Hepatitis C and HIV Coinfection:

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Disclosures and Caveats

• I will discuss investigational agents for hepatitis C (HCV) therapy.
• I will discuss off-label use of telaprevir, boceprevir, and simeprevir in HIV-HCV coinfectected patients.
• I have no financial disclosures.
Objectives

1. Discuss the epidemiology, clinical impact, and risk factors for Hepatitis C (HCV) and HIV-HCV coinfection.

2. Discuss the key issues when considering HCV therapy.

3. Describe current and future HCV therapies as well as their side effects, efficacy, and drug-drug interactions.
Outline

• The Why
  – Why is HCV monoinfection and HIV-HCV coinfection important?

• The Who
  – Who are the patients that are HIV-HCV coinfected?

• The When
  – When should we initiate HCV therapy?

• The How
  – How should we treat HCV and HIV-HCV coinfection in 2014?
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HCV Impact Globally

185 million people infected with HCV globally.

HCV is a major contributor to cirrhosis and liver cancer (the 12th and 16th leading causes of death worldwide).

HCV in the USA

Estimates range from **3.2-5.2 million cases in the USA.**

HCV vs. HIV Impact in the USA

*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.

High HCV prevalence in PLWHA (approximately 15-30%).
Associated with increased all-cause mortality and liver-related mortality.
No improvement in mortality since early cART era in HIV-HCV coinfection.
Why Should We Treat HCV Monoinfection?

Van der Meer AJ et al. JAMA 2012.
Why Should We Treat HIV-HCV Coinfection?

Figure 2. Probability of remaining free of a hepatic decompensation according to hepatitis C virus response to pegylated interferon plus ribavirin treatment. Abbreviation: SVR, sustained virologic response.

Figure 3. Probability of remaining free of death from any cause according to response to hepatitis C virus therapy. Abbreviation: SVR, sustained virologic response.
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People with HIV-HCV Coinfection

• Former or current long-term IVDU
  – HCV infection increasing in young suburban heroin IVDU who often initially use oral prescription opioid drugs.

• MSM
  – Clear increases in prevalence in HIV cohorts.
  – In the Swiss HIV Cohort study, the incidence rates among MSM increased from 0.23 in 1998 to 4.09 in 2011 (an 18-fold increase).

• Blood products prior to 1992 (i.e. hemophiliacs)
• Vertical transmission from coinfected mothers
Challenges of Treating HCV

- Medical comorbidities (including HIV)
- Substance abuse
- Alcohol abuse
- Mental health conditions
- Social circumstances
- Financial circumstances
- Contraindications to interferon (IFN)
  - Present in 71.6-81.6% in HIV-HCV coinfectected patients at academic and VA centers.
Fig. 1. Flow diagram. Of 845 HIV/hepatitis C virus (HCV) co-infected patients in regular care (at least one visit per year for at least 2 years), 277 were referred by their HIV provider for HCV care. Of those referred, 185 completed at least one appointment. A total of 125 had a complete pre-treatment evaluation of whom 29 initiated treatment and six achieved a sustained virologic response.
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A Patient to Ponder

• A 55 y/o man returns to your HIV clinic for follow up.
  – **MSM** now with a single monogamous partner.
  – History of **IVDU** (cocaine) in 1980’s.
  – History of **depression** and **bipolar disorder**, stable on medication therapy.
  – Diagnosed with **HCV** in 1998. **Genotype 1a** and **VL >1,000,000**.
  – **Previously treated** with pegylated interferon and ribavirin but relapsed after completing therapy.
  – Liver biopsy in 2010 revealed **F3 fibrosis**.

• The patient asks about treatment...
What to Consider When Starting HCV Therapy

• **Efficacy of Therapy**
  – HCV genotype
  – Prior response
  – Fibrosis/Stage of Liver Disease

• **Therapy-Related Issues**
  – Adverse effects
  – Drug-drug interactions

• **Access**
  – Insurance vs. Drug assistance program
  – Hepatology support available

• **Patient Specific Factors**
  – Willingness
  – Readiness (i.e. ETOH use)
  – Comorbidities (i.e. mental health, HIV)
  – Risk of reinfection (based on risk factors)

• **Risk-Benefit**
  – Benefits of SVR
  – Risk of decompensation
Fibrosis and Cirrhosis in HIV-HCV Coinfection

• Fibrosis and cirrhosis develop more quickly in HIV-HCV coinfected patients.
  – HIV is independently associated with advanced liver fibrosis and cirrhosis in HCV patients.
  – In one study, persons with HIV-HCV coinfection had liver fibrosis stages similar to persons with HCV monoinfection a decade older.

• Rare but severe cases of rapid decline to ESLD in patients with recent HCV infection have been reported.

• In sum, more aggressive treatment may be appropriate in patients with HIV-HCV coinfection.

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The History of HCV Treatment: The Bad, The Ugly, and The Good (?)

• HCV identified as the cause of non-A, non-B hepatitis in 1989.
• Early therapies had poor efficacy and poor tolerability:
  – Interferon (IFN) in 1986
  – Ribavirin (RBV) in 1998
  – Pegylated interferon (PEG-IFN) in 2001
  – PEG-IFN + RBV (P/R) in 2002
• The addition of telaprevir and boceprevir in 2011 improved efficacy at the expense of additional adverse effects and cost.
• Future therapies may continue to improve efficacy with fewer adverse effects (although with substantial cost).
Treatment Response in DAA Era

HCV Monoinfection SVR

- IFN
- pegIFN
- IFN+RBV
- P/R
- TPV/BOC+P/R
- DAA+P/R
- DAA+/.-RBV

HIV-HCV Coinfection SVR

- IFN
- pegIFN
- IFN+RBV
- P/R
- TPV/BOC+P/R
- DAA+P/R
- DAA+/.-RBV
The HCV Pipeline

**Approved Therapies**
- Interferon
- Ribavirin
- Pegylated Interferon
- Telaprevir
- Boceprevir
- Simeprevir
- Sofosbuvir

**Future Protease Inhibitors**
- Faldaprevir
- Asunaprevir
- ABT-450/r
- Vaniprevir
- Narlaprevir
- Danoprevir
- MK-5172
- Savoprevir
- Vedroprevir
- ACH-2684

**Future NS5A Inhibitors**
- Daclatasvir
- Ledipasvir
- ABT-267
- GS-5816
- MK-8742
- ACH-3102
- SCY-635

**Future Polymerase Inhibitors**
- ABT-333
- BI-207127
- Mericitabine
- BMS-791325
- GS-9669
- VX-222
- VX-135
- IDX719
- Tegobuvir
- Setrobuvir

**Future Other Therapies**
- IFN-lambda
- Miravirsen
- GS-9620
- TT-034
- Silibinin
- Alisporivir
HCV Definitions and Viral Kinetics

- **PegIFN/RBV/DAA**
- **Null response**
- **Partial response**
- **Virologic breakthrough**
- **Relapse**
- **2 log decline**
- **LOD**
- **SVR**

**RVR** = rapid response

**EVR** = early response

**eRVR** = extended rapid response

Standard of Care for HIV-HCV Coinfection in 2013

• HCV Genotype 1
  – Telaprevir (TPV) + P/R for 12 weeks, followed by P/R for 36 weeks
    • With addition of TPV, SVR rates improved from 45% to 74%.
  – P/R for 4 weeks, followed by Boceprevir (BOC) + P/R for 44 weeks
    • With addition of BOC, SVR rates improved from 29% to 63%.

• HCV Genotype 2/3
  – P/R for 48 weeks

Real World Experience with (TPV or BOC) + P/R

• In clinical practice, patients with advanced fibrosis and cirrhosis are treated more commonly than in clinical trials, often with worse outcomes and more adverse effects.

• In the ANRS CO20-CUPIC study (French cohort):
  – SVR 52-71% for prior relapsers.
  – SVR 29-31% for prior partial responders.
  – SVR 0% in prior null responders (0/5).

• In the HCV-TARGET study (US cohort):
  – 76% of patients experienced adverse effects requiring interventions or dose reduction.
  – 38% had severe anemia.
  – 4% developed new liver decompensation.

TPV and BOC In Summary

- Improve efficacy
- Add to side effects (especially GI symptoms, anemia, and rash)
- Add cost
- Add drug interactions
- Add complexity
- Depend on long courses of P/R
Ideal HCV Therapy Regimens

• High efficacy
• Shorter length of treatment
• Fewer adverse events
• Less dependence on IFN and/or RBV
• Daily dosing
• Decreased pill burden
• Minimal drug interactions
Standard of Care for HIV-HCV Coinfection in 2014

• HCV Genotype 1
  – Sofosbuvir (SOF) 400 mg PO daily + P/R for 12 weeks
  
  – Sofosbuvir (SOF) 400 mg PO daily + RBV for 24 weeks in patients who are ineligible for IFN.
  
  – Simeprevir (SMV) 150 mg PO daily + P/R for 12 weeks, followed by P/R alone for 12/36 weeks

• HCV Genotype 2
  – SOF 400 mg PO daily + RBV for 12 weeks

• HCV Genotype 3
  – SOF 400 mg PO daily + RBV for 24 weeks
Simeprevir (Olysio™; SMV; TMC435)

- First generation, second wave NS3/4A protease inhibitor
- Multigenotypic activity including genotypes 1, 2, 4, 5, and 6.
- Once daily dosing
- Not renally cleared
- Drug levels substantially increased patients of East Asian descent and in patients with moderate to severe liver dysfunction due to altered hepatic metabolism.
- Improved safety profile compared to TPV and BOC, but adverse effects include rash, photosensitivity, and hyperbilirubinemia.
- Received unanimous support from FDA advisory board on 10/24/13 and was FDA approved on 11/22/13.
- HIV-HCV coinfection NOT included on FDA label.

SMV: The QUEST 1 & 2, PROMISE, and ASPIRE Studies

SVR12 Rates in SMV Phase 3 Registration Trials

SVR24 in ASPIRE: SVR vs. Placebo

The Role of Resistance: The Q80K Mutation

- **Q80K** is a common baseline HCV mutation in genotype 1a (up to 48% of available sequences in pooled trial analyses).

- SVR rates for patients treated with SMV + P/R who had a baseline Q80K mutation were the same as the P/R control group.

- FDA recommends that all genotype 1a patients be screened for the Q80K mutation before starting SMV therapy.
Drug-Drug Interactions between SMV and Antiretrovirals

• SMV levels significantly **decreased** with efavirenz.
• SMV levels significantly **increased** with boosted darunavir.
• As such, **EFV** and **boosted PIs** have been **excluded** from HIV-HCV coinfection trials studying SMV.
• Raltegravir, rilpivirine, and tenofovir had minimal drug interactions.
SMV in HIV-HCV Coinfection: The C212 Study

- SMV + P/R in HIV/HCV coinfection, including treatment naïve, treatment experienced, and cirrhotics.
- RGT arms for treatment naïve and prior relapse patients included.
- 89% of eligible patients met RGT criteria.
- Worse outcomes with GT1a, Q80K, advanced fibrosis, and if not on ART.
- ART options include tenofovir, emtricitabine, raltegravir, and rilpivirine.

Dieterich D et al. EACS 2013 Abstract PS9/5.
Sofosbuvir (Sovaldi™; SOF; GS-7977)

- Nucleotide analogue inhibitor of NS5B polymerase
- Pangenotypic activity
- Once daily dosing
- Exceptional barrier to resistance
- Minimal hepatic metabolism
- Renally cleared (safety not established for severe CKD or ESRD)
- Received unanimous support from FDA advisory board on 10/25/13 and was FDA approved on 12/6/13.
- HIV-HCV coinfection INCLUDED in FDA label.

SOF and GT 1: The NEUTRINO Trial

- SOF + P/R for 12 weeks in HCV GT 1, 4, 5, and 6.
- **SVR12 90% overall.**
- **SVR12** high in African Americans (87%), cirrhotics (80%), and *IL28B* unfavorable genotype (87%).
- SOF did not increase side effect profile beyond P/R.

SOF and HCV GT 2/3: The FISSION and POSITRON Studies

**FUSION:** SVR12 in GT 2/3 in HCV Treatment Naïve Patients

- SOF+RBV x 12 Wks
- P/R x 24 Wks

**POSITRON:** SVR12 in GT 2/3 in HCV IFN Intolerant, Ineligible, Unwilling

- SOF+RBV x 12 Wks
- Placebo

The FUSION Trial: The Difference Between GT 2 and 3

Jacobson I et al. *NEJM* 2013. Figure courtesy of Dr. Susanna Naggie.
The VALENCE Trial: Extending SOF + RBV in GT 3

- Phase III study of SOF + RBV in HCV GT 2/3
- Initial randomization was to placebo vs. SOF + RBV for 12 weeks.
- Initial data suggested poor response in GT3 (27% SVR 12 in 3/11 patients); protocol changed to extend treatment to 24 weeks.
- In the GT3 arm, 85% (212/250) achieved SVR12 with 24 weeks of therapy.
  - 94% naïve, noncirrhotic
  - 92% naïve, cirrhotic
  - 87% experienced, noncirrhotic
  - 60% experienced, cirrhotic

Zeuzem S et al. AASLD 2013 Abstract 1085.
Drug-Drug Interactions Between SOF and Antiretrovirals

• **Minimal drug interactions** between antiretroviral regimens and SOF.

• SOF concentration **increased** by boosted darunavir but not clinically significant.

• Raltegravir concentrations **decreased** by SOF but not clinically significant.

• SOF concentration **significantly reduced** by boosted tipranavir; recommend avoiding/redosing if combined.
SOF + P/R in HIV-HCV Coinfection

- Pilot study of 19 patients.
- Design similar to the NEUTRINO study (SOF + P/R for 12 weeks).
- **SVR12 89% (17/19).**
- ART regimens included efavirenz, atazanavir, darunavir, raltegravir, and rilpivirine.

 SVR12

SOF + P/R x 12 Wks

Rodriguez-Torres M et al. IDWeek 2013 Abstract 714.
PHOTON-1: SOF + RBV in HIV-HCV Coinfection

- Ongoing phase III, open-label study of SOF + RBV in HIV-HCV coinfected patients.
- Treatment Duration:
  - GT 1 treated with 24 weeks of therapy.
  - GT 2/3 treatment naïve treated with 12 weeks.
  - GT 2/3 treatment experienced treated with 24 weeks.
- ART included efavirenz, atazanavir/ritonavir, darunavir/ritonavir, raltegravir, rilpivirine, tenofovir, emtricitabine, and others.
- 182 patients had been evaluated at time of abstract and 210 included in FDA insert.

Sulkowski M et al. AASLD 2013 Abstract 212. // Sofosbuvir FDA Full Prescribing Information.
Anticipated Future Therapies

- Faldaprevir (2014)
- ABT 450/r + 267 + 333 +/- RBV (2014)
- Daclatasvir (2014)
- Ledipasvir +/- sofosbuvir (2015)
- Deleobuvir +/- faldaprevir (2015)
- Asunaprevir +/- daclatasvir (2015)
Challenges and Unanswered Questions

• How will we identify new cases and successfully link them to care?
• Who will provide care to patients seeking care?
• Who will pay?
• What issues will be noted in post-marketing studies and surveillance?
Great Victories Come At Great Cost…

- Average Wholesale Price (AWP):
  - Pegasys (Pegylated Interferon) = $44,425.20 (48 weeks)
  - Ribavirin = $16,680.00 (48 weeks)
  - Incivek™ (Telaprevir) = $79,386.12 (12 weeks)
  - Victrelis™ (Boceprevir) = $80,313.64 (44 weeks)
  - Olysia™ (Simeprevir) = $63,440.16 (12 weeks)
  - Sovaldi™ (Sofosbuvir) = $100,800.00 (12 weeks)
    - Over $1,000 per pill!
- Additional costs for clinical care, diagnostics, radiology studies, procedures (i.e. biopsy if needed), etc.
- Course of modern HCV therapy likely >$100,000!

Vanderbilt Pharmacy Data.
Take Home Points

• HCV is an increasingly important comorbidity in people living with HIV/AIDS.
• While challenges remain, treatment efficacy and tolerability will dramatically improve with new therapies.
• SOF + P/R and SMV + P/R will likely be the standard of care for HCV GT 1 in 2014.
• SOF + RBV will likely be the standard of care for HCV GT 2/3 in 2014.
Thank You!

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Questions?