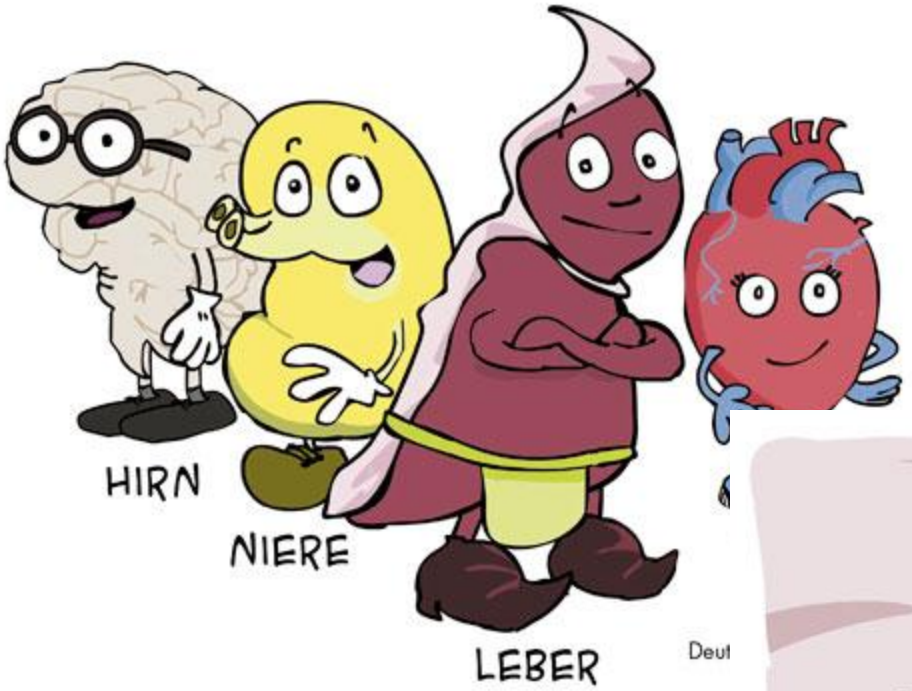
Update Therapie Virushepatitis:

Neue Medikamente, neue Leitlinien…

Heiner Wedemeyer

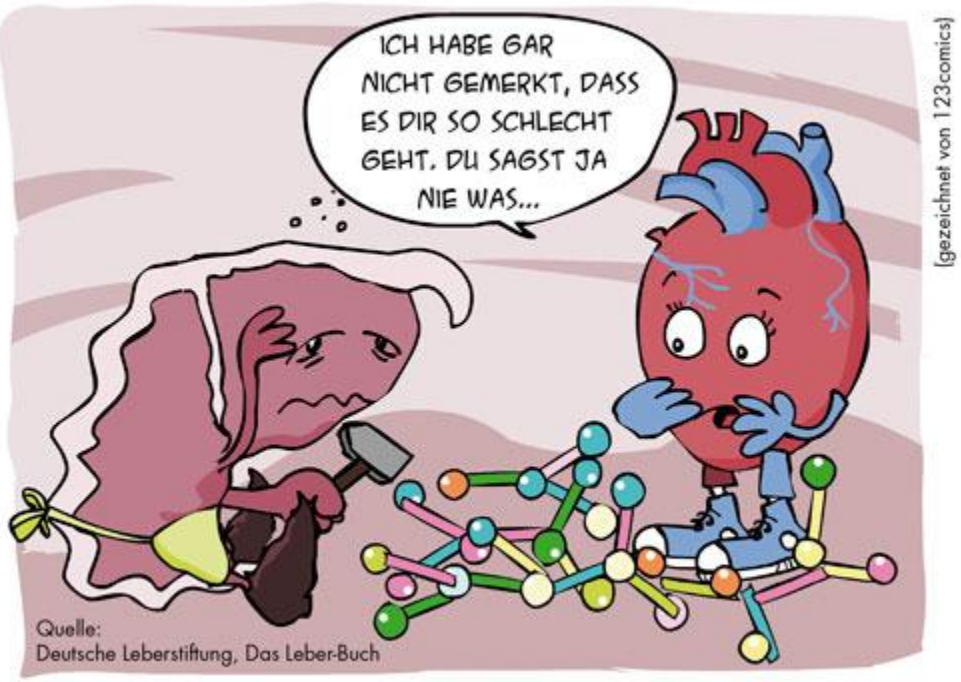
Medizinische Hochschule Hannover

Das Leber-Buch



(gezeichnet von 123comics)

Deut



(gezeichnet von 123comics)

Erkrankungen der Leber bleiben oft sehr lange unbemerkt.

Hepatitisviren

Hepatitis A	Feinstone	1973	RNA
Hepatitis B	Blumberg	1965	DNA
Hepatitis C	Houghton	1988	RNA
Hepatitis D	Rizzetto	1977	RNA
Hepatitis E	**Balayan**	**1980**	**RNA**

Akute Hepatitis E

–

Stets selbstlimitierend?

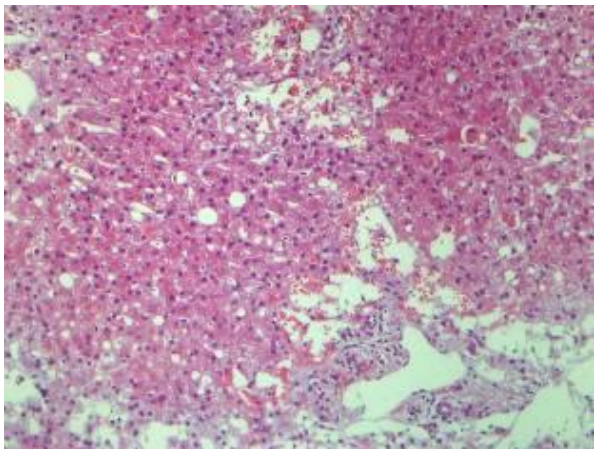
The NEW ENGLAND JOURNAL of MEDICINE

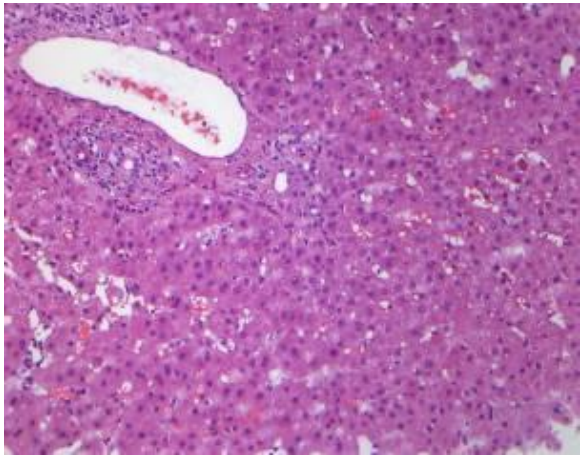
Februar 2008

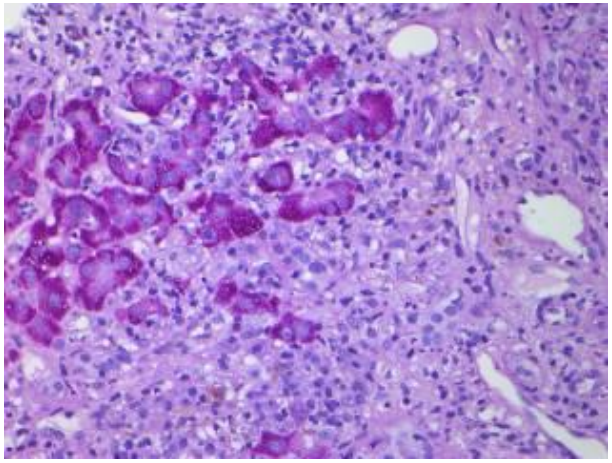
Hepatitis E Virus and Chronic Hepatitis in Organ-Transplant Recipients

Nassim Kamar, M.D., Ph.D., Janick Selves, M.D., Jean-Michel Mansuy, M.D., Leila Ouezzani, M.D., Jean-Marie Péron, M.D., Ph.D., Joëlle Guitard, M.D., Olivier Cointault, M.D., Laure Esposito, M.D., Florence Abravanel, Pharm.D., Marie Danjoux, M.D., Dominique Durand, M.D., Jean-Pierre Vinel, M.D., Jacques Izopet, Pharm.D., Ph.D., and Lionel Rostaing, M.D., Ph.D.

Chronische Hepatitis E bei einem Lebertransplantierten







Monate nach

Transplantation: **0** **6** **19**

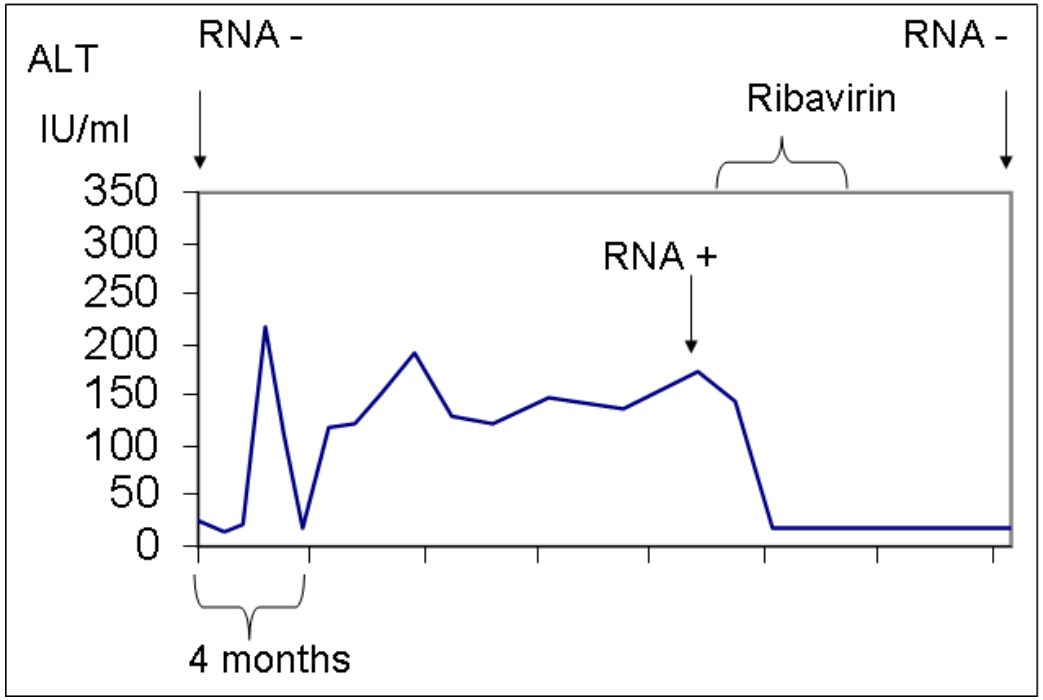
Chronische Hepatitis E mit Fibrose (ISHAK F3) assoziiert

Pischke et al., Liver Transplantation 2010

Hepatitis E
Eine Zoonose?

Therapie der chronischen Hepatitis E: Ribavirin!

Ribavirintherapie einer chronischen Hepatitis E bei einem herztransplantierten Patienten



Pischke et al., Am J Transplantation 2012

Chronische Virushepatitis

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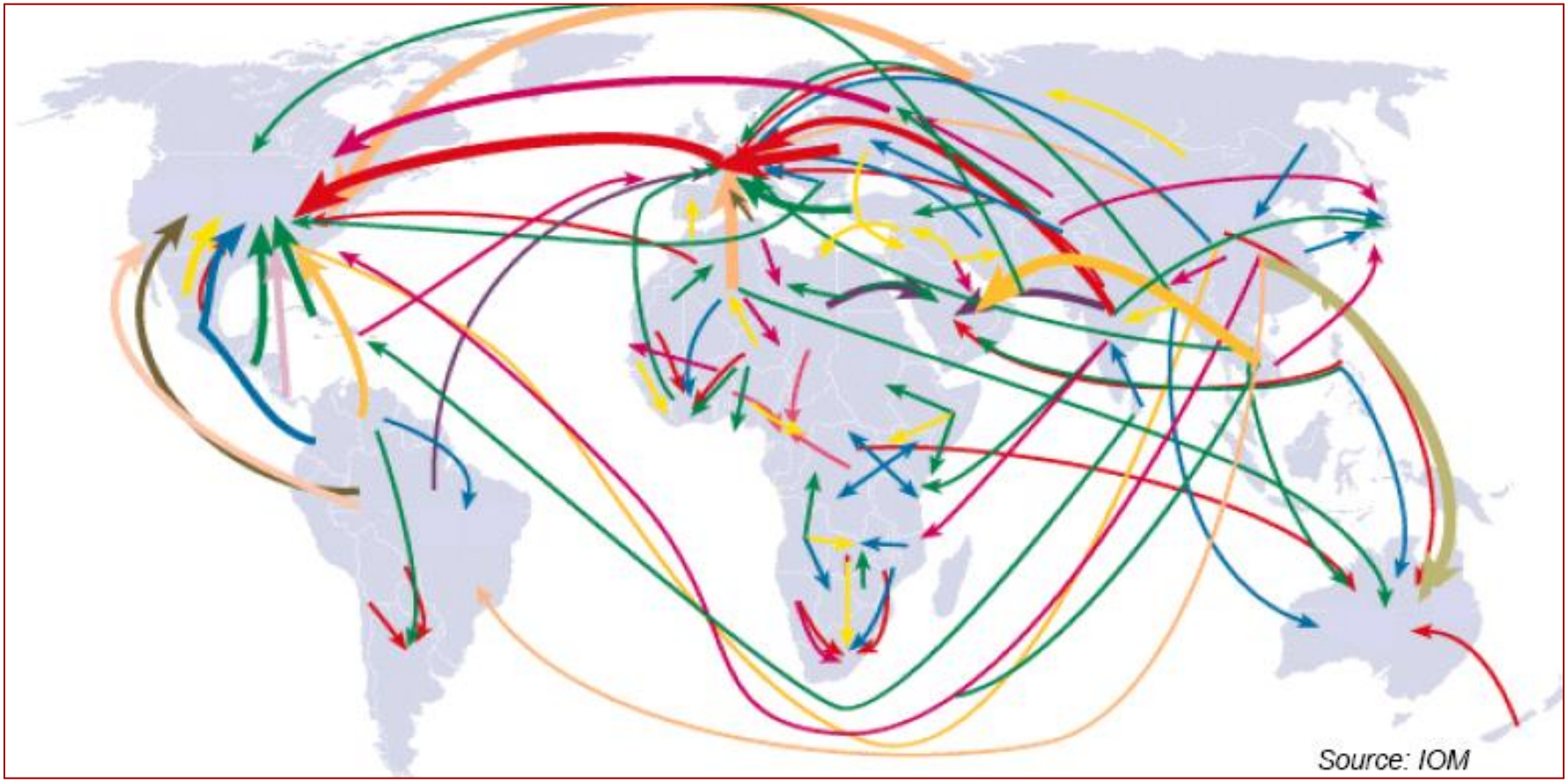
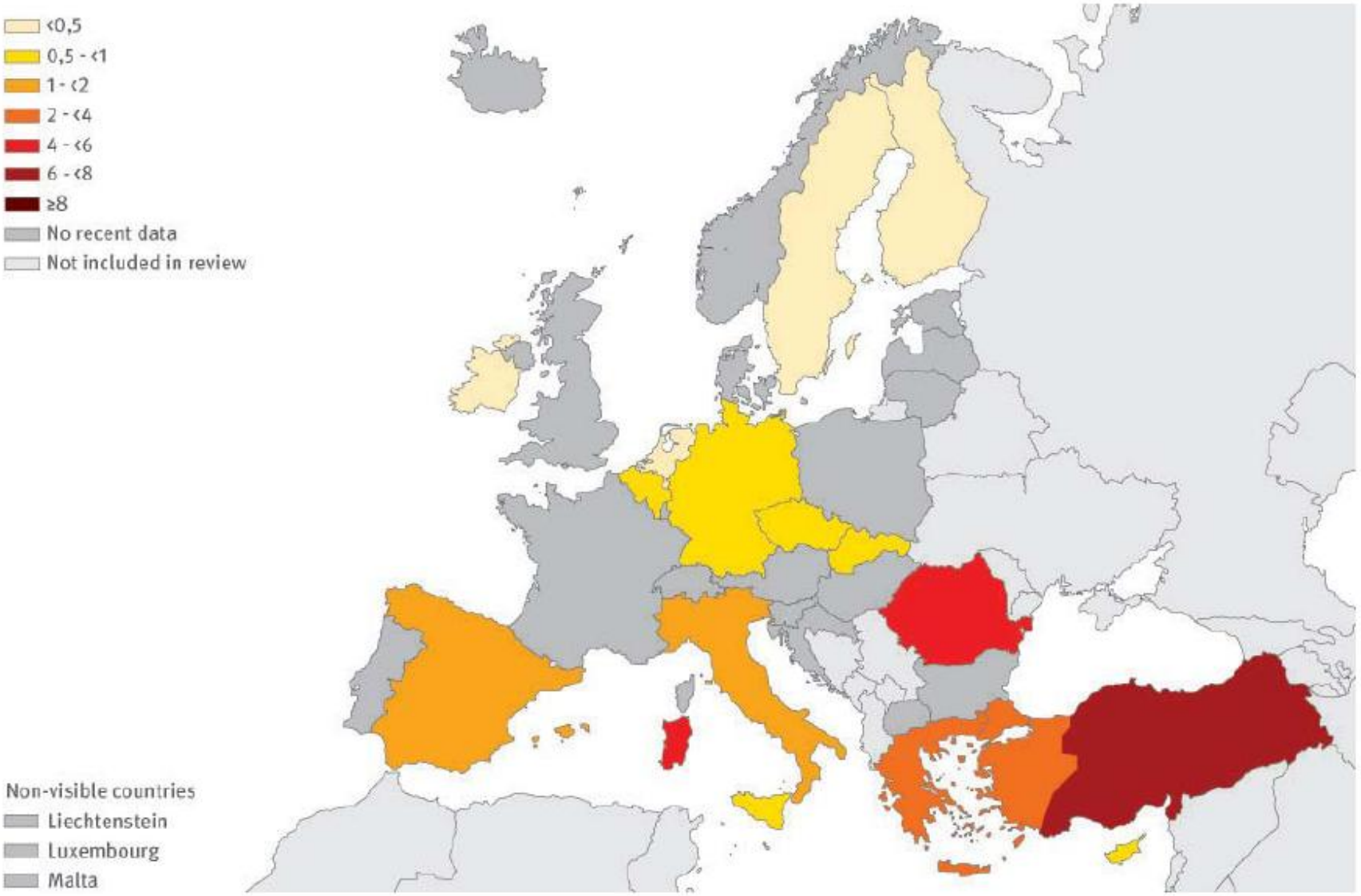
Hepatitis C	**Houghton**	**1988**	**RNA**
Hepatitis D	**Rizzetto**	**1977**	**RNA**
Hepatitis E	Balayan	1980	RNA

Migration and viral hepatitis



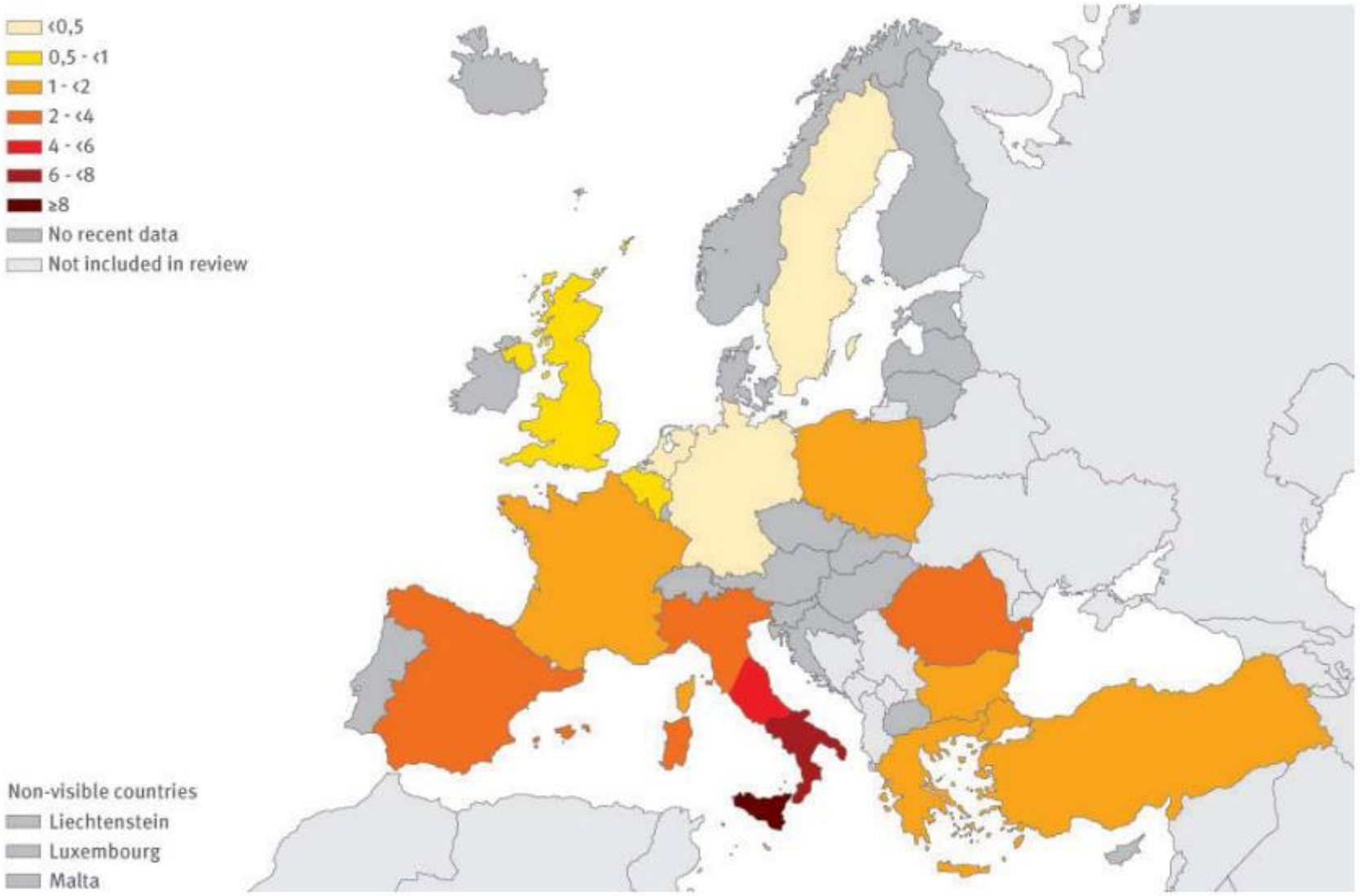
courtesy of Dr Carballo

Hepatitis B prevalence in Europe (general population)

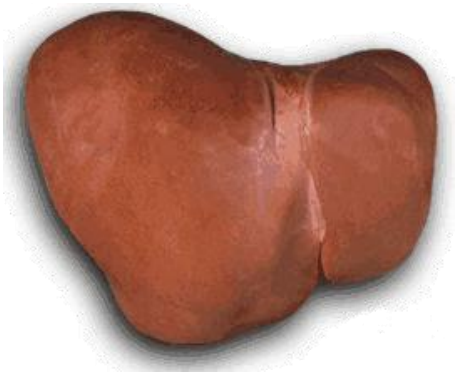


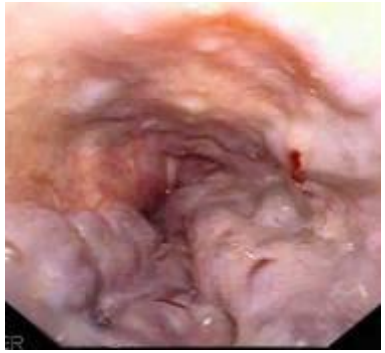
ECDC Technical Report Hepatitis B and C; September 2010

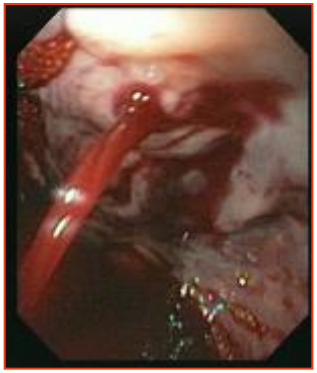
Prevalence of hepatitis C in the general population

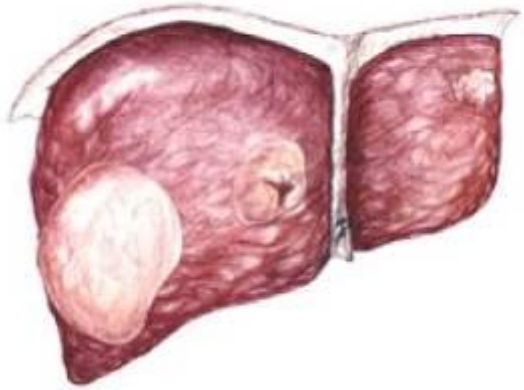


ECDC Technical Report Hepatitis B and C; September 2010









Hepatitisviren

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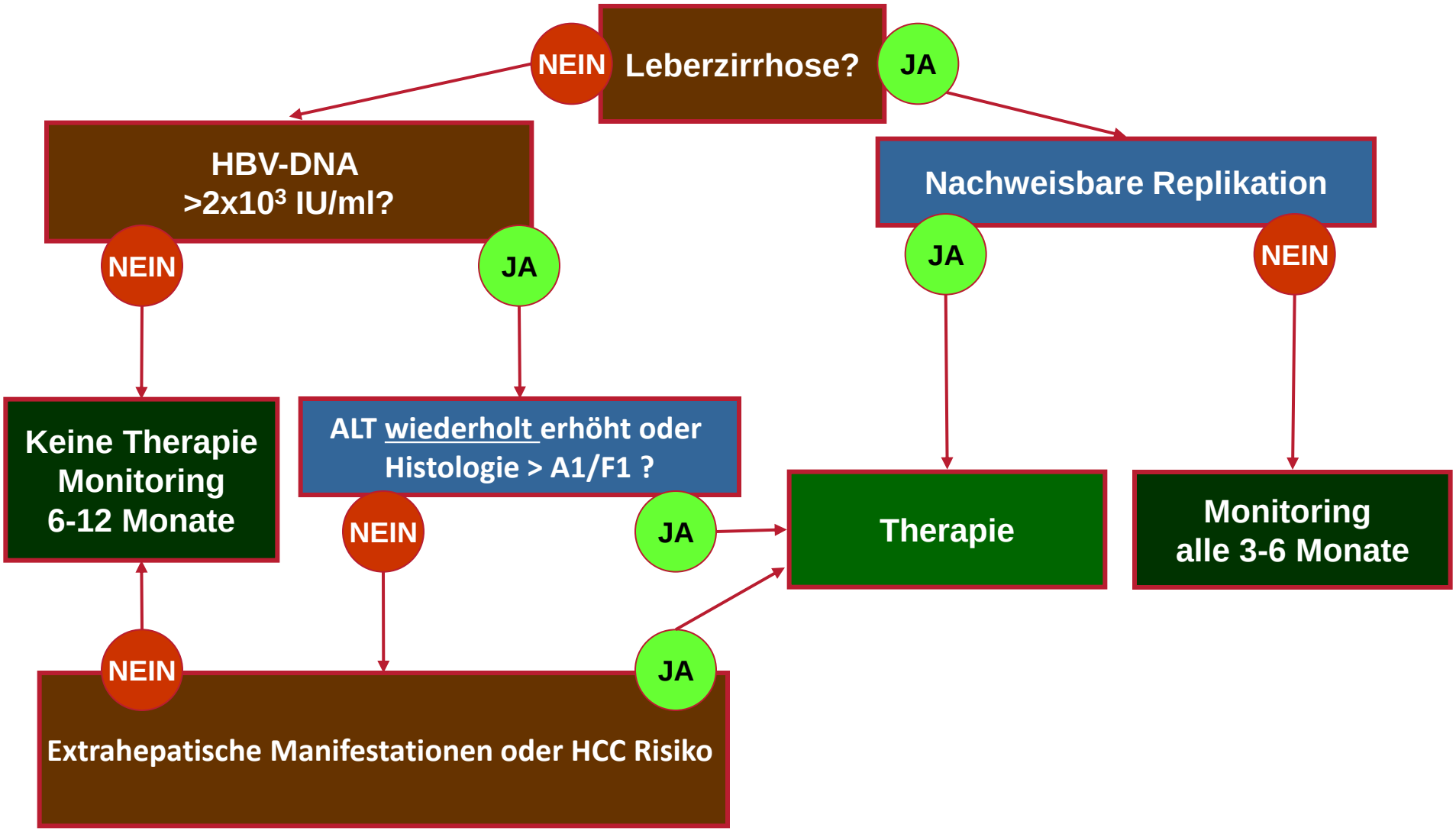
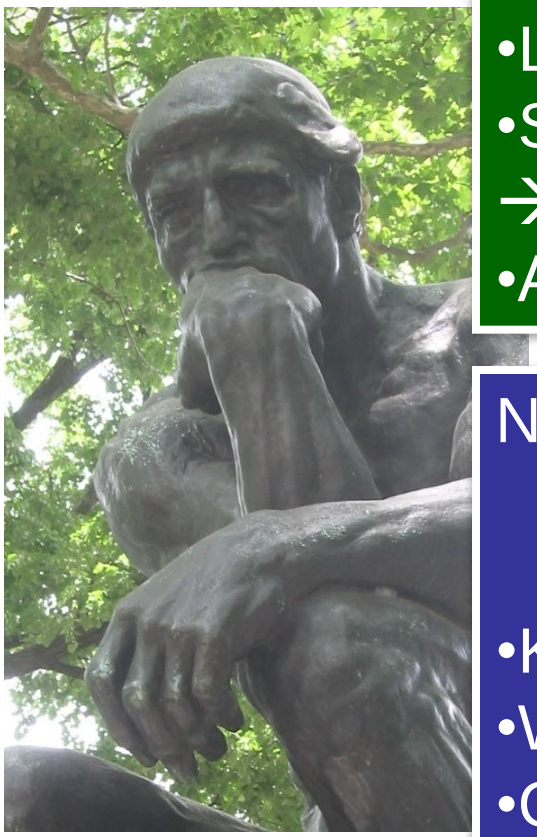
Therapieindikation (Leitlinie 2010/2011)

Deutsche Leberstiftung



Cornberg et al., S3-Leitlinie Hepatitis B Update 2010/2011



(Peg)-Interferon alfa

- Limitierte Therapiedauer möglich!
- Stärkerer HBsAg Abfall

→ häufiger HBsAg Verlust

- Aber Nebenwirkungen…

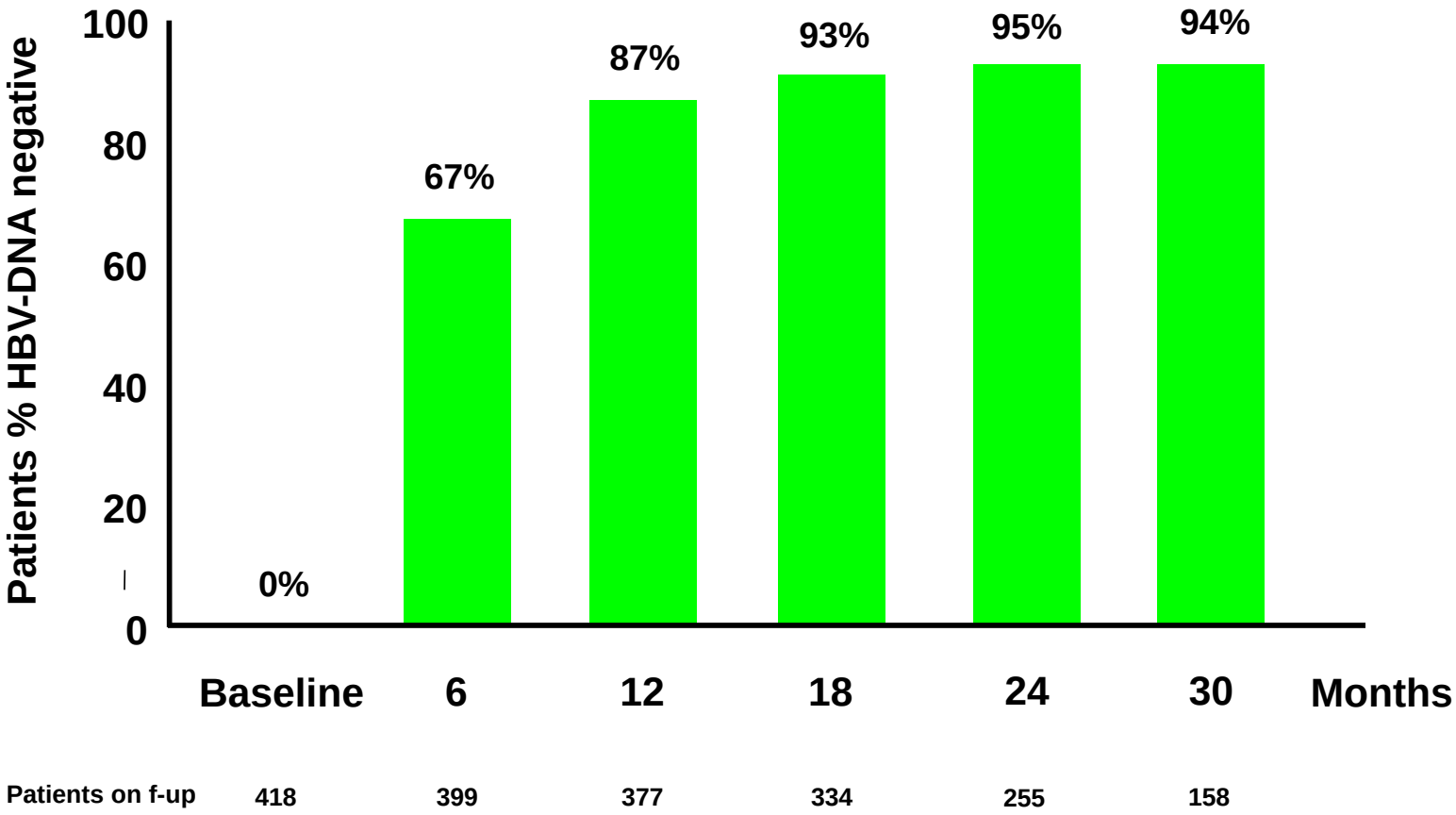
Nukleosid/Nukleotidanaloga





- Keine Nebenwirkungen (nächste Jahre)
- Wie lange therapieren?
- Compliance? Resistenzen?
- Was ist mit Nebenwirkungen bei einer Therapiedauer von > 10 Jahren

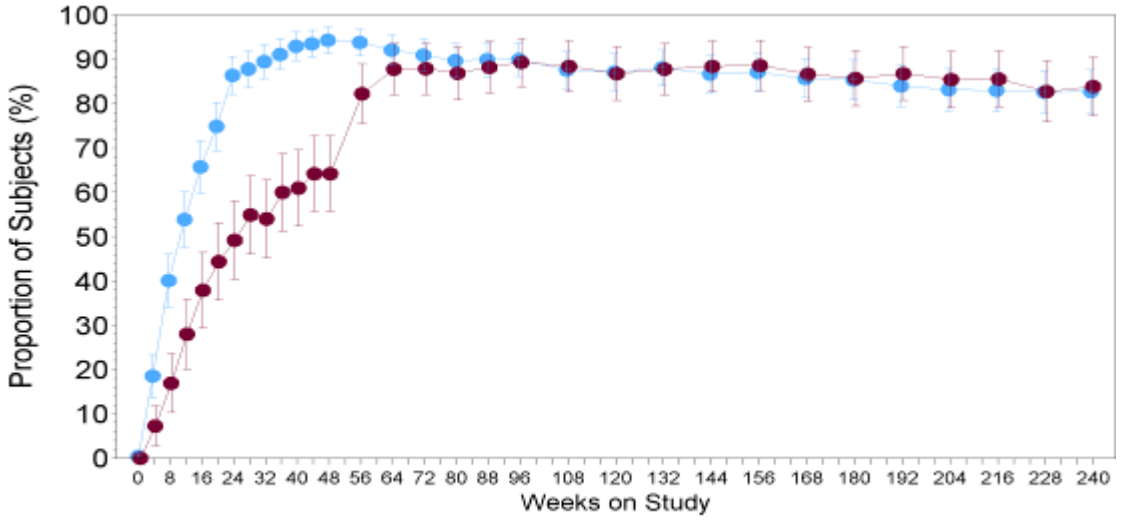
Langzeit-Ansprechen auf eine Entecavir-Therapie:
Italian Real-World Cohort Study



Lampertico et al., AASLD 2010

Langzeit-Ansprechen auf eine Tenofovir-Therapie

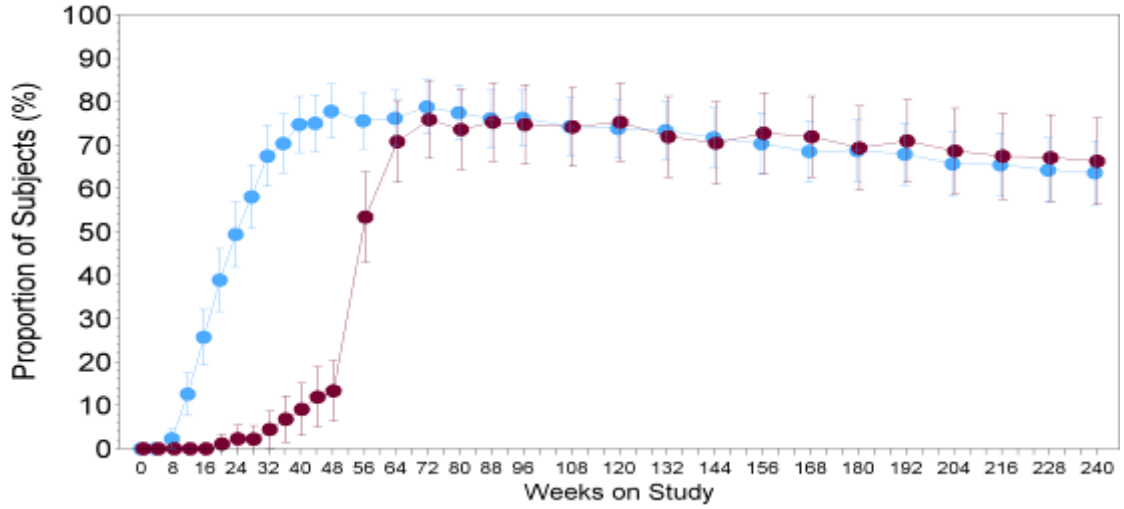
Proportion of patients with HBV DNA <400 copies/mL at Year 5



HBeAg-ve: Week 240:

TDF-TDF 83%
ADV-TDF 84%
Overall: 83%

On-treatment analysis (missing = excluded):
TDF-TDF = 99%
ADV-TDF = 99%

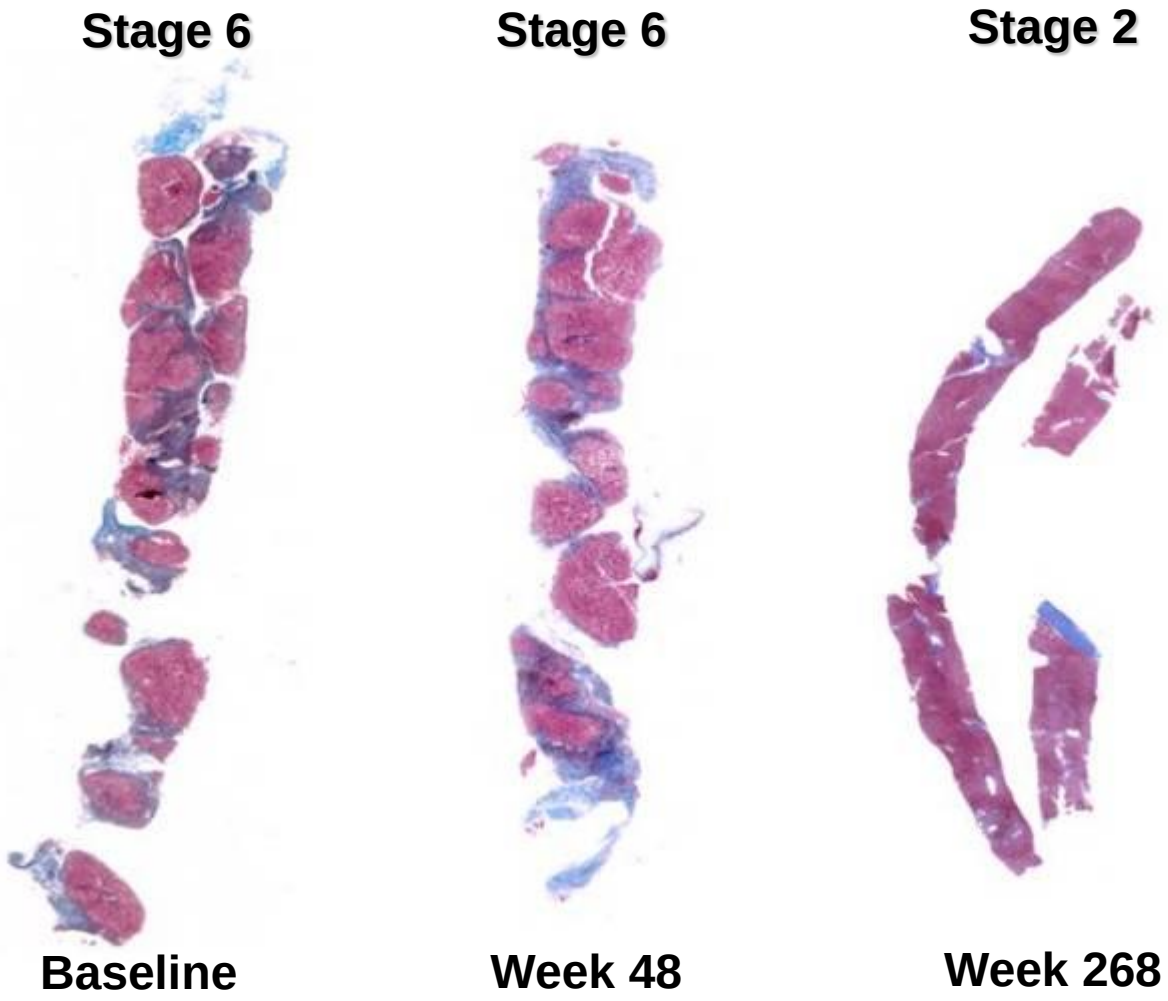


HBeAg+ve: Week 240:
TDF-TDF 64%
ADV-TDF 67%
Overall: 65%

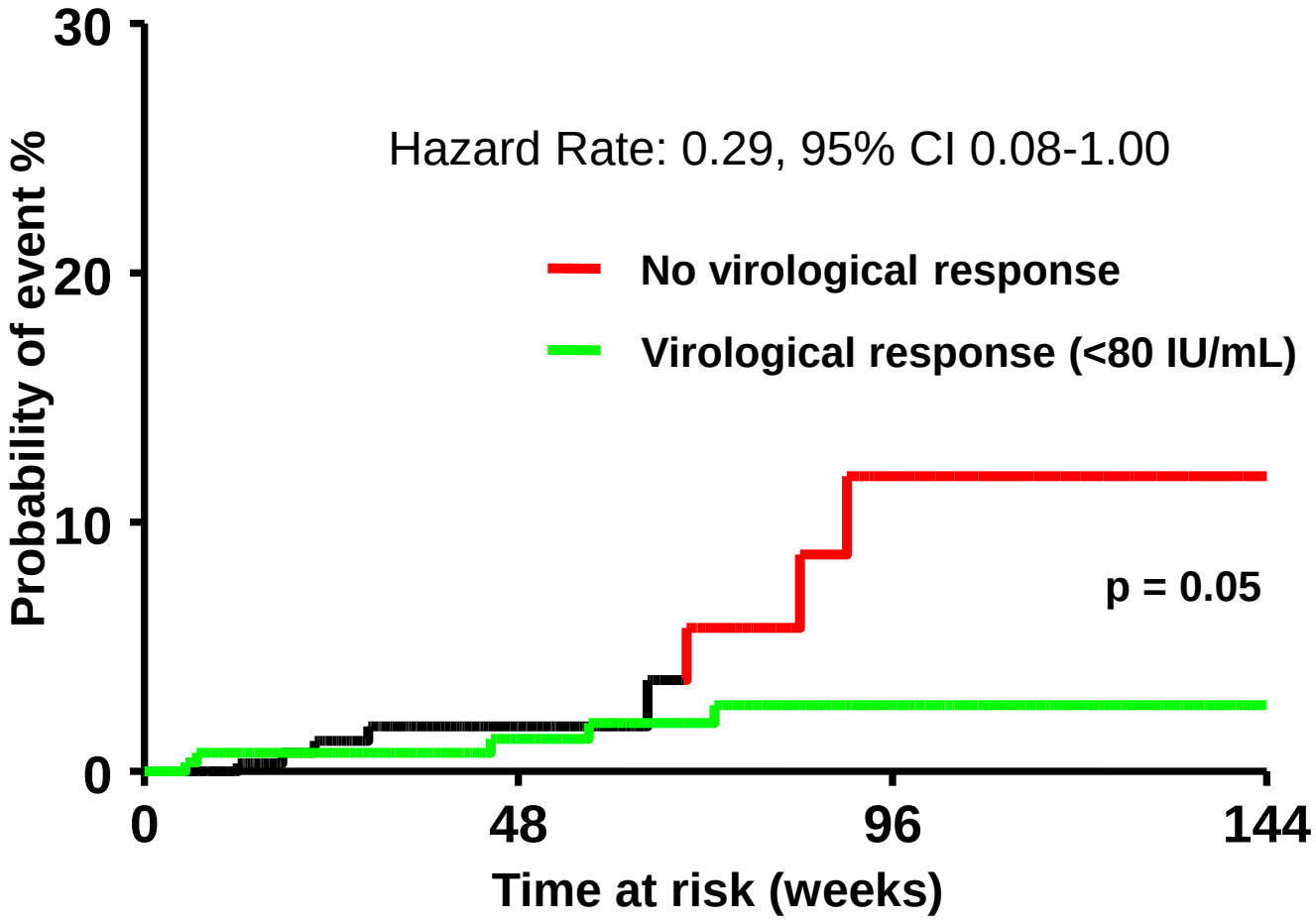
On-treatment analysis (missing = excluded):
TDF-TDF = 96%,
ADV-TDF = 100%

Adapted from Marcellin P, et al. AASLD 2011; Oral #238.

Regression einer Leberzirrhose bei erfolgreicher antiviraler Therapie (hier: Entecavir)



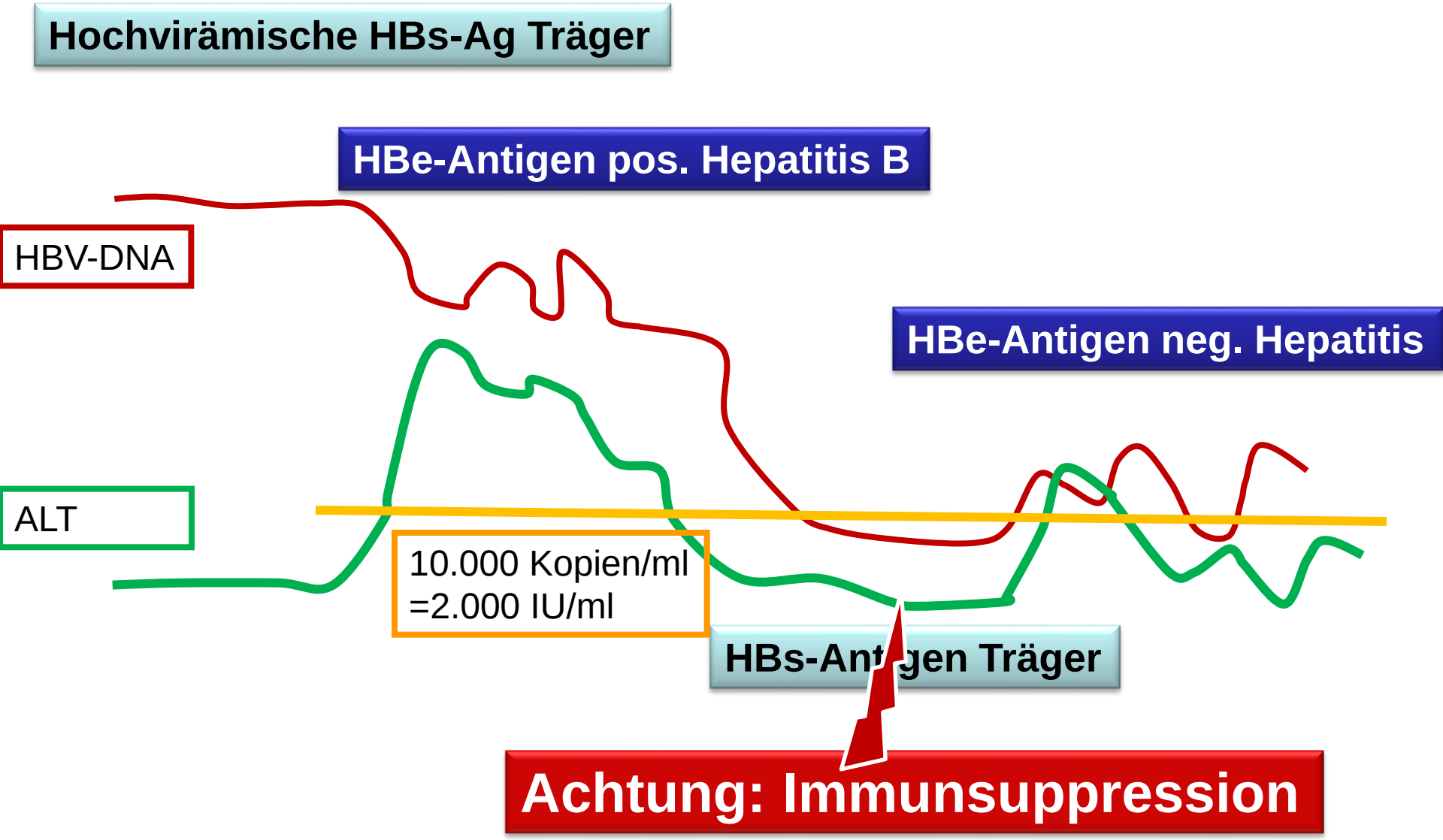
Ein virologisches Ansprechen reduziert das Risiko für klinische Endpunkte



Zoutendijk et al. Gut 2012

Hepatitis B= Dynamischer Verlauf

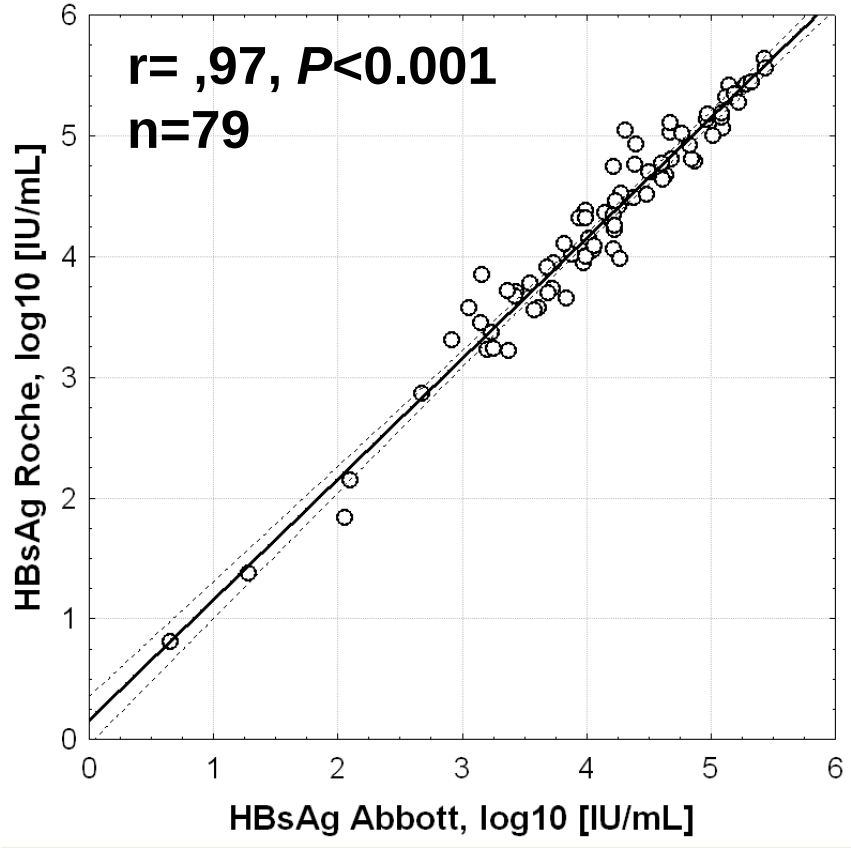
Deutsche Leberstiftung



HBsAg Quantifizierung

Roche

Elecsys® Systems

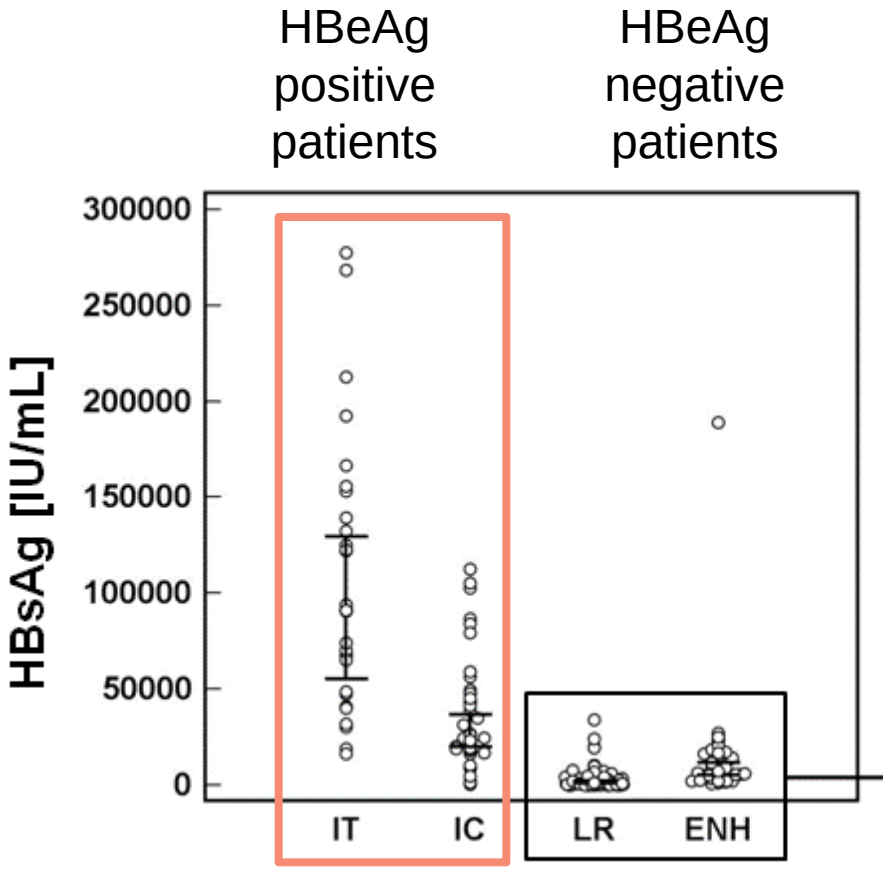


Abbott

ARCHITECT® SYSTEM

Wursthorn et al., J Clin Virol 2011

Unterschiedliche HBsAg-Spiegel in verschiedenen Phasen der Hepatitis B

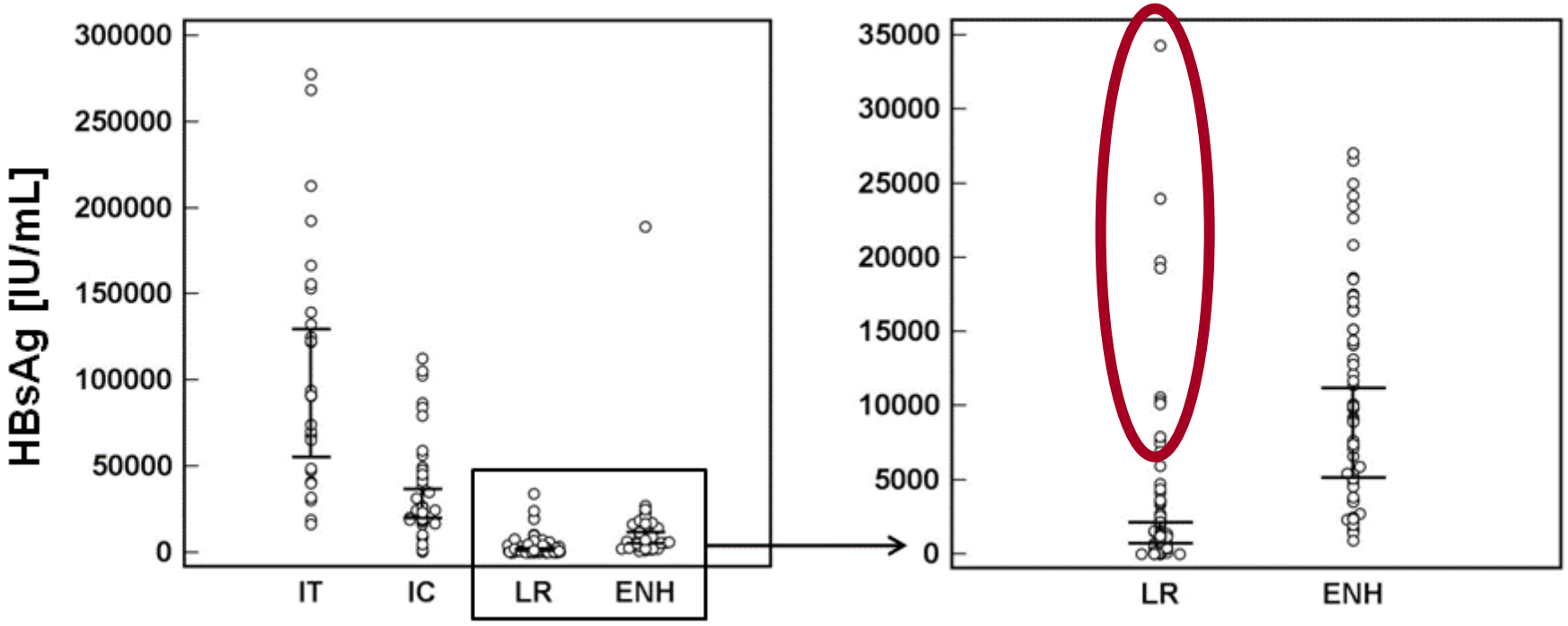


Jaroszewicz, Cornberg et al., J Hepatol 2010

Unterschiedliche HBsAg-Spiegel in verschiedenen Phasen der Hepatitis B

Identifizierung von Patienten mit Risiko für Reaktivierung (Cut-off 1000-3500 IU/ml)

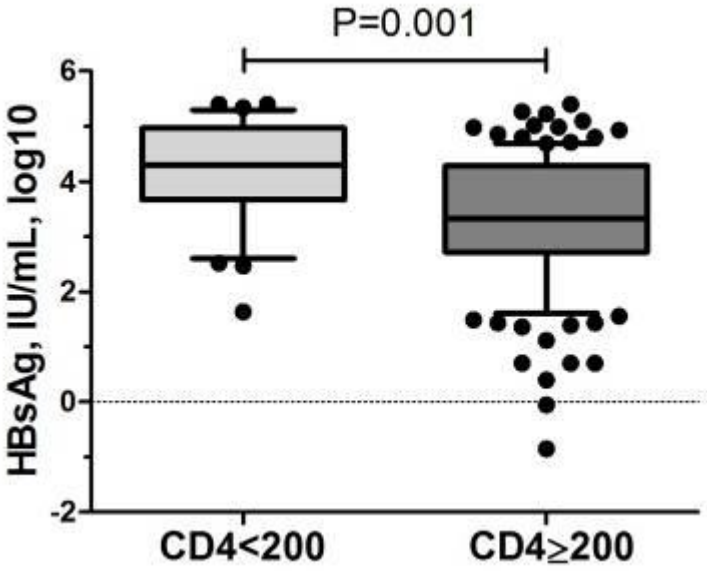
HBsAg carrier
vs.
HBeAg negative Hepatitis



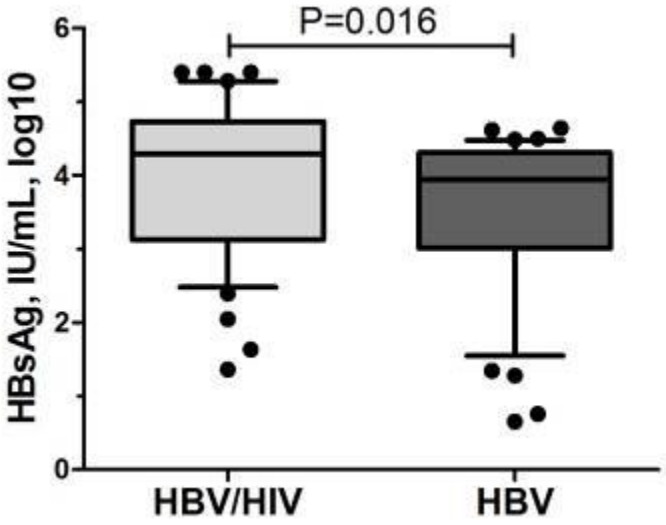
Jaroszewicz, Cornberg et al., J Hepatol 2010

HBsAg levels
in patients with HIV infection

qHBsAg correlates with CD4



HBsAg higher in HIV

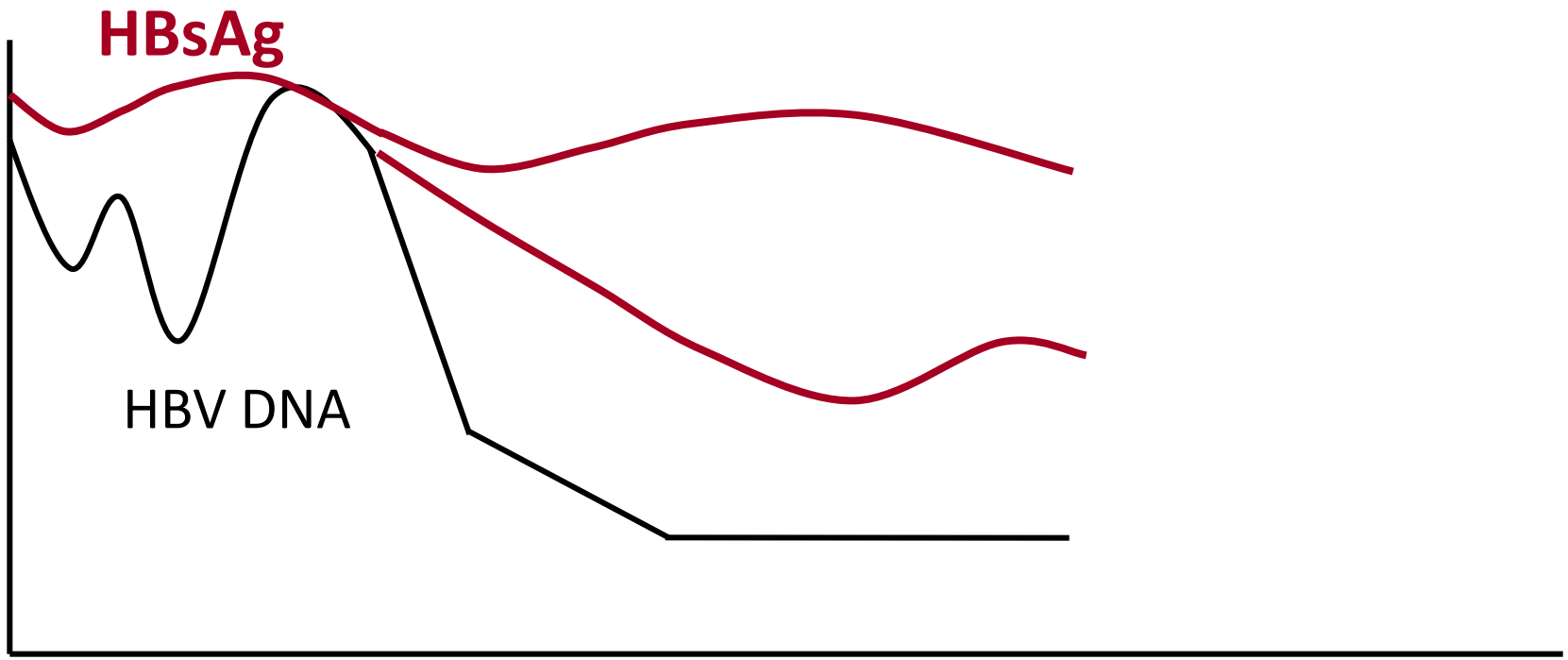


HBV-DNA gleich

Jaroszewicz, Cornberg et al. Plos One 2012

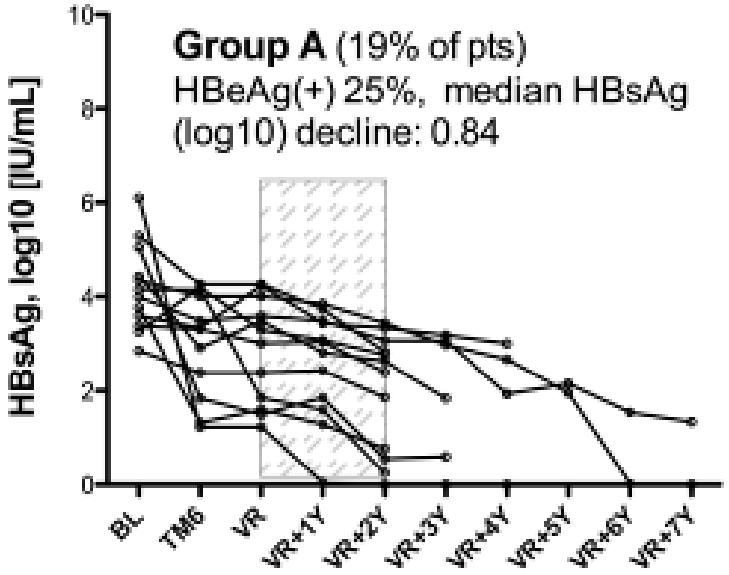
HBsAg Quantifizierung zum Monitoring des Therapieansprechens

Antivirale Therapie

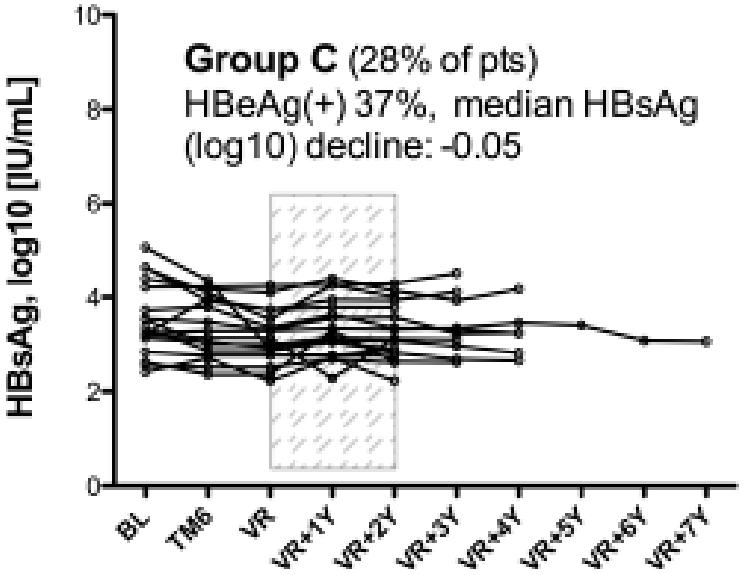


Identifizierung von Patienten, die eine serologische Ausheilung erreichen können

A) >0,5-log decline
6 Months after VR



C) <10% decline
6 months after VR



Jaroszewicz, Cornberg et al., Antiviral Therapy 2011

Hepatitisviren

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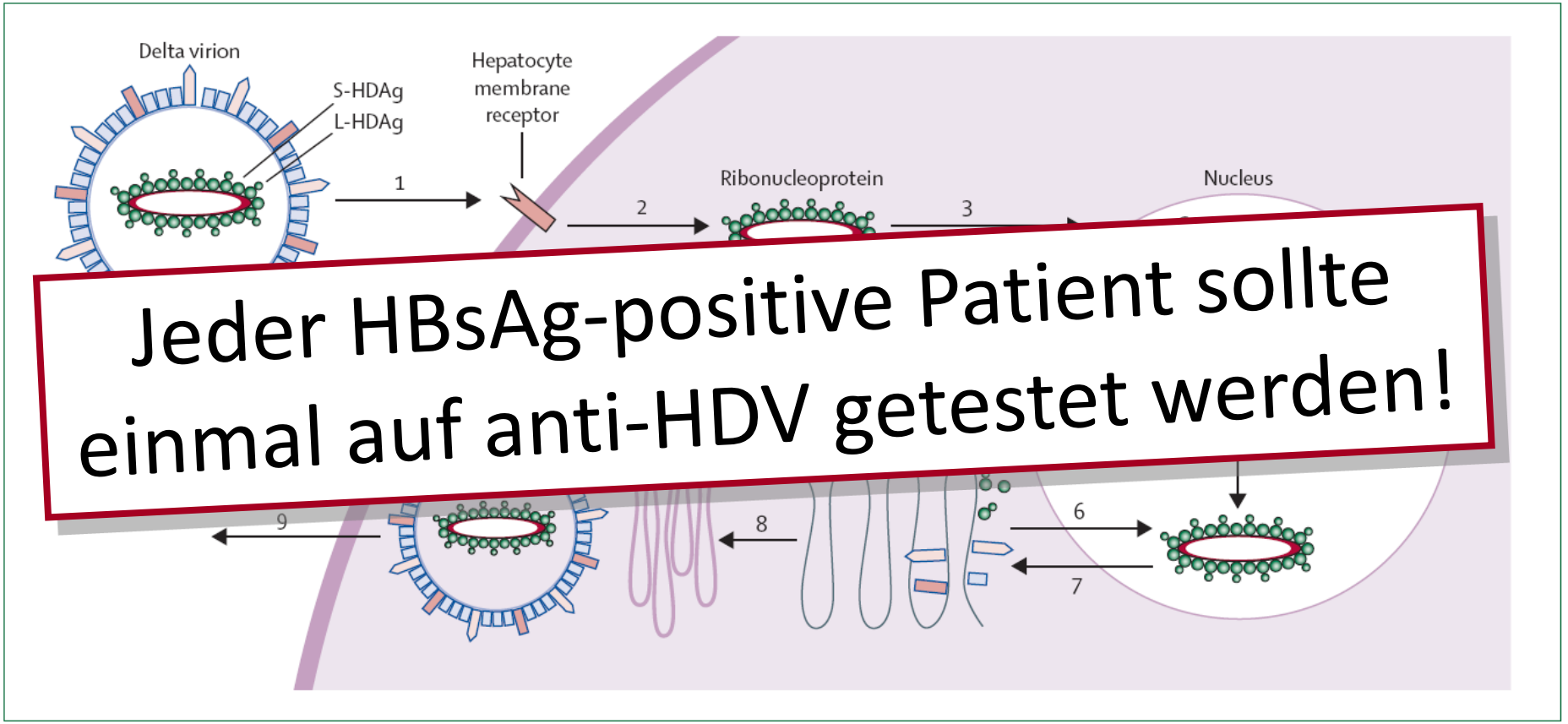
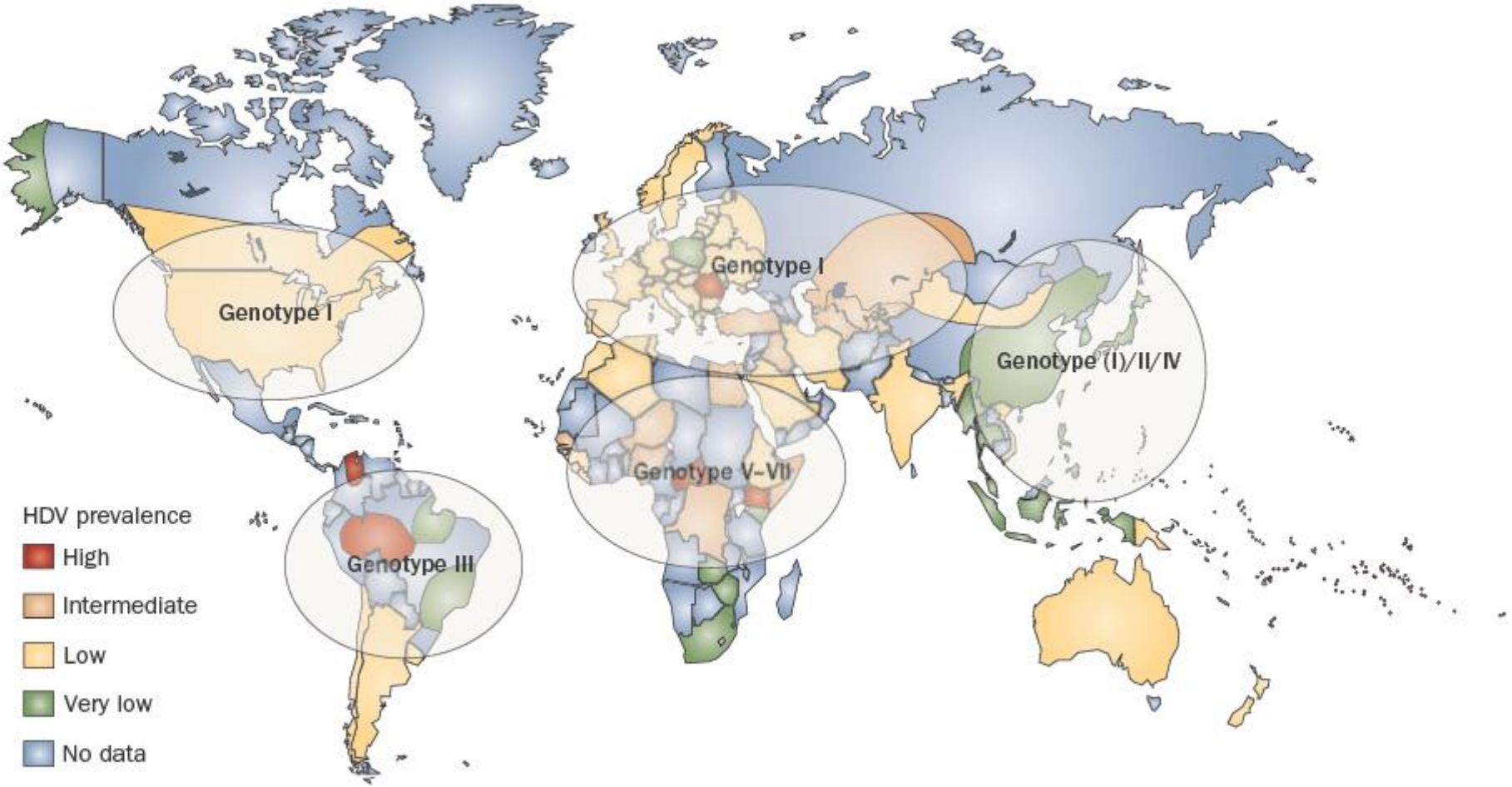
Das Hepatitis D Virus benutzt HBsAg als Hülle



Jeder HBsAg-positive Patient sollte einmal auf anti-HDV getestet werden!

Hughes, Wedemeyer and Harrison, The Lancet 2011

Epidemiologie der Hepatitis D



Wedemeyer & Manns, Nat Rev Gastroenterol 2010

Treatment of Hepatitis Delta with PEG-IFNa-2a: ~25% Sustained HDV RNA clearance

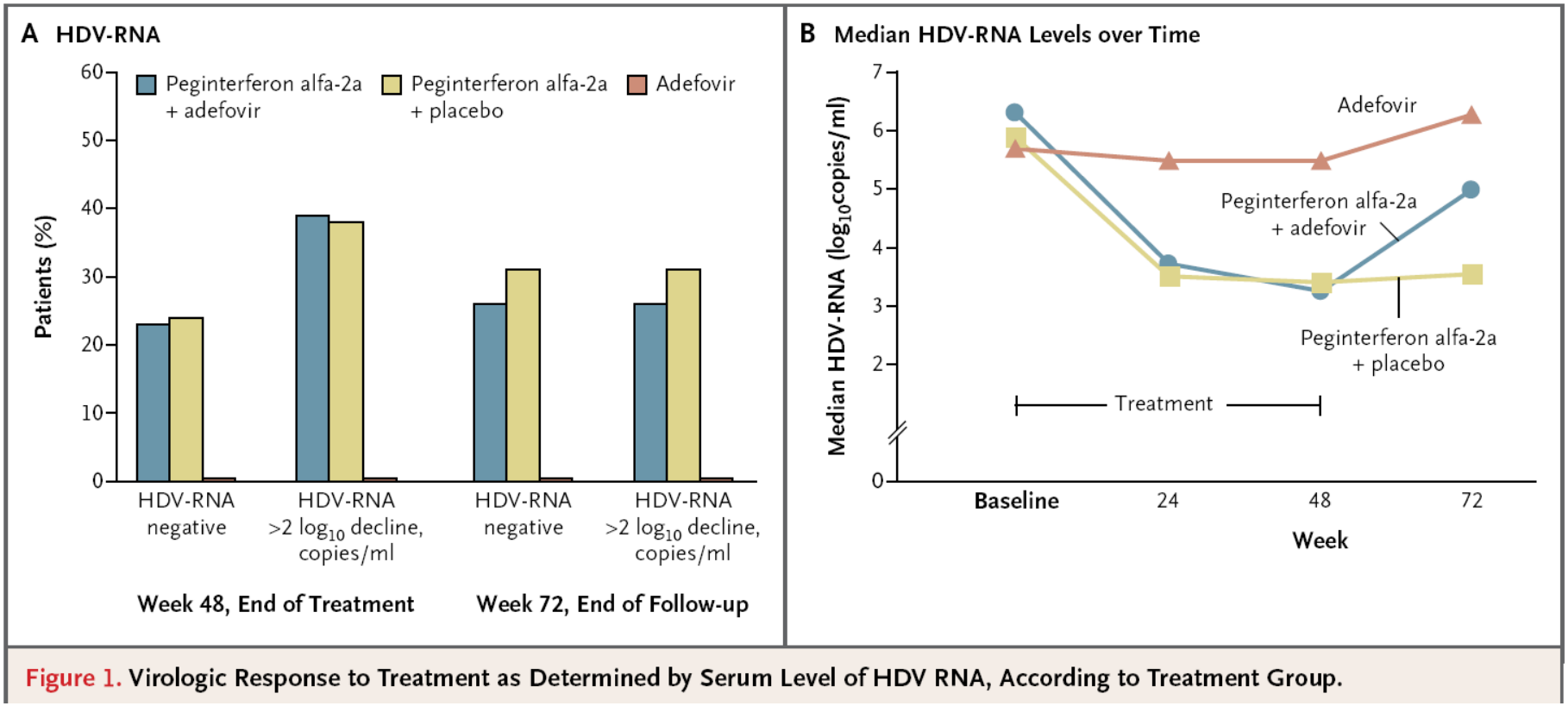


Figure 1. Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.

Wedemeyer et al. NEJM 2011

Hepatitisviren

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Hepatitis E	Balayan	1980	RNA

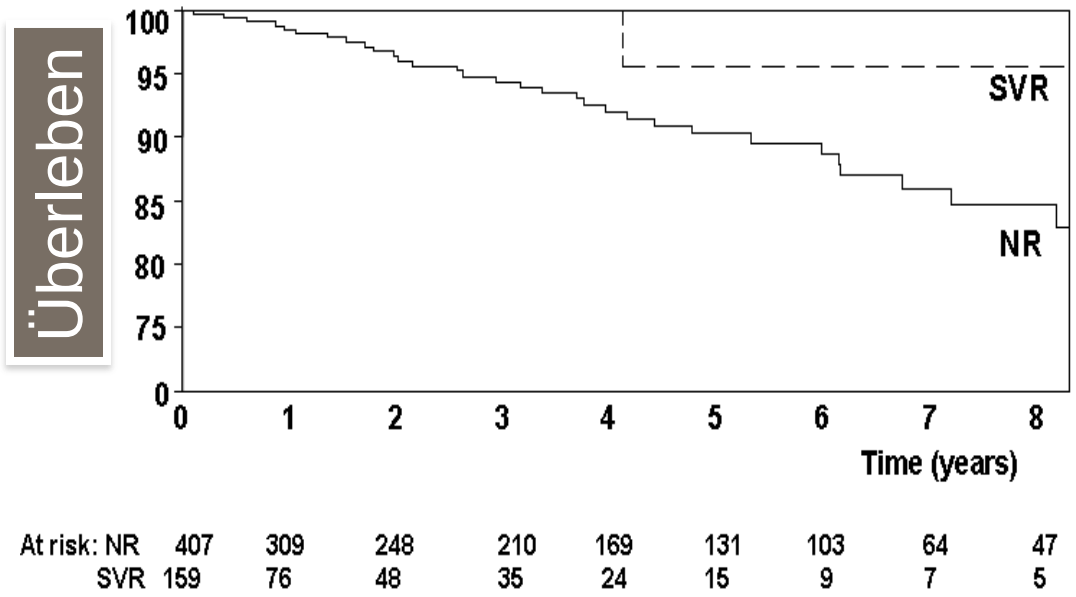

RESPEKT!
DU HAST ABER GANZ SCHÖN ZUGELEGT...
ICH WACHSE EBEN MIT MEINEN AUFGABEN....
PENG!!!
Quelle:
Deutsche Leberstiftung, Das Leber-Buch

Eine erfolgreiche Therapie der chronischen Hepatitis C verlängert das Überleben

479 HCV Patienten
mit Ishak F4-6
5 Zentren Europa und Kanada

→

70% Non-Responder
30% Responder



Veldt, Heathcote, Wedemeyer et al., Ann Intern Medicine 2007

Chronische Hepatitis C:

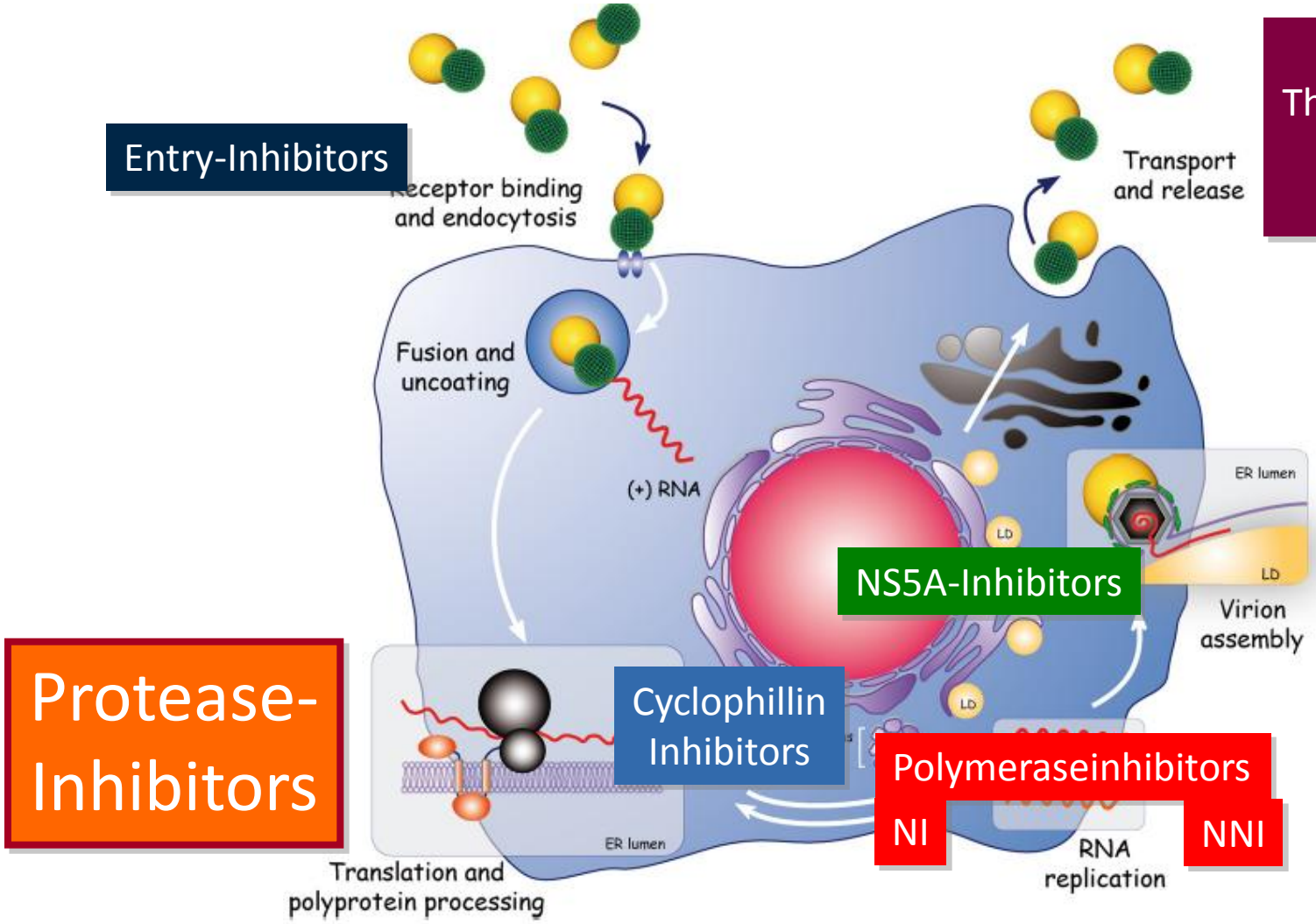
Standardtherapie bis Sommer 2011

Chronische Hepatitis C: Therapie

- PEG-Interferon alpha2a (Pegasys) (180µg)
  PEG-Interferon alpha2b (PegIntron) (1,5µg/kg)
  +
  Ribavirin 800-1200 (1400) mg

  Genotyp 1/4: (24)-48(-72) Wochen: **SVR 40-50%**
  Genotyp 2/3: (16-)24(-48) Wochen: **SVR 60-90%**

Neue Therapieoptionen



Popescu C-L & Dubuisson J. *Biol Cell* 2009;102:63-74.

Boceprevir (Victrelis)

FDA Zulassung 13.5.2011

Europa: 18.7.2011

4x200 mg alle 7-9h

mit Mahlzeit

(3X4 TABLETTEN)

Telaprevir (Incivo)

FDA Zulassung 23.5.2011

Europa: 20.9.2011

2x325 mg alle 7-9h

mit Mahlzeit

(3X2 TABLETTEN)

Behandlung der Hepatitis C: HCV Protease-Inhibitoren

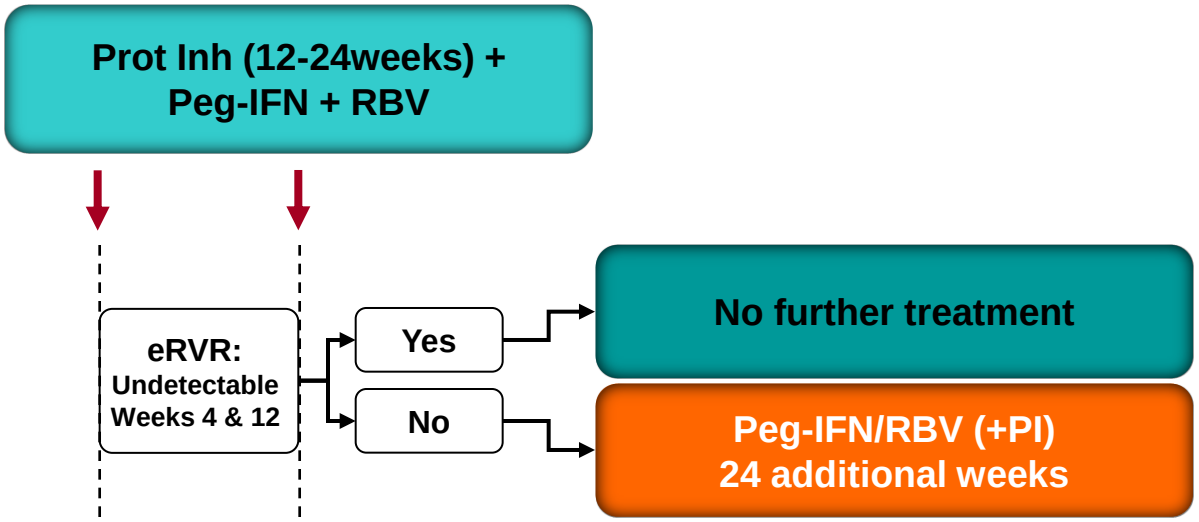
- Sehr starke antivirale Aktivität!
  (HCV-RNA Abfall 3-5 Log innerhalb von 3-7 Tagen)
- Entwickelt nur gegen den HCV Genotyp 1!
- Sehr schnelle Entwicklung von Resistenzen, wenn als Monotherapie eingesetzt
- Kreuzresistenzen!
  (kein Wechsel möglich, keine Kombination sinnvoll)

Neue Standardtherapie der Hepatitis C

- PEG-IFNa + Ribavirin wird weiterhin als Basistherapie benötigt!
- Beide PEG-IFNa-Präparate können mit beiden PIs eingesetzt werden!
- Die Therapiedauer richtet sich nach dem frühem Ansprechen zu Woche der PI-Therapie: 24 vs. 48 Wochen (“Response-guided-Therapy”)

Protease Inhibitor-Therapie der Hepatitis C

Response Guided Therapy!



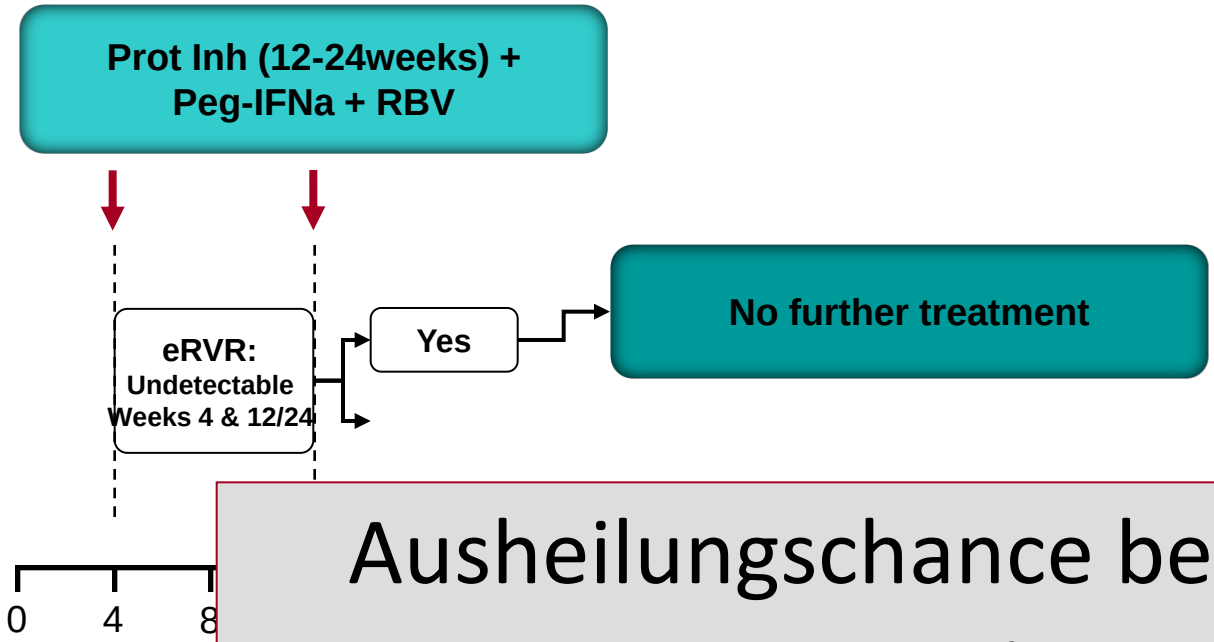
Stopp-Regeln!

Telaprevir: 1000 IU/ml week 4

Boceprevir: 100 IU/ml week 12

Protease Inhibitor-Therapie der Hepatitis C

45-65% der Patienten können kürzer behandelt werden



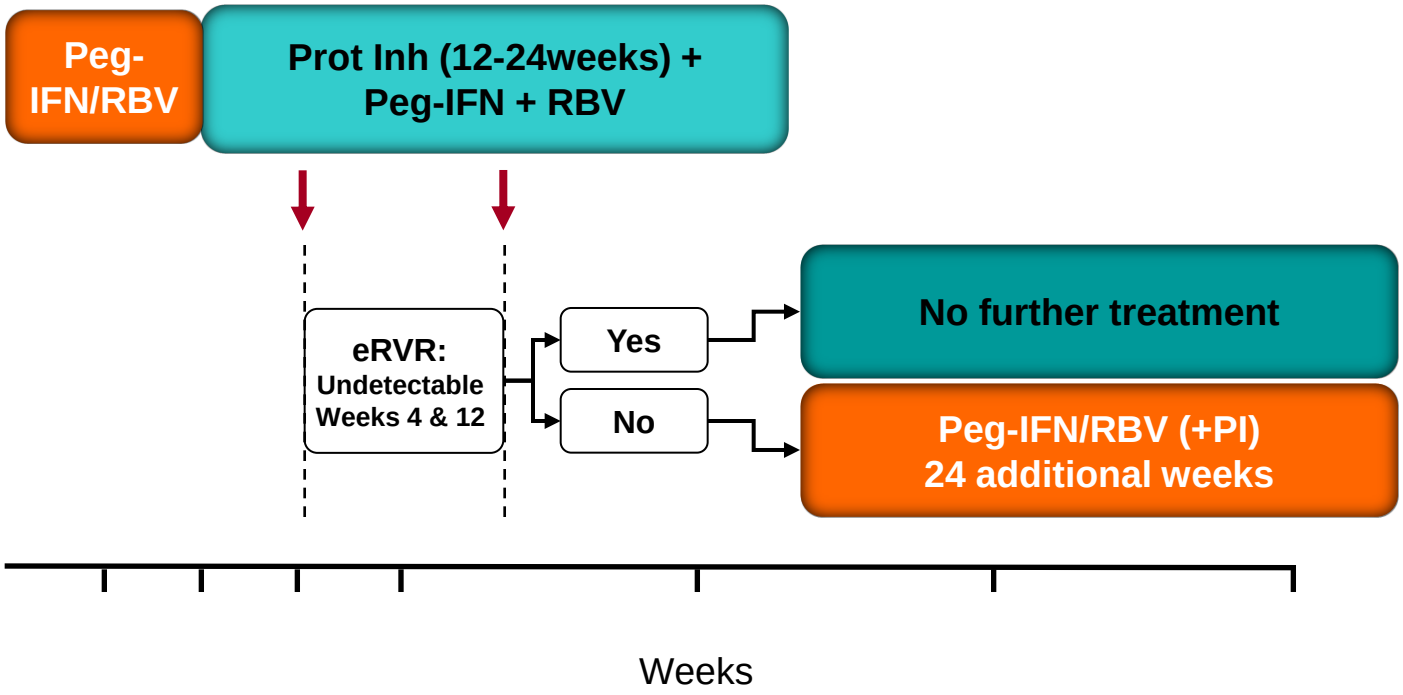
Ausheilungschance bei eRVR: >90%

Neue Standardtherapie der Hepatitis C

- PEG-IFNa + Ribavirin wird weiterhin als Basistherapie benötigt!
- Beide PEG-IFNa-Präparate können mit beiden PIs eingesetzt werden!
- Die Therapiedauer richtet sich nach dem frühem Ansprechen zu Woche der PI-Therapie: 24 vs. 48 Wochen (“Response-guided-Therapy”)
- PEG-IFN/RBV Lead-In Therapie

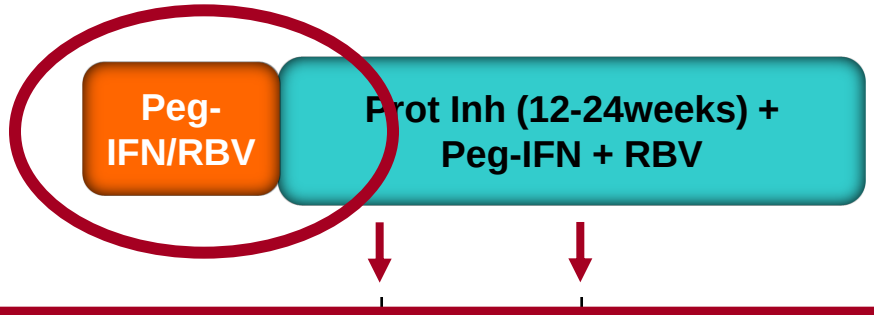
Triple Therapy with Protease Inhibitors

Response Guided Therapy!
+ Lead-in Phase



Triple Therapy with Protease Inhibitors

Response Guided Therapy!
+ Lead-in Phase

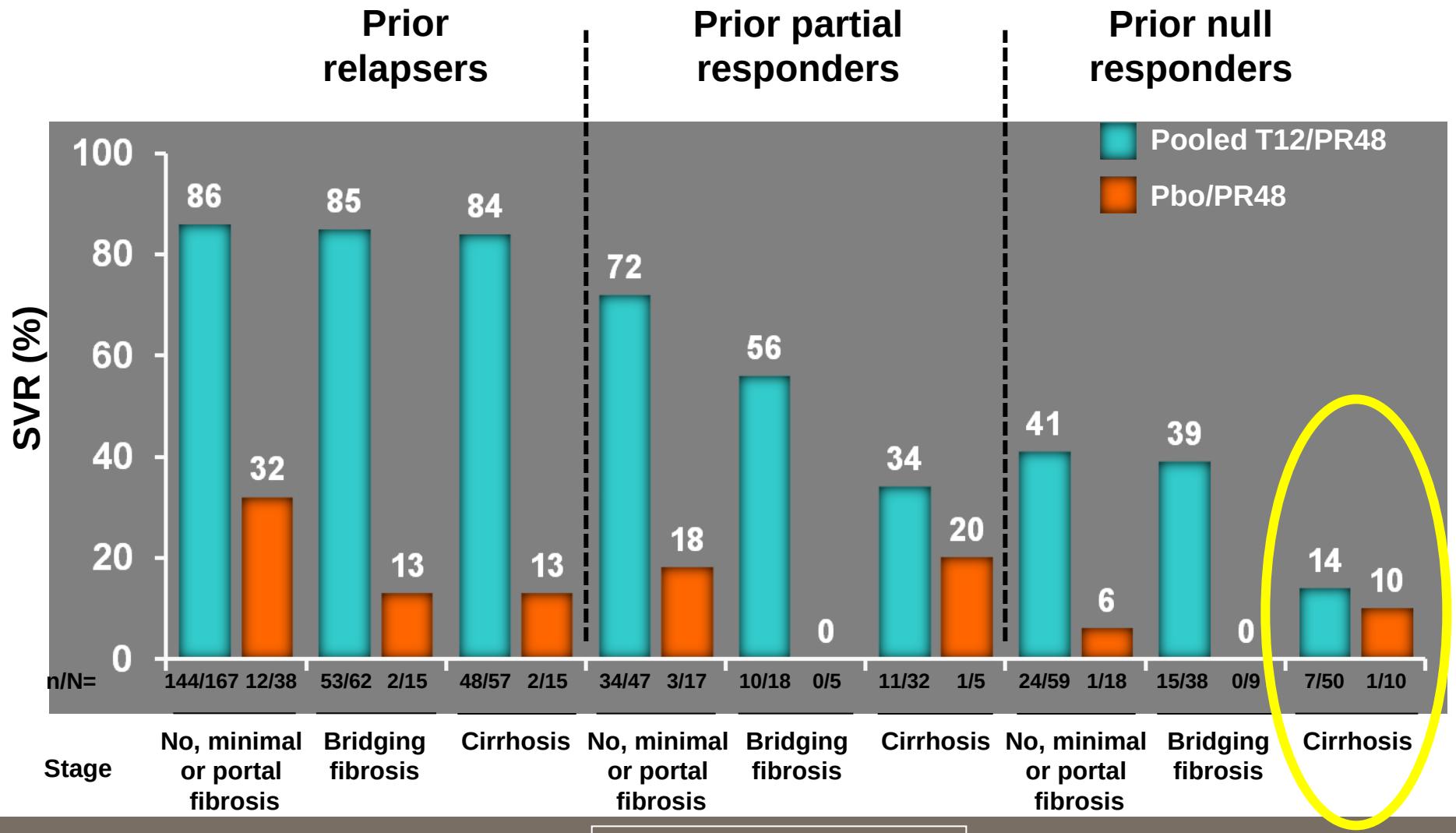


- Identifizierung von IFNa/RBV “intoleranten” Patientne
- Identifizierung von nicht-adhärenten Patienten
- Identifizierung von „Super-Responder“ (keine PI-Therapie notwendig)
- Identifizierung von Patienten mit fehlendem IFN-Ansprechen

Ergebnisse Phase III Studien

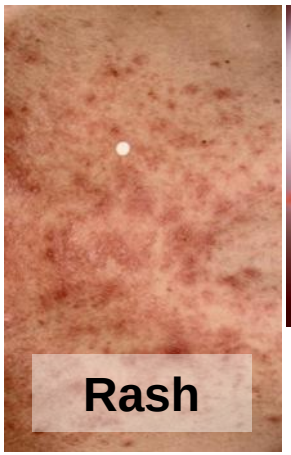
- Steigerung der **Ausheilungsraten** für bisher unbehandelte Patienten um 30% auf **70-80%!**
- "relapse-Patienten": SVR 75-90%
- Nonresponderpatienten: ca. 30% SVR
- Nonresponderpatienten mit Zirrhose: **<15%!**

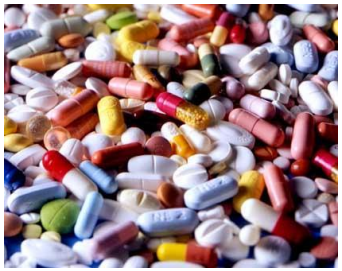
Telaprevir-Realize Studie
SVR by Baseline Fibrosis Stage and Prior Response

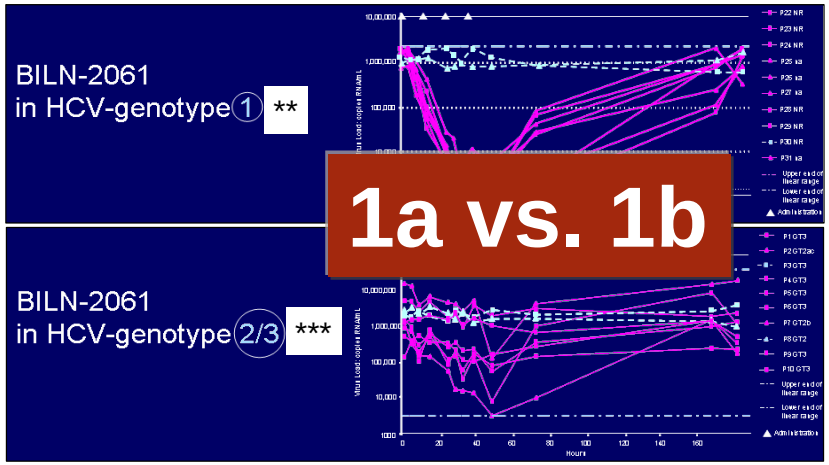


Zeuzem et al. NEJM 2011

Neue Proteaseinhibitoren – alles gut?

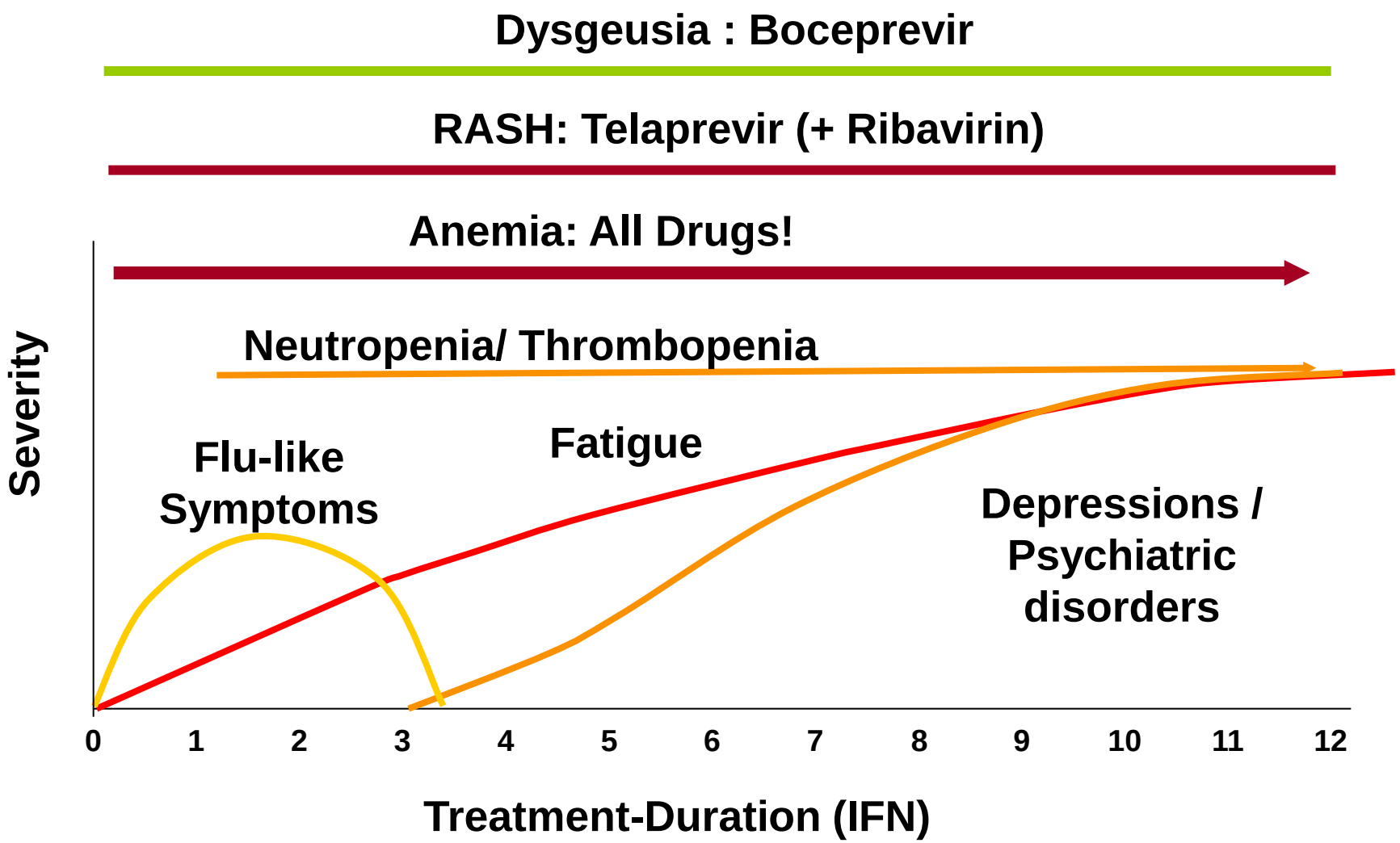




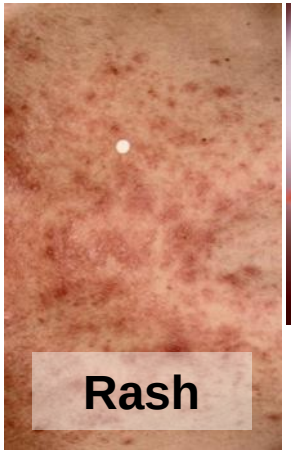


** Hinrichsen et al. *Gastroenterology* 2004; *** Reiser et al. *Hepatology*. 2005

Side effecs during triple therapy

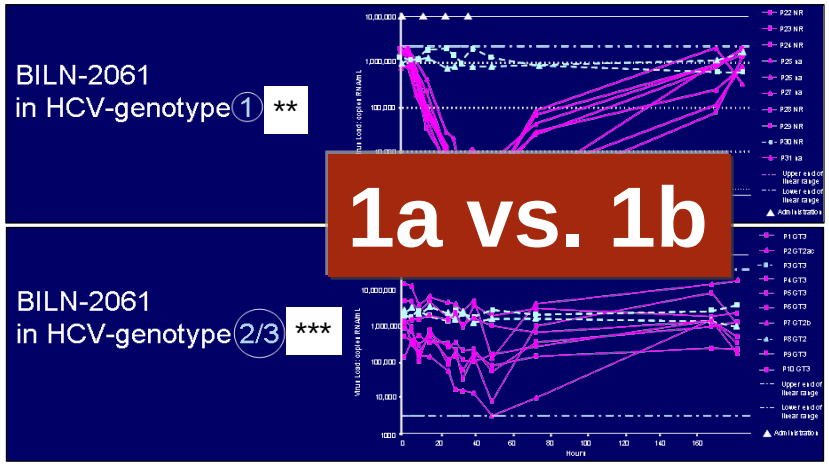


Neue Proteaseinhibitoren – alles gut?



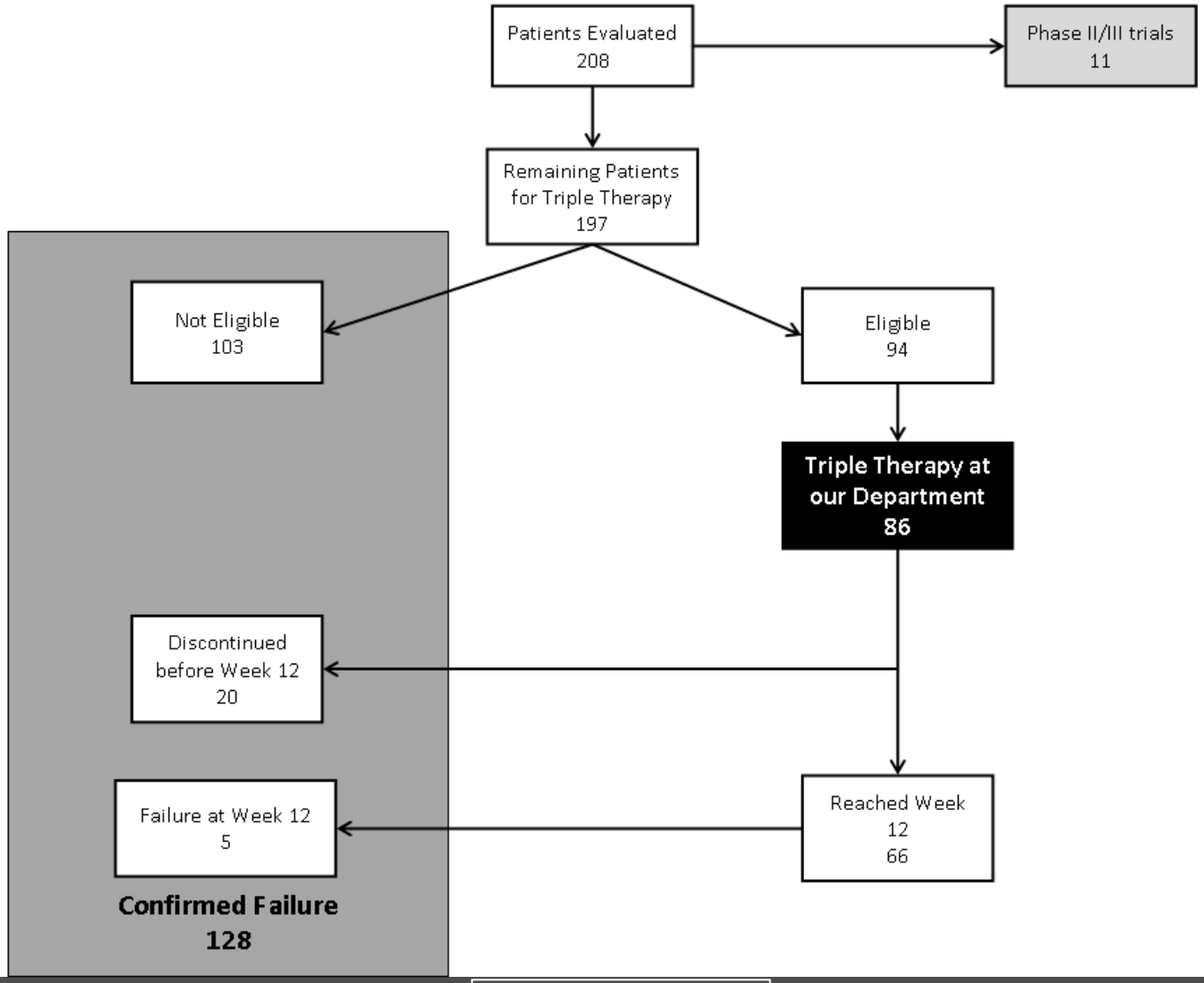
Niedrigere Ansprechraten
-Zirrhose
- Nonresponder
- African Americans

Medikamenteninteraktionen!
Aufwendigere Diagnostik
Kosten!



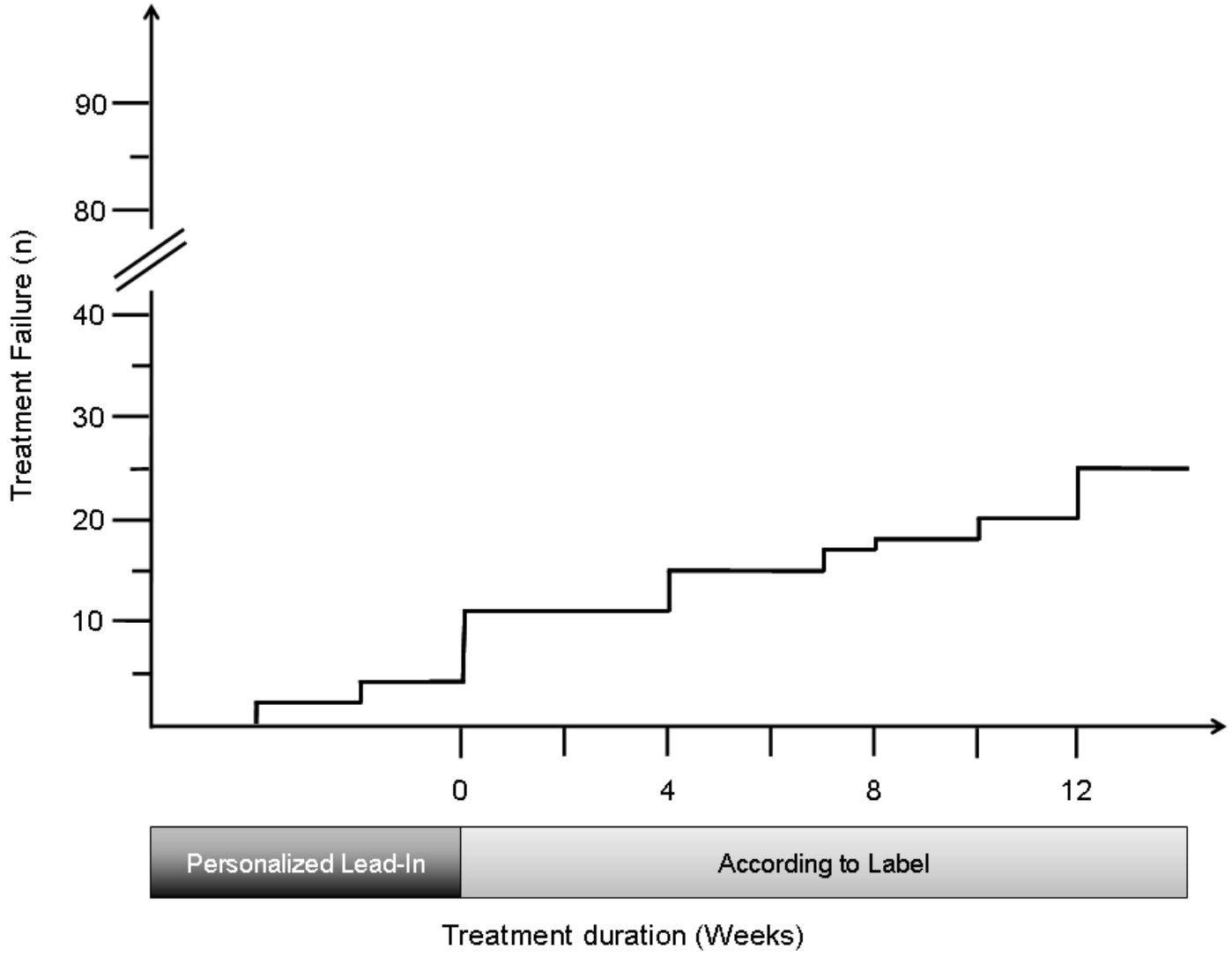
** Hinrichsen et al. *Gastroenterology* 2004; *** Reiser et al. *Hepatology*. 2005

Proteaseinhibitortherapie der Hepatitis C: Erfahrungen MHH



Maasoumy et al.

Proteaseinhibitortherapie der Hepatitis C: Erfahrungen MHH



Maasoumy et al.

… und wann kommen die IFN-freien Therapien?

The NEW ENGLAND JOURNAL of MEDICINE

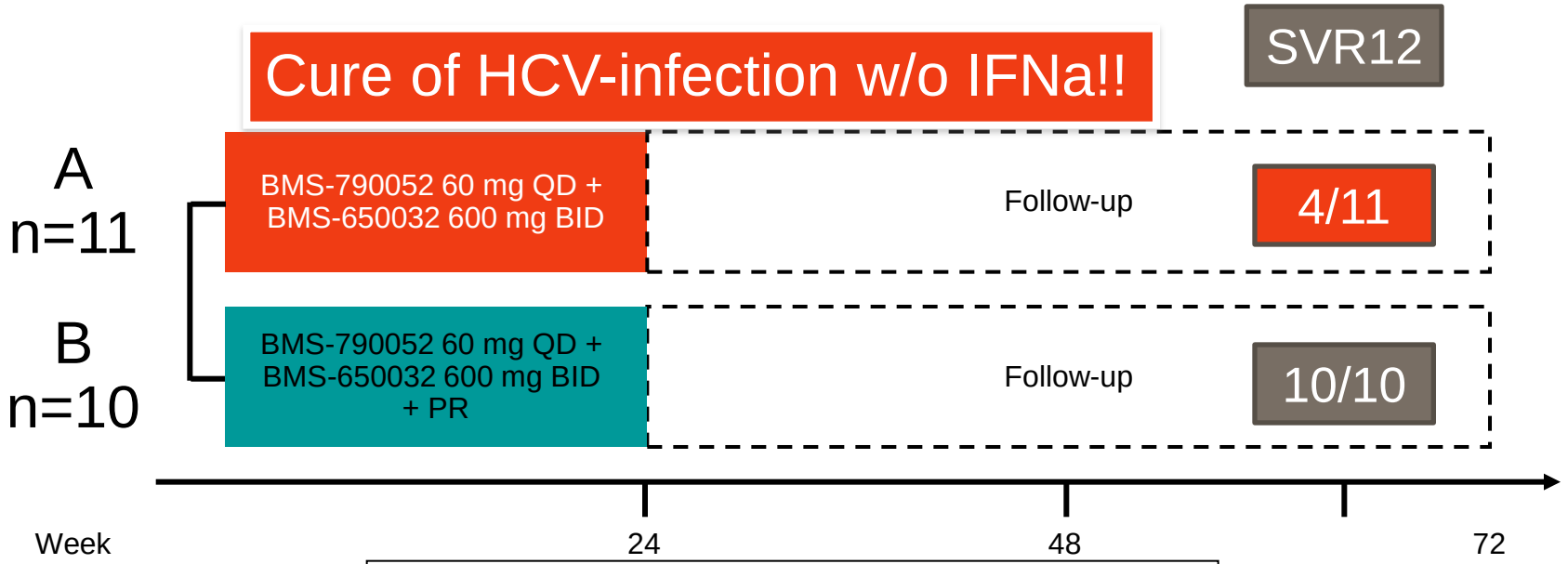
ORIGINAL ARTICLE

Preliminary Study of Two Antiviral Agents for Hepatitis C Genotype 1

Anna S. Lok, M.D., David F. Gardiner, M.D., Eric Lawitz, M.D., Claudia Martorell, M.D., Gregory T. Everson, M.D., Reem Ghalib, M.D., Robert Reindollar, M.D., Vinod Rustgi, M.D., Fiona McPhee, Ph.D., Megan Wind-Rotolo, Ph.D., Anna Persson, Ph.D., Kurt Zhu, Ph.D., Dessislava I. Dimitrova, M.D., Timothy Eley, Ph.D., Tong Guo, Ph.D., Dennis M. Grasela, Pharm.D., Ph.D., and Claudio Pasquinelli, M.D., Ph.D.

BMS-790052 + BMS-650032: AI447011

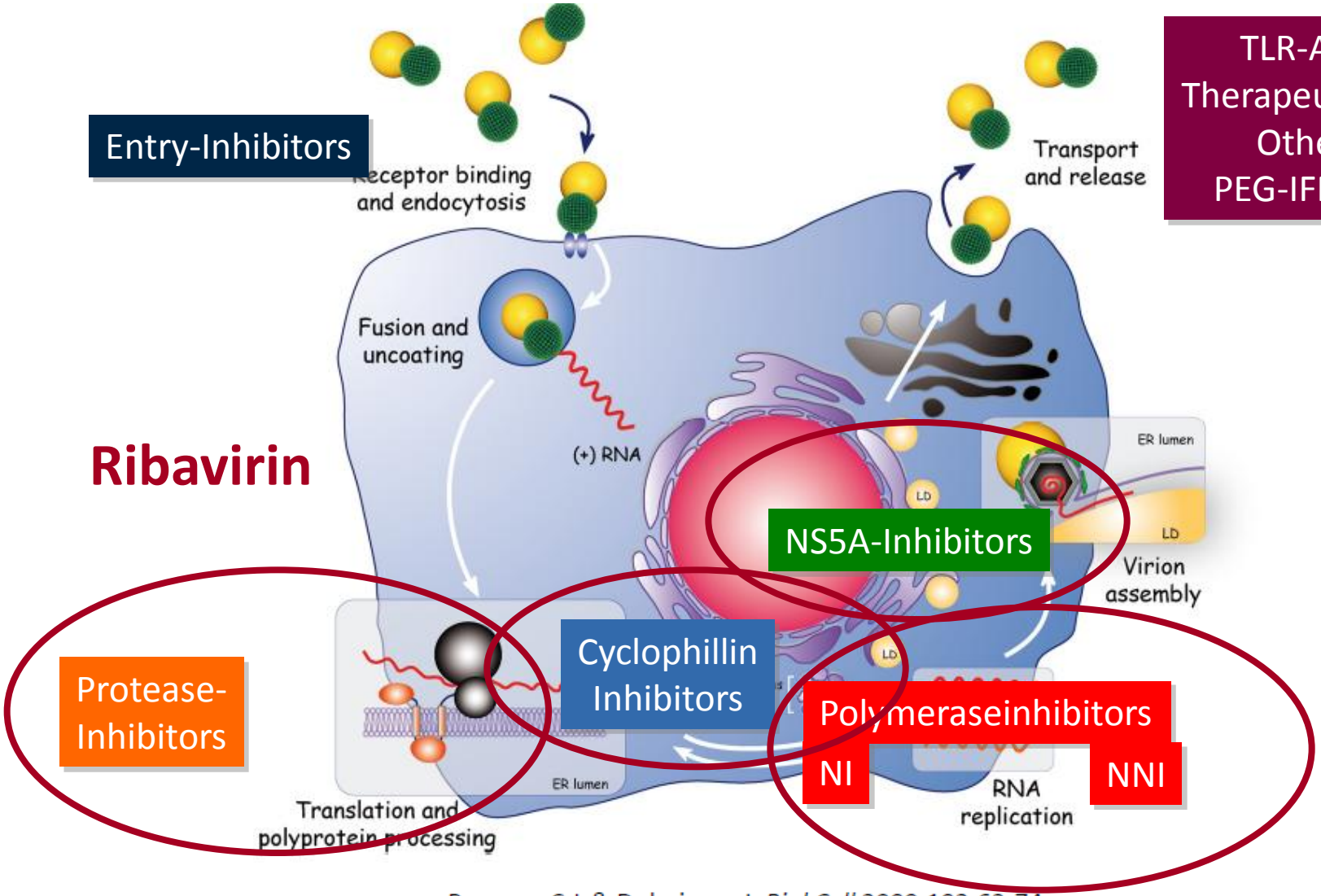
AI447011: phase IIa study of BMS-790052 plus BMS-650032, with or without PegIFN/RBV, for 24 weeks in **HCV genotype-1 null responders**



Genotype 1a: cure in 2/9 patients
Genotype 1b: cure in 2/2 patients

Lok A, et al. NEJM 2012

IFN-free DAA combination therapies

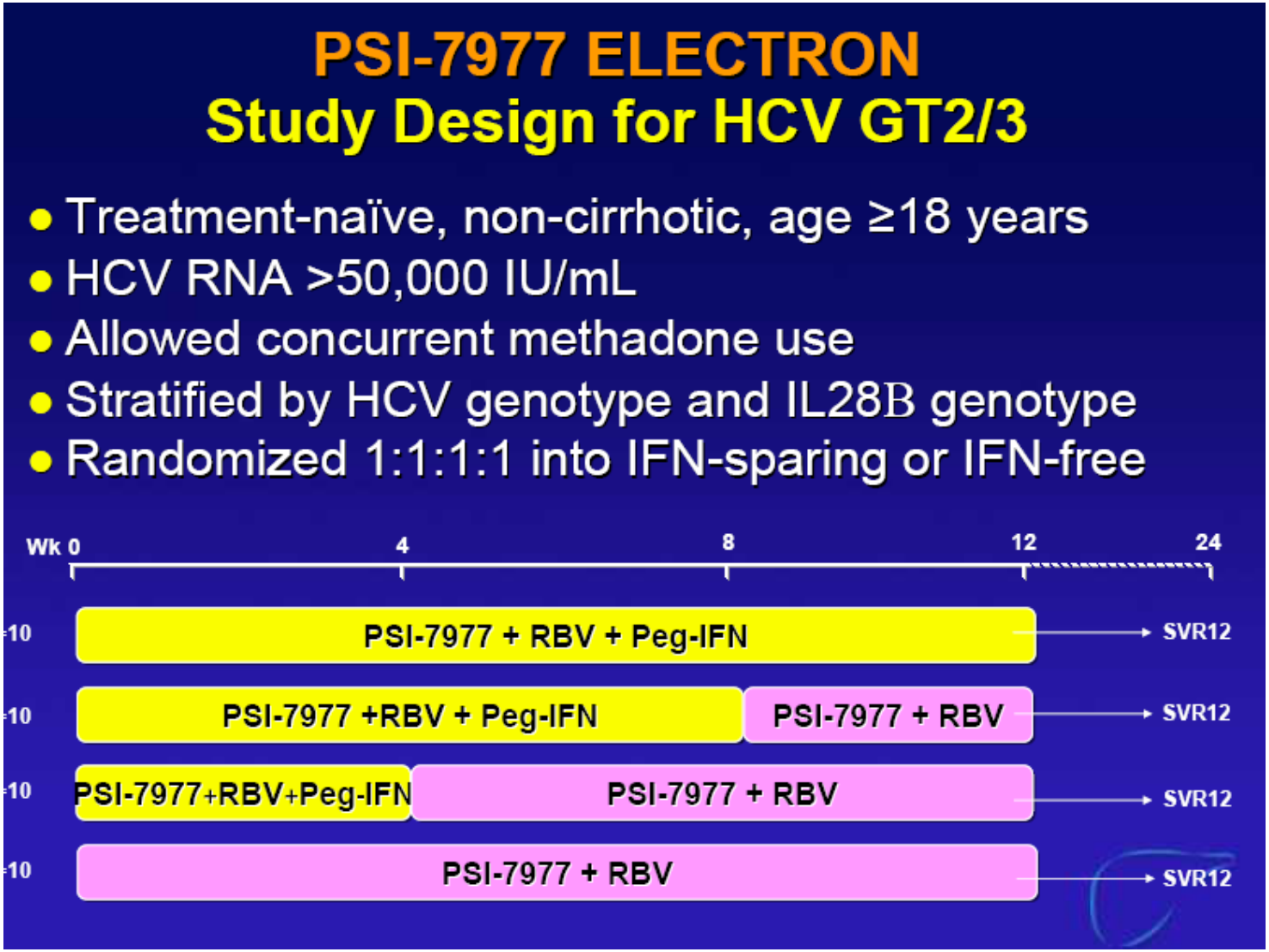


Popescu C-L & Dubuisson J. *Biol Cell* 2009;102:63-74.

DAAs against HCV in clinical development

Protease-Inhibitors *„2nd wave“ vs.* *„2nd generation“*	Potency Pan-genotype efficacy Resistance Barrier	+++ +/++ +/++
Polymerase Inhibitors Non-nucleos(t)ides	Potency Pan-genotype efficacy Resistance Barrier	+-++ + (-) + (-)
Polymerase Inhibitors nucleos(t)ides	Potency Pan-genotype efficacy Resistance Barrier	+-+++ +++ ++/+++
NS5A Inhibitors	Potency Pan-genotype efficacy Resistance Barrier	+++ +/++ +/++
Cyclophilin Inhibitors	Potency Pan-genotype efficacy Resistance Barrier	+/++ +++ ++

GS7-7977: Sofosbuvir



Ed Gane et al., AASLD 2011

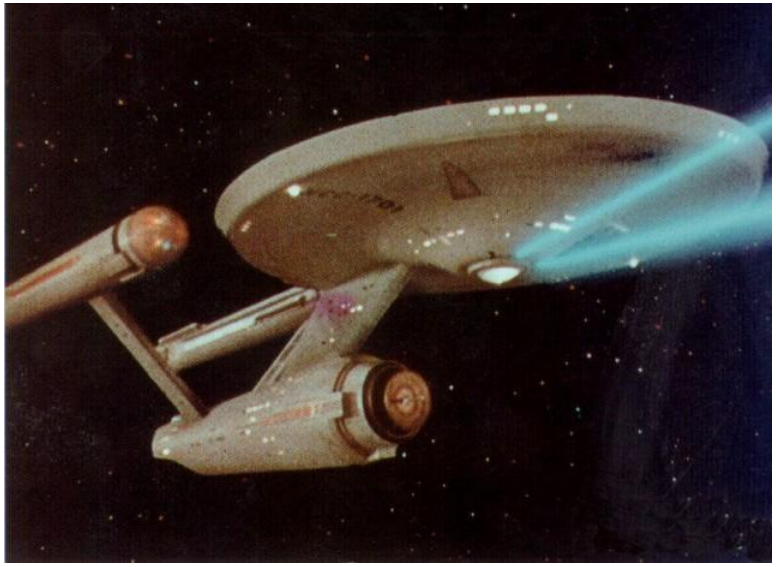
PSI 7977
100% cure in HCV Genotyp 2/3 Patients!!

Time Wk	PSI-7977 RBV 12 weeks PEG		PSI-7977 RBV 8 weeks PEG		PSI-7977 RBV 4 weeks PEG		PSI-7977 RBV NO PEG	
	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
2	9/11	82	7/8	88	8/9	89	8/10	80
4	11/11	100	10/10	100	9/9	100	10/10	100
8	11/11	100	10/10	100	9/9	100	10/10	100
12	11/11	100	10/10	100	9/9	100	10/10	100
SVR4	11/11	100	10/10	100	9/9	100	10/10	100
SVR8	11/11	100	10/10	100	9/9	100	10/10	100
SVR12	11/11	100	10/10	100	9/9	100	10/10	100
SVR24	6/6	100	5/5	100	5/5	100	4/4	100

Ed Gane et al., AASLD 2011

Treatment of Hepatitis C

2012



2014/5

HCV-Therapie 2015:

Kein Interferon

Direkt-Antivirale Substanzen für alle Genotypen

Behandlungsdauer i.d.R. 3 Monate

Heilungsraten >85%