



Viral Hepatitis (2)

University of Jordan

Malik Sallam, M.D., Ph.D.

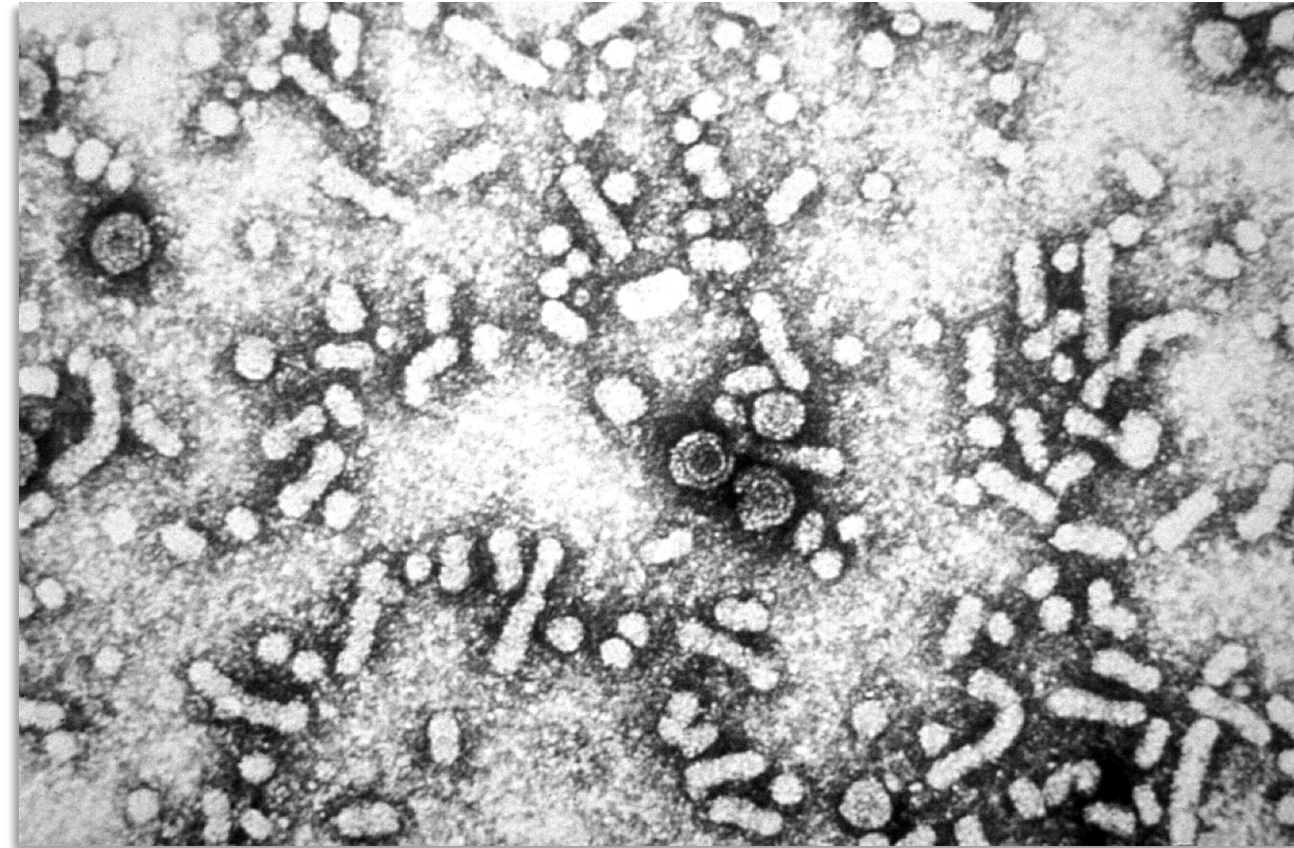
School of Medicine

Department of Pathology, Microbiology and Forensic Medicine



Hepatitis B Virus (HBV) – Background

- HBV is a DNA virus with a peculiar genome that is a circular partially double-stranded DNA of about 3.3 kb (slight length differences are observed in different genotypes).
- HBV is the only human virus that belongs to the family *Hepadnaviridae*, while other animal viruses have been identified that belonged to the same family of viruses which can infect mammals and birds with characteristic tropism for hepatocytes.





Hepatitis B Virus (HBV) – Background

The accidental discovery of association between Australia antigen (HBsAg) and serum hepatitis (type B, compared to type A [infectious hepatitis] caused by HAV) in 1965 by Blumberg et al, marked the start of great strides that were made in the investigation of hepatitis B epidemiology and pathogenesis which eventually led to development of a successful HBV vaccine.



OBITUARY

Baruch Blumberg

(1925–2011)

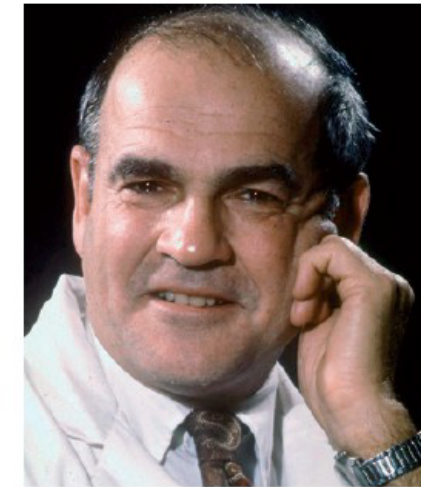
Geneticist whose discovery led to a vaccine for hepatitis B.

In the 2,000 years since Hippocrates described the skin-yellowing condition he termed *ikterus*, no single event has been more pivotal to the understanding and prevention of viral hepatitis than the discovery of the 'Australia antigen' by Baruch (Barry) Blumberg. This antigen, which Blumberg found in the blood of an Australian Aborigine, turned out to be the surface antigen of hepatitis B virus. The finding ultimately led to a test to screen blood donors for the virus and to a hepatitis vaccine.

Although the outcome of Blumberg's research was monumental, his findings were initially serendipitous. In the late 1950s, while working at the US National Institutes of Health (NIH) in Bethesda, Maryland, he showed that cholesterol-transporting proteins called β -lipoproteins exist in varied forms in different populations as a result of genetic polymorphisms. In 1963, while heading the new Geographic Medicine and Genetics Section of the NIH, Blumberg and his co-workers unexpectedly found a precipitate in agar that did not take up the blue stain for lipids but stained red for protein. Blumberg had been using serum samples from haemophiliacs who had received multiple blood transfusions to provide antibodies that would react in agar with diverse proteins. The initially designated

institution. This was the first clue that the Australia antigen might be related to an infectious agent. The specific infection was identified as hepatitis B when two Down's syndrome patients and an investigator in Blumberg's lab were found to carry the antigen only after developing acute hepatitis.

The US company Abbott Laboratories developed a test to screen blood donors for the antigen, which dramatically reduced



York and then graduate work at Columbia University in New York City. At Columbia he first studied mathematics but then transferred to become a medical student at the College of Physicians and Surgeons.

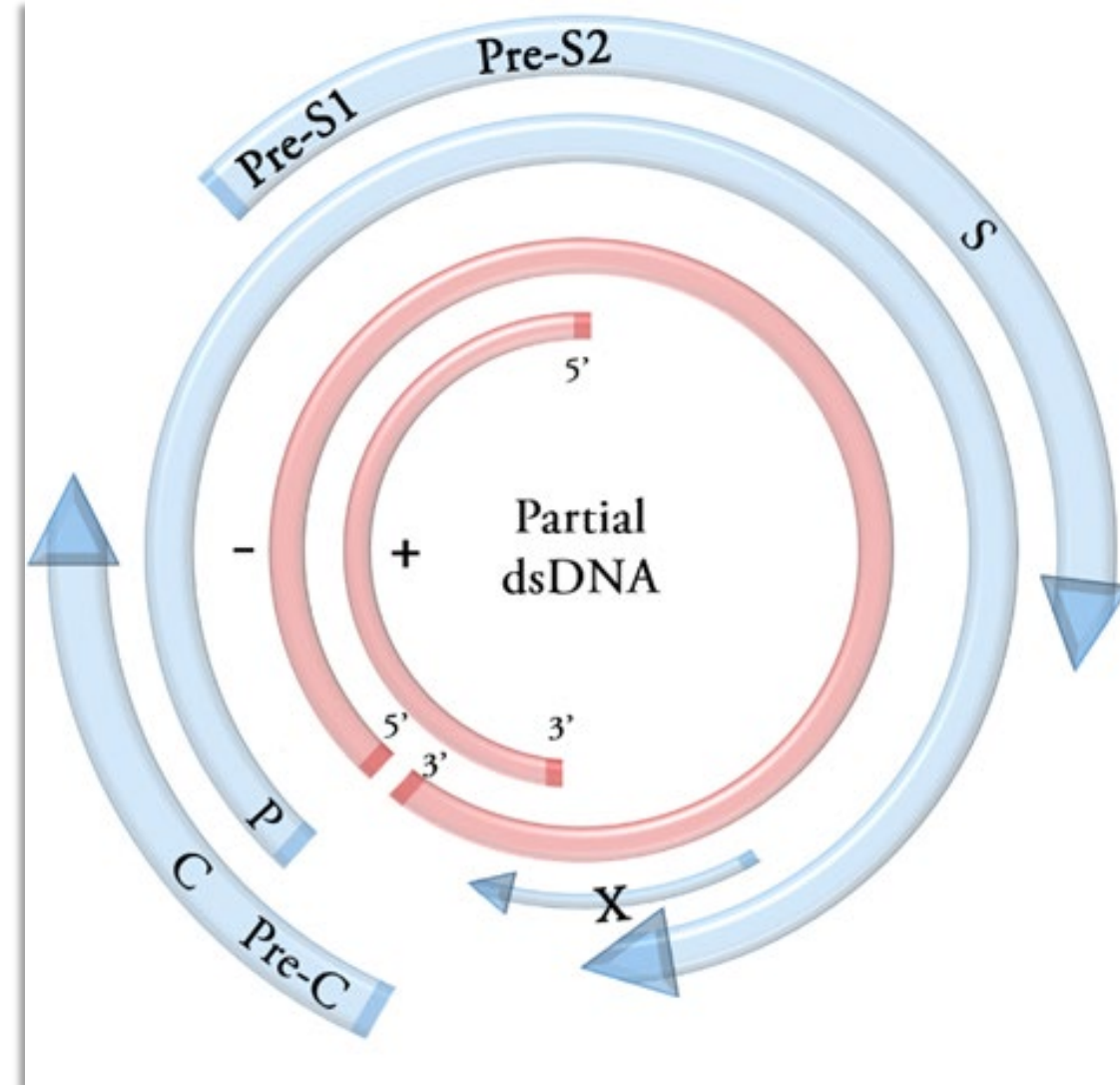
It was at medical school that Blumberg's fascination with population genetics and disease took hold. He spent several months in northern Suriname in South America. A richly heterogeneous population had been brought to the country centuries earlier to work in the sugar plantations and Blumberg was struck by the enormous variation in how these people responded to disease. Yet his life took a few more twists and turns before the Australia antigen transformed it. After completing a medical residency at Bellevue Hospital in New York and a clinical fellowship in arthritis at the Columbia-Presbyterian Medical Center, he moved to Britain. He pursued a PhD in the Department of Biochemistry at the University of Oxford on the physical and biochemical characteristics of hyaluronic acid — a key component of connective, epithelial and neural tissues.

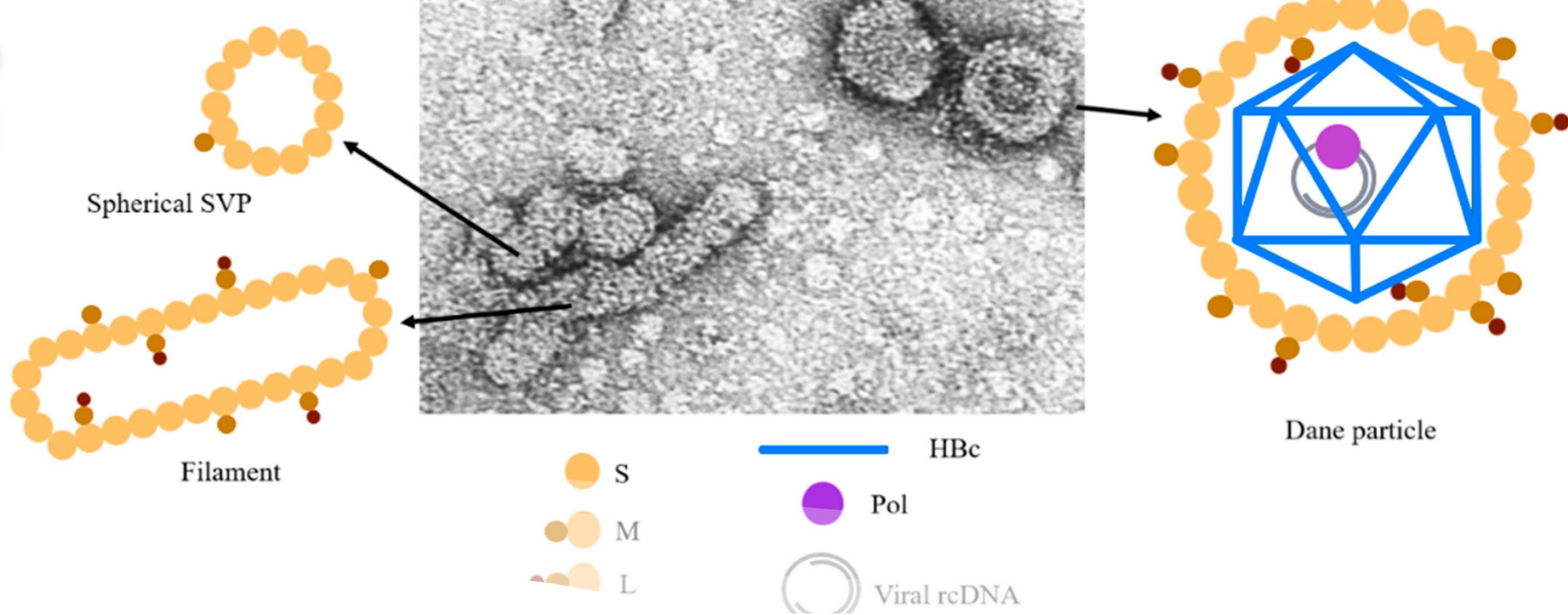
Barry's life after he received the Nobel prize was just as varied. He travelled in China, India and Africa to investigate liver cancer and promote the hepatitis B vaccine. In 1999 he was elected Master of Balliol Col



HBV genome and virion structure

- The genome of HBV consists of four ORFs that encodes seven proteins (*S* that encodes three surface proteins, *X* which encodes the trans-activator of transcription, *C* which encodes two core proteins and the *P* which encodes the HBV polymerase that has DNA polymerase, RT and RNase H activities).
- The extraordinary short length of HBV genome together with the overlapping nature of its genes make HBV a unique human pathogen particularly from an evolutionary point of view



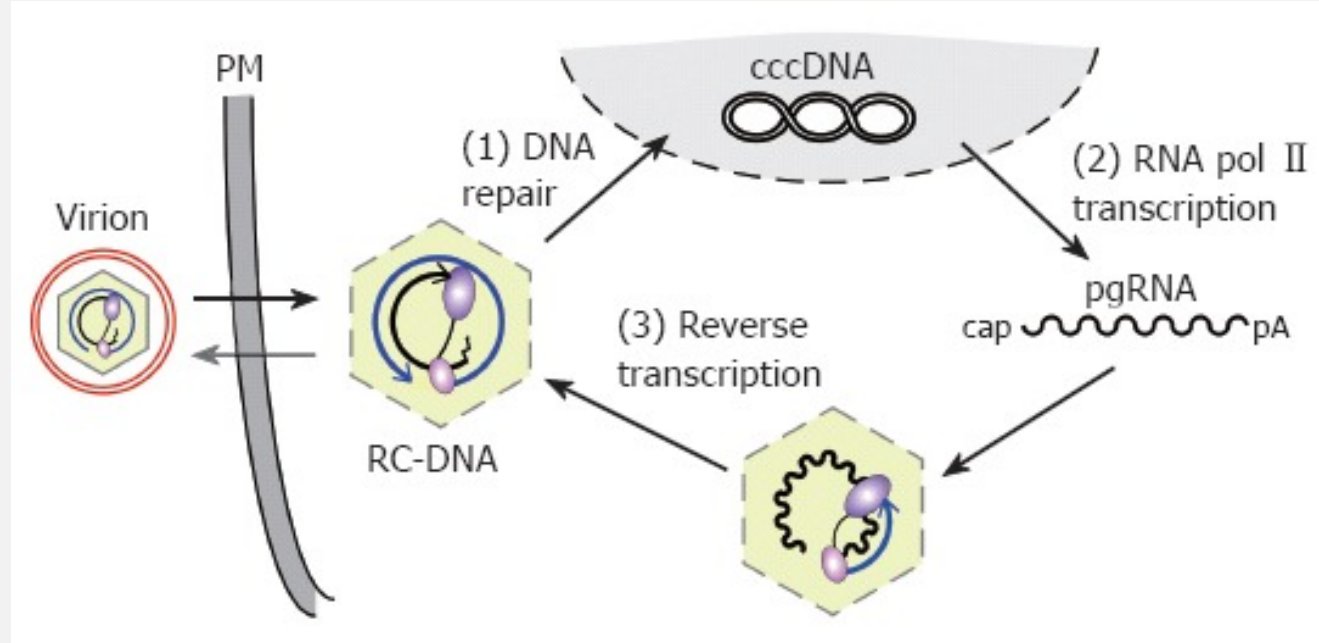


- In the host, HBV is characterized by the circulation of three electron microscope (EM) morphologically recognized structures: The 42-nm virion particles, the 22-nm spherical particles and the 22-nm tubular particles that are up to 200 nm in length.
- The 22-nm particles, that are **non-infectious**, are produced in excess compared to the virions which might be a viral decoy mechanism to trick the immune system.

HBV genome and virion structure



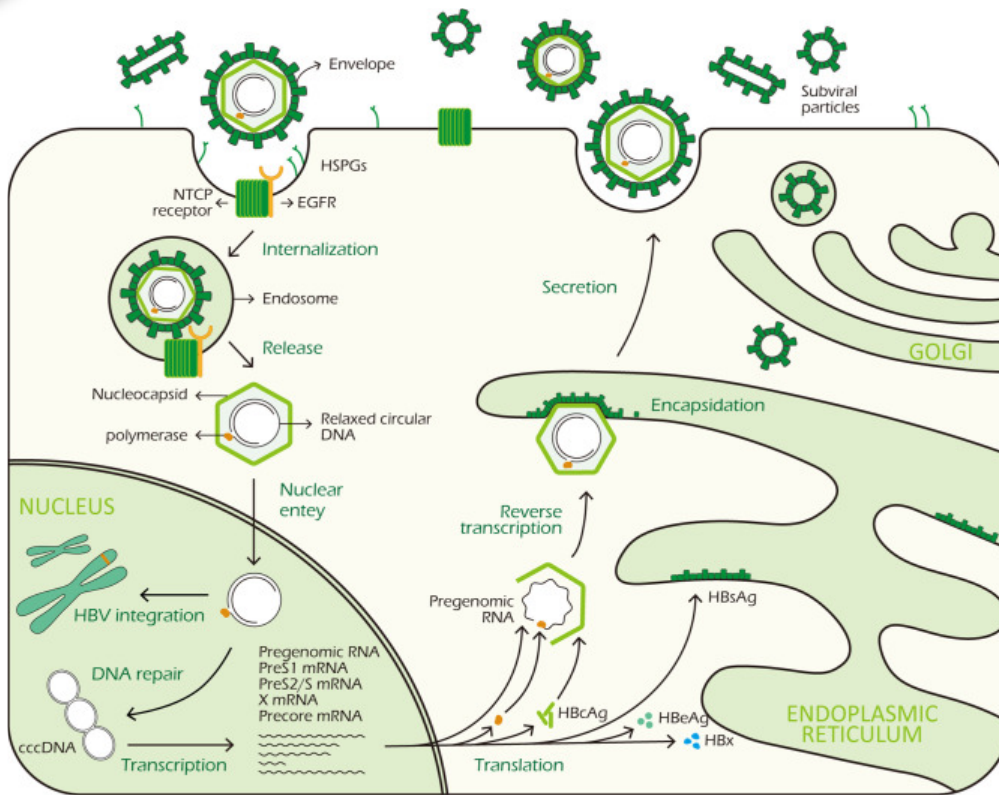
Replication cycle of the hepadnaviral genome



- HBV replication is unique in the way that its replication occurs through an RNA intermediate (the pre-genomic RNA) from the minus DNA strand.
- Then plus DNA strand is transcribed from the minus-strand DNA template by the DNA-dependent DNA polymerase, followed by transfer to the nucleus and forms the covalently closed circular DNA that is the template for mRNA and pre-genomic RNA.



Hepatitis B Virus Proteins



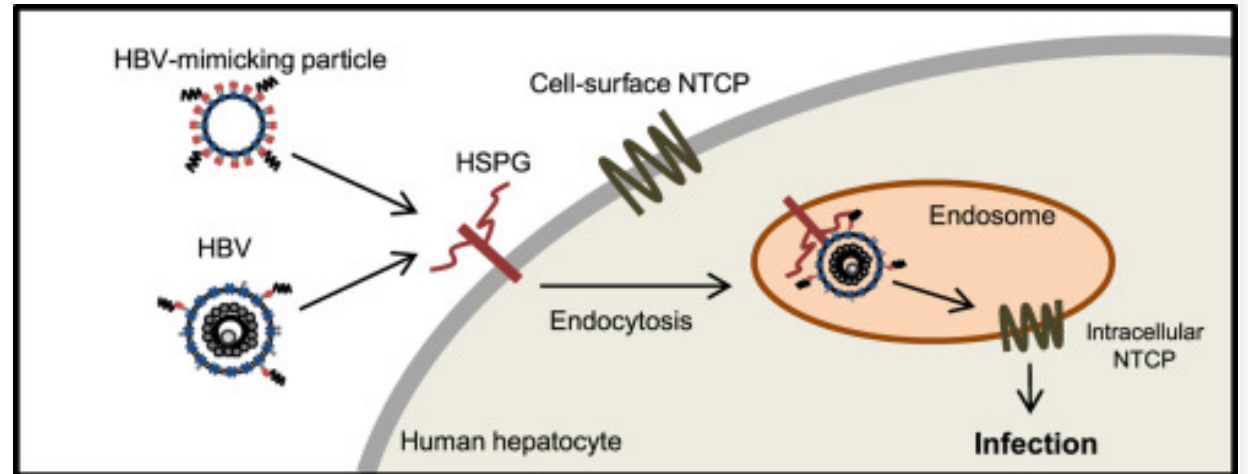
- The polymerase of HBV has the following activities in four domains: terminal protein at the amino end that has a role in initiation of DNA synthesis, a spacer domain that is not critical in function, RT and RNase H.
- The core protein (HBcAg) form the capsid and exists as a dimer.
- Translation of the preCore region results in the production of the soluble form of core protein (HBeAg) with its presence in serum marking higher transmissibility.



Hepatitis B Virus Proteins



- The surface proteins embedded in the envelope are small (S), medium (M) and large (L).
- The most abundant is the S protein that is the product of S while translation of both PreS2 and S results in the production of M protein and translation of PreS1, PreS2 and S all together results in L protein production. The pre-S1 domain of the L protein binds to the hepatic receptor of HBV namely sodium taurocholate co-transporting polypeptide (NTCP).





HBV genetic diversity

- HBV is the only pathogenic human virus that replicates its DNA through an RNA intermediate using reverse transcription which is characterized by low fidelity in spite of restriction in the allowed mutations due to the overlapping nature of some parts of the genome.
- HBV is currently classified into at least eight genotypes designated with capital letters (A-H) with pairwise inter-genotypic distances of more than 8%.

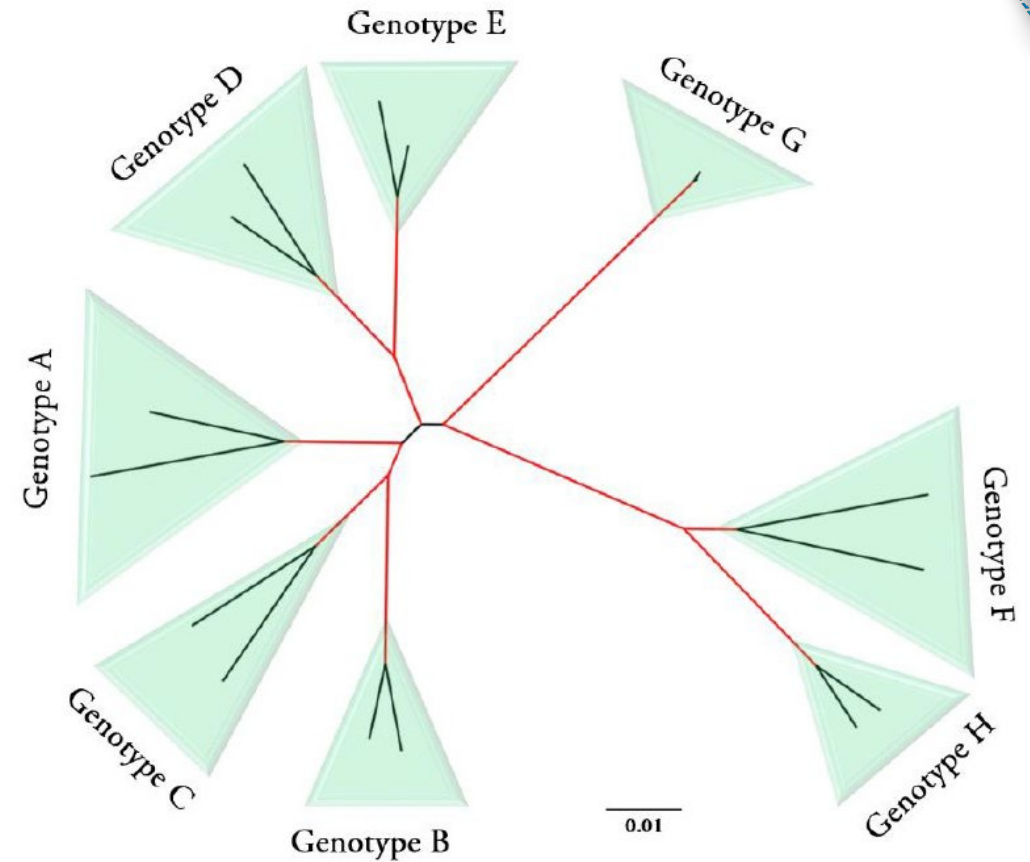
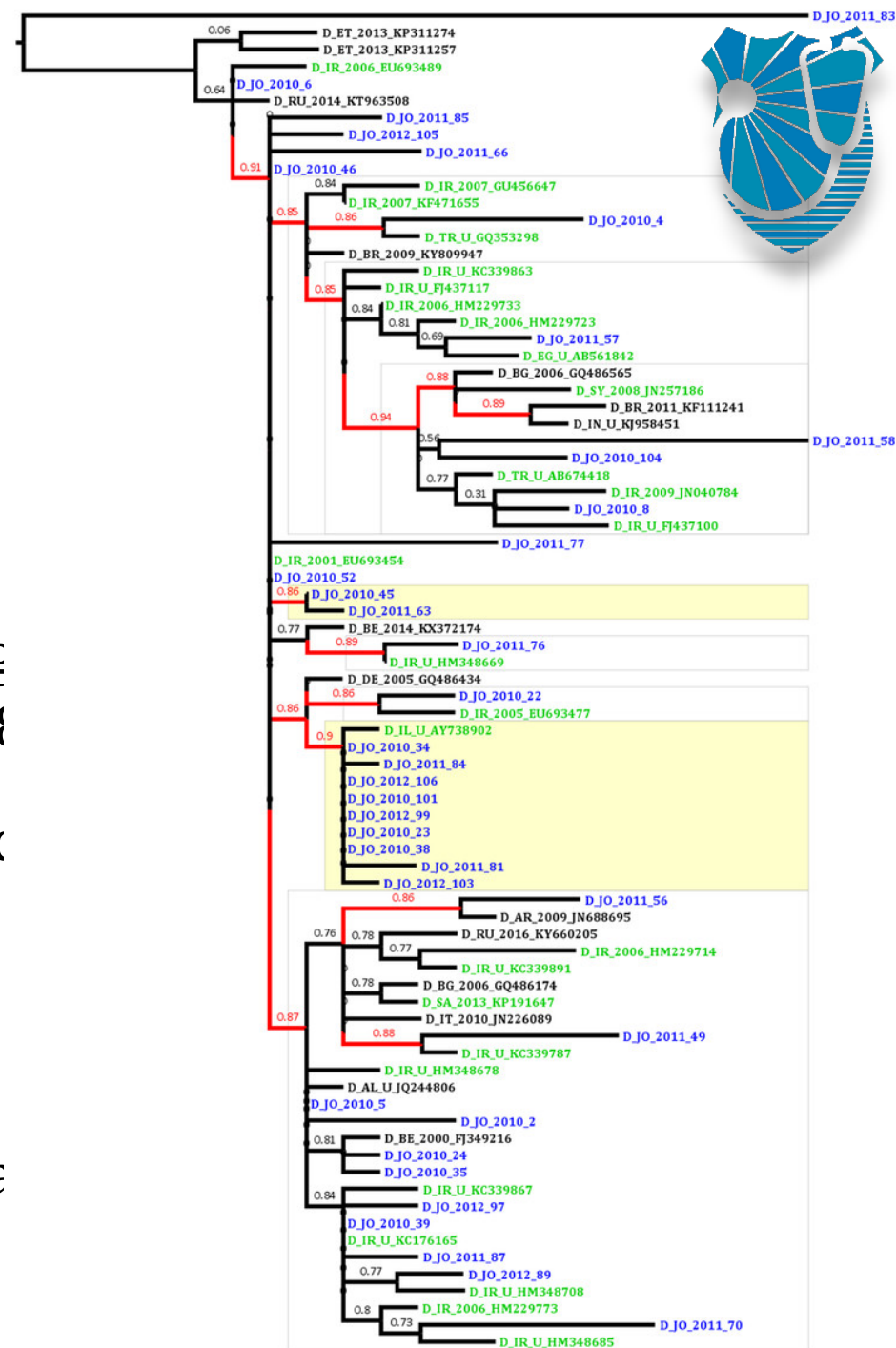


Figure 13. Neighbor joining phylogenetic tree displaying the genetic divergence of H genotypes using reference complete-genomes (16 taxa) with TN93 as the substituit model. Red branches have bootstrap values of ≥ 0.90 . Analysis was conducted in MEG



HBV genetic diversity

- HBV genotypes are further divided into subtypes designated with Arabic numerals with molecular divergence of 4-8%
- The genotypic classification of HBV nowadays replaced the obsolete serotyping system that was based on the serological features of HBsAg.
- Recently, two novel genotypes have been described, genotype I in Vietnam and Laos, and genotype J in Japan



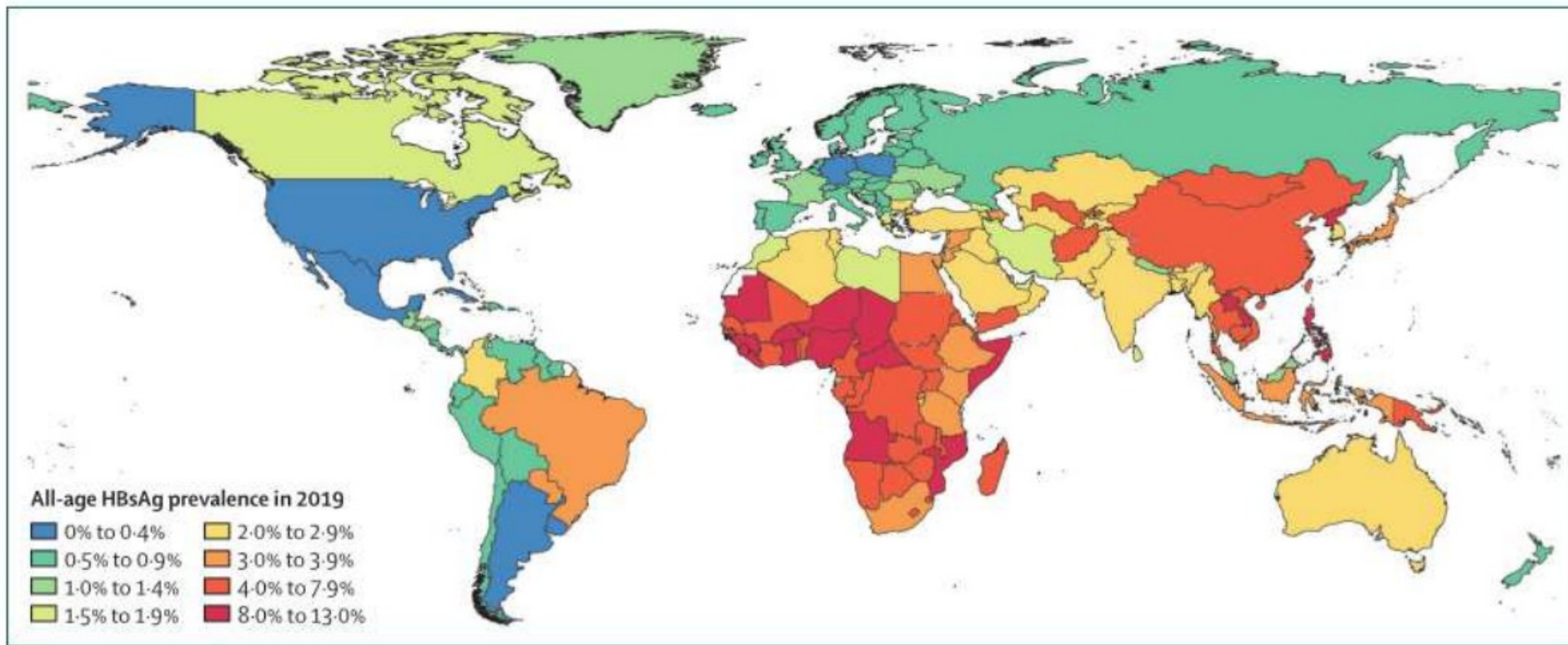


Figure 1: Global prevalence of HBsAg or chronic hepatitis B virus infection
Reproduced from GBD 2019 Hepatitis B Collaborators. HBsAg=hepatitis B surface antigen.

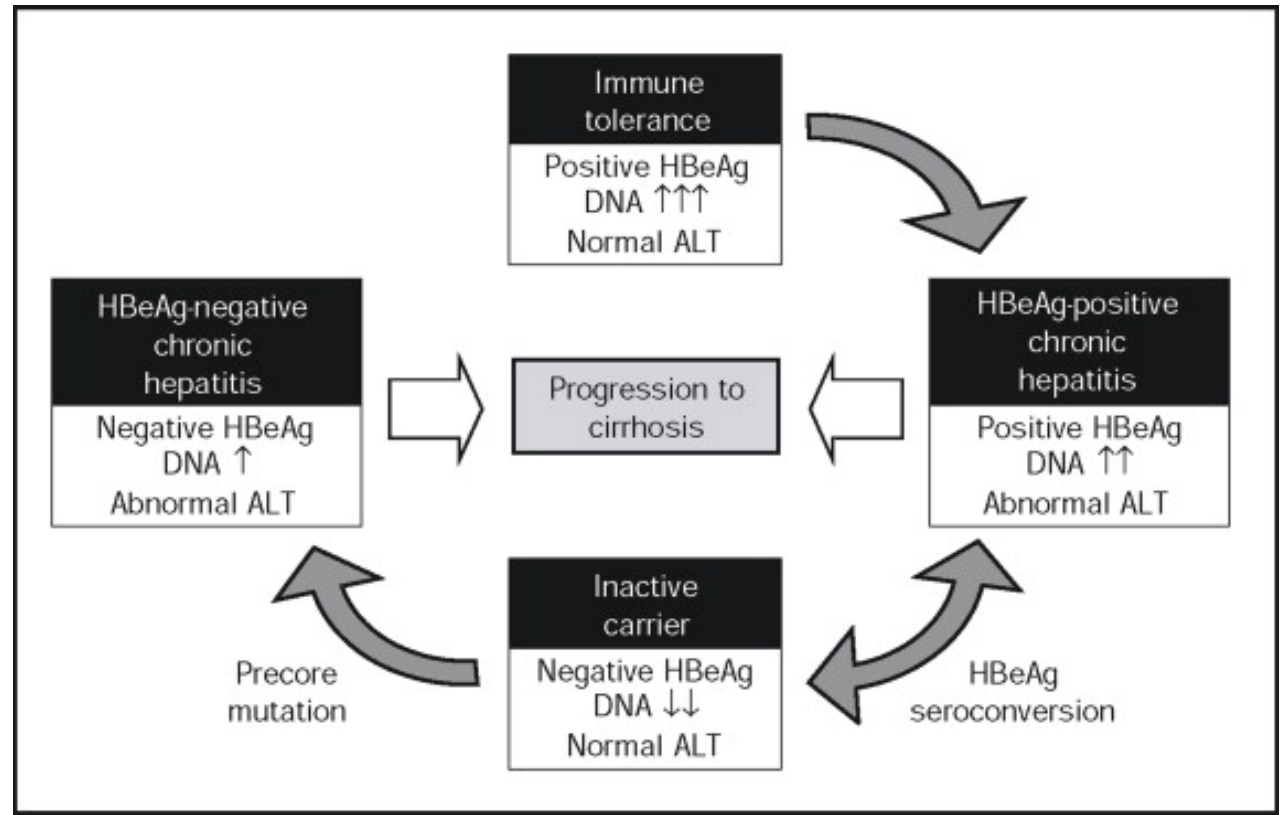
Epidemiologic features and transmission of HBV

- The percutaneous transmission (blood transfusion, IDU, needlestick injury) is the major route for HBV infection. Other major routes of transmission include sexual spread and mother-to-child transmission (MTCT).
- In areas with high endemicity (sero-prevalence $\geq 8\%$, e.g. Southeast Asia), MTCT represents a frequent mode of spread with its subsequent high prevalence of chronicity.



Hepatitis B natural history and clinical features

- HBV can cause both acute and chronic infections, with **age as one of determinants of chronicity**.
- Fulminant hepatitis can follow acute infection.
- Because HBV does not induce a cytopathic effect on the infected hepatocytes, the time from infection till the development of immune response (with clinical signs and symptoms) might take months.
- In adults, the majority clear the infection and a minority develops chronic infection during which, hepatocyte damage occurs as a result of T cell mediated immune attack on hepatocytes expressing HBV antigens on the context of their HLA molecules.



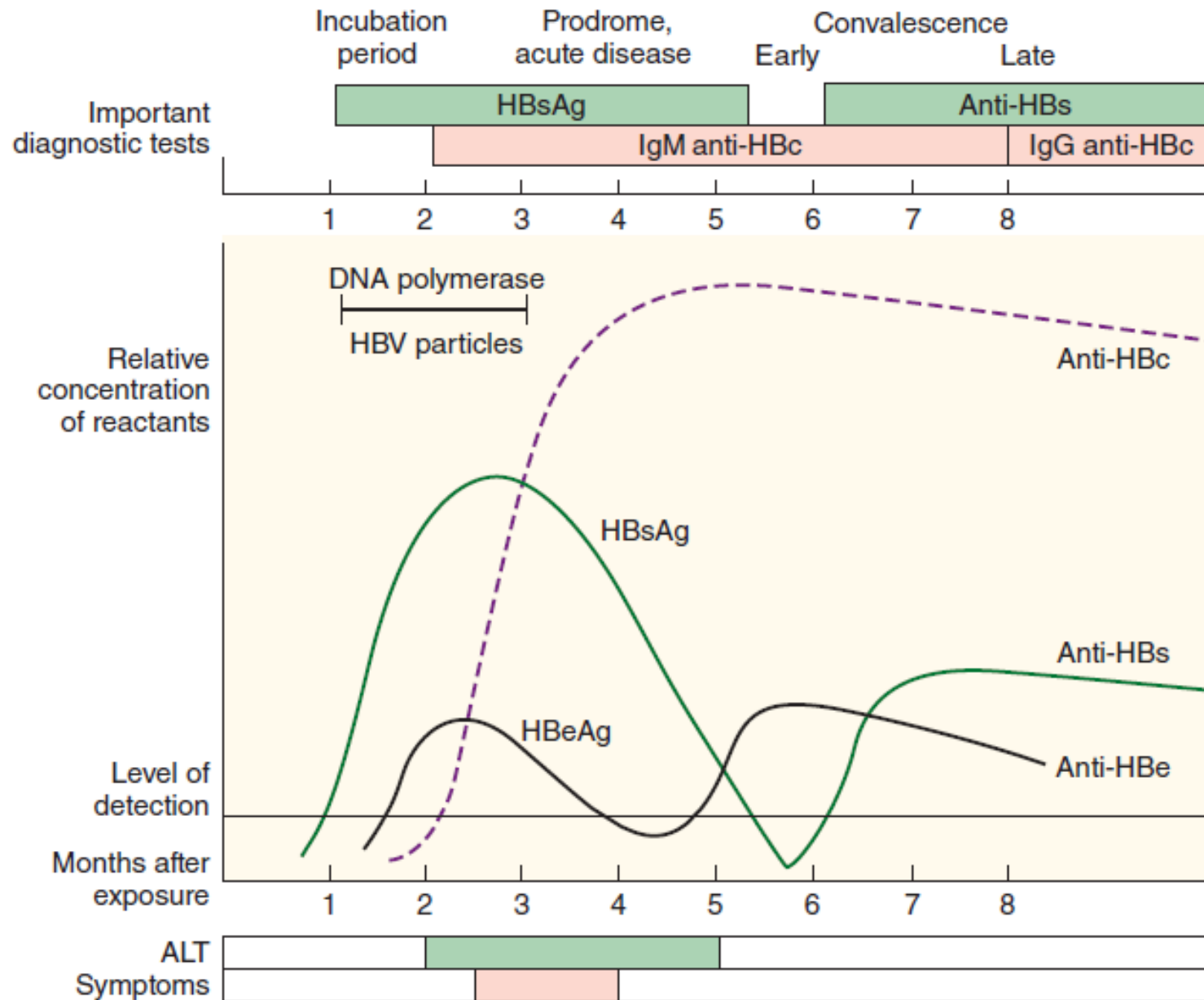


Hepatitis B Diagnosis

- After HBV infection, the first markers of the disease is the appearance of viral DNA in the liver and plasma together with circulating HBsAg. High levels of viremia is followed by rise in the level of markers of hepatocyte damage (mainly ALT) and the appearance of clinical features (fever, malaise and jaundice).
- HBsAg becomes undetectable 1–2 months after the appearance of jaundice.
- The persistence of HBsAg beyond 6 months marks HBV chronicity.
- HBcAb appears within the first two weeks after the appearance of HBsAg and preceding HBsAb.
- The window between decline of HBsAg and rise HBsAb is associated with HBcAb as the only serologic evidence of infection.
- Clearance is associated with the appearance of HBsAb.
- NAT is also available for screening blood/blood products.



Hepatitis B Diagnosis





Hepatitis B management



- Multiple options are available for treatment of chronic hepatitis B including IFNs and several nucleotide and nucleoside analogs with the goal of reducing the viral load to an undetectable level and to reach HBsAg clearance.
- Entecavir and Tenofovir are preferred first-line options due to their high potency and low risk of drug resistance.
- A complete cure is rarely achieved due to the persistence of viral DNA in hepatocytes, current therapies are highly effective at controlling the infection

Table 2. FDA-Approved Treatments for Chronic HBV Infection in Adults

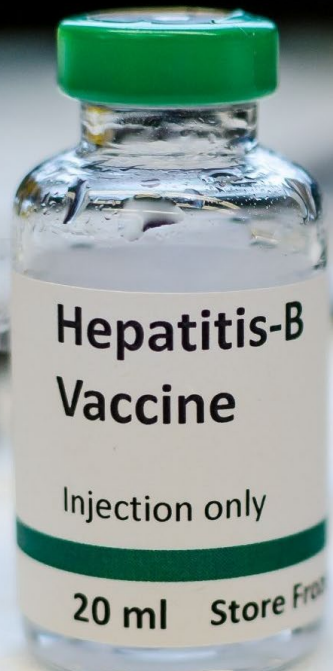
	Drug	Dose	Potential Adverse Events	Drug Resistance	Notes
Preferred Therapies	PEG-IFN $\alpha 2\alpha$	180 mcg weekly	Flu-like symptoms, fatigue, mood disturbances, thrombocytopenia, leukopenia	None	Not well tolerated; high risk of morbidity and mortality
	Entecavir ^a	0.5 mg daily	Lactic acidosis (may occur with decompensated cirrhosis)	Low	Effective against lamivudine-resistant HBV
	Tenofovir disoproxil fumarate	300 mg daily	Nephrotoxicity, osteomalacia	None	Effective against adefovir- or entecavir-resistant HBV
	Tenofovir alafenamide fumarate	25 mg daily	Lactic acidosis	None	Effective against adefovir- or entecavir-resistant HBV
Nonpreferred Therapies	Lamivudine	100 mg daily	Pancreatitis, lactic acidosis	High	None
	Adefovir	10 mg daily	Nephrotoxicity	High	None
	Telbivudine	600 mg daily	Creatinine kinase elevation, myopathy, peripheral neuropathy	High	Discontinued in the United States in 2016

FDA, US Food and Drug Administration; HBV, hepatitis B virus; PEG-IFN, pegylated interferon.

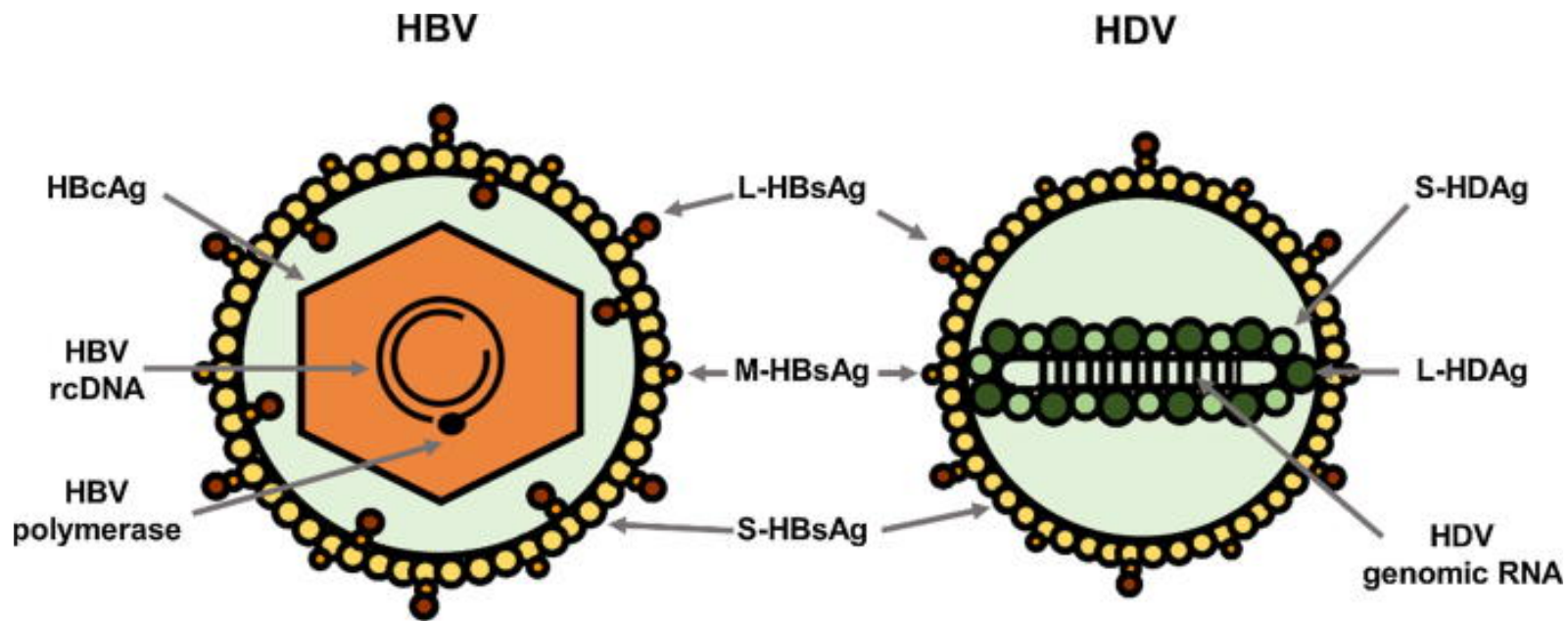
^aEntecavir dose is 1 mg daily if the patient is lamivudine-experienced or has decompensated cirrhosis.



Hepatitis B prevention



- For prevention of HBV infection, an effective vaccine (recombinant HBsAg) has been available from mid-1980s, with many countries worldwide implementing universal vaccination of infants.
- The WHO recommended that all infants receive the HBV vaccine within 24 hours of birth to prevent mother-to-child transmission. The birth dose should be followed by 2 or 3 additional doses to complete the primary series
- Vaccination of groups at highest risk of acquiring HBV infection is recommended. These include health-care workers and others who may be exposed to blood, blood products or other potentially infectious body fluids during their work.



- Delta hepatitis was first recognized following detection of a novel protein, delta antigen (HDAg), by immunofluorescent staining, in the nuclei of hepatocytes from some patients with hepatitis B.
- HDV is now known to be defective and require a helper function from HBV for its transmission. HDV is coated with HBsAg, which is needed for release from the host hepatocyte and for entry in the next round of infection.

Hepatitis D Virus (HDV) - Background



Hepatitis D Virus Coinfection and Superinfection

- Two types of infection are described:
- **Co-infection:** Where a person who is susceptible to HBV is exposed to someone who is co-infected with HBV and delta virus, this results in acute co-infection with both the viruses at the same time.
- **Super-infection:** When an HBV carrier is exposed to infected blood from co-infected patients then the exposure results in super-infection of the existing HBV infection with delta virus; this may result in development of acute hepatitis (due to delta virus) in an HBV chronic carrier.

Table 1. Comparison between the clinical and diagnostic features of HDV infection according to the two patterns of coinfection and superinfection

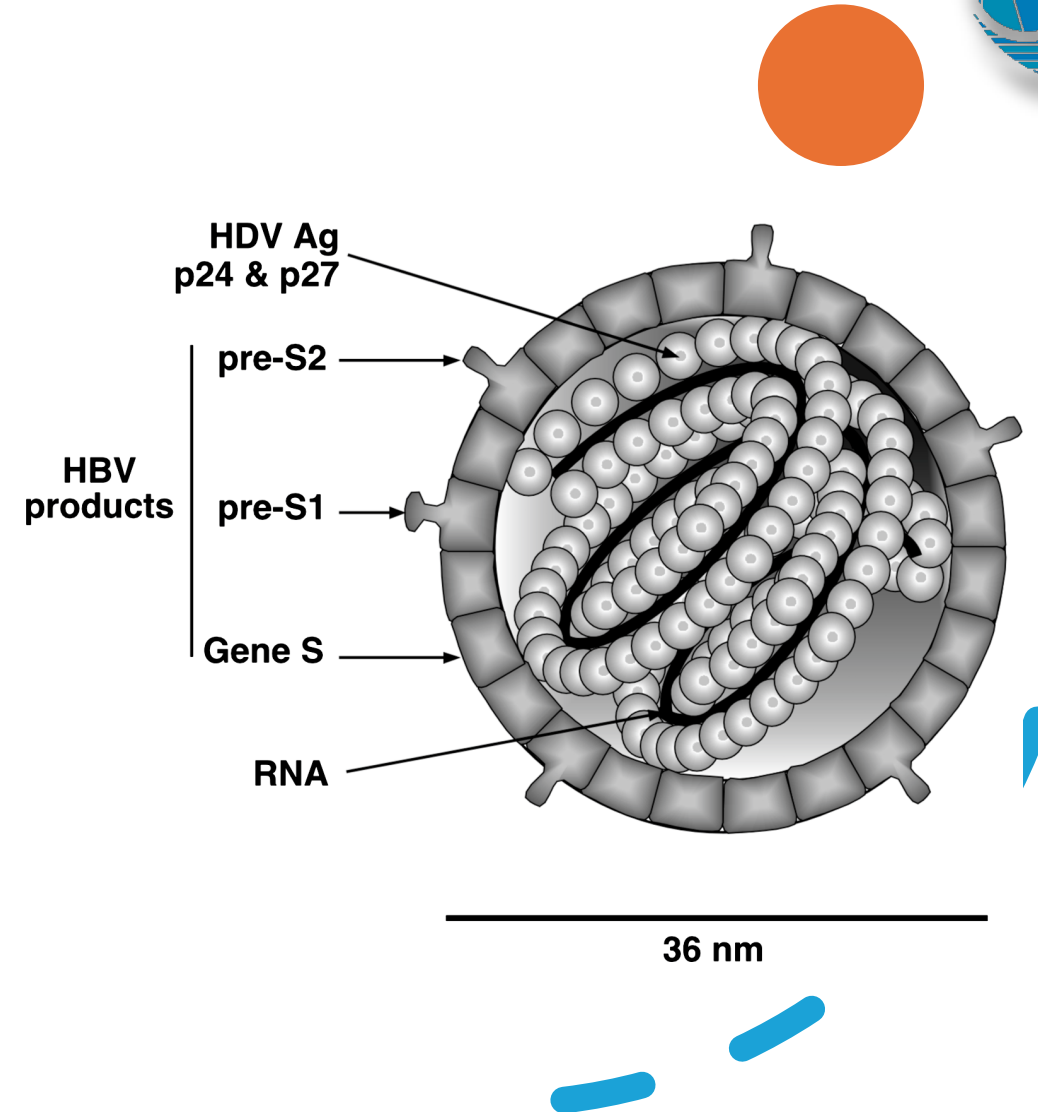
	Coinfection	Superinfection
HBV infection	Acute	Chronic
Outcome	Usually recovery with viral eradication (<5% chronicity)	Usually persistent infection
HBsAg	Present, early, and transient	Preexisting and persistent
IgM anti-HBc	Positive	Negative
Anti-HBs	Appears during the convalescence phase	Negative
HDV infection	Acute	Acute or chronic
Outcome	Usually recovery with viral eradication (<5% chronicity)	Usually persistent infection (80% progress to chronicity)
Serum HDAg	Early and short-lived	Transient and later undetectable because of complexing with antibodies
Liver HDAg	Positive and short-lived	Positive but 50% sensitivity at late stages
Serum HDV RNA	Early positive and transient	Early positive and persistent
Anti-HDV	Late and low titered	Rapidly increasing titers and persistent
IgM anti-HDV	Positive, transient	Positive, high titered



HDV Virion



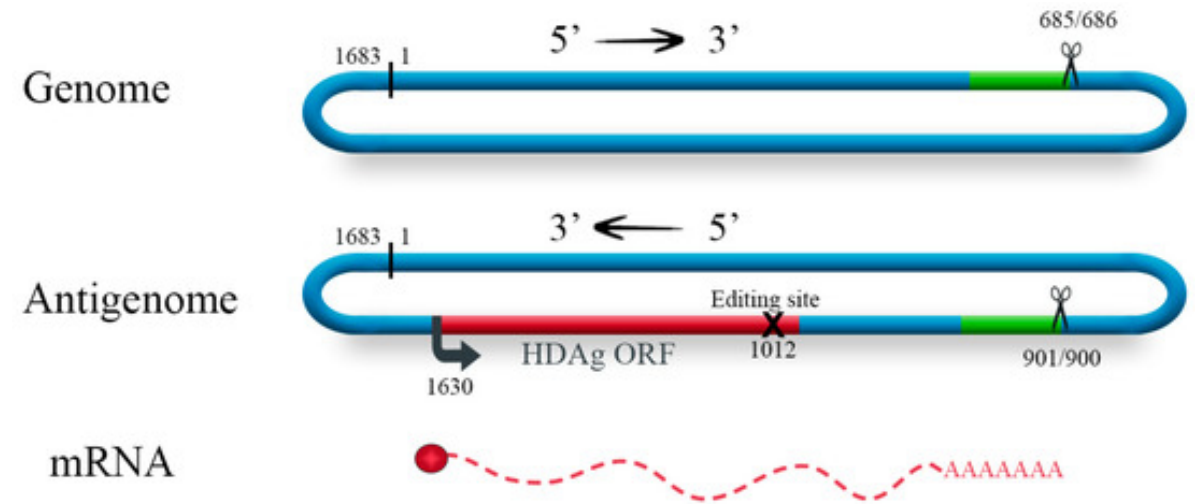
- HDV, is a defective RNA virus that coinfects with and requires the helper function of HBV for its replication and expression.
- Slightly smaller than HBV, delta is a formalin-sensitive, 35- to 37-nm virus. Its nucleocapsid expresses delta antigen, which bears no antigenic homology with any of the HBV antigens, and contains the virus genome.
- The delta core is "encapsidated" by an outer envelope of HBsAg, indistinguishable from that of HBV except in its relative compositions of major, middle, and large HBsAg component proteins.





HDV - Genome

- HDV is unique among human viruses, having an internal nucleocapsid comprising the genome surrounded by the delta antigen and enveloped by an outer protein coat of HBsAg.
- The genome consists of a single-stranded, circular RNA of around 1700 nucleotides, the delta antigen being encoded by antigenomic RNA.

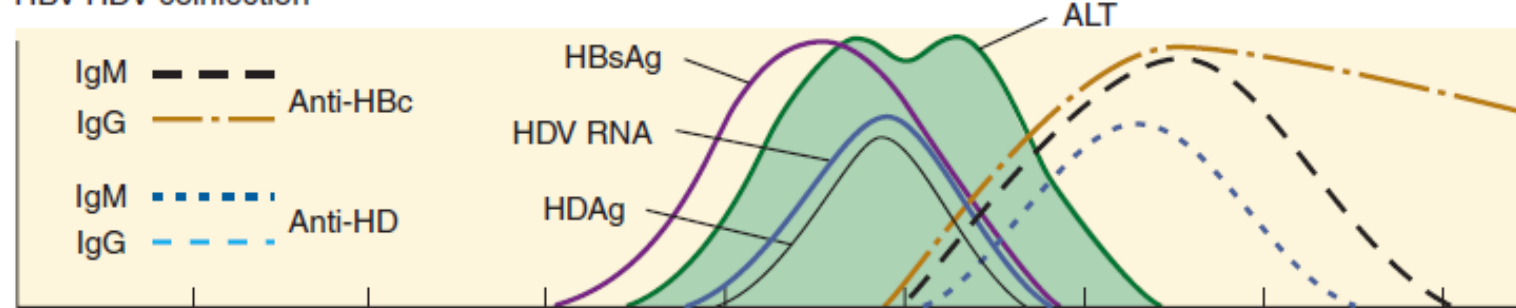




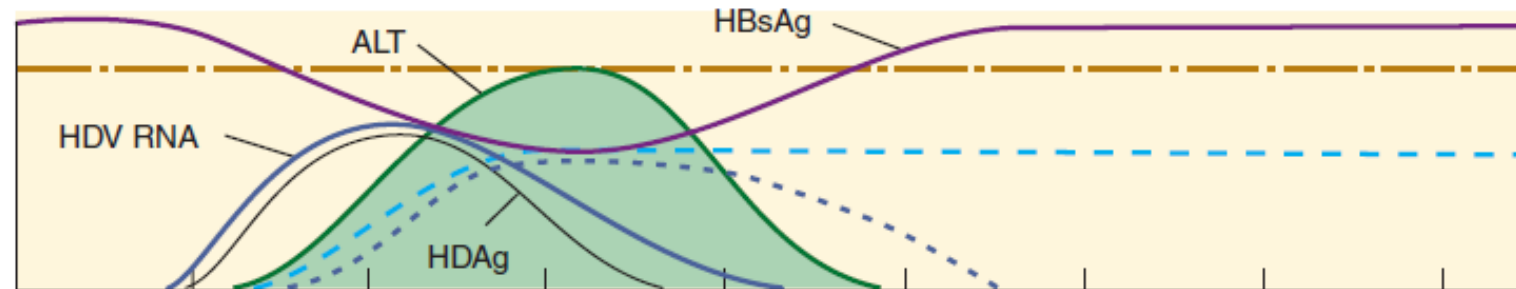
Hepatitis D - Serologic Markers



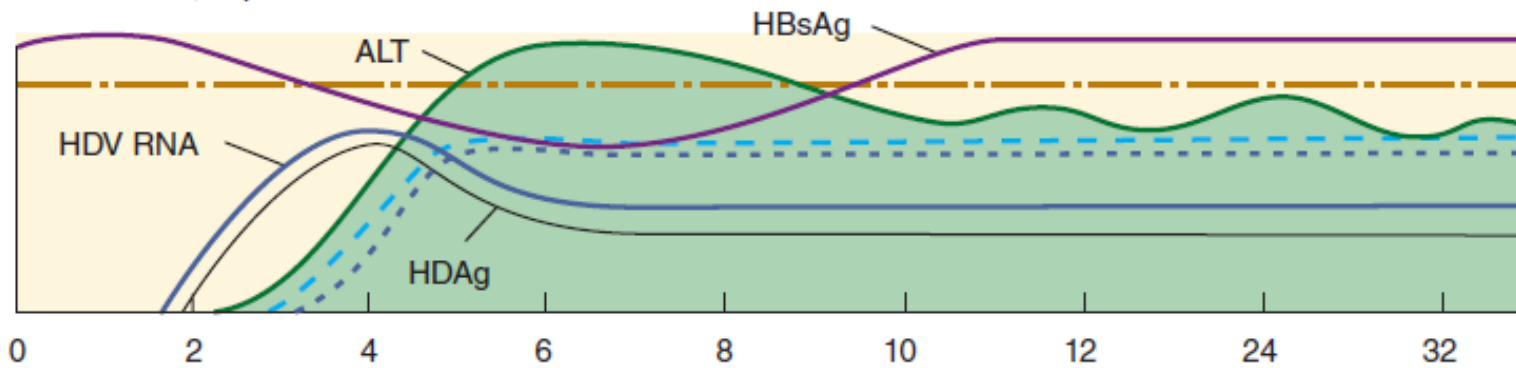
HBV-HDV coinfection



Acute HDV, superinfection



Chronic HDV, superinfection

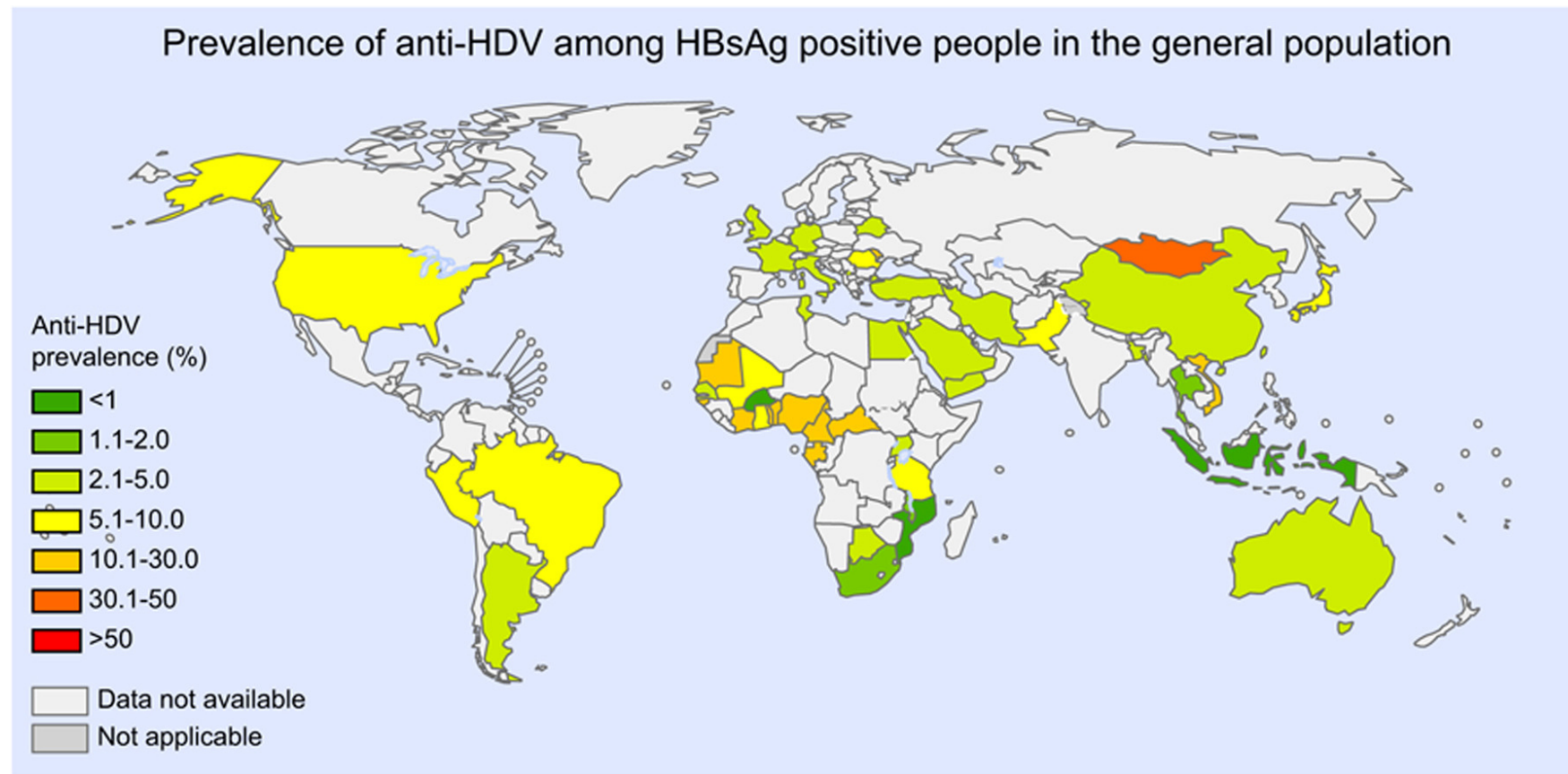


0 2 4 6 8 10 12 24 32

Weeks after exposure



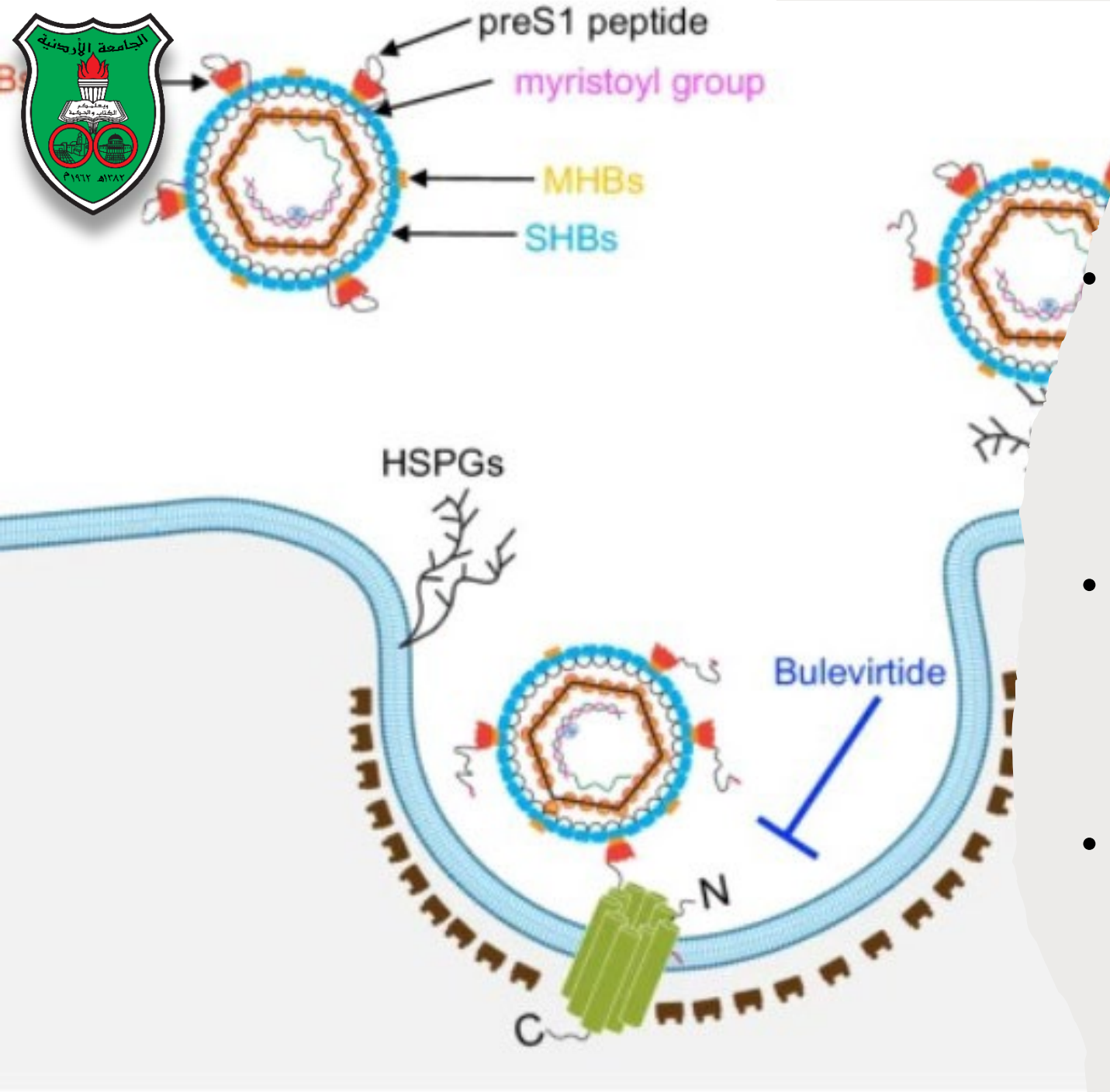
Hepatitis D - Epidemiology



- Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist.
- In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by non-percutaneous means, especially close personal contact.
- In non-endemic areas, such as the United States and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products, primarily injection drug users and hemophiliacs.
- HDV infection can be introduced into a population through drug users or by migration of persons from endemic to non-endemic areas.



Hepatitis D – Diagnosis, Management, and Prevention



- Diagnosis of HDV is done when a patient with a known HBV shows signs of severe liver distress or rapid progression of disease. Anti-HDV antibodies, and RT-PCR test to identify HDV RNA in the blood.
- Management involves the use of pegylated IFN-alpha. Newer entry-inhibitors like Bulevirtide (binding to and blocking the NTCP receptor on hepatocytes) are currently used.
- Prevention is related to the prevention of hepatitis B. The most effective strategy is the universal Hepatitis B vaccination.



Hepatitis C Virus (HCV) – Background



- Before the identification of HCV, it was evident that the culprit infectious agent responsible for the majority of “non-A, non-B hepatitis (NANBH)” cases was a novel virus that is unrelated to other hepatitis viruses known at that time, namely HAV, HBV, HDV and HEV.
- Epidemiologic investigation together with transmission studies in chimpanzees helped to unravel the role of parenteral transmission in the spread of the virus before its identification for the first time by Choo et al. through molecular cloning which helped to study its genome characteristics and to develop serological tests for diagnosis of HCV infection.

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY,
DANIEL W. BRADLEY, MICHAEL HOUGHTON

A random-primed complementary DNA library was constructed from plasma containing the uncharacterized non-A, non-B hepatitis (NANBH) agent and screened with serum from a patient diagnosed with NANBH. A complementary DNA clone was isolated that was shown to encode an antigen associated specifically with NANBH infections. This clone is not derived from host DNA but from an RNA molecule present in NANBH infections that consists of at least 10,000 nucleotides and that is positive-stranded with respect to the encoded NANBH antigen. These data indicate that this clone is derived from the genome of the NANBH agent and are consistent with the agent being similar to the togaviridae or flaviviridae. This molecular approach should be of great value in the isolation and characterization of other unidentified infectious agents.

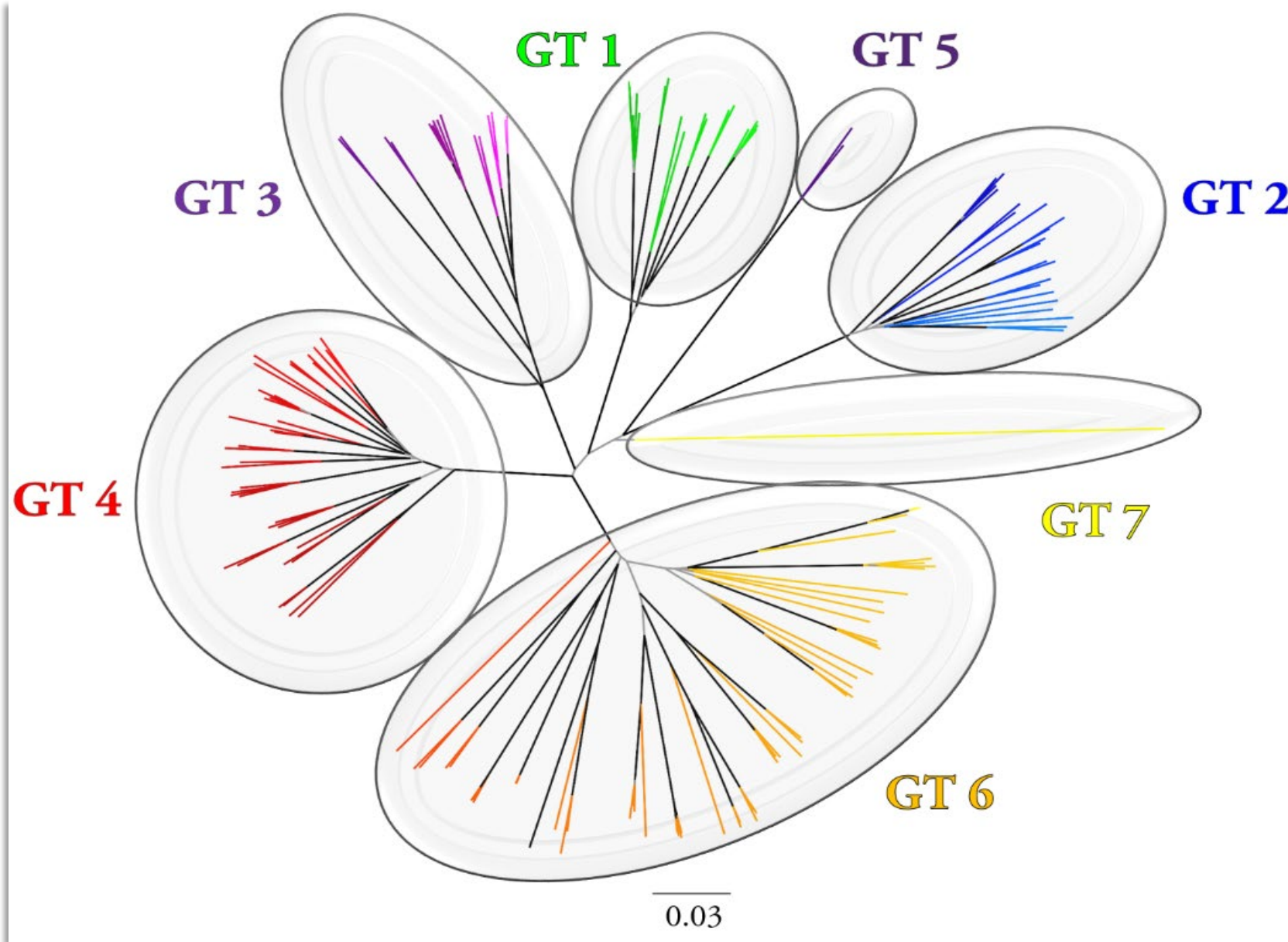


HCV classification

- HCV is a member of the genus *Hepacivirus* that belongs to the family *Flaviviridae*.
- At least seven HCV genotypes, designated with Arabic numerals, and subtypes, designated by small English letters have been described.
- Depending on the genomic region studied, the distinct genotypes differ by more than 30% in the nucleotide sequences, whereas the intra-genotype subtypes differ by 20-25% in the nucleotide sequences.
- Considering the enormous divergence of HCV genotypes from their common ancestor(s), differences in the clinical manifestations and response to treatment appear as a likely outcome.



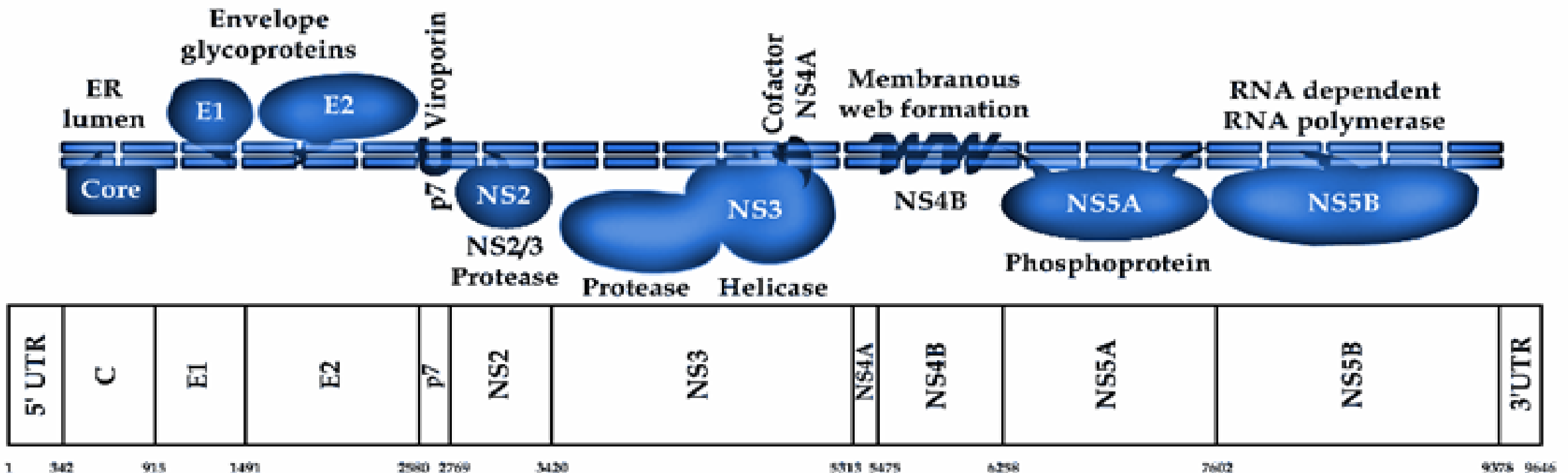
HCV classification





HCV genome

- As a positive-sense single-stranded RNA virus, HCV genome can be viewed as a single ORF which encodes a polyprotein of about 3000 amino acids.
- The HCV polyprotein is processed by cellular and viral proteases with end-products of structural and non-structural proteins. At the 5' end of the HCV resides the highly conserved 5' untranslated region (5' UTR), the region with an internal ribosomal entry site (IRES).





HCV genome and proteins

- Structural proteins include the core protein (C), the envelope glycoproteins (E1 and E2) and the ion-channel viroporin (p7). In contrast to the conserved nature of C, the E1 and E2 display a high level of sequence variability likely as a result of immune selection.
- The non-structural (NS) genes are located towards the 3' end of the genome and encode the following proteins: NS2 which is a cysteine protease that cleaves NS3 from NS2. The second structural protein is NS3 that together with NS4A, forms a serine protease that cleaves all the downstream NS proteins of the virus.
- NS4B acts as a membrane anchor for the replication complex together with the NS5A forming the ER membranous web which has an important role in the induction and regulation of HCV replication.
- NS5B is an RNA-dependent RNA polymerase, the replicating enzyme of the virus.



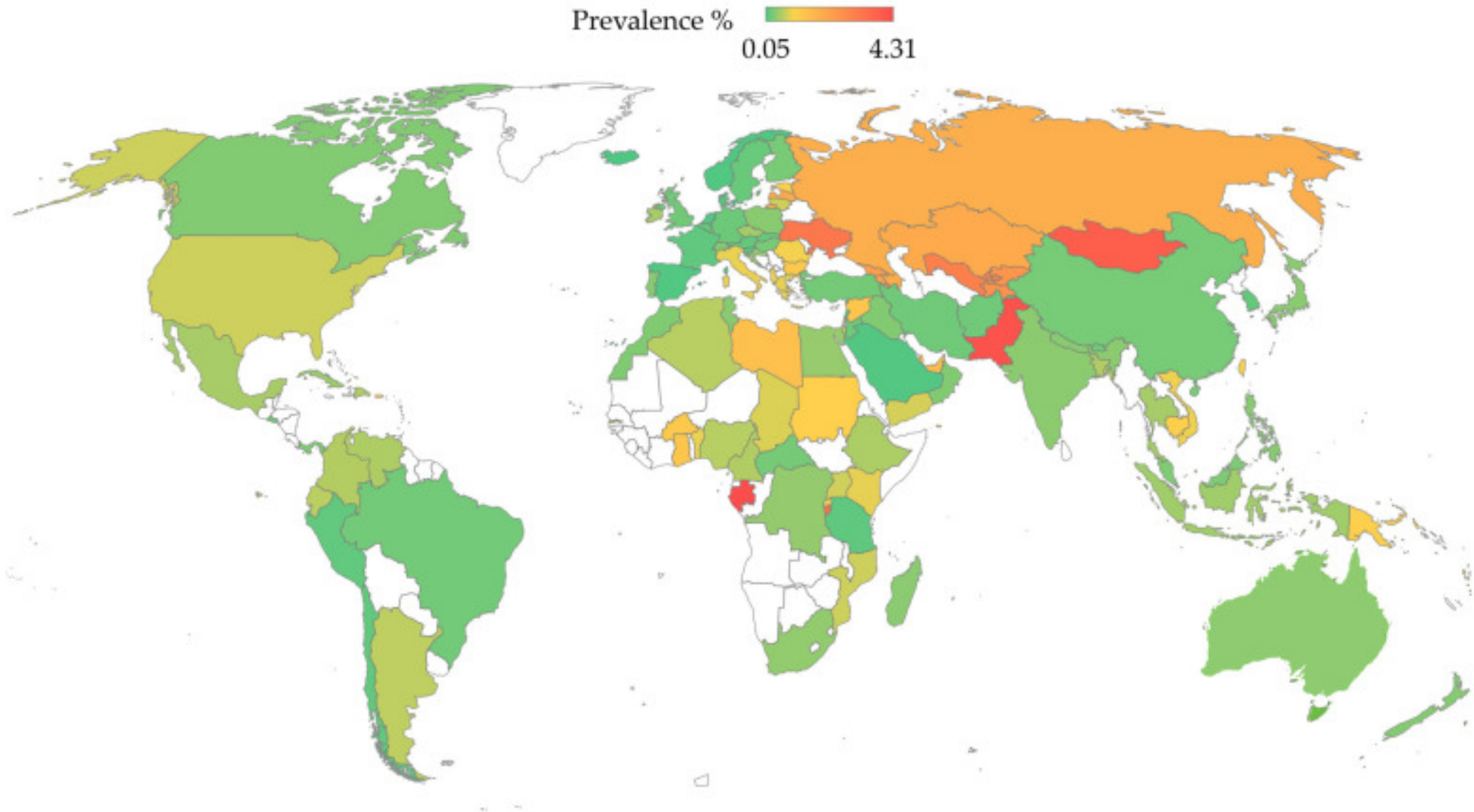
HCV Epidemiology



- Globally, an estimated 50 million people have chronic hepatitis C virus infection, with about 1.0 million new infections occurring per year.
- WHO estimated that in 2022, approximately 242 000 people died from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer).
- Direct-acting antiviral medicines can cure more than 95% of persons with hepatitis C infection, but access to diagnosis and treatment is low.
- Historically, Egypt has experienced the highest prevalence of HCV, particularly among individuals born before 1960, where rates among this particular age demographic had reached as high as 50%. This high prevalence can be traced back to public health campaigns from the 1950s to the 1980s aimed at eradicating schistosomiasis. Currently, China, India, and the United States represent countries with a high burden of HCV disease globally.



HCV Epidemiology





HCV Transmission

- The major route of HCV transmission worldwide is the exposure to contaminated blood mainly through IDU particularly in the high-income countries.
- After the introduction of effective screening of blood/blood products used for transfusion, health-care-related spread of HCV became less common.
- Other lower-risk modes of transmission include high risk sexual behavior, vertical transmission, health-care associated infections (percutaneous exposure through needlestick injuries, hemodialysis surgeries), intrafamilial spread, tattooing, piercing and acupuncture.
- The per-act risk of infection is mainly related to the volume of inoculum together with the viral load of the source of infection, with transfusion as an efficient route.

Table 5. Modes of HCV transmission over time, by income of countries. Number of * in the figure indicates the relative impact of those modes of HCV transmission.

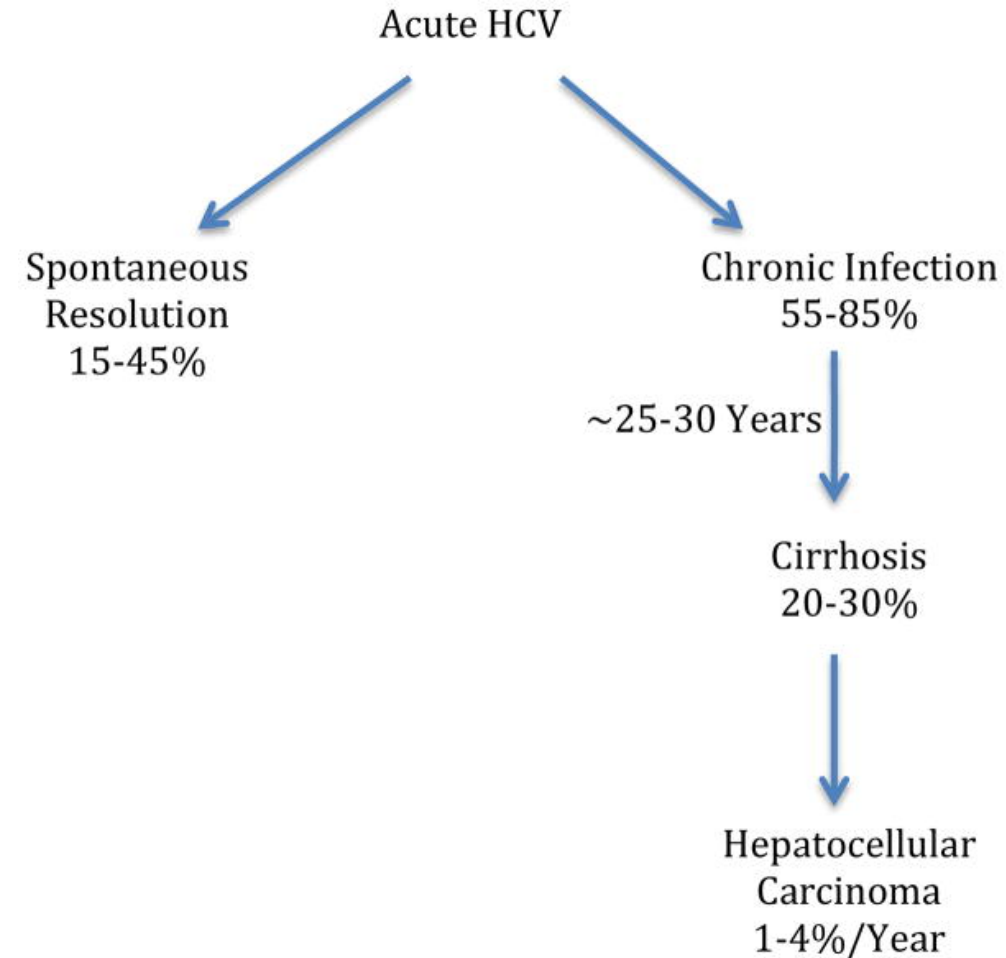
Modalities	High Income		Low/Medium Income	
	Past Decades	Currently	Past Decades	Currently
Blood Transfusion	*****	Near 0	*****	***
PWID	****	*****	**	***
Unsafe medical equipment	****	**	*****	****
Risky sexual behavior	***	***	***	***
Vertical transmission	*	**	*	**
Body grooming and modification	**	***	***	***



Natural history of HCV infection



- After a variable period of incubation (one week to several months), acute HCV infection develops which is mainly asymptomatic, nevertheless about 15-30% of infected individuals develop signs and symptoms of hepatitis (mild fever, malaise, myalgia and obstructive jaundice [dark urine, clay-colored stool and itching]) with elevated liver enzymes
- Spontaneous clearance of HCV (undetectable RNA within six months of infection) occurs in a minority of patients with variable rates in different studies.
- Higher rates of clearance is associated symptomatic acute infection (indicating a strong immune response) and *IL-28B* allele that favors clearance (CC genotype as opposed to CT and TT genotypes).





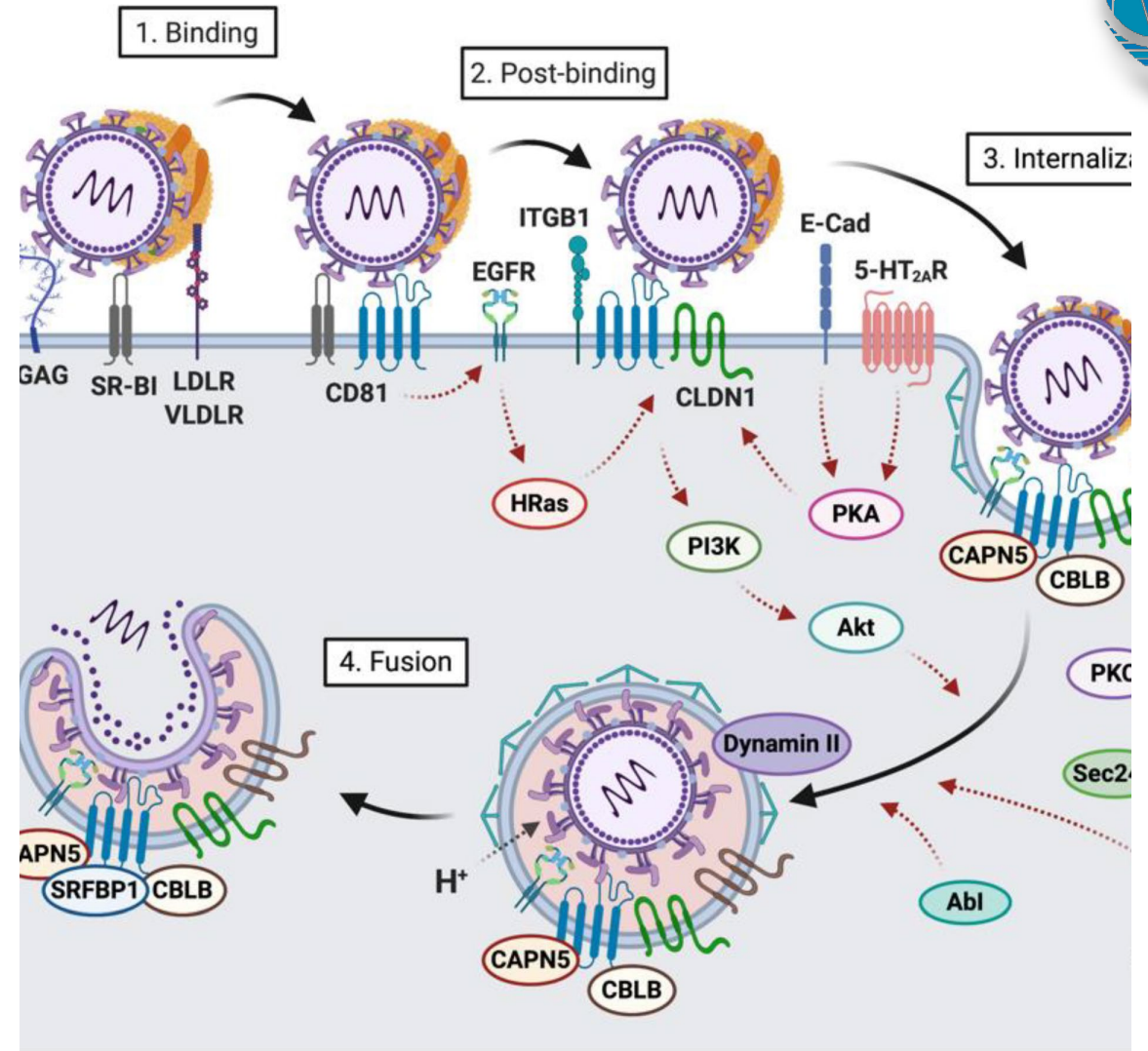
Natural history of HCV infection

- Chronicity that is characterized by high viral load (usually associated with HIV-1 co-infection), follows acute infection in 50–85% of the cases.
- Clearance of RNA during chronic infection is a rare event, with association of clearance with young age, female gender, co-infection with HBV and lower viral load.
- In the chronically infected individuals, the main risk is the progression towards fibrosis, cirrhosis and HCC.



Pathogenesis of hepatitis C

- The tropism of HCV is mostly towards hepatocytes.
- The hepatocyte tropism is related to HCV identified cellular receptors namely CD81, claudin, occludin and scavenger receptor class b type I.
- Hepatic injury is mainly related to immune attack by T helper 1 (Th1)-mediated cytotoxic T lymphocyte (CTL) response on the infected hepatocytes though viral cytopathic effects may play a role.





Pathogenesis of hepatitis C

- In individuals with chronic infection, progression of the disease is associated with old age, male gender, contemporaneous comorbidities causing hepatic damage (alcoholism, chronic HBV infection, and steatohepatitis) and coinfection by HIV-1.
- The role of HCV genotype in disease progression and severity is less certain though some studies suggested that genotype 3 is associated with increased risk.
- Following the development of hepatic cirrhosis, the rate of HCC development is 1-7% each year.



HCV – Diagnosis



- The diagnosis of HCV starts by serologic screening through enzyme or chemiluminescent immunoassays (3rd generation have epitopes from [NS4, C, NS3 and NS5] with a window period of approximately 66 days).
- The serologic assays confirm the history of HCV past infection, nevertheless, the diagnosis of ongoing infection relies on nucleic acid testing which is also used to monitor response to treatment.
- Based on the scientific evidence of genotype correlation with outcome of treatment, particularly for IFN-based therapies, the identification of HCV genotype is considered to have a significant predictive value for treatment success.





HCV - Treatment

- The main goal of HCV treatment is to achieve SVR (i.e. undetectable HCV RNA 24 weeks following the completion of the treatment course).
- The traditional treatment of HCV relied on IFN-based regimens (with ribavirin) that were limited by severe adverse effects and variable efficiency depending on variables like HCV genotype.
- The novel therapeutic options of HCV in the form of direct-acting antivirals (DAAs), have resulted in rising hope among clinicians and patients for better response, less side effects and shorter duration of therapy.

«خبراء وأساتذة كبد»: طرح الجيل الثالث من علاج «سي»
رفع نسب شفاء المرض لـ95%



كتب - إبراهيم جودة :

نشر في: السبت 4 يونيو 2016 - 10:19 ص | آخر تحديث: السبت 4 يونيو 2016 - 10:19 ص



HCV – Treatment

- DAAs were initially used in combination with IFN/ribavirin regimens to improve the overall response, however, this was limited by severe side effects.
- In the current time, DAAs have been shown to give the possibility of HCV eradication from the infected individuals without IFN.
- So far, four classes of DAAs have been approved for treatment of chronic HCV.
- The efficacy of DAAs is generally high with slight differences among HCV genotypes observed in different reports. High cost remains the major obstacle for widespread use of DAAs.



HCV - Treatment



Class	HCV target	Drugs
Protease inhibitor	NS3	Simeprevir, Boceprevir, Telaprevir.
Nucleotide inhibitor	NS5B	Sofosbuvir.
Non-nucleotide inhibitors	NS5B	Dasabuvir, Beclabuvir.
NS5A inhibitors	NS5A	Daclatasvir, Velpatasvir.



HCV – Prevention

- Due to absence of an effective vaccine to HCV infection so far, prevention of transmission relies on identifying individuals at risk and consulting on behavioral changes to decrease the likelihood of forward transmission. In the low-income settings, strict testing of blood/blood products before transfusion is of prime importance.
- In high-income countries where IDU represents the major risk factor for HCV spread, awareness, behavioral changes, treatment as prevention (TasP), opioid substitution treatment (OST) and needle exchange program (NEP) represent important intervention measures to control the HCV epidemics.

Sharing needles can get you more than high...
It can get you HIV and Hep C.



Use clean needles.
Get them at the health department.



Thank You!

References

- Sallam M. (2017). Phylogenetic Inference in the Epidemiologic and Evolutionary Investigation of HIV-1, HCV and HBV. Lund University. Thesis
- de Rocquigny, H.; Rat, V.; Pastor, F.; Darlix, J.L.; Hourieux, C.; Roingeard, P. Phosphorylation of the Arginine-Rich C-Terminal Domains of the Hepatitis B Virus (HBV) Core Protein as a Fine Regulator of the Interaction between HBc and Nucleic Acid. *Viruses* 2020, 12, 738
- Beck, Juergen, and Michael Nassal. "Hepatitis B virus replication." *World journal of gastroenterology* vol. 13,1 (2007): 48-64.
- Zhao, Fenglin et al. "The Functions of Hepatitis B Virus Encoding Proteins: Viral Persistence and Liver Pathogenesis." *Frontiers in immunology* vol. 12 691766. 12 Aug. 2021
- Somiya M, Liu Q, Yoshimoto N, Iijima M, Tatematsu K, Nakai T, Okajima T, Kuroki K, Ueda K, Kuroda S. Cellular uptake of hepatitis B virus envelope L particles is independent of sodium taurocholate cotransporting polypeptide, but dependent on heparan sulfate proteoglycan. *Virology*. 2016 Oct;497:23-32.
- Ababneh NA, Sallam M, Kaddomi D, Attili AM, Bsisu I, Khamees N, Khatib A, Mahafzah A. Patterns of hepatitis B virus S gene escape mutants and reverse transcriptase mutations among genotype D isolates in Jordan. *PeerJ*. 2019 Mar 8;7:e6583.
- Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. *Lancet*. 2023 Mar 25;401(10381):1039-1052.
- Pungpapong S, Kim WR, Poterucha JJ. Natural history of hepatitis B virus infection: an update for clinicians. *Mayo Clin Proc*. 2007 Aug;82(8):967-75
- Tsai, Eugenia. "Review of Current and Potential Treatments for Chronic Hepatitis B Virus Infection." *Gastroenterology & hepatology* vol. 17,8 (2021): 367-376.
- World Health Organization. Hepatitis B vaccines: WHO position paper, July 2017—Recommendations. *Vaccine* 2019, 37, 223–225.
- Mentha, Nathalie et al. "A review on hepatitis D: From virology to new therapies." *Journal of advanced research* vol. 17 3-15. 29 Mar. 2019
- Goodrum, G.; Pelchat, M. Insight into the Contribution and Disruption of Host Processes during HDV Replication. *Viruses* 2019, 11, 21
- Negro, Francesco. "Hepatitis D virus coinfection and superinfection." *Cold Spring Harbor perspectives in medicine* vol. 4,11 a021550. 3 Nov. 2014
<https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>
- Sallam M, Khalil R. Contemporary Insights into Hepatitis C Virus: A Comprehensive Review. *Microorganisms*. 2024 May 21;12(6):1035.
- Stroffolini, Tommaso, and Giacomo Stroffolini. "Prevalence and Modes of Transmission of Hepatitis C Virus Infection: A Historical Worldwide Review." *Viruses* vol. 16,7 1115. 11 Jul. 2024
- Lingala, Shilpa, and Marc G Ghany. "Natural History of Hepatitis C." *Gastroenterology clinics of North America* vol. 44,4 (2015): 717-34.
- Colpitts, C.C.; Tsai, P.-L.; Zeisel, M.B. Hepatitis C Virus Entry: An Intriguingly Complex and Highly Regulated Process. *Int. J. Mol. Sci*. 2020, 21, 2091