Acute Hep C: treatment as prevention?

A Boerekamps, GE van de Berk, FN Lauw, EM Leyten, JE Arends, ME van Kasteren, MAA Claassen, CAB Boucher, BJ Rijnders, for the Dutch Acute HCV in HIV (DAHHS) study group
Conflicts of interest

Within the context of the presentation:
Research grant from MSD (2014-2015-2016 ongoing)
Introduction:

High incidence of Acute HCV (A-HCV) in HIV+MSM observed in many countries.
## Incidence of Acute HCV in MSM

Table 1. Studies determining hepatitis C virus incidence in men having sex with men.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>Study population</th>
<th>N (MSM anti-HCV negative at baseline)</th>
<th>IDUs at baseline (%)</th>
<th>HIV-positive at baseline (%)</th>
<th>Study period</th>
<th>HCV incidence in HIV-positive MSM</th>
<th>HCV incidence in HIV-negative MSM</th>
<th>Overall cumulative incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuliani et al. [43]</td>
<td>Italy</td>
<td>STI clinic attendees</td>
<td>244</td>
<td>n.p.</td>
<td>n.p.</td>
<td>1992–1994</td>
<td>0.4/1000 PYa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alary et al. [40]</td>
<td>Canada</td>
<td>HIV cohort participants</td>
<td>1054</td>
<td>5.4</td>
<td>0</td>
<td>1996–2001</td>
<td></td>
<td>1.2/1000 Pyb</td>
<td>8.3/1000 Pyb</td>
</tr>
<tr>
<td>Rauch et al. [44]</td>
<td>Switzerland</td>
<td>HIV cohort study participants reporting</td>
<td>1571</td>
<td>0</td>
<td>100</td>
<td>1998–2004</td>
<td></td>
<td>0.8/1000 PY</td>
<td></td>
</tr>
<tr>
<td>van de Laar et al. [20]</td>
<td>Netherlands</td>
<td>HIV cohort participants</td>
<td>1812</td>
<td>0.1</td>
<td>27</td>
<td>1984–1999</td>
<td>0/1000 PY</td>
<td>0/1000 PY</td>
<td></td>
</tr>
<tr>
<td>Ruan et al. [48]</td>
<td>China</td>
<td>Cohort study</td>
<td>506</td>
<td>1</td>
<td>0</td>
<td>2006–2007</td>
<td>3.8–7.0/1000 PY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jin et al. [41]</td>
<td>Australia</td>
<td>HIV cohort participants</td>
<td>1542</td>
<td>10.4</td>
<td>10</td>
<td>2000–2007</td>
<td>7.9–13.0/1000 PY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# 2000 - 2009 Incidence of Acute HCV in HIV+ MSM

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Period</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rauch et al. [44]</td>
<td>Switzerland</td>
<td>1998–2004</td>
<td>2 and 7/1000 PY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(in MSM not reporting and reporting unsafe sex, respectively)</td>
</tr>
<tr>
<td>Ghosn et al. [45]</td>
<td>France</td>
<td>&lt;2003</td>
<td>1.2/1000 PY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;2003</td>
<td>8.3/1000 PY</td>
</tr>
<tr>
<td>van de Laar et al. [20]</td>
<td>Netherlands</td>
<td>1984–1999</td>
<td>0.8/1000 PY</td>
</tr>
<tr>
<td>Giraudon et al. [51]</td>
<td>UK</td>
<td>2000–2003</td>
<td>8.7/1000 PY</td>
</tr>
<tr>
<td>Richardson et al. [47]</td>
<td>UK</td>
<td>2000–2006</td>
<td>5.9/1000 PY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11.1/1000 PY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11.4/1000 PY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.5/1000 PY</td>
</tr>
<tr>
<td>van der Helm et al. [49]</td>
<td>Multicentre study (Europe and Canada)</td>
<td>1990–1994</td>
<td>3.8–7.0/1000 PY</td>
</tr>
<tr>
<td>Jin et al. [41]</td>
<td>Australia</td>
<td>2000–2007</td>
<td>7.9–13.0/1000 PY</td>
</tr>
<tr>
<td>Stellbrink et al. [50]</td>
<td>Germany</td>
<td>2002–2009</td>
<td>3.6/1000 PY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.5/1000 PY</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>(2008–2009)</td>
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</tbody>
</table>

≈ 10/1000 PYFU
≈ 1%/year
Introduction:

High incidence of Acute HCV (A-HCV) in HIV+MSM observed in many countries.

Also in the Netherlands:

First reports in 2004:
Sexual transmission of hepatitis C in homosexual men.
Ruyts TA et al. Ned Tijdsch Gen 2004

In 2007:
Incidence 9/1000 PYFU after year 2000
Van der Laar TJ et al. J Infect Dis 2007

In 2014:
Nationwide incidence measured in 19 HIV centers (+- 80% of HIV+MSM in care)
99 A-HCV in 8849 PYFU => 11/1000 PYFU or 1.1% per year
Introduction:

Chronic HCV therapy in the Netherlands.
09/2014: DAA for F3-4 only
11/2015: DAA for all => unrestricted reimbursement for chronic HCV
HIV physicians can prescribe DAA without any other approval/administration

HIV+MSM: Very eager to receive therapy ASAP
⇒ Treatment uptake was most pronounced in HIV+MSM:
05/2017: 76% (n=742/971) of HIV/HCV coinfected MSM were cured of HCV
05/2017: 54% 246/449 of the other HIV+HCV coinfected pts cured of HCV

Acute HCV therapy in the Netherlands:

DAHHS = Dutch Acute HCV in HIV Study group
Study of new therapies for acute HCV in network of HIV centers across NL
Results:

- 2014: A-n = 93, Genotype 1 = 75 (81%), Genotype 4 = 18 (19%)
- 2016: A-n = 49, Genotype 1 = 34 (69%), Genotype 4 = 15 (31%)
Introduction:

DAHHS 1 study: 2014
Pegifn RBV + Boceprevir 12 weeks: genotype 1 only
+- 50% of all gen1 A-HCV infections that year treated in this study
=> 86% cure (ITT)

DAHHS 2 study: 2016 and ongoing
Grazoprevir + elbasvir for 8 weeks: genotype 1 and 4
56 patients included so far (Netherlands + Belgium)

Dutch Modeling study
Will treatment as prevention also work for HCV?

⇒ Immediate DAA treatment is a cost-effective HCV prevention approach that can strongly reduce, but not eliminate, the HCV epidemic among HIV-infected MSM.

Hullegie SJ et al. CROI 2015 abstract nr.536
**Study hypothesis:**
Unrestricted DAA access for HCV positive HIV+MSM will decrease the number of new infections

**Goal:**
To evaluate the results from the modeling study with real-life data

**Methods:**
In the context of the DAHHS1 (2014) and DAHHS2 (2016) studies, the incidence of A-HCV was measured in the participating centers

Remember:
09/2014: DAA for F3-4
11/2015: DAA for all
Methods:

HCV diagnosis in HIV+MSM in the study centers:
Per guideline: HCV testing 1x/year
New ALAT elevation in HIV+MSM => HCV testing
Study centers store left-over plasma => HCV retesting possible

Strict A-HCV definition:

**Definition 1**
Positive HCV IgG or RNA in the presence of negative HCV IgG or RNA in the previous 12 months

**Definition 2:**
Positive HCV IgG or RNA in patient without a documented negative HCV test in last 12 months have to fullfil all these 4 criteria:

1. Pos HCV-RNA + new ALAT elevation >5xULN + documented normal ALAT in last 12 months
2. Documented negative HCV IgG at any time in the past
3. No change in cART and no new other medication that may explain the ALAT elevation
4. No other likely explanation for ALAT rise: In particular, acute HEV, EBV and CMV excluded
Methods:

Incidence per 1000 PYFU in 2014 and 2016 was calculated

# A-HCV infections diagnosed
# PYFU of HIV+MSM in care in 2014

PYFU data from Dutch ATHENA cohort (98% of HIV+ in care in NL)

IRR (95% C.I.) for A-HCV in 2016 versus 2014 was calculated

Incidence in 2016
Incidence in 2014
Results:

**2014**

A-HCV  \( n = 93 \)
- Genotype 1= 75 (81%)
- Genotype 4= 18 (19%)

PYFU  \( n = 8290 \)
- 11.2/1000 PYFU
  (95% CI 9-14)
- 1.1% per year

**2016**

A-HCV  \( n = 49 \)
- Genotype 1= 34 (69%)
- Genotype 4= 15 (31%)

PYFU  \( n = 8961 \)
Results:

<table>
<thead>
<tr>
<th></th>
<th>2014</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-HCV n =</td>
<td>A-HCV n =</td>
<td>A-HCV n =</td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>49</td>
</tr>
<tr>
<td>PYFU n =</td>
<td>8290</td>
<td>8961</td>
</tr>
<tr>
<td>PYFU (95% CI)</td>
<td>11.2/1000 (95% CI 9-14)</td>
<td>5.5/1000 (95% CI 4-7)</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>0.49 (95% CI 0.34 – 0.69)</td>
<td></td>
</tr>
<tr>
<td>Jan-Dec 2014</td>
<td>11.2/1000</td>
<td></td>
</tr>
<tr>
<td>Jan-Jun 2016</td>
<td>6.9/1000</td>
<td></td>
</tr>
<tr>
<td>July-Dec 2016</td>
<td>4.0/1000</td>
<td></td>
</tr>
</tbody>
</table>
What about syphilis in MSM at public health STD clinics:

**First six months of 2015:**
N=446 syphilis infections diagnosed

**First 6 months of 2016:**
N=629 syphilis infections diagnosed (=41% increase ! 95% in MSM)

**Syphilis in HIV+MSM**

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Figuur 5: Percentage positieve infectieuze syfilis testen bij MSM naar hiv status januari t/m december 2007-2015, januari t/m juni 2016

Figuur 2: Aantal LGV-diagnoses per half jaar, januari 2009 - juni 2016

http://www.rivm.nl  Thermometer sexuele gezondheid nov2016
Discussion:

Observational data:
No prove that DAA therapy is the cause of the decline
However, A-HCV was the only STD that decreased in 2016

RCT “impossible” => More (also circumstantial) evidence possible?
Belgium (neighboring country): No unlimited DAA therapy in 2016
Belgium DAHHS2 participating centers: Preliminary data: No decrease

Fylogenetic analysis is ongoing

To what extent is the acute versus the chronic HCV therapy responsible?
=> Fylogenetic analysis will be useful as well
Conclusion:

For the first time in >10 years the incidence of acute HCV has dropped substantially in HIV+MSM in the Netherlands

Unrestricted access and use of DAA for the treatment of chronic (and acute?) HCV is the most likely explanation
In particular: A Boerekamps, SJ Hullegie, Bart Rijnders

Study centers and DAHHS Investigators:

DAHHS2 study coordinators/trial nurses:

Other collaborators:
DAMC van de Vijver, S Popping for mathematical modeling study

ATHENA – SHM:
A.I. van Sighem for providing data on PYFU per center

MSD:
For DAHHS1 and 2 study grants

Last but not least: All patients!
Substantial decline in acute HCV infections among Dutch HIV+MSM after DAA roll out

A Boerekamps, GE van de Berk, FN Lauw, EM Leyten, JE Arends, ME van Kasteren, MAA Claassen, CAB Boucher, BJ Rijnders, for the Dutch Acute HCV in HIV (DAHHS) study group
But will this result in a decline of A-HCV?

Across HIV+ patients in Europe, 63% of new HCV infections were among MSM

Boesecke C et al. Liver Int. 2015

Van de Laar T et al.
Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men.