

Anti-Retroviral Drug Hepatotoxicity and Risk Factors in HIV Patients with or Without Hepatitis B and C: A Review

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Abstract

Physicians are treating patients infected with human immunodeficiency virus and/or hepatitis B or hepatitis C in their practice more often. Long-term complications of these diseases are multifactorial and can be related to the virus itself or to adverse effects of antiretroviral therapy. The liver is the main organ for regulating the internal environment of a body. There is no way to compensate for the loss of a liver function. It has major influences on the flow of nutrients as well as controlling carbohydrate, protein and fat metabolism. Drugs are significant in causing liver injury. More than nine hundred drugs, herbs and toxins have been documented as being hepatotoxic in line with different risk factors. The incidences of severe hepatic injury vary among different study cohorts as well as the differences in risk factors. Patients with a co-infection of HIV and Hepatitis B or C are at a risk of getting liver injury from antiretroviral drugs because the co-infections accelerate liver injury that may lead to cirrhosis or hepatocellular carcinoma. The risk of liver damage for those with a mono-infection of HIV alone is lower than in co-infections. This review explores risk factors for hepatotoxicity, its hepatotoxic antiretroviral drugs and the mechanisms of toxicity. It is meant to highlight the hepatotoxic potential of different antiretroviral drugs currently in use by HIV infected individuals.

Keywords: Hepatotoxicity; Antiretroviral drugs; Risk factors; Mechanisms; Hepatitis B; Hepatitis C; Hepatotoxic potential; Co-infections

Introduction

Survival rates in individuals with human immunodeficiency virus (HIV) infections have improved with access to early treatment; therefore, it has been recommended that individuals with HIV begin antiretroviral therapy (ART) if they have a CD4+ cell count of 500 per mm³ (0.50 or less) [1-4]. Despite this, ART drugs continue to have noteworthy adverse effects that need monitoring for drug interactions and long-term morbidity related to hepatic, cardiovascular, bone, and kidney disease.

Henry J cited by Dietrich et al. states that antiretroviral therapy (ART) has led to reductions in morbidity and mortality associated with HIV infections [5]. Gradually, adverse effects caused by ART on the liver are being documented and are emerging as a major safety concern. Hepatotoxicity is being frequently associated with the use of ARTs [6]. Drug-induced hepatic injury is responsible for >50% of cases of acute liver failure in the United States (US) and is the most frequent reason for withdrawing an approved drug from the market [7]. Most drugs, however, cause liver injury infrequently.

There is a concern for HIV individuals co-infected with Hepatitis B virus (HBV) and/or hepatitis C virus (HCV), because liver disease progression is accelerated in these subjects [8]. Clinical studies indicate that grade 3 aminotransferase levels (levels >5 times the upper limit of

normal (ULN)) and grade 4 aminotransferase levels (levels >10 times the ULN) hepatotoxicity is observed in 5%–10% of HIV positive individuals treated with combination ART for >6 months [8,9].

Hepatic injury due to antiretroviral drugs is constant for each drug as well as consistent for every antiretroviral drug class. Abnormalities in liver enzyme levels are common in patients infected with the Human Immunodeficiency virus (HIV). These abnormalities can be caused by a variety of factors such as drugs used for antiretroviral therapy or co-infections with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) [10]. Hepatitis co-infections with HIV are common in individuals with HIV due to the shared modes of transmission.

According to previous research, chronic viral hepatitis can be associated with a higher risk of antiretroviral hepatotoxicity. Individuals who are using protease inhibitors have the highest risk of developing hepatotoxic related problems [11-13]. Hepatotoxicity is defined by severe changes in the aminotransferase levels.

The clinical manifestations of hepatic toxicity in HIV infected individuals present differently. They may range from elevated transaminase levels that are asymptomatic to hepatic failure and liver function decompensation that may lead to death. Systemic symptoms such as jaundice and coagulopathy also occur [14]. This review explores risk factors for hepatotoxicity, hepatotoxic antiretroviral drugs and the mechanisms of toxicity of these drugs.

Risk factors for the Development of Hepatotoxicity

The incidences of severe hepatic injury vary among different study cohorts as well as the differences in risk factors. Studies indicate that ART related hepatic enzyme elevations are more pronounced in HIV subjects with a co-infection of HBV or HCV [9,15-17].

Drugs used in treatment also present various risk factors to HIV patients. Some studies have documented higher incidences of elevated transaminase levels when protease inhibitors are used, especially ritonavir [9,16,17]. For Non-nucleoside reverse transcriptase inhibitors, nevirapine has been shown to cause more liver damage with efavirenz causing more severe enzyme level abnormalities [18- 20].

Baseline CD4+ counts at the beginning of ART treatment can also be a risk factor. HIV patients on ritonavir with a CD4+ count increase of over 0.05*10⁹/l from baseline have a higher chance of hepatotoxicity than those who have smaller CD4+ increases or decreasing CD4+ counts. Chances of hepatotoxicity also increase in patients with elevated pre-treatment aminotransferase levels [10]. Individuals with chronic viral hepatitis are associated with the onset of severe hepatotoxicity if they are on non-ritonavir containing regimens. A potential justification for higher risk of hepatotoxicity in individuals with elevated baseline aminotransferase levels and a co-infection with hepatitis C maybe that they interfere with drug metabolism [21].

Co-infection with HCV has been documented as one of the leading causes of hepatic injury [9,15-17,22]. For patients who are co-infected with Hepatitis B and are on lamivudine, discontinuation of lamivudine is a risk factor for progression of hepatotoxicity. Alcohol abuse while on ART has also been found to be among the risk factors for the development of liver toxicity [23]. There is a higher chance of hepatotoxicity in older individuals who are on ARTs. It has been well established that age increases the chances of drug related hepatotoxicity [23,24].

Liver fibrosis and its severity at the start of therapy is a critical factor in the risk of liver toxicity associated with ARVs. The severe the fibrosis, the higher the chances of drug-related liver toxicity. Cirrhosis

has also been reported to be a risk factor for total bilirubinemia elevations secondary to atazanavir and/or ritonavir medications [25].

The risk of hepatotoxicity has also been found to be different among experienced and naïve patients. In experienced patients, elevated alanine transaminase level at baseline, a history of liver function test (LFT) elevations and use of non-nucleoside reverse transcriptase inhibitor based drugs were independently linked to the development of grade III hepatotoxicity [25].

Drug Mediated Hepatotoxicity

The most common initial ART regimens are non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) with two nucleoside reverse transcriptase inhibitors (NRTIs) [1]. Common ART toxicities make adherence to therapy difficult. Nevertheless, adherence is imperative to prevent the development of drug resistance. Even with toxicity, a strategy of switching to a different regimen or decreasing dosage to minimize toxicity or maximize adherence may not be possible with ART; the benefits of suppressing HIV supersede other concerns. Identification and cognizance of ART toxicity are necessary in facilitating patient adherence and determine when a change in therapy may be useful [1].

Individuals receiving ART should be routinely monitored for adverse effects every three to six months. Monitoring should encompass a complete blood count and an all-inclusive metabolic panel. A lipid profile and urinalysis for proteinuria should be performed annually. In case of very adverse effects and ART is changed, metabolic panel, a complete blood count, and a lipid profile should be done two to eight weeks subsequently. If the results are abnormal, more frequent tests should be done based on clinical assessments [1,4,26].

In grade 3 aminotransferase levels (levels>5) and grade 4 aminotransferase levels (levels>10), liver toxicity occurs in 5 to 10% of HIV patients on combination ART for a period of over six months [27,28].

Drug	Effect
Abicavir	Can cause fatal hypersensitive reactions, either rash or systemic symptoms. Individuals should be screened for HLA-B*5701 before use, if there are sensitivities, the drug should not be used.
Nevirapine	Can cause severe hepatotoxicity and liver failure leading to death; women with baseline CD4 ⁺ cell counts >250 cells per mm ³ and men with baseline CD4 ⁺ >400 cells per mm ³ are at a highest risk of liver failure
Atazanavir	Can cause asymptomatic indirect hyperbilirubinemia and rash (20% of patients), kidney stones can also be an effect of the drug. For absorption, the drug requires acid in the stomach. Take with food.
Indinavir	Indirect hyperbilirubinemia, the drug should be taken an hour or two after meals and accompanied with about 1.5 litres of water.
Tipranavir	Capable of causing severe hepatitis. Caution should be taken if the patients are allergic to sulfonamide.
Ritonavir	Circumoral and peripheral paresthesia. The drug should be taken with food.
Saquinavir	Rash and hyperprolactinemia. Drug should be used within two hours after meals.

Table 1: Summary of Antiretroviral drugs and their effects on the liver.

Several Protease Inhibitors are used with other drugs for HIV treatment [12]. Metabolization of PIs is by the CYP450 system. In the liver, the PIs majorly cause lipid disorders. About 60% of individuals taking PIs have raised total cholesterol levels (greater than 240 mg per

dL) while 75% have triglyceride levels higher than 500 mg per dL [29]. Atazanavir is the most lipid-favorable PI; boosted darunavir and boosted atazanavir are the next choices if baseline hyperlipidemia is significant [1]. The choice of statins is significant in patients with lipid

disorders who are also taking PIs [26,29,30]. Pravastatin can be used with ART without dosage adjustment, though the lowest dosage should be in patients taking darunavir. Rosuvastatin and atorvastatin are alternative medications. Fibrates, niacin, and omega-3 fatty acids can be used with PIs [31].

Besides indinavir-associated hyperbilirubinaemia, HIV-1 protease inhibitors can also cause hepatitis in patients co-infected with Hepatitis B or C and with raised hepatic aminotransferase concentrations at baseline [10,32] (Table 1).

Hepatotoxicity occurs in association with ART but the risk varies according to the type of medication used. The use of ritonavir has a five-fold increase in chances of getting severe hepatotoxicity while indinavir results in higher chances of hyperbilirubinemia [10]. Ritonavir is a potential inhibitor of cytochrome P450 system that has pharmacokinetic as well as metabolic effects that contribute to hepatotoxicity by interfering with liver functions or raising drug concentrations in the liver [33,34]. In some cases, ritonavir has resulted into fatal acute hepatitis [35]. Cases of hepatotoxicity associated with the consumption of saquinavir have also been documented [8]. Nelfinavir has been found to be less toxic than the other Protease Inhibitors analyzed in 1052 patients [8,36].

There is approximately 2.5 fold increase in risk of developing grade 3 or grade 4 liver toxicity among HCV infected individuals compared to those without HCV co-infection. For example, Sulkowski et al. observed hepatotoxicity among 16% and 13% of HCV infected individuals and 6.5% and 6% of HCV uninfected individuals to prescribed nelfinavir and lopinavir/ritonavir based ART, respectively [8]. Bernstein et al. observed similar incidence rates of hepatotoxicity in HCV-infected individuals randomized to receive nelfinavir (19.2%) or lopinavir/ritonavir (10.5%) based ART. After adjusting the type of ART received and baseline covariates, HCV co-infection was independently associated with approximately 1.7-fold greater risk of hepatotoxicity. NNRTIs are associated with a rash and lipid disorders [1,38,39]. The rash might necessitate stopping NNRTIs and using a different regimen class for ART. Lipid disorders due to NNRTIs can be managed with niacin, statins, omega-3 fatty acids and fibrates [1,31]. Non-nucleoside reverse transcriptase inhibitors have been known to be able to cause hepatitis in the first three months after the onset of therapy sometimes as part of a hypersensitivity reaction [21]. The most common NNRTIs in use are Nevirapine, Efavirenz and Etravirine. In patients receiving nevirapine therapy, the incidences of liver toxicity increase over time. Co-infections with hepatitis B and or C and ALT baseline levels that are abnormal have been reported to be the major risk factors for the onset of hepatic toxicity for individuals on nevirapine [21]. There have been some similarities between liver toxicity by nevirapine and those drugs with protease inhibiting functions [10,21].

Nevirapine is associated with early hypersensitivity reactions that are capable of causing fulminant hepatitis resulting to hepatic failure and death. There is a later onset of direct drug related toxicity resulting to liver enzyme elevations [15]. The World Health Organization (WHO) recommends the use nevirapine with caution and regular monitoring in individuals with baseline grade 1, 2 or 3 liver enzyme elevations and positive or unknown HBV or HCV testing [22]. Nevirapine is not suitable in patients with grade 4 liver enzyme elevations.

Individuals on nevirapine have their toxic levels increase over time with many of them developing hepatitis within the first two to three

months. These observations have also been described in individuals on Protease inhibiting drugs [10].

A South African study in HBV co-infected individuals receiving the less hepatotoxic efavirenz (the second NNRTI used in first-line treatment) found comparable response to ART between mono-infected and co-infected patients despite higher hepatotoxicity in the co-infected [40]. Efavirenz can cause hyperlipidemia and liver toxicity and thus it is not recommended for use during pregnancy. For etravirine, the liver, lipid, and neuropsychiatric effects common with other NNRTIs have not been reported, therefore the drug can be used in patients with resistance to other NNRTIs.

Infections with Hepatitis B or C viruses increase the risk of hepatotoxicity in patients not on ritonavir while chronic HCV infection is associated with a greater than two fold increase in the risk of hepatotoxicity for individuals taking highly active anti-retroviral therapy (HAART) [10]. In chronic HCV infection, hepatic injury may be due to increased viral replication coupled with the activity of CD8+ cells during HAART associated immune reconstitution.

As put forward by Kaplowitz, many serious drug induced hepatic events are random, not related to dosage and are either hypersensitivities mediated by the immune system or are idiosyncratic reactions [41]. However, more frequent adverse liver events like the asymptomatic elevations of the aminotransferase levels can be due to higher levels of the administered drug or a liver metabolite [7].

The most common Nucleoside reverse transcriptase inhibitors (NRTIs) are zidovudine, lamivudine, emtricitabine and tenofovir. NRTIs are capable of causing lactic acidosis, lipodystrophy as well as hepatic steatosis after more than six months of antiretroviral therapy via mitochondrial toxicity [42]. Symptoms of lactic acidosis include nausea and vomiting, fatigue, abdominal pain, diarrhea, and a rise in liver function markers because of hepatic steatosis. This complication can be screened by serum venous lactate level, but should be confirmed by arterial blood gas testing. More than 45.05 mg per dL of the venous or arterial lactate levels should trigger the change from NRTI to a non-thymidine NRTI [26,30]. Studies have documented lower incidences of hepatotoxicity with lamivudine and tenofovir, that is, they are well tolerated. However, in individuals with co-infections of HIV and hepatitis B, discontinuation of these medications can cause a flare up of hepatitis B [23].

A study done by Martinez et al. found that stavudine, is partially responsible for the elevations in liver enzyme levels due to its effects on mitochondrial toxicity [21].

The majority of the NRTI drugs are capable of inducing mitochondrial damage, therefore, have the potential for developing liver injury. Hepatic failure has been reported in patients taking zidovudine, although didanosine and stavudine have been most involved in severe hepatotoxicity. Abacavir and tenofovir have a low potential for mitochondrial damage and seem to have a safer profile regarding liver damage. For those patients with chronic hepatitis B, the removal of lamivudine may be accompanied by a period of hepatitis B replication that results in an increase in transaminase levels [42].

Anti-HBV lamivudine monotherapy has been shown to lead to increased frequencies in drug resistance [43] and possibly to acute hepatitis, fulminant hepatic failure, and death, lamivudine has been shown to be likely effective against HBV in the first months of treatment when episodes of hepatotoxicity occur [16]. Importantly, up

to half of HIV/HBV co-infected patients experience liver enzyme elevations >2.5 times the ULN.

Mechanisms of anti-retroviral toxicity

Anti-retrovirals, like other drugs, induce direct toxicity to the liver. Drug metabolism through the cytochrome pathways cause hepatotoxicity when there are enzyme polymorphisms [44]. Since ARTs are metabolized in the liver, idiosyncratic polymorphisms of the enzymatic complexes are capable of leading to substantial heterogeneity in drug metabolism, predisposing to the development of hepatotoxicity. Antiretrovirals are also capable of activating death receptors and intracellular stress pathways [45].

Hypersensitivity reactions are reactions of the host unrelated to drug dosage. Immune mediated drug reactions involve generation of neoantigens formed by the reaction of liver proteins with reactive drug metabolites. Documentation of hypersensitivity reactions has been done in patients with nevirapine and abacavir as well as those on zalcitabine [46,47].

Mitochondrial toxicity has been known to evolve to acute liver failure. A major feature of hepatic lesion is the buildup of microvesicular steatosis in hepatocytes as well as mitochondrial depletion. This lesion has the capability of evolving to macro vesicular steatosis with fibrosis, focal necrosis, proliferation of biliary ducts, cholestasis and Mallory bodies. Underlying liver disease does not predispose one to this type of lesion [44]. Cumulative exposure to Nucleoside Reverse Transcriptase Inhibitors is a vital factor in the development of lactic acidosis, as it appears after prolonged treatment and has a correlation with the number of concomitant NRTIs [48].

Conclusion

When treating individuals with HIV infection, it is difficult to distinguish liver toxicities in individuals receiving multiple drugs who may have risk factors for hepatotoxicity such as viral hepatitis infections, alcohol abuse and female sex. Many antibiotics, antifungals, and antivirals for HIV-infected patients have been associated with hepatotoxicity. Therefore, as with any decision to prescribe an ARV drug, a careful evaluation of the potential risks and benefits of using it must be made for each individual.

Competing Interests

The authors declare that there were no competing interests

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