

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.

Authors	Location	Study population	N (MSM anti-HCV negative at baseline)	IDUs at baseline (%)	HIV-positive at baseline (%)	Study period	HCV incidence in HIV-positive MSM	HCV incidence in HIV-negative MSM	Overall cumulative incidence
Melbye <i>et al.</i> [42]	Denmark	Cohort participants	246 MSM	n.p.	Minority	1981–1989			1.6% (1981) 4.1% (1984) 4.1% (1989)
Giuliani <i>et al.</i> [43]	Italy	STI clinic attendees	244	n.p.	n.p.	1992–1994	2 and 7/1000 PY (in MSM not reporting and reporting unsafe sex, respectively) 1.2/1000 PY ^b 8.3/1000 PY ^b 9.2/1000 PY 0.8/1000 PY 8.7/1000 PY 6.9/1000 (2002) ^c 11.6 (2006) < 1/1000 PY (1997–1999) 4.6/1000 PY (2002) ^b 5.9/1000 PY (2000–2003) 11.1/1000 PY (2004) 11.4/1000 PY (2005) 17.5/1000 PY (2006) 3.8–7.0/1000 PY 10.8–14.9/1000 PY 7.9–13.0/1000 PY 0/1000 PY (2005–2007) 3.6/1000 PY (2002–2003) 10.5/1000 PY (2008–2009)	0.4/1000 PY ^a	13.7/1000 PY
Alary <i>et al.</i> [40]	Canada	HIV cohort participants	1054	5.4	0	1996–2001			
Rauch <i>et al.</i> [44]	Switzerland	HIV cohort study participants reporting	1571	0	100	1998–2004			
Ghosn <i>et al.</i> [45]	France	HIV cohort participants	241	n.p.	100	<2003 >2003			
Turner <i>et al.</i> [46]	UK	HIV outpatient clinic	308	8.1	100	1999–2005			
van de Laar <i>et al.</i> [20]	Netherlands	HIV cohort participants	1812	0.1	27	1984–1999			
Giraudon <i>et al.</i> [51]	UK	HIV/genitourinary clinic patients	n.p.	n.p.	100	2000–2003 2002–2006			
Browne <i>et al.</i> [17]	UK	HIV and sexual health clinic patients	n.p.	n.p.	n.p.	1997–2002			
Richardson <i>et al.</i> [47]	UK	Sexual health clinic attendees	3536	0	n.p.	2000–2006			
Ruan <i>et al.</i> [48]	China	Cohort study	506	1	0	2006–2007			
van der Helm <i>et al.</i> [49]	Multicentre study (Europe and Canada)	HIV seroconverter cohort	3014	n.p.	100	1990–1994			
Jin <i>et al.</i> [41]	Australia	HIV cohort participants	1542	10.4	10	1995–1999 2000–2007 2001–2007			
Stellbrink <i>et al.</i> [50]	Germany	HIV cohort participants	n.p. (10199 PY)	n.p.	100	2002–2009			

2000 - 2009 Incidence of Acute HCV in HIV+ MSM

Rauch <i>et al.</i> [44]	Switzerland	1998–2004	2 and 7/1000 PY (in MSM not reporting and reporting unsafe sex, respectively)
Ghosn <i>et al.</i> [45]	France	<2003	1.2/1000 PY ^b
		>2003	8.3/1000 PY ^b
Turner <i>et al.</i> [46]	UK	1999–2005	9.2/1000 PY
van de Laar <i>et al.</i> [20]	Netherlands	1984–1999	0.8/1000 PY
		2000–2003	8.7/1000 PY
Giraudon <i>et al.</i> [51]	UK	2002–2006	6.9/1000 (2002)
			11.6 (2006)
Browne <i>et al.</i> [17]	UK	1997–2002	< 1/1000 PY (1997–1999)
			4.6/1000 PY (2002) ^b
Richardson <i>et al.</i> [47]	UK	2000–2006	5.9/1000 PY (2000–2003)
			11.1/1000 PY (2004)
			11.4/1000 PY (2005)
			17.5/1000 PY (2006)
van der Helm <i>et al.</i> [49]	Multicentre study (Europe and Canada)	1990–1994	3.8–7.0/1000 PY
		1995–1999	10.8–14.9/1000 PY
		2000–2007	7.9–13.0/1000 PY
Jin <i>et al.</i> [41]	Australia	2001–2007	0/1000 PY (2005–2007)
Stellbrink <i>et al.</i> [50]	Germany	2002–2009	3.6/1000 PY (2002–2003)
			10.5/1000 PY (2008–2009)

≈ 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

Hullegie SJ et al Clin Microbiol Infect. 2016

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 coinfecting MSM were cured of HCV

05/2017: 54% 246/449 of the other HIV+HCV coinfecting 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:



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

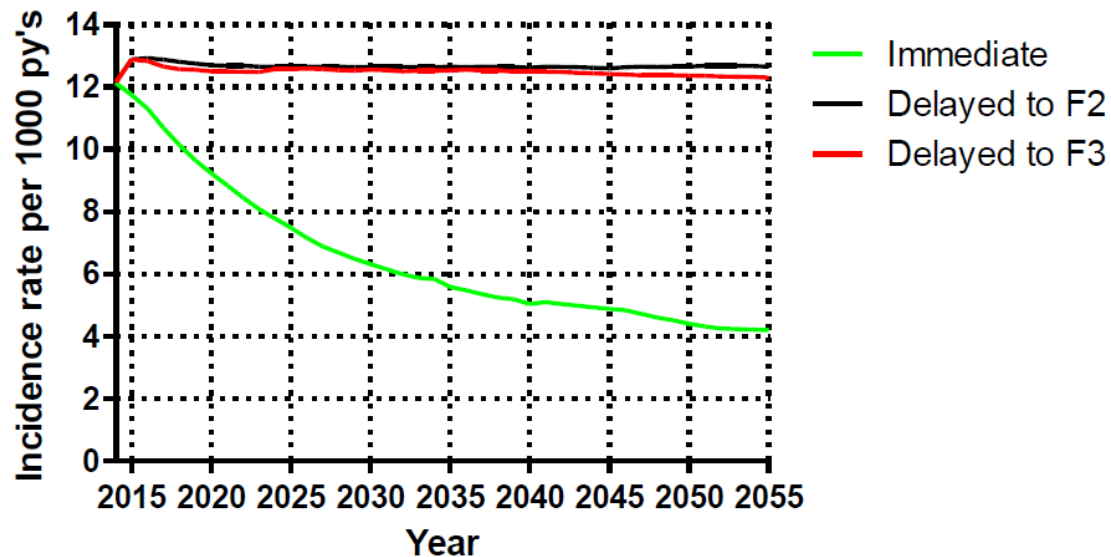
Grazoprevir + elbasvir for 8 weeks: genotype 1 and 4

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.



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 fulfill 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:

2014

A-HCV n = 93

PYFU n = 8290

11.2/1000 PYFU (95% CI 9-14)

1.1% per year

IRR 0.49 (95% CI 0.34 – 0.69)

Jan-Dec 2014 11.2/1000

Jan-Jun 2016 6.9/1000

July-Dec 2016 4.0/1000

2016

A-HCV n = 49

PYFU n = 8961

5.5/1000 PYFU (95% CI 4–7)

0,55% per year



What about syphilis in MSM at public health STD clinics:

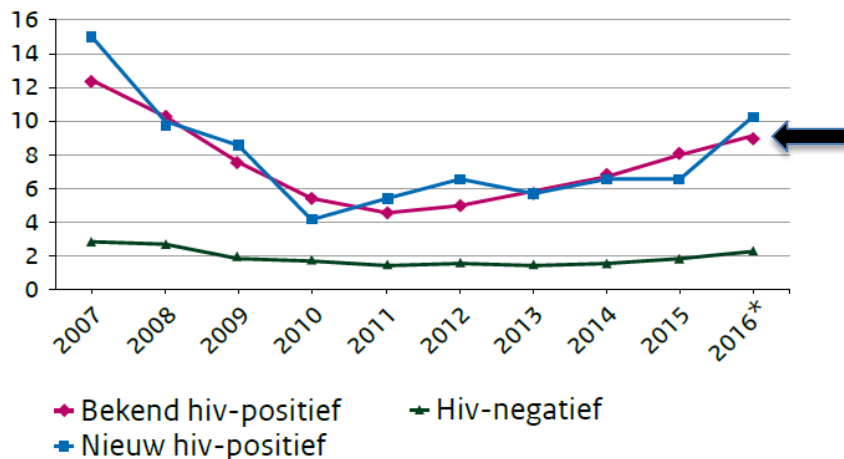
First six months of 2015:

N=446 syphilis infections diagnosed

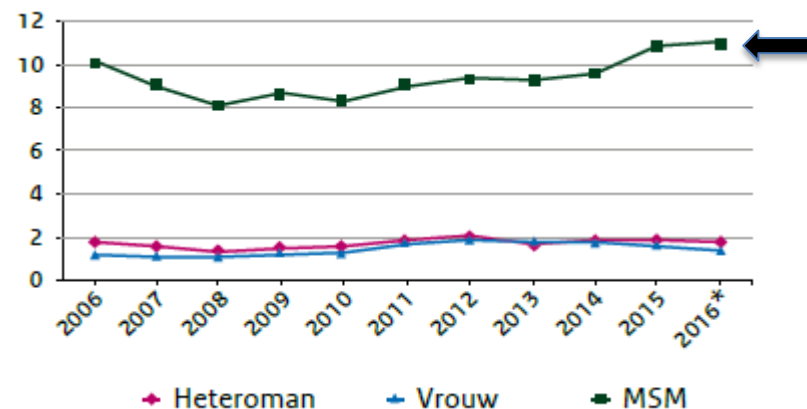
First 6 months of 2016:

N=629 syphilis infections diagnosed (=41% increase ! 95% in MSM)

Syphilis in HIV+MSM



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 halfjaar, januari 2009 - juni 2016

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 usefull 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:

GE van de Berk, FN Lauw, EM Leyten, ME van Kasteren, MAA Claassen, C Richter, A van Eeden, P.H.P. Groeneveld, D. Posthouwer, E.J.G. Peters, F Kroon, E.M.S. Leyten, R Soetekouw, C.E. Delsing, G.J. Kootstra, K.D. Lettinga, A.S.M. Dofferhoff, D.W.M. Verhagen, W.F.W. Bierman, JE Arends

DAHHS2 study coordinators/trial nurses:

K.J.T. Grintjes-Huisman, D.A. de Weerd, M. van Wijk, P.H.M. van Bentum, D Vos, I Hooijenga, D.J. Vlasblom, R.P. Ackens, L.J.M. Elsenburg, M.H.J. Kuipers-Jansen, B.A.F.M. de Kruijff-van de Wiel

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

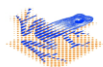
MSD:

For DAHHS1 and 2 study grants

THANKS TO !



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.

Gastroenterology. 2009 May;136(5):1609-17.