HCV Treatment in the HIV co-infected

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Disclosure:
Sources of Research Support

- Merck
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- BMS
- Gilead
- Janssen
- I belong to the ABIM test writing panel for Hepatology. No information about the test will be disclosed.

I WILL DISCUSS AGENTS CURRENTLY UNDER INVESTIGATION
Educational Goals

- Delineate the impact of HIV/HCV co-infected population
- Discuss the new agents introduced into market and how they will change the standard of care
- Discuss the outlook for the HCV for HIV co-infected patients in the next 2 years
- Review a proposed treatment strategy

Disclaimers:
- Recommendations are still germinal
- Need durability, applicability data outside clinical trials
- Will discuss agents that are not yet available
Case Presentation

27 yo man from England
• He is MSM, HIV+ for 5 yrs, normal CD4 count
  • On HAART (on efavirenz+truvada)
• Living in New York for a work assignment
• Presents for fitness to work exam
• LIT’s abnormal, PCP obtains HCV Ab which is positive
• Denies IV drug use
• Genotype 1a

What would you do?

• Check IL28B, wait 3 months and re-evaluate
• Obtain a liver biopsy and write pre-approval for SOF/IFN/RBV
• Obtain liver biopsy and refer to ID specialist
• Obtain liver biopsy and refer to clinical trial
• Obtain HBV serologies, liver biopsy and refer for tretament
The burden of HCV

Worldwide Burden of Disease due to HCV is Increasing

• WHO estimates 130-170 million people, (3% of world’s population) HCV infected and at risk of cirrhosis/HCC

• There are 3 to 4 million new infections/yr

• HCV is responsible for 50–76% of all HCC and 50-60% of all liver transplants in the developed world

• HCV-associated cirrhosis leads to liver failure and death in about 20%-25% of cirrhotic patients
Disease Burden of Patients Infected 20 Years or More is Peaking Now

Complications from chronic hepatitis C develop slowly over a period of 20–30 years

Deaths from HCV in the United States Continue to Rise; Deaths from HBV and HIV are Decreasing

HCV was the contributing or underlying cause of death for 15,106 individuals in 2007
Persons for whom routine HCV testing is recommended

- Persons who ever injected illegal drugs, including those who injected once or a few times many years ago
- Persons who received a blood transfusion or organ transplant before July 1992
- Persons who received clotting factor concentrates before 1987
- Persons who were ever on long-term dialysis
- Children born to HCV-positive women
- Health care, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-positive blood
- Persons with evidence of chronic liver disease
- HIV infected patients
- Persons born between 1945-1965

Background and Epidemiology

- HIV accelerates the natural course of HCV
- Successful antiretroviral therapy can slow fibrosis progression.
  - Not to the rate in HIV-/HCV+ patients
- Liver disease associated with HCV infection has become a leading cause of morbidity and mortality among HCV/HIV-co-infected patients
- HIV/HCV epidemiology
  - Approximately 25% of HIV+ patients are co-infected with HCV
  - Approximately 80% of HIV+ patients who inject drugs are co-infected with HCV
- All patients with HIV infection should be tested for HCV
- HIV/HCV co-infected pts. were considered a “higher need” population
Sexual Transmission of HCV Among HIV+ MSM

- Reports of epidemic of sexually transmitted HCV among HIV+ MSM
  - United States: 6-fold higher incidence rate in HIV+ vs HIV- MSM
  - Swiss HIV Cohort Study: HCV incidence increased 18-fold from 1998 to 2011
  - Australia: 9% of HIV+ MSM co-infected with HCV vs 1.9% HIV- MSM
  - Netherlands: HIV/HCV co-infection prevalence increased from 14.6% to 20.9% from 2000-2007
  - Phylogenetic analysis indicates HCV transmission clusters in some areas
- Sexual practices may influence the incidence of HCV

Risk Factors for Sexual HCV Transmission Among HIV+ MSM

- Multiple factors associated with HCV transmission
  - Unprotected receptive anal intercourse
  - Online casual sexual partners
  - Sex at sex venues
  - Older age
  - Syphilis
  - Recreational drug use
  - Drinking > 13 alcoholic drinks per week
Screening, Surveillance, Treatment Initiation for HCV in HIV+ Patients

• HIV treatment guidelines recommend:
  • HCV screening at HIV diagnosis, then annually and as indicated
  • More frequent surveillance if ongoing risk (MSM, IDU)
  • HCV RNA if HCV Ab+ or suspected acute infection

New Molecular Targets
Direct Antiviral Agents
The current/upcoming arsenal

- **Protease inhibitors**
  - Telaprevir
  - Boceprevir
  - Simeprevir
  - Faldaprevir
  - Asunaprevir
  - ABT-450
  - MK-5172
  - Sovaprevir
  - ACH-2684

- **NS5A Complex Inhibitors**
  - Daclatasvir
  - Ledipasvir
  - Ombitasvir
  - GS-5816
  - ACH-3102
  - PPI-668
  - GSK2336805
  - Samatasvir
  - MK-8742

- **NS5B Nuc. Pol Inhibitor**
  - Sofosbuvir
  - VX-135
  - IDX20963
  - ACH-3422

- **NS5B Non-nuc. Pol Inhibitor**
  - Dasabuvir
  - Deleobuvir
  - BMS 791325
  - PPI-383
  - GS 9669
  - TMC 647055
DAA regimens:
Telaprevir

- Two studies have been presenting data from which we can begin to make plans
- Multi-centric TPV trial (NCT00983853)
  - Reporting on 60 pts (with and without ART) who were HCV treatment naïve
    - Sulkowski Ann Int Med 2013
- French TelapreVIH trial ARNS HC26 (NCT01332955)
  - 69 patients who had prior non response (23% cirrhosis)

DAA regimens:
Boceprevir

- Two studies have been presenting data from which we can begin to make plans
- Multi-centric BOC trial (NCT00959699)
  - Reporting on 60 pts (with and without ART) who were HCV treatment naïve
    - Sulkowski Lancet Inf Dis 2013
- French BoceprenVIH trial ARNS HC27 (NCT01335529)
  - 64 patients who had prior non response (17% cirrhosis)
Promising Results
(Sulkowski Ann Int Med and Lancet Inf Dis 2013)

HIV/HCV Patient
Prior non-responders

- While the SVR data from TelapreVIH and BocepriVIH has not been presented
  - On treatment with TPV (HIV regimens allowed efavirenz) week 16 results are >85%, with close to 90% response for relapsers
  - BOC is quite effective in relapsers (90%) with low null responders on-treatment response (38%)
Challenges With Telaprevir- or Boceprevir-Based HCV Therapy in Coinfected Patients

- Regimen complexity
  - High pill burden
  - Long duration, complex RGT rules
  - Multiple drug-drug interactions
  - Overlapping toxicities
  - With/without food dosing requirements
- Tolerability
  - Additional AEs beyond PEG/ribavirin
    - Rash
    - Asthenia

Specific Risks of Deferring Therapy in HIV/HCV-Coinfected Patients

- Accelerated rate of HCV-related hepatic fibrosis progression in co-infected patients with increasing immune deficiency
  - Progression to cirrhosis risk 3-fold higher in co-infected vs HCV-mono-infected patients
  - Relative risk of decompensated liver disease 6-fold higher in co-infected vs HCV-monoinfected patients
- Co-infected patients have reduced access to liver transplantation and reduced survival
HCV Coinfection vs Monoinfection: Cumulative Incidence of Decompensation

• 10-year hepatic decompensation risk 83% higher in coinfected patients
  • Adjusted HR 1.83 (95% CI: 1.54-2.18)

C212 Study: Simeprevir + PegIFN/RBV in GT1 HCV/HIV Coinfection

• Phase III randomized controlled trial
  • 24- or 48-week regimens: SPV + pegIFN/RBV for 12 weeks, then pegIFN/RBV alone
  • HCV treatment-naive or -experienced HIV+ patients (N = 106)
    • 88% on ART (VL < 50 cells/mL)
    • Excluded: boosted PIs, NNRTIs other than RPV
  • Safety profile similar to monoinfected pts
    • Pruritus and photosensitivity in 20% and 2%, respectively
  • SVR comparable to GT1 HCV-monoinfected pts (80%)
HIV patients should be in GENERAL mix

Advantages of Future HCV Therapies

• Once-daily dosing
• Shorter duration
• Simpler regimens—no response-guided therapy
• Fewer adverse events
• Interferon-free
• High efficacy
PHOTON-1: Sofosbuvir + RBV in GT1/2/3 HIV/HCV Co-infection

- Phase III open-label study
- 12- (GT2/3 treatment-naive) or 24-week regimens (GT1 treatment-naive, GT2/3 treatment experienced): sofosbuvir + RBV
- HCV treatment-naive or -experienced HIV+ patients (N = 223)
- Approximately 76% on ART (VL < 50 cells/mL), various standard regimens
- Safety profile similar to mono-infected patients; consistent with RBV
- Most frequent AEs: fatigue, insomnia, headache, nausea, diarrhea
- 2 patients had transient HIV rebound due to non-adherence

Suñkowski et al AASLD 2013 and CROI 2014
Selected Ongoing or Upcoming Clinical Trials in HIV/HCV Coinfection

- Sofosbuvir + RBV: GT1/4 naive and GT2/3 naive/experienced patients, 12-24 weeks
- ABT450/rl/ABT-267 + ABT-333 + RBV: TURQUOISE-1 study, GT1 naive/experienced patients, 12-24 weeks
- Daclatasvir + pegIFN lambda + RBV: DIMENSION study, GT1-4 naive patients, 24-48 weeks
- Daclatasvir + asunaprevir + pegINF/RBV: QUADRIH study, GT1/4 nulls, 28 weeks
- MK-5172 + MK-8742 + RBV: 047 study, GT2,4,5,6 naive patients

Treatment Recommendations

- HIV/HCV patients should have their disease staged
- Stage >2 patients:
  - G1 SOF+PEG/RBV 12 weeks or SOF+RBV for 24 weeks
  - G2 SOF +RBV for 12 wks
  - G3 SOF +RBV for 24 wks (Add PEG and decrease to 12 wks if appropriate)
- Stage <2 patients:
  - Direct to clinical trial or await IFN free regimens
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Summary

- Liver disease leading cause of morbidity and mortality in HIV/HCV co-infection
  - Antiretroviral therapy may slow progression
- HCV screening at HIV diagnosis and at least annually
- HCV treatment considerations
  - Treat now or wait for future options?
  - First-generation DAAs complex, long duration, AEs, DDIs
  - New agents may improve outcomes with shorter therapy, fewer AEs
  - Consider HCV disease stage and risk of progression

http://www.hcvguidelines.org/