REVIEW ARTICLE

Hepatitis B in Iran

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Introduction

The hepatitis B virus(HBV) is one of the most common chronic pathogens in the world. Over 2 billion of the world's population have been exposed to this virus. About350 million of these, making 5% of the world's population, are chronic carriers.[1] Annually up to 1 million of this population die due to the consequences of this infection such as cirrhosis and hepatocellular carcinoma.[2] The HBV is 100 time more infectious than HIV (Table 1).

The HBV is a DNA virus with 4 major subtypes all of which share a common antigenic determinant, "a" which is located on the HBsAg. There are two additional pairs of mutually exclusive subtypic determinants d or y, and w or r, constituting the four major subtypes: adr, ayr, adw, and ayw. The subtypes have no clinical significance in terms of severity of disease, progression to chronicity or response to treatment but they are used in epidemiological studies to trace an infection.

To date, six different genotypes of the HBV have been identified (A-E). How these genotypes affect pathogenesis or clinical outcome is not known. There is some evidence that genotype C results in more severe liver disease and genotype B may be associated with the development of hepatocellular carcinoma (HCC).[3]

Epidemiology

The only natural host of HBV is the human being and chronic carriers are the only reservoir of this virus in nature.

It is estimated that over 35% of Iranians have been exposed to the HBV and about 3% are chronic carriers[4], ranging from 1.7% in Fars Province to over5% in Sistan and Balouchestan . In a study performed on 250,000 healthy volunteer blood donors in Tehran, 3.6% of male and 1.6% of female donors were HBsAg carriers. Anti-HBc antibody was detected in 37% of this population. Thus, it appears that 8% of Iranians infected by HBV will become chronic carriers.[5]

Among Iranian cirrhotics, 70-84% have evidence of exposure to HBV and 51-56% are carriers.[6,7] In addition, Iranian patients with hepatocellular carcinoma (HCC) show a 72% rate of exposure (as judged by a positive HBcAb) and a 46% carrier rate.[7] These data suggest that HBV is the most common cause of cirrhosis and HCC in Iran.

The neonatal vaccination program launched in 1992 is not expected to change these figures for the general population before the year 2002. Following the neonatal vaccination programs which was begun in 1989 in Saudi Arabia, the overall HBsAg carrier rate in children younger than 12 years

dropped from 6.7% in 1989 to 0.3% in 1997.[8] A similar phenomenon is expected in Iran.

Mode of transmission

HBV is mainly transmitted by the parenteral route. Before routine tests on blood donors, blood transfusion was a very common mode of HBV transmission. Although it is now very rare for blood and blood product transfusion to transmit the disease, it still continues to do so. This could be due to many factors, including testing during incubation period, low level carriers, and S-mutant strains. Some investigators suggest that blood donors also be screened for anti-HBc and/or HBV DNA (Table 2).

Another common mode of transmission is through the percutaneous route which occurs through the sharing of needles by intravenous drug users or reuse of contaminated sharp instruments for tattoos, acupuncture, or ear piercing. Over 25% of intravenous drug users in prison (8.4% of all prisoners) in southern Iran were HBV carriers (unpublished data). As a group, prisoners are considered to be at high risk of developing the infection.

Sexual transmission is the most important mode of spread of HBV in most developed countries and accounts for approximately 30% of acute HBV infections in the United States. Interestingly, in contrast to HIV, the risk of heterosexual transmission is greater when the infected individual is female than when the infected individual is male.[9] Over 75% of the wives of male Iranian carriers have natural immunity against HBV.[10]

The rate of neonatal HBV infection from infected mothers (perinatal transmission) is less than 10% in Western countries. In one Iranian study, over 50% of mothers of HBsAg positive individuals were also carriers.[10] It may be concluded that over 50% of Iranian carriers have contracted the infection perinatally making this route the most likely route of transmission of HBV in Iran. In highly endemic regions, the rate of perinatal infection can be as high as 90%, especially if the mother is HBeAg or HBV DNA positive.[11] Perinatal transmission may occur at three different times: In-utero, during delivery, or after birth. Vaccination of neonates born to HBV positive carriers has a high success rate (95%). Thus, infection probably occurs predominantly at or after birth. Cesarean section does not prevent maternal-infant transmission and is not indicated. Breast-feeding also does not appear to significantly increase the risk of transmission.

Health care environment is another source of viral transmission. There are many reports of HBV infections acquired through infected surgeons, dentists, the equipment they use, and needle stick injuries. Some medical specialties are associated with greater risk of transmission of HBV: dentistry, thoracic surgery, obstetrics and gynecology, general surgery, orthopedic surgery, neurosurgery, cardiology, gastroenterology and nephrology. Needle stick injury by an infected needle can result in transmission of HBV in 12% of cases (2-5% if HBeAg is negative and 27-40% if HBeAg is positive) whereas the probability is only 0.29% for HIV.

Health workers are at particular risk of developing the infection. In a study from Egypt combined HBsAg and anti-HBs frequencies by occupational group were: Nonprofessional staff 60% dentists 32%, graduate nurses 33%, physicians 29%, and student nurses 26%.[12] In a similar study performed on the health workers of the National Iranian Oil Company (NIOC), 23% had evidence of exposure to HBV and 1.8% had a positive HBsAg. In this study, the laboratory personnel were found to be at higher risk than other health workers (RR: 8.8).[13]

In spite of HBsAg screening of hemodialysis patients, this technique is another well-known source of transmission. Unfortunately renal failure patients on hemodialysis fare poorly once infected with HBV. Progression to chronicity and cirrhosis is the rule (over 80%) in these cases and liver transplantation is often not successful.

Acute infection

Acute hepatitis B is the most common cause of hepatitis among Iranian adults. Only a third of acute infections present with an icteric sign, the rest are either totally asymptomatic or only have flu-like symptoms.[5]

During the prodromal period, a serum sickness-like syndrome develops in 10-20% of patients. Malaise, anorexia, nausea, vomiting, low-grade fever, myalgia, and easy fatigability usually follow. Extrahepatic complications are also sometimes observed (Table 3). Occasionally right upper quadrant or midepigastric pain or taste and smell disorders are seen. Smokers may have a

distaste for smoking. Jaundice usually begins within 10 days of the onset of prodromal symptoms as the constitutional symptoms subside and it may persist for 1 to 3 months.

Physical examination may be normal except for jaundice, mildly tender hepatomegaly and a low-grade fever. Splenomegaly may be found in approximately 5 to 15% of patients. Occasionally, mild lymph node enlargement, palmar erythema or spider nevi is also seen.

About0.1 to 0.5% of acute cases progress to fulminant hepatitis. Hepatitis B is the most common cause of fulminant hepatitis in Iran.[5] Such patients present with encephalopathy, spontaneous bleeding due to coagulopathy, and a progressive decrease in liver span. It should be noted that due to massive destruction of hepatocytes, the HBsAg may be undetectable in fulminant hepatitis and serum aminotransferase levels may not be as high as non-fulminant acute hepatitis B. The mortality of fulminant hepatitis B is over 80% and the only effective treatment is urgent liver transplantation. Following fulminant HBV infection the recurrence of HBV in a liver transplant is uncommon.

Chronic infection

Patients not able to clear the virus as judged by a positive HBsAg six months after the acute episode are unlikely to spontaneously recover and are known as chronic cases. In these patients, spontaneous clearance of HBsAg occurs at an annual rate of only 0.5-2%. Spontaneous loss of HBeAg and serum HBV DNA occurs in 10 to 15% of cases.

The risk of chronicity is inversely proportional to the age at infection. Less than 5% of immunocompetent adults with acute HBV infection progress to chronic infection, but 30% of children infected between the ages of 1 and 5 years and up to 90% of those infected during infancy will develop chronic infection.[11, 14] Chronicity seems to be more common in males as also reported in studies from Iran.[15] Although some other Iranian studies do not show such male preponderance.[16] There are many known factors which favor progression to chronicity (Table 4).

The old practice of classifying chronic cases under healthy carriers, chronic persistent or chronic active hepatitis should no longer be used. Instead, the degree of activity of the disease should be assessed by histological examination and staging.

Patients with chronic disease are usually

asymptomatic or have non-specific symptoms such as fatigue. In advanced cases, signs of cirrhosis and liver decompensation such as portal hypertension, ascites, variceal bleedings, hepatic encephalopathy, renal and hepatorenal failure and hepatocellular carcinoma would also prevail. Hepatocellular carcinoma is an important sequel of chronic HBV infection and all chronic carriers should be screened annually, or preferably bi-annually, by a-feto-protein and/or ultrasonography.

Mutants

Among the many mutants of the HBV, the most important are probably the precore mutant, the S mutant, and the YMDD variants.The precore mutant has a mutation in the precore area of its genome, which renders the virus incapable of producing HBeAg. Some investigators believe that the HBeAg is responsible for producing some degrees of immune tolerance. There are many reports that this mutant causes a more severe disease and is less responsive to treatment.[17,18]

Unfortunately, it is estimated that almost 58% of HBV infections in Iran are precore mutants.[19] In addition to being less responsive to treatment, the treatment of precore mutants may be delayed by the false impression that a negative HBeAg indicates a non-replicative infection and thus, does not require treatment. Such practice should be discouraged.

Transaminase levels have been shown to reflect histologic activity in HbeAg-negative chronic HBV carriers with an accuracy of 72-75%.[20] In one study HBV DNA (by bDNA assay) was detectable in 46% of HbeAg-negative patients with ALT above normal versus 7% of patients with normal ALT. If the HBeAg is negative but liver enzyme levels are elevated, an HBV DNA testing and/or histologic examination of the liver is indicated.[21]

Less frequently, a mutation may occur in the S gene affecting the "a" determinant of the HBsAg. Since the "a" determinant is the target for immunization against HBV, such S mutants are vaccine escape mutants and a subject which has received effective immunization against HBV through vaccination may still acquire infection with this mutant. In the future, it may be necessary to produce a bivalent vaccine also covering the mutant "a" determinant. Fortunately, the S mutant is not frequently reported throughout the world. Very few vaccines escape mutants and have been reported in Iran(unpublished data). Another concern with these mutants is that monoclonal commercial tests for HBsAg directed at the "a" determinant may fail to detect the HBsAg produced by these mutants. This phenomenon may partially explain the occasional transmission of HBV hepatitis by blood or blood products in spite of donor screening for HBsAg. Tests using polyclonal antibodies against HBsAg will overcome this problem.

YMDD variants mainly occur during the treatment of chronic HBV. The YMDD region on the viral polymerase is an area where most reverse transcriptor inhibitors such as lamivudine or famciclovir exert their effect. Variations in this area result in partial resistance to these drugs. Unfortunately the appearance of YMDD variants is induced by the use of lamivudine. After a year of lamivudine therapy, 24% of patients show evidence of YMDD variants.

Serologic markers and diagnostic tests:

HBsAg

The HBsAg appears in the serum 1 to 10 weeks after an acute exposure to HBV and approximately 2 to 6 weeks before the onset of symptoms or elevation of transaminases. In patients who recover from HBV infection, HBsAg usually becomes negative after 4 to 6 months. Persistence of HBsAg for more than 6 months defines chronic infection.

Anti-HBs

This is the only protective antibody among antibodies produced against HBV. The appearance of anti- HBs indicates recovery from the acute disease and development of immunity. There may be a gap between the disappearance of HBsAg and appearance of anti-HBs. This period is classically known as the window period during which the only marker of HBV infection is the anti-HBc (see be- low). By the introduction of more sensitive tests for HBsAg and anti-HBs, this phenomenon is less frequently observed.

The protective anti-HBs antibody is directed against the "a" determinant of HBsAg. Coexistence of HBsAg and anti-HBs has been reported in about 24% of HBsAg-positive individuals.[22] In most instances, the antibodies are directed against one of the determinants other than the "a" determinant and are unable to neutralize the circulating virions.[23] These cases should therefore be regarded as chronic infections.

HBeAg

HBeAg is a marker of active HBV replication and infectivity. Its presence is usually associated with high infectivity of blood and increased mother to child transmission. It is usually associated with other replication markers such as HBV DNA polymerase or HBV DNA in serum. Positive HBeAg has been reported in 9.4-13.8% of otherwise healthy Iranian blood donors carrying theHBsAg.[16.24]

Precore mutants do not produce the HBeAg and may be actively replicating in the absence of detectable HBeAg in the serum. Patients with precore mutants may still have anti-HBe antibodies in their sera.

Anti-HBe

The appearance of this antibody follows the disappearance of HBeAg and usually marks non-replicative viral infection and inactive disease or response to treatment. It should be noted however that in Iran about58% of HBV infections are precore mutants[19] and may have anti-HBe in spite of being actively replicating. Thus, an undetectable HBeAg or the presence of anti-HBe per-se should never be assumed to indicate non-replicative infection.

HBcAg

This antigen is an intracellular antigen that is expressed in infected hepatocytes and is not detectable in serum.

Anti-HBc

This is not a protective antibody and its presence indicates exposure to HBV. IgM anti-HBc indicates acute infection and IgG anti-HBc indicates remote exposure or chronic infection. During the window period (see above) in addition to HBV DNA, IgM anti-HBc may be the only serologic marker of acute HBV infection. Occasionally anti-HBc may also be the only indicator of remote infection. In one study on 4930 subjects in Iran, 5.13% were only positive for anti-HBc, without any detectable HBsAg.[16]

HBV DNA

There are various methods for detecting HBV DNA in the serum which can be grouped into PCR assays and non-PCR assays. The non-PCR assays include the hybridization and branched DNA (bDNA) assays which can detect 10^6 and 10^5 particles/ml respectively. The PCR assays can detect as low as 1-10 particles/ml. The PCR test is the first test to become abnormal in HBV infections, often 2-3 weeks before HBsAg can be detected in the serum.

Not recognizing the difference between the extremely sensitive PCR assays and the less sensitive non-PCR ones has been a source of confusion. HBV DNA, when detected using non-PCR assays, just like the HBeAg, can be considered to represent replicative viral infection. On the other hand, HBV DNA when detected by PCR assays does not necessarily indicate active viral replication. HBV DNA may remain detectable by PCR assays for many years even when the patient is considered to

have cleared the infection and HBsAg has become undetectable.[25]

Treatment

Acute cases of HBV infection require no treatment. Over 90% of acute cases will spontaneously clear the virus within 6 months. Again, not all chronic cases require treatment. The usual approach is that if the liver enzymes are not elevated, the patient is only followed every 6 months for signs of activation and progression to HCC. If liver enzymes are elevated, a liver biopsy is indicated. The degree of histologic inflammation should be graded using the HAI system and an HAI score of 4 or greater indicates the need for treatment.

There are currently two treatment modalities approved for treating chronic HBV infections; interferon-a (IFN), an immune modulator, and recently lamivudine (LAM), a reverse transcriptor inhibitor.

Interferon-a

Interferon-a is usually administered as subcutaneous injections in doses of 5 million units (MU) daily or 10 MU three times a week for 16-24 weeks. In Iranian patients we recommend a course of 24 weeks. There is no evidence that prolonging treatment over 24 weeks results in better response rates. Loss of viral replication markers (HBeAg and serum HBV DNA by non-PCR assays) within 12 months of initiation of treatment can be achieved in 30 to 40% of patients. Some patients respond during the follow-up period, after treatment has been stopped.[26 29]

Reactivation occurs in 10-20% of responders and usually occurs in the first post-treatment year.[30,31] Loss of HBsAg is less common and occurs in only 5 to 10% of patients.[29] Among responders, serum HBV DNA (by hybridizing methods) usually becomes undetectable early during treatment but HBeAg to anti-HBe seroconversion may be delayed. Precore mutant infections are more difficult to treat and there is a high relapse rate.[17,18]

Probably the most troublesome side effect of IFN is emotional liability; characterized by anxiety, irritability, depression, and even suicidal tendencies. Another troublesome side effect of IFN is its ability to cause anemia and hemolysis which makes it a poor choice in anemic patients such as thalassemics and hemophiliacs. IFN is an immune system stimulant so it will worsen autoimmune diseases such as autoimmune hepatitis making it essential to rule out autoimmune hepatitis before starting IFN. Thyroid disease is particularly important and thyroid tests are ordered before starting IFN. IFN can promote destruction of hepatocytes and is thus not given to patients with advanced hepatic disease and cirrhosis, it may perpetuate hepatic decompensation. Other side effects include influenza-like symptoms, fatigue, hair loss, anorexia and weight loss.

Predictors of better response to IFN include high pretreatment ALT levels, low serum HBV DNA levels, adult-acquired infection, female sex, active liver inflammation, and absence of HIV and HDV co-infection. Long-term disease and Asian origin is predictive of a poor response.

There is also some evidence that IFN may be helpful in treating patients with extrahepatic manifestations of chronic HBV infection such as polyarteritis nodosa and glomerular diseases.

Lamivudine

Lamivudine (Zeffix®, Epivir®), a reverse transcriptor inhibitor, can be given at a dose of 100mg daily for one year.[32,33] Shorter treatment periods result in high relapse rates but at this dosage, it has an effectiveness comparable to IFN, although recurrence is still a concern.[34] Asians are known to

respond less favorably to lamivudine. But even in these patients, prolonging the treatment period to 2 years results in better response rates. A recent trial on 358 Chinese patients showed a 17% response rate after one year and 27% after two years of therapy.[35] In Iran, we currently recommend 2 years of treatment with 100mg lamivudine daily.

LAM is also effective in HBeAg negative patients[36] where IFN therapy has not been so successful[17,18] Longer treatment periods are under study especially for treating the precore mutants which are less responsive to IFN. LAM is generally better tolerated and, in contrast to IFN, can be safely used in patients with advanced liver disease and anemia.

Acute exacerbations of chronic HBV infection occurs after withdrawal of lamivudine therapy in approximately 16-17% of patients, especially with shorter durations of therapy. But this exacerbation is considered to be of little clinical significance.[37]

Recently, lamivudine has been adopted by the Iranian Ministry of Health and will soon be covered by major insurance companies. LAM could be the first choice for patients in whom IFN is not considered to be safe, i.e. cirrhotics, thalassemics, hemophiliacs, etc. It may also be used as a de-novo therapy for chronic hepatitis B. LAM can induce the appearance of YMDD variants but the variants disappear within 6 months of drug discontinuation . The appearance of these variants is marked by a moderate increase in serum aminotransferase levels. Although, it does not approach the pretreatment levels.[32] The YMDD variants, although partially but still are responsive to LAM and LAM is not discontinued in patients developing these variants.

It is of interest that the combination of IFN and LAM is less effective than either alone[38,39] and they should not be given together.

The D particle

The hepatitis D virus (HDV), also known as the delta or D particle, can only superinfect patients already infected with HBV. There is some evidence that HDV favors the precore variant of HBV.[40,41]

The superinfection of HDV on a previous carrier of HBV usually results in a flare-up of hepatic disease or occasionally, progression to fulminant hepatic failure. These cases also carry a 90% risk of becoming chronic HDV carriers.[42] In the remaining cases, superinfection resolves with persistence of the original HBV infection or rarely, with clearance of the HBsAg. HDV has a strong inhibitory effect on HBV replication. It is frequently observed that HBV DNA becomes undetectable even by sensitive PCR assays.[43]

Depending on region, up to 60% of chronic HBV carriers are also infected with the D particle. About 50% of Iranian cirrhotics are anti-HDV positive.[44]

In Iran, 2.4-14% of otherwise healthy HBsAg carriers and 50% of cirrhotics are infected with the HDV.[16,44,45] A similar report from Uzbekistan states that 14% of HBV carriers under the age of 14 are HDV positive.[46] Similarly, in Saudi Arabia, 13.6% of drug-dependent HBsAg-positive patients are HDV positive.[47] Among HBsAg positive Iranian hemodialysis patients, 44.5% are also infected with HDV.[43]

Patients with chronic hepatitis D often have significant splenomegaly and report a previous episode of acute hepatitis, presumably corresponding to the primary superinfection. This is in contrast to the ordinary HBsAg carrier who rarely gives a history of acute hepatitis.[42]

Treatment of HDV hepatitis is no different from that of the underlying HBV infection but the long-term response rate is only about 15-20%, less than lone HBV infection.

Prevention

Because of the relatively low cost of production and the abundant source of HBsAg positive plasma in endemic countries, worldwide about 80% of all vaccines produced are plasma-derived.[48] However, the vaccine currently available in Iran is a recombinant vaccine. This vaccine is produced by cloning the S gene, which encodes the HBsAg, through the use of a plasmid vector inserted into common baker's yeast.

The vaccine is usually administered in 3 doses of 20µg at 0, 1 and 6 months in the deltoid muscle (not gluteal). The dose for individuals less than 19 years of age is 10µg. For immune suppressed patients or those requiring chronic hemodialysis, a double dose of40 µg is recommended.

Anti-HBs levels of 10 mIU/mL or higher are thought to be protective. Vaccination has been reported to result in adequate protection in about 90% of cases. The overall seroconversion rate to vaccine among 4,087 Saudi children up to 12 years of age was about 77%. Seroconversion rate in those vaccinated at birth was 77% compared with 71% in those vaccinated at school entry.[8] Unpublished data from Zahedan, eastern Iran, also indicates 78.5% effectiveness whereas another study from Sanandaj, western Iran reports 92.6% effectiveness in newborns.[49] Nevertheless, routine post-vaccination testing to document anti-HBs seroconversion is unnecessary except in health care workers, patients on chronic hemodialysis and other individuals who are at risk of recurrent exposure to the HBV. In nonresponders and hyporesponders (anti-HBs < 10 mIU/mL), additional or increased doses have been reported to elicit seroprotective levels in about half of the cases.[50,51,52]Individuals less than 40 years of age respond better than older individuals. Neonates and preterm infants also have a slightly lower response rate.[53] Other conditions showing diminished responsiveness are shown in Table 5. Another group of nonresponders are otherwise healthy individuals in whom the lack of responsiveness appears to be genetically determined.

The duration of protection against infection remains uncertain, but many studies indicate that protection against clinical disease is well prolonged[54], although levels of anti-HBs may fall below the 10 mIU/mL threshold. Anti-HBs disappears from the serum of as many as 40% of vaccinated adults within 10 years Nonetheless, immunity against clinical disease persists for years after the loss of anti-HBs. The need for booster doses, therefore, remains uncertain in healthy adults. Although, in immunosuppressed patients, including those on chronic hemodialysis, anti-HBs levels should be tested annually and booster doses given if levels fall below10 mIU/mL .[55]

Vaccination is recommended for all infants born to HBsAg negative mothers and has been included within Iran's national vaccination program since1992. Furthermore household contacts of patients infected with HBV and high risk groups should also be vaccinated. (Table 6)

Whether or not to test for HBsAg positivity before administering HBV vaccine is a point of controversy. A report based upon commercial retail rate of the hepatitis B vaccine in the United States suggested that prevaccination testing is cost-effective only in populations where the prevalence of anti-HBs positivity exceeds 30%.[56] In Iran however, we currently do not suggest prevaccination testing except in possibly high risk groups where testing has a higher gain and also helps in identifying carriers.

Post-exposure prevention

Infectivity depends on the concentration of viral particles in the blood and the presence or absence of

markers of viral replication (HBV DNA by non-PCR assays, HBeAg, HBV polymerase, etc). The chance of contracting the infection after a needle stick injury will be about 2-5% if HBeAg is negative, and 27-40% if it is positive. The victims of needle stick or splashing incidents or those with sexual exposure should be immediately vaccinated against HBV and should concomitantly receive hepatitis B immunoglobulin (HBIG). HBIG is given at a dose of 0.04 to 0.07 ml/kg and injected at a different site from that of the vaccine. In the case of needle stick incidents the vaccine and HBIG should be administered within 12 hours while in sexual contact prophylaxis is effective even when delayed up to 14 days.[57]

Infants born to HBsAg-positive mothers should receive both HBV vaccine and HBIG (0.5 ml), within 12 hours of birth. Vaccination of these infants is the most important step towards the eradication of chronic HBV infection. Protective efficacy exceeds 95%.[58] In some countries, similarly high protective efficacy rates have been reported without concomitant HBIG administration.[59] However, studies in Taiwan and Hong Kong found that the protective efficacy of vaccine alone was significantly lower being only 75 to 80 percent.[60,61] Infants born to HBsAg-positive mothers should be tested at about 12 months of age to detect vaccine failures.

Recommendations for control of HBV infection in Iran

In spite of the availability of an effective vaccine and the incorporation of HBV vaccination in to the national infant vaccination program,hepatitis B continues to be an important health problem in Iran. Some of the more important reasons for vaccination hold back are summarized in Table 7.

To overcome these problems many steps must be taken among which providing adequate information to the public is probably the most important. Health care providers should also be further informed through continuous medical education programs and actively involved in the control of this disease. According to surveys performed in Iran, less than 60% of health care providers are vaccinated against HBV in spite of the availability of free vaccination programs for this group. This fact underlines the need for promotional programs urging high risk groups to comply with such vaccination routines.

Some third world countries, such as China and Korea, are now producing their own HBV vaccine, which has drastically reduced the cost of vaccination in these countries. We too should plan to accelerate the already begun production of both the vaccine and medications such as IFN and LAM in Iran.

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