Eradicating HCV: Opportunities and Challenges

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Project inform

Disclosures and a Confession

Disclosure

I have no financial relationships to disclose
and
I will not discuss off label use and/or investigational use in my presentation

FULL DISCLOSURE

I’m no Val Robb, you’re regularly scheduled speaker!
Project Inform fights the HIV & hepatitis C epidemics by assuring the development of effective treatments and a cure; supporting individuals to make informed choices about their health; advocating for quality, affordable health care; and promoting medical strategies that prevent new infections.

Overview

• Background
• Eradicating HCV Plans
• Sexual Transmission of HCV in HIV-Positive Gay Men
• Substance Use and HCV
• HCV Re-infection

Selecting therapy
  – Treatment by Genotype
  – Special populations

• Drug procurement
HIV Gardner Cascade

Overall: 3.2 million of U.S. population with chronic HCV

Diagnosed 66%
Linked to Care 37%
Referred to Care 33%
Treated 25%
Successfully Treated 5%

Diagnosed 50% (1.6M)
Referred to Care 32-38% (1.0-1.2M)
Treated 7-11% (220,000-360,000)
Successfully Treated 5-6% (170,000-200,000)

Treatment Cascade for Chronic Hepatitis C Virus Infection in the United States: A Systematic Review and Meta-Analysis

Note: only non-VA studies are included in the above HCV treatment cascade.
14,291 HIV+ patients

7343 ever tested for HCV

1293 (17.3%) HCV+

563 referred for HCV Treatment evaluation (44%)

159 received treatment (28%)

16 cured (2.8% of those referred, 1.2% of with known HCV, likely 0.007% of the total HIV/HCV coinfected patients)

HCV is underdiagnosed & undertreated

Deeb et al, CROI 2012 #751

USPSTF HCV Screening Recommendations

• All baby-boomers (born between 1945-1965) should receive a one-time screening for HCV;
• Persons who inject or have ever injected drugs (including those who may have injected only once);
• Persons who received a blood transfusion, blood products or an organ transplant before 1992;
• Persons who have been on long-term hemodialysis;
• Persons born to an HCV-infected mother;
• Persons who are incarcerated or have a history of incarceration;
• Persons who use (or used) non-injectable, intranasal drugs
• Persons who received an unregulated tattoo;
• Persons with HIV
Screening Recs: Whats missing?

• People who use non-injectable, smokable drugs (sharing crack or crystal meth pipes)

• People who are at risk of sexual transmission

• More specific sexual practices:
  – Fisting
  – Sharing of sex toys
  – Multiple partners
  – Group sex
  – BDSM

HCV Screening in HIV-Infected MSM

• HCV screen upon entry to care;

• Routine monitoring of liver function tests to identify acute HCV infection

• Routine screening (an undefined intervals)

• HCV testing upon diagnosis of an STD

  • Source: CDC 2010 Sexually Transmitted Diseases Treatment Guidelines
Baseline Tests

HCV Disease Progression

- In 10-25% of people with chronic HCV, the disease progresses over 10-40 years.
  - May lead to serious liver damage, cirrhosis, and/or liver cancer.
  - Among people with chronic HCV, 1-5% may die from the disease.
  - HCV is the leading indication for liver transplants.
Overall, sexual transmission accounts for a low number of HCV infections, particularly in HIV-negative persons (Klevens, et al CID 2012).

- One meta-analysis of HIV-negative, heterosexual HCV serodiscordant couples found no sexual transmission in over 9000 person-years and an estimated 750,000 vaginal or anal sex encounters (Thome, et al Hepatol 2010).

- Rates of HCV in HIV-negative MSM are also found to be low, comparable to the heterosexuals of the same status (Yaphe, et al Sex Transm Infect 2012).
HCV Rates in HIV-Negative vs. HIV-Positive MSM

<table>
<thead>
<tr>
<th>Citation</th>
<th>Country</th>
<th>Population</th>
<th>Sample Size</th>
<th>HCV Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin, et al. 2010</td>
<td>Australia</td>
<td>HIV Negative, HIV Positive</td>
<td>1398</td>
<td>1.07% - 9.39%</td>
</tr>
<tr>
<td>Alary, et al. 2005</td>
<td>Canada</td>
<td>HIV Negative</td>
<td>1095</td>
<td>2.9%</td>
</tr>
<tr>
<td>Buffington, et al 2007</td>
<td>United States</td>
<td>HIV Negative, non-PWID</td>
<td>1699</td>
<td>1.5%</td>
</tr>
<tr>
<td>Price, et al. 2013</td>
<td>England</td>
<td>HIV Negative, HIV Positive</td>
<td>953</td>
<td>1.2% - 7.7%</td>
</tr>
<tr>
<td>Schmidt, et al. 2014</td>
<td>Switzerland</td>
<td>HIV Negative, HIV Positive</td>
<td>821</td>
<td>0.38% - 21.1%</td>
</tr>
</tbody>
</table>

Sexual Transmission of HCV: HIV Infection as Syndemic

- Swiss HIV Cohort Study: HCV decreased in PWIDs, remained stable in heterosexual, but increased 18-fold from 1998-2011 (Wandeler, CID 2012)
- Rates of HCV in the United Kingdom have increased 20% each year since 2002 (Thome, et al, Hepatology 2010)
- Studies in France, Amsterdam, and Australia show similar patterns.
- Review of 74 HIV-positive MSM (no injection drug use among them) in New York City from 2005-2010 found clustering of 5 different sexual networks (MMWR, July 22, 2011)
Sexual Transmission of HCV: Additional Risk Factors

- Multiple partners
- Serosorting
- Anal fisting
- Vigorous sex toy play
- Genital ulcerative STDs (herpes, primary syphilis, LGV)
- HPV
- Use of non-injection drugs with sex

Sexual Transmission of HCV: A Summary Quote

“There is a need for specific public health interventions targeting HIV-positive gay men, which address the heightened risk of HCV transmission within their sexual networks. Sexual transmission of HCV seems to occur when HCV-contaminated blood is passed on in a context of situationally-increased HCV prevalence (group sex in HIV-positive gay sexual networks), and mucosal integrity is disrupted due to inflammatory or ulcerative STIs and/or prolonged (PDE-5 inhibitors) or traumatizing genito-anal contacts. This risk is heightened in a setting of fisting and sexually-induced anal haemorrhage, particularly following anorectal surgical interventions... The evidence suggests that public health messages addressing sexual HCV transmission among gay men should focus on the avoidance of sexual or sex-associates exposure to blood rather than seminal fluid. Prevention efforts are needed to communicate sexual or sex-associated routes of transmission for HCV that may not be addressed by messages that focus on the use of condoms.”

The Exceptional Virulence of HCV

- HCV can survive in syringes for up to 63 days (Paintsil E, JID 2010)
- HCV can survive on surfaces for up to 16 days; perhaps longer (Doerrbecker J, JID 2013)
- HCV can survive in water for up to 21 days; certain containers—plastic bottles and aluminum cans—can re-infect fresh water even after cleaning (Doerrbecker J, JID 2013)
- HCV can survive in a cotton filter for 24 hours; 48 hours if wrapped in cotton (Thibault V, JID 2011)
- HCV has been detected in all manner of drug using equipment: cookers, cotton, water, filters, even alcohol wipes (Thibault V, JID 2011)
HCV in People who Use Non-Injection Drugs

• One review of 28 studies of NIDUs (snort or smoke heroin, crack, cocaine or methamphetamine) found prevalence rates ranging from 2.3% to 35.3% (Scheinmann, et al Drug Alcohol Depend 2007)
  – Some limitations, but still high rates

• A review of NIDUs in San Francisco found a prevalence rate of 17% (Hermanstyne, et al, J Public Health 2012)
  – May be undisclosed IDU behavior and/or other risk factors

• Introduction of crack pipe distribution programs in Vancouver, CA led to reductions in HCV incidence over time (Source unknown)

HCV Re-Infection in PWIDs and HIV Positive MSM

• Re-infection of HCV is a commonly misunderstand or even unknown amongst both patients and providers

• Small studies have shown relatively low rates of re-infection among PWIDs

• HIV positive MSM have shown higher rates of HCV-reinfection post-treatment

• Guidelines for screening for re-infection are varied and no clear standard exists
Re-Infection of HCV

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Number of Patients</th>
<th>5-Year Recurrence Rate</th>
<th>Rate per 100 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Mono-Infected, low risk</td>
<td>9419</td>
<td>1.14%</td>
<td>0.23 per 100 person years</td>
</tr>
<tr>
<td>HCV Mono-Infected, high risk</td>
<td>819</td>
<td>13.22%</td>
<td>2.80 per 100 person years</td>
</tr>
<tr>
<td>HIV/HCV Co-Infected</td>
<td>833</td>
<td>21.72%</td>
<td>4.78 per 100 person years</td>
</tr>
</tbody>
</table>

Patient Education Resources: For Patient and Provider

- [http://www.hcvadvocate.org](http://www.hcvadvocate.org)
- [http://www.projectinform.org/](http://www.projectinform.org/)
- **877-HELP-4-HEP** (877-435-7443, hepatitis C helpline, [www.help4hep.org](http://www.help4hep.org))
Curing HCV: The SFGH W86 Model

- Vigorous Screening and Education
- Using EMR to identify HCV viremic and cirrhotic patients
- Working with team based care to prioritize and treat
- 450 patients = elimination possible in 4-5 years
- Staff capacity and procurement become key

Treatment Regimens
HCV Treatments: Let's Start with Pegylated Interferon

Nope, let's not!

• We are in the interferon-free, direct acting antiviral (DAA) era!

• We have several options for all HCV genotypes for both HCV mono-infected and HIV/HCV co-infected persons.

• And we will have several more in the next two years
All Oral DAA Treatment: Available Now

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir (SOF) + ribavirin (RBV)</td>
<td>Sovaldi + (several brand names)</td>
</tr>
<tr>
<td>Sofosbuvir (SOF) + simeprevir (SMV)</td>
<td>Sovaldi + Olysio</td>
</tr>
<tr>
<td>Sofosbuvir (SOF) + ledipasvir (LDV)</td>
<td>Harvoni</td>
</tr>
<tr>
<td>Paritaprevir (PTV)/ritonavir (RTV) + dasabuvir (DSV) + ombitasvir (OMV) with/without ribavirin</td>
<td>Viekira Pack</td>
</tr>
</tbody>
</table>

HCV Drugs No Longer Recommended

- Pegylated interferon
- Telaprevir (Incivek): No longer sold in the U.S.
- Boceprevir (Victrelis)
Interferon Free Options Mean

- Greatly expanded pool of treatment eligible patients
- Paradigm shift to considering treatment in all
- Prioritizing treatment
  - Cirrhotic patients
  - MSM with numerous sexual partners?
  - People who inject drugs (PWIDs) for cure as prevention?
  - Highly motivated
  - EVERYBODY!!! (I wish!)

Ribavirin

- Generally weight based when given with DAA regimens
  - 1000 mg if < 75 kg, 1200 mg if > 75 mg, divided BID
- Side effects:
  - Hemolytic anemia
  - Teratogen, including for men
  - Rash
  - Insomnia
Genotype 1: Options

Patient is genotype 1, is treatment naive, and has no cirrhosis...What should she take?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Length of Treatment</th>
<th>Clinical Trial SVR Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvoni (HCV viral load, less than 6 million)</td>
<td>8 weeks</td>
<td>97%</td>
</tr>
<tr>
<td>Harvoni (HCV viral load, greater than 6 million)</td>
<td>12 weeks</td>
<td>95%</td>
</tr>
<tr>
<td>Viekira Pak (genotype 1a) + ribavirin</td>
<td>12 weeks</td>
<td>97%</td>
</tr>
<tr>
<td>Viekira Pak (genotype 1b)</td>
<td>12 weeks</td>
<td>99.5%</td>
</tr>
<tr>
<td>Sovaldi + Olysio</td>
<td>12 weeks</td>
<td>95%</td>
</tr>
</tbody>
</table>
Sofosbuvir/Ledipasivir

**Figure 2. Efficacy Summary (ITT)**

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<td>12 weeks</td>
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<tr>
<td>Viekira Pak + Ribavirin</td>
<td>12 weeks</td>
<td>94%</td>
</tr>
<tr>
<td>Sovaldi + Olysio</td>
<td>24 weeks</td>
<td>100%</td>
</tr>
</tbody>
</table>

- 97% (1885/1952) overall SVR rate
- 3% (67/1952) did not achieve SVR
  - 1.8% (36) relapsed
  - 1.2% (23) lost to follow-up
  - 0.3% (9) withdrew consent
  - 0.1% (2) virologic breakthrough (both due to non-adherence)

Sulkowski IAS 2014

Patient is genotype 1, is treatment naive, and has cirrhosis...What should he take?
SOF/LED Retreatment in Compensated Cirrhosis

- Compensated cirrhotics enrolled in Phase 2/3 Gilead SOF/LED trials
  - *Need to add RBV or extend therapy to 24 weeks for treatment experienced*

Patient is HIV/HCV coinfection and is genotype 1...What should he take?
HIV/HCV Coinfection: Other Options

- All regimens can be taken in HIV/HCV coinfected
- Very similar response rates as HCV mono-infected
- Sovaldi and Viekira are FDA approved;
- Olysio and Harvoni are not FDA approved, but have been studied in coinfected patients; off-label prescribing is possible
- Must be mindful of drug-drug interactions

Patient is genotype 2...What should she take?

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Prior treatment*</th>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cirrhotic</td>
<td>Naïve or Experienced</td>
<td>Sofosbuvir + Ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>Treatment naive</td>
<td>Sofosbuvir + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced</td>
<td>Sofosbuvir + RBV</td>
<td>12-16 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sofosbuvir + PEG/RBV</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

- Not active: ledipasivir, simeprevir, Viekira Pak
Genotype 3
“3 is the new 1”

Patient is genotype 3...
What should he take?

• Limited current treatment options- better coming soon
• Ledipasvir- limited activity in GT3, not FDA approved

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td><em>Alternative:</em> Sofosbuvir + PEG/RBV</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>
GT3: Limitations of SOF/RBV

GT 3 patients

- SOF/Ribavirin x 24 weeks reasonable for treatment naïve patients (including cirrhotics)

- Consider SOF/PEG/RBV for Treatment experienced if Interferon eligible

- EASL, 2015: BOSON trial found high SVR rates with SOF/PEG/RBV (overall 93%, with high rates for both Tx experienced and cirrhotics)
Coming options for GT3: Daclatasvir

- Daclatasvir: NS5a inhibitor
  - ALLY-3: SOF+ Daclatasvir x 12 weeks
  - Response in cirrhotics still suboptimal

Web Resources

- HCV drug-drug interactions: [www.hep-druginteractions.org](http://www.hep-druginteractions.org)
- HIV drug-drug interactions: [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
- HCV drug-drug interaction tables and news: [http://hcvdruginfo.ca/](http://hcvdruginfo.ca/)

Package inserts

"How do you get the %$!@ medications?!"

Making insurance work

- Specialty pharmacies can be useful to do the leg work
- Identifying a point person who is familiar with the requirements and process
- Advocacy to ensure insurers are actually adhering to their stated guidelines
- California:
  - Project Inform [www.projectinform.org](http://www.projectinform.org)
  - Consumer Health Alliance: [1-855-693-7285](tel:1-855-693-7285), Bay Area legal Aid, Medical issues
Restrictions

• Many insurance programs restrict to cirrhotics & those with narrow definition of HCV complications

• California Department Health Care Services
  – Advanced Fibrosis or extrahepatic manifestations (narrowly defined), PLUS
  – Depression screen & treatment
  – Urine Tox screen and substance abuse treatment
  – Treatment/consultation with HCV “expert”
  – No allowance made for MSM, HIV-coinfection, HCV+ women seeking pregnancy
  
http://www.dhcs.ca.gov/Pages/HepatitisC.aspx

Alternatives to Insurance:
Patient Assistance programs

• Gilead (sofosbuvir, ledipasvir): 855-769-7284
  http://www.mysupportpath.com/
  – Income < 500% federal poverty level (≈ $58K/s
  – appeal is possible)

  – maximum household income of $100,000 for up to a family of three, and 500 percent of federal poverty level for families of four or more

• Requires documentation of rejection by insurance (if applicable)- TWO denials
  – Time consuming- establish point person & process
  – Do Patient Assistance paperwork at same time as PA

• Ribavirin can be difficult to obtain
Alternatives to Insurance (2)

- **ADAP**: Varies by state
- California ADAP covers simeprevir & sofosbuvir, likely will cover sof/ledipasvir
  - Restricted to advanced fibrosis
  - Does not cover patients who are not eligible for ADAP, i.e., have insurance that won’t cover HCV treatment
- **Studies**: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Hard Lessons Learned

- **Tracking dates** (application, initial denial, appeal submission date, denial received, patient assistance application, meds)
- Pt education about process and timeline depending on insurance
- Establishing a connection, understanding process for each insurer & patient assistance program

PATIENCE AND PERSISTANCE!
Summary

• Well tolerated, effective regimens available NOW for majority of patients including hardest to treat populations

• Drug-drug interactions are key when treating the HIV-HCV population

• Drug access remains challenging but can be done

• Pricing and access should improve with approval of new regimens

• HIV providers will be critical in ensuring HIV-HCV patients get access to HCV cure
HCV Testing and Sexual Transmission Awareness for HIV-Infected MSM

Examples of other PI Projects
The End

- Thanks to Emalie Huriaux for few of her slides
- Thanks to Val Robb for giving me her slide deck for today
- Thanks to Alice Asher for reviewing some content

For further discussion, please contact me anytime:
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We can meet over coffee...which it just so happens, is great for the liver!