

**ANNAROSA FLOREANI**

**CHRONIC  
VIRAL HEPATITIS  
B AND C**



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# FOREWORD

The last ten years of the previous century and the first ten years of the new millennium have dramatically changed the history of hepatology. Sensitive and reliable diagnostic assays have become available for hepatitis B and hepatitis C viruses. Studies conducted all over the world have documented the epidemiology and the transmission of hepatitis viruses. More recently, the new therapies for chronic hepatitis have revolutionized the scientific world.

In an impressive editorial published in August 2012, dealing on the clinical trials in *Hepatology*<sup>1</sup>, Jenny Heathcote asks “The future: what will happen?” and “The future: what should happen?”. It is interesting to remember that the incidence of HBV infection has dramatically changed over the last 25 years; moreover, vaccination available for newborns has been shown to reduce the incidence of hepatocellular carcinoma in Taiwan.

The incidence of HCV infection has also declined during the last twenty years. However, HCV in western countries is still the most important risk factor for chronic hepatitis and the most important cause of liver transplant. A vaccine against hepatitis C will be available in the near future. The new antiviral drugs limit the disease progression, improve survival and reduce the risk of hepatocellular carcinoma. The natural history of HCV infection is generally long and characterized by a slow progression to cirrhosis. The study of the natural history together with the role of co-factors of liver disease (including alcohol, iron, genetics, and a number of environmental factors) have furnished an important lesson to hepatologists.

I think that the future is to cure and control early diseases including hepatitis B and C with the aim to reach a real reduction in morbidity and mortality. I wish to thank all the colleagues for their contributions to this up-date on hepatitis B and C. For all of us this work has been a challenge to explore the past and the present knowledge in the field of hepatitis and we are pleased to dedicate this book to the physicians who would like to approach the problems of patients with chronic hepatitis.

ANNAROSA FLOREANI

1. Heathcote J. Clinical trials and their translation in *Hepatology*: past, present and future. *Hepatology* 2012; 56: 399-410.

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# EPIDEMIOLOGY OF HBV INFECTION

# 1

T. Stroffolini

## HOW THE POOL OF SUBJECTS WITH CHRONIC INFECTION HAS ARISEN

Hepatitis B virus (HBV) infection is a major worldwide problem, with more than 2 billion subjects exposed to the virus and 350 to 400 million people having chronic infection.<sup>1</sup>

The likelihood that people will develop a chronic hepatitis B surface antigen (HBsAg) carrier state after acute exposure to the virus depends on their age at the time of infection.<sup>2</sup> Infants whose mother are positive for HBsAg and also positive for hepatitis B “e” antigen (HBeAg), a marker for high viral load, had 90% risk of developing chronic HBV infection; whereas infants whose mothers are HBsAg positive but negative for HBeAg (anti-HBe) have only 15% chance of developing a chronic HBsAg carrier state.<sup>3</sup> A study from Africa showed that children born without HBV but infected during the first 2 years of life had a 50% of chance of becoming chronic HBsAg carriers.<sup>4</sup> Two prospective studies, one in Taiwan<sup>5</sup> and one in Alaska,<sup>2</sup> of children infected between 3 and 5 years of age showed that from 23% to 28.6% develop chronic HBV infection. In contrast, only 3% of subjects 18-24 years old infected with HBV became HBsAg carriers.<sup>6</sup> Finally, with the availability of serological tests for IgM-anti-HBc (a reliable marker for differentiating recent from past HBV infection) it has been firmly shown that acute clinical hepatitis B in adults rarely (0.2%) leads to the chronic carrier state, unless some degree of immune deficiencies exists<sup>7</sup> (Table 1-I). These figures suggest that the pool of chronic HBsAg carriers is likely to have arisen from childhood infections.

Table 1-I – Age at HBV infection as determinant of the HBsAg carrier state.

Age at infection	Likelihood of becoming a chronic HBsAg carrier	Reference
Newborn of HBsAg+/HBeAg+ mother	90%	
Newborn of HBsAg+/anti-HBe+ mother	15%	3
Infants 1-2 years old	50%	4
Infants 3-5 years old	23-28.6%	2, 5
Infants 18-24 years old	3%	6
Immunocompetent adults	<1%	7

Thus, most of the persons in the world with chronic HBV infection become infected in the early childhood.

Because of the inverse association between age and risk of chronic infection, persons infected as children assume a disproportionately large burden of morbidity and mortality attributable to HBV.

Up to 25 per cent of infants and older children who acquire HBV eventually develop HBV-related hepatocellular carcinoma (HCC) or cirrhosis. Adults who have had chronic HBV infection since childhood develop primary HCC at a rate of 5 percent per decade, which is 100-300 fold the rate among uninfected subjects.<sup>8</sup>

## MODES OF TRANSMISSION

HBV transmission may occur in several settings (Table 1-II). The infection is transmitted by percutaneous or mucosal exposure to infected blood or body fluids.



Table 1-II – Setting of HBV transmission.

- Perinatal/mother-to child
- Horizontal/child-to-child
- Household contact (non-sexual)
- Sexual
- Intravenous drug use
- Blood transfusion
- Beauty treatments (tattooing, piercing)
- Health care related:
  - > patient-to-provider
  - > patient-to-patient
  - > provider-to-patients

Table 1-III – Perinatal transmission of HBV.

Serological status of the mother	Risk of infection	Risk of developing chronic HBV infection
HBsAg+/HBeAg+	100%	90%
HBsAg+/anti-HBe+	20%	15%

Perinatal transmission from a chronically infected mother to her infant during delivery is very efficient. In utero transmission may occur, but it accounts for less than 2 per cent of perinatal transmission. The risk of perinatal transmission is virtually 100% if the mother is HBeAg-positive, but it falls to 20% in infants born to a HBeAg-negative mother<sup>3</sup> (Table 1-III). This pattern of transmission had a great impact in the Far East.

Horizontal transmission (child-to-child) occurs in situations of poor sanitation and overcrowding due to sharing of objects contaminated with infectious blood. It is the typical pattern of transmission in Central Africa and India. HBV is efficiently transmitted by sexual contact.<sup>9</sup> Nowadays the infection has mostly become a sexually transmitted disease in the western world, especially in case of occasional sexual intercourse without use of condom.

Injection drug users are at high risk for HBV infection because of behaviours such as sharing of needles, syringes, and other drug paraphernalia. Transmission of HBV via transfusion of blood products has been largely eliminated in most parts of the world by screening blood donors and implementing techniques that ensure viral inactivation of products made from blood,

such as factor concentrates.<sup>10</sup> In high-income countries the risk of acquiring HBV from a single unit of contaminated blood is between 1 in 31000 and 205,000.<sup>11</sup> In these areas the residual risk of HBV transmission is mainly related to blood donations negative for HBsAg that have been collected either during the pre-seroconversion “window period” (WP) defined as the time between infection and detection of a viral antigen or antibody marker, or during the late stages of infection.

In contrast, in underdeveloped countries, like sub-Saharan Africa, the risk of transfusion transmitted HBV is estimated to be much higher (4.3 infections per 1000 units<sup>12</sup>), as a consequence of factors such as the frequent use of paid or replacement donors and incomplete screening coverage.

The use of HBV nucleic acid testing (NAT) significantly reduces the window period and it may also detect occult HBV infection, supporting the long lasting clinical observation that HBsAg negative but anti-HBc positive blood could transmit HBV.

Beauty treatments (such as tattooing and piercing) play an important role in the spread of parenterally transmitted viral infections, including HBV. This practice is of growing diffusion, it involves all social classes and all age-groups, particularly young adults who are not covered by the vaccination campaigns against HBV.

Health care related transmission continues to be an important source of new HBV infections worldwide. Patient-to-provider, patient-to-patient, and provider-to-patient may all occur, even if to a different degree of extent. Patient-to-provider was very common before hepatitis B vaccine became available for health-care-workers. Following needle-stick exposure the risk of HBV infection was 30% with HBeAg-positive blood, but no more than 5% if blood was HBeAg negative.<sup>13</sup> Patient-to-patient transmission is very common in the developing world, as result of percutaneous exposure to contaminated equipment used for injections or other procedures, or from blood or mucosal exposure to contaminated medication. In the developed world, lapses in infection control

practice by health care may cause provider-to-provider HBV transmission. Implicated vehicles for transmission are multidose vials, finger-stick devices, acupuncture needles, and jet injection guns. Contaminated environmental surfaces also play a role particularly in dialysis units. Provider-to-patient HBV transmission is rare, but it may cause small outbreaks.

## GLOBAL PATTERN OF TRANSMISSION

The global epidemiology of HBV infection has traditionally been described according to three levels of endemicity (high, intermediate, and low) on the basis of the prevalence of HBsAg carriers in the general population. The degree of HBV endemicity correlates with the predominant mode of transmission.

Countries with high endemicity are considered those where HBsAg seroprevalence is equal or greater than 8%. Nearly 60% of the world's population lives in highly endemic areas, mainly represented by China, Indonesia, Far East and Central Africa.<sup>14</sup> In these areas perinatal and horizontal (from infected household members) are the predominant routes for HBV transmission.

Countries with intermediate endemicity have a seroprevalence of 2-7%. Middle East, India, South Asia, Eastern Europe and Turkey represent these areas, where a mix of perinatal, horizontal, sexual and health care related routes play a major role in the spread of HBV infection.

Finally, countries with low endemicity (Americas, and Western Europe) are those where seroprevalence is less than 2% and most infections are acquired sexually or through injecting drug use or are health care related (Table 1-IV).

## THE WORLDWIDE CHANGING EPIDEMIOLOGICAL PATTERN OF HBV

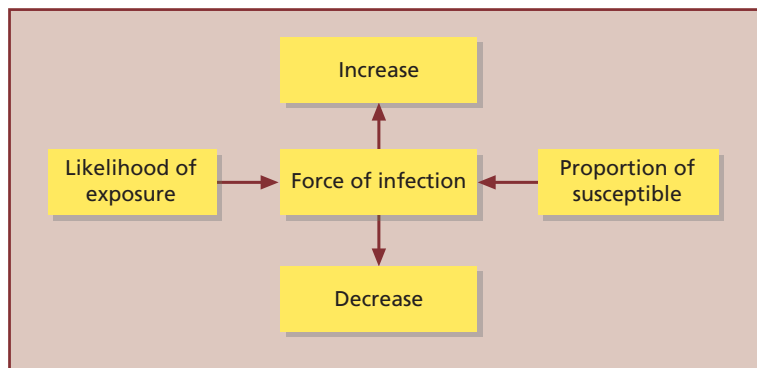
Over the last few decades important changes have occurred in the epidemiology of HBV infection in most areas of the world thanks to the combined effect of non-specific and specific preventive measures that have been adopted.

The force of a given infection (*i.e.* the likelihood of its spread in the community) depends on two factors: the risk of exposure to an infectious agent and the proportion of susceptible people in the community. The balance between these two factors influences the degree of spread of the infection (Figure 1.1). In the case of HBV infection both of these factors have operated. General improvements in quality of living standards and hygiene as well as the introduction of public health measures, such as blood screening for hepatitis virus infection, the use of universal precautions in the medical setting, health education for safe sexual behaviours, and avoidance of all potential risk behaviours for HBV infection all have played a crucial role. The availability of a safe and immunogenic vaccine against HB has further impacted the spread of the infection. By the end of 2008, 177 countries in the world have introduced hepatitis B vaccination into the national routine for neonatal, infant, and /or adolescent immunization programs. Countries that were early to adopt and implement universal infant hepatitis B immunization include Taiwan and Alaska (1984), the Gambia (1986), Italy (1991).

The implementation of vaccination programs has globally resulted in a marked decrease in disease burden, in the carrier state and in hepa-

Table 1-IV – Endemic levels of HBV infection.

Level (HBsAg prevalence in the general population)	Predominant modes of transmission	Geographical areas
High (>8%)	Perinatal/horizontal	Far East, Africa
Medium (2-7%)	Perinatal/horizontal Sexual/health care related	Middle East, Southern Asia, Eastern Europe, Turkey
Low (<2%)	Sexual/intravenous drug use Health care related	Americas, Western Europe



**FIGURE 1.1** Dynamic of a given infection in a general population.

titis B related morbidity and mortality. Taiwan is the best example of a highly endemic area with a substantial and measurable reduction in disease burdening resulting from a long-lasting policy of universal childhood hepatitis B vaccination. HBsAg seroprevalence among Taiwanese children decreased from 9.8% in 1984, the year when universal infant immunization began, to 0.7% in 1999.<sup>15</sup> Mortality from hepatocellular carcinoma decreased 60-70% among children between the period prior to the routine vaccination (1974-1983) and the post-vaccination era (1984-1999).<sup>16</sup>

Universal newborn immunization with hepatitis B vaccine was initiated in 1984 and has eliminated hepatocellular carcinoma (HCC) and acute symptomatic HBV infection among Alaska native children.<sup>17</sup> In fact, the incidence of acute symptomatic HBV infection in subjects <20 years of age fell from cases 19/100,000 in 1981-1982 to 0/100,000 in 1993-1994. No cases of acute HBV have occurred in children since 1992. The incidence of HCC in subjects <20 years decreased from 3/100,000 in 1984-1988 to zero in 1995-1999.<sup>17</sup> In the Gambia, children HBsAg prevalence has decreased from 10% to 0.6% since the introduction of routine infant and childhood vaccination in 1986.<sup>18</sup>

Italy is the best example of a country which has moved from a medium to a low endemic level over the past three decades thanks to the combined effect of non-specific and specific (*i.e.* comprehensive vaccination programme against hepatitis B) preventive measures.<sup>19</sup> The compre-

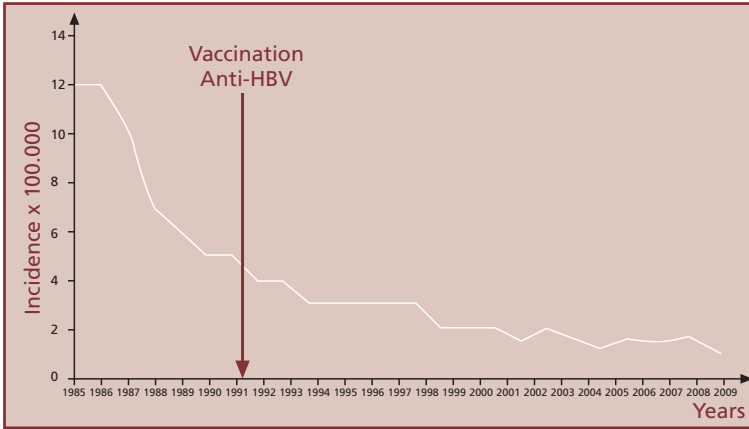
hensive immunization programme for 3-month-old infants and for 12-year-old subjects, introduced in 1991, further contributed to the downward trend of acute hepatitis B incidence (Figure 1.2), particularly in subjects 15-24 years old (Figure 1.3).

Improved sanitation and universal childhood hepatitis B vaccination have also affected the main modes of HBV transmission in the world.

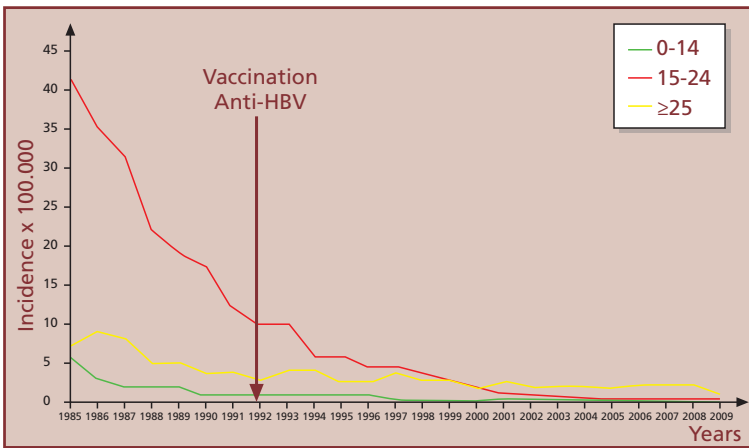
Perinatal and child-to-child transmission no longer play a role. Blood transfusion and intravenous drug use play a minor role than in the past. Health care related and sexual exposure continue to have a major role. Beauty treatments is a source of infection of increasing importance (Table 1-V).

Over the past decade some millions of people have moved from medium-high endemic areas (Eastern Europe, Far East, Central Africa) to Europe (mainly Germany, France, and Italy). This immigration flow may increase the spread of HBV in young adults by sexual route; but it is unlikely that will affect the rise of the carrier reservoir, provided the maintenance of a high coverage of childhood universal immunization in Europe both for naïve and immigrant subjects.

The global epidemiology of hepatitis B continues to evolve, mostly toward a strong decline in the burden of the disease. Nevertheless, the current global burden of HBV remains high, with about 2 million people exposed worldwide and about 350 million individuals with chronic infection.<sup>1</sup> Most of these subjects have acquired the infection in the past and they are at risk for



**FIGURE 1.2** Incidence (cases x 100,000) of acute hepatitis B in Italy, SEIEVA 1985-2009.



**FIGURE 1.3** Age-specific incidence of acute hepatitis B in Italy, SEIEVA 1985-2009.

progressive liver disease and liver cancer. Nowadays hepatitis B is estimated to be the cause of 30% of cirrhosis and 53% of HCC worldwide: an estimated 600,000 deaths each year can be attributed to HBV infection.<sup>20</sup> Several effective drugs against HBV are currently available; how-

ever, they are costly, particularly for developing world.

Although important progress has been made there still is a large void to be filled in the global reduction of HBV burden.

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**Table 1-V – Changing pattern in the modes of HBV transmission as consequence of improved sanitation and universal childhood hepatitis B vaccination.**

Mode of transmission	Past	Current
• Perinatal	+++	-
• Child to child	+++	-
• Household contact	+++	++
• Sexual	+++	+++
• Intravenous drug use	+++	+
• Blood transfusion	+++	+
• Beauty treatments	+	+++
• Health care related	+++	+++

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# NATURAL HISTORY OF CHRONIC HEPATITIS B VIRUS INFECTION AND DISEASE

# 2

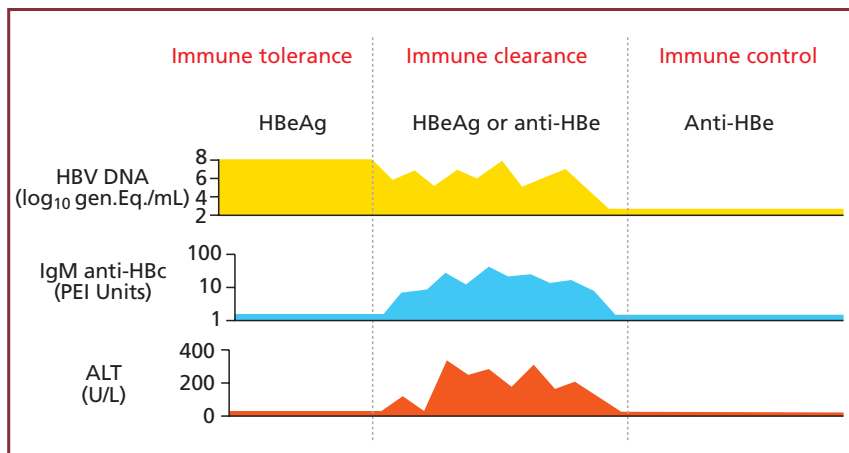
M.R. Brunetto, F. Bonino

Hepatitis B virus (HBV) is not directly cytopathic and florid viral replication may persist for years without significant liver disease because HBV is able to escape the host's immune system circulating a huge excess of its proteins, namely the surface antigen (hepatitis B surface antigen, HBsAg) and the secreted form of the nucleocapsid antigen, hepatitis B "e" antigen (HBeAg).<sup>1-3</sup>

Thus the natural histories of chronic HBV infection and chronic hepatitis B (CHB) are not synonymous and depend on the heterogeneity of the relations between virus, infected hepatocytes and antiviral immune response.<sup>4</sup> Liver necroinflammation occurs only when the immune system recognizes the presence of the virus and triggers an antiviral response aimed to eliminate the virus infected cells. Chronic HBV infection may run with a normal liver and it does not necessarily imply chronic hepatitis B, therefore it necessary to distinguish between chronic HBV infection and CHB.

## PHASES OF CHRONIC HBV INFECTION

Chronic HBV infection results from the ability of HBV to escape the surveillance and control of the immune system.<sup>1-3</sup> During the early phase of the infection viral replication is huge (millions of virions are released in 1 milliliter of the blood and the viral genome, HBV-DNA is detected at the highest levels). The viral nucleocapsidic antigen (HBcAg) can be stained by immune-histochemistry in the nuclei of the great majority (90%) of the hepatocytes, whereas HBsAg is detected on their membranes<sup>5</sup>. This phase of infection is named "immune tolerance" and is not associated with significant virus induced liver damage, liver histology being normal without evidence of necroinflammation (Figure 1). When the immune systems reacts recognizing the virus the antiviral response causes the transition from "immune tolerance" to the next phase, the "immune-elimination",



**FIGURE 2.1** Natural history of Chronic HBV Infection.

where the necro-inflammatory reaction is aimed to eliminate virus infected cells (Figure 2.1). A significant drop of the overexpression of the secretory form of the nucleocapsidic antigen, HBeAg, which is a major inducer of viral tolerance, is observed with the loss of tolerance.<sup>1-4</sup> HBeAg expression is modulated at both transcriptional and translational levels; factors such as cytokines, hormones, drugs, other viral infections and genetic mutations of the HBV genome may all cause a reduction or block of expression and/or secretion of the antigen.<sup>6</sup> The immune tolerance phase lasts longer when HBV infection is acquired at birth or immediately thereafter, particularly when children are born to HBeAg positive mothers since HBeAg crossed the placenta inducing immune tolerance into the fetus.<sup>7</sup> On the contrary the immune tolerance phase is short when HBV infection is acquired during adulthood at exclusion of subjects with reduced immune competence because of diseases and/or immune suppressive therapies.<sup>1-2</sup>

Once immune tolerance is lost liver necro-inflammation begins and it is usually characterized by remittent hepatitis episodes (indicated by elevations of serum levels of liver enzymes  $>5$  x normal values) which are mostly asymptomatic if they occur on previously normal liver. Symptomatic hepatitis with hyperbilirubinemia are more frequent in subjects with underlying liver damage. Thus, the loss of immune tolerance is associated with signs and/or symptoms of liver necro-inflammation (evidence of hepatitis at histology) which in the great majority of cases determines the progressive disappearance of circulating HBeAg and the appearance of its antibody, anti-HBe (seroconversion HBeAg/anti-HBe).<sup>1-3</sup> The yearly incidence of seroconversion varies from 2-15% depending on age, serum transaminases levels, and viral genotype (*i.e.* it is more frequent in patients infected with genotype B than C).<sup>3-4</sup> In highly endemic geographic areas where genotype B and C prevail such as Eastern Asia about 90% of children remain HBeAg positive until 10-15 years of age and 90% of HBeAg/anti-HBe seroconversions occur before the age of 40.<sup>3</sup> In

the Mediterranean basin where the prevalent infection is with HBV, genotype D most of HBsAg carriers present HBeAg/anti-HBe seroconversion before the age of 20.<sup>2</sup> If the antiviral immune response is effective leading to the control of viral replication it determines the transition from the immune-elimination phase to the phase of immune control or inactive infection (see Figure 2.1), which is characterized by the persistence of circulating HBsAg with very low HBV replication (serum HBV-DNA  $\leq 2000$  UI/mL), normal levels of transaminases, disappearance of histologic signs of hepatitis and intrahepatic HBcAg which is not stained anymore at immuno-histochemistry.<sup>1-3</sup> HBsAg may persist within hepatocytes (either focally or diffusely) because of the synthesis of defective forms of surface antigen which can not be secreted and are stored within the endoplasmic reticulum; the cytoplasm of HBsAg storing hepatocytes takes the typical translucent appearance at the usual histologic staining (H&H or Tricrome) and these cells are named *ground glass cells*.<sup>8</sup>

In chronic inactive HBsAg carriers HBV infection may persist indefinitely without new liver damage, however liver fibrosis and even inactive cirrhosis may remain as the scarring consequence of the necro-inflammatory damage which occurred during the previous immune-elimination phase. The chronic inactive HBsAg carrier represents the most frequent prototype of chronic HBV infection (at least in 60% of carriers) which occurs in about 450 millions people worldwide.<sup>9</sup> In this phase of inactive infection the immune system is able to control both viral replication and the transcription of viral genes modulating the activity of viral minicromosomes (circular, closed and coiled HBV-DNA or ccc-DNA) without causing any relevant cell damage.<sup>4</sup> The entity of such immune control on cccDNA and the progressive reduction of the number of infected hepatocytes cause the slow progressive fall of serum levels of HBsAg and its possible disappearance with the rise and positivity of anti-HBs antibody (HBsAg/anti-HBs seroconversion). The incidence of this event varies from 0.7-2.5%



yearly.<sup>4,9</sup> In absence of circulating HBsAg the presence of intrahepatic HBV-DNA with or without antibodies against viral antigens (anti-HBc and anti-HBs) characterizes the *occult* HBV carrier, a condition that is typical of the subjects who spontaneously recovered from an acute self limited acute hepatitis B.<sup>10</sup>

In subjects with normal liver histology both the conditions of chronic inactive HBsAg positive carrier and *occult* HBsAg negative carrier are not associated with CHB and in our geographic area, where HBV infection is mostly caused by genotype D, they do not determine higher risks of hepatocellular carcinoma (HCC); the HCC risk increases if these conditions are reached once irreversible liver damage as cirrhosis has already occurred.<sup>1-4,9</sup> In peoples from Asia and Africa the conditions of inactive HBsAg carrier and *occult* HBV carrier even if associated with normal liver histology are risk factors for HCC even if at lower levels than in cirrhotics: this is explained possibly by the infection with different HBV genotypes and the presence of other HCC cofactors such as aflatoxin.<sup>3,9</sup> HBV infection may reactivate in both chronic inactive HBsAg carriers and *occult* HBV carriers as a consequence of the reduction of the immune control which is induced by concurrent diseases or immune suppressive therapies. In fact the current guidelines foresee that these carriers have to be treated with pre-emptive antiviral drugs whenever immunosuppressive therapies (*i.e.* high dose corticosteroids, chemotherapies...) have to be undertaken and antiviral treatment should be kept for an adequate time (6-12 months) after immune reconstitution.<sup>11-12</sup>

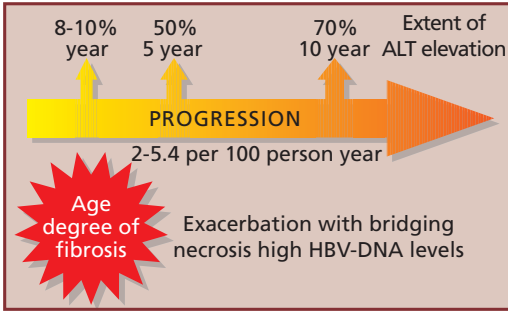
## **CHRONIC HBeAg POSITIVE HEPATITIS B**

In about 30-40% of chronic HBsAg carriers, the antiviral immune response which develops at the time of the loss of immune tolerance is unable to efficiently control HBV replication: this means that liver damage may continue indefinitely over time. Conventional hepatitis B which lasts longer than 6 months is defined as

chronic hepatitis (CHB). HBeAg positive CHB (type I) is characterized by circulating HBeAg and intermediate-high levels of HBV-DNA, elevated serum transaminases and presence of intrahepatic necro-inflammation<sup>1</sup>; viral antigens can be stained within the liver, HBeAg in the nuclei and HBsAg in the cytoplasm of the hepatocytes, but in a spotty fashion at variance from the diffuse staining pattern, which is typical of the immune tolerance phase<sup>5</sup>. If the immune system succeeds to effectively control HBV replication HBeAg/anti-HBe seroconversion occurs with the transition from chronic active hepatitis B to inactive HBV infection which means the recovery from CHB. Such an event happens in about 8-10% of patients per year and more frequently in subjects with higher biochemical activity (elevated serum transaminases). However, if biochemical activity persists at high levels over time without efficacy in controlling viral replication it causes the histologic evolution of liver disease with the development of *bridging necrosis* and the very high risk of transition to the cirrhotic phase (2-5.4 x 100 patients/yearly)<sup>1-2,9</sup> (Figure 2.2).

If HBeAg/anti-HBe seroconversion occurs in late stage, when the structural anatomy is altered with porto-central fibrotic bridges and vascular shunts the stage of irreversible cirrhosis is reached. At this time even the achievement of an inactive HBsAg carrier state (without significant HBV replication and with persistently normal serum transaminases and clearance of intrahepatic necro-inflammation) reduces but does not eliminate the risk of hepatocellular carcinoma. The persistence of a non effective attempt of controlling HBV replication also favours the progressive selection and emergence, within the viral quasispecies, of viral mutants which escape the immunologic pressure. Such mutants as the HBV variants which are unable to secrete HBeAg (HBeAg defective) may become the prevalent population within the viral quasispecies and cause the type II form of CHB, namely HBeAg negative, anti-HBe positive CHB which persist in 5-10% of the patients after HBeAg/anti-HBe seroconversion.<sup>2-4</sup>





**FIGURE 2.2** HBeAg/anti-HBe seroconversion/infection control.

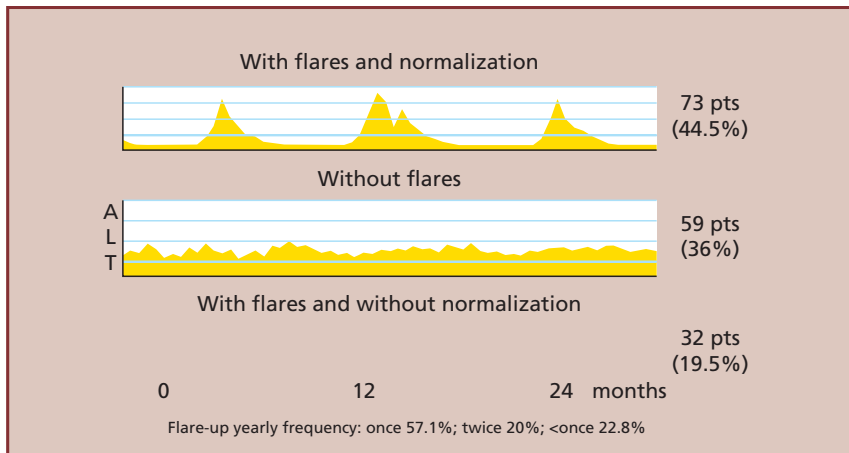
### CHRONIC HBeAg NEGATIVE, ANTI-HBE POSITIVE HEPATITIS B

This form of CHB (type II) is sustained by the infection and replication of a prevalent population of HBeAg defective HBV variants which harbour genetic mutations hampering or blocking the secretion of HBeAg.<sup>6,13</sup> Thus the disease is characterized by the absence of circulating HBeAg and the presence of anti-HBe antibody and active viral replication together with intrahepatic necro-inflammation. At immuno-histochemistry, viral antigens may be stained within the hepatocytes where HBeAg is detected focally in both nuclei and cytoplasm and HBsAg in cytoplasm.<sup>5</sup> In this condition the pathogenesis of CHB stems from the persistent “fighting” equilibrium between active HBV replication and active antiviral immune response which causes

inflammation but is unable to keep the virus under stable control. Type II causes about 85% of CHB in Italy and has become the prevalent CHB form worldwide, even in Asia,<sup>2,4</sup> mainly because of the aging of the HBV-infected population. In the Mediterranean area this disease runs most of its early time asymptotically (90% of cases), is diagnosed on average at the age of 35-40 years and reaches the stage of cirrhosis at histology at the mean age of 45 years; then 25% of the patients experience within 10 years the end stage complications of cirrhosis.<sup>2,13</sup> The viral and biochemical profiles of the disease vary and are often characterized by wild fluctuations of viral replication (serum HBV-DNA levels may fall well below the 2000 IU/mL cut-off) and serum transaminases may normalize<sup>13</sup> (Figure 2.3). In spite of transient and sometimes long lasting remissions (in average a few months) the spontaneous resolution of the disease with transition to the inactive carrier phase is a very rare events (<2%).<sup>9,13</sup>

### OUTCOME

During chronic HBV infection, chronic hepatitis B results from a virus-specific, but ineffective, control of viral replication by the host’s immune system which causes persistent intrahepatic necroinflammation; such a condition determines the progression of disease to cirrhosis and HCC.<sup>9</sup> The evolution of both



**FIGURE 2.3** Outcome of Chronic anti-HBe Positive Hepatitis B. Brunetto MR, J Hep 2002.

forms of CHB is determined by multiple factors, the most important of which is the entity of viral replication.<sup>9, 13-14</sup> In fact both cirrhosis and HCC occur more frequently and earlier in patients with high levels of viral load, independently from the presence of HBeAg.<sup>9, 14</sup> Other risk factors of disease progression, particularly for the HBeAg negative form are the entity and type of necroinflammation which condition the rate of fibrotic progression and correlate with the biochemical profiles of CHB (dynamics of serum transaminases). HBeAg negative CHB presents 3 typical and different biochemical profiles (see Figure 2.3): A) acute hepatitis like flares with intermittent normalizations (in about 45% of cases), B) persistent elevation of transaminases levels without exacerbations (35%), C) hepatitis exacerbations without intermittent normalizations (20% of cases).<sup>13</sup> The C profile, that is associated with the highest HBV-DNA levels, is the one at the highest risk for a quick disease progression to cirrhosis (within 6-10 years); in cases where cirrhosis is already present both profiles characterized by acute hepatitis like exacerbations (A and C) are associated with higher risks of higher rates of liver disease end stage complications such as terminal hepatic failure and HCC.<sup>9, 13</sup> The probability of the appearance of clinical symptoms of cirrhosis in CHB patients in 5 years from diagnosis is about 15-20%, with 4 times higher rate for high viraemic patients. The 5 years survival rate of the patients with evidence of cirrhosis, clinically compensated or decompensated is 85-86% and 15-30% respectively.<sup>9</sup> HBV hepatocarcinogenesis is a stepwise process and the incidence of HCC varies in different geographic areas because of the different impact of the host's genetics (*i.e.* race), viral heterogeneity (genotype and viral quasispecies) and of the environmental cofactors (*i.e.* aflatoxin in food).<sup>3, 9</sup> In white chronic HBsAg carriers from Europe and North-America the HCC incidence varies between 1-13 per 100.000 inhabitants, whereas rises up to 250 in Alaska and 600 in Asia. In Europe the 5 years HCC incidence in cirrhotics is about 10% with 2% year rate; in Asia is 17%.<sup>9</sup>

## HOW TO DIFFERENTIATE THE PHASES OF CHRONIC HBV INFECTION AND DISEASE

Two of the 3 phases of chronic HBV infection are not associated with significant virus induced liver damage: HBeAg positive immune tolerance and HBeAg negative/anti-HBe positive inactive (inactive chronic HBsAg carrier) phases. In both of these conditions, that are characterized by the absence of significant necro-inflammation caused by viral replication (very high in the former and residual in the latter) there is not any indication for antiviral therapy. Thus these two phases of HBV infection without virus induced liver disease have to be distinguished from the immune elimination phase which may be associated with a progressive evolution of liver damage (HBeAg positive or HBeAg negative/anti-HBe positive CHB). Since CHB is mostly asymptomatic and may present periods of normalization of liver enzymes its diagnosis is based exclusively on specific HBV markers.<sup>12</sup> During the HBeAg positive infection the most important diagnostic task is to distinguish between the immune tolerance from HBeAg positive CHB. Usually this is not very difficult since immune tolerance is associated with the highest levels of all HBV markers, HBV-DNA, HBsAg and HBeAg and normal serum transaminase levels which are very rarely normal in HBeAg positive CHB. However, problems come when liver damage is induced by non-viral causes and the elevation of liver enzymes can be mistaken for CHB. In such a case a liver biopsy with the immuno-histochemical staining of viral antigen helps to make the appropriate diagnosis by the identification of the typical *pattern* of immune elimination and CHB, namely the staining of HBcAg in the nuclei of some hepatocytes and cytoplasmic HBsAg which differs from the one characteristic of immune tolerance phase (diffuse HBcAg staining in the nuclei of 90% of hepatocytes with HBsAg on liver cell membranes in the typical *honeycomb* fashion).<sup>5</sup> In addition, the specificity of diagnosis of chronic hepatitis B is confirmed by detection of IgM anti-HBc in serum (>5 IU PEI) which are absent in the immune tolerance phase

(see Figure 2.1). However, commercial assays for detection of IgM anti-HBc, in spite of having a high analytical sensitivity, are set for using the artificial cut-offs (>600 UI PEI) aimed to diagnosis primary acute hepatitis B, this implies the use of different cut-offs for detection of low levels of this antibody associated with CHB.<sup>4</sup>

The differential diagnosis between the HBeAg negative/anti-HBe positive CHB and the chronic inactive HBsAg carrier is much more difficult because type II CHB is characterized, in a significant proportion of patients, by frequent periods of normalization of liver enzymes<sup>13</sup> and in addition serum HBV-DNA levels are usually lower than in the HBeAg positive form (see Figure 2.1) and may fluctuate widely and remain for a long time below the conventional cut-off proposed in guide lines for diagnosis of the inactive HBsAg carrier ( $\leq 2000$  IU/mL).<sup>12</sup> Thus using quantitative HBV-DNA as a single diagnostic tool there is need for long-term monitoring (12 months) with multiple repeated tests of viral load.<sup>12</sup> Differential diagnosis between type II CHB and the inactive HBsAg carrier can be ameliorated with a significant reduction of costs if quantification of HBV-DNA is combined with that of serum HBsAg. Recent data on HBsAg carriers infected with genotype D HBV and followed for more than one year with monthly tests demonstrated that the cut-offs of 2000 IU/mL for HBV-DNA and 1000 IU/mL for HBsAg represent the most specific and sensitive tool to distinguish asymptomatic HBeAg negative/anti-HBe positive CHB from the inactive HBsAg carrier.<sup>15</sup>

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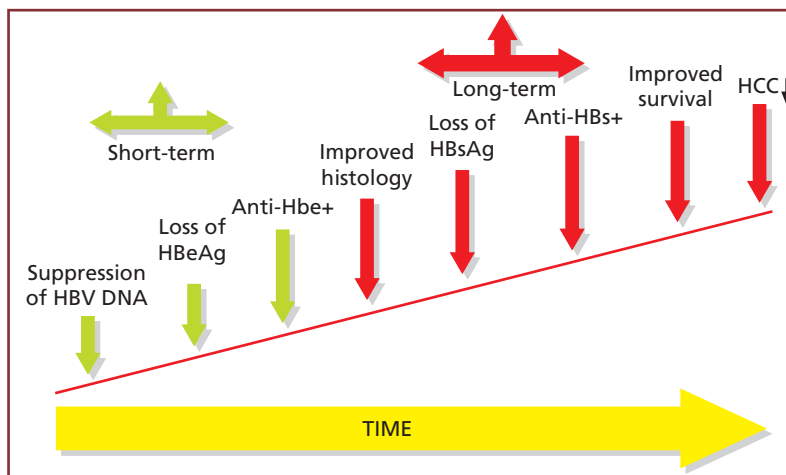
# STANDARD THERAPY FOR CHRONIC HEPATITIS B

# 3

A. Smedile, M.L. Abate, G.P. Caviglia

The hepatitis B virus (HBV) remains the second greatest cause of chronic viral hepatitis in Italy and worldwide besides the general implementation and positive effect of vaccination against HBV. The estimated number of HBV infections in the world is of 450,000,000 with a high prevalence rate in the Far East (China, India, Vietnam) and East Europe (Russia, Romania, Turkey). In Italy, and in the Mediterranean countries the rate HBV infection is in reduction with a recent figure 900,000 of HBV positive carriers in Italy. Chronic hepatitis B is the result of an acute hepatitis, unresolved. The impaired immunological response and the persistence of the virus are the two major triggers inducing necroinflammation and fibrosis leading to cirrhosis and hepatocellular carcinoma. Persistence of infection with high levels of replication (HBV-DNA >20000 UI/mL) and abnormal ALT, are parameters used for the diagnosis and monitoring of the progression of liver disease.<sup>1</sup>

There are two types of chronic hepatitis B; the HBeAg positive chronic hepatitis and the anti-HBe positive chronic hepatitis. These two conditions are different in many ways such as virology status, demographics and disease severity. The most prevalent form of chronic hepatitis B in domestic patients is the anti-HBe positive type. This condition usually affects patients with a longer duration of disease with fluctuating levels of viral replication and flares of liver enzymes is characterized by the selection and detection of HBV mutants (pre-core/BCP) prevailing over the wild type virus. By contrast, in young HBV immigrants, recently infected, the wild type virus is dominant.<sup>2</sup> The major goal of an antiviral therapy is to prevent the evolution of chronic hepatitis to cirrhosis and in cirrhotic patients to prevent complications. There are endpoints which can be achieved in short-term (6-12 months) of successful therapy such as seroconversion



**FIGURE 3.1** Therapeutic endpoints over time.

Table 3-1 – Outcome following HBeAg Seroconversion.

HBeAg seroconversion	<ul style="list-style-type: none"> <li>• Disease remission (↓ HBV DNA; ↓ ALT)</li> <li>• HBsAg loss/seroconversion</li> <li>• Prevention of HCC</li> <li>• Increased survival</li> </ul>
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from HBeAg status to anti-HBe positive antibody, ALT normalization and HBV-DNA negativization. The long-term goals (reduction of fibrosis, cirrhosis and complications) require years of prolonged therapy (Figure 3.1). The seroconversion event in patients with HBeAg-positive CAH is considered extremely relevant to the final outcome of liver disease (Table 3-1). In the anti-HBe positive chronic hepatitis B, the objective of therapy is to achieve reduction of inflammation by total suppression of HBV replication (HBV-DNA <12 IU/mL or HBV-DNA inhibition to inactive carrier status <2000 IU/mL). The suppression of the replication activity is usually followed by the stabilization and even the regression of fibrosis in the liver over time.<sup>3</sup> In this case, therapy with a definite course of Inteferon alpha 2a (alpha-2a IFN), of at least 12 months, should produce a seroconversion from HBsAg positive to anti-HBs antibody. In the case of antiviral therapy with nucleos(t)ide analogues (NUCs) the suppression of HBV-DNA is mandatory lifelong, since the interruption of therapy is followed by a rapid relapse due to the reactivation of the virus occurred in the liver.

Remarkable advances have been made in the cure of chronic hepatitis B with antiviral therapy. The reason for that resides on a better understanding of the different phases (I, II, III, IV) of HBV infection, new molecular and serological assays for diagnosis and monitoring liver disease and primarily the use of NUCs. These are oral drugs that since their approval in 1998, started to replace almost completely the use of the old therapy based on standard Interferon and the Pegylated formulation (Peg-IFN).<sup>4</sup>

## CLINICAL GUIDELINES FOR HBV THERAPY

In recent years Hepatology Societies (AASLD, EASL, AISF) have formulated and updated guidelines in order to help physicians in the current management of chronic hepatitis B (Figure 3.2).<sup>5-7</sup> The reason for that was the rapid evolving spectrum of new drugs and strategies becoming available in the last years. The introduction of NUCs in 1998, with lamivudine (LAM) as the prototype of this new class of drugs for the oral therapy of chronic hepatitis B, was a revolution in the field. Several others drugs such as Adefovir, Telbivudine (second generation) and Entecavir, Tenofovir (third generation) were introduced, increasingly potent and effective in inducing total suppression of HBV replication and in abating the rate of drug-resistance almost to null.

## PATIENTS CANDIDATES

The patients to be considered for therapy are those HBV infected with an active liver disease diagnosed using HBV-DNA levels (HBV-DNA >20000 IU/mL), abnormal liver enzymes and a significant degree of fibrosis (Ishak >S3) by liver biopsy or indirect methods (liver elastometry, LE ≥8KPa). Inactive HBV carriers defined by persistent normal liver enzymes with no replication or low HBV-DNA (<2000 IU/mL), low levels of HBsAg (<1000 IU/mL) and LE <5-7 KPa should not be treated but, monitored and followed over time.<sup>8</sup>

## CHRONIC HEPATITIS B/ HBeAg POSITIVE TYPE

In the past Interferon alpha therapy was the only drug available for the treatment of chronic hepatitis B. Today we also have a wide spectrum of NUCs, all used in this form of chronic hepatitis. Patients with CAH /HBeAg positive considered for treatment, must have: HBV-DNA >20000 IU/mL, HBeAg positive over 6 months, and ALT elevations. In Italian guidelines Inteferon therapy for a definite period of 12 months is recommended as the first line drug with the objective to accelerate the spontane-

Fibrosis	Hepatitis				Cirrhosis	Decompensated cirrhosis
	No	Mild	Moderate	Severe		
METAVIR	FO	F1	F2	F3	F4	
Ishak's	SO	S1-2	S3	S4	S5-6	
	PEG IFN			INDEFINITE Treatment with NAs		
Necroinflamm. activity	>A2 (METAVIR)			ANY		
HBVDNA:	>2000 UI/mL			>15 UI/mL		
ALT:	>UNL			ANY ALT		
	Consider treatment			Treat		

**FIGURE 3.2** The “Stresa Paradigm” summarizing the indications for treatment of patients with HBeAg negative hepatitis B with or without cirrhosis. NA: nucleoside/tide analogues. Treatment of chronic hepatitis B; Update of the recommendations from the 2007 Italian Workshop\* G. Carosi *et al.* /Digestive 2001;40:259-65.

ous seroconversion to anti-HBe positive. In the past, results with standard Interferon therapy were disappointing with a high rate of relapse.<sup>9</sup> With the use of Pegylated-IFN, Lau and coworkers obtained a rate of seroconversion between 30-52% according to different genotypes; genotype D being the most unfavourable (30%). The sustained virologic response and maintenance of anti-HBe seroconversion was stable after 12 months post-therapy.<sup>10</sup> In these patients it is not unusual however, to have a reversion to HBeAg positivity during the follow-up due to an unstable seroconversion.<sup>11</sup> For this reason it is recommended to stop therapy after 6-12 months to stabilize the seroconversion. Predictors of response are elevated ALT (>5 NV), HBV-DNA >20000,000 IU/mL prior therapy, Genotype HBV-A and HBV-B (Table 3-II).<sup>12</sup>

In case the patients do not respond to IFN, develop side effects during therapy or are intolerant to the therapy, NUCs are the second choice of therapy. In other guidelines NUCs are considered as a first choice.

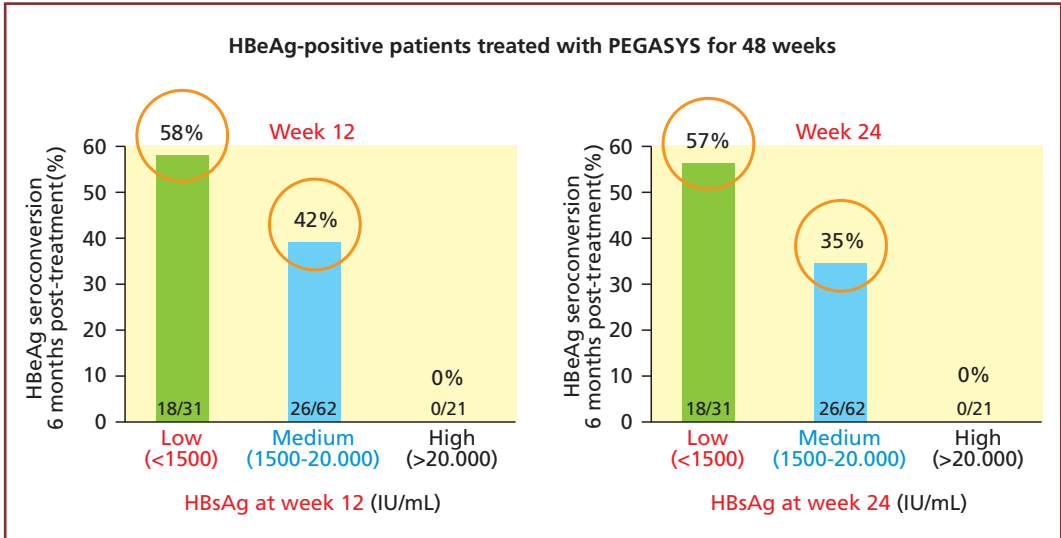
In this type of chronic hepatitis the therapy with NUCs is definite in time, usually 12 months, until the loss of HBeAg and the appearance of anti-HBe antibody. If the patients at histology show a moderate fibrosis (Metavir >F2 and Ishak >S3) or severe fibrosis (Metavir >F3 or Ishak >S4) therapy with NUCs should be considered indefinite in order to completely inhibit the virus. The drug to be used are those with potent antiviral effect such as Entecavir 0.5 mg/die or tenofovir 245 mg/die, adefovir and lamivudine are not indicated because of the risk of developing viral resistance. Monotherapy with NUCs

**Table 3-II – Factors to predict response to PEG-IFN in chronic HBV infection.**

HBeAg positive cases (542 patients Pegasys 180 ug/wk, 48 wk; 266 patient Pegintron 100 ug/wk, 52 wk): better response if

- Female gender
- Younger age
- Lower weight
- HBV genotype A and B
- Lower HBV-DNA
- Higher ALT
- Naive for IFN





**FIGURE 3.3** Low on-treatment HBsAg levels are associated with higher rates of sustained immune control. Gane *et al.* EASL 2011.

is recommended for 12 months until the seroconversion to anti-HBe positive antibody, ALT normalization and HBV-DNA clearance. After 5 years of Entecavir and Tenofovir, the rate of seroconversion from HBeAg to anti-HBe positive was obtained in 50 % and 26% respectively.<sup>13, 14</sup>

## OBJECTIVES AND MONITORING

Overall the clearance of HBsAg with or without the appearance of anti-HBs antibody is considered a surrogate marker of “cure”. This is more evident with IFN therapy (at 5 years 16%) while with NUCs is a rare event (1%), increasing with the duration of therapy.

During therapy with Peg-IFN in HBeAg-positive patients the evaluation of HBV-DNA levels and the quantitation of HBsAg at week 12 and week 24 may predict immune response to therapy (HBeAg seroconversion 6 months post-therapy). In fact, sustained immune control was achieved respectively in 58% and 42% (week 12) and 57% and 35% (week 24) in those with low (<1500) or medium (1500-20000 IU/mL) HBsAg levels at that time point. No immune control was obtained in those with high levels of HBsAg (>20000 IU/mL) (Figure

3.3). In this case therapy should be stopped.<sup>15</sup> The objective of therapy is also to reduce the levels of viremia <2000 IU/mL (inactive carrier) after 12 months of therapy. Patients should then be monitored every 3 and 6 months by testing HBV-DNA and ALT levels. HBeAg and anti-HBe antibody should be assayed every 24 and 48 months.

During NUCs therapy with potent drugs (Entecavir and Tenofovir) the monitoring of HBV-DNA suppression is recommended every 3 months and every 6 months respectively using sensitive PCR assays (HBV-DNA <12 IU/mL). Serological monitoring for the HBeAg/anti-HBe status should be evaluated every 12 months in order to assess stopping therapy.

## CHRONIC HEPATITIS B/ANTI-HBE POSITIVE TYPE

This type of chronic hepatitis B is prevalent in the Mediterranean countries.<sup>16</sup> In Italy there is a cohort of old infected patients that could benefit from the treatment.

The decision to treat these patients is based on histology findings because the degree of fibrosis is determinant to promote progression to cirrho-

sis. Liver biopsy is recommended in the Italian guidelines, because for chronic hepatitis B, liver elastometry is not enough accurate compared for liver biopsy.<sup>17</sup> Patients eligible to therapy are those in phase IV with fluctuating liver enzymes, HBV-DNA >20000 IU/mL and fibrosis (Metavir >F2, Ishak >S3); therapy should be recommended also in patients with normal or borderline enzymes. These patients, with less degree of fibrosis (Metavir <F2, Ishak <S3), could be monitored delaying the therapy or treated with Peg-IFN if there is a concomitant necroinflammatory activity (grading >A2 Metavir score).

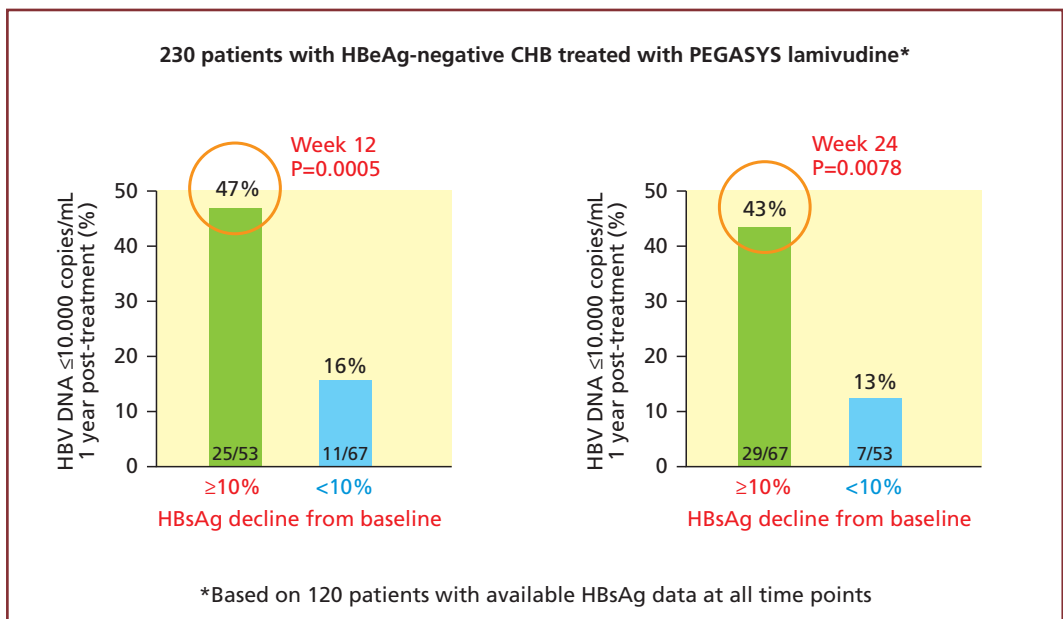
Therapy strategies for these type of chronic hepatitis is similar to HBeAg-positive patients. A definite course of Peg-IFN therapy if patient still naïve to the cytokine or a lifetime course with potent NUCs. The time of initiation of therapy could be deferred in those patients with less fibrosis but is mandatory in case of significant fibrosis (Ishak S4).

Drugs to be used are Entecavir and Tenofovir, the most potent antivirals with a low or almost null rate of HBV resistance.<sup>18, 19</sup> Telbivudine monotherapy could be con-

sidered for those patients with lower HBV-DNA levels (<2,000,000 IU/mL).<sup>20</sup> A recent study using a combination protocol with Entecavir+Tenofovir suggests that there is no advantage in patients with CAH /anti-HBe positive, by contrast this combination was significant in term of HBV-DNA suppression in patients with CAH/HBeAg-positive with high levels of HBV-DNA at baseline.<sup>21</sup>

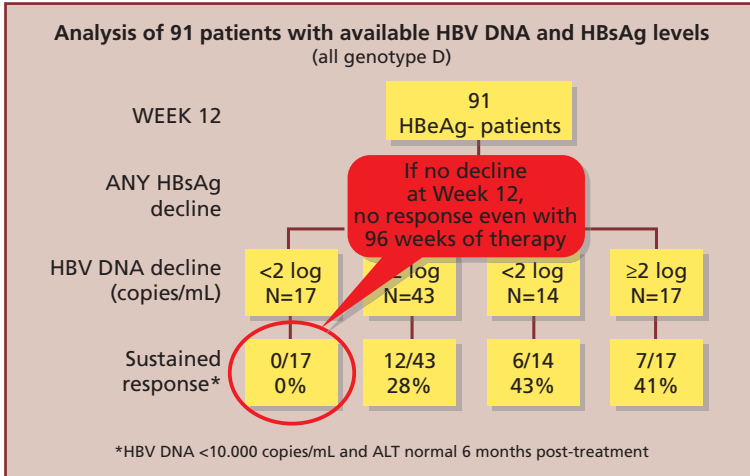
## OBJECTIVES AND MONITORING

In patients with chronic hepatitis anti-HBe positive type, naïve, undergoing treatment with Peg-IFN it is important to identify responsive patients from non-responder in order to reduce side effects. For this reason a major effort has been made to formulate stopping rules during the course of therapy. Marcellin and coworkers report that in 230 patients with HBeAg-negative CHB treated with Pegasys+LAM (qHBsAg available from 120 pts), the sustained immune control (HBV-DNA <10000 IU/mL after 6 months of therapy) was obtained at week 12 in 47% of those who had a decline of qHBsAg



**FIGURE 3.4** HBsAg decline is significantly associated with sustained immune control. Marcellin *et al.* APASL 2010.





**FIGURE 3.5** Independent study confirms findings: Pooled analyses of PEGASYS PegBeLiver and Phase 3. Rijckborst/Lampertico *et al.* APA-SLD 2010.

greater than 10% compared to 16% of those with a decrease less than 10%. At week 24, SVR was achieved in 43% *vs* 13% of those in whom HBsAg decline from baseline was greater than >10% (Figure 3.4).<sup>22</sup> Another analysis confirmed this finding by pooling data from the Pegasys PegBeLiver and Phase 3 study (Lampertico and coworkers).<sup>23</sup> The analysis with available HBV-DNA and HBsAg levels (all genotype D) demonstrated that if there is no at week 12 of HBsAg and HBV-DNA >2 log decline, no response could be obtained even with 96 weeks of therapy (Figure 3.5). By using only qHBsAg decline Lampertico *et al.*, suggest that at week 24 qHBsAg titers >7500 IU/mL had a high negative predictive value (NPV) while qHBsAg <1000 IU/mL at week 48 could be used to identify a subgroup of patients that might benefit from longer duration of therapy. In fact SVR was obtained in 25% after 48 weeks *vs* 80% with 96 weeks (Table 3-III).<sup>24</sup>

The end-points of therapy are ALT normali-

zation, HBV-DNA levels <2000 IU/mL (inactive carrier) at the end of treatment and after 6 months after stopping therapy (SVR). In genotype D patients this is achieved and maintained after 5 years in about 16% of patients; in those who achieved an inactive carriership the clearance of HBsAg is about 70%.<sup>25</sup> HBV-genotype A and B are more favourable for this event, thus explaining the discrepancy in interpreting results of standard IFN therapy obtained in the USA and Far East.<sup>26</sup>

**PRIMARY NON RESPONSE (PNR), PARTIAL RESPONDER (PR), BREAKTHROUGH (BK)**

The definition of primary non response during therapy with NUCs is the failure to obtain a reduction of 1 log at 3 months compared to the basal value. Partial responder is defined by the presence of HBV-DNA at 6 months during therapy with LAM and Telbivudine or 12 months of therapy with potent NUCs such as Tenofovir, Entecavir and Adefovir. The definition of virologic breakthrough is related to the increase of HBV-DNA greater than 1 log compared to the nadir value, observed during therapy in a patient with good compliance to the therapy and confirmed after 1 month. In case of PNR, PR and BK it is necessary to consider an alternative (optional) therapy.

**Table 3-III – Peg-IFN in HBeAg-neg patients New Stopping rule at week 24-48.**

qHBsAg>7500 IU/mL at week 24 (High NPV)
qHBsAg<1000 IU/mL at week 48
SVR Peg-IFN 48 (2/8: 25%) <i>vs</i> 96 (8/19:80%)
Lampertico, EASL 2012

Table 3-IV – Antiviral HBV drug resistance: treatment recommendations.

Resistant drug	Rescue therapy
LAM-R	add TDF
ADV-R	<ul style="list-style-type: none"> <li>• N236T: switch to TDF and add LAM or LdT or ETV or switch to TDF/FTC</li> <li>• A181T/V: switch TDF and add ETV or switch to TDF/FTC</li> </ul>
ETV-R	add TDF
Ldt-R	add TDF
TDF-R??	add ETV, LdT, LDV or FTC
EASL Guidelines. J. Hepatol 2009; Italian Guidelines-Update 2011	

All the guidelines recommend to stop therapy if indication was inappropriate (mild fibrosis), consider Peg-IFN in naïve subjects, change drug with a second line option, consider combination of drugs.

The choice is influenced by the primary drug used and by the pattern of mutations selected during therapy. If this is the case it is important to define the resistance profile in order to make the right choice of the alternative drug to avoid cross-reactions. Unfortunately it is not unusual to deal with patients with multidrug resistance because of the sequential use of monotherapy with NUCs (Table 3-IV).

## HBV CIRRHOSIS

Therapy with NUCs is mandatory in patients with cirrhosis because a pilot study clearly demonstrated the benefit to this category of patients when they were treated with LAM therapy. Clinical events in compensated cirrhotic patients were significantly reduced in patients treated with LAM compared to placebo and even those who developed BK did better than patients included in the placebo arm.<sup>27</sup> This milestone study was the beginning of therapy for compensated and decompensated HBV cirrhosis. All patients with cirrhosis should be treated even with low levels of HBV DNA (<200 IU/mL) and normal ALT. The therapy is urgent in those with initial signs of decompensation.

All guidelines recommend the use of NUCs in patients with compensated cirrhosis HBeAg-positive/anti-HBe positive. The use of Peg-IFN is very limited because of the risk of decompensation. A special category are young cirrhotics,

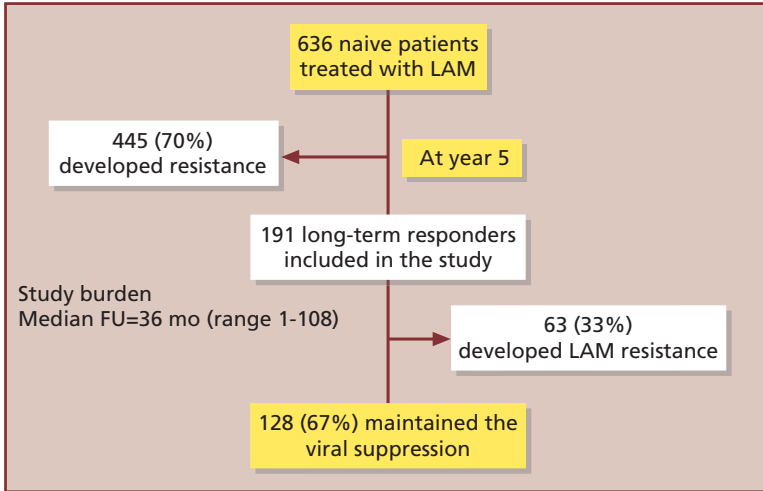
HBeAg positive, genotype non-D, HBV-DNA <2,000,000 IU/mL, abnormal ALT, without portal hypertension that could be considered for a finite course of IFN-Peg, but caution is required. In the prevalent cases of cirrhosis the monotherapy with Entecavir or Tenofovir is recommended.

## LAMIVUDINE/CIRRHOSIS

Lamivudine monotherapy was the historical drug used in this category of patients but, it is today obsolete with the potent new drugs with null risk of resistance. However, there is a small cohort (20%) of CAH/ cirrhotic patients long-term responder (>15 years) still maintaining an efficacious HBV-DNA suppression (Figure 3.6).<sup>28</sup>

In decompensated cirrhotic patients the original studies used LAM and Adefovir monotherapy; in LAM-R adefovir was added with good or partial efficacy.<sup>29</sup> In the transplant setting results were more relevant, even with the second generation drugs, because they allowed the reduction of HBV replication prior to OLT at levels which were considered safe for transplantation.<sup>30</sup> In some cases the amelioration of liver failure scores (Child-Pough, MELD) was so impressive that patients were removed from the waiting list.<sup>31</sup>

Nowadays all decompensated cirrhotic patients are treated prior to OLT with third generation NUCs (Entecavir and Tenofovir) followed by combination with HB-Ig prophylaxis in the post-transplant. This strategy was rewarded by the lowest risk of reinfection and HBV recurrence after OLT (0-5%).<sup>32</sup> There is hope in the future to consider stopping HB-Ig prophylaxis to reduce cost.<sup>33</sup>



**FIGURE 3.6** Long-term outcome of LAM treated CHB patients for over 5 years. Fasano *et al.*, *J. Hepatol* 2012.

## ENTECAVIR: EFFICACY OF LONG-TERM STUDIES

The registration studies with Entecavir in chronic hepatitis B either HBeAg positive or anti-HBe positive have now reached more than 5 years of follow-up.<sup>34,35</sup> The efficacy of the drug is very good with a rate of HBV-DNA inhibition reaching 94% and ALT normalization 86%. The most important data were reported from the analysis of 348 paired liver biopsies before treatment and 5 years. The histological findings were striking, in fact it was demonstrated in 96% of paired liver biopsies either improvement (>1 unit decrease in fibrosis score) or no change at year 5.

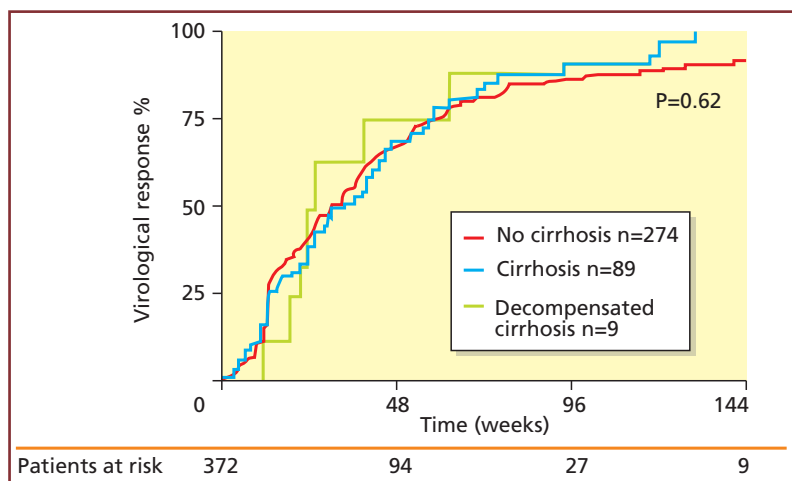
Cirrhosis regression occurred in 74% of patients with cirrhosis at baseline. Drug-resistance rate at 5 years is 0.5% suggesting good tolerability and safety.<sup>36</sup>

Since the introduction of Entecavir in the practical field, many patients naïve or experienced were treated worldwide. We report data from the Italian Cohort of Chronic HBV carriers in which 348 patients were included. Results at 48 months were excellent with 99% of HBV-DNA inhibition.<sup>37</sup> In the study by the Virgil Surveillance Study Group, Entecavir in CAH/cirrhosis reduced significantly the risk of cirrhosis and cirrhosis decompensation (Figure 3.7).<sup>38</sup>

## TENOFOVIR: EFFICACY OF LONG-TERM STUDIES

The registration study with Tenofovir in chronic hepatitis B either HBeAg or anti-HBe positive have now reached more than 5 years.<sup>39,40</sup> The efficacy is excellent, HBV-DNA inhibition in 98%. No drug-resistance so far.

In Europe there are three large cohorts of chronic/experienced HBV treated patients. The first cohort by Lampertico and coworkers consist of 302 patients (80% HBeAg negative, 35% cirrhosis, 43% with concomitant disease, 61 patients HBeAg positive). The mean follow-up is of 36 months. HBV-DNA remission was obtained in 86% of HBeAg positive, 98% of anti-HBe positive, ALT normalization in 83% of cases, 33% of HBeAg seroconversion. Renal impairment was negligible with 3% of Tenofovir dose reduction.<sup>41</sup> In the second cohort, followed in Germany by Petersen and coworkers, 183 naïve CAH patients and 217 experienced were included. HBeAg seroconversion was obtained in 17% at 12 months, HBV-DNA was undetectable in 87% of HBeAg positive and 91% of anti-HBe-positive patients. Clearance of HBsAg was reported in 6.7% at 12 months and safety was good.<sup>42</sup> In the French study by Marcellin and coworkers 441 patients naïve and experienced were treated. Results at 48 months suggest that



**FIGURE 3.7** Entecavir: Clinical outcome in CAH with cirrhosis (VIRGIL Surveillance Study Group). Zoutendijk *et al.*, *J. Gut* 2012.

94% of anti-HBe positive patients were negative for HBV-DNA and 80% of those HBeAg positive. The control of HBV-DNA viremia was good (93%) and comparable in patients with and without mild renal impairment at baseline.<sup>43</sup>

## CONCLUSIONS

The success of therapy for chronic hepatitis B is remarkable. Today chronic hepatitis B is curable, with improvement in life quality, morbidity and mortality. The prevention of fibrosis progression, cirrhosis development and complications were long-term objectives that have become real with a good management of therapy. The hope is also to prevent HCC development which still remain a great risk for cirrhotic patients. The final goal of therapy is the HBsAg clearance and the seroconversion to anti-HBs, this event is rare with NUCs while it is more efficient with the immunostimulation of IFN. Thus a tailored and personalized therapy based on patients characteristics, liver disease activity and virus phases of infection should be recommended to plan a successful strategy.

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