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## **Serotypes and Genotypes of the Hepatitis B Virus in Latin America**

**Rosa María Ribas-Aparicio<sup>1</sup>, Hilda-Alicia Valdez-Salazar<sup>2</sup>,  
Gerardo Aparicio-Ozores<sup>1</sup> and Martha-Eugenia Ruiz-Tachiquín<sup>3\*</sup>**

<sup>1</sup>*Department of Microbiology, National School of Biological Science (ENCB), National Polytechnic Institute (IPN), Mexico City, Mexico.*

<sup>2</sup>*Medical Research Unit in Infectious and Parasitic Diseases (UMAE-Hospital of Pediatrics), XXI Century National Medical Center (CMN-SXXI), Mexican Institute of Social Security (IMSS), Mexico City, Mexico.*

<sup>3</sup>*Medical Research Unit in Human Genetics (UMAE-Hospital of Pediatrics), XXI Century National Medical Center, Mexican Institute of Social Security, Av Cuauhtémoc 330, Col. Doctores, Deleg. Cuauhtémoc, Mexico City, 06720, Mexico.*

### **Authors' contributions**

*This work was carried out in collaboration between all authors. Author RMRA coordinated and participated in writing the manuscript and figures design. Author HAVS helped to draft and critical review the manuscript. Author GAO participated in the writing and editing of the manuscript. Author MERT conceived the review, participated in its design and coordination and was responsible for writing the manuscript.*

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### **ABSTRACT**

The World Health Organization has estimated that 2 billion persons are infected with the hepatitis B virus (HBV) with 360 million persons chronically affected. Worldwide, HBV is the causal agent of cirrhosis (30%) and hepatocellular carcinoma (50%). Methods of transmission for HBV are prenatal, percutaneous, and sexual.

HBV genotypes, subgenotypes, and subtypes represent genetically stable viral populations that share a separate evolutionary history. Additional instable changes arising from mutations and mutant selection have been observed; these viral subpopulations are HBV variants with medical treatment relevance. Expression of the subtype renders antigenically diverse strains. The same region contains an unknown number of epitopes that define the so-called "a" determinant. Thus, we have two mutually exclusive determinants (d/y, w/r)

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\*Corresponding author: Email: [mertachiquin@yahoo.com.mx](mailto:mertachiquin@yahoo.com.mx)

with four variants (w1 - w4 and the expression of a third, q). The difference in 8% of the HBV genome produces different viral groups. Currently, there are ten of these groups (genotypes) classified from A to J, with different geographic distributions. Multiethnic populations present several genotypes and variability is increasing because there are reports of subgenotypes and recombinant intergenotypes, which render the design of effective drugs to combat and eliminate this very difficult virus.

**Keywords:** Serotype; Genotype; HBV; Latin America; Hepatitis B; Review.

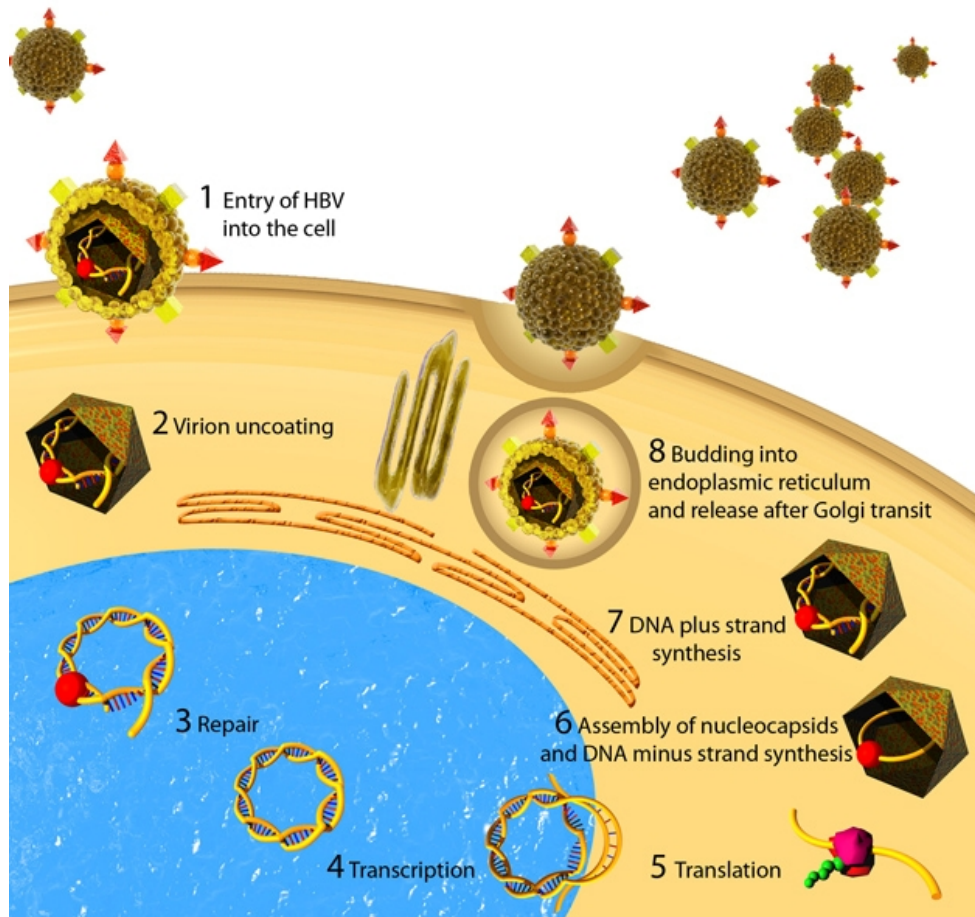
## 1. HEPATITIS B VIRUS

The World Health Organization (WHO) has estimated that 2 billion persons (one third of the world population) are infected with HBV and 360 million persons are chronically affected [1]. At the worldwide level, HBV is the causal agent of cirrhosis (30%) and hepatocellular carcinoma (50%) [2]. HBV is present in other disorders: cancer (lymphoma or leukemia), autoimmune disease, organ transplant (solid organ or bone marrow). HBV can be transmitted perinatally, percutaneously, and sexually [2].

HBV is the first virus to be described from a group of hepadnaviruses. These viruses, which are members of the *Hepadnaviridae* family, manifest marked liver tropism and share a very specific method of replication. The HBV replicative cycle is characterized by the synthesis of a genome of relaxed circular, partially double-stranded 3,200 base-pair DNA, which is synthesized using reverse transcription of an intermediate RNA, the pregenome (Fig. 1). Early events of this cycle such as penetration, loss of the capsid, and release of viral DNA into the nucleus of the host cell have not been clarified due to the absence of cell lines susceptible to infection by hepadnaviruses [3–5].

The HBV genome contains the following four genes: The *X* gene codifies for the X protein (HBX); the *S* gene for the complete surface antigen (HBsAg) and its variants (small, medium, and large); the *P* gene for the polymerase enzyme, and the *C* gene codifies for the endogenous antigen core antigen (HBeAg) and the core antigen (HBcAg) (Fig. 2). It is noteworthy that the polymerase codifying for the *P* gene in hepadnaviruses is an enzyme with the following four activities; 1) DNA-dependent DNA polymerase; 2) RNA-dependent (reverse transcriptase) DNA polymerase; 3) ribonuclease H (RNase H) capable of degrading the RNA present in hybrid DNA-RNA molecules, and 4) the anchor molecule for initiation of DNA synthesis [3–5]. Hepadnaviruses characteristically are not cytopathic, i.e., they do not destroy the host cell [3].

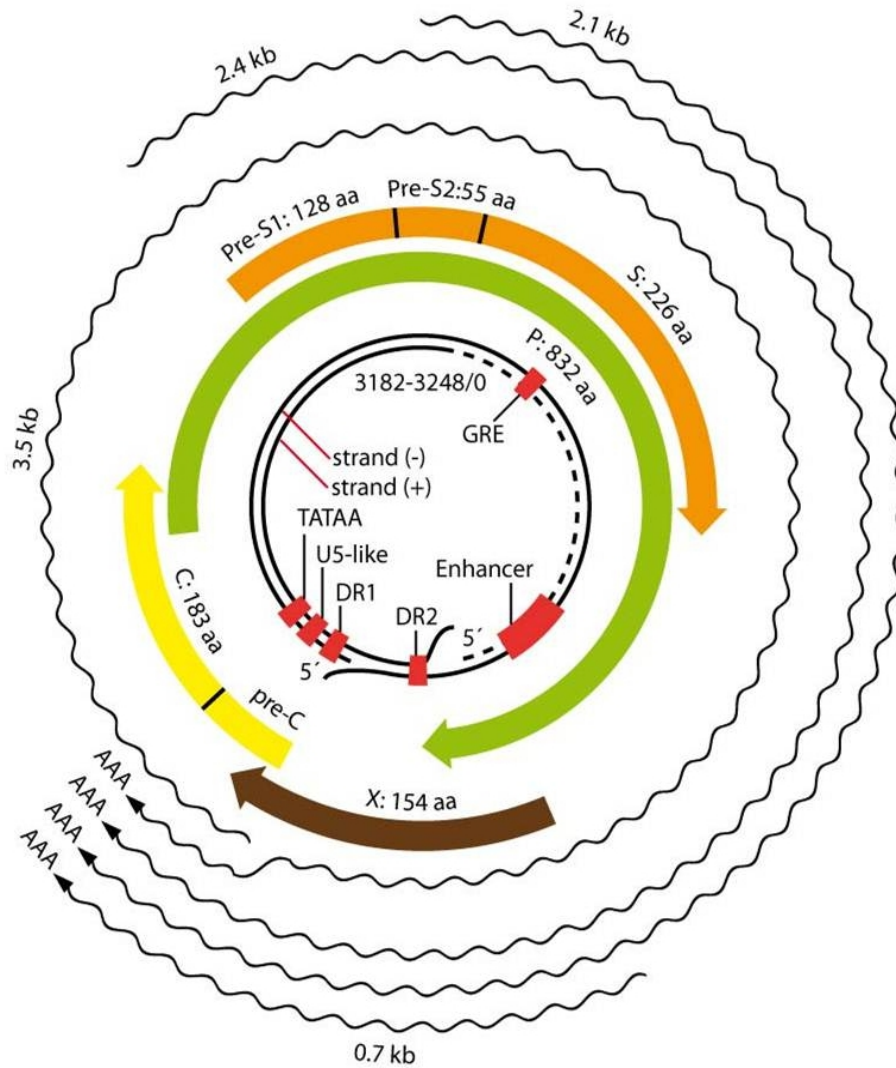
Current knowledge on hepatitis B indicates that liver damage manifests as inflammation of the liver and destruction of the hepatocytes caused by the immune response itself directed against HBV-infected cells, in particular anti-HBV cytotoxic T-lymphocytes, which appear to be those mainly responsible for destruction of the hepatocytes that express HBV antigens in their membranes. It is thought that cases of fulminating, fatal hepatitis B are the consequence of an excessive immune response against the HBV; however, in transgenic mice in whose cells the gene codifying for HBsAg has been experimentally inserted, it has been observed that overprotection of HBsAg can cause hepatocyte destruction [3,6-8].



**Fig. 1. Hepatitis B virus (HBV) life cycle**

1) HBV binds an unidentified receptor on the surface of the hepatocyte; 2) The nucleocapsid is released into the cytoplasm; 3) HBV genome is repaired in the nucleus by host cellular enzymes; 4) The newly repaired genome (covalently closed circular DNA [cccDNA]) serves as the template for transcription of the viral genes as follows pregenome core protein Pol surface antigens (HBsAg) and the X protein; 5,6) The pol-pregenome complex is encapsidated within the oligomerized core protein in the cytoplasm; 7) The pregenome is reversely transcribed; 8) The nucleocapsid buds into the endoplasmic reticulum (ER) at S antigen-concentrated areas and is subsequently secreted via the constitutive secretory pathway (Authors' designed).

The HBV genome is ~3.2 Kb. HBV viral messenger RNA (mRNA) is encoded within four overlapping open reading frames as follows: 3.5 Kb pregenomic RNA (pgRNA) encodes the viral reverse-transcriptase-DNA polymerase-RNaseH (Pol) and core proteins (pre-HBcAg and HBcAg) and serves as the template for viral reverse transcription; envelope proteins (pre-S1, pre-S2, and S) and the X protein (HBx). Fig. 2 modified from Reference [7] (Author's designed).



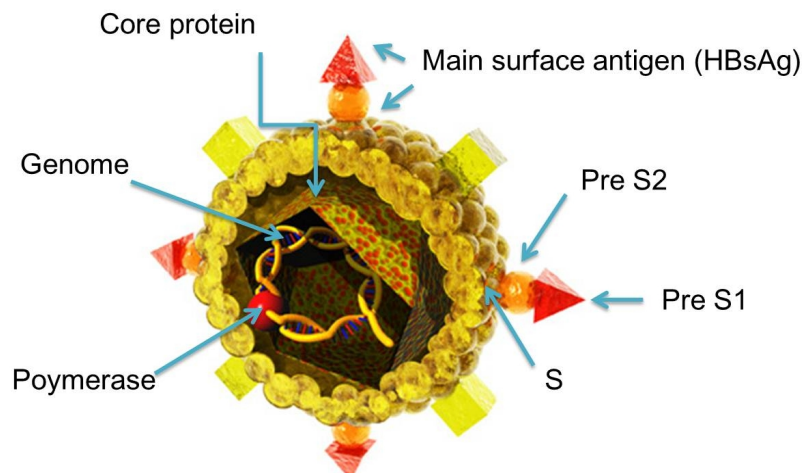
**Fig. 2. Schematic of hepatitis B virus (HBV) genome**

Genotypes, subgenotypes, and subtypes of the HBsAg of the HBV represent genetically stable viral populations that share a separate evolutionary history [9,10]. These emerge in specific human populations and migrate with their hosts to other areas of the world [11,12]. Additional instable changes arising from mutations and the selection of mutants have been observed. These viral subpopulations are referred to as HBV variants; some possess medical and public health relevance [13,14].

## 2. HEPATITIS B VIRUS SEROTYPES

Grouping of HBV isolates into HBsAg subtypes was first performed 30 years ago and constitutes the first demonstration of the diversity of the virus [10]. HBsAg epitopes involved in the expression of the specificities of the subtype are localized in a region that includes the two external loops of the molecule (amino acids 110-180) and that makes the strains

antigenically diverse (Fig. 3). The same region contains an unknown number of epitopes that define the so-called “a” determinant, which is common to all HBV strains known to date [13].



**Fig. 3. Structure of HBV**

Schematic description of the virion. The structure of HBsAg of the HBV is shown at the most external part of the viral envelope, as well as the different protein subunits including Pre S1, Pre S2, and S Fig. 3. (Authors’ designed).

Thus, we have two mutually exclusive determinants (d/y, w/r) with four variants (w1-w4 and the expression of a third, q). Therefore, the serotype is written with an “a”, followed by d/y or w1–4/r, for example, adw2, ayr. At present, the viral subtype can be determined by the amino acid sequence of this region (“a” determinant) of HBsAg [13] (Table 1).

**Table 1. Subtype prediction by the amino acid sequence deduced from the DNA of the HBV**

122*	127*	134*	159*	160*	177*	178*	Subtype
Lys	Pro	Phe	Ala	Lys	Val	Pro	adw2
Lys	Thr	Phe	Ala	Lys	Val	Pro	adw3
Lys	Leu	Phe	Gly	Lys	Val	Gln	adw4q-
Lys	Pro	Phe	Ala	Arg	Val	Pro	adr
Lys	Pro	Phe	Val	Arg	Ala	Pro	adrq-
Arg	Pro	Phe	Ala	Lys	Val	Pro	ayw1
Arg	Pro	Tyr	Gly	Lys	Val	Pro	ayw2
Arg	Thr	Phe	Gly	Lys	Val	Pro	ayw3
Arg	Leu/Ile	Phe	Gly	Lys	Val	Pro	ayw4
Arg	Pro	Phe	Ala	Arg	Val	Pro	ayr

*HBV, hepatitis B virus; \* amino acid number in HBsAg. Modified from Reference [13]*

### 3. HBV GENOTYPES

The genotype of a virus is the order of the puric (adenine [A] and guanine [G]) and pyrimidic bases (cytosine [C], thymidine [T], and uracyl [U]) of the deoxyribonucleic or ribonucleic acid (DNA or RNA) that partially or completely constitutes it. In the case of HBV, it was arbitrarily decided that 8% of the complete genome would form different groups [9,10]. Currently, ten of these groups are classified from A to J and possess different geographic distributions (Table 2) (Fig. 4). Multiethnic populations present multiple genotypes and variability is increasing because there are reports of sub genotypes and recombinant intergenotypes [13,15–17], making difficult the design of effective drugs to combat and eliminate these.

**Table 2. Geographic distribution of HBV genotypes and subtypes**

Genotype	Subgenotype	Subtype	Frequency	Geographic localization
A	A2	adw2	High	Europe, North America, Australia
	A1	ayw1, adw2	High	Africa
	A3			Western Africa
B	B1, B2, B3	adw2	High	Asia
	B4	ayw1	High	Asia
	B2	adw3	Low	Asia
	B5-B9			Asia
C	C1, C2, C3	adr	High	Asia
	C3	adrq-	High	New Guinea, Pacific
	C1, C2	ayr	High	Asia
	C1, C3	adw2	Low	Asia
	C4	ayw3	Low	Asia, Pacific, Australia, Philippines, Vietnam
D	C5			Philippines, Vietnam
	D1, D2, D3	ayw2	High	East Asia & European, Mediterranean
	D2, D3	ayw3	High	Worldwide
	Not identified	adw3	Low	Eastern Europe, Spain,
	D2	ayw4	Low	Eastern Europe, Spain, USA
E	D4-D5			Africa, Europe
	Not identified	ayw4	High	Africa
F	F1, F2	adw4q-	High	Latin America, Alaska, Pacific
	F1, F2	ayw4	Low	Latin America
	F3-F4			Central & South America
G	Not identified	Adw2	Low	Europe, North America
H	Not Identified	ayw4	Low	North & Central America
I				Laos, Vietnam
J				Japan

*HBV, hepatitis B virus. Modified from References [13,18].*

Genotypes A and D have been identified in Europe; B and C in Southeast Asia; F in South America; A, B and D in Argentina; A, B, C and D in Brazil; B and C in Peru; A and H in Nicaragua; A and D in Venezuela, Uruguay and Costa Rica. Genotypes A, C, D, F, G, and H had been identified in Mexico, H being the predominant genotype Fig. 4. (Authors' designed).

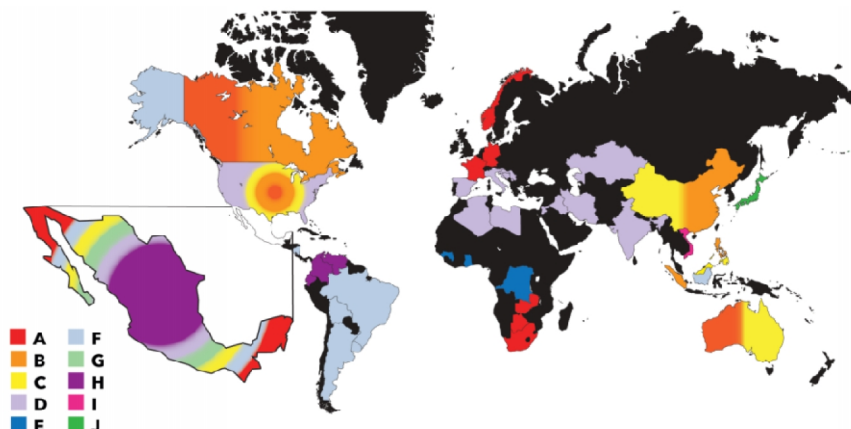


Fig. 4. Geographic distribution of HBV genotypes

#### 4. GENOTYPIC DISTRIBUTION AND MIGRATION OF THE HBV TO LATIN AMERICA

Genotypic distribution of the HBV can reflect the different migration patterns on the American continent. It has been proposed that HBV autochthonous genotypes entered this continent with the first Asian colonizers through the Bering Strait and the latter were displaced to the South. The first Amerindians entered the New World 15,000-20,000 years ago, probably migrating South along the Coast, which allowed rapid expansion to Central and South America. A second migration ensued ~12,500 years ago. Evidence of DNA mitochondrial lineages suggests the isolation of some Amerindian populations immediately after the initial dispersion of colonizers in the Southeastern part of the continent. This isolation is reflected by the geographic locations of the HBV-F subtype and its groups. Distribution of the F subtypes (F1 and F2) correlates with possible entry into South America along the East and West Coasts where the continent becomes narrower. As a result, a mixture of both the F1 and F2 subtypes can be observed in Argentina [6,12] (Fig. 4).

Other HBV genotypes are found in different Latin American countries and mainly reflect migration to other geographic areas within the region. Genotypes A and D are the signature of the European colonization that began in the XVI century, including the trafficking of slaves from Africa (genotype A). Analysis of genotypes B and C indicates recent introduction from Southeast Asia [13].

Genotypes A, B, and D were found in Argentina. Genotypes A, B, C, and D were described in Brazil, with A and D the most common, which differentiates Brazil from other countries in Latin America. Genotype B and C strains were isolated in Peru. Genotypes A, D, H, and G were found in Mexico, whereas genotypes A and H were found in Nicaragua. Genotypes A and D were found in Venezuela, Uruguay, and Costa Rica [11,12,19] (Fig. 4).

The genetic diversity of the HBV and the geographic distribution of its subtypes supply a tool for constructing an evolutionary history of the virus [10,17,20].

## 5. HBV GENOTYPES AND SEROTYPES IN MEXICO

Sánchez *et al.* (2002) carried out a study and reported the presence in the Mexican Republic of serotypes adw2, ayw3, and adw4 with genotypes A, D, F, and G [21]. Alvarado-Esquivel *et al.* (2006) determined the presence of genotypes A (8.2%), G (10.2%), D (6.1%), and H (75.5%) in their analyzed population [22]. Ruiz-Tachiquín *et al.* (2007) reported the presence of serotypes adw4q+, adw1q+, and adrq+ together with genotypes C and H, with H being the predominant genotype [23]. Quiroz-Mercado (2007) found genotypes G and H [24]. Sánchez *et al.* (2007) performed a study in two groups from Western and Central Mexico; group 1 was comprised of chronically infected patients and patients with acute hepatitis, whereas group 2 was comprised of homosexual males. In the first group the authors reported the following genotypes and their corresponding percentages: H (74%), D (21%), and A (5%); for the second group, these genotypes were H (52%), A (32%), and G (28%), and cases reported with genotype G were co-infected with H (86%) and A (14%) [25]. Tanaka *et al.* (2008) reported that the G genotype present in six Mexican male homosexual patients was co-infected with the H genotype, with this genotype exhibiting the greatest prevalence in the country according to later previously cited works [26]. García-Montalvo *et al.* [19] reported that HBV genotype H was detected in 66.7% of samples (blood and liver tissue) followed by genotypes D (20.8%) and F (8.3%). Roman and Panduro (2013) reported in Mexico HVB endemicity is associated with genotypes H and G [27].

## 6. CLINICAL RELEVANCE OF HBV GENOTYPES AND SEROTYPES

HBV infection is combated with the use of the following six U.S. Food and Drug Administration (FDA)-approved drugs: five oral drugs are available for the treatment of chronic hepatitis B including lamivudine (LMV), adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate (TDF). All five drugs act on HBV DNA polymerase and inhibit viral replication, leading to suppression of HBV DNA, HBeAg seroconversion, alanine aminotransferase (ALT) normalization, and histological improvement. Interferon alpha (INF- $\alpha$ ) (and its pegylated formulations) is the unique drug that eliminates the cccDNA of the hepatocytes; thus, it is potentially curative. In comparison, prolonged treatment is required with other antiviral agents due to high rates of relapse. Therapeutic action of treatment is affected by the potential emergence of antiviral resistance. The incidence of resistance varies among the different drugs. The highest resistance rates are observed for LMV, whereas the former are lower for other nucleosides and other inhibitors of reverse-transcriptase nucleotides [6].

Use of these drugs exerts pressure on the virus to change the order of its sequence (mutation) by substituting one nucleotidic base for another, eliminating these, or adding others not included in the sequence origin, producing mutations (precore stop, basal core promoter, and S gene sequences) that can be silenced or not, i.e., that have or do not have an amino acid change in the protein. Thus, these give rise to viral variability that achieves evading their mechanisms of action. Actually, there is not a recommendation in treatment guidelines, due to what has been previously revealed, but it could be necessary to determine the viral genotype that is infecting the individual, whether or not the virus presents mutations in its genome that could confer resistance on the drugs used to combat the virus should also be determined. This, per se, is a useful tool for clinical decision-making. It is also important for the economic determinants of the institutions. Resources designated for safeguarding the health of infected persons would be more effectively



appropriated. Administering a hepatotoxic and ineffective treatment to a sick person without an appropriate response would be unnecessary.

There is growing evidence of the role of genotypes/subgenotypes in the activity and progression of hepatitis B. Some studies have shown a correlation between the genotype and severity of liver damage. In studies conducted in China and Japan in patients with chronic HBV, genotype C was found with greater frequency than genotype B in patients with cirrhosis and hepatocellular carcinoma [28–30]. Recently, long-term studies have shown that the cumulative spontaneous-seroconversion rate of HBeAg into anti-HBeAg is significantly higher in patients with genotype B than in those with genotype C [31]. These studies provide strong evidence that genotype B is associated with less active and slower progression of liver damage as compared with genotype C [31]. In another study of 258 Spanish patients with chronic infection, it was found that elimination of HBsAg occurred more frequently in patients with genotype A than in those with genotype D [32]. The same study also concluded that deaths related to liver damage occurred with greater frequency in patients infected with genotype F [32]. The response to peg-interferon is genotype specific. Studies have shown that HBeAg seroconversion and HBV DNA suppression occur less readily in patients with genotype D infection treated with peg-interferon [33]. Other studies have not shown an effect of genotypes on viral suppression by oral antiviral therapy [33]. This is not unexpected because oral drugs work by only inhibiting viral replication. With the introduction of more potent drugs, the majority of patients would experience HBV DNA suppression regardless of genotypes. Currently, few studies have investigated off-treatment response in relation to genotypes. In a study of 82 LMV-treated patients in Taiwan, 38/62 (61%) patients with genotype B HBV infection sustained HBeAg seroconversion after LMV cessation compared with 5/20 (25%) of those with genotype C infection [30]. This suggests that the result of chronic hepatitis B differs according to the viral genotype that infects the patient [30]. According to a pediatric cohort, Yousef et al. (2012) reported that Asian origin did not affect treatment (LMV) success or spontaneous viral control during follow-up and that the HBV genotype did not influence treatment success [34]. Viral factors associated with outcome of chronic hepatitis B virus (HBV) infection include hepatitis B e antigen status, HBV DNA, genotype, and HBV variants. Progression to chronic infection appears to occur more frequently following acute infection on genotypes A and D. Hepatocellular carcinoma is frequent with genotypes C and D. Genotypes/subgenotypes A1, C, B2-B5 and H were associated with more complications than A2, B1 and B6. Genotypes A and B have a better effect than C, D and I [35, 36]. In patients with hemodialysis in Turkey [37] present genotypes D (99%) and G (1%), with subgenotypes (D1, D2 and D3), and serotypes ayw2 and ayw3. Hemodialysis patients in Central Brazil [38] had genotype D (61.5%), A (30.8%) and F (7.7%). Organ Receptor (solid or bone marrow) with HBsAg positive or negative plus HBcAg positive need to receive prophylaxis after medical evaluation. It is important that the relationship between viral genotype/subgenotype and treatment continues to be investigated.

## **7. CONCLUSION**

It is important that the relationship between viral genotype/subgenotype and treatment continues to be investigated.

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## COMPETING INTERESTS

The authors declared do not have competing interests.

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