

**Author(s):** David Miller, M.D., Ph.D., 2009

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# Hepatitis Viruses

Infectious Diseases/Microbiology Sequence Course

M1 Infectious Diseases Sequence Course

David J. Miller, M.D., Ph.D.

Spring 2010



# Objectives

- **Know the different viruses that cause hepatitis**
- **Appreciate the differences between hepatitis virus genome structures and replication strategies**
- **Understand the differences between acute and chronic hepatitis**
- **Know the different transmission modes for hepatitis viruses**
- **Know the methods to diagnose hepatitis virus infections**
- **Understand the role of vaccination in the prevention of hepatitis virus infections**

Reading assignment: Schaechter' s 4<sup>th</sup> edition, chapter 43

# Hepatitis viruses

## Virology

## Transmission

## Treatment/Prevention

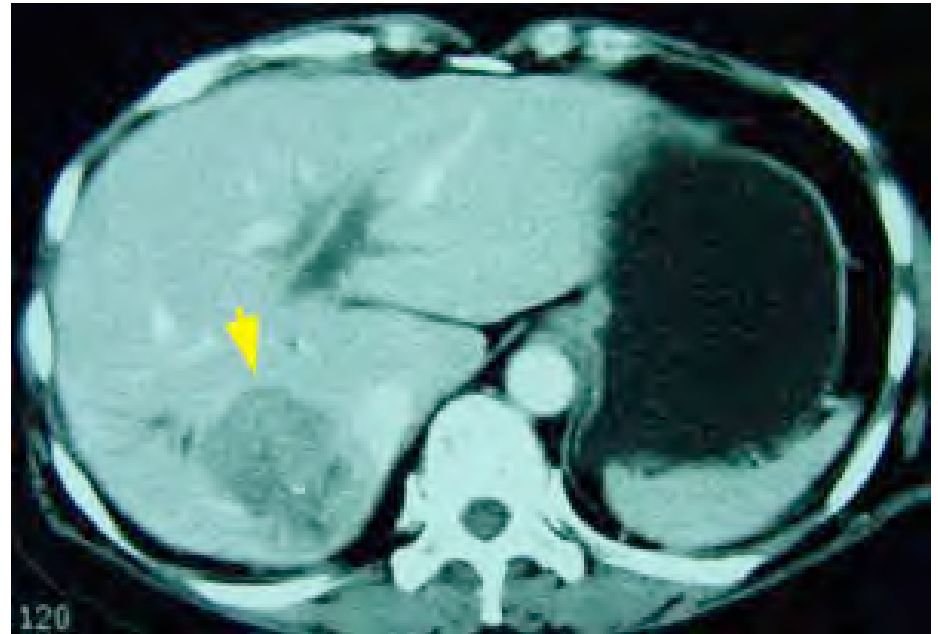
	Structure	Family	Fecal-oral	Sexual-parenteral	Vertical	Chronic infection	Antiviral Rx	Vaccine
<b>HAV</b>	+ssRNA	<i>Picornaviridae</i>	Yes	Maybe	No	No	No	Yes
<b>HBV</b>	“dsDNA” enveloped	<i>Hepadnaviridae</i>	No	Yes	Yes	Yes	Yes	Yes
<b>HCV</b>	+ssRNA enveloped	<i>Flaviviridae</i>	No	Yes	Yes	Yes	Yes	No
<b>HDV</b>	-ssRNA “enveloped”	<i>Deltaviridae</i>	No	Yes	Yes	Yes	No	“No”
<b>HEV</b>	+ssRNA	<i>Hepeviridae</i>	Yes	Maybe	No	No (except transplants)	No	No

43 year old male traveled to Thailand on a business trip. He participated in some of the illicit evening “activities” and didn’t bother to use condoms. Three months later he developed fatigue and mild abdominal pain, and his wife noticed that his eyes were yellow. He didn’t seek medical attention and his symptoms resolved over the next month. However, his wife developed similar symptoms one month later, but these also resolved spontaneously. Twenty years later, she began suffering night sweats, weight loss, and abdominal pain over six months, and was eventually diagnosed with liver cancer.



PD-GOV

Dr. Thomas F. Sellers, Emory  
University CDC PHIL #2860



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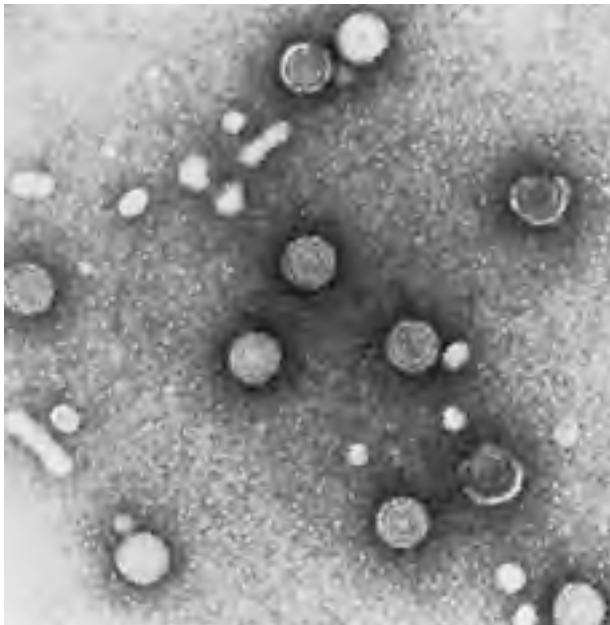
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Diagnosis?

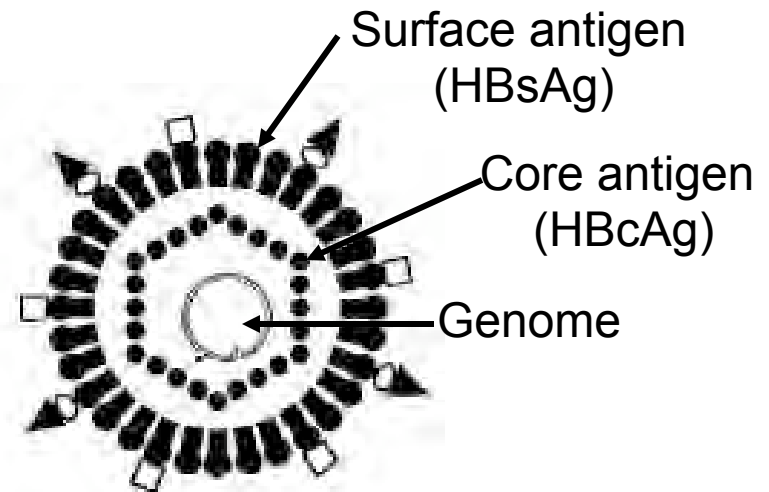


# Hepatitis B virus (HBV)

- **Family: *Hepadnaviridae***
- **Enveloped, partially double-stranded DNA virus**
- **Smallest genome of any human virus (3200 nt)**
- **Complex replication cycle**



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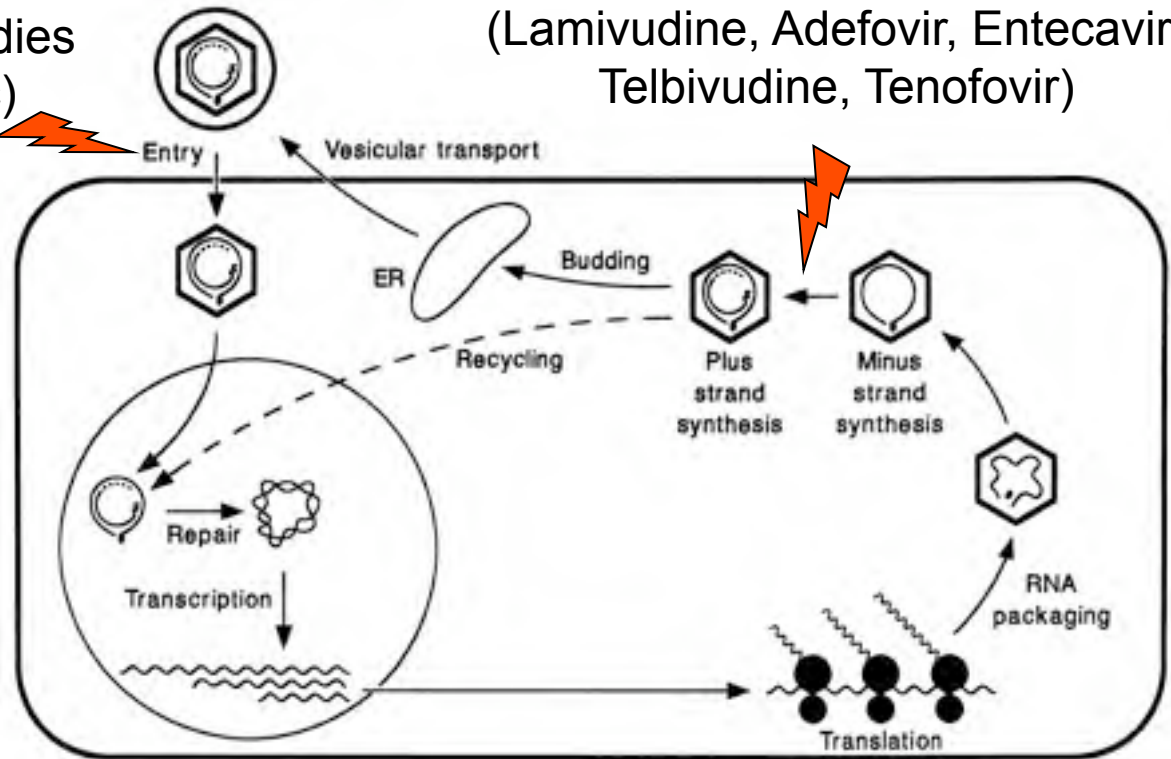
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# HBV life cycle

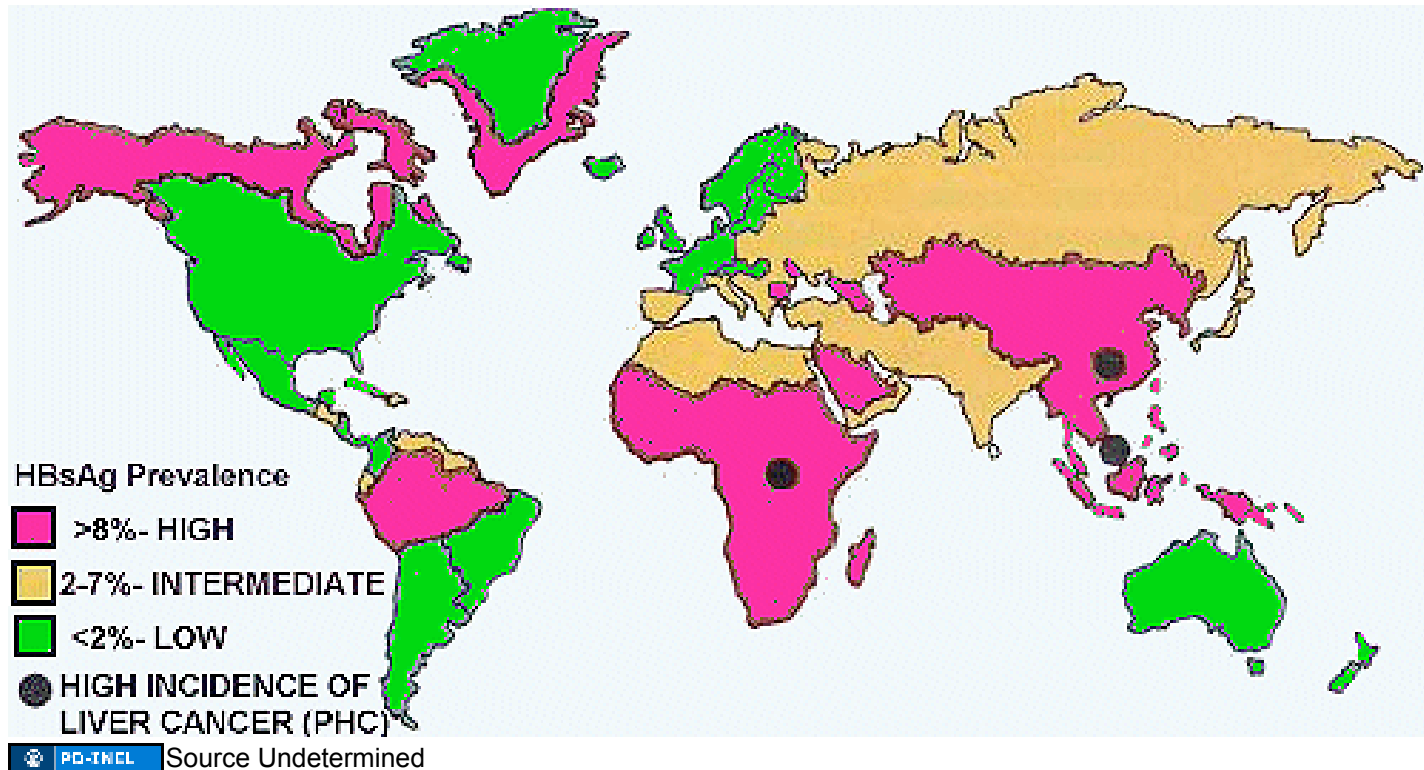
Neutralizing antibodies  
(HBsAg-specific)

HBV polymerase inhibitors  
(Lamivudine, Adefovir, Entecavir,  
Telbivudine, Tenofovir)

- Hepatocyte-specific receptor
- Nuclear steps require liver-specific elements
- Reverse transcription
  - Essential for virion formation
  - Integration *NOT* essential (contrast to retroviruses)



# HBV Epidemiology

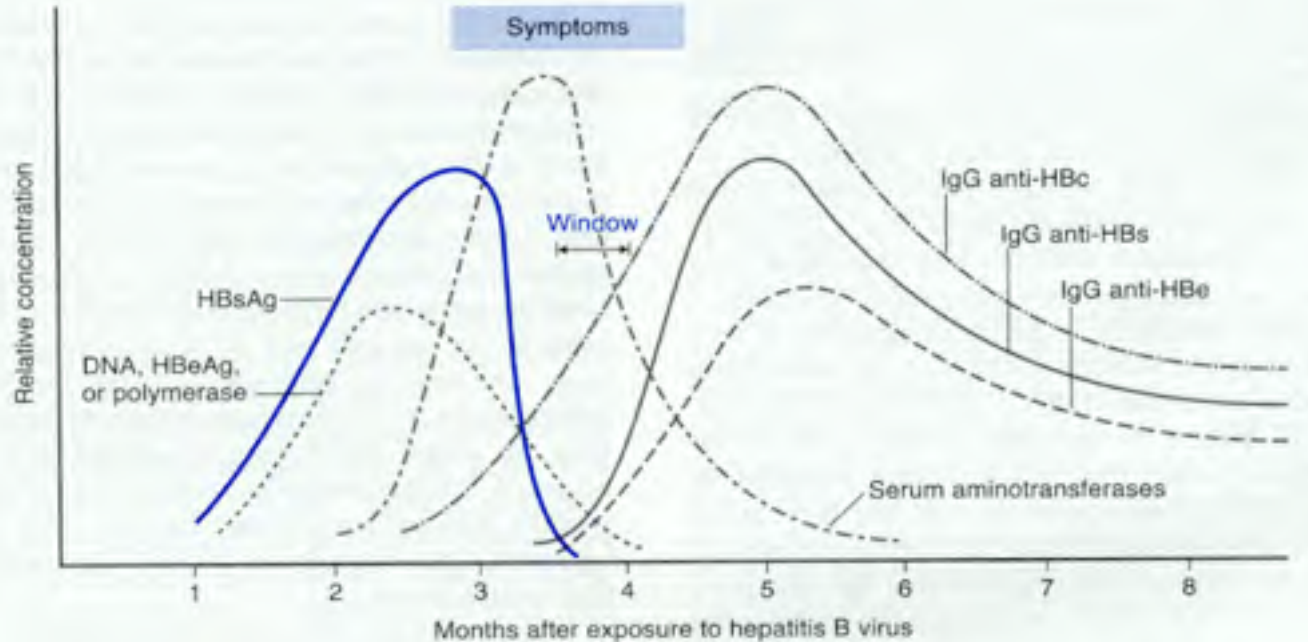


- **Enormous disease burden worldwide**
  - One-third of the world's population exposed
  - More than 300 million people with chronic infection

# HBV Clinical Manifestations

- **Transmission**
  - Parenteral (sexual, IVDU, transfusion, transplant)
  - Vertical
- **Primary symptoms**
  - 6-26 week incubation period
  - Symptoms parallel immune response
  - 95% clear infection (*contrast to HCV*)
- **Complications**
  - 5% progress to chronic infection
    - Immunosuppressed and newborns have increased risk
  - 100-fold increase in HCC after several decades

# HBV Diagnosis



	HBsAg	Anti-HBs	Anti-HBc	HBeAg/PCR
<b>Vaccination</b>	-	+	-	-
<b>Acute infection</b>	+	-	+/-	+
<b>Prior infection, resolved</b>	-	+	+	-
<b>Chronic, inactive</b>	+	-	+	-
<b>Chronic, active</b>	+	-	+	+

# HBV Treatment

- Most effective for chronic active infection
- Interferon  $\alpha$
- HBV polymerase (RT) inhibitors (originally developed for HIV)
  - Lamivudine - resistance frequent
  - Adefovir – resistance uncommon
  - Entecavir - active against Lamivudine-resistant strains
  - Telbivudine
  - Tenofovir (FDA approved in August, 2008)
    - Often combined with emtricitabine (Truvada, Atripla)

# HBV Prevention

- **Active immunization**

- Recombinant subunit vaccine produced in yeast (HBsAg)
- Combination vaccine with HAV available (Twinrix)
- Highly effective
- Component of routine childhood vaccine series
- Recommended for high risk adults
  - Health care and long-term care facility workers, HD patients, IVDU, MSM, commercial sex workers, HIV infection, recent STD, travelers, chronic liver disease
- Seroconversion rate declines with age and immunosuppression
  - >95% for age < 30 yo, but only 50% for age > 60 yo

- **Passive immunization**

- Immune globulin available for post-exposure prophylaxis

# Hepatitis D virus (HDV)

- **Family: *Deltaviridae***
- ***Not true virus***
  - ssRNA genome, but no envelope protein genes
  - Requires HBV co-infection for propagation
- **Associated with increased disease severity**
  - Higher mortality with acute infection
  - Greater risk for chronic complications
- **HBV vaccine protects against HDV infection**



18 year old female college student gave into peer pressure and decided to experiment with intravenous heroin. She had no problems after waking up from her drug-induced stupor, but didn't care much for the experience and never tried it again. Fifteen years later she noticed that her belly was getting larger fairly quickly, even though she was eating less because of generally feeling poorly. Her physician diagnosed her with ascites secondary to liver cirrhosis. Over the next two years she had repeated hospitalization due to ascites, spontaneous bacterial peritonitis (SBP), and bleeding problems. Even though she was placed on the liver transplantation list, she died from liver failure while awaiting an organ.



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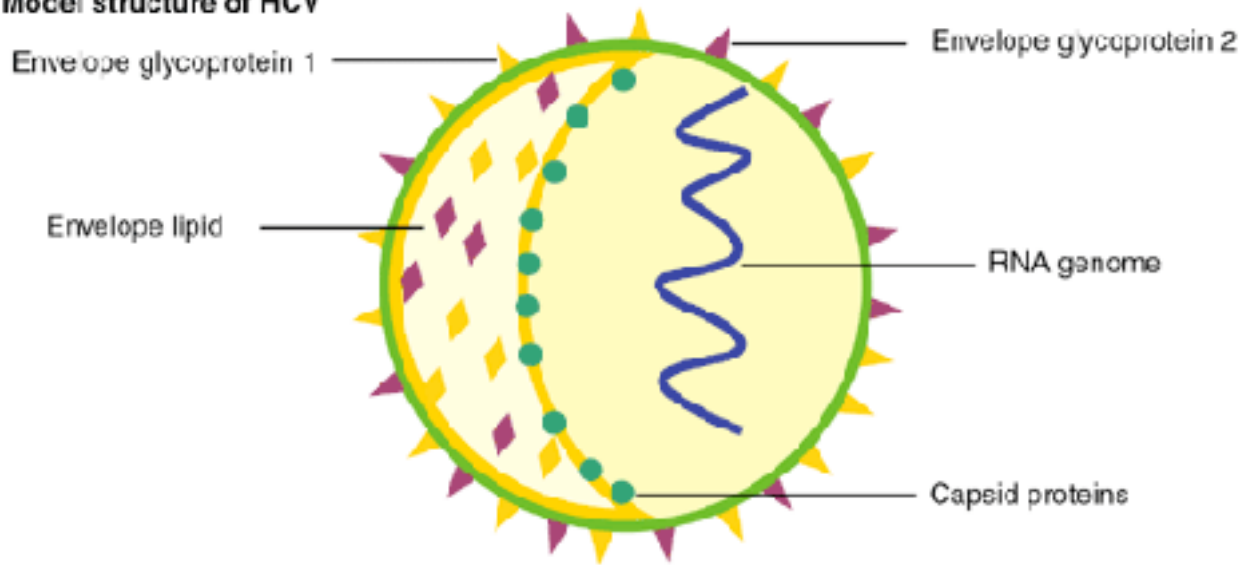
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Diagnosis?

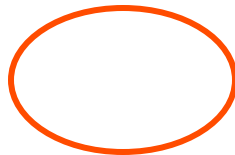
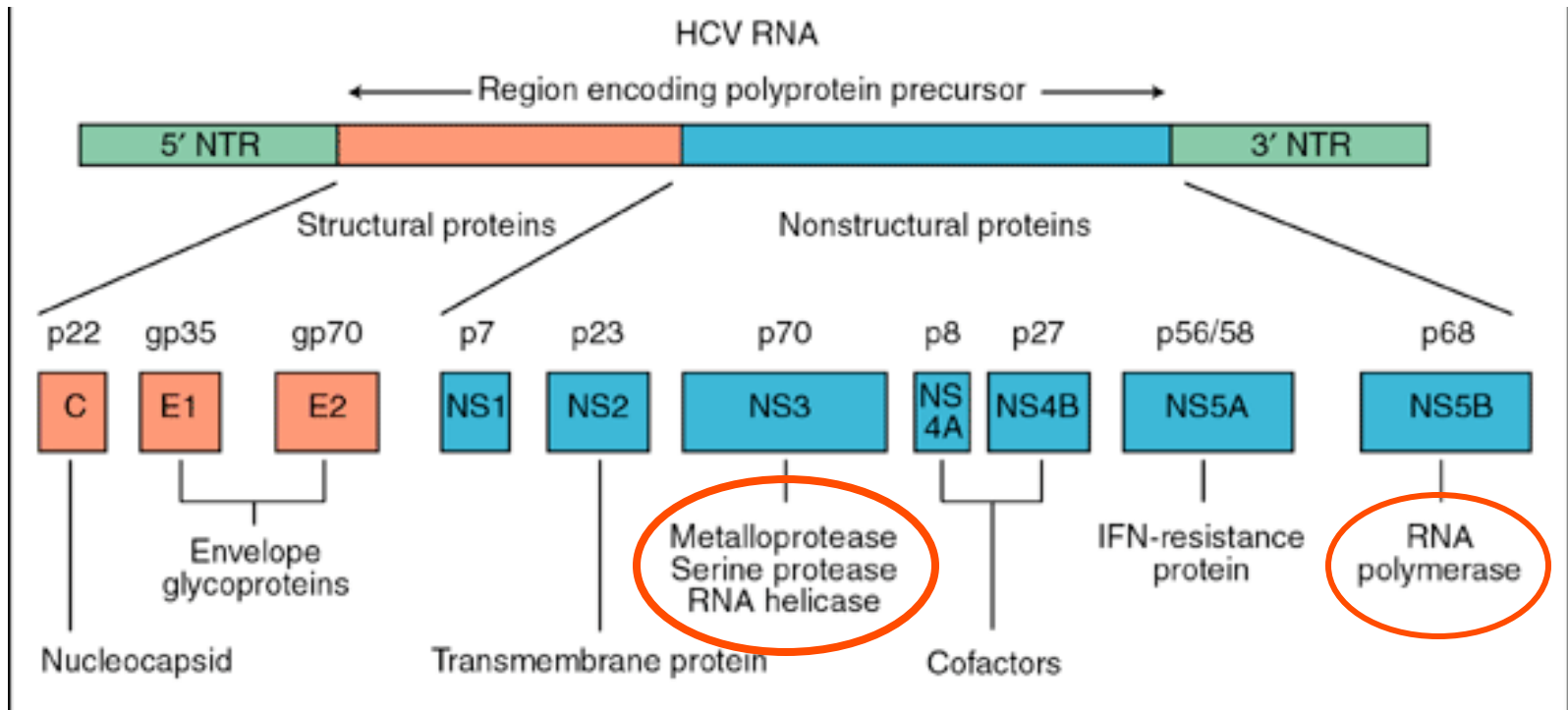
# Hepatitis C virus (HCV)

- **Family: *Flaviviridae***
- **Enveloped**
- **Non-segmented positive (+) strand RNA genome**

a Model structure of HCV



# HCV genome



Active drug targets

# HCV Clinical Manifestations

- **Transmission**
  - IVDU, sexual (less than HBV), transfusion, transplant
  - Vertical
- **Primary symptoms**
  - Acute infection often asymptomatic
  - Only 20% clear infection (*contrast with HBV*)
- **Complications**
  - 70-80% progress to chronic infection
  - 20% will develop cirrhosis (over 20 years)
  - HCC risk increased (1-4% per year)
  - Extrahepatic manifestations
    - Mixed cryoglobulinemia

# HCV Diagnosis and Treatment

- **Diagnosis**
  - Serologies
  - Viral genome detection (RT-PCR)
- **Treatment**
  - Interferon  $\alpha$  (frequent adverse reactions)
  - Ribavirin
    - Rapid resistance if use alone
  - Combination therapy most effective (IFN $\alpha$  + Rib)
    - <50% sustained response
  - Active area of investigation for new targets/drugs
    - R7128 and IDX184 - polymerase inhibitors
    - VX-950 (Telaprevir) - protease inhibitor
    - Debio-025 – cyclophilin inhibitor
  - Liver transplantation

# Potential targets for antivirals

The image is a screenshot of the CDC Health Alert Network (HAN) website. At the top, there is a navigation bar with links: Home, About CDC, Press Room, Funding, A-Z Index, Centers, Institute & Offices, Training & Employment, and Contact Us. Below this is the CDC logo and the text "Department of Health and Human Services" and "Centers for Disease Control and Prevention". There is also a search box and a link to "CDC en Español". A secondary navigation bar contains: Health & Safety Topics, Publications & Products, Data & Statistics, and Conferences & Events.

The main content area is titled "Health Alert Network". On the left, there is a "HAN Menu" with links: Home, News & Events, Training, IT Infrastructure, HAN/PHIN Jurisdictions, Other Jurisdictions, Advanced Practice Centers, and HAN Messages Archive.

The central focus is a "CDC HEALTH ADVISORY" dated Friday, December 19, 2008, 11:50 EST. The advisory title is "CDC Issues Interim Recommendations for the Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance among Circulating Influenza A (H1N1) Viruses, 2008-09 Influenza Season".

At the bottom left, there is a "PD-GOV" logo and the text "Source Undetermined".

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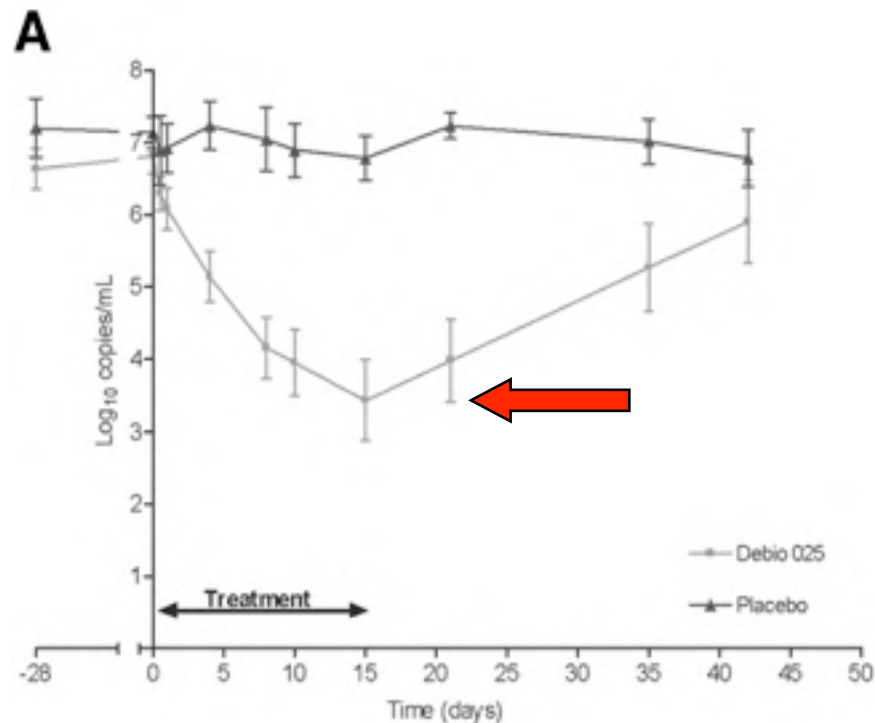
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# The Cyclophilin Inhibitor Debio-025 Shows Potent Anti-Hepatitis C Effect in Patients Coinfected with Hepatitis C and Human Immunodeficiency Virus

Robert Hisiak,<sup>1</sup> Andrzej Horban,<sup>2</sup> Philippe Gallay,<sup>3</sup> Michael Bobardt,<sup>3</sup> Suganya Selvarajah,<sup>3</sup> Alicja Wiercinska-Drapalo,<sup>1</sup> Ewa Siwak,<sup>1</sup> Iwona Cielniak,<sup>2</sup> Jozef Higersberger,<sup>2</sup> Jarek Kierkus,<sup>1</sup> Christian Aeschlimann,<sup>3</sup> Pierre Groscurin,<sup>6</sup> Valérie Nicolas-Métral,<sup>6</sup> Jean-Maurice Dumont,<sup>6</sup> Hervé Porchet,<sup>6</sup> Raf Crabbé,<sup>6</sup> and Pietro Scalfaro<sup>6</sup>



# HCV Prevention

*Why is there no HCV vaccine?*

## Hypervariable region 1

### Patient V5

	1150	1160	1170	1180	1190	1200	1210	1220	1230	
V5-1	TCGACGCGGAGACCCACATCTCCGGGGGAACAGCCGCTACACACACCGGCTTGGCTTTGCTAAACTCTTCACATCAGGCGCTCCGCCAGAACATCCA									(14/26)
V5-2	-----G-----								A-----	(2/26)
V5-3	-----GG--T-G-----AT--G--CA-GT-T---A---GC--C-T-C-----AAG-----									(2/26)
V5-4	-----A-GG--T-G-----AT--G--CA-GT-T---C-A--GC--C-T-C-----AAG-----									(1/26)
V5-5	-----G-----					G-----				(1/26)
V5-6	-----G-----								A-----	(1/26)
V5-7	-----G-----		T-----					C-----		(1/26)
V5-8	-----AAG-----									(1/26)
V5-9	-----G-----						G-----	G-----		(1/26)
V5-10	-----G-----		G-----							(1/26)
V5-11	-----G-----						G-----			(1/26)

### Patient V6

	1150	1160	1170	1180	1190	1200	1210	1220	1230	
V6-1	TCGACGCGGAAACCCACGCTCACCGGGGAACCCCTCCGCCCGCGCGCGCTCTGGACTTACCGGCTCTTCTCACACCTGGCGCCAGCAGAACATCCA									(5/17)
V6-2	-----G-----						T-----GT-----			(4/17)
V6-3	-----G-----		T-----			C--G--T--T--				(3/17)
V6-4	-----G-----					G-----	T-----GT-----			(2/17)
V6-5	--A-----G-----						T-----GT-----			(1/17)
V6-6	-----G-----		T-----			C--G--T--T--		T-----		(1/17)
V6-7	-----G-----	T-----				A--C--T--G--		G-----G-----		(1/17)

### Patient V7

	1150	1160	1170	1180	1190	1200	1210	1220	1230	
V7-1	TCGACGCGCAACTCATGTCACTGGGGGAAGTGCACAGCCACGCGCGCTCTGGGATTGCTAGGTTCTTCAGGCCAGGCGCCAGCAGAACATCCA									(23/30)
V7-2	-----G-----								A-----	(2/30)
V7-3	-----G-----						T-----			(2/30)
V7-4	-----G-----					G-----T-----				(1/30)
V7-5	-----G-----		A-----					C-----		(1/30)
V7-6	-----G--C--C--C-----CCCT--GC--G--G-----AC--CG--TC--TC--CA--T-----									(1/30)

PD-INEL Source Undetermined

## Viral Quasispecies

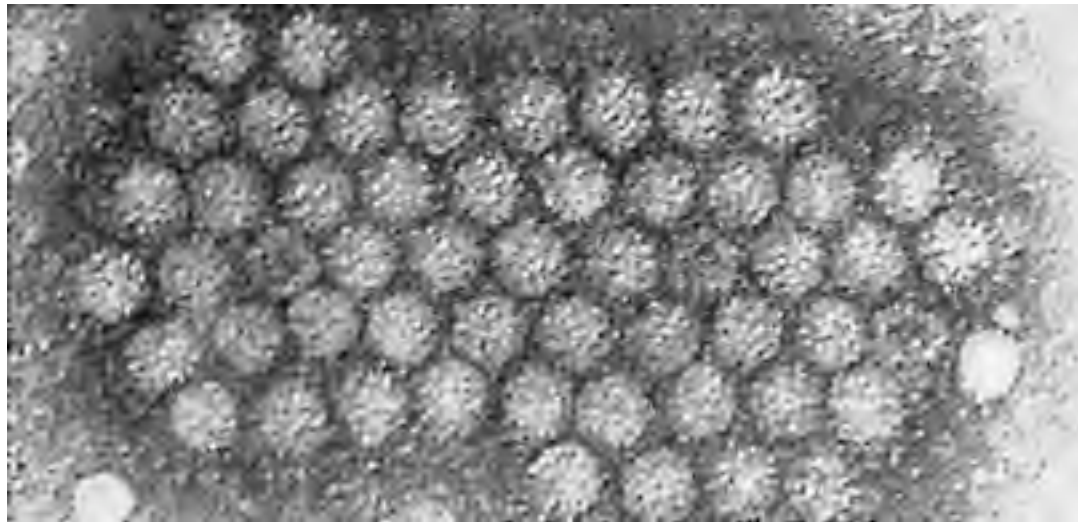
22 year old male college student went to Haiti as a Peace Corp volunteer for one week. He had philosophical issues with vaccines, and declined pretravel vaccinations. While in Haiti, he ate the local food and never boiled his water or used chlorine tablets. Three weeks after returning to the states he developed abdominal pain, nausea, vomiting, and jaundice. His symptoms resolved spontaneously, but one of his co-workers in the college cafeteria developed similar symptoms. Over the next three weeks, 20 college students who routinely ate at the cafeteria became ill, and the State Health Department was contacted immediately. Everyone eventually recovered without problems.


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Diagnosis?

# Hepatitis A virus (HAV)

- **Family: *Picornaviridae***
  - Other members: poliovirus, rhinovirus
- **Non-enveloped (acid stable)**
- **Non-segmented positive (+) strand RNA genome**

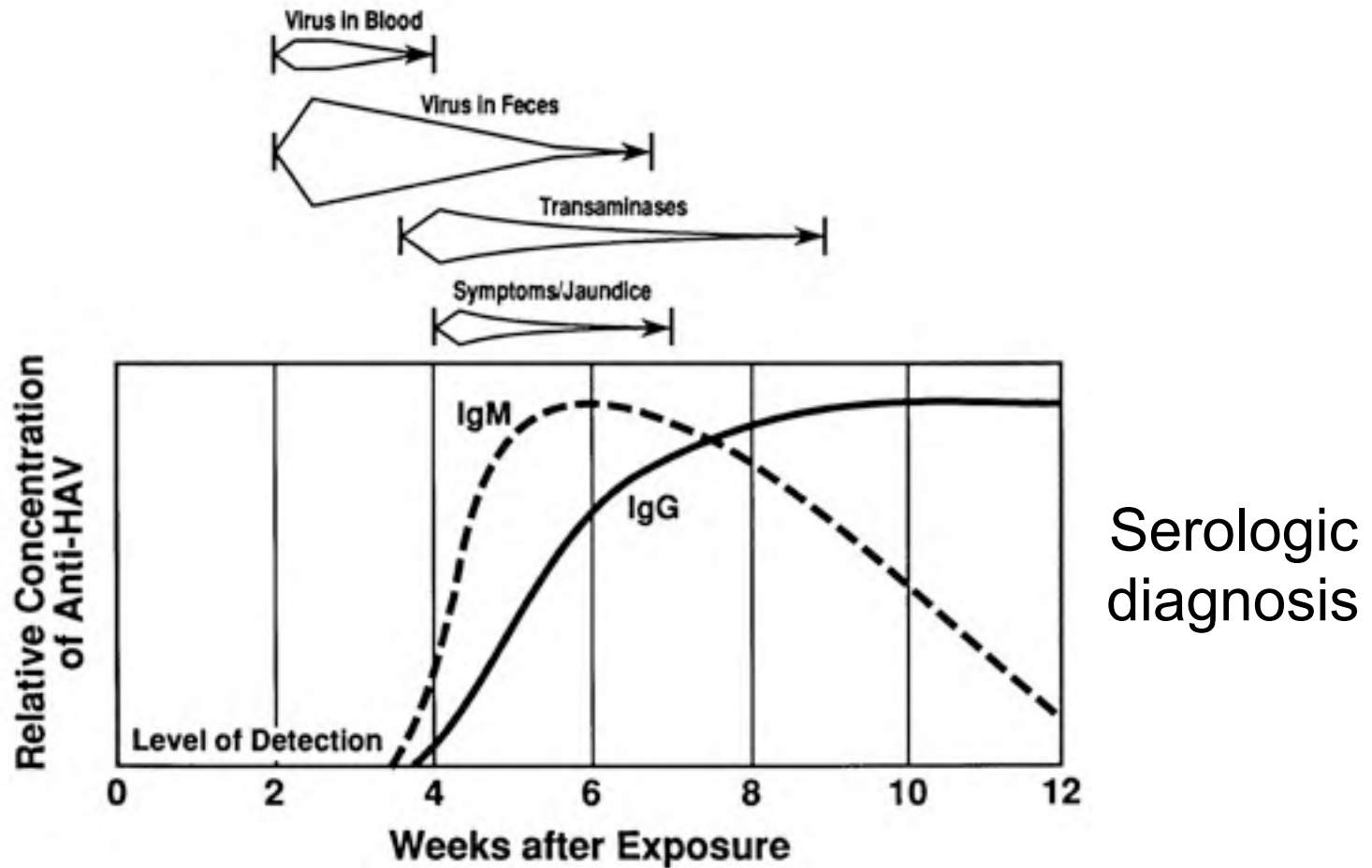


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# HAV Clinical Manifestations

- **Transmission**
  - Fecal-oral (extremely stable virus)
  - More common in underdeveloped countries
- **Primary infection**
  - Frequently symptomatic
  - Due to direct hepatocyte damage
- **Complications**
  - Fatal acute hepatitis rare
  - No chronic infection (*contrast to HBV and HCV*)

# HAV Diagnosis



# HAV Treatment and Prevention

- **Treatment**

- None
- Containment (limit transmission)

- **Prevention**

- Natural infection produces lasting immunity
- Inactivated vaccine available (Havrix, VAQTA)
  - Extremely effective (lasts >10 years)
  - Combination vaccine with HBV (Twinrix)
    - May 2006, recommended for routine childhood vaccination  
(<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5507a1.htm>)
  - Other indications: travel, chronic liver disease, MSM, IVDU
- Immune globulin available for passive prophylaxis



# Hepatitis E virus (HEV)

- **Family: *Hepeviridae* (related to *Caliciviridae*)**
  - Non-enveloped, positive (+) sense RNA virus
- **Similar to HAV**
  - Fecal-oral transmission
  - More frequent in underdeveloped countries
  - Generally no chronic infection in normal patients
  - *Emerging as chronic pathogen in liver transplant patients (NEJM 358:811, 2008)*
- **Potentially life-threatening in pregnant women**
- **No vaccine currently available**

# Additional Source Information

for more information see: <http://open.umich.edu/wiki/CitationPolicy>

Slide 5: David Miller

Slide 7: Dr. Thomas F. Sellers, Emory University CDC PHIL #2860; Source Undetermined

Slide 8: Source Undetermined

Slide 9: Sources Undetermined

Slide 10: Source Undetermined

Slide 11: Source Undetermined

Slide 13: Source Undetermined

Slide 18: Source Undetermined; Source Undetermined

Slide 20: Cambridge University Press, [http://journals.cambridge.org/fulltext\\_content/ERM/ERM5\\_28/S1462399403006926sup009.gif](http://journals.cambridge.org/fulltext_content/ERM/ERM5_28/S1462399403006926sup009.gif)

Slide 21: Cambridge University Press, [http://journals.cambridge.org/fulltext\\_content/ERM/ERM5\\_28/S1462399403006926sup009.gif](http://journals.cambridge.org/fulltext_content/ERM/ERM5_28/S1462399403006926sup009.gif)

Slide 24: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5507a1.htm>

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