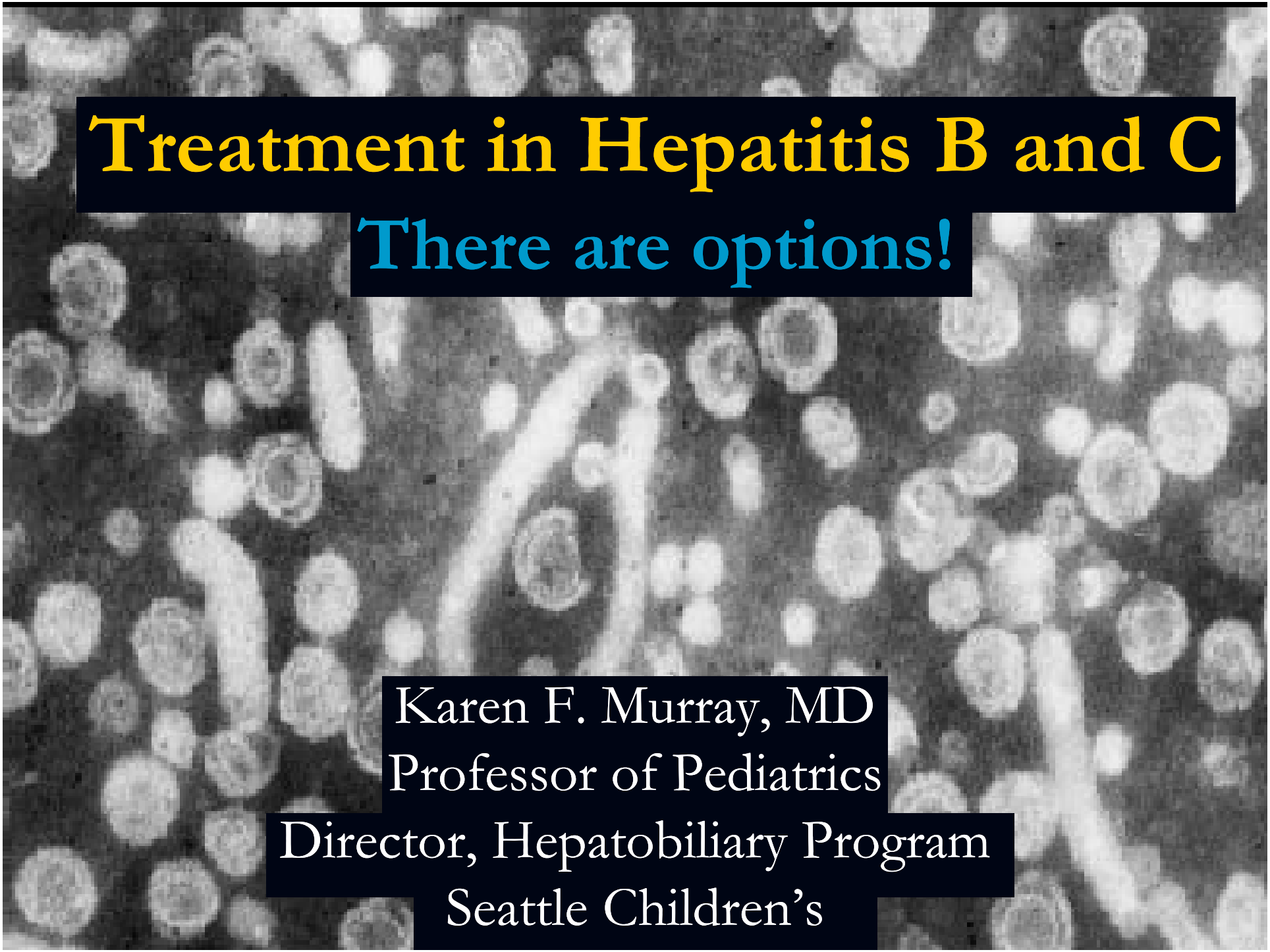
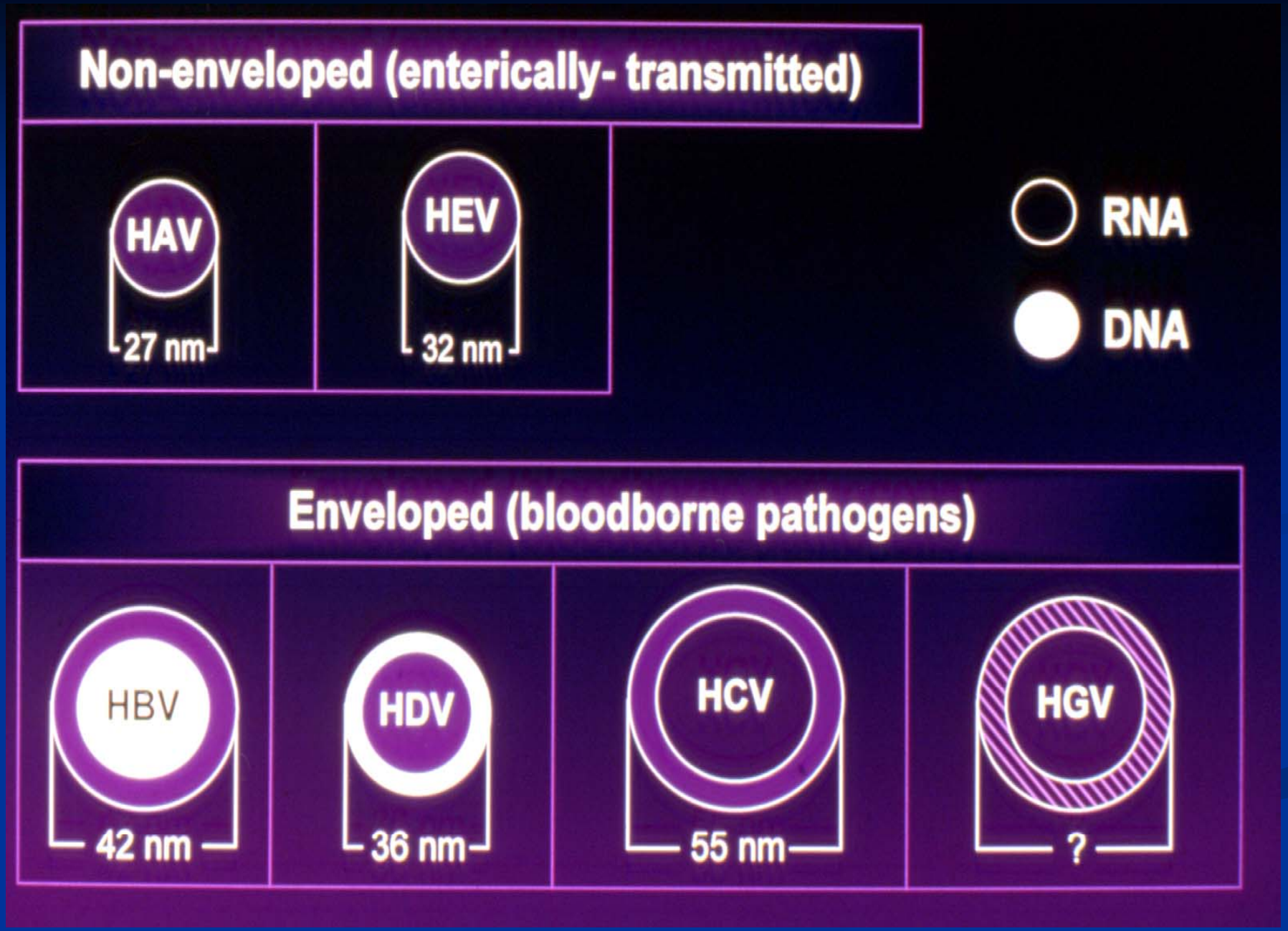


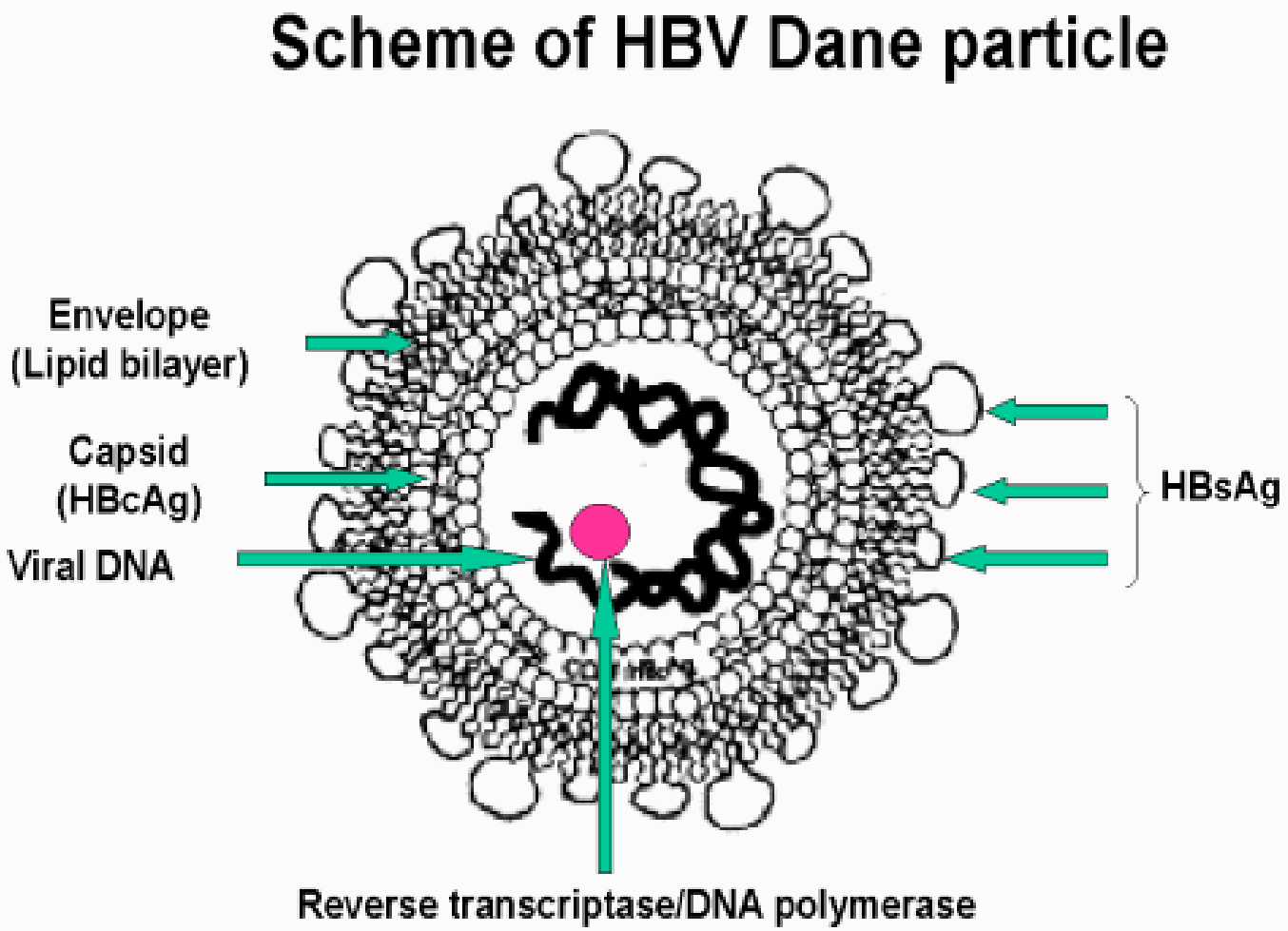
Treatment in Hepatitis B and C

There are options!

Karen F. Murray, MD
Professor of Pediatrics
Director, Hepatobiliary Program
Seattle Children's


Non-enveloped (enterically- transmitted)
HAV
27 nm
HEV
32 nm
RNA
DNA
Enveloped (bloodborne pathogens)
HBV
42 nm
HDV
36 nm
HCV
55 nm
HGV
?

Hepatitis B Virus

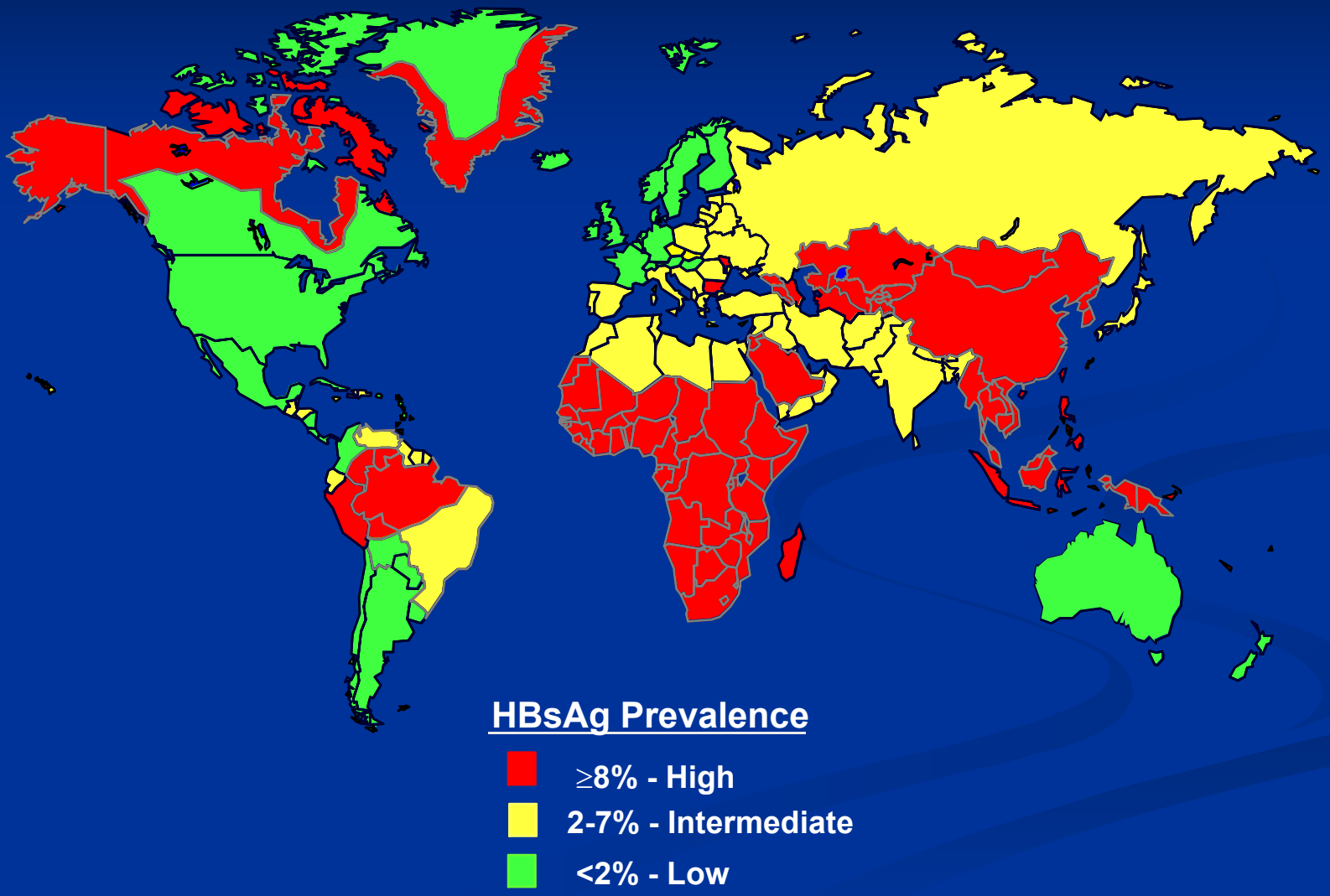


Epidemiology and natural history

- 400 million people with HBV world wide
- Chronic hepatitis B (CHB) is defined as HBsAg+ for more than 6 months
- 90% of children under age 4 years will remain persistently infected
- 15%-40% will develop serious sequelae during their lifetime: cirrhosis, hepatic decompensation, and hepatocellular carcinoma

Gish RG and AC Gadano. J Vir Hep. 2006.

Geographic Distribution of Chronic HBV Infection



Phases of Chronic Hepatitis B Infection

Phase	Labs and Histology	Note
Immune Tolerant	DNA>20,000 IU/ml ALT normal HBsAg and HBeAg detectable Minimal liver inflammation and fibrosis	• Antiviral therapies are generally ineffective • Risk of drug resistance if treated
Immune Active	DNA levels decline ALT elevated HBsAg and HBeAg remain detectable Liver inflammation and fibrosis can develop	• Most children still show no signs or symptoms of disease
Inactive HBsAg Carrier	DNA<2,000 IU/ml or undetectable ALT normalizes HBeAg undetectable, anti-HBe present No liver inflammation, fibrosis may regress	• Age at serocoversion appears to be influenced by HBV genotype • Risk of developing cirrhosis and HCC declines
Reactivation	DNA levels increase ALT normal or elevated HBeAg remains undetectable	• Occurs in 20-30 % of patients • eAg-negative disease • Usually due to a mutant virus

Haber, BA, et al. *Pediatrics*. published online Oct 5, 2009. (doi: 10.1542/peds.2009-0567)

Goals of Treatment

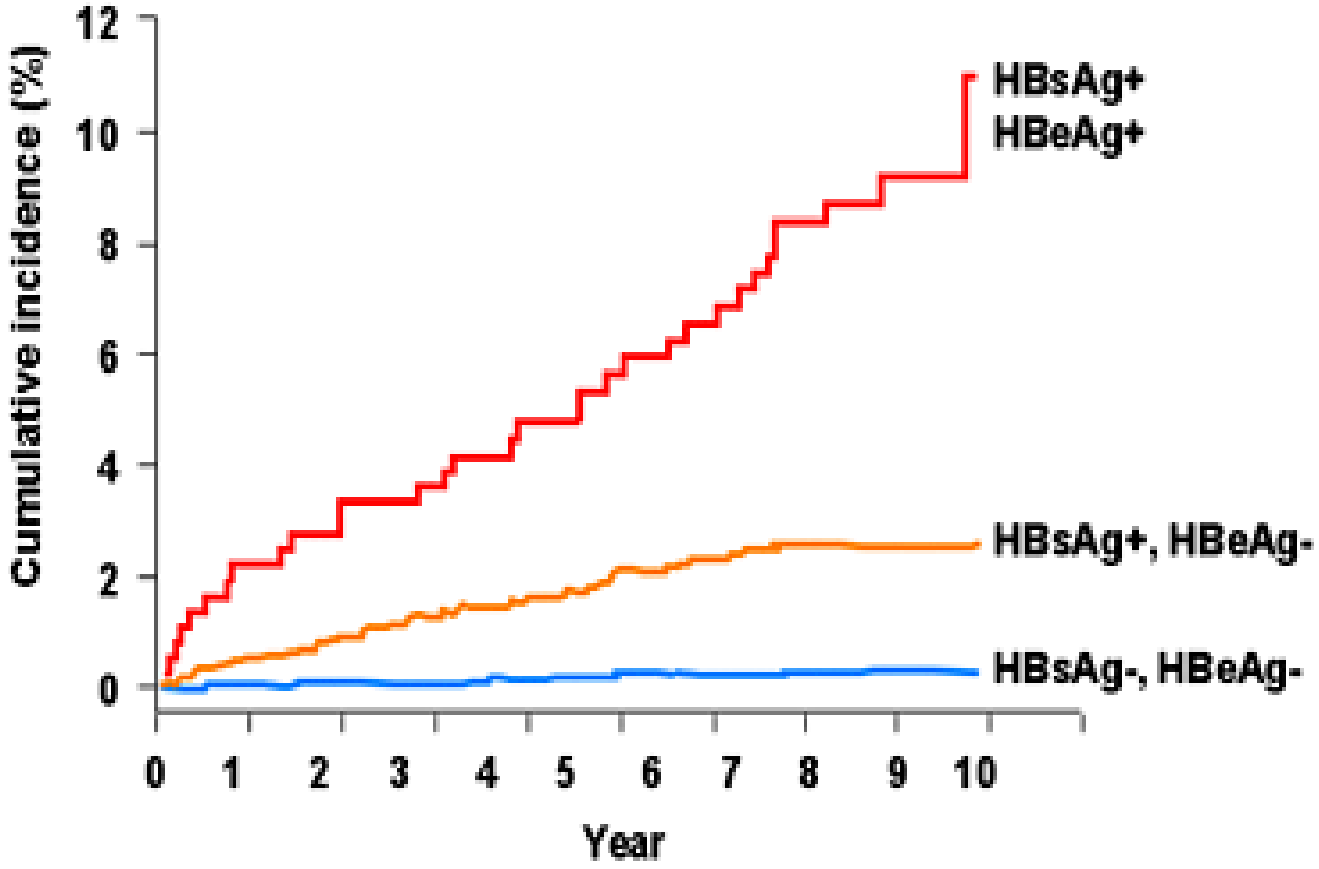
- Decrease risk of chronic liver disease/HCC
- Stabilize/improve the liver health
- Decrease transmission
- Decrease social stigma/isolation
- Eliminate HBV (clear HBsAg)

Measurable Goals of HBV Therapy

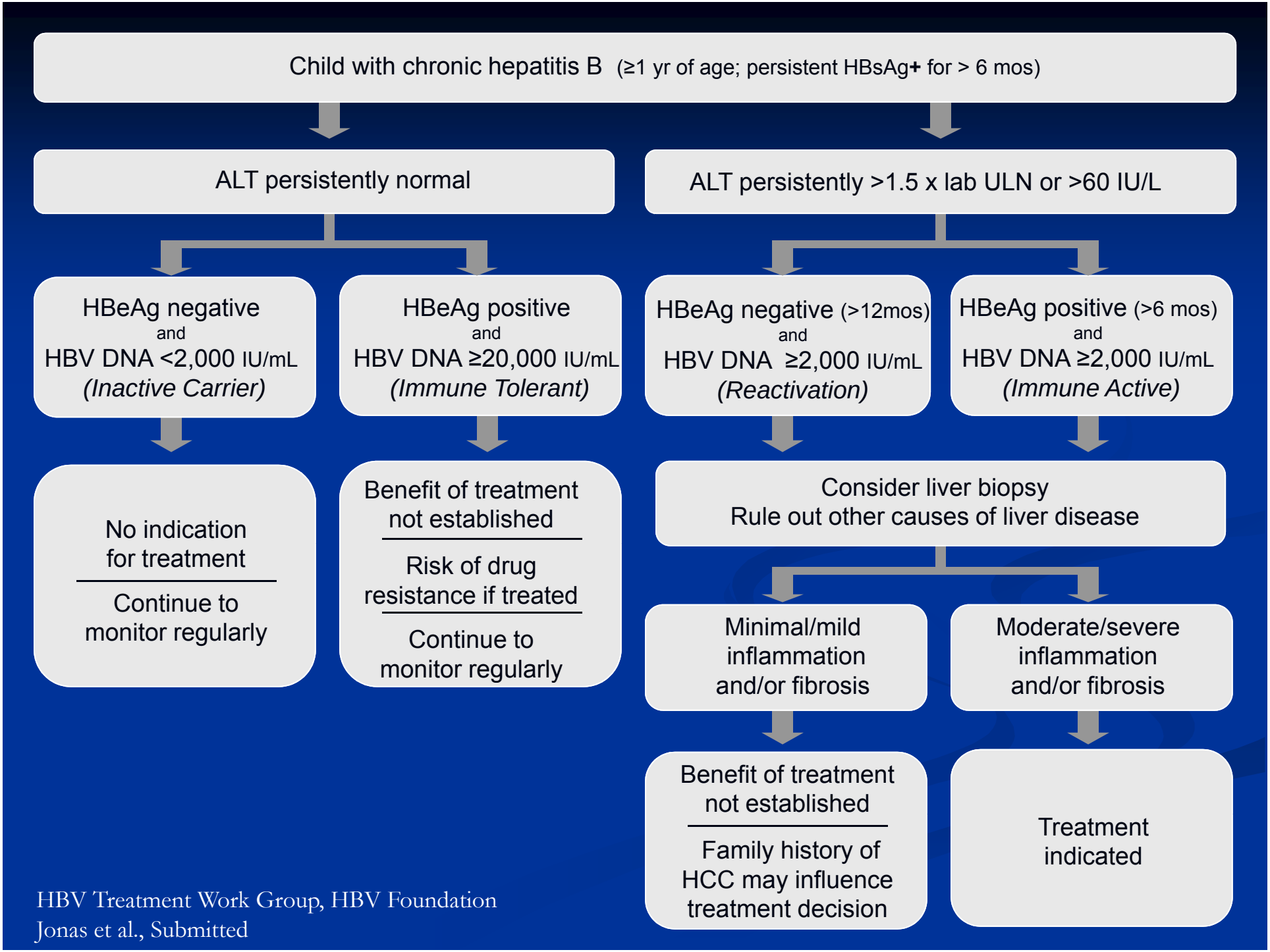
- In HBeAg+ patients
  - HBeAg loss and seroconversion
  - Decrease HBV DNA to $\leq$ 2000 IU/ml
    - Associated with improved long-term outcomes
- In HBeAg+/- patients
  - Normalize the serum aminotransferases
  - HBsAg loss and seroconversion ultimate form of HBV treatment success
    - Best predictor of durable viral suppression
    - Strongest indicator of best long term outcome, lowest risk of cirrhosis and liver cancer
    - Not achieved by the majority of patients

Slide modified from Dr. K Schwarz

HBeAg and the Risk of HCC

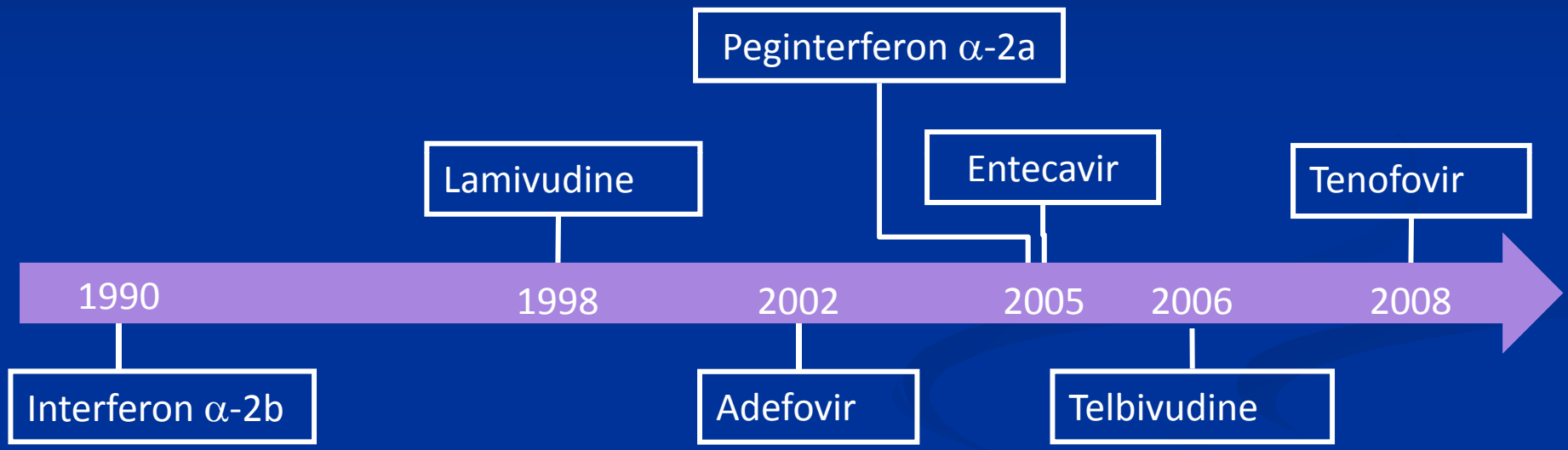


Yang HI, et al. N Engl J Med. 2002 Jul 18;347(3):168-74. Copyright © 2002 Massachusetts Medical Society. All rights reserved.



HBV Treatment Work Group, HBV Foundation
Jonas et al., Submitted

Evolution of USA FDA-Approved HBV Therapy Over Time



Slide by Dr. K. Schwarz

Antiviral Therapy
USA FDA-Approved for Children

Drug	Labeled for	Note
Adefovir	≥ 12 years old	■ Less potent ■ Risk of drug resistance
Entecavir	≥ 16 years old	■ Older teens only
Interferon a-2b	≥ 1 year old	■ Potential adverse effects
Lamivudine	≥ 3 years old	■ Less potent ■ Risk of drug resistance

HBV Treatments Administration and Monitoring

- Interferon:
  - Subcutaneous injection thrice weekly (IFN) or weekly (Peg-IFN)
  - Monitoring discussed in HCV section
- Nucleos(t)ide analogues (Lamivudine, Adefovir):
  - Orally administered once daily
  - Well tolerated!
  - CBC, ALT – every 6 weeks
  - HBV DNA, HBeAg and Ab, Lipase (Lam) – every 3 months

Interferon Treatment for Chronic Hepatitis B in Children

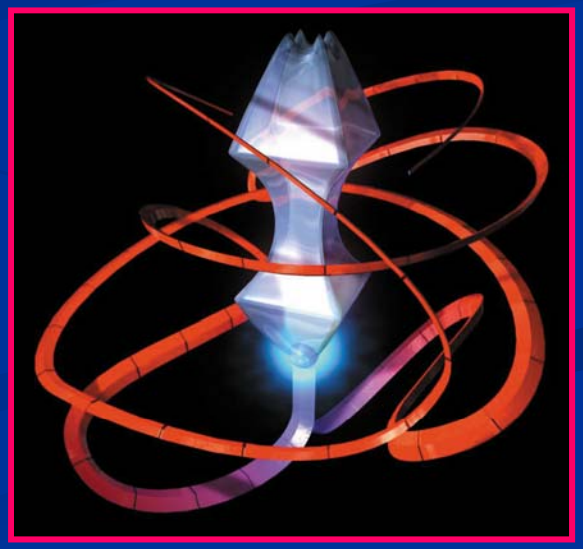
- IFNα 6 MU/m^2 3x/week for 6 months
- Dose reduction in 23% for neutropenia or fever
- Response:
  - HBeAg/DNA in 26% of treated (11% of controls)
  - HBsAg in 10% (1% of controls)

ALT normalized and biopsy improves in responders

Sokal et al: Gastroenterology 1998:114:988-995.

Interferon for Hepatitis B

- Relapse rate in HBeAg+ is 10-20%
- HBeAg - chronic hepatitis B:
  - DNA becomes negative* and ALT normalizes in ~25%
  - 12 months is better than 6 months of therapy
  - Relapse in 50% of responders
- Pegylated-IFN may be better



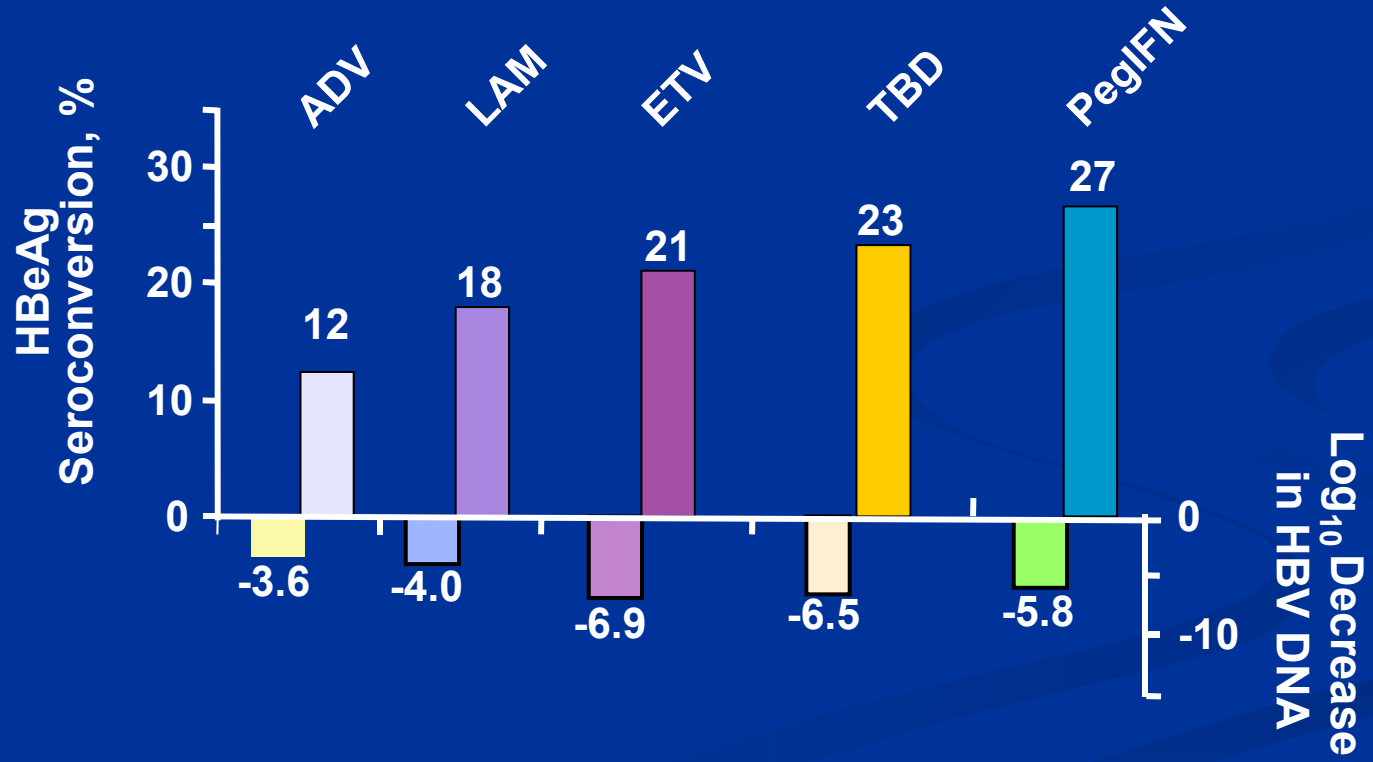
Treatment outcomes in HBV-Infected Children

	IFN-α (Sokal)	Lamivudine (Jonas)	Adefovir dipivoxil (Jonas)
HBeAg clearance	26%	23%	11%*
Suppression of HBV DNA	26%	23%	23%
Side effects	yes	no	no
Resistance to antiviral agent	no	19%	no
HBsAg clearance	10%	3%	0.5%

Slide adapted from Dr. K Schwarz

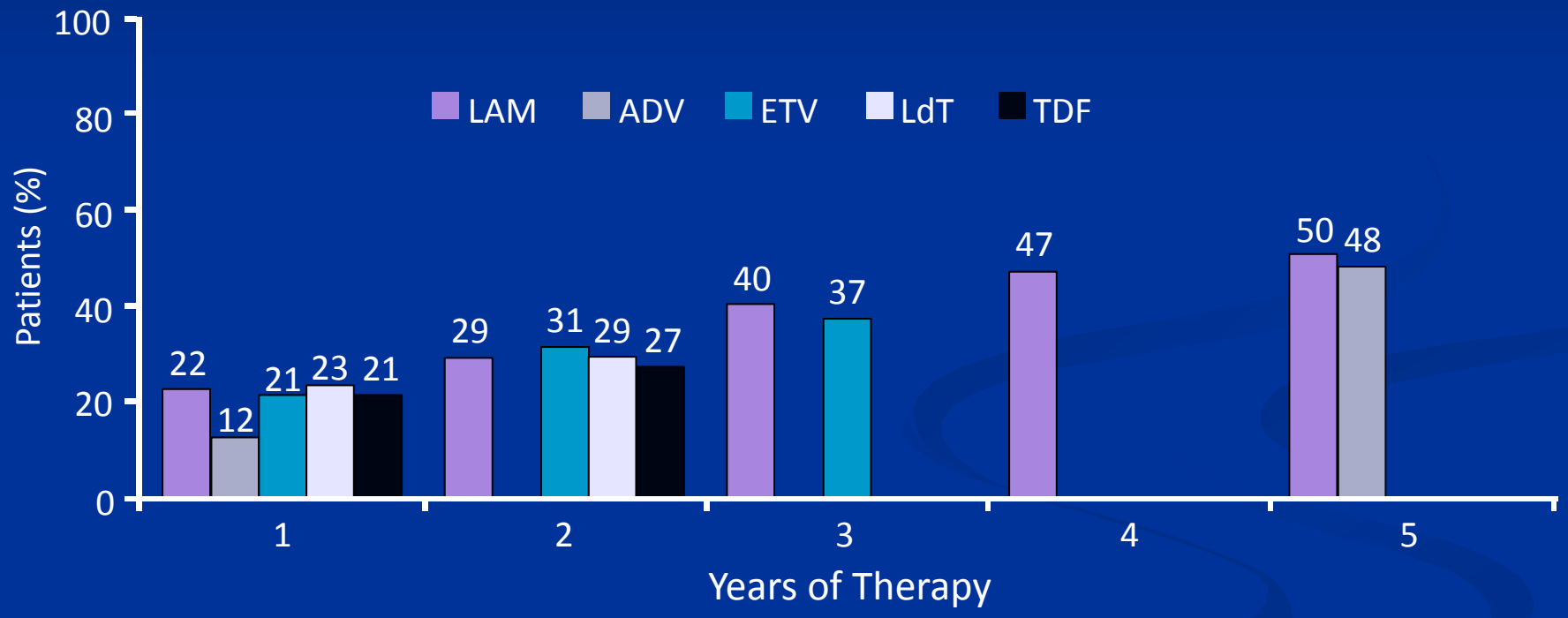
HBV DNA and HBeAg Seroconversion at Year 1 in HBeAg(+) adult Patients

Data from individual studies, not direct comparisons (different populations, baseline values, HBV DNA assays)



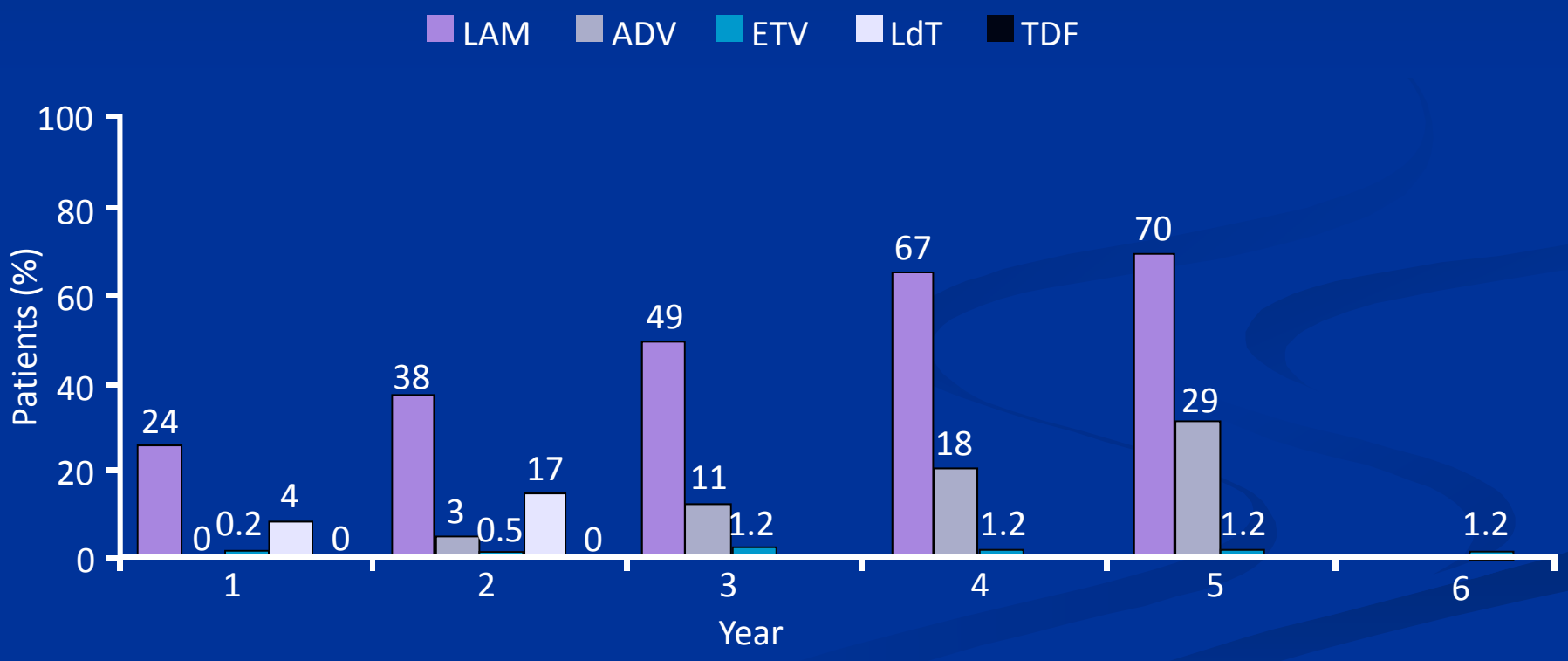
Lau et al. N Engl J Med. 2005;352:2682-2695. Dienstag et al. N Engl J Med. 1999;341:1256-1263. Marcellin et al. EASL 2005. Abstract 73. Lai et al. AASLD 2005. Abstract 72404. Chang et al. AASLD 2004. Abstract 70. Entecavir package insert. Telbivudine package insert.

HBeAg Seroconversion in DNA-negative Patients Extended Treatment



Chang TT, et al. N Engl J Med. 2006;354:1001-1010. Lai CL, et al. N Engl J Med. 2007;357:2576-2588. Marcellin P, et al. N Engl J Med. 2003;348:808-816. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Lok AS, et al. Gastroenterology. 2003;125:1714-1722. Leung NW, et al. Hepatology. 2001;33:1527-1532. Dienstag JL, et al. Hepatology. 2003;37:748-755. Marcellin P, et al. Hepatology. 2008;48:750-758. Liaw YF, et al. Gastroenterology. 2009;136:486-495. Gane E, et al. AASLD 2008. Abstract 729. Heathcote E, et al. AASLD 2008. Abstract 158. *Different patient populations and trial designs.*

Cumulative Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients



EASL HBV Guidelines. J Hepatol. 2009;50:227-242. Tenny DJ, et al. EASL 2009. Abstract 20.

Different patient populations and trial designs.

Contributors to Potential for Resistance

- Potency *
- Pharmacologic barrier to resistance
  - Dose/safety profile
  - Blood levels
  - Tissue concentration
- Genetic barrier to resistance *
  - Genotype differences
  - The number of substitutions needed for primary antiviral drug resistance

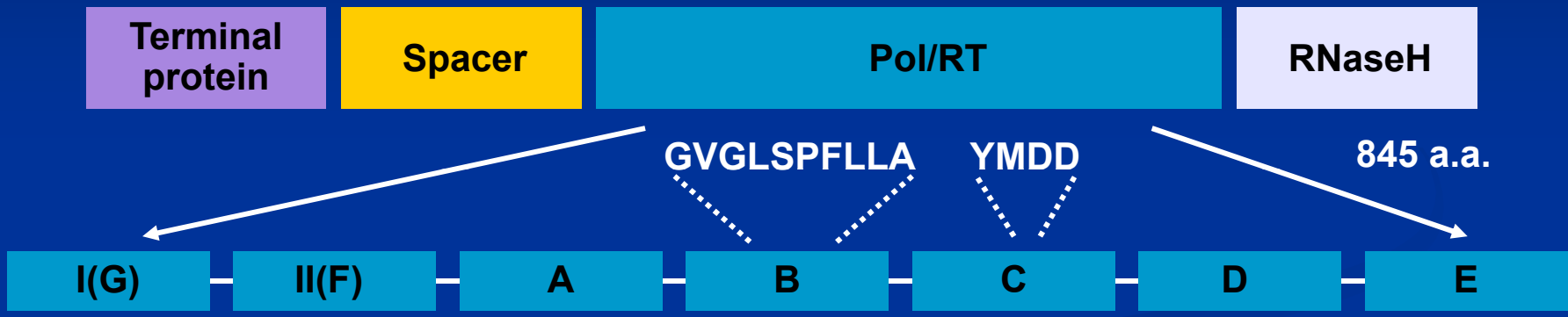
* Most significant

Allen MI, et al. Hepatology. 1998;27:1670-1677. Yatsuji H, et al. Antimicrob Agents Chemother. 2006;50: 3867-3874. Qi X, et al. Antivir Ther. 2007;12:355-362. Villeneuve JP, et al. J Hepatol. 2003;39:1085-1089. Baldick CJ, et al. Hepatology. 2008;47:1473-1482. Seifer M, et al. Antiviral Res. 2009;81:147-155. Heathcote E, et al. AASLD 2008. Abstract 158. Marcellin P, et al. AASLD 2008. Abstract 146. *Adapted from slide of Dr. K. Schwarz.*

HBV Genotypes and Response to Treatment- adults

- Lamivudine – resistance A>D
- Adefovir dipivoxil and Entecavir – no genotype effect
- Interferon and pegylated interferon
  - B >C (40 vs. 20% virologic response)
  - A>D (49 vs. 26% virologic response)
- Pegylated interferon – HBsAg loss
  - A 14%, B 9%, C 3%, D 2%

HBV Resistance Mutations



LAM resistance		rtL80V/I	rtV173L rtL180M	rtM204V/I/S	
ADV resistance			rtA181T/V		rtN236T rtI233V ?
ETV resistance			rtL180M rtT184S/A/I/L	rtM204V/I rtS202G/C	rtM250I/V
TBD resistance		rtL80V/I	rtL180M	rtM204I	

Allen MI, et al. Hepatology. 1998;27:1670-1677. Qi X, et al. J Hepatol. 2004;40(suppl 1):20-21. Tenney D, et al. Antimicrob Agents Chemother. 2004;48:3498-3507. Telbivudine product insert. Lai CL, et al. Gastroenterology. 2005;129:528-536. Schildgen O, et al. N Engl J Med. 2006;354:1807-1812.

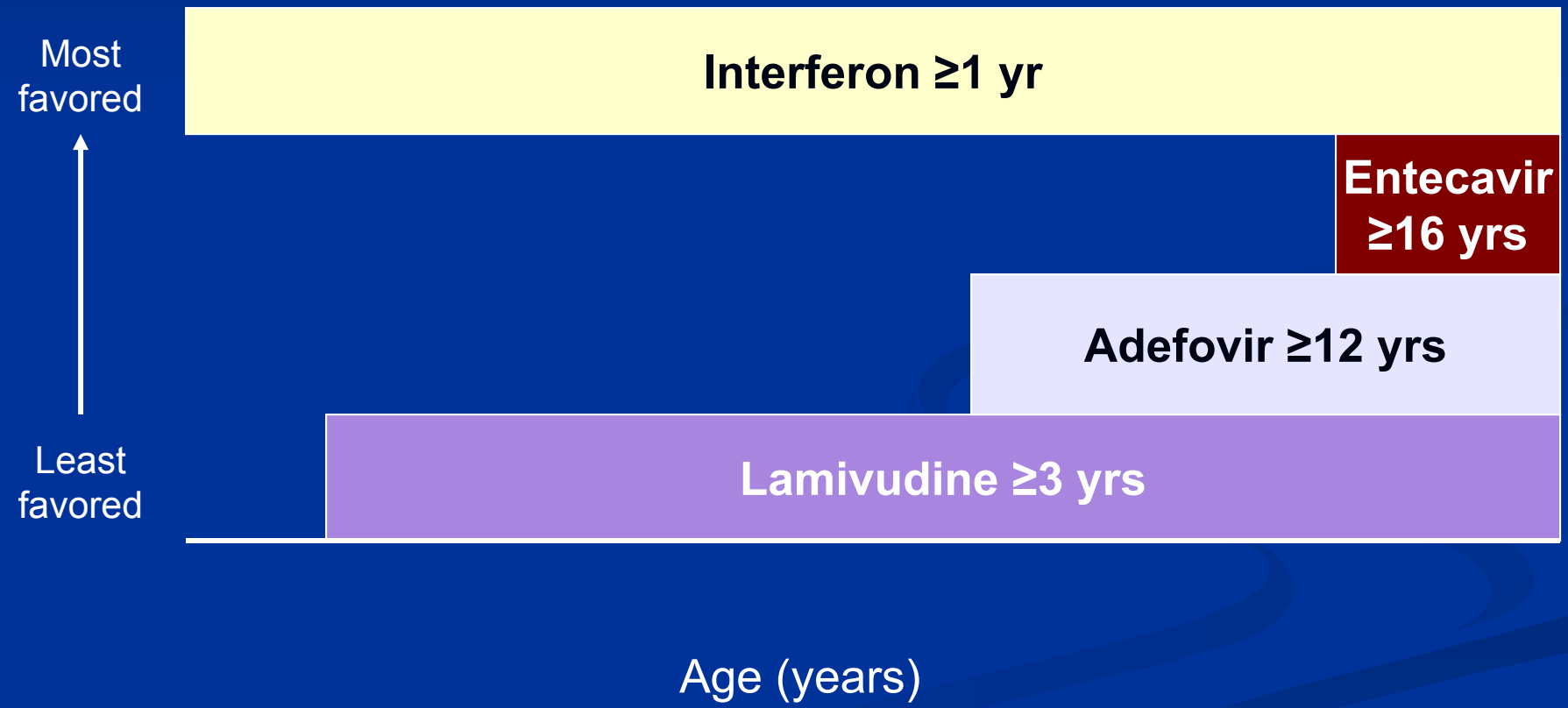
Recommendations for Treatment Initiation in HBeAg-Positive Adults

	AASLD 2007[1]	US Algorithm 2008[2]	EASL 2009[3]
HBV DNA, IU/mL	> 20,000	> 20,000	≥ 2,000
ALT, x ULN*	> 2	> 1	> 1
Disease stage/grade	Moderate/severe necroinflammation and/or significant fibrosis		
First-line therapy	ADV,† ETV, pegIFN	ETV, TDF, pegIFN	ETV, TDF, pegIFN

*Persistent (> 3-6 mos). †TDF not FDA approved at time of publication.

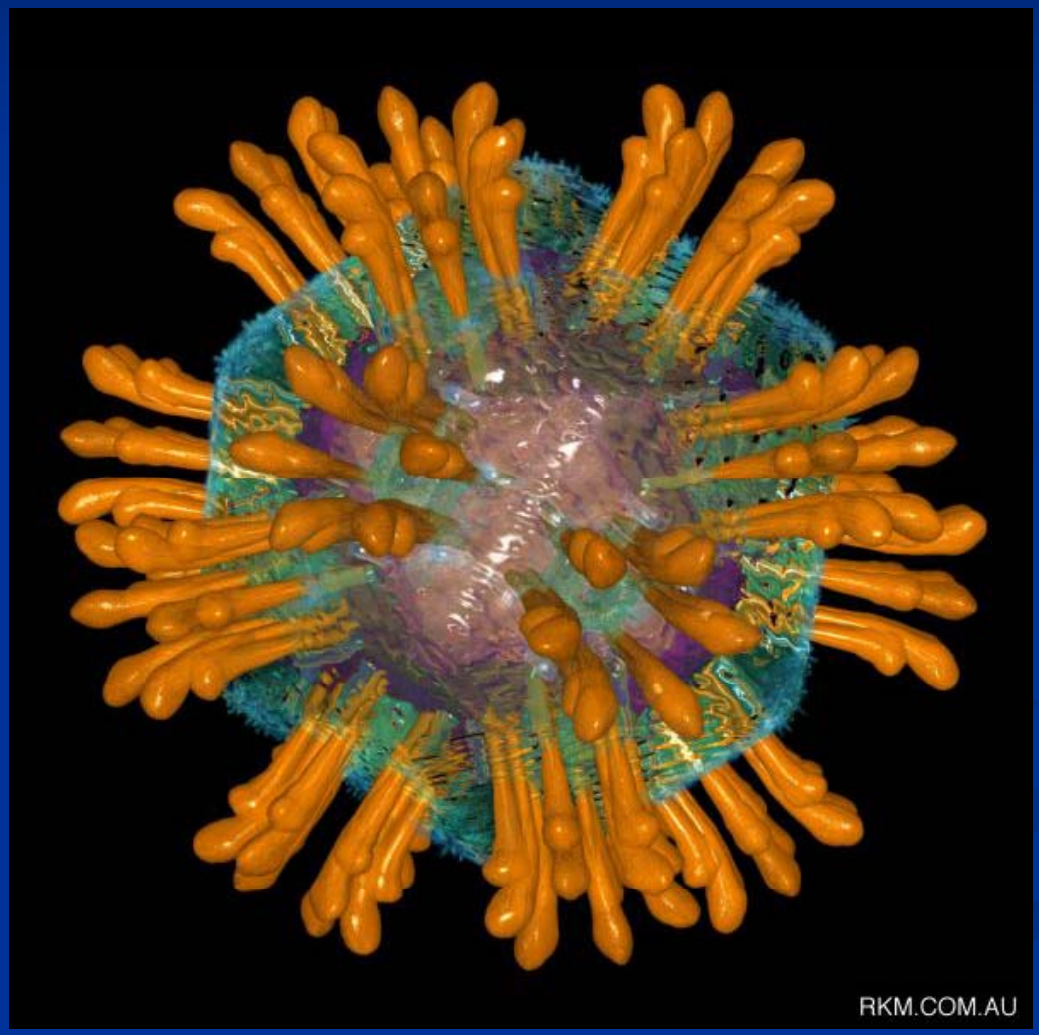
[1] Lok A, et al. Hepatology. 2007;45:507-539. [2] Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341. [3] EASL HBV Guidelines. J Hepatology. 2009;50:227-242. Slide adapted from Dr. K Schwarz

Approved HBV Treatments for Children

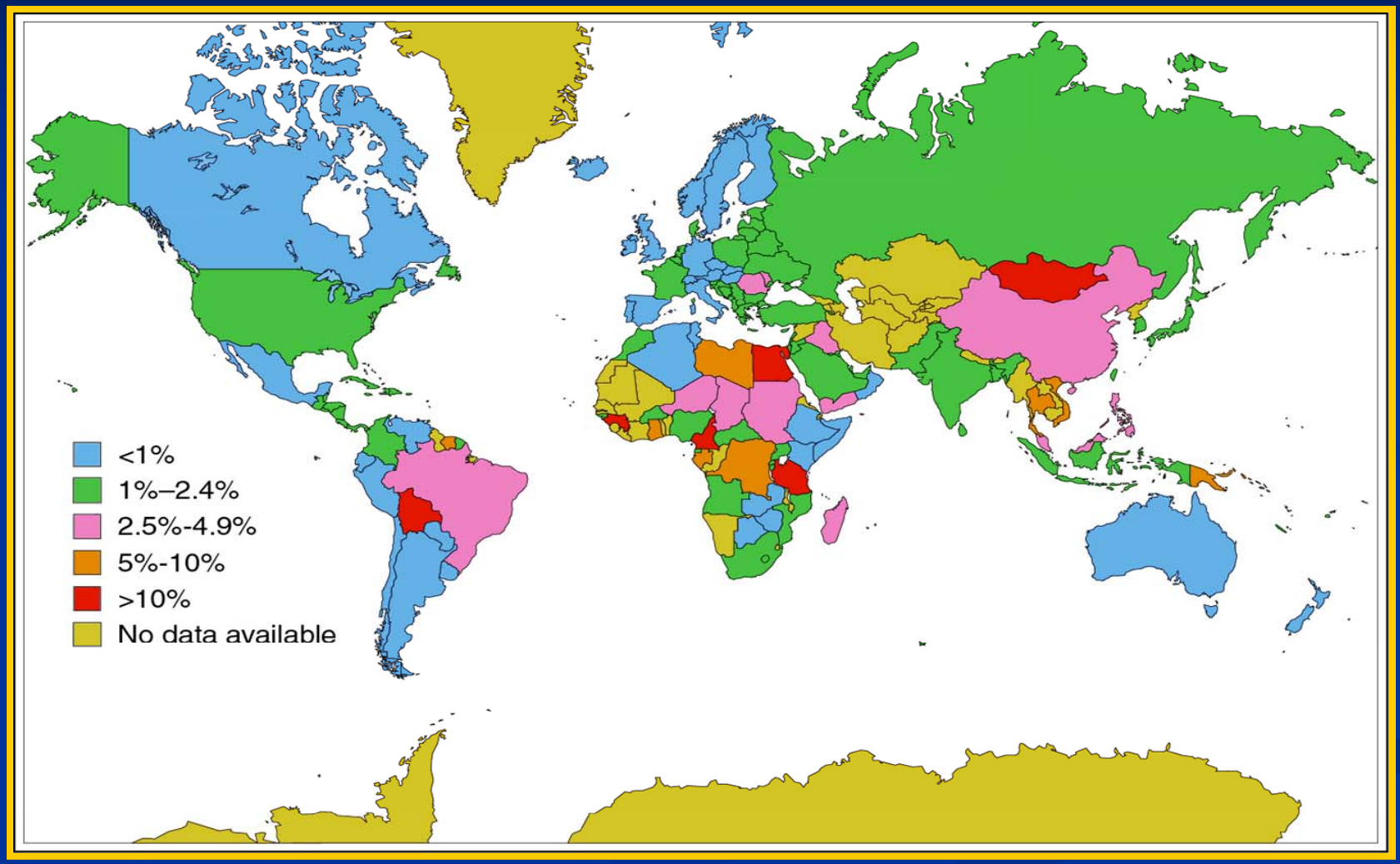


HBV Treatment Work Group, HBV Foundation; Jonas et al., Submitted

Hepatitis C



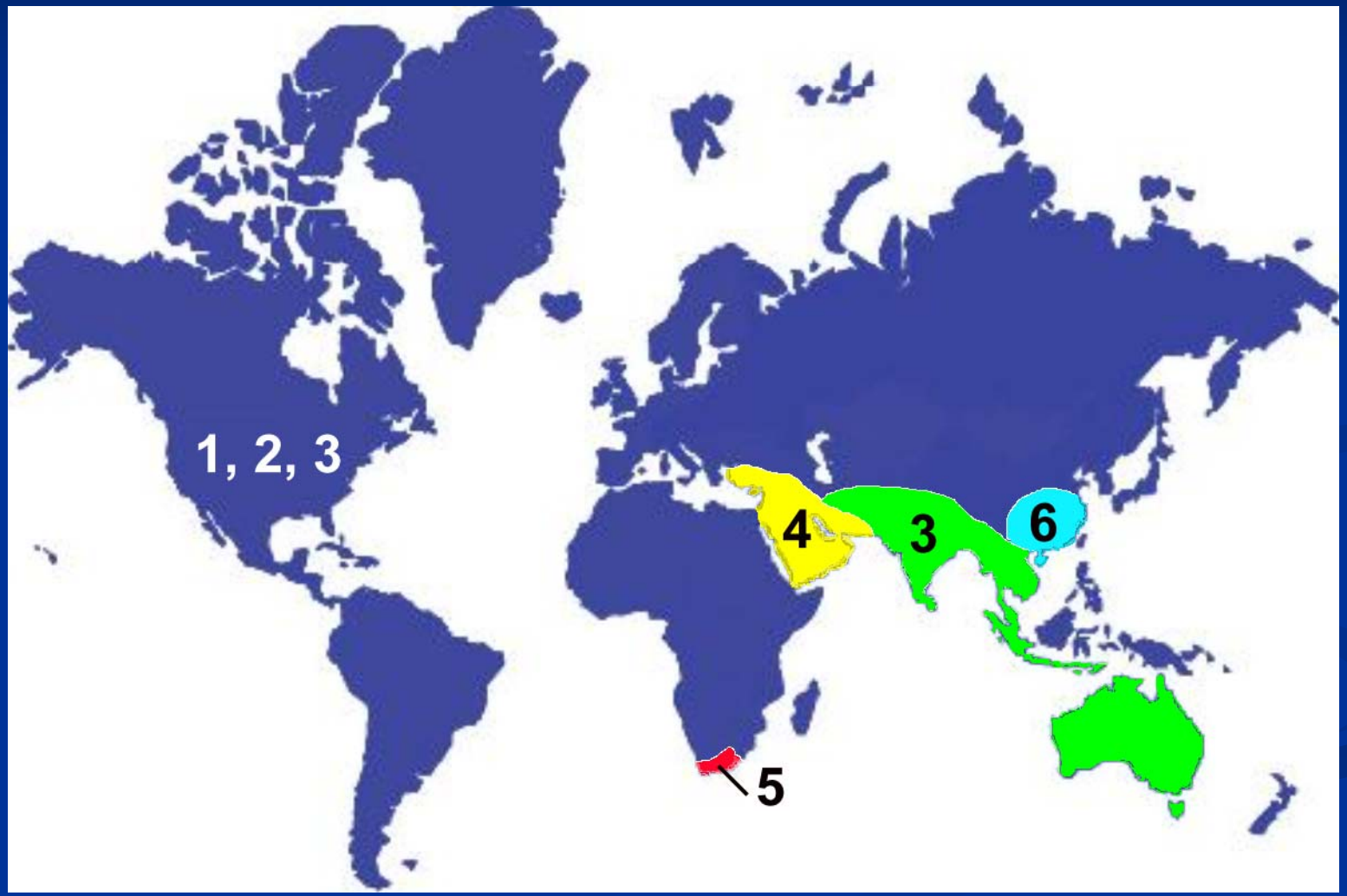
Worldwide Prevalence of HCV



Hepatitis C

- Lifetime risk of death from HCV: 10-20%
- 10,000 deaths/year
- Leading cause for liver transplantation

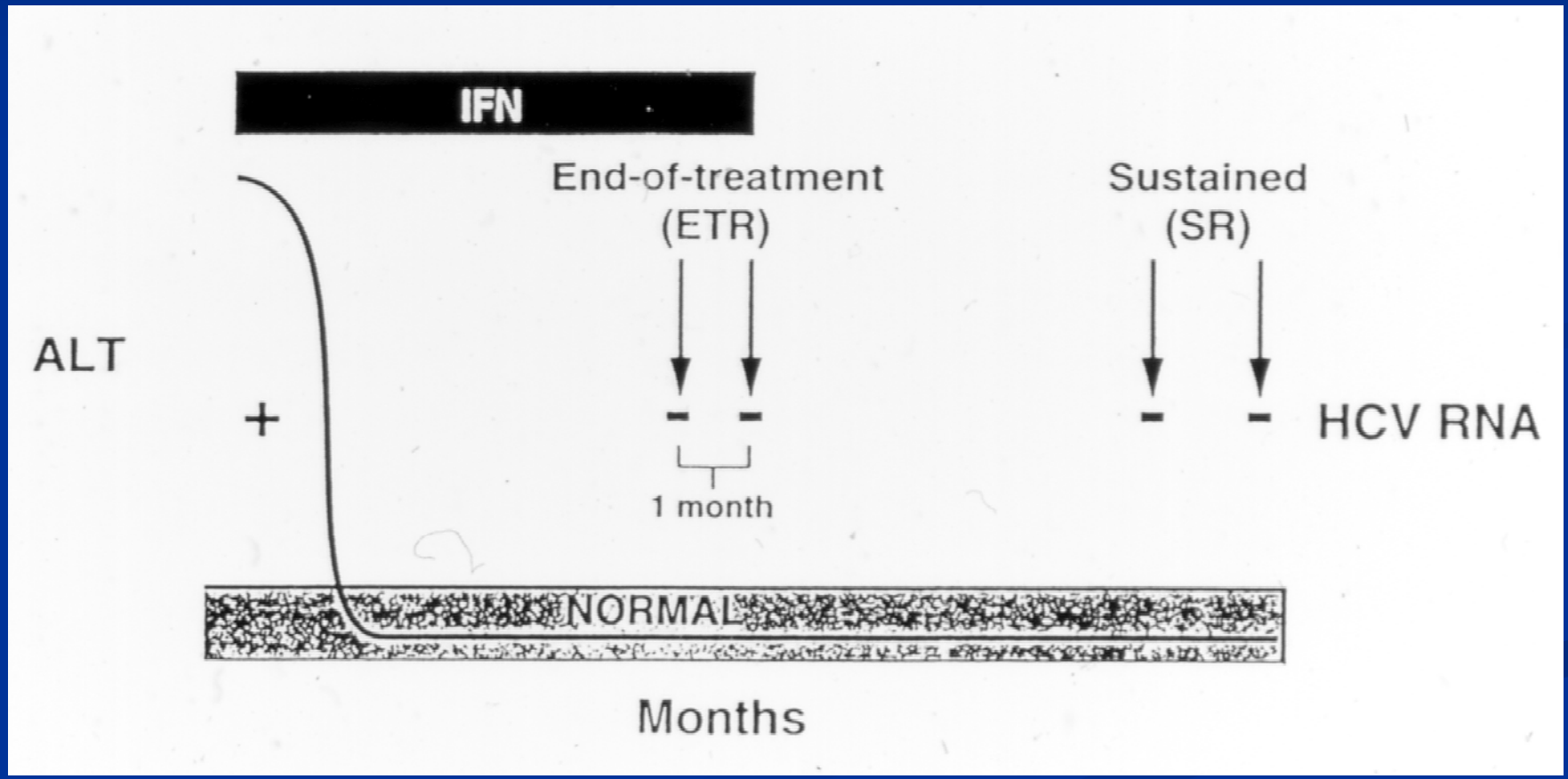
HCV Genotypes Around The World



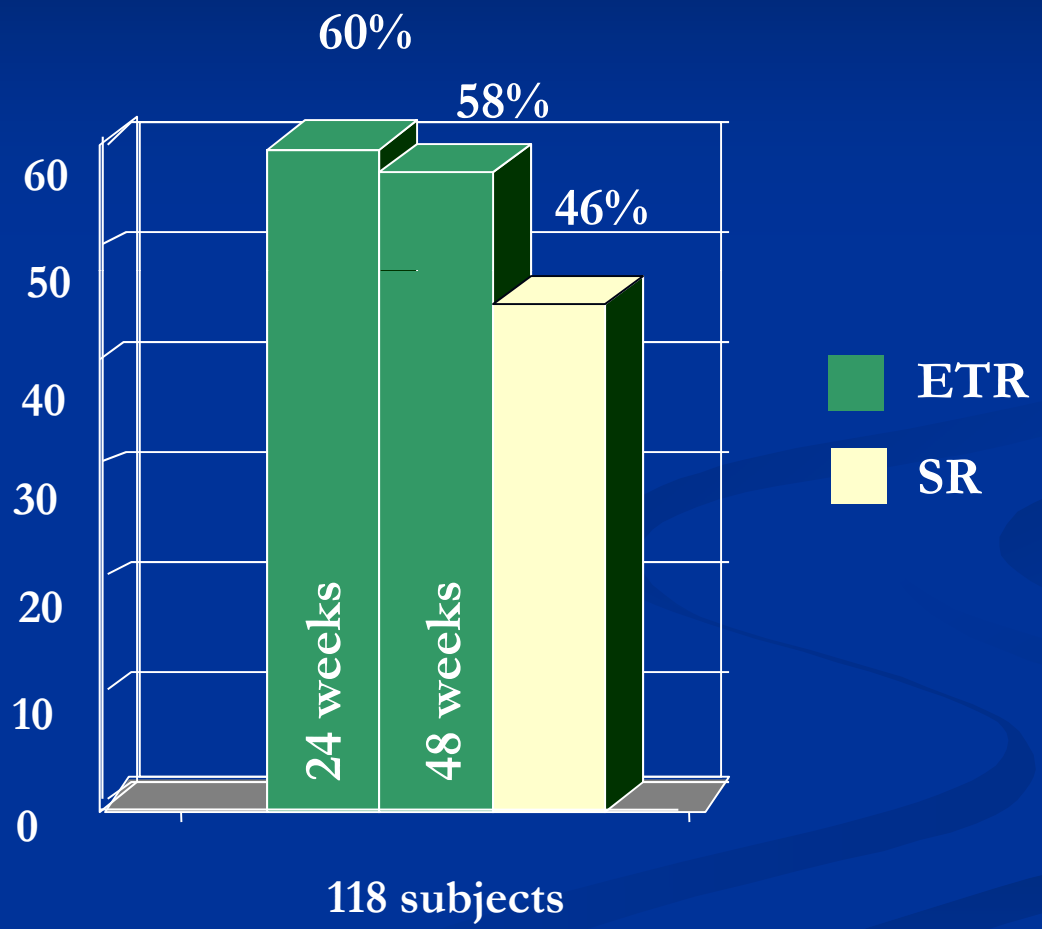
Hepatitis C: Who should be considered for treatment? *individualized*

- Those with advancing liver disease
  - Histology
- Those most likely to respond
  - Genotype, BMI, compliance
- Those who are highly motivated despite the risks of therapy
  - Children > 2 years
  - Normal ALT

HCV IFN Therapy – response definition



Interferon α2b + ribavirin In Children with Chronic HCV

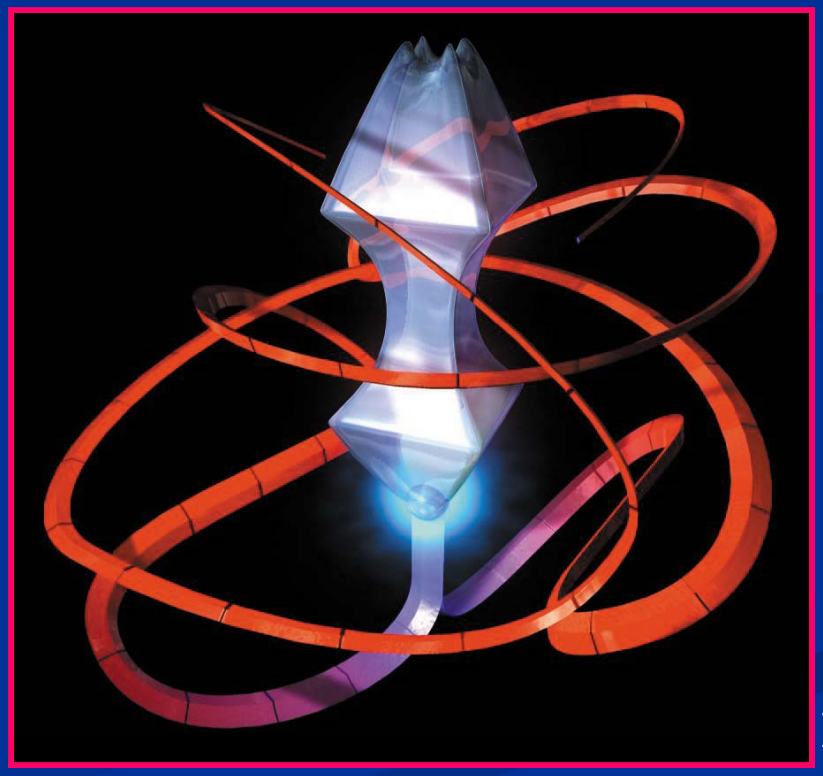


Hepatology, 2005;42:1010-1-18

The PEG Molecules

Peg-Intron
Schering-Plough

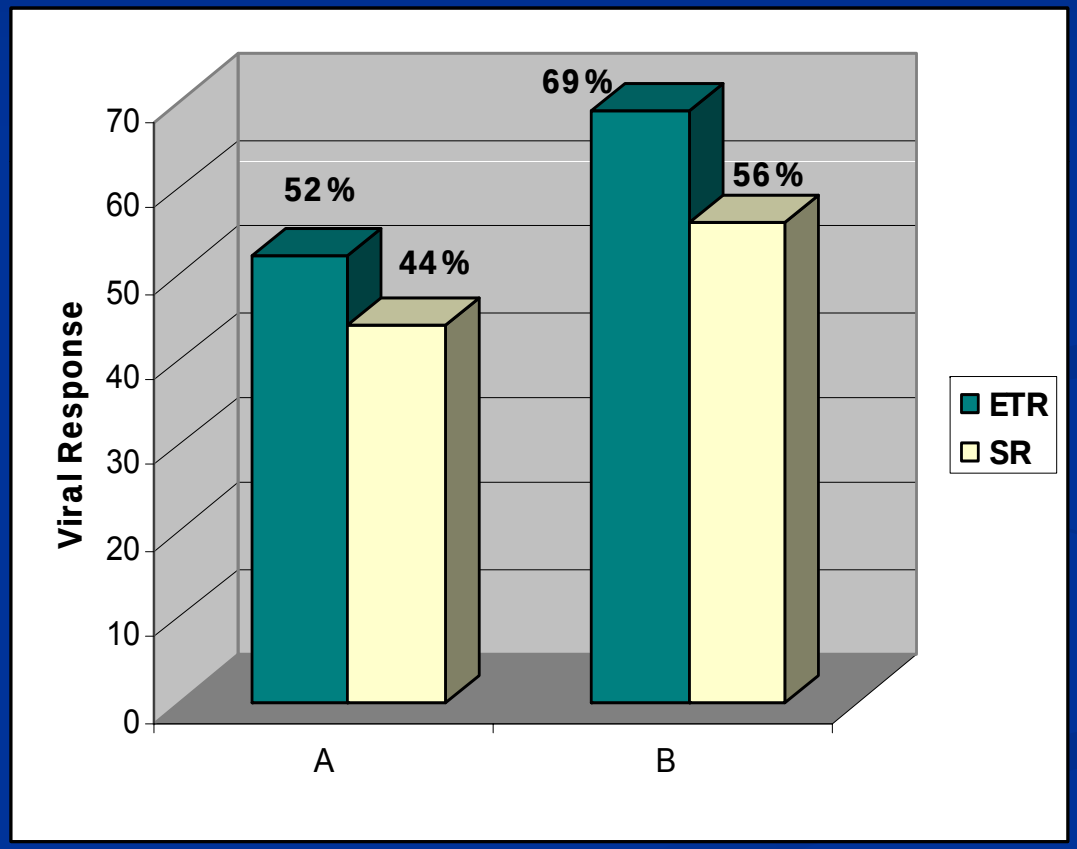
2° and 3° interferon protein structure preserved



Hoff

Slide from Dr. A. Larson

IFN α2b or PEG α2a + Ribavirin In Adults with Chronic HCV

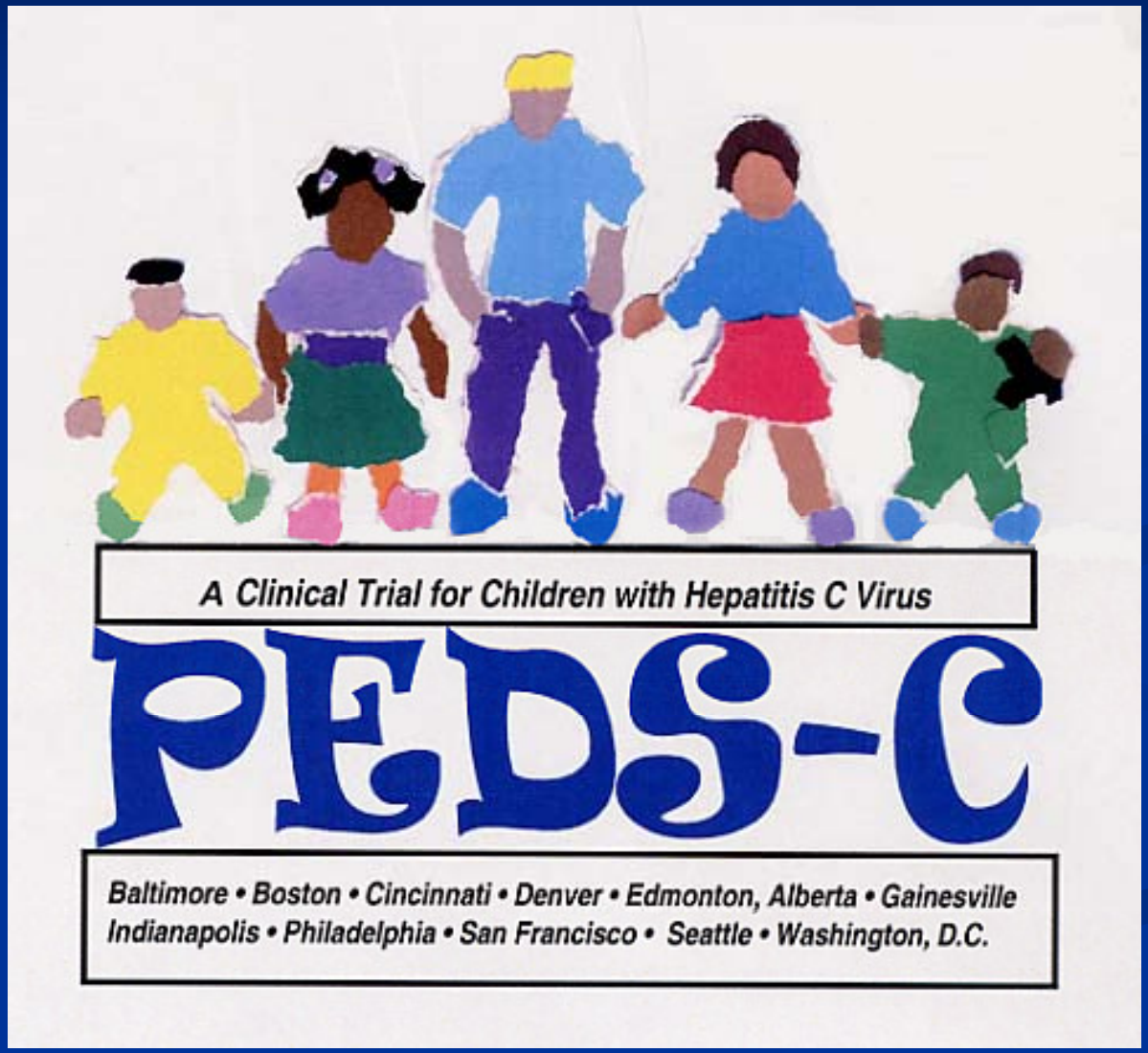


- A = IFN α2b + Ribavirin
- B = PEG 2a* + Ribavirin

*Not approved for pediatric use

N Engl J Med 2002; 347(13)

Results of the PEDS C Trial



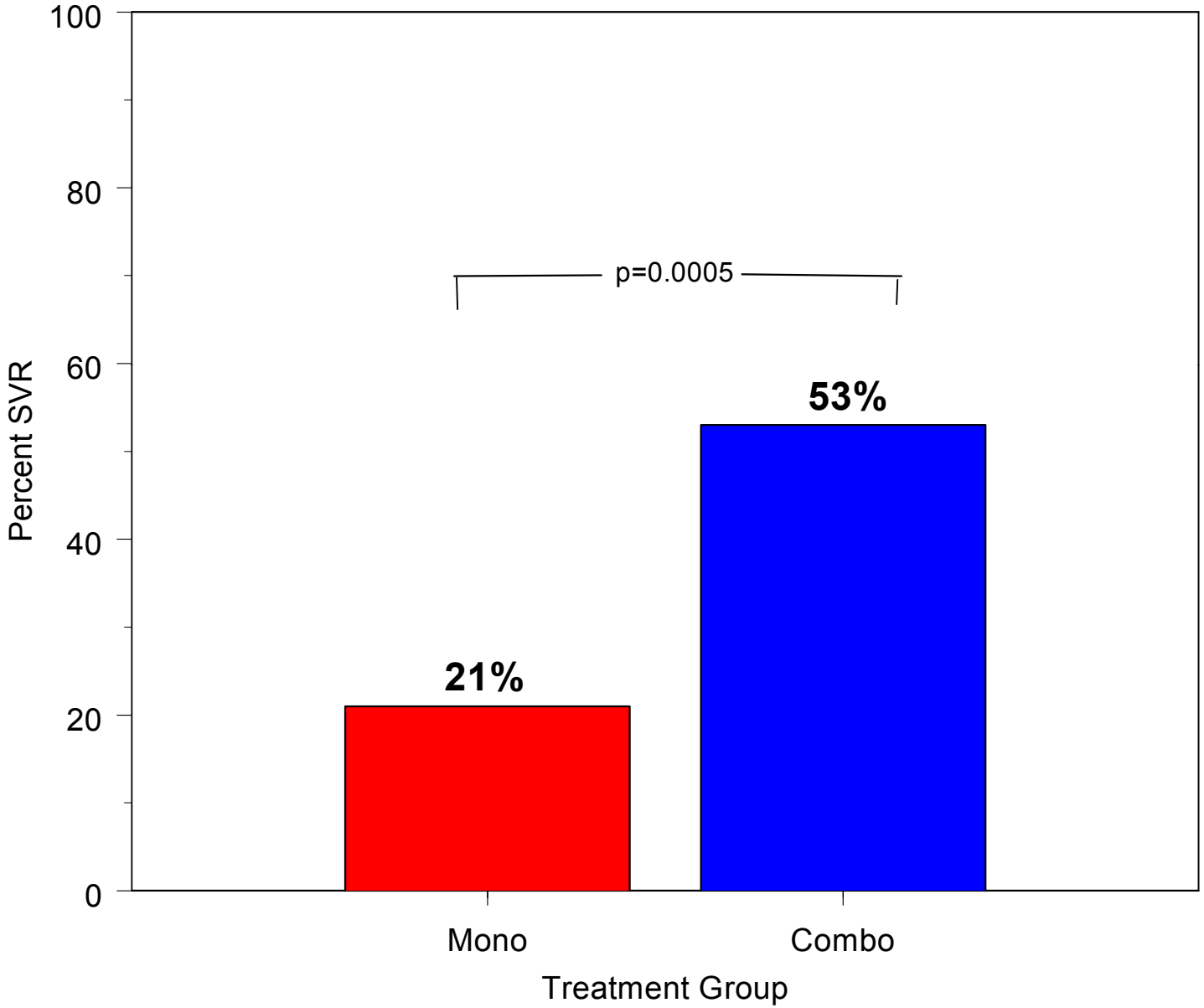
N = 114

Murray Clin Trials 2007

Schwarz Hepatology 2008

Slides from K. Schwarz

Percent SVR by Treatment Group



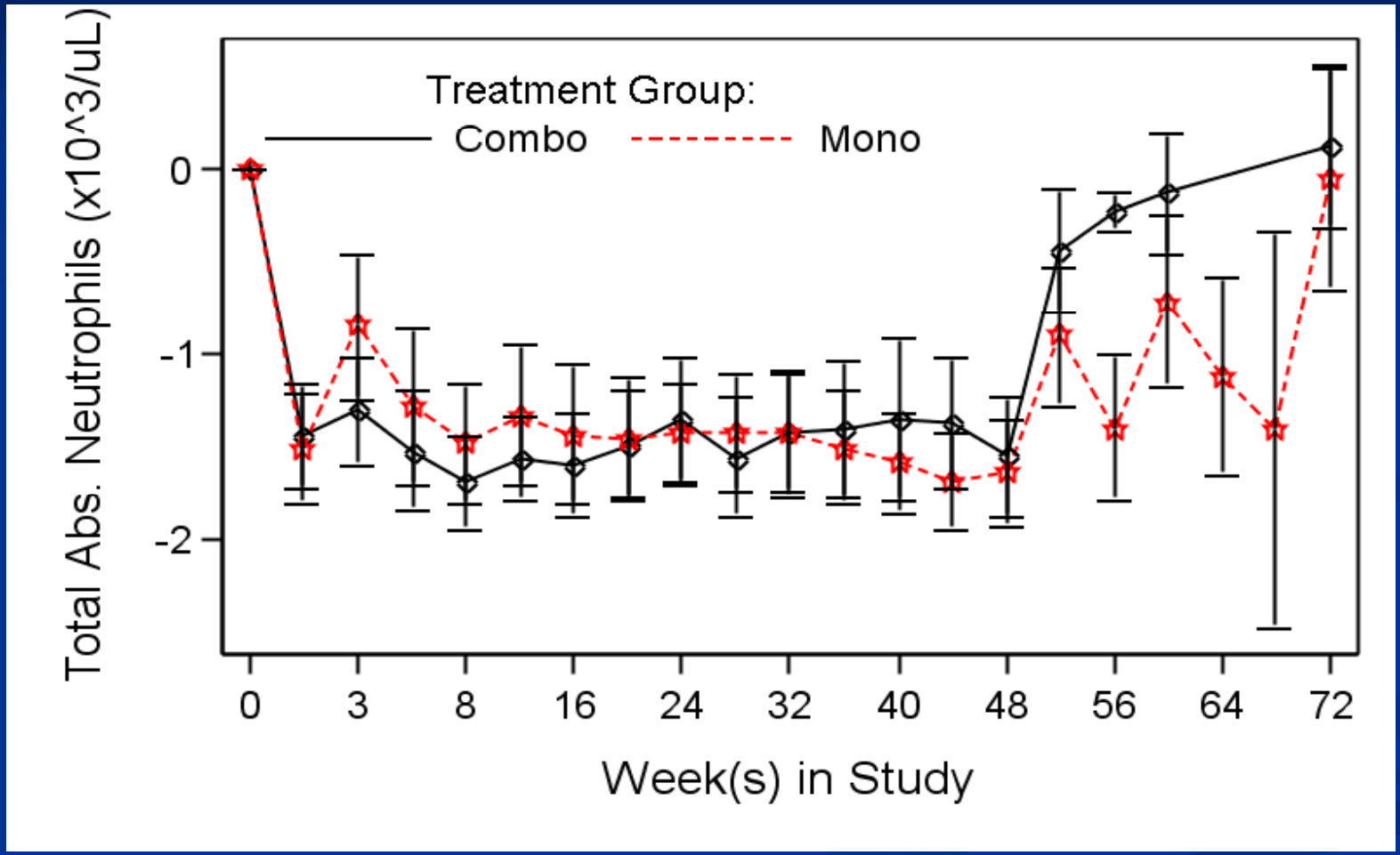
Multivariate Predictors of Viral Response in Children receiving Combination Therapy

Predictor	Odds Ratio	P value
Combo vs mono	5.404	0.0018
Female vs male	3.582	0.0272
Other vs Maternal	6.837	0.0050
Genotype Other vs 1	4.459	0.0231
Mild inflam vs moderate	0.294	0.0328
Mild steatosis vs none	0.150	0.0012

Symptomatic Adverse Events Related to Therapy

	Mono	Combo
Flu	85%	91%
Headache	51	62
GI symptoms	63	56
Injection site rx	46	45
Joint aches	34	36
Irritability	22	31
Rash	24	20
Anorexia	19	13
Depression	12	4

Neutropenia in PEDS-C Trial



Rosenthal AASLD 2008

30% at least 1 dose reduction

No effect on infections or SVR

HCV Treatment Administration and Monitoring

- Interferon- subcutaneous injection
- Ribavirin- orally administered twice a day
  - Teratogen! (Must use effective birth control)
  - Hemolytic anemia
- Monitoring:
  - Week 1, 2, 4, 6, 8, 12, every month
  - Repeat labs weekly if needed
  - CBC with diff, plt count, ALT- with every draw
  - HCV RNA, TSH/T4 – month 1, 3, and every 3 months

Hepatitis B and C Summary

- Hepatitis B and C infections in children commonly become chronic
- Children with HBV or HCV are usually asymptomatic
- Most children with HBV are immunotolerant
- Limited medications are approved for pediatric treatment
- Treatment of children with HBV and HCV is best done under the guidance of a pediatric hepatologist
- Treatment options are increasing