Viral Hepatitis and HIV

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Faculty Disclosures

- **Grant support** - Vertex, Roche, Novartis, Gilead

- **Advisory Board for Scientific Information or Clinical Trial Design**: Roche/Genetech, Gilead, Merck, Biotest, Essai, Bristol-Myers Squibb, Pfizer, Siemens.

*Off-label/investigational uses discussed in this presentation: telaprevir and boceprevir*
Learning Objectives

Upon completion of this presentation, learners should be better able to:

- To describe the burden of liver disease related to HBV and HCV in patients living with HIV
- To recognize the factors – especially those that are modifiable - influencing progression of liver disease and risk of cirrhosis and hepatocellular carcinoma in coinfected patients
- To understand treatment options for HBV and HCV and the expected outcomes of these treatments in HIV patients
HIV and Viral Hepatitis Disease Burden

- Among 33 million HIV infected persons worldwide:
  - 5 million coinfected with HCV
  - 4 million coinfected with HBV

- Prevalence and transmission routes vary geographically; in U.S.
  - HBV: 5-15% of HIV+ are HBsAg-positive
  - HCV: 25% of HIV+ are anti-HCV+

Alter M, J Hepatol 2006;44 (Suppl 1);S6-9.
Importance of Viral Hepatitis in HIV-Infected Persons

- Increased risk of chronic infection following exposure
- Higher levels of viremia
- Increased risk of progression to cirrhosis and its complications
- Increased risk of hepatotoxicity with ART
- Hepatitis viral coinfection may adversely affect course of HIV infection
Causes of Death Among HIV+ Persons with Access to ARVs in NYC

Independent Predictors of Liver-Related Death

- HCV: RR 6.7 (3.9 – 11.2)
- HBV: RR 3.7 (2.4 – 5.9)
- Low CD4: RR 1.23 (1.2 - 1.3)
- IDU: RR 2.0 (1.2 – 3.4)
- Older age: RR 1.3 (1.2 – 1.5)

D:A:D Data Collection on Adverse Events of Anti-HIV Drugs study

Management Approach in Coinfected Patients

- Cure or control of hepatitis viruses is necessary to minimize liver-related complications

**HBV**
- Peg-IFN
- 5 Polymerase inhibitors
  - LMV, Telbivudine, Entecavir
  - Adefovir, Tenofovir

**HCV**
- Peg-IFN + ribavirin ± protease inhibitor
  - Telaprevir
  - Boceprevir

HIV-HBV Coinfection
Natural History of HBV Infection

Acute Infection

<5% of infected immunocompetent adults develop chronic disease

5-30% HIV+ → chronic disease

Chronic Infection

20-30% in 20 yrs

~15-fold higher in HIV+

Liver Cancer (HCC)

<1% per year

Liver Transplantation

2-4% per year

Liver Failure ( Decompensation)

23% of patients decompensate within 5 years of developing cirrhosis

≥4-fold higher in HIV+

Liver Cancer (HCC)

40% higher in HIV+

Death

Which of the following factors is most strongly associated with the risk of liver cancer among HBV-infected patients?

1. Male gender
2. Cirrhosis
3. HBV viral load $\geq 1$ million copies/mL
4. HBV genotype C
5. Alcohol use
Factors Associated with Risk of Cirrhosis in Patients with Chronic HBV

<table>
<thead>
<tr>
<th>Host Factors</th>
<th>Virus Factors</th>
<th>Environmental Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 years of age</td>
<td>High serum HBV DNA concentrations</td>
<td>Concurrent infection (HCV, HDV, HIV)</td>
</tr>
<tr>
<td>Male</td>
<td>Prolonged time to HBeAg seroconversion</td>
<td>Alcohol consumption</td>
</tr>
<tr>
<td>Positive Family Hx</td>
<td>Development of HBeAg(-) chronic hepatitis</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Immune status</td>
<td>Core promoter HBV variant</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Genotype C</td>
<td></td>
</tr>
</tbody>
</table>

Risk of HCC According to Baseline Factors

- **REVEAL**: long-term follow-up (mean, 11.4 yrs) of untreated HBsAg positive individuals in Taiwan (N = 3653)

![Graph showing the risk of HCC according to baseline factors, including HBV DNA levels and cirrhosis status.](image-url)

Question #2

- 45 yo HIV-infected man with chronic HBV infection recently transferred to your practice. HIV infection diagnosed 3 years ago, currently not on ART.
  - CD4 count 890, HIV VL 8900 copies/mL.
  - No history of OIs/ONs
  - HBeAg negative, HBV DNA 5000 IU/mL, ALT 55, AST 48, total bilirubin, albumin, CBC normal
  - Repeat labs 3 months later: ALT 60, AST 55
  - Ultrasound: normal appearing liver without focal lesions
What do you recommend?

1. Liver biopsy to stage disease and determine need for HBV therapy
2. Treat with ART containing tenofovir + emtricitabine
3. Treat with peginterferon
4. Treat with entecavir
5. Treat with combination adefovir and telbivudine
Goals of Treatment in Patients with Chronic HBV

- **Virologic:** suppressed HBV DNA levels
- **Immune:** seroconversion
  - HBeAg $\rightarrow$ HBeAb
  - HBsAg $\rightarrow$ HBsAb
- **Inflammatory:** reduced inflammation and fibrosis $\rightarrow$ less cirrhosis

HBV never “cured” but controlled
Natural History of Chronic HBV

HBeAg

HBV DNA

Anti-HBe

ALT

Immune tolerant

Immune active HBeAg +ve CHB

Immune control (inactive) CHB

Reactivation HBeAg –ve CHB

HBsAg cleared

Lok et al., Arch Intern Med 2006;166:9
Natural History of Chronic HBV

- HBeAg
- Anti-HBe
- HBV DNA
- ALT

Immune tolerant
Immune active HBeAg +ve CHB
Immune control (inactive) CHB
Reactivation HBeAg –ve CHB
HBsAg cleared

Lok et al., Arch Intern Med 2006;166:9
# HBV and HIV Therapies

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>YMDD</th>
<th>HIV Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon</strong></td>
<td>S</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td>S</td>
<td>R</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Adefovir</strong></td>
<td>S</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td><strong>Entecavir</strong></td>
<td>S (0.5)</td>
<td>S (1 mg)</td>
<td>Y*</td>
</tr>
<tr>
<td><strong>Emtricitabine</strong></td>
<td>S</td>
<td>R</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Tenofovir</strong></td>
<td>S</td>
<td>S</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Telbivudine</strong></td>
<td>S</td>
<td>R</td>
<td>N</td>
</tr>
</tbody>
</table>

* HIV activity but not used as part of ART
Treatment Decisions in HBV-HIV Coinfected Patients

If meets criteria for HIV treatment:

- HBV DNA and ALT levels, HBeAg status have little to no role in decision-making
- Choose regimen that is effective against both HIV and HBV

If HIV does not need treatment:

- Decision to treat based on ALT and HBVDNA levels
- Options:
  - Use drugs that have no activity against HIV
  - Treat HIV and HBV simultaneously
Evaluating Need for Treatment in Chronic Hepatitis B

- Cirrhosis
- HBV-DNA
- ALT
- Treatment
- Surveillance
  - HBV-DNA $\geq 2000$ UI
  - HBV-DNA $< 2000$ UI
  - $> N$
  - $N$

Lacombe and Rockstroh Gut 2012
Anti-HBV Therapy in HBV/HIV Coinfected Patients

**ART use**

- **no**
  - Peginterferon*
  - Adefovir (Telbivudine)

- **yes**
  - TDF + LMV or FTC
  - Alternatives
    - ADV + LMV or FTC
    - Entecavir
      - (if fully suppressive ART)

* Not recommended if cirrhosis

DHHS 2012 Guidelines
# Serologic Outcomes in HBV-HIV Coinfected Patients on Treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Population</th>
<th>Follow-up (mos)</th>
<th>HBeAg Loss (anuallized)</th>
<th>HBsAg Loss (anuallized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nunez, 2006</td>
<td>79</td>
<td>LMV (37%) or LMV/TDF (58%)</td>
<td>52</td>
<td>6.5%</td>
<td>3%</td>
</tr>
<tr>
<td>Maylin, 2012</td>
<td>143</td>
<td>ART-experienced on TDF (100%)</td>
<td>30</td>
<td>8.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Martin-Carbonero</td>
<td>92</td>
<td>LMV (94%) TDF (89%)</td>
<td>35</td>
<td>9%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Schmutz</td>
<td>75</td>
<td>TDF (66%) LMV+TDF (33%)</td>
<td>27</td>
<td>12%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Predictors of Response:**
- Higher CD4 count on HAART
- Undetectable HIV RNA

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Martin-Carbonero AIDS 2011;25:73-9
Maylin S, AIDS. 2012 May 15;26(8):939-949
ART including LMV Reduces Risk of Liver-Related Death

- 2,041 HBV-HIV patients
- 7,648 PYFU after starting combination ART
- Liver-related deaths 7.5 per 1,000 PYFU (95% CI: 5.6-9.7)
- LMV-ART associated with reduced risk of liver-related death (LRD)

Factors Independently Associated with LRD

- Age
- CD4 count
- DLD pre-HAART
- DDI and D4T ART (controls)

LMV-ART RR=0.73
P=0.004

Puoti Antivir Ther. 2006;11(5):567-74
Question #3

- 25 yo HIV-infected man with chronic HBV infection on efavirenz, tenofovir and emtricitabine has the following laboratory results:

<table>
<thead>
<tr>
<th></th>
<th>Pre-Tx</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4 count/mm³</strong></td>
<td>400</td>
<td>650</td>
<td>780</td>
<td>900</td>
</tr>
<tr>
<td><strong>HIV RNA copies/mL</strong></td>
<td>19,000</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td><strong>HBV DNA IU/mL</strong></td>
<td>29,000,000</td>
<td>890,000</td>
<td>9,500</td>
<td>1,820</td>
</tr>
<tr>
<td><strong>HBeAg</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
What do you recommend now for management of his HBV infection?

1. Continue current therapy
2. Add entecavir
3. Add peg-IFN
4. Add telbivudine
5. Add famciclovir
HBV-Related Treatment Issues in HIV-Infected Patients

- Management of ART interruptions
- Approach to patients with persistent or intermittently positive low level HBV DNA
- Risks associated with LMVr
- *Treatment options for patients unable to use TDF*
- *Renal and bone toxicities associated with long-term TDF therapy*
Effect of ART Interruptions on HBV Replication Activity

- ART interruptions associated with high rate of HBV DNA rebound
- HBV DNRA rebound:
  - Higher for TDF than LMV reflecting greater HBV DNA suppression from baseline
  - Associated with decline in CD4 count
  - Lead to flares and rarely decompensation

SMART Study

<table>
<thead>
<tr>
<th></th>
<th>Continuous</th>
<th>Interrupted</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=46</td>
<td>N=54</td>
</tr>
</tbody>
</table>

% HBV DNA rebound

- Overall: 31-33%
- TDF-ART: 0%
- LMV-ART: <1%
- 60-89%

“Undesirable” Virologic Responses to Oral HBV Therapy

Change in HBV DNA (log_{10} IU/mL)

- Primary nonresponse
- Suboptimal response
- Nadir
- Virologic breakthrough

1 log

Monitoring on Therapy

- Lack of or suboptimal virologic response weeks
  - Check compliance
  - Check for resistance
  - Add or change to another drug
    - TDF/FTC or LMV with suboptimal response \(\rightarrow\) consider adding ETV\(^1\)

- ART interruptions
  - Risk of HBV flares if ART therapy interrupted and without provision of alternative HBV drug
  - Alternatives limited \(\rightarrow\) adefovir

- Flares of ALT during treatment
  - Generally well-tolerated but may be risk if underlying advanced fibrosis

\(^1\)Ratcliffe L, AIDS 2011;25:1051-6
Effect of Polymerase Mutations on HBsAg

- Pol overlaps S gene
- Reports in HIV-HBV coinfectected patients
- rtV191I mutation caused 44 aa deletion in HBsAg = HBsAg negative in serum
- Triple mutant (rtV163L+rtL180M+rtM204V) → S mutation D164D/I195M = vaccine escape mutant

Matthews G, AIDS 2006;20:863-70
HBV-HIV Summary

- HBV is dynamic disease - close monitoring needed
- Not all liver enzymes elevations in coinfected patients are due to HBV - look for other causes
- Treat all cirrhotics, even if decompensated
- Always treat HBV if treating HIV
- Always treat HBV if “active”
- Monitor for response and make changes if suboptimal virologic responses apparent
Increased Risk of Cirrhosis and ESLD Due to HIV/HCV Coinfection

Histologic Cirrhosis

- Makris (UK)
- Soto (Spain)
- Pol (France)
- Benhamou (France)
- Combined

Relative Risk:
- HCV Only: 0.76
- HIV/HCV: 1.0
- Relative Risk: 2.07
- Combined: 10.83

Decompensated Liver Disease

- Eyster (USA)
- Telfer (UK)
- Makris (UK)
- Lesens (Canada)
- Combined

Relative Risk:
- HCV Only: 0.61
- HIV/HCV: 1.0
- Relative Risk: 6.14
- Combined: 10

Graham, Clin Infect Dis. 2001
Of the following, which factor has NOT been associated with higher risk of cirrhosis in HCV-infected patients?

1. HCV viral load
2. Alcohol use
3. Marijuana use
4. Post-menopausal status
5. Older age at time of HCV exposure
Risk Factors for Progressive Fibrosis and Cirrhosis in HCV Mono-Infection

- Alcohol excess (>50 gm/day)
- Daily marijuana use
- High BMI, obesity, insulin resistance
- Longer duration of infection
- Age >40 years at time of infection
- Male gender, post-menopausal women
- Coinfections: HBV, HIV, Schistosomiasis
- Organ transplantation

Poynard T, Lancet 1997 349:825-32
Benhamou J, Hepatology 1999 30:1054-8
Kamal S, Hepatology 2006;43:771-779
Asselah T, Gut 2006, 55:123-130
### Predictors of Severe Liver Fibrosis in HIV/HCV Coinfected Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at biopsy &gt;35 y</td>
<td>2.95 (2.08 – 4.18)</td>
</tr>
<tr>
<td>Alcohol &gt;50 g/day</td>
<td>1.61 (1.1 – 2.35)</td>
</tr>
<tr>
<td>CD4 count &lt;500 cells/mm³</td>
<td>1.49 (1.06 – 2.08)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.26 (0.94 – 2.06)</td>
</tr>
</tbody>
</table>

- 46% of patients aged >40 had severe liver fibrosis compared to 15% of patients aged <30.
- Severe liver fibrosis was not associated with HCV genotype, HCV viral load, transmission route, or use of HAART.

*Martin-Carbonero, CID, 2004*
Treatment Goals

- **Viral eradication**
  - SVR
  - Sustained loss of HCV RNA in serum (6 mos post-Rx)

- **Prevention of disease progression**
  - Normalization of liver enzymes
  - Improved quality of life
  - Improved liver histology
  - Decreased cirrhosis
  - Decreased HCC
  - Improved survival
# HCV Treatment in 2012

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Drugs Used</th>
<th>Duration</th>
<th>SVR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peg-IFN, ribavirin, telaprevir or Peg-IFN, ribavirin, boceprevir</td>
<td>24-48 wks (RGT) 28-48 wks (RGT)</td>
<td>75% 68%</td>
</tr>
<tr>
<td>2</td>
<td>Peg-IFN, ribavirin</td>
<td>24-48 wks (RGT)</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>Peg-IFN, ribavirin</td>
<td>24-48 wks (RGT)</td>
<td>66%</td>
</tr>
<tr>
<td>4</td>
<td>Peg-IFN, ribavirin</td>
<td>48 wks</td>
<td>43-70% (~55%)</td>
</tr>
<tr>
<td>5</td>
<td>Peg-IFN, ribavirin</td>
<td>48 wks</td>
<td>55%</td>
</tr>
<tr>
<td>6</td>
<td>Peg-IFN, ribavirin</td>
<td>48 wks</td>
<td>70%</td>
</tr>
</tbody>
</table>

## Rationale to Undertake HCV Treatment

<table>
<thead>
<tr>
<th>In Favor</th>
<th>Against</th>
</tr>
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<tbody>
<tr>
<td>Need to reduce risk of progression to cirrhosis and liver-related morbidity</td>
<td>Poor tolerability</td>
</tr>
<tr>
<td>May improve ability to vive HAART</td>
<td>Patients often not treatment candidates</td>
</tr>
<tr>
<td>Decreased pool of infected persons</td>
<td>Drug interactions</td>
</tr>
<tr>
<td></td>
<td>Clinician comfort level low</td>
</tr>
<tr>
<td></td>
<td>Decreased response rates compared to HCV monoinfected</td>
</tr>
</tbody>
</table>
SVR Rates using PEG IFN + RBV in HIV/HCV Patients

First Direct Antiviral Agent (DAA) for Chronic HCV Genotype 1 Infection Approved

Boceprevir (BOC) or Telaprevir (TVR) in combination with peg-IFN and ribavirin (RBV)
  ▪ Indicated for both treatment-naïve and treatment-experienced patients genotype 1 HCV

▪ Telaprevir (Incevik®)
  ▪ 375 mg tablets – take 2 (750 mg total) TID (every 7-9 hours) with food (containing fat)

▪ Boceprevir (Vitrelis®)
  ▪ 200 mg tablets -- take 4 (800 mg total) TID (every 7 - 9 hours) with food
SVR Rates in G1 Treatment-Naive with PI-Combination Therapy

Key Host and Viral Factors Affecting SVR Rates

Treatment-naïve GT1 patients, BOC Triple Therapy

- F0-2 vs 3-4: 67 vs 41
- Non-AA vs AA: 74 vs 50
- CC vs CT vs TT: 82 vs 65 vs 55

Bruno S et al, EASL 2011, Abstract 195
SVR Rates with PI-Combination Therapy in G1 Rx-Experienced

Different Types of “Treatment Experienced”

- Null
- Partial
- Breakthrough
- Relapse

~ 60% of GHCV 1 patients fail Peg-IFN and RBV therapy

Adapted from M. Shiffman
TPV-Combination Therapy
SVR by Prior Response

N=354
Partial Responders N=124
Null Responders N=184
Overall, ITT

86%
57%
31%
65%

Key Elements of PI-Combo Therapy

Similarities
- RGT: early virologic response determines duration
- Futility rules used to minimize resistance
- Extended treatment in cirrhotics

Differences
- Lead-in with BOC
- No lead-in with TPV
- Duration of triple vs dual therapy
- Rules for RGT and futility differ
Treatment of Genotype 1 Chronic HCV with PI-Based Therapy Therapy

- SVR rates superior to Peg-IFN + RBV but several subgroups with suboptimal responses
  - ~15% lower if Black or advanced fibrosis or unfavorable IL28B genotype
  - Prior partial or null response to peg-IFN/RBV (SVR rate with PI is ≤50%)
- RGT offers shorter therapy to ~50-60% of patients
  - Early virologic responses highly predictive of SVR
  - Lead-in with Peg-IFN/RBV identified less responsive patient
  - Cirrhotics not eligible for shorter duration therapy
Increased Potential for Significant Drug-Drug Interactions

- **Telaprevir**
  - CYP3A4 and P-gp substrate
    - Non-cytochrome metabolism as well
  - CYP3A4 inhibitor

- **Boceprevir**
  - Aldoketoreductase (AKR) and CYP3A4/5 substrate
  - CYP3A4 and P-gp inhibitor

- **HIV PIs or NNRTIs, statins, antiarrhythmics, others**
Question #5

- 45 yo HIV-infected woman with chronic HCV infection. She has been on efavirenz, tenofovir and emtricitabine for past 3 years, tolerating well. HIV RNA <50 copies/mL and CD4 count 600/mm³

- HCV history:
  - No prior treatment
  - HCV RNA 3 million IU/mL, Genotype 1b, IL28B CT
  - Prior liver biopsy (2 years ago showed stage 2 fibrosis on scale of 4)
  - ALT 89, AST 100, other liver tests normal. Platelet 250K, Hgb 11.5, WBC 2.3.
She has heard about the drugs to treat HCV and is asking if you recommend treatment. What do you advise at this time?

1. Repeat biopsy to assess for progressive and offer treatment is F3 or higher
2. Treat with telaprevir, peg-IFN and RBV
3. Treat with peg-IFN and RBV, as data on Pis is too preliminary
4. Treat with boceprevir, peg-IFN and RBV
5. Don’t treat – wait for better therapies
Telaprevir Triple Therapy in HIV/HCV Coinfected Patients

Part A: no ART

1:1
T/PR: TVR + PR
PR48 (control): Pbo + PR

Follow-up
SVR

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

2:1
T/PR: TVR + PR
PR48 (control): Pbo + PR

Follow-up
SVR

Weeks 0 12 24 36 48 60 72

Dieterich D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 46
Telaprevir Triple Therapy in HIV/HCV Coinfected Patients (SVR12)

*Patient was defined as SVR12 if HCV RNA was < LLOQ in the visit window

Dieterich D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 46
Boceprevir Triple Therapy

- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization; 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

Sułkowski M, CROI, 2012. Abst. LB146
Virologic Response Over Time†

† Three patients undetectable at FW4 have not yet reached FW12 and were not included in SVR12 analysis.

Sulkowski M, CROI, 2012. Abst. LB146
SVR-12 by ARV Regimen on Day 1
not randomized by ART

<table>
<thead>
<tr>
<th></th>
<th>PR (N=34)</th>
<th>B/PR (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atazanavir/r</strong></td>
<td>8/13 (62%)</td>
<td>12/18† (67%)</td>
</tr>
<tr>
<td><strong>Lopinavir/r</strong></td>
<td>0/10 (0%)</td>
<td>10/15†† (67%)</td>
</tr>
<tr>
<td><strong>Darunavir/r</strong></td>
<td>0/5 (0%)</td>
<td>8/12 (67%)</td>
</tr>
<tr>
<td><strong>Other PI/r</strong>*</td>
<td>0/3 (0%)</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td><strong>Raltegravir</strong></td>
<td>1/3 (33%)</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td><strong>Other††</strong></td>
<td>0</td>
<td>0/2 (0%)</td>
</tr>
</tbody>
</table>

*Includes saquinavir, fosamprenavir and tipranavir; **Raltegrevir without concurrent HIV PI/r; ††Other ARVs were maraviroc and efavirenz

†Excludes 2 patients not yet at FW12 but undetectable at FW4 and ††† 1 not yet at FW12 but undetectable at FW4

Sulkowski M, CROI, 2012. Abst. LB146
HIV Breakthroughs in B/PR Group

- Overall, 7 patients had HIV breakthrough (>50 copies HIV RNA at 2 consecutive visits): 3/64 (5%) randomized to B/PR, and 4/34 (9%) to PR

<table>
<thead>
<tr>
<th>Regimen</th>
<th>BL</th>
<th>TW4</th>
<th>TW12</th>
<th>TW24</th>
<th>TW36</th>
<th>EOT</th>
<th>FW4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>---</td>
<td>659</td>
<td>---</td>
<td>53</td>
<td>2990</td>
</tr>
<tr>
<td>†LPV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>55</td>
<td>59</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>ATV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>243</td>
<td>---</td>
<td>7870</td>
</tr>
</tbody>
</table>

ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir
†The only subject to change ART. LPV/r changed to ATV/r at TW42; ATV/r to DRV/r at FW24.

Sulkowski M, CROI, 2012. Abst. LB146
Boceprevir, Telaprevir in HIV/HCV Patients

- Improved efficacy → 30% over peg-IFN/RBV
  - Similar to HCV monoinfected
  - Tolerability similar to HCV monoinfected
- But ……
  - Only applicable to genotype 1, treatment naïve
  - Still need 48 weeks treatment
  - Limited number of ART regimens that have been studied
HIV HCV Genotype 1 and PI-Peg/RBV Therapy

- If not on ART:
  - Use either boceprevir or telaprevir
- If on RAL + 2-NRTI:
  - Use either boceprevir or telaprevir
- If on ATV/r + 2-NRTI:
  - Use telaprevir
- If on EFV + 2-NRTI:
  - Use telaprevir at increased dose of 1125mg every 7–9 hours

Naggie et al, Gastroenterology 2012;143;1324-34.
PI-Triple Therapy Regimens
The Search for Better

- Treatment regimes more complex
  - Adherence issues, esp. with longer duration therapy
- The “toll” related to drug side effects
- Drug-drug interactions
  - ART, statins, others
- Resistance risk in NRs
  - May limit future treatment options, at least in short-term
Refining Direct Acting Antiviral Agents

Standard of Care for Genotype 1: Boceprevir or Telaprevir Combined with PEG/RBV

- Phase IV
- New Protease Inhibitors Combined with PEG/RBV
- Explore Knowledge Gaps for Special Populations
- Other Drug Classes Combined with PEG/RBV

IFN-FREE Multiple Drug Classes Combined
# Drugs in Development for HCV

*Only represents a sample of agents in development for HCV*

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Direct-acting antiviral agents</th>
<th>Host-targeting agents</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Inhibitor of polyprotein processing</td>
<td>Inhibitor of HCV replication</td>
</tr>
<tr>
<td>Target</td>
<td>NS3 or NS3/NS4A protease</td>
<td>NS5A</td>
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<tr>
<td></td>
<td>Nucleoside analogue</td>
<td>None</td>
</tr>
</tbody>
</table>

| Recently approved   | Irelaprevir (Vertex) | Boceprevir (Merck) | None | None | None | None | None |
|                     | TMC435 (Tibotec and Medvir) | BI201335 (Boehringer Ingelheim) | None | None | None | None | None |

| Phase III           | ABT-267 (Abbott) | Mericitabine (Roche) | IDX184 (Idenix) | Mericitabine (Roche) | PSL-5885 (Pfizer) | IDN-6556 (Idenix) | NIM811 (Novartis) | FEGylated interferon-λ (Bristol-Myers Squibb) | None |
|                     | BMS-790052 (Bristol-Myers Squibb) | BMS-791325 (Bristol-Myers Squibb) | ABT-072 (Abbott) | ANA598 (Novartis) | BAI207127 (Boehringer Ingelheim) | Topirovir (Vertex) | VCH-836 (Vertex) | None |
|                     | Denoprevir (Roche) | GS-9256 (Gilead) | IDX184 (Idenix) | Mericitabine (Roche) | PSL-5885 (Pfizer) | IDN-6556 (Idenix) | NIM811 (Novartis) | FEGylated interferon-λ (Bristol-Myers Squibb) | None |
|                     | GS-9451 (Gilead) | ABT-450/451 (Abbott and Enanta) | Vaniprevir (MK-7006; Merck) | None | None | None | None | None |

| Phase II            | AZD7295 (AstraZeneca) | PPI-461 (Presidio) | GS-6620 (Gilead) | INX-08189 (Inhibitex) | PSL-938 (Pharmasset) | GS-9620 (Gilead) | ITX-5061 (TTherX) | None |
|                     | AZH2028 (Achillion) | BMS-766 (Bristol-Myers Squibb) | EDP-239 (Enanta) | IDX380 and IDX719 (Idenix) | PPI-437, PPI-668, PPI-833 | None | None | None |
|                     | AVL-192 (Aegle) | QNS-227 (GenoScience Pharma) | PSI-661 (Pharmasset) | BILB 1941 (Boehringer Ingelheim) | None | None | None | None |

| Preclinical         | ACH-1095 (Achillion) | ACH-2684 (Achillion) | BMS-766 (Bristol-Myers Squibb) | EDP-239 (Enanta) | IDX380 and IDX719 (Idenix) | PPI-437, PPI-668, PPI-833 | None | None |

Interferon-Free Therapy
Boosted PI + NN-Pol Inhibitor + RBV

Treatment-Naive

Arm 1 (N=19)
ABT-450/r 250/100 mg QD
ABT-333 400 mg BID + RBV
Treatment-naive

Arm 2 (N=14)
ABT-450/r 150/100 mg QD
ABT-333 400 mg BID + RBV
Treatment-naive

Arm 3 (N=17)
ABT-450/r 150/100 mg QD
ABT-333 400 mg BID + RBV
Non-responders

RVR: pre-specified primary analysis based on HCV RNA < LLOD

eRVR: pre-specified primary analysis based on HCV RNA < LLOD

Genotype 1

Poordad F, EASL 2012
Whether to Treat Now vs Awaiting Future Therapies: Considerations*

- Likelihood of response and risk of waiting
  - Stage of fibrosis
  - Prior treatment history
    - Partial and null responders need better drugs

- Tolerability of peg-IFN and ribavirin
  - If previously treated – need details on why Rx stopped
  - Those with cirrhosis require 48 wks treatment – more risk of side effects, especially cytopenias

- Practical issues
  - Insurance status (now and anticipated) and co-pays
  - Support (at work and at home)

* N. Terrault opinion