Chronic hepatitis C and HIV: implications for care

11th Co-infection Workshop, London, Thursday 11th June 2015

Jürgen Kurt Rockstroh
Department of Medicine I,
University Hospital Bonn,
Bonn, Germany
Conflict of Interest

- Honoraria for lectures and/or consultancies from abbVie, BMS, Cipla, Gilead, Janssen, MSD, Roche, ViivV.
- Research grants from Dt. Leberstiftung, DZIF, NEAT ID.
Anti-HCV antibody prevalence in different EuroSIDA regions

- South: 28.8%
- West: 20.1%
- North: 17.3%
- East Central: 34.0%
- East: 57.7%
- Argentina: 20.6%

Peters L et al., BMC Infect Dis. 2014;14 Suppl 6:S13
Global prevalence of HIV/HCV co-infection

Burden of co-infection with HIV and HCV by region, 2013

- Africa
- Eastern Europe
- South East Asia
- North America
- Latin America
- Europe
- Western Pacific
- East Med


HCV, hepatitis C virus; IQR, inter-quartile ratio
GT 1 predominates in HIV/HCV co-infection in Europe

Distribution of GT 1–4 in Europe (EuroSIDA cohort)

52.9%
29.7%
14.2%
3.3%

HCV co-infection in EuroSIDA

- EuroSIDA: prospective, European study of 18,295 HIV-1–infected patients at 105 centres across Europe, Israel and Argentina
- Prevalence of HCV seropositivity in EuroSIDA is 31% (4,044 patients), 74.2% of which were serum HCV RNA-positive

Progression to liver-related death in HIV-positive population

<table>
<thead>
<tr>
<th>HCVAb serostatus:</th>
<th>Events (PYFU)</th>
<th>IRR (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>43 (66,653)</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>175 (26,494)</td>
<td>8.90 (5.60–14.14; p&lt;0.0001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Events (PYFU)</th>
<th>IRR (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1</td>
<td>55 (8122)</td>
<td>1</td>
</tr>
<tr>
<td>GT 2</td>
<td>2 (554)</td>
<td>0.27 (0.07–1.13; p=0.073)</td>
</tr>
<tr>
<td>GT 3</td>
<td>28 (4503)</td>
<td>0.99 (0.62–1.59; p=0.98)</td>
</tr>
<tr>
<td>GT 4</td>
<td>9 (2188)</td>
<td>0.91 (0.44–1.89; p=0.80)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCV-RNA viremia</th>
<th>Events (PYFU)</th>
<th>IRR (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCVAb-</td>
<td>43 (66,653)</td>
<td>0.18 (0.10–0.32; p&lt;0.0001)</td>
</tr>
<tr>
<td>Ab+/RNA-</td>
<td>21 (4838)</td>
<td>1</td>
</tr>
<tr>
<td>Ab+/RNA+</td>
<td>86 (11,302)</td>
<td>2.11 (1.30–3.42; p=0.0025)</td>
</tr>
<tr>
<td>Ab+/unknown</td>
<td>68 (10,354)</td>
<td>1.42 (0.86–2.35; p=0.17)</td>
</tr>
</tbody>
</table>

Multivariate analysis adjusted for gender, exposure group, race, prior AIDS, region of Europe, CD4+ T-cell nadir, HCV treatment status at baseline, age, and baseline date. Starting cART, HBsAg status, diagnosis of a new AIDS-defining illness and CD4+ T-cell count were included as time-updated variables.

HCVAb, anti-HCV antibodies; PYFU, person years of follow-up; IRR, incidence rate ratio; Rockstroh J et al. J Hepatol 2013;59(2):213-220

Adjusted incidence rate ratio (95% CI)
Cumulative incidence of LRD by fibrosis staging and CD4 cell count

145 LRD among 3941 HIV/HCV pts from EuroSIDA

HIV/HCV co-infection burden: Accelerated disease progression and morbidity

- **↑ Prevalence, especially in some populations**\(^1\text{–}^3\)
- **Compared with HCV mono-infected patients, patients co-infected with HIV display:**
  - **↑ viraemia (2–8-fold greater)**\(^1,4\)
    - ↑ infectivity increases risk of transmission from mother to child (20% vs 6%) and risk of sexual transmission (3% vs <1%)\(^1,5\)
  - **↓ likelihood of spontaneously clearing HCV**\(^1,4\)
  - **↑ hepatic fibrosis (2–5-fold greater), cirrhosis, decompensation, hepatocellular carcinoma and liver-related mortality**\(^1,5\)

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Fibrosis
Cirrhosis

- Higher HBV and HCV chronicity rate
- Increased viral replication
- Decreased HCV-specific immune response

Hepatocyte apoptosis

- Direct effect on stellate cells
- Immune dysregulation
- Cytokine alteration
- Hepatocyte apoptosis

LPS

HCV

• HAART

Fibrosis
Cirrhosis
HCC

Adapted from Ingiliz P, Rockstroh JK, Current Opinion in HIV and AIDS 2015
What is the optimal treatment strategy in HIV/HCV co-infected patients?

- Treat HCV first?
- Treat HIV first?
- Treat HIV/HCV simultaneously?
EACS guidelines: when to start

- **Initiation of ART**
  - ART is always recommended if CD4 count < 350 cells/mm³

<table>
<thead>
<tr>
<th>Condition</th>
<th>CD4+ lymphocyte count</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV requiring anti-HBV treatment</td>
<td>&gt;500</td>
</tr>
<tr>
<td>HBV not requiring anti-HBV treatment</td>
<td></td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment is being considered or given</td>
<td></td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment not feasible</td>
<td></td>
</tr>
</tbody>
</table>


C, consider; D, defer; R, recommended
Liver Toxicity due to HAART

- 14-20% of patients will develop elevated liver enzymes.
- 2-10% of patients will need to interrupt HAART due to severe liver injury.
- Risk factors:
  - Viral hepatitis B or C
  - First regimen
  - Nevirapine
  - Full dose ritonavir
  - Female sex

J Infect Dis 2002; 186:23-31
## Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

(Last updated May 1, 2014; last reviewed April 8, 2015)

<table>
<thead>
<tr>
<th>ARVs Generic Name (Abbreviation) Trade Name</th>
<th>Usual Daily Dose</th>
<th>Dosing in Renal Insufficiency</th>
<th>Dosing in Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine (ETR) etravirine</td>
<td>200 mg PO BID</td>
<td>No dosage adjustment necessary</td>
<td>Child-Pugh Class A or B:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dosage adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child-Pugh Class C:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dosage recommendation</td>
</tr>
<tr>
<td>Nevirapine (NVP) Viramune or Viramune XR</td>
<td>200 mg PO BID or</td>
<td>Patients on HD:</td>
<td>Child-Pugh Class A:</td>
</tr>
<tr>
<td></td>
<td>400 mg PO once daily (using Viramune XR formulation)</td>
<td>• Limited data; no dosage recommendation.</td>
<td>• No dosage adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child-Pugh Class B or C:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Contraindicated</td>
</tr>
<tr>
<td>Ribavirine (RPV) Edurant</td>
<td>25 mg PO once daily</td>
<td>No dosage adjustment necessary</td>
<td>Child-Pugh Class A or B:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dosage adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child-Pugh Class C:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dosage recommendation</td>
</tr>
<tr>
<td>Ribavirine (RPV) plus Tenofovir Disoproxil Fumarate (TDF) plus Emtricitabine (FTC) Complera</td>
<td>1 tablet PO once daily</td>
<td>Not recommended for use in patients with CrCl &lt;50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses levels according to CrCl level.</td>
<td>Child-Pugh Class A or B:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dosage adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child-Pugh Class C:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dosage recommendation</td>
</tr>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Atazanavir (ATV) Reyataz</td>
<td>400 mg PO once daily or (ATV 300 mg plus RTV 100 mg) PO once daily</td>
<td>No dosage adjustment for patients with renal dysfunction who do not require HD. ARV/NAve Patients on HD: (ATV 300 mg plus RTV 100 mg) once daily ARV/Experienced Patients on HD: ATV or ATV/rit not recommended</td>
<td>Child-Pugh Class B:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 300 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child-Pugh Class C:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RTV boosting is not recommended in patients with hepatic impairment (Child-Pugh Class B or C).</td>
</tr>
<tr>
<td>Atazanavir (ATV) plus Cobicistat (COBI) Evotaz</td>
<td>1 tablet PO once daily</td>
<td>If Used with TDF:</td>
<td>No dosage recommendation; not recommended in patients with hepatic impairment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not recommended for use in patients with CrCl &lt;70 mL/min.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If Not Used with TDF:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No dosage adjustment for patients with renal dysfunction who do not require HD.</td>
<td></td>
</tr>
</tbody>
</table>
Impact of ART on Overall Liver Mortality in HIV/HCV-Coinfected Patients

- Bonn cohort (1990-2002)
  - 285 HIV/HCV coinfected patients
- Liver-related mortality rates per 100 person-years
  - HAART: 0.45
  - ART: 0.69
  - No therapy: 1.70
- Predictors for liver-related mortality
  - No HAART
  - Low CD4 cell count
  - Increasing age

Antiretroviral therapy reduces the rate of hepatic decompensation among HIV- and hepatitis C virus-coinfected veterans

Objective:
- To evaluate 10,090 HIV/HCV-co-infected males from the Veterans Aging Cohort Study Virtual Cohort, who had not initiated ART at entry, for incident hepatic decompensation between 1996 and 2010

Results:
- Initiation of ART significantly reduced the rate of hepatic decompensation by 28–41% on average

HCV disease progression remains faster in coinfected patients, despite effective ART


Cumulative incidence

Time to hepatic decompensation (years)

HCV-monoinfected patients (n=6079)

Antiretroviral-treated patients coinfected with HIV/HCV (n=4208)

p<0.001

x 1.5

0.048

0.074
HCV disease progression remains faster in coinfection patients, despite effective ART

- If HIV RNA < 1000 copies/mL: +65% excess risk
- If HIV RNA > 1000 copies/mL: +82% excess risk
- If CD4 < 200/mm²: +203% excess risk
- If CD4 > 200/mm²: 56–63% excess risk

ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus.
Modulation of HCV replication after combination antiretroviral therapy in HCV/HIV co-infected patients

Treatment with cART resulted in increased HCV replication and increased ALT in a subset of patients. Subjects with evidence of hepatic injury were more likely to have HCV-specific immune responses. Over time, HCV viral loads declined. Reproducible and biologically important gene expression changes occurred in co-infected patients who underwent successful cART. The effective suppression of HIV by cART initiated a cascade of early and late events in treated patients. Early events involving down-regulation of interferon-stimulate genes may have led to transiently increased viral replication and hepatic injury. At later time points, HCV viral load declined to levels comparable to those seen in the setting of HCV monoinfection. These findings support early antiretroviral therapy in those with HCV/HIV co-infection.

Management of Persons with Chronic HCV/HIV Co-infection

Chronic HCV/HIV

Perform FibroScan® and/or serum markers and/or liver biopsy

F0/F1*
- HCV treatment should be Considered**

F2*
- HCV Treatment must be Considered

F3/F4*
- IFN free HCV Treatment is Recommended

* Metavir fibrosis score: F0=no fibrosis; F1= portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis.
  FibroScan®: F0-F1 < 7.1 KPa; F2 7-10 KPa; F3/F4 > 10 Kpa

** Treatment must be considered independently from liver fibrosis in persons with low CD4 T cell count (<200/µl), ongoing HIV replication, HBV coinfection, debilitating fatigue, high risk of HCV transmission (PWID, prisoners, MSM with high risk behavior, fertile women who want to be pregnant).
HCV Life cycle and therapeutic intervention points

**Cyclophilin A inhibitor**
- Inhibition of cyclophilin A reduces HCV replication

**NS3 inhibitor**
- Inhibits activity of NS3 protease
- Prevents processing of HCV proteins required for replication

**NS5A inhibitor**
- Inhibits activity of NS5A, a multifunctional protein
- Prevents viral replication

**NS5B inhibitor(s)**
- Inhibits NS5B RNA replicase
- Prevents replication of viral genome

**PEG-IFN lambda**
- Type III pegylated interferon
- Expression of receptor is more limited than Alfa, should lead to improved tolerability and safety

**HCV virion**

EASL 2015 HCV recommendations and AASLD/IDSA/IAS-USA HCV recommendations

• Indications for HCV treatment in HIV/HCV co-infected patients are identical to those in HCV mono-infection (Recommendation A1)

• Same treatment regimens can be used in HIV/HCV patients as in patients without HIV infection, as the virological results of therapy are identical (Recommendation A1)

• Treatment should be prioritized regardless of the fibrosis stage in patients with HIV or HBV coinfection, (…) (Recommendation A1)

High Priority for Treatment Owing to High Risk for Complications

- HIV-1 coinfection (AASLD/IDSA)
- Rating: Class I, Level B

Journal of Hepatology DOI: (10.1016/j.jhep.2015.03.025)
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### ARV Interaction Score Card

<table>
<thead>
<tr>
<th></th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>AbbVie 3D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATV/r</strong></td>
<td>No data</td>
<td>ATV ↔ SOF ↔</td>
<td>No data</td>
<td>DCV ↑*</td>
<td>ATV ↔; ABT450 ↑</td>
</tr>
<tr>
<td><strong>DRV/r</strong></td>
<td>SIM ↑; DRV ↔</td>
<td>SOF ↑; DRV ↔</td>
<td>No data</td>
<td>DCV (↑)</td>
<td>DRV ↓; 3D ↓</td>
</tr>
<tr>
<td><strong>LPV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>DCV ↔</td>
<td>LPV ↔; ABT450 ↑</td>
</tr>
<tr>
<td><strong>TPV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>EFV</strong></td>
<td>SIM ↓; EFV ↔</td>
<td>SOF ↔; EFV ↔</td>
<td>LDV ↓; EFV ↓</td>
<td>DCV ↓*</td>
<td>No PK data**</td>
</tr>
<tr>
<td><strong>RPV</strong></td>
<td>SIM ↔; RPV ↔</td>
<td>SOF ↔; RPV ↔</td>
<td>LDV ↔; RPV ↔</td>
<td>No data</td>
<td>ABT450 ↑; RPV ↑</td>
</tr>
<tr>
<td><strong>ETV</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>RAL</strong></td>
<td>SIM ↔; RAL ↔</td>
<td>SOF ↔; RAL ↔</td>
<td>LDV ↔; RAL ↔</td>
<td>No data</td>
<td>3D ↔; ↑ RAL</td>
</tr>
<tr>
<td><strong>ELV/cobi</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>DLG</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>MVC</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>TDF</strong></td>
<td>SIM ↔; TDF ↔</td>
<td>SOF ↔; TDF ↔</td>
<td>LDV ↔; ↑TDF***</td>
<td>DCV ↔; TDF ↔</td>
<td>3D ↔; TDF ↔</td>
</tr>
</tbody>
</table>

- Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD, **3D + EFV led to premature study discontinuation due to toxicities**
- ***when TDF is administered with a boosted HIV-PI and LDV significantly higher TDF levels can be expected warranting closer renal monitoring***

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Personal communication Jennifer Kiser, University of Colorado, Denver, USA
HCV infection can be cured

Clinical events after HCV treatment for 493 patients with no SVR and 218 patients with SVR

Overall mortality

Liver decompensation

SVR, sustained virologic response

• **Treatment of chronic infection: SVR is possible**, **durable**, and **prevents death**

Patients included in the study

- Patients in the database: 1,599
- Patients with F0, F1, F2: 695
- Patients with SVR: 274 (35%)
Kaplan Meier estimates of events

Median FU (IQR): No SVR: 59.3 mo (40.6–79.2); SVR: 59.5 mo (42.8–81.8)

Overall mortality

Liver related mortality

Liver decompensation

Liver related events

Risk of Late Relapse or Re-Infection with Hepatitis C After Sustained Virological Response: Meta-Analysis of 66 Studies in 11,071 Patients

Five-Year Rate (95% CI) of Recurrence Post-SVR, by Risk Group

- **Low Risk**
  - 43 studies
  - N = 9,419
  - Avg. FU = 4.1±2.1y

- **High Risk (IDUs/prisoners)**
  - 16 studies
  - N = 819
  - Avg. FU = 2.9±1.6y

- **HIV/HCV Co-Infected**
  - 7 studies
  - N = 833
  - Avg. FU = 3.1±1.2 years

Five-year recurrence rate post SVR, %

- **Low risk**
  - 1.1% (95%CI 0.9–1.4%)

- **High risk**
  - 13.2% (95%CI 9.9–17.2%)

- **HIV/HCV co-infected**
  - 21.7% (95%CI 18.3–25.5%)

Chronic hepatitis C and HIV: implications for care: Conclusions

- HIV infected individuals with HCV coinfection remain at higher risk for fibrosis progression and hepatic decompensation.
- Therefore HCV therapy is prioritized in most guidelines in this patient group.
- The short- and mid-term effects of ART on the progression of HCV-related liver disease largely outweigh the potential risks for long-term toxicity.
- HIV therapy needs to consider coadministration with all oral DAA combination therapy and possible drug interactions as well as potential dose modifications with advanced liver disease.