Clinical case presentation:
(HIV-HCV patient)

Jürgen Rockstroh, Department of Medicine I,
University of Bonn, Germany
Herbert: 52y old hemophiliac

- **HIV infection 1984**
  - ART history
    - 1993: AZT + DDC
    - 1997: D4T + DDI + Saquinavir
    - 1999: Efavirenz + Indinavir
    - Multiple treatment failures with resistance development
  - Current ART since 2001: TDF + AZT + 3TC + lopinavir/r
    - HIV-1 RNA <50 c/mL,
    - CD4 420 cells/mm³

- **HCV co-infection**
  - Genotype 1a; 6.7 log₁₀
  - ILB28 CT
  - Transient elastography 11.6 kpa (F3 fibrosis)
  - 2008 HCV therapy with PEG-IFN/RBV for 48 weeks, relapse 4 weeks after EOT

- **Other co-morbidities**
  - Hypercholesterolemia: atorvastatin 20mg/d
  - Depression: Escitalopram
Question

» Which impact on SVR rate would the IL28b CT polymorphism have (for traditional PEG-IFN/RBV dual therapy?)

» □ no impact
» □ lower SVR rate to 30%
» □ increase SVR rate to 50%
» □ lower SVR rate to 15%
IL-28B Genotypes and SVR Rates

- Recent studies demonstrate polymorphisms near interleukin 28 B (IL28B) gen predict sustained virological response (SVR) to treatment with Peg-IFN + RBV in HCV-monoinfected pts harboring genotype 1.
- Study assessing potential role of the IL-28B treatment induced clearance of rs12979860 polymorphism in acute and chronic hepatitis C in HIV-positive patients.

Question

» Should we treat Herberts HCV?

» ☐ Yes
» ☐ no
Management of newly diagnosed HIV-HCV co-infected genotype-1 patients

Newly diagnosed chronic HCV GT 1 infection

Perform Fibroscan® and/or serum marker and/or liver biopsy

F0F1a

In general, treatment can be deferred. Consider treatment with Peg/RBV and an HCV protease inhibitor or Peg/RBV alone if low HCV viral load, IL28B CC genotype, absence of insulin resistance and high CD4 count.

F2F3a

Treatment with Peg/RBV and an HCV protease inhibitor.

F4a

Treatment with Peg/RBV and an HCV protease inhibitor if compensated disease. Treatment should be undergone in specialised centres.

aMetavir fibrosis score: F0=no fibrosis; F1= portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis; Peg, pegylated interferon; RBV, ribavirin

Ingiliz P, Rockstroh J. Liver International 2012
EACS guidelines, version November 2012
Telaprevir + PegIFN + RBV in HIV/HCV Co-infected Patients with Virologic Failure on IFN + RBV

Single Arm, Phase 2 Clinical Trial

- **Complete RVR$_8$** (HCV-RNA < 15 IU/mL): 32 weeks PR phase (Total treatment: 48 weeks)
- **Partial RVR$_8$** (15 IU/mL < HCV-RNA < 1,000 IU/mL) 56 weeks PR phase (Total treatment: 72 weeks)

Cotte L, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 36.
Telaprevir + PegIFN + RBV in HIV/HCV Co-infected Patients with Virologic Failure on IFN + RBV

**Main Inclusion Criteria**
- Chronic HCV genotype 1 infection and HIV-1 infection
- **Previous virological failure** after ≥12 weeks PegIFN + RBV ≥600 mg/day
- Stable ART for ≥3 months
- Authorized antiretrovirals: ATV, ATVr, EFV, RAL, TDF, FTC, 3TC
- CD4 ≥200 cells/mm$^3$ and ≥15%, plasma HIV-RNA levels <50 copies/mL
- Liver biopsy <3 years or cirrhosis on any previous biopsy

**Main Exclusion Criteria**
- HVB coinfection, HIV-2 infection
- Past history of decompensated cirrhosis
- **Previous null response with cirrhosis**

**Important patient characteristics**
- F3 16%, F4 23%; HCV GT1a 70%
Telaprevir + PegIFN + RBV in HIV/HCV Co-infected Patients with Virologic Failure on IFN + RBV: Virologic Response

- RVR<sub>8</sub>: 88%
- EVR<sub>16</sub>: 88%
- 1.5% <LLOQ (<15 IU/mL)

Cotte L, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 36.
Telaprevir + PegIFN + RBV in HIV/HCV Co-infected Patients with Virologic Failure on IFN + RBV: Early Virologic Response by Patient Group
## Grade 3-4 AEs and treatment discontinuations up to W16

<table>
<thead>
<tr>
<th>AEs Type</th>
<th>N (%)</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3 AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>6 (9%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>General</td>
<td>5 (7%)</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 4 AEs</strong></td>
<td></td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Blood</td>
<td>4 (6%)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Reasons for treatment discontinuations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric AEs</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous AEs</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Others AEs</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Virological failure</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>
BOC/IFN/RBV Following Virologic Failure: Results by ARV Regimen

Patients (%) with HV-RNA <15 IU/mL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>All (n=64)</th>
<th>2NRTI/ATVr (n=32)</th>
<th>2NRTI/RAL (n=27)</th>
<th>Others (m=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W4</td>
<td>44%</td>
<td>63%</td>
<td>56%</td>
<td>40%</td>
</tr>
<tr>
<td>W6</td>
<td>20%</td>
<td>37%</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>W8</td>
<td>16%</td>
<td>37%</td>
<td>70%</td>
<td>40%</td>
</tr>
<tr>
<td>W12</td>
<td>10%</td>
<td>37%</td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>W16</td>
<td>4%</td>
<td>37%</td>
<td></td>
<td>40%</td>
</tr>
</tbody>
</table>

RVR_8
EVR_16

Pizot-Martin I, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 37.
Question

»How many clinically relevant drug-drug-interactions do you need to work on before starting telaprevir based triple HCV therapy in this patient?

»1) only HCV and HIV PI
»2) only HCV and HIV PI and atorvastatin
»3) HIV and HCV PI and atorvastatin and escitalopram
»4) none of the above
Telaprevir increases exposure of atorvastatin

Effect on atorvastatin

GLS Mean Ratio (90% CI)

$C_{\text{max}}$ 10.6 (8.7 – 12.9)

AUC 7.9 (6.8 – 9.1)

Contraindication!!

Telaprevir decreases exposure of Escitalopram

<table>
<thead>
<tr>
<th>Co-medication</th>
<th>TVR effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram (SSRI) Metabolised by CYP2C19 &amp; CYP3A4</td>
<td>↓ 35%</td>
</tr>
</tbody>
</table>

- Mechanism: Not clearly determined but INDUCTION of CYP2C19?
- Doses may need to be increased when combined with telaprevir

van Heeswijk R, et al. IWCPHT 2010. Abstract 12; Telaprevir SmPC;
Telaprevir exposure decreased with HIV PIs

Variable effect of telaprevir on HIV PI exposure

Herbert: 52y old hemophiliac

**HIV infection 1984**
- ART history
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  - 1999: Efavirenz + Indinavir
  - Multiple treatment failures with resistance development
- Current ART since 2001:
  TDF + AZT + 3TC + lopinavir/r
  - HIV-1 RNA <50 c/mL,
  - CD4 420 cells/mm³

**HCV co-infection**
- Genotype 1a; 6.7 log\(_{10}\)
- ILB28 CT
- Transient elastography 11.6 kpa (F3 fibrosis)
- 2008 HCV therapy with PEG-IFN/RBV for 48 weeks, relapse 4 weeks after EOT

**Other co-morbidities**
- Hypercholesterolemia:
  - atorvastatin 20mg/d
- Depression: Escitalopram
Herbert

RT: 67N, 103N, 184V, 219Q

| Lamivudine | Efavirenz |
| Abacavir   | Etravirine |
| Zidovudine | Nevirapine |
| Stavudine  | Rilpivirine |
| Didanosine |            |
| Emtricitabine |        |
| Tenofovir  |            |

PRO: 10I, 46I, 90M

| Atazanavir/r | Darunavir/r |
| Fosamprenavir/r | Indinavir/r |
| Lopinavir/r | Nelfinavir |
| Saquinavir/r | Tipranavir/r |
Question

Which HIV therapy would you suggest to be co-administered with a HCV PI based therapy plus PEG-IFN and ribavirin?
# Telaprevir: Drug-Drug Interactions With ARVs

<table>
<thead>
<tr>
<th>HIV Antiretroviral</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies completed</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>Clinical and laboratory monitoring for hyperbilirubinaemia is recommended</td>
</tr>
<tr>
<td>Darunavir/r, Fosamprenavir/r</td>
<td>Coadministration not recommended</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>TVR dose increase necessary (1125 mg q8h)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Etravirine and rilpivirine</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Increased clinical and laboratory monitoring is warranted</td>
</tr>
<tr>
<td><strong>Studies not completed</strong></td>
<td></td>
</tr>
<tr>
<td>Abacavir; zidovudine</td>
<td>An effect of telaprevir on UDP-glucuronyltransferases cannot be ruled out and</td>
</tr>
<tr>
<td></td>
<td>may affect plasma concentrations of abacavir or zidovudine (not studied)</td>
</tr>
</tbody>
</table>

*UDP, glucuronosyltransferase: uridine 5'-diphospho-glucuronosyltransferase.*

Telaprevir EU SmPC.
Boceprevir: DDIs with HIV antiretrovirals

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<tr>
<td><strong>Studies completed</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>In general not recommended; EMEA says can be considered on a case-by-case basis if patient has no prior HIV drug resistance and is suppressed</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Etravirine</td>
<td>No dose adjustment requires</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>No dose adjustment required</td>
</tr>
</tbody>
</table>

Hulskotte E et al., 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 771LB
De Kanter C et al., 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 772LB
FDA Safety Announcement, dated 08 Feb 2012
EMA press release, dated 17 Feb 2012
Merck "Dear Health Care Provider" letter, dated 06 Feb 2012

DDI – Drug-drug interactions
Patient is switched from his antiretroviral therapy to Darunavir/r and Raltegravir and screened for the BI coinfection study where Darunavir/r and Raltegravir are both allowed as ART

Patient is undetectable at week 48 (EOT) and relapses 4 weeks after treatment discontinuation

Transaminases increase to 300 IU/l and Fibroscan has progressed to 18 kpa (F4 fibrosis)

What therapy or management strategy do you recommend now?
Jens: 45y old msm

• HIV infection 2004
  – ART history
    • GT resistance testing prior to ART: D67N, K219E
    • 2008: 3TC, FTC, LPV/r
    • Current ART since 2001:
      FTC + 3TC + fosamprenvir/r
      HIV-1 RNA <50 c/mL,
      CD4 704 cells/mm³

• Acute HCV co-infection 8/2010
  – 2010 HCV therapy with PEG-IFN/RBV for 12 weeks, discontinuation because of rise in HCV at week 12 (partial response)

• 12/2011
  – Genotype 1a; 3.148.649 copies/ml
  – ILB28 CC
  – Transient elastography 32 kpa (F4 fibrosis)

• Other co-morbidities
  – 2009 NHL, 6 cycles R/CHOP + Radiation
Question

» Should we treat Jens HCV ?

» Yes

» no
Question

»How would you treat Jens HCV?

1. with Boceprevir + PEG-IFN/RBV
2. with Telaprevir + PEG-IFN/RBV
3. other
Do we need to change ART and if how?

1) maintain therapy as is (never change a winning team)
2) continue ART with FTC, Fosamprenavir/r
3) switch to raltegravir + TDF + FTC
4) none of the above
Patient had previously undergone chemotherapy for NHL and was on a simplified FTC daily and fos-amprenavir 700mg/ritonavir 100mg twice-daily regimen. Liver stiffness was 32 kPa suggestive of liver cirrhosis.

Schwarze-Zander C et al., HIV 11; Glasgow 2012, p130
Patient remains on FTC, Fosamprenavir/r for the entire duration of his HCV therapy.

Patient shows negative HCV-PCR at week 48 (EOT) and SVR (24 weeks after treatment discontinuation).