behaviors that impact HCV progression
    • Alcohol, body weight, smoking
• Offer HCV related care
  – Immunizations for HAV and HBV
Awareness of HCV and Risk Behaviors

- Injecting drug practices
  - Studies suggest that HCV+ have more severe addiction, no consistent change in sharing practices with awareness\(^1\)-\(^4\)
- Alcohol
  - Some studies suggest awareness of HCV associated with less alcohol use\(^5\)-\(^7\)

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Awareness of HCV and Risk Behaviors

• “Risk behaviors after HCV seroconversion in young injection drug users in San Francisco”
  – Data from prospective study of young IDU
  – 112 participants seroconverted during study
  – Examined behaviors before/after seroconversion

## Awareness of HCV and Risk Behaviors

<table>
<thead>
<tr>
<th></th>
<th>Immediately After Seroconversion</th>
<th>6 months After Seroconversion</th>
<th>12 months After Seroconversion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Past Month Alcohol Use</td>
<td>0.52</td>
<td>0.27–1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Past Month Injection Drug Use</td>
<td>0.84</td>
<td>0.35–2.05</td>
<td>0.7</td>
</tr>
<tr>
<td>Past 3 Month Non-injection Drug Use</td>
<td>0.4</td>
<td>0.20–0.81</td>
<td>0.01</td>
</tr>
<tr>
<td>Past 3 Month Lending of Syringes</td>
<td>0.80</td>
<td>0.29–2.25</td>
<td>0.68</td>
</tr>
<tr>
<td>Past 3 Month Sharing of Injection Equipment</td>
<td>0.61</td>
<td>0.22–1.71</td>
<td>0.35</td>
</tr>
<tr>
<td>Past 3 Month Sex without Condom</td>
<td>1.65</td>
<td>0.77–3.58</td>
<td>0.2</td>
</tr>
<tr>
<td>Current Depression</td>
<td>0.76</td>
<td>0.23–2.53</td>
<td>0.65</td>
</tr>
</tbody>
</table>

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**Footnotes:**

* Adjusted for secular trends plus drug use, recent incarceration and homelessness; fixed covariates (age, sex, race, etc.), which represent between- rather than within-subject differences, have no influence in the conditional logistic model.

* OR for behavior immediately after seroconversion; model assumes change at seroconversion followed by linear trend.
Future Research Opportunities

- Interventions to prevent transmission (treatment as prevention?)
- Interventions to improve screening and linkage to care
- Improving systems for delivery of care/expanding access to care for HCV in IDU
- Monitoring/improving adherence in IDU
- Elucidating non-hepatic effects of HCV
- Finding an effective vaccine for HCV