Hepatitis B and C

And the rest of the alphabet…

Adapté des exposés de la Chaire Franqui 2003
"Antiviral drugs and Discoveries in Medicine"
Prof. E. De Clercq, KU-Leuven
http://www.md.ucl.ac.be/chaire-francqui/

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)		●	●	?	

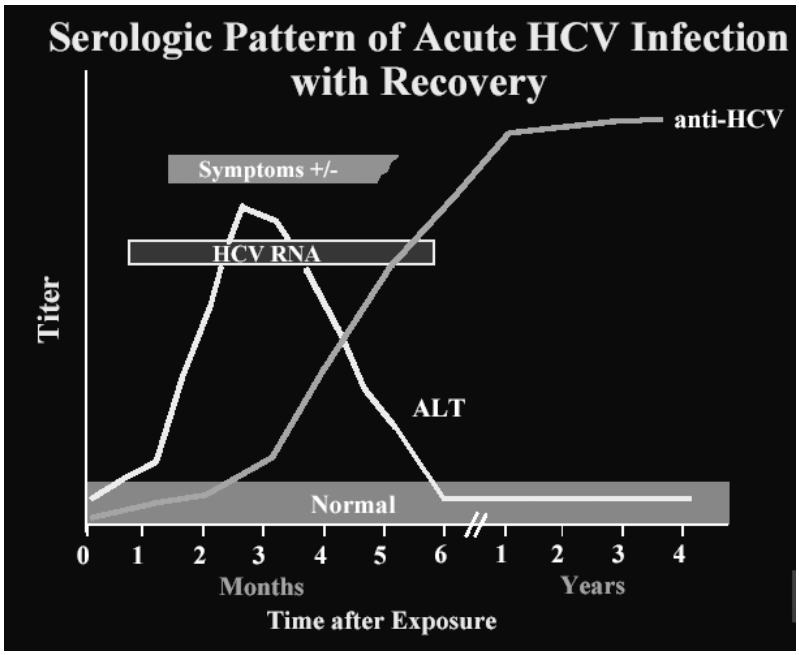
Hepatitisvirus infections: vaccination

HAV	HBV	HCV	HDV	HEV
Yes	Yes	No	No	No

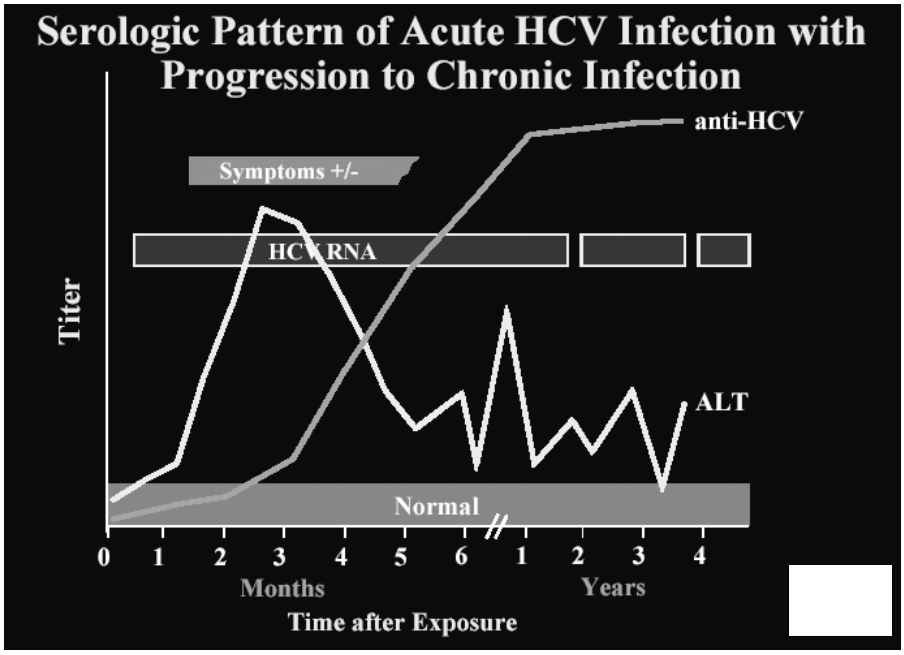
Features of hepatitis C virus infection

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



Centers for Disease Control and Prevention



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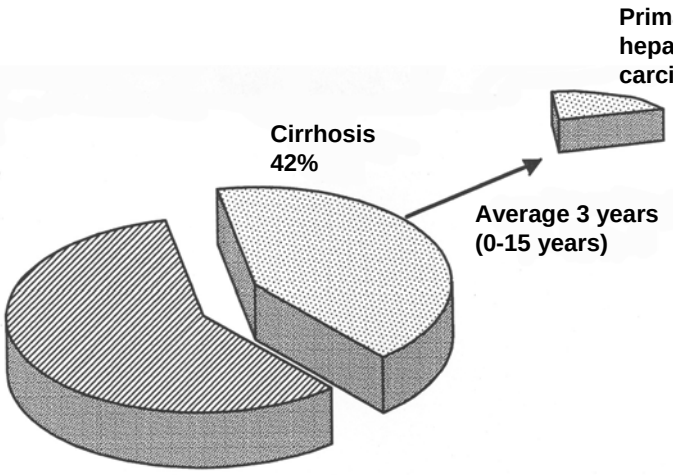
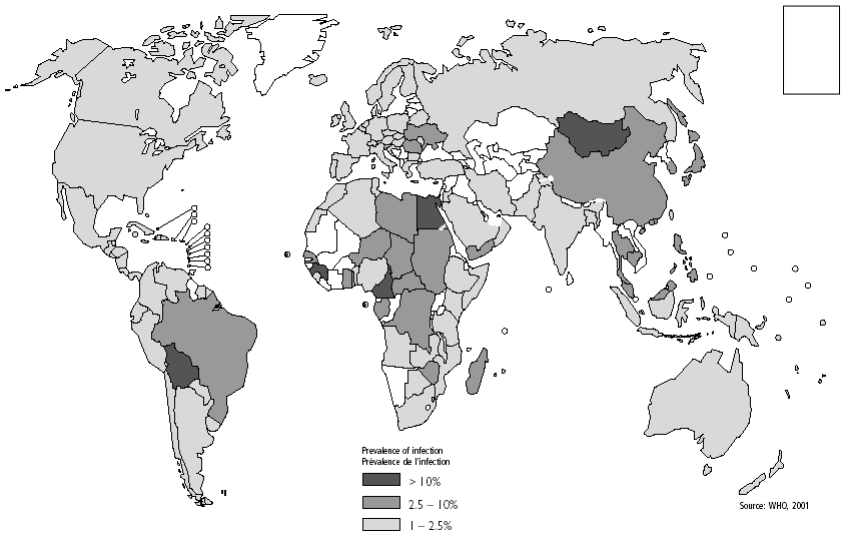
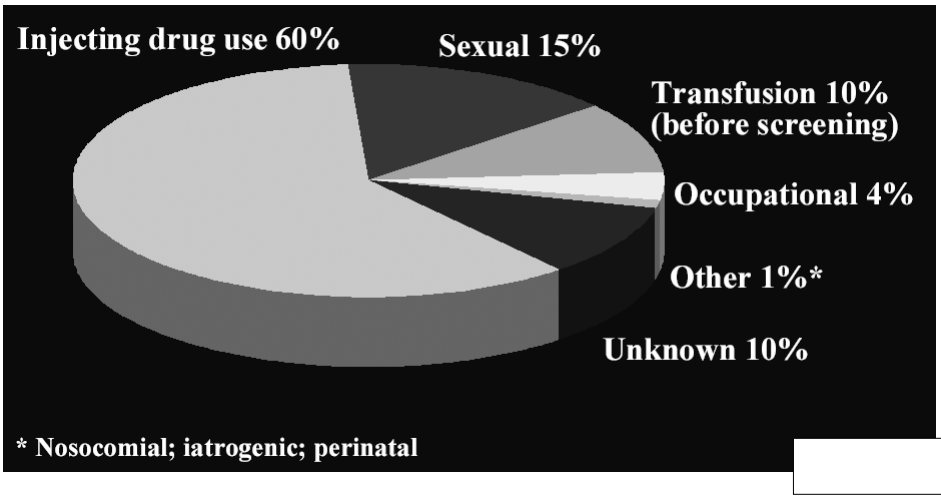
Evolution of chronic hepatitis C



Global distribution of HCV infection

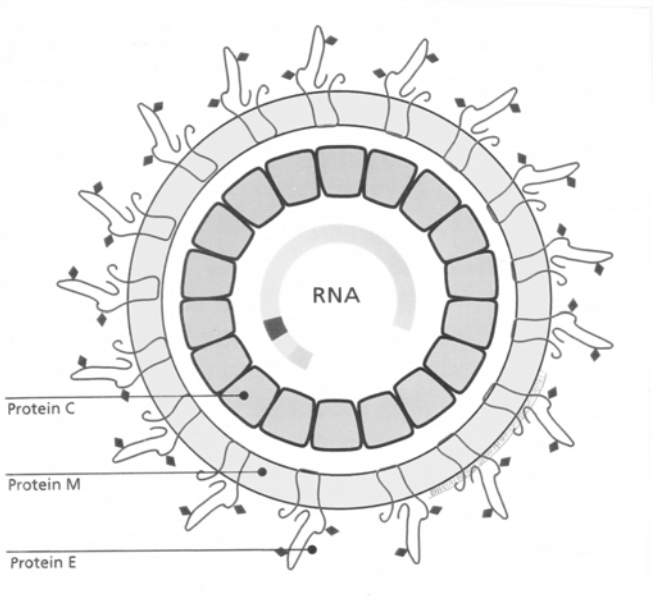


Transmission routes for HCV



Centers for Disease Control and Prevention

GENERAL STRUCTURE OF A FLAVIVIRUS



Most effective therapies for the treatment of HCV infection

Drug name	Launched
Monotherapy	
Intron A (IFN-α2b, recombinant)	1995
Roferon A (IFN-α2a, recombinant)	1996
PEG-INTRON (PEGylated IFN-α2b)	2001
Pegasys (PEGylated IFN-α2a)	2001
Combination therapies	
PEG-Intron and ribavirin	2001
Pegasys and ribavirin	2002

Interferons

(Schorderet 1999)

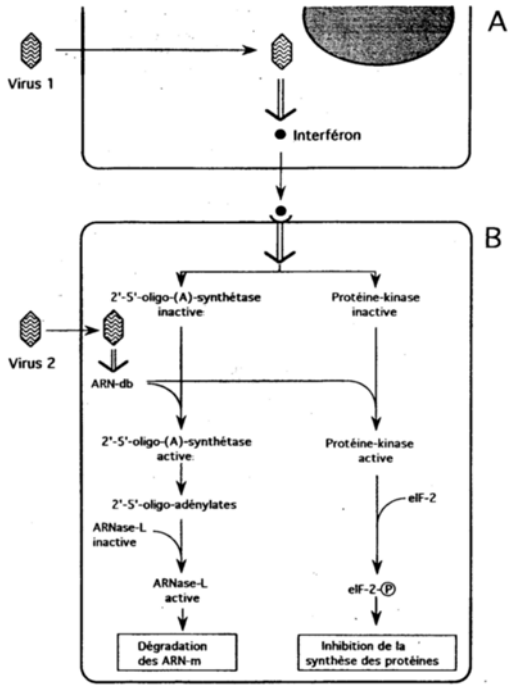


Figure 2. Représentation schématique de l'activité antivirale de l'interféron. En A, la cellule infectée par le virus 1 génère et sécrète l'interféron. En B, la cellule sensibilisée par l'interféron produit par la cellule A est infectée par le virus 2. Plusieurs mécanismes antiviraux sont alors mis en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

PEG

Polyethylene glycol

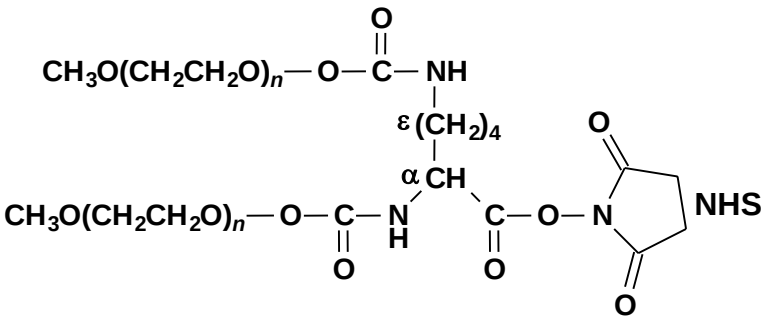
$CH_3(OCH_2CH_2)_nOH$

$CH_3OCH_2CH_2OCH_2CH_2.....OCH_2CH_2OCH_2CH_2OH$

Glycol
$HOCH_2CH_2OH$

Polyethylene
$-(CH_2CH_2)_n-$

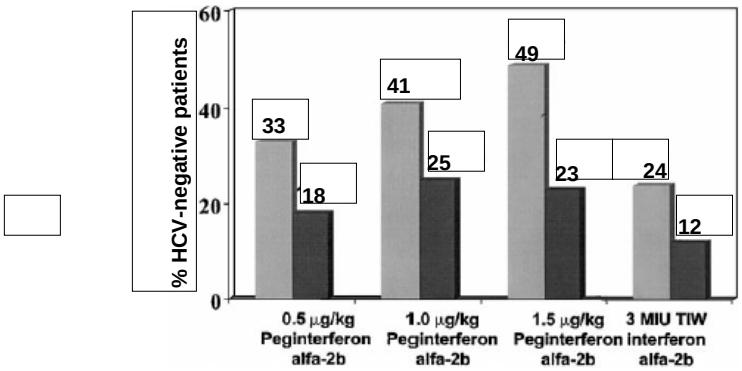
Ethylene
$-CH_2-CH_2-$



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)

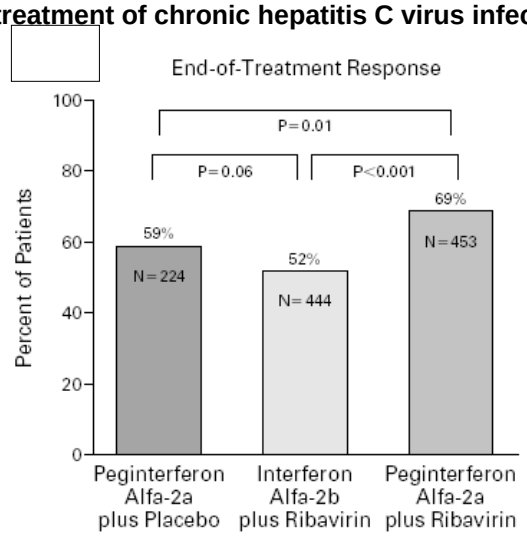
Pegylated interferon α-2b compared to interferon α-2b for the initial treatment of chronic hepatitis C
Virologic response at end of treatment and end of follow-up



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

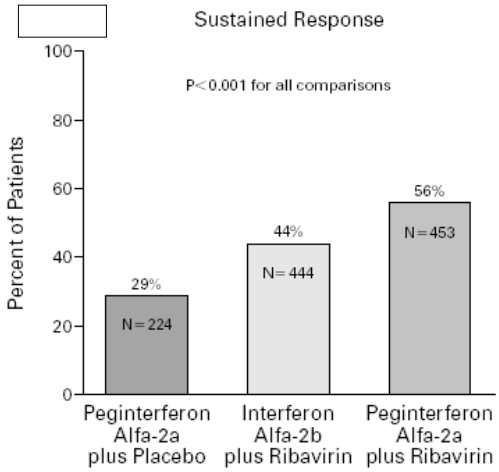
Lindsay *et al*., Hepatology 34: 395-403 (2001)

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]

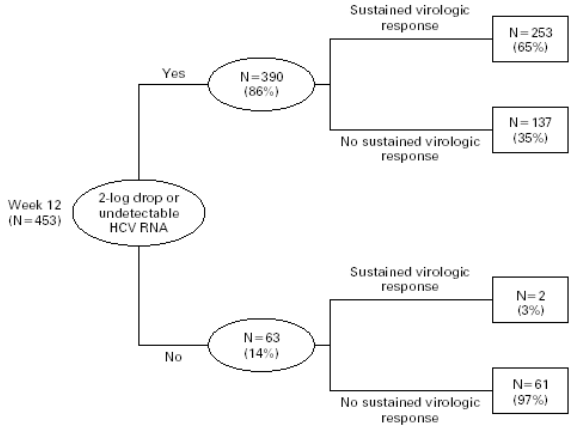
	Peginterferon alfa-2a plus ribavirin (N = 453)	Interferon alfa-2b plus ribavrin (N = 444)	Peginterferon alfa-2a plus placebo (N = 224)
		No./total no. (%)	
HCV genotype[b]			
All patients	255/453 (56)	197/444 (44)	66/224 (29)
Genotype 1	138/298 (46)	103/285 (36)	30/145 (21)
Genotype 2 or 3	106/140 (76)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

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

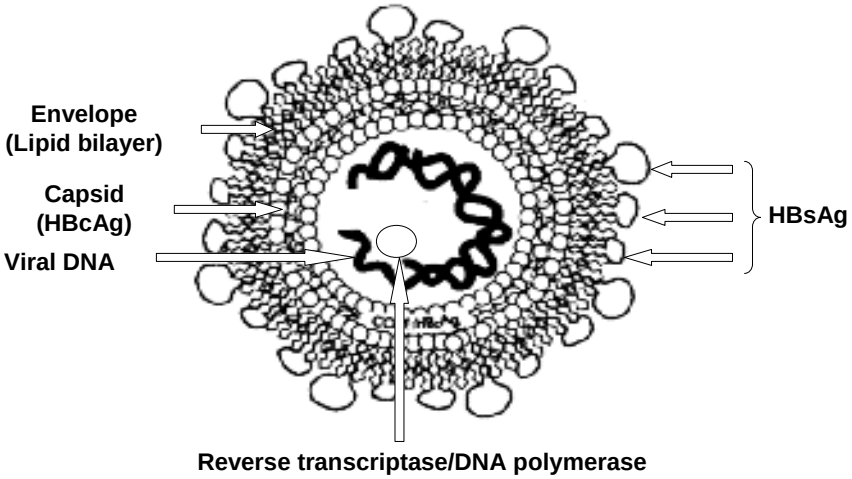
Adverse events	Peginterferon alfa-2a plus ribavirin	
Fatigue*	242	(54)
Headache*	211	47)
Pyrexia*	195	(43)
Myalgia*	189	(42)
Insomnia	168	(37)
Nausea	130	(29)
Alopecia	128	(28)
Arthralgia	121	(27)
Irritability	109	(24)
Rigors*	106	(24)
Pruritus	101	(22)
Depression	100	(22)
Decreased appetite	96	(21)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

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

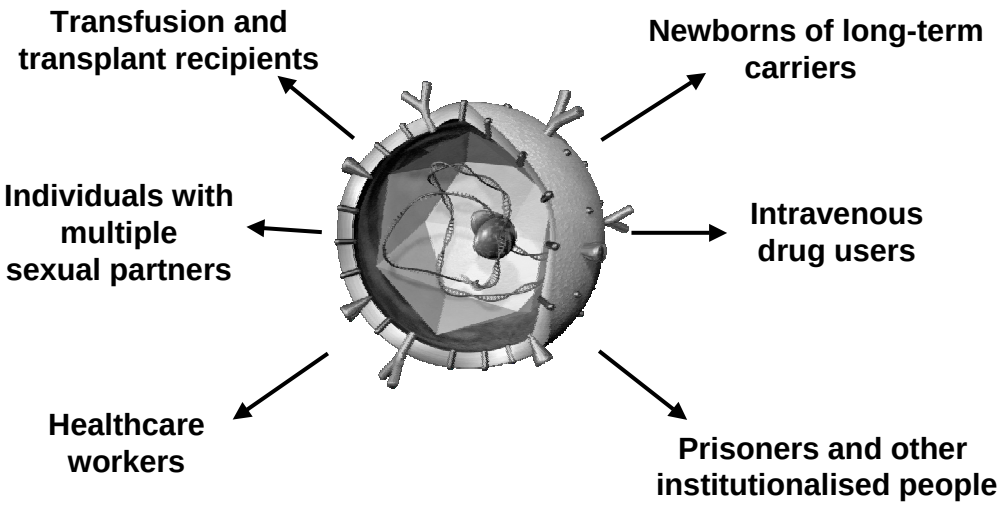
Fried *et al*., N. Engl. J. Med. 347: 975-982 (2002)

Hepatitis B

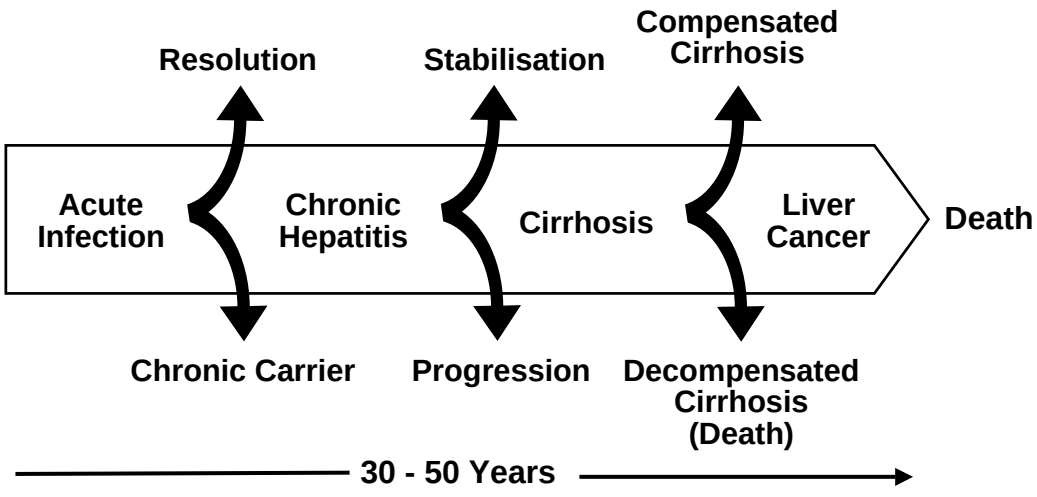
Scheme of HBV Dane particle



Transmission of Hepatitis B Infection

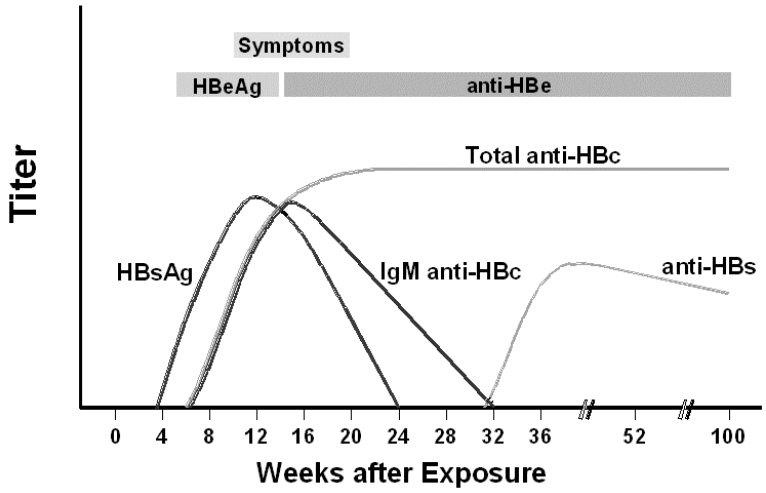


Natural History of Chronic HBV Infection



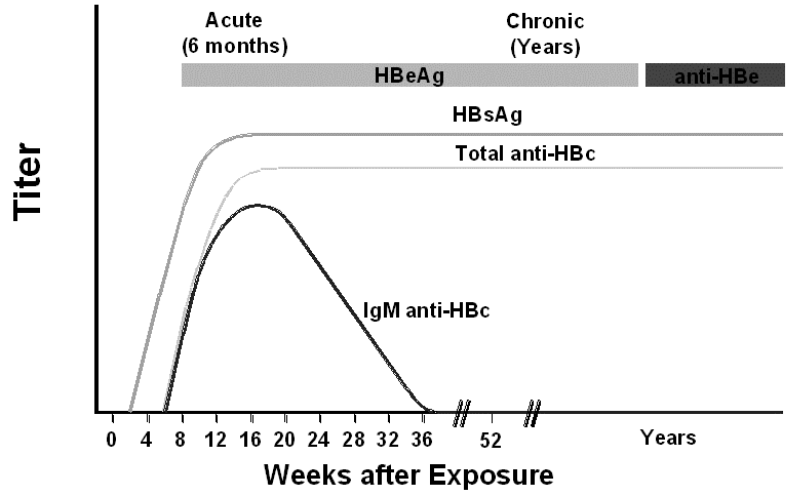
Feitelson, Lab. Invest. 71, 324-349 (1994)

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

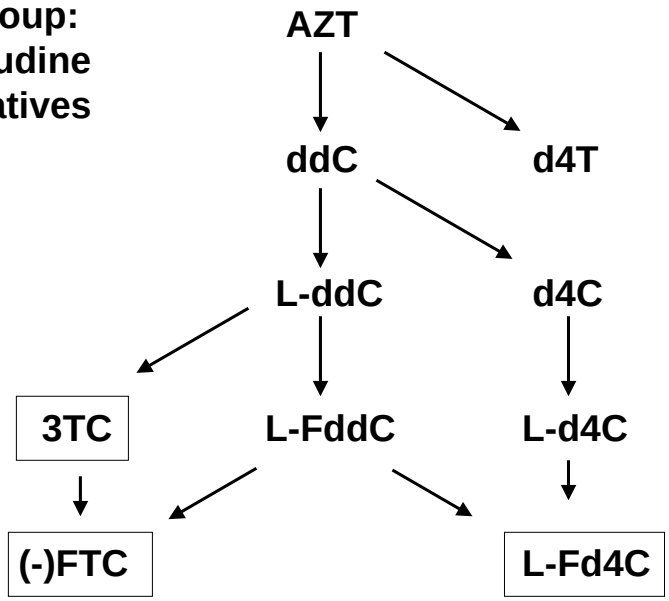
- 350 million chronic carriers worldwide
- Ninth leading cause of death
- Nearly 75% of HBV chronic carriers are Asian

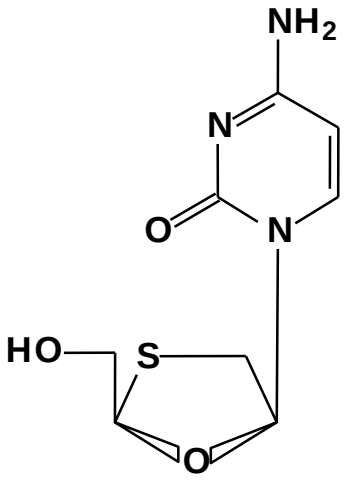
HBsAg Prevalence (%)

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

Prevalence of HBsAg Positivity in Europe

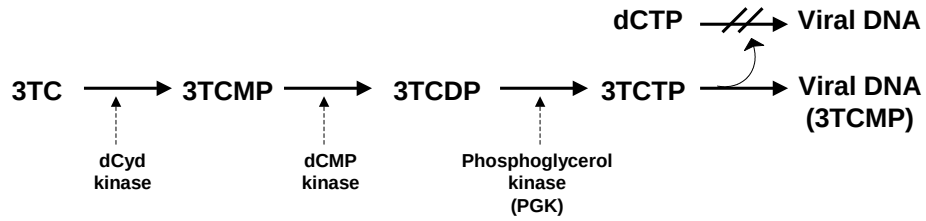
1st group: zidovudine derivatives



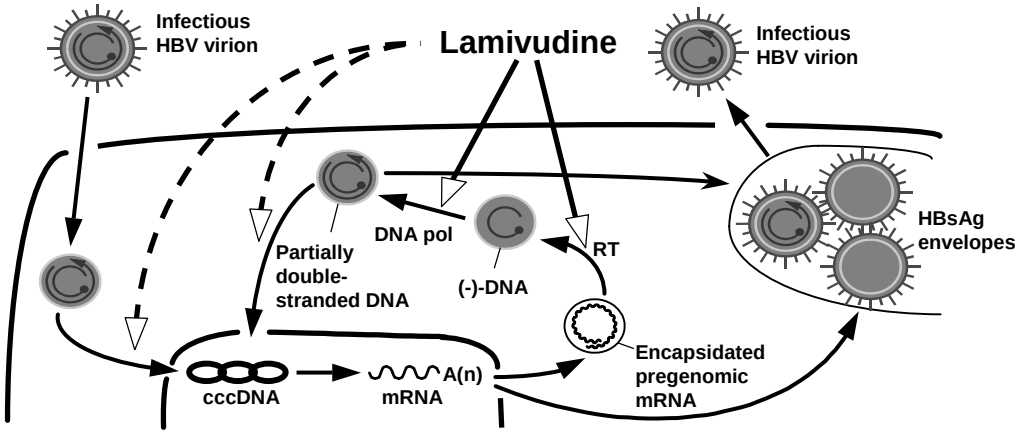


3TC
Lamivudine

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

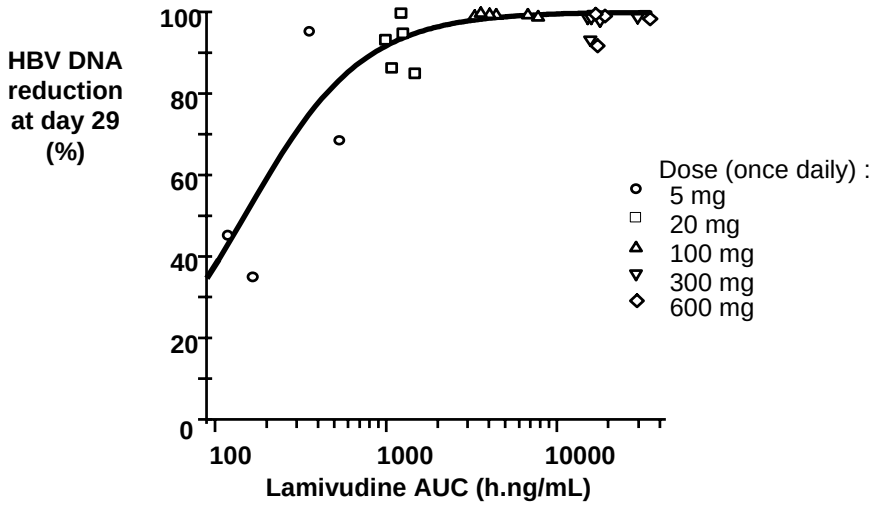


Replication Cycle of Hepatitis B Virus; Mechanism of Action of Lamivudine



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

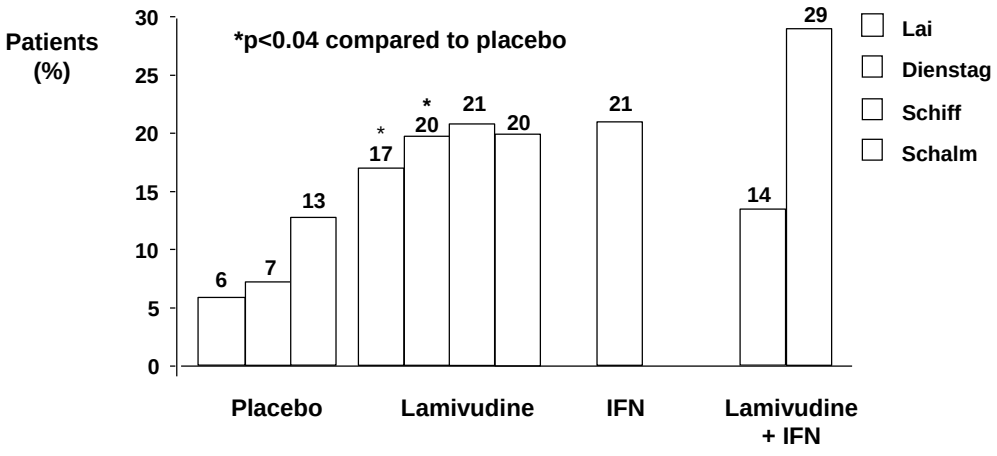
HBV DNA Reduction versus Lamivudine Bioavailability



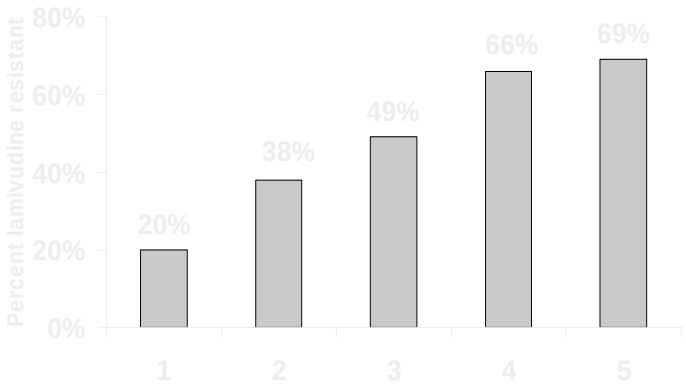
Johnson *et al.,* Clin. Pharmacokinet. 36, 41-66 (1999)

HBeAg Seroconversion After One Year of Therapy

Seroconversion = HBeAg-ve and anti-HBe+ve

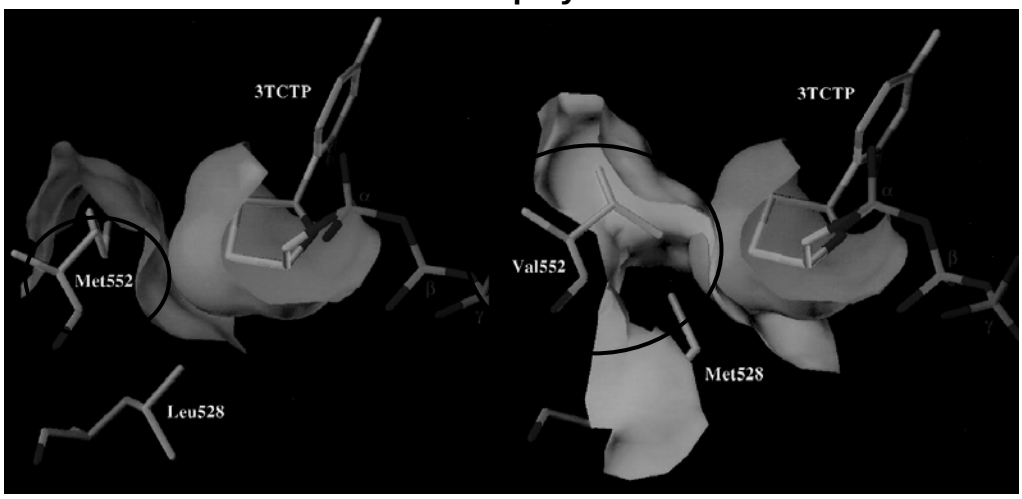


Incidence of lamivudine resistance in chronic hepatitis B



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.

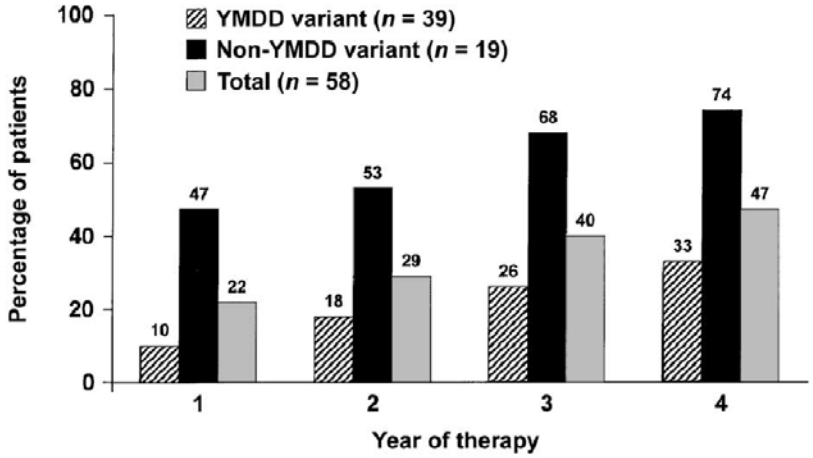
Interaction of 3TCTP (lamivudine triphosphate) with YMDD region of HBV DNA polymerase



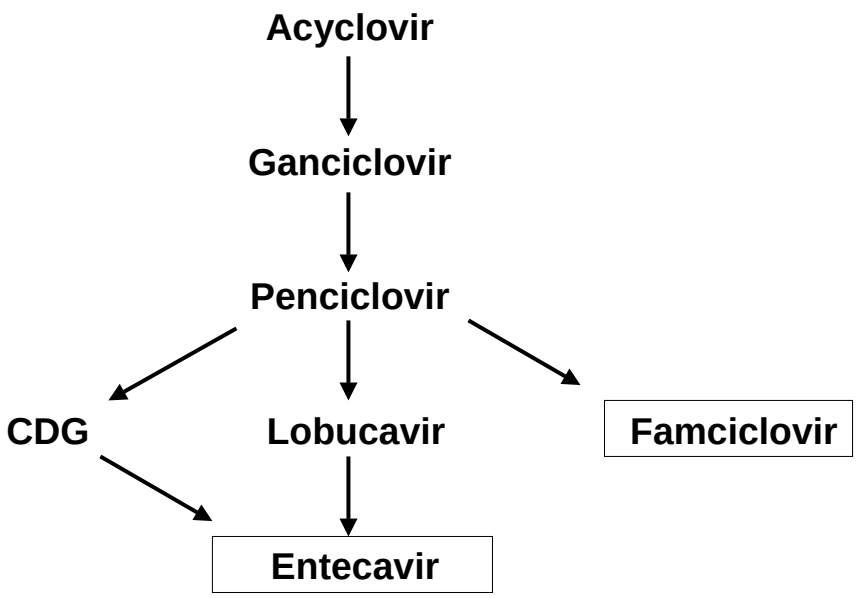
Binding of 3TCTP to wild-type (left) and Met552Val mutant (right) HBV DNA polymerase. Molecular modeling suggests that steric hindrance (right) between 3TCTP and the mutated amino acid, Val552, is the primary cause of 3TCTP resistance. This steric conflict is not observed in the binding of 3TCTP to the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

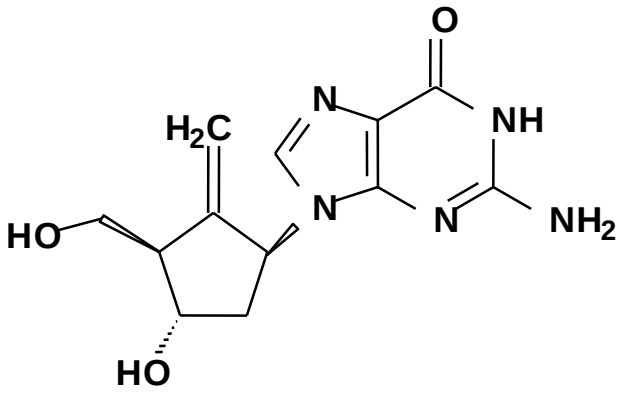
Das et al., J. Virol. 75: 4771-4779 (2001)

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



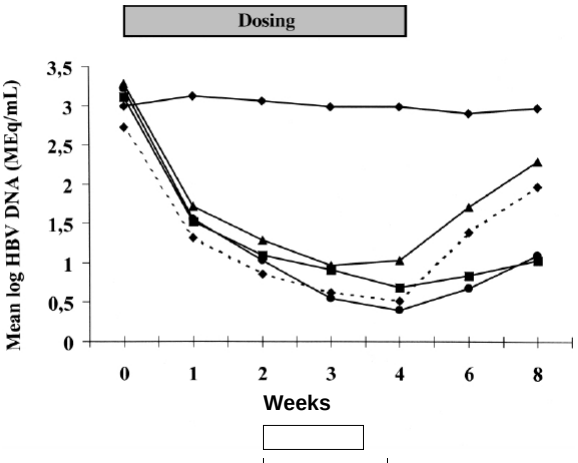
Lai *et al*., Clin. Infect. Dis. 36, 687-696 (2003)





Entecavir

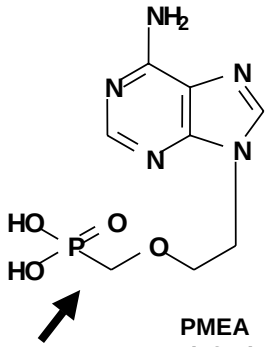
Oral Entecavir in the treatment of patients with chronic hepatitis B virus infection



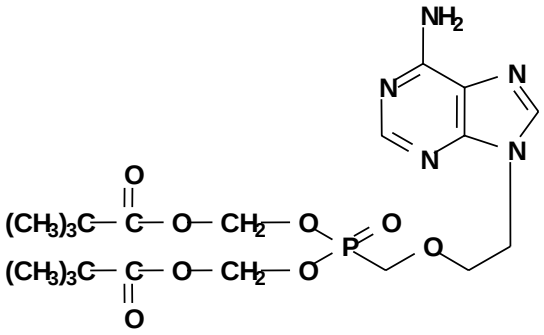
Mean HBV DNA during therapy and 1 month follow-up. (—◆—) placebo, (--◆--) 0.05 mg, (—▲—) 0.1 mg, (—●—) 0.5 mg, (—■—) 1.0 mg

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

Adefovir

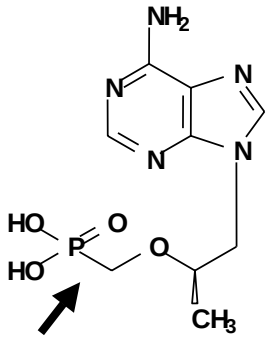


PMEA
Adefovir

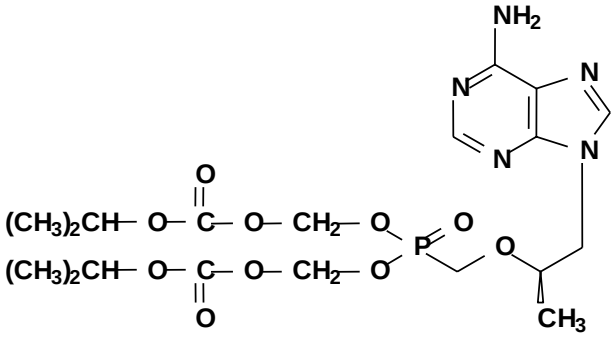


Bis(POM)PMEA
Adefovir dipivoxil

Tenofovir



PMPA
Tenofovir



Bis(POC)PMPA
Tenofovir disoproxil
Tenofovir disoproxil fumarate

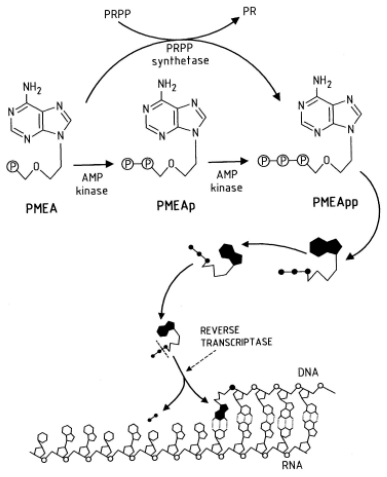
Antiviral activity spectrum of PMEA (Adefovir) and PMPA (Tenofovir)

	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)

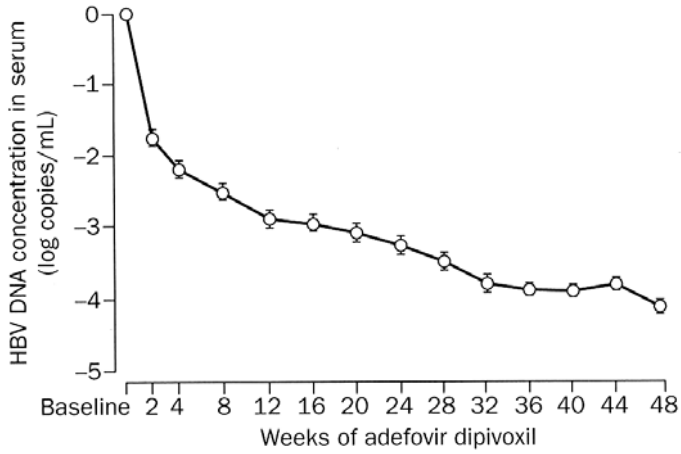
	Adefovir	Tenofovir
Retroviridae		
Human immunodeficiency virus type 1 (HIV-1)	●	●
Human immunodeficiency virus type 2 (HIV-2)	●	●
Simian immunodeficiency virus (SIV)	●	●
Feline immunodeficiency virus (FIV)	●	●
Visna/maedi virus	●	●
Feline leukemia virus	●	●
LP-BM5 (murine AIDS) virus	●	●
Moloney (murine)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

Mechanism of action of adefovir (PMEA)



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

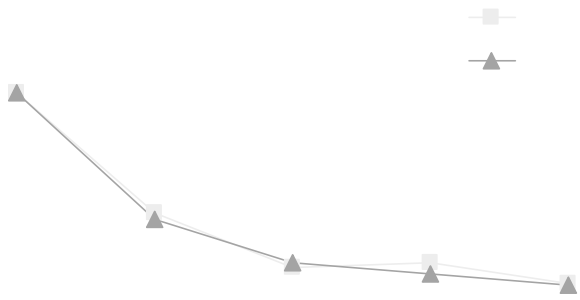
Mean (SE) changes from baseline in serum HBV DNA concentration



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

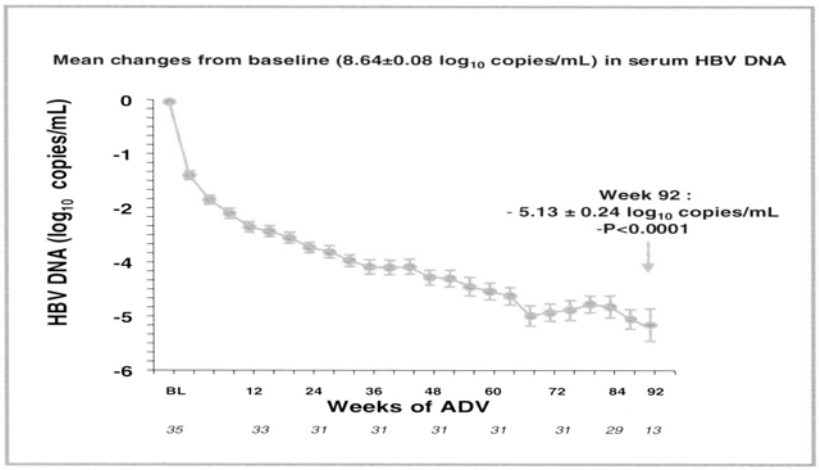
Adefovir dipivoxil in lamivudine-resistant hepatitis B patients – Study 461

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)