Cases: Issues in Hepatitis C in Active or Recently Active Substance Abuse and Renal Failure

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Learning Objectives

After attending this presentation, learners will be able to:

▪ Describe special considerations for hepatitis C treatment for people with recent history of drug use
▪ Describe considerations for the treatment of hepatitis C for people with advanced chronic kidney disease

Off-Label Disclaimer

I will discuss the following off-label use in this presentation:
Treatment of acute HCV infection
Case

- 21 y/o woman with congenital ureteropelvic junction obstruction progresses to ESRD requiring dialysis by age 17. PMH also notable for ADHD, anemia, growth retardation. On waiting list for deceased donor renal transplant for 2 years. She presents with new HCV Ab seroconversion upon testing at dialysis center.
- Negative testing 1 year earlier
- Adherent to dialysis center visits
- Use of intermittent substances, including snorted cocaine and heroin
- Denies injection drugs, no new tattoos, no blood transfusions for over 10 years
- Testing shows: ALT 274 U/L, HCV RNA 35,000 IU/mL, genotype 3a
- HIV, syphilis negative, HBSAg negative, HBSAb negative

ARS Question 1

- 21 y/o woman with congenital UPJ obstruction progresses to ESRD requiring dialysis by age 17. PMH also notable for ADHD, anemia, growth retardation. On waiting list for deceased donor renal transplant for 2 years. She presents with new HCV Ab seroconversion upon testing at dialysis center. ALT 274 U/L, HCV RNA 35,000 IU/mL

What is the most likely scenario?

1. Chronic HCV (previous false negative antibody) with cocaine-related ischemic hepatitis
2. Chronic HCV (previous false negative antibody) with alcohol use
3. Acute HCV infection due to contaminated medical equipment
4. Acute HCV infection related to opioid drug use
5. Other
Outcomes of acute HCV

Factors associated with viral clearance

- Female
- Young age
- Race (non-African-American)
- Immunocompetence
- Jaundice
- Cell-mediated immunity
- Genes related to the immune system
  - Interleukin-28b (interferon-lambda)
Lab values may resemble chronic or cleared infection

Finding acute HCV requires a high clinical suspicion
Consider in any new diagnosis with risk factors or newly elevated transaminases
Many underreport or may not be aware of risk
History
– Ask about past testing of HCV.
– Specifics of injection drug use (or sexual risks for HIV+MSM)
– Duration of behaviors, paraphilia
– Systematic screening results in increased identification
Laboratory testing
– HCV RNA even if HCV Ab negative
– Repeat evaluations, seroconversions, viral fluctuations

ARS Question 2

• 21 y/o woman with new diagnosis of acute HCV

Should we treat her HCV now?
1. Yes
2. No, wait for spontaneous clearance
3. No, recent drug use means she will reinfect herself after treatment
Can treatment as prevention be applied for HCV among people who inject drugs (PWID)? Modeling DAAs
The number of people that one sick person will infect (on average) is called $R_0$. Here are the maximum $R_0$ values for a few viruses:

- smallpox: 2.7
- measles: 12.5
- influenza: 3.1

$R_0 = C \times P \times D$

- $C$ = # of contacts per unit of time
- $P$ = probability of transmission per contact with infectious person
- $D$ = duration that patient is infectious to others

Smaller or limited networks may decrease $C$

Clean injection equipment may decrease $P$

Behaviors that affect $C$ and/or $P$ amongst PWID cycle over time/locale.

Knowledge of infectious status may affect behaviors.

Ultimately, duration of infectiousness is a major barrier as most infected persons remain infectious without treatment.

Treat social networks

"Bring your friends"
What were the effects of de-restricting access to DAAs in the Netherlands?

- Late 2015: unrestricted access with very rapid uptake in Dutch HIV/HCV coinfection (~70% treated)
- No associated decrease in syphilis or LGV so behavior unlikely explanation
- Indirect evidence of “cure as prevention” for HCV

Rijnders et al. CROI Abstract 137LB

What were the effects of de-restricting access to DAAs in Iceland?

Prevalence of HCV viremia among PWID at Vogur Addiction Hospital 2010-2017 – recent iv use

Thorarinn Tyrfingsson et al. EASL 2018

Recommendations for Screening and Treatment of HCV Infection in People Who Inject Drugs (PWID)

**Recommendation for Screening**
- Annual HCV testing is recommended for PWID with no prior testing, or past negative testing and ongoing injection drug use. Depending on the risk of use, recent-negative testing may be advised.
- Substances use in PWID treatment programs and needle exchange programs should offer routine, annual HCV testing with T200 assay or immediate confirmatory HCV-RNA testing and linkage to care for those who are infected.

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**Recommendation for Treatment**
- PWID should be encouraged about measures to reduce the risk of HCV transmission to others.
- PWID should be offered linkage to therapy treatment services when available, including needle exchange services and substituting with buprenorphine treatment programs.
- Active or recent drug use or a screen for reinfection is at risk for retransplantation in HCV treatment.

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**Recommendation for Testing for Reinfection in People Who Inject Drugs (PWID)**
- At least annual HCV/RNA testing is recommended for PWID with recent injection drug use after they have spontaneously cleared HCV infection or have been successfully treated.
HCV is rising among reproductive-aged women and children in the U.S., 2006-2014

ARS Question 3

Patient is ready to treat, genotype 3a
Fibrosure is confounded, Fibroscan shows 4 kPa
What would be your choice of antiviral regimen?
1. Ledipasvir/sofosbuvir x 6 weeks
2. Ledipasvir/sofosbuvir x 12 weeks
3. Elbasvir/grazoprevir x 12 weeks
4. Glecaprevir / pibrentasvir x 8 weeks
5. Glecaprevir / pibrentasvir x 12 weeks
6. Sofosbuvir / velpatasvir x 12 weeks
7. Something else

Treatment of HCV

"It's the only treatment option he has under his current health plan."
Glecaprevir and pibrentasvir (G/P):
Renal Impairment

- GT 1-6 for 12 weeks
- Stage 4 or 5 CKD
- GFR<30 including HD
- TN or TE (42%) with IFN, P/R or SOF-P-R
- Including compensated cirrhosis (19%)
- GT1a 22%, GT1b 26%, GT2 16%, GT3 11%, GT4 19%, GT5 1, GT6 1

Gane et al. NEJM 2017

EBR/GZR - C-SURFER established safety and efficacy in patients with chronic kidney disease (CKD) stage 4/5

Treatment naive and experienced Mean age 56
-6% cirrhosis
Hypertension or diabetes were primary etiologies
Prior renal transplant n=17
SAE 14.4% in treatment
SAE 16.8% in deferred

Roth et al. Lancet 2015

Patients With CKD Stagea 4 or 5 (eGFR <30 mL/min or End-Stage Renal Disease)

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>GENOTYPE</th>
<th>DURATION</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of glecaprevir (50 mg)/pibrentasvir (150 mg)</td>
<td>1a, 1b, 4</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)</td>
<td>1, 2, 3, 4, 5, 6</td>
<td>8 to 16 weeks</td>
<td>I, B²</td>
</tr>
</tbody>
</table>

a Chronic kidney disease (CKD) stages: 1 = normal (GFR >90 mL/min/1.73 m²), 2 = mild (GFR 60-89 mL/min/1.73 m²), 3 = moderate (GFR 30-59 mL/min/1.73 m²), 4 = severe (GFR 15-29 mL/min/1.73 m²), 5 = ESRD (GFR <15 mL/min/1.73 m²)

b Patients in this group should be treated as mild patients without CKD. Duration of glecaprevir/pibrentasvir should be based on presence of cirrhosis and prior treatment experience. Please refer to appropriate sections for each treatment group.

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www.hcvguidelines.org | Last Updated: May 24, 2018
Direct-Acting Antiviral Prophylaxis in Kidney Transplantation From Hepatitis C Virus-Infected Donors to Noninfected Recipients

An Open-Label Nonrandomized Trial

Christine M. Durand, MD; Mary G. Boering, MPH; Glenn M. Brown, MD; Michael A. Cutlerberg, MD; Philip M. Kolakowski, MD; Michelle B. Ryan, MD; Sameer S. Khan, MD; William M.Ackerson, MD; Ron H. Rabin, MD; Robert H. Borello, MD; Paul G. Van Arkel, MD; David A. Vail, MD

Background: Given the high mortality rate for patients with end-stage kidney disease waiting on dialysis and the efficacy and safety of hepatitis C virus (HCV) treatments, deceased kidney donors with HCV-coinfected donors may be a neglected public health resource.

Objectives: To determine the feasibility and feasibility of using antiviral agents elvitegravir/cobicistat at posttransplant day 1 and after 12 weeks of treatment in HCV-infected recipients (n = 15, HCV D′ genotype) in this randomized trial. The primary outcomes were the incidence of adverse events related to HCV treatment and the proportion of recipients with an HCV RNA level below the lower limit of quantification 12 weeks after prophylaxis.

Results: Among 15 HCV D′ genotype recipients, no treatment-related adverse events occurred, and HCV RNA was undetectable in 14 of 15 recipients at 12 weeks after prophylaxis.

Limitations: Nonrandomized study design and a small number of patients.

Conclusion: The use of antiviral prophylaxis HCV treatment results.

Recommended Treatment for Patients With Acute HCV Infection

Recommended Regimens for Patients With Acute HCV Infection

What are exceptions to the waiting period for acute HCV?

- HCV transmission prevention
  - a surgeon
  - a person with ongoing intravenous drug use
  - an HIV-positive man who engages in sex with other men
- Mitigation of clinical consequences
  - a patient with cirrhosis who is acutely superinfected with HCV
- Reduction in the likelihood of loss to follow-up
  - a patient who may not be engaged in care in 3 to 6 months

www.hcvguidelines.org | Last Updated: May 24, 2018

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www.hcvguidelines.org | Last Updated: May 24, 2018

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## Clinical trials of acute HCV with DAAs, interferon-sparing

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
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</tbody>
</table>

### Can PWID be cured with novel HCV regimens?

**Original Research**

Elbasvir–Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy

*Annals of Internal Medicine*

Gregory J. Dore, MD; Fredrik B. Allin, MD; Alan P. Leung, MD; Glenn Delcogli, MD; Edward J. Gane, MD; Dave Elliott, MD; Anne E. Agur, MD; Michael Stedman, MD; Yue He, MD; Steven R. Sacktor, MD; Yrymichon, MD; David Solomon, MD; Guanping Ge, MD; David Wunderer, MD; Joseph Englebert, MD; Brent S. West, MD; Sherif van Eys, MD; Jionna Mar, MD; Elina Ber, MD; Michael R. Koster, MD; and Jonathan P. Elton, MD; on behalf of the NICE CSU COSTAR Study Group

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**C-EDGE COSTAR**

Treatment naive PWID on opiate agonist therapy for 3 months, keeping 80% of appointments

*Annals of Internal Medicine*

Gregory J. Dore, MD; Fredrik B. Allin, MD; Alan P. Leung, MD; Glenn Delcogli, MD; Edward J. Gane, MD; Dave Elliott, MD; Anne E. Agur, MD; Michael Stedman, MD; Yue He, MD; Steven R. Sacktor, MD; Yrymichon, MD; David Solomon, MD; Guanping Ge, MD; David Wunderer, MD; Joseph Englebert, MD; Brent S. West, MD; Sherif van Eys, MD; Jionna Mar, MD; Elina Ber, MD; Michael R. Koster, MD; and Jonathan P. Elton, MD; on behalf of the NICE CSU COSTAR Study Group
What is the rate of positive toxicology screens?

[Image of a graph showing urine drug screen results for two treatment phases.]


What was adherence in PWID?

[Image of a bar graph showing adherence among subjects in immediate and deferred treatment arms.]


HCV treatments are compatible with opioids and medication-assisted therapies

[Image of a table listing opioid substances and their compatibility with different HCV treatments.]

www.hep-druginteractions.org
HCV treatments are compatible with other drugs of abuse

<table>
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<th>SOF/VEL</th>
<th>PCD</th>
<th>GZ囚IR</th>
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<td>Monitor*</td>
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<td>Monitor*</td>
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<td>Monitor*</td>
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<td>Use lowest dose</td>
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<td>✓</td>
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</tbody>
</table>

Data courtesy of James Mackintosh, University of Liverpool. [www.mackintoshlab.org]

Numerous studies show compatibility of HCV medications with methadone and buprenorphine

Integrated analysis across phase III ION studies (ledipasvir/sofosbuvir) showed no decrement in SVR

Naltrexone

No changes in dosing for mild-to-moderate hepatic impairment

Early studies associated naltrexone use with hepatotoxicity; however, many patients had other reasons for transaminase elevations, such as HCV

Later studies have suggested safety; warnings about hepatotoxicity were removed from label

Generally, advise choosing MAT independent of HCV and liver status (except decompensated cirrhosis)


HCV and medication-assisted therapies

Case

- 23 y/o woman with acute HCV infection
- Genotype 3 infection, HCV RNA doesn’t clear
- She initiates therapy with G/P

What other counseling measures are important?

Liver health
Reinfection
Other associated risks
Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs

High coverage NSP + OST results in 74% incidence reduction

Contrasts in opioid abuse services

Netherlands pop 16.8 million
Massachusetts pop 6.75 million
Indiana pop 6.6 million

Amsterdam: Universal access to methadone & NEP

39 methadone programs opioid overdose
2x national average

13 methadone programs in Illinois was from 3,464 in 1998 to 14,089 in 2011 to 15,000 in 2014
58% were between 18 and 34 years old, 44% women compared to just 20% women a decade ago.

Center for Health Information and Access, Access to substance use disorder treatment in Massachusetts, April 2005.


Center for Health Policy, IUPUI. Opioid Treatment Programs in Indiana – The Use of Medication in Addiction Treatment, January 2013.

OST associated with 50% incidence reduction
Outbreaks of other viruses:
HAV, HBV, HIV

HAV  
HIV  
HBV  
HAV

PWID are at risk for re-infection for HCV and other infections

- Preventive measures:
  - Parenteral exposures
  - Clean needles, syringes, cookers, cottons, water
  - Opiate agonist therapy may be protective
  - Safe tattoos
  - Sexual transmission
  - HAV & HBV immunization
  - Prevention of skin, soft tissue infections, endocarditis
  - Especially young men, watch for use of anabolic steroids

Reinfection incidence in PWID following SVR

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>SVR</th>
<th>Treatment</th>
<th># reinfection</th>
<th>Incidence reinfection</th>
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<tr>
<td>Martinello et al</td>
<td>Curr HIV/AIDS Rep 2017</td>
<td></td>
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</tbody>
</table>

- Deve 2014  
- Wdlaus 2014  
- Rhee 2016  
- Fouchier 2015  
- Centers 2015  
- Stengel 2015  
- Deve 2016  
- Lee 2016  
- Mavroudis 2017  

- Parenteral exposures
- Clean needles, syringes, cookers, cottons, water
- Opiate agonist therapy may be protective
- Safe tattoos
- Sexual transmission
- HAV & HBV immunization
- Prevention of skin, soft tissue infections, endocarditis
- Especially young men, watch for use of anabolic steroids
What were re-infection rates in CO-STAR?

**INCREASED RISK OF REINFECTION BASED ON REPORTED INJECTION DRUG USE DURING FOLLOW-UP**

- 59 participants (72%) reported injection drug use
- 139 participants (88%) reported HB injection drug use

**Rate of re-infection:**
- 0.2 reinfections/100 person-years
- 0.6 reinfections/100 person-years

3 of 10 re-infections cleared viremia spontaneously

*Dore et al. AASLD 2017*

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**“Toolbox” for HCV prevention for PWID**

**Before exposure**
- HCV testing and counseling
- Drug treatment
- Reducing transmission from positive partners
- Vaccine

**Point of transmission**
- Change injecting behavior
- Clean injecting equipment
  - Syringes/needles
  - “extras”
  - Safe injecting locations

**After exposure**
- Viral titer testing
- Antiviral treatment

*Adapted from Kim Page, UNM*

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**Restrictions often specifically exclude PWID**

*Comparing 2014 & 2016 Medicaid FFS Sobriety Requirements*
Co-localization of HCV care

- HIV/HCV co-infection clinics
- Integrated primary care/ SUD / HCV/HIV/STD care
- Training PCPs and SUD providers to treat HCV
- Training specialists that treat HCV regarding SUD
- ECHO models
- ? mobile clinics

What physicians/providers can do

- Diagnosis and testing
- Screening for other infections
- Counseling about risk reduction, transmission
- Provide treatment
- Provide culturally competent care
- Don’t let your clinic be the barrier!
- Build teams: enlist peers, other providers
- Advocate for harm reduction & derestricting access to DAAs

Conclusions and recommendations regarding HCV and PWID

- In 2018, HCV can be prevented, diagnosed, and cured for PWID
- To achieve elimination, we must:
  - Reduce silence by increasing testing and knowledge of HCV
  - Reduce stigma
  - Address substance use
  - Build structures that enhance access to comprehensive care
  - Prevent new cases, via harm reduction, medication assisted therapies, development of vaccine
  - Remove counterproductive restrictions to treatment based on lack of evidence, cost-containment, and discrimination
- People: Enlist patients, peers, providers, policymakers
<table>
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<th>Question-and-Answer</th>
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<td>Remember to raise your hand and wait until you have the microphone before you ask your question—we are recording!</td>
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