Erasmus MC
University Medical Center Rotterdam

Charleroi
Belgian HIV
society
2016

Acute Hepatitis C

Why treat? How treat? Why not?

BJ Rijnders, MD, PhD
Dep. Internal Medicine
Section of Inf Dis
Erasmus MC
Rotterdam, NL

Disclosures

Research grants from MSD (2014-2015-2017)

Research grants from Gilead (2013-2015-2016-2017)

Investigator of trials sponsored by MSD, Gilead, Jansen-Cilag

Invited speaker for Gilead, MSD, Pfizer, Jansen-Cilag

Advisory board : BMS, ViiV Abbvie, MSD, Gilead, Jansen-Cilag

Conference invitations: BMS, Abbvie, MSD, Gilead, Jansen-Cilag

✓ *My wife earns more than I do*

Epidemiology

- Worldwide
- In the Netherlands and Belgium

Diagnosis

To treat or not to treat ?

And if yes, how to treat?

Epidemiology

IVDU, nosocomial transmission, sexual transmission, unknown

IVDU

IVDU remains a major risk factor for A-HCV:

≈1 million active IVDUsers in Europe alone

Incidence 2-16/100 PYFU

Prevalence of anti-HCV AB in IVDU throughout the world : 60-80%

USA :

ongoing AHCV epidemic in young white heroin IVDU in rural areas

Not only IVDU:

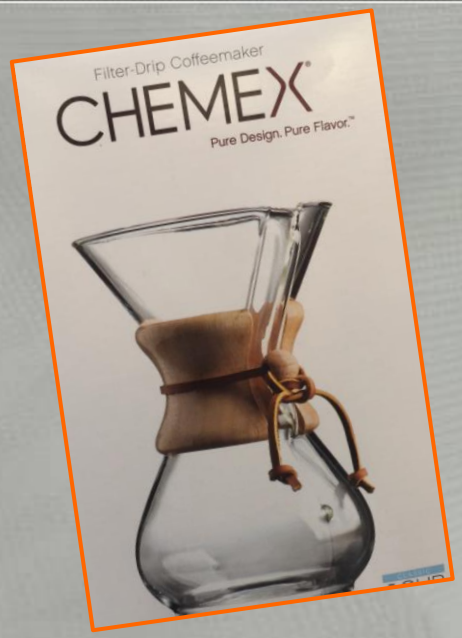
Transmission also occurs via straws shared while sniffing drugs !

European Monitoring Centre for Drugs and Drug Addiction , 2010
SJ Hullegie et al. CMI 2015

Lucidarme D et al. Epidemiol Infect, 2004
Nelson P.K. et al. Lancet, 2011

IVDU

Not only the classical user : In the context of ***chem - sex***



Cam - sex

Epidemiology

Nosocomial transmission

Major route in resource limited settings, genotype 4 in Egypt

In Europe:

- Risk via transfusion, inadequate sterilization, needle injections nearly absent
- Nosocomial HCV transmission still occurs:

National surveillance system France: Nosocomial HCV = 25% of all A-HCV infections
Risk populations : hemodialysis patients, health care workers

Dutch study in 2286 dialysis patients in 1995 2.9% => 1997 3.4%
Incidence 0.5/100 PYFU !

J Infect Dis. 2000 Nov;182(5):1291-9

Epidemiology

Sexual transmission

Heterosexual transmission is very limited, even with anal intercourse:

As low as 1 per 190.000 sexual contacts or 0.07% per year

Transmission in men who have sex with men (MSM):

Starting in 2000 clusters were seen of HCV transmission in non-IVDU HIV+ MSM

Problem has not been tackled/increases !

Large majority is genotype 1 or 4

Terrault et al. Hepatology, 2013

Epidemiology

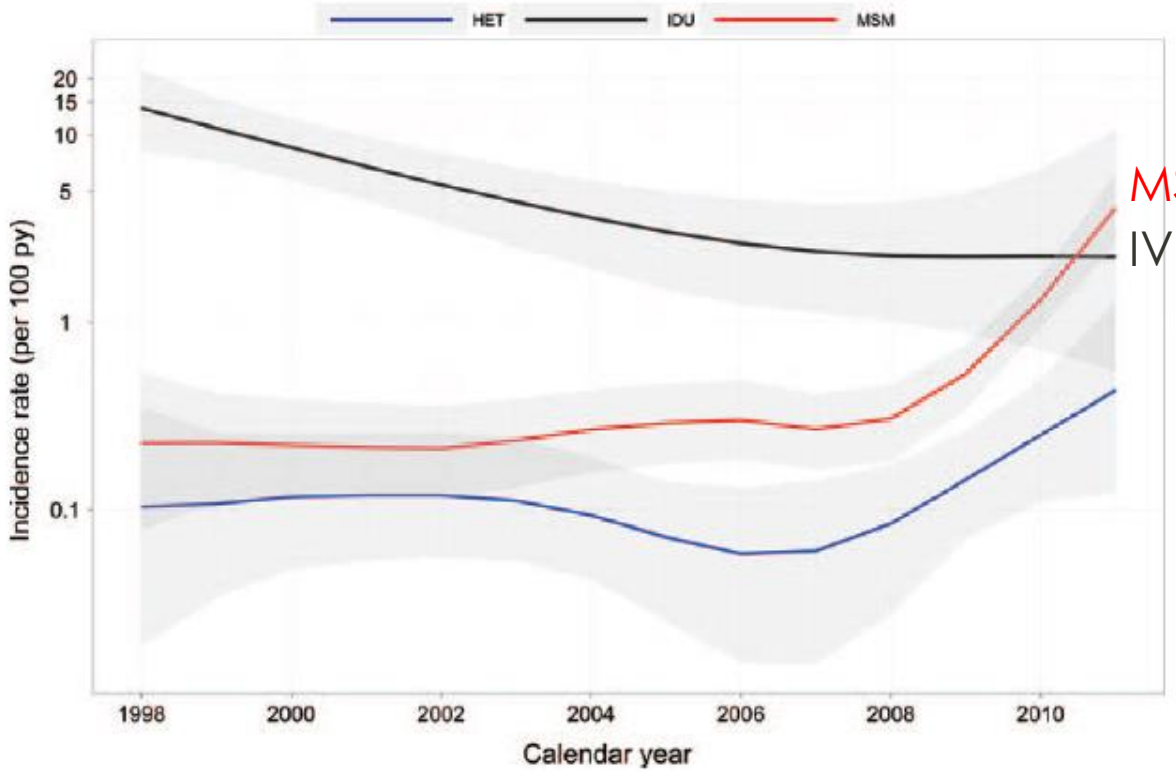


Figure 2. Hepatitis C virus infection incidence rates by transmission group (shaded: 95% credible intervals). Abbreviations: HET, heterosexual; IDU, injection drug user; MSM, men who have sex with men; py, person-year.

Wandeler G et al. Clin Inf Dis 2012

Epidemiology

Sexual transmission

Transmission in men who have sex with men (MSM):

Netherlands 2014

- **n=99** A-HCV diagnosed in 12 months in 19 HIV centers in HIV+MSM
- 80% = genotype 1 / 19% = genotype 4
- Incidence 1.1% per 100 PYFU

Risk factors:

Recreational drug use / Serosorting / UAI / ulcerative STD

Receptive fisting / Sharing straws while sniffing drugs

History of acute HCV => Extremely high reinfection rates from 5 to 15.2/100 PYFU

SJ Hulllegie et al. CMI 2015 Martin TC et al. Aids, 2013 Lambers FA et al. Aids, 2011 Xiomara T et al. AIDS 2015
Van Hommerig J et al. Open forum ID 2015

Epidemiology

Sexual transmission

Transmission in men who have sex with men (MSM):

Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001-2009

- 69 episodes of newly acquired HCV infection
- 14% symptomatic
- Annual incidence in HIV-infected MSM:

0.2% in 2001 1.5% in 2008 2.9% in 2009

5% of 370 HIV negative PREP candidates in Amsterdam : HCV + at screening visit !!!

Several acute HCV infections during PREP use in Antwerp

Bottieau E et al. Euro surveillance 2010

Epidemiology

- Worldwide
- In the Netherlands and Belgium

Diagnosis

To treat or not to treat ?

And if yes, how to treat?

Diagnosis

QUESTION about a case:

HIV+ patiënt, CD4 700/ml, HIV-RNA <20c/ml HAART (TDF/FTC/EFV)
No alcohol abuse, no other medication and no symptoms
Non-responder to HepB vaccination
Comes for his biannual HIV check-up

Lab calls you that his ALAT is 400 (was 30 IU 6 months earlier)

He tells that he went to Antwerp (or Amsterdam) 3 months earlier and points this as the very likely date of infection

Diagnosis

Question:

The most likely diagnosis is acute HCV

The most likely diagnosis is acute HBV

Both are +- as likely

Diagnosis

Remember:
The patients was on TDF (Tenofovir-DF) as are +-75% of HIV+ patients in NL/BE

The most likely diagnosis is acute HCV

The most likely diagnosis is acute HBV

Both are +- as likely

Diagnosis

Remember:
The patients was on TDF (Tenofovir-DF) as are +-75% of HIV+ patients in NL/BE

The most likely diagnosis is acute HCV

~~**The most likely diagnosis is acute HBV**~~

~~**Both are +- as likely**~~

Diagnosis

Question:

3 months after (probable date of) infection, HCV antibodies will be positive in:

A/ +- 90%

B/ +- 75%

C/ +- 50%

D/ < 50%

Diagnosis

A heterogeneity in case definition of AHCV infection is currently used

Best:	PCR- → PCR+ within period of 6 (-12) months; often impossible
Very good:	Antibody seroconversion within 6 (-12)months; often impossible
Very Good:	HCV RNA positive + Antibody negative + ALAT >5-10ULN
Good:	PCR+ and no other cause of transaminitis in pnt with documented HCV negative status somewhere in the past in pnt with possible exposure within 6 (-12) months
Reasonable	PCR+ Ab+ ALAT >5-10xULN No other cause of transaminitis in pnt with possible exposure within 6 (-12) months

Hajarizadeh B et al. J Hepatol. 2012 Thomson EC et al. AIDS 2009

Diagnosis

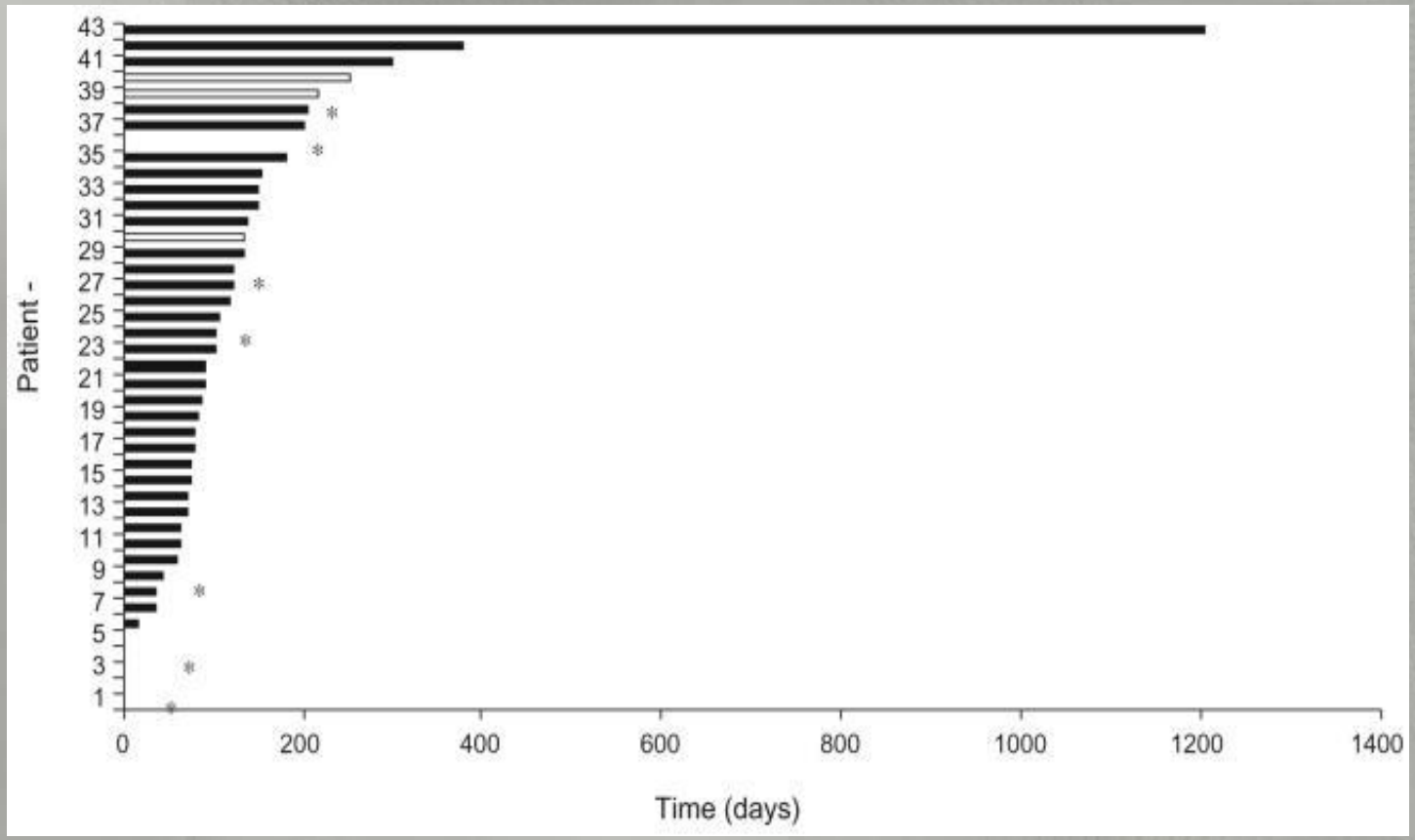
ALAT rise may initially remain absent, seroconversion takes time:

43 HIV+ patients (CD4 570):

ALAT at first HCV PCR+ was low at 65 IU and was <ULN in 25% !

88% had ALAT >ULN at least once during first 6months after first PCR+

Diagnosis



Antibody response:

- 50% Ab negative 100 days after infection
- 10% Ab negative after 1 year

Thomson EC et al. AIDS 2009

Diagnosis

HCV antigen instead of HCV RNA to diagnose acute HCV?

SJ Hullegie et al. Submitted

Diagnosis

HCV antigen instead of HCV RNA to diagnose acute HCV?

Architect HCV Ag assay, Abbott

42/44 had HCV Ag detected above the limit of detection

39/44 had HCV Ag detected above 3.0 fmol/L (chronic HCV Ag cut-off)

1/23 HCV neg controls (with ALT elevation but HCV RNA-) had HCV Ag (<3.0)

- Sensitivity 89% (3.0 fmol/L) or 95% (> limit of detection)
- Specificity 100% (3.0 fmol/L) or 96% (> limit of detection)

Antibodies: Liaison XL anti-HCV, Diasorin

32/35 pts with acute HCV had antibodies at time of first HCV detection

35/35 pts had HCV IgG at start of therapy (<26wks after infection)

SJ Hullegie et al. Submitted

Diagnosis

Question:

3 months after (probable date of) infection, HCV antibodies will be positive in:

A/ **+- 90%**

B/ **+- 75%**

C/ **+- 50%**

D/ **< 50%**

Diagnosis

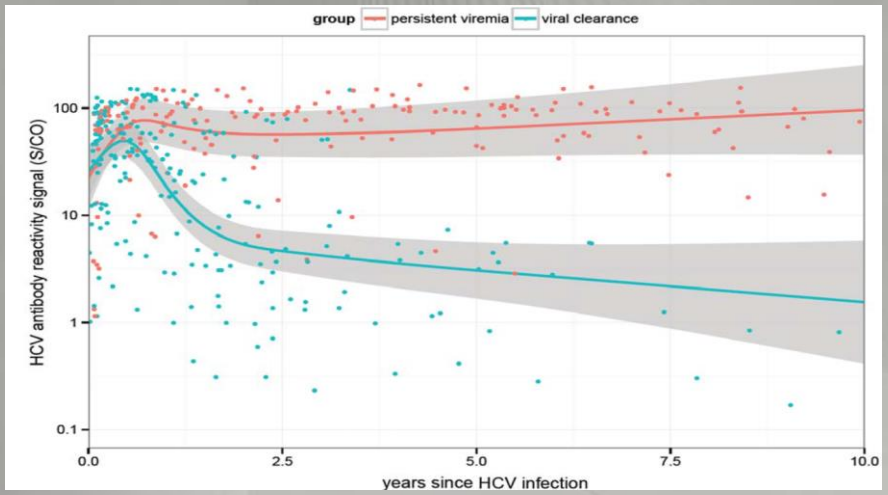
How to diagnose reinfection?

*** Relapse versus reinfection?**

Sequencing needed as up to 80% is genotype 1a

Essential if acute HCV therapy is studied in population with 5% reinfection/year

*** After SVR: Can reinfection be diagnosed with antibody testing?**



No SVR

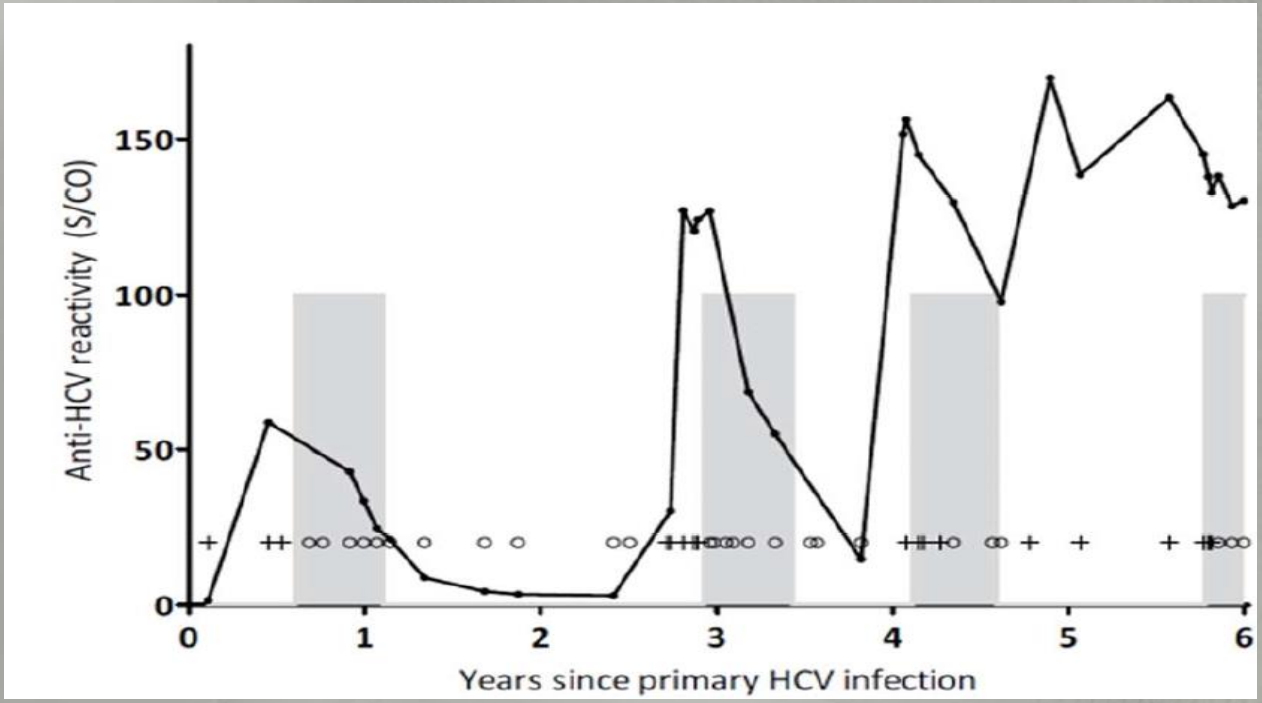
SVR or spontaneous clearance

At 3 yrs: 1/3th of successfully treated acute HCV pts became antibody negative !

Vanhommerig J et al Clin Inf Dis 2014

Diagnosis

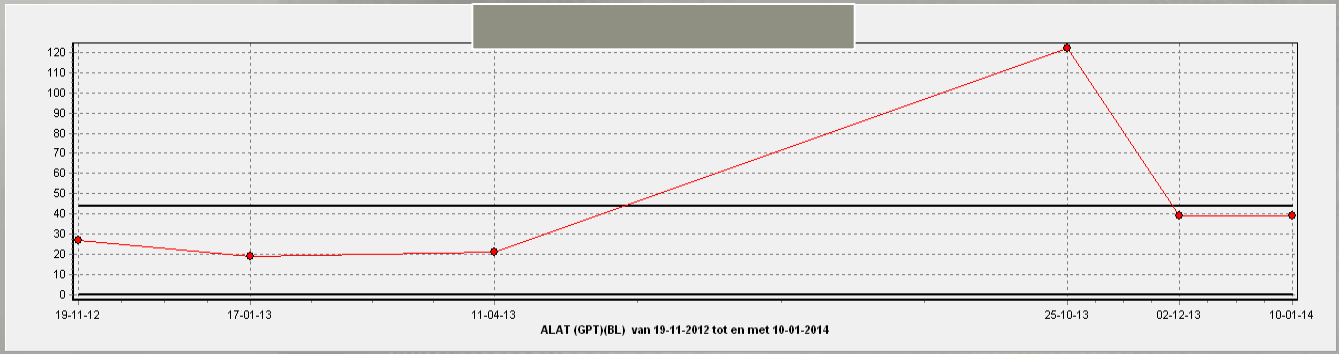
After SVR: Can reinfection be diagnosed with antibody testing?



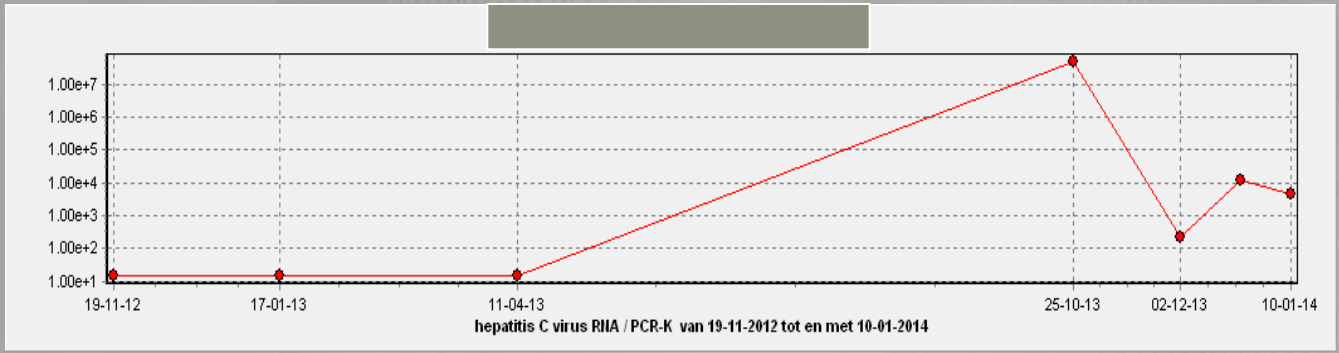
Vanhommerig J et al Clin Inf Dis 2014

Diagnosis

Some examples of pitfalls: **Fluctuating viremia first 6 months after infection:**



Single ALAT peak



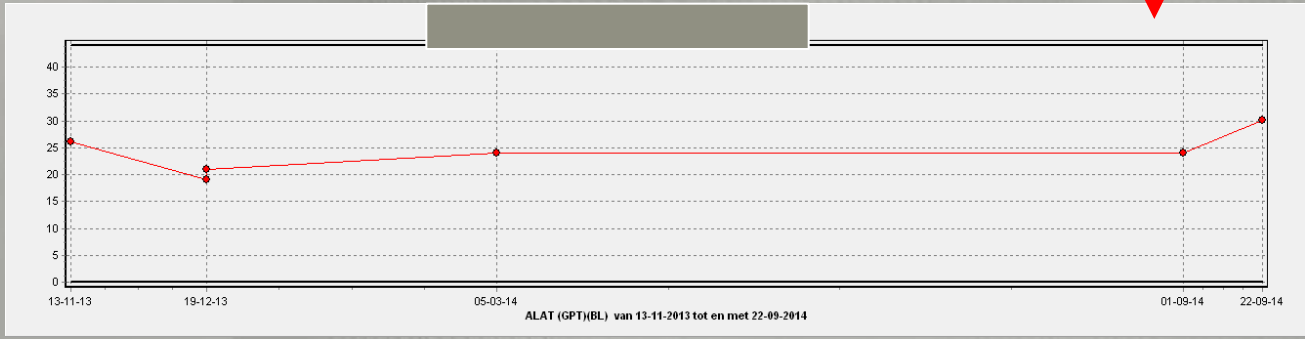
But ongoing fluctuating viremia:

10^e8 => 10^e2 => 10^e4

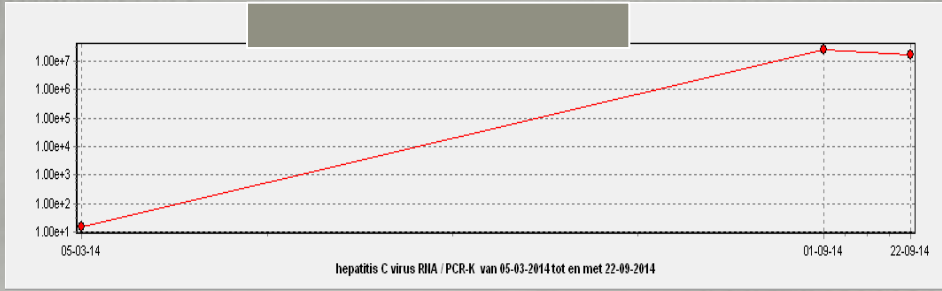
Diagnosis

Some examples of pitfalls: **No ALAT during first months after infection:**

GGD HCV Partner notification



Normal ALAT



But very high viremia

Epidemiology

- Worldwide
- In the Netherlands and Belgium

Diagnosis

To treat or not to treat ?

And if yes, how to treat?

Treatment

What should I tell you?

? Overview of all the IFN/PegIFN studies:

Is becoming more of historical interest for resource rich settings

? Studies on DAA for acute HCV

Only small studies have been completed with mixed results.

Larger studies on DAA for acute HCV are recruiting now or will start in near future

Treatment

PegIFN based therapy: SVR in HIV negative?

Table 1 Treatment of acute hepatitis C (AHC) with pegylated interferon alfa for monoinfected patients

Study	Study design	No. of pts	Treatment	Treatment duration (weeks)	Start of therapy	SVR (%)
Kamal et al. [65]	R	20	Peg-IFNα[b]	24	12 weeks from onset	16/20 (80)
		20	Peg-IFNα[b] + RBV (800 mg/day)	24	12 weeks from onset	17/20 (85)
Santantonio et al. [58]	Non-R	16	Peg-IFNα-2b (1.5 μg/kg/week)	24	12 weeks from onset	15/16 (94)
Broers et al. [64]	Non-R	14	Peg-IFNα-2b (1.5 μg/kg/week)	24	100 days from onset of symptoms or 63 days from first HCV detection	8/14 (57)
Wiegand et al. [57]	Non-R	89	Peg-IFNα-2b (1.5 μg/kg/week)	24	76 days after infection	63/89 (71)[a]
Kamal et al. [59]	R	129	Peg-IFNα-2b (1.5 μg/kg/week)	12	8, 12, and 20 weeks from onset	41/43 (95)
						40/43 (93)
						33/43 (77)
Kamal et al. [63]	R	131	Peg-IFNα-2b (1.5 μg/kg/week)	8	12 weeks from onset	23/24 (68)
				12		28/34 (82)
				24		31/34 (91)
De Rosa et al. [81]	Non-R	23	Peg-IFNα-2b (1.0–1.6 μg/kg/week)	12	13.5 days after diagnosis	17/23 (74)
Calleri et al. [62]	Non-R	46	Peg-IFNα-2b (1.0–1.5 μg/kg/week)	12	15 days after ALT peak	33/46 (72)
Deterding et al. [60]	R	55 sympt.	Peg-IFNα-2b (1.5 μg/kg/week)	24	At diagnosis	37/55 (67)[c]
		52 sympt.	Peg-IFNα + RBV (>10.6 mcg/kg/day)	24	12 weeks from onset	28/52 (54)[c]
		25 asympt.	Peg-IFNα-2b (1.5 μg/kg/week)	24	At diagnosis	18/25 (72)[c]
Santantonio et al. [61]	R	44	Peg-IFNα-2b (1.5 μg/kg/week)	24	12 weeks from onset	31/44 (70.5)[d]
		43	Peg-IFNα-2b (1.5 μg/kg/week)	12		31/43 (72.1)[d]
		43	Peg-IFNα-2b (1.5 μg/kg/week) + RBV (10.6 mcg/kg/day)	12		31/43 (72.1)[d]

R randomized study, *Non-R* non-randomized study, *SVR* sustained virological response, *sympt.* symptomatic patients, *asympt.* asymptomatic

542/711
= 76%

Treatment

PegIFN based therapy: SVR in HIV positive?

Table 2 Treatment of AHC with pegylated interferon alfa for HCV/HIV-coinfected patients

Study	Study design	No. of pts	Treatment	Treatment duration (weeks)	Start of therapy	SVR (%)
Gilleece et al. [70]	Retrospective/ prospective	27	Peg-IFNα + RBV	24	NA	59
Serpaggi et al. [71]	Retrospective	10	IFNα ± RBV Peg-IFNα	6–48	49 days from onset	0
Luetkemeyer et al. [72]	Retrospective	4	Peg-IFNα + RBV	48 24 (1pt)	8 weeks after diagnosis	66
Vogel et al. [73]	Prospective	111	Peg-IFN (G 2,3) Peg-IFNα + RBV (G 1)	24 48	7 weeks after diagnosis	62%
Dominguez et al. [74]	Prospective	14	Peg-IFNα + RBV	24	14 weeks after diagnosis	71
Matthews et al. [75]	Prospective	22	Peg-IFNα + RBV	24	22 weeks after infection	80
Piroth et al. [76]	Prospective	40	Peg-IFNα + RBV Peg-IFNα (2 pts)	39 ± 17	5 months after diagnosis	82
Grebely et al. [77]	Prospective	35	Peg-IFNα + RBV	24	>26 weeks after infection in 66 % of pts	74

310/467 = 66%

+ Lambers et al. 38/50 Boesecke 68/105 Fierer 30/48

Note:

- Mostly + RBV
- Mostly 24 weeks (or longer) and no study on 12w therapy
- Several studies showed that RVR4 is very good predictor of SVR with PPV of +-90%

Treatment

PegIFN + 1th generation DAA + RBV in HIV+

Dutch **A**cute **H**CV in **H**IV **S**tudy **(DAHHS)**

10 HIV reference centers: 70% of all HIV+ MSM in care in 2014

N=57 acute HCV genotype 1 infections

R/ Boceprevir PegIFN RBV for 12 weeks, no lead-in

Primary endpoint:

SVR in patients with cRVR4 (Target not detected)?

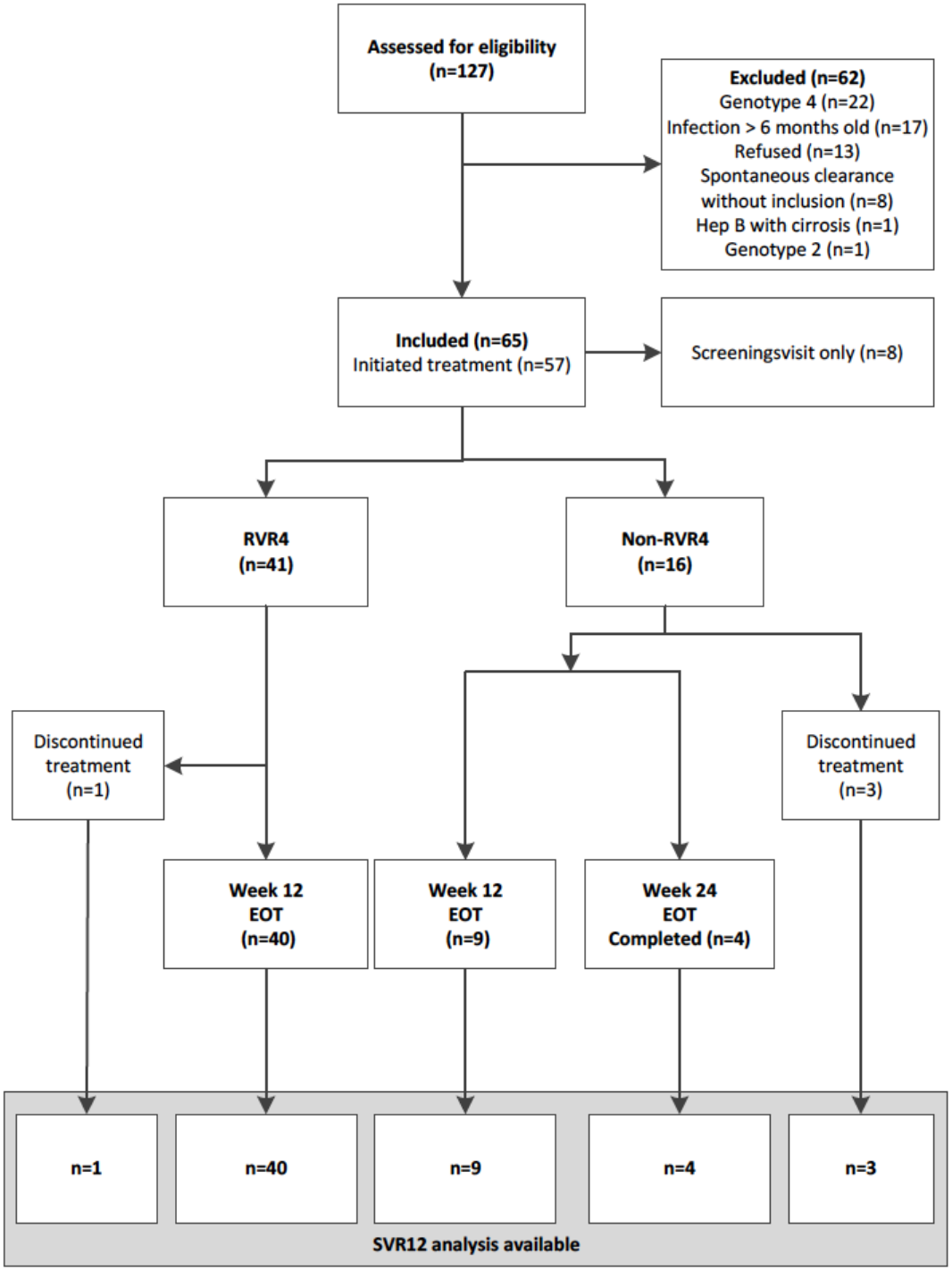
Secundary endpoints:

SVR in ITT population

Is 12w boceprevir pegIFN RBV as good as historical 24w PegIFN RBV?

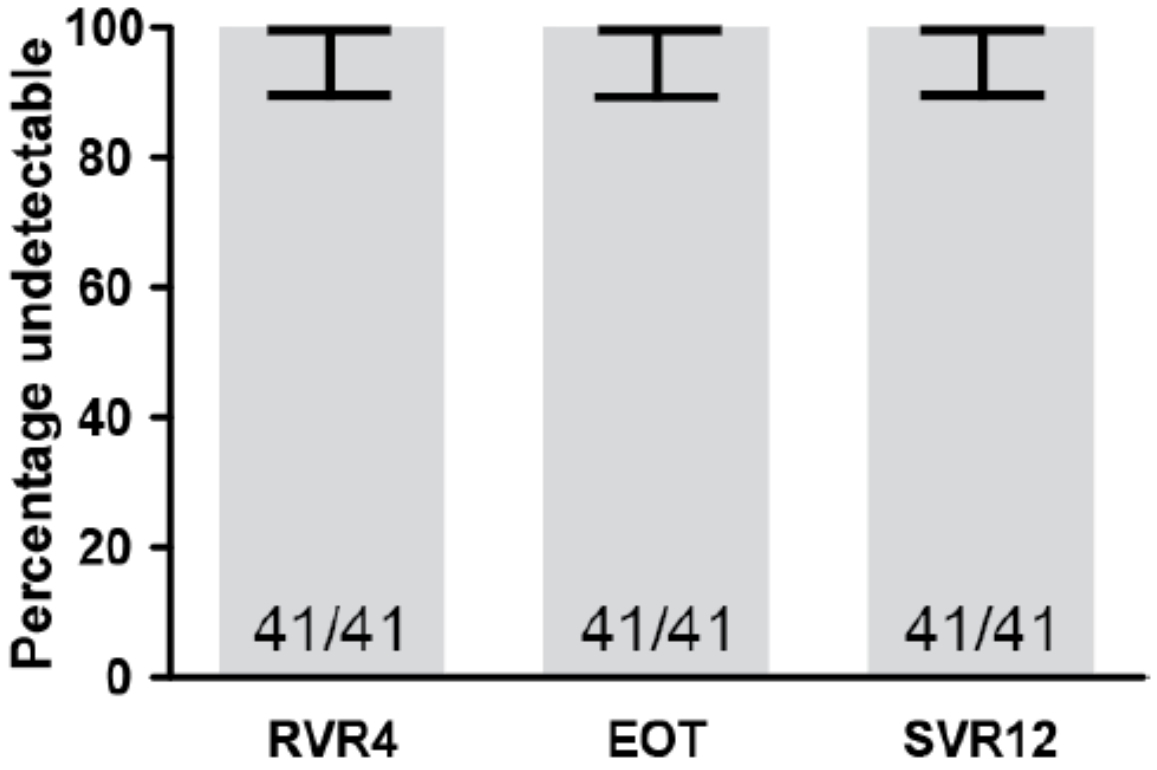
SJ Hullegie et al. J Hepatology 2016

DAHHS


Assessed for eligibility (n=127)
Excluded (n=62)
Genotype 4 (n=22)
Infection > 6 months old (n=17)
Refused (n=13)
Spontaneous clearance without inclusion (n=8)
Hep B with cirrosis (n=1)
Genotype 2 (n=1)
Included (n=65)
Initiated treatment (n=57)
Screeningsvisit only (n=8)
RVR4 (n=41)
Non-RVR4 (n=16)
Discontinued treatment (n=1)
Discontinued treatment (n=3)
Week 12 EOT (n=40)
Week 12 EOT (n=9)
Week 24 EOT Completed (n=4)
n=1
n=40
n=9
n=4
n=3
SVR12 analysis available

Treatment:

Figure 2a. Virological response in RVR4 patients

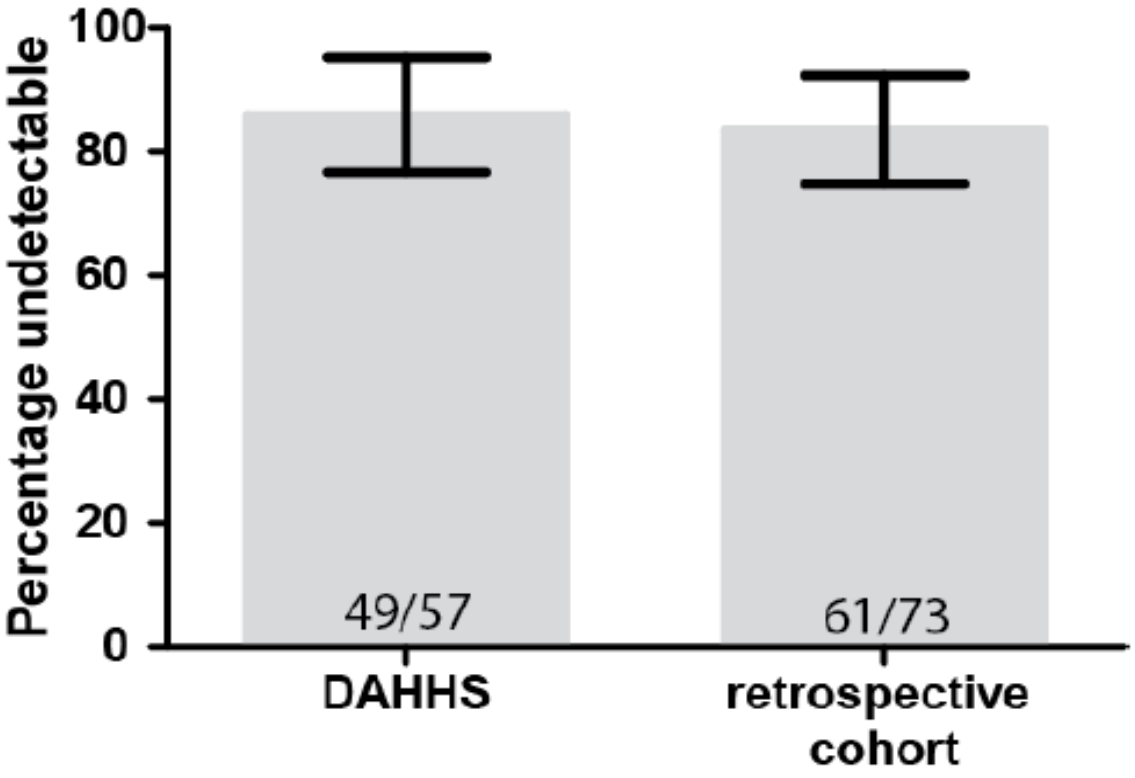


41/41=
100% SVR12

SJ Hullegie et al. J Hepatology 2016

Treatment:

Figure 2b. Virological response in ITT population



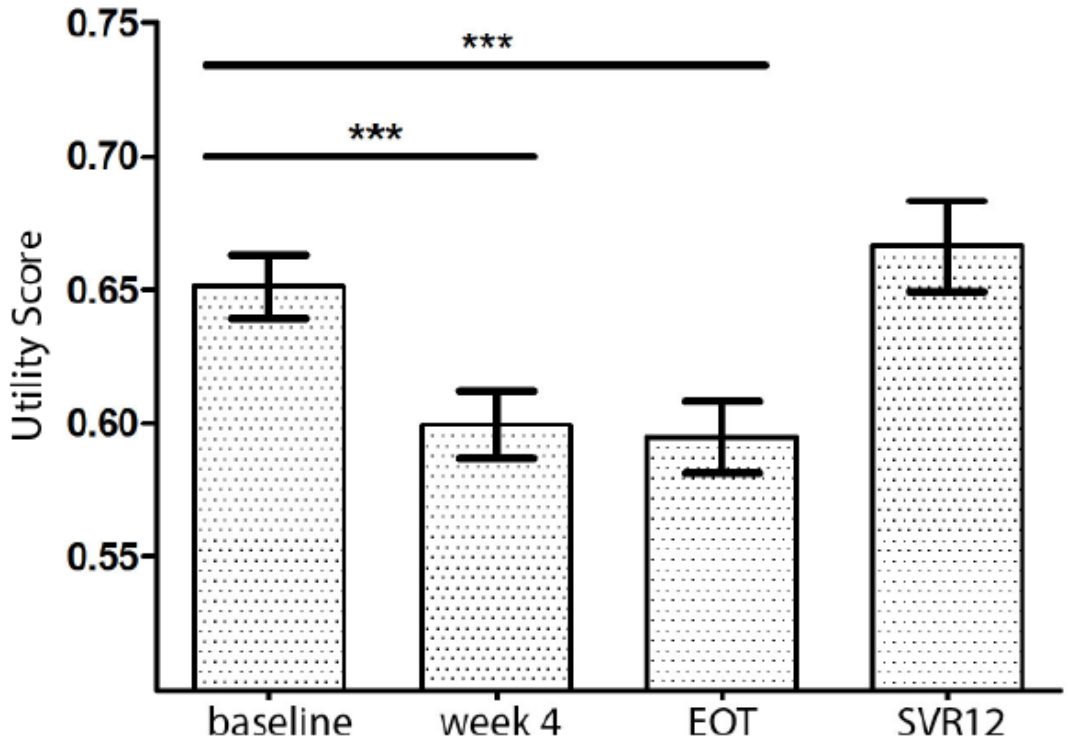
49/57=
86% SVR12

SJ Hullegie et al. J Hepatology 2016

Controls : from MOSAIC study

Treatment:

Figure 4. Change in utility score during treatment with peginterferon, ribavirin and boceprevir



Acute HCV treatment with DAA only?

Study name	Coordinator	Therapy	HCV genotype	Duration (weeks)	HIV status	Number of patients
DAHHS2	EMC	GZP+EBV	1+4	8	+	80
REACT	Kirby Institute	SOF/VEL	All	6-12	-/+	250
TARGET3D	Kirby Institute	DSV+PTV/r+ OBV	1	8-6	-/+	60
DARE-C2	Kirby Institute	SOF+RBV	All	8-6	-/+	20
SWIFT-C	ACTG	SOF+ rbv	All	8	+	50
SOL	UKB	SOF+LDV	1,4	6	+	26
Hep-Net Acute HCV	MHH	SOF+LDV	1	6	-	20
SAHIV	France	GZP+EBV	1,4	8	+	50
SLAM-C	USA	SOF LED	1	4	-	14
		SOF SIM	1	8	-	15

SJ Hullegie et al. CMI 2015

Acute HCV treatment with DAA only?

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DAHHS2	EMC	GZP+EBV	1+4	8	+	80
REACT	Kirby Institute	SOF/VEL	All	6-12	-/+	250
TARGET3D	Kirby Institute	DSV+PTV/r+ OBV	1	8 ➡ 6	-/+	30+30
DARE-C2	Kirby Institute	SOF+RBV	All	8-6	-/+	20
SWIFT-C	ACTG	SOF+ rbv	All	8	+	50
SOL	UKB	SOF+LDV	1,4	6	+	26
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SJ Hullegie et al. CMI 2015

Acute HCV treatment with DAA only?

Study name	Coordinator	Therapy	HCV genotype	Duration (weeks)	HIV status	Number of patients	
DAHHS2	EMC	GZP+EBV	1+4	8	+	80	*Recruiting (n=48/80)*
REACT	Kirby Institute	SOF/VEL	All	6-12	-/+	250	*2017-2019 ?*
TARGET3D	Kirby Institute	DSV+PTV/r+ OBV	1	8 ➡ 6	-/+	30+30	*Recruiting*
DARE-C2	Kirby Institute	SOF+RBV	All	8-6	-/+	20	*Completed*
SWIFT-C	ACTG	SOF+LDV	All	8	+	35?	*Recruiting*
SOL	UKB	SOF+LDV	1,4	6	+	26	*Completed*
Hep-Net Acute HCV	MHH	SOF+LDV	1	6	-	20	*Completed*
SAHIV	France	GZP+EBV	1,4	8	+	50	*2017-2018 ?*
SLAM-C	USA	SOF LED	1	4	-	14	*Completed*
		SOF SIM	1	8	-	15	

SJ Hullegie et al. CMI 2015

Acute HCV treatment with DAA only?

DARE CII study **SVR12**

HIV pos or neg, all genotypes
n=19, within 1 year after infection
sofosbuvir ribavirin for **6 weeks**

SWIFT-C study

HIV pos, n=15 genotype 1
n=17, within 6 months after infection
sofosbuvir ribavirin ***12 weeks***

Acute HCV treatment with DAA only?

SLAM-C study **SVR12**

HIV neg, Ab- RNA+, gen1

n=14 Sofosbuvir ledipasvir ***4 weeks***

n=15 sofosbuvir simeprevir ***8 weeks***

HepNet IV study

HIV neg gen1

n=20, within 4 months after infection

sofosbuvir ledipasvir **6 weeks**

SOL study

HIV pos gen1 (n=19) or 4 (n=7)

n=26, within 6 months after infection

Sofosbuvir ledipasvir ***6 weeks***

Post-hoc: 22/22 with HCV VL <9.000.000 had SVR12

Acute HCV treatment prospects?

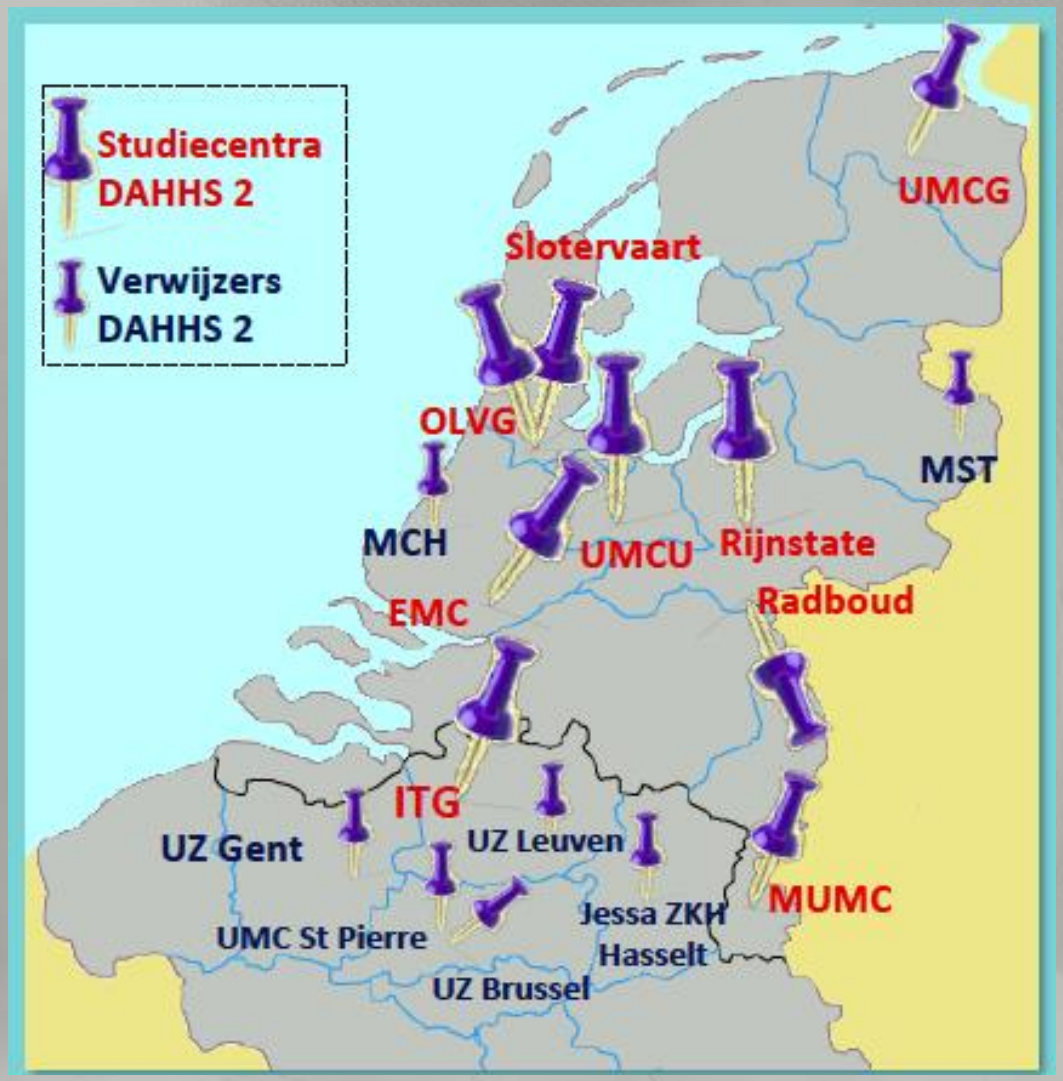
DAHHS-2:

Netherlands + Belgium

n=80 genotype 1 or 4

QD Grazoprevir Elbasvir STR 100/50mg for 8 weeks

Acute HCV treatment prospects?



Acute HCV treatment prospects?

DAHHS-2:

48/80 included
41 started therapy
HAART change needed in +-50% (DTG, RAL, RPV)
AE: No treatment discontinuations so far
17 have reached post-treatment w12 => SVR in 17/17
1 relapse/reinfection (pending) (C.I. 78% - 100% ...)

Hoofdonderzoeker
Dr. Bart Rijnders (MD, PhD)
b.rijnders@erasmusmc.nl
Dagelijkse coördinatie
Anne Boerekamps (MD)
a.boerekamps@erasmusmc.nl
*Trial-mobiel: **06-12725005***

Treating acute HCV?

Why bother about PegIFN based acute HCV therapy?

- New DAA not registered for acute HCV
- In many countries, second generation DAA are not (yet) available for all because of costs

Why not wait 12 months until its chronic and treat with 95% cure with latest DAA?

VERY expensive when compared with 86% SVR with 12w IFN RBV Boceprevir or 24w PegIFN

Chronic HCV	12w PegIFN SOF RBV	= 40.000 euro	(official Dutch
	12w Sofosbuvr ledipasvir	= 48.700 euro	price
	12w Paritaprevir/Ombitasvir/dasabuvir	= 21.000 euro	settings)
	12w Grazoprevir/elbasvir	< 20.000 euro	???
Acute HCV	12w PegIFN RBV ~~Boceprevir~~	= +- 12.700 euro	
	24w PegIFN RBV	= +- 5.000 euro	
	8w Grazoprevir/elbasvir	< 14.000 euro ??	

To prevent ongoing transmission in MSM and IVDU !

Modeling the Acute HCV epidemic in the DAA era

Reliable Dutch data available on :

Number of HIV+ MSM in NL: ATHENA cohort

Number of new HCV infections in HIV+MSM (Hullegie SJ et al. 2014, ATHENA)

Number of sex partners per year from questionnaires from DAHHS

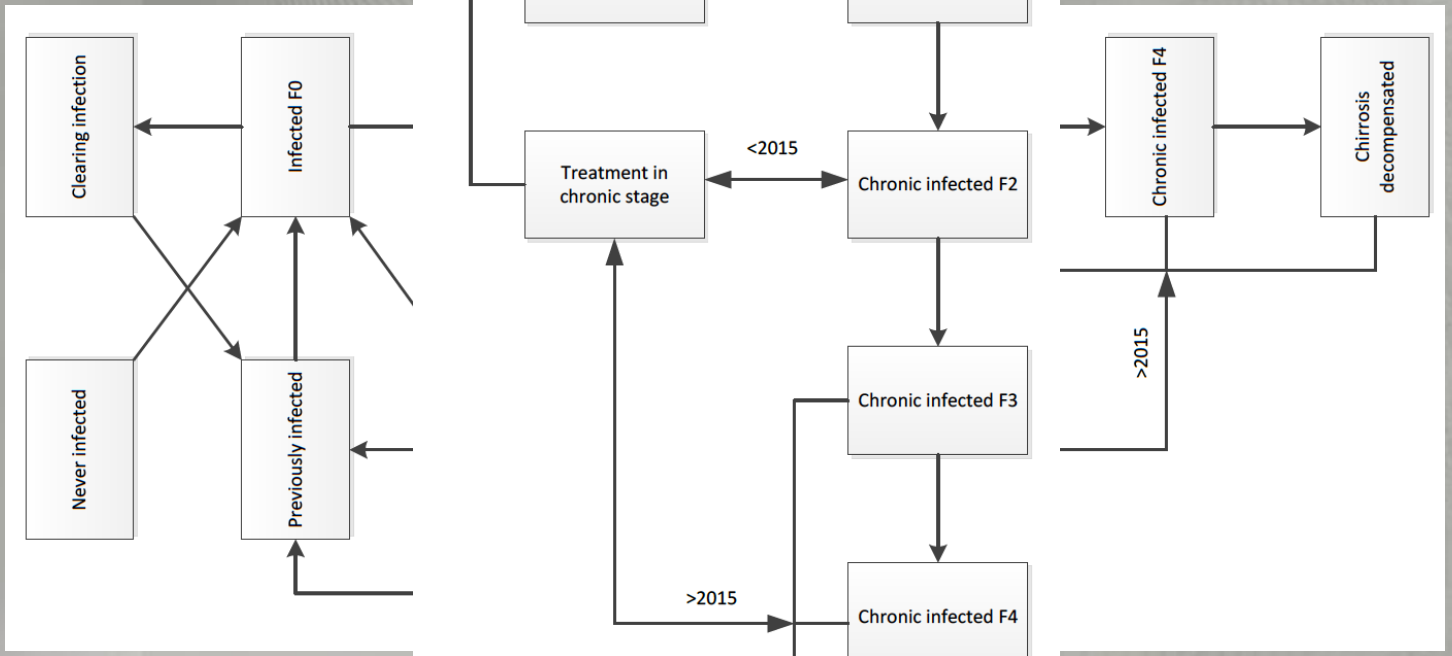
What happens over the next 40 years if we treat all Acute HCV diagnosed among HIV+MSM with DAA right away ?

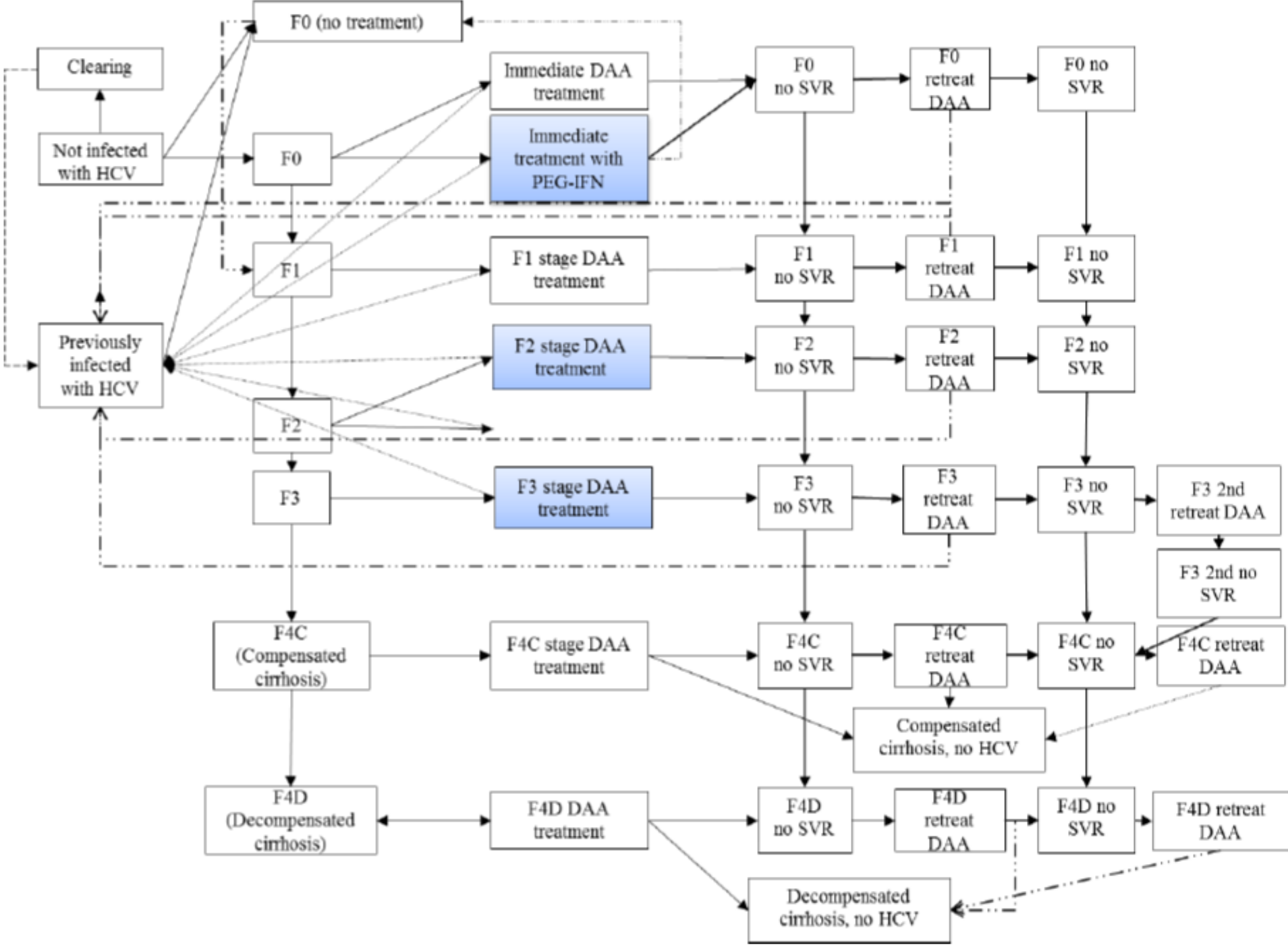
SJ Hullegie, ... D Vandevijver, submitted

Modeling the A … nic in the DAA era

What happens if we … DAA right away ?

HCV lifetime model:




F0 (no treatment)
Clearing
Immediate DAA treatment
F0 no SVR
F0 retreat DAA
F0 no SVR
Not infected with HCV
F0
Immediate treatment with PEG-IFN
F1
F1 stage DAA treatment
F1 no SVR
F1 retreat DAA
F1 no SVR
Previously infected with HCV
F2 stage DAA treatment
F2 no SVR
F2 retreat DAA
F2 no SVR
F2
F3
F3 stage DAA treatment
F3 no SVR
F3 retreat DAA
F3 no SVR
F3 2nd retreat DAA
F3 2nd no SVR
F4C (Compensated cirrhosis)
F4C stage DAA treatment
F4C no SVR
F4C retreat DAA
F4C no SVR
F4C retreat DAA
Compensated cirrhosis, no HCV
F4D (Decompensated cirrhosis)
F4D DAA treatment
F4D no SVR
F4D retreat DAA
F4D no SVR
F4D retreat DAA
Decompensated cirrhosis, no HCV

Modeling the Acute HCV epidemic in the DAA era

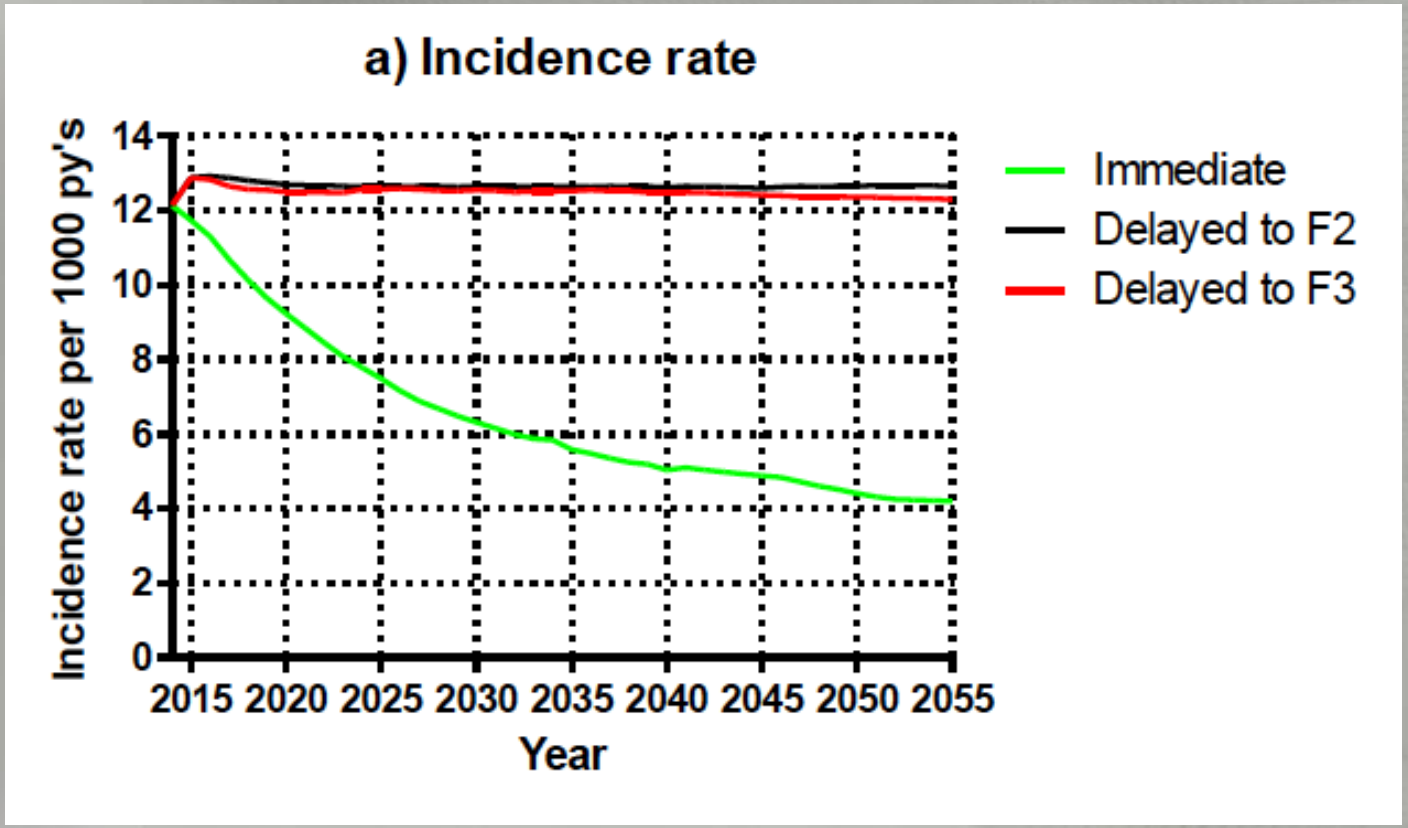
Parameter	Range	Range in model	Source/rationale
Transmission parameters			
Transmissibility	0-0.05	0-0.05, uniform	Calibrated
Clearance of HCV	15-25%	15-25%, uniform	[24]
Time to clearance	40-170 days	40-170 days, triangular peak (40)	[24]
New HIV MSM per year	737		[2]
Reinfection rate	8-26.5%, per year	8-26.5% per year.	[5]
Disease progression parameters			
F0 to F1	0.098 – 0.122, per year	0.098-0.122, uniform	[23]
F1 to F2	0.095 – 0.140, per year	0.095-0.140, uniform	[23]
F2 to F3	0.097 – 0.159, per year	0.097-0.159, uniform	[23]
F3 to F4	0.098 – 0.135, per year	0.098-0.135, uniform	[23]
F4 to decompensated cirrhosis	0.029 – 0.063, per year	0.029-0.063	[25]
F4 to Hepatocellular carcinoma	0.01 – 0.03, per year	0.01 – 0.03, per year	[26]
Mortality parameters			
General	Life expectancy of 39 years	1/39	Patients are infected with HCVat a median age of 40 years[13]. The life expectancy is normal if patients have a CD4>350 [27]. The life expectancy of men in the Netherlands is 79 years
HCV-infected, treatment, F0-F3	Life expectancy of 39 years	1/39	
Compensated	0.024 – 0.055 per year	0.024-0.055, uniform	[25]
Decompensated	0.19 – 0.35 per year	0.19-0.35, uniform	[25]
Treatment related parameters			
SVR in AHCV treated with	52-84%		[5, 28](DAHHS artikel)

Modeling the Acute HCV epidemic in the DAA era

Parameter	Range	Range in model	Source/rationale
pegIFN and RBV			
SVR, double or triple DAA combination	89%-100%		[29-32]
Percentage AHCV that is diagnosed	75%-100%		Clinical practice EMC.
Proportion that will receive pegIFN+ RBV in AHCV	67-75%		Clinical practice EMC.
Time to start treatment after transmission	16.5 – 25 weeks		[13]
Risk behavior related parameters			
Annual new sexual partners			Calibrated
Highest risk group	10-85	10-85, trian (peak 20)	
Risk group 2	1-10	1-10, triangular(10)	
Risk group 3	0.5-1	0.5-1 (uniform)	
Risk group 4	0-0.5	0-0.5 (uniform)	
Proportion per risk group			Calibrated
Highest risk group	0.01-0.11	0.01-0.11, triang(0.08)	
Risk group 2	0-0.2	0-0.2	
Risk group 3	0-0.3	0-0.3, uniform	
Risk group 4	0.4-0.9	0.4-0.9, triangle (0.67)	
Rate of assortative mixing	0-0.8	0-0.8, uniform	Calibrated

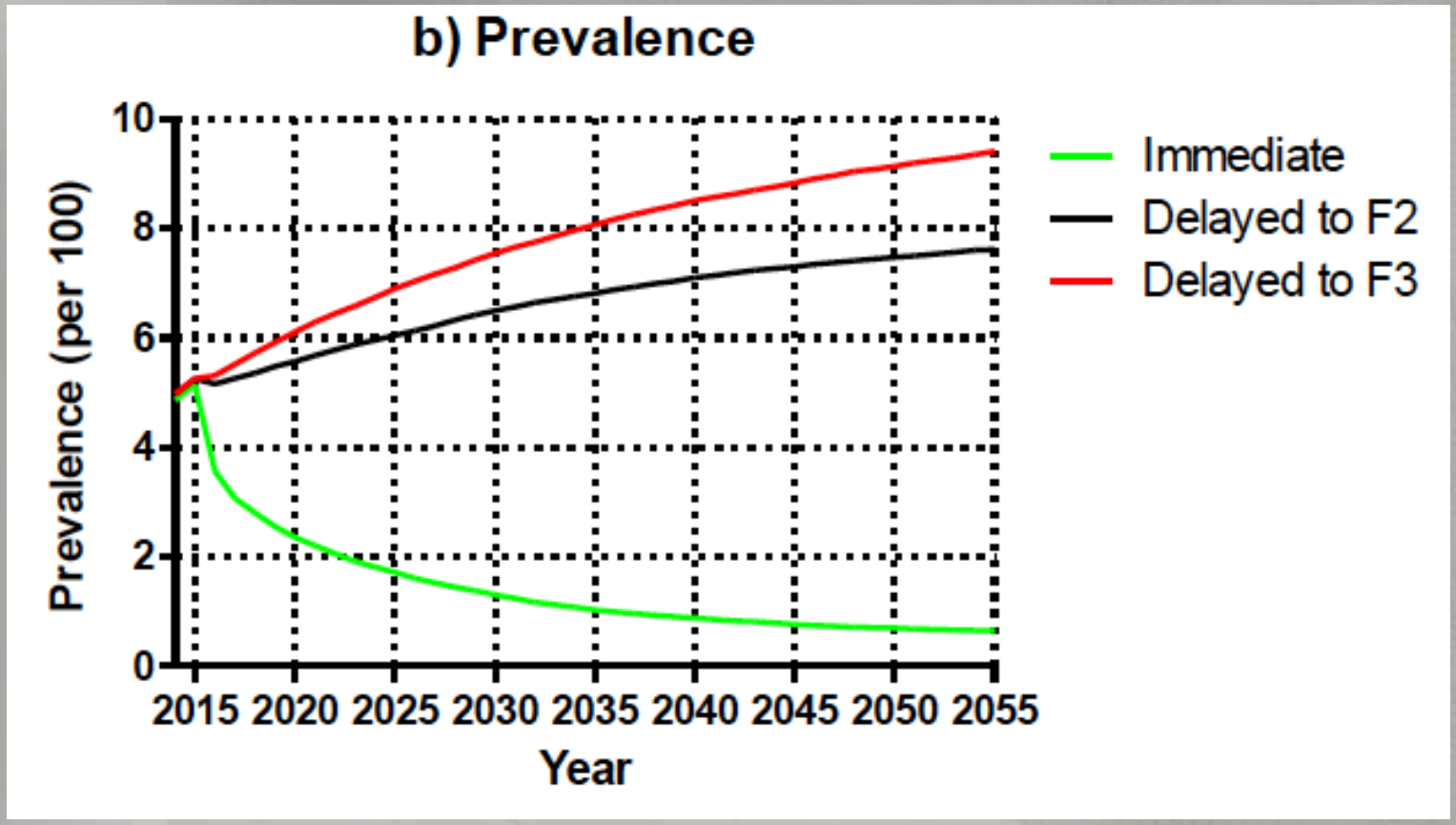
Modeling the Acute HCV epidemic in the DAA era

What will happen if we treat all Acute HCV with DAA right away ?



Modeling the Acute HCV epidemic in the DAA era

What will happen if we treat all Acute HCV with DAA right away ?



Modeling the Acute HCV epidemic in the DAA era

What will happen if we treat all Acute HCV with DAA right away ?

- *Prevalence 5% => 0,6% in 2055*
- *Incidence 1.2% => 0,4% in 2055*
- *Cirrhosis will become rare*

Elimination not realistic ... unless we can diagnose earlier

⇔ *acute HCV is mostly asymptomatic*

⇔ *HIV+MSM are seen every 6 months*

Modeling the Acute HCV epidemic in the DAA era

What will happen if we treat all Acute HCV with DAA right away ?

Next question => What will it cost? What is the cost per QALY?

Immediate DAA for all cost society €135 million over 40 years.
Delayed DAA at F2 costs €117 million and €105 million at F3

Immediate DAA leads to 2148 more QALYs compared to F2
Immediate DAA leads to 2596 more QALYs compared to F3

Modeling the Acute HCV epidemic in the DAA era

At a DAA price of 40.000€ per 12 weeks
And taking into account, the decreased transmission of acute HCV
And taking into account PegIFN therapy in 67% and cure in 70%

Immediate treatment with DAAs after HCV diagnosis costs:
€9,000/QALY compared to treatment at F2
€12,000/QALY compared to treatment at F3
= VERY COST EFFECTIVE, but still you can use money only once

!! ICER strongly depends on DAA price:
50% reduction to €20,000 => **immediate DAA therapy = *cost saving !***

PS. More cost-effective if no PegIFN therapy during acute infection

Modeling the Acute HCV epidemic in the DAA era

Modeling the Acute HCV epidemic in the DAA era

But models are models, what about real numbers?

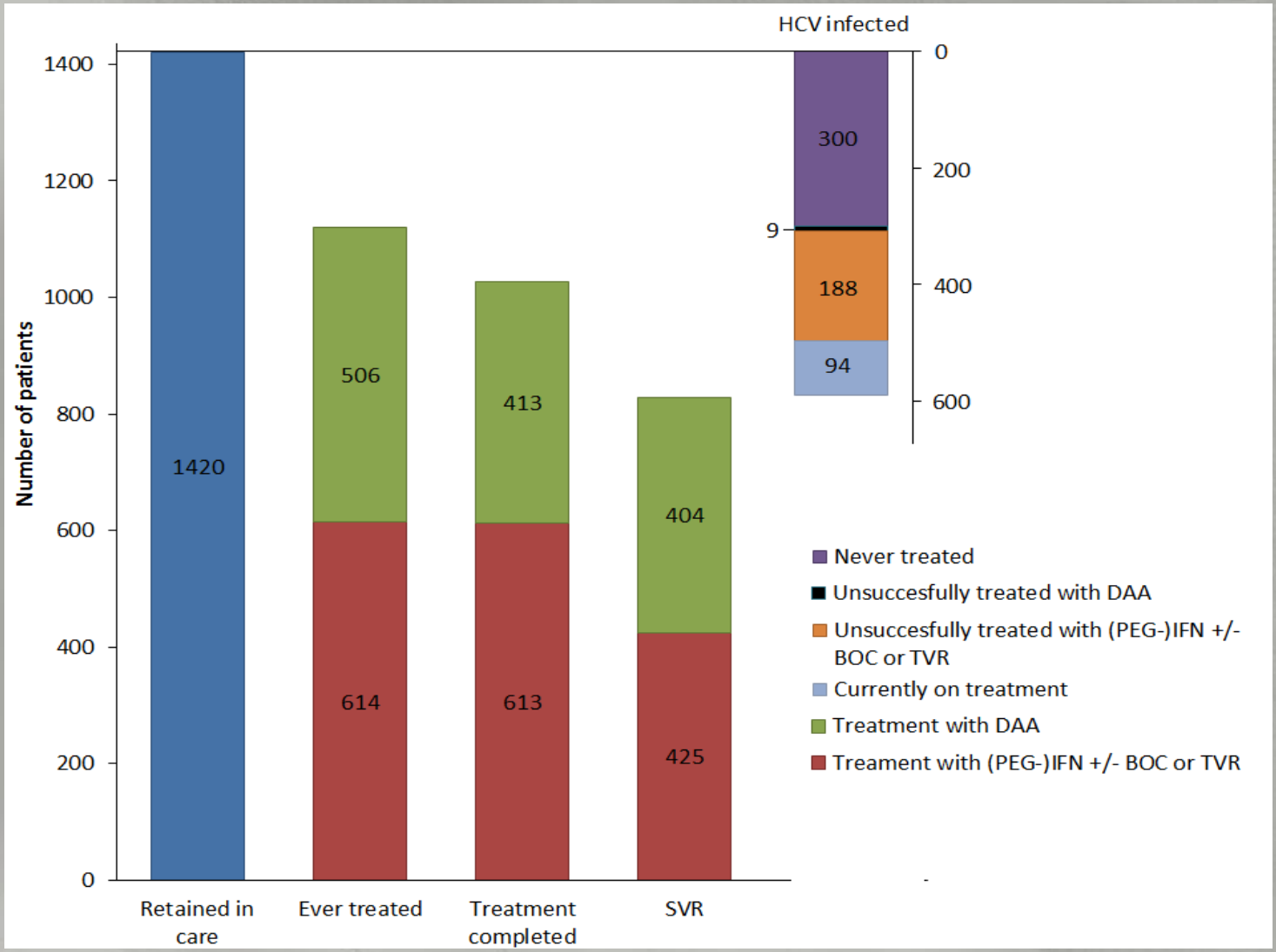
HCV treatment uptake in HIV + HCV+ patients

Data from Dutch Athena cohort up to may 2016

2 years after F3-4 DAA therapy became reimbursed in the Netherlands

½ year after F0-4 DAA therapy became reimbursed

Modeling the Acute HCV epidemic in the DAA era



A Boerekamps et al. CROI 2017

Modeling the Acute HCV epidemic in the DAA era

But models are models, what about real numbers?

We hope to proof this model with nationwide incidence numbers soon

But already now there is something going on

	DAHHS1 *(12 months of 2014)*	***DAHHS2*** *(11 months in 2016)*
	GENOTYPE 1 and 4	***GENOTYPE 1 and 4***
Site OLVG		
Site UMCU		
Site UMCG		
Site MUMC		
Site Radboud		
Site Rijnstate		
Site Erasmus MC		
Site Den Haag		
TOTAL		

Modeling the Acute HCV epidemic in the DAA era

Future plans to "prove" that TASP works

2014-2015-2016-2017 incidence in all HIV centers in Netherlands (ATHENA)

2014-2015-2016-2016 incidence in Antwerp Leuven Gent Hasselt

Well,
That's all I have to say about that!

Treatment

PegIFN based therapy: How long to treat?

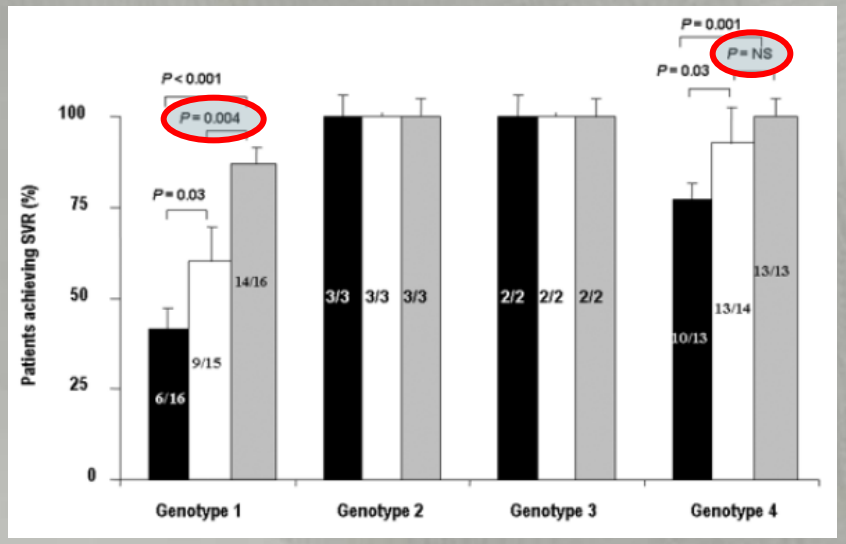
8 versus 12 versus 24w? 2 large RCT

Kamal et al. : After 12w observation, 77% asymptomatic, all genotypes (mostly 1 and 4)

8w PegIFN alone 68% (n=34)
12w PegIFN alone 82% (n=34)
24w PegIFN alone 91% (n=34)

RVR4 pts : **88%** had SVR !

Genotype 1 conclusion not as robust :



SVR in patient with RVR4 according to treatment duration and genotype: black=8w, white=12w, gray=24w

Kamal et al. Gastroenterology 2006

Treatment

PegIFN based therapy: How long to treat?

- **12w versus 24w?**
- **12w with RBV versus 12w without RBV?**

Santantiono et al. : After 12w observation, 58% asymptomatic, all genotypes (mostly 1 and 4)

24w PegIFN alone 70% (n=44)

12w PegIFN alone 72% (n=43)

12w PegIFN + RBV 72% (n=43)

RVR4 pts : **87%** had SVR. Genotype did not correlate with SVR, only RVR4 did

My conclusion in HIV negative patients:

- RVR4 (target not detected!): 12 weeks is OK
- RVR4 and genotype 1 and PegIFN is well tolerated: 24wks
- No RBV needed

Treatment

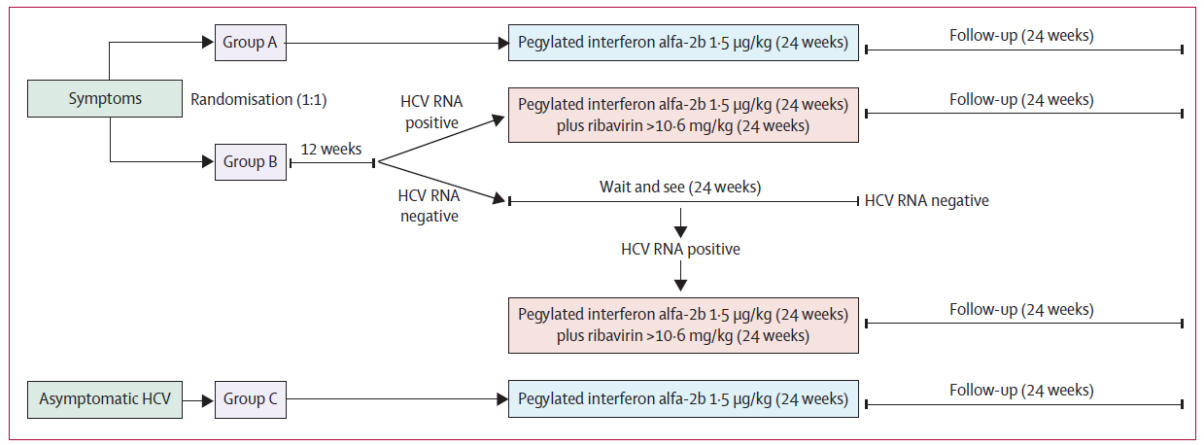
PegIFN based therapy: When to start? When to wait?

Kamal et al. 2006: All genotypes, 80% asymptomatic, mostly occuptional transmission: RCT n=129, ITT results

Table 2. Effect of Treatment Onset on End of Treatment and Sustained Response Rates in All Patients Using Intent-to-Treat Analysis

Virologic response (undetectable HCV-RNA)	Onset week 8 (n = 43)	Onset week 12 (n = 43)	Onset week 20 (n = 43)
End of treatment N (%)	42 (97.6)	41 (95.3)	38 (88.3)
Sustained response N (%)	41 (95.3)	40 (93.2)	33 (76.6)

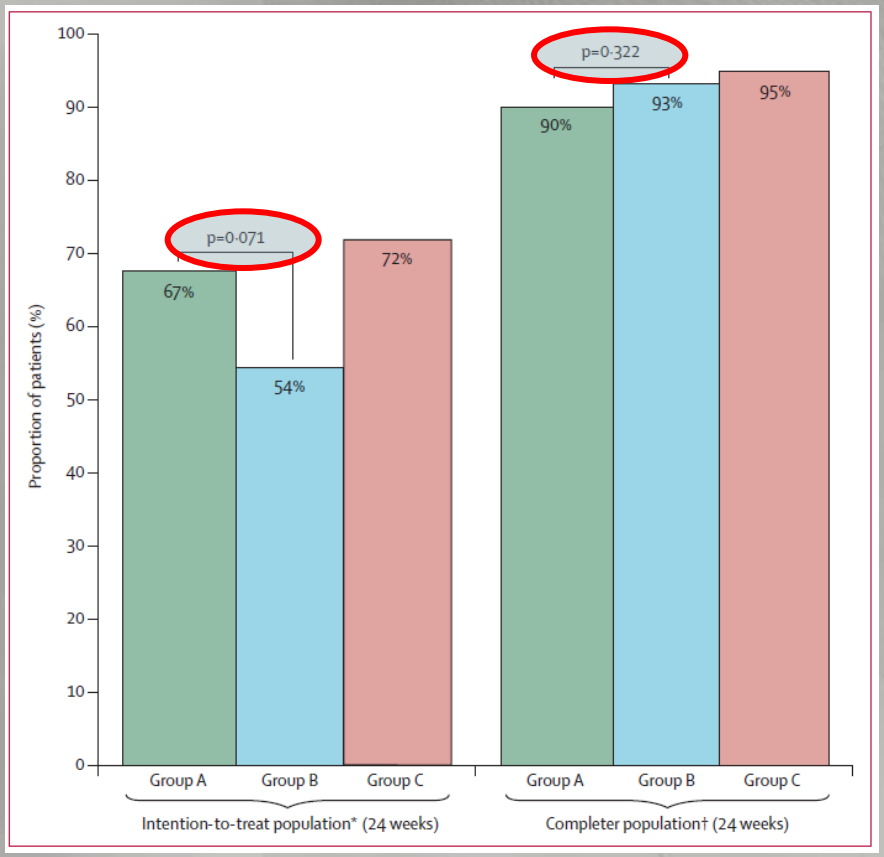
Deterding et al. 2013:



Treatment

PegIFN based therapy: When to start? When to wait?

Deterding et al. 2013:



Study prematurely stopped due to low enrollment (n=132/6years)

ITT: Delayed therapy was not non-inferior

ITT: Group B (12w delay) failures were often result of LTFU

Kamal et al. Gastroenterology 2006

Deterding et al. Lancet Inf Dis 2013