

Adverse drug reactions to antiretroviral medication

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1. ABSTRACT

Antiretroviral therapy has greatly improved prognosis of HIV infection, with a dramatic reduction of morbidity and mortality worldwide. Nevertheless, the condition is still a common cause of death in many underdeveloped countries, where effective treatment is not always unavailable. More than 20 drugs active against HIV are commercially available, which belong to one of four groups: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and fusion/entry inhibitors. In the near future new drugs are expected, including those of a novel group, the integrase inhibitors. To avoid viral resistance, combinations of the drugs must always be used in clinical practice. Adverse reactions are common with antiretrovirals, and they are an important cause of medication non-adherence and suboptimal control of HIV infection. In this article we review the most relevant of those toxicities.

2. INTRODUCTION

The advent of effective antiretroviral therapy more than one decade ago greatly improved prognosis of HIV infection, and a dramatic reduction of morbidity and mortality related to the condition took place. Nevertheless, adequate control of the condition is only feasible with medication that must be taken on a daily basis.

As of October 2007, a total of 23 drugs active against HIV are commercially available. All of them belong to one of four groups: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and fusion/entry inhibitors (Table 1). In the near future new drugs are expected to be approved, including representatives of a novel group, the integrase inhibitors (1). To avoid viral resistance, combinations of the drugs must always be used in clinical practice (2,3).

Table 1. Commercially available antiretroviral agents.

	Generic name	Abbreviation
Nucleoside reverse transcriptase inhibitors (NRTI)	Zidovudine Didanosine Zalcitabine Stavudine Lamivudine Abacavir Tenofovir ¹ Emtricitabine	AZT or ZDV ddI ddC d4T 3TC ABC TDF FTC
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Nevirapine Delavirdine Efavirenz	NVP DLV EFV
Protease inhibitors (PI)	Saquinavir ²¹ Ritonavir Indinavir ²¹ Nelfinavir Amprenavir Lopinavir ² Atazanavir ²¹ Fosamprenavir ²¹ Tipranavir ² Darunavir ²	SQV RTV IDV NFV APV LPV ATV f-APV TVP DRV
Fusion and entry inhibitors	Enfuvirtide Maraviroc	T-20 MVC

¹ Nucleotide; ² always used with ritonavir as a pharmacokinetic-booster; ²¹ commonly used with ritonavir as a pharmacokinetic-booster.

Adverse reactions have been reported with all antiretrovirals, and they are among the most common reasons for switching of therapy and for medication non-adherence (4). The problem is especially important in underdeveloped countries, where many times only the cheaper and more toxic medications are available. Herein we describe the most relevant of those toxicities.

3. HYPERSENSITIVITY REACTIONS

3.1. Hypersensitivity to nevirapine and other NNRTIs

Hypersensitivity reactions are more common in HIV-infected patients than they are in the general population (5). These reactions have been described with all groups of antiretroviral medications, but they are especially common with regimens that include nevirapine, a NNRTI. As much as one third of patients who are treated with the drug develop a cutaneous rash, especially during first few weeks of therapy. The reaction generally consists of a mild, self-limited, erythematous or maculopapular eruption. But there are occasional cases of severe life-threatening reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis. Pruritus, mucosal sores and fever are commonly seen in affected patients.

The other two available NNRTIs, efavirenz and delavirdine, may also cause the reaction, but prevalence is lower than with nevirapine, and severe cases are exceptional.

Patients who start treatment with NNRTIs should be advised of the possible presentation of the reaction, and should be recommended to report symptoms promptly, if they occur. To diminish the likelihood that patients develop hypersensitivity to nevirapine, therapy with the drug is recommended to be initiated at 200 mg daily for the first two weeks and then increased to the therapeutic dose of

200 mg twice daily. This approach is not necessary with efavirenz or delavirdine.

When patients taking one NNRTI develop a rash, it is the seriousness of the condition that generally determines whether the medication should be continued. Mild reactions do not require drug discontinuation. But more serious reactions, for example those involving desquamation, high fever or edema, may require hospitalization, as well as permanent discontinuation of the NNRTI. Patients who have recently started nevirapine and experience only mild eruptions may be maintained at 200 mg daily until symptoms abate, after which the dose is increased (6).

3.2. Hypersensitivity to abacavir

Abacavir, a NRTI, produces hypersensitivity reaction in about 6 % of treated patients. The condition presents in a variety of ways including high fever, chills, sore throat, cough, dyspnea, tachypnea, nausea, vomiting, diarrhea, loss of appetite, abdominal pain, arthralgia, myalgia, malaise, fatigue, dizziness, and a generalized macular rash. This reaction has been considered by some authors a modality of the drug-rash with eosinophilia and systemic symptoms (DRESS) syndrome. It usually develops within the first few weeks of therapy, and does not appear to be dose-related.

If therapy is stopped symptoms usually subside within a few days. But when therapy is continued symptoms tend to worsen, typically involve multiple organ systems, and may include hypotension, respiratory distress, anaphylaxis, and even death.

Restarting therapy may cause severe reactions within hours of drug administration. Therefore, rechallenge is contraindicated in patients who have developed the condition.

The association of abacavir hypersensitivity reaction with *HLA-B₁5701* allele is particularly important and provides a basis for genetic screening and prevention of the reaction in the clinic setting (7). A patch test may also be useful to detect the persons at risk.

3.3. Hypersensitivity to other antiretrovirals

PIs, including the newer ones such as darunavir, produce occasional hypersensitivity reactions, generally during the first month of treatment. Systemic or cutaneous symptoms may occur, with pruritus as a prominent complaint in most cases. Patients should be aware of the mild risk of the reaction, and should be encouraged to report it promptly. Careful rechallenge is feasible for mild cases. But discontinuation of the drug is recommended after more severe reactions. A different PI, or a drug of other group, may be employed instead.

Rare cases of hypersensitivity reactions have also been reported with other antiretrovirals, including enfuvirtide, a fusion inhibitor, and maraviroc, a recently approved entry inhibitor (8).

3.4. Treatment of hypersensitivity reactions

Patients should be advised to seek medical advice immediately if any rash or unexplained fever develops while taking antiretroviral therapy, especially if symptoms occur during the first few weeks of therapy.

Once a decision has been made regarding continuation or not of the offending drug, symptoms should be treated. For mild pruritic eruptions topical treatment with corticosteroid preparations or systemic antihistamine drugs may be enough. More intense reactions with systemic symptoms should be assessed immediately. If anaphylaxis develops, the patient will require epinephrine, antihistamines, corticosteroids, and general supportive care (9).

4. HYPERLACTATEMIA-STEATOSIS SYNDROME

The NRTIs, especially stavudine, zidovudine and didanosine, may disrupt mitochondrial function, specifically oxidative phosphorylation, through inhibition of DNA polymerase. The dysfunction induces pyruvate and fatty acid accumulation, and their conversion to lactate and triglycerides, respectively. The final result is lactic acidosis and hepatic steatosis, among other metabolic consequences.

The syndrome generally manifests months to years after starting therapy. Obesity and female gender are known risk factors.

Mild cases are common, and clinically are characterized by vague and persistent complaints of malaise, fatigue, nausea and abdominal pain. More severe cases are uncommon, and manifest with weight loss, vomiting, jaundice, pancreatitis, mental status changes, breathlessness and cardiac arrhythmias. Liver failure as well as multiorgan failure and death can occur. Blood analyses disclose metabolic acidosis, with an elevated anion gap caused by persistently increased serum levels of lactic acid. Hypoalbuminemia is frequent, and bilirubin and liver enzymes are usually elevated. Creatine phosphokinase is generally increased, and a decreased ratio of mitochondrial to nuclear DNA is also present. Histologically microvesicular or macrovesicular hepatic steatosis is commonly seen in severe cases.

Diagnosis is based on drug history, clinical picture and lactic acid level. Prognosis is worse with high lactic acid levels.

The antiretroviral therapy should be discontinued immediately. Otherwise treatment is essentially symptomatic. Case reports have suggested a possible role for supplementation with cofactors such as thiamine or riboflavin, but their authentic efficacy is unclear. The syndrome slowly resolves after discontinuation of the offending drugs. Reintroduction of therapy should be considered only when lactic acid levels are completely normal. The new regimen should include the NRTIs with less propensity to provoke mitochondrial toxicity, i. e., lamivudine, emtricitabine, tenofovir and abacavir (10).

5. LIVER TOXICITY

Hepatotoxicity has been described with virtually every antiretroviral agent, although prevalence and severity of the side effect varies from drug to drug. Direct toxicity of the medications is the principal mechanism. Clinical hepatitis can occur, although asymptomatic elevation of liver enzymes is much more frequent. Hepatotoxicity occurs more commonly in the first weeks of treatment, but it may present at any time during therapy.

Among PI, severe hepatotoxicity, defined as aminotransferase level higher than 5 times the upper limit of normal, is especially common with ritonavir. When the drug is used at full dose as many as one fourth of patients may experience the toxicity. Tipranavir provoke the side effect in about 10 % of patients, while the other PIs, including low dose ritonavir used to boost other medications, cause the reaction in less than 5 % of patients.

Nevirapine, a NNRTI, provoke acute hepatitis in about 5 % of patients. Fulminant hepatic failure can occasionally occur. This reaction is more common in patients without advanced immunodeficiency, e. i., with CD4 cells counts over 350 per mm³, and about one half of affected subjects also present symptoms of the nevirapine hypersensitivity reaction (see above).

The NRTIs may also cause hepatotoxicity, generally as a part of the hyperlactatemia-steatosis syndrome (see above).

The risk of hepatic side effects is increased in patients who abuse alcohol or take other hepatotoxic medications, and in those who present hepatitis B or C coinfection. Nevertheless, antiretroviral therapy may improve long-term prognosis of hepatitis B and C.

Liver toxicity of maraviroc, a newly approved entry inhibitor, seems to be uncommon.

Management of severe hepatotoxicity includes immediate discontinuation of the whole antiretroviral treatment, and introduction of a new regimen when aminotransferase levels are normalized. The potential offending agents should be avoided in the new treatment. Other potential causes of concomitant hepatotoxicity should be considered, and treated as needed.

In mild cases, if aminotransferase levels are lower than 5 times the upper limit of normal, continuation of treatment with close monitoring of patients may be appropriate (11).

6. PANCREATITIS

Pancreatitis occurs in about 3 % of patients who take didanosine, a NRTI, generally one to six months after starting treatment. Factors that increase the risk of the reaction include: taking high dose of the medication, alcohol ingestion, previous history of pancreatitis, advanced HIV infection, and concomitant administration of

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drugs that can cause pancreatitis, such as valproic acid or pentamidine.

Pancreatitis can also occur as a part of the hyperlactatemia-steatosis syndrome, provoked by the NRTIs (see above). And cases of pancreatitis have been reported with lamivudine in the pediatric population.

PI, especially full dose ritonavir, can cause a significant increase in serum triglycerides. Levels as high as 1,000 mg/dL are occasionally seen, which may be associated with pancreatitis.

Patients usually present with post-prandial abdominal discomfort, nausea and vomiting. Serum amylase and lipase concentrations are typically elevated, and therefore should be monitored in all patients with suspected pancreatitis. Increases in serum triglycerides or glucose concentrations can also occur.

The reaction usually resolves within one or two weeks after drug discontinuation, but severe fatal cases occasionally occur. Treatment is essentially symptomatic (12).

7. GASTROINTESTINAL INTOLERANCE

Gastrointestinal symptoms are among the most common side effects of antiretroviral medications. NRTIs, especially zidovudine and didanosine, and all PIs frequently produce nausea, vomiting and abdominal discomfort. PIs, principally nelfinavir and lopinavir, frequently produce diarrhea.

These symptoms present with the very first doses of the drugs, are generally mild, and tend to diminish over time despite continuing treatment.

Taking the medications with food may substantially reduce gastrointestinal symptoms, although there are drugs, such as didanosine, that must necessarily be taken on an empty stomach. Antiemetics or antidiarrheals efficiently ameliorate symptoms in many patients. But in the most severe cases substitution of the responsible drug may be the best option (13).

8. NERVOUS SYSTEM TOXICITY

8.1. Central nervous system side effects of efavirenz

The NNRTI efavirenz frequently produces drowsiness, dizziness, impaired capacity of concentration, diurnal somnolence, insomnia, abnormal dreams, depression, hallucination and other psychic complaints. These symptoms begin with the very first doses of the drug, and occur in more than half of the patients who take it. Suicidal ideation, exacerbation of psychiatric disorders and psychosis can also occur.

Preexisting psychiatric illnesses and concomitant use of drugs with effects on the central nervous system promote the appearance of symptoms and increase their intensity. Efavirenz is metabolized via the enzyme CYP2B6P of the cytochrome P450. Presence of polymorphism 516TT of the gene that codifies the enzyme is

associated with diminished clearance of efavirenz and increased risk of central nervous system toxicity of the drug.

Patients who take efavirenz should be advised to restrict potentially risky activities, such as driving vehicles or operating dangerous machinery during the first weeks of therapy. Taking the medication at bedtime is recommended to reduce the impact of side effects. Ingesting the drug on an empty stomach can reduce drug concentration and ameliorate symptoms.

Central nervous system toxicity of efavirenz completely disappears or substantially diminishes after 2 to 4 weeks of treatment. Nevertheless, if symptoms are severe and persistent, cause significant impairment in daily function or exacerbate psychiatric illness, the best option may be switching to other drug (14).

8.2. Ascending neuromuscular weakness

NRTIs, especially stavudine, may rarely provoke a progressive ascending demyelinating polyneuropathy. The disorder tends to occur months after initiating treatment, but develops rapidly, generally within days to weeks. It may mimic Guillain-Barré syndrome, and carries the risk of respiratory paralysis and death. This side effect tends to occur as a part of the hyperlactatemia-steatosis syndrome (see above).

Early recognition of the disorder and withdrawal of the offending drug are key to avoid progression of weakness. Treatment is basically supportive. Measures such as plasmapheresis, corticosteroid, and intravenous immunoglobulin are of limited value, if any. Recovery often takes months, and substantial residual deficits are common. Rechallenge with the drug is contraindicated in patients who have suffered the condition (15).

8.3. Peripheral neuropathy

NRTIs, especially stavudine, didanosine and zalcitabine, may produce a symmetrical peripheral neuropathy, generally weeks to months after starting treatment. First symptoms usually consist of numbness and paresthesia, which are followed by painful sensation. Complaints appear distally, in toes and feet, and slowly progress proximally to calves and the entire legs. Upper extremities are less frequently involved. The condition is disabling in some cases, and may be irreversible despite discontinuation of the offending drugs.

Risk factors to develop peripheral neuropathy are: increased age, preexisting peripheral neuropathy, combined use of the NRTIs that cause the disorder, concomitant use of drugs that produce peripheral neuropathy, and advanced HIV infection.

Treatment consists of discontinuation of the responsible agents and avoidance of other potential causes of peripheral neuropathy, if present. Gabapentin, pregabalin, tricyclic antidepressants, lamotrigine, and a variety of analgesics and topical anesthetics may provide symptomatic relief (16).

9. HEMATOLOGIC TOXICITY

9.1. Bone marrow suppression

Zidovudine, a NRTI, may produce myelosuppression, generally weeks to months after starting treatment. Anemia, frequently severe, occurs in about 3 % of patients. Typical symptoms of the condition, such as fatigue, weakness, dizziness and breathlessness, are usually present. Neutropenia occurs in about 5 % of patients. When severe, the blood abnormality may favor the development of a variety of infections.

Advanced HIV infection, preexisting hematologic diseases, and concomitant use of other myelotoxic drugs increase the risk of zidovudine related anemia and neutropenia.

Replacement of zidovudine with another NRTI is generally the best solution for affected patients. Red blood cell transfusion and erythropoietin for anemia, and filgrastim or similar agents for neutropenia may be indicated in some cases. Avoidance of other myelotoxic drugs is also recommended (17).

9.2. Excess bleeding

PIs have been shown to increase the risk of bleeding in hemophiliac subjects. Joints, muscles and soft tissues are especially affected. Use of NNRTIs based regimes or increased dose of factor VIII are generally adequate alternatives for affected patients.

Tipranavir has been associated with increased risk of intracranial hemorrhage. The side effect may occur months after initiating treatment, and tends to occur in patients with predisposing conditions, such as central nervous system lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, or concomitant therapy with anticoagulants and antiplatelet agents (18).

10. URINARY TRACT TOXICITY

10.1. Urolithiasis

Indinavir, a PI, induce de formation of stones composed of monohydrated indinavir throughout the urinary tract. The stones are typically invisible with radiographs. The side effect may occur in as much as one third of the patients who take the drug, and present at any time during treatment. Symptoms are those of typical renal colic, consisting of intense flank pain that may radiate to the genital area or the abdomen, hematuria, dysuria and frequency.

The antecedent of nephrolithiasis of any cause, inadequate fluid intake, high peak serum concentration of Indinavir, and prolonged exposure to the drug are factors that favor the development of lithiasis.

To prevent the side effect it is recommended that patients take at least 2 liters of water, or other fluids, per day. Treatment is symptomatic, and basically consists of

hydration and analgesics. Stent placement in the urinary tract may be required in some cases. Withdrawal of the medication is not mandatory, but switching to an alternative agent is the most practical approach in most cases (19).

10.2. Nephrotoxicity

Indinavir can also produce interstitial nephritis, sometimes with medullary calcification and cortical atrophy. Crystals of monohydrated indinavir seem to be responsible of the side effect. Increased serum creatinine may occur, but end-stage renal failure is uncommon. Asymptomatic leukocyturia is typically present in urinalysis. The disorder is generally reversible after discontinuation of the drug.

Tenofovir, a nucleotide reverse transcriptase inhibitor, may also produce renal dysfunction, generally weeks to months after initiating treatment. Risk factors for nephrotoxicity are a low CD4 cell count, anemia, hypertension, impaired renal function, injection drug use, diabetes, and the use of ritonavir, which slightly increases tenofovir levels. Blood analysis may show increased serum creatinine, hypophosphatemia, hypokalemia and non-anion gap metabolic acidosis. Urine analysis may show abnormalities consistent with the Fanconi syndrome, i. e., proteinuria, glycosuria and phosphaturia. End-stage renal disease is rare. Resolution of the disorder generally takes place with discontinuation of the drug (4,20).

11. METABOLIC AND CARDIOVASCULAR SIDE EFFECTS

Metabolic side effects of antiretrovirals are common. PIs (except unboosted atazanavir) have been shown to increase total cholesterol, LDL-cholesterol and triglyceride concentrations, and decrease HDL-cholesterol level. Efavirenz, stavudine and zidovudine may increase triglyceride concentration. NRTIs such as stavudine and PIs such as ritonavir or lopinavir induce insulin resistance, as defined by inadequate response of tissues to the action of insulin, which may manifest by hyperglycemia, hyperinsulinemia and other metabolic derangements. Moreover, other cardiovascular risk factors, such as smoking, are overrepresented in HIV-infected patients, compared to the general population. As a result, cardiovascular disease is becoming especially prevalent in HIV-infected people (21).

For that reason all cardiovascular risk factors should be assessed before starting antiretroviral treatment and regularly thereafter. Use of antiretrovirals without metabolic side effects is always desirable. Cessation of smoking, when present, is probably the single most efficient intervention. Diet and exercise are useful for many patients, but specific medication is commonly required for metabolic disorders.

Dyslipidemia is commonly treated with statins. Atorvastatin and other statins are appropriate in most cases,

but they must be used with care, because plasma levels may be substantially increased by PIs. Pravastatin has fewer interactions with PIs, but plasma concentration of the drug is significantly increased by darunavir. Ezetimibe may also be employed.

Metformin improves insulin sensitivity and therefore is useful in patients with insulin resistance. Other oral antidiabetic drugs, insulin and antihypertensives are also commonly indicated in patients with HIV-infections, and most of them can be safely used concomitantly with antiretroviral treatment (4).

12. LIPODYSTROPHY

Lipodystrophy, or abnormal distribution of the body's adipose tissue, is one of the most relevant side effects of antiretroviral medication. The condition appears gradually after months to year of treatment, and is frequently associated with metabolic abnormalities such as insulin resistance, dyslipidemia or the hyperlactatemia-steatosis syndrome. Inhibition of mitochondrial DNA polymerase may be the responsible mechanism of all these side effects.

There are two types of lipodystrophy: lipoatrophy, or abnormal loss of fat, and lipohypertrophy, or abnormal accumulation of fat. Both frequently coexist in affected patients.

12.1. Lipoatrophy

Lipoatrophy is related to stavudine and to a less extent to zidovudine and didanosine. The role of the rest of NRTIs and the other groups of antiretrovirals is much more debatable, if any. HIV itself has also been proposed as a possible cause. Low baseline body mass index, advanced age and low CD4 cell count seem to favor the development of the condition.

Fat loss is predominantly peripheral and generally more evident in the face, buttocks and extremities. The abnormality causes a typical image of the face, which results stigmatizing for many patients. Prominent veins in the extremities are also characteristic.

Switching stavudine or zidovudine to other drugs tends to improves lipoatrophy, but normalization can take years. Cosmetic interventions in the face, such as poly-L-lactic acid injections, can give acceptable results in many patients. Drugs such as thiazolidinediones and pravastatin have a small or no effect at all (22).

12.2. Lipohypertrophy

Lipohypertrophy is related PIs. High baseline body mass index, advanced age and low CD4 cell count seem to favor the development of the condition.

Fat accumulation is predominantly central and generally manifests as an increase in abdominal girth and breast size. Visceral fat content is augmented. Appearance of a dorsocervical fat pad (buffalo hump) and subcutaneous lipomas is also typical.

Switching PIs to other agents may slow or halt progression, however, may not reverse the side effect. Removal of fat either by surgery or liposuction can attain satisfactory results in many cases. A variety of diets and drugs have been used to treat lipohypertrophy, with poor results in general. Growth hormone may diminish abdominal fat accumulation, but may aggravate lipodystrophy as well as insulin resistance and dyslipidemia. Metformin has been shown to improve visceral adiposity, but the effect is mild (23).

13. OSTEOPENIA AND OSTEONECROSIS

Patients who take antiretroviral medication have a higher incidence of osteopenia than the general population. Tenofovir seem to predispose to the abnormality more than other medications, although HIV itself and perhaps other factors might also contribute. No study so far has clearly demonstrated an increased risk of bone fractures among patients who take antiretroviral medication. Alendronate may be used when significant osteopenia is present.

PIs have been associated with increased risk of avascular necrosis of bone. Other risk factors for the condition, such as diabetes, corticosteroid use, alcohol abuse, obesity or dyslipidemia, are generally present in affected patients. One or both femoral heads are involved in most cases. The disorder presents insidiously with moderate local pain, commonly triggered by movement or weight bearing. Image studies, especially magnetic resonance (MRI) are useful for diagnosis. Conservative treatment, with analgesics and control of risk factors, may be enough in early stages. Surgical decompression or total joint substitution is frequently required in more advanced or severe cases (24).

14. IMMUNE RECONSTITUTION

During the first weeks after starting antiretroviral therapy an inflammatory syndrome may take place as a consequence of a rapidly improving immune function. The condition is more common in patients with advanced immunodeficiency, and may occur with any conventional antiretroviral treatment.

The syndrome presents with general symptoms such as fever and malaise and local inflammation at the site of a previously recognized or unrecognized opportunistic infection. Symptomatic treatment with analgesics or corticosteroids is generally successful (25).

15. LOCAL REACTIONS

Enfuvirtide, a fusion inhibitor that is administered via subcutaneous injection, produces an inflammatory reaction at the site of injection in virtually every patient. The side effect occurs since the very first doses, and consists of pain, discomfort, pruritus, erythema, warmth, ecchymosis, nodules and cysts. The inflammatory process is generally 1 to 3 cm in diameter and spontaneously resolves within two or three days, but there

are cases of more severe reactions as well as occasional infections at the site of injection.

To prevent the reaction, patients must be educated to use a sterile technique of injection, rotate injection sites and avoid injection into sites with little subcutaneous fat. Treatment is generally unnecessary. In severe cases symptomatic measures, such as analgesics or local cold application, may be useful (26).

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