TRIPLE E for HCV

Satellite Symposium Series
Engagement
Education
And
Eradication

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Provided by:
TRIPLE E for HCV

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Faculty Disclosures

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- **Speakers Bureau:** AbbVie and Salix Pharmaceuticals

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- **Consultant:** Abbott Diagnostics, AbbVie, Chronic Liver Disease Foundation, and Merck
- **Speakers Bureau:** Chronic Liver Disease Foundation
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AbbVie
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Educational Objectives

• Discuss data on the incidence, prevalence and transmission of HCV in persons who use drugs (PWUD)

• Describe the detrimental effects of chronic HCV, including the extrahepatic manifestations, to emphasize the need for diagnosis and treatment in PWUD

• Discuss updates in screening mandates and treatment guidelines for HCV including the importance of harm reduction and prevention of reinfection

• Propose that HCV elimination is possible now that many prior HCV treatment obstacles have been removed
Transmission, Epidemiology and Natural History of Hepatitis C
Hepatitis C by the Numbers

170 million people worldwide

#1 blood-borne infection in US

5.2 million people in US

0 indication for liver transplantation

0 cause of liver cancer in US

0 FDA-approved vaccines

Chak, Talal, Sherman, Schiff, & Saab. 2011.
Transmission and Liver Disease

- **Injection drug use** is the principle risk factor for transmission
- Spontaneous resolution of acute infection occurs in 15-25% cases
- **Chronic disease** develops in most patients and can lead to cirrhosis, liver cancer, liver failure, and death
- **Sustained Viral Response (SVR)** can be achieved in the majority of cases = cure!
Populations at Risk

Baby Boomers (born 1945-1965)

1960s
Up to 300,000 cases of acute HCV per year; risk of exposure via blood transfusion up to 33%

1970s
Volunteer donor system reduces risk of exposure via blood transfusion

1989
HCV discovered

1992
HCV Antigen introduces widespread introduction of HCV antibody testing

People Who Use Drugs (PWUD)

30-70% prevalence


Such expansion of HIV prevention services resulted in very large reductions in HIV incidence.
Reduction in HCV Transmission Among PWUD Has Been Lower Than HIV

- HCV easier to transmit than HIV
  - Less sharing is needed for transmission
  - Sharing of drug preparation equipment will transmit HCV
- Prevalence of HCV much higher in PWUD than HIV
Transmission Via Contact with Contaminated Blood: Needles and Syringes

Fixed

Detachable

Zibbell J. CDC. Presented as part of Hepatitis C Prevention Opportunities Among PWID, April 28, 2015.
Transmission Via Contact with Contaminated Blood: Needles and Syringes

Mean Volume of Fluid Retained with Plunger Depressed

**DETACHABLE Needle**
Low dead-space QD syringe

**FIXED Needle**
Low dead-space syringe

**HIGH dead-space syringe**

Zibbell J. CDC. Presented as part of Hepatitis C Prevention Opportunities Among PWID, April 28, 2015.
Transmission Via Contact with Contaminated Blood: Preparation Equipment

Filters

Cookers

Water

Surfaces

Zibbell J, CDC, Presented as part of Hepatitis C Prevention Opportunities Among PWID, April 28, 2015.
HCV Transmission

Bloody fingers

Fingers on cooker and in solution

Zibbell J, CDC, Presented as part of Hepatitis C Prevention Opportunities Among PWID, April 28, 2015.
Hepatitis C and Other Drugs: More Than Just Injecting

- HCV can be spread through straws and pipes!
- HCV in nasal drug users ranges from 2.3% to 35.3%
- HCV has been found on the stems of crack pipes
- USPSTF and AASLD/IDSA Guidance recommend screening for persons with history of intranasal drug use
- Consider HCV in people who smoke crack or crystal meth, especially if linked to sex ("chem-sex")

How Long Can HCV Survive on Inanimate Objects?

- **Syringe**: 64 days
- **Water container**: 21 days
- **Surface**: 21 days
- **Foil**: 3 days
- **Filter**: 1 day

HCV-contaminated solution needs to be heated for almost 90 seconds and reach temperatures of 144°F for the virus to be at undetectable levels.

Duration of Infection Drives Transmission Among PWUD

• Patients with chronic HCV infection are infectious until they are successfully treated

• To reduce viral transmission
  – Reduce number of contacts & probability of transmission per contact
    • Safe injection equipment
    • Regular testing within networks
  – Reduce duration that patient is infectious with HCV treatment
Likelihood of HCV Infection: Initiation and Duration of Injection Drug Use Matters

The Changing Face of Heroin Use in America

948,000¹ Americans reported heroin use in 2016

170,000¹ Americans started using heroin in 2016; nearly double the number of people than in 2006 (90,000)

US Overdose Deaths Involving Heroin: Number Among All Ages, 1999-2017²

Of the 1,118 acute HCV case reports that contained information about IDU, 68.6% (n=767) indicated use of injection drugs.

Impact of the US Opioid Epidemic:
Opioid Overdose Deaths Increased from 2016 to 2017

Opioids were involved in 70,237 deaths in 2017 and the age-adjusted rate of overdose deaths increased significantly by 9.6% from 2016 to 2017.

Red indicates statistically significant increases from 2016 to 2017.
Available at: https://www.cdc.gov/drugoverdose/data/statedeaths.html Accessed April 1, 2019
Increasing Deaths Due to Opioids


CDC: Reported Number of Acute HCV Cases: United States, 2001–2016

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS).
Acute Hepatitis C in the United States, 2016

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS).

*National goal: 0.25 cases/100,000 populations
Natural History of HCV

HCV Infection

Acute Infection, 20-30% with symptoms

Clearance of HCV RNA, 15%-25%

Fulminant Hepatitis, Rare

Chronic Infection, 75%-85%

Extrahepatic Manifestations

Chronic Active Hepatitis

Cirrhosis, 10%-20% over 20 years

Decompensated Cirrhosis, 5-year survival rate of 50%

HCC, 1%-4% per year

Chen & Morgan. 2006.
Chronic HCV Infection May Lead to Liver Disease and Liver Cancer

- ~75% of patients infected with HCV will develop a chronic infection
- 65% with chronic infection will develop chronic liver disease
The Future of Chronic Hepatitis C

- Burden of HCV liver disease expected to triple in next 10-15 years
- Prevalence of cirrhosis 45% by 2030
- HCV deaths doubled 1999-2007 to current > 17,000 (projected peak 35,000/yr)
- Economic burden > $10 billion per year

Impact of HCV on Survival

Mean Age at Death
NYC, 2000-2011

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Mean Age at Death (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infection</td>
<td>78</td>
</tr>
<tr>
<td>HCV mono-infection</td>
<td>59</td>
</tr>
<tr>
<td>HIV/HCV coinfection</td>
<td>52</td>
</tr>
</tbody>
</table>

Premature Death (<65 years old)
NYC, 2000-2011

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Premature Death, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infection</td>
<td>26</td>
</tr>
<tr>
<td>HCV mono-infection</td>
<td>67</td>
</tr>
<tr>
<td>HIV/HCV coinfection</td>
<td>94</td>
</tr>
</tbody>
</table>

- Time period covers ART introduction for PWUD in NYC
- Many of the HCV mono and co-infected patients die from causes other than HCV and HIV
Increasing Deaths Due to HCV

More people are dying of HCV than all 60 other nationally notifiable infectious diseases combined.

Source: Center for Disease Control and Prevention

Conclusions

- HCV transmission occurs mostly via contact with contaminated blood, but other routes also spread the virus (e.g. pipes, intranasal).
- HIV transmission reduction techniques resulted in decreased incidence; HCV is easier to transmit than HIV.
- HCV and opioid injection use are rising in parallel.
- HCV incidence is increasing, particularly in white females.
- Untreated chronic HCV increases morbidity and mortality.
- HCV care in PWUD is a significant issue that requires immediate attention.
HCV Screening, Diagnosis and Linkage to Care
Bottleneck in HCV Cascade to Cure: Screening and Linkage to Care Remain Low

- Only 50% of patients living with HCV are *aware*
- 5 to 9% of patients living with HCV are *cured*

EMR Prompt for HCV Antibody Test

Common EMR for large healthcare system, >5,000 clinicians and > 1.5 million patients

Beth Israel Deaconess Medical Center, Boston, MA, Quality Outcomes Data.
HCV Screening is Straightforward: Algorithm for Screening/Diagnosis of Asymptomatic Persons


Hepatitis C Screening Update

USPSTF Recommendations

1. HCV screening in persons at high risk of infection

2. 1-time HCV screening for adults born between 1945 and 1965 (B recommendation)

Is Reactive HCV Antibody Test a Diagnosis for Chronic HCV Infection?

- No! It’s a SCREENING test
- Some individuals become infected with HCV and then spontaneously clear the infection
- Approximately 15%-25% of individuals clear the virus without treatment and do not develop chronic infection
- HCV RNA (viral load) is required to confirm chronic infection

Recent/active IDU should *not* be seen as contraindication to HCV therapy\(^1\)

EASL
Treatment should be prioritized in those at risk of transmitting HCV *including* active PWUD\(^2\)

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Detection of HCV Infection Should Result in Linkage to Care

*For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Telemedicine-Based HCV Evaluation: An Example

Entry
- Two onsite patient education sessions
- HCV RNA +

Patient Evaluation

Study Flow
- HCV medications delivered to program
- HCV medications dispensed with methadone
- Electronic bill submission
- Discussion with physician assistant
- Documentation in electronic health record

Continuum of Care in PWUD

The continuum of care for PWUD in Philadelphia 2013-17

- HCV Ab(+)
- Ever Tested for HCV RNA
- HCV RNA (+)
- Initiated HCV Care*
- Treatment**

Younger (≤ 35) PWUD (N=1,239)
Older (> 35) PWUD (N=1,151)

Poor linkage to care and very low treatment rates, especially in younger PWUD

*In HCV Care= seeing a specialist or having another RNA > 180 days from 1st RNA result.
**Treatment= report that treatment initiated or the infection resolved.
Barriers Persist – Poor Access for Medicaid Patients in the US (Varies by State)

Impact of Care Coordination: Triple E Model

• CLDF designed a self-sustaining, comprehensive HCV education, screening and treatment model

• This program provided 4 important fundamentals to substance abuse centre sites:
  – Staff education
  – Patient education and counselling
  – Antibody (Ab) screening and secondary blood draw (if Ab positive)
  – Linkage to care: links patient directly hepatitis specialist (onsite or via telemedicine in areas where HCV providers are limited) and a CLDF healthcare provider for onsite counselling and management

Impact of Care Coordination: Triple E Model (cont’d)

- Patient screening and outcomes data
- 19 substance abuse centre sites involved

**Results***

<table>
<thead>
<tr>
<th></th>
<th>Ab Screened</th>
<th>Ab Positive</th>
<th>Blood Draw Completed (on Ab Positive Patients)</th>
<th>Linked to Care (Patients who had Blood Drawn)</th>
<th>HCV RNA Detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Pts</td>
<td>1475</td>
<td>658</td>
<td>531</td>
<td>384</td>
<td>369</td>
</tr>
</tbody>
</table>

*Data from March, 2017 - November, 2018
Impact of Care Coordination: Triple E Model (cont’d)

- HCV education, screening and effective linkage to care are necessary to effectively integrate these treatments into disease management.

- Broadening the Triple E model could result in recovery center-focused eradication of HCV.

Impact of Care Coordination

- RCT of patients attending ORT clinics in SF and NYC (N=489)
- Intervention arm received onsite screening, education, counseling, and case management
- 59% HCV seropositive
- Intervention arm
  - ↑ Linkage to care
  - 6 month follow up
  - OR 4.1 (2.35-7.17)

OR, odds ratio; RCT, randomized controlled trial.
Accessing the Drug Involved Population Beyond the Conventional Healthcare Setting

- Accessing drug-involved persons at venues where they habitually congregate or receive treatment can potentially overcome the:
  - Stigmatization associated with HCV and
  - Reluctance to seek care within a conventional health care setting

Conclusions

- HCV screening and diagnosis is straightforward
- Screening and linkage to care remain low in PWUD
- Even when PWUD test HCV seropositive, nearly half need better linkage to care
- Society guidelines *recommend* HCV treatment in PWUD
- HCV education, screening and effective linkage are necessary to provide treatment to PWUD
HCV Management and Treatment Update
Decrease in HCV-Related Mortality Coincides with the Introduction of Direct Acting Antivirals (DAA’s)

Direct-Acting Antivirals (DAA)

**NS3/4a protease:**
- simeprevir
- paritaprevir
- grazoprevir
- voxilaprevir
- glecaprevir

**NS5A replication complex:**
- ledipasvir
- ombitasvir
- daclatasvir
- velpatasvir

**NS5B polymerase:**
- sofosbuvir
- dasabuvir
- elbasvir
- pibrentasvir
Efficacy of Antiviral Therapy

Sustained Virologic Response (%)

- 5-19% (24 wks)
- 11-19% (48 wks)
- 10-22% (78 wks)
- 33-36% (IFN + RBV x 48 wks)
- 42-52% (PegIFN + RBV x 48 wks)
- 63-75% (BOC/TVR + PegIFN + RBV)
- 92-100% (DAA 2015-2017)
Baseline factors associated with all-cause mortality

- Older age
- GT 3 (2-fold increase in mortality and HCC)
- Higher fibrosis score
- Diabetes
- Severe alcohol use

10-yr Cumulate Occurrence Rates Among Patients with Cirrhosis (N=530)

- All-cause mortality
- Liver-related mortality or liver transplant
- HCC
- Liver failure

*Median follow-up 8.4 years.
Impact of Antiviral Therapy (cont’d)

- Large-scale VA observational cohort studies
- Survival benefit and deceased HCC risk even in patients without advanced liver disease

FIB-4 ≤3.25
No cirrhosis
No decomp
No HCC
No OLT

(n=103,346)

Direct-Acting Antiviral HCV Regimens

• Choice of regimen, treatment duration, and use of ribavirin depends on several factors
  – Presence/absence of cirrhosis
  – Prior treatment experience
  – Genotype (1-6)

• All oral, virtually no side effects, no interferon

• Methadone/buprenorphine/naloxone are safe to use during therapy
Effect of Opiates on the Liver

Heroin
- No hepatotoxicity
- Street heroin may be contaminated with toxic substances (e.g., lead)

Methadone
- No hepatotoxicity

Buprenorphine
- Elevated transaminases possible
- Anecdotal cases of liver failure

References:
HCV Treatment in PWUD

- Treatment has no impact on ORT or increased drug use
- Drug use within 6 months of HCV therapy does not affect response
- However, more frequent drug use decreases HCV treatment efficacy

Social functioning and attendance are better indicators of treatment outcome; independently associated with SVR after adjusting for drug use

HCV Treatment in PWUD is a Priority

- CO-STAR and real-world study results support DAA use in ORT patients
  - Including those with recent drug use
- Adherence and response in these patients is comparable to other HCV-infected populations
- Reducing HCV transmission means treating HCV in patients with recent (previous 6–12 months) or ongoing IDU
- Time from HCV infection to the development of cirrhosis among PWUD is 30–40 years; delaying treatment may prolong period of infectiousness and potential transmission
- International guidelines support the prioritization of HCV treatment among PWUD

ORT = Opioid Replacement Therapy
HCV Treatment and Drug Use

- Prospective RCT in patients with high HCV treatment adherence despite drug use

- ~60% of patients had positive urine test for ≥1 of 8 drug classes
  - Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, propoxyphene

- 6/18 (2%) with recurrent viremia had evidence of reinfection

**SVR12 Rates Among Patients with High HCV Treatment Adherence**

GT, genotype; RCT, randomized controlled trial.
HCV Treatment and ORT

- Patients on stable regimen of ORT
- Methadone vs. buprenorphine: No difference in antiviral efficacy, pharmacokinetics, no dose adjustments
- No difference in efficacy, adherence, adverse events vs. non-ORT

High SVR in PWUD Despite Imperfect Adherence

**Anchor Study:** Active IDU within 3 m treated with SOF/VEL x 12w

Adherence generally high but even missed doses and finishing late had little effect on SVR

HCV Treatment and ORT

• Post-hoc analyses focus on restricted PWUD populations
  – Small sample sizes, recent drug users were excluded\(^1\)

• However, these analyses provide important outcomes data\(^1\)

• Treatment of mild-to-moderate HCV in PWUD is more cost-effective than delaying treatment until cirrhosis develops\(^2\)

HCV Treatment in Patients *Not* Receiving ORT

- Patients with IDU history might *not* be receiving ORT, but *are* receiving HCV care
  - Treatment provided at hospital-based HCV clinics, drug treatment clinics, community health centers, and needle and syringe programs
- Real-world studies of DAA therapy in these patients demonstrate efficacy
  - 93–100% treatment completion
  - 80–96% SVR

Data on HCV Treatment in Patients Receiving and Not Receiving ORT: The ION Studies

- Stored blood samples tested for illicit drugs
  - 8% ($n = 70$) of samples showed illicit, non-cannabis drug use by participants during therapy
- SVR12 stratified by treatment duration for participants receiving and not receiving ORT
- Among people without drug use at the time of therapy initiation, subsequent illicit drug use during therapy did not have a major effect on SVR

Additional Data on HCV Treatment in Patients Not Receiving ORT:

- In a study of 174 participants with a history of IDU in the last year:\(^1\)
  - 63% cirrhosis, 37% treatment experienced, 58% genotype 1
  - 95% completed therapy
  - 93% achieved SVR
- Data strongly support DAA treatment in patients not on ORT with recent IDU\(^2\)
- More data needed on PWUD who are not on ORT\(^2\)

Improvements in Patient Reported Outcomes and Quality of Life in HCV-Treatment Patients with or without ORT

- 8450 patients enrolled in phase 3 clinical trials of sofosbuvir
- PRO instruments completed before, during, and after treatment
  - 4.8% (407) were receiving ORT
- At baseline, ORT recipients had significantly (P < .0001) lower PRO scores (by -3.5 to -15.6 on a 0-100 scale)

Clinical Trials on Patient Reported Outcomes during HCV Treatment

**A**

PROs for the General Population Infected with HCV

- Fatigue: 55% (IFN+RBV+DAA+ regimen), 39% (IFN-/RBV+/DAA+ regimen), 20% (IFN-/RBV-/DAA+ regimen)
- Psychiatric Disorders: 45% (IFN+RBV+DAA+ regimen), 45% (IFN-/RBV+/DAA+ regimen), 28% (IFN-/RBV-/DAA+ regimen)

**B**

PROs for Persons with Substance Use Disorders Who Are Receiving ORT

- Fatigue: 71% (IFN+RBV+DAA+ regimen), 43% (IFN-/RBV+/DAA+ regimen), 27% (IFN-/RBV-/DAA+ regimen)
- Psychiatric Disorders: 65% (IFN+RBV+DAA+ regimen), 22% (IFN-/RBV+/DAA+ regimen), 14% (IFN-/RBV-/DAA+ regimen)

References:

- Perumalswami PV, Talal AH. *J Infect Dis.* 2018;217:1020-1023
Improvements in Patient Reported Outcomes and Quality of Life in HCV-Treatment Patients with or without ORT (cont’d)

- SVR results in improved PROs for 12 consecutive weeks after HCV treatment cessation (SVR-12)
- PRO improvements are more dramatic in patients on IFN/RBV-free regimens
- DAAs may have more dramatic positive effects in patients receiving ORT (A) than in those not receiving ORT (B) when compared to older regimens

Reinfection – It Will Happen

- Drug use persisted after cure but remained stable
- Reinfection more common early after SVR

Part A: Through FW12

Part A: Through FW24

Part B: Through 36 months of follow-up

Reinfection rate among all persons* (N = 199):

10 reinfections | 564 person-years | 1.8 reinfections per 100 person-years (95% CI: 0.8, 3.3)

Reinfection rate among persons with reported injection drug use* (n = 80):

6 reinfections | 212 person-years | 2.8 reinfections per 100 person-years (95% CI: 1.0, 6.2)

Conclusions

• Promising new direct-acting antiviral drug regimens offer the possibility of eradication of HCV
• International guidelines support the prioritization of HCV treatment among PWUD
• Adherence and response in these patients is comparable to other HCV-infected populations
• Treatment has no impact on ORT or increased drug use
• Drug use within 6 months of HCV therapy does not affect response
• Broadening the treatment of HCV in PWUD will have an invaluable effect on public health
Conclusions
Specific Challenges Faced by PWUDs

- Stigmatization regarding diagnosis of HCV
- Poor knowledge and inaccurate perceptions about HCV infection, the long-term consequences and associated treatment
- Perceived low need for treatment
  - Absence of noticeable symptoms
  - Belief that HCV is a “benign disease”
- In many states, restrictions on HCV medication provisions still exist
- Variations in reimbursement for HCV therapy create challenges in expanding pool of treating providers

Overall Conclusions: The Need to Prioritize Treatment of PWUD

- Development of tolerable antiviral therapies have revolutionized HCV treatment, but “we are far from having won the war against the virus”

- HCV care among PWUD remains severely restricted, largely because of their inability to access appropriate HCV management

- More effective tools are needed to screen, diagnose and cure HCV-infected PWUDs
  - e.g. telehealth approaches, integrated care models, and point-of-care diagnostics

- The CDC, NIH and other federal and industrial partners have active research programs designed to engage HCV-infected persons with PWUDs into care

- Research gaps need to be addressed to eliminate HCV infection in this population

Panel Discussion/Q&A
Clinical Trials on Patient Reported Outcomes during HCV Treatment

A

PROs for the General Population Infected with HCV

B

PROs for Persons with Substance Use Disorders Who Are Receiving ORT

Panel Discussion/Q&A