

Review Article

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## Antiretroviral Therapy that Includes, Protease Inhibitors - Induced Hepatotoxicity: A Review

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### ABSTRACT

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Human immunodeficiency virus (HIV) is a retro virus known to be the primary aetiological agent of Acquired Immunodeficiency syndrome (AIDS). It is reported that about 39 million people globally are living with HIV. HIV infected patients are frequently present with elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). This has been often attributed to the hepatic effects of Antiretroviral- Protease Inhibitor drugs (PI's). A review of cohort studies investigating the incidence of hepatotoxicity among patients receiving Antiretroviral- Protease inhibitor drugs suggests that the overall rate of ALT and AST elevations is similar among all Protease inhibitor drugs and considering the importance of drug induced hepatotoxicity as major cause of liver damage, this review also throws light on protease inhibitor drugs which induce hepatotoxicity, with their mechanism of liver damage and clinical scenario.

### Introduction

HIV is a retrovirus known to be the primary cause of Acquired Immune deficiency Syndrome (AIDS). Due to the large scale of morbidity and mortality it causes, HIV is fast becoming a major threat in developing countries including the Indian sub-continent. Infection with HIV is associated with prolonged latent period during which the virus continues to actively replicate, usually resulting in symptomatic illness. (1)

#### Antiretroviral Therapy

The introduction of combination of antiretroviral therapy has led to significant

reduction in morbidity and mortality associated with HIV infections.(2) There are different combination therapies presenting activity against both wild-type and multidrug resistant HIV.

Pharmaceutical agents that can be combined to make up highly active antiretroviral therapy (HAART) can be divided into three categories, namely, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), based on their mechanism of action.

With inception of highly active antiretroviral therapy (HAART), the quality of life of HIV infected individuals is gradually improving. The number of people contacting new infections has been on decline globally and those having access to HAART are increasing.

### **Hepatotoxicity**

Hepatotoxicity is a general term for liver damage. Medications, including those used to treat HIV infection, may cause hepatotoxicity. Drug induced hepatic injury is currently responsible for < 50% of cases of acute liver failure in the united states.(3) The mechanisms of antiretroviral-induced hepatic toxicity include dose-dependent toxicity, idiosyncratic reactions, hypersensitivity reactions, mitochondrial toxicity and immune reconstitution.(4)

Antiretroviral drugs, particularly nevirapine and ritonavir-boosted protease inhibitors, may cause hepatitis.(5-10) The risk of development of hepatitis is higher in patients with pre-existing liver problems, especially those with HBV and HCV co-infection.(11-13)

### **Classification of Hepatotoxicity**

Liver toxicity is defined as an increase in Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) levels 5 times above the upper limit of normal (corresponding to WHO grade 3-4 toxicity). There has been discrepancy in the classification of hepatotoxicity.

A standard toxicity grade scale is available and is used by AIDS research group. Patients with normal AST and ALT levels before treatment are classified with respect to changes relative to the upper limit of normal UNL.

Hepatotoxicity is classified as grade 0 (<1.25× ULN); grade 1(1.25-2.5× ULN); grade 2 (2.6- 5× ULN); grade 3 (5.1-10× ULN) and grade 4 (>5×ULN). Severe hepatotoxicity is defined as grade 3 and grade 4 changes in AST and/or ALT levels during highly active antiretroviral therapy.

### **Protease Inhibitors**

**Ritonvir:** 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.(14) 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 in to therapy. (15, 16) However the most common laboratory finding in patients on indinavir is unconjugated hyperbilirubinaemia seen in upto 40% of patients. (17) This occurs due to inhibition of the enzyme uridinediphosphoglucoronoside (UDP) – Glucuronosyl transferase that is the enzyme involved in Gilbert's syndrome mutant allele.(18) 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. (19)

**Nelfinavir:** It appears to be safer than the other protease Inhibitors, A retrospective study of 118 HCV/ HIV coinfecting patients

receiving PI therapy for longer than 3 months was performed.(20) 38% of patients receiving NFV therapy and remainder received other protease Inhibitors, indinavir 32%, saquinavir 16%, ritonavir 13% and ampernavir 1%. The rate of grade 3-4 hepatotoxicity was 3 & in 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. (21)

**Mechanism of PI – related Hepatotoxicity**

Substrates of P-glycoprotein, an ATP-dependent efflux membrane multidrug resistance transporter, comprise one class of molecules that can limit the absorption of most PIs. For example, oral administration of saquinavir, indinavir, or nelfinavir in

knockout mice lacking this transporter resulted in two- to fivefold increases in plasma drug concentrations.(37) Higher plasma drug of Hepatology concentrations can therefore produce toxicities in human patients that might lack P-glycoprotein. While drug interactions should be examined closely whenever prescribing medication in combination with PIs, this is a particularly important consideration with ritonavir, given its powerful inhibition of cytochrome p450 (CYP) 3A4 and its effects on several other mechanisms of drug interactions.(38) These can lead to increased levels of many coadministered medications, and consequently ADRs. Moreover, there is a potential for interaction with nutritional supplements.(39) Physicians should also be aware that patients with chronic viral hepatitis coinfection have additional impairment of CYP3A activity in the presence of ritonavir, compared to HIV patients without viral hepatitis, even at the low doses of 100 mg/day typically used for pharmacokinetic boosting.(40)

**Table.1** Incidence of hepatotoxicity in registration trials for selected HIV-1 Protease inhibitors

<b>Drug</b>	<b>Definition of liver injury</b>	<b>No. of patients studied</b>	<b>Incidence,cases/100 patients exposed</b>
Saquinavir (22)	ALT or AST >5* ULN	442	5.7
Indinavir (23)	ALT or AST >5* ULN Total bilirubin, 2.5* ULN	1220	2.6–4.9 6.1–11.9
Ritonavir (24)	ALT >215 IU/L, AST >180 IU/L	1270	5.3–9.5
Lopinavir/ritonavir (25)	ALT >215 IU/L, AST >180 IU/L	612	2.2–9.5
Nelfinavir (26)	ALT or AST >5*ULN	1297	1–2
Atazanavir (27)	ALT or AST >5*ULN Total bilirubin >2.5*ULN	1056	22–47

**Note:**Data are abstracted from the US Food and Drug Administration–approved prescribing information for each drug. AST, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

**Table.2** Incidence of hepatotoxicity in published cohort studies for selected HIV-1 protease inhibitors (PIs).

Study Design	No. of Patients studied	Prevalence of HCV infection %	Definition of Hepatotoxicity	Incidence of Hepatotoxicity, in cases/100 patients exposed, by drug or regimen.						Reference
				Over all	R T V	I D V	S Q V	N F V	other regimens	
Retrospective	748	28	ALT >5*ULN or ALT >200 IU/mL	8.5	-	-	-	-	-	(28)
Prospective	211	52	AST or ALT >5*ULN or 3.5*abnormal baseline level	10.4	27.3	6.8	5.9	5.9	-	(29)
Retrospective	1047	26	ALT or ALT >5*ULN	5	-	-	-	-	-	(30)
Retrospective	394	14	AST or ALT >5*ULN and 1100 IU above baseline ALT level	18	-	-	-	-	-	(31)
Prospective	208	19.2	AST or ALT >5*ULN and 1100 IU above baseline ALT level	-	-	-	-	-	RTV + SQV	(32)
Retrospective	222	38	AST or ALT >5*ULN or 3.5* abnormal baseline level	10	-	-	-	-	-	(33)
Retrospective	1250	46.5	ALT *200 IU/mL	7.9	6.1	4.1	6.1	1.3	-	(34)
Retrospective	1477	48.1	ALT or AST above baseline level	7.8	9.1	4.7	5.2	3.4	-	(35)
Retrospective	560	10.7	AST or ALT >10*ULN and 1200 IU above baseline ALT level	7.9	-	-	-	-	-	(36)

**NOTE.** ALT, alanine aminotransferase; AST, aspartate aminotransferase; d4T, stavudine; HBV, hepatitis B virus; HCV, hepatitis C virus; LAM, lamivudine; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NVP.

## Tests

### Liver function tests (LFTs)

These tests measure whether liver is being damaged. (Things that can damage the liver are viral hepatitis, alcohol, medications, and street drugs.) These tests measure alkaline phosphatase, ALT, AST, albumin and bilirubin. It is important to have a baseline measure of liver health, because it may need to take HIV medications in the future, and some of these medications can cause liver damage.

## Hepatitis A, B, and C

Liver is an organ that processes almost everything put into body, including drugs. The three most common types of viral hepatitis (A, B, and C) can damage liver.

Some of the same behaviours that put people at risk for HIV (unprotected sex, injection drug use) can put them at risk for hepatitis.

If you have both HIV and hepatitis B or C, your treatments for either disease can be affected. If you have HIV, your hepatitis may progress faster. If your liver is damaged

from hepatitis, it may be harder for your body to process your HIV medications. What's more, some HIV treatments can damage your liver, so if you have hepatitis, your doctor may want you to try other treatments

In conclusion, hepatotoxicity of Ritonavir, Indinavir, Saquinavir, Nelfinavir became more evident after the introduction of ART (Anti retrovirals) of high activity, which initially included invariably protease Inhibitors.

Based on the review of drug induced hepatotoxicity, it has been found that none of the studies has been able to prove the higher potential for liver toxicity of this particular family of drugs.

Among the PI's, in some studies full dose ritonavir (RTV) has been found to be more hepatotoxic.(41) Although these results have not been confirmed by others. (42,43) In certain cases, RTV has caused fatal acute hepatitis.(44) Several cases of liver toxicity associated with the use of indinavir (IDV ) and saquinavir (SQV) have also been reported.(45) Nelfinavir was found to be less hepatotoxic than the other PI's analyzed (RTV, IDV, SQV, APV) in study evaluating 1052 patients. (46)

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