Review Article

Challenges in Providing Treatment and Care for Viral Hepatitis among Individuals Co-Infected with HIV in Resource-Limited Settings

Wirach Maek-a-Nantawat, Anchalee Avihingsanon, and Pirapon June Ohata

The HIV Netherlands Australia Thailand Research Collaboration, Thai Red Cross AIDS Research Centre, 104 Rajdumri Road, Pathumwan, Bangkok 10330, Thailand

Correspondence should be addressed to Wirach Maek-a-Nantawat, wirach.m@hivnat.org

Received 26 September 2011; Accepted 6 December 2011

1. Introduction

Most countries in Southeast Asia currently have limited resources in providing universal coverage for HIV treatment and care. Since the start of the global AIDS epidemic, Thailand has become the only country within this region with a high prevalence of HIV infection (>1%). In 2009, the HIV prevalence has decreased to 2.3 million because of the HIV prevention campaigns. These HIV prevention campaigns focused on promoting the use of condoms among commercial sex workers and their clients which achieved >90–95% success in preventing HIV transmission. Another campaign known as the prevention of mother-to-child transmission (PMTCT) was also successful. However, in recent years, the rates of new HIV infection have increased among hard-to-reach groups such as the men having sex with men (MSM), injection drug users (IDUs), and adolescents. It has been shown that only 20–30% of sexually active young people used condoms consistently. Furthermore, these HIV-infected high risk groups have sexually transmitted hepatitis infection, especially HCV.

Antiretroviral drugs are provided through the national health schemes and international funding agencies such as the Global Fund and PEPFAR. These antiretroviral therapy (ART) programs provide financial support for ARV protocol development, professional health care training, drug supply chain management, formation of a laboratory network, monitoring and evaluation, and other needs requested by the multisector and various people living with HIV/AIDS (PLWHA) groups. The program has scaled up but mostly lacks local leadership, comprehensive training, and coordination to achieve and sustain the success of the program. Furthermore, patients coinfected with hepatitis are currently being ignored. Screening and treatment for hepatitis coinfection should be included in the national policy to reduce problems in the future.
2. Epidemiology of HBV and HCV Coinfection

It has been documented that HBV infection in the general population is high (>8%) in many countries from the Southeast Asia region [1–4]. Reports showing lower infection rates of 3.2–6% from Brunei Darussalam, Indonesia, Philippines, and Thailand [5–9] are based on cases infected through vertical transmission. In tertiary care settings, HBV infection in HIV-infected population was approximately 8.7–11% [10–14]. MSMs and IDUs are at a higher risk of being infected with HBV and HIV. However, the infection rate of HBV in PLWHA is not that much different compared to the general population of which majority are infected perinatally. The most common HBV genotypes are C [15–17] and B [18, 19] followed by A. The most common genotypes found among migrants living in Thailand are C (86%) and B (11.6%) [20]. The prevalences of HBsAg among migrants from Cambodia, Laos, and Myanmar living in Thailand were 10.8%, 6.9%, and 9.7%, respectively [20]. In the last 10 years, chronic perinatal infection has decreased when the national program expanded its immunization protocol to include HBV vaccination in all children. Even though the HBV subtypes of the surface antigen [15, 18, 21] reported are adr and adw, this is not clinically significant because the HBV vaccine of either ayw or adw subtype can yield anti-a which is protective against crossinfection with other HBsAg subtypes as well [22].

In contrast to HBV, HCV co-infection is moderately high in PLWHA, especially among IDUs and MSMs. If HIV prevalence in IDUs is high, eventually HCV co-infection will become a major problem as currently seen in Thailand and Vietnam [23]. Among PLWHA, it has been estimated that approximately 5–40% have contacted HIV from injecting drugs. In Thailand and Vietnam, at least 50% of IDUs are living with HIV/AIDS, and about 90–95% have also contracted HCV. The estimated prevalence of HCV/HIV co-infection is 7.2–10.1% [10, 11, 14, 24, 25]. Unlike Thailand and Vietnam, in the Philippines, 83–89% of IDUs are infected with HCV whereas only 0.34% are infected with HIV. Hence, the prevalence of HCV/HIV co-infection is low [26]. Factors such as males [10, 27] and IDUs are at a higher risk of becoming infected with HCV and HIV. Among the general population, the most common genotypes of HCV in Thailand, Vietnam, and Indonesia are 3a (70%), 6a (32.5%), and 1b (47.3%), respectively [25, 28, 29]. However, in HIV-infected individuals, genotype 1 is increasingly found [27]. The prevalence of HCV/HBV-HCV triple infection is rare (0.4%) but can be found among IDUs and MSMs [11]. The predominant HCV genotypes detected in migrants from Cambodia, Laos, and Myanmar living in Thailand were 1a, 1b, 3, and 6, respectively. However, this data may not accurately reflect the real HCV genotypes among these groups of people because few samples were collected from that study [30].

3. Approach in Diagnosing HBV or HCV among HIV-Infected Patients

Many individuals infected with HBV at birth or during early childhood and subsequently infected with HIV have asymptomatic HBV chronic infection with or without amino-transaminase elevation. Patients who develop acute hepatitis B during their adulthood will have abrupt and progressive jaundice with GI symptoms such as nausea, abdominal pain, flatulence, and bloated abdomen. The general symptoms include fatigue, dizziness, weight loss, or anorexia. The liver is usually not enlarged, and the cutaneous stigmata of chronic liver disease is not detected unless the disease has progressed to decompensated cirrhosis. Cirrhosis is more common in patients with lower levels of ALT and CD4 compared to those monoinfected with HBV [31, 32]. HIV-HBV co-infected men are much more likely to die of liver-related causes compared to monoinfected HBV patients [33]. The risk of HCC is somewhat increased in HIV-infected individuals with low CD4 counts [34]. Patients with genotype C have exhibited earlier progression of cirrhosis and HCC than those with genotype B [17].

Similarly, patients co-infected with HCV and HIV have asymptomatic acute HCV infection. It is also possible that many IDUs co-infected with HCV and HIV may not have reported their symptoms, and this may not necessary reflect an accurate account of HCV infection among these groups of people. Usually, in non-IDUs, acute hepatitis C is detected in PLWHAs currently on treatment and diagnosed with sexually transmitted infections (e.g., syphilis, gonorrhea) because of elevated enzyme levels. HIV positive individuals with acute HCV infection can develop chronic HCV infection. In contrast to HBV, in HCV co-infected patients, disease progression to liver cirrhosis and hepatocellular carcinoma (HCC) occurs very quickly and may exist prior to HCV treatment. As a result of this, physicians need to closely monitor these patients, even those that have sustained viral response to HCV treatment. Routine HBV and HCV screening are not routinely performed at tertiary care setting. Many HIV patients with undetectable HIV RNA and elevated liver enzymes are screened for hepatitis and eventually found to be co-infected with HBV [14, 35].

Currently, the national guidelines for antiretroviral therapy in HIV-infected adults and adolescents in most countries recommend HIV-infected persons to be screened for HBV before initiating ART. The reason for this is because this will help guide physicians in designing the patient’s HAART regimen which should contain at least 2 antiretroviral drugs with activity against both HIV and HBV, that is, tenofovir plus lamivudine or tenofovir plus emtricitabine. The viral hepatitis serology is widely available but not routinely used to screen those patients most at risk such as IDUs and MSMs. Tests for HBs antigen are recommended to all HIV-infected patients, but recently, in actual practice, 53–69% of HIV-infected adults were tested for hepatitis [12, 13, 36]. Asymptomatic chronic infected cases are not unmasked and may continue to transmit the viruses through contaminated blood and genital secretions. If HIV-infected people are aware of the effects of HBV and the accessibility of HBV treatment, then the rate of HBV screening prior to ART may improve. The results of HBV serologic profiles are interpreted as mono-HBV infection (see Table 1). However, isolated positive core antibodies are more frequently (20–30%) found in co-infected patients [37] compared
to those monoinfected with HBV, especially in advanced immunocompromised [38], HCV co-infected cases [39–41], or IDUs. The clinical significance of having a positive anti-HBc antibody is not well understood, but there is more evidence indicating that people with this serologic finding has an occult infection with frequent hepatic flares [42] and potential of transmitting the infection [43–46]. In certain cases, some may have undetectable HBV DNA with isolated core antibody [47, 48].

Since HBV/HIV co-infection is common, it is highly recommended that in every HIV-infected individuals, serologic screening tests for hepatitis B should include HBs Ag, anti-HBs, and anti-HBc antibody. If all 3 serologic tests are negative, then it is highly recommended that the patients get a hepatitis B vaccine to prevent infection. If an isolated core antibody is detected, then a confirmatory HBV-DNA or complete liver function workup is needed to help guide the patients’ long-term care management. It is not conclusive whether HIV-infected individuals with isolated core antibody should get a Hepatitis B vaccine [37]. If HBs antigen is positive, then it is important to assess whether the patient also has HBe Ag, anti-HBe antibody, HBV-DNA and liver enzymes to rule out viral replication, liver complications and whether treatment is needed.

Majority of patients presenting acute HBV infection will have elevated levels of liver enzymes (ALT > AST with >10 times ULN). However, as for those currently infected with HBV or have tested positive for HBs antigen, it is difficult to differentiate whether they are HBV carriers or have chronic infection with low or nonreplicative phase. In healthy carriers, HBV-DNA may not be detectable because of transient viremia and therefore would require retesting. HBV-DNA is somewhat useful but is too expensive for some countries with limited resources. Certain places may not have access to machines to detect HBV-DNA, and some patients may not be able to afford such diagnostic tests. In order to detect and differentiate chronic active HBV patients from positive serostatus for HBe Ag, physicians would need the patients’ medical history, risk behaviors or predisposing factors, and physical findings such as stigmata of chronic liver.

Liver enzymes can be used as a surrogate marker for detecting hepatic necroinflammation, but its elevation may also indicate a hepatic flare from any causes including the virus itself. Serum aminotransferase levels are less reliable in determining whether the patient would need therapy or not. Serum aminotransferase levels can be lower in patients co-infected with HIV and HBV or within normal range in some patients with significant hepatic fibrosis. Even though liver pathology can specifically detect fibrosis and necroinflammation by using a scoring system; however, its procedure is invasive, time-consuming and may not be sensitive if there is bias in the way the samples are collected or assessed. Assessing the extent of the underlying liver damage is important because it will affect the prognosis of the infection as well as the choices for treatment. Another noninvasive test known as the hepatic elastography (Fibroscan) can be used to measure the liver’s stiffness or evaluate hepatic fibrosis. The results from the Fibroscan can guide treatment and care but may not be possible in resource-limited settings. Some of the limitations of the fibroscan are its inability to accurately predict the degree of injury seen on a liver biopsy or subsequent clinical events. Close monitoring is necessary to detect early cases.

In regards to HCV co-infection, the national guidelines recommend to screen for anti-HCV antibody before initiating ART in HIV-infected adults exhibiting symptoms or those with risk factors such as intravenous drug use. The treatment cost for HCV is extremely expensive and is not covered by the national health schemes. Patients with HCV who need treatment must pay for their own treatment. Aside from that, the national health schemes do not provide free diagnostic tests for HCV genotype and HCVRNA load. At the present, in majority of the countries, there is insufficient epidemiological data on HIV/HCV co-infection. Hence this may be one of the reasons why the national health schemes will not offer free HCV testing in HIV-infected individuals. According to the physicians who have done anti-HCV tests in their HIV-infected patients, there is a high prevalence of HCV co-infection. This result indicates that an appointed committee should include HCV tests in the national guidelines for HIV-infected patients.

It is possible to use tests to detect for anti-HCV antibody to screen those groups at risk for acquiring the infection. However, it is important to note that anti-HCV seroconversion occurs much slower in HIV-infected patients, and it is still possible to have anti-HCV negative results despite ongoing viral replication for a year [49]. Currently, HCV antibody tests cost around 6–9 USD. In a resource-limited setting, this cost is affordable yet it is not included in the national health care program. This test can be used to screen and diagnose HCV in HIV-infected patients even though

### Table 1: Findings and interpretations of HBV serologic markers.

| HBs Ag | Anti-HBs | Anti-HBc | Hbe Ag | Interpretation |
|--------|----------|----------|--------|---------------|
| +      | −        | −        | +      | Chronic replicative phase or acute infection |
| +      | −        | +        | −      | Chronic nonreplicative/carrier (DNA neg) |
| +      | −        | −        | −      | Precore mutants |
| −      | −        | +        | −      | Isolated core antibody |
| −      | +        | −        | −      | Recovery from acute infection |
| −      | −        | −        | −      | Occult infection (DNA positive) |
| −      | −        | −        | +      | Previously immunized with HBV vaccine |

### Notes:
- ALT > AST with >10 times ULN.
- HBV-DNA is somewhat useful but is too expensive for some countries with limited resources.
- Certain places may not have access to machines to detect HBV-DNA.
- Some patients may not be able to afford such diagnostic tests.
- Liver enzymes can be used as a surrogate marker for detecting hepatic necroinflammation.
- Serum aminotransferase levels are less reliable in determining whether the patient would need therapy or not.
- Serum aminotransferase levels can be lower in patients co-infected with HIV and HBV or within normal range in some patients with significant hepatic fibrosis.
- Liver pathology can specifically detect fibrosis and necroinflammation by using a scoring system.
- The procedure is invasive, time-consuming, and may not be sensitive if there is bias in the way the samples are collected or assessed.
- The results from the Fibroscan can measure the liver’s stiffness or evaluate hepatic fibrosis.
- The fibroscan has limitations such as its inability to accurately predict the degree of injury seen on a liver biopsy or subsequent clinical events.
- Close monitoring is necessary to detect early cases.
- In regards to HCV co-infection, the national guidelines recommend to screen for anti-HCV antibody before initiating ART in HIV-infected adults exhibiting symptoms or those with risk factors such as intravenous drug use.
- The treatment cost for HCV is extremely expensive and is not covered by the national health schemes.
- Patients with HCV who need treatment must pay for their own treatment.
- The national health schemes do not provide free diagnostic tests for HCV genotype and HCVRNA load.
- At the present, in majority of the countries, there is insufficient epidemiological data on HIV/HCV co-infection.
- Hence this may be one of the reasons why the national health schemes will not offer free HCV testing in HIV-infected individuals.
- According to the physicians who have done anti-HCV tests in their HIV-infected patients, there is a high prevalence of HCV co-infection.
- This result indicates that an appointed committee should include HCV tests in the national guidelines for HIV-infected patients.
- It is possible to use tests to detect for anti-HCV antibody to screen those groups at risk for acquiring the infection.
- However, it is important to note that anti-HCV seroconversion occurs much slower in HIV-infected patients, and it is still possible to have anti-HCV negative results despite ongoing viral replication for a year.
- Currently, HCV antibody tests cost around 6–9 USD. In a resource-limited setting, this cost is affordable yet it is not included in the national health care program.
- This test can be used to screen and diagnose HCV in HIV-infected patients even though...
it may not be perfect. It can be used in clinical settings or as requested. In most of the cases, there are no or very little clinical symptoms as seen in people with acute HCV infection. Therefore, acute HCV infection is defined as having detectable HCV-RNA in the first 6 months after infection. Transaminase levels can also be used to accurately detect acute HCV infection. Elevated levels of alanine transaminase (ALT) are more sensitive in detecting acute HCV when compared to anti-HCV antibody tests. Tests to detect HCV-RNA are used to determine the virus's replicative state. Hence results from HCV-RNA tests can detect early infection better than the antibody tests and are usually used to exclude false positive results obtained from the serologic tests when the patients have disclosed not having any risk behaviors. Sometimes it is also used to determine whether the result from the serology test is a false positive or not. Past resolved HCV infection may yield false positive results in the serology test. HIV positive individuals who need to start antiviral treatment should be screened for HCV by using the HCV-RNA tests and monitored regularly [50]. Chronic hepatitis C infection is defined as having ongoing viral replication for more than 6 months. Without the patient's past hepatitis C test results, it is difficult to determine the HCV status of the patient based only on the patient's history, current physical and laboratory examinations. It is very difficult to distinguish between acute and chronic infection because flares during chronic hepatitis C may mimic acute infection.

Genotyping should be done in every case who will need HCV treatment because this will help guide the physician in determining the length of treatment, predict treatment response and prognosis of HCV (see Figure 1). However, if genotyping tests are not available, then physicians from resource-limited setting can use regional epidemiological data to determine the subtype of HCV. As for those patients not on HCV treatment due to no indication, treatment intolerability or failure and drug availability, it is important to continue to monitor and assess the progression of the disease. Liver enzymes should regularly be checked every 3 months and repeated if there are significant elevations. The degree of histologic injury is a better predictor of subsequent clinical events than is the degree of elevated serum aminotransferase levels, genotype, or viral load. The result of the Fibroscan can support the physician's decision to start antiviral treatment regardless of symptoms. However, in the middle of 2011, there is evidence that this is not implemented throughout the region. Therefore, it is important to assess the treatment rates in cases with CD4 of 200–350 cell/μL to ensure treatment coverage and care among these people in order to reduce opportunistic infections in severely immunocompromised patients. Some nucleoside/nucleotide analogs for HIV treatment are effective to both HIV and HBV and therefore can be used to treat HIV/HBV co-infected patients. Furthermore, the results from the study on Tenofovir in HBV Coinfection (TICO) which was conducted in Thailand showed that a combination of tenofovir and emtricitabine or lamivudine was better than using only tenofovir [55, 56]. There was an increased loss of HBsAg when a longer follow-up period was implemented to assess HBV treatment outcome. Hepatic flares were observed in 19–25% of the patients without any severe complications. Interestingly, long-term use of tenofovir in HIV/HBV co-infected patients may prevent disease progression to end-stage liver disease in the Thai population, by slowing or reversing liver fibrosis. Currently, the Thai national guideline recommends using tenofovir with either lamivudine or emtricitabine for any HBV co-infected individuals regardless of their baseline CD4+ T-cell count. Since HBV treatment is cheap (approximately 55 USD/mo. for tenofovir plus lamivudine and 70 USD/mo. for tenofovir plus emtricitabine), this is covered by the national health scheme. However, the cost for monitoring HBV-DNA is not included in the national AIDS

In conclusion, routine screening using serologic tests for hepatitis B and C is beneficial for the patient to determine when to start treatment or those who cannot afford such care to closely monitor the disease progression and complications. The use of stavudine, didanosine, and nevirapine, which are unfriendly to the liver, should be used with caution because it can lead to liver toxicities. For public health concerns, this will also help reduce the risk of transmission if treatment is provided and reduce risk behaviors. As for those patients at risk of acquiring hepatitis such as immunocompromised patients, physicians can recommend HBV vaccinations. It is highly recommended that in resource-limited settings where there is a high prevalence of hepatitis, HBV and HCV should be screened in HIV-infected patients prior to ART.

4. Management of Coinfected Patients

Recently, the international HIV treatment guidelines 2011 recommend that antiretroviral therapy should be started in all HBV/HIV co-infected adolescents and adults who require treatment for chronic active hepatitis B irrespective of their CD4 cell counts. According to these new guidelines, all HIV-infected individuals with CD4 ≤ 350 cells/μL are required to start antiretroviral therapy regardless of symptoms. However, in the middle of 2011, there is evidence that this is not implemented throughout the region. Therefore, it is important to assess the treatment rates in cases with CD4 of 200–350 cell/μL to ensure treatment coverage and care among these people in order to reduce opportunistic infections in severely immunocompromised patients. Some nucleoside/nucleotide analogs for HIV treatment are effective to both HIV and HBV and therefore can be used to treat HIV/HBV co-infected patients. Furthermore, the results from the study on Tenofovir in HBV Coinfection (TICO) which was conducted in Thailand showed that a combination of tenofovir and emtricitabine or lamivudine was better than using only tenofovir [55, 56]. There was an increased loss of HBsAg when a longer follow-up period was implemented to assess HBV treatment outcome. Hepatic flares were observed in 19–25% of the patients without any severe complications. Interestingly, long-term use of tenofovir in HIV/HBV co-infected patients may prevent disease progression to end-stage liver disease in the Thai population, by slowing or reversing liver fibrosis. Currently, the Thai national guideline recommends using tenofovir with either lamivudine or emtricitabine for any HBV co-infected individuals regardless of their baseline CD4+ T-cell count. Since HBV treatment is cheap (approximately 55 USD/mo. for tenofovir plus lamivudine and 70 USD/mo. for tenofovir plus emtricitabine), this is covered by the national health scheme. However, the cost for monitoring HBV-DNA is not included in the national AIDS
program, and the patients have to pay for this by themselves. Other nucleoside analogs such as adefovir, telbivudine, and entecavir are also not included because the government has decided that these drugs are not essential for the mass treatment of HBV. Moreover, it is still unclear which HBV drugs should be used for the preferred regimen in pregnant women, and infants born to HBV co-infected mothers.

The situation is even worse for those co-infected with HIV and HCV. The current national treatment guideline recommends pegylated interferon α2a or 2b plus ribavirin (Figure 1). Pegylated interferon and ribavirin are not on WHO and Asian national essential medicines lists for all HCV patients and hence are not freely provided through the national health schemes. As for other low and middle-income countries, many patients cannot afford pegylated interferon and ribavirin due to its costs. Currently, patented pegylated interferon from Roche (Pegasys) and Merck (PegIntron) is packaged and sold with generic ribavirin. Because of these patents, hepatitis C treatment remains to be expensive. For a 48-week treatment course, it costs approximately $26,000–30,000 USD. Thus, most health care systems cannot provide treatment for HCV and will refuse to offer treatment to majority of patients with HCV. This price does not include other related investigations such as HCV genotyping and HCV RNA as well as treatment for unexpected complications. HCV RNA should be assessed before commencing treatment and used to assess the efficacy of the treatment regimen. The most common adverse events are neuropsychiatric symptoms and marrow toxicity which can add to the cost of treatment and contribute to premature treatment termination. Therefore, in order to minimize adverse effects, antiretroviral therapy needs to be adjusted. Concomitant use of zidovudine is contraindicated due to its effect on the bone marrow; bone marrow suppression is worsened by the use of zidovudine. The use of didanosine is also not recommended during HCV therapy due to increased risks of hepatic decompensation. Problems are further exacerbated if the patient is co-infected with HCV and HIV and receiving treatment concomitantly. It is not possible for all HCV/HIV co-infected patients to get HCV treatment because it is very expensive and has several intolerable side effects. Patients on ART also suffer from pill burdens and side effects of antiretroviral drugs.

As a result of this, images of the liver by using ultrasound, levels of serum aminotransaminase, and α-fetoprotein are regularly monitored in HCV co-infected patients (see Table 2 for summary). Liver biopsy is rarely done to avoid complications and risks for contamination, especially in HIV-infected treatment-naïve patients. Most Thai patients with HCV infection have genotype 3, the type which responds well to treatment, allowing physicians to reduce the treatment duration to 12–16 weeks in those achieving rapid virological response (RVR); this is based on the findings that 82% of patients were successfully treated for HCV which is comparable to a 24-week treatment course [57] and is still also cost-effective if retreating the cases with relapses for 24 weeks [58]. During treatment, RVR measured at week 4 is a strong predictor of sustained virological response (SVR) [59]. Because of this, short-course treatment for 24 weeks is recommended to the patients infected with genotype 2/3, and a shorter treatment course (12–16 weeks) may be an option for patients unable to tolerate treatment with close RVR monitoring. The response-guided therapy aims to optimize treatment outcomes without compromising SVR rates [60].

IL28B gene polymorphisms modulate early virological response to peginterferon/ribavirin treatment and is associated with SVR in patients infected with genotype 2/3 HCV who did not achieve RVR [61]. The favorable CC genotype, as compared to either the CT or TT genotypes, has been associated with a 3-fold increase in the rate for spontaneous clearance of HCV [62] and 2-3 folds higher rate of SVR.

---

**Figure 1:** Treatment scheme for HCV coinfection guided by genotype and HCV-RNA load assessment at baseline, wks 4, 12, and 24 [48, 72]. Patients having baseline HCV-RNA load <400,000 IU/ml with minimal fibrosis.
in HCV genotype 1 chronically infected individuals treated with combination pegylated interferon/ribavirin therapy [63]. In contrast to HCV genotype 1 patients, despite the faster initial viral response in the patients carrying C/C, SVR rates of mono-HCV genotype 3 infection were not different compared to the patients carrying T-allele [64, 65]. Quantitative evaluation of interferon-γ-inducible protein-10 (IP-10) may add on the predictive value of IL28B polymorphisms for HCV treatment responses [66]. The clinical outcomes of an earlier viral decline and a shorter course treatment in CC patients infected with HIV/HCV genotype 2/3 are warranted. Nonetheless, access to treatment in Thailand is still hindered by the costs of the medications. Furthermore, drug toxicities may contribute to incomplete treatment for HCV among HIV-infected individuals. In order to sustain the effectiveness of HCV treatment, evidence base information on epidemiology and IL28B polymorphism in specific population can be used to minimize the duration of treatment but may compromise the cost instead. Therefore, policy makers need to strongly reconsider integrating optimized treatment regimen for HCV co-infection into the national program for the future.

5. Prevention Programs

After successful integration of the national expanded program on immunization (EPI) on HBV immunization, coverage of the vaccinations has increased in most countries up to 80% as seen by the results from many studies on incidence reduction of HBV and hepatocellular carcinoma in the young age group [68–72]. Due to the high prevalence of HBV infection in the region, HBV serology screening prior to vaccination in high risk groups is not necessary, for example, MSMs, IDUs, and health care workers (HCWs).
Many adults, including health care workers (HCWs), cannot reimburse for HBV vaccinations. Currently, the guideline recommendation for HBV treatment and care for HCWs is not well defined. If people are aware of the complications and prognosis of chronic hepatitis, this may encourage people to have HBV serology screening and HBV vaccinations in adults older than 30 years old. For postexposure prophylaxis, hepatitis B immunoglobulin (HBIG) is required in cases that have been exposed to blood from HBV-infected individuals and are not immune to HBV according to the postexposure HBV screening test. Occupational risks can be prevented if high risk groups such as HCWs and health-related students have been immunized. This preventive policy targeting professional health care workers (i.e., hospitals and clinics) at risk of acquiring HBV infection should be integrated into the national health care system. Currently, HBV immunization is recommended to all HIV-infected patients who are susceptible and have achieved immunological success after antiretroviral therapy. However, it is important to conduct a serologic test for HBV to confirm the person’s immune status before vaccination because low CD4 levels or the use of NNRTI may affect the response to the vaccine [67]. It has been shown that in HIV-infected individuals, the immune response of generating HBs antibodies was 71.4% which was much lower compared to healthy HIV seronegative individuals. However, no adverse event has been detected.

Since HCV vaccines are not available for the prevention of the disease, hence it is essential for all high risk groups, including MSMs and IDUs, to continuously receive updated information on HCV transmission and outcomes to reduce their behavior risk of blood-to-blood contamination. Lack of free access to clean injecting equipment for IDUs may not be a critical issue because syringes and needles are available cheaply in drug stores. However, due to social stigmatization, discrimination, and illegal issues, IDUs are afraid to access clean needles and syringes resulting in higher rates of HIV and HCV infection. Even though the Needle and Syringe Program, a harm reduction effort, is successful in Australia in preventing HCV and HIV infection among IDUs, but such a program is difficult to launch in resource-limited setting with a conservative society. Hence, continuing education and health promotion are required to provide correct information to the community to change their perception as a preventive strategy. HIV/HCV co-infection among IDUs is a public health emergency that is currently being ignored by the policy makers. The need for proper policy and advocacy are needed and should be presented through health promotion campaigns in collaboration with working groups and peer educators to successfully implement and launch harm reduction programs properly. Community advocates and appropriate waste disposal need to be worked out before rolling out the harm reduction programs. Regular HCV screening for high risk groups, especially HCWs and patients with chronic renal failure on hemodialysis, is necessary. Voluntarily unpaid donor blood must be routinely screened for HBV and HCV serology at every blood bank unit throughout the region as currently being performed by the Red Cross blood banks.

6. Perspectives on Hepatitis B and C Coinfection among HIV-Infected Patients for Testing and Treatment

Since HBV co-infection is more chronic, therefore the national guidelines have recommended sufficient and early screening to initiate proper treatment and care. Despite this, there are still problems for those patients who have developed resistance and have limited selection of drugs to choose from and/or intolerability. It will be a continued struggle to provide alternative treatment and other drug choices for these patients. Hepatitis B vaccination should be implemented at all levels of the population, especially high risk groups and health care workers; HBV vaccination is an urgent and necessary action that should be in place in order to reduce HBV infection. The strategic plan must cover adults older than 30 years old who may become infected and transmit the virus to others via the sexual route. Hepatitis B is preventable and immunization is better than acquiring the virus. The cost of the immunization program is incomparable to the people’s quality of life. Recently 2 new protease inhibitors, boceprevir and telaprevir, were approved by the US FDA in May 2011 and by the European Medicine Agency (EMA) in August and September 2011, respectively, for HCV treatment. The drugs can increase the efficacy and RVR when used as a triple drug therapy (with pegylated interferon and ribavirin) in HCV patients with genotype 1 [73–77], but the cost is 2-3 times higher than the standard treatment. For these new drugs, the US FDA is concerned about the adverse events such as suicidal tendencies and lack of efficacy in certain groups of people; boceprevir has been shown to cause rash and gout whereas telaprevir has been associated with TB. Both boceprevir and telaprevir can cause anemia in HCV patients. However, it should be noted that anemia is a common laboratory abnormality among patients infected with both HIV and HCV due to treatment; physicians will need to reduce the dose of their HCV medications in patients with anemia [78]. Aside from additional drug toxicities, evidence-based information from monoinfected HCV clinical trials on shorter triple drug treatment, pharmacokinetics guided optimized dose of new drugs, and potential drug-drug interactions warrant further investigations in Asian population living with HIV/AIDS.

HCV Direct-Acting Antivirals (DAAs), new polymerase and protease inhibitors that are under clinical investigations with or without interferon, provide HCV patients with more treatment options. Quad therapy (2 different protease inhibitors plus pegylated interferon and ribavirin) is another option that will become available in the future regardless of the cost of the drugs. To improve tolerability and treatment coverage, the interferon-free DAA-based combination therapy may be an alternative choice for some people [79].

HCV infection is a curable disease and the international clinical guidelines already have provided recommendations for screening, diagnostics, and treatment for HCV/HIV co-infected patients. Yet majority of the patients, especially IDUs co-infected with HIV and HCV, still have problems in getting the proper treatment and care. The social stigma around drug use pervades many aspects of the society,
creating huge barriers that IDUs face when seeking health care. The barriers in the health care setting, including prejudice and stigmatization, are worse than HIV monoinfection because the medical service providers and policy makers have insufficient experience in dealing with co-infected patients resulting in limited care and financial support. Physicians may refuse treatment to IDUs because of their perceptions that these patients have poor adherence to treatment. In fact, treatment adherence among IDUs substantially increased when they have access to health and social services with harm reduction support and mental health care. A challenge can be met through educating medical staff and providing support for patients. Access to treatment and healthcare should be abrogated by national policymakers when it comes to treating HCV in HIV co-infected patients. The main economic benefit to treating people with HCV is that it will lower the cost and amount of medical care needed for HCV in the long term, including treatment for severe liver disease and HCV-related liver malignancy. Moreover, it is absolutely impossible to put a price on the patient’s quality of life as it is priceless and invaluable. Successful treatment can also prevent new HCV infections.

Acknowledgments

All authors declare no affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the paper apart from those disclosed. The authors would like to thank the Australasian Society for HIV Medicine (ASHM) and ASHM-AusAID ALAF Training Program on HIV and Viral Hepatitis Co-infection Management in Asia for inspiring us to write the paper.

References

[1] S. Vong, J. F. Perz, S. Sok et al., “Rapid assessment of injection practices in Cambodia, 2002,” BMC Public Health, vol. 5, article 56, 2005.
[2] H. T. T. Tran, H. Ushijima, V. X. Quang et al., “Prevalence of hepatitis virus types B through E and genotypic distribution of HBV and HCV in Ho Chi Minh City, Vietnam,” Hepatology Research, vol. 26, no. 4, pp. 275–280, 2003.
[3] P. Jutavijittum, A. Yousukh, B. Samountry et al., “Seroprevalence of hepatitis B and C virus infections among Lao blood donors,” Southeast Asian Journal of Tropical Medicine and Public Health, vol. 38, no. 4, pp. 674–679, 2007.
[4] V. Wiwanitkit, “An overview of a hepatitis B serology screening check-up program among Thai workers,” Viral Immunology, vol. 15, no. 4, pp. 647–649, 2002.
[5] E. J. Nelwean, R. Van Crevel, B. Alisjahbana et al., “Human immunodeficiency virus, hepatitis B and hepatitis C in an Indonesian prison: prevalence, risk factors and implications of HIV screening,” Tropical Medicine and International Health, vol. 15, no. 12, pp. 1491–1498, 2010.
[6] Y. Yanase, T. Ohida, Y. Kaneita, D. M. D. Agdamag, P. S. A. Leaño, and C. J. Gill, “The prevalence of HIV, HBV and HCV among Filipino blood donors and overseas work visa applicants,” Bulletin of the World Health Organization, vol. 85, no. 2, pp. 131–137, 2007.
[7] V. J. Sebastian, S. Bhattacharya, S. Ray, and J. H. Daud, “Prevalence of hepatitis-B surface antigen in the pregnant women of Brunei Darussalam,” The Southeast Asian Journal of Tropical Medicine and Public Health, vol. 21, no. 1, pp. 123–127, 1990.
[8] M. J. Alexander, A. S. Sinnatamby, M. J. Rohaimah, A. H. Harun, and J. S. Ng, “Incidence of hepatitis B infection in Brunei Darussalam—analysis of racial distribution,” Annals of the Academy of Medicine Singapore, vol. 19, no. 3, pp. 344–346, 1990.
[9] P. Luksamijaruluk, W. Kaepan, and S. Klampakhorn, “Hepatitis B virus sero-markers, hepatitis C virus antibody and risk behaviors among middle age and older Thai males,” Southeast Asian Journal of Tropical Medicine and Public Health, vol. 38, no. 1, pp. 45–52, 2007.
[10] S. Sungkanuparp, A. Vibhagool, W. Manosuthi et al., “Prevalence of hepatitis B virus and hepatitis C virus co-infection with human immunodeficiency virus in Thai patients: a tertiary-care-based study,” Journal of the Medical Association of Thailand, vol. 87, no. 11, pp. 1349–1354, 2004.
[11] W. P. Law, G. J. Dore, C. J. Duncombe et al., “Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001,” AIDS, vol. 17, no. 15, pp. 2191–2199, 2003.
[12] S. Kiertiburanakul, D. Chatiprasitsakul, K. Atamasirikul, and S. Sungkanuparp, “Late and low compliance with hepatitis B serology screening among HIV-infected patients in a resource-limited setting: an issue to improve HIV care,” Current HIV Research, vol. 9, no. 1, pp. 54–60, 2011.
[13] S. Sungkanuparp, P. Wongprasit, W. Manosuthi, and K. Atamasirikul, “Compliance with hepatitis B and hepatitis C virus infection screening among HIV-1 infected patients in a resource-limited setting,” The Southeast Asian Journal of Tropical Medicine and Public Health, vol. 39, no. 5, pp. 863–866, 2008.
[14] N. S. W. Leeratanapetch, “Hepatitis B virus and hepatitis C virus co-infection with HIV patients at Khon Kaen Hospital,” Khon Kaen Hospital Medical Journal, vol. 32, no. 2, pp. 229–238, 2008.
[15] A. Theamboonlers, P. Tangkijvanich, C. Pramoolsinsap, and Y. Poovorawan, “Genotypes and subtypes of hepatitis B virus in Thailand,” Southeast Asian Journal of Tropical Medicine and Public Health, vol. 29, no. 4, pp. 786–791, 1998.
[16] A. Theamboonlers, P. Jantaradsamee, N. Kaew-In, P. Tangkijvanich, P. Hirsch, and Y. Poovorawan, “The predominant genotypes of hepatitis B virus in Thailand,” Annals of Tropical Medicine and Parasitology, vol. 93, no. 7, pp. 737–743, 1999.
[17] P. Tangkijvanich, V. Mahachai, P. Komolmit, J. Fongsarun, A. Theamboonlers, and Y. Poovorawan, “Hepatitis B virus genotypes and hepatocellular carcinoma in Thailand,” World Journal of Gastroenterology, vol. 11, no. 15, pp. 2238–2243, 2005.
[18] A. Utama, S. Purwantomo, M. D. Siburian et al., “Hepatitis B virus subgenotypes and basal core promoter mutations in Indonesia,” World Journal of Gastroenterology, vol. 15, no. 32, pp. 4028–4036, 2009.
[19] A. Utama, T. I. Octavia, R. Dhenni, I. Yusuf, and S. Tai, “Hepatitis B virus genotypes/subgenotypes in voluntary blood donors in Makassar, South Sulawesi, Indonesia,” Virology Journal, vol. 6, article 128, 2009.
[20] P. Sa-nguanmoo, P. Tangkijvanich, N. Thawornsuk et al., “Molecular epidemiological study of hepatitis B virus among migrant workers from Cambodia, Laos, and Myanmar to Thailand,” Journal of Medical Virology, vol. 82, no. 8, pp. 1341–1349, 2010.
[21] K. Suwannakarn, P. Tangkijvanich, N. Thawornsuk et al., "Molecular epidemiological study of hepatitis B virus in Thailand based on the analysis of pre-S and S genes," *Hepatology Research*, vol. 38, no. 3, pp. 244–251, 2008.

[22] W. Ilg, C. Delhoune, and F. Deinhardt, "Hepatitis B surface antigen (HBsAg) subtype-specific antibodies in persons vaccinated against hepatitis B," *Journal of Medical Virology*, vol. 13, no. 2, pp. 171–178, 1984.

[23] V. M. Quan, V. F. Go, L. V. Nam et al., "Risks for HIV, HBV, and HCV infections among male injection drug users in northern Vietnam: a case-control study," *AIDS Care*, vol. 21, no. 1, pp. 7–16, 2009.

[24] A. Jatapai, K. E. Nelson, T. Chuenchitra et al., "Prevalence and risk factors for hepatitis C virus infection among young Thai men," *American Journal of Tropical Medicine and Hygiene*, vol. 83, no. 2, pp. 433–439, 2010.

[25] T. Tanimoto, N. H. Cuong, A. Ishizaki et al., "Multiple routes of hepatitis C virus transmission among injection drug users in Hai Phong, Northern Vietnam," *Journal of Medical Virology*, vol. 82, no. 8, pp. 1355–1363, 2010.

[26] S. Kageyama, D. M. D. Agdamag, E. T. Alesna et al., "Tracking the entry routes of hepatitis C virus as a surrogate of HIV in an HIV-low prevalence country, the Philippines," *Journal of Medical Virology*, vol. 81, no. 7, pp. 1157–1162, 2009.

[27] D. J. Jamieson, N. Skunodom, T. Chaowananchit et al., "Infection with hepatitis C virus among HIV-infected pregnant women in Thailand," *Infectious Diseases in Obstetrics and Gynecology*, vol. 2008, Article ID 840948, 7 pages, 2008.

[28] S. Akkarakharomrongsin, K. Praiannathavorn, N. Hacharoen et al., "Geographic distribution of hepatitis C virus genotype 6 subtypes in Thailand," *Journal of Medical Virology*, vol. 82, no. 2, pp. 257–262, 2010.

[29] A. Utama, N. P. Tania, R. Dhenni et al., "Genotype diversity of hepatitis C virus (HCV) in HCV-associated liver disease patients in Indonesia," *Liver International*, vol. 30, no. 8, pp. 1152–1160, 2010.

[30] S. Akkarakharomrongsin, K. Praiannathavorn, N. Hacharoen, A. Theamboolers, P. Tangkijvanich, and Y. Povororawan, "Seroprevalence and genotype of Hepatitis C virus among immigrant workers from Cambodia and Myanmar in Thailand," *Intervirology*, vol. 54, no. 1, pp. 10–16, 2010.

[31] J. F. Colin, D. Cazals-Hatem, M. A. Loriot et al., "Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men," *Hepatology*, vol. 29, no. 4, pp. 1306–1310, 1999.

[32] V. Di Martino, T. Thevenot, J. F. Colin et al., "Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B," *Gastroenterology*, vol. 123, no. 6, pp. 1812–1822, 2002.

[33] C. L. Thio, E. C. Seaberg, R. Skolasky Jr. et al., "HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS)," *Lancet*, vol. 360, no. 9349, pp. 1921–1926, 2002.

[34] G. M. Clifford, M. Rickenbach, J. Polese et al., "Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma," *AIDS*, vol. 22, no. 16, pp. 2135–2141, 2008.

[35] D. W. F. Chotiprasitsakul, K. Atamasirikul, and S. Sungkanuparp, "Screening of hepatitis B virus infection among HIV infected patients receiving antiretroviral therapy," *Journal of Infectious Diseases and Antimicrobial Agents*, vol. 27, no. 2, pp. 69–75, 2010.

[36] J. Zhou, G. J. Dore, F. Zhang, P. L. Lim, and Y. M. A. Chen, "Hepatitis B and C virus coinfection in the TREAT Asia HIV Observational Database," *Journal of Gastroenterology and Hepatology*, vol. 22, no. 9, pp. 1510–1518, 2007.

[37] Y. Jongirawisan, P. Ungulkraiwit, and S. Sungkanuparp, "Isolated antibody to hepatitis B core antigen in HIV-1 infected patients and a pilot study of vaccination to determine the anamnestic response," *Journal of the Medical Association of Thailand*, vol. 89, no. 12, pp. 2028–2034, 2006.

[38] C. C. Hung, C. F. Hsiao, R. T. Gandhi, B. McGovern, H. Lee, and P. Sax, "Isolated Antibody to Hepatitis B Core Antigen in Individuals Infected with HIV-1," *Clinical Infectious Diseases*, vol. 37, no. 9, pp. 1275–1277, 2003.

[39] D. Neau, M. Winnoch, A. C. Jouvencel et al., "Occult hepatitis B virus infection in HIV-infected patients with isolated antibodies to hepatitis B core antigen: aquainte cohort, 2002–2003," *Clinical Infectious Diseases*, vol. 40, no. 5, pp. 750–753, 2005.

[40] R. T. Gandhi, A. Wurcel, H. Lee et al., "Isolated antibody to hepatitis B core antigen in human immunodeficiency virus type-1-infected individuals," *Clinical Infectious Diseases*, vol. 36, no. 12, pp. 1602–1605, 2003.

[41] A. L. French, M. Y. Lin, C. T. Evans et al., "Long-term serologic follow-up of isolated hepatitis B core antibody in HIV-infected and HIV-uninfected women," *Clinical Infectious Diseases*, vol. 49, no. 1, pp. 148–154, 2009.

[42] A. Eduarde Silva, B. J. McMahon, A. J. Parkinson, M. H. Sjogren, J. H. Hoofnagle, and A. M. Di Bisceglie, "Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine," *Clinical Infectious Diseases*, vol. 26, no. 4, pp. 895–897, 1998.

[43] M. Hofer, H. I. Joller-Jemelka, P. J. Grob, R. Lüthy, and M. Opravil, "Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only," *European Journal of Clinical Microbiology and Infectious Diseases*, vol. 17, no. 1, pp. 6–13, 1998.

[44] H. T. Chung, J. S. K. Lee, and A. S. F. Lok, "Prevention of posttransfusion hepatitis B and C by screening for antibody to hepatitis C virus and antibody to HBCAg," *Hepatology*, vol. 18, no. 5, pp. 1045–1049, 1993.

[45] R. C. Dickson, J. E. Everhart, J. R. Lake et al., "Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen," *Gastroenterology*, vol. 113, no. 5, pp. 1668–1674, 1997.

[46] J. H. Hoofnagle, L. B. Seef, Z. B. Bales, and H. J. Zimmerman, "Type B hepatitis after transfusion with blood containing antibody to hepatitis B core antigen," *New England Journal of Medicine*, vol. 298, no. 25, pp. 1379–1383, 1978.

[47] M. Núñez, P. Rios, M. Pérez-Olmeda, and V. Soriano, "Lack of "occult" hepatitis B virus infection in HIV-infected patients," *AIDS*, vol. 16, no. 15, pp. 2099–2101, 2002.

[48] D. D. Douglas, H. E. Taswell, J. Rakela, and D. Rabe, "Absence of hepatitis B virus DNA detected by polymerase chain reaction in blood donors who are hepatitis B surface antigen negative and antibody to hepatitis B core antigen positive from a United States population with a low prevalence of hepatitis B serologic markers," *Transfusion*, vol. 33, no. 3, pp. 212–216, 1993.

[49] E. C. Thomson, E. Nastouli, J. Main et al., "Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV," *AIDS*, vol. 23, no. 1, pp. 89–93, 2009.

[50] C. Scott, S. Day, E. Low, A. Sullivan, M. Atkins, and D. Asboe, "Unselected hepatitis C screening of men who have sex with men attending sexual health clinics," *Journal of Infection*, vol. 60, no. 5, pp. 351–353, 2010.
[51] Y. C. Gilleece, R. E. Browne, D. Asboe et al., “Transmission of hepatitis C virus among HIV-positive homosexual men and response to a 24-week course of pegylated interferon and ribavirin,” Journal of Acquired Immune Deficiency Syndromes, vol. 40, no. 1, pp. 41–46, 2005.

[52] V. Wiwanitkit, “Alpha fetoprotein for screening for hepatocellular cancer in populations with viral hepatitis B: an appraisal of Thai reports,” Asian Pacific Journal of Cancer Prevention, vol. 6, no. 4, pp. 535–536, 2005.

[53] P. Tangkijvanich, N. Anukulkarnkusol, P. Suwangool et al., “Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels,” Journal of Clinical Gastroenterology, vol. 31, no. 4, pp. 302–308, 2000.

[54] A. Komindr, N. Pradithpol, S. Suphanpayak et al., “Correlation of HBV and HCV with CH, LC, HCC in liver biopsied tissue at Rajavithi Hospital,” Journal of the Medical Association of Thailand, vol. 88, no. 6, pp. 788–809, 2005.

[55] A. Avihingsanon, S. R. Levin, S. Kerr et al., “Efficacy of tenofovir disoproxil fumarate/entecavir compared with emtricitabine alone in antiretroviral-naive HIV-HBV coinfected in Thailand,” Antiviral Therapy, vol. 15, no. 6, pp. 917–922, 2010.

[56] G. V. Matthews, A. Avihingsanon, S. R. Levin et al., “A randomized trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naive individuals in Thailand,” Hepatology, vol. 48, no. 4, pp. 1062–1069, 2008.

[57] S. Slavenburg, I. Weggelaar, M. G. H. Van Oijen, and J. P. H. Drenth, “Optimal length of antiviral therapy in patients with hepatitis C virus genotypes 2 and 3: a meta-analysis,” Antiviral Therapy, vol. 14, no. 8, pp. 1139–1148, 2009.

[58] A. K. Singal and B. S. Anand, “Tailoring treatment duration to 12 to 16 weeks in hepatitis C genotype 2 or 3 with rapid virologic response: systematic review and meta-analysis of randomized controlled trials,” Journal of Clinical Gastroenterology, vol. 44, no. 8, pp. 853–857, 2010.

[59] L. Martin-Carbonero, M. Nuñez, A. Mariño et al., “Undetectable hepatitis C virus RNA at week 4 as predictor of sustained virological response in HIV patients with chronic hepatitis C,” AIDS, vol. 22, no. 1, pp. 15–21, 2008.

[60] T. Berg and G. Carosi, “Optimizing outcomes in patients with hepatitis C virus genotype 2 or 3,” Antiviral Therapy, vol. 13, no. 1, pp. 17–22, 2008.

[61] A. Mangia, A. J. Thompson, R. Santoro et al., “An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response,” Gastroenterology, vol. 139, no. 3, pp. 821–827, 2010.

[62] D. L. Thomas, C. L. Thio, M. P. Martin et al., “Genetic variation in IL28B and spontaneous clearance of hepatitis C virus,” Nature, vol. 461, no. 7265, pp. 798–801, 2009.

[63] D. Ge, J. Fellay, A. J. Thompson et al., “Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance,” Nature, vol. 461, no. 7262, pp. 399–401, 2009.

[64] T.-M. Scherzer, H. Hofer, A. E. Staettmayer et al., “Early virologic response and IL28B polymorphisms in patients with chronic hepatitis C genotype 3 treated with peginterferon alfa-2a and ribavirin,” Journal of Hepatology, vol. 54, no. 5, pp. 866–871, 2011.

[65] A. Moghaddam, E. Melum, N. Reinton et al., “IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection,” Hepatology, vol. 53, no. 3, pp. 746–754, 2011.

[66] J. M. Darling, J. Aerssens, G. Fanning et al., “Quantification of pretreatment serum interferon-γ-inducible protein-10 improves the predictive value of an IL28B gene polymorphism for hepatitis C treatment response,” Hepatology, vol. 53, no. 1, pp. 14–22, 2011.

[67] M. L. Landrum, K. H. Hullsiek, A. Ganesan et al., “Hepatitis B vaccine responses in a large U.S. military cohort of HIV-infected individuals: another benefit of HAART in those with preserved CD4 count,” Vaccine, vol. 27, no. 34, pp. 4731–4738, 2009.

[68] K. Wichajarn, P. Kosalaraksa, and S. Wiangnon, “Incidence of hepatocellular carcinoma in children in Khon Kaen before and after national hepatitis B vaccine program,” Asian Pacific Journal of Cancer Prevention, vol. 9, no. 3, pp. 507–510, 2008.

[69] V. Chongsrisawat, Y. Poovorawan, A. Theamboonlers et al., “Hepatitis B seroprevalence in Thailand: 12 Years after hepatitis B vaccine integration into the national expanded programme on immunization,” Tropical Medicine and International Health, vol. 11, no. 10, pp. 1496–1502, 2006.

[70] Y. Poovorawan, V. Chongsrisawat, A. Theamboonlers, H. L. Bock, M. Leysen, and J. M. Jacquet, “Persistence of antibodies and immune memory to hepatitis B vaccine 20 years after infant vaccination in Thailand,” Vaccine, vol. 28, no. 3, pp. 730–736, 2010.

[71] Y. Poovorawan, V. Chongsrisawat, A. Theamboonlers et al., “Evidence of protection against clinical and chronic hepatitis B infection 20 years after infant vaccination in a high endemicity region,” Journal of Viral Hepatitis, vol. 18, no. 5, pp. 369–375, 2011.

[72] Y. Poovorawan, V. Chongsrisawat, A. Theamboonlers et al., “Long-term benefit of hepatitis B vaccination among children in Thailand with transient hepatitis B virus infection who were born to hepatitis B surface antigen-positive mothers,” Journal of Infectious Diseases, vol. 200, no. 1, pp. 33–38, 2009.

[73] F. Poordad, J. McCone Jr., B. R. Bacon et al., “Boceprevir for untreated chronic HCV genotype 1 infection,” New England Journal of Medicine, vol. 364, no. 13, pp. 1195–1206, 2011.

[74] B. R. Bacon, S. C. Gordon, E. Lawitz et al., “Boceprevir for previously treated chronic HCV genotype 1 infection,” New England Journal of Medicine, vol. 364, no. 13, pp. 1207–1217, 2011.

[75] J. G. McHutchison, M. P. Manns, A. J. Muir et al., “Telaprevir for previously treated chronic HCV infection,” New England Journal of Medicine, vol. 362, no. 14, pp. 1292–1303, 2010.

[76] J. G. McHutchison, G. T. Everson, S. C. Gordon et al., “Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection,” New England Journal of Medicine, vol. 360, no. 18, pp. 1827–1838, 2009.

[77] K. E. Sherman, S. L. Flamm, N. H. Afdhal et al., “Response-guided telaprevir combination treatment for hepatitis C virus infection,” New England Journal of Medicine, vol. 365, no. 11, pp. 1014–1024, 2011.

[78] P. Deming and I. R. McNicholl, “Coinfection with human immunodeficiency virus and hepatitis C virus: challenges and therapeutic advances—insights from the Society of Infectious Diseases Pharmacists,” Pharmacotherapy, vol. 31, no. 4, pp. 357–368, 2011.

[79] G. J. Dore, G. V. Matthews, and J. Rockstroh, “Future of hepatitis C therapy: development of direct-acting antivirals,” Current Opinion in HIV and AIDS, vol. 6, no. 6, pp. 508–513, 2011.