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/

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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)		●	●	?	

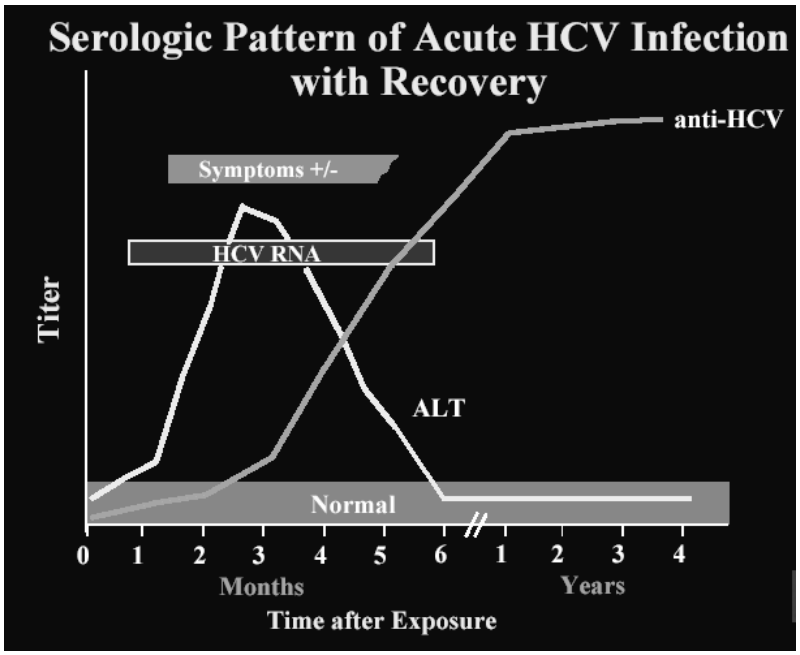
Hepatitisvirus infections: vaccination

HAV	HBV	HCV	HDV	HEV
Yes	Yes	No	No	No

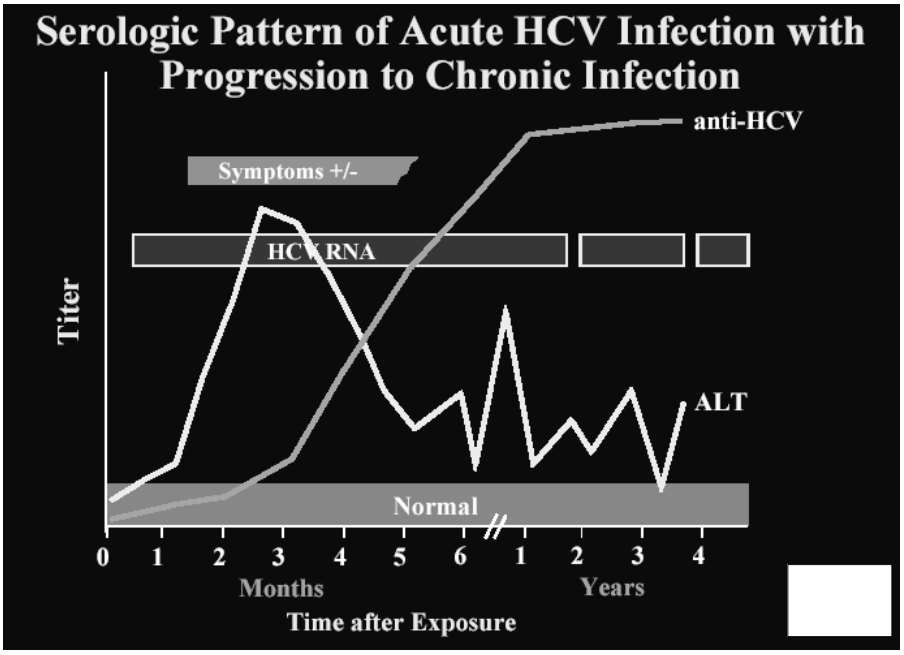
Features of hepatitis C virus infection

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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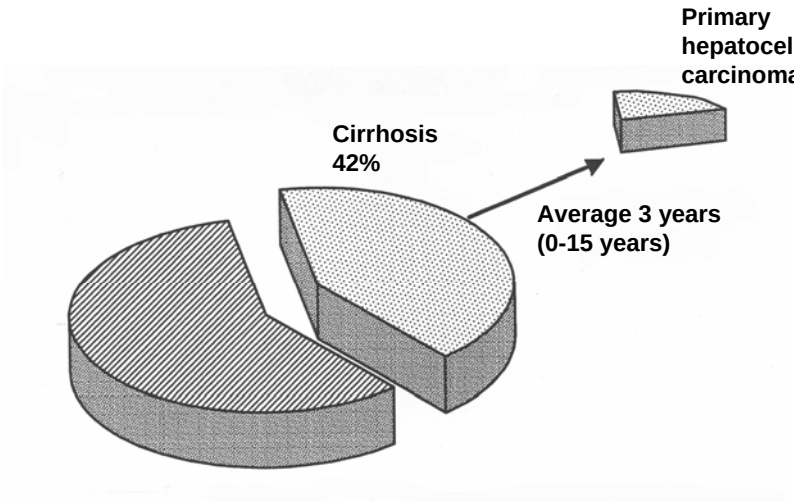
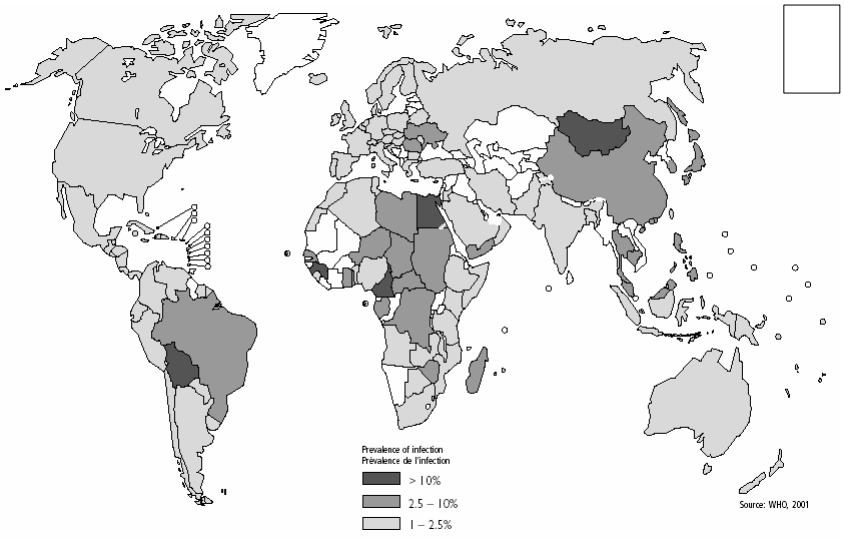
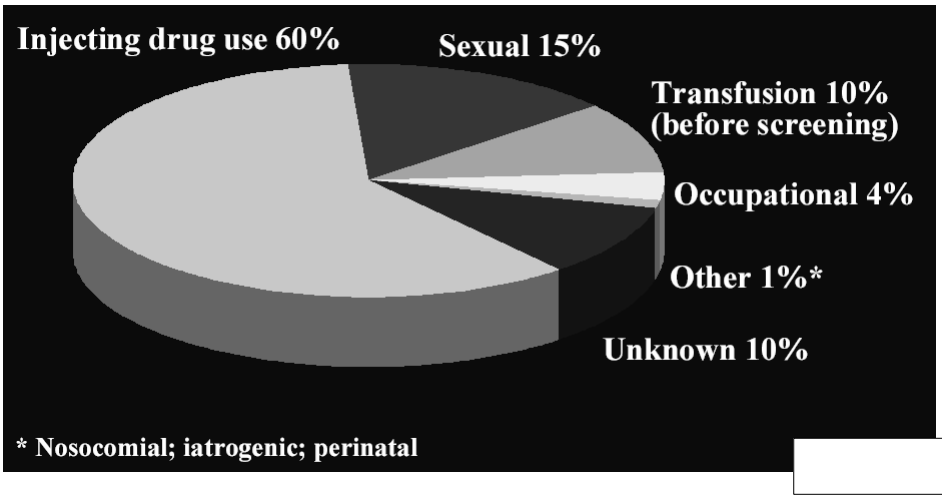
Evolution of chronic hepatitis C



Global distribution of HCV infection

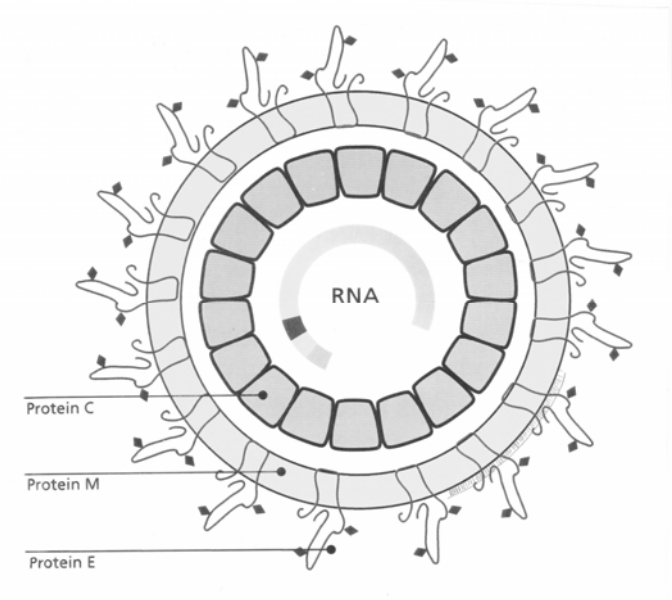


Transmission routes for HCV



Centers for Disease Control and Prevention

GENERAL STRUCTURE OF A FLAVIVIRUS



Most effective therapies for the treatment of HCV infection

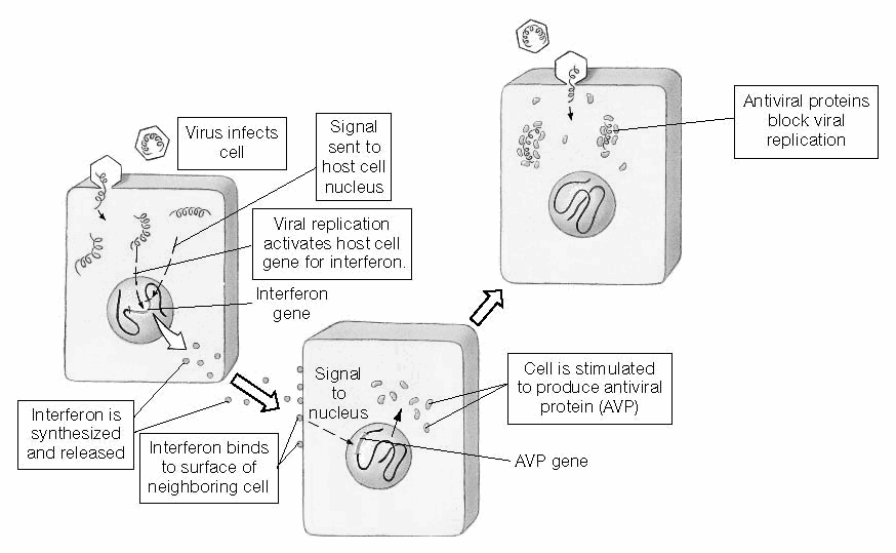
Drug name	Launched
Monotherapy	
IFN-α2b, recombinant (Intron®)	1995
IFN-α2a, recombinant (Roferon A®)	1996
PEGylated IFN-α2b (PEG-Intron®)	2001
PEGylated IFN-α2a (Pegasys®)	2001
Combination therapies	
PEG-Intron and ribavirin	2001
Pegasys and ribavirin	2002

Interférons

- 1957: Isaacs and Lindenman found that chicken cells exposed to influenza virus produced a substance that could protect other cells from influenza infection. It was named interferon.
- Replication of virus not required
- Induced by double stranded RNA, and several other compounds
- Host specific, not viral specific
- 3 main classes of interferons (IFN-alpha, IFN-beta and IFN-gamma)
- 2 receptors; one of alpha and beta INF, one for gamma INF
- Interferon induces an “antiviral state”
  - Over 100 genes induced including "antiviral proteins"
  - Increases NK cell’s lytic ability
  - Reduces amino acid biosythesis
  - Increase MHC gene expression in uninfected cells
- Large amounts produce fever, chills, nausea and malaise.
- Prolonged INF induction may lead to apoptosis (death, not only of infected cells but of neighboring ones as well).

http://www.uccs.edu/~rmelamed/MicroFall2002/Chapter%2016/Interferon.html

Interferons: mode d'action antivirale



http://www.uccs.edu/~rmelamed/MicroFall2002/Chapter%2016/Interferon.html

PEG

Polyethylene glycol

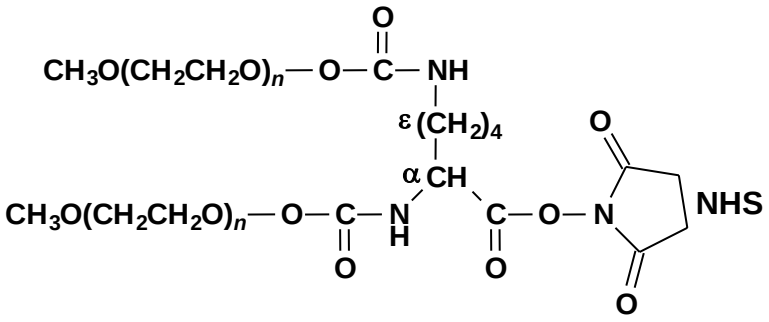
$CH_3(OCH_2CH_2)_nOH$

$CH_3OCH_2CH_2OCH_2CH_2.....OCH_2CH_2OCH_2CH_2OH$

Glycol
$HOCH_2CH_2OH$

Polyethylene
$-(CH_2CH_2)_n-$

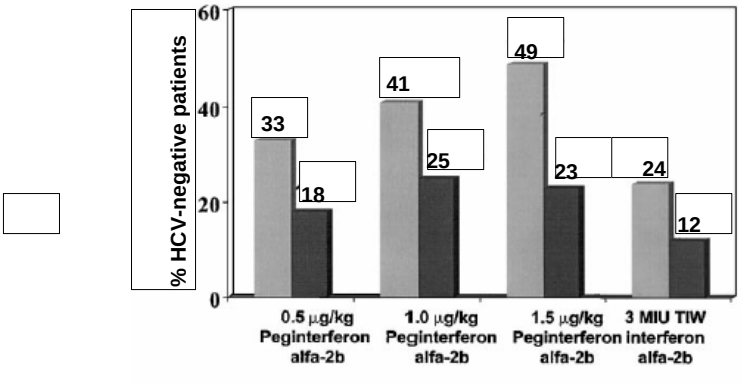
Ethylene
$-CH_2-CH_2-$



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)

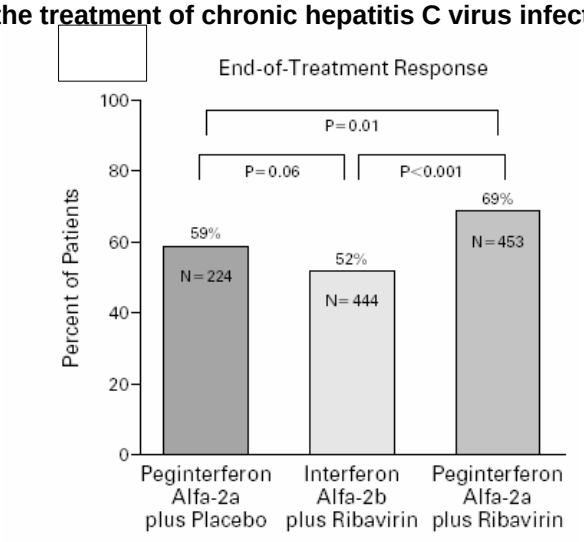
Pegylated interferon α-2b compared to interferon α-2b for the initial treatment of chronic hepatitis C
Virologic response at end of treatment and end of follow-up



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)

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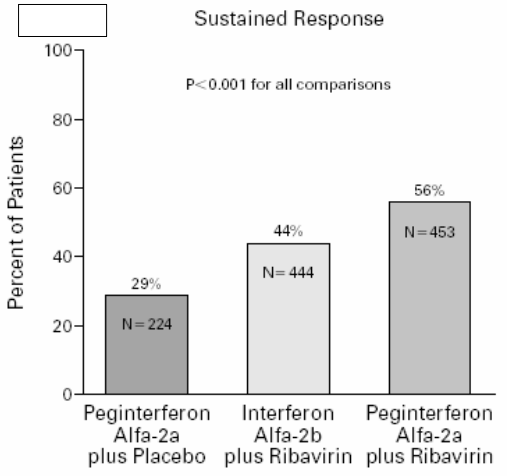


Fried *et al*., N. Engl. J. Med. 347: 975-982 (2002)

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]

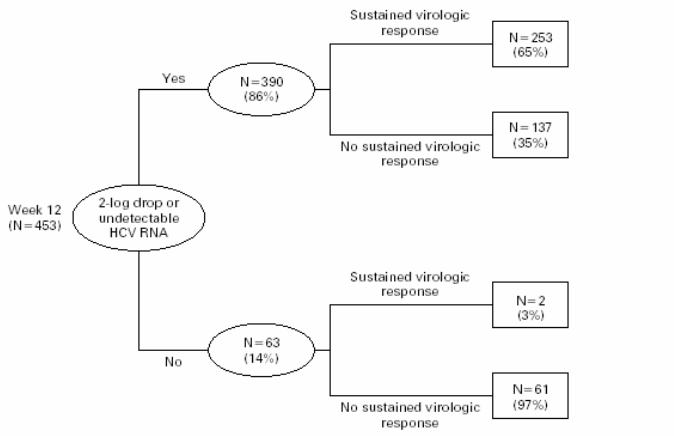
	Peginterferon alfa-2a plus ribavirin (N = 453)	Interferon alfa-2b plus ribavrin (N = 444)	Peginterferon alfa-2a plus placebo (N = 224)
		No./total no. (%)	
HCV genotype[b]			
All patients	255/453 (56)	197/444 (44)	66/224 (29)
Genotype 1	138/298 (46)	103/285 (36)	30/145 (21)
Genotype 2 or 3	106/140 (76)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

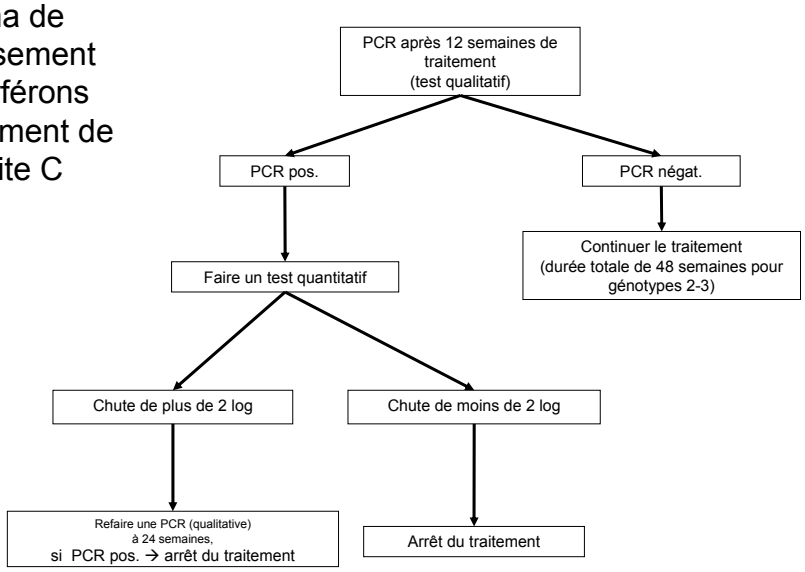
Fried *et al*., N. Engl. J. Med. 347: 975-982 (2002)

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)

Schéma de remboursement des interférons pour traitement de l'hépatite C



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

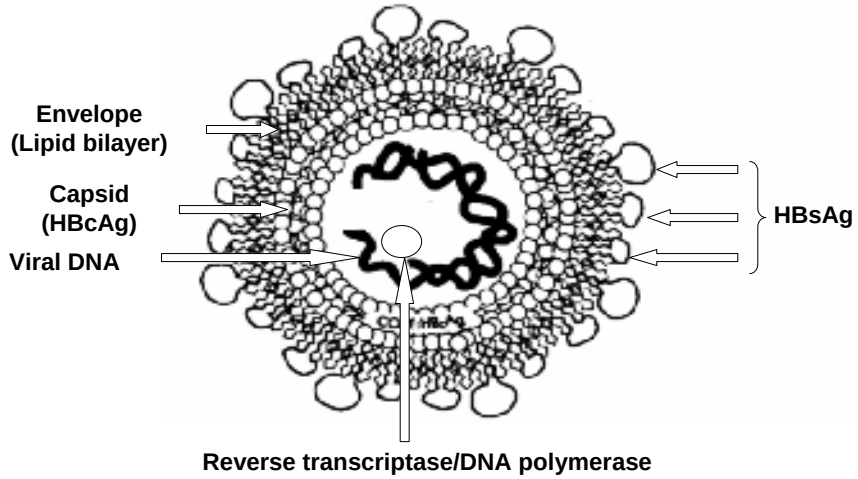
Adverse events	Peginterferon alfa-2a plus ribavirin	
Fatigue*	242	(54)
Headache*	211	47)
Pyrexia*	195	(43)
Myalgia*	189	(42)
Insomnia	168	(37)
Nausea	130	(29)
Alopecia	128	(28)
Arthralgia	121	(27)
Irritability	109	(24)
Rigors*	106	(24)
Pruritus	101	(22)
Depression	100	(22)
Decreased appetite	96	(21)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

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

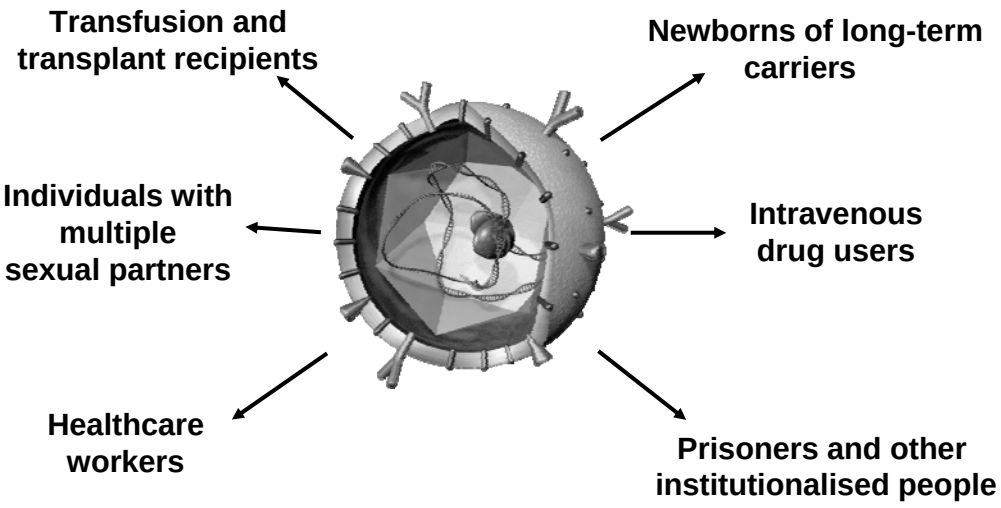
Fried *et al*., N. Engl. J. Med. 347: 975-982 (2002)

Hepatitis B

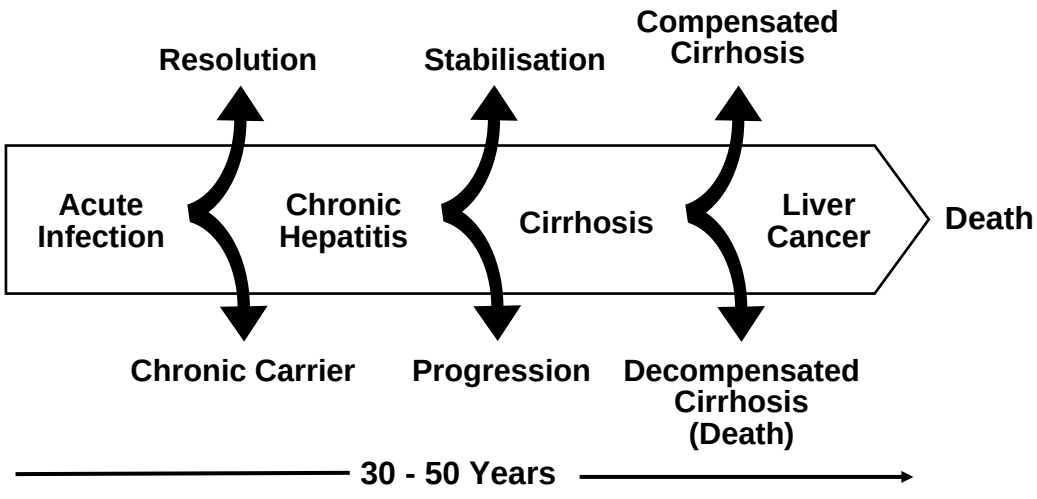
Scheme of HBV Dane particle



Transmission of Hepatitis B Infection

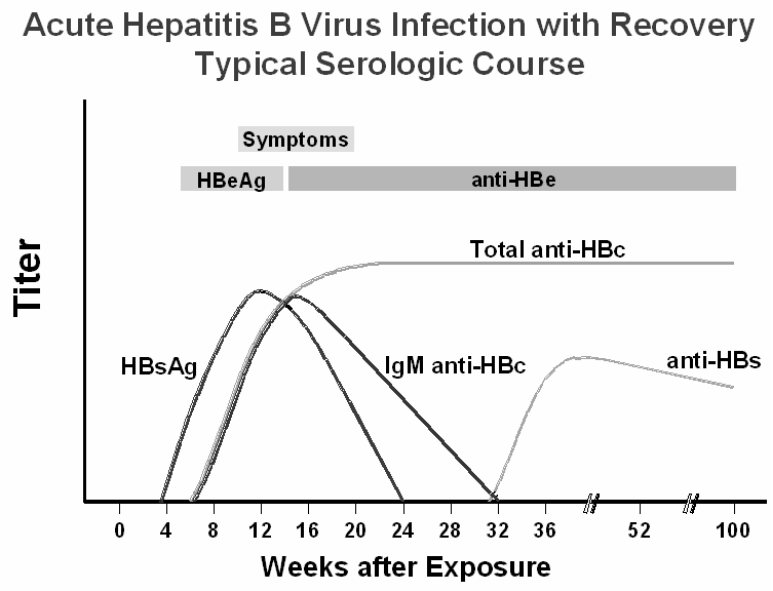


Natural History of Chronic HBV Infection



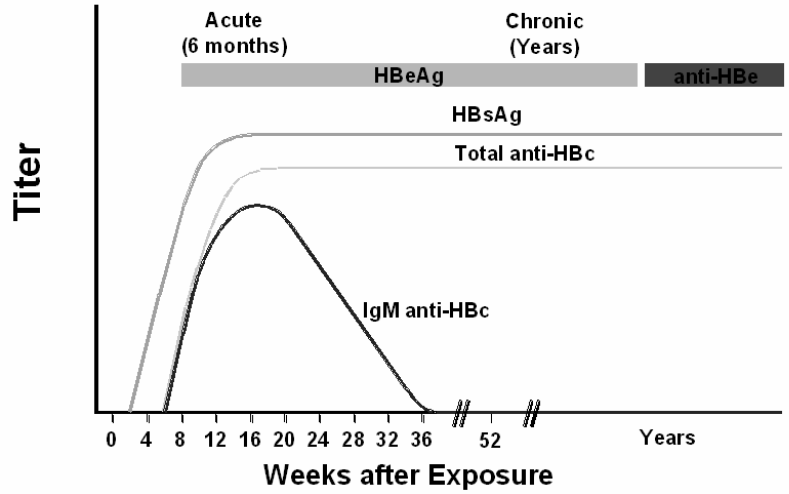
Feitelson, Lab. Invest. 71, 324-349 (1994)

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

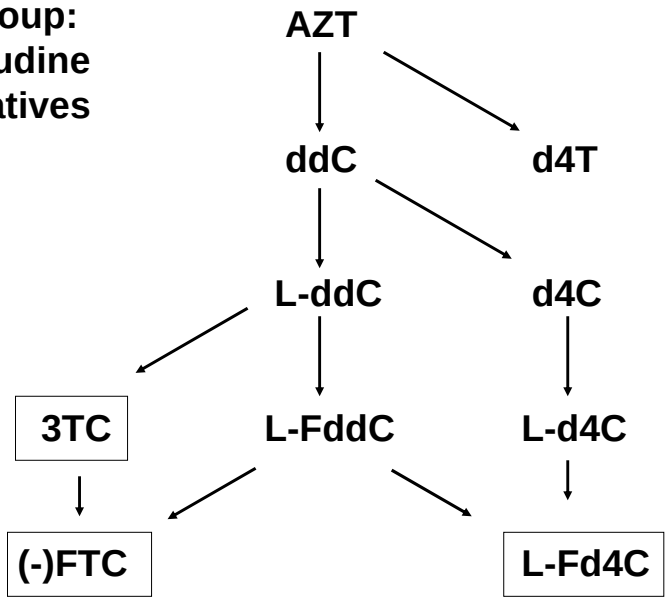
HBsAg Prevalence (%)

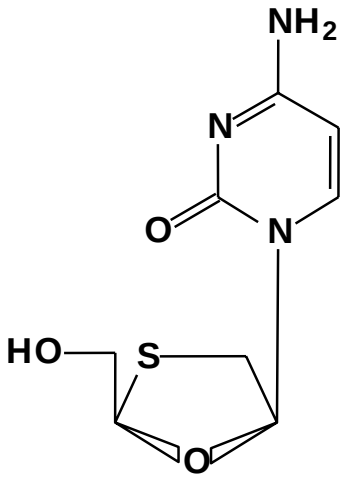
- ☐ ≥8: High
- ☐ 2-7: Intermediate
- ☐ <2: Low

Prevalence of HBsAg Positivity in Europe

- ≤ 0.2% Very Low
- 0.3-1.0% Low
- 1.1 - 5.0% Intermediate
- >5.0% High
- No data

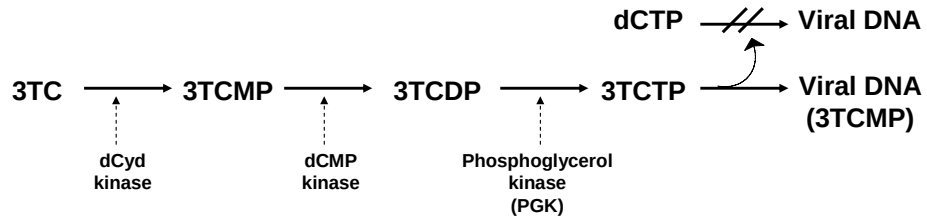
1st group: zidovudine derivatives



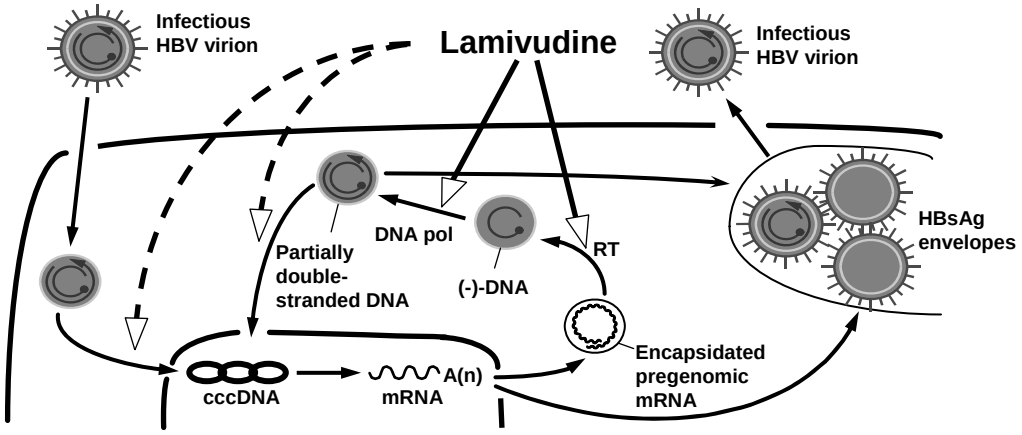


3TC
Lamivudine

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

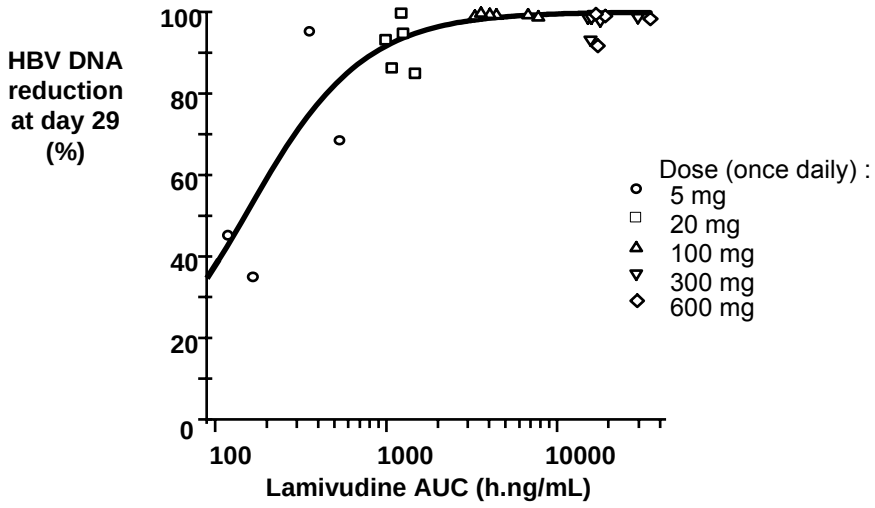


Replication Cycle of Hepatitis B Virus; Mechanism of Action of Lamivudine



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

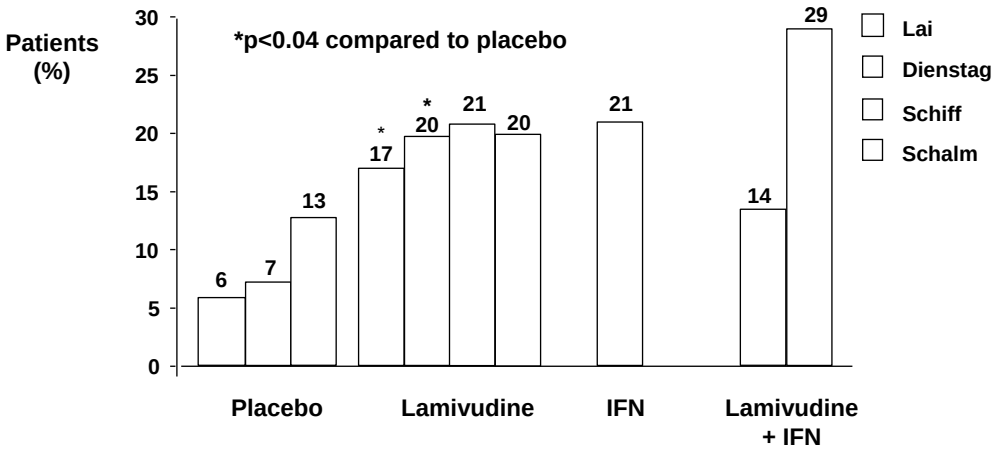
HBV DNA Reduction versus Lamivudine Bioavailability



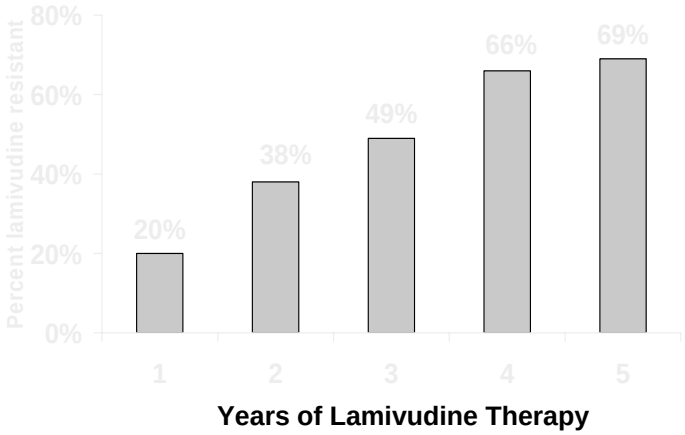
Johnson *et al.,* Clin. Pharmacokinet. 36, 41-66 (1999)

HBeAg Seroconversion After One Year of Therapy

Seroconversion = HBeAg-ve and anti-HBe+ve

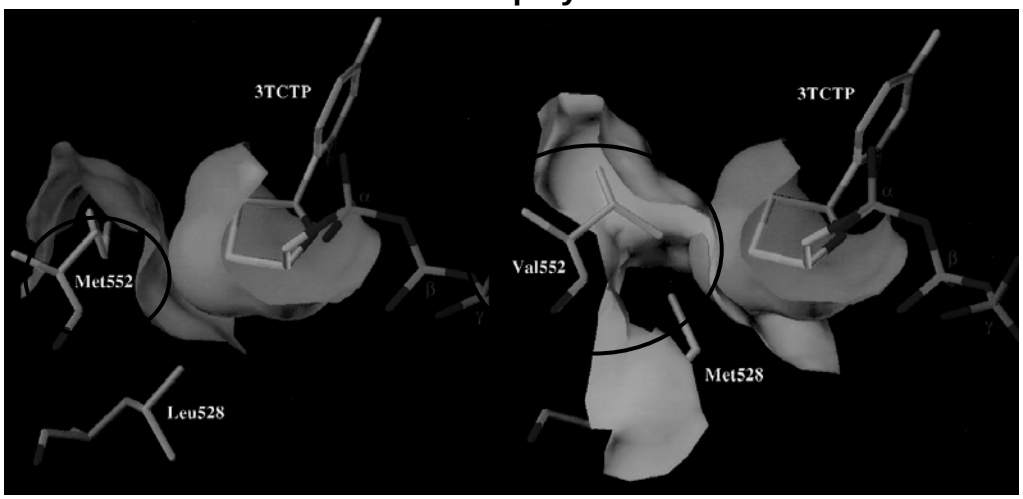


Incidence of lamivudine resistance in chronic hepatitis B



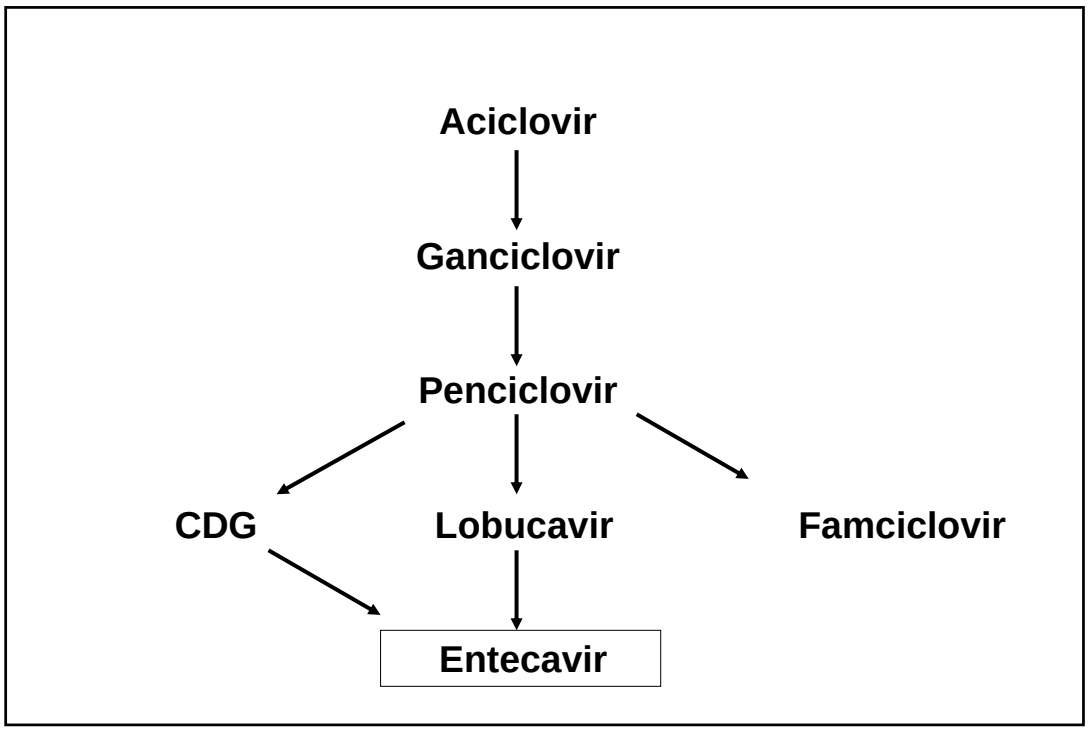
Westland *et al*., 37th Annual Meeting of the European Association for the Study of Liver Diseases, Madrid, Spain, 17-21 April 2002. Oral presentation 568.

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.

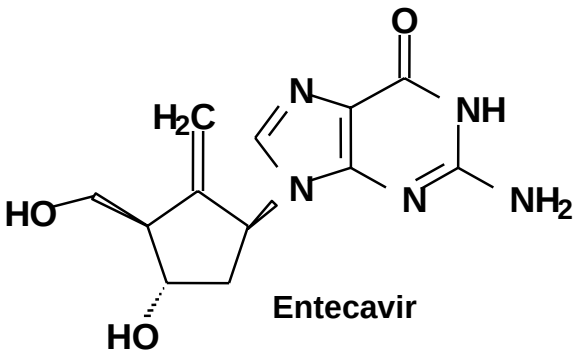
Das et al., J. Virol. 75: 4771-4779 (2001)



Mécanisme d'action:
inhibition des 3 fonctions de la polymérase virale:
- amorce des polymérases du VHB,
- transcription inverse du brin négatif d'ADN à partir de l'ARN messager prégénomique,
- synthèse du brin positif d'ADN du VHB.

Le Ki de l'entecavir tri-phosphate pour l'ADN polymérase du VHB est de 0,0012 µM.

L'entecavir tri-phosphate est un faible inhibiteur des ADN polymérases cellulaires (Ki 18-40 µM)

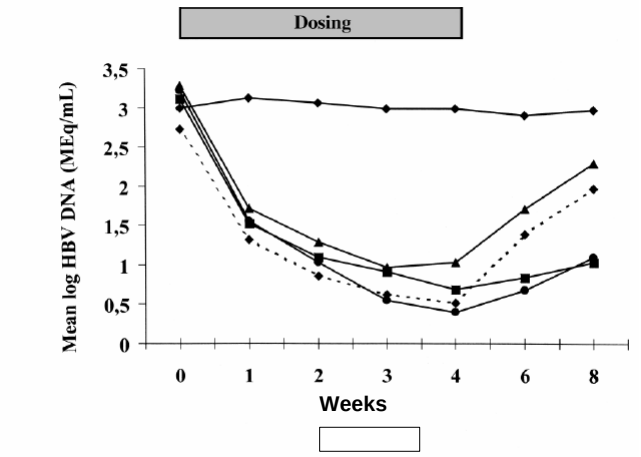


Entecavir

Indiqué dans le traitement des patients adultes atteints d'une infection chronique par le virus de l'hépatite B (VHB) présentant une maladie hépatique compensée avec la mise en évidence d'une réplication virale active, une élévation persistante des taux sériques d'alanine aminotransférase (ALAT), une inflammation hépatique active et/ou une fibrose histologiquement prouvées. Cette indication est basée sur des données provenant d'études cliniques chez des patients AgHBe positifs et des patients AgHBe négatifs pour l'infection par le VHB, des patients n'ayant jamais reçu de traitement par un analogue nucléosidique et des patients ayant un VHB résistant à la lamivudine

Notice européenne en date du 26/06/2006
http://www.emea.europa.eu/humandocs/Humans/EPAR/baraclude/baraclude.htm
(mais non encore disponible en Belgique)

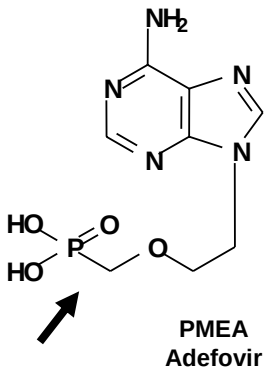
Oral Entecavir in the treatment of patients with chronic hepatitis B virus infection



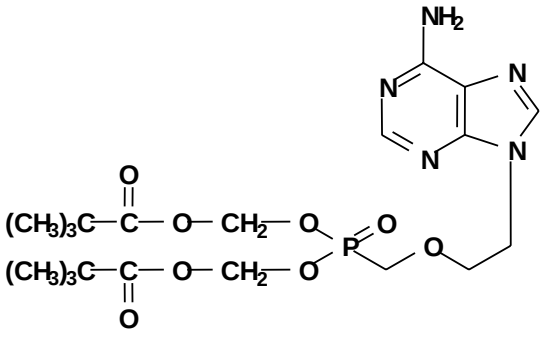
Mean HBV DNA during therapy and 1 month follow-up. (—◆—) placebo, (--◆--) 0.05 mg, (—▲—) 0.1 mg, (—●—) 0.5 mg, (—■—) 1.0 mg

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

Adefovir

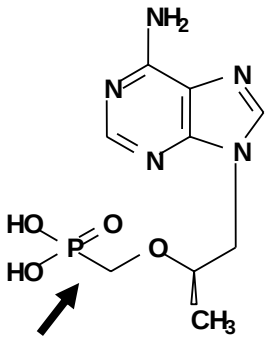


PMEA
Adefovir

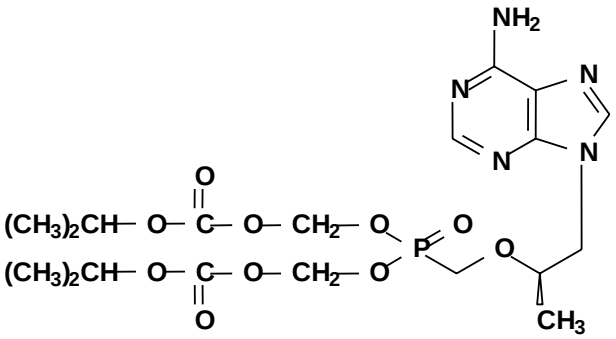


Bis(POM)PMEA
Adefovir dipivoxil

Tenofovir



PMPA
Tenofovir



Bis(POC)PMPA
Tenofovir disoproxil
Tenofovir disoproxil fumarate

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

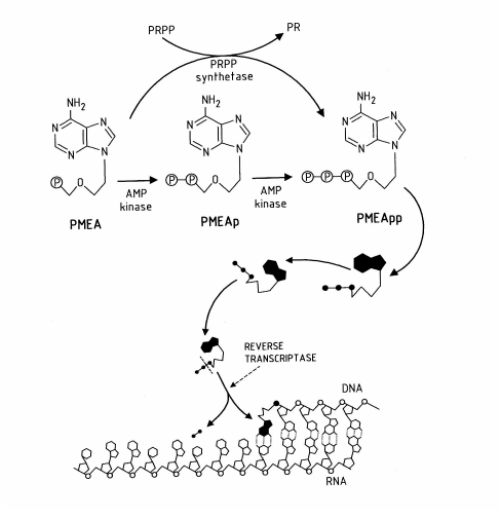
	Adefovir	Tenofovir
Herpesviridae		
Herpes simplex virus type 1 (HSV-1)	●	
Herpes simplex virus type 2 (HSV-2)	●	
Varicella-zoster virus (VZV)	●	
Epstein-Barr virus (EBV)	●	
Human cytomegalovirus (HCMV)	●	
Thymidine kinase-deficient HSV (TK HSV)	●	
Thymidine kinase-deficient VZV (TK VZV)	●	
Hepadnaviridae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

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

Retroviridae	Adefovir	Tenofovir
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	●	●

Pour des raisons de stratégies de développement
- **l'adéfovir a été enregistré pour l'hépatite B**
- **le ténofovir pour les patients infectés par le HIV-1**

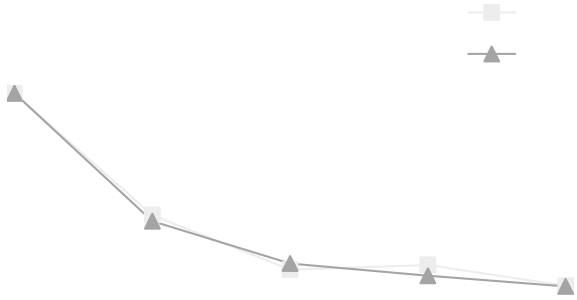
Mechanism of action of adefovir (PMEA)



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

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.

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

- Remarkably, no YMDD or other mutations occurred with therapy…

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

- The cumulative incidence of ADV resistance at month 6, 12, 18 and 24 was 0%, 6.5%, 24.6% and 38.3% respectively. Patients with ADV resistance were associated with higher HBV DNA levels and lower HBV DNA reduction in first 6 months of ADV treatment…

Chen et al. Antivir Ther. 2006;11(6):771-8.

Sasadeusz et al.
Why do we not yet have combination chemotherapy for chronic hepatitis B?
Med J Aust. 2007 Feb 19;186(4):204-6.