AIDS Rev 2003;5:36-43

Hepatotoxicity of Antiretroviral Therapy

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Abstract

Hepatotoxicity is a serious complication in patients taking HAART. Coinfection with hepatitis viruses increases the risk of liver toxicity while taking antiretroviral therapy. Baseline transaminases should be checked before beginning antiretorviral therapy and all patients should be screened for pre-existing liver disease, most notably hepatitis B and C infections. Regular monitoring of transaminases is mandatory when commencing antiretroviral therapy. In patients with normal liver function, transaminases may be checked monthly after commencing HAART for the first 3 months. If stable this can be broadened to 3 month intervals. In patients with pre-existing liver disease monitoring should be performed more frequently (every 2 weeks) when initiating therapy. Once stable liver enzymes should be checked monthly.

The less hepatotoxic drugs such as lamivudine and abacavir should be preferred in patients at high risk for hepatotoxicity. Risks include co-infection with hepatitis B and C viruses, a previous record of hepatotoxicity, cirrhosis, obesity and female gender. Minor enzyme elevations (<5-fold upper normal limit) are generally safe to tolerate and usually resolve. Patients must be closely observed with regular liver function tests and a hypersensitivity type drug reaction should be excluded. The onset of clinical symptoms, elevated serum lactate or evidence of severe hepatic dysfunction (coagulopathy or elevation of ammonia levels) are suggestive of severe toxicity and HAART should be withheld.

Treatment of suspected HAART related hepatotoxicity should first involve withdrawal of therapy. Hypersensitivity reactions may be treated with corticosteroids. Nucleoside-induced mitochondrial damage may improve with riboflavin or thiamine therapy.

Key words

Hepatotoxicity. Hepatitis C. Liver toxicity. Nevirapine.

Introduction

The differential diagnosis of liver disease in a patient with HIV infection is often a difficult task. Abnormalities in liver function are common and may be caused by HIV itself, hepatitis viruses, systemic opportunistic infections, malignancies and drug-induced hepatotoxicity[1]. Co-infection with hepatitis B and C viruses is common in HIV patients and liver disease is becoming a leading cause of death in this group. There are three different classes of highly active antiretroviral therapy (HAART): nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). HAART has significantly improved surviv-

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al and reduced progression of disease in this population but is frequently implicated in drug-related toxicity. Hepatotoxicity, liver enzyme elevation and drug interactions are a significant problem in HIV patients on HAART. In patients commencing anti-retroviral therapy 14-20% will experience elevations of liver enzymes[2,3]. 2-10% will need to interrupt anti-retroviral therapy due to severe hepatic injury and marked elevation of liver enzymes. Co-infection with chronic viral hepatitis B and C is very common in HIV infected patients and increases the risk of hepatotoxicity.

Definition of hepatotoxicity

There has been variability in the classification of hepatotoxicity –particularly in early studies. A standardized toxicity grade scale is now widely used by the AIDS Clinical Trials Group. Patients with normal pre-treatment ALT and AST levels are classified based on changes relative to the upper limit of normal (ULN): grade 0 (<1.25 x ULN), grade 1 (1.25-2.5 x ULN); grade 2 (2.6-5 x ULN); grade 3 (5.1-10 x ULN) and grade 4 (>10 x ULN). Patients with elevated pre-treatment ALT and AST (often viral hepatitis patients) are classified as above, but based on changes relative to baseline rather than ULN. Cholestasis is a feature of HAART hepatotoxicity and changes in bilirubin are classified based on changes relative to ULN: grade 0 (<1.1 x ULN), grade 1 (1.1-1.5 x ULN), grade 2 (1.6-2.9 x ULN), grade 3 (3-5 x ULN) and grade 4 (>5 x ULN). Severe hepatotoxicity is defined as grade 3 or 4 change in AST or ALT levels during anti-retroviral treatment. Severe hyperbilirubinemia is defined as grade 3 or 4 change during treatment and is analysed independent of serum ALT and AST.

Mechanisms of hepatotoxicity

Mitochondrial damage

Nucleoside analogues act by incorporating into viral nucleic acids and inhibiting viral replication. Human mitochondrial DNA polymerase _, an enzyme that is required for normal mitochondrial replication, is inhibited by nucleoside analogues[4]. Depletion of mitochondrial DNA impairs the cellular respiratory chain and inhibits pyruvate and fatty acid oxidation pathways. Mitochondria appear enlarged and swollen with matriceal densities and occasional vacuoles on electron microscopy[5]. With more severe NRTI mitochondrial toxicity microvesicular hepatic steatosis, giant mitochondria and intrahepatic cholestasis are characteristic on light microscopy. Clinically severe NRTI mitochondrial toxicity is manifested by the development of hepatomegaly and steatosis and occasionally may be associated with lactic acidosis and liver failure.

Electron transfer in the mitochondrial respiratory chain is interrupted resulting in an increase in intracellular release of reactive oxygen species[6]. These oxygen free radicals cause lipid peroxidation of fatty acids, release of proinflammatory cytokines, induce fibrosis and damage nuclear DNA. An important final step is the release of cytochrome C, an intermembrane protein, from damaged mitochondria into the cytosol. Cytochrome C activates caspases and triggers cellular apoptosis[7].

Hypersensitivity reactions

Hypersensitivity reactions are idiosyncratic, immune mediated adverse drug effects that are most frequently observed with NNRTIs. Nevirapine in particular has been implicated but have also been documented with the NRTI abacavir and the new PI amprenavir. Clinical features that may suggest an acute, immune-mediated hypersensitivity response include fever, skin rash and eosinophilia. Hepatic histopathology can vary considerably and includes hepatocellular necrosis, cholestasis, tissue eosinophilia, parenchymal and periportal infiltrates with a predominance of lymphocytes and plasma cells. The reaction tends to resolve following withdrawal of the offending agent and typically recurs on re-challenge, usually after a shorter time interval[6].

The exact immunological mechanisms and triggers are not known but the occurrence of constitutional symptoms such as fever and hypotension suggest a cytokine mediated reaction.

Lipodystrophy syndrome and steatohepatitis

Lypodystrophy can be a long-term side effect of protease inhibitors. The syndrome consists of central obesity, a buffalo hump, wasting of extremities, hyperlipidemia and insulin resistance[8]. The pathological mechanism is believed to be due to homology of the catalytic region of HIV-1 protease, the drug binding target, with two proteins that regulate lipid metabolism: cytoplasmic retinoic acid-binding protein type I (CRAB P1) and low-density-lipoprotein receptor-related protein (LRP). PI bind to LRP and impair hepatic chylomicron uptake and triglyceride clearance by the LRP-lipoprotein lipase complex[9,10].

Insulin resistance is believed to be the metabolic hallmark of predisposition to non-alcoholic steatohepatitis (NASH). Steatohepatitis is a common feature in patients on HAART and mitochondrial toxicity is often implicated. However the precise mechanism is not well defined and insulin resistance may also have an important role in the HIV setting[11].

Hepatotoxicity due to drug interactions

Side effects and toxicity may result from interaction with other hepatically metabolised drugs. The protease inhibitors, in particular ritonavir are potent inhibitors of several cytochrome P450 iso-

forms and thus alter plasma levels of drugs that share the same routes of metabolism. Dose dependent hepatotoxicity may result from toxic levels of drugs whose clearance is reduced. Along with the protease inhibitors, the NNRTIs efavirenz, nevirapine and delaviridine are also metabolised by cytochrome P450 enzymes.

An example is ritonavir, a powerful enzyme inhibitor, which can significantly increase levels of other antiretrovirals[12]. In particular, co-administration with saquinavir produced a 20 fold increase in steady state concentrations. Indinavir levels are also markedly elevated.

HIV patients frequently require treatment with anti-microbial agents whose half lives may be significantly prolonged by concomitant antiretroviral use. Levels of the antifungals ketoconazole and itraconazole are increased to toxic levels by indinavir and ritonavir. Anti-tuberculous therapy can be particularly difficult in HIV patients as these drugs may be hepatotoxic themselves and are metabolised by the cytochrome P450 enzymes. The risk of hepatotoxicity increased significantly after commencement of treatment for tuberculosis in a recent study[13]. Rifabutin should be used instead of rifampicin. A pharmacokinetic study demonstrated that the concomitant administration of ritonavir and rifabutin resulted in an approximate fourfold and 35-fold increase in the area under the curve (AUC) of rifabutin and its active metabolite 25-O-defacetyl rifabutin, respectively. Therefore concomitant use of the two drugs is contraindicated[14].

The role of co-infection with hepatitis B and C viruses

The prevalence of HCV and HIV co-infection ranges from nearly 30% to over 50% depending on the population. A higher mortality due to liver disease and hepatitis C in HIV-infected patients first appeared in the literature in 1997[15]. In 1999 the US Public Health Service (USPHS) and the Infectious Disease Society of America (IDSA) described hepatitis C as an opportunistic infection in their guidelines[16].

Viral hepatitis has been shown to be an important independent risk factor for development of hepatotoxicity during HAART therapy. Melvin, et al. demonstrated that HAART discontinuation rates due to hepatotoxicity were increased more than two-fold in the presence of hepatitis C[17]. Den Brinker, et al. presented data from their cohort of 394 patients that demonstrated an increased risk of developing liver enzyme elevations (LEE) in their co-infected patients[II]. Patients co-infected with hepatitis B had a relative risk (RR) of developing LEE of 2.78 times and those with hepatitis C had a relative risk of 2.46 times. Progression to AIDS or death was 1.7 times greater in the HCV/HIV-co-infected patients compared to HIV-infected only patients in the Swiss HIV Cohort Study. In addition, HCV-seropositivity was associated with a CD4 cell count that remained 50 cells/μl lower than HCV-seronegative patients 36 months after beginning antiretroviral therapy[19].

Studying a cohort of 1,255 patients, 46.0% of whom had a positive HCV antibody test, D'Arminio-Monforte, et al.[20] found the probability of reaching ALT plasma levels ≥ 200 IU/l (approximately 5 x ULN {grade 3}) was 7.9% in a 24-month period in their patients. The authors demonstrated that HCV infection was the most important factor associated with reduced time to ALT plasma levels ≥ 200 IU/l. HCV-infected individuals were at an adjusted fourfold greater risk of severe hepatic damage compared with persons negative for both HCV and HBV markers. Monga, et al.[21] noted that liver decompensation developed in 10% of patients with HIV/HCV coinfection. In contrast, no liver-related deaths or decompensation occurred in patients without coinfection ($p < 0.05$).

In a recent study of 222 HIV-infected patients receiving HAART[22], predictors of hepatotoxicity were evaluated in subgroups of patients co-infected with HCV, HBV, or hepatitis D virus (HDV). In this analysis, the overall toxicity rate was 9% for NNRTI- and 10% for PI-based regimens. Independent predictors of liver toxicity were found to be HCV, increasing age, and alcohol abuse.

Immune reconstitution disease

Patients with chronic hepatitis C will frequently experience a flare in transaminases after commencing anti-retroviral therapy. This phenomenon has been attributed to immune reactivation due to a rapid increase in cytotoxic T cells, leading to immune-mediated destruction of HCV-infected hepatocytes. In one study, protease inhibitors temporarily increased viremia and transaminases[23]. HCV RNA levels returned to baseline after 8 months of therapy.

An alternative explanation is that HIV infection results in an increase in endogenous interferon alfa production that may suppress transaminase levels. Following anti-retroviral therapy interferon levels then return to normal.

Spectrum of drug-related liver toxicities

Ribavirin

It is a guanosine nucleoside analogue that may reduce the efficacy of the pyrimidine nucleoside analogues zidovudine, stavudine and zalcitabine by inhibiting intracellular phosphorylation[24]. This effect has been demonstrated *in vitro* but may not be relevant in clinical practice. However, ribavirin markedly increases didanosine levels which may cause fatal mitochondrial toxicities, pancreatitis and lactic acidosis[25]. This has prompted a Black Box Warning in the Didanosine package concerning use with ribavirin and we would recommend avoiding the combination completely.

Nucleoside analogue reverse transcriptase inhibitors

Hepatotoxicity related to NRTIs was first documented in the early 1990s with zidovudine monotherapy. The most serious toxicity was shown with the experimental drug FIAU[26]. Combination therapy was subsequently found to further increase the risk of hepatotoxicity. Asymptomatic enzyme elevations greater than five times normal have been recorded in approximately 6% of patients[27]. More severe reactions evoking symptoms have been recorded with an incidence of 1.3 patients per 1000 person/year. All the nucleoside analogues have been implicated but hepatotoxicity may be more prevalent with stavudine (d4T), zalcitabine (ddC), and didanosine (ddI). These three drugs have a higher affinity for mitochondrial polymerase γ, and have a higher rate of toxicity than abacavir (ABC), zidovudine (AZT), lamivudine (3TC) or tenofovir[28,29] (Fig. 1).

A variant of the lipodystrophy syndrome, the lipoatrophy syndrome, originally attributed to protease inhibitor therapy, may be caused by NRTIs. It is believed to be due to hepatic mitochondrial toxicity and is and is characterised by wasting of the peripheral fat in the face, legs and arms. It differs from the PI induced lipodystrophy syndrome that is characterised by central obesity, gynaecomastia and a buffalo hump[30].

Laboratory features most commonly involve elevation of transaminases but cholestatic pictures are also noted with elevations of alkaline phosphatase and GGT. Extra-hepatic mitochondrial toxicity is manifest by elevated creatine kinase, lipase, amylase, hyperlactemia and lactic acidosis (Fig. 2).

Plasma lactate and HCO_3 levels are useful in the assessment and monitoring of NRTI toxicity. A normal plasma lactate value of 1-2 mmol/l may be raised to 3-5 mmol/l, causing symptomatic hyperlactatemia in patients experiencing mitochondrial toxicity. Acidosis may occur at lactate levels of 5 mmol/l or above. Compensated or asymptomatic hyperlactatemia is chronic and stable over time with an HCO_3 plasma level ≥ 20 mmol/l. It is worth noting that d4T and ddI are associated with a higher risk of hyperlactatemia than ZDV, 3TC and other NRTIs. Decompensated or symptomatic lactic acidosis/hepatic steatosis is fortunately rare but, when it occurs, it is rapidly progressive and life-threatening with HCO_3 plasma levels < 20 mmol/l. Risks for the latter are female gender, HCV/HBV co-infection, liver disease, pregnancy and obesity.

Zidovudine. It has been implicated in cases of fatal hepatic failure in advanced AIDS patients. These patients developed massive hepatomegaly and microvesicular steatosis which progressed to fulminant hepatic failure[31]. Four out of the six deaths occurred in obese females, raising the possibility of pre-existing steatohepatitis. Lactic acidosis with hepatomegaly and steatosis has also been described. This can be severe with a 50% mortality and has also been noted with didanosine and stavudine therapy[32]. Zidovudine can also cause acute hepatitis due to hypersensi-

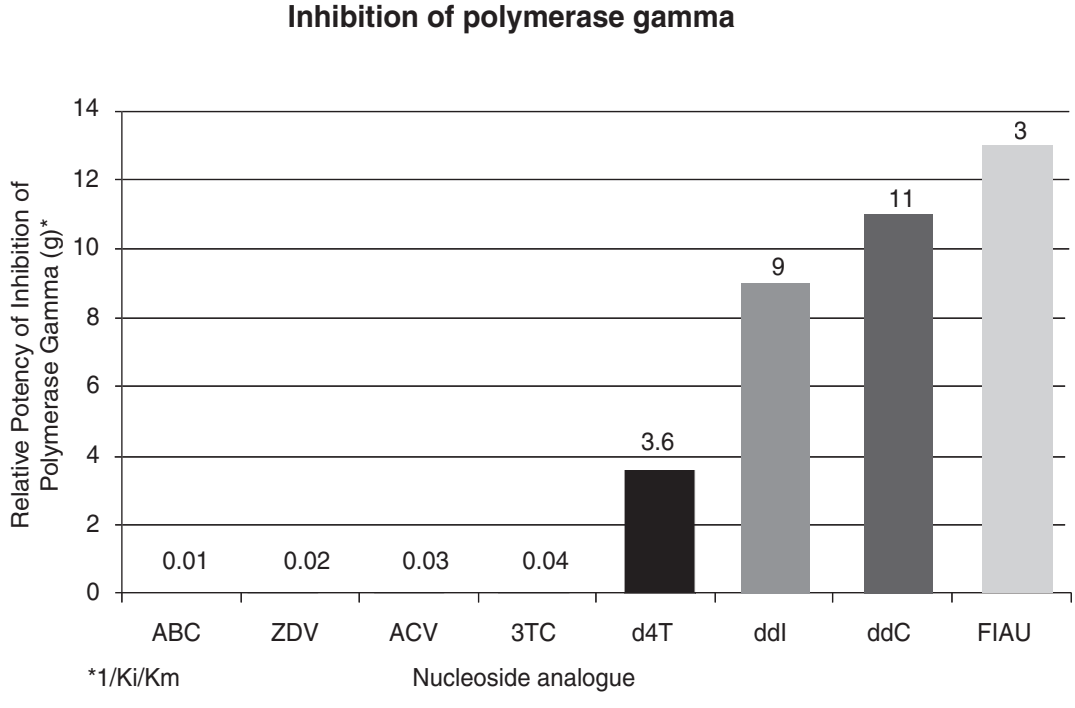


Figure 1. *Potency of polimerase gamma inhibition by nucleoside analogues.*

tivity, which resolved approximately 10 days after cessation of therapy. In these patients AZT was replaced with DDI or DDC without recurrence of toxicity[33,34].

Didanosine. Its toxicity appears to be more common than AZT. The most common toxicity seen is microvesicular steatosis and is usually dose dependent (>10 mg/kg)[35,36]. A major risk for didanosine hepatotoxicity is concomitant ribavirin therapy as mentioned above, prompting the FDA to recommend use with extreme caution.

Stavudine. It has been most frequently associated with hepatotoxicity in patients on antiretroviral therapy. Many case reports of hepatotoxicity have frequently involved d4T –especially when used in with ddI–, a combination that is no longer recommended[37].

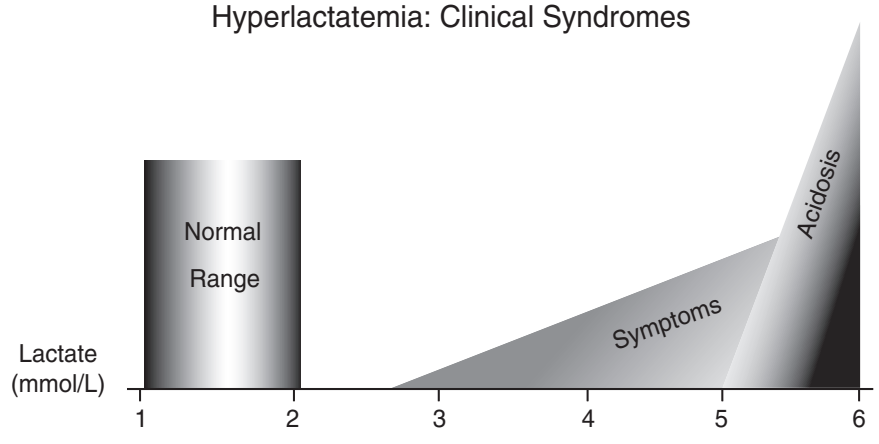
Lamivudine and abacavir. They have been least reported to cause hepatotoxicity of all the NRTIs. A proposed reason is the low affinity of these drugs for mitochondrial DNA polymerase γ.

Non-nucleoside analogue reverse transcriptase inhibitors

Nevirapine. Hepatotoxicity is commonly seen with nevirapine therapy with a significant number of patients developing abnormal liver function tests. It can cause a several types of hepatotoxicity including asymptomatic aminotransferase elevation, hypersensitivity reaction and late-onset dose-related hepatotoxicity. The hypersensitivity reaction can develop in the first few weeks of therapy and may cause symptoms of rash, fever, hypotension along with hepatic dysfunction. Reactions may be severe and may progress to Stevens-Johnson syndrome. Laboratory features to suggest hypersensitivity include a leucocytosis with eosinophilia and increased IgE levels. This type of reaction has been observed more frequently in patients with high CD4 counts (females with CD4 count > 250 and males with CD4 count > 400 cells/ml), moderate immunodeficiency who were not being treated[38]. The reaction will usually abate following discontinuation of the drug and therefore fatal outcomes are rarely seen.

There are reports of late onset "nevirapine hepatotoxicity" typically occurs after 4-5 months of therapy. Other evidence suggests that this effect may be due to NRTI mitochondrial toxicity as it occurred mainly in patients taking concomitant stavudine[39,40]. Predisposing factors may include a high cumulative dose of the drug, high serum levels and concomitant liver disease –typically chronic viral hepatitis. Liver function tests usually improve following discontinuation of the drug.

Efavirenz and delavirdine. The Adult AIDS Clinical Trials Group (AACTG) analysed 21 studies that had included 10,611 patients. Similar rates of severe hepatotoxicity and subsequent discontinuation were reported for the nevirapine-treated and efavirenz-treated patient populations[41]. The incidence of grade 3 or 4 elevations was 10.8% in the efavirenz-treated group and 8.9% in the nevirapine-treated group. However, the incidence of severe



Compensated or asymptomatic hyperlactatemia
chronic
stable over time
HCO_3>=20mmol/L
common
risk factors- NRTIs, (d4T>ZDV)

Decompensated or symptomatic lactic acidosis / hepatic steatosis
rapidly progressive
life-threatening
HCO_3<20mmol/L
rare
risks-female gender, HCV/HBV co-infection, liver disease, pregnancy, obesity

Figure 2. *Clinical and laboratory features of nucleoside analogue-induced hyperlactatemia.*

hepatotoxicity in the delaviridine treated group was only 3.6%. The authors concluded that patients treated with nevirapine or efavirenz were significantly more likely to experience a grade 3 or 4 hepatic event than patients treated with delavirdine (Fig. 3).

A recent retrospective analysis of patients treated with one of three NNRTIs showed that there was more liver toxicity in hepatitis B or C co-infected patients, but there was no difference in the incidence of liver toxicity (defined as grades 3-4 elevations of AST or ALT plasma levels) in patients treated with nevirapine, efavirenz or delavirdine[42].

Protease inhibitors

Hepatotoxicity is a well recognised side effect of PI therapy with over 50% of patients developing asymptomatic mild elevation of transaminases. In some series up to 10-20% developed severe hepatotoxicity with liver enzymes rising above 5 times the upper limit of normal[43]. Transaminases usually rise after 3 months of therapy and most will return to normal over the next 3-5 months, however approximately 10% will stay persistently elevated[44]. Symptomatic hepatotoxicity is less common with 2-5% of patients developing right upper quadrant pain, nausea and vomiting, jaundice and pruritis[27,43,45].

The histological pattern observed in patients with PI hepatotoxicity is variable without definite pathognomonic features. Features include bile duct injury and proliferation, hepatocellular necrosis and Mallory bodies. Ballooning of hepatocytes, Kupffer cell activation and peri-cellular fibrosis in zone 3 has recently been described in a series and are believed to be features of PI hepatotoxicity[46].

Ritonavir. Ritonavir has been the most frequently implicated PI to cause hepatotoxicity. Sulkowski, et al. recorded severe hepatotoxicity defined as a rise in transaminases greater than 5 times normal in 27.3% of patients treated with ritonavir[43]. Cytochrome P450 inhibition is an important factor in ritonavir hepatotoxicity.

Indinavir. Severe acute hepatitis has been reported with indinavir therapy and this may occur early or late into therapy[47,48]. However the most common laboratory finding in patients on indinavir is unconjugated hyperbilirubinemia seen in up to 40% of patients[49]. This occurs due to inhibition of the enzyme uridinediphosphoglucoronoside (UDP)-glucuronosyltransferase that is the enzyme involved in Gilbert's syndrome. Hyperbilirubinemia is significantly higher in patients homozygous or heterozygous for the Gilbert's syndrome mutant allele[50]. Despite this frequency, severe hepatotoxicity has been reported in only 3.4% of patients and in whom therapy must be ceased.

Saquinavir. Severe hepatitis due to saquinavir is uncommon. In clinical trial NV 14256 less than 1% of patients developed hypertransaminemia. Levels of saquinavir, when used in combination with ritonavir may rise 20 times and the combination is discouraged[51].

Nelfinavir. It appears to be safer than the other protease inhibitors. A retrospective study of

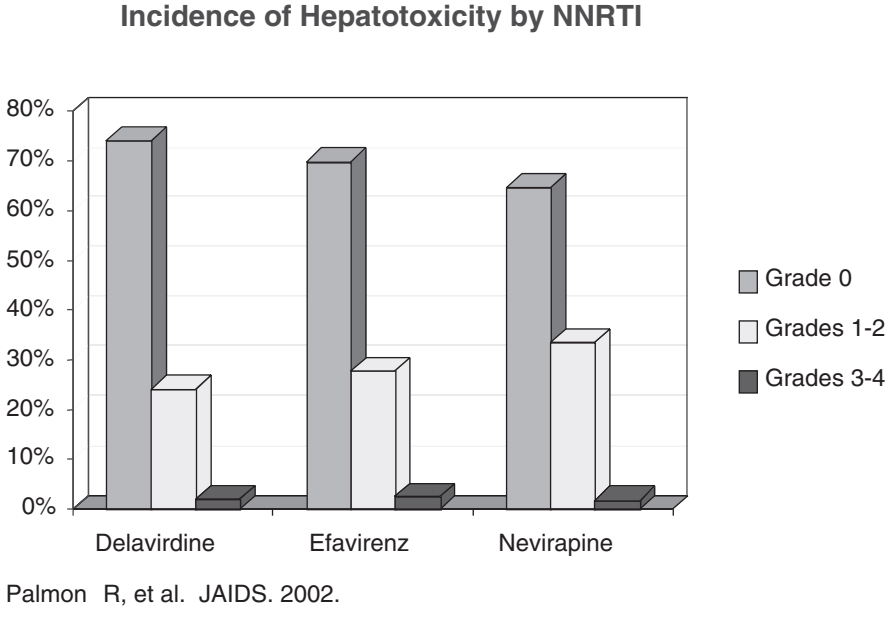


Figure 3. *Incidence of mild, moderate and severe hepatotoxicity in patients treated with NNRTIs.*

1168 HCV/HIV co-infected patients receiving PI therapy for longer than 3 months was performed[52]. 38% of patients received NFV therapy and the remainder received other protease inhibitors: indinavir (32%), saquinavir (16%), ritonavir (13%) and amprenavir (1%). The rate of grade 3-4 hepatotoxicity was 3% in the NFV treated group compared to 8% in the non-NFV group.

Amprenavir. There are few reports of amprenavir hepatotoxicity in the literature. In a review of data from 358 adults and 268 children enrolled in phase II and III studies severe hepatotoxicity related to amprenavir was rare[53].

Conclusions

Hepatotoxicity is a serious complication in patients taking HAART. There is strong evidence that coinfection with hepatitis viruses increases the risk of hepatotoxicity while taking antiretroviral therapy. Certain precautions may be taken to reduce this risk. Baseline transaminases should be checked and all patients should be screened for pre-existing liver disease, most notably hepatitis B and C infections. Hepatitis C in HIV-infected patients may not be easily detectable, as coinfection tends to reduce seropositivity with the usual anti-HCV antibody tests (EIA or RIBA). Thus all HIV-infected patients should be further evaluated for the presence of HCV-RNA using a sensitive polymerase chain reaction (PCR) assay.

Regular monitoring of transaminases is mandatory when commencing antiretroviral therapy. Patients may be splitted in two groups –those with normal liver function and those with pre-existing liver disease or cirrhosis. In patients with normal liver function, we recommend transaminases be checked monthly after commencing HAART for the first 3 months. If stable this can be broadened to 3 monthly intervals. In patients with pre-existing liver disease monitoring should be performed more frequently (2 weekly) when initiating therapy. Once stable LFT should be checked monthly.

The less hepatotoxic drugs such as lamivudine and abacavir should be preferred in patients at high risk for hepatotoxicity. Risks include coinfection with hepatitis B and C viruses, a previous record of hepatotoxicity, cirrhosis, obesity and female sex. Minor enzyme elevations (<5 x normal limit) are generally safe to tolerate and usually resolve. Patients must be closely observed with regular liver function tests and a hypersensitivity type drug reaction should be excluded. The onset of clinical symptoms, elevated serum lactate or evidence of severe hepatic dysfunction (coagulopathy or elevation of ammonia levels) are suggestive of severe toxicity and HAART should be withheld.

Severe liver enzyme elevations should not only prompt evaluation for HAART related hepatotoxicity, but also other causes of liver injury. Acute viral hepatitis, opportunistic infections and alcohol or drug abuse need to be considered in the differential diagnosis. Biochemical, toxicological and virological testing should be performed. Liver biopsy will frequently provide the diagnosis.

Treatment of suspected HAART related hepatotoxicity should first involve withdrawal of therapy. Hypersensitivity reactions may be treated with corticosteroids. NRTI-induced mitochondrial toxicity may improve with riboflavin or thiamine therapy[54,55].

Careful monitoring is required in patients with HIV infection who are receiving HAART and thoughtful consideration should be given to all potential causes of liver enzyme elevation. As is many other medical decisions, an individual analysis of the risk to benefit ratio must be made with all drug therapy.

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