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REVIEW ARTICLE

Treatment of chronic hepatitis B virus infection in resource-constrained settings: expert panel consensus

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Abstract

Most of the estimated 350 million people with chronic hepatitis B virus (HBV) infection live in resource-constrained settings. Up to 25% of those persons will die prematurely of hepatocellular carcinoma (HCC) or cirrhosis. Universal hepatitis B immunization programmes that target infants will have an impact on HBV-related deaths several decades after their introduction. Antiviral agents active against HBV are available; treatment of HBV infection in those who need it has been shown to reduce the risk of HCC and death. It is estimated that 20–30% of persons with HBV infection could benefit from treatment. However, drugs active against HBV are not widely available or utilized in persons infected with HBV. Currently recommended antiviral agents used for treatment of human immunodeficiency virus (HIV) infection do not adequately suppress HBV, which is of great concern for the estimated 10% of the HIV-infected persons in Africa who are co-infected with HBV. Progressive liver disease has been shown to occur in co-infected persons whose HBV infection is not suppressed. In view of these concerns, an informal World Health Organization consultation of experts concluded that: chronic HBV is a major public health problem in emerging nations; all HIV-infected persons should be screened for HBV infection; HIV/HBV co-infected persons should be treated with therapies active against both viruses and that reduce the risk of resistance; standards for the management of chronic HBV infection should be adapted to resource-constrained settings. In addition, a research agendum was developed focusing on issues related to prevention and treatment of chronic HBV in resource-constrained settings.

The World Health Organization (WHO) is developing guidance for the treatment of persons who are chronically infected with the hepatitis B virus (HBV) in resource-constrained settings. WHO called for a technical consultation as an informal process of getting expert input into the next steps for dealing with the significant public health problem posed by HBV infection and its related disease burden. This consultation included representatives from professional medical associations dedicated to the study of liver diseases who were familiar with treatment guidelines in well-resourced settings as well as clinicians from resource-constrained settings and partner agencies. The findings and recommendations of this consultation do not constitute formal WHO policy or

recommendations; however, they will be important in addressing the needs of millions of HBV-infected persons globally.

Background

Worldwide, an estimated 2 billion people have been infected with the HBV, and more than 350 million have chronic (long term) HBV infections. The WHO estimates that 500 000–700 000 people die from HBV infection worldwide each year (1). A recent analysis indicated that 1.4 million persons born in 2000 would die prematurely because of HBV infection (2).

Globally, HBV is estimated to account for 53% of all cases of hepatocellular carcinoma (HCC), the most frequent type of liver cancer (3). As many as 25% of those with chronic hepatitis B are at risk for developing cirrhosis, resulting in decompensated cirrhosis, liver failure and/or HCC during their lifetimes (4). In some countries in Asia, HCC – in large part because of HBV – is one of the top three causes of death in males (3). In developed countries, most persons with chronic HBV infection were born in endemic countries from where they migrated. HBV infection is a major public health threat on a similar scale of magnitude as human immunodeficiency virus (HIV), malaria and tuberculosis (5).

The greatest risk of acquiring chronic HBV infection is by perinatal transmission (90%), followed by horizontal transmission during the first 5 years of life (30%) (6, 7). Vaccines against HBV have been available since 1982. Vaccination of infants is 90–95% effective in preventing HBV infection. To decrease transmission of HBV, the WHO has recommended universal hepatitis B vaccination for all infants (8). This strategy has resulted in a dramatic decrease in the prevalence of young children who are positive for HBsAg, the serological marker of chronic HBV infection, in regions of the world where universal infant vaccination programmes have been implemented. However, as the highest incidence of serious complications of HBV infection occurs later in life, usually in persons older than 40 years, a large residual pool of chronically infected individuals remain (2). It will require several decades after the initiation of hepatitis B vaccination programmes to realize a decline in the incidence of HBV-related HCC, cirrhosis and overall liver-related disease in endemic regions.

Chronic HBV infection is a dynamic state in which people can move through several phases of disease. Many persons will eventually develop an inactive form of chronic hepatitis B and may not need treatment. The phases of chronic hepatitis B are listed in Table 1. However, between 20 and 30% of persons have active liver inflammation that can progress to cirrhosis and HCC. Treatment of those high risk persons with chronic HBV infection is a means of reducing the morbidity from the disease in the next 30–40 years until the effect of universal infant vaccination.

Currently, seven antiviral agents are approved for the treatment of chronic HBV infection in industrialized countries, and have been shown to delay progression of cirrhosis, reduce the incidence of HCC and improve long-term survival (9). Several professional, international Hepatology organizations have developed guidelines for treatment of chronic HBV infection (9–11). Treatment, however, is not readily accessible in many resource-constrained settings, where most people infected with HBV live. Published guidelines often require diagnostic methods (e.g. liver biopsy) to determine eligibility for treatment. Also, several antiviral drugs cannot be used generally in countries because of their unavailability and the lack of clear guidelines on their use.

This concept paper discusses the feasibility of providing antiviral treatment for persons with chronic HBV infection in resource-constrained settings (including selection of patients, selection of therapeutic agents and follow-up of patients in treatment) and outlines a global strategy for increasing access to treatment to decrease hepatitis B-related mortality and morbidity.

Therapeutic options for hepatitis B virus control

Some of the drugs available for the treatment of HBV, including tenofovir, lamivudine and emtricitabine, are also active against HIV; entecavir has weak anti-HIV activity (12). Table 2 shows the activity of these drugs against HBV and HIV. In a recent double-blind controlled trial of lamivudine for treatment of people with chronic HBV and compensated cirrhosis, recipients of lamivudine showed a significantly decreased incidence of decompensated cirrhosis, liver-related death and HCC compared with the placebo group over a 3-year period (13). The outcome was less favourable after the onset of lamivudine resistance. This trial provided strong

Table 1. Phases of chronic hepatitis B virus infection

HBV phase	HBeAg	ALT level	HBV DNA level	Liver biopsy: inflammation and fibrosis	Treatment indicated
Immune tolerant	Positive	Normal	Very high: > 10 million IU/ml	None to minimal	No
Immune active	Positive or negative	Elevated	High: > 20 000 IU/ml	Mild to severe	Yes, in selected persons
Inactive Phase	Negative	Normal	Low: < 2 000 IU/ml	None to mild	No
HBsAg clearance	Negative	Normal	Low: < 2 000 IU/ml	None to mild	No

ALT, alanine aminotransferase; HBV, hepatitis B virus.

Table 2. Antiviral agents active against hepatitis B virus infection

Antiviral agent	Potency against HBV	Resistance barrier	Activity against HIV	Cost*
Interferons	Moderate	None	Moderate	High
Lamivudine	Moderate–high	Low	High	Low
Tenofovir	High	High	High	Low
Emtricitabine	Moderate	Low	High	Low†
Telbivudine	High	Low	Unclear	High
Adefovir	Low	Moderate	None (at 10 mg dose)	High
Entecavir	High	High	Weak	High

*For resource restricted countries.

†Emtricitabine is not available as a single agent.

HBV, hepatitis B virus; HIV, human immunodeficiency virus.

evidence that the risk of serious complications of HBV infection could be reduced by effectively treating advanced liver disease. However, the cost of several agents and licensing or distribution agreements still preclude their use or optimum use in many endemic regions.

Lessons from human immunodeficiency virus control

In the past few years, various organizations have developed comprehensive programmes to reduce the substantial mortality rate from HIV, especially in countries in Africa (14). In addition to measures to prevent HIV infection, four key strategies have been used to reduce the mortality from HIV: (i) identifying infected persons by screening and confirming HIV infection; (ii) determining candidates for antiviral therapy by ascertaining HIV–RNA concentrations and CD4 cell counts; (iii) selecting appropriately effective combinations of antiretroviral agents based on antiviral resistance patterns, efficacy and cost; (iv) monitoring patients for antiviral resistance. These programmes have had a dramatic effect in preventing death from chronic HIV infection in areas where they have been introduced and in returning persons previously ill with AIDS to a state of health where they can again care for their families, attend school or resume working (14).

Rationale for programmes for the treatment of hepatitis B virus monoinfection and hepatitis B virus/human immunodeficiency virus co-infection in resource-constrained settings

It is estimated that perhaps 10% of the 40 million people infected with HIV worldwide are co-infected with HBV; the majority live in resource-constrained settings. As many as 3 million HIV-HBV co-infected persons live in Africa (15). Although HBV infection appears to have a minimal effect on the progression of HIV, the presence of HIV markedly accelerates the progression of liver fibrosis, and thereby may increase the risk of developing HCC and cirrhosis by accelerating the progression to these adverse consequences in many co-infected persons (16–18). Moreover, the more widespread use of antiretroviral therapy may lead to immune restitution and worsening of immune-mediated chronic hepatitis. A recent meta-analysis of studies examining overall mortality showed an increase in mortality among HIV-positive persons because of co-infection with HBV both before and after commencement of HAART (19). Furthermore, a multicentre prospective study showed that persons with HBV/HIV co-infection were eight times more likely to die of liver disease than HIV patients infected with HIV alone and 19 times more likely than those with HBV alone (20). Thus, hepatitis B will contribute significantly to morbidity in HIV-HBV co-infected patients unless treated appropriately.

In resource-constrained settings, treatment of HIV usually comprises two nucleoside reverse transcriptase inhibitors (one of which is lamivudine), and one non-nucleoside reverse transcriptase inhibitor such as nevirpaine or a protease inhibitor. HBV testing is not routinely performed before HIV antiviral therapy is started. This can result in major untoward consequences. First, this HBV-blind therapy may lead to HBV resistance. In fact, up to 90% of HIV/HBV co-infected persons treated with lamivudine are resistant to lamivudine after 4 years of treatment, leading to the potential progression of hepatitis B disease. There is a critical need, therefore, to identify HBV and HIV coinfection in order to optimize the therapy of both diseases. At the time of this consultation, recommended HAART was inadequate in the 10% of HIV patients with HBV co-infection. In 2010, the WHO recommended that tenofovir plus either 3-TC (lamivudine) or emtricitabine be included in the HAART regimen for HBV/HIV co-infected persons. However, no recommendation for screening HIV persons for HBV was made. Therefore, there is a need to develop strategies to identify HIV/HBV co-infection to meet the new 2010 WHO recommendations.

Apply preexisting infrastructure developed for human immunodeficiency virus programmes to hepatitis B virus treatment programmes

The existing infrastructure for the HIV programmes could be adapted to accommodate both HBV and HIV screening and treatment programmes. The important components for successful HBV treatment programmes include: (i) the ability to diagnose persons infected with HBV by testing for HBsAg; (ii) tests to determine high viral replication, HBeAg and lower viral replication, antibody to HBeAg; (iii) testing for aminotransferase activities [primarily alanine aminotransferase (ALT) and aspartate aminotransferase (AST)]; (iv) ideally, testing for HBV-DNA concentrations with polymerase chain reaction technology that is also utilized to measure HIV–RNA levels; (v) making available the most potent antiviral agents with high barriers to resistance that suppress HBV in both mono-infected and co-infected patients; (vi) the ability to test for antiviral resistance in persons receiving HBV therapy.

All these components can be implemented with minimal impact to existing programmes in areas where HIV programmes are in place. Testing for HBsAg can be carried out with the same diagnostic instrumentation used for HIV, usually an enzyme-linked immunosorbent assay. In addition, rapid, relatively inexpensive tests for HBsAg that do not need complicated equipment have been developed and are already used in some resource-constrained countries for screening blood donors. Measuring aminotransferase activities is a routine procedure in most hospital laboratories. Laboratory equipment already used to test for HIV–RNA levels, if available, can be used to determine HBV–DNA concentrations utilizing appropriate primers. This same technology, used for HIV resistance testing can be used for HBV resistance testing.

How to select people for hepatitis B virus treatment in resource-poor settings

Liver biopsy is neither readily available nor affordable in many regions of the world. Therefore, criteria for treatment that do not mandate invasive procedures such as liver biopsy are more practical for selecting persons for HBV treatment.

Selection of candidates with hepatitis B virus mono-infection for treatment in resource-poor settings

Ideally, treatment should be given to persons with evidence of progressive disease. However, as in most emerging nations, testing for HBV-DNA and liver biopsy are not readily available, and identification of such patients is difficult. Treatment should be given to persons diagnosed with cirrhosis (by any means available, including physical examination, AST/ALT ratio, platelet count, ultrasound, histology, physical imaging studies or fibrosis markers). Patients with decompensated cirrhosis (ascites, bleeding oesophageal varices, splenomegaly, encephalopathy or coagulopathy) should be treated, as antiviral therapy can be life saving, but is also less effective at this stage.

The following should also be offered treatment: HBeAg-positive subjects above the age of 40 years with elevated ALT in whom the risk of HCC has been shown to be extremely high; individuals positive for HBsAg and HBeAg with ALT levels more than twice the upper limit of normal for at least 1 year: individuals negative for HBeAg and ALT more than twice the upper limit of normal for at least 1 year and over the age of 40; and HBsAg-positive persons with ALT levels > 10 times the upper limit of normal regardless of HBeAg status.

Recommendations

Whenever possible, guidelines established by Continental Liver Societies should be followed. Recommendations for countries with restricted resources are listed below.

General recommendations

1. Viral hepatitis (B and C) should be recognized as a major public health threat on a similar scale of magnitude as HIV, malaria and tuberculosis.
2. More precise data, should be obtained by all means, of the burden of disease because of viral hepatitis (B and C).
3. WHO should facilitate the mobilization of adequate funding from the governments of WHO's Member States and other non-government donors for programmes in viral hepatitis (B and C).
4. Comprehensive HBV programmes should be developed in all countries, especially in areas of high endemicity, because effective hepatitis B immunization programmes will not significantly reduce the global burden of HBV-related disease for four to seven decades.
5. HBV management programmes should be coordinated with other well-established health programmes (such as HIV) in countries where such programmes exist.

Strategy for increasing access to treatment for HBV infection

Goal: Decrease morbidity and mortality from hepatitis B virus-related diseases

Diagnosis and screening for hepatitis B infection

1. Guidelines for screening and diagnosis of HBV in resource-limited settings should be developed in order to identify and manage people with chronic infection.
   a. HBsAg testing is the primary tool for screening and diagnosis, and should be made available in all countries.
   b. Confirmation of positive HBsAg findings (a measure of chronicity) should be confirmed by a second test at a different time point.
   c. Target populations for screening should be defined according to local epidemiology and programme goals.
   d. Screening programmes for HBV infection should be linked, when possible, to other existing screening programmes.
   e. All blood donors should be screened for HBsAg, HIV, HCV and syphilis infection.
2. All HIV-positive subjects should be screened for HBsAg as a marker of HBV infection.
3. All HBsAg-positive subjects should be screened for HIV.
4. All people found to be HBsAg positive should be referred for management, which should include:
   a. Patient education as a minimum.
   b. Contact follow-up including vaccination of susceptibles.
   c. Advice on alcohol consumption.
   d. Further diagnostic measures, and/or treatment.
   e. Lack of any of these measures should not be grounds for a lack of referral.

Table 3. Treatment decisions for persons with human immunodeficiency virus/hepatitis B virus co-infection by treatment indication*

Treatment indication*	No indication for treatment of HBV infection	Indication for treatment of HBV infection
Indication for treatment of HIV infection	Treat for both infections	Treat for both infections
No indication for treatment of HIV infection	No treatment	Consider earlier ART initiation and treat both HBV and HIV

*Treatment indication according to existing Continental Liver Society (for HBV) or World Health Organization (for HIV) treatment guidelines.
ART, antiretroviral therapy; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

5. Advocacy and health education should be initiated in all countries in order to alert the general population and health-care workers of the risk and need for screening and management for HBV infection.

*Priority for treatment where resources are limited**

1. Patients with compensated cirrhosis
   - Persons diagnosed with compensated cirrhosis using clinical, laboratory, imaging and histological information according to availability, should be tested for HBsAg.
   - Treat all who are confirmed to be HBsAg-positive.
   - Monitor for HCC occurrence and decompensation.
2. Patients with decompensated cirrhosis
   - Test all persons with a clinical diagnosis of decompensated cirrhosis for HBsAg using clinical, laboratory, imaging and histological information according to availability.
   - Treat all who are confirmed to be HBsAg positive, with appropriate monitoring for further decompensation.
   - Monitor for HCC occurrence.
3. Subjects with HIV/HBV co-infection
   - All persons with HIV infection should be tested for HBsAg.

All HBV/HIV co-infected subjects with or without cirrhosis should be assessed to determine if there is an indication for either HIV or HBV treatment, or both, or neither (Table 3).

Patient evaluation utilizing tests that are not currently available in countries where resources are limited

1. Quantitative HBV DNA assays should be developed for resource-constrained regions that are robust, reliable, sensitive, standardized, affordable, quality controlled and validated under field conditions or in referral laboratories to guide management of HBV infections.
2. Liver biopsy is useful if available, provided it can be performed safely and interpreted appropriately.
3. Alternatively, non-invasive tests of liver fibrosis may be considered when available.

Treatment options where resources are limited

1. Selection of antiviral agents for first-line treatment of HBV monoinfection:
   (a) Tenofovir should be made available in all countries for treatment of HBV infection.
   (b) Either entecavir or tenofovir should be used as first-line monotherapy for mono-infected patients if available.
   (c) Monotherapy with lamivudine, emtricitabine and telbivudine should be avoided if at all possible because of the risk of resistance and difficulties with access to monitoring for viral resistance.
   (d) When entecavir and tenofovir are not available, the combination of adefovir+lamivudine, or adefovir+telbivudine should be recommended.
   (e) Interferon-α can be used for specific subgroups as recommended in the practice guidelines of continental liver associations, provided that appropriate monitoring can be provided.
2. Selection of antiviral agents for first-line treatment of HBV/HIV co-infection
   (a) Co-infected patients with an indication for treatment of either HBV and/or HIV should receive a triple combination of antiretroviral agents, including two that are active against HBV (either emtricitabine+tenofovir or lamivudine+tenofovir, preferably as fixed-dose formulations) as per 2010 WHO Recommendations.
   (b) In patients who are already being treated with lamivudine without tenofovir and are subsequently found to be HBsAg-positive, treatment should be changed to include two drugs that target HBV, one of which should be tenofovir (either emtricitabine+tenofovir or lamivudine+tenofovir.
   (c) The endpoints of therapy are outlined in existing practice guidelines of continental liver associations.

Monitoring issues modified for resource-constrained settings

1. The following steps should be taken when monitoring HBV mono-infected patients on therapy if testing HBV DNA concentrations are not available:
   (a) monitor compliance in all patients,
   (b) for treatment with entecavir, measure ALT activities every 6 months,
   (c) for treatment with tenofovir: measure baseline serum creatinine, spot urine protein creatinine ratio if possible and ALT and serum creatinine every 6 months.
2. When monitoring patients for co-infection who are on treatment with tenofovir+lamivudine or tenofovir+emtricitabine: Measure ALT and creatinine and/or spot urine protein/creatinine ratio concentration at baseline

   i. if normal, then measure again every 6 months,
   ii. if renal tests are abnormal, use tenofovir with caution and reduced dosing,
   iii. manage any comorbidities particularly diabetes or hypertension to reduce the risk of nephrotoxicity.
3. Children with HBV rarely have progressive disease and should only be treated if they have advanced fibrosis or cirrhosis.
4. For HCC surveillance, follow existing practice guidelines of continental liver associations.

Research issues discussed

Overall, the research strategy needs to consider how studies can enhance the recommendations of the WHO consultation on hepatitis B and provide technical resources to include more patients for treatment who are at risk for complications. Several possible projects were discussed at the consultation:

1. In order to determine the burden of disease with more accuracy, data should be mined from existing death registries in countries where there is good data collection and where the prevalence of hepatitis B infection is known with more certainty. In these countries, the number of cases of HCC and liver-related death may be evaluated by examining registries and death certificates.
2. The prevalence of HBV co-infection in patients with HIV infection is variable in different regions. Surveys should determine the burden of co-infection in existing HIV programmes. This survey could be easily performed by testing representative samples of persons known to be HIV positive for HBsAg in several countries.
3. It would be important to know the prevalence of HCV co-infection.
4. One participant discussed a proposal for a 5-year programme to study hepatitis B prevalence, treatment and outcome in an African country. The project could be a pilot project from which this WHO consultative group could provide input and obtain data to answer questions about how to best treat and monitor HIV/HBV co-infection and HBV mono-infection. In addition, a project in Asia could be planned using a similar study design. Such projects should examine disease burden by evaluating effectiveness of screening programmes, and establishing the infrastructure to collect data on liver-related mortality including HCC. Infrastructure for testing, monitoring and evaluating patients should also be established together with effectiveness of treatment to improve outcomes.
5. Participants at the consultation reached the consensus that a thorough methodological evaluation needs to be preceded by a systematic review of best practices for surveillance of hepatitis B outcomes.
6. Population-based monitoring for HBV resistance should be performed in same settings where monitoring for HIV resistance is performed.
7. Other proposals regarding HBV DNA testing were to:
   a. Encourage the development of inexpensive tests for HBV DNA that can readily be performed in clinic laboratories under field conditions; for example, DNA hybridization assays with a cutoff of $>$ 2000 IU/ml (10 000 genomic copies/ml) to better determine who with HBV mono-infection would be candidates for antiviral therapy.
   b. Encourage the use of dried blood spot testing for HBsAg and HBV DNA for prevalence and diagnostic studies.
   c. Support the creation of quality control panels for measuring HBV DNA concentrations.
   d. Support the development of inexpensive surrogate tests for fibrosis that might be used to determine candidates for treatment that could replace liver biopsy.

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