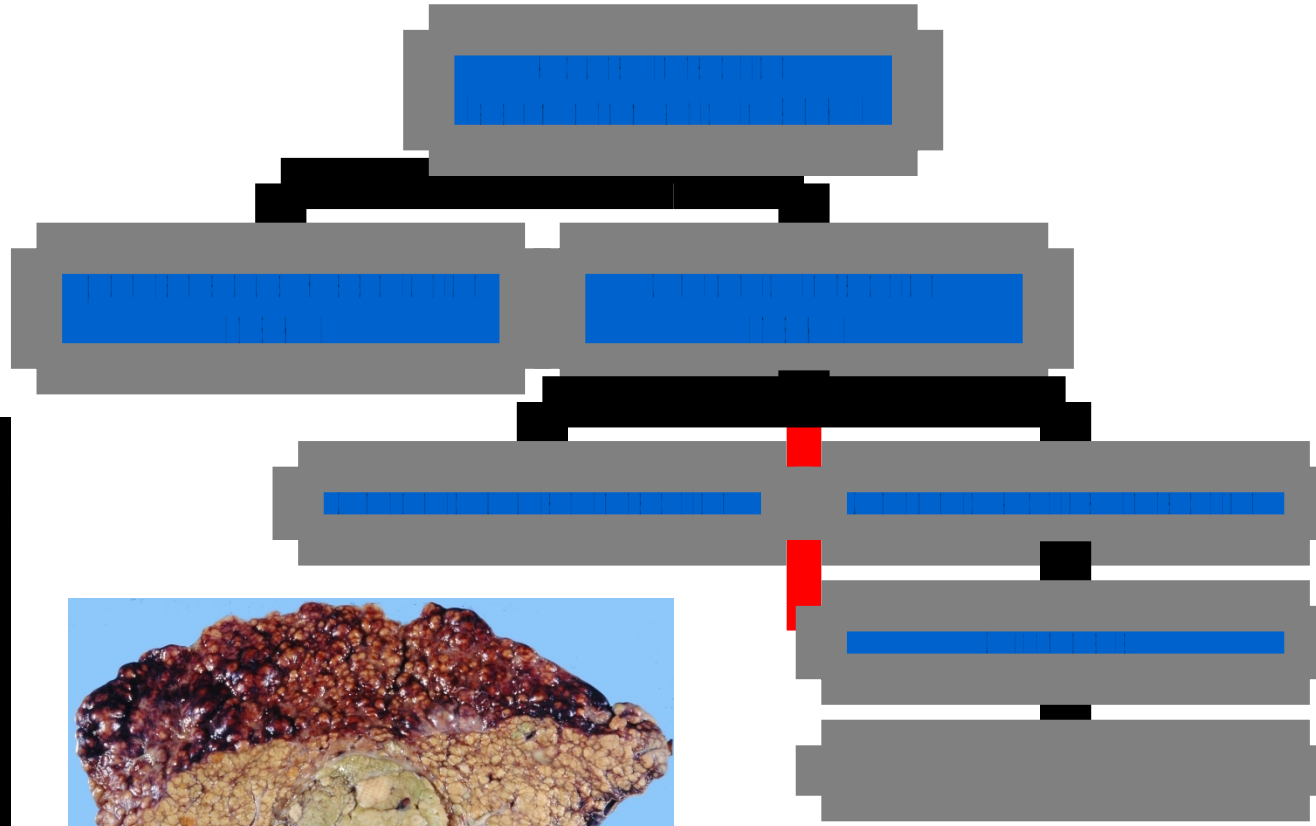
GGD Amsterdam

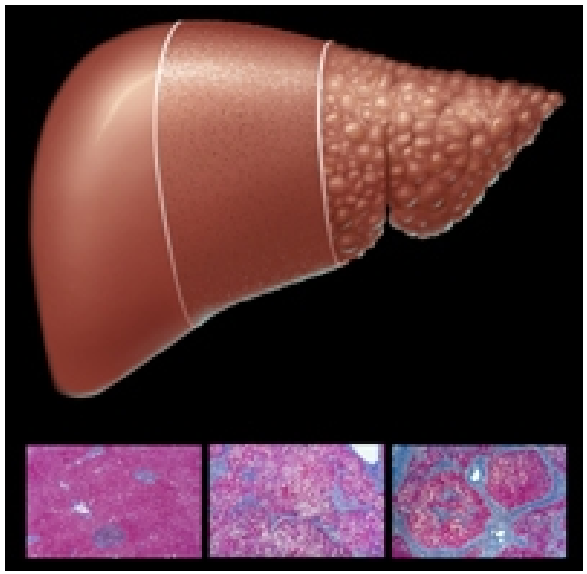
Hepatitis C treatment of drug users

K. Lindenburg

Buitenpolikliniek GGD/AMC
Cluster Infectious Diseases
Research Department
Public Health Service Amsterdam

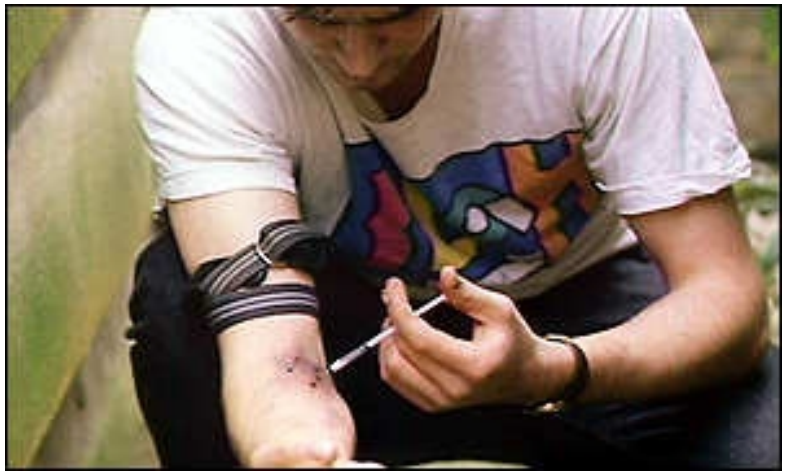
Hepatitis C virus (HCV) infection





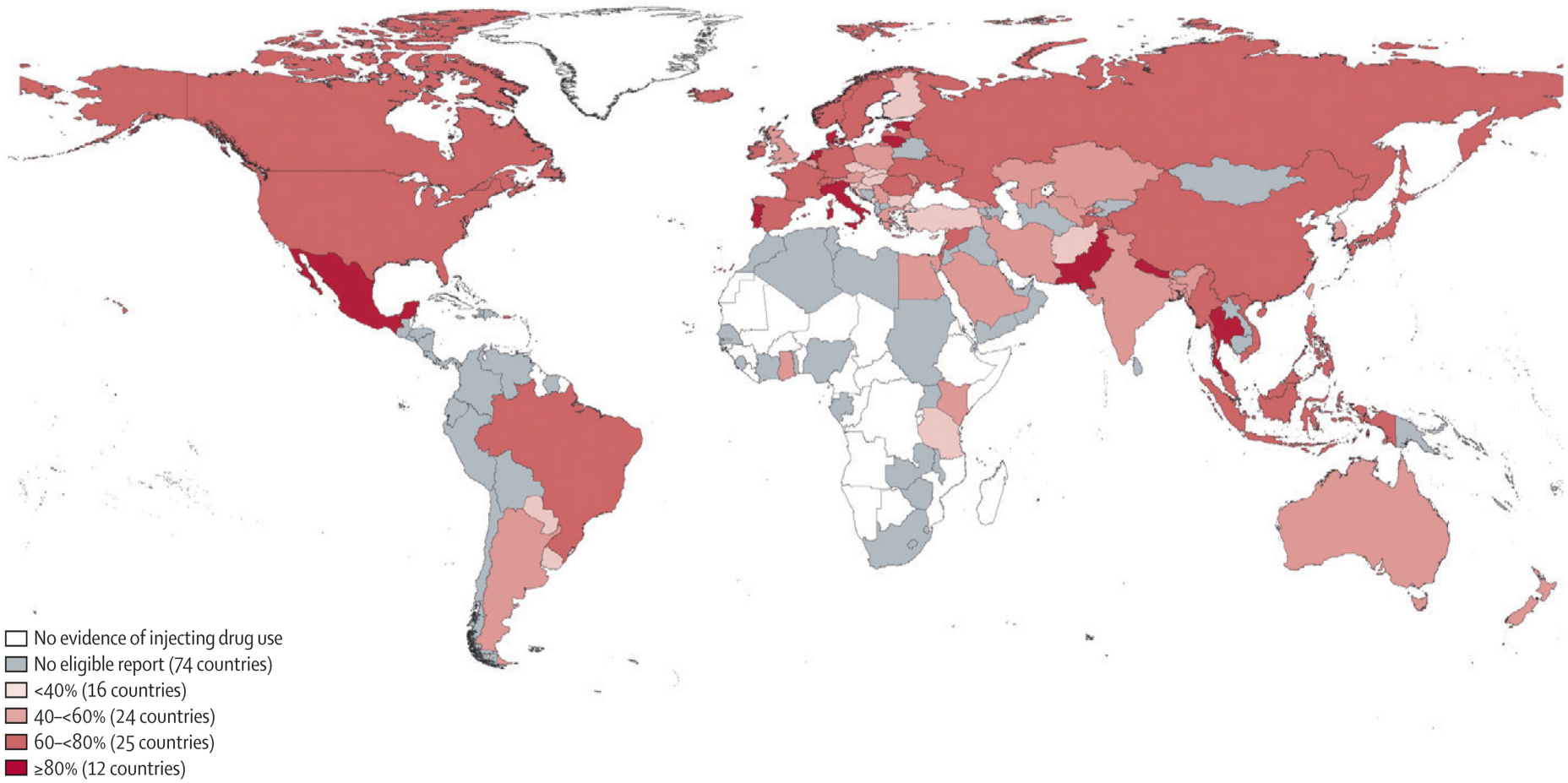
Prevalence intravenous drug use (IV(DU))

2007 estimate: 16 million worldwide



Sources: Mathers et al, Lancet 2008; EMCDDA 2010; Wiessing et al, Eurosurveillance 2010

IVDU: Prevalence HCV AB positive



Nelson et al, Lancet 2011

HCV Treatment DU: Actual situation

Active DU largest group infected with

and largest group un(der)treated for HCV

(Volk et al. 2009)

Treatment of Hepatitis C

Peg-Interferon and Ribavirine since 2001

Duration: 24-48 weeks depending on HCV genotype

Sustained virologic response (SVR = treatment succes): 60% over-all

50% genotype 1 and 4

80% genotype 2 and 3

Treatment of Hepatitis C

Peginterferon/Ribavirine:

- Many side effects!
  - *Physical*
  - *Psychiatric*
- Cost

April 2012: Direct acting antivirals (DAA) ….. SVR increased …… More side-effects and challenges!

HCV treatment & DU: barriers for physicians

Complex lifestyle DU

Compliance

(Psychiatric) side effects

Effect active alcohol/drug use on SVR

Sustained virologic response (SVR)

Re-infection

None HCV related mortality risk

HCV treatment & DU: barriers for DU

Limited acces to:

- Healthcare
- Information
- Testing

HCV treatment guidelines for DU

DO NOT TREAT!

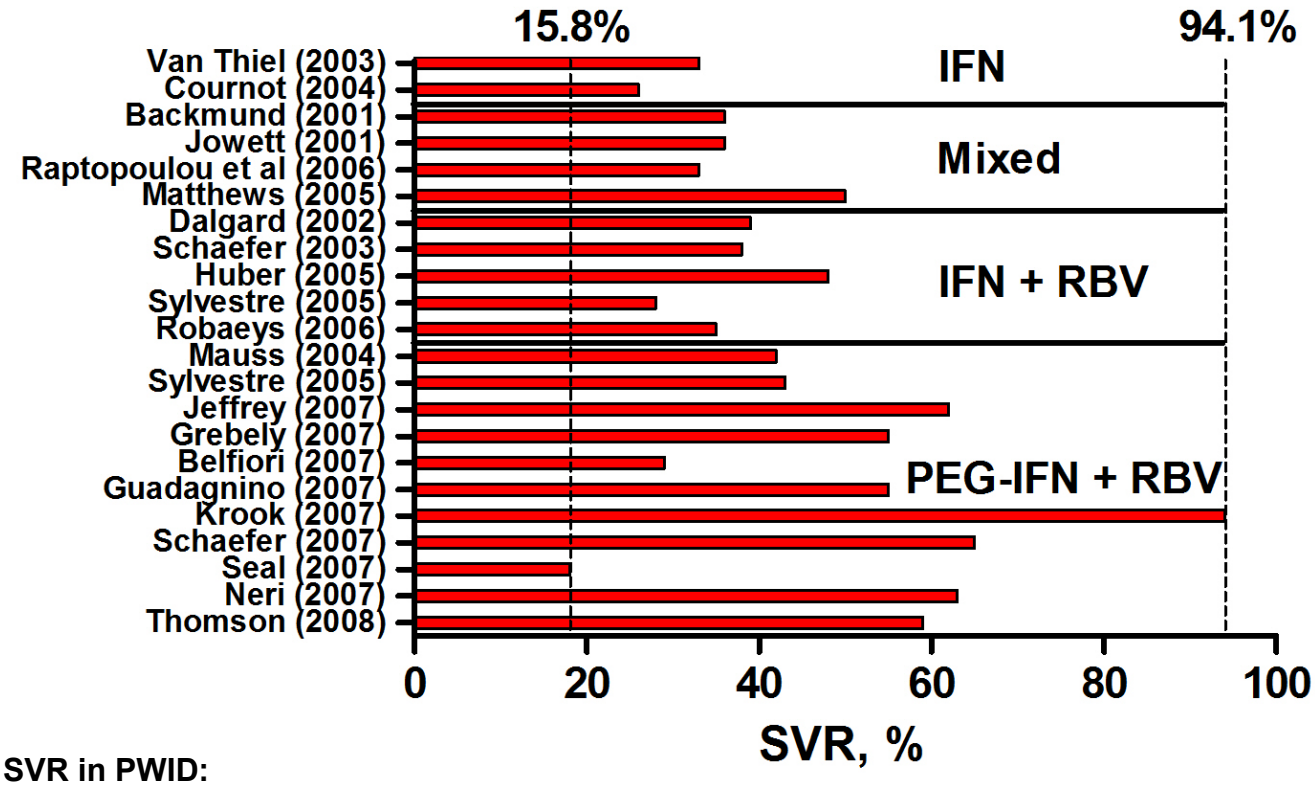
AASLD, EASL en Dutch Nat. Guidelines:

"Individual HCV treatment decision for each DU"

Studies HCV treatment of DU

- Few studies, small numbers of DG included
- Review Hellard, 2009:
  - Data compliance: limited (varying results)
  - (I)DU complete treatment : 50-100%
  - SVR studies (DU and non-IDU): no difference in SVR
  - Reinfection after HCV treatment: 0-2 cases per 100/p.y.

PWIDs can be successfully treated for HCV



Median SVR in PWID:

Peg-IFN alfa + RBV: 54.3% (range 18.1-94.1)
Regardless of treatment regimen: 40.6%

Hellard M, et al.
Clinical Infectious Diseases 2009

Dutch-C (drug users treatment for HCV)

- Amsterdam Cohort Study
- Pilot ACS: Dutch-C
- Goal: test and treat DU for HCV plus protocol development

Dutch-C (drug users treatment for HCV)

- Multidisciplinairy unit
- Treatment location at Public Health Service
- Hepatologist responsible for HCV treatment
- Personel experienced with DU
- Separation methadone/psychofarmaca and HCV subscription

Dutch-C (drug users treatment for HCV)

- Delivering methadone together with ribavirine
- Weekly observed Peginterferon administration
- Extensive screening before treatment
- Standard psychiatric evaluation before/during treatment
- Network information and involvement before/during treatment

Dutch-C (drug users treatment for HCV)

- Continuity of care (detention; hospital)
- Individual treatment, flexible and individual decisions
- Safe environment, respectful attitude
- One focus!
- We find it rewarding and valuable!

HCV screening DU ACS

449/497 (90%) test for HCV AB

↓

267/449 (60%) HCV AB positive

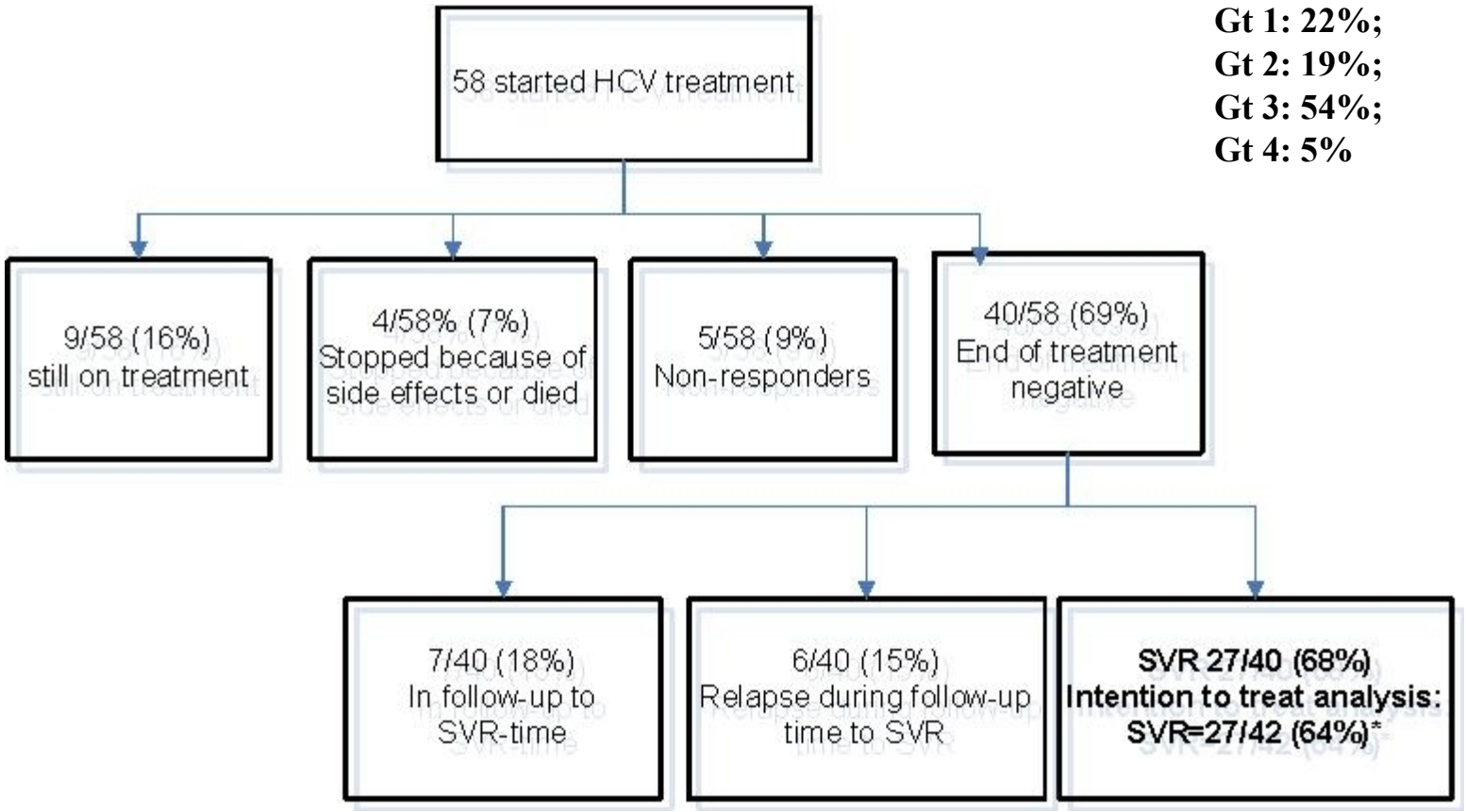
↓

183/267 (69%) HCV PCR positive

↓

49/183 (27%) HIV pos/HCV pos

Flow-Chart 2010: HCV treatment of DU in Dutch-C



Gt 1: 22%;
Gt 2: 19%;
Gt 3: 54%;
Gt 4: 5%

2012 (n=90) Depression: <5% Compliance: 95%

Psychiatric characteristics 58 DU in HCV treatment Dutch-C

Personality disorder	12%
Depression	9%
Psychotic disorder	14%
Personality dis. and depression	3%
Personality and anxiety dis.	3%
Psychofarmaco (prescription)	47%

Baseline Characteristics 58 DU during HCV treatment in Dutch-C project

Alcohol	62%
IDU	19%
DU	97%
Methadone	80%

Dutch-C and HCV re-infection

Overall incidence HCV re-infectie after SVR:

0.76 per 100 person-years (95% CI, 0.04–3.73)

2012 (n=90) 1 man …….. who cleared HCV

B. Grady et.al.

HCV reinfection following SVR in PWID

Study	Study Population	Median Age	IDU post-treatment	Median Follow-up (years)	New infection	HCV reinfection incidence rate
Backmund 2004	n=18	32	50%	2.8 (0.8-5.1)	2/18	4.1/100 py
Dalgard 2005	n=27	NA	33%	5.4 (1.1-6.8)	1/27	0.8/100 py
Currie 2008	n=9	46	22%	3.6 (3.2–6.0)	1/9	0.6/100 py
Grebely 2010	n=35	44	54%	2.0 (0.4-5.0)	2/35	3.2/100 py
Bate 2010	n=57	34	NA	3.4 (0.2-11.5)	5/57	NA
Grebely 2012	n=87	36	NA	1.2 (0.1-3.0)	4/87	3.7/100 py
Grady 2012	n=42	51	21%	2.5 (1.6-3.7)	1/42	0.8/100 py

Cost effectiveness: HCV treatment of DU

A systematic review by John-Baptiste A. et al. (2012)

- Lack of quality data
- 8 studies HCV treatment: Screening and treatment interventions involving pegylated interferon and ribavirin generally cost effective.

Dutch-C and direct acting antivirals (DAA)

- Policy Dutch-C up until april 2012:

  HCV genotype 1 and < F2 Fibrosis? Wait for DAA!

- Currently +/- 100 naive HCV genotype 1 patients …….

  40% F3 or F4 Fibrosis ……

DAA and DU

Pill-burden and compliance

Interactions!

Dermatological side-effects

Future regimes

Cost!

DAA and drug interactions

Drug	DAA	Expected effect
XTC	TVR/BOC	Increase XTC level
Cannabis	TVR/BOC	Possible increase THC level
GHB	TVR/BOC	Possible increase GHB level
Paddo's	TVR/BOC	No expected interaction
Poppers	TVR/BOC	No expected interaction
Heroïne	TVR/BOC	No expected interaction
Methadone	TVR/BOC	Decrease total methadone level; no change in free methadone level?
Cocaïne	TVR/BOC	Possible increase cocaïne level; decrease hepatotoxic metabolite

Prof. D. Burger, UMCN

DAA and DU

Dutch-C and DAA: 1 (Telaprevir)

Good virologic response

Compliance 100%

Dermatological issues

Fatty food issues

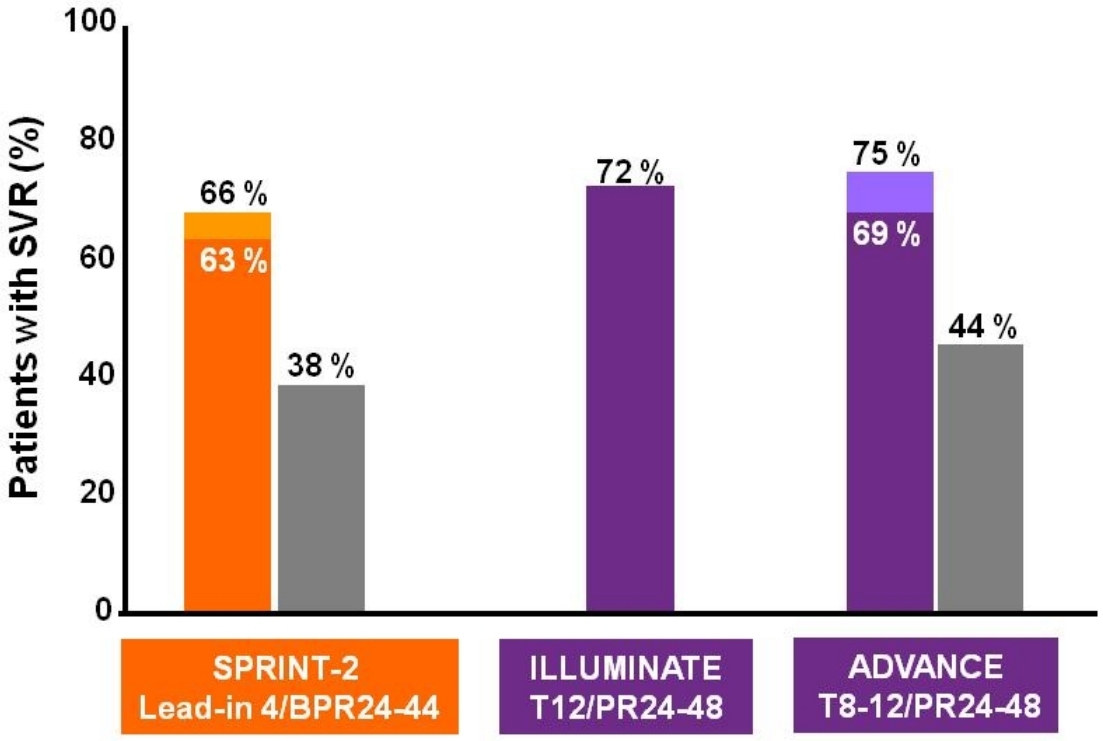
Feasibility?

Learning and protocol development (and do no harm ……)

Personnel time X 2!

Results of phase 3 studies

SVR rates in treatment-naive patients



Control arms: PR48

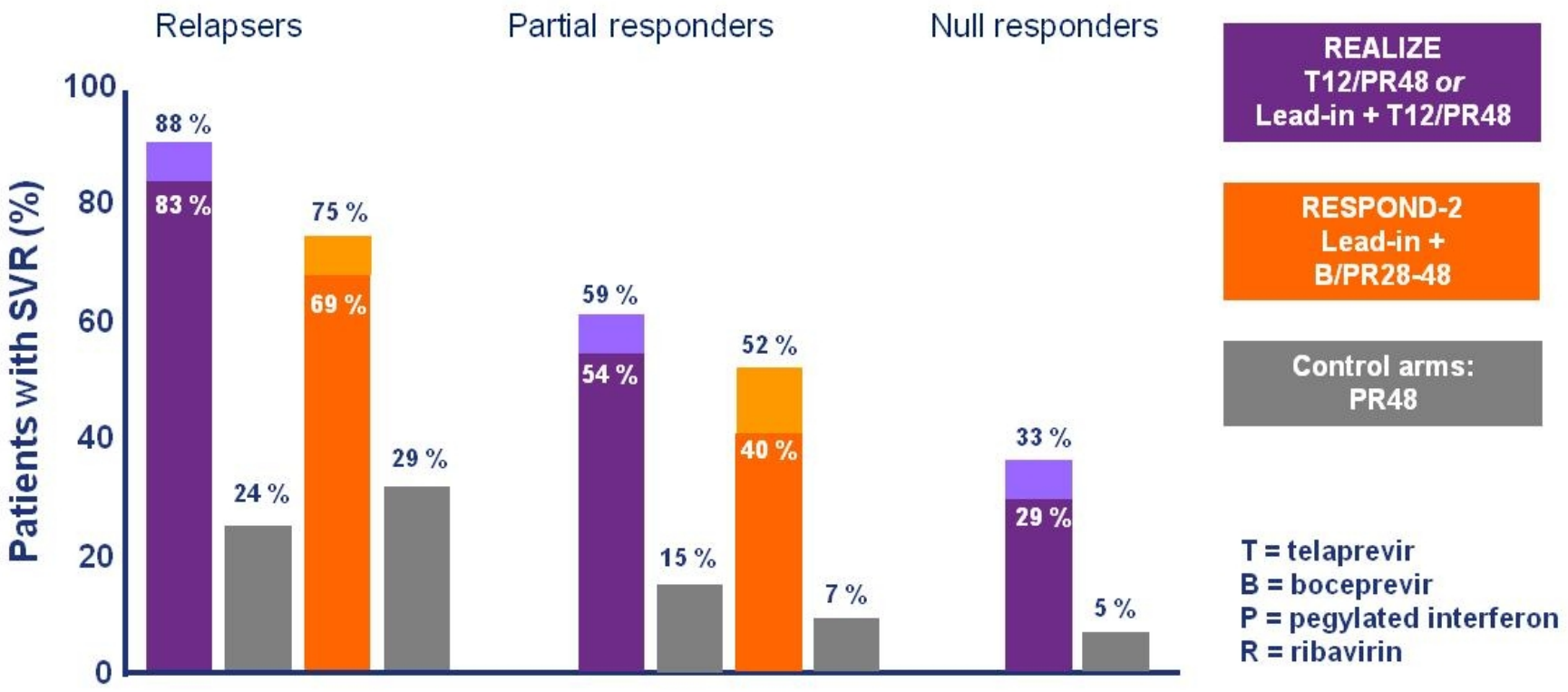
B = boceprevir
T = telaprevir
P = pegylated interferon
R = ribavirin

Note that there are inherent limitations of comparing findings from across trials

H. Reesink, personal communication
Graph is based on:
Poordad F, et al. N Engl J Med 2011;364:1195–1206
Sherman KE, et al. N Engl J Med 2011;365:1014–1024
Jacobson IM, et al. N Engl J Med 2011; 364: 2405–241

SVR rates in treatment-experienced patients: Non (IV)DU!

Results of phase 3 studies

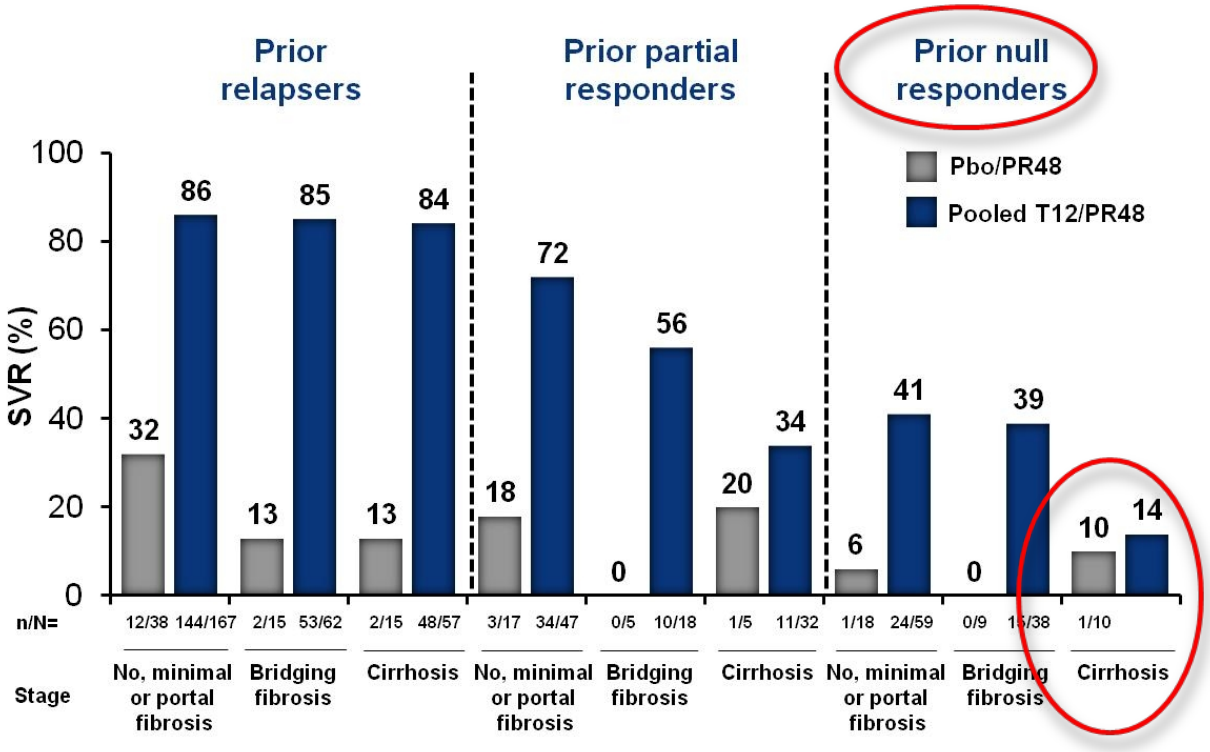


Note that there are inherent limitations of comparing findings from across trials

H. Reesink, personal communication
Graph is based on:
Bacon BR, et al. N Engl J Med 2011;364:1207–1217
Zeuzem S, et al. N Engl J Med 2011;364:2417–2428

SVR by fibrosis + prior response Peg-IFN/RBV therapy

Telaprevir (REALIZE study)



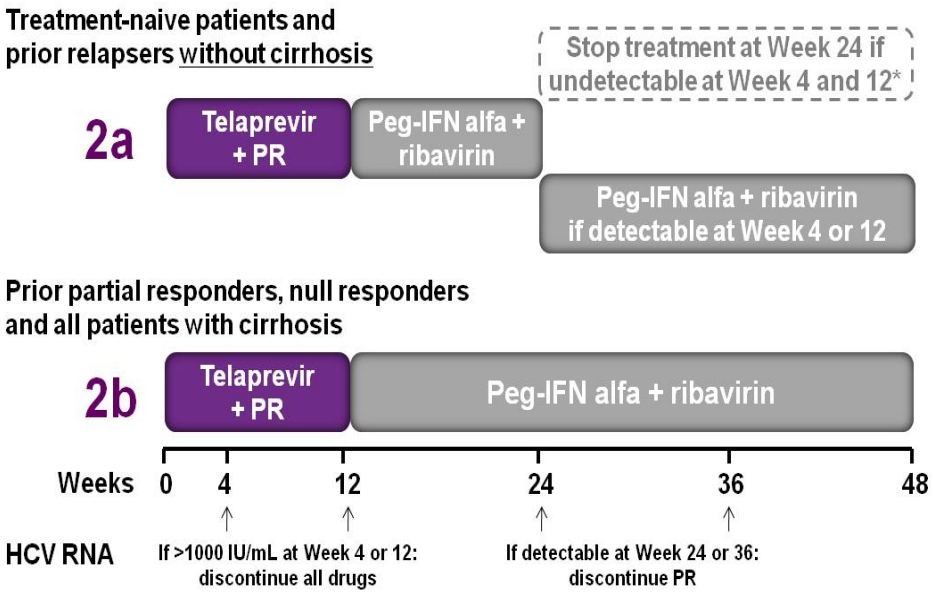
Boceprevir:

no null responders in phase 3 studies

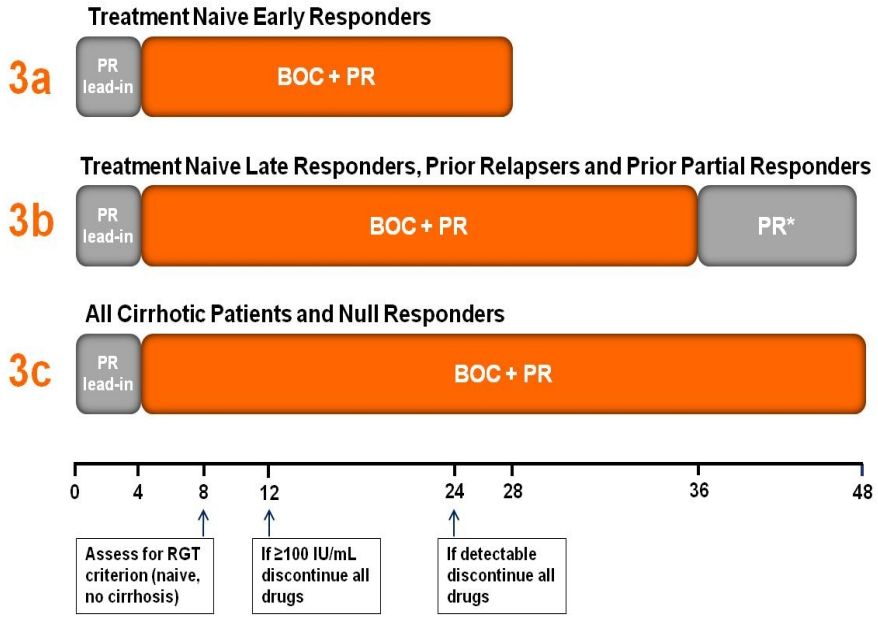
Zeuzem S, et al. J Hepatol 2011;54(Suppl.):S

New HCV treatment guidelines

Telaprevir treatment strategies[1]



Boceprevir treatment strategies[2]



1. Telaprevir SPC
2. Boceprevir SPC

Frequent (>10%) side effects during peg-IFNα, ribavirin, and telaprevir or boceprevir

Frequency	Peg-IFNα / Ribavirin	Telaprevir	Boceprevir
Frequent > 10%	**(Hemolytic) Anemia** **Headache** **Fatigue** **Pyrexia** **Myalgia, arthralgia** **Insomnia** **Alopecia** **Mood disorders** **Depression** **Lack of concentration / motivation** **Emotional instability** **Agitation, irritability** **Diarrhea** **Thrombocytopenia** **Neutropenia** **Anorexia** **Nausea** **Irritation at injection site** **Pruritus**	**Anemia** **Pruritus** **Rash** **Proctalgia** **Diarrhea** **Nausea**	**Anemia** **Neutropenia** **Headache** **Fatigue** **Flu-like symptoms** **Dysgeusia** **Anorexia** **Depression** **Diarrhea**

Lamers et al. 2012; Treatment of chronic hepatitis C – Dutch national guidelines (dra

Not so many patients are being treated as expected; Outcomes in Clinical Practice: Retro-spective Studies in the United States

Data from medical records review including patients with HCV-1 infection[1,2]

- 2 centers in Dallas and Miami with 12-wk follow-up[1]
- Exclusions: transplantation, dialysis, HIV co-infected
- Of 498 patients identified
  - 19% began triple therapy
  - 21% discontinued triple therapy < Wk 12

- Mount Sinai Medical Center and Montefiore with 12-wk follow-up[2]
- Of 174 patients who initiated TVR-based triple therapy
  - 32% discontinued TVR prematurely (20% RCT)
  - 21% discontinued treatment due to adverse events (13% RCT)

1. Chen EY, et al. AASLD 2012. Abstract 133.
2. Bichoupan K, et al. AASLD 2012. Abstract 1755.

Experience in cirrhosis, Outcomes Clinical Practice: CUPIC Study 'French Early Access Program'

- Patients received one of the following
  - Boceprevir-based therapy*
  - Telaprevir-based therapy†
- Patients had compensated cirrhosis and were previous nonresponders
- Wk 16 interim analysis
  - 497 patients

* 4-wk pegIFN 1.5 µg/kg/wk + RBV 800-1400 mg/day lead-in and then boceprevir 800 mg TID + pegIFN/RBV for 44 wks.

† Telaprevir 750 mg TID + pegIFN 180 µg/wk + RBV 1000-1200 mg/day for 12 wks and then pegIFN/RBV for 36 wks.

Hezode C, et al. AASLD 2012. Abstract 51

CUPIC: Cirrhotic Safety of Telaprevir to week 16

Patients, n (% patients with at least one event)	Telaprevir n=292	Boceprevir n=205
Serious adverse events (SAEs)	132 (45.2%) *	67 (32.7%)**
Premature discontinuation	66 (22.6%)	54 (26.3%)
Due to SAEs	43 (14.7%)	15 (7.3%)
Death		
Telaprevir: *Septicemia, Septic shock, Pneumonia, Endocarditis, EVH*	5 (2.6%)	1 (0.5%)
Boceprevir: *Pneumonia*		
Infection (Grade 3/4)	19 (6.5%)	5 (2.4%)
Hepatic decompensation (Grade 3/4)	6 (2.0%)	6 (2.9%)
Asthenia (Grade 3/4)	16 (5.5%)	12 (5.8%)
Rash Grade 3/SCAR	14 (4.8%)	0

* 334 SAEs in 132 patients;
** 159 SAEs in 67 patients;
SCAR: severe cutaneous adverse reaction

Hezode C. et al. oral presentation at AASLD 2012 (abstract 51)

Multivariate analysis: baseline predictors of severe complications*

Predictors	OR	95%CI	p-value
Platelet count ≤100,000	3.11	1.32-7.73	0.0098
Albumin level <3.5 g/dL	6.33	2.66-15.07	<0.0001

* Death, severe infection and hepatic decompensation, n=32

Hezode C, et al. AASLD 2012. Abstract 51

	↑SVR	↓SEs	↓Pills	Freq	No IFN?
Triple Regimens with PR					
TMC-435	+	√	√	qd	-
BI-201335	+	√	√	qd	-
Daclatasvir	+	√	√	qd	-
Sofosbuvir (G1)	++	√	√	qd	-
Danoprevir/r	++	√	√	bid	-
QUAD Regimens					
BMS (PR+NS5A+PI) nulls	+++	±	√	bid	-
VX (PR+PI+NNI)	+++	±	-	bid	-
Roche (PR+DNV/r + MCB)	++	±	-	bid	-
GS (PR+PI+NS5A) short course	+++	±	-	bid	-
All Oral Regimens					
BMS (NS5A+PI) G1b null	+	√	√	qd	√
BMS (NS5A+PI+NNI) G1a/b	+++	√	√	qd	√
BI (PI+NNI+/- RBV)	++	√	√	bid	√
GS (NI+RBV) G2/3, 1	+++, ++	√	√	qd	√
GS (NI+NS5A+RBV)	+++	√	√	qd	√
Alisporivir ± RBV G2/3	+	√	±	qd	√
VX (PI+NNI) + RBV	+-++	√	±	bid	√
ABT (PI/r+NS5A+NNI)+/-R	+++	√	±	bid	√

Future

- 2014: expected registration of new oral DAAs (Sofosfubir, Daclatasvir, TMC435)
- 2015: various other DAAs and Lambda IFN

Conclusion

DU can and should be tested and (if necesary and possible) treated for HCV infections

Knowledge, experience and guidelines for treating (active) DU with new antiviral HCV therapy should be collected in clinical trials and/or multidisciplinairy and experienced treatment centers

Acknowledgements

- C Weegink/H.W. Reesink
- S Moll/J vd Werff
- J Schinkel
- P Jansen
- B Grady
- G Casteelen/A. V. Ekeren
- G van Santen/A. Miedema
- D van Baarle
- C van den Berg
- A Kok
- R Coutinho/M. Borgdorff
- M Prins
- A. Kox/N. Grave

Health Service of Amsterdam:

Cluster Infectious Diseases

Cluster for Mental Health

AMC:

Department of Hepatology

Department of Psychiatry

Department of Human Retrovirology

Department of Clinical Virology

UMC Utrecht:

Department of Immunology

National Institute of Public Health and the Environment

Participants ACS