Identification & Treatment of Acute HCV in HIV-infected Patients

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Transmission

- Injection drug use is the chief mode of transmission
- Other modes of transmission include blood transfusions, organ transplant, exposure to an infected sexual partner, exposure to blood in health care workers and perinatal exposure
- Other possible modes of transmission: tattoos, piercings
- Estimated risk with blood transfusion is now < 1 in a million per unit transfused (since 1990 when screening donors for Hep C antibodies was initiated)
Sexually transmitted HCV

An epidemiological puzzle

- HIV and HCV are known for more than one decade
- Except for rare cases of sexual transmission IDU (blood-to-blood) remains main transmission route
- Why are we observing an epidemic of sexually transmitted HCV infections?
  - Is it the host?
  - Is it behaviour?
  - Is it the virus?
HIV as a risk factor for HCV transmission

- HCV-RNA is more often detected in semen of HIV+ patients than in HIV-negative\(^1\)
- HIV+ patients have a higher risk for a chronic course of HCV-infection\(^2\)
- HIV+ patients – dependent on CD4 cell-count – have a reduced capability to mount cellular immune responses against HCV\(^3\)

Acute HCV in HIV+ MSM

**Australia** 11: 47 cases
Prevalence chronic HCV/HIV 6,19
<1%: 1,000

**USA** 1,2: 55 cases
Prevalence chronic HCV/HIV 12-14
15-30%: 180,000 - 360,000

**Europe:** 1,197 cases
Prevalence chronic HCV/HIV 14,15
25%: 185,500
- UK: 3,4 582
- Germany: 5,18,27 157
- France: 6,7 126
- Netherlands: 8,17 97
- Belgium: 20 69
- Switzerland: 9 23
- Italy: 10 21
- Austria: 27 20
- Denmark: 97
- Spain: ~97

**Lebanon** 22: 1 case
Prevalence chronic HCV/HIV 25
49%: 1,500

**Canada** 23: ~30 cases
Prevalence chronic HCV/HIV 4
19%: 11,200

**Japan** 31: 35 cases
Prevalence chronic HCV/HIV 29
55%: 8,800

**Taiwan** 28: 28 cases
Prevalence chronic HCV/HIV 29
55%: 8,800

**Australia** 11: 47 cases
Prevalence chronic HCV/HIV 6,19
<1%: 1,000

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Incidence Rate Ratio (IRR): 1.24 (95% C.I. 1.16 – 1.33; p<0.0001)

Rockstroh J et al., 12th International Congress on Drug Therapy in HIV Infection, Glasgow, 2012
AHC Incidence in HIV+ MSM

Incidence of acute HCV by risk group

Interaction between transmission group and year p-value=0.044

EuroSIDA in EuroCoord

Rockstroh, JIAS 2012
### Number of Seroconversions

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Events</th>
<th>PYFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>95</td>
<td>11196</td>
</tr>
<tr>
<td>IDU</td>
<td>16</td>
<td>376</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>29</td>
<td>6267</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>1339</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>150</strong></td>
<td><strong>19178</strong></td>
</tr>
</tbody>
</table>

- In total 150 seroconversion in a total of 19178 PYFU
- Overall incidence = 0.79 (95% CI: 0.67 – 0.92) /100 PYFU
- Of 1940 HCV seropositive patients in EuroSIDA 8% were msm

Rockstroh J et al., 12th International Congress on Drug Therapy in HIV Infection, Glasgow, 2012; Soriano V, Mocroft A, Rockstroh J et al., JID 2008
Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference

The European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel

AIDS 2011, 25:399–409

(1) Positive anti-HCV immunoglobulin G (IgG) in the presence or absence of a positive HCV-RNA and a documented negative anti-HCV IgG in the previous 12 months.

(2) Positive HCV-RNA and a documented negative HCV-RNA and negative anti-HCV IgG in the previous 12 months.
# Initial presentation acute HCV

## HIV- vs. HIV+ patients

<table>
<thead>
<tr>
<th></th>
<th>HIV-positive n=157</th>
<th>HIV-negative n=259</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39 (35 - 44)</td>
<td>37 (27 - 48)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>99%</td>
<td>58%</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>Transmission risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>97%</td>
<td>2%</td>
</tr>
<tr>
<td>heterosexual</td>
<td>1%</td>
<td>20%</td>
</tr>
<tr>
<td>IVDA</td>
<td>1%</td>
<td>17%</td>
</tr>
<tr>
<td>HCV Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV-GT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/4</td>
<td>84%</td>
<td>69%</td>
</tr>
<tr>
<td>2/3</td>
<td>15%</td>
<td>29%</td>
</tr>
<tr>
<td>anti-HCV positive</td>
<td>83%</td>
<td>79%</td>
</tr>
<tr>
<td>HCV-RNA (log10)</td>
<td>5.8 (5.4 - 6.4)</td>
<td>5.0 (4.0 - 5.8)</td>
</tr>
<tr>
<td>Laboratory presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum ALT (IU/l)</td>
<td>261 (92 - 499)</td>
<td>660 (363 - 1213)</td>
</tr>
<tr>
<td>ALT &gt; 20 x ULN</td>
<td>7%</td>
<td>37%</td>
</tr>
<tr>
<td>Bilirubin &gt; 2 mg/dl</td>
<td>10%</td>
<td>58%</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days transm. - sympt.</td>
<td>62 (42 - 101)</td>
<td>48 (30 - 63)</td>
</tr>
<tr>
<td>Symptoms or signs</td>
<td>32%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Vogel, Deterding et al. CID 2009
Caveat diagnostics: anti-HCV in HIV+ individuals

- testing for anti-HCV may not be enough
- after a first positive HCV-RNA
  - 37% anti-HCV positive 3 months later
  - 86% anti-HCV positive 6 months later
  - 5% without seroconversion after 1 year

Thomson et al. AIDS 2009, 23:89–93
Natural course of AHC in HIV+

- Spontaneous cure in 0 – 40% of all patients
  - Within treatment protocols\(^1,^2\): 25%
  - Observational cohorts\(^3,^4\): 15%

- Prognostic favorable factors:
  - High CD4 cell-count
  - Low HCV-RNA
  - Negative HCV-RNA at week 12\(^5\)

1 Vogel, Antiviral Therapy 2006
2 Gilleece, JAIDS 2005
3 Jones, AASLD 2008, Abstract 1383
4 Thomson, AIDS 2009
5 Azwa, EACS 2007
Consensus recommendation screening for acute HCV infection (grade A, level II, grade C, level II)

(1) All newly diagnosed HIV individuals should be screened for anti-HCV antibody.

(2) HIV-infected MSM at risk for contracting acute hepatitis C infection should be screened at 6-month interval with ALT and annually with anti-HCV antibody.

(3) HIV-infected patients with newly diagnosed STI or continued IVDU should be screened 3 months after diagnosis/last exposure.

(4) A NAT test for HCV-RNA should be performed if a diagnosis of acute HCV infection is suspected.
Screening for acute HCV in HIV

Cost-effective Screening for Acute Hepatitis C Virus Infection in HIV-Infected Men Who Have Sex With Men

Benjamin P. Linas, Angela Y. Wong, Bruce R. Schackman, Arthur Y. Kim, and Kenneth A. Freedberg

Results:
- With HCV protease inhibitor–based therapy, screening with 6-month LFTs and a 12-month HCV Ab test was the optimal strategy when the HCV infection incidence was ≤1.25 cases/100 person-years. The 3-month LFT strategy was optimal when the incidence was >1.25 cases/100 person-years.

Conclusions:
- Screening for acute HCV infection in HIV-infected MSM prolongs life expectancy and is cost-effective. Depending on incidence, regular screening with LFTs, with or without an HCV Ab test, is the optimal strategy.

Linas BP et al. CID 2012
Future of acute HCV?

- Increased cases in even more countries and rising incidence among the MSM population
- Increased reports of acute HCV in HIV- MSM
- Cost of effective screening discussed for such a long time until it has reached all communities……
- Chance of early intervention missed because of high cost and unwillingness to study impact of IFN-free DAA therapy in larger cohorts and the impact of well tolerated therapies with short treatment cycles in a well defined high risk patient population
Reinfection – an alarming reality!

553 patients from 7 NEAT centers with cured acute HCV since 6/2001

141 with at least one reinfection (25.5%)

1509 patient-years of FU, median 2.1 years

Incidence rate: 7.82/100 patient-years

Treated patients: 7.9/100 patient years

Spontaneous clearers: 3.3/100 patient-years

Ingiliz et al., EASL 2014, Martin et al., AIDS 2013
EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

European Association for the Study of the Liver*

Recommendations

- Pegylated IFN-α monotherapy (pegylated IFN-α2a, 180 μg/week or pegylated IFN-α2b, 1.5 μg/kg/week) for 24 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases (Recommendation A1)

- Pegylated IFN-α (pegylated IFN-α2a, 180 μg/week or pegylated IFN-α2b, 1.5 μg/kg/week) should be combined with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks in patients with acute hepatitis C who are HIV-coinfected (Recommendation B1)

- Although no data is available yet, IFN-free regimens can theoretically be used in these patients and are expected to achieve high SVR rates. The same doses and durations as for patients with chronic hepatitis C must be used, until new data indicate whether shorter and/or less intensive treatment is sufficient to achieve high infection cure rates (Recommendation B1)
In 60/483 (12.6%) episodes AHC resolved spontaneously.

In 309/483 (64%) treatment with pegIFN/RBV was initiated within 24 weeks of AHC diagnosis.

Median time from diagnosis to treatment initiation was 8 weeks.

SVR rate was 70% (217/309).
Annual rates of treatment initiation for new AHC diagnoses from 2007 to 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated uptake per newly diagnosed AHC episodes (%)</td>
<td>7/15 (46.7)</td>
<td>15/30 (50)</td>
<td>26/40 (65)</td>
<td>35/49 (71.4)</td>
<td>66/105 (62.9)</td>
<td>82/108 (76)</td>
<td>64/105 (61)</td>
<td>14/31 (45)</td>
</tr>
<tr>
<td>Relative change in treatment uptake</td>
<td>N/A</td>
<td>+3.3%</td>
<td>+15%</td>
<td>+6.4%</td>
<td>-8.5%</td>
<td>+13.1%</td>
<td>-15%</td>
<td>-16%</td>
</tr>
</tbody>
</table>
### Acute HCV in HIV+ MSM: Updated TVR Results

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>White (%)</th>
<th>IL28B CC (%)</th>
<th>Geno 1a (%)</th>
<th>SVR 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TVR total</strong></td>
<td>33</td>
<td>79</td>
<td>52</td>
<td>91</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>48</td>
<td>58</td>
<td>42</td>
<td>90</td>
<td>63%</td>
</tr>
</tbody>
</table>

\[ p = 0.04 \]

Fierer D et al. AASLD 2013
## Current & future studies with DAAs in acute HCV

<table>
<thead>
<tr>
<th>Study name</th>
<th>Coordinator</th>
<th>DAAs</th>
<th>HCV genotype</th>
<th>Duration (weeks)</th>
<th>HIV Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAHHS</td>
<td>UMC Utrecht</td>
<td>BOC + pegIFN + RBV</td>
<td>1</td>
<td>12</td>
<td>pos</td>
</tr>
<tr>
<td>CHAT</td>
<td>UKB</td>
<td>TPV + pegIFN + RBV</td>
<td>1</td>
<td>12</td>
<td>pos</td>
</tr>
<tr>
<td>SWIFT-C</td>
<td>ACTG</td>
<td>SOF + RBV</td>
<td>all</td>
<td>8 vs. 12</td>
<td>pos</td>
</tr>
<tr>
<td>DARE C III</td>
<td>Kirby Institute</td>
<td>SOF + RBV</td>
<td>all</td>
<td>6</td>
<td>neg + pos</td>
</tr>
<tr>
<td>SOL</td>
<td>UKB</td>
<td>SOF + LDV</td>
<td>1, 4</td>
<td>6</td>
<td>pos</td>
</tr>
<tr>
<td>Hep-Net Acute HCV</td>
<td>MHH</td>
<td>SOF + LDV</td>
<td>1</td>
<td>6</td>
<td>neg</td>
</tr>
</tbody>
</table>
Conclusions
1. The amount of patients diagnosed with acute HCV remains high (15.5/1000 years of follow-up).
2. 30 of 53 patients prescreened, fulfilled all inclusion and exclusion criteria.
3. Participation rate of the patients fulfilling inclusion and exclusion criteria was extremely high (>90%).
4. Personal communication: so far all 9 patients at week 12 are HCV-RNA negative.
Study design

* patients who do not achieve an RVR will be treated for 48 weeks
* patients who do not achieve an RVR will be treated for 24 weeks (12 weeks TPV/Peg-IFN/RBV followed by 12 weeks Peg-IFN/RBV)
* patients with a HCV RNA > 1000 IU/ml at week 4 will be discontinued from Telaprevir and continued with Peg-IFN/RBV for additional 44 weeks
* patients who do not achieve a ≥ 2 log_{10} drop in HCV RNA at week 12 will stop treatment
* patients who do not achieve an undetectable HCV RNA at week 24 will stop treatment
Interim analysis

- 14 pts. screened (1 screening failure)
- SVR: 3 pts (arm 2)
- 4 ETR (2 arm 1, 2 arm 2)
- 1 Tx discontinuation due to AE (arm 2)
- 1 re-infection under Tx (arm 2)
- 4 virologic failures (2 arm 1, 2 arm 2)
CHAT patient: HCV kinetics

HCV RNA Baseline: 10,852,811 IU/ml
HCV RNA Week 2: 355 IU/ml
HCV RNA Week 4: 28,762 IU/ml
HCV RNA Week 5: 996,909 IU/ml → Tx discontinuation

2 reasons for non-response:
Reinfection -> again GT 1a infection
HCV PI resistance
Resistence analysis @ week 4

**geno2pheno®**

HCV resistance prediction from genotype (version 1.0)

II. Substitutions

| NS3 region | V36M, T40A, V71I, Q80K, S91A, L153I, R155K |

III. Resistance analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prediction</th>
<th>Scored Mutations</th>
<th>Fold change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>resistant</td>
<td>36M,155K,80K</td>
<td>5.1</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>resistant</td>
<td>36M,80K,155K</td>
<td>62</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>resistant</td>
<td>80K,155K</td>
<td>420</td>
</tr>
<tr>
<td>Faldaprevir</td>
<td>resistant</td>
<td>36M,80K,155K</td>
<td>360</td>
</tr>
</tbody>
</table>

-> Pre-existent?
## Resilience analysis @ baseline

**geno2pheno®**

HCV resistance prediction from genotype (version 1.0)

### II. Substitutions

<table>
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### III. Resistance analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prediction</th>
<th>Scored Mutations</th>
<th>Fold change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>susceptible</td>
<td>none</td>
<td>-</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>susceptible</td>
<td>none</td>
<td>-</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>resistant</td>
<td>80K</td>
<td>14</td>
</tr>
<tr>
<td>Faldaprevir</td>
<td>resistant</td>
<td>80K</td>
<td>2.2</td>
</tr>
</tbody>
</table>

HCV RNA Baseline: 10.852.811 IU/ml
Detection of a Sexually Transmitted HCV Protease Inhibitor-Resistance Variant in a HIV-infected Homosexual Man

Sandra Franco¹, Cristina Tural²-⁵, María Nevot¹, José Moltó²-⁵, Jürgen Kurt Rockstroh⁶, Bonaventura Clotet¹-⁵, and Miguel Angel Martinez¹

To appear in: Gastroenterology
Accepted Date: 9 May 2014
A pilot trial of sofosbuvir and ledipasvir for 6 weeks in the treatment of acute hepatitis C genotype 1 and 4 infection in patients with HIV-1 co-infection (SOL Study)

Other ongoing trials:

- ACTG 12 weeks Sofosbuvir + RBV
- Australia 6 weeks Sofosbuvir and RBV
- Germany Hepatitis Competence network SOF+LDV
Summary

- Increased cases in even more countries and rising incidence among the msm HIV+ and – population
- First all oral DAA combinations demonstrate cure rates in >95% after 6 weeks of therapy
- Extended roll-out of IFN free simple and short DAA combination treatments leads to a decrease in new infections
- Efforts to address the increasing drug use in HIV+ msm as well as psychological interventions to deal with issues around high risk sexual risk behaviour are needed to eventually end this epidemic