Review Article

HIV-Antiretroviral Therapy Induced Liver, Gastrointestinal, and Pancreatic Injury

Manuela G. Neuman,1, 2 Michelle Schneider,3 Radu M. Nanau,1, 2 and Charles Parry3, 4

1 Departments of Clinical Pharmacology and Toxicology, and Global Health, University of Toronto, ON, Canada M5G 1X8
2 In Vitro Drug Safety and Biotechnology, University of Toronto, MaRS Discovery District, 101 College Street, Suite 300, Lab 351, Toronto, ON, Canada M5G 1L7
3 Alcohol & Drug Abuse Research Unit, Medical Research Council, Tygerberg (Cape Town), South Africa
4 Department of Psychiatry, Stellenbosch University, Tygerberg (Cape Town), South Africa

Correspondence should be addressed to Manuela G. Neuman, Manuela.neuman@utoronto.ca

Received 26 November 2011; Revised 30 December 2011; Accepted 1 January 2012

Academic Editor: Lawrence Cohen

Copyright © 2012 Manuela G. Neuman et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The present paper describes possible connections between antiretroviral therapies (ARTs) used to treat human immunodeficiency virus (HIV) infection and adverse drug reactions (ADRs) encountered predominantly in the liver, including hypersensitivity syndrome reactions, as well as throughout the gastrointestinal system, including the pancreas. Highly active antiretroviral therapy (HAART) has a positive influence on the quality of life and longevity in HIV patients, substantially reducing morbidity and mortality in this population. However, HAART produces a spectrum of ADRs. Alcohol consumption can interact with HAART as well as other pharmaceutical agents used for the prevention of opportunistic infections such as pneumonia and tuberculosis. Other coinfections that occur in HIV, such as hepatitis viruses B or C, cytomegalovirus, or herpes simplex virus, further complicate the etiology of HAART-induced ADRs. The aspect of liver pathology including liver structure and function has received little attention and deserves further evaluation. The materials used provide a data-supported approach. They are based on systematic review and analysis of recently published world literature (MedLine search) and the experience of the authors in the specified topic. We conclude that therapeutic and drug monitoring of ART, using laboratory identification of phenotypic susceptibilities, drug interactions with other medications, drug interactions with herbal medicines, and alcohol intake might enable a safer use of this medication.

1. Introduction

Knowledge about indications for antiretroviral therapy (ART) use in chronically human immunodeficiency virus (HIV-) infected patients, relative efficacy of different regimens, patient evaluation, and laboratory monitoring are essential in the success of viral eradication. There are different combination therapies presenting activity against both wild-type and multidrug resistant HIV.

Side effects of these therapeutic interventions include adverse drug reactions (ADRs) such as direct hepatocytotoxicity, hypersensitivity syndrome reactions (HSRs), nausea, headache, diarrhea, and pancreatic toxicity. An ADR represents any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy [1].

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), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs), based on their mechanism of action. 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 [2]. Higher plasma drug
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 [3]. These can lead to increased levels of many coadministered medications, and consequently ADRs. Moreover, there is a potential for interaction with nutritional supplements [4].

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 [61].

The various ADRs associated with ART use encountered predominantly in the liver, including HSRs, as well as throughout the gastrointestinal (GI) system, including the pancreas, are presented hereinafter and summarized in Table 1.

2. Hepatotoxicity

Mendes-Corrêa et al. argue that liver damage exists in HIV patients independent of ART exposure [62].

In general, severe hepatic injury occurs in HAART patients, regardless of their treatment [63]. In his last published work, Zimmerman stated unequivocally that the necroinflammatory changes that can be seen in drug-related hepatotoxicity can overlap with those of chronic viral hepatitis [64].

The importance of histological changes in the diagnosis of drug-induced toxicity, its disease spectrum, and the fine structures of hepatocytotoxicity are considered in the discussion section. In the present section, we bring forth only evidence shown by investigators in their work, which is also summarized in Table 1.

Careful review of medication, both prescription and nonprescription, should be compiled in patients with new symptoms or signs of hepatitis, in order to address the possibility of drug toxicity.

Hepatic mitochondrial damage was found in ART-naive patients as well as patients exposed to the NRTIs zidovudine or didanosine [62]. The intensity of dense granules was higher in mitochondria from previously untreated patients, compared to current ART patients (P < 0.05). Qualitative analyses showed areas of mitochondrial hyperplasia, with changes in shape (elongation, baloonization, bizarre shapes) and size (megamitochondria) in both groups. There were also increases in the numbers of dense granules, matrix condensation, crista loss, lamellar distributed filamentous material, and crystallloid material [62].

The levels of $^{13}$C-methionine exhaled, a measure of hepatic mitochondrial function, increased significantly in ART-naive patients after treatment initiation (P < 0.001) [5]. $^{13}$C exhalation continued to decrease in ART-naive patients who continued to remain naive (P = 0.04), as well as patients who stopped treatment (P = 0.043). No changes in the $^{13}$C-methionine breath test results were observed among ART-experienced patients who did not change their treatment (P = 0.31) or changed only the PI and NNRTI components of their treatments (P = 0.34), or among patients who remained on structured treatment interruption (P = 0.068). Reinitiation of ART led to significant improvements (P = 0.008) [5]. A switch from didanosine or stavudine to tenoforiv or abacavir also led to a significant improvement in $^{13}$C-methionine breath test performance (P < 0.001) [5].

Hepatotoxicity is a relatively common ADR leading to treatment interruptions in HIV patients, observed with different drug combinations (Table 1) [6–27]. Among these, nevirapine was often associated with the development of hepatotoxicity [8, 9, 12, 13, 15, 16, 18, 20, 22, 23, 25]. Nevirapine use was associated with a higher incidence of liver toxicity than efavirenz use [14]. The use of PIs in combination with either efavirenz or nevirapine was associated with an increased risk of hepatotoxicity compared to efavirenz or nevirapine alone (odds ratio (OR) 3.07, 95% confidence interval (CI) 1.01–9.32, P = 0.04) [65].

Increases in liver enzymes are also common ADRs characteristic of different ART regimes (Table 1) [20, 28–35, 66]. Increases in alanine aminotransferase (ALT) or/and aspartate aminotransferase (AST) are common symptoms of hepatotoxicity, while increases in alkaline phosphatase and y-glutamyl transpeptidase were indicative of cholestasis in one study [66].

The median delay between HAART initiation and occurrence of hepatotoxicity was 2.5 months (interquartile range (IQR) 1 to 11 months) in one study [17] and 5 weeks (IQR 3 to 29 weeks) in another study [18]. While a similar number of patients discontinued nevirapine due to hepatotoxicity before month 3 and after a mean number of 9 months in another study [13], van Griensven et al. observed that only 27.6% of 29 cases of nevirapine hepatotoxicity occurred after 6 months of treatment [18].

One study found hepatitis to occur with a similar frequency among zidovudine/lamivudine, zidovudine/didanosine, or stavudine/lamivudine patients [27], whereas a separate study found a higher incidence of hepatotoxicity among stavudine/lamivudine patients [19].

Hepatic events were the most common drug ADRs associated with atazanavir/ritonavir [24]. Jaundice was also observed among atazanavir/ritonavir patients [24, 33, 36], but not among lopinavir/ritonavir patients [33]. Similarly, grade ≥3 increases in total bilirubin levels occurred more frequently in the atazanavir/ritonavir group than in the lopinavir/ritonavir group [33]. Acute liver failure, accompanied by jaundice, fever, vomiting, and hepatomegaly, was observed in a 10-year-old male [67]. The patient’s condition started improving following liver transplantation and replacement of efavirenz with raltegravir [67]. Bilirubin levels did not affect the rate of hepatotoxicity in another study [35]. Grade 3 hyperbilirubinemia/liver toxicity was also observed with nevirapine [21].

Unconjugated bilirubin levels should be monitored in PI patients. The microsomal enzyme uridine diphosphate
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|------------------|----------------------------|---------|
| 113 patients, 97 (85.8%) men | Germany | Stavudine/didanosine-based \((n = 73 (64.6\%))\) | Hepatic mitochondrial toxicity | | Stavudine and didanosine | [5] |
| 122 patients, 90 (73.8%) men | Germany | Zidovudine, lamivudine, abacavir, tenofovir | Hepatotoxicity | 1 (0.8\%) case | Tenofovir | [6] |
| 600 adults, 430 (71.7\%) women | Uganda | Zidovudine, lamivudine, abacavir \((n = 300 (50.0\%))\), lamivudine, nevirapine \((n = 300 (50.0\%))\) | Grade 4 liver function test abnormalities (ALT or/and AST raised >10 times over the upper limit of normal), including acute hepatitis/hepatic failure | | Zidovudine Lamivudine Nevirapine | [7] |
| 133 pregnant women | Brazil | Nevirapine-based | Grade ≤3 hepatotoxicity (ALT or/and AST raised ≤5 times over the upper limit of normal) | 6 (4.5\%) cases | Nevirapine | [8] |
| 409 patients | Thailand | Zidovudine, lamivudine, nevirapine Stavudine, lamivudine, nevirapine | Hepatotoxicity, including asymptomatic hepatitis, symptomatic hepatitis or hepatitis occurring concomitant with rash | 64 (15.6\%) cases, including 19 (4.6\%) symptomatic cases | Likely nevirapine | [9] |
| 142 patients: 105 (73.9\%) men, 124 (87.3\%) white | Spain | Nevirapine-based Zidovudine, lamivudine \((n = 65 (45.8\%))\), Stavudine, lamivudine \((n = 34 (23.9\%))\), Stavudine, didanosine \((n = 33 (23.2\%))\) Other combinations \((n = 10 (7.0\%))\) | Hepatotoxicity (ALT or/and AST raised >5 times over the upper limit of normal) Clinical hepatitis (ALT or/and AST raised >5 times over the upper limit of normal and/or nausea, asthenia, jaundice) | 8 (5.63\%) cases | Nevirapine | [10] |
| 157 pregnant women | Brazil | Zidovudine, lamivudine, nevirapine | Grade ≤3 hepatotoxicity | 7 (4.4\%) cases | Nevirapine | [11] |
| 540 patients | Niger | Stavudine, lamivudine, nevirapine | Grade ≤3 hepatotoxicity (ALT or/and AST raised ≤5 times over the upper limit of normal) Cutaneous ADRs | 78 (15.7\%) cases, including 6 (1.2\%) grade 3 cases 7 (1.3\%) cases, including 5 (0.9\%) rash cases and 2 (0.4\%) pruritus cases | Nevirapine | [12] |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|------------------|---------------------------|---------|
| 315 children median age 7.2 years: 158 (50.2%) girls | Rwanda | Stavudine, lamivudine, nevirapine ($n = 281$ (89.2%)). Stavudine, lamivudine, efavirenz ($n = 6$ (1.9%)) Zidovudine, lamivudine, nevirapine ($n = 19$ (6.0%)). Zidovudine, lamivudine, efavirenz ($n = 9$ (2.9%)) | Severe hepatotoxicity, including asymptomatic hepatitis, symptomatic hepatitis, and clinical hepatitis | 5 (1.7% of 300 nevirapine patients) cases before month 3, including 4 clinical hepatitis cases and 1 grade 3 asymptomatic case | Nevirapine | [13] |
| 8736 patient records | Tanzania | Various combinations | Liver toxicity | Higher in nevirapine patients than in efavirenz patients | Nevirapine Efavirenz | [14] |
| 253 women, 42 (16.6%) pregnant | United States | Nevirapine-based Zidovudine/lamivudine most common NRTI backbone | Hepatitis, including late-onset hepatitis Rash with concomitant hepatitis Grade 1 rash | 3 (1.2%) cases 2 (0.8%) cases 1 (0.4%) case | Nevirapine | [15] |
| 1110 patients, 631 (56.8%) men | Argentina | Nevirapine-based | Hepatotoxicity (ALT or/and AST raised >5 times over the upper limit of normal for patients with previously normal levels or >3.5 times over the baseline level for patients with abnormal basal levels) Severe rash | 35 (3.2%) cases 49 (4.4%) cases | Nevirapine | [16] |
| 290 women, 125 (43.1%) pregnant | Côte d’Ivoire | Zidovudine, lamivudine, nevirapine ($n = 265$ (91.4%)). Stavudine, lamivudine, nevirapine ($n = 25$ (8.6%)) | Hepatotoxicity (ALT or/and AST raised >5 times over the upper limit of normal) Rash | 10 (3.4%) cases 15 (5.2%) cases | Not specified Likely nevirapine | [17] |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|------------------|---------------------------|---------|
| 2190 adults, 1567 (71.5%) women | Rwanda | Stavudine, lamivudine, nevirapine | Hepatotoxicity (assessed based on ALT levels) | 29 (1.3% of entire sample and 21.0% of 138 patients who stopped treatment due to nevirapine toxicity) cases | Nevirapine | [18] |
| | | | Skin rash | 108 (4.9% of entire sample and 78.3% of 138 patients who stopped treatment due to nevirapine toxicity) cases | Nevirapine | |
| 546 patients, 378 (69.2%) men | Peru | Lamivudine with either zidovudine (76% of cases), stavudine, or didanosine. Other drugs were nevirapine (n = 314 (57.5%)), efavirenz (n = 210 (38.5%)), lopinavir/ritonavir (n = 19 (3.5%)), atazanavir/ritonavir (n = 2 (0.4%)), or indinavir (n = 1 (0.2%)) | Hepatotoxicity | 7 (2.3%) cases | Not specified | [19] |
| 765 patients: 614 (80.3%) men, 311 (40.6%) white, 265 (34.6%) black, 161 (21.0%) Hispanic | United States | Zidovudine, lamivudine, efavirenz (n = 380 (49.7%)). Zidovudine, lamivudine, abacavir, efavirenz (n = 373 (48.8%)) | Grade 4 hepatotoxicity (ALT or/and AST, total bilirubin, direct bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase raised >10 times over the upper limit of normal) | 3 (4.3% of 70 patients who substituted efavirenz with nevirapine due to efavirenz toxicity) cases | Nevirapine | [20] |
| | | | Grade 3 hyperbilirubinemia (bilirubin raised 3–10 times over the upper limit of normal) | 18 (2.4%) cases 5 (33.3% of 15 patients who substituted efavirenz with nevirapine due to efavirenz toxicity) cases | Nevirapine | |
| | | | Skin symptoms | 2 (2.2% of 92 HAART-treated pregnancies) cases | Likely nevirapine | |
| 103 pregnant women: 38 (36.9%) Caucasian, 24 (23.3%) Aboriginal | Canada | Nevirapine-based (n = 56 (54.4%)) | Grade 4 hepatotoxicity (ALT or/and AST raised >10 times over the upper limit of normal) Grade 3 hyperbilirubinemia (bilirubin raised 3–10 times over the upper limit of normal) Grade 2 rash and fever | 1 (1.1% of 92 HAART-treated pregnancies) cases | Nevirapine | [21] |
| | | | | 2 (2.2% of 92 HAART-treated pregnancies) cases | Likely nevirapine | |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|-------------------|---------------------------|---------|
| 137 patients, 103 (75.2%) men | Spain | Didanosine, stavudine, nelfinavir ($n = 67$ (48.9%)), Didanosine, stavudine, nevirapine ($n = 70$ (51.1%)) | Grade 4 rash | 1 (1.1% of 92 HAART-treated pregnancies) cases | Nevirapine | [22] |
| 573 patients, 366 (63.9%) men | Italy | Nevirapine-based 213 (37.2%) were taking zidovudine. 289 (50.4%) were taking stavudine. 71 (12.4%) were taking thymidine analogues. 97 (16.9%) were taking PIs | Hepatotoxicity | 44 (22.3% of 197 toxicity-related treatment interruptions) cases, including 5 cases of grade 3 AST elevations and 11 cases of grade 3 ALT elevations | Nevirapine and/or NRTIs | [23] |
| 1318 patients, 967 (73.4%) men | Switzerland | Tenofovir, emtricitabine, atazanavir/ritonavir ($n = 144$ (10.9%)), Tenofovir, emtricitabine, efavirenz ($n = 374$ (28.4%)), Tenofovir, emtricitabine, lopinavir/ritonavir ($n = 216$ (16.4%)), Tenofovir, emtricitabine, nevirapine ($n = 50$ (3.8%)), Zidovudine, lamivudine, efavirenz ($n = 77$ (5.8%)), Zidovudine, lamivudine, lopinavir/ritonavir ($n = 204$ (15.5%)), Abacavir, lamivudine, efavirenz ($n = 77$ (5.8%)) | Hepatic events | 152 (11.5%) cases, including 42 (29.2%) of 144 atazanavir/ritonavir patients | Atazanavir/ritonavir (OR 2.55, 95% CI 1.01–6.42, $P = 0.047$) | Other drugs | [24] |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|------------------|---------------------------|---------|
| Zidovudine/lamivudine, zidovudine/didanosine, or stavudine/lamivudine. 325 (50.0%) were taking nevirapine and 325 (50.0%) were taking efavirenz | Botswana | Zidovudine/lamivudine | Hepatotoxicity | 11 (3.4% of 325 nevirapine patients) cases | Nevirapine | [25] |
| Efavirenz-based (n = 117 (62.2%). Lopinavir/ritonavir-based (n = 71 (37.8%)) | Spain | Efavirenz-based | Hepatotoxicity | 8 (5.1% of 117 efavirenz patients and 2.8% of 71 lopinavir/ritonavir patients) cases | Efavirenz | [26] |
| Zidovudine, lamivudine (n = 1336 (59.8%)). Zidovudine, didanosine (n = 1022 (45.8%)). Stavudine, lamivudine (n = 1154 (51.7%)). Stavudine, didanosine (n = 772 (34.6%)). Didanosine, lamivudine (n = 258 (11.6%)) | United States | Zidovudine, lamivudine | Hepatitis | 56 (1.6% of 1336 zidovudine/lamivudine patients, 1.6% of 1022 zidovudine/didanosine patients, 1.6% of 1154 stavudine/lamivudine patients) cases | Zidovudine and lamivudine | [27] |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|-------------------|---------------------------|---------|
| Bilirubin elevations | 11 (0.5%) cases | Stavudine and lamivudine | 27 (4.4%) cases | Grade ≥2 liver enzyme elevations (graded according to the Toxicity Tables of the Division of Acquired Immunodeficiency Syndrome) | Stavudine and lamivudine Stavudine and didanosine Lamivudine and didanosine Zidovudine and lamivudine Zidovudine and didanosine | [31] |
| Pancreatitis (assessed by routine monitoring of total amylase levels) | 13 (1.7% of 772 stavudine/didanosine patients) cases | Stavudine and didanosine | 3 (6.1%) cases | Grade ≤3 elevated AST and γ-glutamyl transpeptidase | Treatment-related | [28] |
| Pancreatitis (assessed by routine monitoring of total amylase levels) | 2 (6.1%) cases | Nevirapine and hepatitis A virus coinfection | 6 (2.1%) cases | Grade ≤3 elevated ALT/AST | Nevirapine and nevirapine | [29] |
| Pancreatitis (assessed by routine monitoring of total amylase levels) | 6 (2.1%) cases | Zidovudine and didanosine | 27 (4.4%) cases | Grade ≥2 liver enzyme elevations (graded according to the Toxicity Tables of the Division of Acquired Immunodeficiency Syndrome) | Stavudine | [30] |
| Rash | 2 (1.2%) cases | Zidovudine and didanosine | 27 (4.4%) cases | Grade ≥2 rash (graded according to the Toxicity Tables of the Division of Acquired Immunodeficiency Syndrome) | Nevirapine and/or other drugs | [31] |
| Rash | 30 (5.7%) of 526 patients who developed a new rash after therapy initiation | Nevirapine and/or other drugs | 27 (4.4%) cases | Grade ≥2 liver enzyme elevations (graded according to the Toxicity Tables of the Division of Acquired Immunodeficiency Syndrome) | Nevirapine and/or other drugs | [31] |
| Rash | 1 (0.6%) of 152 nevirapine patients | Nevirapine | 27 (4.4%) cases | Grade ≥2 liver enzyme elevations (graded according to the Toxicity Tables of the Division of Acquired Immunodeficiency Syndrome) | Nevirapine and/or other drugs | [31] |
| Rash | 1 (0.6%) of 152 nevirapine patients | Nevirapine and/or other drugs | 27 (4.4%) cases | Grade ≥2 liver enzyme elevations (graded according to the Toxicity Tables of the Division of Acquired Immunodeficiency Syndrome) | Nevirapine and/or other drugs | [31] |
| Rash | 1 (0.6%) of 152 nevirapine patients | Nevirapine and/or other drugs | 27 (4.4%) cases | Grade ≥2 liver enzyme elevations (graded according to the Toxicity Tables of the Division of Acquired Immunodeficiency Syndrome) | Nevirapine and/or other drugs | [31] |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|-------------------|---------------------------|---------|
| 88 children mean age 10.2 years: 51 (58.0%) girls, 38 (43.2%) white, 26 (29.5%) black | Switzerland | Lopinavir/ritonavir-based | AST elevation (185 IU/L) | 1 (1.1%) case | Lopinavir/ritonavir | [32] |
|                   |                |           | HSR  |                   | Lopinavir/ritonavir        |         |
|                   |                |           | GI toxicity, including hepatic and pancreatic symptoms | 5 (5.7%) cases | Lopinavir/ritonavir |         |
|                   |                |           | Amylase elevation without serum lipase elevation (870 IU/mL) | 1 (1.1%) case | Lopinavir/ritonavir |         |
| 883 patients, 606 (68.6%) men | Worldwide | Tenofovir, emtricitabine, atazanavir/ritonavir (n = 440 (49.8%)). Tenofovir, emtricitabine, lopinavir/ritonavir (n = 443 (50.2%)) | Grade ≥3 increases in ALT/AST | 25 (3.9%) of 435 atazanavir/ritonavir patients and 1.8% of 431 lopinavir/ritonavir patients cases | Atazanavir/ritonavir | [33] |
|                   |                |           | Grade ≥3 increases in total bilirubin levels | 146 (33.6%) of 435 atazanavir/ritonavir patients cases | Lopinavir/ritonavir |         |
|                   |                |           | Jaundice No mention of Gilbert syndrome or hemolysis | 3 (0.7% of 440 atazanavir/ritonavir patients) cases | Atazanavir/ritonavir |         |
|                   |                |           | Diarrhea and grade ≥2 nausea | 4 (0.9% of 443 lopinavir/ritonavir patients) cases | Lopinavir/ritonavir |         |
| 40 patients, 20 (50.0%) women | Uganda | Zidovudine, didanosine, lopinavir/ritonavir (n = 36 (90.0%)). Stavudine, didanosine, lopinavir/ritonavir (n = 4 (10.0%)) | Elevated AST levels | 2 (5.0%) cases | Not specified | [34] |
|                   |                |           | Nausea or vomiting | 7 (17.5%) cases | Didanosine and unspecified drugs | Not specified |
|                   |                |           | Diarrhea | 9 (22.5%) cases | Likely didanosine | [35] |
| 49 children, 30 (61.2%) boys | Burkina Faso | Didanosine, lamivudine, efavirenz | Increases in liver enzyme levels | 2 (4.1%) cases | Likely didanosine | [35] |
|                   |                |           | Increases in pancreatic enzyme levels without pancreatitis | 1 (2.0%) case | Likely didanosine | [35] |
| 3333 patients | England | Not specified | Jaundice No mention of Gilbert syndrome or hemolysis | 7 (3.4% of 203 treatment switches) cases | Atazanavir | [36] |
|                   |                |           | Suspected/actual HSR | 5 (2.5% of 203 treatment switches and 62.5% of 8 treatment switches due to abacavir toxicity) cases | Abacavir | [36] |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|------------------|---------------------------|---------|
| 158 patients, 104 (65.8%) men | Italy | Tenofovir, emtricitabine, efavirenz ($n = 41$ (25.9%)). Tenofovir, emtricitabine, various boosted PIs ($n = 46$ (29.1%)). Abacavir, lamivudine, efavirenz ($n = 12$ (7.6%)). Abacavir, lamivudine, various boosted PIs ($n = 41$ (25.9%)). Other combinations including boosted PIs ($n = 18$ (11.4%)) | Early HSR | 2 (3.8% among 53 abacavir patients) cases | Abacavir | [37] |
| 56 patients: 49 (87.5%) men, 26 (46.4%) white, 18 (32.1%) black | United States | Tenofovir, another NRTI, lopinavir/ritonavir, fosamprenavir ($n = 28$ (50.0%)). Tenofovir, other NRTIs, lopinavir/ritonavir ($n = 14$ (25.0%)). Tenofovir, other NRTIs, fosamprenavir/ritonavir ($n = 14$ (25.0%)) | HSR | Abacavir | [38] |
| 600 patients, 430 (71.7%) women | Uganda | Zidovudine, lamivudine plus either abacavir or nevirapine | Suspected HSR (grade ≥3) | 15 (3.0% of 300 nevirapine patients and 2.0% of 300 abacavir patients) cases | Nevirapine | Abacavir | [39] |
| 357 HLA B*5701-negative adults: 348 (97.5%) men, 307 (86%) white | Australia | Tenofovir and emtricitabine, or abacavir and lamivudine. Other drugs included zidovudine, didanosine, stavudine, atazanavir, lopinavir, efavirenz or nevirapine | HSR | Abacavir | [40] |
| 385 HLA-B*5701-negative adults 313 (81.3%), men 56 (14.5%) black | Europe | Abacavir, lamivudine, efavirenz. Tenofovir, emtricitabine, efavirenz | HSR | Abacavir | [41] |
| Study population                  | Study settings | Treatment                                                   | ADRs                              | Incidence of ADRs                                                                 | Drugs associated with ADRs | Ref. no. |
|----------------------------------|----------------|-------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------|---------------------------|----------|
| 211 children mean age 5 years: 111 (52.6%) boys | Zambia         | Stavudine, lamivudine, nevirapine                           | Grade ≤ 2 rash                    | 15 (7.1% of 211 nevirapine patients and 37.5% of 40 ADRs judged to be definitely/probably related to nevirapine) cases | Nevirapine                | [42]     |
| 57 patients, 39 (68.4%) men      | China          | Stavudine, didanosine, nevirapine (n = 38 (66.7%)), Stavudine, lamivudine, nevirapine (n = 10 (17.5%)), Zidovudine, lamivudine, nevirapine (n = 9 (15.8%)) | Rash (including grade 3 rash)     | 3 (5.3%) cases                                                                   | Likely nevirapine          | [43]     |
| 173 adults, 107 (61.8%) men      | Cambodia       | Efavirenz was substituted with nevirapine                   | Cutaneous HSR                     | 10 (5.8% of 173 patients substituting efavirenz with nevirapine and 52.6% of 19 patients who developed nevirapine-induced treatment-limiting HSRs) cases | Nevirapine                | [44]     |
|                                  |                |                                                             | Hepatic HSR                       | 10 (5.2% of 173 patients substituting efavirenz with nevirapine and 47.4% of 19 patients who developed nevirapine-induced treatment-limiting HSRs) cases | Nevirapine                |          |
| 394 patients, 263 (66.8%) men    | Cambodia       | Stavudine, lamivudine, nevirapine                           | Minor rash                        | 17 (4.3% of 394 patients who switched efavirenz with full-dose nevirapine and 32.7% of 52 cases of nevirapine-induced ADRs cases 49 (7.4% of 661 ART-naive patients commencing nevirapine-based HAART and 51.6% of 95 cases of nevirapine-induced ADRs cases) | Nevirapine                | [45]     |
| Study population                        | Study settings               | Treatment                                                                 | ADRs                                                                                                      | Incidence of ADRs                                                                                                                                                                                                 | Drugs associated with ADRs | Ref. no. |
|----------------------------------------|-----------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|---------|
| Severe HSR, including severe rash,    | Jamaica                     | 77 (63.6%) receiving HAART Zidovudine/lamivudine-based (n = 72 (93.5%)).  | HSR                                                                                                      | 3 (4.2% of 72 nevirapine patients and 3.9% of 77 HAART patients) cases                                                                                                                                       | Nevirapine               | [46]    |
| SJS, TEN and/or hepatitis              |                             | Nevirapine-based (n = 72 (93.5%)). Zidovudine, lamivudine, nevirapine (n = 67 (87.0%)) |                                                                                                           |                                                                                                                                                                                                            |                          |         |
|                                                                                     |                             | Grade ≤ 4 hepatitis                                                                                      |                                                                                                           |                                                                                                                                                                                                            |                          |         |
| 121 adolescents mean age 7 years: 70  | Jamaica                     | Zidovudine/lamivudine-based (n = 72 (93.5%)). Zidovudine, lamivudine,     | Nevirapine                                                                                                 | 124 (1.9% of 4620 nevirapine patients and 27.1% of 458 patients who interrupted nevirapine due to HSRs) cases 334 (5.1% of 4620 nevirapine patients and 72.9% of 458 patients who interrupted nevirapine due to HSRs) cases | Nevirapine               | [47]    |
| (57.8%) boys                          |                             | nevirapine (n = 4620 (45.4%))                                                                 |                                                                                                           |                                                                                                                                                                                                            |                          |         |
| 10186 patients: 7395 (72.6%) men,     | Europe and Canada           | Nevirapine-based (n = 6547) Zidovudine, lamivudine, nevirapine (n = 4620 | Hepatotoxicity without concomitant skin rash                                                               | 124 (1.9% of 4620 nevirapine patients and 27.1% of 458 patients who interrupted nevirapine due to HSRs) cases 334 (5.1% of 4620 nevirapine patients and 72.9% of 458 patients who interrupted nevirapine due to HSRs) cases | Nevirapine               | [47]    |
| 6227 (61.1%) Caucasian                 |                             | (45.4%))                                                                                                 |                                                                                                           |                                                                                                                                  |                          |         |
|                                                                                     |                             |                                                                                                           |                                                                                                           |                                                                                                                                                                                                            |                          |         |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|------------------|---------------------------|---------|
| 217 patients, 122 (56.2%) men | Senegal | Didanosine, lamivudine, efavirenz ($n = 63$ (29.0%)). Stavudine, didanosine, efavirenz ($n = 44$ (20.3%)). Stavudine, lamivudine, efavirenz ($n = 11$ (5.7%)). Zidovudine, lamivudine, efavirenz ($n = 52$ (24.0%)). Lamivudine, zidovudine, nevirapine ($n = 28$ (12.9%)). Didanosine, lamivudine, nevirapine ($n = 8$ (3.7%)). Stavudine, didanosine, nevirapine ($n = 8$ (3.7%)). Stavudine, lamivudine, nevirapine ($n = 3$ (1.4%)) | Hepatitis, including hepatitis with concurrent skin rash | 3 (6.4% of 47 nevirapine patients) cases, including 2 (4.2%) cases with concurrent skin rash | Nevirapine | [48] |
| 230 adults, 172 (74.8%) men | India | Stavudine, lamivudine, nevirapine ($n = 157$ (68.3%)). Stavudine, lamivudine, efavirenz ($n = 18$ (7.8%)). Zidovudine, lamivudine, nevirapine ($n = 41$ (17.8%)). Zidovudine, lamivudine, efavirenz ($n = 14$ (6.1%)) | Hyperamylasemia | 10 (4.6%) cases | Likely efavirenz or nevirapine | 
| 126 patients, 109 (86.5%) men | Spain and Italy | Lamivudine, abacavir, efavirenz ($n = 63$ (50.0%)). Lamivudine, abacavir, lopinavir/ritonavir ($n = 63$ (50.0%)) | HSR/rash | 8 (6.3%) cases | Lopinavir/ritonavir | [50] |
| 21 Caucasian patients, 16 (76.2%) men | France | Efavirenz-based ($n = 7$ (33.3%)). Nevirapine-based ($n = 14$ (66.7%)) | HSR | 6 (28.6%) cases | Efavirenz Nevirapine | [51] |
| 650 adults, 451 (69.4%) women | Botswana | Either zidovudine and lamivudine, zidovudine and didanosine, or stavudine and lamivudine, plus either nevirapine or efavirenz | SJS | 16 (2.5%) cases | Likely nevirapine or efavirenz | [52] |
| Study population | Study settings | Treatment | ADRs | Incidence of ADRs | Drugs associated with ADRs | Ref. no. |
|------------------|----------------|-----------|------|-------------------|---------------------------|----------|
| **66 patients, 56 (84.8%) men** | Spain | Lopinavir/ritonavir-based ($n = 33$ (50.0%)). Nevirapine-based ($n = 33$ (50.0%)). NRTIs were didanosine, stavudine, and/or zidovudine | Diarrhea | 10 (15.2%) cases | Likely nevirapine or lopinavir/ritonavir | [53] |
| **70 patients, 50 (71.4%) men** | Spain | Lopinavir/ritonavir-based | Unspecified GI symptoms assessed using the Gastrointestinal Symptom Rating Scale | 1 (1.4%) case | Lopinavir/ritonavir | [54] |
| **23 patients, 18 (78.3%) men** | Spain | Zidovudine, lamivudine, abacavir, tenofovir | Unspecified GI symptoms | | Lopinavir/ritonavir, tipranavir | [55] |
| **115 patients, 70 (60.9%) men** | France | Indinavir/ritonavir-based | Unspecified GI ADRs | 4 (12.5% among 32 lopinavir/ritonavir patients) cases | Lopinavir/Ritonavir | [56] |
| **1771 patients, 1204 (68.0%) men** | South Africa | Zidovudine, didanosine, efavirenz ($n = 444$ (25.1%)). Stavudine, lamivudine, efavirenz ($n = 444$ (25.1%)). Zidovudine, didanosine, lopinavir/ritonavir ($n = 440$ (24.8%)). Stavudine, lamivudine, lopinavir/ritonavir ($n = 443$ (25.0%)) | Nausea, constipation, fatigue | | Zidovudine and didanosine. Stavudine and lamivudine | [57] |
| **630 patients, 494 (78.4%) men** | Worldwide | Saquinavir/ritonavir-based ($n = 309$ (49.0%)). Lopinavir/ritonavir-based ($n = 163$ (25.9%)). Indinavir/ritonavir-based ($n = 158$ (25.1%)) | Unspecified GI toxicity, including grade ≥3 GI ADRs | | Saquinavir | [58] |
| **12 patients: 11 (91.7%) men, 9 (75.0%) Caucasian, 3 (25.0%) black** | United Kingdom | Saquinavir/ritonavir-based | Mild nausea and diarrhea | 5 (41.7%) cases | Likely treatment-related | [59] |
| **1081 patients, 708 (65.5%) men** | Italy | Not specified | Pancreatic toxicity (at least 3-fold increases in serum pancreatic enzymes) | 166 (38.2% of 435 patients with confirmed laboratory pancreatic abnormalities) cases | Concurrent use of didanosine, stavudine, lamivudine | [60] |
glucuronosyltransferase (UGT) mediates conjugation of bilirubin.

Hyperbilirubinemia is an adverse effect that occurs in approximately 25% of indinavir patients, with total bilirubin rising to the 2.5 to 5 mg/dL range [68]. This represents largely indirect bilirubin and is insignificant except as a possible complication of pregnancy [68, 69]. Atazanavir also appears to impair UGT activity [70], such that the PIs atazanavir and indinavir are associated with hyperbilirubinemia. The relationship between underlying genetic risk factors and the risk of developing hyperbilirubinemia remains unclear. UGT1A1*28 allele was associated with jaundice in a study in which bilirubin levels were not measured [24]. In a study of patients who underwent genotypic analysis for polymorphisms associated with increased unconjugated bilirubin, 64 (66.7%) of 96 patients were positive for the UGT1A1*28 allele. [70]. Ocama et al. found that 23 (29.9%) of 77 consecutive HIV-infected patients presenting with hepatotoxicity (jaundice, right upper quadrant pain with fever or malaise, ascites, and/or tender hepatomegaly) had increased transaminase levels as a result of nevirapine and/or isoniazid hepatotoxicity [71]. Of these 23 patients with drug-induced liver disease, 14 (60.9%) presented with jaundice and recovered after drug discontinuation. Hepatitis B surface antigen was positive in 11 (14.3%) patients while antihapatitis C antibody was reactive in only 2 (2.6%). Granulomatous hepatitis due to tuberculosis was diagnosed in 7 (9.1%) patients. Other diagnoses included alcoholic liver disease, AIDS cholangiopathy, hepatocellular carcinoma, schistosomiasis, hemangiomata, and hepatic adenoma. Twelve (15.6%) patients died during follow-up, of which 7 (9.1%) died because of liver disease [71].

The overall incidence of severe hepatic injury was not significantly different between NRTIs, NNRTIs, and PIs in a sample of 222 patients, of which 84 (37.8%) were coinfected with hepatitis C virus (HCV) [63]. Coinfection with hepatitis viruses is often associated with a higher risk of hepatotoxicity [63, 65]; however this is not always the case [24]. Elevated baseline liver function tests and older age are additional risk factors for hepatotoxicity [18].

3. Hypersensitivity Syndrome Reaction

HSRs have been associated with the NRTI abacavir, the NNRTIs nevirapine and efavirenz, and the PI amprenavir [72–74]. The potential for HSR development symbolizes a treatment-limiting and potentially life-threatening ADR.

Abacavir HSR is the major treatment-limiting toxicity of HAART regimens containing this drug. This ADR usually occurs in the first 6 weeks of treatment [75]. An HSR characterized by some combination of flu-like symptoms, fever, rash, as well as GI symptoms, including hepatotoxicity, generally occurs in 3–5% of patients starting abacavir [76]. Other symptoms of HSR include malaise, lethargy, myalgia, myolysis, arthralgia, edema, pharyngitis, cough, dyspnea, headache, and paresthesia. Physical findings may include lymphadenopathy, mucous membrane lesions (i.e., conjunctivitis, mouth ulcerations), and rash, which usually appears as maculopapular or urticarial, but can also lead to Stevens-Johnson syndrome (SJS).

Differentiation between abacavir HSR and viral respiratory infections can be problematic. Rash (OR 13.1, \( P = 0.02 \)), nausea (OR 30, \( P < 0.001 \)), vomiting (OR 17.1, \( P = 0.001 \)), and diarrhea (OR 22, \( P < 0.001 \)) were associated with HSR in 15 cases of abacavir HSR matched with 30 controls with culture-proven influenza A with no abacavir exposure [77]. The number of GI symptoms was also predictive of HSR (\( P < 0.001 \)). Multivariate analysis confirmed that the number of GI symptoms (OR 8.6, \( P = 0.0032 \)) and rash (OR 16.9, \( P = 0.07 \)) was associated with abacavir HSR. Abacavir HSR-associated rash was typically mild to moderate in this study, occurring after an average of 9–11 days since treatment initiation [77]. Abacavir HSR was found to resolve itself rapidly following treatment modifications [37]. This reaction was observed in other studies as well [36–41].

Abacavir HSR is strongly associated with GI symptoms [77]. Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase or creatinine, and lymphopenia. Liver failure and death have occurred in association with HSR. Symptoms associated with HSR worsen with continued therapy but often resolve upon discontinuation of the drug [78, 79].

It is highly recommended that HSR patients avoid rechallenge with full-dose abacavir, as extremely severe symptoms and even death may result [80]. Reports describe the mechanisms of action, efficacy, and ADRs of abacavir in HIV-1-infected patients and illustrate the danger of serially rechallenging patients with this agent even if the patient was previously desensitized [78, 81–83].

A strong statistical association was identified between the human leukocyte antigen (HLA)-B*5701 allele, part of the major histocompatibility complex, and clinically diagnosed abacavir HSR [84]. While abacavir HSR occurs in approximately 5% of HIV patients treated with this drug, the HLA-B*5701 allele was discovered in 6.3% of 11000 genetic screens performed in a Canadian population [75]. As a consequence, prospective HLA-B*5701 screening is performed to identify patients at high risk for abacavir HSR before they are treated [85]. Genetic screening of potential abacavir patients can greatly help prevent HSRs and it can lead to individualizing of HAART in order to prevent toxicity and to improve adherence [75]. Carriers of HLA-B*5701 should avoid abacavir-based HAART [84, 86–91]. Despite prior HLA genotyping, the incidence of abacavir HSR was higher in an abacavir/lamivudine-based regimen compared to a tenofovir/emtricitabine-based regimen [40, 41]. This phenomenon indicates that an additional metabolic or immune mechanism might contribute to the ADR.

Approximately 17% of patients starting nevirapine and 10% of patients starting efavirenz will develop rash of varying severity with or without systemic features, typically between 1 and 3 weeks after starting the drug [92]. As HLA genotyping has the potential to reduce the incidence of abacavir HSR, nevirapine is the pharmaceutical agent most often associated with cutaneous HSRs (Table 1) [9–14, 16–18, 20–25, 31, 39, 42–48]. Moreover, Warren et al. [93] report that nevirapine can be associated with SJS. Albeit
infrequent, SJS and toxic epidermal necrolysis (TEN) are sometimes observed in conjunction with nevirapine and can be fatal [9, 13, 31, 45, 48, 49]. The median time for skin rash occurrence was 1.0 month (IQR 3 weeks to 3 months) [17, 18, 45]. The majority of patients who discontinued nevirapine due to HSR did so within 18 weeks (for both skin rash and hepatotoxicity without concomitant skin rash) [47].

Hepatitis is observed with relative frequency in HSR patients [15, 45, 48]. No patient suffered from both skin rash and liver abnormality in other studies [8, 11, 44, 47]. Hepatic involvement in HSR can also be observed without concomitant cutaneous reactions [44, 47].

Nevirapine-associated HSRs are usually moderate to severe and often require treatment change for the elimination of the agent that caused the reaction [8, 9, 13, 15, 16, 18, 20, 23, 31, 42, 44–46]. Nevirapine is usually substituted with efavirenz in HSR cases [42]. Dermal lesions were observed only in combinations that contained nevirapine and lamivudine in one study [66]. There was a higher incidence of severe rashes (grade ≥3) among nevirapine patients, compared to nonnevirapine patients (P = 0.002) in another study. While the same trend was observed overall for grade ≥2 rash, this association was no longer significant (P = 0.099) [31]. Efavirenz itself has been associated with skin symptoms [20, 50]. In such cases, a switch to nevirapine often results in the development of similar reactions on nevirapine as well, showing cross-reactivity between the two NNRTIs [20]. Efavirenz treatment did not lead to the development of cutaneous HSRs in a separate study [25].

The HLA-DRB1*01 allele was significantly associated with isolated rash alone in patients exposed to nevirapine or efavirenz (P = 0.04), whereas immunologic and genetic factors are associated with hepatotoxicity and systemic ADRs [51].

Lopinavir/ritonavir [50] and atazanavir/ritonavir [24] were also associated with HSR. Among other NRTIs, the development of rash led to zidovudine and stavudine substitution [30] and the development of pruritis led to didanosine substitution [35] in other studies.

There are also studies in which the drugs responsible for the HSR are not specified, but certain hypotheses can be made based on the medication regimen. In such instances, patients are often exposed to either nevirapine or efavirenz [19, 52].

Older age (P < 0.003) and a higher CD4+ cell count (P < 0.03) were predictors of rash development [42]. No significant differences in plasma nevirapine concentrations were observed between patients who experienced skin rash and patients who did not [14]; however significantly more cases of grade ≥2 rash were identified in a group receiving a full dose of nevirapine, compared to a half-dose of the drug (P = 0.003) [42]. A strong association between grade ≥2 rash and nevirapine-based treatment was observed when only subjects with CD4+ >250 cells/mm3 were considered (P = 0.001), suggesting an interaction between the treatment and the CD4+ count [42].

In addition, a trend of increasing risk of developing grade ≥2 rash was observed in pregnant subjects (P = 0.054). Pregnant subjects with baseline CD4+ >250 cells/mm3 were significantly at risk of developing grade ≥2 rash (P = 0.042). However, pregnancy alone is not a predictor of ADR development for women initiating nevirapine therapy. This is an important finding, as pregnant women were both more likely to start nevirapine-based treatment (P < 0.001) and to have higher baseline CD4+ counts (P < 0.001) [31]. No independent risk factors for skin rash were identified in a separate study [18].

### 4. Gastrointestinal Intolerance

GI complaints, mainly diarrhea, vomiting, and abdominal disturbances, were the most frequently observed ADRs in several studies [24, 53]. These types of ADRs appeared mainly during the first 12 weeks of therapy and were mild (grade <2) and transient in most patients [53]. Gastroenterological intolerance (dyspepsia, nausea, vomiting, and diarrhea) is common effects of different drug combinations [66]. GI intolerance was the main cause of lopinavir/ritonavir therapy modification or interruption (Table 1) [24, 32, 36, 54]. GI symptoms associated with lopinavir/ritonavir and tipranavir were the most common type of ADRs in patients exposed to these pharmaceutical agents [55]. Cases of GI toxicity associated with lopinavir/ritonavir discontinuation occurred between day 3 and week 15 [56]. While diarrhea was the most common ADR that led to lopinavir/ritonavir treatment changes, this ADR was less commonly associated with efavirenz discontinuations [26]. Compared with patients assigned to efavirenz, patients assigned to lopinavir/ritonavir had higher rates of nausea, diarrhea, and vomiting (P < 0.01) [57].

Nevirapine is another drug associated with a high rate of treatment discontinuations as result of GI intolerance [22, 47]. Nevirapine discontinuations caused by GI symptoms often occur within the first 18 weeks of treatment [47].

The incidence of GI ADRs (mainly diarrhea) was higher in patients treated with nelfinavir compared to patients treated with nevirapine (P = 0.01) [22]. Vomiting and diarrhea were observed in other samples of patients treated with nelfinavir [28, 56].

GI intolerance was the main cause of saquinavir therapy modification or interruption as well [36]. A higher saquinavir Cmin was associated with a higher incidence of serious GI ADRs [58]. In addition, higher saquinavir Cmin was more prevalent in individuals with grade ≥3 GI side effects, compared with individuals with grade ≤2 GI side effects (P = 0.028) [58]. Mild nausea and diarrhea were also observed among saquinavir patients [59].

No patient on atazanavir/ritonavir discontinued treatment due to GI intolerance. More patients receiving lopinavir/ritonavir experienced grade ≥2 nausea, compared to patients receiving atazanavir/ritonavir [33].

GI symptoms were associated with treatment modifications in patients receiving treatment with dual-boosted PIs [94]. The drugs responsible for the observed ADRs are not specified [94]. GI toxicity was also reported in relation to didanosine [34]. Patients assigned to zidovudine and didanosine had higher rates of nausea, constipation, and
fatigue when compared to patients assigned to stavudine and lamivudine (P < 0.05) [57]. Drug-related GI toxicity leads to poor medication adherence and ultimate virological failure [34]. Mild GI intolerance that did not require treatment modifications was observed in a couple of other studies [46, 95].

5. Pancreatic Toxicity

Acute pancreatitis is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes (serum amylase, isoamylase, and/or lipase). Abnormal exocrine and endocrine function can also occur during an acute attack.

Banks and Freeman argue that acute pancreatitis is characterized by two of either abdominal pain characteristic of acute pancreatitis, serum amylase, and/or lipase raised ≥3 times over the upper limit of normal, and characteristic findings of acute pancreatitis on computed tomography (CT) scan [96]. Based on this characterization, Manfredi and Calza found 46 (3.7%) patients who presented with serum amylase and/or lipase raised ≥3 times over the upper limit of normal and acute pancreatitis on CT scan [60]. A further 120 (11.1%) patients presented only with serum amylase and/or lipase raised ≥3 times over the upper limit of normal and were thus classified as asymptomatic. Only 31 (2.9%) patients had mild-to-moderate symptoms of abdominal pain, which 163 (22.0%) abused alcohol (≥0.5) [57]. Drug-related GI toxicity leads to poor medication adherence and ultimate virological failure [34]. Mild GI intolerance that did not require treatment modifications was observed in a couple of other studies [46, 95].

A relatively high incidence of at least one confirmed laboratory pancreatic abnormality, relating to at least two serum pancreatic enzymes over a mean follow-up period of 33.6 consecutive months, was observed in this large study [60]. The use of NRTIs like didanosine, stavudine, and lamivudine and coadministration of other medications such as pentamidine, cotrimoxazole, antituberculosis therapy, lamivudine and coadministration of other medications such as cyclosporin, dapsone, and/or emetine led to elevations in another study [32].

Pancreatitis likely attributable to didanosine was observed in a couple of studies (Table 1) [27, 35]. Grade ≥3 serum amylase elevations were similar in patients receiving either didanosine/lamivudine/efavirenz or lamivudine/zidovudine/efavirenz [97]. Hyperamylasemia and hyperuricemia were eventual findings without clinical relevance in another study [66]. Among NNRTIs, nevirapine was associated with pancreas-related toxicities [25, 47, 48], whereas efavirenz was not [25].

Recurrent episodes of acute pancreatitis may also suggest a misuse of alcohol or use of concomitant medication. There is no mention of how many drinkers were in a large study, yet the incidence of symptomatic and asymptomatic cases was similar between alcohol drinkers and abstainers [60].

6. HAART Interaction with Alcohol Consumption

Hepatic injury is often more common in individuals with alcohol abuse and in those with HCV coinfection. HAART-induced hepatic injury has the potential to limit the usefulness of this medication in HIV treatment [63]. Twelve (5.4%) patients were found to abuse alcohol in a sample of 222 patients, of which 84 (37.8%) were coinfected with HCV. Alcohol abuse was identified as a risk factor for developing hepatic injury of any grade (OR 3.42, 95% CI 1.04–11.19, P < 0.05), especially severe hepatic injury (OR 8.66, 95% CI 2.47–30.40, P < 0.05), measured by elevations in transaminase levels [63]. Alcohol intake greater than 40 g per day (OR 3.09, 95% CI 1.27–7.54, P = 0.01) was associated with a greater risk of severe hepatotoxicity in a sample of 108 patients [65].

Fourteen (10.6%) patients were alcohol abusers in a small sample of 132 HIV patients coinfected with HCV. Due to the low number of alcohol abusers in this sample, no association between alcohol abuse and hepatotoxicity was observed [98]. Alcohol consumption, both at baseline and during follow-up, was not linked to progression of fibrosis by ≥1 stages among 135 patients coinfected with HCV, of which 31 (23.0%) patients had an alcohol intake of >50 g/day [99].

Excessive alcohol consumption had no effect on the development of mild-to-moderate rash. However, severe rash plus/or hepatotoxicity was observed among 741 patients, of which 163 (22.0%) abused alcohol (≥168 g of alcohol per week for women and ≥252 g of alcohol per week for men) [16].

Since the primary metabolic pathways of abacavir are mediated by microsomal UDP glucuronol transferase and cytosolic alcohol dehydrogenase, use and misuse of alcohol can lead to hepatotoxicity. A significant pharmacokinetic interaction was found following the coadministration of abacavir and ethanol. Twenty-four HIV-positive men received either a single 600 mg dose of abacavir, 0.7 g/kg ethanol (the equivalent of 5 alcoholic drinks), or a 600 mg dose of abacavir plus 0.7 g/kg ethanol on separate occasions. With coadministration, there was a 41% increase in abacavir area under the curve and a 26% increase in abacavir t1/2, with no change in the pharmacokinetic profile of ethanol [100].
While not all studies found an association between alcohol consumption and a greater risk of HAART toxicity, studies where such parameters are investigated often use small population sizes, with a low proportion of alcohol abusers, making it difficult to uncover interactions.

7. Discussion

The present paper discusses hepatic, GI, and pancreatic ADRs related to various ART drugs and drug combinations. We also introduce a section on HSR, since HSRs encompass many of the clinical entities of hepatic and GI representations. We further describe some of the interactions between ART and other drugs and alcohol. Moreover, we briefly explore the influence of certain comorbidities, such as viral hepatitis, on ART-induced hepatotoxicity.

As with all ART medications, many clinically significant interactions are possible with PIs. For example, atazanavir cross-reacts with nevirapine. Atazanavir exposure is significantly lower when combined with this drug, and the risk of nevirapine toxicity may increase due to increased nevirapine exposure. In addition, atazanavir in combination with efavirenz is not recommended in treatment-experienced patients, since efavirenz significantly lowers atazanavir exposure. Concomitant didanosine/lamivudine exposure is not recommended in ART-naive patients receiving unboosted atazanavir due to potential toxicities. In addition, the virological response to abacavir may be diminished significantly by multiple NRTI-associated mutations and/or by reductions in phenotypic susceptibility to abacavir. However, many subjects showing evidence of baseline resistance to NRTIs respond to abacavir.

Of particular relevance to the HIV-infected population is coinfection with HCV. Hepatitis with aminotransferase elevations was reported, and it should be appropriately monitored [101].

Hepatocytotoxicity, or drug-induced liver injury, can be classified based upon clinical presentation and laboratory features, the mechanism of toxicity, and/or histological findings. The presence of serum bilirubin raised >3 times over the upper limit of normal along with aminotransferase elevations is associated with a more drastic prognosis than isolated aminotransferase abnormalities [102], an observation known as Hy’s Law [103].

In addition to these acute hepatic presentations, some drugs are associated with chronic histological inflammatory changes and a clinical syndrome resembling autoimmune hepatitis, while others cause endothelial damage or thrombosis, leading to vascular complications such as venoocclusive disease [104]. Withdrawal of the offending drug usually leads to reversal of the injury. The patterns of acute injury may present as hepatocellular (cytotoxic) damage, cholestasis, a mixed pattern of cytotoxic and cholestatic injury, or, less commonly, steatosis [102]. Discontinuation of the offending agent usually results in complete recovery, although the prognosis is generally worse in patients with hepatocellular injury presenting with jaundice when compared to cytotoxic injury alone.

HIV per se may influence the ultrastructural architecture of the liver. In the liver of a patient living with AIDS, Phillips et al. found tubular structures mainly in the cytoplasm of endothelial cells and less frequently in Kupffer cells, macrophages, fibroblasts, and biliary cells. These changes were associated with the endoplasmic reticulum, representing a cellular response to virus-induced injury [105].

Drug-induced steatohepatitis may also resemble alcoholic liver disease [106, 107]. In addition, ethnicity plays a role in antiretroviral-induced toxicity [108].

Some of the subjects living with HIV that were included in these studies have a history or past or present alcohol consumption. From a histological point of view, alcoholic hepatitis presents enlargement of hepatocytes that may increase the vascular pressure in the acinus [109]. Mitochondrial changes, including megamitochondria or irregular mitochondria, as well as Mallory bodies, are also encountered. Mallory bodies (alcoholic hyalin) correspond to cytokeratine conglomerations of proteins that form filaments.

The predominant cell in the liver is the hepatocyte, which contains abundant cytoplasm. There are little amounts of carbohydrates and phospholipids in filaments seen in hepatocytes. These cytokeratine filaments represent an abnormal expression of the cytoskeleton. Ultrastructurally, irregular inclusions, which range from small conglomerates of filaments to large inclusions, occupy most of the cytoplasm [105]. A wide range of other ultrastructural changes in alcoholic liver disease can be seen in conjunction with HAART, such as cell necrosis, increased peroxisome numbers, and crystalloid inclusions. Also, with are infrequent bile duct proliferation and ground glass cytoplasmic inclusions that can be resolved after alcohol abstinence.

The genetic value of UGT in PI-induced hyperbilirubinemia is further discussed [110]. Rotger et al. showed that individuals homozygous for the A(TA)$_7$TAA allele of UGT1A1*28 enzyme receiving atazanavir or indinavir were at increased risk of experiencing hyperbilirubinemia in the jaundice range. They studied in parallel a group of patients that have not been genotyped for UGT1A1 allele before prescribing atazanavir or indinavir as first-line agents versus patients that have been genotyped for UGT1A1*28. The “genotype-guided ART” narrowed the use of atazanavir or indinavir to individuals without the UGT1A1*28 allele. The authors conclude that genetic screening would lead to a theoretical 75% reduction in the incidence of hyperbilirubinemia in the jaundice range. The high incidence of the UGT1A1*28 allele might lead to high risk of developing jaundice in the setting of Gilbert syndrome when exposed to specific PIs [110]. UGT1A1 promoter A(TA)$_7$TAA variant was most common among African Americans and least common among subjects of Asian origin [111]. Therefore, the use of genetic screening for the A(TA)$_7$TAA allele before initiation of antiretroviral therapy is controversial [112].

Ideally, genetic testing for this allele, in conjunction with testing for markers of immunotoxicity such as lymphocyte toxicity assay, may be used in the future in the clinical setting to prevent, diagnose, or monitor drug-induced ADRs in people living with HIV [113].
We conclude that antiviral pharmacodynamics is affected by a broad array of factors ranging from individual pharmacokinetic and pharmacogenetic parameters, to medication adherence and drug-drug interactions. Therefore, therapeutic and drug monitoring of HAART plays an important role. Using laboratory techniques to identify phenotypic susceptibilities, as well as knowing the interactions between ART and other drugs or herbal medicines, might enable a safer use of this beneficial type of medication in HIV patients. Adding to the complexity, many HIV-infected patients are unable to keep therapeutic medication safe due to their behavior patterns, such as alcohol misuse. Lack of pharmacovigilance is associated with HIV disease progression as well as toxicities.

The major objective of this article is to increase awareness on the possible toxicity of therapeutics prescribed in HIV. Moreover, there are other health products including traditional small molecule drugs, natural health products, biologics, and biotechnology products that are prescribed in HIV. These products may cause not only significant liver direct toxicity but also unpredictable, idiosyncratic hepatotoxicity. Therefore, in the process of achieving pharmacovigilance objectives, the investigational approach used for a particular therapeutic may have to be individualized based on the safety characteristics of the product as well as its proposed clinical application.

**Abbreviations**

ADR: Adverse drug reaction  
ALT: Alanine aminotransferase  
ART: Antiretroviral therapy  
AST: Aspartate aminotransferase  
CI: Confidence interval  
CYP: Cytochrome P450  
GI: Gastrointestinal  
HAART: Highly active antiretroviral therapy  
HCV: Hepatitis C virus  
HIV: Human immunodeficiency virus  
HLA: Human leukocyte antigen  
HSR: Hypersensitivity syndrome reaction  
IQR: Interquartile range  
NRTI: Nucleoside reverse transcriptase inhibitor  
NNRTI: Non-nucleoside reverse transcriptase inhibitor  
OR: Odds ratio  
PI: Protease inhibitor  
SJS: Stevens-Johnson syndrome  
UGT: Uridine diphosphate glucuronosyltransferase.

**References**

[1] F. E. Karch and L. Lasagna, “Adverse drug reactions. A critical review,” *Journal of the American Medical Association*, vol. 234, no. 12, pp. 1236–1241, 1975.

[2] R. B. Kim, M. F. Fromm, C. Wandel et al., “The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors,” *Journal of Clinical Investigation*, vol. 101, no. 2, pp. 289–294, 1998.

[3] R. B. Pollard, “Use of protease inhibitors in clinical practice,” *Pharmacotherapy*, vol. 14, no. 6, pp. 215–295, 1994.

[4] L. S. Lee, A. S. A. Andrade, and C. Flexner, “Interactions between natural health products and antiretroviral drugs: pharmacokinetic and pharmacodynamic effects,” *Clinical Infectious Diseases*, vol. 43, no. 8, pp. 1052–1059, 2006.

[5] M. Banasch, J. Frank, K. Serova et al., “Impact of antiretroviral treatment on 13C-methionine metabolism as a marker of hepatic mitochondrial function: a longitudinal study,” *HIV Medicine*, vol. 12, no. 1, pp. 40–45, 2011.

[6] C. Stephan, B. Dauer, P. Khaykin et al., “Quadruple nucleos(t)ide reverse transcriptase inhibitors-only regimen of tenofovir plus zidovudine/lamivudine/abacavir in heavily pre-treated HIV-1 infected patients: salvage therapy or backbone only?” *Current HIV Research*, vol. 7, no. 3, pp. 320–326, 2009.

[7] P. Munderi, A. S. Walker, C. Kityo et al., “Nevirapine/zidovudine/lamivudine has superior immunological and virological responses not reflected in clinical outcomes in a 48-week randomized comparison with abacavir/zidovudine/lamivudine in HIV-infected Ugandan adults with low CD4 cell counts,” *HIV Medicine*, vol. 11, no. 5, pp. 334–344, 2010.

[8] W. Kondo, E. A. Carraro, E. Prandel et al., “Nevirapine-induced side effects in pregnant women—experience of a Brazilian University Hospital,” *Brazilian Journal of Infectious Diseases*, vol. 11, no. 6, pp. 544–548, 2007.

[9] N. Phanuphak, T. Apornpong, S. Teeratakulpisarn et al., “Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women,” *HIV Medicine*, vol. 8, no. 6, pp. 357–366, 2007.

[10] H. Knobel, A. Gueral, M. Montero et al., “Risk of side effects associated with the use of nevirapine in treatment-naïve patients, with respect to gender and CD4 cell count,” *HIV Medicine*, vol. 9, no. 1, pp. 14–18, 2008.

[11] W. Kondo, A. D. A. F. De Astori, S. E. K. Gomes, R. D. B. Fernandes, M. D. G. Sasaki, and R. L. Sbalqueiro, “Evaluation of the adverse effects of nevirapine in HIV-infected pregnant women in a South Brazilian University Hospital,” *Revista Brasileira de Ginecologia e Obstetricia*, vol. 30, no. 1, pp. 19–24, 2008.

[12] V. Meyssonnier, D. Costagliola, and P. E. Caumes, “Nevirapine-associated toxicity in Niger,” *HIV Medicine*, vol. 9, no. 1, pp. 62–63, 2008.

[13] J. van Griensven, L. De Naeyer, J. Uwera, A. Asiimwe, C. Gazille, and T. Reid, “Success with antiretroviral treatment for children in Kigali, Rwanda: experience with health center/nurse-based care,” *BMC Pediatrics*, vol. 8, article 39, 2008.

[14] O. M. Minzi, H. Irunde, and C. Moshiro, “HIV patients presenting common adverse drug events caused by highly active antiretroviral therapy in Tanzania,” *Tanzania Journal of Health Research*, vol. 11, no. 1, pp. 5–10, 2009.

[15] S. J. Bersoff-Matcha, D. Bourse, and J. Blank, “Evaluation of the safety of nevirapine therapy during pregnancy,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 54, no. 5, pp. 560–562, 2010.

[16] E. G. Bottaro, M. J. Huberman, M. D. C. Iannella et al., “Nevirapine-associated toxicity in clinical practice in Buenos Aires, Argentina,” *Journal of the International Association of Physicians in AIDS Care*, vol. 9, no. 5, pp. 306–312, 2010.
[17] P. A. Coffie, B. Tonwe-Gold, A. K. Tanon et al., “Incidence and risk factors of severe adverse events with nevirapine-based antiretroviral therapy in HIV-infected women. MTCT-Plus program, Abidjan, Côte d’Ivoire,” BMC Infectious Diseases, vol. 10, article 188, 2010.

[18] J. van Griensven, R. Zachariah, F. Rasschaert, J. Mugabo, E. F. Atté, and T. Reid, “Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda,” Transactions of the Royal Society of Tropical Medicine and Hygiene, vol. 104, no. 2, pp. 148–153, 2010.

[19] J. H. Willig, J. Echevarria, A. O. Westfall et al., “Durability of initial antiretroviral therapy in a resource-constrained setting and the potential need for zidovudine weight-based dosing,” Journal of Acquired Immune Deficiency Syndromes, vol. 53, no. 2, pp. 213–221, 2010.

[20] J. T. Schouten, A. Krambrink, H. J. Ribaudo et al., “Substitution of nevirapine because of efavirenz toxicity in AIDS clinical trials group A5095,” Clinical Infectious Diseases, vol. 50, no. 5, pp. 787–791, 2010.

[21] J. E. Van Schalkwyk, A. Alimenti, D. Khoo et al., “Serious toxicity associated with continuous nevirapine-based HAART in pregnancy,” BJOG: An International Journal of Obstetrics and Gynaecology, vol. 115, no. 10, pp. 1297–1302, 2008.

[22] J. Mallolas, J. L. Blanco, J. Pich et al., “A randomized trial comparing the efficacy and tolerability of two HAART strategies at two years in antiretroviral naive patients,” Revista Clinica Espanola, vol. 207, no. 9, pp. 427–432, 2007.

[23] M. Colafiglì, S. Di Giambenedetto, L. Bracciale et al., “Long-term follow-up of nevirapine-treated patients in a single-centre cohort,” HIV Medicine, vol. 10, no. 8, pp. 461–469, 2009.

[24] L. Elzi, C. Marzolini, H. Furrer et al., “Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008,” Archives of Internal Medicine, vol. 170, no. 1, pp. 57–65, 2010.

[25] C. W. Wester, A. M. Thomas, H. Bussmann et al., “Non-nucleoside reverse transcriptase inhibitor outcomes among combination antiretroviral therapy-treated adults in Botswana,” AIDS, vol. 24, no. 1, pp. 527–536, 2010.

[26] M. J. Pérez-Elias, A. Moreno, J. L. Casado et al., “Observational study to evaluate clinical outcomes after first-line efavirenz- or lopinavir-ritonavir-based HAART in treatment-naive patients,” Journal of the International Association of Physicians in AIDS Care, vol. 8, no. 5, pp. 308–313, 2009.

[27] R. B. Van Dyke, L. Wang, and P. L. Williams, “Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children,” Journal of Infectious Diseases, vol. 198, no. 11, pp. 1599–1608, 2008.

[28] Y. J. Bryson, M. Mirochnick, A. Stek et al., “Pharmacokinetics and safety of nevirapin when used in combination with zidovudine and lamivudine in HIV-infected pregnant women: pediatric AIDS Clinical Trials Group (PACTG) protocol 353,” HIV Clinical Trials, vol. 9, no. 2, pp. 115–125, 2008.

[29] D. Podzamczer, M. Olmo, J. Sanz et al., “Safety of switching nevirapine twice daily to nevirapine once daily in virologically suppressed patients,” Journal of Acquired Immune Deficiency Syndromes, vol. 50, no. 4, pp. 390–396, 2009.

[30] C. Laurent, A. Bourgeois, E. Mpoudi-Ngole et al., “Tolerability and effectiveness of first-line regimens combining nevirapine and lamivudine plus zidovudine or stavudine in Cameroon,” AIDS Research and Human Retroviruses, vol. 24, no. 3, pp. 393–399, 2008.

[31] E. Aaron, M. C. Kempf, S. Criniti et al., “Adverse events in a cohort of HIV infected pregnant and non-pregnant women treated with nevirapine versus non-nevirapine antiretroviral medication,” PLoS ONE, vol. 5, no. 9, Article ID e12617, 8 pages, 2010.

[32] C. Rudin, M. Wolbers, D. Nadin et al., “Long-term safety and effectiveness of lopinavir/ritonavir in antiretroviral-experienced HIV-1-infected children,” Archives of Disease in Childhood, vol. 95, no. 6, pp. 478–481, 2010.

[33] J. M. Molina, J. Andrade-Villanueva, J. Echevarría et al., “Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study,” The Lancet, vol. 372, no. 9639, pp. 646–655, 2008.

[34] B. Castelnuovo, L. John, F. Lutwama et al., “Three-year outcome data of second-line antiretroviral therapy in Ugandan adults: good virological response but high rate of toxicity,” Journal of the International Association of Physicians in AIDS Care, vol. 8, no. 1, pp. 52–59, 2009.

[35] D. Hirt, C. Bardin, S. Diagbouga et al., “Didanosine population pharmacokinetics in West African human immunodeficiency virus-infected children administered once-daily tablets in relation to efficacy after one year of treatment,” Antimicrobial Agents and Chemotherapy, vol. 53, no. 10, pp. 4399–4406, 2009.

[36] I. Davidson, H. Beardsell, B. Smith et al., “The frequency and reasons for antiretroviral switching with specific antiretroviral associations: the SWITCH study,” Antiviral Research, vol. 86, no. 2, pp. 227–229, 2010.

[37] R. Manfredi and L. Calza, “Recent availability of two novel, fixed formulations of antiretroviral nucleoside analogues: a 12-month prospective, open-label survey of their practical use and therapeutic perspectives in antiretroviral-naive and -experienced patients,” AIDS Patient Care and STDs, vol. 22, no. 4, pp. 279–290, 2008.

[38] A. C. Collier, C. Tierney, G. F. Downey et al., “Randomized study of dual versus single ritonavir-enhanced protease inhibitors for protease inhibitor-experienced patients with HIV,” HIV Clinical Trials, vol. 9, no. 2, pp. 91–102, 2008.

[39] A. S. Walker, P. Muyengy, C. Kitty et al., “Twenty-four-week safety and tolerability of nevirapine vs. abacavir in combination with zidovudine/lamivudine as first-line antiretroviral therapy: a randomized double-blind trial (NORA),” Journal of Acquired Immune Deficiency Syndromes, vol. 55, no. 1, pp. 6–16, 2008.

[40] A. Martin, M. Bloch, J. Amin et al., “Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial,” Clinical Infectious Diseases, vol. 49, no. 10, pp. 1591–1601, 2009.

[41] F. A. Post, G. J. Moyle, H. J. Stellbrink et al., “Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study,” Journal of Acquired Immune Deficiency Syndromes, vol. 55, no. 1, pp. 49–57, 2010.

[42] V. Mulenga, A. Cook, A. S. Walker et al., “Strategies for nevirapine initiation in HIV-infected children taking pediatric fixed-dose combination “baby pills” in Zambia: a
randomized controlled trial,” *Clinical Infectious Diseases*, vol. 51, no. 9, pp. 1081–1089, 2010.

[43] H. Y. Zhou, Y. H. Zheng, Y. He et al., “Evaluation of a 6-year highly active antiretroviral therapy in Chinese HIV-1-infected patients,” *Intervirology*, vol. 53, no. 4, pp. 240–246, 2010.

[44] J. Van Griensven, P. Un, T. Phe, S. Thai, and L. Lynen, “Substituting nevirapine for efavirenz: risk factors for toxicity in nonnaive patients in a resource-constrained setting,” *AIDS*, vol. 23, no. 17, pp. 2374–2376, 2009.

[45] D. Laureillard, N. Prak, M. Fernandez et al., “Efavirenz replacement by immediate full-dose nevirapine is safe in HIV-1-infected patients in Cambodia,” *HIV Medicine*, vol. 9, no. 7, pp. 514–518, 2008.

[46] C. Pryce, R. B. Pierre, J. Steel-Duncan et al., “Safety of antiretroviral drug therapy in Jamaican children with HIV/AIDS,” *West Indian Medical Journal*, vol. 57, no. 3, pp. 238–245, 2008.

[47] A. M. Kesselring, F. W. Wit, C. A. Sabin et al., “Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy,” *AIDS*, vol. 23, no. 13, pp. 1689–1699, 2009.

[48] P. De Beaudrap, J. F. Etard, F. N. Guéye et al., “Long-term efficacy and tolerance of efavirenz- and nevirapine-containing regimens in adult HIV type I Senegalese patients,” *AIDS Research and Human Retroviruses*, vol. 24, no. 6, pp. 753–760, 2008.

[49] A. Sivadasan, O. C. Abraham, P. Rupali et al., “High rates of regimen change due to drug toxicity among a cohort of South Indian adults with HIV infection initiated on generic, first-line antiretroviral treatment,” *Journal of Association of Physicians of India*, vol. 57, no. 5, pp. 384–388, 2009.

[50] P. Echeverría, E. Negredo, G. Carosi et al., “Similar antiviral efficacy and tolerability between efavirenz and nevirapine/ritonavir, administered with abacavir/lamivudine (Kivexa), in antiretroviral-naïve patients: a 48-week, multicentre, randomised study (Lake Study),” *Antiviral Research*, vol. 85, no. 2, pp. 403–408, 2010.

[51] Z. G. Vitezica, B. Milpied, C. Lonjou et al., “HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz,” *AIDS*, vol. 22, no. 4, pp. 540–541, 2008.

[52] H. Bussmann, C. W. Wester, A. Thomas et al., “Response to zidovudine/didanosine-containing combination antiretroviral therapy among hiv-1 subtype c-infected adults in botswana: two-year outcomes from a randomized clinical trial,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 51, no. 1, pp. 37–46, 2009.

[53] E. Negredo, O. Miró, B. Rodriguez-Santiago et al., “Improvement of mitochondrial toxicity in patients receiving a nucleoside reverse-transcriptase inhibitor—sparring strategy: results from the multicenter study with nevirapine and kaletra (MULTINEKA),” *Clinical Infectious Diseases*, vol. 49, no. 6, pp. 892–900, 2009.

[54] J. S. de la Fuente, V. Granja, I. Escobar, E. C. De La Fuente, V. Moreno, and R. Rubío, “Study of the gastrointestinal tolerance of a new tablet formulation of the lopinavir/ritonavir antiretroviral in HIV-infected patients,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 50, no. 3, pp. 294–298, 2009.

[55] A. Bonjoch, M. I. Buzon, J. M. Llibre et al., “Transient treatment exclusively containing nucleoside analogue reverse transcriptase inhibitors in highly antiretroviral-experienced patients preserves viral benefit when a fully active therapy was initiated,” *HIV Clinical Trials*, vol. 9, no. 6, pp. 387–398, 2008.

[56] X. Duval, F. Mentré, E. Rey et al., “Benefit of therapeutic drug monitoring of protease inhibitors in HIV-infected patients depends on PI used in HAART regimen—ANRS 111 trial,” *Fundamental and Clinical Pharmacology*, vol. 23, no. 4, pp. 491–500, 2009.

[57] A. Ratsela, M. A. Polis, S. Dhlimo et al., “A randomized factorial trial comparing 4 treatment regimens in treatment-naïve HIV-infected persons with AIDS and/or a CD4 cell count < 200 Cells/µl in South Africa,” *Journal of Infectious Diseases*, vol. 202, no. 10, pp. 1529–1537, 2010.

[58] U. S. Justesen, Z. Fox, C. Pedersen et al., “Pharmacokinetics of two randomized trials evaluating the safety and efficacy of indinavir, saquinavir and lopinavir in combination with low-dose ritonavir: the MaxCmin1 and 2 trials,” *Basic and Clinical Pharmacology and Toxicology*, vol. 101, no. 5, pp. 339–344, 2007.

[59] K. Singh, L. Dickinson, A. Chaikan et al., “Pharmacokinetics and safety of saquinavir/ritonavir and omeprazole in HIV-infected subjects,” *Clinical Pharmacology and Therapeutics*, vol. 83, no. 6, pp. 867–872, 2008.

[60] R. Manfredi and L. Calza, “HIV infection and the pancreas: risk factors and potential management guidelines,” *International Journal of STD and AIDS*, vol. 19, no. 2, pp. 99–105, 2008.

[61] T. A. Knox, L. Oleson, L. L. Von Moltke, R. C. Kaufman, C. A. Wanke, and D. J. Greenblatt, “Ritonavir greatly impairs CYP3A activity in HIV infection with chronic viral hepatitis,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 49, no. 4, pp. 358–368, 2008.

[62] M. C. Mendes-Corrêa, H. F. Andrade Jr., C. Fumíca Takakura, and M. I. Seixas Duarte, “Hepatic ultrastructural mitochondrial changes prior to antiretroviral therapy in HIV-infected patients in Brazil,” *Journal of the International Association of Physicians in AIDS Care*, vol. 7, no. 5, pp. 252–258, 2008.

[63] M. Núñez, R. Lana, J. L. Mendoza, L. Martín-Carbonero, and V. Soriano, “Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 27, no. 5, pp. 426–431, 2001.

[64] H. J. Zimmerman, Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver, Lippincott Williams and Wilkins, Philadelphia, Pa, USA, 2nd edition, 1999.

[65] J. Ena, C. Amador, C. Benito, V. Penoll, and F. Pasquau, “Risk and determinants of developing severe liver toxicity during therapy with nevirapine-and efavirenz-containing regimens in HIV-infected patients,” *International Journal of STD and AIDS*, vol. 14, no. 11, pp. 776–781, 2003.

[66] E. A. Soria, I. I. Cadile, L. R. Allende, and L. E. Kremer, “Pharmacoepidemiological approach to the predisposing factors for highly active antiretroviral therapy failure in an HIV-positive cohort from Cordoba City (Argentina) 1995–2005,” *International Journal of STD and AIDS*, vol. 19, no. 5, pp. 335–338, 2008.

[67] A. Turkova, C. Ball, S. Gilmour-White, M. Rela, and G. Mieli-Vergani, “A paediatric case of acute liver failure associated with efavirenz-based highly active antiretroviral therapy and effective use of raltegravir in combination antiretroviral treatment after liver transplantation,” *Journal of Antimicrobial Chemotherapy*, vol. 63, no. 3, pp. 623–625, 2009.
[68] M. S. Hirsch, F. Brun-Vezinet, B. Clotet et al., “Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 Recommendations of an International Aids Society-USA panel,” *Clinical Infectious Diseases*, vol. 37, no. 1, pp. 113–128, 2003.

[69] S. M. Hammer, J. J. Eron Jr., P. Reiss et al., “Antiretroviral treatment of adult HIV infection: 2008 Recommendations of the international AIDS society-USA panel,” *JAMA—Journal of the American Medical Association*, vol. 300, no. 5, pp. 555–570, 2008.

[70] S. D. Zacker, X. Qin, S. D. Rouster et al., “Mechanism of indinavir-induced hyperbilirubinemia,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 22, pp. 12671–12676, 2001.

[71] P. Ocama, M. Katwere, T. Piloya et al., “The spectrum of liver diseases in HIV infected individuals at an HIV treatment clinic in Kampala, Uganda,” *African Health Sciences*, vol. 8, no. 1, pp. 8–12, 2008.

[72] P. J. Bayard, T. G. Berger, and M. A. Jacobson, “Drug hypersensitivity reactions and human immunodeficiency virus disease,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 5, no. 12, pp. 1237–1257, 1992.

[73] S. A. Coopman, R. A. Johnson, R. Platt, and R. S. Stern, “Cutaneous disease and drug reactions in HIV infection,” *The New England Journal of Medicine*, vol. 328, no. 23, pp. 1670–1674, 1993.

[74] P. P. Koopmans, A. J. A. M. van der Ven, T. B. Vree, and J. W. M. van der Meer, “Pathogenesis of hypersensitivity reactions to drugs in patients with HIV infection: allergic or toxic?” *AIDS*, vol. 9, no. 3, pp. 217–222, 1995.

[75] R. G. Lalonde, R. Thomas, A. Rachlis et al., “Successful implementation of a national HLA-B*5701 genetic testing service in Canada,” *Tissue Antigens*, vol. 75, no. 1, pp. 12–18, 2010.

[76] R. H. Foster and D. Faulds, “Abacavir,” *Drugs*, vol. 55, no. 5, pp. 729–738, 1998.

[77] P. Keiser, N. Nassar, D. Skiest et al., “Comparison of symptoms of influenza A with abacavir-associated hypersensitivity reaction,” *International Journal of STD and AIDS*, vol. 14, no. 7, pp. 478–481, 2003.

[78] A. E. Loeliger, H. Steel, S. McGuirk et al., “The abacavir hypersensitivity reaction and interruptions in therapy,” *AIDS*, vol. 15, no. 10, pp. 1325–1326, 2001.

[79] P. Bossi, J. C. Roujeau, F. Bricaire, and E. Caumes, “Stevens-Johnson syndrome associated with abacavir therapy,” *Clinical Infectious Diseases*, vol. 35, no. 7, p. 902, 2002.

[80] R. P. Walensky, J. H. Goldberg, and J. P. Daily, “Anaphylaxis after rechallenge with abacavir [6],” *AIDS*, vol. 13, no. 8, pp. 999–1000, 1999.

[81] M. Shapiro, K. M. Ward, and J. J. Stern, “A near-fatal hypersensitivity reaction to abacavir: case report and literature review,” *AIDS Reader*, vol. 11, no. 4, pp. 222–226, 2001.

[82] S. Hetherington, A. R. Hughes, M. Mosteller et al., “Genetic variations in HLA-B region and hypersensitivity reactions to abacavir,” *The Lancet*, vol. 359, no. 9312, pp. 1121–1122, 2002.

[83] W. Symonds, A. Cutrell, M. Edwards et al., “Risk factor analysis of hypersensitivity reactions to abacavir,” *Clinical Therapeutics*, vol. 24, no. 4, pp. 565–573, 2002.

[84] F. Vidal, F. Gutiérrez, M. Gutiérrez et al., “Pharmacogenetics of adverse effects due to antiretroviral drugs,” *AIDS Reviews*, vol. 12, no. 1, pp. 15–30, 2010.

[85] A. R. Hughes, W. R. Spreen, M. Mosteller et al., “Pharmacogenetics of hypersensitivity to abacavir: from PGx hypothesis to confirmation to clinical utility,” *Pharmacogenomics Journal*, vol. 8, no. 6, pp. 365–374, 2008.

[86] S. Hetherington, S. McGuirk, G. Powell et al., “Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir,” *Clinical Therapeutics*, vol. 23, no. 10, pp. 1603–1614, 2001.

[87] H. A. Kessler, J. Johnson, S. Follansbee et al., “Abacavir expanded access program for adult patients infected with human immunodeficiency virus type 1,” *Clinical Infectious Diseases*, vol. 34, no. 4, pp. 535–542, 2002.

[88] A. Lucas, D. Nolan, and S. Mallal, “HLA-B*5701 screening for susceptibility to abacavir hypersensitivity,” *Journal of Antimicrobial Chemotherapy*, vol. 59, no. 4, pp. 591–593, 2007.

[89] S. Rodriguez-Nóvoa, P. García-Gascó, F. Blanco et al., “Value of the HLA-B*5701 allele to predict abacavir hypersensitivity in Spaniards,” *AIDS Research and Human Retroviruses*, vol. 23, no. 11, pp. 1374–1376, 2007.

[90] L. J. Waters, S. Mandalia, B. Gazzard, and M. Nelson, “Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience,” *AIDS*, vol. 21, no. 18, pp. 2533–2534, 2007.

[91] D. Zucman, P. D. Truchis, C. Majerholc, S. Stegman, and S. Caillat-Zucman, “Prospective screening for human leukocyte antigen-B*5701 avoids abacavir hypersensitivity reaction in the ethnically mixed French HIV population,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 45, no. 1, pp. 1–5, 2007.

[92] A. Barner and M. Myers, “Nevirapine and rashes,” *The Lancet*, vol. 351, no. 9109, p. 1133, 1998.

[93] K. J. Warren, D. E. Boxwell, N. Y. Kim, and B. A. Drollet, “Nevirapine-associated Stevens-Johnson syndrome,” *The Lancet*, vol. 351, no. 9102, p. 567, 1998.

[94] R. B. Osih, P. Taffé, M. Rickenbach et al., “Outcomes of patients on dual-boosted PI regimens: experience of the Swiss HIV Cohort study,” *AIDS Research and Human Retroviruses*, vol. 26, no. 11, pp. 1239–1246, 2010.

[95] P. Isaakidis, M. E. Raguenaud, T. Phe et al., “Evaluation of a systematic substitution of zidovudine for stavudine-based HAART in a program setting in rural cambodia,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 49, no. 1, pp. 48–54, 2008.

[96] P. A. Banks, M. L. Freeman, R. Fass et al., “Practice guidelines in acute pancreatitis,” *American Journal of Gastroenterology*, vol. 101, no. 10, pp. 2379–2400, 2006.

[97] J. Berenguer, J. González, E. Ríbera et al., “Didanosine, lamivudine, and efavirenz versus zidovudine, lamivudine, and efavirenz for the initial treatment of hiv type 1 infection: final analysis (48 weeks) of a prospective, randomized, noninferiority clinical trial, GESIDA 3903,” *Clinical Infectious Diseases*, vol. 50, no. 5, pp. 5701–5706, 2005.

[98] J. Macías, J. Berenguer, M. A. Japón et al., “Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus,” *Hepatology*, vol. 50, no. 4, pp. 1056–1063, 2009.

[99] J. S. Walsh, M. J. Reese, and L. M. Thurmond, “The metabolic activation of abacavir by human liver cytoisol and expressed human alcohol dehydrogenase isozymes,” *Chemico-Biological Interactions*, vol. 142, no. 1-2, pp. 135–154, 2002.
[101] M. S. Sulkowski, D. L. Thomas, R. E. Chaisson, and R. D. Moore, “Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection,” *Journal of the American Medical Association*, vol. 283, no. 1, pp. 74–80, 2000.

[102] H. J. Zimmerman, “Drug-induced liver disease,” in *Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver*, pp. 353–365, Appleton-Century-Crofts, New York, NY, USA, 1st edition, 1978.

[103] A. Reuben, “Hy’s law,” *Hepatology*, vol. 39, pp. 574–578, 2004.

[104] K. G. Ishak, “Hepatic histopathology,” in *Diseases of the Liver*, L. Schiff and E. R. Schiff, Eds., pp. 175–187, JB Lippincott Company, Pennsylvania, Pa, USA, 1993.

[105] M. J. Phillips, S. Poucell, J. Patterson, and P. Valencia, *The Liver: An Atlas and Text of Ultrastructural Pathology*, vol. 395, Raven Press, New York, NY, USA, 1987.

[106] H. J. Zimmerman and J. H. Lewis, “Chemical- and toxin-induced hepatotoxicity,” *Gastroenterology Clinics of North America*, vol. 24, no. 4, pp. 1027–1045, 1995.

[107] D. Larrey, “Drug-induced liver diseases,” *Journal of Hepatology*, vol. 32, no. 1, pp. 77–88, 2000.

[108] A. I. Akhtar and M. Shaheen, “Jaundice in African-American and Hispanic patients with AIDS,” *Journal of the National Medical Association*, vol. 99, no. 12, pp. 1381–1385, 2007.

[109] L. M. Blendis, H. Orrego, and I. R. Crossley, “The role of hepatocyte enlargement in hepatic pressure in cirrhotic and noncirrhotic alcoholic liver disease,” *Hepatology*, vol. 2, no. 5, pp. 539–546, 1982.

[110] M. Rotger, P. Taffé, G. Bleiber et al., “Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia,” *Journal of Infectious Diseases*, vol. 192, no. 8, pp. 1381–1386, 2005.

[111] E. Beutler, T. Gelbart, and A. Demina, “Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism?” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 14, pp. 8170–8174, 1998.

[112] R. E. Nettles, M. J. Child, R. J. Bertz, and S. Schnittman, “Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia: genetic screening is unnecessary,” *Journal of Infectious Diseases*, vol. 193, no. 11, pp. 1611–1612, 2006.

[113] M. G. Neuman, I. M. Malkiewicz, E. J. Phillips et al., “ Monitoring adverse drug reactions to sulfonamide antibiotics in human immunodeficiency virus-infected individuals,” *Therapeutic Drug Monitoring*, vol. 24, no. 6, pp. 728–736, 2002.