Hepatitis B & hepatitis C in HIV-infection

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Human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) are the three most common chronic viral infections seen in the world. All three viruses share modes of transmission and hence co-exist in the same host at significantly high rates. HIV-induced immunosuppression has deleterious effects on the natural history, pathophysiology, diagnosis, therapeutic responses to hepatitis viruses. Responses to HBV vaccination are impaired in persons with HIV infection. Co-infection with the hepatitis viruses and HIV is likely to become a major health care catastrophe in the coming years. This review discusses the current trends in the understanding of the biology of co-infection and implications for treating these viruses effectively.

Key words HBV - HCV - HIV - highly active antiretroviral therapy (HAART)

Hepatitis B/HIV co-infection

Hepatitis B virus (HBV) infection is one of the most common infections in the world with approximately 2 billion people infected with it1. Of these, approximately 5 per cent suffer from chronic liver disease1. Also, over two-thirds of all cases of liver cancers worldwide are also caused by HBV2. While chronic HBV infection in the setting of HIV infection is not listed as an opportunistic infection by the US Centers for Diseases Control, it is a common co-existing infection seen in HIV infected individuals because of the shared modes of transmission of HBV and HIV. HIV positive individuals, particularly those with suppressed immune systems, are less likely to respond to vaccination against HBV and are more likely to develop chronic disease after being exposed to HBV. Moreover, individuals co-infected with HBV and HIV more frequently present with atypical serologies, have higher HBV DNA levels, and experience more profound liver disease as a result of chronic infection3.

Virology: HBV belongs to the family of DNA viruses that preferentially infect hepatocytes and are referred to as hepadnaviridae4. Each complete virion consists of an inner core (nucleocapsid or hepatitis core antigen, HBcAg) surrounded by an outer protein coat or envelope (the hepatitis B surface antigen, HBsAg)4. The HBV genome is a circular, partially double-stranded DNA of approximately 3,000 base pairs. There are four overlapping open reading frames (ORF), which encode for the envelope, precore/core, polymerase, and X proteins. The envelope ORF encodes for the large middle and small surface glycoproteins of HBsAg. The precore/core ORF is translated into a precore polypeptide, which is secreted as hepatitis B ‘e’ antigen, which is detectable in the blood as HBeAg and HBcAg, which is only detected in the liver. Upon entering the hepatocytes,
the HBV genome is transported to the nucleus and is converted into closed circuit circular DNA (cccDNA). The HBV cccDNA serves as a template for transcription of mRNA and the RNA pregenome. Once transferred to the cytoplasm, HBV polymerase uses reverse transcription to convert the RNA genome into new circular genomic DNA. Most virologists consider HBV as a non-cytopathic virus. Replicative HBV, either during the acute or chronic stages of infection, causes liver disease because of vigorous cytotoxic T lymphocyte (CTL) and/or cytokine-mediated elimination of HBV-infected hepatocytes.

Epidemiology: Chronic hepatitis B infection causes chronic liver disease and hepatocellular cancer. World-wide, it is estimated that more than one million people infected with HBV will die every year and approximately 25 per cent of all patients with chronic HBV infection will die of liver disease. The prevalence of chronic hepatitis B is higher in China and sub-Saharan Africa (20%) than in North America, Western Europe and in Australia (0.5%). Transmission of HBV is predominantly via parenteral means, even though this infection is also transmitted by sexual contact and acupuncture. Mother-to-child transmission and occupational transmission from HBV infected patients to health care workers are also major modes of transmission. One of the major distinctive features of HBV infection is that risk of developing chronic liver disease varies greatly with age of acquiring the infection. For neonates and infants who acquire HBV, the risk of chronicity is almost 90 per cent, while it decreases to 30 per cent for children 1-5 yr, and up to 2 per cent for older children and adults.

Natural history/clinical features

Acute HBV infection: HBV infection can manifest as an asymptomatic infection, acute hepatitis and rarely fulminant liver failure. Asymptomatic infection, which is the most common presentation, begins with active HBV replication within the hepatocytes. Detectable levels of HBV DNA in the peripheral blood may be present even before elevations in the levels of serum transaminases. HBsAg and HBeAg become detectable in blood within two weeks before the core antigen can be detected and may persists for up to 8 wk. IgM antibodies to HBeAg occur early and decrease after six months; however, total anti-HBc remains for life. Anti-HBs become positive after loss of active replication, usually after six months. Anicteric infection is typically associated with a flu-like illness without jaundice. Icteric infection is associated with symptoms ranging from mild jaundice to non-fatal subacute hepatic necrosis to fatal fulminant hepatitis in <1 per cent of symptomatic cases. In those with acute hepatitis, HBV DNA levels and serum transaminases are usually higher and persist longer. Outcome of acute HBV infection is largely determined by host factors, particularly age and immune competence at the time of exposure.

Regardless of the clinical course, most HBV-infected adults are capable of mounting broad-based CTL and antibody responses to the virus. With the development of a protective immune response and serological evidence of immunity, infection becomes latent and usually remains so for the life of the patient. If the patient with latent infection becomes immunosuppressed at a later date such as after an organ transplantation, HBV can reactivate, as intact virions may be hidden from the immune system in the nucleus of hepatocytes as cccDNA.

Chronic HBV-infection: Three phases of chronic hepatitis B infection are widely recognized. Children and adolescents may have a long period of immune tolerance phase with near normal liver histology, high concentrations of HBV DNA, and HBeAg positivity; the immune clearance phase with seroconversion from HBeAg to antibody against HBeAg accompanied by active hepatic inflammatory response and fibrosis and fluctuating serum alanine transaminase (ALT) concentrations, and lastly, the residual phase with low concentrations of HBV DNA and normal concentrations of ALT. For Caucasians who acquire the disease during adolescence or adulthood, there is no immune tolerance phase. Instead, the disease progresses directly to the immune clearance phase and is of short duration, which probably accounts for the better response to immunomodulatory therapy in Caucasian patients than in those from other ethnic origins. By contrast, those who acquire infection during the neonatal period and early childhood (mainly
seen within Asians and African populations), the response to immunotherapy is worse. The disease continues to progress after HBeAg seroconversion. Although Asian patients who are HBeAg negative, have lower levels of HBV DNA than those who are HBeAg positive, the course of their disease is marked by frequent exacerbations. Severe exacerbations occur with equal frequency in patients who are HBeAg positive and in those who have antibodies to HBeAg. Also, precore mutations, those associated with mutations in the core promoter region and absence of HBeAg in serum with elevated HBV DNA and ALT, can be detected in about 44 per cent of patients who are HBeAg positive. Furthermore, disease activity after HBeAg seroconversion has no relationship to the presence or absence of precore and core promoter mutants.

**Hepatitis B genotypes:** There are seven different genotypes (A-G) of HBV recognized worldwide. Of these, A is pandemic, B and C are seen predominantly in Asia, D in Southern Europe, E in Africa, F in the USA, and G in the USA and France. A newly discovered genotype H is seen predominantly in Central America. B genotype is further divided into Bj, seen in Japan, and Ba, seen in rest of Asia. Unlike HCV, HBV genotypes may affect disease profiles but not treatment responses. Caucasians infected with genotype A have a higher likelihood of clearance of HBV DNA and HBeAg, sustained remission after HBeAg seroconversion and a better histologic activity index (HAI) compared with patients infected with genotype D. Asian patients with genotype B when compared to those infected with genotype C, have HBeAg seroconversion at an earlier age, less serious liver disease, and a better response to interferon.

**Pathophysiology:** Recent studies using chimpanzees and acute HBV infection in man have clearly unraveled several mechanisms by which HBV is eliminated during the acute phase of HBV infection. These studies have clearly shown that the elimination of virus is mainly through non-cytolytic mechanism mediated through cytokines released by CD8 \(^+\) T cells. Tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and interferon-\(\gamma\) (INF-\(\gamma\)) are the major cytokines involved in the clearance of HBV in chimpanzees. In the chronic phase of HBV infection, the immune clearance phase is triggered by a decrease in host tolerance to HBV antigens with a concomitant increased expression of class I HLA molecules, resulting in a decrease of HBV DNA and an increase in ALT. The process of liver fibrosis and cirrhosis continues with low level of viremia even after HBeAg seroconversion. However, the notion of non-cytolytic CD8 \(^+\) T cell response occurring in acute infection might also be true for chronic infection.

**Diagnosis:** Of all the viral hepatitides, HBV is the most complicated infection with respect to interpretation of serologic tests. Co-infection with HIV results in even more atypical serologies. Both acute and chronic HBV infections are characterized by the presence of hepatitis B surface antigen (HBsAg) and the absence of antibodies to HBsAg (anti-HBs). Most often, antigen disappearance is associated with a resolved infection. However, transplanting a liver from someone with a resolved infection into a HBV naïve individual, rarely, may result in an acute HBV infection. This suggests that HBV infection is most probably latent and not resolved, and immunocompromised individuals are unable to control re-activation of latent HBV DNA in the liver. HBeAg in his serum reflects high levels of HBV replication in the liver with elevated levels of ALT. The presence of anti-HBe indicates either that there is no viral replication and normal ALTs or the presence of pre-core mutants with high levels of HBV replication and elevated ALTs. Anti-HBV treatment can be discontinued if HBeAg to an anti-HBe seroconversion is maintained for over 6 months. However, those with a precore mutant do not have HBeAg from the beginning and anti-HBV therapy should be continued indefinitely in these individuals.

In HIV-positive individuals, the interpretation of serologies is often complicated. Many of these patients often present with anti-HBc alone. During a median of 31 months between the first and the last samples collected, anti-HBc remained the sole marker for HBV infection in over 98 per cent of patients. HBV DNA encoding for the surface and core antigens was detected in 63 and 60 per cent respectively of all 202 samples tested. Over time HBV DNA was detectable in over 89 per cent of all patients. Those patients who had HBVDNA and no anti-HBV
antibodies (36%) had necroinflammatory liver disease attributable to HBV infection. These data indicate that HIV positive patients with anti-HBc antibodies are more likely to have active HBV infection than their HIV negative counterparts with anti-HBc antibodies.

HBV DNA: There are two commonly used commercial qualitative assays for detecting HBV DNA in the serum: one is a branched chain DNA assay and the other is a hybrid capture test. The lower limits of detection in these two assays are 700,000 and 140,000 copies/ml respectively. Another PCR-based assay allows for detection of 200 copies of HBV DNA/ml. Recent studies have indicated that after six months of lamivudine treatment, 64 per cent of patients with HBV DNA concentrations of more than 10^3 copies/ml will develop lamivudine resistance, compared with 13 per cent of persons with HBV DNA levels less than 10^3 copies/ml. Thus, quantitative PCR (qPCR) is the preferred assay to monitor the progression of disease and the effectiveness of treatment. Recently, there has been new interest in following the levels of cccDNA. The cccDNA is super-coiled DNA that does not replicate, it is resistant to nucleoside analog treatment and is considered as the probable source for DNA rebound once therapy is stopped.

Liver biopsy: Liver biopsy is indicated for assessment of the severity of liver disease in chronic HBV infection. However, biopsy is not essential for determining whether treatment is needed, even though it is preferable to have a baseline histological assessment. Treatment decisions are made based on the clinical information like elevations of ALTs more than 1.5 times the normal limits and detection of HBV DNA by sensitive assays.

TREATMENT

General principles: The primary goals of treatment in chronic HBV infection are to arrest the progression of liver disease by suppressing HBV replication. Even though HBV is not considered a cytopathic virus, immune responses directed against HBV epitopes will continue to cause hepatic damage in the presence of viraemia. Once viral replication is shut off, surface antigen is lost and there will be no evidence of viral peptides on the surface of hepatocytes. However, the cccDNA will still be in the nucleus and potentially lead to relapse of HBV infection in the presence of immune suppression induced by chemotherapy, steroids or immunosuppressive drugs associated with transplantation.

Therapeutic end points that are used to assess treatment response include normalization of ALT levels, inability to detect HBV DNA in the peripheral blood by qualitative assays, loss of HBeAg with or without emergence of anti-HBe, and improvements in liver histology. Some of these assays are expensive for many developing countries and following ALT levels is probably the best single clinical parameter that can be used to follow therapeutic response. Baseline ALT levels are also good predictors of therapeutic responses. High levels of ALT indicate that there is an immune response directed against HBV occurring in the liver and combined with antiviral therapy may lead to clearance of virus-infected hepatocytes. Baseline ALT levels higher than two times the upper limit of normal carry a good prognostic value in treating HBV with nucleoside analogs. However, current consensus suggests that low levels of viral replication can lead to continued progression of liver disease therefore use of quantitative HBV DNA assays are considered optimal as treatment end points.

There are two modes of anti-HBV treatment available (Table I). One is immunomodulation using INF-α and the other, viral suppression using nucleoside/nucleotide analogs. Since chronic HBV is unlikely to be eradicated, an adequate therapeutic response to anti-HBV treatment is defined as suppression of HBV re-application, normalization of ALT levels and/or HBeAg and HBsAg seroconversion. Liver transplantation is effective and should be considered in patients with end-stage disease not responding to treatment.
Interferons: INF-α used at a dose of 5 million units per day or 10 million units three times a week is associated with HBeAg clearance in approximately 30 per cent and HBsAg clearance in 10 per cent of immunocompetent patients. INF-α monotherapy is also effective in reducing HBV DNA levels and normalizing levels of ALT. However, it is associated with a high degree of relapse. INF-α monotherapy is less effective in patients with high baseline HBV DNA levels and patients with normal ALT levels prior to treatment, as is often seen with HIV co-infected HBV patients. Interferon is also associated with significant adverse events including fever, myalgias, thyroid dysfunction, bone marrow suppression, and psychiatric disturbances. When used in persons with cirrhosis, interferon therapy may be associated with immune enhancement in the liver that may lead to decompensation. Unfortunately, several studies have demonstrated that an effective response to interferon therapy is seen only with those HIV/HBV co-infected individuals with CD4+ T cell counts greater than 350 cells/μl.

Recent studies using pegylated interferons have been promising. A recent study using pegylated interferon α-2a vs conventional interferon α-2a indicated superior therapeutic response rates for pegylated interferon α-2a with greater HBV DNA suppression, greater loss of HBeAg, and ALT normalization (24 vs 12%) in patients with higher CD4+ T cell counts, normal synthetic function, normal haematological profile, elevated transaminases, and no clinical evidence of hepatic decompensation.

Lamivudine: Lamivudine, first approved for treatment of HIV infection, was approved for the treatment of HBV infection in 1998. The treatment of HBV infection is with 100mg of lamivudine once daily vs 300 mg once daily for HIV infection. HIV/HBV co-infected patients should be treated with the higher dose.

One year of lamivudine treatment of HBeAg-positive chronic HBV infection with persistent ALT elevations resulted in HBeAg seroconversion in about 16-18 per cent of patients compared with 4-6 per cent of untreated controls. Improvement in liver histology was seen with 49-56 per cent of lamivudine treated patients and only in 23-25 per cent of controls. HBeAg negative chronic HIV infected individuals with elevated ALT levels treated with lamivudine for 24 wk, resulted in a 63 per cent virologic and biochemical response compared to 6 per cent response in the control group. Of those who completed one year of treatment, 39 per cent had no detectable HBV DNA by PCR assay, and 60 per cent had improvement in hepatic histology. Similar findings were seen with other studies as well indicating long term therapy with lamivudine increases the possibility of HBeAg seroconversion.

Follow-up data of these clinical trials have indicated that lamivudine resistance mutations occurred in 15 to 32 per cent of patients treated with lamivudine for 52 wk and as many as 67 per cent of HIV-mono-infected patients. As many as 90 per cent of HIV/HBV co-infected patients treated with lamivudine for over 4 yr develop lamivudine resistance mutations. These resistance mutations generally fall within the YMDD motif, a highly conserved domain of HBV reverse transcriptase. Interestingly, patients with lamivudine resistance mutations continue to experience HBeAg seroconversion, partial suppression of HBV DNA, and biochemical and histologic parameters, probably because of decreased fitness or replicative capacity of the mutant strain. However, HBV can develop compensatory mutations in the DNA polymerase genes (V173L and L180M) that can restore the replicative capacity and can cause HBV DNA levels to return to pre-treatment levels.

Table I. Various modes of anti-HBV therapy

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<th>A. Antiviral agents</th>
<th>B. Immunomodulators</th>
<th>C. Liver Transplantation</th>
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<tr>
<td>Lamivudine</td>
<td>Interferon (Peg-IFN)</td>
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<td>Adefovir dipivoxil</td>
<td>Thymosin-α1</td>
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<td>Tenofovir</td>
<td>Steroid withdrawal</td>
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<td>Entecavir</td>
<td>Therapeutic vaccines</td>
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<td>Clevudine (L-FMAU)</td>
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<td>Emtricitabine (FTC)</td>
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**Adefovir dipivoxil:** Adefovir was recently approved in the US by the Food and Drug Administration (FDA) for treatment of HBV infection at a dose of 10mg once daily. Daily doses of 60mg and greater evaluated for the treatment of HIV infection were associated with unacceptable rates of renal toxicity (proximal renal tubular necrosis). Adefovir has shown activity against both the wild type and lamivudine resistant HBV. Several phase I and II studies demonstrated that adefovir is associated with a 4-log reduction in HBV DNA as well as seroconversion rates from HBeAg to anti-HBe antibodies in the range of 20 to 27 per cent.

A recent double-blind, placebo controlled phase III clinical trial evaluating the safety and efficacy of adefovir once daily versus placebo in patients with HBeAg-positive chronic HBV infection established the efficacy of adefovir in treatment of HBV infection. After 48 wk of treatment of patients who received 10 mg and 30 mg daily and placebo, there was significant improvement in liver histology in 53, 59 and 25 per cent of patients respectively. There was significant reduction in the levels of HBV DNA in the treatment groups when compared with placebo (3.52 log copies/ml for 10 mg; 4.76 log copies/ml for 30 mg; and 0.55 log copies/ml for placebo). At the end of 48 wk, there were also significantly higher number of patients with no detectable HBV DNA (<400 copies/ml) in the adefovir groups (21 and 39%) compared to placebo (0%); 48 per cent of patients receiving 10mg of adefovir and 55 per cent of those receiving 30mg of adefovir had normalization of ALT when compared to the placebo (15%). HBeAg seroconversion also occurred more frequently with the treatment groups (12 and 14%) compared to the placebo (6%). No adefovir-associated mutations were identified during the 48 wk of therapy, and the safety profile for the 10 mg dose group was similar to that of the placebo.

Another recent international, industry-sponsored, multi-center double-blind placebo controlled phase III clinical trial also reported favourable data for the use of adefovir among HBeAg-negative chronic HBV infected individuals without evidence of hepatic decompensation. After 48 wk of treatment with 10 mg of adefovir, 64 per cent had significant histologic improvements compared to 33 per cent in the placebo group; 51 per cent in the treatment arm had no detectable HBV DNA levels at the end of 48 wk compared to the placebo arm (0%); and 72 per cent of all patients treated with adefovir had normalization of ALT values compared to 29 per cent of those receiving placebo.

**A recent study reported efficacy of adefovir in the treatment of lamivudine resistant HBV.** Patients receiving lamivudine as part of their antiretroviral regimen were started on 10mg of adefovir daily. Significant reductions in median HBV DNA levels 3.97 log (48 wk), 4.80 log (96 wk), 5.55 log (144 wk) and 5.62 log copies/ml (192 wk) were seen, indicating a continued effect on HBV viraemia. Similar results were also observed with regards to the percentage of patients with undetectable levels of HBV DNA (6% at 48 wk, 27% at 96 wk, 46% at 144 wk and 59% at 192 wk). Rates of ALT normalization were also significant (19% after 48 wk, 37% after 96 wk, 64% after 144 wk, and 67% 192 wk). There were no reports of adefovir-resistant mutations in this study.

**Adefovir resistance can occur in vivo with a N236T mutation in the D domain of HBV polymerase.** However, it does not seem to occur nearly as frequently as HBV resistance to lamivudine. Adefovir resistance is only seen with extended therapy and even then, only in a small percentage of patients, particularly in those with HBeAg negative, precore mutant HBV infection.

**Tenofovir:** Tenofovir, a nucleotide analog recently approved as a treatment for HIV infection, also has activity against HBV. However, no large, controlled study addresses the efficacy of tenofovir in the treatment of HBV infection. Some sub-studies have evaluated the efficacy of tenofovir for HIV/HBV co-infection within the context of two, large, phase III randomized controlled studies involving HIV infected patients. In a study involving therapy-experienced HIV-infected patients, the mean decrease in HBV DNA was 4.9 log copies/ml 24 wk after receiving tenofovir (N=10) compared with a mean increase of 1.2 log copies/ml in the placebo group (N=2). In another study involving ARV-naïve HIV infected patients, the mean decrease in HBV DNA was 3 log copies/ml.
copies/ml after 48 wk of therapy with lamivudine (N=6), compared with a mean decrease of 4.7 log copies/ml among those who received both lamivudine and tenofovir (N=5). A follow up of this study showed that combined therapy with tenofovir and lamivudine had greater sustained anti-HBV activity than lamivudine alone and a greater number of subjects who had normalization of ALT values without evidence of emergence of resistance mutations to tenofovir.

When considering the use of tenofovir for the treatment of HBV infection, it should be noted that the safest and most effective anti-HBV dose has not been established. Randomized controlled clinical trials to address this question have not been performed. Further, no clinical trials have been completed so far to address the safety and efficacy among HIV negative HBV positive individuals.

Cross resistance of anti-HBV agents: It is clear from early clinical trials that lamivudine resistance is associated with mutations in the YMDD motif and adefovir resistance is associated with a N236T mutation in the DNA polymerase. However, there has not been any evidence of cross resistance between these two agents in clinical trials. Adefovir is active against HBV strains with YMDD mutations and lamivudine is active against mutants with N236T mutations. However, it is not known whether either lamivudine or adefovir resistance mutations can lead to cross resistance to newer anti-HBV agents under development like entecavir, emtricitabine and telbivudine. *In vitro*, YMDD mutants are less sensitive to entecavir, but remain sensitive to this drug *in vivo*. N236T mutants are also less sensitive to entecavir *in vitro* but the *in vivo* results are not yet available. Emtricitabine appears to be less active against YMDD mutants but fully active against strains with N236T mutants. *In vivo* data are not yet available. Telbivudine is not active against YMDD mutants both *in vitro* and *in vivo*, and there is no data on the activity of this drug against HBV strains with a N236T mutation.

Treatment of HIV/HBV infection: All HIV-infected individuals should be screened for the presence of HBV infection, given their shared routes of transmission. The most appropriate time to initiate anti-HBV therapy is always difficult to determine. For co-infected individuals, most experts recommend that when therapy for HIV infection is initiated, HBV should also be treated. For those HIV/HBV co-infected patients who do not meet the guideline requirements to initiate therapy for HIV infection, treatment of HBV infection should still be considered. Patients with active liver disease as indicated by elevated ALT and necroinflammatory liver disease, and those with high HBV DNA levels (over 100,000 copies/ml for HBeAg positive patients and over 10,000 copies for precore mutants) should initiate therapy. This recommendation is mainly based on the fact that those who are infected with the precore mutants tend to have more aggressive and prolonged liver disease. Liver biopsies are often helpful to assess the severity of liver disease, but are used mainly for patients with atypical clinical presentations such as individuals with normal ALT levels, high HBV DNA levels, or those with elevated ALTs and low HBV DNA levels. Unlike immunocompetent patients, it is not uncommon to see significant necroinflammatory liver disease in HIV/HBV co-infected individuals with normal ALTs and HBV DNA levels.

The emergence of HBV resistant to lamivudine or adefovir generally takes a much longer time than does the emergence of resistant HIV. Hence, it is general practice to continue these drugs in a HIV/HBV co-infected patient even after genotypic and/or phenotypic tests show resistance to HIV. In patients with chronic HBV infection who were receiving lamivudine, rebound in HBV replication leading to severe liver disease has been seen, even in patients with no detectable HBsAg prior to discontinuation of therapy. Such patients must be closely monitored. Due to its potent activity against HBV, a similar approach should be followed when discontinuing tenofovir. Continuing either lamivudine or tenofovir as a single agent to prevent such a rebound runs the risk of inducing resistance by HIV to that agent, unless resistance by HIV has been previously documented (e.g., presence of the M184V mutation in a patient receiving lamivudine). Adefovir at doses approved for HBV infection can potentially be used to prevent or control such rebounds, since the low dose used for treatment of HBV infection does not have activity against HIV and does not appear to select for virus resistant to tenofovir. Thus,
consensus is to treat HBV with one of the three drugs, regardless of the HIV drug resistance profile.

HIV/HBV co-infected individuals are more likely to develop severe hepatotoxicity due to antiretroviral regimens. All agents used to treat HIV can cause severe hepatotoxicity, however, among the non-nucleoside reverse transcriptase inhibitor analogs (NNRTI) nevirapine is associated with severe hepatotoxicity, as is ritonavir among the protease inhibitors. Hepatic steatosis, most commonly associated with the nucleoside analogs (NRTI), didanosine, stavudine and zalcitabine can lead to severe hepatotoxicity in HIV/HBV co-infected patients.

The goal of treatment should be suppression of HBV for as long as possible and to stop progression of liver fibrosis. Most HIV/HBV co-infected patients require therapy indefinitely. However, if an HBeAg-positive patient undergoes rarely seen seroconversion while on anti-HBV therapy, therapy can be stopped after six months.

Unlike interferon, nucleoside analogs can be used to treat both compensated and decompensated liver disease. Combination therapy (e.g., lamivudine with tenofovir), although most probably more efficient in HBV suppression, has yet to be tested in larger clinical trials to validate their use in the context of treatment of HIV/HBV patient.

**HBV vaccination:** Vaccination against HBV is strongly recommended for all HIV infected individuals who have not been exposed to HBV. It should be noted that the success rate of vaccination are much lower in HIV infected individuals, particularly those with lower CD4+ T cell counts. Brugera et al. showed that standard HBV vaccination schedules induce anti-HBV protective immunity in 30 to 40 per cent of HIV infected individuals. Patients with CD4+ T cell counts lower than 200 cells/µl have poor response rates while those with higher CD4+ T cell counts should expect a protective antibody response in 70 per cent of cases. At least one study subsequent to this has tested whether doubling the dose of standard HBV vaccination would increase the antibody response rates among HIV infected individuals. The overall response rates were 55 per cent and those with lower CD4+ T cells (200-500 cells/µl) having a lower response rates of 33 per cent and compared to 87.5 per cent in those individuals with a CD4+ T cell counts > 500cells/µl. However, one year after vaccination, only 58 per cent of these patients had persistent protective antibody titres. Hence, it is less likely that repeated vaccination can induce persistent protective antibody titres in HIV infected individuals. Currently, several strategies are being employed to augment the efficacy of HBV vaccine in HIV infected individuals by using cytokines as adjuvants.

**Relevance to India:** Hepatitis B is a major public health problem in India. The average carrier rates of HBV in the general population are considered to be approximately 4 per cent. Among these, professional blood donors constitute a major risk factor group with a prevalence rate of 14 per cent. Thalassaemic and renal dialysis patients also have a high risk of acquiring HBV infection. These studies have indicated that HBV infection is established in early childhood, probably associated with crowded living conditions and poor hygiene. However, HBV is also associated with acute and sub acute liver failure in adults as well as with a significant proportion of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Community based epidemiological studies have indicated a slightly higher rates of chronic HBV infection in a south Indian tribal population. Several tribal customs including scarification, tribal treatment practices like blood-letting and other practices like tattooing, ear and body-piercing are all suggested to be contributing to the high prevalence rates of HBV. However, it should be noted that many of these studies have very small sample sizes and may have selection biases and may not accurately reflect the real prevalence of HBV infection in India. Use of molecular diagnosties have indicated a higher prevalence rate of HBV infection among the general population in India, surprisingly slightly higher among rural than urban population. In summary HBV infection remains a significant public health hazard in India and will probably remain so until nationwide vaccination programs and other control measures are fully implemented.
Management of hepatitides is expensive, especially when one needs lifelong treatment. Testing for resistance mutations, assays to monitor disease progression and treatment progress and the drugs that are required to treat the infection are all expensive. Availability of new generic drugs in India would definitely be important in the management of HBV/ HIV co-infected individuals. There are several obstacles one could envision in the management of HBV infection in developing countries like India. One major obstacle is the cost and availability of assays that monitor HBV DNA levels in blood as well as of anti-HBV therapy.

For those patients who are infected with HIV and HBV, proper diagnosis of chronic HBV is important. Measuring HBeAg is a more cost-effective assay than HBV DNA assays in detecting HBV in chronic HIV infected individuals. HBV DNA assays should be restricted to those who are suspected of having precore mutants. Following HBeAg and anti-HBe is sufficient to monitor patients who undergo treatment. Monitoring of ALT is also a very sensitive and cost-effective assay to diagnose and monitor those patients undergoing treatment. Normalization of ALT in someone with elevations prior to initiation of therapy is a good indication of adequate suppression of HBV replication. Monitoring of ALT is probably sufficient for monitoring of those with precore mutants with elevated ALT prior to therapy. Liver biopsy and evaluation of necroinflammatory scores in hepatic histology would be useful in the management of these individuals with precore mutants.

There have been recent reports from India of successful treatment of HCV patients using interferon α and ribavirin. This is a promising trend and as clinicians gather more experience in managing patients for interferon associated toxicities and managing the adverse events in a timely fashion, interferons will also be used to treat HBV in India. Lamivudine, which has already been widely used in India, is easily the best option to treat HBV infection. Adefovir and tenofovir are not yet available in India; however, both could potentially add to the armamentarium to treat HBV. Inclusion of lamivudine in the initial HIV regimen of all those individuals coinfected with HBV is the best therapeutic strategy that can be recommended. Monitoring of these patients with ALT and hepatitis serologies is important to ensure adequate HBV suppression.

Vaccination of all individuals is probably the most cost-effective way to control HBV infection in India. Even though HBV is not a predominant cause of acute liver failure in India, it could potentially lead to chronic liver disease and decompensation over time, particularly in HIV infected individuals. Immunization of HIV infected individuals may not have great success, as seen with the studies conducted in the US. However, it is recommended that all HIV infected patients, particularly those with higher CD4+ T cell counts, should be offered immunizations. Currently, there are no strong clinical data to routinely recommend repeated immunization to achieve protective immunity against HBV.

In conclusion, screening all HIV infected patients for HBV, vaccination of all patients who have not been exposed to HBV, and careful scrutiny of atypical HBV serologies, and consideration of treatment with a nucleoside analog against HBV are some of the recommendations for management of HBV infection. When newer medications are validated in clinical trials, we will be able to treat HBV with combination therapy and extend the duration of HBV suppression in HIV infected individuals.

**HCV and HIV co-infection**

Over 170 million people worldwide are suffering from chronic HCV infection. Recent WHO reports indicate that chronic liver disease is responsible for over 1.4 million deaths due to cirrhosis and primary liver malignancies. It is estimated that HCV is responsible for at least one-fifth of these deaths. HIV infection is found in approximately 40 million individuals. Both HCV and HIV are transmitted by blood and blood products, but HCV is ten times more infectious than HIV. Co-infection with HCV is more common in people with high exposure to contaminated blood and both viruses infect approximately 60-90 per cent of haemophiliacs and 50-70 per cent HIV positive intravenous drug users (IDUs) in the US and Europe.
Epidemiology: Chronic HCV is a major cause of chronic liver disease associated morbidity and mortality around the world.\textsuperscript{1,6,1,61,62} The eradication rates with treatment of individuals infected with HCV alone can approach 60 per cent; however, due to lack of detection and the cost and difficulty of treatment, mortality rates associated with HCV are on the rise in most countries.\textsuperscript{65,66} With the advent of routine blood screening for HCV, transfusion-related transmission has almost disappeared in most countries. By contrast with HBV, sexual transmission of HCV is less efficient, though patients with high risk sexual behaviour still have a high risk of acquiring HCV infection sexually.\textsuperscript{66} HCV is detectable in 2-4 per cent of infants born to HCV infected mothers. Co-infection with HIV increases the rate of transmission of both viruses and high HCV viral levels in mothers increase the risk of perinatal transmission. The perinatal risk of HCV transmission can be significantly reduced to <1 per cent in infants born to HIV/HCV co-infected mothers if the mother is on ART and undergoing caesarean section delivery. Occupational transmission of HCV among health care workers is also a major mode of transmission.

Natural history

(i) Acute HCV infection: Acute HCV infection is often asymptomatic with resolution in approximately two-thirds to one-half of all patients.\textsuperscript{69-71} Although incidence of acute HCV has significantly declined in many developed nations through routine screening of blood and blood products, it does occur through shared needles, sexual transmission and as a nosocomial infection in health care professionals. The incubation period for acute HCV infection is 2 to 26 wk and the most common clinical presentation is with jaundice (in about 20-30%). The symptoms resolve and a significant proportion (30-80%), in contrast to HBV infection, progress to chronicity.\textsuperscript{73} A recent study has provided overwhelming cure rates (98%) for treating acute HCV infection within four months of seroconversion.\textsuperscript{74} However, many acutely infected individuals will go on to clear the virus and hence may not require any intervention. Spontaneous resolution of acute HCV infection is more common with children, women and those who are symptomatic with jaundice during the acute stage of infection.\textsuperscript{69,76}

Severl ongoing clinical trials treating acute HCV infection will probably be able to answer whether and when we need to treat acute HCV infection.

(ii) Chronic HCV infection: Chronic HCV infection leads to cirrhosis, oesophageal varices, portal hypertension, hepatic decompensation, and hepatic malignancies. HCV is currently the major cause for liver transplantation in Europe and the US. Recent evidence suggests that the increase in the number of deaths from hepatocellular carcinoma in most countries is due to HCV infection.\textsuperscript{62} Cirrhosis is the end-stage of progressive liver fibrosis. Chronic HCV infection leads to cirrhosis among HCV mono-infected individuals in approximately 30 yr.\textsuperscript{72-79} There are several factors that may affect the rate of liver disease progression\textsuperscript{77,80,81} (Table II).

HCV infection can also present with extrahepatic manifestations which usually manifest much earlier than hepatic manifestations. Recent studies have indicated that three-fourths of all HCV infected individuals have at least one extra hepatic manifestation.\textsuperscript{82-84} These include rheumatic (myalgias, arthralgias, paraesthesias), mucocutaneous (pruritus, sicca syndrome, Raynaud’s phenomenon), vasculitic (cryoglobulinemia) and psychiatric (depression and anxiety) symptoms.\textsuperscript{82-84} Extrahepatic manifestations also include biochemical abnormalities like the presence of anti-nuclear antibodies, cryoglobulins, anti-Sm antibodies, and abnormal thyroid tests.\textsuperscript{82-84} Even though mixed cryoglobulinaemia is relatively common in chronic HCV patients, associated vasculitis is rare (2%). The clinical significance of these biochemical abnormalities is not yet clearly understood.

Natural history of HCV/HIV co-infection: Since the advent of ART, the outcome of HIV infection has been dramatically altered. Maximal suppression of HIV replication has led to effective restoration of immune function, resulting in a dramatic reduction in mortality associated with HIV infection. Recently causes other than opportunistic infections have been implicated in affecting the morbidity and mortality of HIV infected individuals. These include long-term toxicities of antiretroviral therapy such as metabolic abnormalities and cardiovascular events and...
hepatotoxicity and progressive liver disease due to both ART and chronic hepatitides. In developed countries, liver disease has already emerged as a major cause of mortality.

**Effect of HCV on HIV:** HCV does not appear to have a direct effect on HIV viral levels. However, in patients with progressive liver disease, portal hypertension and splenomegaly, the peripheral CD4+ T cell counts may be lower, giving the clinical picture of a more severe immunodeficiency state than is actually present. Large cohorts have provided conflicting results regarding risk of progression of HIV infected individuals to AIDS in the presence or absence of HCV co-infection. In the Swiss cohort study, patients who were co-infected with both HIV and HCV had a more rapid progression to AIDS than those who did not have HCV coinfection. Interestingly, this study also found that CD4+ T cell count increased less in patients with HCV than those without HCV after effective ART was instituted, suggesting that HCV infection may blunt immune recovery of HIV infected individuals on ART. Another large study failed to show an increase in progression of HIV infected individuals to AIDS among those who were coinfected with HCV. It is reasonable to believe that HIV/HCV coinfected patients differ in many important aspects from those with mono-infection. It has been suggested that decreased compliance with ART across the entire group could dilute the ability to discern differences in progression to AIDS. Understanding how HCV infection modifies the outcome of HIV infection is also complicated by the dramatic effects of ART on the natural history of HIV infected individuals.

**Effect of HIV on HCV:** HIV-associated immunosuppression has striking effects on several aspects of the natural history of HCV. First, the presence of HIV appears to be associated with higher HCV viral loads in serum and in liver tissue. Although one would assume that this is probably due to the immunosuppression associated with HIV infection, clinical trials have failed to demonstrate a clear relationship between the CD4+ T cell counts and HCV RNA levels. Moreover, HCV viral kinetic modeling does not support the hypotheses of higher viral production among HIV infected patients.

| Table II. Factors that predict liver fibrosis progression among HCV infected individuals |
|---------------------------------|---------------------------------|
| 1. Stage of liver fibrosis      | 2. Age at infection              |
| 3. Duration of HCV infection    | 4. Age at biopsy                 |
| 5. Consumption of alcohol >50 g per day | 6. HIV co-infection             |
| 7. CD4 count <200/µl             | 8. Male sex                     |
| 11. Absence of protease inhibitors in antiretroviral therapy regimen |

However, higher HCV viral loads definitely will have a negative impact on therapeutic response among HIV/HCV patients to anti-HCV therapy. Second, co-infected patients are less likely to clear HCV virus spontaneously. Third, HIV infected individuals are more likely to have false positive and false negative tests for serologic assays to detect HCV. This is more likely due to the presence of non-specific hypergammaglobulinaemia seen in HIV infected patients with lower CD4+ T cell counts. Finally, HIV/HCV co-infection is associated with a more rapid progression of liver disease to cirrhosis, liver failure and hepatocellular carcinoma. Benhamou et al. estimated the annual rate of fibrotic progression by dividing the METAVIR score by estimated duration of infection. Multivariate analysis of this study indicated that a low CD4+ T cells count (< 200 cells/µl) and alcohol consumption in excess of 50 g/day were highly associated with increased risk of disease progression (Table II). A subsequent study comparing patients on ART, a less effective ART, or no treatment, clearly indicated that effective suppression of HIV viral levels was associated with a decrease in liver-associated mortality. In a haemophiliac cohort, there was a higher risk for mortality from hepatic decompensation and hepatoma in persons with HIV co-infection than in mono-infected individuals. The overall risk of development of liver-related mortality for those who were exposed to HCV alone was 1.4,
compared with 6.5 among those who were infected with both viruses over those individuals who were negative for both viruses. It is conceivable that as survival of HIV infected individuals increases with potent viral suppressive therapies and appropriate prophylaxis of opportunistic pathogens, HCV-related morbidity and mortality will be more prevalent. In many developed countries, HCV-related liver disease is already among the predominant causes for death among HIV infected individuals.

**Effect of HCV on ART:** ART has been associated with hepatotoxicity leading to multiple interruptions causing significant morbidity and mortality. Several studies have demonstrated that hepatotoxicities associated with ART are more common in people coinfected with HCV and HIV, particularly those taking protease inhibitors. Several cohort studies have demonstrated a higher proportion of elevated transaminase levels among those with HCV infection. Management of liver toxicities in the presence of underlying liver disease is often cumbersome. Severe hepatotoxicities are more commonly associated with HBV and HCV infection. A recent review on the manifestations and current management trends of hepatotoxicity associated with ART in HIV/HCV co-infection covers the topic in greater depth.

**Effect of ART on HCV:** Several studies have suggested that initiation of ART leads to an increase in HCV viral levels. This increase is transient, and the viral load returns to baseline levels within six months of initiation of ART. Chung et al. recently showed that even though the viral loads increased in all patients, it continued to increase only in those with lower CD4+ T cell counts. Most studies used multiple ART regimens that makes it difficult to conclude any treatment-specific differences. Serum HCV RNA level increases are associated with increases in ALT and Aspartate transaminase (AST) increases as well. The mechanism of HCV RNA level increase in association with ART-associated immune reconstitution is not clearly established. This may be true in the case of HBV co-infection, where the increases in ALT coincides with a decrease in HBV DNA levels, suggesting an immune-mediated viral clearance as a mechanism for this phenomenon. However, the paradoxical increase in HCV RNA levels seen with HCV co-infection may reflect increased replication in some extrahepatic reservoirs or an altered immune-mediated HCV clearance in these patients.

**Pathogenesis:** Both HCV and HIV are RNA viruses whose genomes are transcribed frequently, producing greater than 10^10 virions in a day. Since both viruses replicate by means of a polymerase enzyme lacking the ability to proofread error, the replication results in the accumulation of a swarm of variants. The HIV genome is reverse transcribed and the complementary DNA strand is integrated into the DNA of latently infected CD4+ T cells contributing to the persistence of a HIV reservoir. HCV infection, on the other hand, is maintained by ongoing replication. In other words, since the HCV genome does not integrate into the host cell genome, but rather replicates in the cytoplasm, it is possible to eradicate HCV infection with effective therapy.

HCV predominantly replicates in hepatocytes. HCV is not considered as a cytopathic virus (Poynard), and chronic HCV is generally considered to be the result of an intermediate immune response that is large enough to induce hepatic cell destruction and fibrosis but not enough for eradication of HCV. HCV-specific humoral and cellular responses are weaker in the chronic phase than in the acute phase of the infection. Also, patients with poor immune responses in the acute phase are often asymptomatic and are more likely to become chronic carriers than those with good immune responses against HCV. It is arguable that one of the mechanisms by which immunomodulatory therapy (interferons) eradicates HCV infection is by restoration of a specific immune response.

**HCV genotypes:** HCV consists of six genotypes: genotypes 1a and 1b are prevalent in the US, genotype 1, 2, and 3 are common in Europe and Australia, genotype 4 is common in the middle east and North Africa, genotypes 1b, 2a and 2b are common in Japan, genotypes 1b and 2a in China, genotype 6 in Hong Kong, Macau and Vietnam, genotype 5 in Sub-Saharan Africa and genotype 3 in Thailand, Malaysia and Singapore. In India, genotype 1b is predominant in southern India and 3 and 2b are common in northern India.
Knowledge of genotypes is helpful for prediction of therapeutic response and the choice of treatment duration\textsuperscript{127, 128}. Response rates to therapy for genotypes 2 and 3 with pegylated interferon and ribavirin is around 88 per cent, but only 48 per cent for genotypes 1, 4, 5, and 6\textsuperscript{78}. Genotypes do not change during the course of infection. Genotyping all HCV patients for the purpose of management without treatment is recommended. Interestingly, no studies have shown any relationship between genotypes and severity of liver disease\textsuperscript{129}.

**Diagnosis:** There are currently two types of tests available to detect HCV: one is a serologic assay for the presence of antibodies and the other is a molecular test for detection of viral particles. Initial screening is done by detection of antibodies against HCV in the serum. Antibodies against HCV are often detected by using enzyme immunoassays (EIAs) that are very sensitive and specific. The third generation EIA currently used can detect both the core proteins and the non-structural proteins enabling diagnosis of HCV within 4 to 10 wk of infection. False positive results can be expected for immunosuppressed individuals, like those with HIV infection, chronic renal failure, and essential cryoglobulinemia\textsuperscript{78}.

Molecular assays for detection of HCV RNA are of two types. One is the qualitative assay, based on a PCR technique and has a lower limit of detection of 100 HCV RNA copies/ml. This test is particularly useful when transaminase levels are normal, when other causes of liver disease are present, in immunosuppressed individuals and in the acute stage of HCV infection. The second type of assay is the quantitative type and there are two different assays currently available. One is a qPCR assay and the other a bDNA assay. The HCV RNA viral loads from different assays are reported as standardized international units in order to make it clinically relevant for routine use in clinical practice\textsuperscript{130, 131}. Knowledge of HCV viral load is important as a predictor of therapeutic response and relapse. Patients with high HCV viral loads prior to therapy will experience higher rates of treatment relapses. Also, patients with less than two-log reduction in baseline viral levels at 12 wk after initiation of therapy have been shown to have a very low likelihood of achieving sustained virologic response\textsuperscript{130, 131}. However, baseline HCV viral loads have not been shown to correlate with the severity of liver disease\textsuperscript{130, 131}.

All HIV infected individuals should be screened for the presence of HCV infection\textsuperscript{132}. Screening is done with EIA followed by a confirmatory test or qualitative RNA test for positive patients\textsuperscript{72}. Detection of HCV RNA along with a positive antibody test indicates active HCV infection. It should be noted that HCV antibody titres decrease to levels below the level of detection in persons co-infected with HIV and HCV, particularly in those with CD4$^+$ T cell counts $< 200$/ml\textsuperscript{84}. Therefore, it is recommended that HCV RNA tests be done in persons with negative anti-HCV results and elevated ALT levels.

**Liver biopsy:** A liver biopsy for HCV patients is usually recommended for evaluation of the severity of liver disease. It is useful to stage the fibrosis and grade the degree of inflammation\textsuperscript{133, 134}. Biopsy is also helpful in diagnosing other causes for liver disease like autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), alcoholic liver disease, haemochromatosis and drug toxicities. One of the major limitations of liver biopsy is sampling error. The co-efficient of variation of the staging of 15 mm biopsy sample is around 55 per cent\textsuperscript{135}. Liver biopsy is also associated with several serious adverse events and carries a mortality rate of 0.3 per 1000\textsuperscript{136}.

Recently, a number of studies have attempted to validate the utility of non-invasive tests such as serum biochemical markers to predict the extent of HCV-induced liver disease. These markers, which include α2-macroglobulin, haptoglobin, γ-glutamyl transpeptidase (GGT), total bilirubin and apolipoprotein A1, have been shown to have high predictive value for the diagnosis of significant fibrosis when combined with ALT\textsuperscript{137, 138}. However, their utility in detecting early hepatic fibrosis has not been proven. Such markers, if validated, would be extremely helpful in assessing and monitoring liver disease among HCV/HIV coinfected patients.

**Management of HCV infection**

**General principles:** HCV does not integrate into the host genome, but replicates in the cytoplasm. Hence, it is conceivable that HCV can be eradicated with
adequate suppressive therapy. However, to date we do not have HCV-specific antiviral therapy available. Current treatment regimens include interferon-α, (standard or pegylated) and ribavirin. Although interferon may have some direct effects on HCV replication, the exact mechanism of action of both these agents is not yet clearly understood. It is believed that the antiviral effects of combination therapy include suppression of HCV replication in hepatocytes, enhancement of immune-mediated elimination of HCV infected hepatocytes, and prevention of new infection of hepatocytes. Some genotypes of HCV confer resistance to interferon and are less responsive to treatment (e.g., genotype 1, 4, 5 and 6). Until newer HCV-specific drugs are available, treatment for HCV is recommended for persons with chronic HCV who are at the greatest risk of developing cirrhosis. The risk is estimated by several biochemical, viral and histologic factors, including portal or bridging fibrosis or moderate degree of necroinflammatory response. Since liver fibrosis progression is more rapid in HIV/HCV co-infected patients, and the life expectancy of HIV infected individuals has significantly improved, it is recommended that these patients should be considered for anti-HCV treatment. Factors that are associated with a poor prognosis to achieve sustained virologic response (SVR) are summarized in Table III.

There are four potential benefits for treating HCV in HIV/HCV co-infected patients (Table IV). First, treatment of HCV could lead to viral eradication or SVR, as defined as undetectable HCV RNA at the end of treatment and 6 months later (See definitions of treatment responses in Table V). SVR is considered a cure in HCV mono-infected individuals, as several studies with 3 to 13 yr of follow up have shown that viral clearance is durable. Second, suppression of HCV can lead to a reduction in the risk of liver failure and hepatoma. Although only a few available data link HCV treatment to long-term clinical benefits, it is noteworthy that such benefits are not restricted to those with SVR. These studies have treated patients who are at the greatest risk of developing liver failure and hepatoma, without regard to SVR. Such approaches are relevant to HIV/HCV infected individuals who have lower rates of achieving a SVR, and limited access to liver transplantation compared to monoinfected individuals. Third, the treatment of HCV among HIV/HCV co-infected individuals may allow these individuals to better tolerate antiretroviral therapy for HIV. Many HIV/HCV co-infected patients have multiple interruptions of ART, due to higher rates of severe hepatotoxicity following initiation of ART. Treatment of underlying HCV infection can lead to normalization of transaminases and enable these patients to tolerate ART without interruptions. Finally, patients who

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**Table III.** Factors associated with poor sustained virologic response to combination therapy

<table>
<thead>
<tr>
<th>A. Viral factors</th>
<th>B. Host factors</th>
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<tr>
<td>HCV genotype 1</td>
<td>Age</td>
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<tr>
<td>HCV pre-treatment viral load &gt; 2 million copies/ml</td>
<td>Male sex</td>
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<tr>
<td>Chronicity of infection</td>
<td>Race- African American</td>
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<td>Alcohol consumption</td>
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<td>Liver fibrosis &gt; grade 3</td>
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<td>HIV co-infection</td>
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<td></td>
<td>CD4 T cell count &lt;500 cells/µl</td>
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<td></td>
<td>Prior treatment with interferon</td>
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<td></td>
<td>Body mass index (BMI)</td>
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<td></td>
<td>Ribavirin usage</td>
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*Source: References 81,127,128*
show no decline in plasma HCV levels may derive clinical benefit from therapy as evidenced by a decrease in the elevated transaminase levels, improved tolerance of antiretroviral therapy, and the decreased inflammation on the repeat liver biopsies (Fig.). Whether this benefit will be durable following discontinuation of therapy is uncertain. Long-term follow up of co-infected patients in a clinical trial setting to examine hepatic histologic response after discontinuation of therapy is needed to determine the durability of such benefit.

It should be noted that while no therapies have been specifically approved by the US FDA for the treatment of chronic HCV in HIV infected individuals, there are several treatments approved for HCV mono-infected individuals: monotherapy with interferon-α 2b, interferon alfacon-1, pegylated interferon-α 2b, and pegylated interferon-α 2a and combination therapy with interferon-α 2b, pegylated interferon-α 2b, or pegylated interferon-α 2a with ribavirin.

Interferon-α monotherapy: Interferon-α monotherapy has been used to treat both HCV monoinfected and HIV/HCV co-infected individuals. The results of interferon-α monotherapy are disappointing, although HCV mono-infected individuals fare better than HIV/HCV co-infected individuals. One study treated 90 HIV/HCV co-infected individuals with CD4+ T cell counts > 200 cells/µl with interferon-α for 12 months. In an intent to treat analysis, 20 per cent of these individuals achieved SVR: better responses were associated with a pretreatment CD4+ T cell count of >500 cells/cmm.

Addition of polyethylene glycol to the interferon-α molecule allows once-weekly administration and provides continuous exposure to interferon-α. Studies have shown that in HCV mono-infected patients pegylated interferon-α 2a, a branched 40 kDa PEG and pegylated interferon α2b, a linear 12 kDa PEG are more effective than standard interferon alone and have a similar tolerability profiles.

Combination therapy with interferon-α and ribavirin: Several randomized controlled trials have shown that interferon-α with ribavirin is a more effective therapy than interferon monotherapy in HCV mono-infected individuals. Many studies have suggested that combination therapy with interferon-α and ribavirin is well tolerated by HIV/HCV co-infected patients and may eradicate HCV in a small percentage of patients.

Two large multi-center international clinical drug registration trials in HCV-monoinfected individuals have clearly demonstrated that combination therapy with pegylated interferons (both α 2a or α 2b) is superior to that of combination therapy with standard interferon plus ribavirin, with SVR of 54 per cent (pegylated interferon-α 2b) and 56 per cent (pegylated interferon-α 2a). Given the ease of administration and its superior efficacy, combination therapy with pegylated interferons and ribavirin has largely replaced the use of standard interferon-α with ribavirin. There are four major clinical trials which have used pegylated interferon plus ribavirin for the treatment of HIV/HCV infected individuals. The Spanish study was an open label study using pegylated interferon-α and ribavirin to treat HIV/HCV co-infected patients. This study had a significantly higher proportion of HCV genotype 3 patients.
Liver biopsy slides showing necroinflammatory and fibrotic process in liver of an HIV/HCV patient who underwent successful treatment with pegylated interferon and ribavirin. (A) The necroinflammatory score (H & E staining) shows marked improvement from baseline biopsy (i) at the end of one year of treatment (ii). (B) On the other hand, the liver fibrosis scores (Masson staining) shows no significant change from baseline (i) after one year of treatment (ii) despite eradication of HCV.

A. H & E staining, i. Baseline, ii. After treatment
B. Masson staining, i. Baseline, ii. After treatment
who appear to respond better to the combination therapy than individuals with genotype 1. Despite this advantage, overall SVR rates were only 28 per cent, which is much lower than rate seen with monoinfected patients\textsuperscript{158}. The second trial, ACTG 5071, a multi-center, randomized clinical trial, enrolled 134 patients in the US. Patients were randomized to receive pegylated interferon-\(\alpha\) 2a in doses of 180 \(\mu\)g weekly along with escalating doses of ribavirin (600 mg to 1000 mg/d),\textsuperscript{159} or standard interferon-\(\alpha\) 2a using an induction regimen (6 million units three times a week to 3 million units three times a week) plus ribavirin (as escalating doses). This study reported an SVR of 27 per cent for the pegylated interferon-\(\alpha\) 2a with ribavirin group, lower than the other that seen with HCV monoinfected patients who underwent similar treatment. The RIBAVIC study,\textsuperscript{160}, sponsored by the French National Research Group, treated 412 patients and compared responses in HIV/HCV co-infected individuals receiving pegylated interferon-\(\alpha\) 2b with ribavirin or standard interferon-\(\alpha\) 2b with ribavirin. The SVR for this study was only 26 per cent (pegylated interferon arm) vs 18 per cent (interferon arm). The fourth study, the AIDS Pegasys Ribavirin International Co-infection Trial (APRICOT) was a multi-center, international, industry sponsored randomized controlled study that used three arms\textsuperscript{157}. Patients received pegylated interferon-\(\alpha\) 2a 180 \(\mu\)g/wk with or without ribavirin (800mg daily) or interferon-\(\alpha\) 2a (3 million units three time s a week) with ribavirin (800 mg/day). Of the 868 patients who completed the trial, SVR was attained in 40 per cent of the pegylated interferon-\(\alpha\) 2a with ribavirin arm, 20 per cent of the pegylated interferon-\(\alpha\) 2a alone arm, and 12 per cent of the interferon-\(\alpha\) 2a with ribavirin arm.

Overall efficacy of pegylated interferon-\(\alpha\) 2a with ribavirin in HIV/HCV co-infected patients is modest compared to HCV mono-infected individuals. Subtle yet significant differences between these trials could be key factors to why the response rates are different between these trials. ACTG 5071 used a dose-escalation regimen for ribavirin initiating at a lower dose (600 mg) and then increased this to 1000mg within the first twelve weeks\textsuperscript{159}. On the other hand, APRICOT study used a fixed dosing schedule for ribavirin at 800 mg/day\textsuperscript{157}. This approach has led investigators to speculate that higher SVR could have been achieved in the ACTG trial, if higher doses of ribavirin were used with initiation of treatment\textsuperscript{107}. The other key difference is the trial population, (US vs other countries). Baseline weight of US participants seems to be higher than those from other countries who participated in these trials and obesity is associated with decreased interferon response. Moreover, African-Americans appear to have lower response rates to interferon treatment than patients from other races that were represented at a higher proportion in ACTG than in APRICOT. Furthermore, liver pathology was more advanced in the ACTG study, which could have had a negative effect on treatment response.

Special consideration should be given to those patients with advanced liver disease. Persons with hepatic decompensation are not optimal candidates for interferon therapy. Hence, persons with advanced liver disease need to be screened for evidence of ascites, hepatoma, portal hypertension, and encephalopathy. Liver transplantation for HIV/HCV co-infected individuals is being explored as a feasible option in many centers in the US\textsuperscript{161}. Current guidelines recommend treating patients who are co-infected with HIV and HCV prior to development of severe liver disease\textsuperscript{81}. Given the high rates of relapse among HIV/HCV co-infected patients with genotype 2 and 3, current recommendations suggest these patients should be treated for 48 wk instead of 24 wk as with HCV mono-infected individuals\textsuperscript{81}. Also, HIV/HCV co-infected individuals have a higher relapse rate after stopping treatment for 48 wk when compared with that of HCV mono-infected individuals\textsuperscript{81}. Studies are currently addressing the need for prolonged, 48 wk treatment regimens for HIV/HCV co-infected patients in order to improve the rate of SVR.

Adverse events associated with anti-HCV treatment: Immunomodulatory therapy with interferon-\(\alpha\) has many adverse events\textsuperscript{162}. Most persons experience flu-like symptoms with initial doses, such as fatigue and malaise and other side effects such as anorexia, weight loss, hair loss, and skin rash. Neuropsychiatric disturbances (depression, irritability, insomnia, and cognitive changes) are
reported in over 50 per cent of patients. Depression can be severe and suicides have been reported with use of interferon for the treatment of HCV. Interferon can also lead to thyroid dysfunction in less than 5 per cent of patients and can also cause dose-dependent cytopenias, including leucopenia and thrombocytopenia. Lymphopenia that follows is usually associated with a decrease in absolute CD4+ T cell counts; however, the percentage of CD4+ T cells remains unchanged, and there is no apparent additional risk for opportunistic infection.

Ribavirin is associated with haemolytic anaemia and interferon also induces bone marrow suppression leading to anaemia. This may be a more serious problem with HIV infected individuals because of the high prevalence of anaemia and limited myeloid reserves due to comorbid diseases and/or associated drug toxicity. Ribavirin can also cause birth defects and hence should not be administered to pregnant women. Both men and women should be advised to use effective measures of contraception during therapy and for six months after the drug is discontinued.

Since combination therapy has been used for treating HIV/HCV co-infected patients, newer adverse events have been reported. A recent study reported loss of Colour vision and other ophthalmologic changes in patients undergoing therapy with pegylated interferon-α 2b and ribavirin. These findings suggest that all patients undergoing therapy for HCV should undergo complete ophthalmologic examination at baseline and at regular intervals while undergoing treatment. Another concern has been drug interactions that may be involved with the use of ribavirin with other nucleoside analogs. Several years ago, it was shown that ribavirin, which is a guanosine nucleoside analog has antagonistic activity in vitro against the anti-HIV activity of pyrimidine nucleoside analogs: zidovudine, stavudine and zalcitabine. However, many small clinical trials have failed to detect any clinically significant antagonism when ribavirin was used along with pyrimidine nucleoside analogs. In contrast, ribavirin inhibits inosine 5’ phosphate dehydrogenase, which facilitates the intracellular conversion of didanosine to its inactive metabolite. This enhances HIV activity in vitro but may also increase in vivo toxicity, including mitochondrial effects. Further, symptomatic hyperlactataemia has been reported in some patients co-infected with HIV and HCV and receiving ribavirin and didanosine concomitantly. Therefore it is not recommended that those two drugs be used concomitantly.

Prevention: Compared to HCV mono-infection, co-infection with both HIV and HCV results in accelerated liver fibrosis, hepatocellular carcinomas, intolerability to ART, multiple interruptions in ART, lack of adequate response to existing anti-HCV treatment and problems associated with orthotopic liver. Overall, the best strategy in fighting HCV among HIV co-infected individuals is to prevent acquiring HCV infection. Unlike HBV, we do not have an effective HCV vaccine that prevents infection. All these factors reiterate the significance of developing efficient preventive strategies to thwart HIV infected persons from acquiring HCV infection. First, persons with HIV infection who are not yet infected with HCV should undergo counseling to stop using injection drugs; those unable to do so should pursue safe injection practices (Table VI). Second, use of barrier methods of contraception must be employed to adequately prevent sexual transmission of HCV. Third, pregnant mothers who have risk factors to acquire HCV infection must be screened for the presence of HCV. It should be noted that interferon-α and ribavirin are contraindicated in pregnancy. Elective caesarian section prior to rupture of membranes has shown to reduce maternal fetal transmission rates of HCV (and HIV) significantly, but is still not routinely recommended by the experts. Finally, although post-exposure prophylaxis with ART is recommended for all HIV infection, it is not recommended to prevent HCV infection.

Relevance to India: There have been a few studies in India that provided information on prevalence of HCV infection. A community-based study using serologic assays indicated a HCV prevalence rate of 0.87 per cent. The prevalence increased from 0.31 per cent for children <10 yr to 1.85 per cent among those who are older than 60 yr. Although these percentages are far below what has been projected world-wide, these represent a significant reservoir of...
infection calling for public health measures to address the magnitude of this problem. Another study from a tertiary care hospital\textsuperscript{173} in southern India demonstrated an overall 6\% prevalence of HCV infection and a 21\% seroprevalence of HCV among HIV infected individuals. These numbers probably do not represent that in the general population, but are of concern. Surprisingly, a study evaluating the knowledge of HCV among family physicians in one of the provinces in northern India indicated that there were deficiencies in the awareness about HCV, its detection and transmission\textsuperscript{174}. However, this study had a low physician response rate and probably does not represent the practice of family physicians over the entire country. These results reiterate the need for health education for health care providers regarding all aspects of health care (Table VII).

Several studies\textsuperscript{52,122-126} have evaluated the prevalence of HCV genotypes in India. HCV genotype 3 is more common in northern and western parts of India\textsuperscript{123,125,126} whereas, genotype 1 is more common in the southern region\textsuperscript{53,122}. Genotype 3 infections have a greater response to treatment and HIV-negative individuals require 24 wk of therapy, compared to 48 wk for genotype 1\textsuperscript{127,128,151,152}. Unlike HBV treatment, several studies reported treatment of HCV patients with interferon with or without ribavirin\textsuperscript{57-59}. These studies have been done in cohorts which are predominantly genotype 3 and have reported excellent SVR rates\textsuperscript{57,59}. These data indicate that it is conceivable to diagnose and treat HCV patients and obtain cure rates similar to that seen with larger clinical trials reported worldwide\textsuperscript{127,128,149-152}. These clinical trials also demonstrated excellent adherence and follow up of patients who underwent 48 wk of treatment. Overall, these data suggest it is very possible to successfully manage HCV infection in a resource-limited setting. However, it should be noted that management of HCV patients in settings with limited resources like community hospitals and

### Table VI. Who should we screen for HCV?

<table>
<thead>
<tr>
<th>A. Based on increased risk for infection</th>
<th>B. Based on need for exposure management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior use of injected illegal drugs</td>
<td>Healthcare, emergency, public safety workers after needle stick/mucosal exposures to HCV-positive blood</td>
</tr>
<tr>
<td>Received clotting factors made before 1987</td>
<td>Children born to HCV-positive women</td>
</tr>
<tr>
<td>Received blood/organisms before July 1992</td>
<td></td>
</tr>
<tr>
<td>Previously on chronic haemodialysis</td>
<td></td>
</tr>
<tr>
<td>Evidence of liver disease</td>
<td></td>
</tr>
</tbody>
</table>

*Source*: Reference 72

### Table VII. Methods to reduce risk of acquiring HCV infection

| Screen and test donors for blood, blood products and organs |
| Virus inactivation of plasma-derived products |
| Risk-reduction counseling and services: |
| Obtain history of high-risk drug and sex behaviours |
| Provide information on minimizing risky behaviour, including referral to other supportive services |
| Vaccinate against hepatitis A and/or hepatitis B |
| Safe injection and infection control practices |
| Identify persons at risk for HCV and test to determine infection status: |
| Routinely identify at risk persons through history, record review |
| Provide HCV-positive persons: |
| Medical evaluation and management |
| Counselling |
| Prevent further liver damage |
| Prevent transmission to others |

*Source*: Reference 72
clinics is going to be extremely challenging. Anti-HCV therapy is not without severe adverse events and has high drop out rates outside of clinical trials settings. Monitoring these patients and managing adverse events can be challenging. Also, the studies mentioned above only represent a very small portion of the total number of patients infected with HCV in the Indian subcontinent, reiterating the need for prioritizing limited resources. Further, the response rates of the majority of patients with genotype 1 are not going to be as high as those seen with genotype 3. Finally, HIV/HCV co-infected individuals are unlikely to respond to treatment to the same degree as HCV mono-infected individuals. Management of these individuals will obviously be challenging. HIV infected individuals are susceptible to opportunistic infections associated with a high degree of morbidity and mortality. Management of HIV infection should be prioritized for control of ongoing HIV replication using ART, prophylaxis and specific therapy for opportunistic infections. With regards to HCV infection, prompt diagnosis and counselling of these patients is the most effective strategy (Tables VI & VII). Vaccination of these patients against HBV and hepatitis A virus is recommended (CDC). Moreover, these patients should be advised to avoid alcohol and other hepatotoxic agents like acetaminophen, as these agents can worsen the underlying liver disease.

In summary, HCV co-infection is an emerging opportunistic infection that could have a catastrophic effect on the morbidity and mortality of HIV infected patients. Screening susceptible individuals and offering counselling are the first steps in the management of HCV infection. Treatment for HCV in HIV infected individuals is expensive, associated with severe side effects, and has only modest cure rates. Availability of resources may require that treatment be reserved for select patients until less expensive and more effective therapies are available.

**Conclusion**

HCV and HIV co-exist in a large proportion of patients due to their shared modes of transmission. HIV accelerates HCV-associated liver fibrosis and HCV leads to higher rates of discontinuation of HAART due to severe hepatotoxicity. HCV treatment responses to the current standard of care are only modest in HIV co-infected individuals. Moreover, current treatments are associated with significant side effects. HCV treatments that are more effective, less expensive, associated with fewer side effects, and preferably not immune-based are required to eradicate HCV. Current research is focused on defining the optimal management of chronic HCV patients including the role of liver transplantation. Future studies should focus on the pathogenesis of HCV in HIV infected individuals, thereby enabling clinicians to develop novel therapeutic approaches to impede liver disease progression.

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