Faculty and Planning Committee Disclosures:
Please consult your program book.

Off-Label Disclosure:
The following off-label/investigational uses will be discussed in this presentation: investigational NAFLD/NASH medications
Objectives

• To recognize unique aspects of treating HCV in the setting of HIV infection
• To describe the post-SVR management of HIV/HCV-coinfected patients who achieve HCV cure
• To review the work-up of abnormal liver tests in HIV-infected patients without viral hepatitis coinfection
Meet the Professor: Hepatitis and Other Liver Diseases in Individuals with HIV

Jennifer Price, MD, PhD
Assistant Professor of Medicine
Division of Gastroenterology and Hepatology
University of California, San Francisco
Case 1

- 50 y/o man with HIV/HCV, history of IDU
- HIV history:
  - Stable on TAF/FTC/elvitegravir/cobicistat (Genvoya)
- HCV history:
  - Treatment naïve
  - Genotype 1b
- PMH: negative
- Other medications: methadone maintenance
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- Labs
  - Albumin 4, t bili 0.5, AST 40, ALT 35, Cr 0.6, INR 1.0, platelets 250
  - CD4 568; HIV RNA not detected
  - HBsAb+, HBsAg-, HBcAb-

- Fibroscan
  - Median liver stiffness 6.1 consistent with F0-F1 fibrosis
Case 1

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He is interested in HCV treatment- is he a candidate?
AASLD/IDSA and DHHS Guidance: HIV/HCV Coinfection

• All pts with HIV should be screened for HCV\textsuperscript{[1]}
• HCV treatment candidacy nearly universal\textsuperscript{[2]}
  – HIV coinfection creates unique considerations for pts with HCV, particularly potential drug interactions between HCV and HIV antivirals
• Even with potent HIV ARVs, pts with HIV/HCV coinfection are at increased risk for rapidly progressive liver disease\textsuperscript{[2]}

“HIV ARV therapy is not a substitute for HCV treatment”\textsuperscript{[2]}

AASLD/IDSA Recommendations for First-line HCV Treatment in HIV/HCV Coinfection

Treatment in HIV/HCV should be the same as in HCV monoinfection after consideration of potential drug–drug interactions between DAAs and ARVs

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*If GT1a with BL NS5A RASs for EBR, 12 wks not recommended; can increase duration to 16 wks with RBV (alternative). † Some data to support 8 wks in GT1, but 8 wks not recommended in HIV/HCV coinfection. ‡ If decompensated cirrhosis, do not use HCV protease inhibitors. § If BL Y93H RAS present in GT3, add RBV or consider SOF/VEL/VOX. ‡‡ If also cirrhotic, increase duration to 12 wks.


Slide credit: clinicaloptions.com
## HIV/HCV Drug–Drug Interactions

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<td>X</td>
</tr>
<tr>
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<td>✓*</td>
<td>✓*†</td>
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<tr>
<td>LPV + RTV</td>
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<td>EVF</td>
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<tr>
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*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes owing to lack of clinical safety data.

Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
## Case 1 Continued

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</table>

- Insurance company strongly prefers GZR/EBR based on their formulary
- His HIV has been treated with TAF/FTC/Elvitegravir/cobi (Genvoya)

Is this regimen suitable for him?
## HIV/HCV Drug–Drug Interactions

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<td>✓*</td>
<td>X</td>
</tr>
<tr>
<td>ETV</td>
<td>X</td>
<td>X</td>
<td>✓*</td>
<td>X</td>
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</tr>
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<tbody>
<tr>
<td>zepatier</td>
<td>Elvitegravir</td>
<td>Check HEP/ HEP drug interactions</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>Elvitegravir</td>
<td>Do Not Coadminister</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>Elvitegravir</td>
<td></td>
</tr>
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https://www.hep-druginteractions.org/checker
HEP Drugs | Co-medications
---|---
zepatier | Elvitegravir
Elbasvir/Grazoprevir | Elvitegravir/cobi/FTC/TAF
Elbasvir/Grazoprevir | Elvitegravir/cobi/FTC/TAF

Summary:
Coadministration is not recommended as it may substantially increase grazoprevir exposure. Coadministration with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide has not been studied. However, coadministration with elvitegravir/cobicistat/emtricitabine/tenofovir-DF increased grazoprevir exposure by ~5.4-fold. A similar increase would be expected with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

Description:
Coadministration of elbasvir/grazoprevir and OATP1B inhibitors such as cobicistat is contraindicated because it may significantly increase grazoprevir plasma concentrations.


https://www.hep-druginteractions.org/checker
Case 1 Continued

Options:

1. Petition for different HCV regimen
   - GLE/PIB x 8 weeks
   - SOF/LDV x 12 weeks
   - SOF/VEL x 12 weeks

2. Change HIV regimen
   - Consider Dolutegravir/ABC/3TC or Rilpivirine/TAF/FTC

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Insurance approves SOF/LDV. Are there any other concerns?
# AASLD/IDSA Recommendations for LDV or VEL With Tenofovir


## Guidance for Coadministration With TDF[^1]*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Without COBI or RTV</th>
<th>With COBI or RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/LDV</td>
<td>Monitor[^2]</td>
<td>Monitor; consider TAF or ART switch</td>
</tr>
<tr>
<td>SOF/VEL</td>
<td>Monitor</td>
<td>Monitor; consider TAF</td>
</tr>
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<td>SOF/VEL/VOX</td>
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## Guidance for Coadministration With TAF[^1]

<table>
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<tr>
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<th>Guidance</th>
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<tbody>
<tr>
<td>SOF/LDV, SOF/VEL, SOF/VEL/VOX</td>
<td>No significant interaction</td>
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</table>

[^1]: Guidance assumes normal renal function (eGFR > 60 mL/min).

[^2]: Monitor for potential drug interactions.

---

*If eGFR < 60 mL/min, avoid TDF coadministration with SOF/LDV, SOF/VEL, or SOF/VEL/VOX.
# AASLD/IDSA Recommendations for LDV or VEL With Tenofovir

**Guidance for Coadministration With TDF**

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**Guidance for Coadministration With TAF[^1]**

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*If eGFR < 60 mL/min, avoid TDF coadministration with SOF/LDV, SOF/VEL, or SOF/VEL/VOX.

**“For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended”**
Case 2

- 47 y/o MSM with HIV/HCV
- HIV history:
  - Stable on EFV/FTC/TDF (Atripla)
- HCV history:
  - Treatment naïve
  - Genotype 3a
- Compensated cirrhosis
Case 2

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• HIV history:
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What are your preferred treatment options?
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Treatment in HIV/HCV should be the same as in HCV monoinfection after consideration of potential drug–drug interactions between DAAs and ARVs

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Slide credit: clinicaloptions.com
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<td>✓</td>
</tr>
<tr>
<td>TDF</td>
<td>✓</td>
<td>✓*</td>
</tr>
</tbody>
</table>

*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes owing to lack of clinical safety data.

Slide credit: clinicaloptions.com
Alternative Options for Treatment-Naive GT3 HCV With Compensated Cirrhosis?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration, Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td></td>
</tr>
<tr>
<td>▪ GLE/PIB</td>
<td>12</td>
</tr>
<tr>
<td>▪ SOF/VEL*</td>
<td>12</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td></td>
</tr>
<tr>
<td>▪ SOF/VEL/VOX</td>
<td>12</td>
</tr>
<tr>
<td>▪ DCV + SOF ± weight-based RBV</td>
<td>24</td>
</tr>
</tbody>
</table>

*If Y93H, add RBV or use SOF/VEL/VOX as alternative.

### HIV/HCV Drug–Drug Interactions

<table>
<thead>
<tr>
<th>ARV(s)</th>
<th>GLE/PIB</th>
<th>SOF/VEL</th>
<th>SOF/VEL/VOX</th>
<th>SOF + DCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV + (RTV or COBI)</td>
<td>![X]</td>
<td>![✓*]</td>
<td>![X]</td>
<td>![↓ DCV dose]</td>
</tr>
<tr>
<td>DRV + (RTV or COBI)</td>
<td>![X]</td>
<td>![✓*]</td>
<td>![✓*†]</td>
<td>![✓]</td>
</tr>
<tr>
<td>LPV + RTV</td>
<td>![X]</td>
<td>![✓*]</td>
<td>![X]</td>
<td>![✓]</td>
</tr>
<tr>
<td>EFV</td>
<td>![X]</td>
<td>![X]</td>
<td>![X]</td>
<td>![↑ DCV dose]</td>
</tr>
<tr>
<td>RPV</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
</tr>
<tr>
<td>DTG</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
</tr>
<tr>
<td>RAL</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
</tr>
<tr>
<td>EVG/COBI/FTC/TDF</td>
<td>![✓*†]</td>
<td>![✓*]</td>
<td>![✓*†]</td>
<td>![↓ DCV dose]</td>
</tr>
<tr>
<td>EVG/COBI/FTC/TAF</td>
<td>![✓†]</td>
<td>![✓]</td>
<td>![✓†]</td>
<td>![↓ DCV dose]</td>
</tr>
<tr>
<td>3TC/ABC</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
</tr>
<tr>
<td>TAF</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
<td>![✓]</td>
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<tr>
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*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes owing to lack of clinical safety data.


Slide credit: clinicaloptions.com
Principles of Regimen Switching in Virologically Suppressed Pts

- Review ART history for:
  - Prior intolerance or HIV virologic failure
  - HIV resistance test results
- If prior HIV resistance uncertain, consider switch only if new regimen likely to maintain suppression of resistant virus
- In pts with HIV/HBV, continue ARVs active against HBV (even if not needed for HIV suppression)
  - (TAF or TDF) plus (3TC or FTC)

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- If prior HIV resistance uncertain, consider switch only if new regimen likely to maintain suppression of resistant virus
- In pts with HIV/HBV, continue ARVs active against HBV (even if not needed for HIV suppression)
  - (TAF or TDF) plus (3TC or FTC)
- Switches usually maintain HIV suppression if no resistance to drugs in new regimen
- Check HIV-1 RNA during first 3 months after switch to ensure suppression
- Boosted PI or INSTI monotherapy not recommended

My approach: ≥ 4-wk adjustment before starting HCV DAAs to ensure ART is tolerated and effective

Does Switching ART Affect Likelihood of HCV Cure?

- Real-world, single-center, cohort study of HIV/HCV-coinfected pts treated with DAAs (N = 255)

Pt's Achieving SVR (%)

<table>
<thead>
<tr>
<th>Change in ART</th>
<th>n/N = 72/78</th>
<th>92.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Change in ART</td>
<td>n/N = 174/177</td>
<td>98.3</td>
</tr>
</tbody>
</table>

P = .02
Case 2 Continued

• 47 y/o MSM with HIV/HCV
• HIV history:
  – Stable on EFV/FTC/TDF (Atripla)
• HCV history:
  – Treatment naïve
  – Genotype 3a
• Compensated cirrhosis

• Pt switched to DTG + FTC/TAF
• Other options:
  – EVG
  – RAL
  – RPV
• Treated with SOF/VEL x 12 weeks and achieved SVR12 (cure)
Case 2 Continued

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- HIV history:
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- HCV history:
  - Treatment naïve
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- Compensated cirrhosis

What are the next steps in management?

- Pt switched to DTG + FTC/TAF
- Other options:
  - EVG
  - RAL
  - RPV
- Treated with SOF/VEL x 12 weeks and achieved SVR12 (cure)
HCV Care Continues Past Achievement of SVR

- Diagnosis
  - Linkage to care
  - Treatment
  - Cure

Persons at risk for infection:
- Counseling
- Harm reduction (injection and sex practices)
- Surveillance for reinfection

Persons with advanced fibrosis (stage 3/4):
- Counseling
- Harm reduction (alcohol and obesity)
- Surveillance for HCC

HCV Reinfection Risk After SVR in HIV/HCV-Coinfected Pts

Prospective cohort study of risk factors for HCV reinfection in HIV/HCV-coinfected pts achieving SVR (N = 257)


Slide credit: clinicaloptions.com
## HCV Care Continues Past Achievement of SVR

### Post-Treatment Follow-Up for Patients Who Achieved a Sustained Virologic Response

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients who do not have advanced fibrosis (i.e., those with Metavir stage F0, F1, or F2), recommended follow-up is the same as if they were never infected with HCV.</td>
<td>I, B</td>
</tr>
<tr>
<td>Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV-RNA test rather than an HCV-antibody test is recommended to assess for HCV recurrence or reinfection.</td>
<td>I, A</td>
</tr>
<tr>
<td>Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for patients with advanced fibrosis (i.e., Metavir stage F3 or F4) who achieve SVR.</td>
<td>I, C</td>
</tr>
<tr>
<td>A baseline endoscopy is recommended to screen for varices if cirrhosis* is present. Patients in whom varices are found should be treated and followed as indicated.</td>
<td>I, C</td>
</tr>
<tr>
<td>Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving SVR.</td>
<td>I, C</td>
</tr>
</tbody>
</table>

* For decompensated cirrhosis, please refer to the appropriate section.

Case 3

- 60 y/o man with HIV, CKD, DM, hyperlipidemia presents with elevated liver enzymes
- HIV history:
  - Diagnosed in 1985
  - Started treatment in late 1990’s
    - History of d4t
    - Treatment interruption for a year in early 2000’s
    - Currently on EFV + FTC/TAF (Descovy)
  - Other meds: aspirin 81 mg daily, fenofibrate, ezetimibe, niacin, metformin, DHEA
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  - Other meds: aspirin 81 mg daily, fenofibrate, ezetimibe, niacin, metformin, DHEA
- Family history
  - Cryptogenic cirrhosis in father, paternal grandmother, paternal aunt & uncle
- Social history
  - Never smoker; No illicit drugs, 2 alcoholic drinks/week
  - Sexually active, male partners, condoms with HIV- partners
Case 3

• Labs:
  – Cr 1.36, albumin 4.5, t bili 1.2, AST 78, ALT 56, alk phos 41
  – WBC 7.0, Hgb 42.5, platelets 195, INR 1.0
  – CD4 592, HIV not detected
  – HgA1C 6.1
  – Total cholesterol 204, triglycerides 238, HDL 38, LDL 118
• Imaging:
  – Abdominal ultrasound: mildly enlarged liver with diffuse fatty infiltration, borderline enlarged spleen
• Vitals: BP 128/82, HR 59, BMI 28.6
• Physical exam: appears fit with central obesity
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  – Cr 1.36, albumin 4.5, t bili 1.2, AST 78, ALT 56, alk phos 41
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Work-up Suspected NAFLD

Evaluate for other causes EtOH, HBV, HCV, autoimmune hepatitis, iron overload

- Evaluation of other causes of liver disease
  - EtOH: 2 drinks/week
  - HBsAg, HBsAb, HBcAb negative
  - HCV Ab negative (HCV RNA checked previously and negative)
  - ANA negative, Anti-smooth muscle antibody negative, IgG normal
  - A1AT normal
  - Ferritin, iron, and % saturation normal

Adapted from Rinella ME, Nat Rev Gastroenterol Hepatol, 2016
Work-up Suspected NAFLD

Evaluate for other causes EtOH, HBV, HCV, autoimmune hepatitis, iron overload

Risk stratification for liver-related outcomes
• Age, features of metabolic syndrome
• Non-invasive serum and imaging surrogates for fibrosis

High risk features:
– Age 60, diabetes, dyslipidemia, central obesity

Noninvasive surrogates:
– FIB-4: 3.21
– APRI: 0.952
– NAFLD fibrosis score: 2
– Fibroscan: LS 7.3 kPa

Adapted from Rinella ME, Nat Rev Gastroenterol Hepatol, 2016
Risk stratification in NAFLD

**Suspected NAFLD**

Evaluate for other causes: EtOH, HBV, HCV, autoimmune hepatitis, iron overload

**Risk stratification for liver-related outcomes**

- Age, features of metabolic syndrome
- Non-invasive serum and imaging surrogates for fibrosis

**Low-risk profile**
- Age <40
- No diabetes or metabolic syndrome features
- Non-invasive serum and imaging surrogates for fibrosis suggest F0-F1*
  - APRI < 0.5
  - FIB-4 < 1.30
  - NFS < -1.455
  - VCTE < 7 kPa

Follow, reassess as risk factors, tests evolve

**Intermediate-risk profile**
- Age > 40
- Multiple metabolic syndrome features
- Non-invasive serum fibrosis markers for indeterminate*
  - APRI 0.5-1.5
  - FIB-4 1.30-2.67
  - NFS -1.455-0.675
  - VCTE 7-10 kPa

Consider liver biopsy

**High-risk profile**
- AST > ALT
- Platelets < 150,000
- Non-invasive serum or imaging surrogates for fibrosis suggest ≥ F3*
  - APRI > 1.5
  - FIB-4 > 2.67
  - NFS > 0.675
  - VCTE > 10 kPa

Consider liver biopsy in absence of overt cirrhosis

*optimal cut-offs unclear, especially in HIV+

Adapted from Rinella ME, Nat Rev Gastroenterol Hepatol, 2016
Case 3

• Liver biopsy:
  – Portal tracts with mild lymphoplasmacytic inflammation
  – Hepatic parenchyma shows severe steatosis (grade 3, scale 0-3) with rare non-classical ballooned hepatocytes
  – Centrizonal pericellular and portal fibrosis (stage 2, scale 0-4)
  – Iron stain negative
  – Overall, features are of steatohepatitis with centrizonal and portal fibrosis (F2)
Treatment of NAFLD

• Weight loss: goal 7-10% or more weight loss
  – Improve NASH and fibrosis
  – 3-5% weight loss improves steatosis

• Diet
  – Decrease calorie intake by 500-1,000 kcal/day
  – Avoid fructose-sweetened beverages, added sugars

• Exercise alone reduces steatosis
  – Aerobic >150-250 minutes/week; should reach moderate or vigorous intensity
  – Resistance training 45 minutes/day x 3 days/week

• Treat diabetes, hypertension, dyslipidemia
Pharmacologic Treatment of NASH

- Pioglitazone 30 mg/day
  - Improved NASH and fibrosis in PIVENS trial but did not achieve statistical significance in primary endpoint
  - Associated with weight gain, bone fractures, long-term safety
- Vitamin E for confirmed NASH in non-diabetic; 800 IU/day
  - Improved NASH in PIVENS trial
  - Increased risk of bleeding, prostate cancer, and possibly hemorrhagic stroke
- Metformin is not recommended
- Liraglutide: histologic improvement in LEAN trial; premature to recommend
- Statins: inconsistent results as treatment for NASH
  - Safe in patients with NAFLD/NASH- do not withhold

ART Considerations in NAFLD

- Avoid stavudine and didanosine
- Choose regimen with favorable metabolic profile
- Study of 39 pts on efavirenz + TDF/FTC or ABC/3TC, 19 randomized to switch from efavirenz to raltegravir
  - RAL group had decreased CAP-measured fatty liver and lower proportion with fatty liver compared to EFV group

# NAFLD/NASH: Emerging Treatments, Phase III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Study Population</th>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elafibranor</td>
<td>PPAR α/δ agonist</td>
<td>NASH with fibrosis (stage 1-3)</td>
<td>RESOLVE-IT⁴</td>
<td>NASH resolution without fibrosis worsening; long-term composite of all-cause mortality, cirrhosis, and liver-related outcomes</td>
</tr>
<tr>
<td>Obeticholic acid</td>
<td>FXR agonist</td>
<td>NASH with fibrosis (stage 1-3)</td>
<td>REGENERATE⁵</td>
<td>Fibrosis improvement without NASH worsening; NASH resolution without fibrosis worsening; all-cause mortality and liver-related outcomes</td>
</tr>
<tr>
<td>Selonsertib</td>
<td>ASK1 inhibitor</td>
<td>NASH with fibrosis (stage 3)</td>
<td>STELLAR 3⁶</td>
<td>Fibrosis improvement without NASH worsening, EFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NASH with compensated cirrhosis</td>
<td>STELLAR 4⁷</td>
<td>Fibrosis improvement without NASH worsening</td>
</tr>
<tr>
<td>Cenicriviroc</td>
<td>CCR2/5 antagonist</td>
<td>NASH with fibrosis (stage 2/3)</td>
<td>AURORA⁸</td>
<td>Fibrosis improvement without NASH worsening; composite of progression to cirrhosis, liver-related outcomes, and all-cause mortality</td>
</tr>
</tbody>
</table>

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¹ClinicalTrials.gov. NCT02704403. ²ClinicalTrials.gov. NCT02548351. ³ClinicalTrials.gov. NCT03053050. ⁴ClinicalTrials.gov. NCT03053063. ⁵ClinicalTrials.gov. NCT03028740. ⁶Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
NAFLD Pharmacologic Treatment in HIV+

• Tesamorelin
  – Synthetic growth hormone-releasing hormone, targets visceral fat
  – 50 HIV+ patients randomized to tesamorelin 2 mg (n=28) or placebo (n=22) SC daily x 6 months
  – Modest but significant reduction in liver fat in tesamorelin group vs placebo
  – ClinicalTrials.gov Identifier: NCT02196831

• Aramchol
  – Fatty acid-bile acid conjugate
  – Reduction in liver fat in phase 2 trial in primary NAFLD
  – 50 HIV+ patients with lipodystrophy and NAFLD
  – Failed to meet primary endpoint of improvement in liver fat at 12 weeks

Case 4

• 60 y/o man with HIV, DM, lipodystrophy, and h/o CMV retinitis presents with refractory ascites and hepatic encephalopathy s/p TIPS.

• HIV history:
  – Diagnosed in 1980’s
  – Sequential monotherapy for years; exact history unknown
  – On truvada/maraviroc/darunavir /ritonavir since 2000s
  – CD4 171, HIV VL undetectable for many years
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- Liver disease history:
  - Abnormal liver tests in 2000’s, asymptomatic, attributed to ART
  - 2010 admitted with melena; EGD revealed varices requiring banding; no further treatment
  - 2014 developed LE edema and ascites, SBP
    - Liver biopsy performed
    - TIPS place for refractory ascites
    - Developed hepatic encephalopathy
Case 4

• What is the most likely cause of his liver disease?
Case 4

• What is the most likely cause of his liver disease?
  – Serologic work-up unrevealing
  – Liver biopsy:
    • Limited, fragmented sample, only 2 incomplete portal tracts
    • No significant inflammation, steatosis, ballooned hepatocytes, iron deposition, and no PAS-D+ globules suggesting A1AT
    • No diagnostic features of cirrhosis but trichrome stain showed septal to bridging fibrosis
    • Reticulin stain shows focal regenerative change, which would be expected in both NRH and advanced fibrosis
  – DDx: cryptogenic cirrhosis vs NASH cirrhosis vs NRH
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  – DDx: cryptogenic cirrhosis vs NASH cirrhosis vs NRH

• What do you recommend next in his management?
History of Liver Transplantation

• **1963** - First human liver transplant by Dr. Tom Starzl
• **1980’s** - Rapid growth of liver transplantation with introduction of cyclosporine
• **1983** - National Institutes of Health Consensus Development Conference: liver transplantation no longer considered an experimental treatment
• **1990’s** – Refined surgical techniques, more potent immunosuppressive drug regimens
• **1995** - Adult-to-adult living donor transplant in the US
• **2002** - MELD system of liver allocation
• **2016** - MELD-Na modified system for liver allocation
• **2016** - Many centers can achieve 5-yr survival > 75%
Timing of Liver Transplant Referral

• Need to consider the natural history of liver disease
• Complications of cirrhosis (Child Pugh B or C)
  – Ascites
  – Portal hypertensive bleeding
  – Hepatic encephalopathy
  – Spontaneous bacterial peritonitis (SBP)
  – Synthetic function abnormalities: bilirubin, albumin, INR
• Waiting list priority is based on liver disease severity (MELD-Na) NOT waiting time
Liver Transplantation
Absolute Contraindications

- Severe, irreversible co-morbid medical conditions that adversely impact short-term life expectancy
- Severe, untreated pulmonary hypertension
- Extra-hepatic malignancy
- Advanced HCC with vascular/lymph node invasion
- Severe, uncontrolled systemic infection
- Extensive portal-mesenteric venous thrombosis
- Active substance abuse or unacceptable risks for recidivism
- Non-compliance
- Lack of social support
Liver Transplantation

“Relative” Contraindications*

- Severe obesity
- Advanced age
- Frailty
- Other malignancy

* Criteria still not well defined and may be center specific
Liver Transplantation in HIV+

• Pre-HAART outcomes relatively poor compared to HIV-persons

• HAART era:
  – Excellent outcomes in HIV/HBV
  – Lower survival in HIV/HCV vs HCV-monoinfected in the pre-DAA era
    • Recipient and donor characteristics strongly influence outcomes
  – Fewer concerns with HIV/HCV in DAA era
Liver Transplantation in HIV+

• Criteria for liver transplant:
  – CD4 >100
  – HIV RNA suppressed (or predicted suppression post-transplant)
  – Stable ART regimen
  – No active OI or neoplasm
  – No history of chronic cryptosporidiosis, primary CNS lymphoma, or PML
  – No history of multidrug resistant fungal infections

• ART considerations post-transplant
  – DDI’s between CCR5 antagonists or integrase inhibitors and post-transplant immunosuppressants unlikely
  – PI’s inhibit P450 3A4 system leading to increased CNI’s and sirolimus levels
  – Efavirenz induces P450
  – Many antibiotics and antifungals used post-transplant can inhibit P450

**HIV Organ Policy Equity (HOPE) Act**

- HOPE Act November 21, 2013: organs infected with HIV may be transplanted into individuals who are:
  1) HIV-infected before receiving such an organ
  2) Participating in clinical research approved by an IRB until participation in such research is no longer warranted
Case 4 Continued

• He was evaluated for liver transplant and listed.
  – Blood type O+, MELD 10
  – Multiple admissions for various complications
    • Ascites recurred → TIPS occluded requiring revision
    • Multiple admissions for HE
    • L hip fracture
    • Portal vein thrombosis requiring anticoagulation → MELD increased to 20 on Coumadin
Case 4 Continued

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  – Blood type O+, MELD 10
  – Multiple admissions for various complications
    • Ascites recurred → TIPS occluded requiring revision
    • Multiple admissions for HE
    • L hip fracture
    • Portal vein thrombosis requiring anticoagulation → MELD increased to 20 on Coumadin

• Potential living donor is worked up and approved
  – Successfully undergoes living donor liver transplant
  – Explant path:
    • Cirrhosis without features to suggest a definite etiology
Living Donor Liver Transplantation

Right Lobe Graft

Left Lobe Graft

Slide credit: Dr. Francis Yao
Advantages of LDLT

- Decreased waiting time
- Increased survival
- Transplant before critically ill
- Semi-elective procedure
- Favorable donor characteristics: young, non-steatotic, short cold ischemia time

A2ALL Study:

Berg CL, Hepatology, 2011.
Disadvantages of LDLT

Recipient Risks
- Small-for-size syndrome
  - Encephalopathy, ascites
  - Graft dysfunction → failure
- Biliary complications
  - 32% vs 10% DDT
- Vascular complications
  - 10% vs 3% DDT

Donor Risks
- Mortality
  - 0.5% right lobe, 0.1% left lobe
- Surgical morbidity (14-28%)
  - Post-operative pain
  - Pleural effusions
  - Infections, including wound
  - Neuropraxia
  - DVT
  - Hernias
  - Psychiatric

95% resolve by 1 year post-op except hernia (75%) and psychiatric (42%)

Case 5

- 50 y/o man with HIV, hyperlipidemia, and HTN
- HIV history:
  - Diagnosed in 2008
  - Well-controlled on EFV/FTC/TDF (Atripla)
  - CD4 639, VL not detected
  - No prior OI’s
- No other medications
- No family history of liver disease
- 2 EtOH drinks/night during week, 5-7 drinks/night on weekends
Case 5

- 50 y/o man with HIV, hyperlipidemia, and HTN
- HIV history:
  - Diagnosed in 2008
  - Well-controlled on EFV/FTC/TDF (Atripla)
  - CD4 639, VL not detected
  - No prior OI’s
- No other medications
- No family history of liver disease
- 2 EtOH drinks/night during week, 5-7 drinks/night on weekends
- Labs:
  - AST 104, ALT 171, alk phos 127, t bili 0.5
  - INR 1.1, platelets 112
- Liver ultrasound:
  - Increased echogenicity of the liver may be related to fatty infiltration or parenchymal liver disease.
Case 5

• Liver biopsy:
  – Hepatocytes show mild to moderate ballooning and moderate micro and macrovesicular steatosis.
  – Cirrhosis; the hepatic lobular architecture is replaced by nodules separated by near complete fibrous septa tapping proliferating bile ducts
  – Mild to moderate lymphocytic infiltrates are seen in the septa with focal interface activity into the nodules and residual hepatic lobules
Alcohol and Liver Disease

• What is the “safe” amount of alcohol consumption?

• NIAAA defines unhealthy drinking:
  – Men
    • >14 standard drinks per week on average
    • >4 drinks on any day
  – Women
    • >7 standard drinks per week on average
    • >3 drinks on any day

• Higher risk of liver injury in patients with chronic liver disease- unclear what amount, if any, is “safe”

Case 5 Continued

• Liver biopsy:
  – Hepatocytes show mild to moderate ballooning and moderate micro and macrovesicular steatosis.
  – Cirrhosis; the hepatic lobular architecture is replaced by nodules separated by near complete fibrous septa tapping proliferating bile ducts
  – Mild to moderate lymphocytic infiltrates are seen in the septa with focal interface activity into the nodules and residual hepatic lobules

What do you recommend next?
**Management of Compensated Cirrhosis**

- Goals of management of compensated cirrhosis: Treat etiology, Screen/Prevent complications
- Treatment of etiology: Complete alcohol abstinence, alcohol intervention, NASH treatment
- Screening for complications: EGD to assess for varices, HCC screening every 6 months with ultrasound +/- AFP
- Vaccinate against HAV, HBV; Avoid drugs that may worsen volume/renal status: NSAIDS, ARB’s, ACE-I’s
Case 5 Continued

- Stops drinking alcohol entirely
- EGD: no varices
  - Recommend repeat in 2-3 years
- Clinically remains stable
- Abdominal ultrasound in 2016 shows a 2 cm lesion
- Quad-phase CT scan shows a 2.1 cm lesion in segment 4a typical for HCC (LI-RADS 5)
Case 5 Continued

• Stops drinking alcohol entirely
• EGD: no varices  
  – Recommend repeat in 2-3 years
• Clinically remains stable
• Abdominal ultrasound in 2016 shows a 2 cm lesion
• Quad-phase CT scan shows a 2.1 cm lesion in segment 4a typical for HCC (LI-RADS 5)

What do you recommend next?
Liver Transplant for HCC

- HCC Exception Points:
  - Those meeting Milan T2 criteria are given adjusted MELD priority score 28 after being listed for 6 months
  - MELD exception upgraded every 3 months

- UCSF has expanded criteria with down-staging protocol

1 lesion ≤ 5 cm

2-3 lesions, none >3 cm

No evidence of macroscopic vascular invasion or extra-hepatic spread

Case 5 Continued

- Evaluated and listed for transplant
- TACE performed to the segment 4A lesion
- Post-TACE imaging showed treated lesion but new 2 cm LI-RADS 5 lesion segment 5
- TACE performed to segment 5 lesion
- EFV/FTC/TDF (Atripla) switched to FTC/TAF (Descovy) and dolutegravir (Tivicay)
  - In anticipation of transplant to minimize post-transplant drug-drug interactions
- Is awaiting liver transplant
Case 6

• 45 y/o man with cirrhosis due to HIV/HBV coinfection, ESRD due to hypertension and glomerulonephritis

• Initially seen to determine candidacy for kidney transplant alone.

• HIV and HBV well controlled, initially on lopinavir/ritonavir (Kaletra), tenofovir (Viread), lamivudine (Epivir).
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Is he a candidate for kidney transplant alone?
Case 6

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- Initially seen to determine candidacy for kidney transplant alone.
- HIV and HBV well controlled, initially on lopinavir/ritonavir (Kaletra), tenofovir (Viread), lamivudine (Epivir).
- No history of decompensation
- EGD normal: no varices, no portal-hypertensive gastropathy
- Transjugular liver biopsy with portal pressure measurements
  - Cirrhosis with grade 1 inflammation
  - HVPG 6 mmHg (clinically significant portal hypertension HVPG ≥ 10 mmHg)

Is he a candidate for kidney transplant alone?
Case 6 Continued

- He underwent deceased donor kidney transplant, no postoperative complications and no signs of hepatic decompensation
- 2.5 years post-kidney transplant, his liver enzymes are elevated

<table>
<thead>
<tr>
<th></th>
<th>Pre-KT</th>
<th>Time post-KT</th>
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<tbody>
<tr>
<td></td>
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<td>2.5yr</td>
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<tr>
<td>ALT</td>
<td>18</td>
<td>80</td>
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<tr>
<td>HBV DNA</td>
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<td>&lt;20 detected</td>
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</tbody>
</table>
Case 6: Diagnostic Studies

- **Infectious:** CMV PCR <200 copies/mL, HAV IgM negative, HCV Ab negative, HBV DNA <20 IU/mL but detected, HCV RNA <15 IU/mL, HDV Ab negative
- Ferritin 593
- ANA negative, ASMA negative, IgG 1684
- A1AT 132
- AMA negative
- MRI abdomen: Cirrhosis. Wedge-shaped hypodense lesion in segment 7 consistent with remote post-biopsy hemorrhage
Case 6: Diagnostic Studies

• Liver biopsy:
  – Cirrhosis, HVPG 14mmHg
  – Mild predominately lymphocytic inflammation in the portal zones and lobules, with mild interface activity
  – Immunostain for HBcAg is negative, HBsAg is positive in a few hepatocytes
Case 6: Diagnostic Studies

- Liver biopsy:
  - Cirrhosis, HVPG 14mmHg
  - Mild predominately lymphocytic inflammation in the portal zones and lobules, with mild interface activity
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- Additional lab testing
  - Hepatitis E IgM reactive
  - Hepatitis E PCR positive
Hepatitis E Virus

• Single-stranded, non-enveloped RNA virus of the *Hepeviridae* family

• Genotypes 1-4 infect humans

• Genotypes 1 & 2: Classic Epidemic HEV
  – Fecal-oral
  – No known animal reservoir

• Genotypes 3 & 4: Autochthonous/Sporadic HEV
  – Genotype 3: Animal reservoirs: pigs (especially farmed swine), deer, wild boar, shellfish, rodents
  – Genotype 4: Detected in pigs
Classic Epidemic HEV (G1,2)

- Most common cause of acute hepatitis in endemic areas
- Typically occurs in adolescents/young adults
- Clinical features:
  - High rate of jaundice, cholestasis
  - High fatality rate among pregnant women
- Consider in patients with acute hepatitis and recent travel to endemic area

Genotype 3,4 HEV

- Typically transient, anicteric, and asymptomatic
- Most often clinically apparent in older men
- Fatality rate is not increased in pregnant women
- Can become chronic in immunosuppressed patients
- Consider in patients with:
  - Unexplained hepatitis, particularly if older, solid organ transplant recipient, or HIV+
Hepatitis E and Cirrhosis

• Prevalence of HEV infection reported to be 3.2-6.5% in decompensated alcoholic cirrhosis in a small French cohort

• HALT-C cohort overall prevalence based on HEV IgG: 21%
  – 10 cases were incident cases that developed during follow-up
  – Coinfection associated with older age (52.5 vs 50.1)
  – No association with decompensation

Hepatitis E and HIV

• Unclear seroprevalence of HEV IgG: 1-45%
  – Likely higher than in HIV-negative patients

• Factors associated with HEV-HIV coinfection
  – CD4 count <100-200
    • Higher CD4 counts may be associated with clearance
  – Cirrhosis (bidirectional relationship)
  – Increased age (no clear cutoff)

Hepatitis E and Transplant Recipients

• Tacrolimus can increase the risk of chronic HEV in solid organ transplant recipients by almost 2-fold in comparison to cyclosporine
• Uncommon to see spontaneous clearance of HEV beyond 3-6 months after infection identified
• Limited data on fibrosis progression
  – Small series demonstrated 1 stage increase in fibrosis over a median of 22 months

Hepatitis E: Treatment

• In transplant recipients, reduce immunosuppression
  – Sustained virologic response rate of 30%

• Ribavirin
  – Cannot give to pregnant women
  – Emergence of mutations in HEV genotype 3 associated with nonresponse to ribavirin
  – Optimal dose and length not clear

• Pegylated interferon

• Sofosbuvir: in vitro effects, not yet studied in humans

Questions?