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Non-Hepatic Adverse Effects of Antiretroviral Therapy for HIV Treatment and Care

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Abstract

High-level viral replication occurs when HIV enters the body. Due to frequent mutations, the virus becomes resistant in the body and persists in memory T cells making it incurable. Lifelong therapy is then required to suppress replication of the virus in the cells. The drugs available for HIV care such as Non-nucleoside reverse transcriptase inhibitors, Protease Inhibitors, Nucleoside reverse transcriptase inhibitors, Entry and Fusion Inhibitors and Integrase inhibitors have been documented to cause adverse effects in patients. Non-nucleoside reverse transcriptase inhibitors and protease inhibitors are metabolized by the cytochrome P450 system, resulting to numerous drug-drug interactions. Adverse effects of antiretroviral therapy should be monitored frequently. Monitoring should include complete blood counts and comprehensive metabolic profiles every three to six months. Lipid profiles and urinalysis for proteinuria should be done after every year. Long-term morbidity due to antiretroviral therapy includes renal, liver, glucose, and lipid abnormalities, and bone disease as well as cardiovascular disease. With some exceptions for lipid management, these morbidities can be managed. This review aims at describing different non-hepatic adverse effects of antiretrovirals as well as factors associated with them.

Keywords: Non-nucleoside reverse transcriptase inhibitors; Protease inhibitors; Nucleoside reverse transcriptase inhibitors; Entry and Fusion Inhibitors; Integrase inhibitors; Adverse effects; Cytochrome P450; Antiretroviral therapy

Introduction

The advancement of antiretrovirals (ARVs) has improved the management of HIV disease. Currently, a treatment-naïve individual with HIV infection is given a 3-drug regimen from at least 2 classes or drug groups [1]. Antiretroviral therapy (ART) has reduced morbidity as well as mortality while increasing survival times of HIV patients to closely the life expectancy of healthy individuals [2,3]. Nonetheless, ART is associated with the onset of adverse events (AEs). While the AEs can be serious, many are considered to be mild to moderate in nature. These adverse effects are capable of significantly reducing the quality of life [4].

The objective of this review is to describe the different non-hepatic adverse effects of antiretrovirals as well as the factors associated with these effects.

HIV drugs are classified into different classes by their modes of action on the virus. Currently, there are eight classes of HIV regimens [5,6]. They include,

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) that block reverse transcriptase, the enzyme that HIV uses to replicate itself. These drugs include; abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) that bind to and alter reverse transcriptase. They include; delavirdine, efavirenz, etravirine, nevirapine and rilpivirine.

Protease Inhibitors (PIs) that block viral protease enzyme. Protease is needed in replication. These drugs include; atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir.

Fusion inhibitors that block the virus from entering the CD4+ T cells of the immune system. Example include enfuvirtide.

Entry inhibitors that block the proteins on the CD+ T cells that the virus needs to enter these cells. Example include maraviroc.

Integrase inhibitors that block HIV integrase, an enzyme needed in HIV replication. Examples include, dolutegravir, elvitegravir and raltegravir

Pharmacokinetic enhancers, are used to increase the effectiveness of a HIV medicine that's been included in a regimen.

Combination HIV medicines that contain two or more HIV medicines from one or more of the above drug classes. These combinations include; abacavir and lamivudine; abacavir, dolutegravir and lamivudine; abacavir, lamivudine and zidovudine; atazanavir and cobicistat; darunavir and cobicistat; lamivudine and zidovudine [5,6].

Major Adverse ART reactions

These drugs are capable of causing both short term and long term toxicities in the body. Short term toxicities in the body include toxicities to the kidney and the bone marrow; cutaneous reactions such as Steven-Johnson syndrome (SJ syndrome) and the hypersensitivities (Table 1). Long term toxicities include morphologic complications

such as lipoaccumulation/lipohypertrophy, visceral adiposity, breast enlargement, dorso-ventral fat pad, lipomas and cosmetic disfigurement; Metabolic abnormalities such as dyslipidimias, abnormalities of glucose metabolism, insulin resistance, lactic acidosis, hepatosteatosis, osteonecrosis, osteopenia, osteoporosis and increased bleeding in hemophiliacs [7].

These medium and long-term side effects of ART are due to the inhibitions of mitochondrial DNA polymerase enzyme resulting to impaired synthesis of mitochondrial enzymes required to generate ATP by oxidative phosphorylation [7]. This is referred to as mitochondrial toxicities and they include; myopathy which is caused by zidovudine; neuropathy which is caused by stavudine, didanosine and zalcitabine; Peripheral neuropathy which is caused by all NRTIs but predominantly stavudine and pancreatitis that's caused by didanosine [7,8].

Mitochondrial toxicities represent with different symptoms in different organs such as fatigue, myalgia and proximal weakness in the muscles; dilated cardiomyopathy; distal pain, numbness, paresthesia and reduced reflexes in the nerves; abdominal pain for the pancreas and peripheral lipoatrophy [9]. For management of mitochondrial toxicities, cease the prescription of the causative drug.

Drug hypersensitivities in HIV-1 infected individuals are very common in the general population. These hypersensitivities manifest themselves as pruritic rashes, erythematous maculopapular rash with or without accompanying fever. Hypersensitive rashes begin 1-2 weeks after the onset of therapy. All NNRTIs and the NRTI such as abacavir and the PI (amprenavir) cause hypersensitivity [9]. The symptoms of hypersensitivities include maculopapular rash, fever, myalgia, fatigue and mucosal ulceration. Others include, hypotension, acute interstitial nephritis and acute interstitial pneumonitis. Nearly 50% of these hypersensitivities resolve spontaneously. However, in cases of mucosal involvement, exfoliation, blistering and significant hepatic dysfunction, therapy should be stopped [10].

For lipodystrophy syndrome, the main clinical features are peripheral fat loss and central fat accumulation within the abdomen, breasts and over dorsocervical spine and other peripheral lipomatosis. Lipodystrophy syndrome starts after about 12-18 months of therapy [9]. The main metabolic features associated with the lipodystrophy syndrome include hypertriglyceridemia, hypercholesterolemia, insulin resistance, type-2 diabetes mellitus and lactic acidosis. Risk factors for lipodystrophy are genetic factors, raised C-peptides and triglyceride concentrations after 1 year, use of dual combinations of ritonavir-saquinavir and stavudine [7]. Management entails, aerobic exercises, low fat foods, use of anabolic steroids, metformin, restorative surgery and withdrawal or substitution of the causative ART.

Cutaneous manifestations of antiretroviaral drugs are as many as they are varied. NNRTIs have resulted in cutaneous eruptions and hypersensitivity syndrome. NRTIs have altered nails, nail and mucocutaneous pigmentation, led to hair changes, vasculitis, and morbilliform eruptions [11].

Myocardial infarction has been shown by many epidemiological studies to increase with duration of exposure to combination ART containing NNRTI / PI. These regimens can be substituted by abacavir (3 NRTI regimen) or atanazavir [12,13].

ART can have adverse effects on the gastrointestinal tract such as transient nausea, vomiting or diarrhoea early in therapy. Nausea is pronounced in zidovudine and didanosine while indinavir is associated with esophageal reflux and should not be given with antacid. Indinavir can be used with H2 blockers and proton pump inhibitors.

Drug	Cutaneous reaction
Protease inhibitors	Lipodystrophy, Hypersensitivity reactions and acute generalized exanthematous pustulosis
Indinavir	Acute porphyria, Stevens-Johnson syndrome, gynecomastia, alopecia and paronychia with nail fold pyogenic granuloma-like lesions
Ritonavir	IgA-mediated hypersensitivity reactions and Hematoma formation
Nelfinavir	Morbilliform eruption and Generalized urticarial
Saquinavir	Gynecomastia, Stevens-Johnson syndrome and hypersensitivity syndrome
Zidovudine	Nail hyperpigmentation, Mucocutaneous hyperpigmentation, hypertrichosis, eyelash hypertrichosis, hypersensitivity syndrome, leukocytoclastic vasculitis
Didanosine	Leukocytoclastic vasculitis, Stevens-Johnson syndrome, papuloerythroderma, acute gouty arthritis, alopecia
Lamivudine	Allergic contact dermatitis, paronychia with lateral nailfold pyogenic granuloma-like lesions

Table 1: Cutaneous reactions to different ART drugs Adapted from Ref. [7].

Classes of ARVS and Their Adverse Effects

Nucleoside Reverse Transcriptase Inhibitors: NRTIs are the backbone of ART and are majorly associated with lactic acidosis and lipodystrophy [14,15]. Lactic acidosis manifests with fatigue, nausea and vomiting, abdominal pain, diarrhea, and an increase in liver function markers because of hepatic steatosis. Lipodystrophy involves lipoatrophy which is the loss of subcutaneous fats in the extremities and the face. It also includes lipohypertrophy which is the central abdominal fat accumulation and dorsocervical fat pad. For facial lipoatrophy, calcium hydroxylapatite and polylactic injections are recommended [16,17]; while for lipohypertrophy, liposuction and recombinant growth hormone administration are recommended [16,17]. Decrease in the intake of polyunsaturated fats and an increase in fiber intake and Glucophage have been documented to decrease lipohypertrophy [17].

Zidovudine leads to bone marrow suppression, fatigue, nausea and vomiting and headache. Lamivudine and emtricitabine are well tolerated. Tenofovir has been linked to renal abnormalities such as glycosuria, increased creatinine levels, hypophosphatemia and the potential for acute tubular necrosis. However, the risk of acute renal failure associated with tenofovir is 1%; risks of renal failure increase with advancement of the HIV disease or a pre-existing renal problem

[18]. Cumulative tenofovir exposure also increases the risk of chronic kidney disease (Table 2) [19].

Drug	Adverse Reactions
Didanosine	Peripheral neuropathy, gastriontesinal effects, pancreatitis, optic neuritis, retinal changes,
Emtricitabine	hyperpigmentation of palms and soles,
Stavudine	Lactic acidosis and pancreatitis, peripheral sensory neuropathy; hyperlipidemia; lipoatrophy; glucose intolerance and diabetes mellitus. Co-administration with didanosine should be avoided.
Tenofovir	Asthenia, diarrhea, headache, vomiting, nausea, proteinuria, flatulence, renal toxicity, renal failure and decreased bone mineral density.
Zidovudine	Anemia, nausea, neutropenia, headache, vomiting, fatigue, myopathy, hyperpigmentation of oral mucosa as well as the nail beds and low white blood cell count

Table 2: Adverse effects of Nucleoside Reverse Transcriptase Inhibitors.

Non-Nucleoside Reverse Transcriptase Inhibitors: NNRTIs majorly cause rashes and lipid disorders [14,15,20]. The ART being administered should be stopped or changed in case of a rash while the lipid disorders can be managed with niacin, statins, omega-3 fatty acids and fibrates [14,21].

Efavirenz disrupts the central nervous system by causing sleep, mood and cognitive disorders within the first month. This happens in about 50% of HIV patients and this prevalence decreases to 23% within 3 months. However, the disorders subside after 6 months of therapy [14,22,23]. Efavirenz is not recommended during pregnancy because it can cause hyperlipidemia and liver toxicity.

A single mutation (K103N) has conferred resistance to the first generation NNRTIs thus the second generation etravirine is recommended because multiple mutations are needed for the virus to become resistant. However, etravirine has been documented to cause a rash and nausea. The rash is more pronounced in women than in men with a ratio of 30:18. Incase of a rash, the drug should be stopped or changed. Steven-Johnson syndrome and toxic epidermal necrolysis and erythema have been reported too for etravirine (Table 3) [24].

Drug	Adverse effects
Efavirenz	Dizziness, headache, insomnia and absent mindedness due to damage to the central nervous system; lipoatrophy if consumed with stavudine or zidovudine, potential teratogenicity, false-positive cannabinoid and benzodiazepine screening assays and it's teratogenic.
Etravirine	Nausea, hypertension, peripheral neuropathy, hypersensitivity reactions, Steven – Johnson syndrome, erythema and epidermal necrolysis

Table 3: Adverse effects of Non-Nucleoside Reverse Transcriptase Inhibitors.

Protease Inhibitors: Most ART regimens are boosted with the use of ritonavir, although some patients cannot tolerate ritonavir because of its adverse gastrointestinal effects. Their metabolization by the CYP450 increases the chances of drug-drug interactions. Gastrointestinal effects include lipohypertrophy, diabetes mellitus, glucose intolerance and lipid disorders. Cholesterol levels are elevated (>240 mg per dL) in 60% of patients taking PIs while 75% have elevated triglyceride levels (>500 mg per dL) [25].

PIs are linked to glucose intolerance in 15 to 20% of those with a HIV infection and diabetes develops in 6% of those on PIs [14,15]. Regardless, diabetes medications can be taken without adjusting the dosage for individuals with HIV on PI therapy [14]. However, metformin and thiazolidinediones which are insulin sensitizing agents are recommended (Table 4) [17].

Drug	Adverse effects
Atazanavir	Asymptomatic indirect hyperbilirubinemia, rash and kidney stones, needs acid in the stomach for absorption.
Darunavir	Rash
Ritonavir	Adverse effects on GIT such as lipohypertrophy, lipid disorders, diabetes mellitus, glucose intolerance, altered taste, circumoral and peripheral paresthesia and raised cholesterol and triglyceride levels.
Lopinavir	Pancreatitis, risk of myocardial infarction with long-term use.
Nelfinavir	Diarrhoea
Indinavir	kidney stones, alopecia, renal insufficiency, dry skin and mucous membranes, paronychia, gallstones and ingrown toenails

Table 4: Adverse Effects of Protease Inhibitors.

Because of the metabolization of PIs by the CYP450 system, statins used are important especially for patients with lipid disorders [16,17,25]. Pravastatin can be used without adjusting the dosage even though the lowest possible dosage should be used in individuals taking darunavir. Rosuvastatin and atorvastatin, niacin, omega-3 fatty acids and fibrates can also be used with PIs. Simvastatin and lovastatin should not be used with PIs [21].

Entry and Fusion Inhibitors: The entrance of HIV into the CD4+ cell is by fusing with the cell membrane and attaching to chemokine receptors on the surface. These receptors are blocked by the entry and fusion inhibitors. Enfuvirtide, which is a fusion inhibitor, is used in treating experienced HIV individuals with restricted therapeutic options. It is rarely used because it has to be administered subcutaneously by injection. Adverse effects comprise neutropenia and a risk of pneumonia [14,15,26].

Some of the C-C chemokine receptors on CD4+ T cells include CCR5 (R5) and CXCR4 (X4). Maraviroc, which is an entry inhibitor is a CCR5 antagonist and is used in both treatment-naïve and treatment-experienced HIV individuals [27,28]. Maraviroc works on R5 cells only. When maraviroc is combined with lamivudine/zidovudine, it is as effective as efavirenz. However, maraviroc is better tolerated than efavirenz even though the drug causes bronchitis and nasopharyngitis, fever, headache and esophageal candidiasis when both drugs are compared to a placebo (Table 5) [27].

Drug	Adverse effects
Maraviroc	Cough, bronchitis, nasopharyngitis, headache, fever, rash, upper respiratory symptoms, abdominal pain, musculoskeletal symptoms, orthostatic hypotension, esophageal candidiasis.
Enfuvirtide	Injection site reactions, increased risk of bacterial pneumonia, eosinophilic hypersensitivity reactions and neutropenia; may increase risk of bacterial pneumonia
Raltegravir	Diarrhea, nausea, headache, myopathy, rhabdomyolysis

Table 5: Adverse Effects of Entry, Fusion and Integrase Inhibitors.

Integrase Inhibitors: Integrase inhibitors such as raltegravir prevent viral DNA from integrating into host DNA. This is achieved by inhibiting the integrase enzyme [26-28]. Due to viral resistance to the drug, its long-term effectiveness has been limited. Its adverse effects include myopathy and rhabdomyolysis [26,27].

Cytochrome P450 Interactions

Many PIs and NNRTIs interact with isoforms of cytochrome P450 isoforms especially CYP3A4 and CYP2D6. Common interactions and outcomes before starting therapy are; decreased loads of oral contraceptives and increased concentrations of non-sedating antihistamines, macrolides and cisapride; rifabutin and rifampicin; benzodiazepines and opiates; ergot derivatives and sildenafil [7].

Ritonavir is used as a pharmacokinetic booster and it aids in the inhibition of cytochrome P450 mediated metabolism of other PIs. This allows for fewer and reduced doses of other PIs [7].

HIV Treatment with ART, Principles in Adverse Reaction Management

There should be increased screening of cardiac, bone and kidney diseases in patients with HIV who are on ART [16,29]. Ten percent of death in HIV is due to cardiovascular diseases. ARVs such as indinavir, lopinavir, didanosine and abicavir raise the chances of heart complications [30,31].

Multiple studies show that low CD4+ T counts, high viral load, and increasing exposure to ART increase chances of heart diseases [14,30,32]. Heavy alcohol use (more than 14 drinks a week) also increases the risks of heart disease. There should be annual screening for traditional cardiac risk factors such as diabetes and hypertension and tobacco use [14,16,17,25]. Osteopenia occurs in 52% of HIV patients while osteoporosis occurs in 15% [33]. Tenofovir and didanosine are associated with low bone mineral densities [34]. Deficiency in Vitamin D is linked to the use of NNRTIs [35]; screening is recommended for patients on these drugs. Osteoporosis screening has to be done after the age of 50 for those individuals on tenofovir or didanosine, and should be done on all patients who are over 50 years in age and have HIV [16,17]. Treatment of osteoporosis should be done by the aid of calcium, vitamin D and bisphosphonates [36-38].

Abnormal kidney functions occur in about 30% of those with HIV [16,39]. With the exceptions of NNRTIs and PIs, many ARVs should have their dosages adjusted if glomerular filtration rates are below 50 ml per min per 1.73 m^2 [39].

For drug initiation, drugs with non-overlapping toxicities should be administered first. Pregnancies and pediatric age groups should be considered, injecting drug users, those with hepatitis B or C, hemophilia and post exposure prophylaxis should also be considered [7]. In case of adverse reactions, dosage reductions are not advised because of risks of drug resistance while a switch to a drug with a different toxicity profile is advised for those who've got good control of viral replication. If the reactions are severe, all drugs should be stopped and new drugs with different toxicity profiles used. For individuals with uncontrollable viral replications, the responsible drug should be stopped and a new drug introduced [7].

In conclusion, the type of ARV therapy and its timing will be based on their toxicities, there should be assays to predict drug induced adverse reactions as well as therapeutic monitoring of ARTs. Patients with HIV should be encouraged to go for ART and should be given supplements that reduce the chances of developing adverse reactions.

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