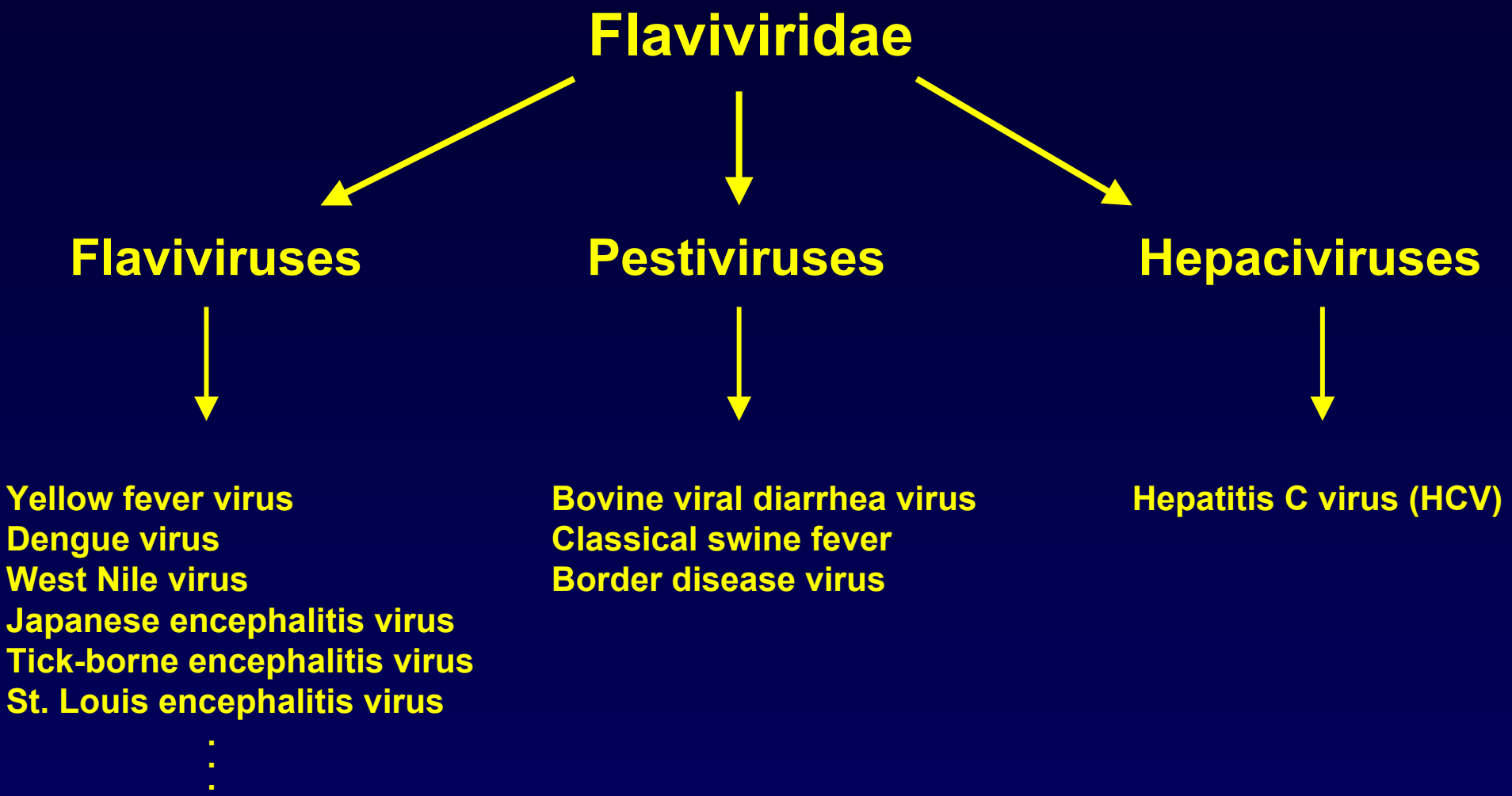
Hepatitis C and B,
and the rest of the alphabet


Flaviviridae
Flaviviruses
Pestiviruses
Hepaciviruses
Yellow fever virus
Dengue virus
West Nile virus
Japanese encephalitis virus
Tick-borne encephalitis virus
St. Louis encephalitis virus
:
Bovine viral diarrhea virus
Classical swine fever
Border disease virus
Hepatitis C virus (HCV)

Hepatitisviruses

HAV	HBV	HCV	HDV	HEV
Enterovirus type 72	Hepadnavirus	Hepacivirus	δ-agens [circular (-)RNA]	Calicivirus
Picornaviridae	Hepadnaviridae	Flaviviridae		Picornaviridae

Transmission of hepatitisviruses

HAV	HBV	HCV	HDV	HEV
Faeco-oral	Parenteral Sexual Perinatal	Parenteral Sexual (Perinatal)	Parenteral Sexual (Perinatal)	Faeco-oral

Hepatitisvirus infections

	HAV	HBV	HCV	HDV	HEV
Acute hepatitis	●	●	●	●	●
Chronic carrier (risk)		●	●	●	
Chronic hepatitis (risk)		●	●	●	
Cirrhosis (risk)		●	●	●	
Hepatocellular carcinoma (risk)		●	●	?	

Hepatitisvirus infections: vaccination

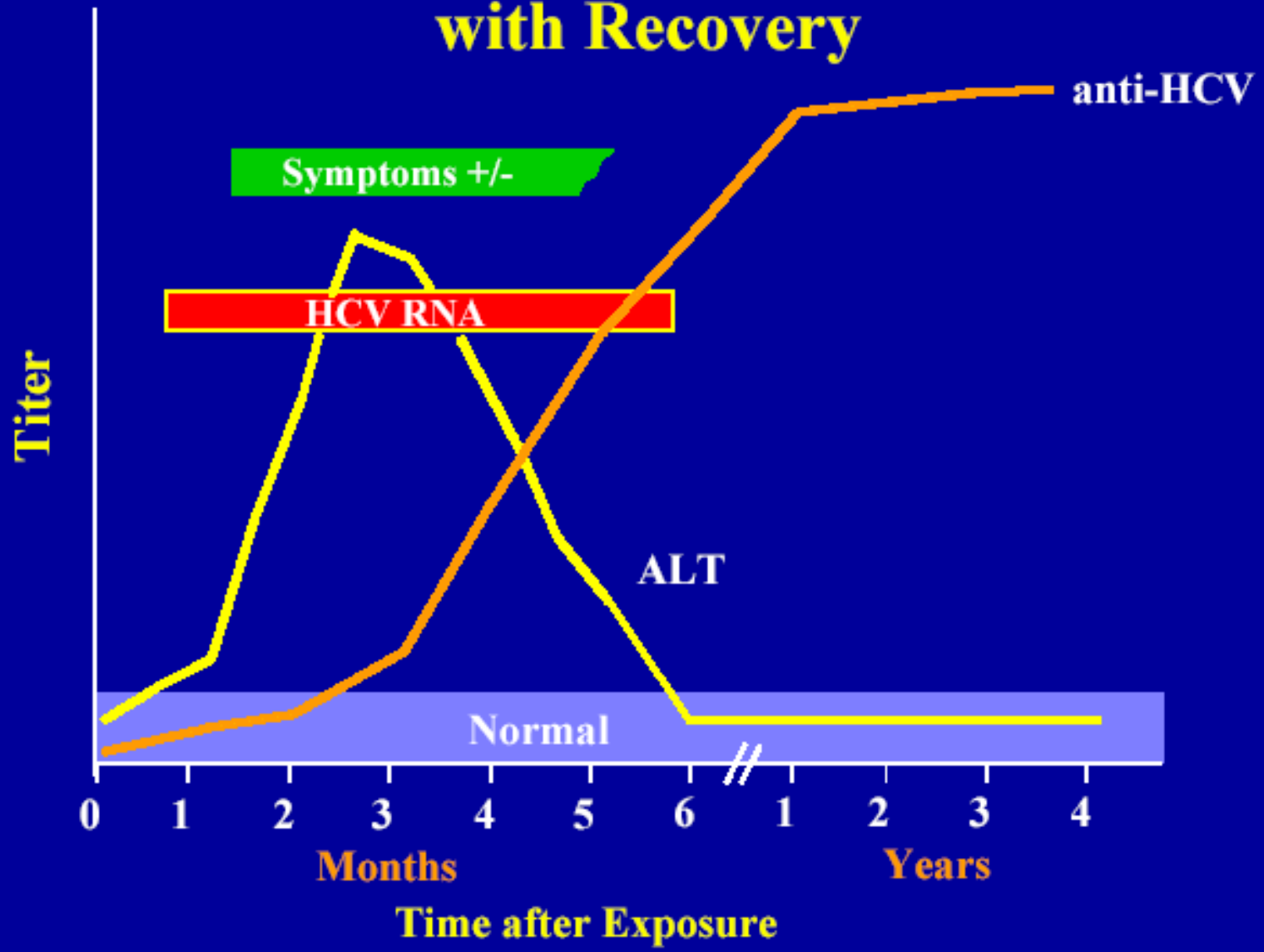
HAV	HBV	HCV	HDV	HEV
Yes	Yes	No	No	No

Features of hepatitis C virus infection

Incubation period	Average 6-7 weeks Range 2-26 weeks
Acute illness (jaundice)	Mild (≤ 20%)
Case fatality rate	Low
Chronic infection	60%-85%
Chronic hepatitis	10%-70%
Cirrhosis	< 5%-20%
Mortality from CLD	1%-5%

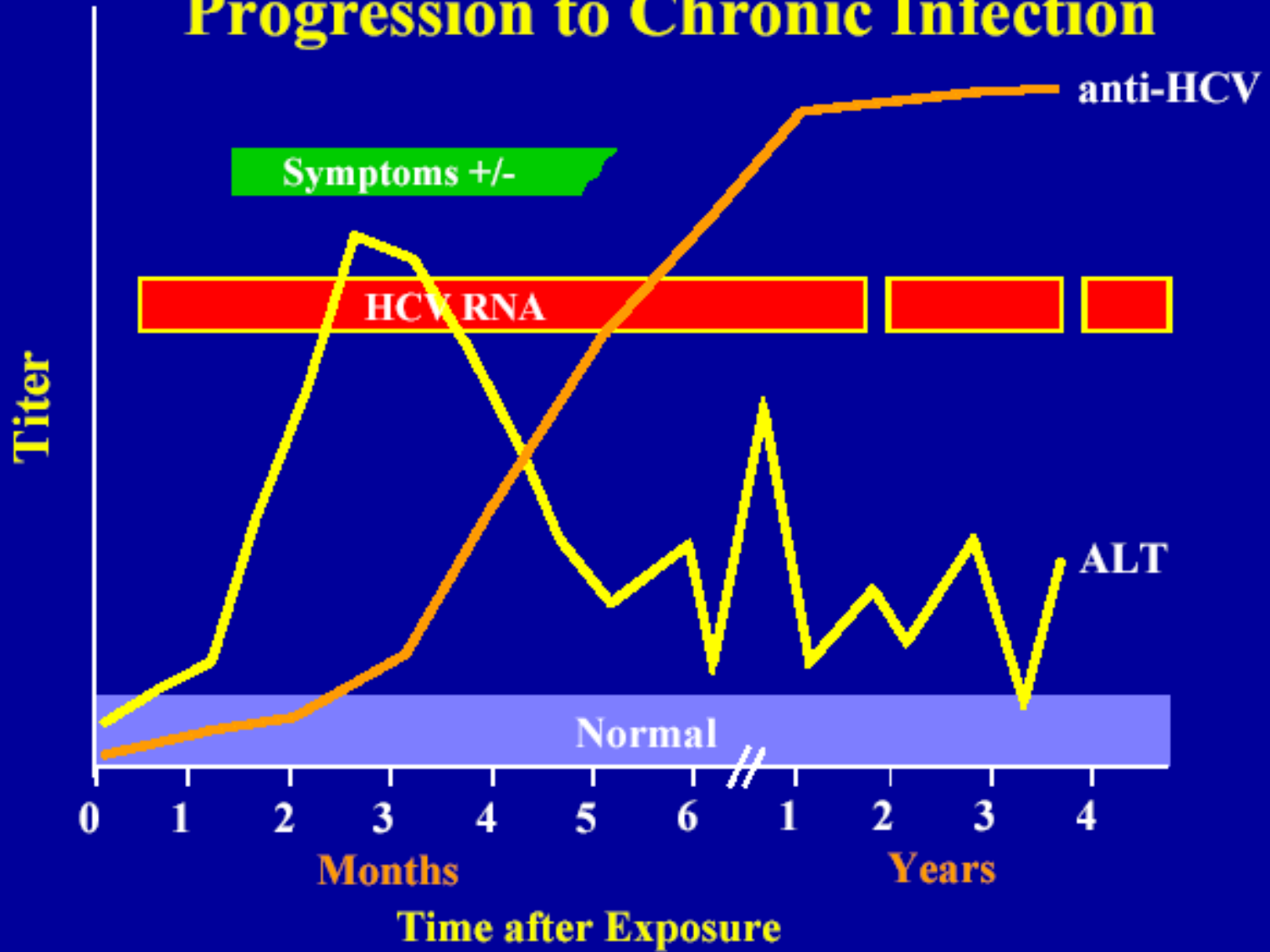
Centers for Disease Control and Prevention

Serologic Pattern of Acute HCV Infection with Recovery



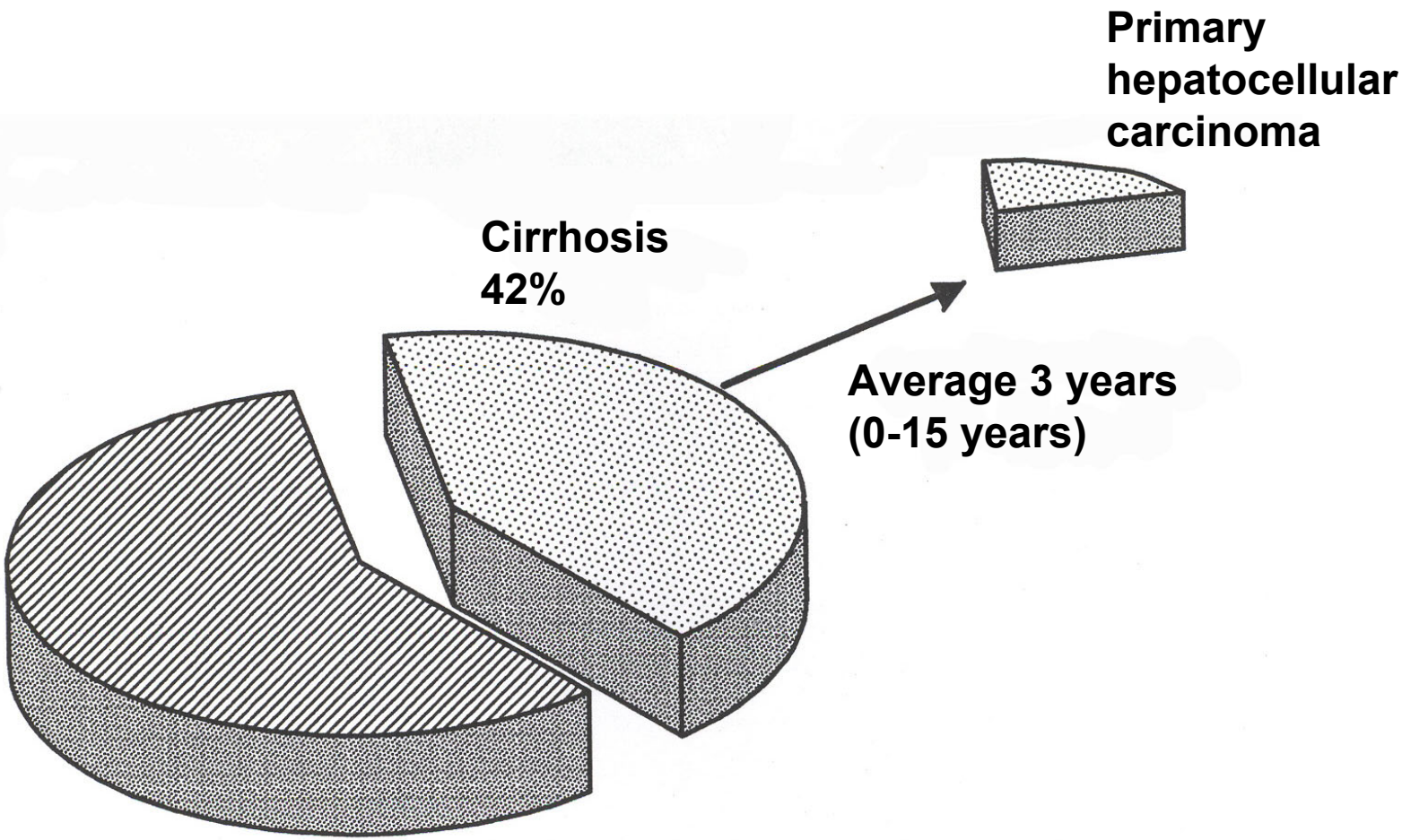
Centers for Disease Control and Prevention

Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

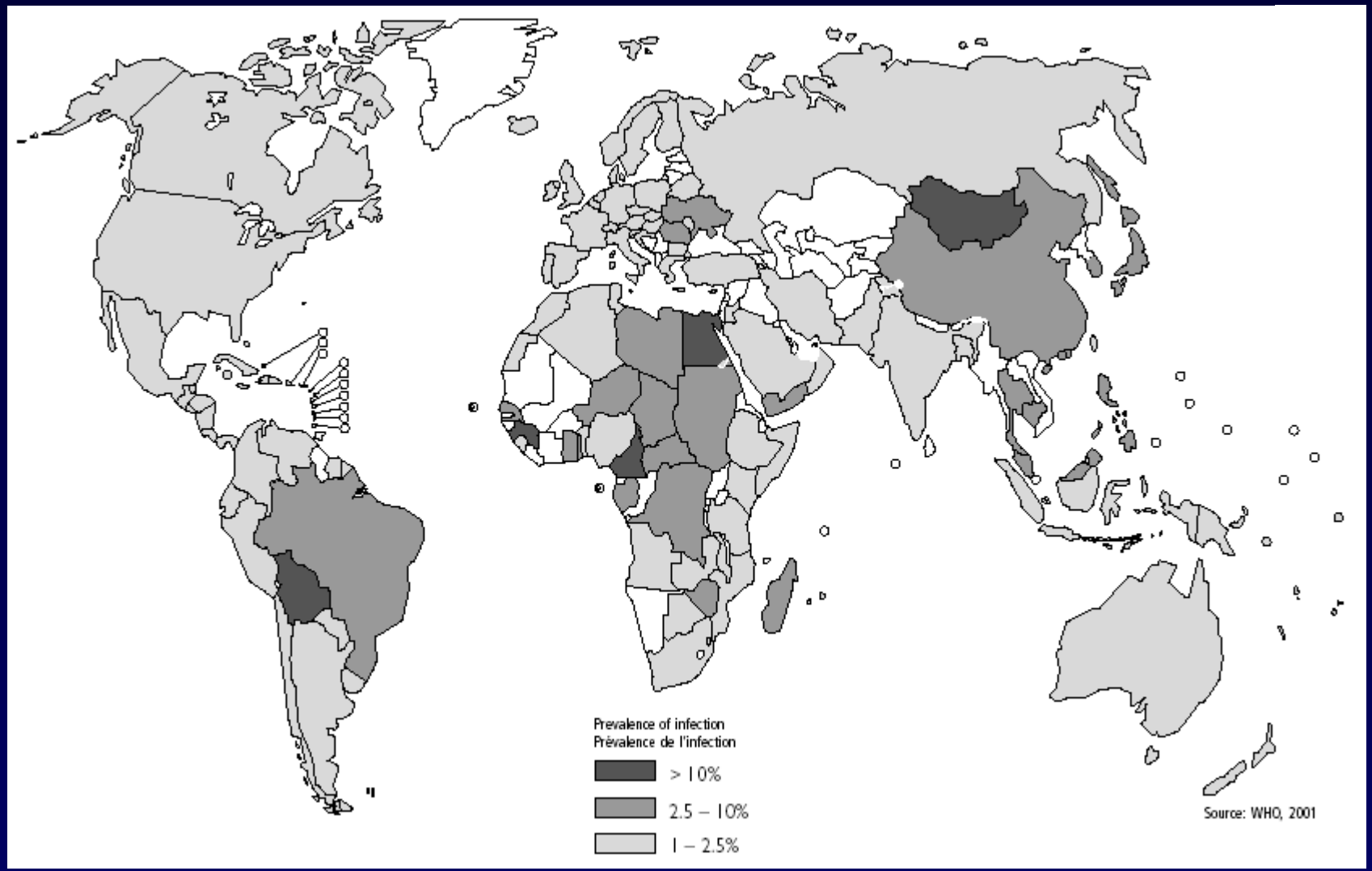


Centers for Disease Control and Prevention

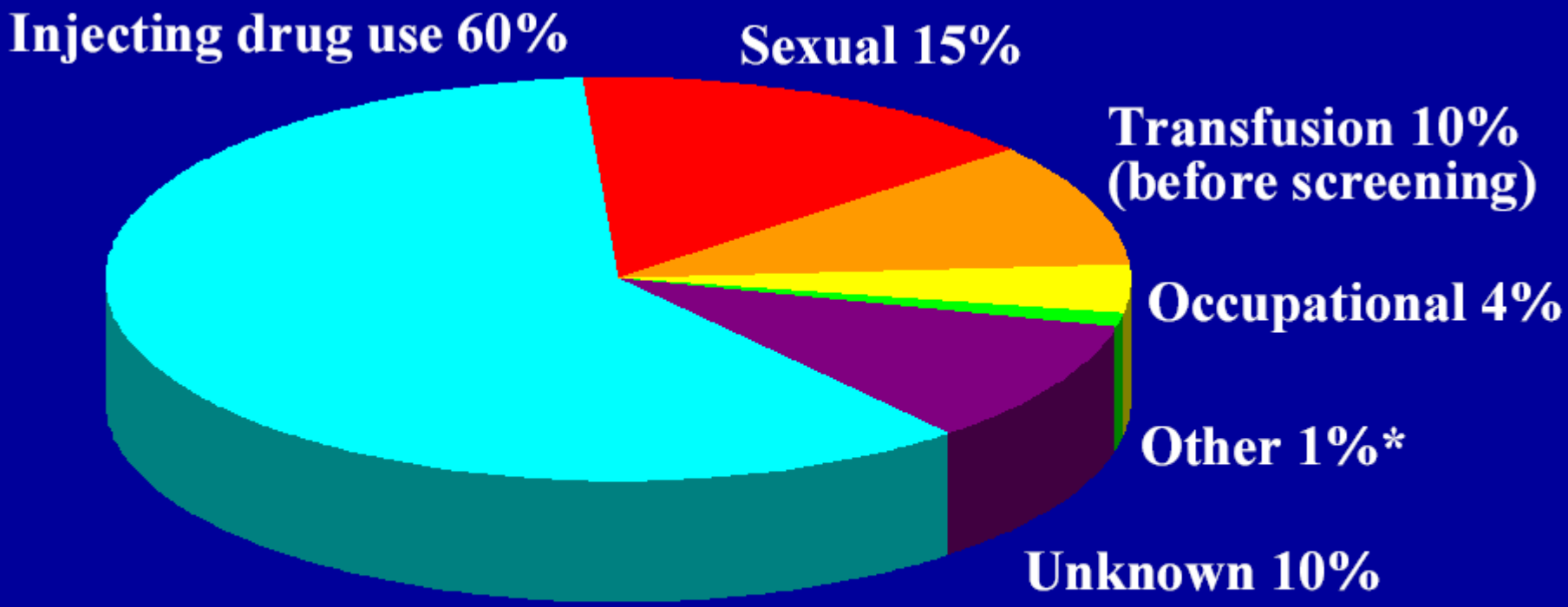
Evolution of chronic hepatitis C



Global distribution of HCV infection



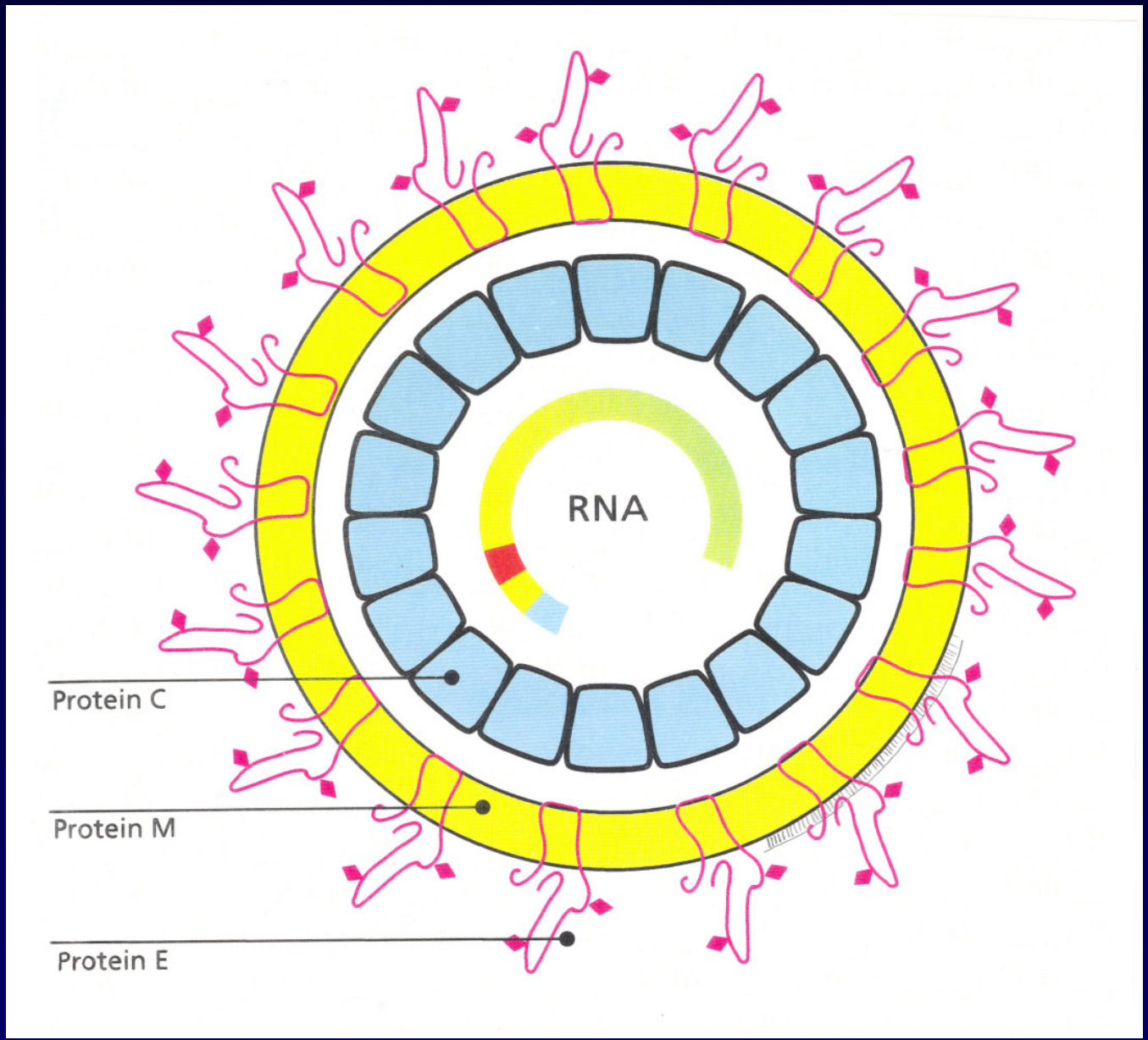
Transmission routes for HCV



* Nosocomial; iatrogenic; perinatal

Centers for Disease Control and Prevention

GENERAL STRUCTURE OF A FLAVIVIRUS



Interferons

(Schorderet 1999)

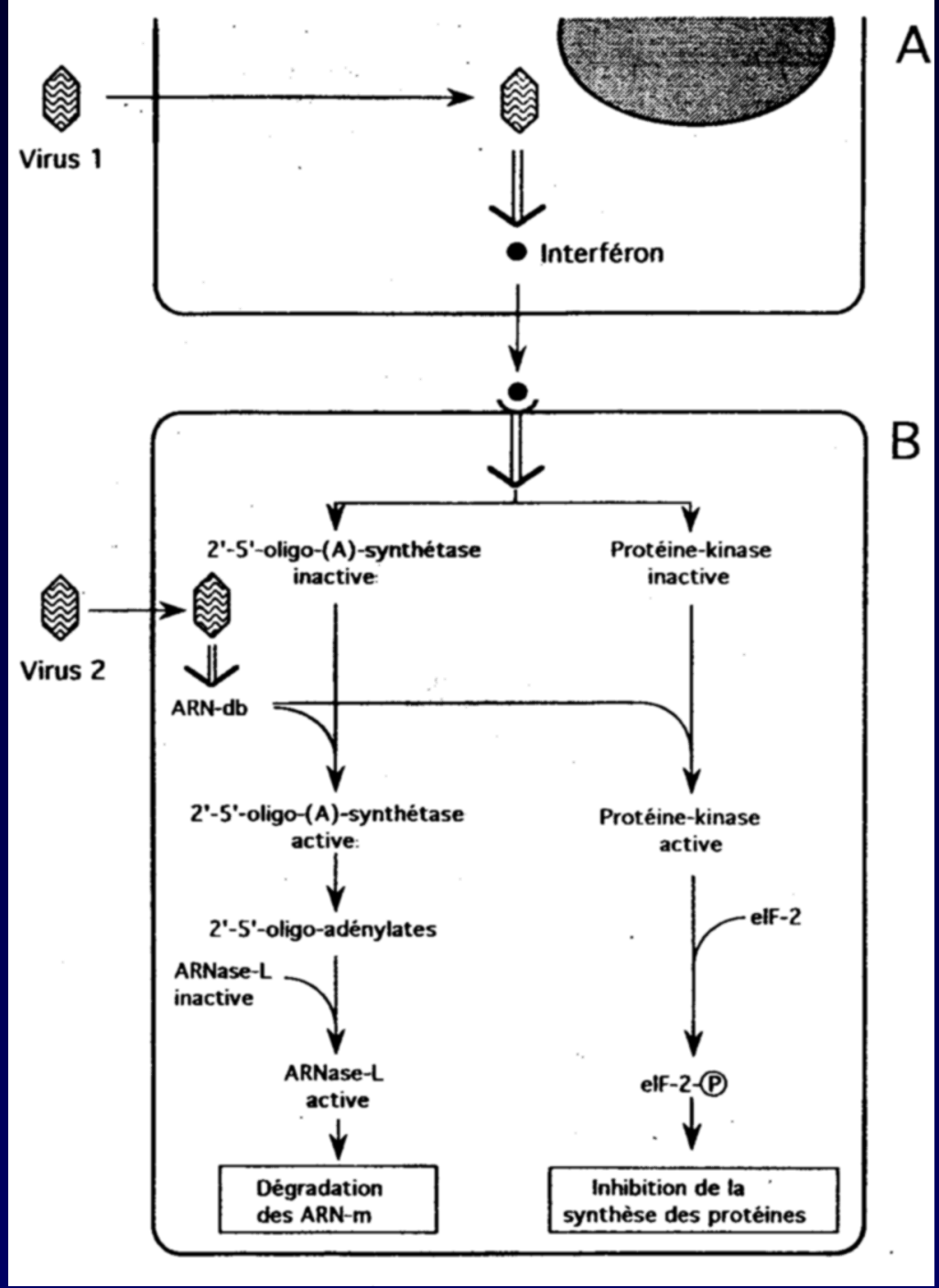


Figure 2. Représentation schématique de l'activité antivirale de l'interféron. En A, la cellule infectée par le virus 1 génère et sécrète l'interféron. En B, la cellule sensibilisée par l'interféron produit par la cellule A est infectée par le virus 2. Plusieurs mécanismes antiviraux sont alors mis en jeu (ARN-db = ARN à deux brins)

PEG

Polyethylene glycol

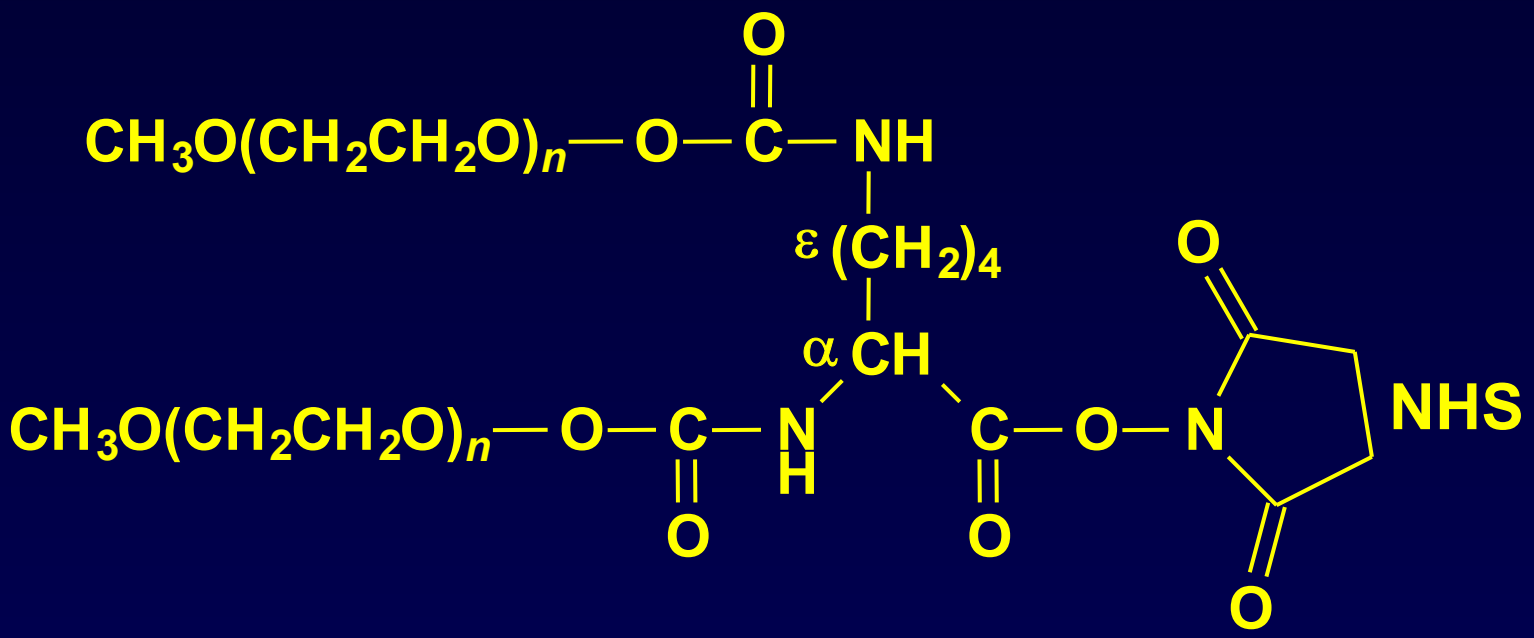
$CH_3(OCH_2CH_2)_nOH$

$CH_3OCH_2CH_2OCH_2CH_2.....OCH_2CH_2OCH_2CH_2OH$

Glycol
$HOCH_2CH_2OH$

Polyethylene
$-(CH_2CH_2)_n-$

Ethylene
$-CH_2-CH_2-$



Branched polyethylene glycol (PEG) that was created by coupling a monofunctional PEG (mPEG)-benzatriazole carbonate of molecular mass 40 kDa to lysine. Conjugation of this PEG moiety to interferon-α2a (IFN- α2a) results in an agent with a significantly longer half-life, which requires less frequent administration and has an improved toxicity profile. NHS, *N*-hydroxysuccinimide.

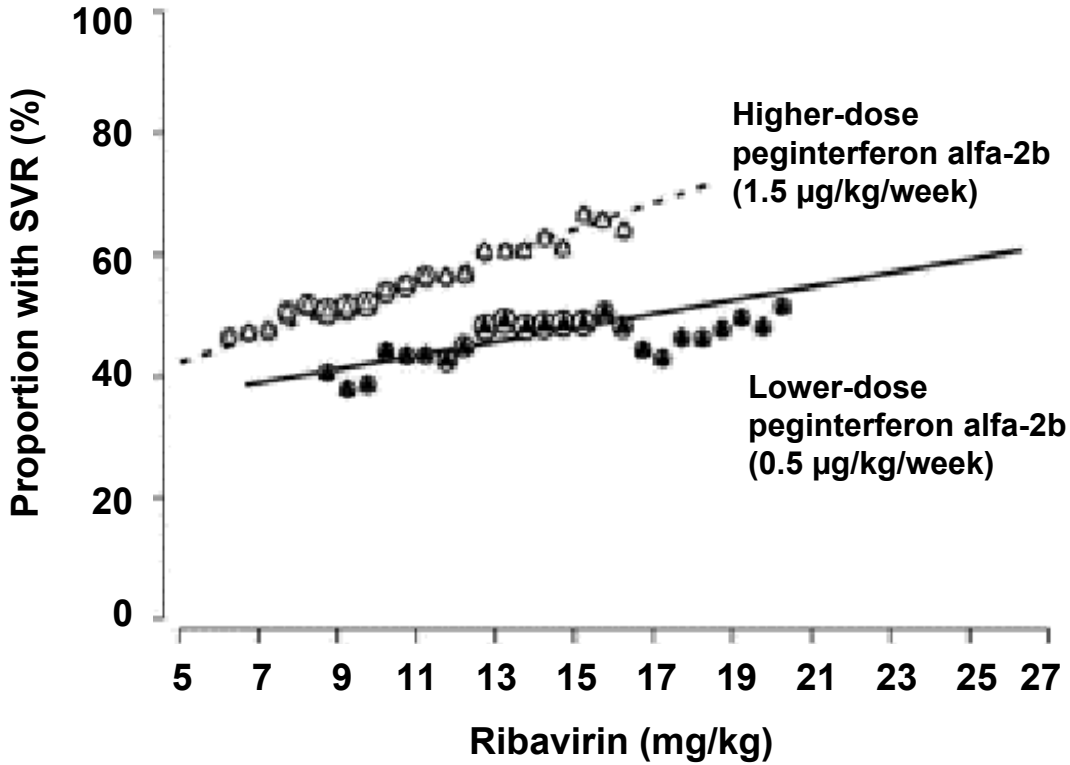
Tan *et al.*, Nature Reviews/Drug Discovery 1: 867-881 (2002)

Pegylated interferon α-2b plus ribavirin compared with interferon α 2b plus ribavirin for the initial treatment of chronic hepatitis C
Virological response at the end of treatment and follow-up

Endpoint	Sustained viral response (SVR) rate (number responding/total treated)		
	Higher-dose peginterferon 1.5 µg/kg/week + Ribavirin (800 mg/day)	Lower-dose peginterferon 0.5 µg/kg/week + Ribavirin (1000-1200 mg/day)	Interferon 3 MU x 3/week + Ribavirin (1000-1200 mg/day)
Overall			
End of treatment: all patients	65% (333/511)	56% (289/514)	54% (271/505)
SVR at end of follow-up: all patients	54% (274/511)	47% (244/514)	47% (235/505)
SVR by genotype			
1	42% (145/348)	34% (118/349)	33% (114/343)
2/3	82% (121/147)	80% (122/153)	79% (115/146)
4/5/6	50% (8/16)	33% (4/12)	38% (6/16)

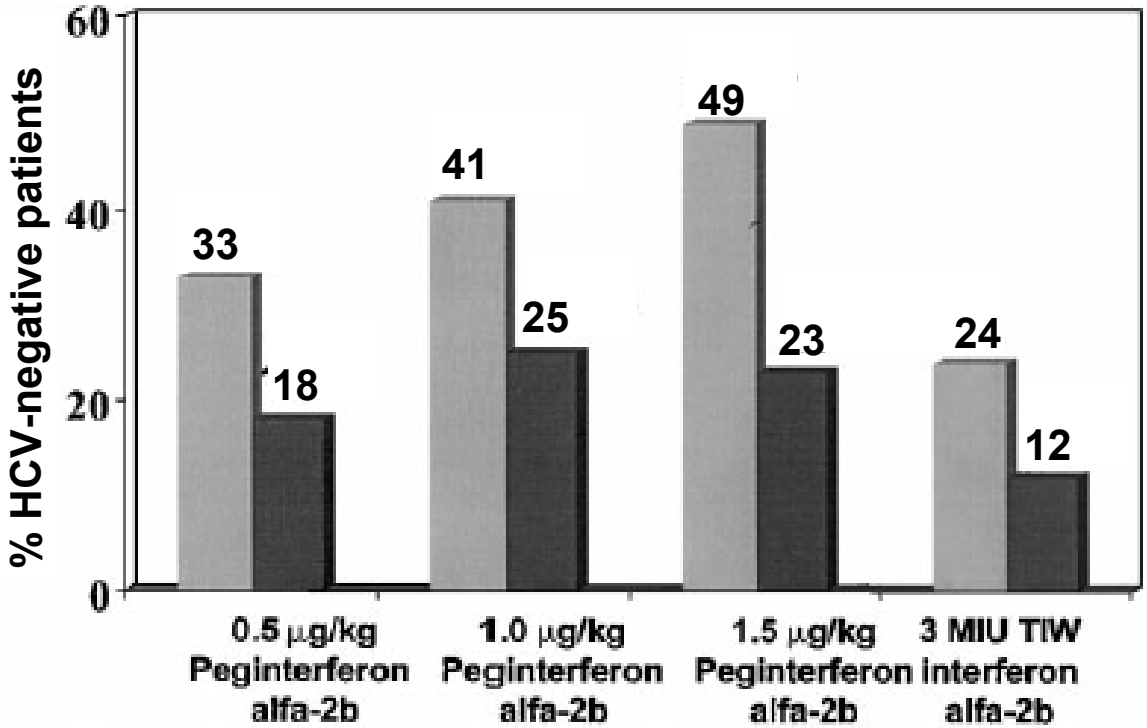
Manns *et al.*, Lancet 358: 958-965 (2001)

Peginterferon α-2b plus ribavirin for initial treatment of chronic hepatitis C
Logistic regression analyses
Sustained virological response (SVR) as a function of ribavirin dose (mg/kg) and dose of peginterferon alfa-2B



Manns *et al.*, Lancet 358: 958-965 (2001)

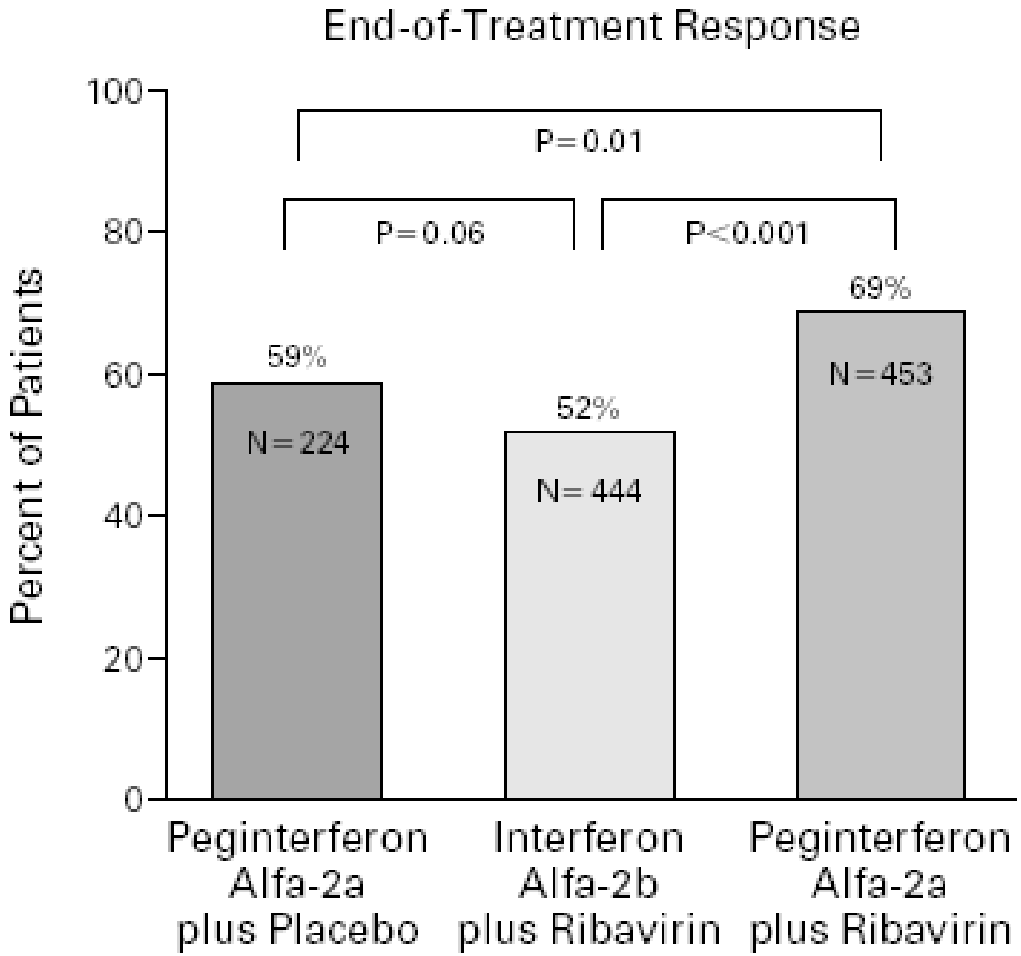
Pegylated interferon α-2b compared to interferon α-2b for the initial treatment of chronic hepatitis C
Virologic response at end of treatment and end of follow-up



Percentage of subjects with virologic responses (loss of detectable serum HCV RNA) at the end of treatment (▭) and at the end of follow-up (■)

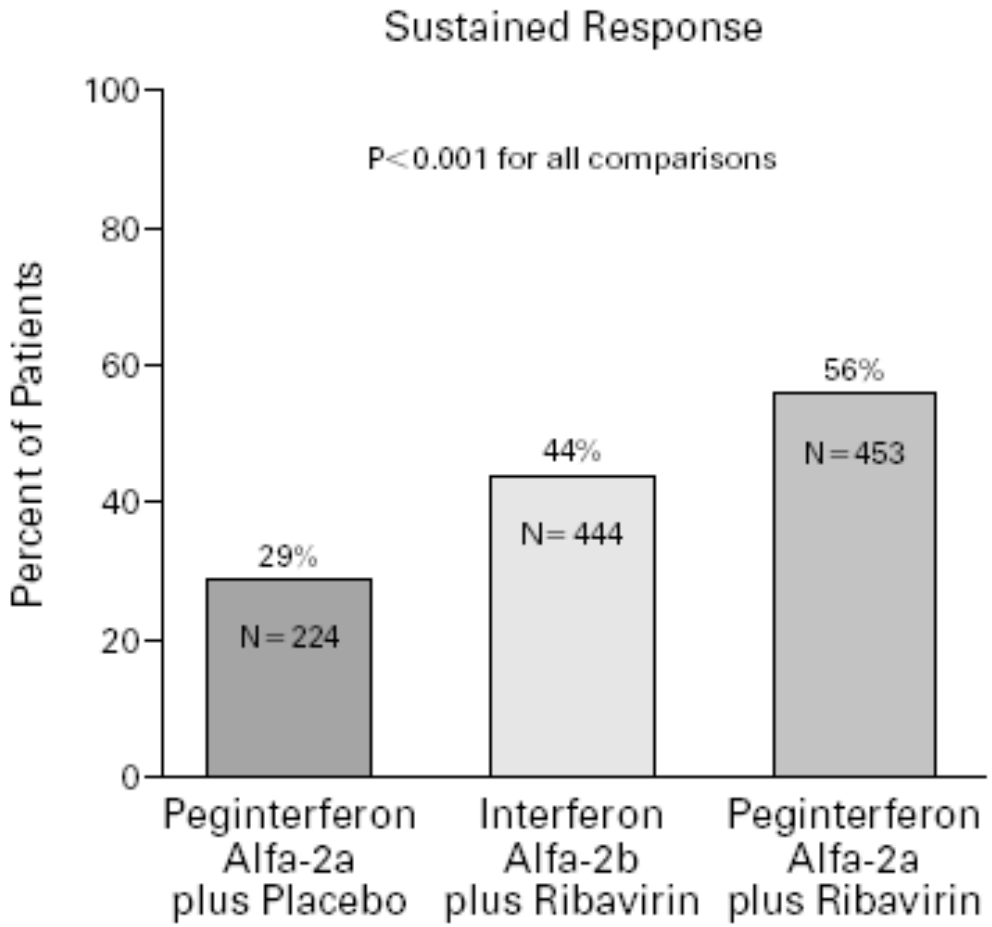
Lindsay *et al.*, Hepatology 34: 395-403 (2001)

Pegylated interferon α-2a, as compared to interferon α-2b, plus ribavirin for the treatment of chronic hepatitis C virus infection



Fried *et al.*, N. Engl. J. Med. 347: 975-982 (2002)

Pegylated interferon α-2a, as compared to interferon α-2b, plus ribavirin for the treatment of chronic hepatitis C virus infection



Fried *et al.*, N. Engl. J. Med. 347: 975-982 (2002)

Pegylated interferon α-2a, as compared to interferon α-2b, plus ribavirin for the treatment of chronic hepatitis C virus infection Proportion of patients with a sustained virologic response as a function of HCV genotype[a]

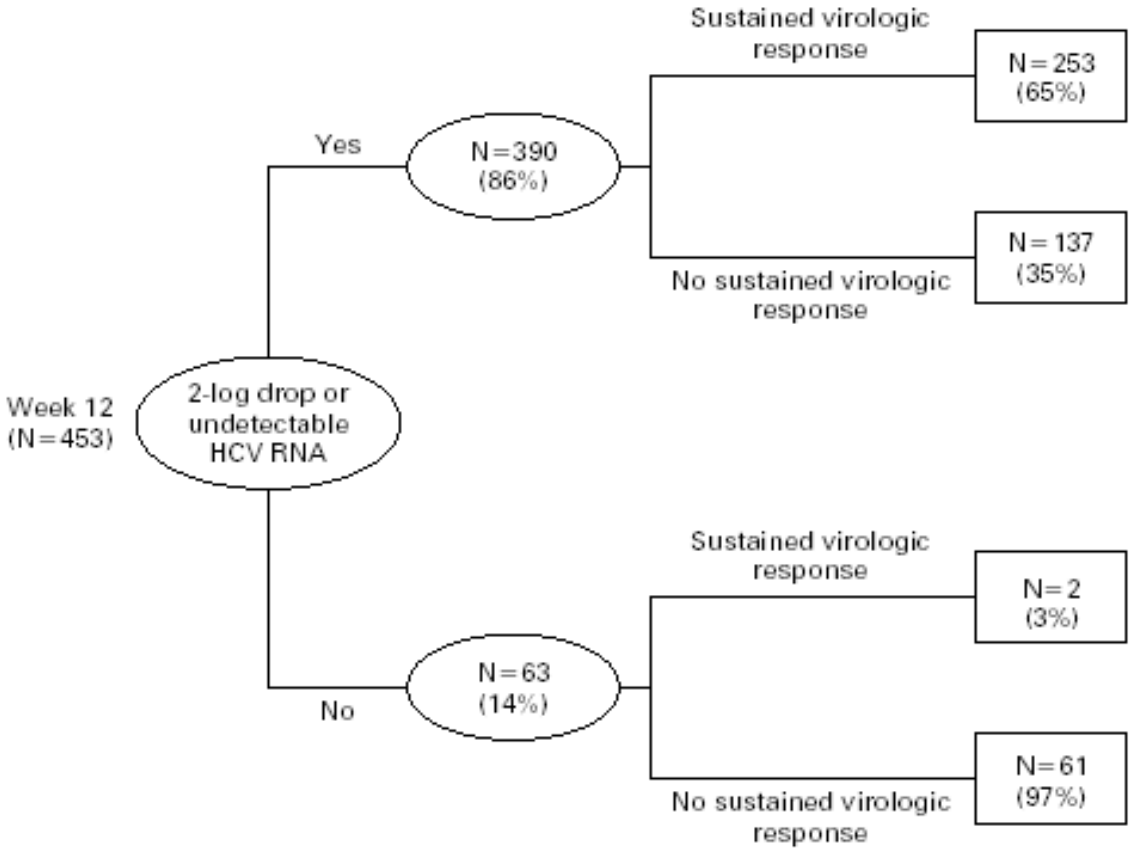
	Peginterferon alfa-2a plus ribavirin (N = 453)	Interferon alfa-2b plus ribavrin (N = 444)	Peginterferon alfa-2a plus placebo (N = 224)
	No./total no. (%)		
HCV genotype[b]			
All patients	255/453 (56)	197/444 (44)	66/224 (29)
Genotype 1	138/298 (46)	103/285 (36)	30/145 (21)
Genotype 2 or 3	106/140 (76)	88/145 (61)	31/69 (45)
Genotype 4	10/13 (77)	4/11 (36)	4/9 (44)

[a]A sustained virologic response was defined as no detectable hepatitis C virus (HCV) RNA 24 weeks after the cessation of therapy.

[b]Six patients had other genotypes

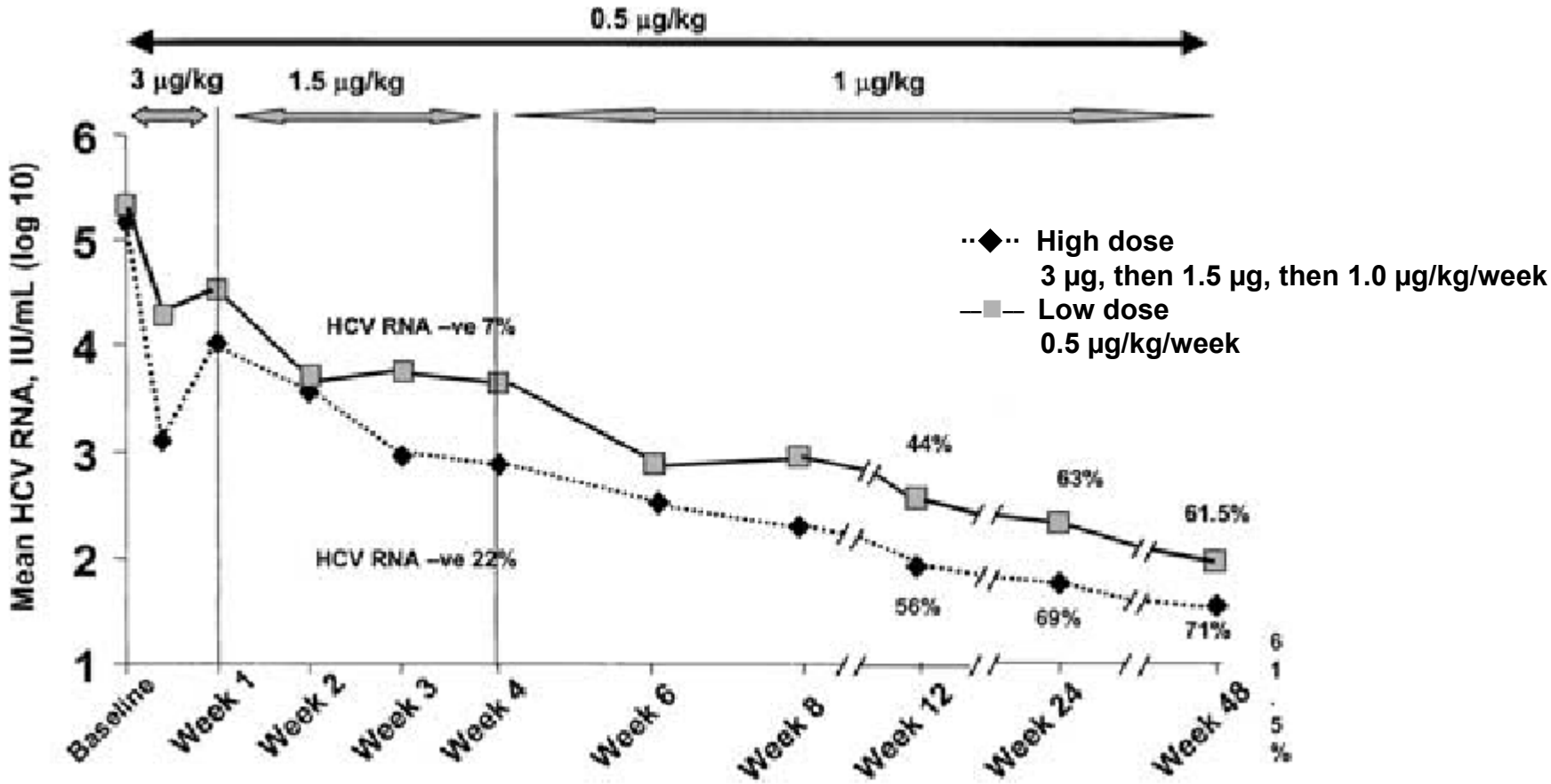
Fried *et al.*, N. Engl. J. Med. 347: 975-982 (2002)

Pegylated interferon α-2a plus ribavirin for the treatment of chronic hepatitis C virus infection
Predictability of sustained virologic response



Fried *et al.*, N. Engl. J. Med. 347: 975-982 (2002)

Kinetics of HCV RNA and proportions of patients who became HCV RNA negative at different times with the high and low doses of peginterferon α-2b plus ribavirin



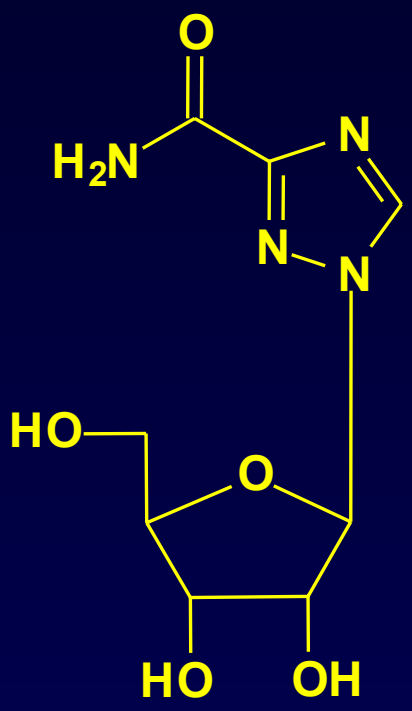
Buti *et al.*, Hepatology 35: 930-936 (2002)

Adverse events in 453 patients with chronic hepatitis C virus infecton who received peginterferon alfa-2a plus ribavirin (percentage of patients in parentheses)

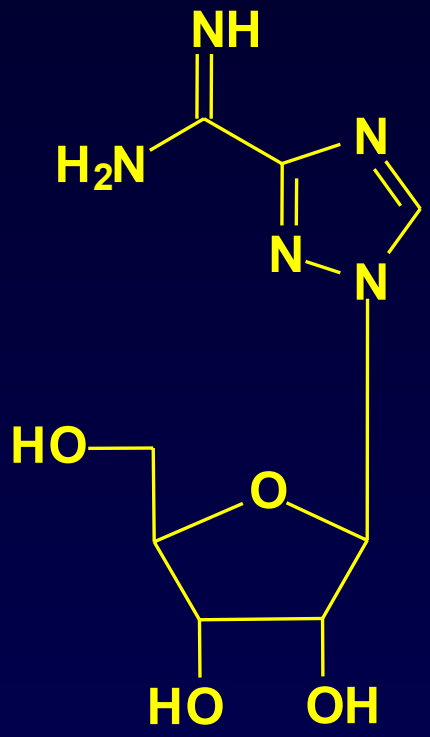
Adverse events	Peginterferon alfa-2a plus ribavirin	
Fatigue*	242	(54)
Headache*	211	47)
Pyrexia*	195	(43)
Myalgia*	189	(42)
Insomnia	168	(37)
Nausea	130	(29)
Alopecia	128	(28)
Arthralgia	121	(27)
Irritability	109	(24)
Rigors*	106	(24)
Pruritus	101	(22)
Depression	100	(22)
Decreased appetite	96	(21)
Dermatitis	95	(21)

*This symptom is one of the influenza-like symptoms often seen with interferon treatment

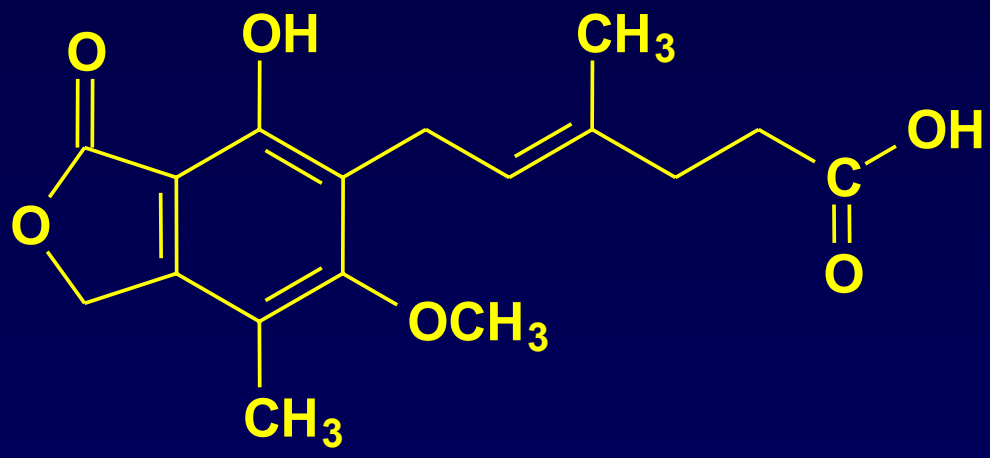
Fried *et al.*, N. Engl. J. Med. 347: 975-982 (2002)



Ribavirin



Viramidine



Mycophenolic acid

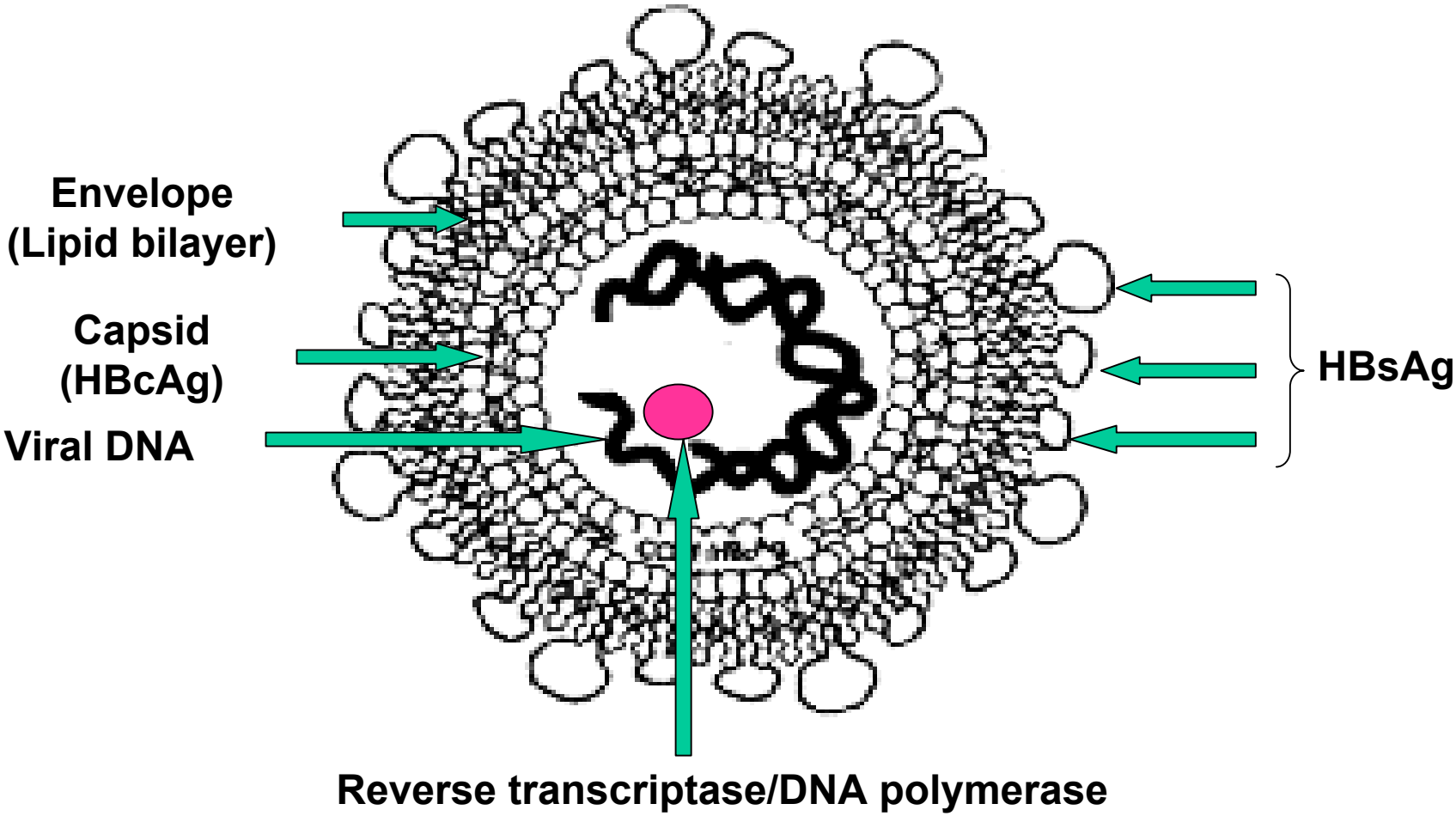
Selected IFN-based therapies for the treatment of HCV infection

Drug name	Company	Clinical phase
Monotherapy		
Intron A (IFN-α2b, recombinant)	Schering-Plough	FDA approval, 1995
Roferon A (IFN-α2a, recombinant)	Roche	FDA approval, 1996
Infergen A (IFN alfacon-1)	InterMune Pharmaceuticals	FDA approval, 1997
Welferon (lymphoblastoid IFN-αn1)	GlaxoSmithKline	FDA approval, 1999
PEG-INTRON (PEGylated IFN-α2b)	Schering-Plough	FDA approval, 2001
Pegasys (PEGylated IFN-α2a)	Roche	FDA approval, 2001
Omniferon (natural IFN-α)	Viragen (Scotland)	Phase II
Omega IFN (IFN-ϖ)	BioMedicines	Phase II
Albuferon- α (albumin-IFN-α2b)	Human Genome Sciences	Phase I
Rebif (IFN-β1a)	Serono	Preclinical
Combination therapies		
Rebetron (Intron A and ribavirin)	Schering-Plough	FDA approval, 1998
PEG-INTRON and ribavirin	Schering-Plough	FDA approval, 2001
Pegasys and ribavirin	Roche	FDA application, submitted

Tan *et al.*, Nature Reviews/Drug Discovery 1: 867-881 (2002)

Hepatitis B

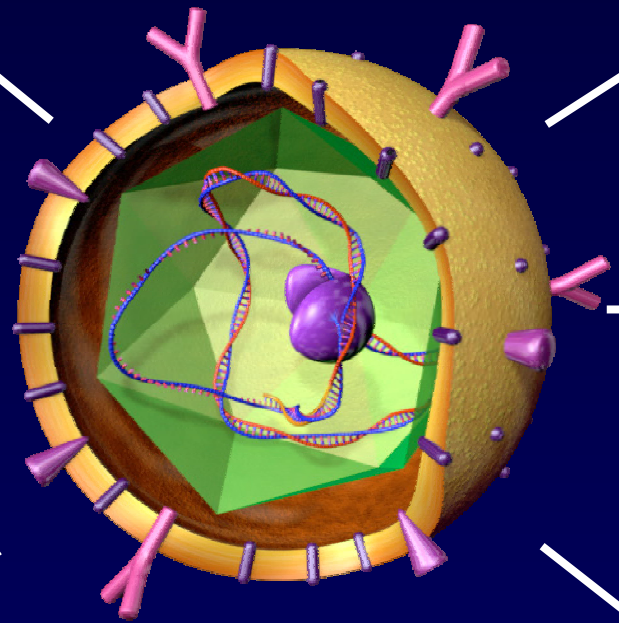
Scheme of HBV Dane particle



Transmission of Hepatitis B Infection

Transfusion and transplant recipients

Newborns of long-term carriers



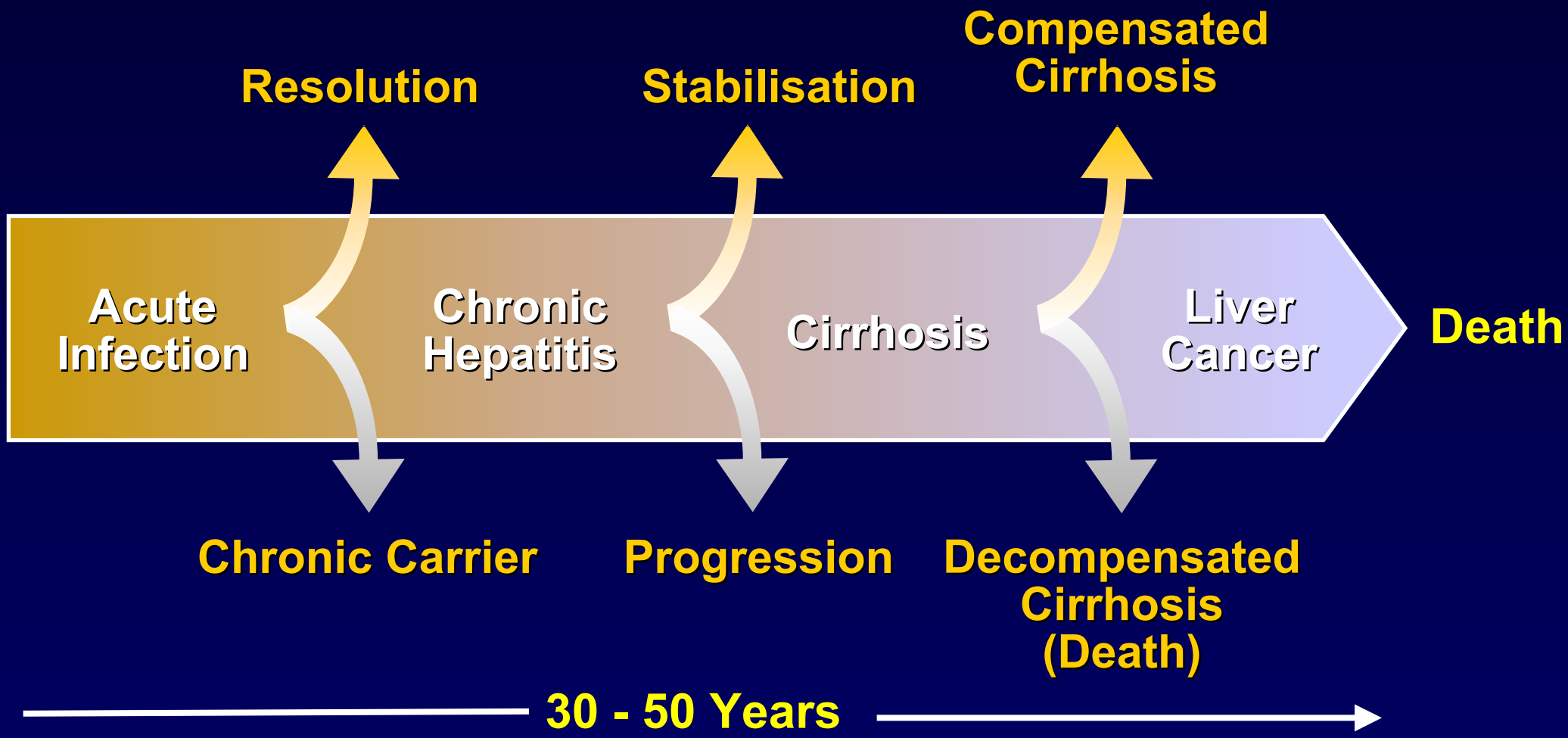
Individuals with multiple sexual partners

Intravenous drug users

Healthcare workers

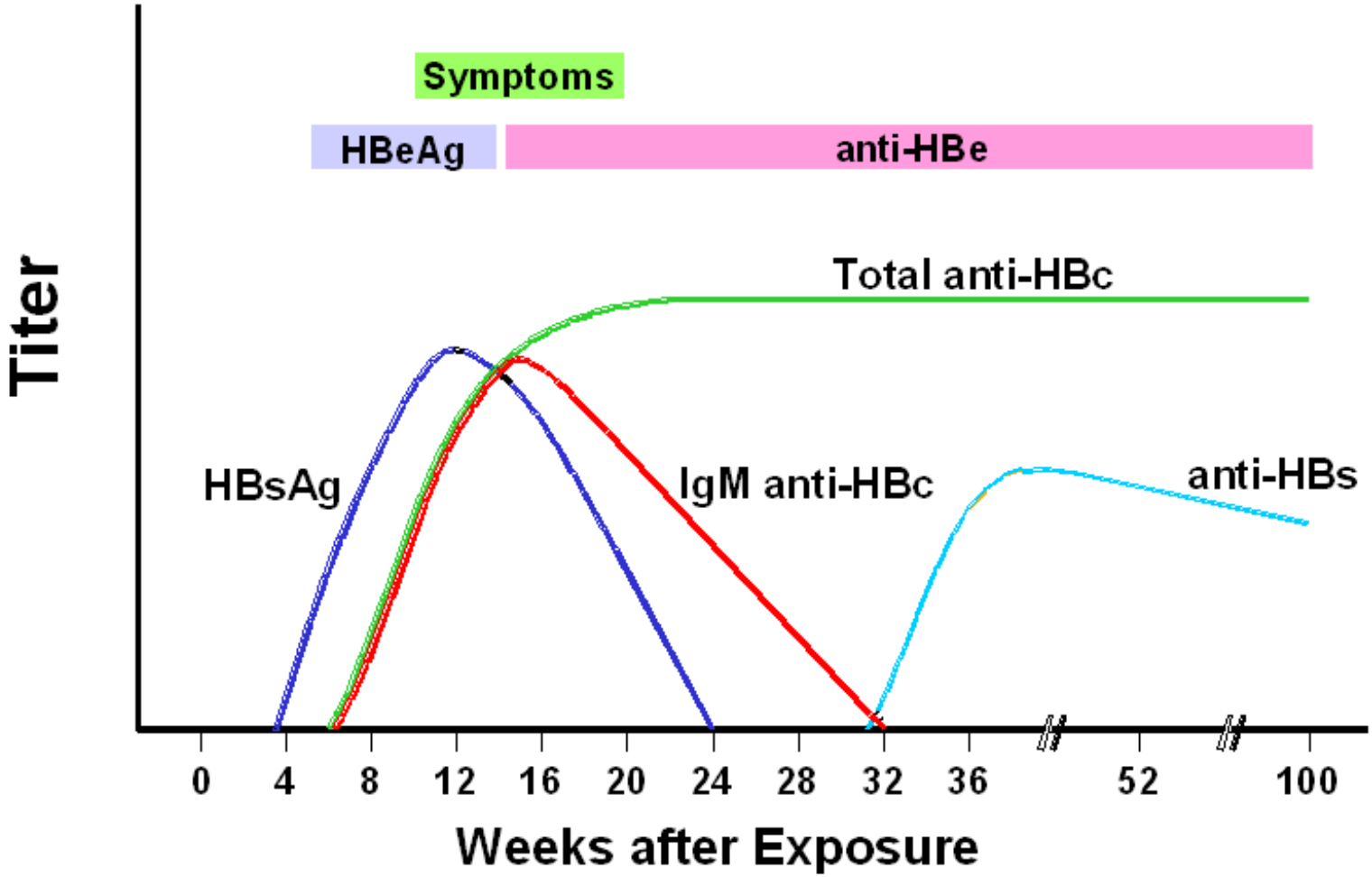
Prisoners and other institutionalised people

Natural History of Chronic HBV Infection



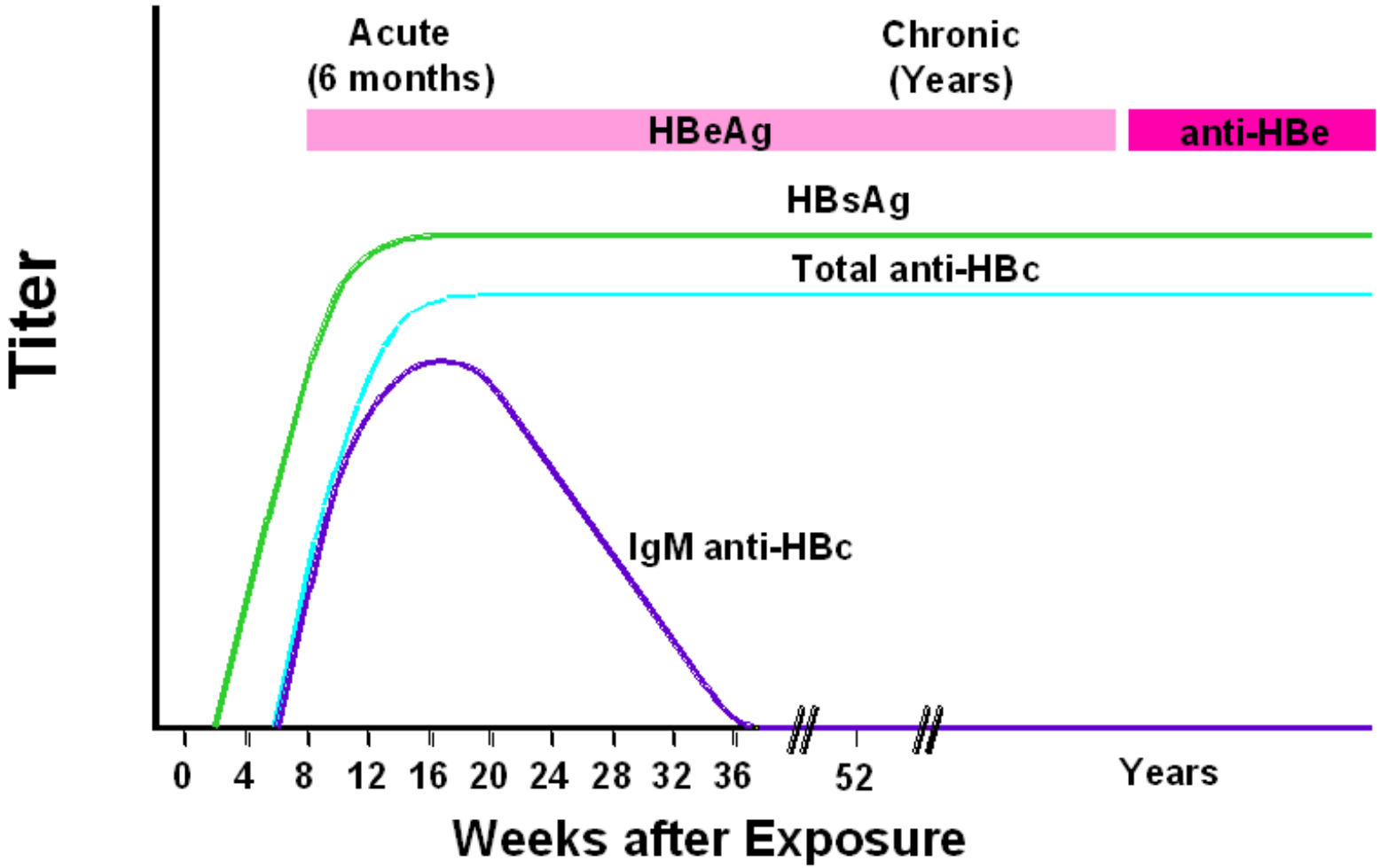
Feitelson, Lab. Invest. 71, 324-349 (1994)

Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



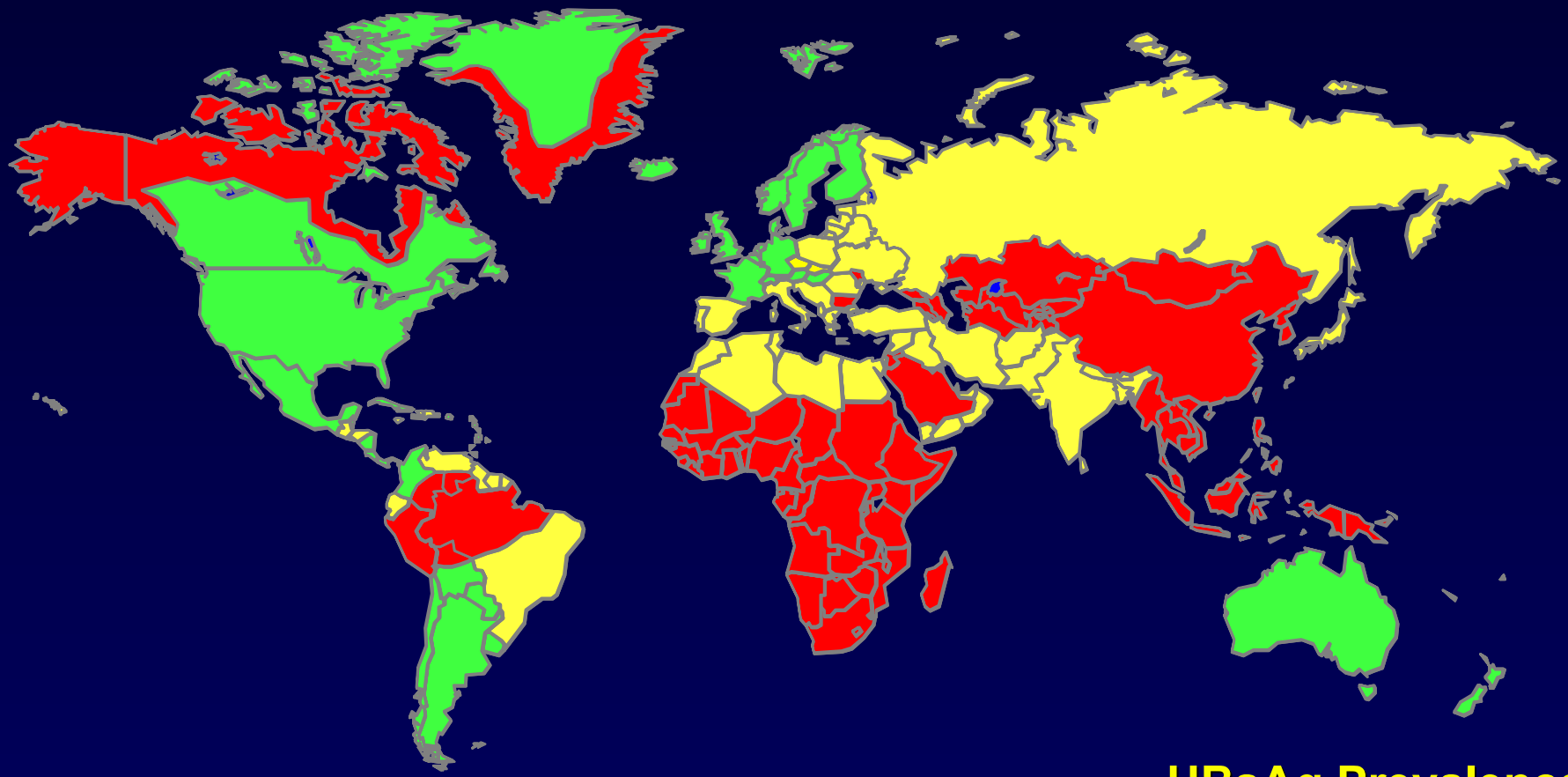
Source: http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_b/slide_3.htm

Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course



Source: http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_b/slide_3.htm

Global Distribution of Chronic HBV Infection

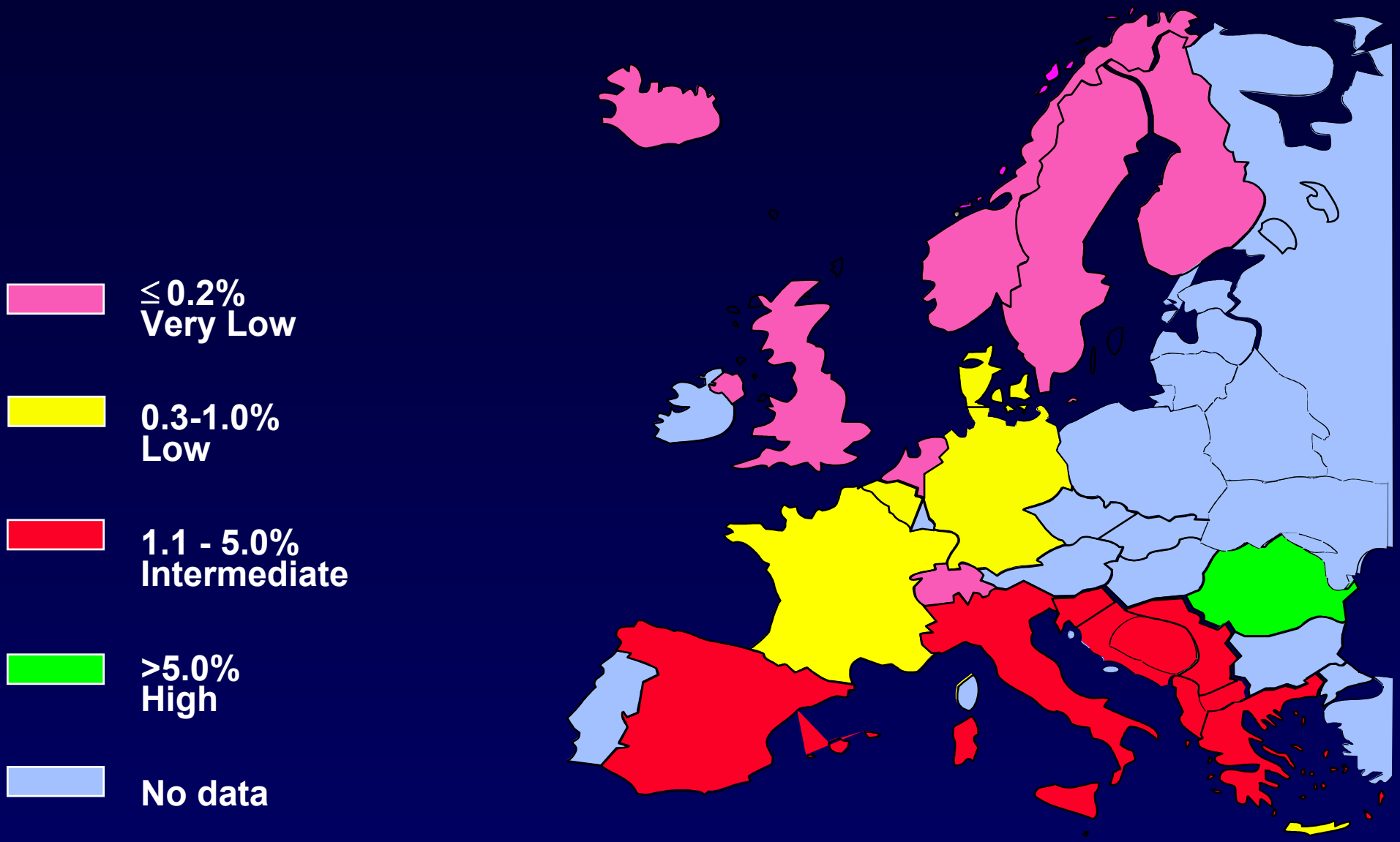


- 350 million chronic carriers worldwide
- Ninth leading cause of death
- Nearly 75% of HBV chronic carriers are Asian

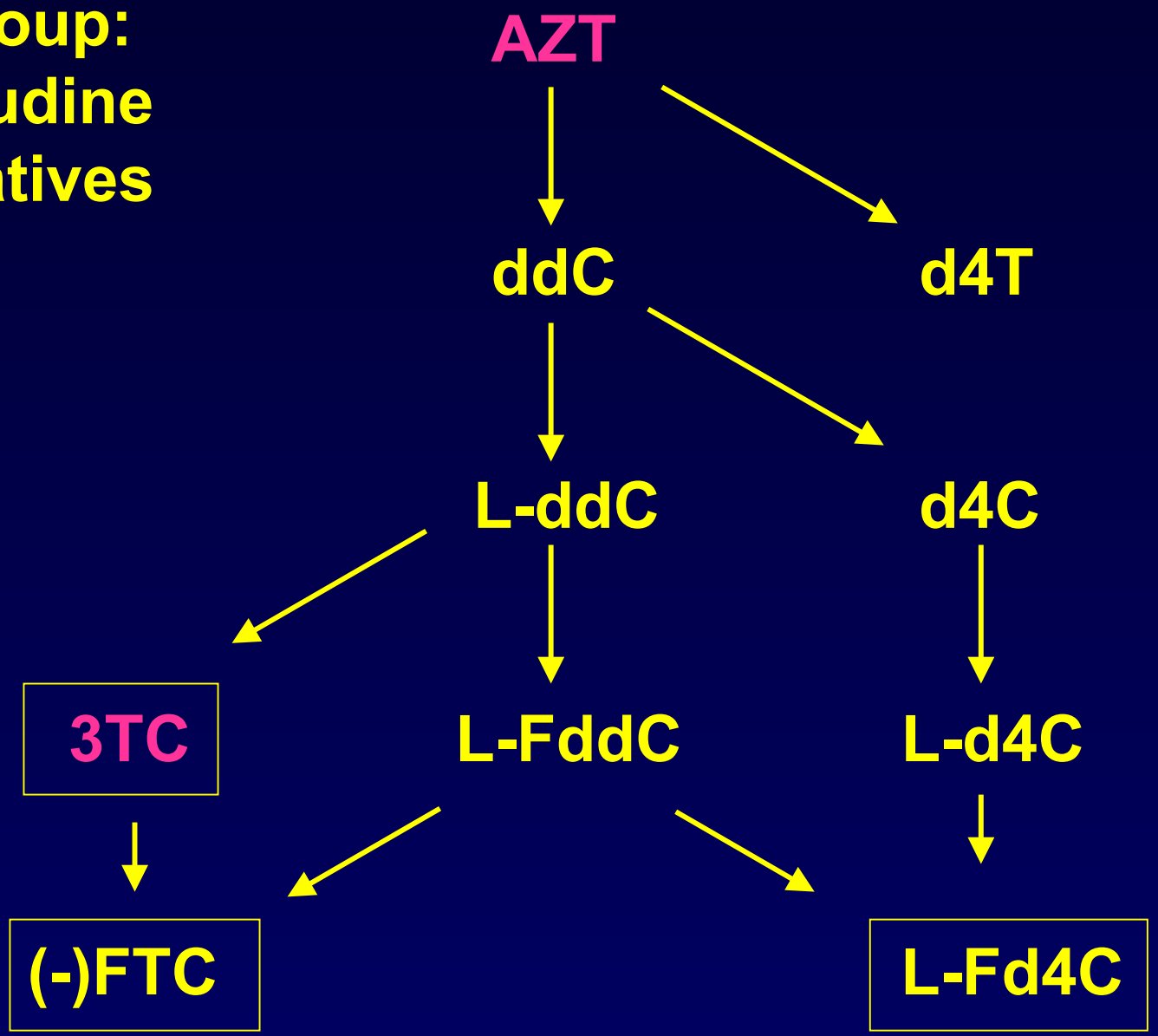
HBsAg Prevalence (%)

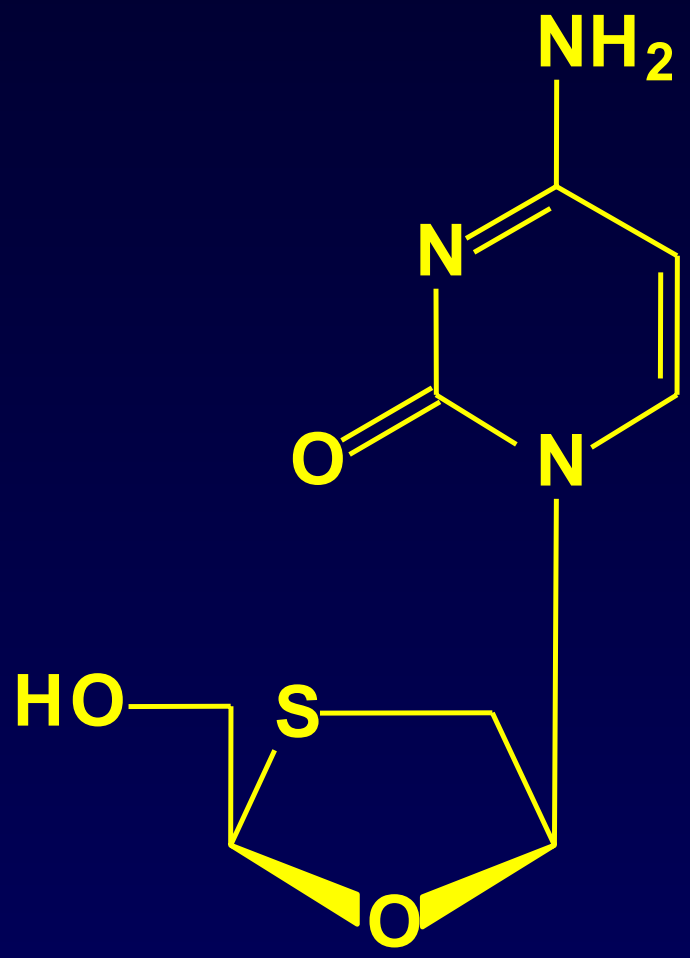
- ≥8: High
- 2-7: Intermediate
- <2: Low

Prevalence of HBsAg Positivity in Europe



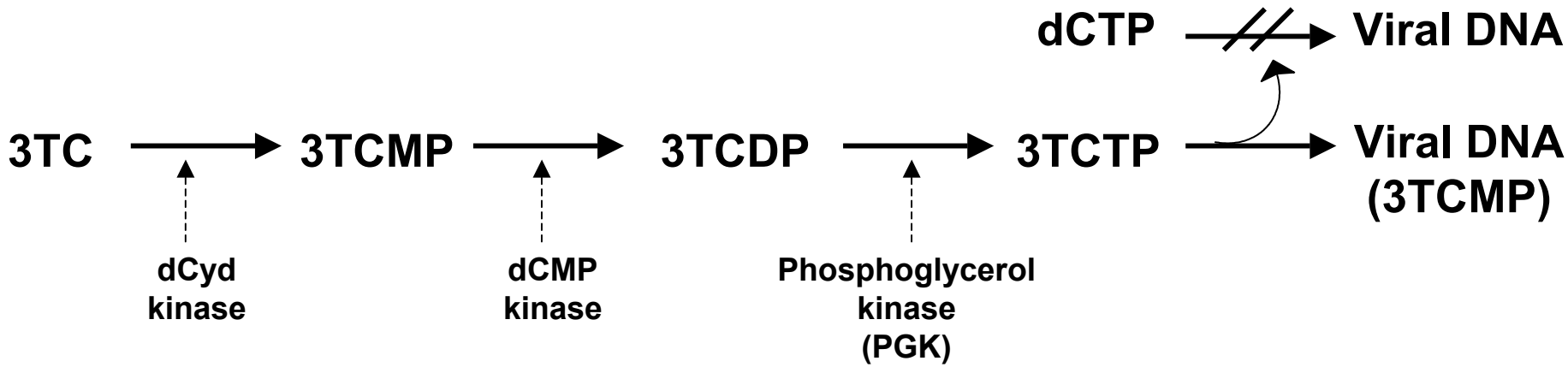
1st group: zidovudine derivatives



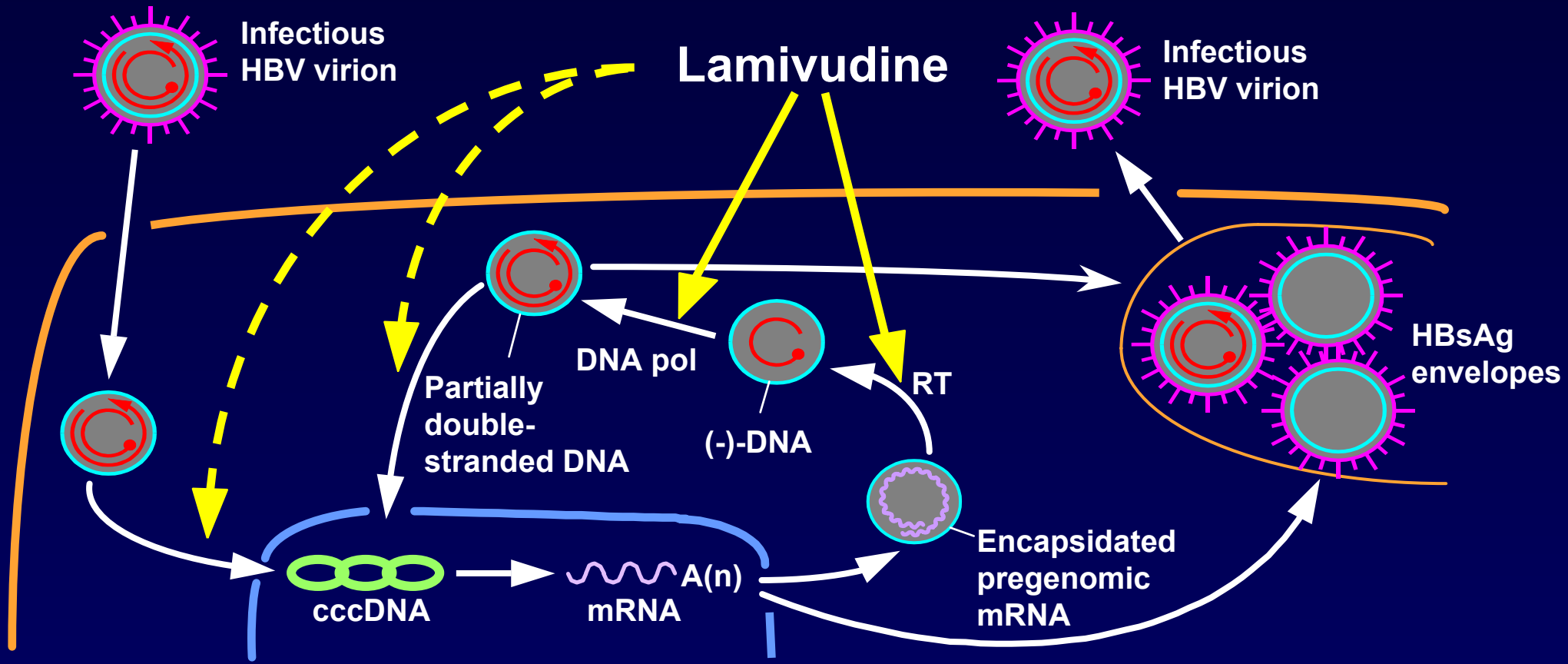


3TC
Lamivudine

Metabolic pathway of 3TC (Lamivudine) and interaction with HIV and HBV DNA

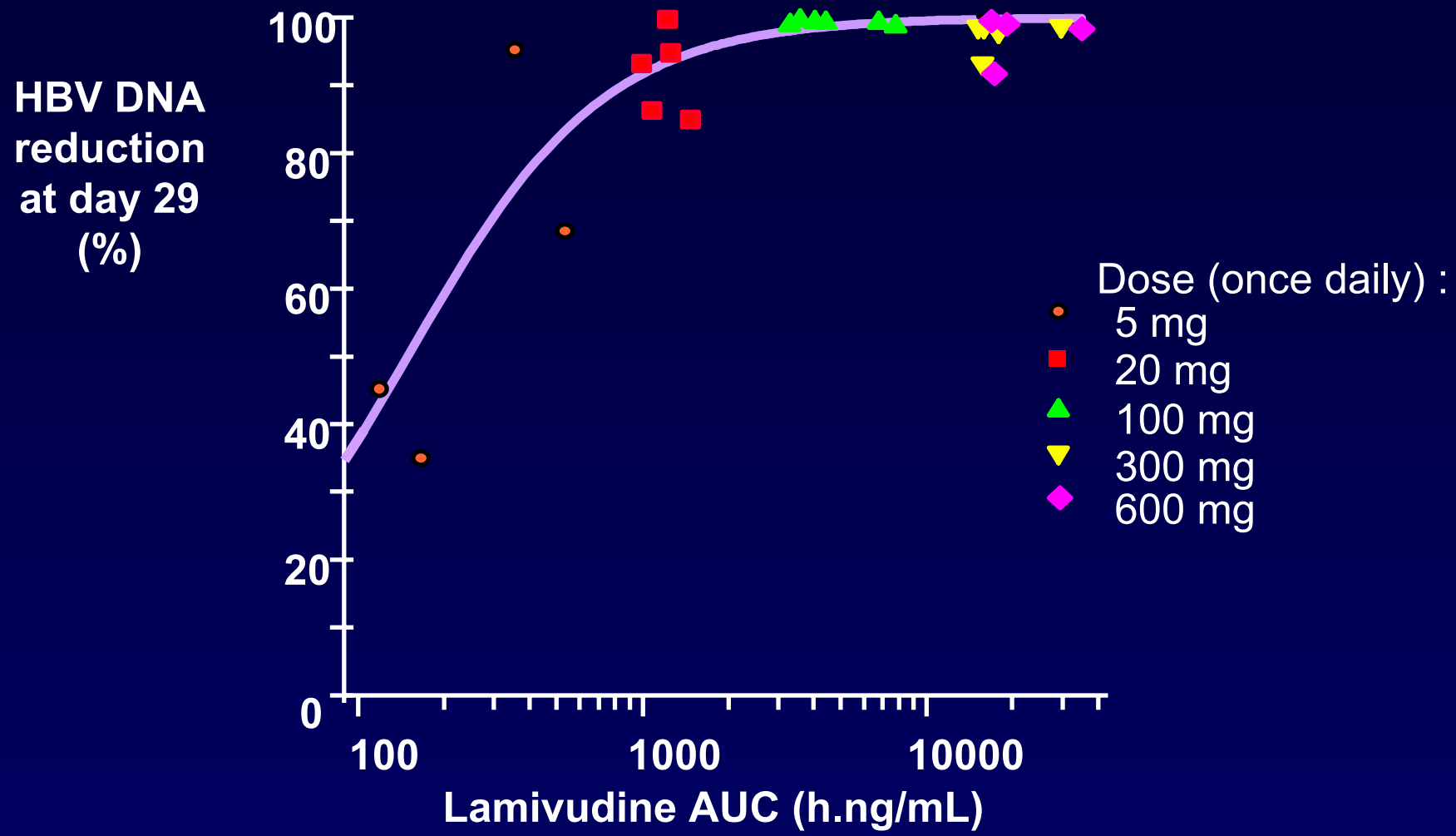


Replication Cycle of Hepatitis B Virus; Mechanism of Action of Lamivudine



Lai and Yuen, J. Med. Virol. 61, 367-373 (2000)

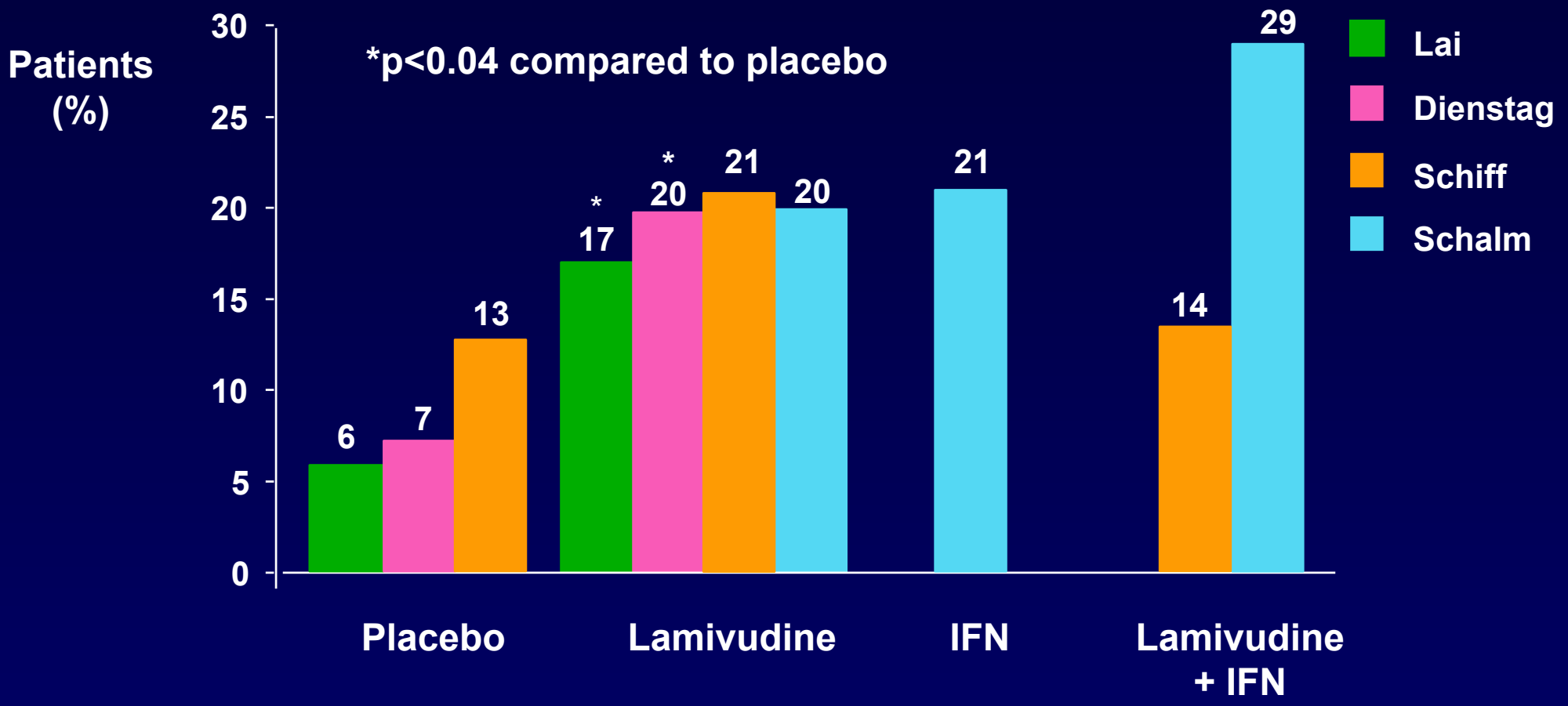
HBV DNA Reduction versus Lamivudine Bioavailability



Johnson *et al.*, Clin. Pharmacokinet. 36, 41-66 (1999)

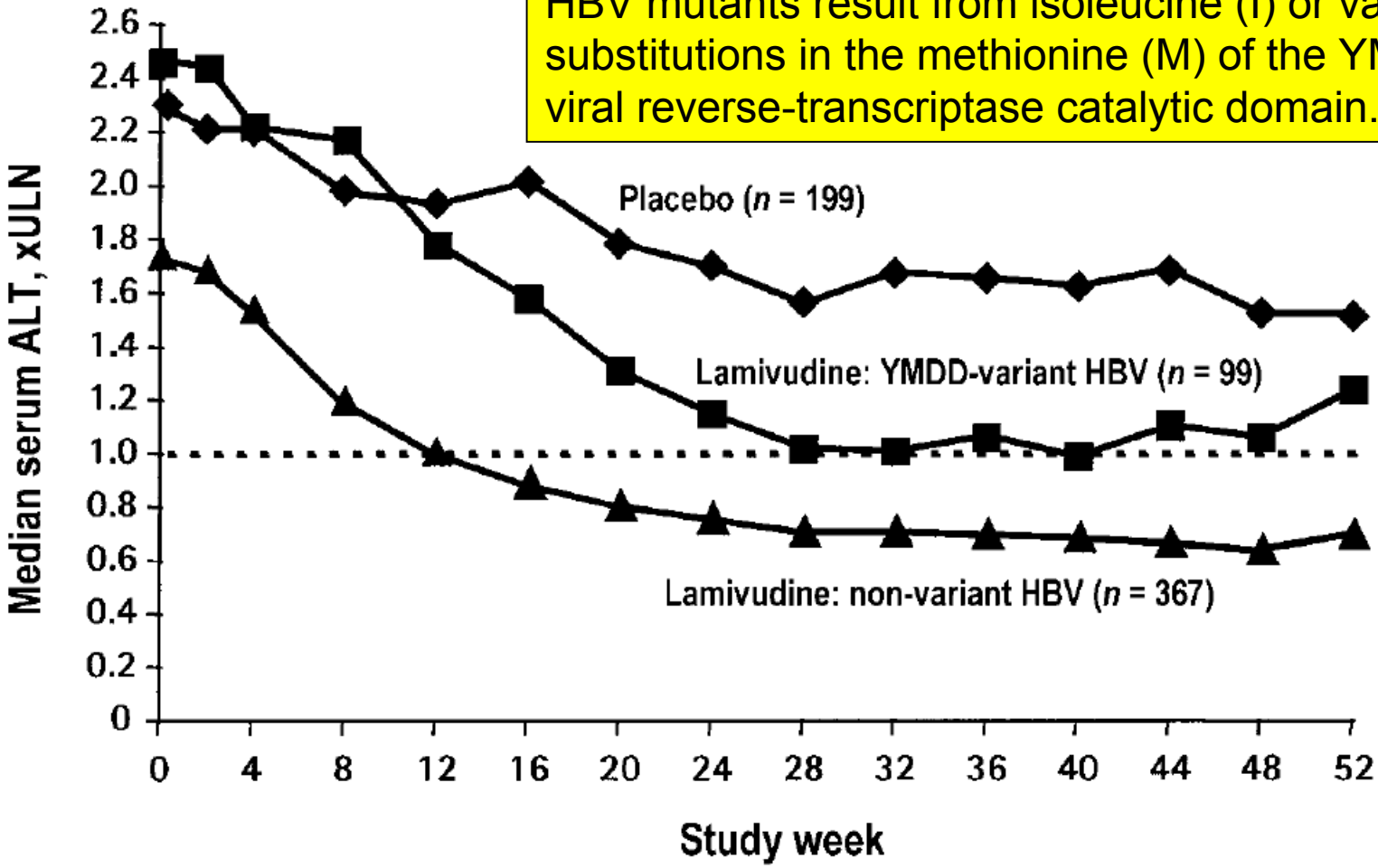
HBeAg Seroconversion After One Year of Therapy

Seroconversion = HBeAg-ve and anti-HBe+ve



Median serum alanine aminotransferase (ALT) level during 1 year of lamivudine therapy in patients with and without detectable YMDD-variant hepatitis B virus infection at the end of the year

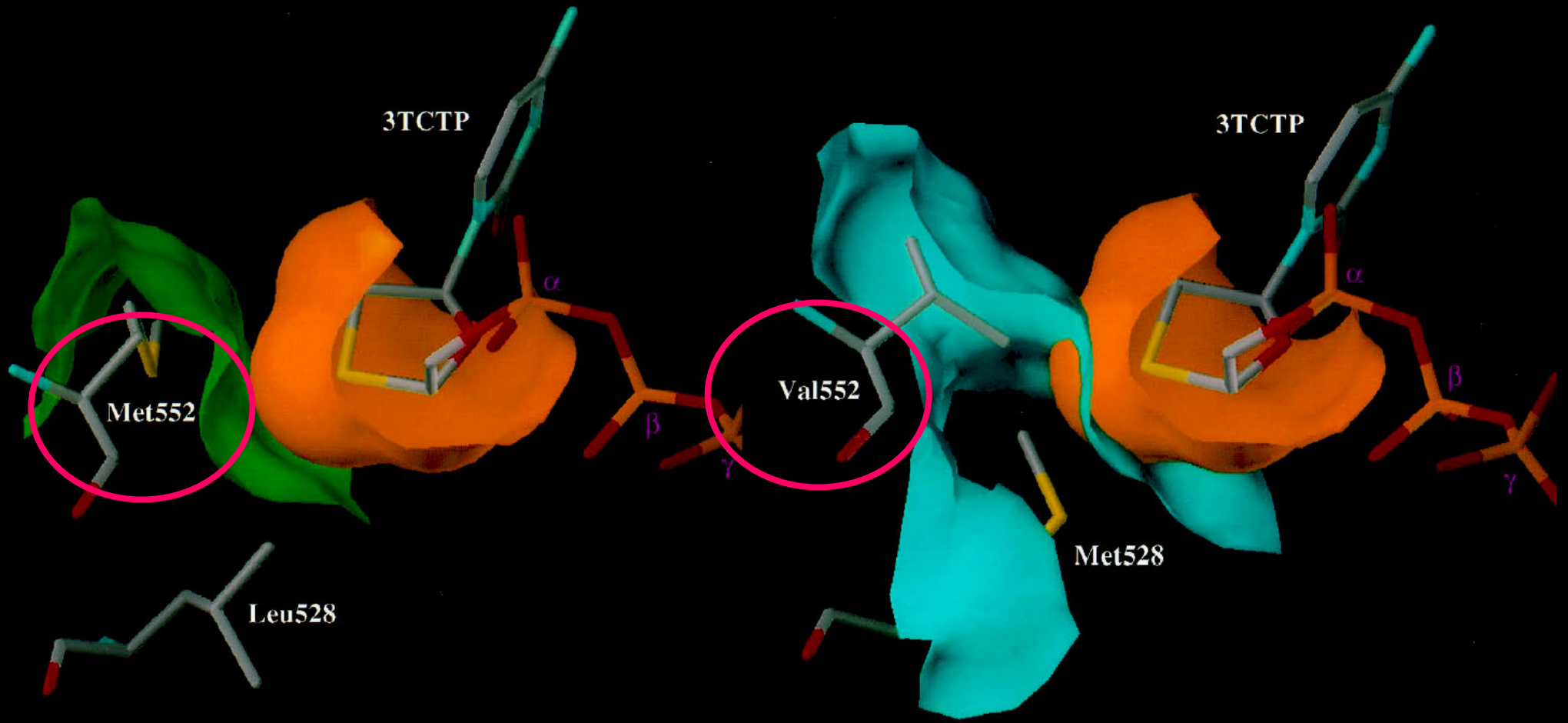
HBV mutants result from isoleucine (I) or valine (V) substitutions in the methionine (M) of the YMDD motif in the viral reverse-transcriptase catalytic domain.



ULN, upper limit of normal.

Lai *et al.*, Clin. Infect. Dis. 36, 687-696 (2003)

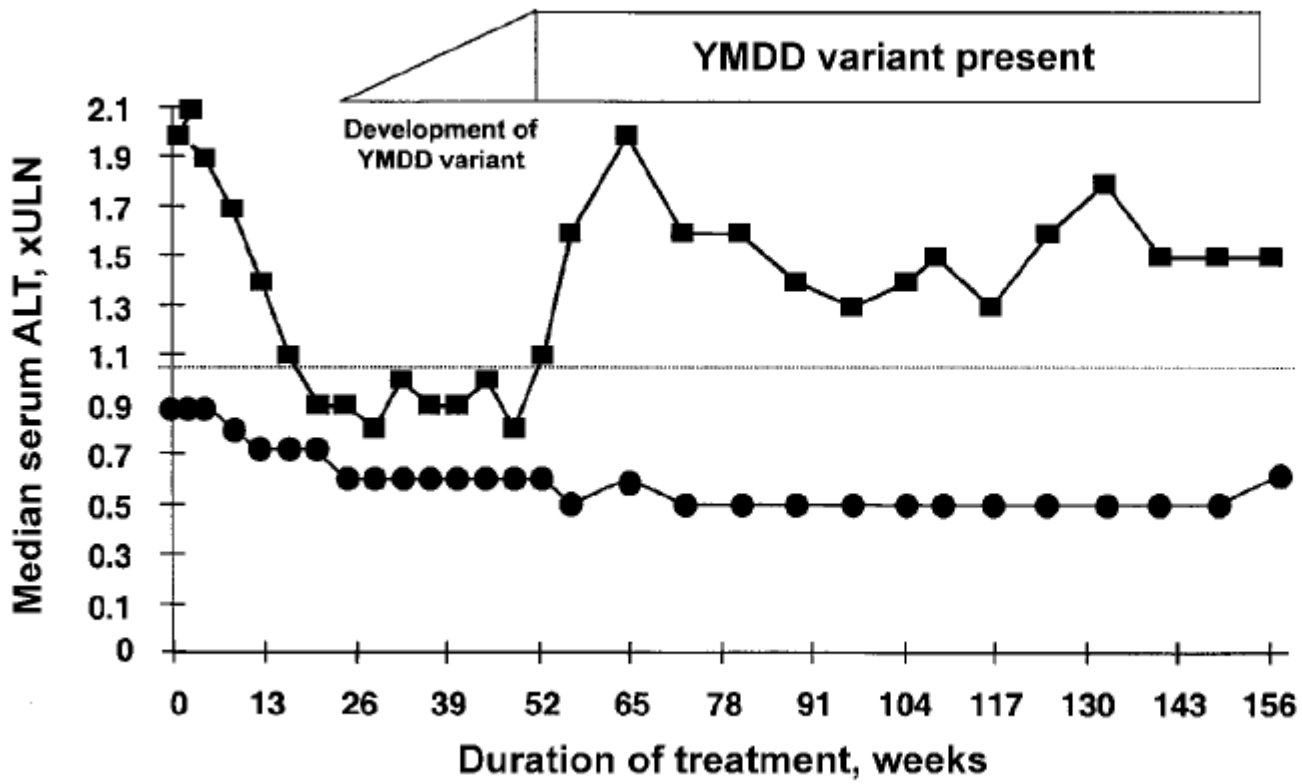
Interaction of 3TCTP (lamivudine triphosphate) with YMDD region of HBV DNA polymerase



Binding of 3TCTP to wild-type (left) and Met552Val mutant (right) HBV DNA polymerase. Molecular modeling suggests that steric hindrance (right) between 3TCTP and the mutated amino acid, Val552, is the primary cause of 3TCTP resistance. This steric conflict is not observed in the binding of 3TCTP to the wild-type HBV polymerase.

Das et al., J. Virol. 75: 4771-4779 (2001)

Median serum alanine aminotransferase (ALT) level during 3 years of daily lamivudine (100 mg) therapy in the subset of study participants in whom YMDD variants developed during year 1 of therapy and persisted for ≥ 2 years.



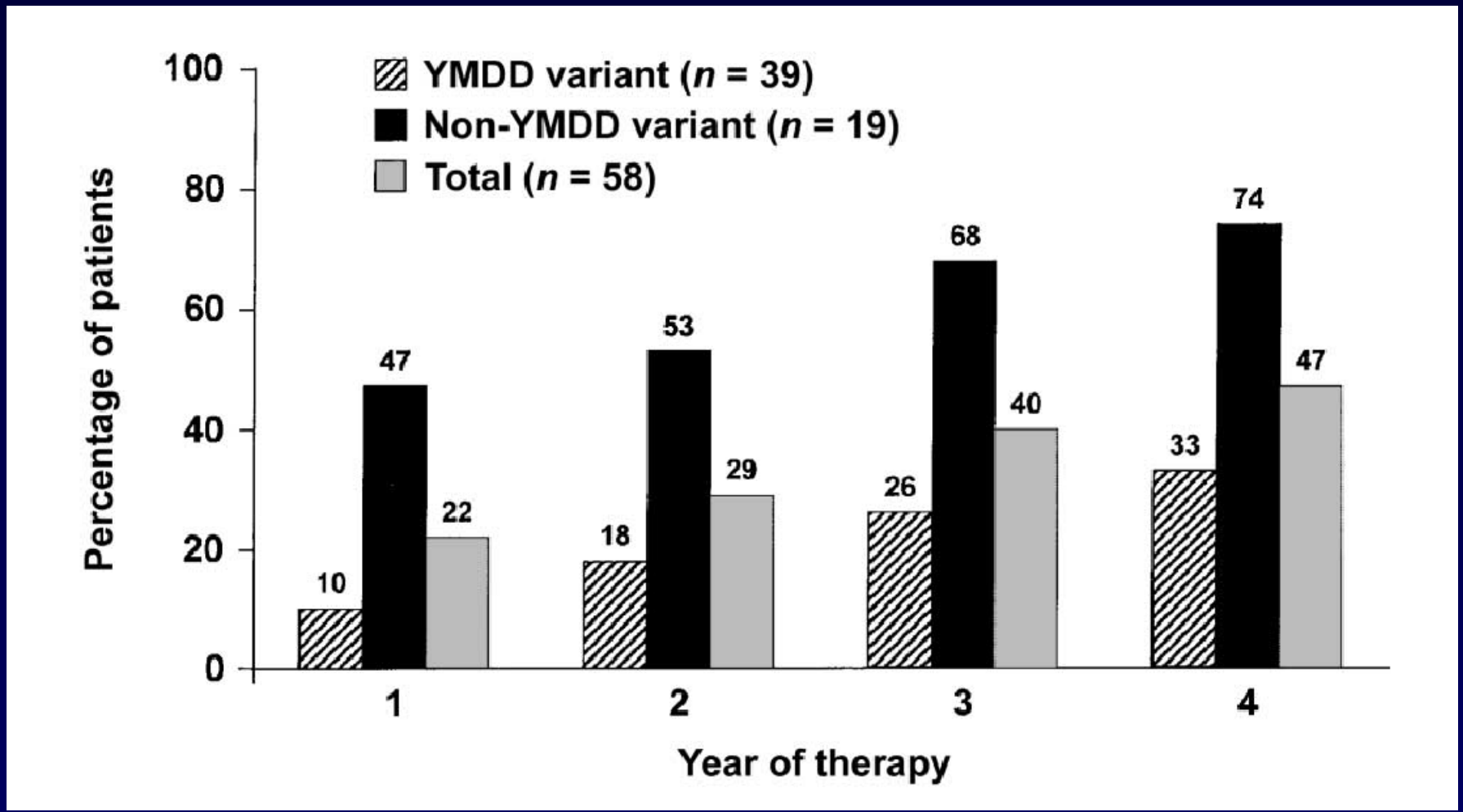
■ YMDD variant (*n* = 24)

● Wild-type/undetectable HBV DNA (*n* = 95)

ULN, upper limit of normal.

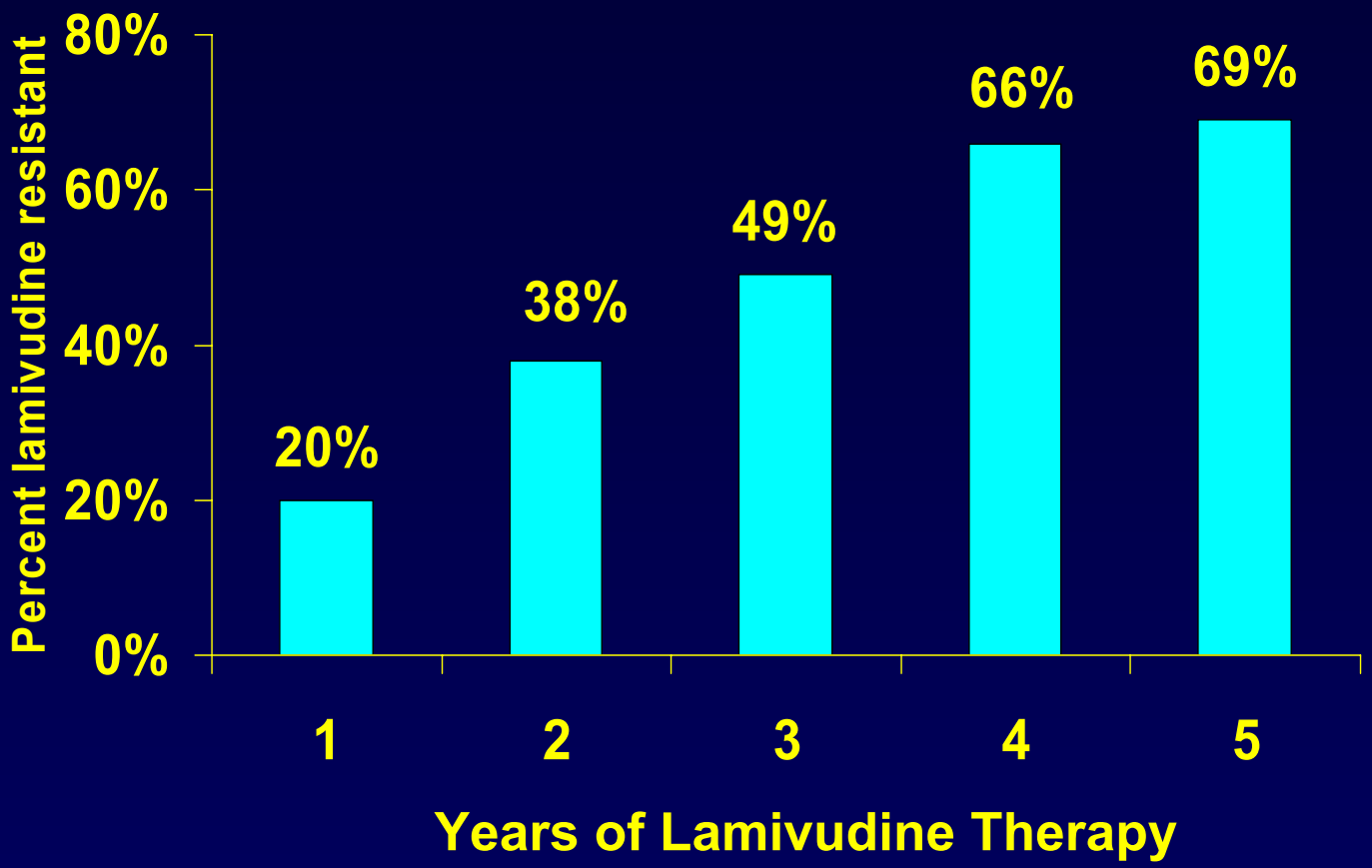
Lai *et al*., Clin. Infect. Dis. 36, 687-696 (2003)

Proportion of patients with hepatitis B e antigen seroconversion at the end of 1-4 years of therapy with lamivudine (100 mg), analyzed with respect to whether YMDD-variant hepatitis B virus was detectable

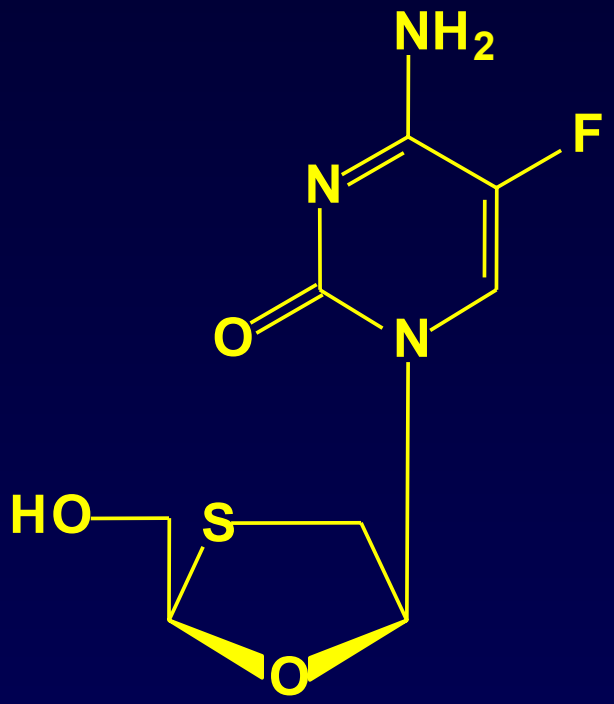


Lai *et al.*, Clin. Infect. Dis. 36, 687-696 (2003)

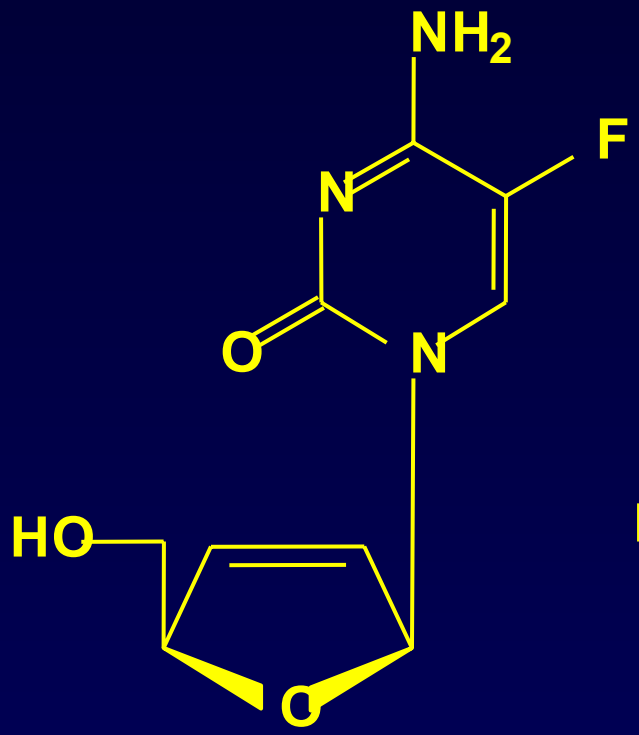
Incidence of lamivudine resistance in chronic hepatitis B



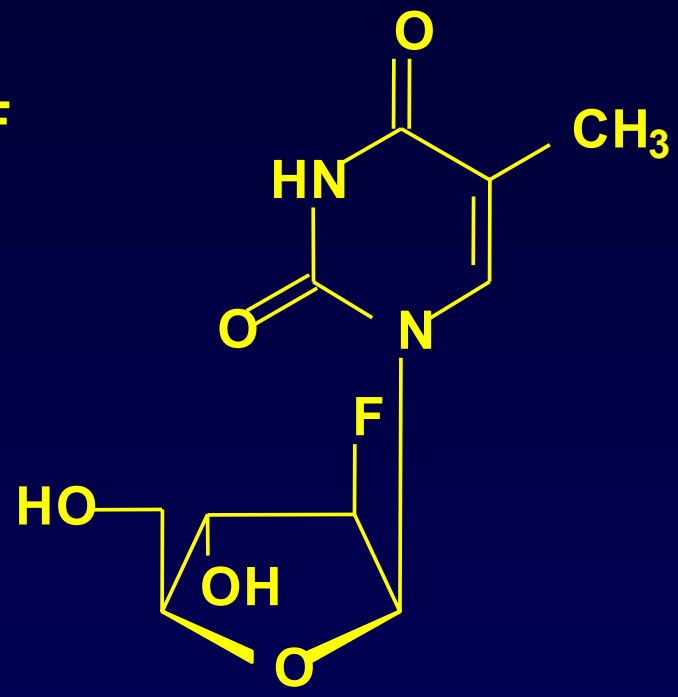
Westland *et al*., 37th Annual Meeting of the European Association for the Study of Liver Diseases, Madrid, Spain, 17-21 April 2002. Oral presentation 568.



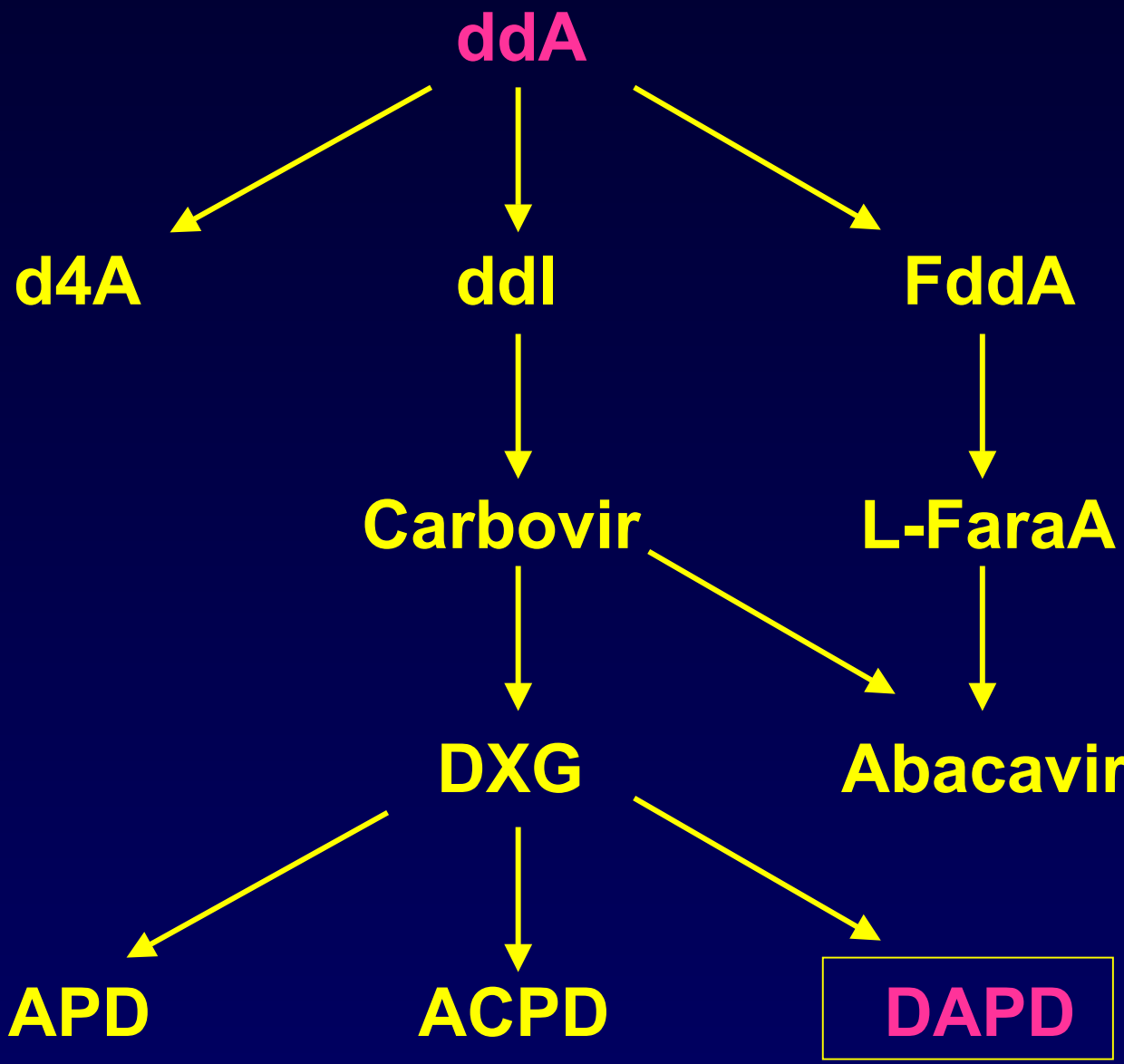
(-)FTC
Emtricitabine



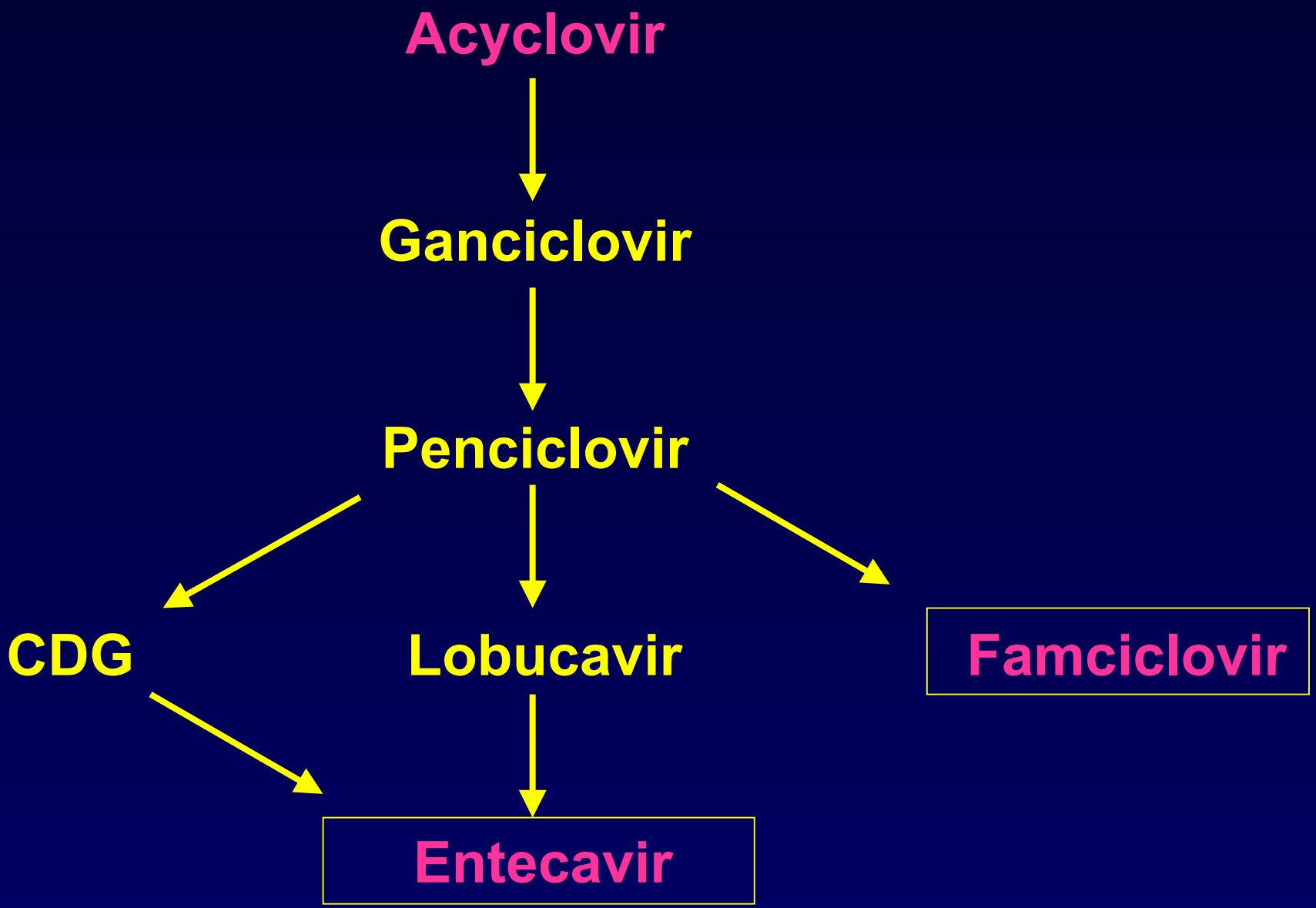
L(-)Fd4C

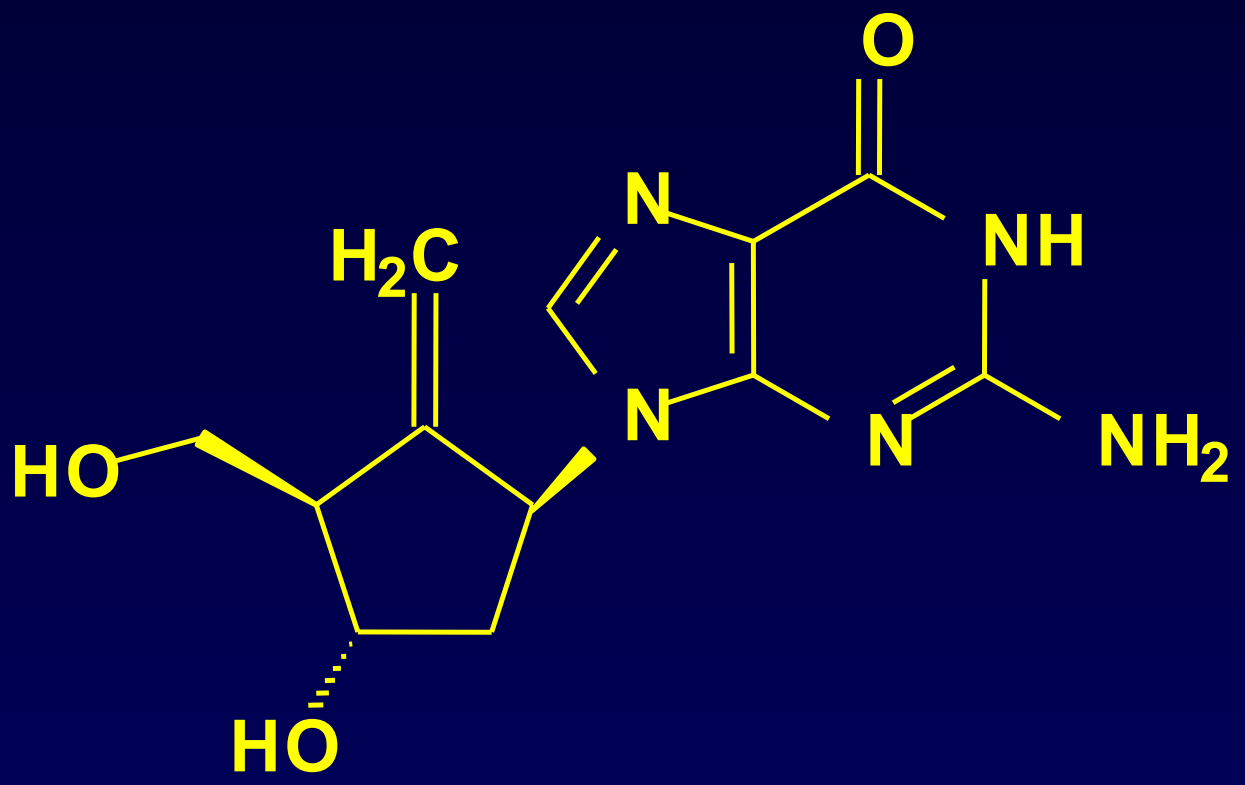


L-FMAU


ddA
d4A
ddI
FddA
Carbovir
L-FaraA
DXG
Abacavir
APD
ACPD
DAPD

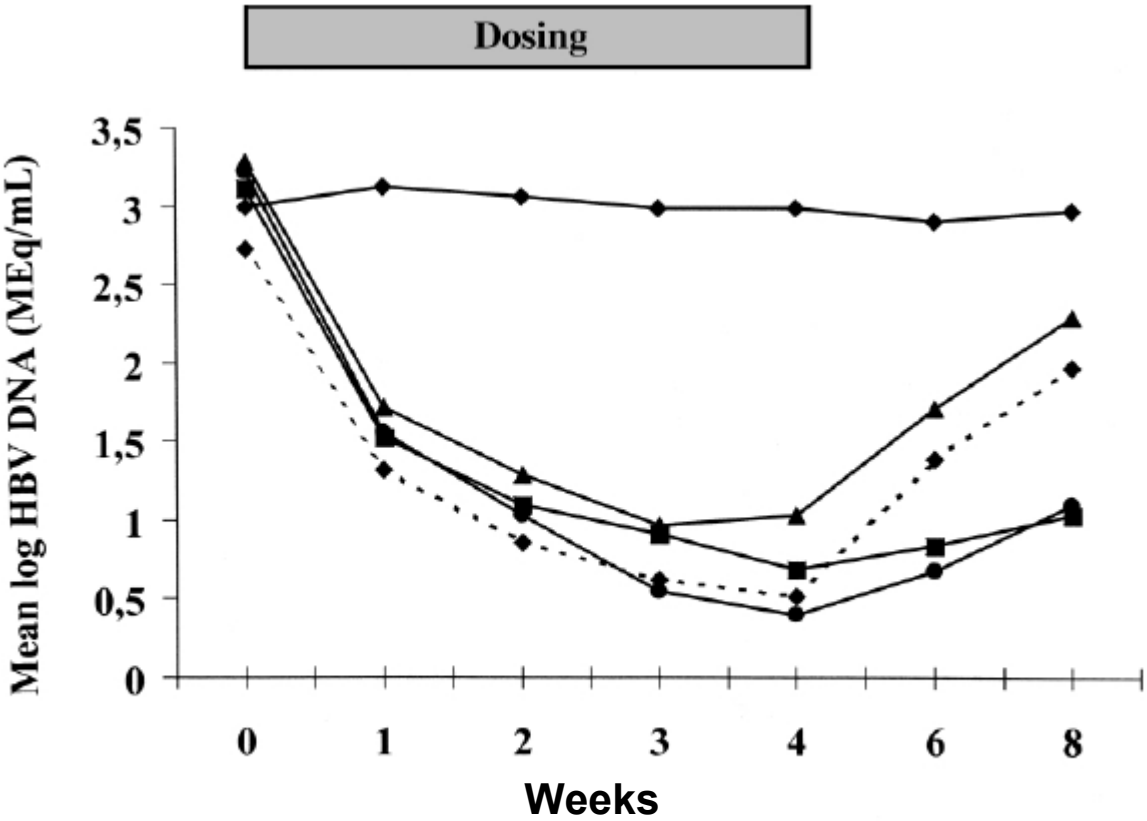
DAPD
Amdoxovir


Acyclovir
Ganciclovir
Penciclovir
CDG
Lobucavir
Famciclovir
Entecavir



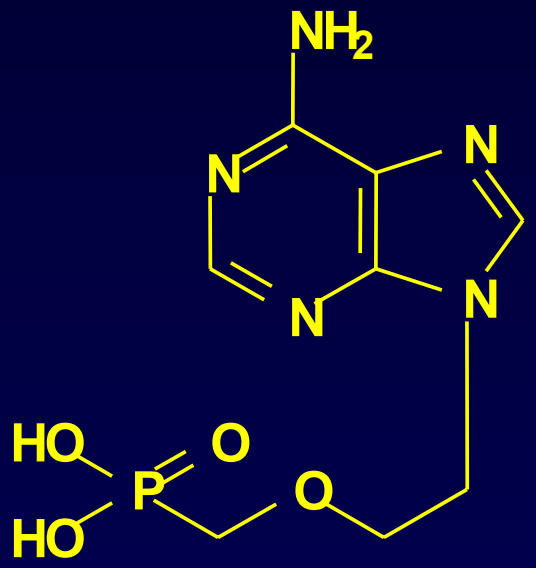
Entecavir

Oral Entecavir in the treatment of patients with chronic hepatitis B virus infection

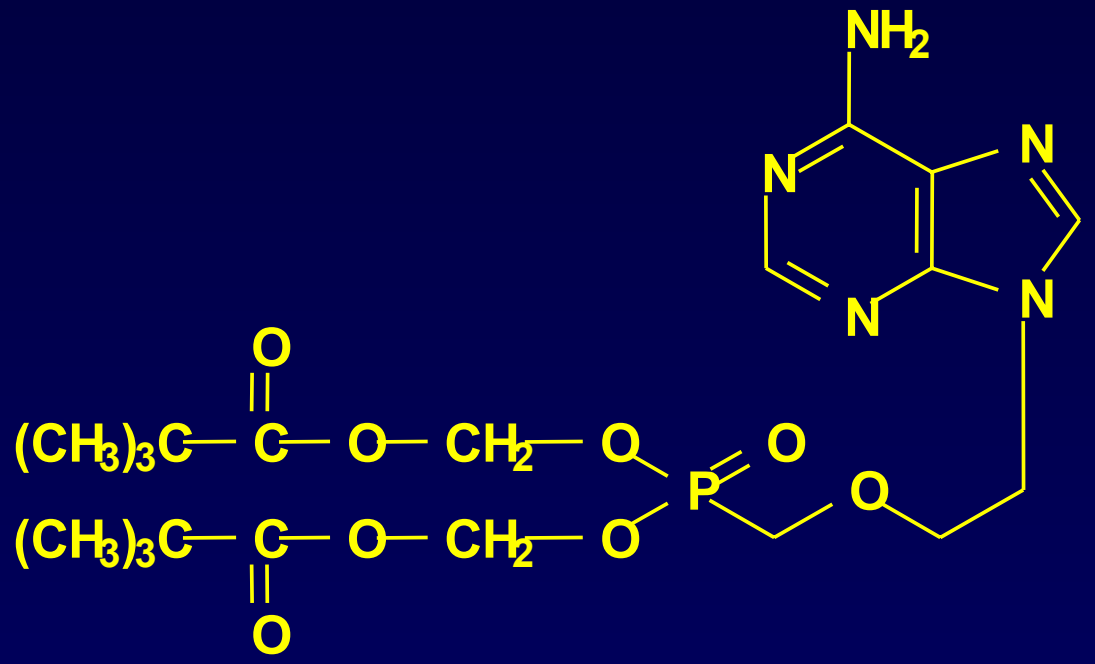


Mean HBV DNA during therapy and 1 month follow-up. (—◆—) placebo, (--◆--) 0.05 mg, (—▲—) 0.1 mg, (—●—) 0.5 mg, (—■—) 1.0 mg

de Man *et al.*, Hepatology, 34: 578-582 (2001)



PMEA
Adefovir



Bis(POM)PMEA
Adefovir dipivoxil

PMPA
Tenofovir

Bis(POC)PMPA
Tenofovir disoproxil
Tenofovir disoproxil fumarate

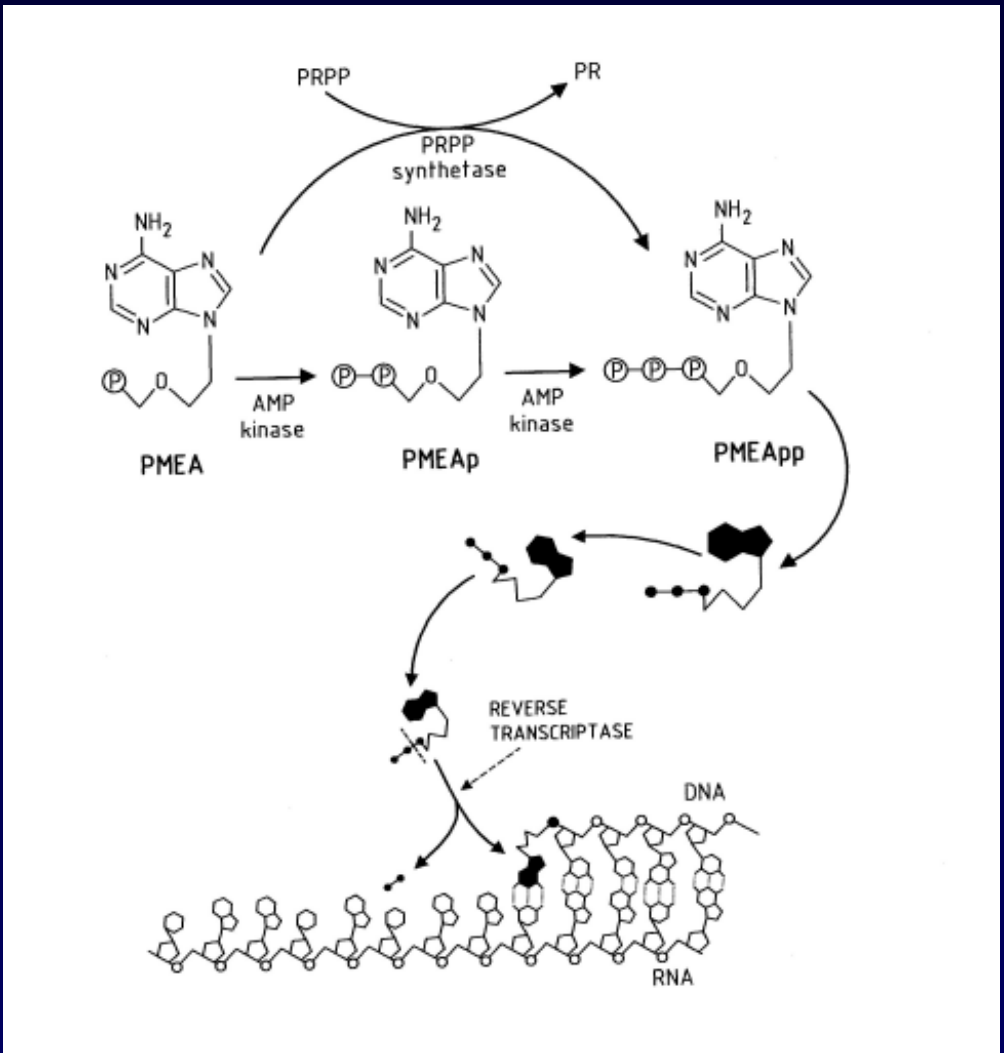
Antiviral activity spectrum of PMEA (Adefovir) and PMPA (Tenofovir)

	Adefovir	Tenofovir
Herpesviridae		
Herpes simplex virus type 1 (HSV-1)	●	○
Herpes simplex virus type 2 (HSV-2)	●	○
Varicella-zoster virus (VZV)	●	○
Epstein-Barr virus (EBV)	●	
Human cytomegalovirus (HCMV)	●	○
Thymidine kinase-deficient HSV (TK⁻ HSV)	●	○
Thymidine kinase-deficient VZV (TK⁻ VZV)	●	○
Hepadnaviridae		
Human hepatitis B virus (HHBV)	●	●
Duck hepatitis B virus (DHBV)	●	●

Antiviral activity spectrum of PMEA (Adefovir) and PMPA (Tenofovir) (continued)

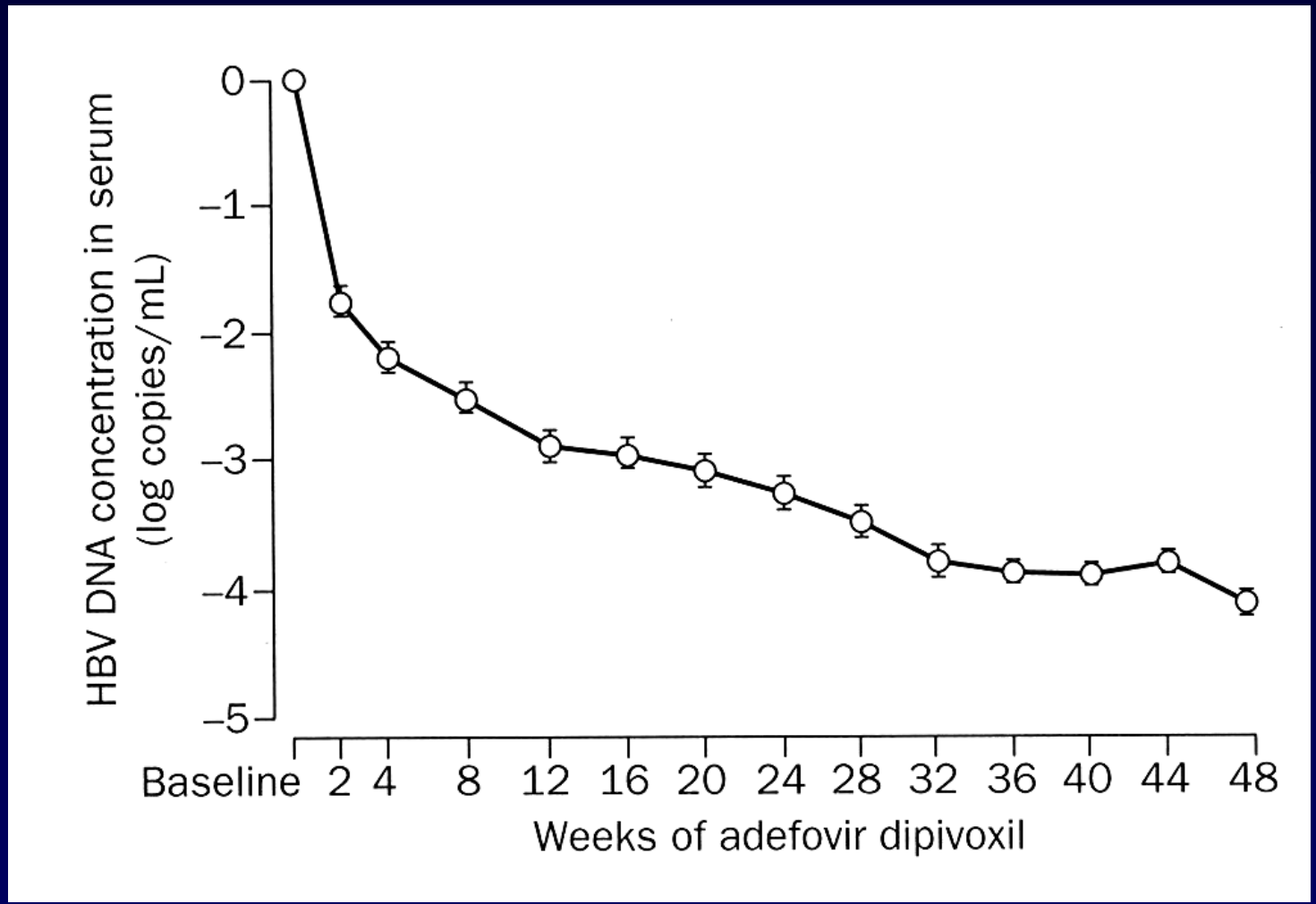
	Adefovir	Tenofovir
Retroviridae		
Human immunodeficiency virus type 1 (HIV-1)	●	●
Human immunodeficiency virus type 2 (HIV-2)	●	●
Simian immunodeficiency virus (SIV)	●	●
Feline immunodeficiency virus (FIV)	●	●
Visna/maedi virus	●	●
Feline leukemia virus	●	●
LP-BM5 (murine AIDS) virus	●	●
Moloney (murine) sarcoma virus	●	●

Mechanism of action of adefovir (PMEA)



Adefovir dipivoxil for lamivudine-resistant HBV in patients coinfected with HIV

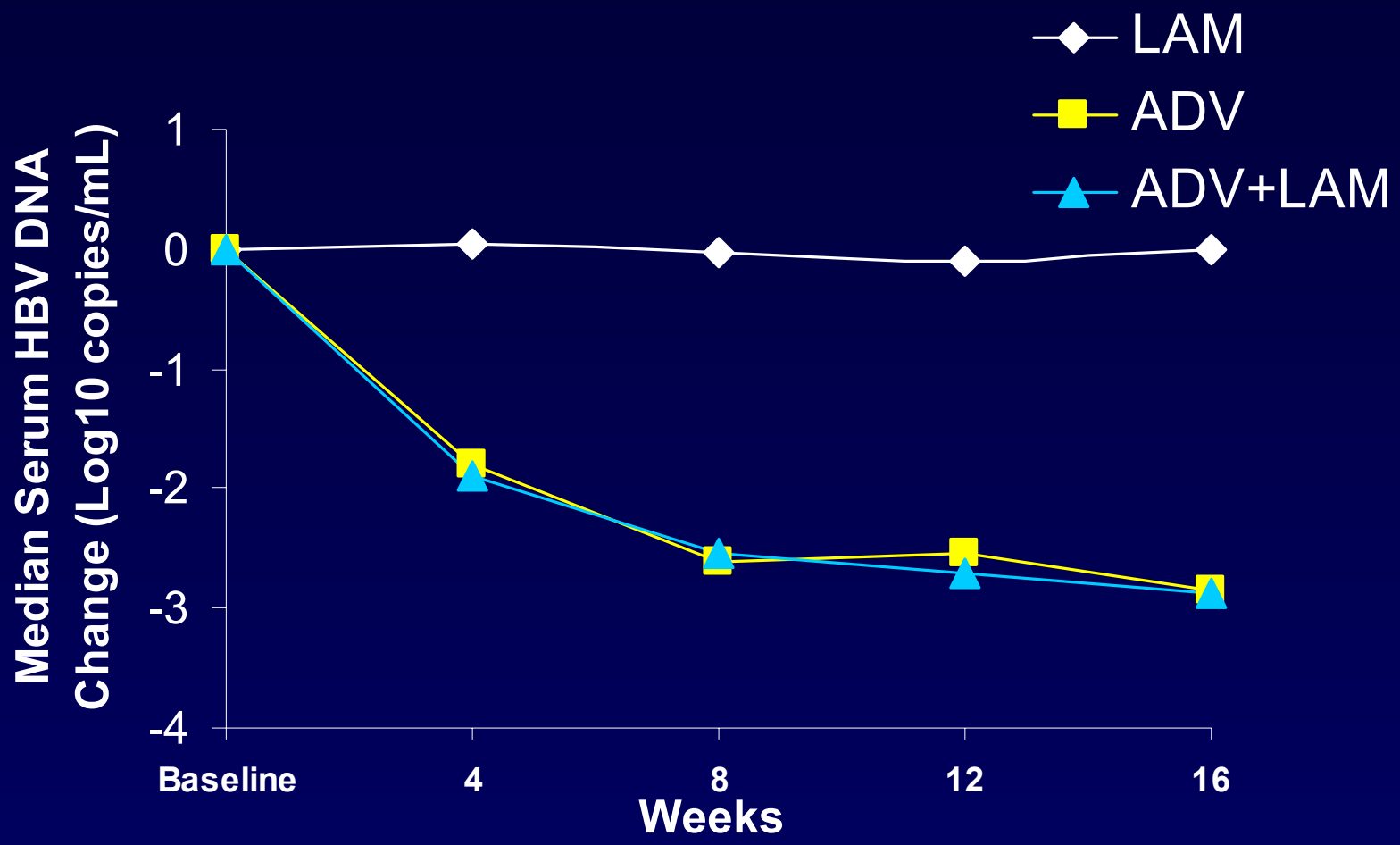
Mean (SE) changes from baseline in serum HBV DNA concentration



Benhamou *et al.*, Lancet 358, 718-723 (2001)

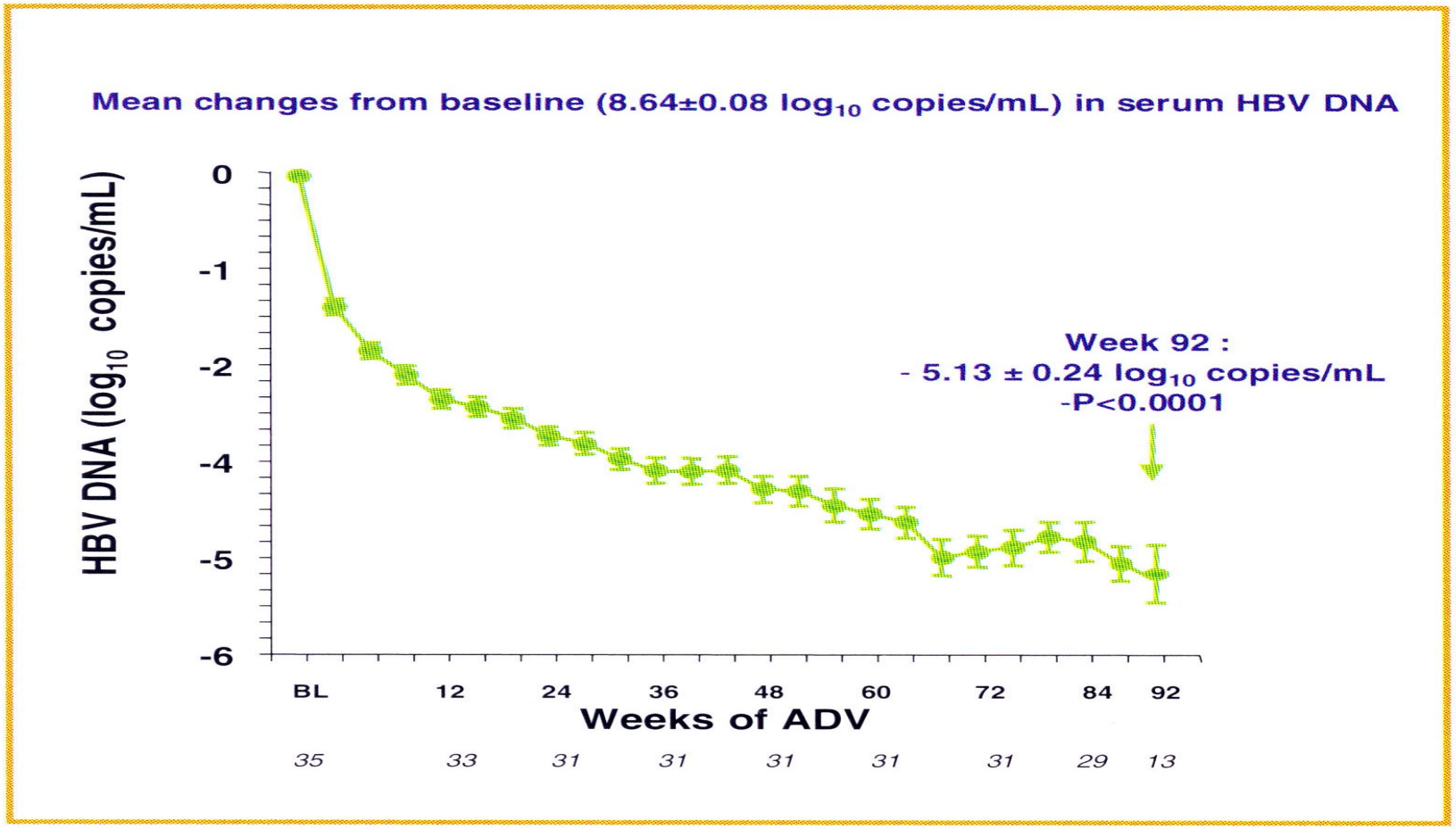
Adefovir dipivoxil in lamivudine-resistant hepatitis B patients – Study 461

Median change in serum HBV DNA



Peters *et al*., 37th Annual Meeting of the European Association for the Study of Liver Diseases, Madrid, Spain, 17-21 April 2002. Oral presentation 646.

Long-Term Adefovir Dipivoxil for Lamivudine-resistant HBV in Patients Coinfected with HIV



Benhamou *et al*., 37th Annual Meeting of the European Association for the Study of Liver Diseases, Madrid, Spain, 17-21 April 2002. Poster 245.

"Suppressing Hepatitis B without Resistance – So Far, So Good"

- Remarkably, no YMDD or other mutations occurred with therapy at either dose of adefovir (10 mg or 30 mg, daily) during the 48-week course, either in HBeAg-positive patients or in HBeAg-negative patients, nor was there evidence of virologic resistance.
- An increasing duration of adefovir therapy was associated with increasing efficacy in terms of the absence of detectable HBV DNA, highlighting the applicability of adefovir for long-term treatment of chronic HBV infection.

Mailliard & Gollan, N. Engl. J. Med. 348, 848-850 (2003)