Safety Aspects of Antiretroviral Therapy for Management of HIV Infection

R.Rajesh[*1], Sudha vidyasagar[2], Patel Naren[1], ManjuVarghese[1]

1) Department of Pharmacy Practice, Manipal college of Pharmaceutical Sciences, Manipal University, Manipal – 576 104, Karnataka, India.
2) Department of Medicine, Kasturba Medical College, Manipal University, Manipal – 576 104, Karnataka, India.

ABSTRACT: There are four classes of antiretroviral agents used in the treatment of HIV/AIDS. Adverse effects to Highly Active Antiretroviral Therapy (HAART) are common and often difficult to avoid. In many cases, research is not able to identify the exact cause of an adverse event. The severity of adverse reactions varies greatly and difficult to manage; typically prevention is more desirable than treatment. However, this is not always true. This paper will review safety aspect of class-wide Highly Active Antiretroviral Therapy, mechanism of action. A class-wide adverse effect for Reverse transcriptase inhibitors includes lactic acidosis, peripheral neuropathy and lipoatrophy. Class wide adverse effects to non-nucleoside reverse transcriptase inhibitors include rash and hepatotoxicity, while efavirenz has its own unique CNS reactions. Protease inhibitor side effects include hyperglycemia, lipoaccumulation, dyslipidemia, and gastrointestinal (GI) intolerance. Coreceptor CCR5 antagonists, which provide a novel mechanism of action, are a recent addition to the armamentarium of antiretroviral agents. Antiretroviral are an important break-through in the treatment of HIV/AIDS. However, adverse reactions from these drugs can range from mild to life-threatening, and determining which agent is the cause is frequently difficult to discern. Fortunately, side effects can be monitored, treated and in many cases, prevented.

INTRODUCTION

Highly Active Antiretroviral Therapy (HAART), are essential to the life-expectancy of most people infected with HIV today.[1] HAART has revolutionized the treatment of human immunodeficiency virus (HIV) infection over the past 10 years. The advent of HAART has reduced morbidity, mortality and the incidence of opportunistic infections, thus improving the outlook for patients with HIV/AIDS. Patients and clinicians have more choices in antiretroviral agents now than in the early 1990s or even at the beginning of this decade.

Currently, there are twenty six medications comprising four classes of antiretroviral (ARV) agents: reverse transcriptase inhibitors, protease inhibitors, entry inhibitors and integrase inhibitor. Despite these advances in the treatment of HIV, the complete eradication of infection with the virus is still not possible. Not only is the combining of ARVs necessary to treat HIV infection, it is also important for patients to be highly adherent to their regimen in order to achieve and maintain maximal efficacy and to prevent resistance. However, increasing resistance, nonadherence to medications, and toxicity has fueled virological failure and the need for additional agents active against HIV. The concept of HIV-entry inhibition was introduced into practice in 2003 with the approval of enfuvirtide, the first HIV fusion inhibitor.[2] Maraviroc was approved by the food and drug administration (FDA) for use in combination with other antiretroviral agents in the treatment of HAART-experienced patients whose HIV infection is resistant to multiple classes of antiretroviral drugs. In addition, maraviroc is labeled for use only

*Corresponding Author:
E-mail: rrajesh3775@gmail.com; rajesh.r@manipal.edu

in patients infected with CCR5-tropic HIV-1, who have evidence of ongoing viral replication, and who are resistant to multiple antiretroviral agents.[3] However, as with any drug, there is a propensity for adverse drug reactions (ADR). Each class of ARVs has side effects that affect the entire (or at least most) of the class, while the individual drugs within each class typically have additional, sometimes unique, ADRs. These side effects have the potential to greatly impact a patient's adherence to medications and consequently, the benefit he or she may derive from the HAART regimen. This paper will discuss safety aspects of antiretroviral therapy for management of HIV infection.

Reverse Transcriptase Inhibitors

Reverse transcriptase inhibitors include the nucleoside analogues zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine; the nucleotide analogue tenofovir; and the nonnucleoside reverse transcriptase inhibitors nevirapine, delavirdine, efavirenz and etravirine. These were the first class of drugs that were licensed for the treatment of HIV infection. They are indicated for this use as part of combination regimens. It should be stressed that none of these drugs should be used as monotherapy for HIV infection. The reverse transcriptase inhibitors block the HIV replication cycle at the point of RNA-dependent DNA synthesis, the reverse transcription step. While the non nucleoside reverse transcriptase inhibitors are quite selective for the HIV-1 reverse transcriptase, the nucleoside and nucleotide analogues inhibit a variety of DNA polymerization reactions in addition to those of the HIV-1 reverse transcriptase.

Zidovudine

Anemia can be associated with zidovudine therapy.[4–6]Anemia greatly impacts quality of life (QOL), mostly because of its association with nausea, fatigue and weakness.[6] Lower CD4 cell counts, increased age have been shown to increase the risk for anemia.[7] Careful monitoring of complete blood count (CBC) in patients on zidovudine can be an essential method to prevent clinically significant anemia. Recombinant human erythropoietin, blood transfusion and cessation of zidovudine and other myelosuppressive therapies (such as gancyclovir or sulfamethoxazole trimethoprim) are viable treatment options for zidovudine induced anemia.[5, 8]

Nausea is another common side effect that may be present in early zidovudine use[4]. Other side effects of zidovudine may include: granulocytopenia, myopathy, lacticacidosis, hepatomegaly with steatosis, headache. Myopathy may occur within 6–12 months of initiating zidovudine, and has an insidious onset that involves proximal muscle weakness and exercise-induced myalgias[4]. The mechanism of myopathy is believed to be mitochondrial toxicity within myocytes.[4] Zidovudine should be used with caution in patients who have anemia (hemoglobin less than 9.5 grams/deciliter). Reduction of hemoglobin may occur as early as 2 to 4 weeks. Severe anemia may require dose adjustment, discontinuation, and/or blood transfusions. Doses should be reduced until bone marrow recovers if the anemia is significant (hemoglobin less than 7.5 grams/deciliter or reduction of greater than 25% of baseline). Monitor blood counts frequently in patients with advanced human immunodeficiency virus (HIV) disease and periodically in patients with asymptomatic or early HIV disease.

Didanosine

Pancreatitis is a known complication of didanosine use occurring in approximately 1 to 7% of patients[9]. Fatal and nonfatal pancreatitis has occurred during therapy with didanosine alone or in combination regimens, such as concomitant use of hydroxyurea and stavudine. It has occurred in experienced patients, regardless of degree of immunosuppression. The frequency of pancreatitis is dose related. Peripheral neuropathy manifested by numbness, tingling, or pain in the hands or feet is a major dose-limiting toxicity reported with didanosine use. It occurs more frequently in patients with advanced HIV disease, history of neuropathy or in patients treated with neurotoxic drug therapy. The onset of neuropathy ranges from 55 to 201 days after initiation of therapy.

Elevated liver enzymes, hepatitis, hepatic failure and necrosis have occurred with didanosine therapy. Severe hepatomegaly with hepatic steatosis, sometimes fatal, has been reported.Pre-existing liver dysfunction increases the risk of liver function abnormalities, including severe and potentially fatal hepatic events.

Lactic acidosis has also been a noted complication of didanosine treatment. Lactic acidosis is a life-threatening reaction and is defined as lactate con-

centrations exceeding 5mmol/L, with a blood pH of <7.3 and end organ failure[10].If the lactate level is > 2 mmol/L, with clinical symptoms reflective of lactic acidosis, the medication should be discontinued and supportive therapy initiated. [11]

Stavudine

Peripheral neuropathy, lactic acidosis, and lipoatrophy are all side effects seen with stavudine[12,13,14,15,16].

TABLE 1: ADVERSE REACTIONS ASSOCIATED WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN THE MANAGEMENT OF HIV INFECTION.

Drugs	Adverse effects
Reverse Transcriptase Inhibitors	
Zidovudine	• Anemia, granulocytopenia, myopathy • Lactic acidosis, hepatomegaly with steatosis • Headache, nausea
Didanosine	• Pancreatitis, peripheral neuropathy • Abnormalities on liver function tests, lactic acidosis • Hepatomegaly with steatosis
Stavudine	• Peripheral neuropathy, pancreatitis, lactic acidosis • Hepatomegaly with steatosis, ascending neuromuscular Weakness, lipodystrophy
Lamivudine	• Hepatotoxicity • >10%: Headache, fatigue, nausea, diarrhea • Vomiting, pancreatitis, peripheral neuropathy • Paresthesia, musculoskeletal pain
Emtricitabine	• Hepatotoxicity • >10%: dizziness, fever, insomnia, abnormal dreams, Hyperpigmentation, diarrhea, cough
Tenofovir	• Potential for renal toxicity • >10%: Pain, diarrhea, nausea, weakness
Nevirapine	• Skin rash, hepatotoxicity
Efavirenz	• Rash, headache, dizziness, nausea, diarrhea • >10%: insomnia, anxiety
Reverse Transcriptase Inhibitors	
Ritonavir	• Nausea, abdominal pain, hyperglycemia • Fat redistribution, lipid abnormalities
Indinavir	• Nephrolithiasis, indirect hyperbilirubinemia • Hyperglycemia, fat redistribution, lipid abnormalities
Entry Inhibitors	
Enfuvirtide	• Local injection reactions, hypersensitivity reaction • Increased rate of bacterial pneumonia
Maraviroc	• Hepatotoxicity, nasopharyngitis, fever, cough, rash • Abdominal pain, dizziness, musculoskeletal symptoms
Integrase Inhibitor	
Raltegravir	• Headache, Dizziness, Insomnia, Nausea, Fatigue, Diarrhea and rash

These side effects are generally attributed to mitochondrial toxicity caused by mitochondrial DNA polymerase-γ inhibition[17, 16]. Lactic acidosis is a severe consequence of stavudine use that can arise within several months of therapy[18, 19, 20]. When compared to other NRTIs, lipoatrophy is most-commonly seen with stavudine.[21, 22, 12, 16] The risk of adipocyte apoptosis increases with duration of stavudine therapy, concurrent protease inhibitor therapy, concurrent elevation of serum lactate levels, older age, white race, longer NRTI- experience, and lower pre-treatment body fat.[16] Other symptoms of fat depletion include: facial atrophy ("sunken cheeks") and venomegaly[22, 12]. Peripheral fat wasting can be seen in approximately 63% of patients who take stavudine for greater than one year. Switching from stavudine to zidovudine or abacavir may help to slow the progression of lipoatrophy, and to a lesser extent reverse it.[16] Stavudine-induced lipoatrophy can adversely affect adherence secondary to decreased Quality of life.[22]

Lamivudine/Emtricitabine

Lamivudine and emtricitabine have reported frequently occurring ADRs such as: nausea, increased appetite, headache, rash and dry skin. Most of the adverse events and laboratory abnormalities were rated as Grade 1 – 2 in severity. Emtricitabine shown to cause asymptomatic hyperpigmentation of the palms and soles[23,24]. In clinical practice, both lamivudine and emtricitabine are considered well-tolerated antiretrovirals, and prevention or treatment of side effects should be considered on an individual basis. Pronounced hepatotoxicities including severe hepatomegaly with steatosis and fatalities have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. It has occurred mostly in women. Risk factors may include obesity and prolonged exposure.

Tenofovir

Potential adverse effects related to tenofovir include renal toxicity . There are several case reports of renal toxicity associated with tenofovir. Peyriere et al. reported seven cases of renal tubular dysfunction associated with tenofovir use. Patients experienced hypophosphatemia, hypokalemia, proteinurea, proximal renal tubular acidosis, and a 20–78% decrease in creatinine clearance. Laboratory abnormalities in these studies improved when tenofovir contain-

ing regimens were discontinued. Karrs etal[25] also reported three cases of renal impairment associated with tenofovir use. One patient developed diabetes insipidus, two patients had glucosuria and two had acidosis and hypokalemia[26]. Decreases in bone mineral density (BMD) have been reported in association with tenofovir disoproxil fumarate therapy. Patients with HIV and a history of bone fractures should be monitored closely. Supplementation with calcium and vitamin D may be beneficial for all patients receiving tenofovir disoproxil fumarate.

Nevirapine

Skin Rash is the major adverse effects with nevirapine therapy, and usually occurs within the first 6 weeks of treatment. Most rashes tend to be mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus. The location of the rash is usually the trunk, face, and extremities and women appear to be at higher risk for developing severe nevirapine-associated rash. An initial dose of 300 milligrams (mg) once daily in adults and 4 mg/kilograms/day for the first 14 days is imperative to reduce the frequency of rash. The dose should not be increased until the rash resolves. Treatment of mild to moderate rash depends upon symptomatic presentation and includes antihistamine and/or corticosteroid agents; treatment of more severe rashes would also include discontinuation of the drug. Patients who are presenting with rash should have liver function tests performed, because rash and hepatotoxicity may occur simultaneously[11]. Patients with severe rash or SJS should seek immediate medical attention for proper treatment. Severe and life-threatening hepatotoxicity, including hepatic failure, fulminant and cholestatic hepatitis, and fatal hepatic necrosis, has been reported, especially during the first 18 weeks of nevirapine therapy. Patients must discontinue nevirapine and seek medical attention immediately if they develop signs or symptoms of hepatitis, or with increased transaminases combined with rash or other system symptoms.

Efavirenz

Certain central nervous system (CNS) side effects are unique to efavirenz. Several studies have observed some or all of the following CNS side effects such as insomnia, dizziness, light-headedness, nervousness, irritability, impaired concentration, abnormal/vivid dreaming and hallucinations[27, 28, 29]. Efavirenz-related CNS side effects have been shown by different groups to last for a median of 13 days, with a range of 1–116 days[27, 28] CNS symptoms usually decrease within two to four weeks. Administration of efavirenz at bedtime may help reduce the impact of some side effects on patient's daily lives. Elimination of alcohol and close attention to psychoactive medications may also decrease CNS abnormalities.[11] Other psychiatric symptoms (including severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behavior, paranoid reactions, and manic reactions) have been reported among patients using efavirenz.

Protease Inhibitors

Saquinavir was the first of the HIV-1 protease inhibitors to be licensed. The class of antiretroviral agents that first had a large impact on treatment outcomes of people with HIV infection was the protease inhibitors. While the effects of the PIs on wild-type virus are quite dramatic and can last for long periods (when combined with 2 NRTIs), side effects often limit long-term tolerability of these agents. Thus, management of these side effects is essential for optimal outcomes in patients. Currently, there is Ten FDA-approved PIs. All PIs appear to be associated with some risk of lipodystrophy, hepatotoxicity, and hyperglycemia, increased bleeding episodes among patients with hemophilia, GI disturbances (e.g. nausea, vomiting, and diarrhea) and lipid abnormalities [2]. The four most common class-wide side effects are GI complaints, lipid abnormalities, hyperglycemia, and lipoaccumulation.

Ritonavir

Ritonavir has been shown to increase transaminase levels. Clinical hepatitis and jaundice have occurred when transaminase levels are > 5x the upper limit of normal (ULN). Other side effect includes nausea, abdominal pain, hyperglycemia, fat redistribution, lipid abnormalities. During post marketing surveillance, first-, second-, and third-degree atrioventricular block has been reported with ritonavir therapy. Ritonavir should be used with caution in patients at risk for cardiac conduction abnormalities (eg, underlying structural heart disease, ischemic heart disease, cardiomyopathies) and in patients receiving ritonavir concurrently with other medications which may prolong the PR interval (eg, calcium channel blockers, beta-adrenergic blockers, digoxin, atazanavir), especially ones which are metabolized by CYP3A4.

Additionally, clinical monitoring is recommended. Even at low doses, ritonavir has been shown to elevate total cholesterol and triglycerides. Paresthesia is another reported side effect of ritonavir, with a possible dose-effect relationship.

Indinavir

Adverse effects that were only seen in indinavir were dry skin, dry lips and alopecia. Patients using indinavir had the highest incidence of metabolic alterations,such as: lipodystrophy, weight gain, triglyceride and cholesterol increases and diabetes[30]. Nephrolithiasis, including flank pain with or without hematuria, has been reported in 4% to 5% of patients receiving indinavir, presumably related to crystallization of the drug.In some cases, kidney stones have been associated with renal insufficiency, acute renal failure, and pyelonephritis with or without bacteremia.Several studies have examined possible causes or risk factors for developing nephrolithiasis or urolithaisis. The kindney stones were discovered between day 1 and 102 weeks after the initiation of treatment.

Some measures for preventing nephrolithiasis or urolithaisis include monitoring or indinavir plasma concentration, administering indinavir without food, not exceeding 2.4 grams/day of indinavir, and consuming adequate fluid intake of at least 1.5 liters (approx 48 oz) a day for adults [31, 32]. If nephrolithiasis is caused by super-therapeutic plasma concentrations of indinavir, dose reduction to 600mg three times a day can be effective[33]. If nephrolithiasis develops, treatment options include temporary interruption (i.e. 1–3 days) or complete discontinuations of therapy[31].Other effects of indinavir include hyperglycemia, indirect hyperbilirubinemia (via inhibition of the conversion of indirect bilirubin to direct bilirubin), tubulointerstitial nephritis, and fat redistribution.

Entry Inhibitors

The need for new classes of antiretroviral drugs has become apparent because of increasing concern about the long-term toxic effects of existing drugs, the need to combat HIV-1 variants that are resistant to treatment, and the frequency of treatment change in drug-experienced patients. Currently, most regimens are combinations of inhibitors of two viral enzymes — reverse transcriptase and protease. Nevertheless, several steps in the HIV replication cycle are potential targets for intervention. These steps can be divided into entry steps, in which viral envelope glycoproteins and their receptors are involved and post entry steps, involving viral accessory gene products and the cellular proteins with which they interact. New treatment options target viral entry into the cell. These treatments include the HIV fusion inhibitor enfuvirtide and new HIV coreceptor antagonists in advanced stages of clinical development or in different stages of preclinical development. Here, we review safety aspects of new HIV entry inhibitors, their adverse effects in clinical trials, and their possible role in anti-HIV therapy.

Enfuvirtide

Enfuvirtide inhibits the fusion of the virus with the host CD4 cell surface, preventing the virus from entering the cell. The drug is a large polypeptide which is the reason for its high cost and requirement for parenteral administration. Enfuvirtide is known to cause injection site reactions (ISRs) and hypersensitivity reactions (HSRs), and increases the risk for pneumonia[34]. Patients on enfuvirtide have been shown to develop pneumonia, caused by either Gram-positive or Gram-negative bacteria.[34, 35]

Maraviroc

Maraviroc is the first CCR5 coreceptor antagonist approved from the food and drug administration (FDA) for the treatment of CCR5-tropic human immunodeficiency virus (HIV) infection as part of an optimized antiretroviral regimen in treatment-experienced patients. As 50% or more of treatment experienced patients infected with CXCR4-tropic virus, a tropism assay should be performed before initating maraviroc therapy. Maraviroc carries a black –box warning regarding hepatotoxicity[3]. Hepatotoxicity may be preceded by systemic allergic symptoms, including itchy rash or increased eosinophils. Immediate medical attention should be sought by patients exhibiting signs or symptoms of allergic reaction or liver inflammation while taking maraviroc. Caution is warranted for patients with preexisting hepatitis B or C infection or liver dysfunction[3]. Maraviroc should be used with caution in patients with an increased risk of cardiovascular events. Postural hypotension was considered to be dose related[36, 37]. Other adverse effects are nasopharyngitis, fever, cough, rash, abdominal pain, dizziness, musculoskeletal symptoms.

INTEGRASE INHIBITOR

Raltegravir

Raltegravir is a novel HIV-1 integrase inhibitor to be approved by the US Food and Drug Administration for use in antiretroviral treatment–experienced adult patients with viral resistance. Raltegravir prevents proviral DNA-strand transfer. The drug has potent in vitro activity against strains of HIV-1 that are susceptible or resistant to other classes of antiretroviraldrugs.[38–44] In the BENCHMRK studies,[45,46] use of raltegravir with an optimum background regimen was generally well tolerated and provided superior HIV-1 suppression compared with optimum background treatment alone, despite infection with virus resistant to reverse transcriptase and protease inhibitors. Raltegravir is used in combination with other antiretroviral agents in treatment experienced patients with evidence of ongoing HIV-1 replication. An adverse effect includes Headache, Dizziness, Insomnia, Nausea, Fatigue, Diarrhoea and rash.

Conclusions

Highly Active Antiretroviral therapy is becoming increasingly effective but also increasingly complex. The adverse effects of Highly Active Antiretroviral Therapy may cause symptoms affecting a variety of organ systems. Although current antiretroviral regimens are potent from an antiviral perspective, they often fail because of patient nonadherence. To optimize adherence, and hence efficacy, clinicians must focus on preventing adverse effects. As efforts continue in the development of newer HAART, treating physicians and Pharmacists must remain aware of new and developing syndromes associated with Highly Active antiretroviral use.

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