Berlin 23.10.2014

Hepatitis C and Drug Use - turn the page

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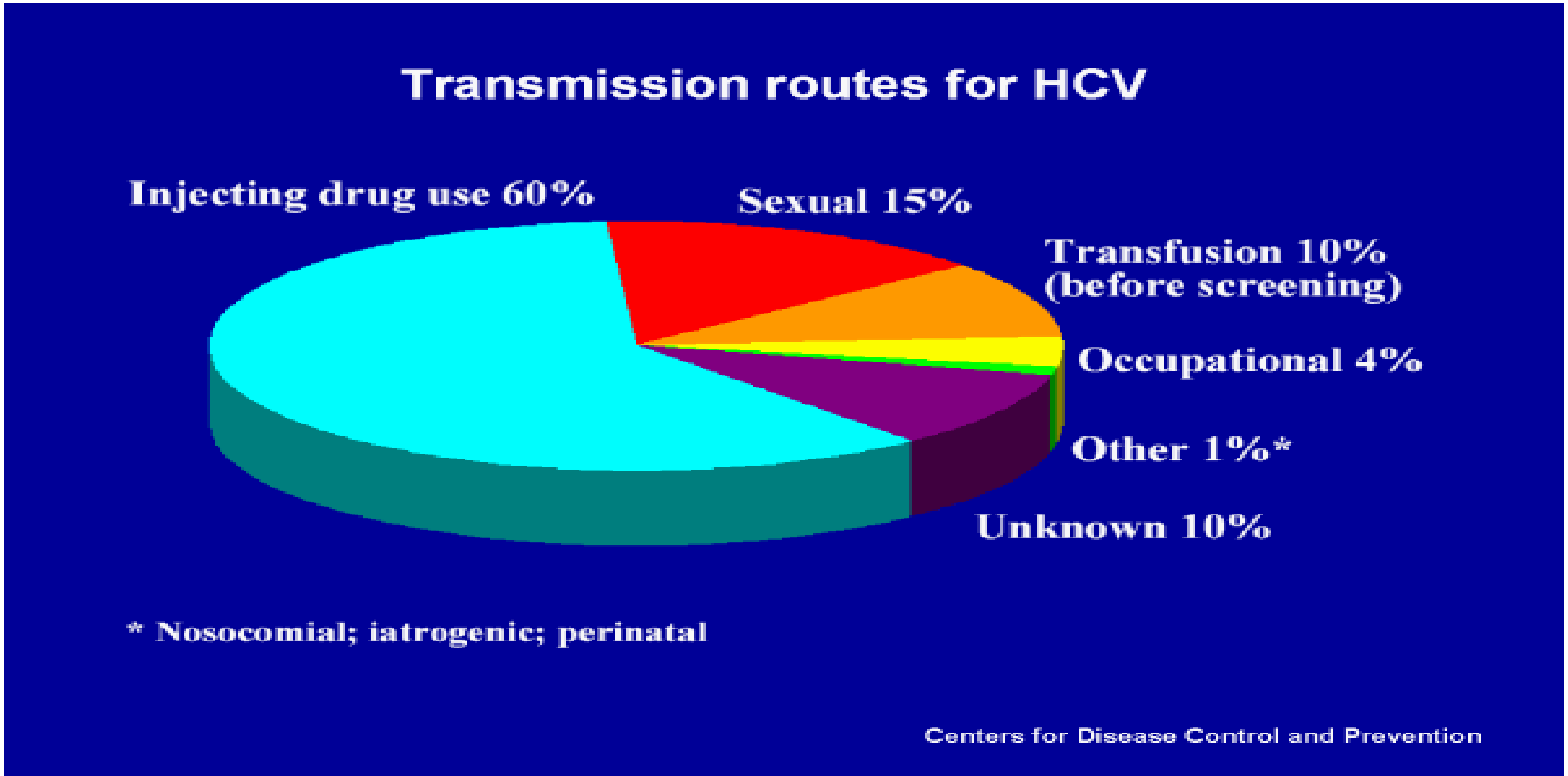
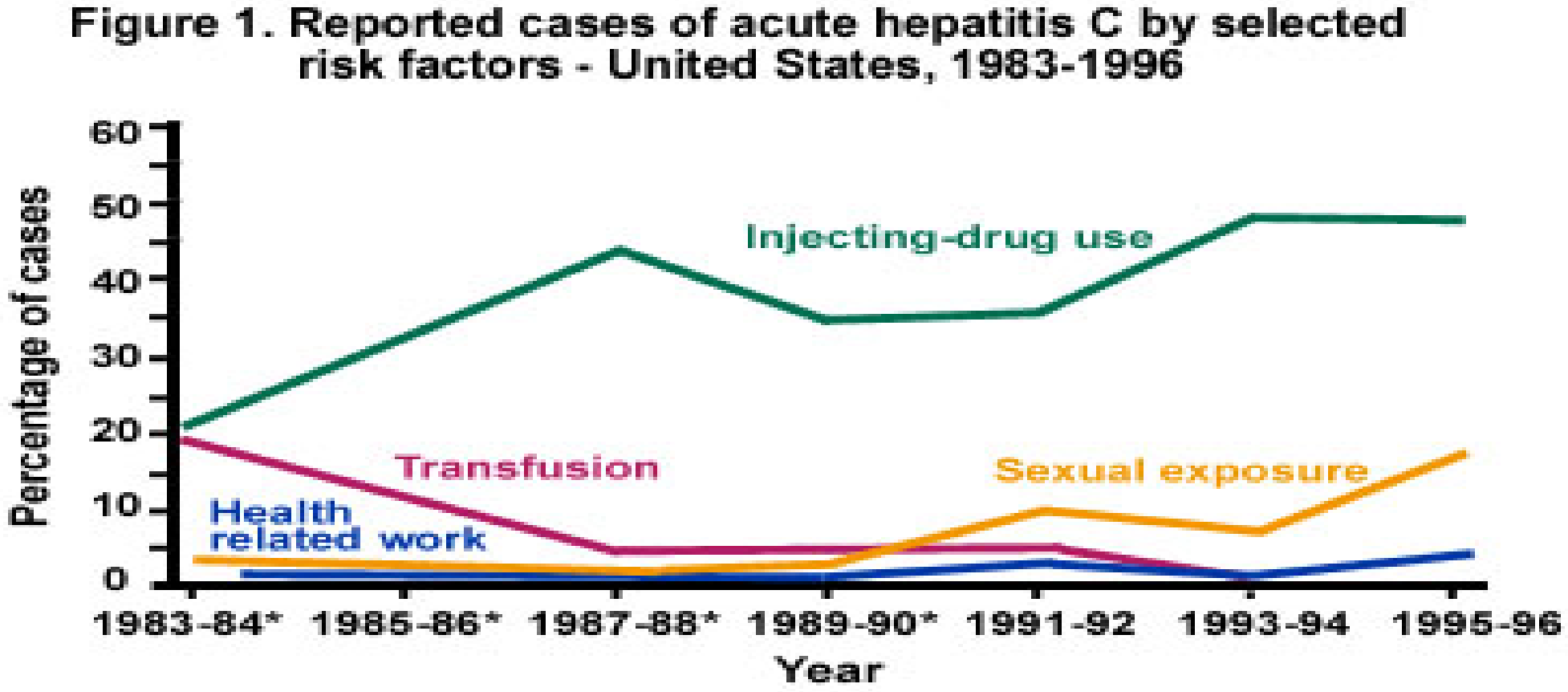
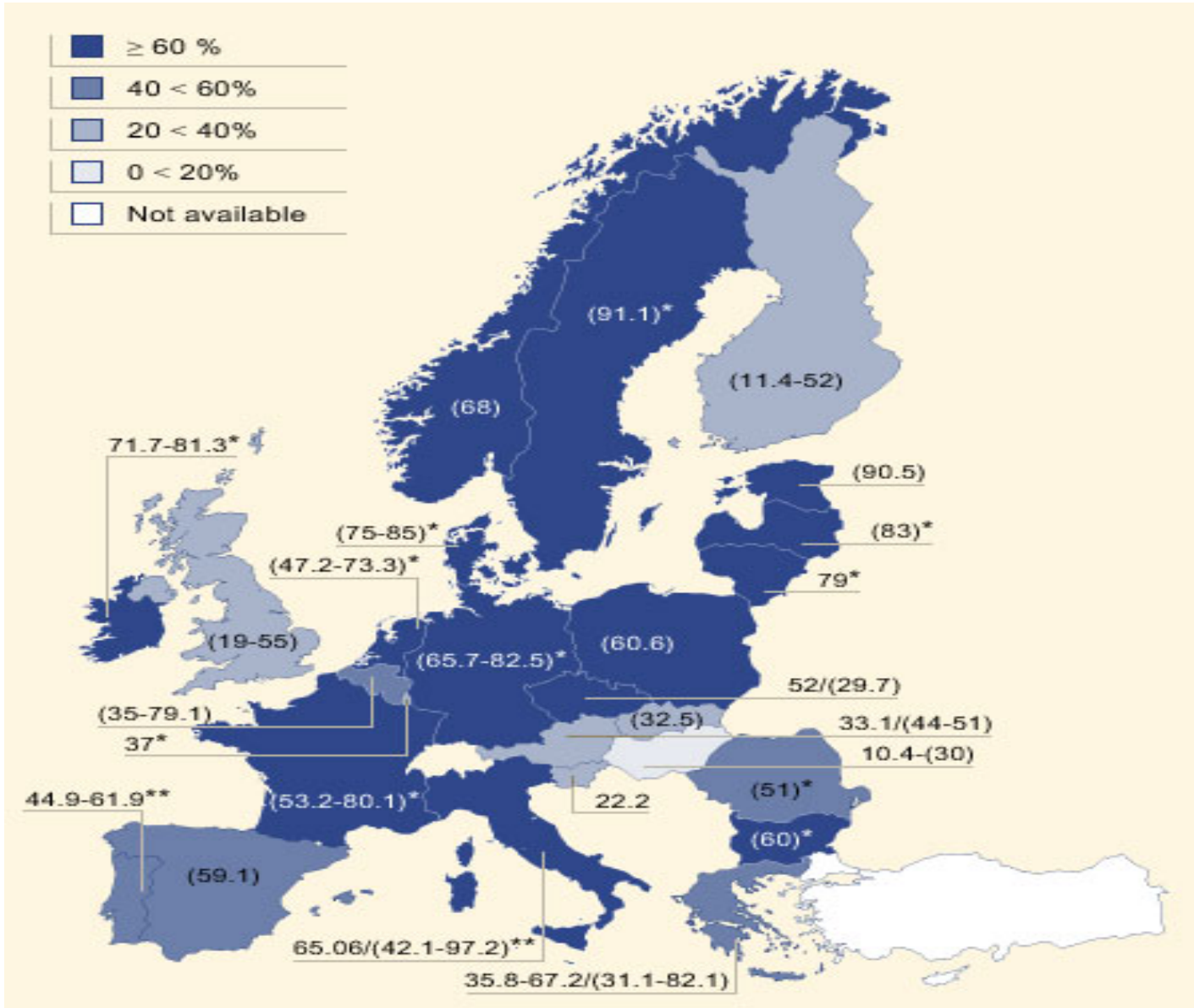
Number of HCV-infections by intravenous use



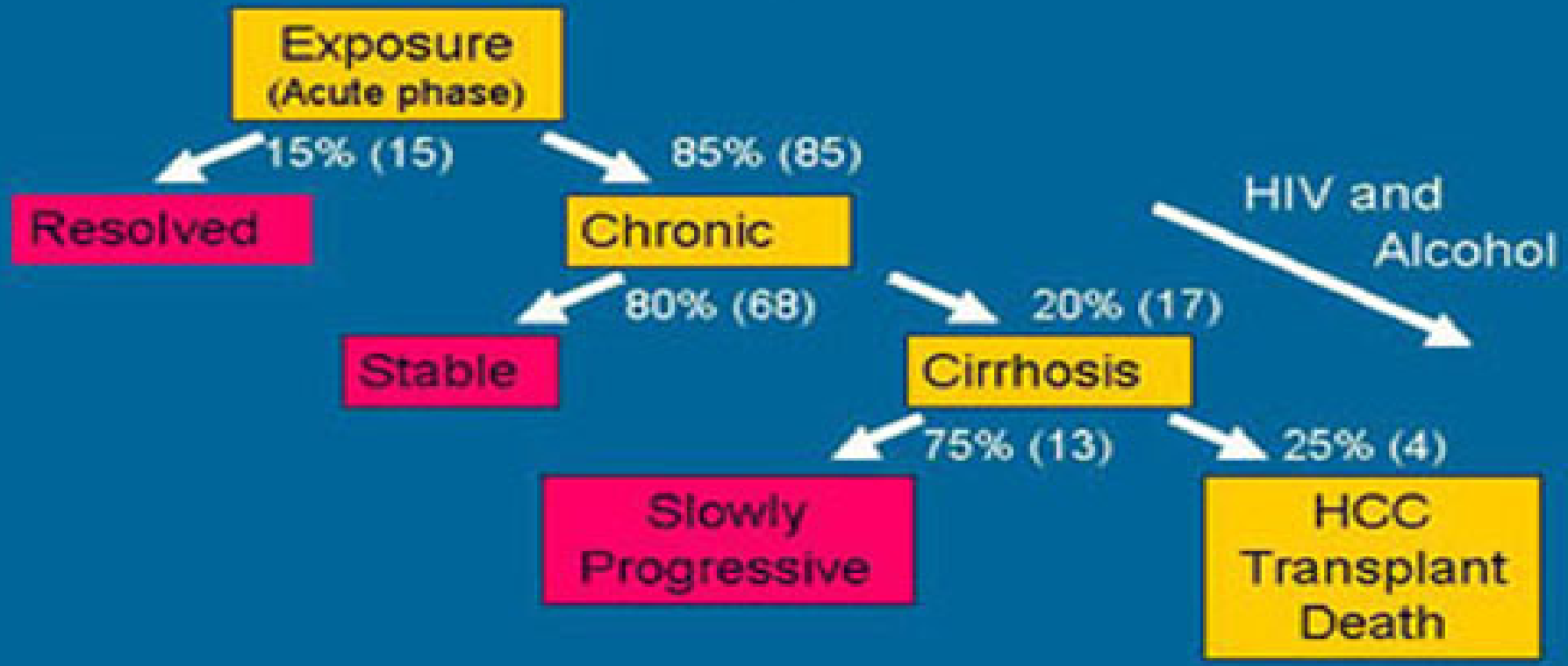
Prevalence of acute HCV-infection in IDU



HCV-prevalence in IDU in Europe



Natural History of HCV Infection



Alter, MJ. Epidemiology of Hepatitis C in the West. Semin Liver Dis. 1996; 15:5-14.
Management of Hepatitis C. NIH Consensus Statement. 1997 March 24-26; 15(3).

Pro and Con for the treatment decision in the past

PRO

- high morbidity and mortality
- physical insensitivity
- stabilisation by substitution treatment
- good compliance by proper selection

CON

- high rate of re-infections
-high rate of death
- bad compliance
- Social instability
- Somatic and psychiatric comorbidity
- stop due to imprisonment
- politoxicomania
- Illegal trade with medicaments

Premos Study

5-6 year follow up of patients on opioid maintenance treatment

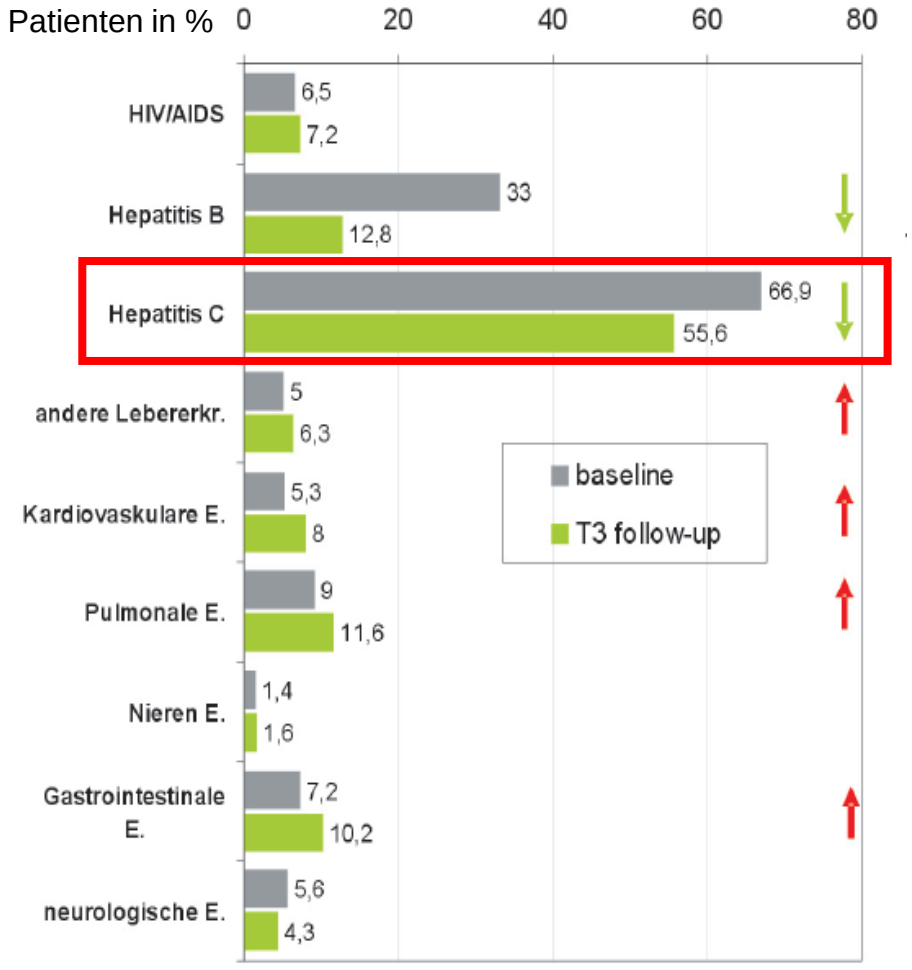
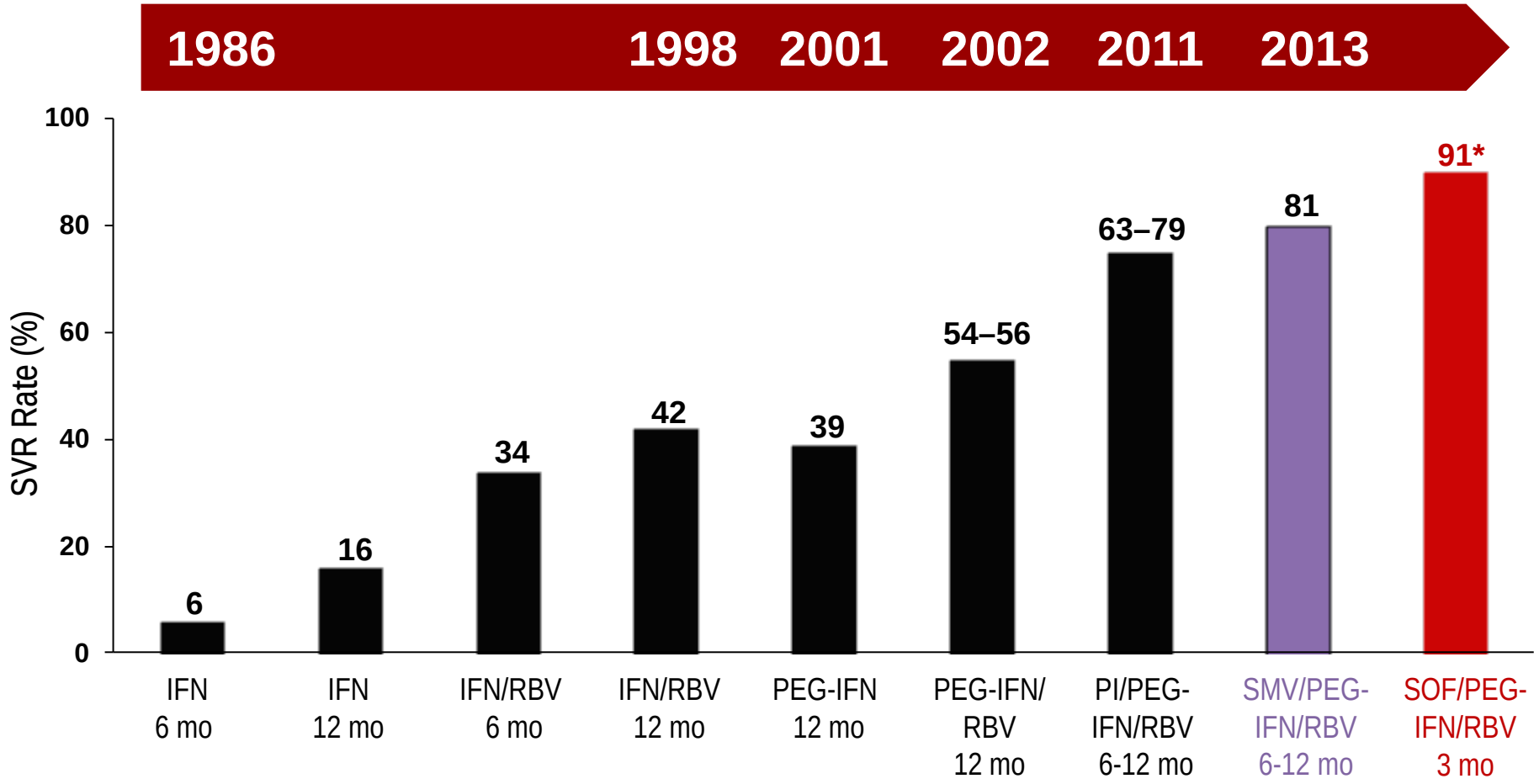


Abb. 9: Veränderungen der somatischen Morbidität von t_1 zu t_3 (n=1.493)

- 223 Centers for opiate maintenance therapy in Germany
- Period of observervation 2003-2010
- T3 = after 5-6 years
- n=1493

Wittchen et al. Suchtmed 13 (5) 280-286 (2011)

SVR Rates in Patients With HCV



***SVR12 rate of 90% among GT 1 patients in the Phase 3 NEUTRINO trial (12 weeks of SOF+PEG-IFN+RBV)**

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71; INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals, 2013; VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co, 2014; Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425; Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413; Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02.

Duration of HCV-treatment

•IFN	48 weeks
•PegIFN GT 1,4	48 weeks
•PegIFN GT 2,3	24 weeks
•PegIFN +RBV GT 1,4	48 weeks
•PegIFN +RBV GT1,4 RVR	24 weeks
•PegIFN + TPV + RBV	24 weeks
•PegIFN + BOC + RBV	24 weeks
•PegIFN + SOF + RBV	12 weeks
•SOF + DCV	12 weeks
•SOF + LPV	8 weeks

Cost-development of HCV-treatment

Regimen	per month	duration	total cost
PegIFN+RBV	1 800.-	6-11	11 000.- 20 000.-
PegIFN+RBV+BOC	4 500.-	6	27 000.-
PegIFN+RBV+TPV	6 800.-	6	41 000.-
PegIFN+RBV+SOF	21 600.-	3	65 000.-
SOF+SMV	36 000.-	3	108 000.-
SOF+DCV	36 000.-	3	108 000.-
SOF+RBV (GT 3)	20 600.-	6	123 600.-

Direct Acting Antivirals (DAA of the first generation)

- NS3 Protease-Inhibitoren:
-

• Boceprevir	(Victrelis®)	BOC	2011
• Telaprevir	(Incivo®)	TVR	2011
• Simeprevir	(Olysio®)	SMV	2014
• Faldaprevir			
• Asunaprevir			2015
• ABT 450/r			2015
• MK-5172			

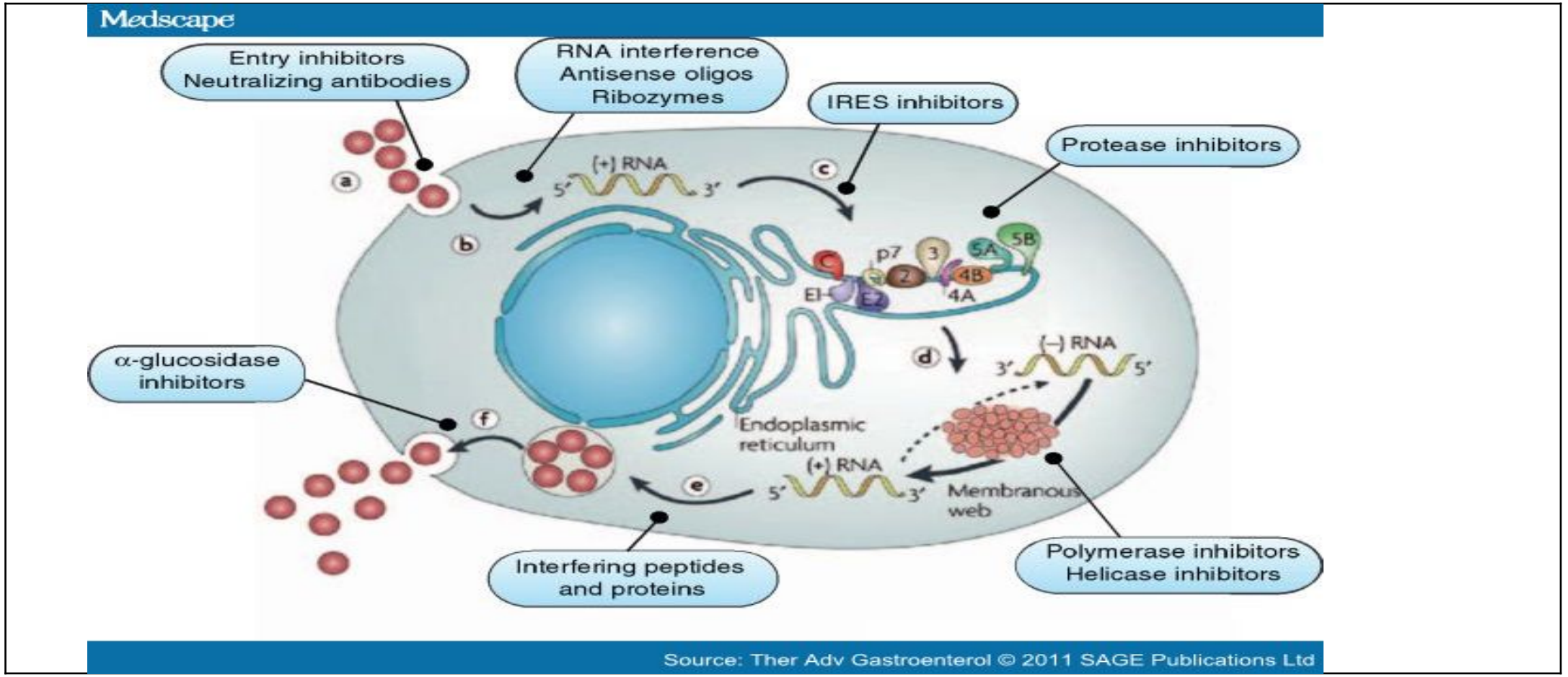
Direct Acting Antivirals (DAA) of the 2. generation:
NS5B Polymerase-Inhibitors

- Sofosbuvir (Sovaldi®) SOF 2013
- Mericitabine

Direct Acting Antivirals of the 2. generation: NS5A-Inhibitors

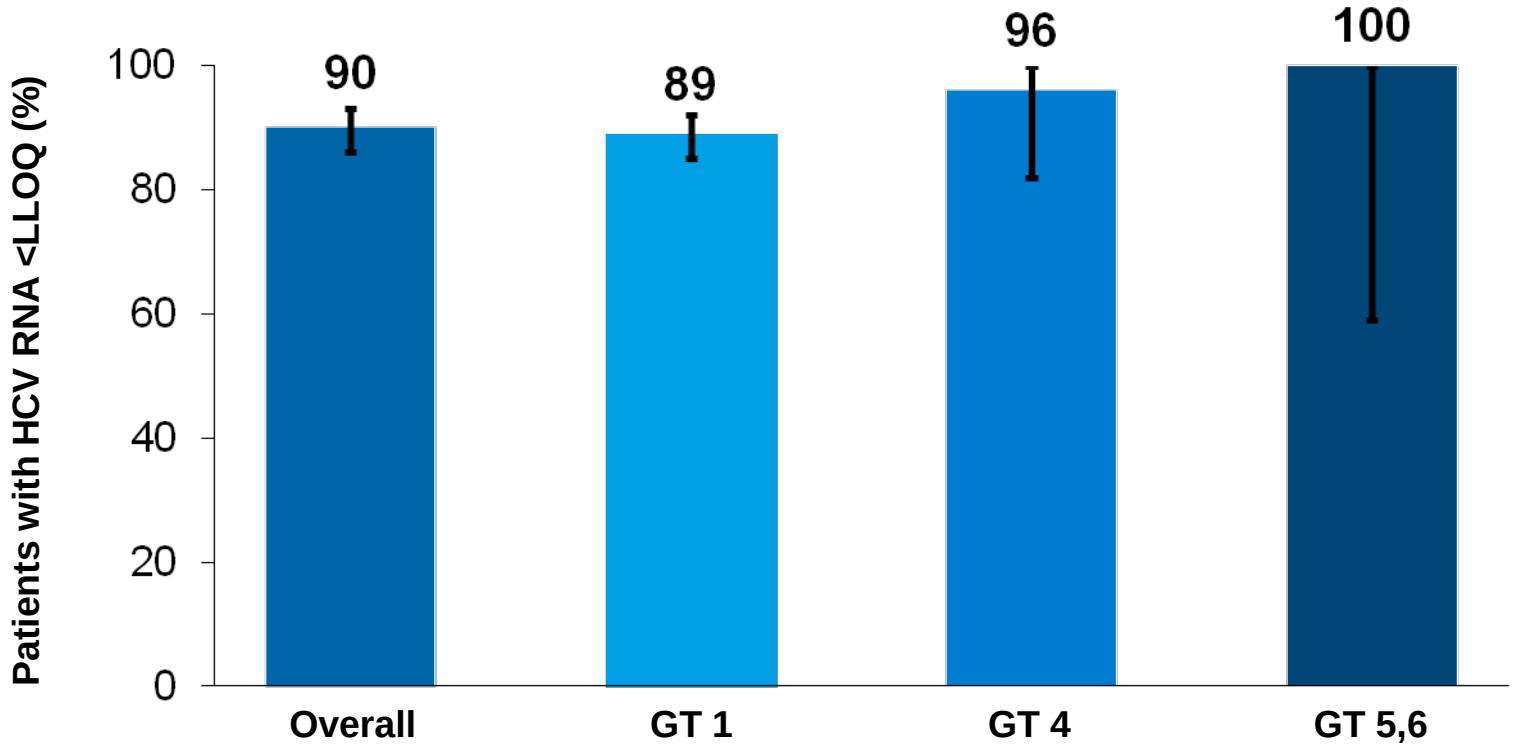
•Daclatasvir	(Daklinza®)	DCV	2014
•Ledispavir		LDV	2014
•Ombitasvir		OBV	2015
•PPI-668			
•MK-8742			
•GS-5816			
•GSK2336805			

How Protease and Polymerase-Inhibitors work



NEUTRINO: sustained virological response

GT 1, 4, 5, 6 Treatment-Naïve: SOF+PEG-IFN+RBV x 12 Weeks



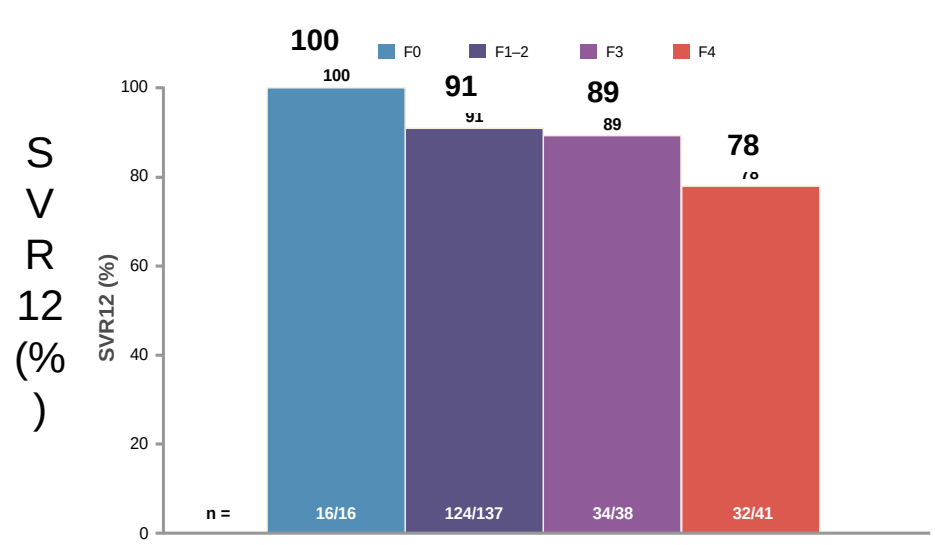
Lawitz E, et al. EASL 2013. Amsterdam, The Netherlands. Oral #1411;
Lawitz E, et al. N Engl J Med. 2013;368(20):1878–87.

Error bars represent 95% confidence intervals

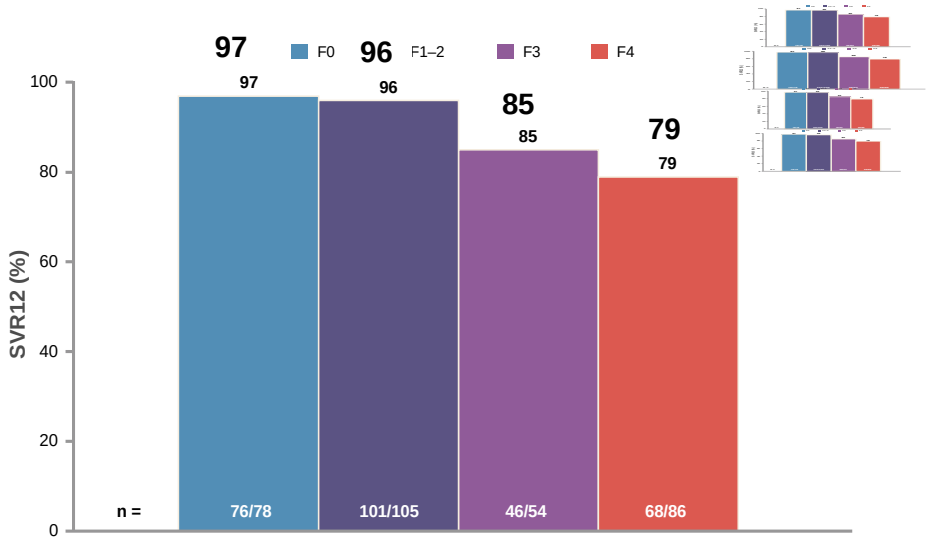
NEUTRINO SVR Rates by Fibrosis Analysis

GT 1, 4, 5, 6 Treatment-Naïve: SOF+PEG-IFN+RBV x 12 Weeks

SVR12 Rates by Biopsy Fibrosis Stage (n=232)



SVR12 Rates by FibroTest® Stage (n=323)

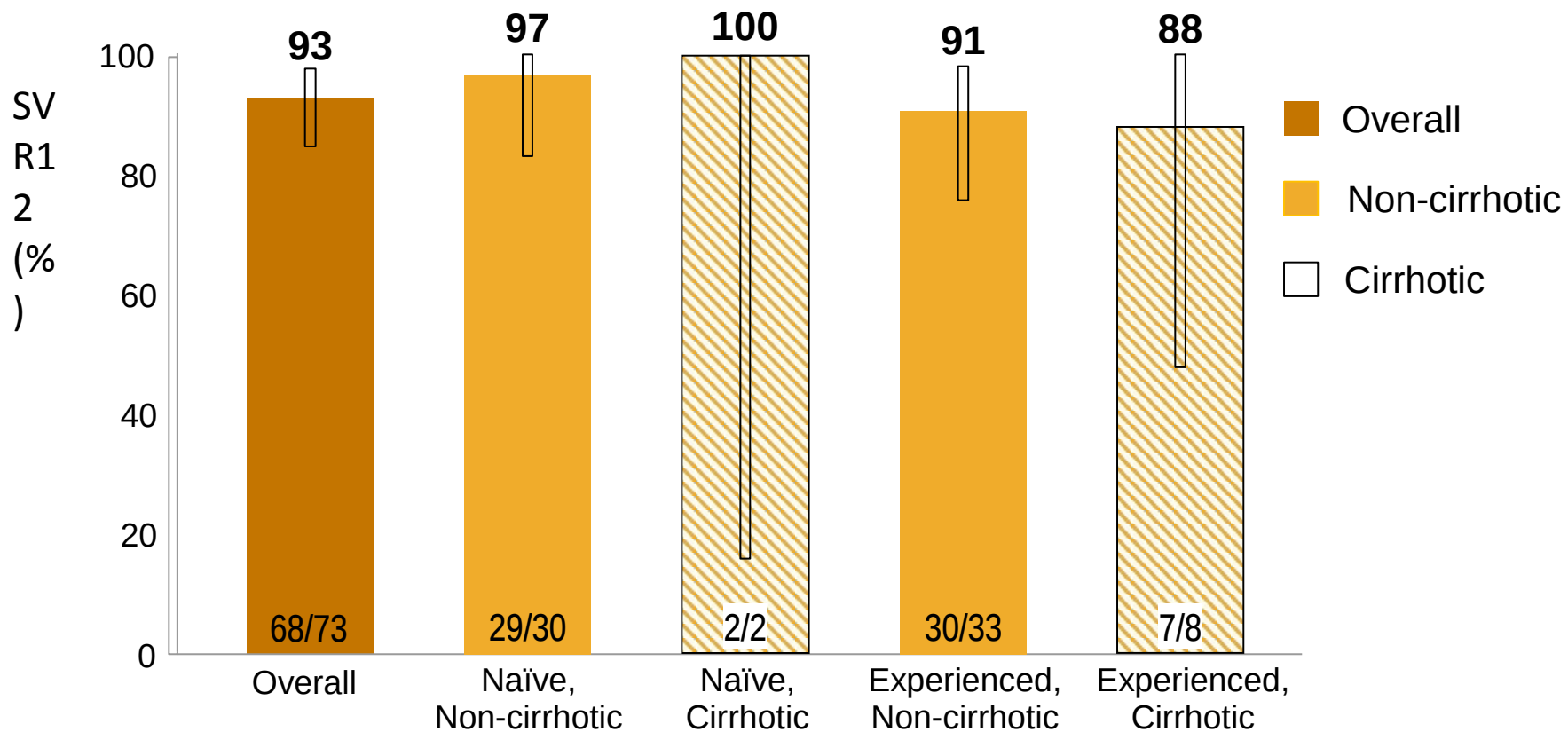


SVR12 (%)

Patel K, et al. AASLD 2013. Washington, DC. #1093.

VALENCE: sustained virological response

HCV GT2 Treatment-Naïve and -Experienced SOF + RBV for 12 Weeks

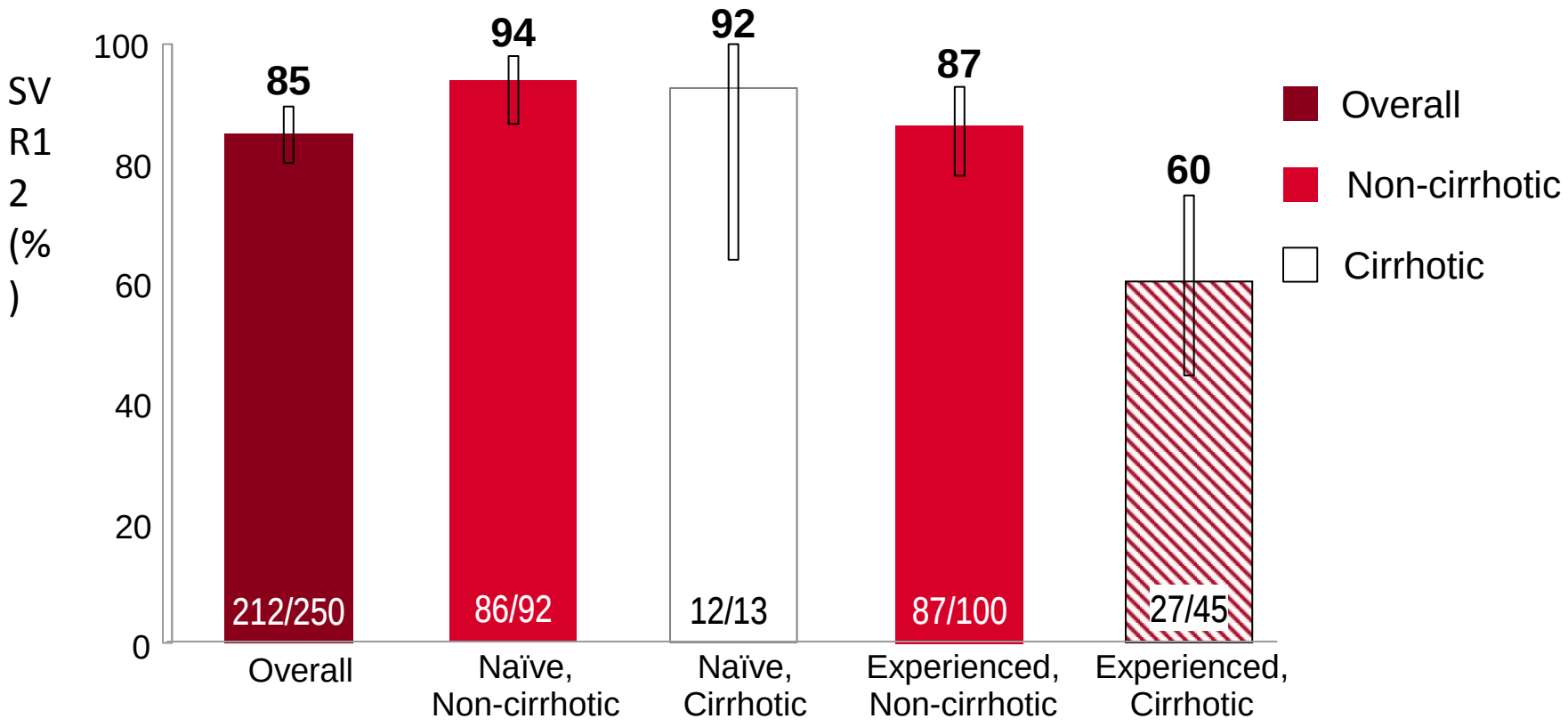


- 100% of patients had HCV RNA < LLOQ at Week 4
- Relapse after completion of therapy accounted for all virological failures
- No S282T mutations were observed by population or deep sequencing

Zeuzem S, et al. AASLD 2013. Washington, DC. #1085.

VALENCE: sustained virological response

HCV GT3 Treatment-Naïve and -Experienced SOF + RBV for 24 Weeks

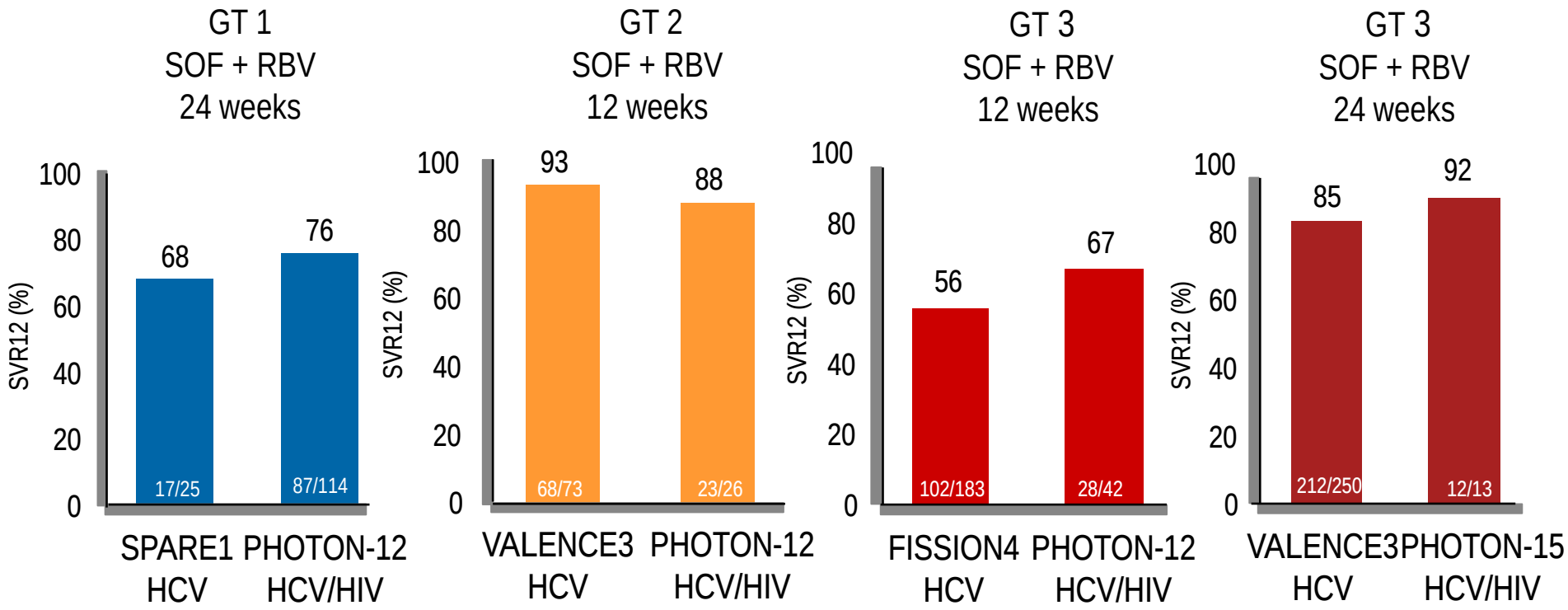


- 1 patient experienced virological breakthrough – PK documented non-adherence
- Relapse after completion of therapy accounted for all other virological failures
- No S282T mutations were observed by population or deep sequencing

Zeuzem S, et al. AASLD 2013. Washington, DC. #1085.

SVR in HCV Mono-infected and HCV/HIV Co-infected

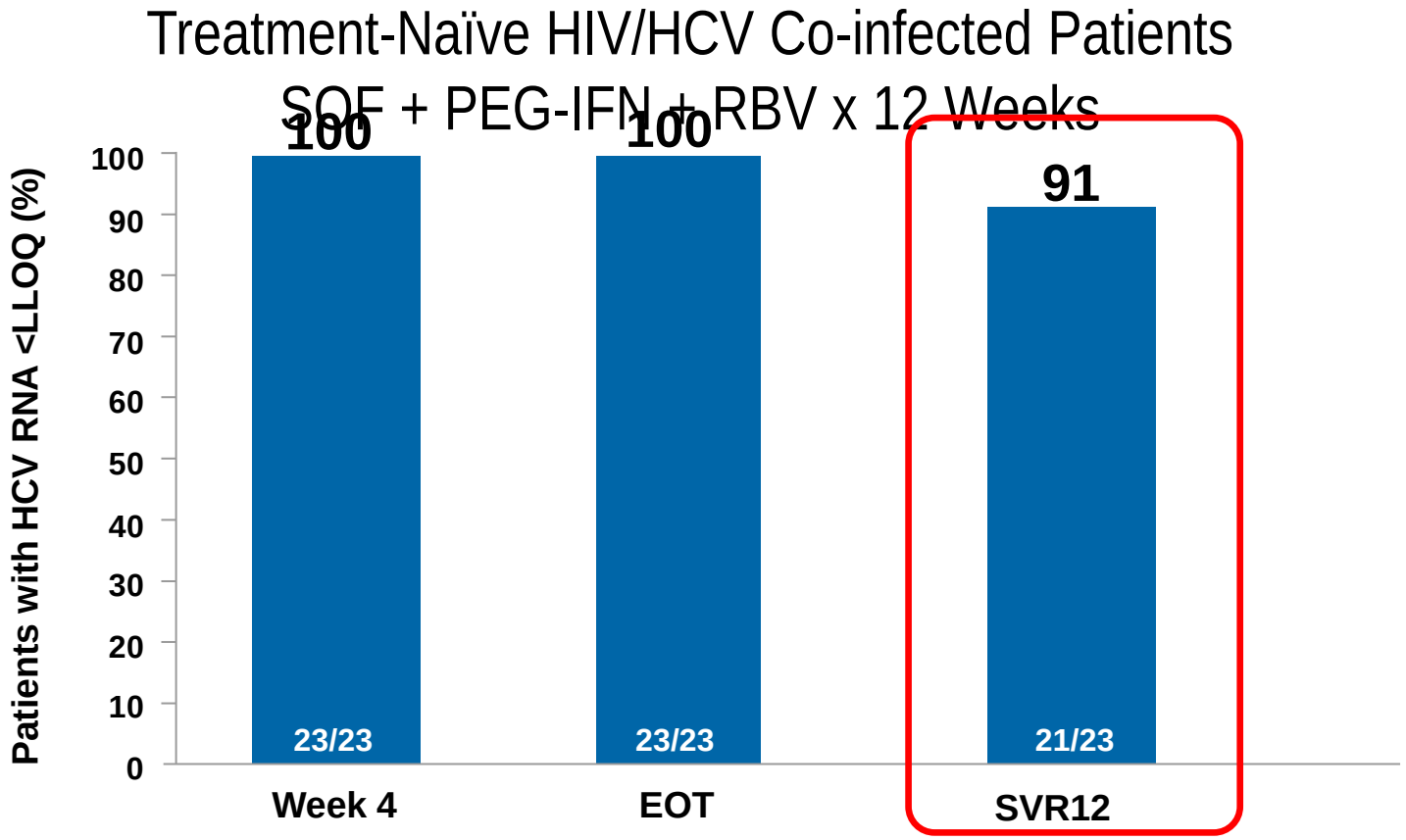
All-Oral SOF + RBV x 12 or 24 Weeks



Similar response rates in HCV/HIV co-infected patients compared to HCV mono-infected patients

1. Osinusi A, et al. JAMA. 2013;310(8):804-811. 2. Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212.
3. Zeuzem S, et al. AASLD 2013. Washington, DC. #1085. 4. Lawitz E, et al. N Engl J Med. 2013 May 16;368(20):1878-87.
5. Gilead Sciences EAME. SOVALDI (sofosbuvir), Summary of Product Characteristics, January 2014.

Study 1910: HIV-HCV-Coinfected



- SVR12 was similar by HCV GT and by HIV ARV regimen
- There was no on-treatment HCV or HIV virological breakthrough
- Relapse occurred in 1 patient and accounted for all virological failures
- 2 patients discontinued treatment early due to adverse events
  - 1 patient discontinued at week 6 and was lost to follow-up
  - 1 patient achieved SVR12 after 8 weeks of SOF + RBV therapy

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714.

Currant Conditions for a therapy with 2 DAA without pegIFN/RBV

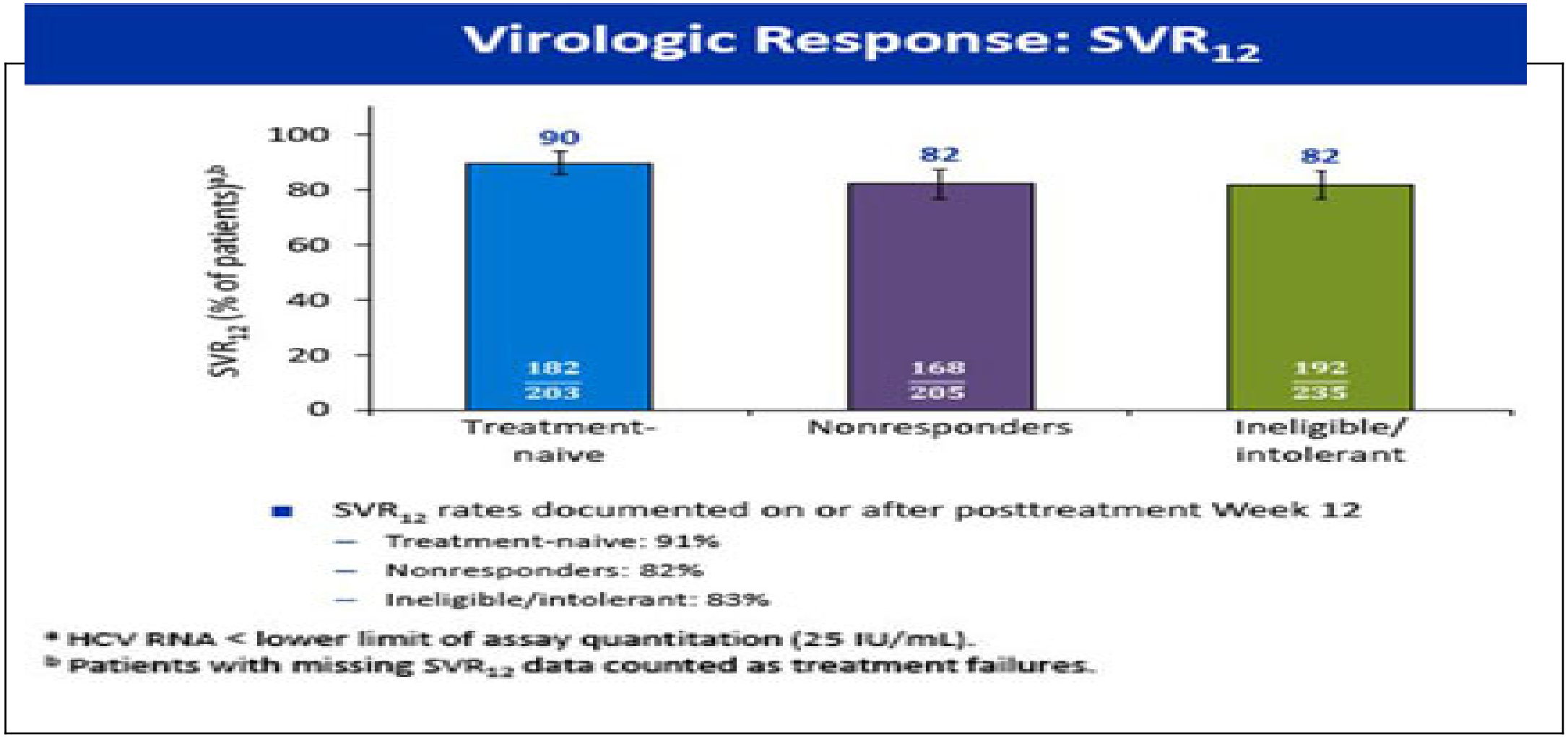
- urgent therapy : Fibroscan > 10, Metavir > F3
- (advanced fibrosis)
-
- Contraindikations: for pegIFN or for RBV
-
- IL28B-Gene: T/T : low reaction to pegIFN
-
- Non-response/relapse:
- dual therapy with pegIFN +RBV or
- triple therapy with TPV+pegIFN+RBV or
- triple therapy with BOC+pegIFN+RBV
-

Contraindications for the use of pegIFN or RBV

- pegIFN: - severe psychiatric comorbidity
- - autoimmune disease
- - neurological disease
- - retinal disease
- - thyreoid disease
- - neutropenia
- - thrombocytopenia

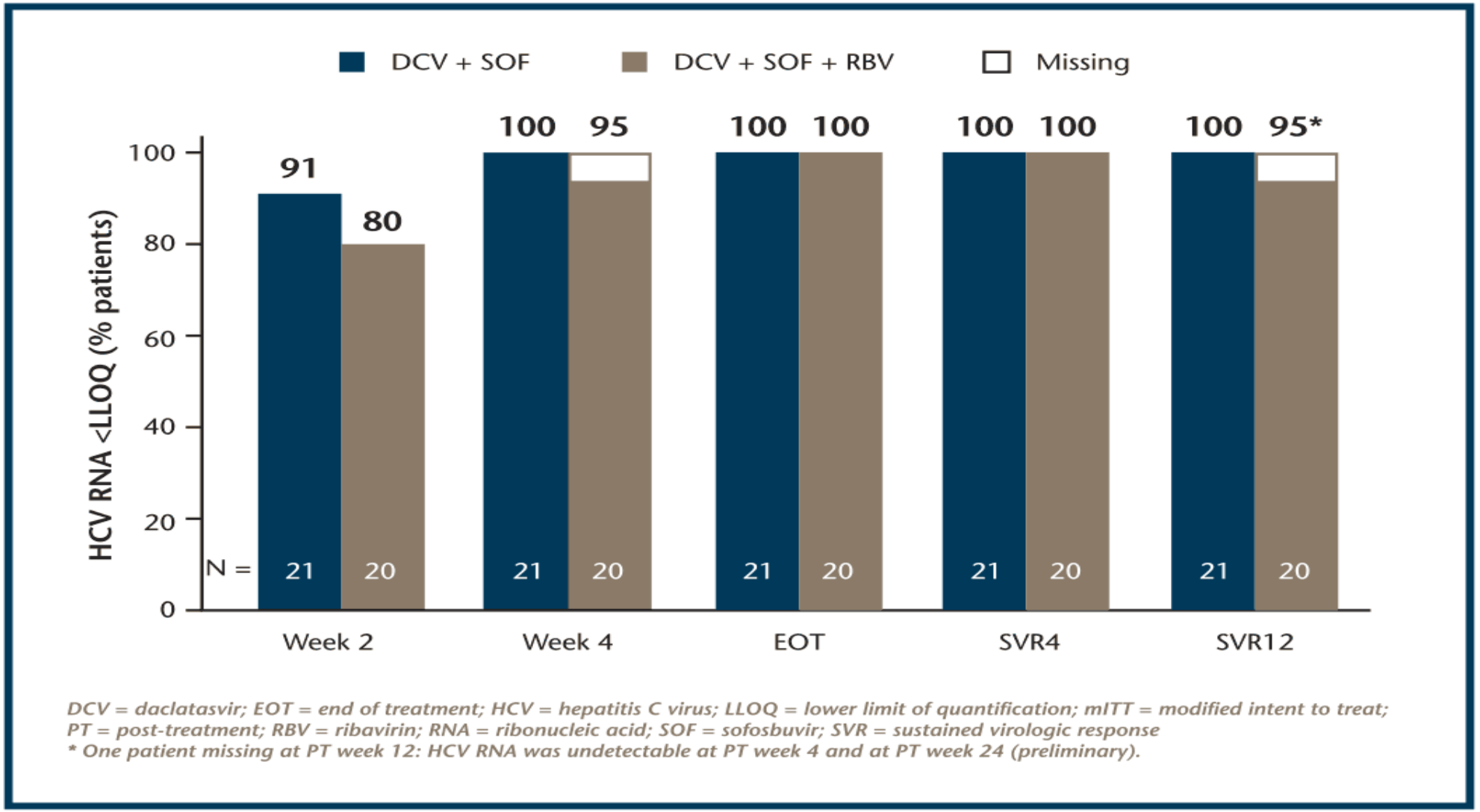
- RBV: - cardiac desease
-

Sustained virological response with 2 DAA (Daclatasvir + Asunaprevir)



Sustained virological response with 2 DAA (Sofusbuvir + Daclatasvir + - RBV)

Figure 1. Virologic response during and after treatment (mITT)



DCV = daclatasvir; EOT = end of treatment; HCV = hepatitis C virus; LLOQ = lower limit of quantification; mITT = modified intent to treat; PT = post-treatment; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR = sustained virologic response
** One patient missing at PT week 12: HCV RNA was undetectable at PT week 4 and at PT week 24 (preliminary).*

Recent Therapy of HCV by Genotype

Therapie	GT1	GT2	GT3	GT4
SOF + PegIFN + RBV	x		x	x
SOF+RBV		x		
SOF + SMV +/- RBV	x			x
SOF + DCV +/- RBV	x		x	x

Side effects of pegIFN and RBV

- Ribavirin:
- Anemia, fatigue, loss of concentration, headache, pruritus, skin rash, visual defects, tachycardia, nausea, vomiting, and other 35 side effects
- pegIFN :
- neutropenia, fever, arthralgia, headache, chest pain, cough,
- anorexia, depression, attempted suicide, anxiety, psychosis, emotional lability, pruritus, hair loss, multiple infections, thyropathy
- and other 50 side effects
-
- **Clearly more and severe side effects than DAA**

Side effects of DAA

- Sofosbuvir:
- fatigue, headache,

- Daclatasvir:
- fatigue, headache,

- Simeprevir:
- photoallergy, skin rash, elevation of liver enzymes
-
- **Clearly less side effects than pegIFN und RBV**
-

Summary

•With DAA-combination-therapy finally patients can be treated,
•in which pegIFN and RBV was contrandicated
•Therapy with DAA is nearly free of side effects
•The duration of HCV-therapy today is limited to 12 weeks
•The healing from HCV is 90 – 100% with 2 DAA or with
•pegIFN/RBV and one DAA of second generation, even for
•HIV-HCV-coinfected patients
•The only remaining problem are the costs of a therapy with
•2-3 DAA. Nowadays these therapies are therefore limited to
•special conditions