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Molecular Evolution of Hepatitis Viruses

Flor H. Pujol, Rossana Jaspe and Héctor R. Rangel
Laboratorio de Virología Molecular, CMBC, IVIC, Caracas, Venezuela

1. Introduction

Five hepatitis viruses (HV) are known to date. Infection by enterically-transmitted viruses (HAV and HEV) causes acute hepatitis and is generally benign compared to the disease caused by parenterally-transmitted viruses (HBV, HCV and HDV), for which chronic infection may lead to hepatocellular carcinoma (HCC). Some types of HDV have also been associated to a high frequency of fulminant hepatitis (Table 1). In addition to these viruses, other viruses have been discovered and initially proposed as causative agents of hepatitis, like GBV-C, TTV and SenV. The association with hepatitis was later discarded.

This chapter addresses the molecular evolution of these viruses. An overview on molecular biology and replication of each HV, with emphasis on aspects leading to generation of diversity, is discussed. The diversity of each HV, both at the intrahost and the population level, and the implication of HV diversity on pathogenicity is described. In addition, the possible origin of these viruses is discussed. The chapter also covers how co-infection with HIV may modulate the diversity of HV, in terms of genotypic variability and intrahost evolution.

Hepatitis Virus	**Genome and size**	**Chronicity and HCC**	**Genotypes**	**Salient molecular feature**
A	sRNA 7.5 Kb[1]	No	7: 4 in humans 8 and simian genotypes	Codon usage
B	dDNA 3.2 Kb	Yes		Reverse transcriptase
C	sRNA 9.5 Kb	Yes	7	Quasispecies
D	spRNA 1.7 Kb	Yes	8	Ribozyme, viroid-like genome
E	sRNA 7.2 Kb	No[2]	4	Zoonotic transmission of some genotypes

[1]: s for single stranded, d for partially double stranded, sp for single stranded with intrapairing as a viroid structure. 2: HEV has not been associated to chronicity, except in immunocompromised patients (Kaba et al., 2011).

Table 1. Molecular characteristics of hepatitis viruses

2. Molecular biology and replication of hepatitis viruses

All but one (HBV) of the HV are RNA viruses. This fact implies that they use RNA polymerases – and for HBV a retrotranscriptase - for replication, which lack proofreading

capacity, leading to generation of mutations 10^4 more frequently than human DNA polymerase, for example.

2.1 Enterically transmitted viruses

HAV is a non-enveloped virus which belongs to the genus *Hepatovirus*, of the family *Picornaviridae* (Cristina & Costa-Mattioli, 2007). As an RNA virus, replication occurs entirely in the cytoplasm. HAV genome is a single positive stranded ARN of 7.5 Kb, with an Internal Ribosome Entry Side (IRES) at its 5´ non-coding region. It encodes for a polyprotein of aproximately 2.200 aminoacids (Figure 1) (Cristina & Costa-Mattioli, 2007). This polyprotein is cleaved by celular and viral proteases to produce 11 proteins and among them the viral RNA-dependent RNA polymerase. This polymerase produces the antigenomic negative strand RNA which serves as template for generation of genomic positive strand RNAs, which will be inserted into the assembling viral capsids to be liberated by exocytosis throughout the cell (Cuthbert, 2001).

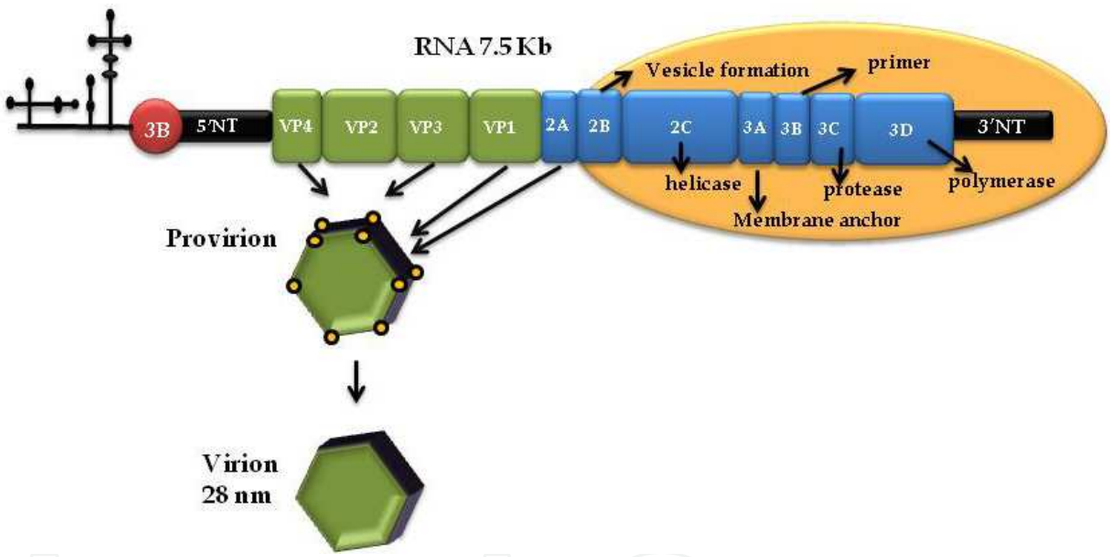

Fig. 1. **HAV virion and genome organization.** The positive-strand RNA genome contains a single open reading frame which encodes a polyprotein proteolytially processed by a cellular protease and the viral protease 3Cpro. Structural proteins (VP) are indicated in green, and nonstructural proteins in blue. The RNA secondary structure of the IRES is shown in the 5´end.

HEV is a non-enveloped virus classified as a *Hepevirus*, in the family *Hepeviridae* (Jameel, 1999). Infection with HEV is responsible for a high percentage of fulminant hepatitis in pregnant women (Dalton et al., 2008). The HEV genome is a positive single-stranded RNA of aproximately 7.2 kb, with a 5´-methylguanine cap and a 3´- polyA stretch. It contains three partially overlapping open reading frames (ORFs) (Figure 2):

- ORF1, coding for non structural proteins including the RNA-dependent RNA polymerase,
- ORF2, coding for the viral capsid protein,

- and ORF3, which might function as a viral accessory protein affecting the host response to infection. (Ahmad et al., 2011).

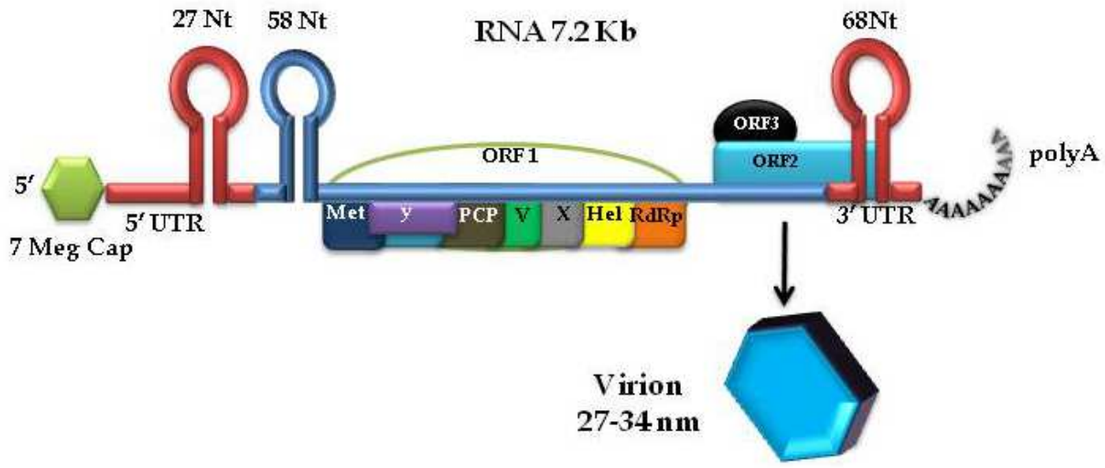

Fig. 2. **HEV virion and genome organization.** The positive strand RNA genome is capped at the 5′ end and polyadenylated at the 3′ end. The three open reading frames (ORFs) are shown. ORF1 encodes the nonstructural polyprotein with various functional units – methyltransferase (MeT), papain-like cysteine protease (PCP), RNA helicase (Hel) and RNA dependent RNA polymerase (RdRp). ORF2 encodes the viral core protein. ORF3 encodes a small regulatory phosphoprotein.

HEV replication is not completely known. After releasing of viral RNA in the cytosol, ORF1 is translated into the polyprotein, generating the replication complex. It is believed that negative RNA intermediates are then produced, for the synthesis of genomic as well as subgenomic positive RNAs, these latter translated into the capsid and ORF3 proteins. Positive genomic RNA is package in the capsids for liberation of HEV through exocytosis (Ahmad et al., 2011).

2.2 Hepatitis B virus

HBV is an enveloped virus belonging to the genus *Hepadnavirus*, in the family *Hepadnaviridae*. This family includes several genera of partially double stranded DNA generated from an intermediate RNA through reverse transcription (Ganem, 1991). HBV genome is around 3,200 bases long (Figure 3), the smallest of all known animal viruses.The viral genome encodes four overlapping ORFs:

- S, coding for the viral surface envelope proteins,
- C, coding for the capsid and e antigen proteins,
- P, coding for the polymerase, functionally divided into the terminal protein domain, which is involved in encapsidation and initiation of minus-strand synthesis; the reverse transcriptase (RT) domain, which catalyzes genome synthesis; and the ribonuclease H domain, which degrades pregenomic RNA.
- X, coding for a protein with multiple functions, including signal transduction, transcriptional activation, DNA repair, and inhibition of protein degradation (Liang, 2009).

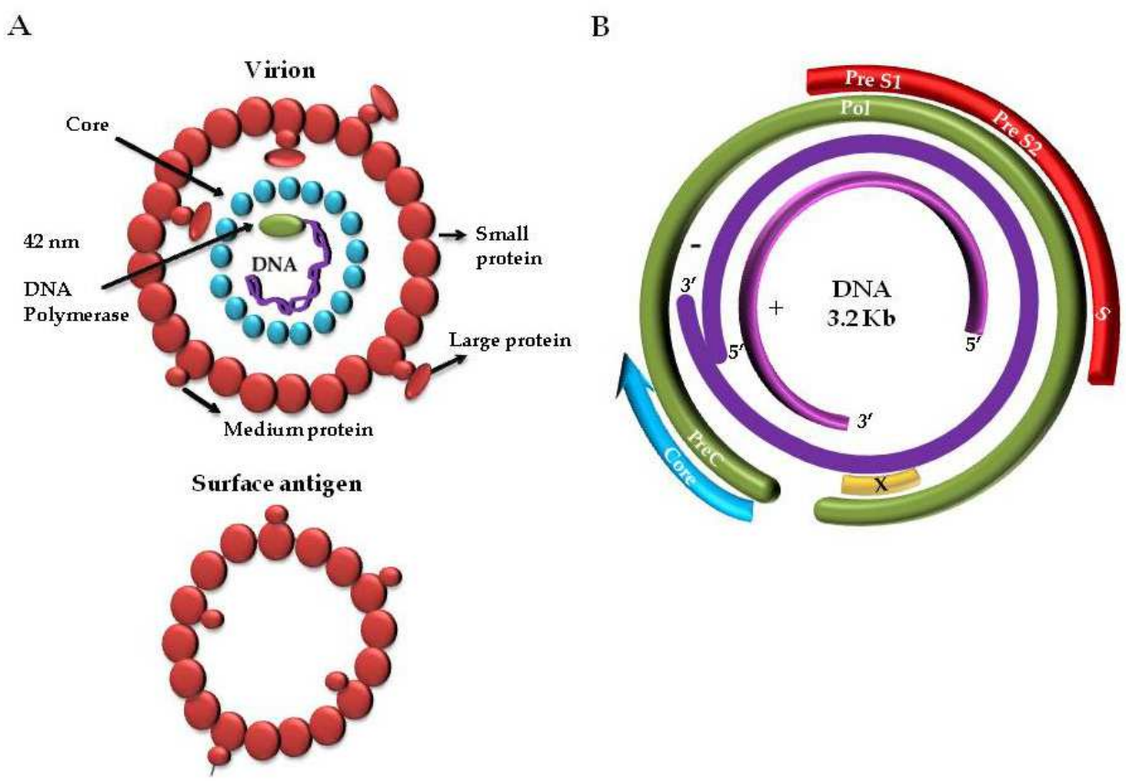

Fig. 3. **HBV virion and genome organization. A.** Enveloped virion of 42 nm. The 3 forms of HBV surface antigen (small, medium ans large) are embedded in the lipid envelop which covers que core which interacts with the partially double stranded DNA, which is covalently linked to the polymerase. Cellular heat shock proteins inside the virion are not shown. In addition to the virion, HBV surface antigen empty particles are secreted both as spherical or cylindrical particles. **B.** The DNA genome and the 4 ORFs are shown, describing the compact nature of this genome.

After entry into the cell, the viral capsids are directed to the nucleus. The single-stranded gap region in the viral genome is repaired and circularized to a covalently closed circular form. This circular DNA is the template for transcription of the pregenomic and several subgenomic messenger RNAs. Pregenomic RNA is retrotranscribed inside the capsids by the HBV polymerase. The nucleocapsids are then directed to the endoplasmic reticulum to interact with the envelope proteins and assemble into mature virions, which are then secreted outside the cell (Liang, 2009).

2.3 Hepatitis D virus

HDV, genus *deltavirus*, is the smallest animal RNA virus (1,700 bases), and is related to plant viroids and satellite viruses (Figure 4). In contrast to plant satellite viruses, HDV is able to

perform autounomous replication, but depends on coinfection with HBV, since it uses its viral surface antigen for assembling its virion (Taylor, 2009). Unlike other RNA viruses, HDV lacks an RNA-dependent RNA polymerase, by using the cellular RNA polymerases of the host, which recognize its genome because of its folded, rod-like structure. Three forms of RNA are made in the host during replication: circular genomic and antigenomic RNA, and polyadenylated antigenomic mRNA, which codes for the only protein coded in this genome, the HDAg. Two forms of HDAg are produced by RNA edition. Replication of the circular HDV RNA template occurs via a rolling mechanism similar to that of plant viroids. A viral ribozyme selfcleaves the linear HDV RNA. These monomers are then ligated to form circular RNA, which interacts with HDAg and uses HBV empty surface antigen particles for assembling the HDV virions (Hugues et al., 2011; Taylor, 2009).

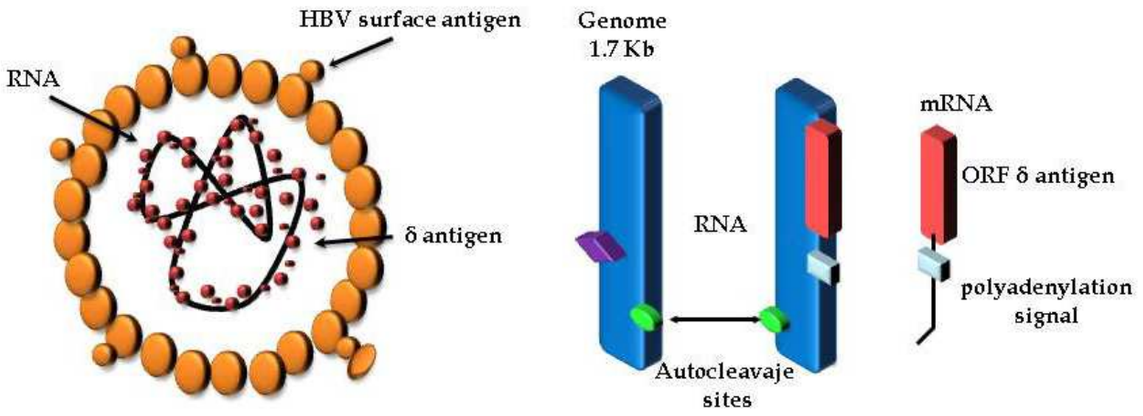

Fig. 4. **HDV virion and genome organization.** HDV RNA is packed through interaction with HDV antigen, who presents in two forms, large (with an N-terminal strech of amino acids intercating with RNA) and small form. HDV RNA and antigens are inside HBV surface antigen empty particles, provided by HBV replication. During replication, 3 HDV RNAs accumulate in the cell: the single negative strand genome and the antigenome, each possessing a ribozyme, with cleavage sites indicated by green circles, and the 800-nucleotide mRNA, that has a 5´-cap and a 3´-poly(A) tail.

2.4 Hepatitis C virus

HCV belongs to the genus *Hepacivirus*, in the family *Flaviviridae*. It is an enveloped virus with a positive RNA of around 9.5 Kb, which codes for a polyprotein of around 3,000 amino acids, including an RNA-dependent RNA polymerase (Figure 5). HCV interacts with a series of receptor to enter the cell via endocytosis, from which the capsid released the viral RNA in a membranous web close to the Endoplasmic reticulum, where replication takes place. The translated polyprotein is co- and post-translationally modified to produce mature viral proteins which can form replication complexes and assemble into new virions. These progeny virions bud into the lumen of the ER and leave the host cell through the secretory pathway (Poenisch & Bartenschlager, 2010; Tang & Grise, 2009).

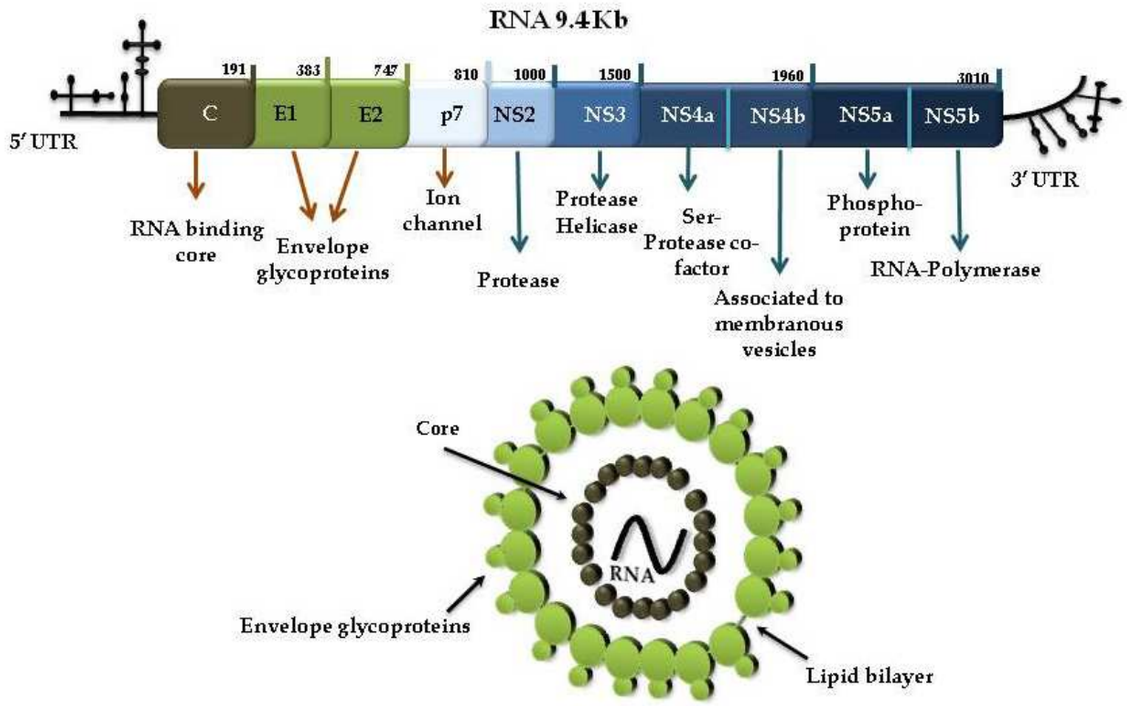

Fig. 5. **HCV virion and genome organization.** The positive-strand RNA genome contains a single open reading frame which encodes a polyprotein proteolytially processed by cellular and viral proteases. Structural proteins (VP) are indicated in green and nonstructural proteins in blue. The RNA secondary structure of the IRES is shown in the 5´end. At the 3´end, the RNA exhbit also a secondary structure involved in replication.

2.5 Other parenterally-transmitted viruses historically associated with hepatitis

In addition to the well established hepatitis viruses, 3 other parenterally-transmitted viruses have been identified, GBV-C (formerly known as HGV), TTV and SEN-V (Figure 6). However, the real role of these new viruses as causative agents of hepatitis is uncertain. There is no evidence at the present that these viruses cause any pathology in humans (Allain et al., 2002). A tentative genus has been proposed for GBV-C, *Pegivirus*, and 6 genotypes of GBV-C have been described (Smith et al., 2000; Stapleton et al., 2011). Genotype 1 is more prevalent in Africa, genotype 2 in Europe and North America, and genotypes 3, 4 and 5 are found mainly in Asia. GBV-C genotype 3 circulates among Central and South American population groups, a finding that may be related to the Asiatic origin of the American man (Loureiro et al., 2002; Smith et al., 2000). These findings suggest an old origin of GBV-C.

TTV is a single-stranded DNA virus, of around 3.8 Kb, distantly related to circoviruses and classified in the genus Arnellovirus (Biagini, 2009; Hino & Miyata, 2007). TTV represents in fact a swarm of viruses, which chronically infects human and other animals, and was originally thought to be associated with hepatitis. However, there does not seem to be any link between TTV infection and HCC or chronic hepatitis. Up to 23 genotypes of TTV have been described, which are grouped in 5 genogroups. One of these genogroups comprises SEN-V, another virus initially associated with hepatitis. Preliminary evidence suggests that some SEN-

V types may be associated to hepatitis, although this association could be a casual event, and then not meaning that SEN-V is actually a true hepatotropic virus (Hino & Miyata, 2007).

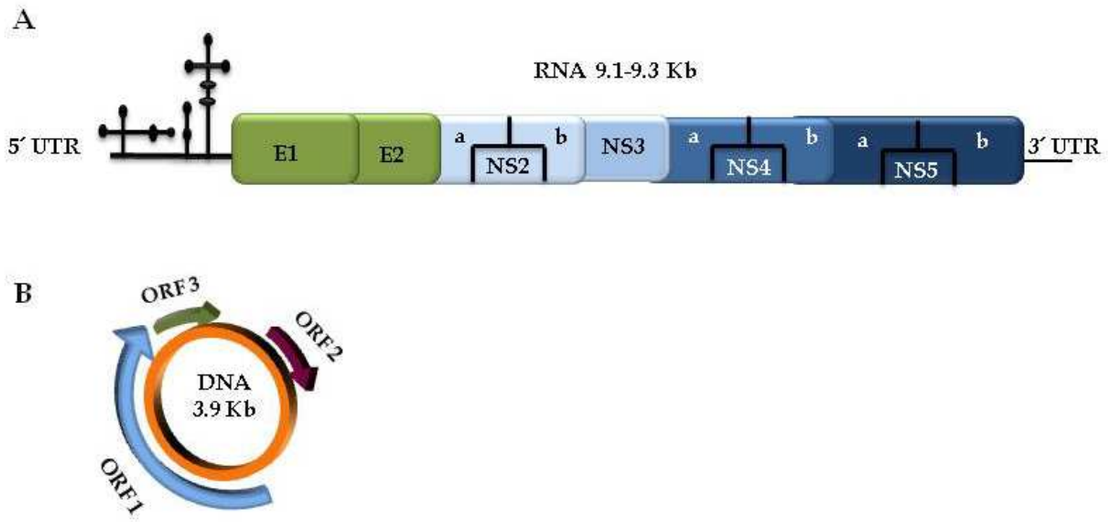

Fig. 6. **Genome organization of GBV-C and Arnellovirus. A: GBV-C genome.** The positive-strand RNA genome contains a single open reading frame which encodes a polyprotein proteolytially processed by cellular and viral proteases. Structural proteins (VP) are indicated in green and nonstructural proteins in blue. A core coding region is absent in the GBV-C genome. The RNA secondary structure of the IRES is shown in the 5´end. **B. Arnellovirus genome.** TTV and Sen-V single-stranded DNA viruses of negative polarity. ORF1 (DNA polymerase), ORF2 (non-structural protein), and ORF3 (core), all present in the plus strand complementary to the virion, are displayed in colours.

3. Genetic diversity of hepatitis viruses

3.1 Enterically transmitted viruses

HAV variants can be classified in 6 genotypes, 3 of them infecting humans and the other 3 other primates from the Old World (Cristina & Costa-Mattioli, 2007; Robertson, 2001) (Table 1). Genotype I, and particularly subgenotype IA, is the most prevalent around the world (Cristina & Costa-Mattioli, 2007). Interestingly, in countries with intermediate to high prevalence of HAV infection, like Latin America and Africa, HAV genotype I is highly predominant, being exclusively found in several countris from South America, where a higher diversity would be expected due to the high frequency of infection (Cristina & Costa-Mattioli, 2007; Sulbarán et al., 2010). A founder effect, like observed for human immunodeficiency virus (HIV) subtype B in the Americas, may account for this situation (Y. Sulbaran et al., 2010; Tebit et al., 2007). In addition, HAV has adopted a naturally highly deoptimized codon usage with respect to that of its cellular host. This characteristic suggests a fine-tuning translation kinetics selection as the underlying mechanism of the codon usage bias in this specific genome region (Aragones et al., 2010). Moreover, significant differences in codon usage are found among the different genotypes (D´Andrea et al., 2011). These differences might be a factor that might bring some adaptative advantage to HAV genotype I and particularly subgenotype IA.

Four genotypes have been reported for HEV (Purcell & Emerson, 2008) (Table 1). Two of these genotypes are endemic among swines and other mammals. An interesting feature of this disease is that two modes of transmission seem to prevail in different geographic regions:

- human to human transmission in highly endemic regions, like Central and Southeat Asia, the Middle East and North Africa, where the most commons genotypes are 1 and 2, the human ones, and
- a zoonotic transmission linked to contact and/or consumption of swines and other susceptible mammals, in non-endemic regions, like Europe, Japan and the Americas, with a more frequent circulation of the animal genotypes 3 and 4 (Purcell & Emerson, 2008). These zoonotic reservoirs might explain the presence of HEV infection in non endemic areas and in isolated populations, like Amerindians, where evidence of exposure to HEV has been documented (Pujol et al., 1994).

3.2 HBV

The absence of proof reading capacity of the HBV reverse transcriptase leads to a high mutation rate. On the other hand, the extreme overlapping of the open reading frames of this small viral genome reduces the viability of many of these mutations (Torresi, 2002). For these opposite characteristics, the substitution rate of HBV is intermediate between RNA and DNA viruses (Kidd-Ljunggren et al., 2002). Another implication of this enhanced potential variability is the generation of a quasispecies-like viral population (Gunther et al., 1999), harboring viral mutations that can be eventually selected under particular selection pressures (Pawlotsky, 2005). The quasispecies complexity is however modulated by the compact genome organization of this virus (Pawlotsky, 2005).

In addition to the diversity which occurs during the natural course of infection, another degree of variability is displayed by HBV strains circulating worldwide. This variability includes the vaccine escape mutants and the genotypic and subtypic variability.

Vaccine escape mutants occur by point mutations in the "a" determinant of the surface antigen, the main immunogenic region, induce conformational changes that prevent the binding of neutralizing antibodies. The most frequent substitutions observed with these characteristics are G145R and D144A (Pawlotsky, 2005; Torresi, 2002). In addition to their transmission between individuals, vaccine escape mutants might be selected under the pressure of neutralizing antibodies or antiretroviral drugs (Lada et al., 2006).

Eight human HBV genotypes (A–H) have been described, based on a minimum divergence of 8% of the complete genome sequences (Table 1) (Figure 7) (Araujo et al., 2011; Norder et al., 2004). Genotypes A and D are predominant in the Old World but are also widely distributed in all the continents. Genotypes B and C are found mainly in South East Asia and the Far East, while genotype E circulates in sub-Saharan West Africa (Norder et al., 2004; Pujol & Devesa, 2005). HBV genotype E might be a recent genotype, exhibitig a low intragenotypic variation not being introduced to the Americas during slave trade (Kramvis et al., 2005; Quintero et al., 2002).

The distribution of genotype G is not fully known. This genotype exhibit several interesting characteristics. A low intragenotypic variability has been found among different isolates

from different countries (Lindh, 2005). A high frequency of mutations in the core and precore regions and a frequent association of co-circulation with HBV genotype A have also been reported. This last finding has lead even to the suggestion that the genotype G represents an impaired virus which needs a helper virus for effective replication (Lindh, 2005). However, transmission and infection with exclusively HBVgenotype G has recently been documented (Chudy et al., 2006). On the other hand, a segment of the preS region is identical in genotype E and G strains, suggesting an eventual recombination between these two genotypes. This last assumption might also suggest an African origin for genotype G, although this genotype has not been found yet circulating in Africa (Lindh, 2005). This genotype is might be found more frequently in co-infection with HIV (Dao et al., 2011). Alternatively, HBV genotype G is found frequently infecting men who have sex with men (MSM) (Bottechia et al., 2008; Osiowy et al., 2008; Sanchez et al., 2007). The core variability displayed by HBV genotype G (a 12 amino acid insertion at the N-terminal end) has been shown frecently that migh be affecting the ability of assembly and secretion of the viral particle (Cotelesage et al., 2011), which supports the assumption for the need of a co-infecting strain for an efficient replication of this genotype.

Some of the HBV genotypes are divided into subgenotypes, based on a divergence of more than 4%. Seven subgenotypes are described at the moment for genotype A, 9 for genotype B (Thedja et al., 2011), 12 for genotype C (Mulyanto et al., 2011), 7 for gebnotype D (Meldal et al., 2009) and 4 for genotype F (Devesa et al., 2008). No subgenotypes have been found at present inside genotypes E, G and H. This fact migh be due to the fact that these genotypes might be more recent than the other ones.

HBV genotype F is the most divergent of the HBV genotypes, is autochthonous to and highly predominant in some countries of South America (Devesa & Pujol, 2007). HBV genotype H is closely related to genotype F and seems to be restricted to Central and North America (Arauz-Ruiz et al., 2002). In addition to human HBV genotypes, several simian genotypes have also been identified, one in a monkey from the New World (woolly monkey), while the others have been found infecting simians from the Old World (Figure 7) (Devesa & Pujol, 2007).

In addition, a new genotype I has been proposed for a recombinant of genotypes A, C, and G mainly found in Laos and Vietnam (Tran et al., 2008), genotype J for a recombinant strain between human and ape viruses (Tatematsu et al., 2009). Indeed, several studies have pointed that recombination seems to play an important role in shaping the evolution of HBV (Fares & Holmes, 2002; Simmonds & Midgley, 2005). The exact mechanism of recombination of HBV genomes is not clear, but it seems more likely to occur in the nucleus, by illegitimate replication (Yang & Summers, 1998), or by recombination with integrated HBV DNA (Bowyer & Sim, 2000).

HBV variability seems to play a role in HCC development. Pathogenic differences in causing HCC have been reported among hepatitis B virus (HBV) variants, but also genotypes. HBV genotype C is associated with a more severe disease. (Yang et al., 2008; Yu et al., 2005), and genotype D seems to evolve worse than genotype A (Thakur et al., 2002). HBV genotype F was associated to a higher frequency of HCC development at younger age in Alaskan individuals (Livingston et al., 2007). However, the risk of HCC may differ among subgenotypes (Pujol et al., 2009).

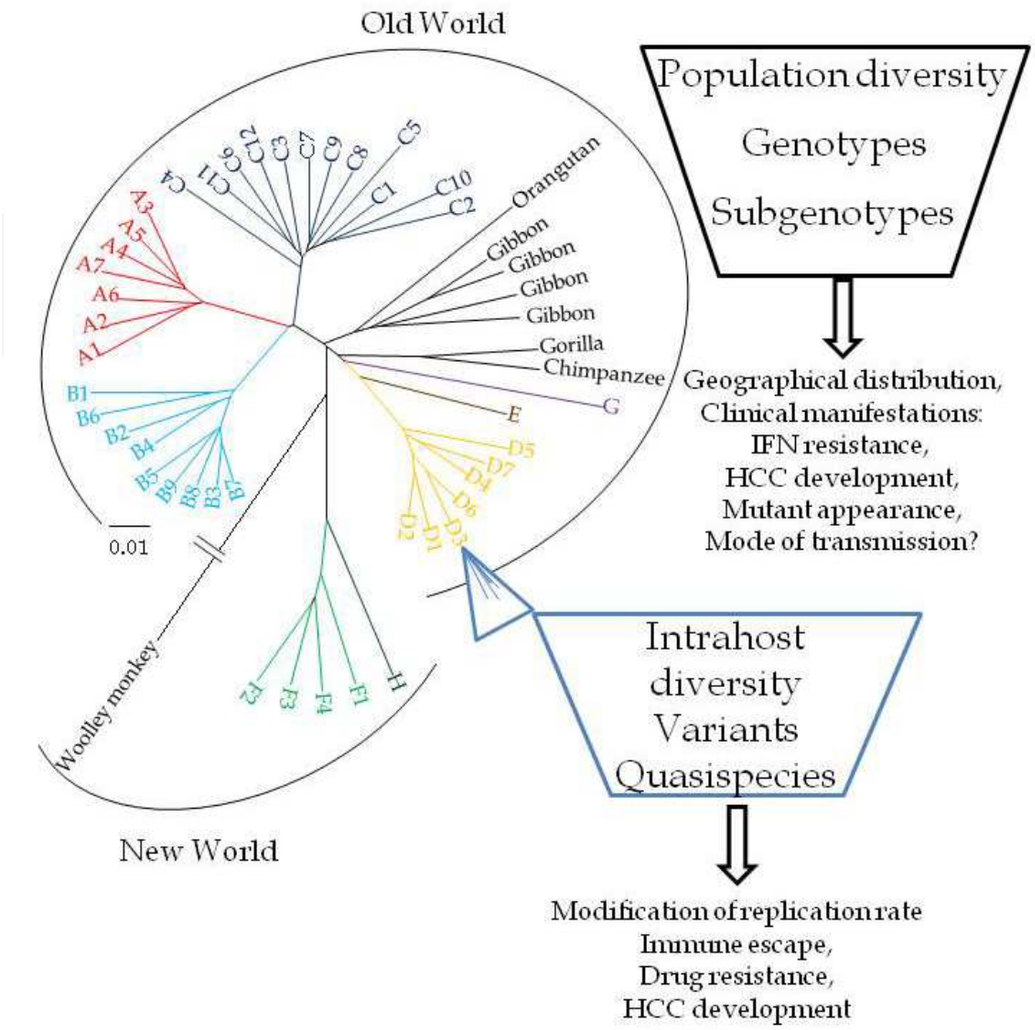

Fig. 7. **HBV molecular evolution.** Human and non-human primates HBV genotypes and subgenotypes are shown in the phylogenetic tree. Intrahost diversity is shown in blue. The implication of HBV variability is also shown.

Several variants are generated during the course of the chronic infection in response to the host or exogenous immune pressures and drug therapy. Mutations in the Precore, Core, X, Pre-S, S and Pol gen, have been reported. Particular interest has been directed toward the generation of translational stop codon mutation at the precore region (mostly G1896A) inside the ε structure, and mutations in the basal core promoter region (especially A1762T, G1764A) and the upstream regulatory sequences (nt1643-1742). The selection of the G1896A seems to be genotype-dependent (Devesa & Pujol, 2007). The basal core promoter overlaps with the X region of the HBV genome, and mutations in the amino acid sequences at positions 130 and 131 in this region (K130M and V131I) has been proposed as prognostic markers for the development of liver cancer (Kuang et al., 2004, Pujol et al., 2009). Some genotypic variability may also occur in terms of interferon sensitivity and development of drug resistance (Kramvis & Kew, 2005; Ramos et al., 2007).

The current treatment for HBV involves the use of Interferon (IFN) and/or antiretroviral drugs, since some of the anti-HIV reverse transcriptase drugs can also inhibits the HBV polymerase. Although no specific mutations have been associated to IFN resistance, some genotypes are more susceptible to this immunomodulator, like genotypes A and B, compared to D and C (Lin & Kao, 2011). Five nucleoside and nucleotide analogues inhibit HBV reverse transcriptase: Adefovir, Entevavir, Lamivudine, Telbivudine and Tenefovir. Drug resistance mutations emerge during treatment with these drugs, consisting of point mutation in one of the 5 domains of the HBV polymerase (Table 2) (Yuen et al., 2009).

The origin of HBV is still an unsolved question (Jazayeri et al., 2009). The reduced size of HBV genome, together with the high degree of overlapping of its open reading frames, has impaired the drawing of an evolutionary picture of this virus. With the advent of sequences from several HBV strains circulating in non human primates (Figure 7), an alternative hypothesis has been proposed: human HBV genotypes might have emerged through several zoonotic introductions from simian strains, both at the Old and New World (Devesa & Pujol, 2007).

3.3 HDV

Eight genotypes of HDV have been identified (Table 1) (Deny, 2006). HDV genotype 1 is present worldwide. Genotype 2 is found in Japan, Taiwan, Russia. Genotype 3 is the most divergent genotype and is found in the Amazon Basin, and has been shown to infect individuals from Peru, Venezuela and Colombia, where severe cases have been documented. This genotype is actually the most frequently associated to fulminant hepatitis. Genotype 4 circulates in Taiwan and Japan. The remaining HDV genotypes (5–8) are found Africa (Deny, 2006).

As other RNA viruses, HDV circulates as a quasispecies distribution of variants, in which defective mutants have being described (Wu et al., 2005). In addition mutants appearing under the immune pressure, as detected by the presence of amino acids under positive selection, target of cytotoxic T lymphocytes, have also been described (Wang et al., 2007).

3.4 HCV

HCV has been classified in 7 genotypes, according to a genetic divergence of more than 30-35% in the complete genome and in several subtypes inside each genotype, according to divergences of more than 20% (Figure 8) (Le Guillou-Guillemette et al., 2007; Chayama & Hayes, 2011). Infections with HCV genotype 1 are associated with the lowest therapeutic success (Zeuzem et al., 2000). HCV genotypes 1, 2, and 3 have a worldwide distribution. HCV subtypes 1a and 1b are the most common genotypes in the US and are also are predominant in Europe, while in Japan, subtype 1b is predominant. Although HCV subtypes 2a and 2b are relatively common in America, Europe, and Japan, subtype 2c is found commonly in northern Italy. HCV genotype 3a is frequent in intravenous drug abusers in Europe and the United States. HCV genotype 4 is prevalent in Africa and the Middle East, and genotypes 5 and 6 seem to be confined to South Africa and Asia, respectively (Simonds, 2001; Zein, 2000). HCV genotype 7 was more recently identified in Canada, in an emigrant from the Democratic Republic of Congo.

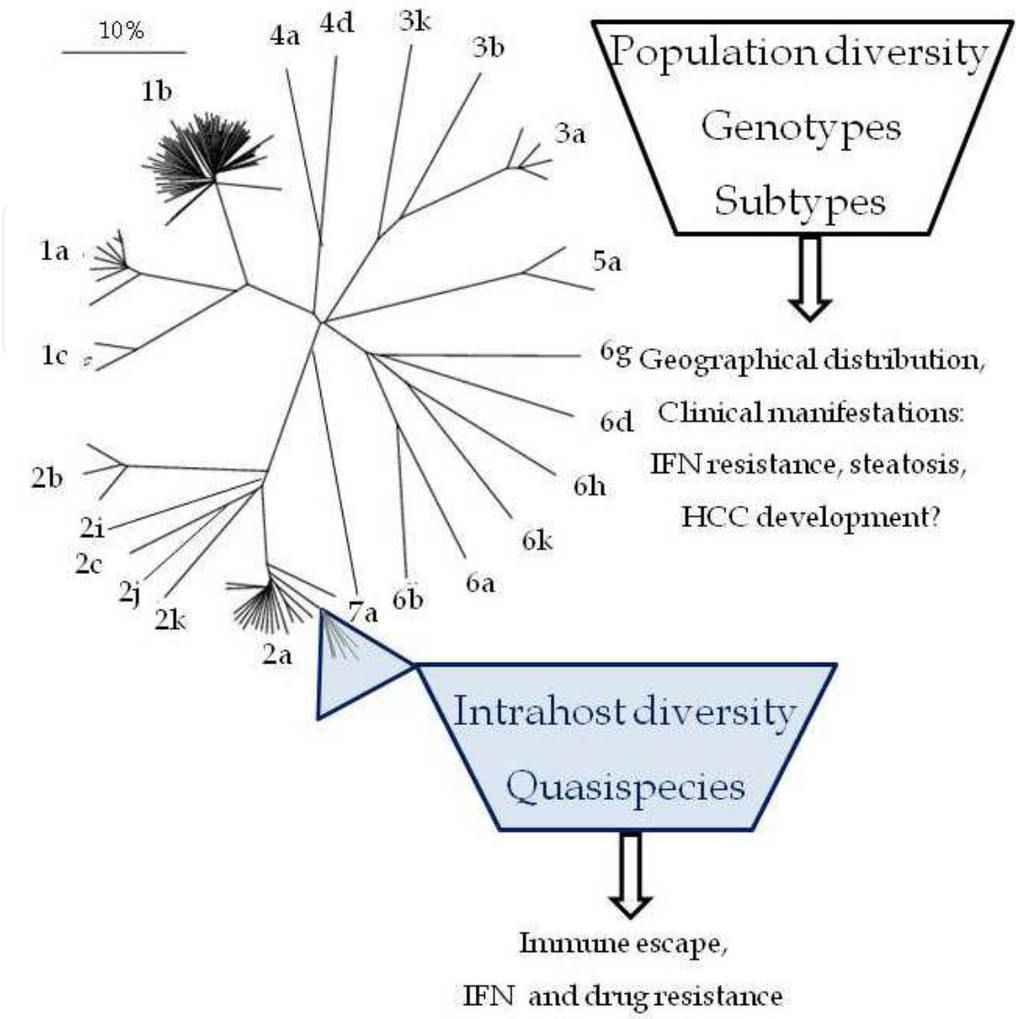

Fig. 8. **HCV molecular evolution**. HCV genotypes and subtypes for which at least one complete genome has been sequenced, are shown in the phylogenetic tree. Intrahost diversity inside each subtype is shown in blue. The implication of HCV variability is also shown.

In contrast with HBV, recombination between HCV genotypes seems to be a rare event. *In vitro* studies suggest a low frequency of recombination for this virus (Reiter et al., 2011), in agreement with the low number of recombinant strains identified so far (Morel et al., 2011). However, intergenotypic incompatibility might be a factor involved in the low frequency of recombinants observed, and intragenotypic recombination might be more frequent than expected (Mes & Doomum, 2011).

Changes in hepatitis C virus (HCV) genotype distribution with time have been reported in several countries. In Venezuela, for example, a significant reduction of the circulation of HCV genotype 1b was observed in the last decade, with the increase of circulation of genotype 2j (Pujol & Loureiro, 2007; M.Z. Sulbaran et al., 2010). Several subtypes of HCV genotype 2 and 4 were introduced in some countries of the Americas during slave trade in

Martinique (Martial et al., 2004) and of HCV genotype 2 in Venezuela (Sulbarán M.Z. et al., 2010). It is difficult to estimate for how long HCV has been present in human populations. HCV may have been endemic in Asia and Africa for a considerably longer time than in Western countries. HCV subtypes might have diverged around 200-250 years ago and genotypes around 500-2000 years ago (Bostan & Mahmood, 2010; Cantaloube et al., 2003; Smith et al., 1997).

HCV genotype 1b has been frequently associated with a more severe liver disease. Nevertheless, this association might be due to the fact that individuals infected with this genotype have a longer mean duration of infection (Zein, 2000). A recent meta-analysis showed however HCV subtype 1b associated to a higher risk factor for HCC development (Raimondi et al., 2009). Hepatic steatosis is a common consequence of HCV infection, has been recently associated with the development of HCC, and is more frequently found among HCV genotype 3 infected patients (Monto et al., 2002). More studies are needed to confirm the correlation between HCV genotype 3, the presence of steatosis and progression to HCC (Zhu & Chung, 2003).

Within an infected individual, HCV circulates as a collection of closely related variants named quasispecies (Fishman & Branch, 2009). HCV like others RNA virus has a high level of genetic variability, especially in the E1 and E2 genes (envelope glycoproteins). Humoral pressure on the hypervariably region of E2 has been associated with quasispecies diversification through immune escape mechanisms (Weiner et al., 1992). The quasispecies nature of HCV populations in an infected individual might contribute to the viral persistence in the host, IFN and drug resistance (Fishman & Branch, 2009) (Figure 8).

4. HIV co-infection

HIV co-infection with HCV and/or HBV is frequent, since these viruses share many modes of transmission, and exacerbates the natural history of these viral infections. A decreased immune clearance and more rapid progression of liver disease has been documented, leading to an increased incidence of cirrhosis, risk of drug-related hepatoxicity, HCC development, and death. On the other hand, liver disease has emerged as a major cause of morbidity and mortality in HIV-infected patients. Viral hepatitis co-infection increases the risk of drug-related hepatoxicity of highly active antiretroviral therapy (HAART), impacting the selection of specific agents (Sulkowski, 2008).

HIV-1 co-infection increases HCV viral load in dually infected patients. This effect seems to be both related to the acquired immunodeficiency and to a direct interaction between the viruses (Rotman & Liang, 2009). In addition, HIV-1 co-infection seems to impact the quasispecies complexity exhibited by HCV. Both an increase and a decrease of quasispecies heterogeneity has been described, when compared to HCV mono-infected patients (Sherman et al., 1996; Toyoda et al., 1997). In spite of the conflicting results, many reports suggest a relatively low level of HCV quasispecies diversity before HAART, and an increase in diversity after prolonged treatment, principally due to a significant increase in both synonymous and non-synonymous substitution rates in the hypervariable region 1 of HCV E2 (Bernini, et al, 2011). This exponential growth of the quasispecies populations in immunological responders coincides with a peak in CD4 cell counts, positive selection in several proteins of HCV, and a frequent increase in HCV viral load (Bernini, et al, 2011).

Patients co-infected with HBV and HIV-1 have a higher likelihood of chronicity after acute HBV infection compared with HIV-negative patients (Lacombe et al., 2010). The natural history of HBV-related disease is modified by HIV infection in several ways. Co-infected patients have higher HBV DNA levels, lower aminotransferase levels, decreased spontaneous loss of hepatitis B early antigen (HBeAg), accelerated progression to cirrhosis, and increased risk of liver-related morbidity and mortality compared with HBV monoinfection (Lacombe et al., 2010). As previously mentioned, a number of clinically significant HBV genome mutations have been reported in HBV mono-infection, and differences in disease evolution and treatment response have been associated to a particular genotype and to some of these mutations. Many of these mutations appears during the long term evolution of infection and during exposure to nucleos(t)ides analogs, used to treat HIV (Lacombe et al., 2010). In HIV-1/HBV co-infected individuals, a novel –1G mutation in the HBV core and precore gene was found to be more frequent compared to mono-infected patients. This mutation results in premature termination of the deduced HBV precore and core genes and was associated with high HBV viral load. PreS2 deletions were observed more frequently in co-infection (Audsley et al., 2010).

An interesting observation is that the natural course of HIV-1 might be modulated by the presence of GBV-C. GBV-C co-infection seems to exert a beneficial effect on HIV disease progression (Maidana et al., 2005), although this evidence has not been consistently corroborated (Baggio-Zappia et al., 2009). The mechanism by which GBV-C interferes with AIDS progression is not yet fully undestood. *In vitro* studies have shown that the inhibitory effect of GBV-C on HIV-1 replication might be related to solubles factors induced by GBV-C (Jung, 2005), and specifically with chemokines, Rantes, MIP-1 and SDF-1, which may compete with HIV-1 envelop glycoprotein 120 for the correceptor CCR5 and CXCR4 in CD4 cells. This effect may reduce a successful HIV-1 interaction with infected cell (Xiang, 2004). Several lines of evidence suggest a possible inhibition of HIV-1 by GBV-C through increase in soluble ligands for HIV-1 correceptor and activation of innate immunity (Lalle, 2008; Mohr & Stapleton, 2009). In addition, the beneficial effect of GBV-C on survival of HIV-1 infected patients might be genotype specific (Schwarze-Zander et al., 2006). Two GBV-C proteins, E2 and NS5A, have been shown to modulate CD4+ T-lymphocyte chemokine receptor expression and chemokine release in vitro, then inhbiting HIV replication. The inhibitory effect of GBV-C NS5A on HIV-1 replication was exerced *in vitro* by the non structural proteins from all the genotypes tested (Chang et al., 2007), failing then to describe a genotype specific inhibition of this protein in HIV-1 replication. More studies are needed to clarify the exact role of GBV-C co-infection on HIV-1 replication.

5. Conclusions

There are still 5 viral entities named hepatitis viruses, which share only their tropism for the hepatocyte. Parenterally transmitted viruses are normally the ones associated to chronicity and to more severe sequela, like cirrhosis and HCC. Due to the error prone nature of their polymerases, these viruses display a substantial degree of genetic diversity. Within these 5 viral entities, viral variants (genotypes, subgenotypes, diversity of quasispecies, mutants) might exhibit particular characteristics in term of pathogenesis and mode of transmission. Thus, instead of 5 viruses, we are in fact dealing with a multiplicity of viral variants with different consequences and evolution inside the infected host. Vaccines are not available for

all these entities, only for HAV and HBV, and partially for HDV. The significant degree of variability exhibited by these viruses is an unresolved limitation for the development of effective vaccines against them. Some of these variants might have originated separately in the New and the Old World, as for HBV and HDV, for example. Some of these viruses may have a long time of co-evolution with human host, as for GBV-C, while others might have been introduced more recently, like HCV.

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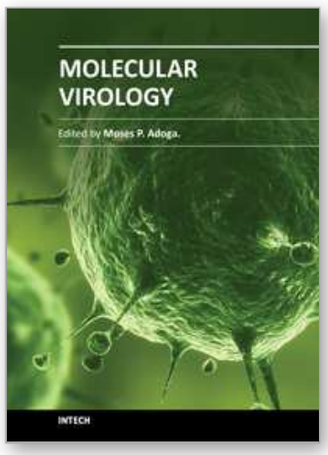

Molecular Virology

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This book covers various aspects of Molecular Virology. The first chapter discusses HIV-1 reservoirs and latency and how these twin phenomena have remained a challenge to eradication. Aspects regarding the molecular evolution of hepatitis viruses including their genetic diversities with implications for vaccine development are treated in the second chapter. Metabolic disorders that are a consequence of hepatitis C virus infection are discussed in the succeeding chapter. The following two chapters discuss influenza C virus and the applications of viral vectors in therapeutic research. Avian influenza is handled in the sixth chapter and the therapeutic potential of belladonna-200 against japanese encephalitis virus infection is discussed in the succeeding chapter. The last two chapters discuss baculoviruses and their interaction with polydnaviruses. Researchers, lecturers and students will find this book an indispensable companion.

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