Current Standard of Care for Treating Chronic HCV

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Learning Objectives

At the conclusion of this presentation, learners will be better able to:

• Determine appropriate treatment candidates for Hepatitis C therapy in the current therapeutic era
• Review available data on current Hepatitis C therapies in order to practically apply that data to clinical care

Off-Label Disclosure

• This presentation will include off-label discussion of Boceprevir and Telaprevir in HIV
Outline

- Deciding to treat – or not
  - Staging – various methods used to stage
- Data on currently available HCV protease inhibitors
- Baseline assessment
- Monitoring on therapy
- Monitoring response
- Stopping rules
- Response guided therapy
- Toxicity/Symptom management
- Adherence management
Treating now vs. waiting

- Transitional period
- **Breathtaking** treatments on the near horizon
- Currently, breathlessness inducingly difficult treatment with IFN-based therapy
  - But it cures frequently
  - Some patients cannot afford to wait
Main question now:
Can this patient afford to wait?
Current Standard of Care for Treating Chronic HCV

- **HCV GT1:**
  - Telaprevir + PEG-IFN + weight based ribavirin (WBR)
  - Boceprevir + PEG-IFN + WBR

- **HCV GT2, 3**
  - PEG-IFN + 800mg/day ribavirin
  - No clinical trials data for current PIs
    - TPV active in GT2

- **HCV GT 4**
  - PEG-IFN + WBR +/- Nitazoxanide

Ghany et al, Hepatology, 2011
Deciding whom to treat

• Patient factors
  – **Stage of liver disease**
  – **Treatment history**
    • Prior null responder, partial responder or relapser
  – **Motivated to be treated**
  – Lack of absolute contraindications
  – HCV genotype
  – IL28B polymorphism status - ?
  – Other non-hepatic sequelae of HCV

• Systemic factors
  – Capacity to treat
    • Adequate resources for monitoring and management
      – Infrastructure
Treating now vs. watchful waiting in holding pattern

- Benefit of waiting for new drugs and IFN-free therapy ('warehousing')
  - Better quality of life
  - Better efficacy
  - Less toxicity/safer
  - Shorter course
  - ?Less resistance issue

- Potential Risk of waiting
  - Progression of liver disease
    - Risk of decompensation
      - Decreased response rates in advanced fibrosis/cirrhosis
    - Stakes potentially higher in HIV/HCV coinfected
      - More rapid progression
  - Non-hepatic risks of chronic HCV
  - Public health
  - Bird in the hand
Informed deferral

• “With safe and effective therapy available, treatment deferral is no longer a passive decision, but rather an action in itself that requires its own unique consent process: an informed deferral.”

• Argument:
  – Limitations in accurately staging liver disease
  – Limitations in predicting progression
  – Timing and availability of more potent and safer agents not fully known
  – Insurance status may change over time
  – New health comorbidities may arise over time
    • Making therapy more complicated
  – If high-risk behaviors, deferring may put others at risk

Aronsohn and Jensen, Hepatology November, 2012
Patient selection right now

- **Staging patient’s disease**
- Abstaining from alcohol
- Control depression
- Motivated patient
  - Treatment is hard
  - Importance of drug adherence
  - Importance of adherence to follow up (travel)
  - Coping skills/ ability to cope with potential toxicities
- Social support
  - Helpful
    - Not absolutely needed
- No hepatic decompensation
  - Can be subtle
- Other comorbidities well managed
  - HIV well controlled
    - HIV and non-HIV drug interactions addressed/ HIV regimen altered if needed
  - Insulin resistance
  - Vitamin D deficiency
  - Thyroid disease, CAD, etc
- Baseline cytopenias addressed/manageable
Staging disease becomes key decision point
Staging disease

• Liver biopsy still considered ‘imperfect’ gold standard

• Clinical
  – History suggesting decompensation
  – PE: jaundice, liver firmness, splenomegaly, gynecyomastia, ascites, spider angiomata

• Biochemical
  – Platelets, AST/ALT/GGT/bilirubin, PT, albumin, haptoglobin
  – Models – ‘non-invasive markers’

• Imaging
57 yo AA woman HCV GT1b, VL 500K with hx of relatively controlled depression and IVDU (15 years ago). PE c/w obesity and otherwise normal. AST 135, ALT 150, TB 0.5, albumin 4, INR 1, WBC 7, HGB 12, Platelets 235 and HCV fibrosure c/w F0-F1 and mild inflammation. HIV negative. She has no desire to be in a clinical trial and is not keen on IFN.
What is your next course of action?

A. Recommend liver biopsy
B. Tell her that she is unlikely to have significant liver disease and should return in 2 years when she may get treated with IFN-free therapy
C. Tell her odds are better than 50/50 that she will be cured of the HCV and recommend that she initiate treatment with TPV or BOC +PEG-IFN+WBR
D. Check IL28B genotype
E. Ask her to follow up in 6 months for a visit and labs
F. Address her obesity
Liver Bx Fibrosis Staging

F0 (Ishak 0)  F1 (~Ishak 1,2)  F2 (~Ishak 3)

F0 = no scarring  
F1 = portal fibrosis without septa  
F2 = portal fibrosis with rare septa/occasional portal-portal bridging  
F3 = numerous septa, marked bridging (portal-portal and portal-central) without cirrhosis  
F4 = cirrhosis/advanced scarring of the liver

Metavir

G Everson via K Sherman, Topics in Antiviral Medicine, 2011
Assessing fibrosis: Liver biopsy

- Can assess hepatic architecture
- Diagnose concomitant etiologies of liver disease
  - e.g., Steatosis
- Subject to sampling error
  - Need adequate specimen
- Subjectivity
  - Pathologist interpretation
- Access
  - Cost
  - Invasive
    - Potential morbidity

Assessing fibrosis: Biomarkers

- Predicts disease at the extremes – cirrhosis or minimal disease
  - Less good discerning mild-moderate fibrosis
- Examples
  - Platelet count, APRI, FIB-4, SHASTA
  - Commercial tests (Fibrosure, FibroTest, Fibroscore, hepascore)
  - Combining through algorithms (eg, APRI+Fibrosure) improves sensitivity/specificity
- In an individual patient confounders may exist
  - Can be ‘indeterminant’
- Can follow longitudinally, cheaper, safe

Assessing fibrosis: Imaging

• Ultrasound, CT, MRI
  • Cannot ‘r/o’ cirrhosis
  • Can assess liver nodularity, signs of portal HTN
    • Portal venous flow
• Research settings in US
  • Transient elastometry (Fibroscan)
    • Reliable for significant fibrosis and cirrhosis
    • Observer expertise required
    • Nonspecific: Other things influence shear waves:
      • Inflammation
      • Steatosis, age, BMI, visceral adiposity
    • Not FDA approved in U.S.
• MR elastography

After staging, key conversations

• In patient without significant fibrosis
  – Often wont recommend treating right now BUT
    • Unpredictability of progression
    • Importance of regular follow up
    • Continue to urge EtOH avoidance, discuss obesity, other modifiables
    • Discuss current treatment available
    • A goal is to retain in hepatitis care

• In patient with significant fibrosis
  – Review risks of advanced liver disease
  – Review response rates based on Rx history and other factors
  – Discuss current treatment available, trials
Data on treatment response with currently available PI based triple therapy: Telaprevir and Boceprevir
Telaprevir in treatment naïve GT1 HCV monoinfected: SVR

ADVANCE
Jacobson et al, NEJM, 2011(Ghany et al, Hepatology 2011)
SVR by Stage of Fibrosis in Rx naive

ADVANCE
Jacobson et al, NEJM, 2011
Terminology in IFN treatment experienced

• Null responder
  – Different definitions
    • Classic definition

• Partial responder

• Relapser

• Virologic breakthrough
Telaprevir in treatment experienced GT-1 HCV monoinfected: SVR

REALIZE
Zeuzem et al, NEJM, 2011 (Ghany et al, Hepatology 2011)
Rationale for Telaprevir RGT in naive

Sherman, NEJM, 2011 (Ghany et al, Hepatology, 2011)
Boceprevir in treatment naïve GT1 HCV monoinfected

SPRINT-2
Poordad et al, NEJM, 2011 (Ghany et al, Hepatology 2011)
Boceprevir in treatment experienced GT-1 HCV monoinfected

Prior null responders were excluded from this trial

RESPOND-2 Bacon et al, NEJM, 2011 (Ghany et al, Hepatology 2011)
Boceprevir in treatment experienced (PROVIDE)

- SVR was also achieved in all 4 patients with ‘other’ prior non-response.
- Overall, 81 of 138 patients (59%) achieved SVR.

SVR rates if lead-in dropouts included: nulls 38% (19/50), partials 68% (53/78), relapers 50% (5/10), overall 57% (81/142)

† denominator for relapse rate = patients with undetectable HCV RNA at EOT and not missing end of follow-up data.
IL28B

- Genetic polymorphism on chromosome 19
  - Initial described as predictive of response to PEG/RBV*
  - Commercial tests available

- How should this be used in practice?
  - Currently treating those who can’t wait
    - Motivate those with higher likelihood of response
  - Though less predictive than viral load decline after 4 wk lead-in

- Future
  - Predict those eligible for shorter course therapy

‘Real world’ safety data in cirrhotics

- French early access study to TPV and BOC
- Compensated cirrhosis
- Prior non-responders
- Partial, relapsers (then nulls)
- 16 week interim analysis
  - Toxicity findings

Hezode et al, AASLD 2012
### Telaprevir: week 16 safety findings

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients, n (% patients with at least one event)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events (SAEs)</strong></td>
<td>132 (45.2%)</td>
</tr>
<tr>
<td><strong>Premature discontinuation Due to SAEs</strong></td>
<td>66 (22.6%), 43 (14.7%)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td>Septicemia, Septic shock, Pneumopathy, Endocarditis, Oesophageal varices Bleeding</td>
<td></td>
</tr>
<tr>
<td><strong>Infection (Grade 3/4)</strong></td>
<td>19 (6.5%)</td>
</tr>
<tr>
<td><strong>Hepatic decompensation (Grade 3/4)</strong></td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td><strong>Asthenia (Grade 3/4)</strong></td>
<td>16 (5.5%)</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>14 (4.8%)</td>
</tr>
<tr>
<td>Grade 3/SCAR</td>
<td></td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
<td>5 (1.7%)</td>
</tr>
</tbody>
</table>

*334 SAEs in 132 patients; SCAR: severe cutaneous adverse reaction

Hezode et al, AASLD 2012
# Telaprevir: week 16 safety findings

<table>
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<tr>
<th>Patients, n (% patients with at least one event)</th>
<th>Telaprevir n=292</th>
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<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 2 (8.0 – ≤9.0 g/dL)</td>
<td>55 (18.8%)</td>
</tr>
<tr>
<td>Grade 3/4 (&lt;8.0 g/dL)</td>
<td>34 (11.6%)</td>
</tr>
<tr>
<td>EPO use</td>
<td>157 (53.8%)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>47 (16.1%)</td>
</tr>
<tr>
<td>RBV dose reduction</td>
<td>38 (13.0%)</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 3 (500 – &lt;750/mm³)</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Grade 4 (&lt;500/mm³)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>G-CSF use</td>
<td>7 (2.4%)</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 3 (20,000 – &lt;50,000/mm³)</td>
<td>28 (9.6%)</td>
</tr>
<tr>
<td>Grade 4 (&lt;20,000/mm³)</td>
<td>9 (3.1%)</td>
</tr>
<tr>
<td>Thrombopoietin Use</td>
<td>4 (1.4%)</td>
</tr>
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EPO: Erythropoietin; G-CSF: granulocyte-colony stimulating factor

Hezode et al, AASLD 2012
## Boceprevir: week 16 safety findings

<table>
<thead>
<tr>
<th>Patients, n (% patients with at least one event)</th>
<th>Boceprevir n=205</th>
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<tr>
<td>Serious adverse events (SAEs)*</td>
<td>67 (32.7%)</td>
</tr>
<tr>
<td>Premature discontinuation Due to SAEs</td>
<td>54 (26.3%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.5%)</td>
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<tr>
<td>Pneumopathy</td>
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<td>Infection (Grade 3/4)</td>
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<td>Asthenia (Grade 3/4)</td>
<td>12 (5.8%)</td>
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<tr>
<td>Rash</td>
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</tr>
<tr>
<td>Grade 3/SCAR</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
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*152 SAEs in 67 patients; SCAR: severe cutaneous adverse reaction.

Hezode et al, AASLD 2012
## Boceprevir: week 16 safety findings

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<th>Boceprevir n=205</th>
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<tbody>
<tr>
<td>Grade 2 (8.0 – ≤9.0 g/dL)</td>
<td>48 (23.4%)</td>
</tr>
<tr>
<td>Grade 3/4 (&lt;8.0 g/dL)</td>
<td>9 (4.4%)</td>
</tr>
<tr>
<td>EPO use</td>
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<td>Grade 3 (20,000 – &lt;50,000/mm³)</td>
<td>10 (4.9%)</td>
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<td>3 (1.5%)</td>
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EPO: Erythropoietin; G-CSF: granulocyte-colony stimulating factor
# Multivariate analysis: baseline predictors of severe complications*

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<tr>
<th>Predictors</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count ≤100,000/mm³</td>
<td>3.11</td>
<td>1.32-7.73</td>
<td>0.0098</td>
</tr>
<tr>
<td>Serum albumin level &lt;35 g/L</td>
<td>6.33</td>
<td>2.66-15.07</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Death, severe infection and hepatic decompensation, n=32 (6.4%)
## Multivariate analysis: baseline predictors of anemia <8g/dL or blood transfusion*

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<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Gender: Female</td>
<td>2.19</td>
<td>1.11-4.33</td>
<td>0.023</td>
</tr>
<tr>
<td>No lead-in phase</td>
<td>2.25</td>
<td>1.15-4.39</td>
<td>0.018</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>3.04</td>
<td>1.54-6.02</td>
<td>0.0014</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>5.30</td>
<td>2.49-11.25</td>
<td>&lt;0.0001</td>
</tr>
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* n=71 (14.3%)

Hezode et al, AASLD 2012
Boceprevir: week 16 efficacy data

- Week 4: 3% (5/194), 2% (5/205)
- Week 8: 42% (77/191), 38% (77/205)
- Week 12: 64% (112/174), 55% (112/205)
- Week 16: 77% (118/154), 58% (118/205)

Hezode et al, AASLD 2012
Data on Telaprevir and Boceprevir in HIV/HCV coinfected
Telaprevir in HIV/HCV GT1 treatment naive

Part A: no ART

<table>
<thead>
<tr>
<th>T/PR</th>
<th>TVR + PR</th>
<th>PR</th>
<th>SVR12</th>
<th>SVR24</th>
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PR48 (control)

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Part B: ART (EFV/TDF/FTC or ATV/r + TDF + FTC or 3TC)

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</table>

Weeks

0 12 24 36 48 60 72

EFV = efavirenz; TDF = tenofovir; FTC = emtricitabine; ATV/r = ritonavir-boosted atazanavir; 3TC = lamivudine; T/TVR = telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo = placebo; P/Peg-IFN = pegylated interferon alfa-2a (40 KD) 180 μg/wk.

Sułkowski et al. AASLD 2012
SVR: Telaprevir in HIV/HCV GT1 treatment naive

Sulkowski et al, AASLD 2012

*Prior to Week 24 visit, 1 patient in this cohort was lost to follow up. SVR24 was imputed based on SVR12 for this patient.
SVR: Telaprevir in HIV/HCV GT1 treatment naive

Sulkowski et al, AASLD 2012

*Prior to Week 24 visit, 1 patient in this cohort was lost to follow up. SVR24 was imputed based on SVR12 for this patient.
Treatment experienced

• Trials ongoing
• Early virologic data encouraging
Boceprevir dose 800 mg TID

4-week lead-in with PEG2b/RBV for all patients

- PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID

Futility rules: Week 12 <100, Week 24 <LLD
Boceprevir in HIV/HCV GT1 Treatment naïve

Sulkowski et al, CROI 2012
Boceprevir in HIV/HCV GT1 Treatment naïve

Sulkowski et al, CROI 2012
Safety of BOC, TPV HIV/HCV

• Clinical practice
  – Similar to monoinfected
  – TPV - Less severe rash and perianal pruritis

• Boceprevir
  – Anemia common
    • Trials – 40% epo, 6% transfusions
  – Neutropenia common (1/3)
  – Still unsettled drug interaction issues
    • In trial, 3 HIV breakthroughs (2 ATZ/r, 1 LPV/r) vs. 4 placebo

• Telaprevir
  – Overall anemia less common
    • Greater subset in whom it is more severe (11% transfusions)
  – Rash is common (~1/3)

Kostman et al, #677, CROI; Martel-Laferriere, #679, CROI, 2013
BOC, TPV in HIV/HCV coinfected: ‘Game changers’

• Similar response rates to HCV mono
• Similar safety profile to HCV mono
• Increased liver failure, liver cancer in HIV/HCV vs. HCV*
  – HIV becomes reason to treat rather than not to treat HCV
  – In near future likely should treat HCV in all HIV

*LoRe et al, IAS 2012
AASLD Treatment recommendations for treatment naive HCV monoinfected GT 1 infected patients

If GT1, liver bx suggested

No fibrosis or portal fibrosis only

More than portal fibrosis

Consider no treatment

Treat with PEG/RBV and add BOC at 4 wks

Treat with PEG/RBV with TPV 1st 12 weeks

Cirrhosis

Continue Rx for 48 wks

No cirrhosis

<LLD week 8+24, consider 28wk (vs. 48)

>100IU/ml wk 12 or detectable wk 24, DC Rx

<LLD week 4+12, consider 24wk (vs. 48)

>1000IU/ml wk 4 or 12 or detectable wk 24, DC Rx

Ghany et al, Hepatology 2011
Treatment recommendations for treatment naïve HCV monoinfected GT 2 or 3 infected patients

GT2 or 3: liver bx ‘optional’

- No fibrosis or portal fibrosis only

More than portal fibrosis

- Treat with PEG/RBV 24 wks (HIV 48 weeks)
  * Increased RBV or 48w therapy

Consider delay treatment

Ghany et al, Hepatology 2011
Telaprevir

- 12 weeks of TPV, PEG-IFN, WBR followed by a tail of PEG-IFN/RBV (variable duration)
- 750 mg (2 pills) q8 (7-9h) with food
  - ~30 minutes after **high fat meal** (20gm)
    - High fat increases AUC by 230 - 330% vs. fasting (vs. 120% low fat meal)
    - 1125 q12 in treatment naïve HCV monoinfected (Buti et al, LB-8 AASLD, 2012)
- Metabolism
  - Substrate and inhibitor of CYP3A4, P-gp
  - 80% eliminated in feces, 1% urine
Boceprevir

• 4 week lead in of PEG-IFN/WBR then BOC added to this for 24-44 more weeks
• 800 mg (4 pills) q8 (7-9h) with food
• Metabolism
  – Some unpredicted interactions
  – Substrate of aldo-ketoreductase – metabolized to a ketone-reduced metabolite
  – Minor substrate for CYP3A4/5 – lesser pathway
    • Inhibits CYP3A4
  – Substrate and inhibitor of P-gp
  – Eliminated via feces mainly
    • No renal dose adjustment recommendation
PI companions: Still PEG-IFN and RBV

• **PEG-IFN-alfa**
  
  – Timing of the weekly injection
    • 2a (Pegasys) – 180mcg/wk
    • 2b (Pegintron) – 1.5 mcg/kg/wk (dosing tables/calculator)
  
  – Dose adjust for renal insufficiency

• **Ribavirin**
  
  – Begin with weight based dose
    • 1200 QD ≥ 75kg, 1000 QD <75kg
    • Dose adjust for renal insufficiency
  
  – Long half life
    • Can pair it with the PI doses
    • When dose reduce can give QD
Baseline assessment prior to therapy

- HIV, Hepatitis A, B test (vaccinate if non-immune)
- Quantitative HCV viral load
- HCV genotype
- Discuss pregnancy potential and birth control
- Baseline ‘safety’ labs
  - CBC (with WBC differential)
  - Chemistries
  - Liver function tests
  - TSH
  - (pregnancy test)
- Assess mental health and support system
- Clinical assessment of cardiac and pulmonary functioning
  - Stress test if concerns
- Assess for drug interactions
  - HIV drug interactions
- Diabetic
  - Ophthalmologic exam
- Cirrhotic
  - EGD screening, U/S screening
  - Closer monitoring
Assess for drug interactions with Boceprevir, Telaprevir

- http://www.hep-druginteractions.org

- Hormonal contraceptives
  - Cannot rely upon for birth control
    - Barrier methods, IUDs
      - 2 non-hormonal methods recommended

- Statins
- PDE-5 inhibitors
- HIV medications
## For Both Boceprevir and Telaprevir

- Avoid ddI, d4T, AZT if possible
- Specific issues with different PIs, NNRTIs - unpredictable two-way interactions
- Maraviroc - ?dose adjustment (CYP3A4 metabolized) – data pending
- ?Abacavir – no data
  - Ribavirin dose reduction hasn’t effected response in HCV monoinfected
  - BUT different viral kinetics in coinfected AND in particular, on abacavir, will this be an issue? (more aggressive epo/less RBV dose reduction?)

- Treating HCV prior to HIV (CD4>500, HIV VL <50K) - Controversial

### Boceprevir
- Generally avoid boosted PIs and efavirenz until further data (ACTG clinical trial)
- No significant interaction with rilpivirine
- Raltegravir without significant interaction

### Telaprevir
- Data with ATZ-ritonavir
  - Avoid other HIV PIs
  - Efavirenz acceptable with high dose telaprevir
  - Raltegravir without clinically significant interaction

Rhee et al, #537, CROI 2013, deKanter et al, CROI 2012 Sulkowski, AASLD 2012, van Heeswijk, ICAAC 2011
Initiating therapy

- Patient education
  - Dietary requirements
  - Adherence
  - Birth Control
  - Expectation regarding toxicities
    - Flu-like symptoms
      - Fever, headache, nausea
    - Fatigue
    - Mental health
      - Irritability...depression
    - Anemia, blood counts
    - Rash (TPV)

- Preemptive symptom management
Follow up

• Frequency
  – Patient and practice specific
    • Frequent
• Monitoring for response
  – Determining to STOP
  – Response guided therapy
    • Determining Duration
• Symptom, toxicity management
• Reinforce and assess adherence
Telaprevir: Determining total duration of therapy and response guided therapy (RGT)

- Prior partial or null responder, cirrhotic or HIV positive
  - NO
    - UND HCV VL at W4 and W12
      - NO
        - 48 weeks total
      - YES
        - 24 weeks total
  - YES
    - Plan 48 weeks

Telaprevir package insert, Sulkowski AASLD 2012
RGT: Undetectable early timepoints

- HCV viral load assays have
  - Lower limit quantification
    - Unquantifiable
      - Virus can be unquantifiable but still detectable
  - Lower limit detection
    - Should be at least <25IU/mL
    - Speak to lab

- To qualify for RGT need undetectable VL
- Not ‘unquantifiable’ but undetectable
Telaprevir: Monitoring for response: Stopping (futility) rules

- Likely no chance of SVR
- Risk - further resistance to the PI, further toxicity to the patient
- RULES
  - Week 4 HCV RNA >1000 IU/mL $\rightarrow$ STOP
  - Week 12 >1000 $\rightarrow$ STOP
  - Week 24 confirmed detectable $\rightarrow$ STOP
Boceprevir: Determining duration of therapy, RGT

- **Cirrhotic or HIV positive:**
  - **YES:** Plan 4+44 weeks
  - **UND HCV VL at W8 and W24**
    - **YES:** 4+32 (36wks total)
    - **NO:** 4+32+12 (48wks total)
  - **NO:** Rx naive
    - **NO**

- **Rx naive:**
  - **NO**
    - **UND HCV VL at W8 and W24**
      - **YES:** 28 weeks (4+24)
      - **NO:** 4+32+12 (48wks total)

*Prior partial or relapser

Boceprevir package insert, Sulkowski et al, CROI 2012
Boceprevir: Monitoring for response: Stopping (futility) rules

- **RULES**
  - Week 12 HCV RNA >100 IU/mL → STOP
  - Week 24 confirmed detectable → STOP
Frequency of HCV VL monitoring

• Clinical trials
  – Monitored every 4 wks (at least)

• Clinical practice
  – At least every 4 wks for first 12 weeks
  – Week 24, (Week 36), end of treatment (ETR), 24 weeks after end of treatment (SVR)

• More frequently if concern for breakthrough
  – VL remains detectable at week 8 and week 12
  – LFTs bump
  – Adherence concern
Frequency of HIV VL/CD4 monitoring

• NO more than ordinarily
  – Unless in *poorly chartered* territory
    • In terms of drug interactions

• On HCV Rx
  – CD4 will drop with WBC
  – CD4% shouldn’t
  – Engenders anxiety

• OI prophylaxis
  – Consider case by case
  – Few OIs reported
50 year old 80kg AA man with HIV/HCV coinfection, HCV GT1a prior partial responder with cirrhosis initiates therapy with PEG-IFN/WBR leadin anticipating triple rx with BOC (4+44). His baseline hemoglobin was 15.9 and is now 11.9 after 4 week leadin. He is mildly fatigued but doing well. His stools are heme negative.
Which of the following is your next course of action?

A. Decrease the ribavirin dose
B. Initiate erythropoieten
C. Decrease the ribavirin and initiate erythropoieten
D. Initiate the Boceprevir and recheck HGB in 2 weeks
E. Given the anemia issue, attempt to obtain Telaprevir for use instead of BOC
Hematologic toxicities

• Anemia
• Leukopenia
• Thrombocytopenia
Hematologic toxicities: Anemia

• 2 hits
  – Ribavirin hemolysis
    – Renally cleared – dose adjustments for GFR
  • Genetically influenced by ITPA activity
    – Low activity, less likely anemia
  – Interferon BM suppression
• Significantly Worsened with the PIs
• Confirm no concomitant process
  – Assess iron, B12 and folate levels, heme-check stool
  – Particularly when unresponsive
Dose adjustments for anemia

• Now, dose reduction is **first line** for anemia
  • Historically, with PEG-IFN+RBV, RBV dose reduction → decreased response

• Boceprevir
  – Randomized trial in those with HGB <10 to dose reduction vs. epo
  – SVR rates same in either strategy
  – Regardless of timing or magnitude of reduction

• Telaprevir
  – Recent data – increases serum and intracellular RBV levels 1.5 – 3X
  – Retrospective analysis of REALIZE, ADVANCE and ILLUMINATE clinical trials
    • No difference in SVR rates in naïve or experience with dose reductions (down to <600mg)

Poordad et al, abstract #1419, AASLD 2012; Sulkowski et al, abstract #594, DDW 2012; Hammond et al, abstract #34, CROI 2013
HIV/HCV

• Anemia common
  – Similar frequency to monoinfected

• Little data on effect of dose reduction on treatment response
  – But treatment responses are just as good...

• Currently extrapolating from monoinfection data
Anemia management

• **Close monitoring**
  – Much harder to ‘dig out of a hole’

• **First line - RBV dose reduce early**
  – If Hgb <10 or if drops significantly
  – Different dose reduction strategies – can cont. to reduce

• **PEG-IFN dose reduction**
  – Particularly if other cytopenias

• **Erythropoieten**

• **If <10, (Goal 10-11), other select situations**

• **Blood transfusions**
  – Severely symptomatic, <8

• **Weighing when time to stop - individualized**

Poordad et al, abstract #1419, AASLD 2012; Sulkowski et al, abstract #594, DDW 2012
Leukopenia

• ANC declines on PEG-IFN based therapy
  – Up to ~20% neutropenia

• Cirrhotics at risk of bacterial infection/sepsis
  – In general
    • See this on therapy (?more)

• PEG-IFN dose reduction
  – Strategies individualize
    • <750cells/mm3

• WBC growth factor
  – GCSF/neupogen to increase ANC
    • ? Clinical benefit – treating the number
    • Used to maintain therapy
Thrombocytopenia

- On average platelets drop 30-50%
- PEG-IFN dose reduction
  - Platelets <~50K
  - Discontinue <~25K
- Eltrombopag
  - Orally bioavailable thrombopoietin-receptor agonist
  - Goal
    - To allow patients to begin or maintain HCV therapy who would otherwise stop (>~50K)
    - NOT to normalize platelets
      - 25mg dose
    - Thromboembolic risk – with higher plt counts
      - Portal vein thrombosis
  - Hepatotoxicity
  - Some drug interactions
  - Close monitoring of CBC
Mental health

- Antidepressants
- PEG-IFN dose reduction
- Family support/understanding
- Involvement of therapist/etc.
Telaprevir rash: mild to moderate

• **Common**
  – ~1/3 patients

• **As is pruritis and perianal pruritis**

• **Mild to moderate rash (< 50% BSA)**
  – Topical steroids and oral antihistamines
  – Apply Cream, Loose clothing, Limit sun/heat exposure
  – ‘treat through’

• **Treat pruritis similar to rash**
Telaprevir rash: more severe

- Systemic signs or symptoms associated with a rash
  - ’Red-flag features’ → **stop telaprevir**
    - Mucosal involvement, blisters
    - Progressing to >50% BSA
    - Dermatology consult
  - Often resolves within 7-10 days after TPV cessation
    - Can persist for weeks (maybe RBV)
  - PEG-IFN, RBV can cont.
    - If rash stops within 10d
    - **Cannot restart TPV once stopped**
  - **SJS/TEN, DRESS**
    - Stop all drugs
    - Emergent derm/medicine involvement
Perianal itching

• About 25% on telaprevir
• Examine
• Tucks pads
• Corticosteroid creams
  – Proctofoam-HC (Hydrocortisone/pramoxin rectal foam)
• Lidocaine cream
  – If burning
• Any hemorrhoidal cream may soothe
Adherence management

• Data on PEG-IFN/RBV suggest that harder to adhere to the oral therapy*
  – Becomes an issue many months into BOC

• Different models of treatment
  – Modified DOT – unlike HIV, this is possible given delimited time
  – Patients have transportation issues

*LoRe et al, Annals, 2011
Different HCV treatment models

• Current therapy is very labor intensive for all
  – This will change and become simpler
• Team approach can be effective
  – Weekly team meetings to review patients in care
    • Hepatologists
    • ID physicians
    • Clinical pharmacists
    • ID/HIV nurse practitioners and PAs
  – Support staff
    • Nursing, Behavioral health/psych, Social work, Dietician
Summary

• Unique therapeutic era
• Treat those with advanced disease or with specific HCV sequelae
  – Treatment requires close monitoring
    • Toxicity and symptom management
• Monitor consistently those in whom treatment is deferred – attempt to retain them in care
• Boceprevir and Telaprevir cure rates are as high in HIV infected treatment naïve patients as HCV monoinfected