Academic Journal of Life Sciences
ISSN(e): 2415-2137, ISSN(p): 2415-5217
Vol. 3, No. 7, pp: 36-46, 2017
URL: http://arpgweb.com/?ic=journal&journal=18&info=aims

Hepatitis B Virus and Immunity

Obeagu Emmanuel Ifeanyi* Diagnostic Laboratory Unit,Department of University Health Services,Michael Okpara University of Agriculture,Umudike,Abia State,Nigeria

Obeagu Getrude Uzoma Department of Nursing Science,Ebonyi State University,Abakaliki,Nigeria

Abstract: Hepatitis B is one of the most common infectious diseases of the liver in the world and a major public health problem. The predominant routes of transmission vary according to the endemicity of HBV infection. In areas of high endemicity, perinatal transmission is the main rout of transmission, where as in areas of low endemicity, sexual contact amongst high-risk adults is predominant. All three coat proteins of HBV contain HBsAg, which is highly immunogenic and induces anti-HBs. The stability of HBV does not always coincide with that of HBsAg. Exposure to ether, acid (pH 2.4 for at least 6 hrs) and heat (98°C for 1 min; 60°C for 10 hrs) does not destroy immunogenicity or antigenicity. Antigenicity and probably infectivity are destroyed after exposure of HBsAg to 0.25% sodium hypochlorite for 3 minutes. Infectivity is lost after autoclaving at 121°C for 20 min or dry heat treatment at 160°C for 1hr. HBV occurs worldwide. The highest rates of HBsAg carrier rates are found in developing countries with primitive or limited medical facilities .In areas of Africa and Asia, widespread infection may occur in infancy and childhood. The overall HBsAg carrier rates may be 10 to 15%.The prevalence is lowest in countries with the highest standards of living, such as Great Britain, Canada, United States, Scandinavia, and some other European Nations. During HBV infection, the host immune response causes both hepatocellular damage and viral clearance. Innate immunity generally plays a role immediately after infection to limit the spread of the pathogen and initiate efficient development of an adaptive immune response. Innate immune response during the early phases of viral infections are mainly characterized by the production of type 1 interferon (IFN) α-/β cytokines and the activation of natural killer (NK) cells.

Keywords: Hepatitis; Hepatitis B virus; Immunity.

1. Introduction

Hepatitis B is one of the most common infectious diseases of the liver in the world and a major public health problem. The virus is transmitted by direct injection into the bloodstream (through any method of injection under the skin). The predominant routes of transmission vary according to the endemicity of HBV infection. In areas of high endemicity, perinatal transmission is the main rout of transmission, where as in areas of low endemicity, sexual contact amongst high-risk adults is predominant. HBV is a DNA – containing virus which is capable of infecting human liver cells and other cells in the body, once it gains access to the blood stream. One of the interesting features of the hepatitis B virus is that the virus itself does not damage the liver, the damage being caused by the individuals, s own immune system attacking the virus-infected cells [1]. The virus has complex life cycle. Hepatitis B is one of a few known non-retroviral viruses which use reverse transcription as a part of its replication process .The virus gains entry into the cell by binding to an unknown receptor on the surface of the cell and enters it by endocytosis. Because the virus multiples via RNA made by a host enzyme, the viral genomic DNA has to be transferred to the cell nucleus by host proteins called chaperones. The partially double stranded viral DNA is then made fully double stranded and transformed into covalently closed circular DNA (cccDNA) that serves as a template for transcription of four viral mRNAs. The largest mRNA, (which is longer than the viral genome), is used to make the new copies of the genome and to make the capsid core protein and the viral DNA polymerase. These four viral transcripts undergo additional processing and go on to form progeny virions which are released from the cell or returned to the nucleus and re-cycled to produce even more copies. The long mRNA is then transported back to the cytoplasm where the virion P protein synthesizes DNA via its reverse transcriptase activity.

2. Antigenicity

All three coat proteins of HBV contain HBsAg, which is highly immunogenic and induces anti-HBs (humoral immunity). Structural viral_proteins induce specific T-lymphocytes, capable of eliminating HBV-infected cells (cytotoxic T-cells; cellular immunity) [2].

*Corresponding Author

HBsAg is heterogeneous antigenically, with a common antigen designated a, and two pairs of mutually exclusive antigens, d and y, and w (including several subdeterminants) and r, resulting in 4 major subtypes: adw, ayw, adr and ayr [3].

The distribution of subtypes varies geographically [4]. Because of the common determinants, protection against one subtype appears to confer protection to the other subtypes and no difference in clinical features have been related to subtypes.

In the United State, northern Europe, Asia, and Oceania, the d determinant is common, but the y determinant is found at lower frequency. The d determinant to the near exclusion of y is found in Japan. The y determinant, and rarely d, are found in Africa and in Australia aborigines. y is also frequently found in India and around the Mediterranean. In Europe, the US, Africa, India, Australia, and Oceania, the w determinant predominates. In Japan, China, and Southeast Asia, the r determinant predominates. Subtypes adw, ady, and adr are each found in extensive geographic regions of the world. Subtype ayr is rare in the world, but it is commonly found in small populations in Oceania [5].

The c antigen (HBcAg) is present on the surface of core particles. HBcAg and core particles are not present in the blood in a free form, but are found only as internal components of virus particles [6].

The core antigen shares its sequences with the e antigen (HBeAg), identified as a soluble antigen, but no cross-reactivity between the two proteins is observed.Viral oligopeptides of 8-15 amino acids are loaded on host cell MHC-class I molecules and are transported to the surface of the cell. HBV-specific T-lymphocytes can then detect infected cells and destroy them. This cell deletion triggered by inflammation cells may result in acute hepatitis. When the infection is self-limited, immunity results. If HBV is not eliminated, a delicate balance between viral replication and immunodefence prevails which may lead to chronic hepatitis and liver cirrhosis. In chronically infected cells the HBV DNA may integrate into the host cell DNA. As a long term consequence, integration may lead to hepatocellular carcinoma [2].

3. Stability

The stability of HBV does not always coincide with that of HBsAg. Exposure to ether, acid (pH 2.4 for at least 6 hrs) and heat (98°C for 1 min; 60°C for 10 hrs) does not destroy immunogenicity or antigenicity. However, inactivation may be incomplete under these conditions if the concentration of virus is excessively high.

Antigenicity and probably infectivity are destroyed after exposure of HBsAg to 0.25% sodium hypochlorite for 3 min [4, 7]. Infectivity is lost after autoclaving at 121°C for 20 min or dry heat treatment at 160°C for 1hr.

HBV is inactivated by exposure to sodium hypochlorite (500 mg free chlorine per litre) for 10 min, 2% aqueous glutaraldehyde at room temperature for 5 min, heat treatment at 98°C for 2 min, Sporicidin (Ash Dentsply, York, PA) (pH 7.9), formaldehyde at 18.5 g/l (5% formalin in water), 70% isopropylalcohol, 80% ethyl alcohol at 11°C for 2 min, Wescodyne (a iodophor disinfectant, American Sterilizer Co., Erie, PA) diluted 1:213, or combined β-propriolactone and UV irradiation.

HBV retains infectivity when stored at 30°C to 32°C for at least 6 months and when frozen at –15°C for 15 years. HBV present in blood can withstand drying on a surface for at least a week [2].

4. Types of Hepatitis B Virus Infection

The infection has two possible phase-Acute and Chronic.

Acute phase of hepatitis B virus refers to newly acquired infections. This occurs during the first one to four months after acquiring the virus. Only about 30% to 50% of adult develop significant symptoms during acute infection, majority of infected adults successfully clear the virus and acquire immunity.

Chronic hepatitis B virus occurs when the hepatitis B virus remains in a person's body for more than 6 months or years. More than 90% of new born, 50% of children, 5% of adults infected with hepatitis B virus develop chronic hepatitis [8, 9].

5. Prevalence

HBV occurs worldwide. The highest rates of HBsAg carrier rates are found in developing countries with primitive or limited medical facilities [6]. In areas of Africa and Asia, widespread infection may occur in infancy and childhood. The overall HBsAg carrier rates may be 10 to 15%.

The prevalence is lowest in countries with the highest standards of living, such as Great Britain, Canada, United States, Scandinavia, and some other European Nations.

In North America infection is most common in young adults. In the USA and Canada, serological evidence of previous infection varies depending on age and socioeconomic class. Overall, 5% of the adult USA population has anti-HBc, and 0.5% are HBsAg positive.

In developed countries, exposure to HBV may be common in certain high-risk groups .Adults infected with HBV usually acquire acute hepatitis B and recover, but 5 to 10% develop the chronic carrier state. Infected children rarely develop acute disease, but 25 to 90% become chronic carriers. About 25% of carriers will die from cirrhosis or primary liver cancer as adults [10].

In the past, recipients of blood and blood products were at high risk for HBV infection . Over the last 25 years, testing blood donations for HBsAg has become a universal requirement. Testing procedures have made major

progress in sensitivity in the last 15-20 years. However 19% of countries reported that they were not testing all blood donations for HBsAg [11] Global Database on Blood Safety, unpublished data). In the many countries where pre-transfusion screening of blood donations for HBsAg is carried out systematically, the residual risk of HBV transmission is minimal. Moreover, plasma derived medicinal products (including antihaemophilic factors) undergo additional viral inactivation and removal procedures resulting in greatly reduced or no transmission of HBV by these products.

However, the risk is still present in many developing countries. Contaminated and inadequately sterilized syringes and needles have resulted in outbreaks of hepatitis B among patients in clinics and physicians' offices. Occasionally, outbreaks have been traced to tattoo parlors and acupuncturists [12]. Rarely, transmission to patients from HBsAg positive health care workers has been documented.

Reductions in the age-related prevalence of HBsAg in countries where hepatitis B is highly endemic and universal immunization of infants has been adopted suggest that it may be possible to eradicate HBV from humans.

Hepatitis B vaccines have been available since 1982 and have been used in hundreds of millions of individuals with an outstanding record of safety and impact on the disease. Carriage of HBV has already been reduced from high prevalence to low prevalence in immunized cohorts of children in many countries [13, 14].

6. Epidemiology

In endemic areas of Africa and Asia, the epidemiological patterns differ from those seen in North America and Western Europe. In these regions, most infections occur in infants and children as a result of maternal-neonatal transmission or close childhood contact, although percutaneous exposure with contaminated needles or following unsafe injections is always a possibility in these countries [2].

The chronic liver disease and HCC associated with HBV infections are among the most important human health problems in high-prevalence regions.

The disease has caused epidemics in parts of Asia and Africa, and it is endemic in China [15]. About a third of the world's population, more than 2 billion people have been infected with the hepatitis B virus [16]. This includes 350 million chronic carriers of the virus. Despite the existence of a safe and effective vaccine, Nigeria has remained a hyper-endemic area for hepatitis B virus infection, with an estimated 12% of the total population being chronic carriers [17]. Hepatitis B virus infection continues to be a substantial and devastating health problem with new cases still being reported annually [18]. Studies done in Nigeria showed HBV carrier rate in the range of 9 to 39% [19]. Glebe and Urban [20] stated that HBV infection has reached endemic proportions in developing countries including Nigeria, where an estimated 18 million people are infected. The disease burden is large and of public health concern. The morbidity and mortality associated with the Hepatitis B virus (HBV) infection is considerable with serious complications including acute viral hepatitis, chronic viral hepatitis, liver cirrhosis and primary liver cell carcinoma [21].

Multimer, *et al.* [22] found that blood transfusion clearly increased the risk of HBV infection as shown by significantly higher markers of HBV infection (HBsAg and anti HBc) in subjects who were transfused. Samuel, *et al.* [23] in Ibadan determined markers of HBV infection and detected the presence of its occult infection in serum of a cohort of adult Nigerians showed that occult HBV infection is present among Nigerians adults [24]. Abiodun and Omoike [25] in Benin observed that HBV infection increased with increasing units of blood transfused. In Awka, Ezegbudo, *et al.* [19] found that the prevalence of HBsAg among pregnant women decreases with increasing social status. Sirisena, *et al.* [26], Mustapha and Jibrin [27] in Gombe and Jos respectively found that having multiple sex partners increased the carriage of HBsAg. Ola, *et al.* [28] in Ibadan found that 57.1% of patients with primary liver cell carcinoma were positive for HBsAg.

Amazigo and Chime [29] in Eastern Nigeria found that HBsAg carriage and exposure rate to HBV were significantly higher in rural than in urban population. This was attributed to overcrowding and clustering. They also demonstrated that by 40years of age 87% of indigenous population of Eastern Nigeria has at least one HBV marker in their serum.

Olubuyide, *et al.* [30] found that a high (39%) prevalence of HBsAg was associated with surgeons and dentists, with high potential of transmissibility. They speculated that it was due to lack of vaccination and frequent application of universal precaution. Recent studies on HBsAg prevalence in Jos and Gombe among patients with human immune deficiency syndrome (HIV) showed a prevalence of 26.9% and 26.5% respectively. These high values could be because HIV and HBV share similar modes of transmission and risk factors. [27, 31].

7. Transmission

Currently, there are four recognized modes of transmission [2].

1. From mother to child at birth (perinatal)
2. By contact with an infected person (horizontal)
3. By sexual contact
4. By parenteral (blood-to-blood) exposure to blood or other infected fluids.

There is considerable variation between areas, countries and continents as to the age at which most transmission takes place. There can be carriers with or without hepatitis [3].

There is no convincing evidence that airborne infections occur and faeces are not a source of infection, since the virus is inactivated by enzymes of the intestinal mucosa or derived from the bacterial flora. HBV is not transmitted by contaminated food or water, insects or other vectors [2]. HBsAg has been found in all body secretions and excretions. However, only blood, vaginal and menstrual fluids, and semen have been shown to be infectious [6].

Transmission occurs by percutaneous and permucosal exposure to infective body fluids. Percutaneous exposures that have resulted in HBV transmission include transfusion of unscreened blood or blood products, sharing unsterilized injection needles for intravenous drug use, haemodialysis, acupuncture, tattooing and injuries from contaminated sharp instruments sustained by hospital personnel [3]. Nester, *et al.* [1] stated that Sexual and perinatal HBV transmission usually result from mucous membrane exposures to infectious blood and body fluids. Perinatal transmission is common in hyperendemic areas of south-east Asia and the far East, especially when HBsAg carrier mothers are also HBeAg positive. Infection may also be transmitted between household contacts and between sexual partners, either homosexual or heterosexual, and in toddler-aged children in groups with high HBsAg carrier rates [2].

Immune globulins, heat-treated plasma protein fraction, albumin and fibrinolysin are considered safe when manufactured appropriately.

HBV is stable on environmental surfaces for at least 7 days, and indirect inoculation of HBV can occur via inanimate objects like toothbrushes, baby bottles, toys, razors, eating utensils, hospital equipment and other objects, by contact with mucous membranes or open skin breaks [3].

Infectious HBV can be present in blood without detectable HBsAg, so that the failure to detect antigen does not exclude the presence of infectious virus [32]. The source of infection cannot be identified in about 35% of cases.

The natural reservoir for HBV is man [33]. Closely related hepadnaviruses have been found in woodchucks and ducks, but they are not infectious for humans. The reuse of the same, unsterilized needle and syringe for vaccination of many different children accounts for many unnecessary HBV infections [12].

People depending on repeated transfusion should be vaccinated against HBV. HBV is about 100 times more infectious than HIV.

8. Risk Groups

Here is a list of groups of people who are at risk of contracting HBV.

- infants born to infected mothers
- young children in day-care or residential settings with other children in endemic areas
- sexual/household contacts of infected persons
- health care workers
- Patients and employees in haemodialysis centres [34].
- injection drug users sharing unsterile needles
- people sharing unsterile medical or dental equipment
- people providing or receiving acupuncture and/or tattooing with unsterile medical devices
- Persons living in regions or travelling to regions with endemic hepatitis B [35].
- sexually active heterosexuals
- men who have sex with men

Frequent and routine exposure to blood or serum is the common denominator of healthcare occupational exposure. Surgeons, dentists, oral surgeons, pathologists, operating room and emergency room staff, and clinical laboratory workers who handle blood are at the highest risk.

HBV infection is the major residual post-transfusion risk in developed countries because of the long window period, HBV mutants, the low viraemia (difficulties for PCR on pooled samples) and the very high infectivity. Over one-third of patients with acute hepatitis B do not have readily identifiable risk factors [10].

Efforts to vaccinate persons in the major risk groups have had limited success because of the difficulties in identifying candidates belonging to high risk groups. Moreover, regulations have to be developed to ensure implementation of vaccination programs [33].

High risk persons should be post-tested within 1-2 months of receipt of the third dose of HBV vaccine, to identify good responders to vaccination. This policy is cost-saving since adequate responders do not need to be retested or given HBIG whenever they later are exposed to HBV. They also do not need to be offered booster doses of vaccine periodically.

9. Signs and Symptoms of Hepatitis B Virus Infection

Many people have no symptoms when they are first infected with HBV. Others may feel like they have flu, with fever, fatigue, loss of appetite, nausea, vomiting, light stool, dark urine, pain in the upper right abdomen (due to inflamed liver), jaundice, weight loss and aching joints and muscles.

Similarly, people living with chronic HBV infection often feel perfectly healthy. Others may experience bouts of fatigue, lost appetite and nausea.

10. Immune Response during Hepatitis B Virus Infection

There is little evidence that humoral immunity plays a major role in the clearance of established infection. Cell-mediated immune responses, particularly those involving cytotoxic T-lymphocytes (CTLs), seem to be very important [4].

CD8-positive, class I major histocompatibility complex (MHC)-restricted CTLs directed against HBV nucleocapsid proteins are present in the peripheral blood of patients with acute, resolving hepatitis B. Such cells are barely detectable in the blood of patients with chronic HBV infection, suggesting that the inability to generate such cells may predispose to persistent infection, although their absence from the blood in chronic infection may be due to their sequestration elsewhere.

CTLs against envelope glycoprotein determinants, that are often CD4-positive, class II MHC-restricted, have also been detected. Primary infection leads to an IgM and IgG response to HBcAg shortly after the appearance of HBsAg in serum, at onset of hepatitis. Anti-HBs and anti-HBe appear in serum only several weeks later, when HBsAg and HBeAg are no longer detected, although in many HBsAg-positive patients, HBsAg-anti-HBs complexes can be found in serum.[6].

During HBV infection, the host immune response causes both hepatocellular damage and viral clearance. Innate immunity generally plays a role immediately after infection to limit the spread of the pathogen and initiate efficient development of an adaptive immune response. Innate immune response during the early phases of viral infections are mainly characterized by the production of type 1 interferon (IFN) α-/β cytokines and the activation of natural killer (NK) cells. Production of type 1 IFN_S can be triggered directly by virus replication through cellular mechanisms that detect the presence of viral RNA or DNA [36, 37] ; while NK cells are activated by the recognition of stress induced molecules and the modification of the quality of major histo- compatibility complex (MHC) class 1 molecule on the surface of infected cells [38].

Experimental data collected, mainly in animal models but also in humans [39], show that after inoculation, HBV does not immediately start to replicate efficiently. HBV – DNA and HBV antigens are not detectable in serum or liver until 4-7 weeks post infection [40]. Following this period, HBV begins a Logarithmic expansion phase that can be detected in the liver and serum, reaches levels of $10^9 – 10^{10}$ copies Ml^{-1} [41] and infects most hepatocytes.

The peculiarity of the kinetics of HBV replication has been largely ignored and only the comparison with Hepatitis C virus (HCV). Viral kinetics has drawn attention to the unusual pattern of HBV replication [42, 43]. The initial lag phase of HBV replication does not appear to be a consequence of HBV inhibition by elements of innate and adaptive immunity. The activation of IFN-Y, interleukin (IL)-2 and turmor necrotic factor (TNF) –α and intrahepatic recruitment of inflammatory cells is delayed until the logarithmic expansion of HBV in experimentally infected wood chucks [44-46] and Chimpanzee [47].

A further characteristic of HBV in relation to early host defense mechanism reside in the lack of IFN α and β production. HBV replication can be efficiently limited by α and β IFN [48, 49], but data on acutely infected Chimpanzees suggest that such antiviral cytokines are not triggered by HBV replication [50]. HBV might have evolved strategies to escape the initiated antiviral defence mechanism activated by the toll-like receptor system. Because HBV replicates within nuclocapsid particles, viral replicative intermediate of single stranded RNA or viral DNA, it has been proposed that generally strong activators of type 1 IFN genes [37, 51] are protected from cellular recognition [50].

Caution should follow the analysis of the data. Hepatitis after HBV infection is generally mild in Chimpanzees compared with humans. It is possible that the inability to detect activation of genes related to innate immunity is a reflection of a mild profile of the disease. Still the striking difference between the early detection of type 1 IFN activation during early phase of HCV infection in Chimpanzees [52, 53] and its absence in HBV – infected animals is a further indication of the ability of HBV to sheak through the front line host defence mechanism. Such early events are difficult to analyse during natural infection in humans. HBV infected patients are mainly detected after onset of clinical symptoms nausea and hycterus , which occur well after infection 10-12 weeks . Never the less, it is interesting to note that the lack of early symptoms in HBV-infected patients such as fever and malaise, which are characteristics of other human viral infections, constitutes indirect evidence of the defective type 1 IFN production during the early phases of HBV infection.

11. Triggering HBV Immunity

According to Guidotti, *et al.* [47] immediately after the experimental phase of HBV expansion, chimpanzees able to control the virus show a typical acute phase of disease with the robust activation of IFN-y and TNF. Also many cellular genes linked to a T helper type 1 (T h I) of cellular response [50]. It is also possible that the initial host response to HBV is primarily sustained by NK and NK-T cells. Although we lack direct evidence for the role of NK and NK-T-cell. During natural HBV infection the experimental data on animal are consistent with the possibility that the initial burst of IFN-y and the subsequent rapid inhibition of HBV could be mediated by these components of innate immunity. Work on acutely infected chimpanzees is again providing the strongest evidence that NK and NK-T cells could be responsible for the initial control of HBV replication. In chimpanzees that are able to ultimately resolve the infection, a rapid drop in virus replication occurs in the presence of intrahepatic IFN-α production before the massive recruitment of T-cells [47]. Despite the data in animal models, the only experimental evidence of NK-cells involvement in human HBV infection are represented by an analysis of NK-cells frequencies in patients studied

during the incubation phase of acute Hepatitis B. Here increase number of circulating NK cells were concomitant with the peak HBV replication, while 2-4 weeks later, HBV specific CD8-Tcells appear when virus replication had already drooped.

In the case of chronicity a different pattern is observed. When virtually all patients that experience acute hepatitis B resolve the infection, development of chronicity is often associated with absent or mild symptoms of acute hepatitis. In line with the clinical observation, neonatally infected wood chucks that develop chronicity lack the large IFN-Y and TNF – α production observed in resolved animals [44, 46, 54] and fail to develop an efficient antiviral specific immune response. Thus activation of elements of innate immunity able to produce large amount of IFN-Y seems to be a factor that determines the subsequent induction of humoral immunity (adaptive immunity) and ultimately outcome of HBV infection, what triggers the activation is still unknown. What seems well established is that the differences in adaptive immune response to HBV that characterized chronic and resolved patients are heavily influenced by the immunological events occurring in the initial phase of HBV replication.

12. Patterns of Adaptive Immunity in HBV Infection

The adaptive immune response is comprised of a complex web of effector cell types, all of which play key roles in development of immunity to HBV. CD4 T cells, classically referred to as helper T cells are robust producers of cytokines. The CD4 T cells are required for efficient development of effector cytotoxic CD_8 T cells and B cell antibody production.

The level of circulating HBV is reduce through non cytolytic and cytolytic mechanism carried out by CD_8 T cells on HBV infected Hepatocytes [47] while B cell antibody production neutralizes free viral particles and can prevent (re) infection [8, 55].

Despite the cellular immune response being a major contributor to HBV clearance, humoral responses also play a role in controlling HBV. HBV clearance is associated with the production of anti envelope antibodies [8] and sera with high levels of antiviral antibodies (specific for the viral envelope) that can control HBV infection [55] Therefore it is likely that the integration activation of both the cellular and humoral arms of adaptive immune response allows the host to control infection, the different components being so inter connected that the failure of one of them clearly affects the expansion and protective efficacy of the others. A lack of CD_8 T cells help can impair CD_8 T cell activity and antibody production while the inability to mount a virus specific CD_8 T cell response result in a level of circulating virus that cannot be cleared by antibodies alone [56]. According to Penna, *et al.* [57], HBV specific, HLA- class 11 restricted CD_4 T cell responses have been characterized mainly in patient with self limited acute hepatitis.

In HBV infected patients, the frequency and function of circulating and intra-hepatic HBV specific CD_8 T cell is inversely proportional to the level of HBV-DNA [58]. HBeAg a secretory form of nucleocapsid antigen is produced in large excess during HBV replication [59]. Exacerbation of chronic epatitis B are often associated with selection of HBV unable to produce HBe Ag [60]. In addition HBV replication is linked to the production of excessive amount of the soluble form of HBsAg. Particles composed of only surface antigen are present in 10^3-10^6 fold excess over whole virions [59]. These particles are not infectious but the evolution of such impressive levels of synthetic effort by HBV may deliberately cause a state of low T cell response and T-cell deletion. Other factors in addition to the quantity of viral antigens, have been suggested to explain the state of virus specific T cell collapse present in chronic hepatitis B patients. Dendritic cells, they represent a specialized antigen presenting cell population necessary for induction of an adaptive immune response [61]. The relation to their crucial role in T-cell priming functional alterations of dentritic cell populations could explain the state of T and B cell hypo- responsiveness present in chronic hepatitis B patients.

13. Diagnosis

There are several tests that can be used to determine if a patient has been exposed to HBV, if it's a new (acute) or old (chronic) infection and if HBV is affecting the liver.

HB_SAg – This test identifies the hepatitis B surface antigen (Hb_SAg), a part of the outer coat of the virus. This is the most common test used to find out if someone has been exposed to HBV or currently infected with the virus.

HB_eAg – This test identifies the hepatitis B e antigen (HB_eAg), another part of the virus. If this antigen is found, it means that the virus is actively multiplying and the patient is contagious and can pass the virus onto someone else.

Antibody tests - These tests can identify several differently antibodies including the hepatitis B surface antibody (HB_SAb), the hepatitis B core antibody (HB_CAb), and the hepatitis B e antibody (HB_eAb). If antibodies are found, it means the immune system is able to fight the virus either because the patient has been vaccinated against HBV or because the body has recovered from HBV infection.

ALT and AST- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are liver enzymes that are normally present in the blood. A higher than normal amount of these enzymes in a sample of blood can be a sign of liver damage.

Liver biopsy – A liver biopsy involves removing a tiny piece of tissue from the liver. The biopsy sample is stained and examined under a microscope to see if scar tissue is present. A biopsy can indicate if scarring is present, what type of cells are involved and how far the scaring has spread. Although it is an invasive procedure, a liver biopsy is a fast and safe way to asses liver damage in most people [62]. For hemophiliacs, however, there is always the risk of

serious bleeding. Chronic hepatitis B virus infection may be classified as replicative or non-replicative. In replicative infections (also known as chronic active hepatitis), the virus is replicating at a high rate, HBV viral load is usually high and the 'e' antigen (HB_eAg) is present in the blood. In non-replicative infections (chronic persistent hepatitis), the virus is still replicating but at a fairly low level. HBV viral load is generally low and the 'e' antigen is not found. Generally, people with non-replicative hepatitis are at much lower risk of developing serious liver damage than those with replicative infection.

14. Serological Markers of HBV Infection

During HBV infection, the serological markers vary depending on whether the infection is acute or chronic [63].

HBV serological markers in hepatitis patient

Antigens	**Antibodies**
HBsAg Hepatitis B surface antigen is the earliest indicator of acute infection and is also indicative of chronic infection if its presence persists for more than 6 months. It is useful for the diagnosis of HBV infection and for screening of blood.	anti-HBs This is the specific antibody to hepatitis B surface antigen. Its appearance 1 to 4 months after onset of symptoms indicates clinical recovery and subsequent immunity to HBV. Anti-HBs can neutralize HBV and provide protection against HBV infection.
HBcAg Hepatitis B core antigen is derived from the protein envelope that encloses the viral DNA, and it is not detectable in the bloodstream. When HBcAg peptides are expressed on the surface of hepatocytes, they induce an immune response that is crucial for killing infected cells. The HBcAg is a marker of the infectious viral material and it is the most accurate index of viral replication.	anti-HBc This is the specific antibody to hepatitis B core antigen. Antibodies to HBc are of class IgM and IgG. They do not neutralize the virus. The presence of IgM identifies an early acute infection. In the absence of HBsAg and anti-HBs, it shows recent infection. IgG with no IgM may be present in chronic and resolved infections. Anti-HBc testing identifies all previously infected persons, including HBV carriers, but does not differentiate carriers and non-carriers.
HBeAg Hepatitis B e antigen appearing during weeks 3 to 6 indicates an acute active infection at its most infectious period, and means that the patient is infectious. Persistence of this virological marker beyond 10 weeks shows progression to chronic infection and infectiousness. Continuous presence of anti-HBe indicates chronic or chronic active liver disease. HBeAg is not incorporated into virions, but is instead secreted into the serum. Mutant strains of HBV exist that replicate without producing HBeAg. HBeAg's function is uncertain.	anti-HBe This is the specific antibody to hepatitis B e antigen. During the acute stage of infection the seroconversion from e antigen to e antibody is prognostic for resolution of infection. Its presence in the patient's blood along with anti-HBc and in the absence of HBsAg, anti-HBs and core HBV mutants indicates low contagiousness and convalescence. [31]
HBxAg Hepatitis B x antigen is detected in HBeAg positive blood in patients with both acute and chronic hepatitis. HBxAg is a transcriptional activator. It does not bind to DNA.	anti-HBx This is the specific antibody to hepatitis B x antigen. It appears when other virological markers are becoming undetectable.
HBV DNA HBV DNA is detectable by hybridization assays or PCR as soon as 1 week after initial infection. The tests are generally performed for monitoring of antiviral treatment or to detect mutants that escape detection by current methods.	
HBV DNA polymerase Tests for the presence of HBV DNA polymerase, detectable within 1 week of initial infection, are only performed for research purposes.	

Source: [63]

15. Treatment

Acute hepatitis B infection does not usually require treatment because most adults clear the infection spontaneously [64]. Early antiviral treatment may only be required in less than 1% of patients, whose infection takes

a very aggressive course (fulminant hepatitis) or who are immunocompromised. On the other hand, treatment of chronic infection may be necessary to reduce the risk of cirrhosis and liver cancer.

Chronically infected individuals with persistently elevated serum alanine aminotransferase, a marker of liver damage and HBV DNA levels are candidate for therapy [65]. Although none of the available drugs can clear the infection, they can stop the virus from replicating, thus *minimizing* liver damage. Medications for hepatitis B have been improving continually and are usually effective at reducing viral loads markedly or even to undetectable levels. Currently seven therapeutic agents are approved by the Food and Drug Administration for the treatment of chronic hepatitis B, including two formulations of interferon (interferon alpha and pegylated interferon) and five nucleoside or nucleotide analogs (Lamuvidine, telbivudine, abacavir, entecavir and tenofovir). Among the approved analogs both entecavir and tenofovir have antiviral activity as well as very low rates of drug resistance. Treatment with these agents reduces HBV DNA levels to undetectable or nearly undetectable levels in most treated persons [66].

Virtually, all treated patients even those few still receiving older agents eg lamuvidine can expect to achieve a reduction of HBV DNA viral load to very low levels within weeks or months of initiating therapy [67]. The newer medications are effectively in suppressing viral replication and it is expected that they will be used for a newly identified HBV infected health –care provider who is performing exposure prone procedures and who has HBV virus levels above the threshold suggested in this report (1,000 IU/ml i.e about 5,000 genome equivalents (ml) or as adopted by his or her institution's expert review panel. However, clinicians caring for infected health-care providers or students who are not performing exposure prone procedures and who are not subject to expert panel review should consider both the benefits and risks associated with life-long antiviral therapy for chronic HBV started at young ages [67].

Infants born to mothers known to carry hepatitis B virus can be treated with antibodies to the hepatitis B virus (HBIg). When given with the vaccine within twelve hours of birth, the risk of acquiring hepatitis B is reduced to 90% [68]. This treatment allows a mother to safely breastfeed her child.

16. Control

There are broadly three strategies for controlling HBV infection. Immunization for at risk population, antiviral drugs and Immunostimulatory therapy with alpha – interferon for those affected.

Immunization is the most effective means of controlling HBV worldwide [69]. The vaccine has 95% record of safety and efficacy in preventing development of the chronic carrier state. The vaccine is administered in either two to three or four dose schedules into infants and adults which provides protection for 85-90% of individuals (JCVI). Protection has been observed to last 12years in individuals who show adequate initial response to the primary course of vaccinations and that immunity is predicted to last at least 25 years [70]. Since HBV is transmitted through body fluids and blood, prevention is thus the avoidance of such transmission like unprotected sexual contact, blood transfusions, re-use of contaminated needles and syringes and vertical transmission during child birth. Infants should be vaccinated at birth. Shi, *et al.* [14] shows that besides the WHO recommended immunoprophylaxis starting from the new born, multiple injections of small dose of hepatitis B immune globulin (HBlg, 200-400IU per month) [71] or oral lamivudine (100mg per day) in HBV carrier mothers with high degree of infectiousness ($>10^6$ copies/ml) in late pregnancy effectively and safely prevent HBV intrauterine transmission, which provide new insight into prevention of HBV at the earliest stage.

In addition to the above measures where it is feasible, HBV infection in Nigeria can be drastically reduced through health education of the general population on the various mode of transmission of HBV and preventive measures [26].

Also discouraging communal sharing of blade/sharp instruments used for shaving, barbing, manicure and body piercing / cutting and high level sexual networking. Those adults at risk for HBV infection should be discouraged for pre-chewing of solid food for children because saliva is known to transmit HBV [72].

Vaccination campaigns have shown that control of the disease is feasible, even in endemic areas. Some countries incorporate hepatitis B immunoglobulin (HBIG) in their vaccination strategies.

In endemic areas, procurement of low cost vaccine, education and acceptance, vaccine integration in the expanded program of immunization (EPI), prevention of vertical transmission, antibody escape mutations, protective efficacy, long term immunity and natural boosting are important questions and issues.

Since most HBV carriers are unaware of their condition, they therefore pose a significant risk to health care workers and other people exposed to their blood. Workers are advised to assume that all patients are potentially infectious, and should practice "universal precautions".

17. Conclusion

Hepatitis B viral infection is a major a public health challenge especially in the developing countries with low health facilities and manpower.It causes immunological derangements with its complications.Hepatitis B is one of the most common infectious diseases of the liver in the world and a major public health problem. The predominant routes of transmission vary according to the endemicity of HBV infection. In areas of high endemicity, perinatal transmission is the main rout of transmission, where as in areas of low endemicity, sexual contact amongst high-risk adults is predominant. All three coat proteins of HBV contain HBsAg, which is highly immunogenic and induces anti-HBs. The stability of HBV does not always coincide with that of HBsAg. Exposure to ether, acid (pH 2.4 for at

least 6 hrs) and heat (98°C for 1 min; 60°C for 10 hrs) does not destroy immunogenicity or antigenicity. Antigenicity and probably infectivity are destroyed after exposure of HBsAg to 0.25% sodium hypochlorite for 3 minutes. Infectivity is lost after autoclaving at 121°C for 20 min or dry heat treatment at 160°C for 1hr. HBV occurs worldwide. The highest rates of HBsAg carrier rates are found in developing countries with primitive or limited medical facilities .In areas of Africa and Asia, widespread infection may occur in infancy and childhood. The overall HBsAg carrier rates may be 10 to 15%.The prevalence is lowest in countries with the highest standards of living, such as Great Britain, Canada, United States, Scandinavia, and some other European Nations. During HBV infection, the host immune response causes both hepatocellular damage and viral clearance. Innate immunity generally plays a role immediately after infection to limit the spread of the pathogen and initiate efficient development of an adaptive immune response. Innate immune response during the early phases of viral infections are mainly characterized by the production of type 1 interferon (IFN) α-/β cytokines and the activation of natural killer (NK) cells.

Adequate health education should be given to the public on the preventive measures and the treatment procedures of those infected and the control as well. This will help to improve the lives of the populace and enhanced productivity in the society.

References

[1] Nester, E. W., Anderson, D. G., Roberts, E. C., and Nester, T. M., 2009. *Microbiology*. 6 ed. A Human perspective McGraw Hill, pp. 606–608.

[2] Hollinger, F. B. and Liang, T. J., 2001. *Hepatitis B Virus. In: Knipe, D.M. Fields Virology*. 4 ed. Philadelphia: Lippincott Williams and Wilkins. pp. 2971-3036.

[3] Robinson, W. S., 1995. *Hepatitis B virus and hepatitis D virus. In: Mandell, G.L., Bennett, J. E. and Dolin, R. Principles and Practice of Infectious Diseases*. 4 ed. New York: Churchill Livingstone. pp. 1406-1439.

[4] Robinson, W. S., 1994. *Hepatitis B viruses. General Features (human). In: Webster RG and Granoff A, eds. Encyclopedia of Virology*. London: Academic Press Ltd. pp. 554-569.

[5] Zuckerman, A. J., 1996. *Hepatitis Viruses. In Baron's Medical Microbiology*. 4 ed. University of Texas Medical Branch, pp. 132-136.

[6] Mahoney, F. J. and Kane, M., 1999. *Hepatitis B vaccine. In: Plotkin, S. A., and Orenstein, W.A., Vaccines*. 3 ed. Philadelphia, W.B. Saunders Company, pp. 158-182.

[7] World Health Organization, 2008. "Hepatitis B Fact sheet." Available: http://www.who.int/mediacentre/factsheets/fs204/en/

[8] Alberti, A., Chemello, L., and Benvegnu, L., 1999. "Natural history of hepatitis C." *Journal of Hepatology*, vol. 31, pp. 17-24.

[9] Lok, A. S. and McMahon, B. J., 2001. "Chronic hepatitis B." *Hepatology*, vol. 34, pp. 1225–1241.

[10] Centers for Disease Control and Prevention, 1991. "Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination recommendations of theimmunization practices advisory committee (ACIP)." *Morbidity and Mortality Weekly Report*, vol. 40, pp. 1-19. Available: http://www.cdc.gov/ncidod/diseases/hepatitis/v40rr13.htm

[11] World Health Organization, 2001. " Introduction of hepatitis B vaccine into childhood immunization services." Geneva, (unpublished document WHO/V&B/01.31 available on request from Department of Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland).

[12] Viral Hepatitis Prevention Board, 1998. "Ensuring injection safety and a safe blood supply." Available: http://hgins.uia.ac.be/esoc/VHPB/vhfs3.html

[13] Li, X. M., Yang, Y. B., Hou, H. Y., Shi, Z. J., Shen, H. M., Teng, B. Q. L. A. M., Shi, M. F., and Zou, L., 2003. "Interruption of HBV intrauterine transmission, a clinical study." *World Journal of Gastroenterol*, pp. 1501 – 1503.

[14] Shi, Z., Li, X., Ma, L., and Yang, Y., 2010. "Hepatitis B immunoglobulin injection in pregnancy to interrupt hepatitis B virus mother-to-child transmission a meta analysis." *International Journal of infectious Diseases. Official publication of the international society for infectious Diseases*, vol. 14, pp. 622–634.

[15] Williams, R., 2006. "Global challenges in Liver disease." *Journal of Hepatology*, vol. 44, pp. 521-526.

[16] World Health Organisation, 2009. "No scientific Justification to suspend Hepatitis B Immunization." Available: http/W.H.O.int/inf-fr-en/prq8-67.htm.

[17] Ugwuja, E. I., 2010. "Seroprevalence of Hepatitis B surface Antigen and Liver function tests among adolescents in Abakaliki South Eastern." *Internet Journal of Tropical Medicine*, vol. 6, pp. 1-6.

[18] Seyed, M. A., 2006. "Immunization an important strategy to control hepatitis." *Journal of infectious disease*, vol. 6, pp. 3-5.

[19] Ezegbudo, C. N., Agbonlahor, D. E., Nwobu, G. O., Igwe, C. U., Agba, M. I., and Okpala, H. O., 2004. "The seroprevalence of hepatitis b surface antigen and human immunodeficiency virus (hiv) among pregnant women in Anambra State." *Shiraz E-Medical Journal*, vol. 5, pp. 1-8.

[20] Glebe, D. and Urban, S., 2007. "Viral and cellular determinants involved in Hepadnaviral entry." *World Journl of gastroenterology*, vol. 13, pp. 22-38.

[21] World Health Organisation, 2005. "Department of Communicable Disease, Surveillance and Response." Available: http/www/WHO/hepatitis/200.htm

[22] Multimer, J., Olomi, A., Skidmore, S., Olomu, N., Ratcliffe, D., and Rodger, S., 1994. "Viral hepatitis in Nigeria – Sickle cell disease and commercial blood donors." *QJM*, vol. 87, pp. 407-411.

[23] Samuel, O., Jesse, A., Otegbayo, J. A., Georgina, N., Odaibo, G., David, O., Olaleye, O., Itunu, O., Olubuyide, I., *et al.*, 2009. "Occult HBV infection, HCV in Nigeria." *Journal of infect. Dev. Ctries*, pp. 442-446.

[24] Abiodun, P. O. and Ihongbe, J. C., 1985. "Hepatitis B surface Antigen and blood donors in Beni City." *East Afric Journ*, vol. 62, pp. 883-888.

[25] Abiodun, P. O. and Omoike, I. U., 1990. "Hepatitis B surface Antigenaemia in children in Benin City." *Nig. Journal of Paed*, vol. 17, pp. 27-31.

[26] Sirisena, N., Njoku, M., and Idoko, J., 2002. "Carriage rate of Hepatitis B surface antigen in Urban community in Jos." *Nig. Postgrad. J.*, vol. 9, pp. 7-10.

[27] Mustapha, S. K. and Jibrin, Y. B., 2004. "The prevalence of Hepatitis B surface Antigenaemia in patients with Human Immunodeficiency Virus infection in Gombe, Nigerian." *Afr. Med.*, vol. 3, pp. 10-12.

[28] Ola, S. O., Olubude, I. O., and Ayoola, E. A., 1994. "Serum Alpha Foetoprotein, Hepatitis B virus infection and primary Hepatocellular Carcinoma in Nigeria." *Agri Med Journal*, pp. 783-793.

[29] Amazigo, U. O. and Chime, A. B., 1990. "Hepatitis B virus in rural and urban population of Eastern Nigeria prevalence of serological markers." *East Africa Med. J.*, vol. 67, pp. 539-544.

[30] Olubuyide, I. O., Ola, S. O., Dosumu, O. O., Arotiba, J. T., Olaleye, O. A., and Odaibo, G. N., 1997. "Hepatitis B and C in Doctors and Dentists in Nigeria." *J. M ed.*, vol. 90, pp. 422-431.

[31] Ukaeje, C. J., Ogbu, O., Inyama, P. U., Anyanwu, G. I., and Njoku, I. M., 2005. "Prevalence of Hepatitis B surface antigen among blood donors and human immunodeficiency virus infected patients in Jos, Nigeria." vol. 100, pp. 13-16.

[32] Tacket, C. O., Roy, M. J., Widera, G., Swain, W. F., Broome, S., and Edelman, R., 1999. "Phase safety and immune response studies of a DNA vaccine encoding hepatitis B surface antigen delivered by a gene delivery device." *Vaccine*, vol. 17, pp. 2826-2829.

[33] Viral Hepatitis Prevention Board, 1996. "Antwerp VHPB Report. Editorial. Control of viral hepatitis in Europe." *Viral Hepatitis*, vol. 4, Available: http://hgins.uia.ac.be/esoc/VHPB/vhv4n2.html

[34] Centers for Disease Control and Prevention, 1998. "Control measures for hepatitis B in dialysis centers." Available: http://www.cdc.gov/ncidod/hip/control.htm

[35] World Health Organisation, 1999. "Health risks and their avoidance - hepatitis B. In: International travel and health. Vaccination requirements and health advice. Geneva, W.H.O:67."

[36] Alexopoulon, L., Hon, A., Medzhitov, R., and Flavell, R., 2001. "Recognition of double stranded RNA and activation of NF-KB by Toll-like receptors Nature." vol. 413, pp. 732-738.

[37] Heil, F., Hemmi, H., Hochrein, H., Ampenberger, F., Kirschning, C., Akira, S., Lipford, T., H., W., and Bauer, S., 2004. "Species-specific recognition of single- stranded RNA via toll-like receptor-7 and 8." *Science*, vol. 303, pp. 1526–1529.

[38] Moretta, L., Bottino, C., Pende, D., Vitale, M., Mingari, M., and Moretta, A., 2005. "Human natural killer cells, molecular mechanisms controlling NK cell activation and tumor cell lysis." *Immunol let*, vol. 100, pp. 7-13.

[39] Fong, T. L., DiBisceglie, A. M., Biswas, R., Waggoner, J. G., Wilson, L., Claggett, J., and Hoofinagle, J. H., 1994. "High levels of viral replication during acute Hepatitis B infection predict progression to chronicity." *J. Med. Virol*, vol. 43, pp. 155-158.

[40] Thimme, R., Wieland, S., Steiger, C., Ghrayeb, J., Reimann, K., Percell, R., and Chisari, F., 2003. "CD8+ T-cells mediate viral clearance and disease pathogenesis during acute hepatitis B virus infection." *J. virol*, vol. 77, pp. 68-76.

[41] Whalley, S. A., Murray, J. M., Brown, D., Webster, G. J., Emery, V. C., Dusheiko, G. M., and Perelson, A. S., 2001. "Kinetics of acute hepatitis B virus infection in humans." *J. Exp. Med.*, vol. 193, pp. 847-854.

[42] Bertolleti, A. and Ferrari, C., 2003. "Kinetics of immune response during HBV and HCV infection." *Journal of Hepatology*, vol. 38, pp. 4–13.

[43] Wielland, S. F. and Chisari, F. V., 2005. "Shealth and cunning; hepatitis B and c viruses." *Journal of virology*, vol. 79, pp. 9369-9380.

[44] Cote, P. J., Toshkov, I., and Bellazza, C., 2000. "Temporal pathogenesis of experimental neonatal woodchuck hepatitis virus infection: increased initial viral load and decreased severity of acute hepatitis during the development of chronic viral infection." *Hepatology*, vol. 32, pp. 807-817.

[45] Hodgson, P. D. and Michalak, T. I., 2001. "Augmented hepatic interferon gamma expression and T-cell influx characterize acute hepatitis progressing to recovery and residual lifelong virus persistence in experimental adult woodchuck hepatitis virus infection." *Hepatology*, vol. 34, pp. 1049–1059.

[46] Nakamura, I., Nupp, J., Cowlen, M., Hall, W., Tennant, B., Casey, J., Gerin, J., and Cote, P., 2001. "Pathogenesis of experimental neonatal Woodchuck hepatitis virus infection: Chronicity as an outcome of infection is associated with a diminished acute hepatitis that is temporally deficient for the expression of interferon gamma and tumor necrosis factor alpha messenger RNAs." *Hepatology*, vol. 33, pp. 439-447.

[47] Guidotti, L., Rochford, R., Chung, J., Shapiro, M., Purcell, R., and Chisari, F., 1999. "Viral clearance without destruction of infected cells doing acute HBV infection." *Science*, vol. 284, pp. 825–829.

[48] McClary, H., Koch, R., Chisari, F., and Guidotti, L., 2000. "Relative sensitivity of hepatitis B virus and other hepatotropic viruses to the antiviral effects of cytokines." *Journal of Virology,* vol. 74, pp. 2255–2264.

[49] Wieland, S. F., Guidotti, L. G., and Chisari, F. V., 2000. "Intrahepatic induction of alpha/beta interferon eliminates viral RNA-containing capsids in hepatitis B virus transgenic mice." *Journal of virology,* vol. 74, pp. 4165-4173.

[50] Wieland, S., Thimme, R., Purcel, R., and Chisari, F., 2004. "Genomic analysis of the host response to hepatitis B virus infection." *Proc Natl Acad sci USA,* vol. 101, pp. 6669–6674.

[51] Lund, J., Sato, A., Akira, S., Medzhitov, R., and Iwasaki, A., 2003. "Toll – like receptor 9-mediated recognition of herps simpler virus-2 by plasmacytoid dendritic cells." *Journal Exp. Med.,* vol. 198, pp. 513–520.

[52] Bigger, C. B., Brasky, K. M., and Landford, R. E., 2001. "DNA microarray analysis of chimpanzee liver during acute resolving hepatitis C virus infection." *Journal of virology,* vol. 75, pp. 7059–7066.

[53] Su, A. I., Pezacki, J. P., and L., W., 2002. "Erenomic analysis of the host response to hepatitis C virus infection." *Proc Natl Acad Science USA,* vol. 99, pp. 15669–15674.

[54] Menne, S., Roneker, C., Roggendorf, M., Eterin, J., Cote, P., and Tennant, B., 2002. "Deficiences in the acute-phase cell-mediated immune response to viral antigens are associated with development of chronic Woodchuck hepatitis virus infection following neonatal inoculation." *Journal of virology,* vol. 76, pp. 1769-1780.

[55] Grady, G. F., Lee, V. A., and Prince, A. M., 1978. "Hepatitis B immune globulin for accidental exposures among medical personnel: final report of a multicenter controlled trial." *Journal of infect disease,* vol. 138, pp. 625–638.

[56] Ciurea, A., Hunziker, L., Klenerman, P., Hengartner, H., and Zinkernagel, R., 2001. "Impairment of CD4+ T cell responses during chronic virus infection prevents neutralizing antibody responses against virus escape mutants." *Journal of Exp. Med.,* vol. 193, pp. 297-305.

[57] Penna, A., Delprete, G., and Cavalli, J., 1997. "Predominant T-helper I cytokine profile of hepatitis B virus nucleocapsid – specific T-cells in acute self-limited hepatitis B." *Hepatology,* vol. 25, pp. 1022-1027.

[58] Sobao, Y., Tomiyama, H., and Sugi, K., 2002. "The role of hepatitis B virus-specific memory CD8 T cells in the control of viral replication." *Journal of Hepatology,* vol. 36, pp. 105–115.

[59] Seeger, C. and Masan, W., 2000. "Hepatitis B virus biology." *Microbiol Mol Biol Rev.,* vol. 64, pp. 51-68.

[60] Brunetto, M., Giarin, M., and Oliver, F., 1991. "Wild type and e antigen minus hepatitis B virus and course of chronic hepatitis." *Proc Natl Acad Science USA,* vol. 88, pp. 4186–4190.

[61] Banchereau, J., Briere, F., Caux , C., Davoust, J., Lebecque, S., Liu, Y., Pulendran, B., and Palucka, K., 2000. "Immunobiology of dendritic cells." *Annu cev. Immunol,* vol. 18, pp. 67- 811.

[62] Bessesen, M., Ives, D., and Condreay, L., 1999. "Chronic active hepatitis B exacerbation in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine." *Clinical infectious diseases,* vol. 28, pp. 1032-1035.

[63] Gitlin, N., 1997. "Hepatitis B: diagnosis, prevention, and treatment." *Clinical Chemistry,* vol. 43, pp. 1500-1506.

[64] Hollinger, F. B. and Lau, D. T., 2006. "Hepatitis B: the pathway to recovery through treatment." *Gastroent clinics of North Am.,* vol. 35, pp. 895-931.

[65] Lai, C. L. and Yuen, M. F., 2007. "The natural history and treatment of chronic hepatitis B: a critical evaluation of standard treatment criteria and end points." *Annals of Internal Medicine,* vol. 147, pp. 58-61.

[66] Ribeiro, R., Germanidis, G., and Powers, K., 2010. "Hepatitis B virus kinetics under antiviral therapy sheds light on differences in hepatitis." *Journal of infectious disease,* pp. 1309-1318.

[67] Hoofnagle, J. H., Doo, E., Liang, T., Fleischer, R., and Lok, A., 2007. "Management of hepatitis B: Summary of clinical research workshop [Review]." *Hepatitis,* vol. 45, pp. 1056-1075.

[68] Libbus, M. K. and Phillips, L. M., 2009. "Public health management of perinatal hepatitis B virus." *Public Health Nursing (Boston, Mess),* vol. 26, pp. 353-361.

[69] Kire, C. F., 1993. "The epidemiology and control of hepatitis B in sub Saharan Africa." *Prog Med. Virology,* vol. 40, pp. 143-156.

[70] Vandamme, P. and Van, H., 2007. "A review of the long term protection after hepatitis A and B vaccination." *Travel medicine and infectious disease,* vol. 5, pp. 79-84.

[71] Li, X. M., Shi, M. F., Yang, Y. B., Shi, Z. J., Hon, H. Y., Shen, H. M., and Teng, B. Q., 2004. "Effect of Hepatitis B immunoglobulin on interruption of HBV intrauterine infection." *World Journ Gastroenterol,* vol. 10, pp. 3215-3217.

[72] Household, K., 1999. *Hepatitis disorders. In: Codna, H. M., Wilteberg, D. F. Paediatrics and child health Cape Town*. 4 ed. Oxford University press, pp. 559-573.