# HIV Co-infected Patients with HBV And HCV- A Review

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ABSTRACT

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The prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection with HIV is significant. Co-infection with the two viruses is not uncommon. It is well established that worldwide approximately 4 to 5 million persons are co-infected with HIV. There is a considerable variation in the prevalence of co-infection in different areas. In the treatment of HIV infection, the use of highly active antiretroviral therapy (HAART) is measured and its discovery has been one of the most useful and dramatic advances in the field of medicine. Highly active antiretroviral therapy was introduced in Malaysia in 1997 for treating HIV infection. The purpose of this study is to investigate the prevalence of HBV and HCV co-infection with HIV. The initiation of HAART for human immune deficiency virus has led an era to focus on other leading causes of morbidity such as hepatitis B and hepatitis C. We will review the evaluating effects of highly active antiretroviral therapy on HIV positive patients co-infected with HBV and HCV and find out its possible outcomes. Knowledge of the effects of various treatments as well as interaction between these viruses is the key to understanding and effectively treating these patients. Recent reviews have discussed many aspects of treatment. We summarize the advanced studies regarding to the progression of HAART including effects of co-infection with hepatitis B and C virus as well as its pharmacotherapeutic outcomes.

## INTRODUCTION

Approximately 350 million people are infected with Hepatitis B virus (HBV) worldwide, and the World Health Organization (WHO) estimates that approximately 170 million people are infected with Hepatitis C virus (HCV). HBV and HCV infection account for a substantial proportion of liver diseases throughout the world. Because the two hepatotropic viruses share same modes of transmission, co-infection with the two viruses is not uncommon, especially in areas with a high prevalence of HBV infection and among people at high risk for parenteral infection. The exact number of patients infected with both HCV and HBV is unknown.[1]

HBV and Human Immunodeficiency Syndrome (HIV) are mostly found co-infecting a single patient because the pathogens share transmission routes. The prevalence of HBV/HIV co-infection varies by geographic region and risk factor exposure, but studies suggest that up to 10% of patients with HIV have chronic HBV co-infection.[2,3]

### Epidemiology

Globally, there are an estimated 130 million chronic hepatitis C virus (HCV) infections, with an overall prevalence of 3%. Approximately 4 to 5 million persons are co-infected with HIV.[4] Infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are among the 10 leading causes of death from infectious disease.[5] The introduction of highly active antiretroviral therapy (HAART) has led to a marked reduction of morbidity and mortality in HIV infected patients,[6,7] with subsequently increased importance of co-morbidities such as chronic liver diseases.[8,9] In HIV-HBV co-infected individuals receiving HAART, unique mutations in HBV have been defined which may directly alter pathogenesis,[10] and high rates of HBV mutations conferring drug resistance have also been demonstrated.[11] Studies on people co-infected with HIV-1 and HBV have been limited by small size, cross sectional design, co-infected with HCV, or selection bias of a referral clinic population, which sees more severe cases.[12-16]

Although most studies demonstrate increased mortality among co-infected individuals, a recent meta-analysis of over 30 studies with over 100,000 patients found no increase in mortality in co-infected patients in the pre- HAART era. Post-HAART, co-infection increased risk of overall mortality but not of AIDS-defining conditions.[17]

The endemicity of HBV infection is influenced primarily by the age at which most infections occur. Endemicity of infection is high in those parts of the world where almost all infections occur during the perinatal period or early in childhood (for example, Southeast Asia and sub-Saharan Africa). At least 8% of the population in these areas is chronically infected and 70–90% has serological evidence of previous HBV infection.[18]

The estimated worldwide prevalence of HCV infection is 2.2%. Similar to HBV, geographic differences in the endemicity of HCV infection can be described based on

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regional prevalences; high (prevalence 3%) moderate (prevalence 2–2.9%), low (prevalence 1.0–1.9%), and very low (prevalence 1.0%).[19,20]

Among the estimated 40 million persons infected with HIV worldwide, an estimated 2–4 million are chronically infected with HBV and an estimated 4–5 million are chronically infected with HCV. Several factors influenced these co-infection estimates, including geographic differences in the prevalence of chronic infection by age, the efficiency of exposures that account for most transmission, and the prevalence of persons at high risk for infection.

Dual infection with HBV and HCV is not uncommon in geographic areas where a high endemic level of both infections is reported, such as Southeast-Asia and Mediterranean.[1]

Differences in infectivity between HBV, HCV and HIV have been observed in several settings. HBV and HIV are more efficiently transmitted perinatally and sexually than HCV. In the perinatal setting, maternal coinfection with HIV facilitates the transmission of HCV to newborns.[22] Despite the infection rates in these high-risk groups, rates of infection in the general population have remained low (< 0.5% among adults aged 15–49) in several countries with large populations including China, Malaysia, and Philippines.[23]

**Human immunodeficiency virus (HIV)**

Human immunodeficiency virus (HIV) is the worldwide disseminated causative agent of acquired immunodeficiency syndrome (AIDS). HIV is a member of the *Lentivirus*genus of Retroviridae family and is grouped in two types named HIV-1and HIV-2. These viruses have a notable ability to mutate and adapt to the new conditions of human environment.[66]

In many parts of the world, the predominant mode of transmission has always been heterosexual contact. However, the rates of HIV seen in different geographical settings vary widely as the result of a complex interplay of behavioral, biological, social and structural risks (direct determinants) and vulnerabilities (i.e. factors which may not be directly linked to the transmission of the virus, but may increase the chances of the virus spreading in a particular population).Many social and demographic factors also influence the epidemiology of HIV.[66]

This striking difference suggests that young girls are particularly susceptible to infection, through having unprotected sex with older, infected, men and perhaps due to starting sex at a very young age.[67]

The south-east Asian epidemic has been well documented in Thailand, where HIV initially spread rapidly in the late 1980s among injecting drug users and between sex workers and their clients. The government acted quickly to set up a comprehensive prevention campaign including enforced condom use in establishments used by sex workers and a mass advertising campaign.[68] In the past 2 decades, the human immunodeficiency virus (HIV) has rampaged across the globe leaving virtually no country untouched. Despite advances in our understanding of the social, behavioural and biological factors that directly increase the risk of HIV transmission, approximately 14,500 individuals are infected daily.[65]

**Hepatitis B Co-Infection with HIV**

HBV is a deoxyribonucleic acid (DNA) virus. In the United States, the prevalence of chronic carriage of hepatitis B surface antigen (HBsAg) is present in less than 1% of the population.[24,25] The course of hepatitis B in HIV co-infected patients is characterized by the increased prevalence of markers of active viral replication (hepatitis B e antigen [HBeAg], HBV DNA). Indeed, viral replication is even further enhanced when CD4 counts continue to decrease over time.[26,15]

Throughout the world more than 350 million persons are chronically infected with HBV and approximately 33 million persons are infected with HIV.[27-28] HBV is transmitted by percutaneous and mucous membrane exposures to infectious

**Table 1: Social and demographic factors that influenced the epidemiology of HIV.[66]**

| Individual Factors | Social and Demographic Factors | Structural Factors |
|---|---|---|
| Age | Age structure of population | Income distribution |
| Gender | Gender-based education rates | Policy environment |
| Lack of knowledge | Rates of urbanization | Position of women |
| Type of partnerships | Access to effective STI treatment | Wealth of population |
| Protective Behaviours (e.g. use of condoms) | Availability and use of commercial sex | |
| Presence of other sexually transmitted infections (STIs) | Sexual mixing patterns | |
| Injecting drug use | Population mobility | |
| Male circumcision status | Services for drug users | |
| Denial of risk | Safety of blood transfusion | |
| | Rates of male circumcision | |

blood and body fluids that contain blood.[18] The prevalence of chronic infection ranges from 1 to 7% of the population and serological evidence of past infection is found in 10–60%. In most developed parts of the world (for example, Western Europe, Australia, USA), the endemicity of HBV infection is low and most infections occur among high risk adult populations that include injection drug users, persons with multiple heterosexual partners, and men who have sex with men (MSM). The prevalence of chronic HBV infection is 1% and the overall infection rate is 5–7%.[18]

HBV does not change the course of HIV disease, but HIV does alter the course of HBV.[29] Patients with chronic HBV infection were 3.5 times more likely to have liver disease than those with no HBV infection ($p<0.02$).[30] HIV infected persons are less likely to clear acute HBV infection spontaneously and face a higher risk of liver-related death than those who are infected with only HIV.[31] The presence of chronic HBV can also lead to an increased risk of hepatotoxicity related to the administration of HAART.[32]

HAART induced immune restoration may switch the immune reaction to HBV from a tolerant to an intolerant phase, leading to either the complete control of HBV replication or more often to an exacerbation of chronic hepatitis. Patients who spontaneously recover from HBV infection mount vigorous CD4 and cluster of differentiation 8 (CD8) T-cell responses to various HBV epitopes.[33-34]

**Hepatitis C Co-infection with HIV**

HCV is a RNA flavivirus that infects 4 million (1.8%) people in the United States and 150-200 million worldwide.[35] Co-infection with HIV and HCV is common since both infections share similar routes of transmission. In the United States, approximately 30% of patients who are HIV-infected are also co-infected with HCV.[36] Main routes of Hepatitis C transmission include IVDU (Intravenous Drug Users), transfusion of blood products, needle sticks and to a lesser extent sexual intercourse (although rates are rising due to anal intercourse especially in MSM). Since the relative efficiency of transmission differs according to route, the prevalence of co-infection varies markedly among various risk groups.[37]

The presence of both HIV and HCV infection may complicate the natural history of both viruses and their treatment.[38] For example; co-infected patients have higher HCV viral loads than patients infected with HCV alone. In addition, individuals who are co-infected with both viruses are at risk of progressive liver disease and consequently cirrhosis, liver failure, and hepatocellular carcinoma.[39] In some studies, HIV-HCV co-infection was associated with a more rapid progression to AIDS and death.[40]

HCV infection leads to chronic hepatitis in 85% of patients, and those patients have a 20% risk of developing cirrhosis during the subsequent 2 decades.[41-43] Many studies suggest that HIV disease modifies the natural history of chronic HCV infection; this leads to an accelerated course of progression from chronic active hepatitis to cirrhosis, end-stage liver disease, and death.[44-48]

Risk factors associated with acquiring HCV infection include transfusion of blood and blood products and transplantation of solid organs from infected donors, illegal injection drug use, unsafe therapeutic injections, occupational exposure to blood (primarily contaminated needle sticks), birth to an infected mother, sex with an infected partner, and sex with multiple partners.[49]

Prior to HAART, people with HIV-HCV co-infection were reported to have higher HCV viral load and accelerated hepatic fibrosis. Rates of HCV-related liver disease progression appeared to be 5±10 fold higher in people with HIV-HCV co-infection.[50] In contrast; there was inconclusive evidence to support a role for HCV in acceleration of HIV disease progression.[51]

A 20 year prospective study found increased risk of hepatitis/liver-related deaths despite HAART among co-infected drug users (DUs) compared to HCV-mono infected DUs, providing further support that HIV accelerates liver disease in the HAART era.[52] Hepatic steatosis (HS), a common (40%–75%) complication of HCV monoinfection and HCV-HIV co-infection, is associated with rapid fibrosis progression[53], although a recent meta-analysis found that it is not necessarily more common in co-infected than HCV monoinfected patients.[38] HS is associated with increased body mass index, diabetes, elevated ALT levels, HCV genotype 3, necro inflammation, and fibrosis.[53,54]

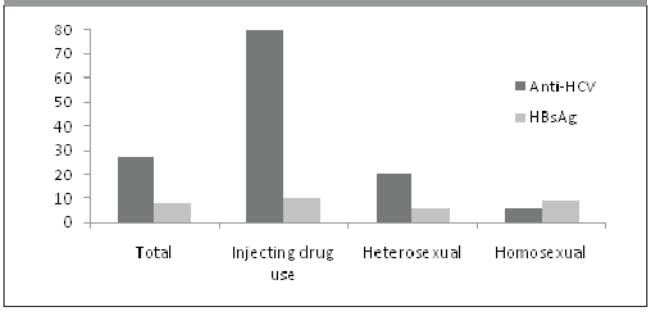
**The impact of viral hepatitis co-infection on HIV**

The impact of viral hepatitis co-infection on HIV natural history remains uncertain. Some studies have suggested poorer outcomes in co-infected patients.[55-56] HBV infections acquired at young ages are more likely to progress to chronic infections, resulting in a high prevalence of chronic HBV infection among the general population of adolescents and adults at risk for sexually-acquired HIV. Sexual (and injection drug use) exposures account for most HBV and HIV infections in developed countries, but among HIV-positive persons in some risk groups, the prevalence of chronic HBV infection may be 10-fold higher than the background prevalence.[57-61]

Understanding of HBV and HCV co-infection with HIV is particularly important in Asian countries due to high background HBV and HCV prevalence [62] and the significant

role injecting drug use plays in transmission of HIV in the region.[63] The interactions between HIV, HBV and HCV have now extended from the epidemiological, where partially overlapping modes of transmission and bi-directional impacts on natural history are features, to the therapeutic domain. The impact of HIV therapies on both HBV and HCV co infection is seen through the duplicate antiviral action of some therapeutic agents, against both HIV and HBV, the impacts of immune function restoration on the natural history of underlying HBV and HCV, and the increasing issue of hepatotoxicity.[64]

**Fig. 1: Prevalence of HIV among HBV and HCV Patients**




Differences in infectivity between HBV, HCV and HIV have been observed in several settings. As indicated above, HBV and HIV are more efficiently transmitted parentally and sexually than HCV. In the prenatal setting, maternal co-infection with HIV facilitates the transmission of HCV to newborns.[69]

**Pharmacotherapeutic Outcomes**

Treatment of hepatitis B in an HIV-infected patient should be considered upon initial diagnosis of hepatitis B. For assessing disease activity and possible indications for HBV therapy, a quantitative determination of HBV DNA and of liver transaminases is recommended. Serum HBV DNA levels are associated with a linear increased risk for development of liver cirrhosis and hepatocellular carcinoma.[70]

The management of chronic HBV disease in HIV infected patients is complex due to the dynamic nature of the disease, drug toxicities, antiviral resistance, potential for hepatitis flares, and the paucity of data regarding treatment of this subpopulation of patients.[71-72]

As of 1989, all HCV testing was performed using ELISA, followed by confirmatory testing of positive samples with recombinant immunoblot assay (RIBAs).[73] Although there have been several case reports of the impact of HAART on HIV-HBV co-infection, relatively few studies have specifically examined this issue. A recent Dutch study that retrospectively assessed rates of hepatotoxicity following initiation of HAART, also reported on the impact of HAART on HIV-HBV co-infection.[74]

**Table.2 Recommended Initial Testing for Patients with HIV/HBV + Coinfection**

| |
|---|
| **Complete blood count (CBC) and biochemical profile** |
| Asparate aminotransferase, alanine aminotransferase, bilirubin, Albumin, international normalized ratio, prothrombin time |
| **Hepatitis B serology** |
| Hepatitis B surface antigen (HBsAG) |
| Hepatitis B surface antibody (anti-HBs) |
| Hepatitis B core antibody (anti-HBc) |
| Hepatitis B e antigen (HBeAg) |
| Hepatitis B e antibody (anti-Hbe) |
| **HBV DNA** |
| Antibodies to hepatitis A,C and D |
| Cd4 cell count, HIV RNA |
| **Monitoring if HBV treatment is initiated** |
| CBC, biochemical profile, CD4 cell count, HIV RNA, HBV DNA, |
| HBeAg, anti-HBe (depending upon pretreatment status) every 3 mo |
| Liver ultrasound and alpha-fetoprotein level every 6-12 mo |

HBV= hepatitis B virus

The timing of initiation of HAART in relation to anti-HCV therapy in co-infected patients poses challenges for clinicians. HAART may slow liver disease progression and might therefore be initiated earlier in co-infected than HIV mono-infected patients.[75-76] On the other hand, HAART might increase fibrosis in co-infected patients through cumulative hepatotoxicity.[75, 77-78] Treatment of chronic HCV in co-infected individuals is apriority because of their more rapid progression to ESLD, poor tolerance of ART, and greater risk of hepatoxicity.[79]

There are no guidelines for the clinical management and treatment of co-infected children, and the limited experience in their management and lack of evidence base to guide policy is a barrier to achieving optimal care.[80]

**Implication of HAART in Malaysia**

Since the first few cases of HIV infection were detected in Malaysia in 1986, the rate of new HIV infections reported annually has increased exponentially. At the end of 2008, there were 84,630 reported cases of HIV infections and 14,576 reported cases of AIDS.WHO, newly reported cases of HIV in Malaysia have been declining from the peak of 6,978 cases in 2002 to 3,692 cases in 2008.Since 1997, infections among women in Malaysia are up by 11% and 75% of these patients are between the ages 20 to 39. 60% of these women are married.

The discovery of antiretroviral therapy has been one of the most dramatic advances in the history of medicine. The introduction of the first nucleoside reverse transcriptase inhibitor (NRTI), zidovudine, in the late 1980s marked the

first therapeutic advances in the field of human immunodeficiency virus (HIV) infection. This was supported by randomized controlled trials (RCTs) documenting prolonged survival.[82]

In Malaysia, HAART can be accessed through the medical clinics of all general hospitals and some district hospitals (i.e., those with specialist physicians).Some local university hospitals also provide ARV treatment. All HIV clinics are run by specialist physicians, who have had some training in HIV medicine, and are supported by nurse counselors, who have undergone attachments at the Infectious Diseases Clinic in Hospital Kuala Lumpur. The frequency of these clinics varies from once in 2 weeks to every day.[83]

ART was first made available in Malaysia in 1989 and since then much effort has been put in to ensure its availability to the population via infectious diseases clinics in major hospitals and primary health clinics with family medicine physicians trained in HIV medicine. In 2006, the Malaysian government made nationwide two significant initiatives, namely the Methadone Maintenance Therapy (MMT) and the Needle Syringe Exchange Program (NSEP) targeted at intravenous drug users in an effort to encourage the use of clean sterile syringes and needles to feed their habits. In the same year, first-line ART without cost was made available for all eligible HIV infected citizens. These initiatives are starting to bear fruit as more HIV infected individuals can now access the beneficial effects of treatment and the rate of HIV infection amongst intravenous drug users has declined.[84]

In 2006, antiretroviral drugs available in Malaysia were of three categories namely NRTI, NNRTI and PI. The list of drugs are as follows: NRTI [zidovudine (AZT), didonosine (ddI), zalcitabine(ddC), stavudine (d4T), lamiduvine (3TC) and AZT þ 3TC], NNRTI(efavirenz and nevirapine) and PI (indinavir, ritonavir, saquinavir, lopinavir and nelfinavir).[85]

Advances in ART therapy have changed the course of HIV infection. What used to be a disease with early morbidity and mortality is now a chronic manageable disease. Benefits of HAART have been reported in many western countries. HAART superiority was again proven in the present study in terms of a reduction in mortality and ADEs.[86-89]

## DISCUSSION

Advances in ART therapy have changed the course of HIV infection. HAART superiority was again proven in the present study in terms of a reduction in mortality and ADEs.[86-89] Choice of HAART regimen did not seem to be influenced by hepatitis status. Immunological and virological responses to antiretroviral treatment were similar among patients with and without hepatitis, and hepatitis co-infection status had no independent effect on survival. Co-infection with HBV or HCV, however, was independently associated with elevated ALT levels in patients on HAART. Estimated prevalence of HBV is high in the Asia–Pacific region, with at least 8% of the population chronically infected and 70–90% having serological evidence of previous HBV infection.[4]

The prevalence of HIV and hepatitis co-infection depends on several factors, including geographic location and background population HBV and HCV prevalence, age and distribution of HIV and hepatitis risk-exposure categories.[90] The assessment of mortality using death certificates is generally well accepted. However, liver disease may have been overshadowed by AIDS-related diagnoses and not been included. For example, hepatocellular cancer was diagnosed in less than 1% of patients, thus under diagnosis is a distinct possibility. In addition, there may be differences in the assessment of the type of liver disease on death certificates.

Recently, high hepatic mortality rates in HIV/HBV co-infected patients were studied in the MACS cohort; co infected patients were eight times more likely to die of liver disease as compared with HIV infection alone.[91]

Mortality due to end-stage liver disease occurred in patients with HCV infection, although other cofactors, such as alcohol use, chronic HBV infection, and use of hepatotoxic medications, may have played a contributory role in either progression or decompensation of chronic liver disease.[92]

However, a recent prospective study of hepatotoxicity in HIV-positive patients who were receiving antiretroviral therapy found that 88% of patients who had concomitant chronic HCV or HBV infection tolerated their medications without serious adverse effects as evidenced by liver function tests.[93]

Hepatotoxicity was clearly a limiting factor in the use of HAART in this cohort. The likelihood of drug-related toxicities is increased by underlying viral hepatitis. Co-infected patients should have careful assessment of possible underlying liver disease and a close laboratory evaluation when starting HAART, because abnormal transaminase levels and hepatic decompensation during antiretroviral therapy have been reported in the literature.[94-98]

## CONCLUSION

HIV- infected patients should be monitored regularly for HBV/HCV co-infection. More aggressive and early treatment is required for the co-infected patients with high progression rates of AIDS. Initiation of HAART should be implicated before anti-HCV therapy but treatment of HBV infection should always be closely coordinated with HIV therapy.

Co-infection with HIV alters the natural history of chronic hepatitis B with faster progression to liver cirrhosis. Toxicity from antiretroviral medications explains an increased

frequency of hepatitis from HAART has been reported in individuals with HBV or HCV infection.

**Future Suggestions**

- Emerging data on development of resistance focuses the need for combination therapy instead of monotherapy.
- Patients should be monitored to detect antiviral resistance and reactivation of HBV.
- Additional research is needed to better understand the interaction of these viruses and identify better correlates of disease progression and treatment responses.

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