Preparing for a new era in HCV treatment in the HIV-infected patient

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Tufts University School of Medicine
What is our understanding of HIV/HCV coinfection in 2011?

• What have we learned about HCV treatment responses with PEG/RBV in the HIV-infected patient to date?
• Will DAA agents truly make a difference in overall response rates in our patients?
• What else can we do to slow down fibrosis progression while we await new therapies?
PEG-IFN + Ribavirin lead to greater rates of SVR in HCV patients

Fried, M. NEJM 2002;347:975
Torriani, F. NEJM 2004; 351:348
What are the differences that set HIV/HCV patients apart?

Torriani, F. NEJM 2004; 351:348
PARADIGM trial examines role of weight-based RBV

Randomized 1:2

Wk 48

Interferon-naive patients coinfected with HIV and genotype 1 HCV (N = 410)

Peginterferon alfa-2a
180 μg/wk + Ribavirin 800 mg/day (n = 135)

Peginterferon alfa-2a
150 μg/wk + Ribavirin 1000-1200 mg/day (n = 275)

SVR rates similar (19 and 22%)

Rx discontinuation rates high (57 and 59%)

Ribavirin 1000 mg/day < 75 kg and 1200 mg/day ≥ 75 kg.

Sulkowski AASLD 2010
SVR rates in PROVE 2 trial with TPV

Lack of RBV leads to lower SVR

Hezode NEJM 2009; 360:1836
Effect of baseline HCV RNA on SVR

Torriani, F NEJM 2004; 351:438-450
HCV RNA levels are generally higher in HIV-infected patients

- In one study of 1266 hemophiliacs with HCV, concomitant HIV infection was associated with an increased risk of higher levels of HCV RNA compared to patients with HCV alone; (OR = 1.4)

Gadalla, SM J Viral Hep March 2010
Daar E JAIDS 2001;26:466

Lin Gastroenterology 2008; 134:803

*gp120 enhances HCV replication in a TGF-beta-1 dependent manner*
Slower viral clearance on PEG/RBV due to higher baseline levels

Baseline HCV RNA

No differences in Phase 1
No difference in Phase 2

HIV/HCV patients clear viremia an estimated 20 days later than patients with HCV alone

Sherman, K. Gastroenterology 2005; 128:313
PARADIGM Trial:
RVR predicts SVR in HIV/HCV G1

Sulkowski, MS AASLD 2010 Boston #920
PARADIGM: But the RVR+ patients make up a small piece of the pie

- RVR+: 8%
- RVR-: 92%

n=410
Week 4 response predicts SVR

Sulkowski, MS AASLD 2010 Boston #920
Of the patients who do achieve a 3 or 2 log drop...

- 3 log: 42%
- 2 log: 17%
- 1 log: 32%
- < 1 log: 9%

26% of remaining patients
Virologic clearance in HIV/HCV G 1 (n=176)

Rodriguez-Torres, M. AASLD 2007 #1300
Rates of virologic clearance in HIV/HCV genotype 1 (n=176)

Rodriguez-Torres, M. AASLD 2007 #1300
What we really need are....
Directly acting antivirals for HCV

McHutchison, J. NEJM 2009 360:1827-30
Seden, K. J Antimicrob Chemother March 2010
McGovern, B. Hepatology 2008; 48:1700-1712
Sorting out drug interactions....

- Telaprevir is a substrate and inhibitor of CYP3A
- Likely to interact with PIs and NNRTIs
Telaprevir AUC declines with PIs

Mean TVR PK Profiles

Best profile with atazanavir
How does TPV effect PI concentrations?

DRV AUC down 40%
FOS AUC down 47%
TPV dose escalations required with EFV

**Mean EFV PK Profiles and Statistics**

![Graph showing PK profiles and statistics for EFV with TPV dose escalations](image)

<table>
<thead>
<tr>
<th>TVR dose</th>
<th>Effect of TVR on EFV</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C\textsubscript{min}</td>
<td>C\textsubscript{max}</td>
<td>AUC\textsubscript{24h}</td>
<td></td>
</tr>
<tr>
<td>1125 mg q8h</td>
<td>0.90 (0.81–1.01)</td>
<td>0.76 (0.68–0.85)</td>
<td>0.82 (0.74–0.90)</td>
<td></td>
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<tr>
<td>1500 mg q12h</td>
<td>0.89 (0.82–0.96)</td>
<td>0.80 (0.74–0.86)</td>
<td>0.85 (0.79–0.91)</td>
<td></td>
</tr>
</tbody>
</table>
**Tenofovir PK profile similar regardless of increased TPV dosing**

**Mean Tenofovir PK Profiles and Statistics**

![Graph showing Tenofovir PK profiles](image)

<table>
<thead>
<tr>
<th>TVR dose</th>
<th>$C_{\text{min}}$</th>
<th>$C_{\text{max}}$</th>
<th>AUC$_{24\text{h}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1125 mg q8h</td>
<td>1.17 (1.06–1.28)</td>
<td>1.22 (1.12–1.33)</td>
<td>1.10 (1.03–1.18)</td>
</tr>
<tr>
<td>1500 mg q12h</td>
<td>1.06 (0.98–1.15)</td>
<td>1.24 (1.13–1.37)</td>
<td>1.10 (1.03–1.17)</td>
</tr>
</tbody>
</table>
Telaprevir in HIV/HCV patients with genotype 1 infection

**Study Design**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Part A: no ART</th>
<th>Part B: ART (EFV/TDF/FTC or ATV/r + TDF + FTC or TMC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/P/R</td>
<td>TVR + PR</td>
<td>TVR + PR</td>
</tr>
<tr>
<td>PR48 (control)</td>
<td>PR</td>
<td>PR</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up SVR</td>
<td>Follow-up SVR</td>
<td>Follow-up SVR</td>
<td></td>
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</tbody>
</table>

**No ART**

**With ART**

Courtesy of M. Sulkowski
Eligibility criteria

• All HCV treatment naive patients
• Liver biopsy within one year
• Compensated cirrhotics allowed
• **Part A:** No ART
  (CD4>500 cells; RNA<100,000 c/mL)
• **Part B:** ART with EFV or ATV + TDF/FTC
  (CD4>300 cells/mm3; NDVL)
Objectives

• Safety and tolerability
• Proportion with no detectable HCV RNA at 12 weeks
• Selection of resistant variants
Interim analysis

• Based on 59 of 60 patients who received one dose of treatment
• 41 of 59 reached 12 week point:
  ◦ 13 in Part A
  ◦ 46 in Part B
Undetectable HCV RNA at Week 4 (ITT)

RVR 70% vs 5%

Courtesy of M. Sulkowski
Undetectable HCV RNA at Week 12 (ITT)

![Chart showing treatment outcomes for HCV RNA levels with various treatment regimens.](chart.png)

Courtesy of M. Sulkowski

eRVR 68% vs 14%
PROVE 2: Phase 2 Clinical trial of Telaprevir

Hezode NEJM 2009;360:1839
Median Telaprevir Trough Plasma Concentrations were Similar with and without ART

TPV levels stable

Courtesy of M. Sulkowski
ART levels are stable
Mean HIV RNA Changes from Baseline

Probably PEG-related

Courtesy of M. Sulkowski
### Most Common Adverse Events*

<table>
<thead>
<tr>
<th></th>
<th>T/PR N=37</th>
<th>PR N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>38%</td>
<td>41%</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>Dizziness</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Reported in ≥ 15% of patients regardless of severity. Mild events: 5% or <5% greater than 15% points in any 1 group vs PR.

Mild and moderate rash events occurred in 15% and 11% of T/PR patients, respectively and in 14% and <1% of PR patients.

Courtesy of M. Sulkowski
**Serious Events and Treatment Discontinuation**

<table>
<thead>
<tr>
<th></th>
<th>Part A</th>
<th>Part B</th>
<th>Part C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No ART</td>
<td>EFV/TDF/FTC</td>
<td>ATV/r + TDF + FTC/3TC</td>
</tr>
<tr>
<td>T/PR</td>
<td>N=7</td>
<td>N=16</td>
<td>N=14</td>
</tr>
<tr>
<td>PR</td>
<td>N=6</td>
<td>N=8</td>
<td>N=14</td>
</tr>
<tr>
<td>Any AE, n(%)</td>
<td>7 (100)</td>
<td>15 (94)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Serious AE, n(%)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation at all study drugs due to AE, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Due to jaundice</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Due to anemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Due to rash</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Bacterial infection (n=2), anemia (n=1)

**Increased hyperbilirubinemia reported with ATV plus RBV**

Courtesy of M. Sulkowski; Rodriguez-Novoa  AIDS 2008; 22:2535
Interim analysis summary

- Higher proportions of patients achieve viral suppression at week 4 and 12 with TPV compared to SOC
- PK interactions acceptable
  - Remember higher doses of TPV with EFV!
- No unexpected effects on CD4/HIVRNA
- Side effects similar to trials in HCV
Is telaprevir ready for “prime-time” in HIV patients who are HCV treatment-naive?

• Still months away from SVR data...
• Small data set; more trials will be needed
• Background ART is an issue...
• Will HIV/HCV patients need 48 weeks of total treatment? Will 24 weeks be “good enough”
Second phase declines with DAA agents

IFN effectiveness

Telaprevir effectiveness

Guedj Hepatology 2011
What about the HIV G1 patient who is HCV Rx-experienced?

- Chance of SVR will likely follow same patterns as in HCV alone being treated with a HCV PI plus PEG/RBV...

- Is the patient a former....
  - Relapser?
  - Partial responder?
  - Null responder?

- Also the group at highest risk of drug resistance if rapid clearance is not attained - particularly G1a patients
Emergence of resistance-associated variants (RAVs) during SPRINT-2 and RESPOND-2

RAVs more common among G1a patients who received boceprevir

16-19% versus 10-11%

Brass CA EASL 2011 Berlin
Emergence of resistance-associated variants (RAVs) during SPRINT-2 and RESPOND-2

Risk of emergence of RAVs higher among Non-SVR patients

42% to 58% of patients with non-SVR have RAVs
What will be the impact of drug resistance in the HIV/HCV patient?

• Will levels of HCV viremia in the HIV-infected host be a stumbling block again?
• Will the relative lower efficacy of PEG/RBV come to haunt us again with our nonresponder patients?
Implications of HCV drug resistance

- Broad cross-resistance among first generation HCV PIs (BOC, TPV, BI, TMC435)
- Polymerase inhibitors less potent but with high genetic barrier to resistance
- Urgent question:
  ◦ Will resistance be archived?
- The answer will directly impact whether we need a strategy for “drug sequencing” or not....
Does HCV drug resistance fade with time?

- HCV is not integrated into the host genome
  - Replicates in cytoplasm
- Phase 3 clinical trial of TPV demonstrate that wild-type replaces resistant variants in 71% of patients by one year of follow-up
  - Caveat: population sequencing assays were used
- In the patient with advanced fibrosis, the clock is ticking....

Sullivan, JC EASL 2011 Berlin; Zeuzem, S Hepatology 2010; 52:S436A
Boceprevir and the HIV/HCV patient

- Phase 2 treatment trial in progress
- Biotransformation via cyp3A4 and aldo keto reductase (AKR)
- No meaningful interaction with tenofovir
- 44% declines seen in BOC Cmin when given with efavirenz

Kassera CROI 2011; Abstract #118
Boceprevir and HIV/HCV

• Side effects:
  ◦ Anemia
  ◦ Dysgeusia
Until more data are available, what can we do to...

- Slow the pace of fibrosis progression?
- Limit hepatic steatosis?
ART for “liver health”
Liver deaths remain important cause of mortality in HIV infected patients*

- 23,441 patients (11 cohorts in Europe, USA, Australia)
- 1248 deaths (5.3%) 2000-2004
- 14% liver-related
  - Risk higher with low CD4+ T cell counts

Risk of drug-induced liver injury increased in HIV-infected patients with chronic viral hepatitis

Early ART and drug toxicity

Arch Intern Med. 2006; 166:1632-41; JIAPAC 2011;10:5-11
Getting “SMART” about HIV pathogenesis

- Trial stopped early because of increased mortality in AIDS (OR=2.2) and non-AIDS deaths (OR=1.6) in the discontinuation arm.

- Risk of mortality higher in those with baseline elevations in IL-6, CRP...

Neuhaus, J. AIDS 2010; 24:697-706
Could a “leaky gut” be linked to chronic immune activation?

Microbial translocation as a cause of immune activation

Plasma LPS (pg/ml)

- Uninfected
- Acute/early
- Chronic
- AIDS

P-values:
- P < 0.0001
- P = 0.842
- P < 0.0001
- P < 0.0001

ART leads to decline in LPS

Giorgi, JV. J Infect Dis 1999; 179:859
Role of LPS in other liver diseases

- Alcoholic liver disease
- Activation of TLR4, which increases stellate cell susceptibility to injury
- Progression of HCV
  - IFN treatment lowers LPS levels in HCV infected patients
- Role in hepatotoxicity
Microbial translocation and liver disease

- Well characterized cohort of patients with well-defined course of HIV and HCV disease
  - 17 HCV cases with cirrhosis or ESLD
  - 71 controls with minimal liver disease
- 32% with HIV seroconversion

Balagopal, A. Gastroenterology 2008; 135:226
Microbial translocation and liver disease

- Cross-sectional findings of Brenchley’s group were confirmed:
  - Markers of microbial translocation (eg, LPS, sCD14) were associated with CD4 depletion
  - LPS was strongly associated with cirrhosis (OR 19)
Inflammatory markers in HBV or HCV without concomitant HIV

**NIH cohort:**
- 16 HBV or HCV patients with minimal fibrosis
- 68 with cirrhosis; 40 controls

sCD14, IL-6, LPS and I-FABP (marker of enterocyte death) at enrollment and following antiviral treatment for HCV or HBV....

sCD14 and IL-6 correlated with inflammation/fibrosis

Successful antiviral therapy for HBV or HCV led to declines in IL-6 and I-FABP levels...**but not in sCD14 or LPS** levels

SCD14 levels independently predict mortality in HIV-infected patients

We need to know the coinfection status of HIV patients when we study microbial translocation
death) at enrollment and following antiviral treatment for HCV or HBV....

Similar factors that drive disease progression in HIV also apply to HCV and HBV...

Sandler, N CROI 2011 Abstract #939; Sandler N JID 2011;203:780-90
HIV suppression associated with slower fibrosis progression rates

Brau, N. J Hep 2006; 44:47
SLAM-C trial halted due to non-progression in ART alone arm
HIV and the liver

HCV/HIV co-infection: time to re-evaluate the role of HIV in the liver?
J. T. Blackard and K. E. Sherman. Division of Digestive Diseases, University of Cincinnati College of Medicine, Cincinnati, OH, USA

• Increased oxidative stress
• Kupffer cell depletion in AIDS

Lin Gastroenterology 2008; 134:803; Balagopal, A AIDS 2009; 23:2397
“A one-two punch to the gut by HIV”

Kim, AY Chung, RT. Gastroenterology 2009; 137:795
“A one-two punch to the gut by HIV....”

...leading to collateral damage to the liver...

Kim, AY Chung, RT. Gastroenterology 2009; 137:795
APRICOT conducted in the early ART era

Which antiretroviral drugs were available at this time?

HIV/HCV patients

Torriani, F. NEJM 2004; 351:348
### 2002

**Nucleoside analogs**
- AZT
- Lamivudine
- Abacavir
- Didanosine
- Stavudine
- Tenofovir (approval end of 2001)

**Non-Nucleoside reverse transcriptase inhibitors**
- Efavirenz
- Nevirapine

**Protease inhibitors**
- Lopinavir
- Nelfinavir
- Indinavir
- Ritonavir

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**HIV guidelines:**
Treat patients with CD4 count <200 cells

Dybul, M. Annals IM 2002; 137:381
Early days of potent ART in treatment-naive patients

Importance of ritonavir “boosting”

Walmsley, S. NEJM 2002; 346: 2039-46
Now...virologic suppression in vast majority of patients

qMRK trial with RAL with 89% SVR in BID arm

Ortiz, R. AIDS 2008; 22:1389
Treatment survey of HIV/HCV patients

- SVR
- CD4>350
- NDVL

Provider expertise?
Better HIV parameters?

Cacoub J Hep 2010; 53:230
“Hit hard, hit early...” returns...

- Timing of the initiation of ART continues to shift......

>500 cells?

"HIV treatment may reduce inflammation and immune activation, which may contribute to high rates of other co-morbidities"

DHHS HIV Treatment Guidelines December 2009
Fibrosis of the gut limits immune reconstitution

Estes, J. J Infect Dis 2008; 198:456-64
The other side of the coin of ART...

- Drug-induced liver injury
  - Nevirapine and hypersensitivity
  - Didanosine and nodular regenerative hyperplasia
- Hepatic steatosis
- Insulin resistance and hyperlipidemia
Drug-induced liver injury: nevirapine

• Early reports of liver toxicity and fatal cases of liver failure
• Strict parameters for use of NVP according to CD4 counts
• “Switch studies” showing there is no increased risk of hepatotoxicity in virologically suppressed patients....even those with a high CD4 cell count....

• Favorable lipid profiles

What is the trigger for drug-induced liver injury?

- Role of LPS and other pro-inflammatory cytokines

Roth, R J Pharm and Exp Ther 2010; 332:692
Eradication of HCV is critically important!

- SVR associated with a decreased risk of HTOX
- Treatment for HCV enables treatment for HIV
- Related to improved liver fibrosis?
- Related to changes in the milieu of proinflammatory cytokines?

Labarga JID 2007; 196:670; McGovern CID; 45:1386
Hepatic steatosis

• Associated with:
  • HCV genotype 3

Steatosis of any etiology supplies the “fuel for the fire” of lipid peroxidation

• Hyperlipidemia
• Diabetes
• Visceral adiposity
Lipodystrophy Syndrome | HCV genotype 3 infection | Nucleoside analogs

Hepatic steatosis

ETOH | Reactive oxygen species | MTOX

Oxidative stress

Inflammation

Lipid peroxidation

TNF, IL-6

Stellate cell activation

Fibrosis

Hepatic steatosis associated with central body fat

- DEXA scans in 173 HIV/HCV coinfected patients within 12 months of liver biopsy
- Steatosis associated with:
  - Central body fat and...
  - Detectable HIV RNA....

Brown, T. AIDS 2010; 24:811
Natural history of steatosis in HIV/HCV

- 222 mainly AA patients

Risk factors for steatosis progression:
- Alcohol abuse
- Overweight/obesity

Implications: As ART has improved, risk of hepatic steatosis may decline...

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**Graph:**
- Percentage of patients with stable, increasing, and decreasing fibrosis levels for Trivial fat and Significant fat.

- Stable: Black bars
- Increase: Gray bars
- Decrease: White bars

- Y-axis: Percentage
- X-axis: Fibrosis status (Stable, Increase, Stable, Decrease)
Mortality continues to decrease: D:A:D cohort from 1999-Feb 2008

Median CD4 count of 408 cells/mm³; 49% had NDVL

Hypertension and diabetes associated with increased liver-related and all-cause mortality

DAD cohort AIDS 2010; 24:1537-1548
Importance of insulin resistance

- Insulin resistance associated with:
  - Decreased SVR rates
  - Fibrosis progression
  - Certain antiretroviral medications (ZDV, older PIs)

Merchante, N. Gut 2009; 58;1654; Blanco, F. J Viral Hepatitis 2010
Scrutinize the patient from a “liver-point of view”

- Decrease risk of mitochondrial toxicity (e.g., avoid stavudine, didanosine)
- Maintain HIV suppression with potent ART
- Education about the harms of alcohol abuse
- Address insulin resistance (e.g., review antiretroviral medications; treatment of HCV genotype 1)

Interventions to decrease/prevent hepatic steatosis in HIV/HCV coinfected patients

- Switch ART in treatment-experienced patients who are taking older agents
- Use of “metabolically friendly” antiretroviral medications (e.g., atazanavir, darunavir, nevirapine, raltegravir)
- Early treatment of HIV, regardless of CD4 T cell count
- Viral eradication of HCV genotype 3
- Weight reduction/exercise counseling for overweight patients

Address hyperlipidemia (consider switch to nevirapine, raltegravir, atazanavir; initiate lipid-lowering agents)

McGovern, BH Gastroenterology 2011
Will STAT-C be the “great equalizer” for HIV/HCV coinfected patients?

Courtesy of M. Sulkowski
Importance of SVR in HIV/HCV

- 711 patients undergoing HCV therapy 2000-2005
- 31% achieve SVR
- Follow-up over mean of 21 months

Similar overall mortality benefit after SVR in VA cohort

SVR associated with decreased liver-related mortality and... overall mortality!

Rx of HIV

Rx of HCV

Decreased overall mortality
Rx of HIV

Decreased overall mortality

Common link?

Rx of HCV
What will be the therapeutic landscape within the next decade?

Antiviral therapy
Earlier ART
Cytokine targets
Anti-fibrotic agents
Agents that influence gut microbiota
Will the outlook regarding liver disease improve for our HIV-infected patients?