Original Research Paper

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ADVERSE EFFECTS OF ANTI RETROVIRAL THERAPY

Dermatology

KEYWORDS: Antiretroviral ,Adverse Effects

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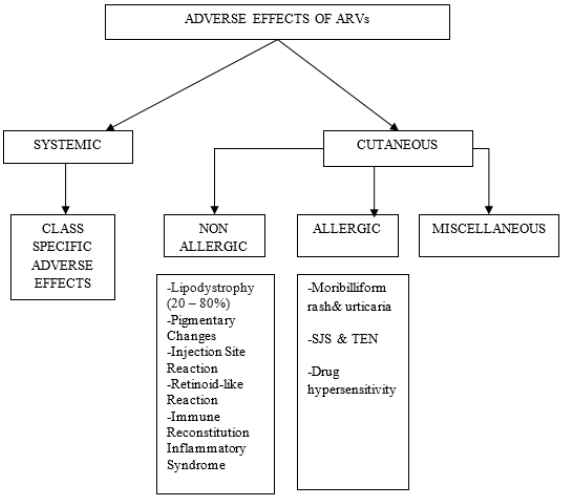
ABSTRACT

Antiretroviral (ARV) toxicity is an increasingly important issue in the management of HIV-infected patients. With the sustained declines in opportunistic complications, HIV infection is a more chronic disease, and so more drugs are being used in patients for longer periods. However, prolonged treatment with ARVs can be difficult to sustain because of problems with adherence and toxic effects. All ARVs have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from class to class, and from patient to patient. A better understanding of the adverse effects of ARVs is of interest not only for HIV specialists as they try to optimize therapy, but also for other physicians who care for HIV-positive patients

INTRODUCTION

Adverse effects have been reported with use of all antiretroviral (ARV) drugs; they are among the most common reasons for switching or discontinuing therapy and for medication nonadherence



CLASS SPECIFIC ADVERSE EFFECTS

DRUG CLASS	CLASS SPECIFIC ADVERSE EFFECTS
NRTI	Lactic acidosis, hepatic steatosis, and body fat redistribution (lipodystrophy)
Nucleotide reverse transcriptase inhibitor	GI, Renal insufficiency, fanconi's like syndrome
NNRTI	Rash ,SJS, TEN, Drug interactions
PI	Dyslipidemia, hyperglycemia, insulin resistance, and lipodystrophy. increase risk of bleeding
Fusion inhibitors	Injection site reactions
CCR5 antagonists	Constitutional symptoms
Integrase inhibitors	Pruritus

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS[NRTI]

NRTIs are associated with mitochondrial toxicities i.e .lactic acidosis, hepatic steatosis, and body fat redistribution (lipodystrophy).

LACTIC ACIDOSIS-

Hyperlactatemia is defined as blood lactate level greater than 2mM. Lactic academia without symptoms or mild symptoms in seen in 8 to 20% patients.

Patients may be asymptomatic, chronically ill or acutely ill. They can also present with non specific symptoms like fatigue, myalgia, nausea vomiting diarrhea abdominal distension weight loss and / or dyspnea. [1]

The other common lab test abnormalities that suggest this diagnosis are elevated CPK, LDH, amylase or AST, increased anion gap, low serum albumin, pH or bicarbonate and CT scan, ultrasound or biopsy of liver showing hepatic steatosis. [2]

The treatment depends on the lactic acid levels.
If the levels are less than 5mM then no treatment, or modification of NRTI is required.

If the levels are greater than 5mM then discontinuation of NRTI is recommended.

If the levels are greater than 10mM then emergency medical intervention and supportive care is required.

HEPATIC STEATOSIS

The risk factors included elevated liver enzymes pretreatment, chronic Hepatitis B or C, concomitant hepatotoxic medications,old age, female,high alcohol intake, high viralload or renal dysfunction. Monitoring of liver enzymes is mandatory. If the levels are greater than 3.5 of the upper limit of normal values then nevirapine should be stopped immediately. Further, if clinical hepatitis occurs nevirapine should be stopped immediately and never readministered.

LIPODYSTROPHY SYNDROME

It is fat accumulation i.e. abdomen (Crix belly), upper back (Buffalo hump),breasts (gynecomastia) and subcutaneous tissue (peripheral ;lipomatosis) with fat atrophy i.e. loss of subcutaneous fat in the face, extremities and buttocks. The treatment includes a low fat diet, exercise[3], Growth hormone, Growth hormone releasing hormone[4], Thiazolidinediones, Testosterone, Metformin, Restorative surgeries, regimen changes.

Zidovudine (AZT,ZDV) side effects include Anemia within 4 to 6 weeks, neutropenia after 12 to 24 weeks, Fatigue, malaise, headache,Nausea, vomiting which resolve 2-4 weeks after initiation, Myalgia, myopathy and hyperpigmentation of skin and nails.[5] It is important to adjust the dosage for renal insufficiency or failure.

Stavudine (d4T)

Of the NRTIs, stavudine appears to convey the greatest risk of lipodystrophy and other mitochondrial toxicity. The side effects include peripheral neuropathy in 5 to 15%, pancreatitis, dyslipidemia, diarrhoea [6]. There is increased risk of lactic acidosis

and hepatic steatosis when combined with didanosine, therefore this combination should be avoided whenever possible, especially during pregnancy. There is also increased risk of peripheral neuropathy when combined with didanosine. It is therefore important to consider dosage adjustment for peripheral neuropathy, and adjust dosage for renal insufficiency or failure.

Lamivudine (3TC)
The adverse effects of lamivudine occur infrequently, and usually manifest as mainly Headache and dry mouth. In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of lamivudine[7]. The dose must be adjusted for renal insufficiency or failure

Emtricitabine (FTC)
It is active against hepatitis B virus (not approved by the U.S. Food and Drug Administration [FDA] for treatment of hepatitis B). In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of emtricitabine. The common adverse effect include headache, nausea, insomnia, hyperpigmentation of palms and soles (occurs most frequently in dark-skinned people).

Abacavir (ABC)
It is known to cause Drug Hypersensitivity syndrome(DHS) i.e. fever, myalgia, malaise, nausea, vomiting, symptoms suggestive of upper respiratory tract infection, as well as anorexia, with symptoms progressively worsening with each subsequent dose [8]. Rash occurs in about half of the cases and usually occurs in the first 6 weeks of treatment and may be more severe with once-daily abacavir dosing.
DHS occurs in 2.3–9% of patients and the risk of hypersensitivity is related to certain genetic factors, particularly HLA B*5701; and therefore screening for this should be considered before prescribing abacavir. In case of hypersensitivity syndrome, abacavir must be discontinued permanently.

Didanosine (ddI)
The adverse effects include pancreatitis in 1 to 9% patients which can be fatal in 6%, peripheral neuropathy in 5 to 12% patients, nausea, diarrhea. Concomitant alcohol intake may increase the risk of pancreatitis. A lower frequency of diarrhea has been found with the use of enteric-coated capsules.

There is increased risk of lactic acidosis and hepatic steatosis when combined with stavudine; this combination should be avoided when possible, especially during pregnancy. There is increased risk of peripheral neuropathy when combined with stavudine. It I necessary to adjust dosage for renal insufficiency or failure.

Zalcitabine (ddC) has been withdrawn from market.

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR
Tenofovir (TDF)
The side effects include flatulence, nausea, diarrhea, abdominal discomfort, asthenia, acute renal insufficiency. Other adverse effects include Fanconi's like syndrome : disorder of proximal tubule leading to electrolyte imbalance and Hypophosphatemia , Hypocalcemia, Normoglycemic Glycosuria, and Chronic renal insufficiency. [9]

It is active against hepatitis B but not FDA approved for treatment of hepatitis B. In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of tenofovir.

It may worsen gastrointestinal symptoms in lactose-intolerant patients; and hence tenofovir is formulated with lactose.

It is necessary to adjust dosage for renal insufficiency or failure.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS [NNRTI]
NNRTIs are associated with rash, and may cause Stevens-Johnson syndrome and toxic epidermal necrolysis.
All NNRTIs may have significant interactions with other drugs; dosage adjustment of interacting agents may be required.

Nevirapine (NVP)
It causes elevations in liver function tests, hepatitis, liver failure, rash, SJS, and TEN.

Nevirapine causes a rash in 18% of patients, with 8% of patients on the drug having either DHS or SJS[10]. Most of the associated rashes occur in the first 8 weeks after initiation. Risk factors for development of a rash include female sex, being treatment-naive, and having a plasma concentration near 5.3 mg/l. A lower lead-in dose of nevirapine i.e.Initial dose of 200 mg per day for first 14 days, then 200 mg twice daily (immediate-release formulation) or 400 mg once daily (extended-release formulation), decreases frequency of rash.

- Hepatotoxicity may be life threatening. It is more common at higher CD4 cell counts, in women, and in patients with hepatitis B or C. Nevirapine should not be initiated for women with CD4 counts of >250 cells/μL or men with CD4 counts of >400 cells/μL, unless the benefit clearly outweighs the risk. Monitor liver tests closely for the first 16 weeks of treatment

Efavirenz (EFV)
Central nervous system symptoms due to Efavirenz are common; the severity usually decreases within 2-4 weeks. Abnormal dreams, drowsiness, dizziness, confusion, mood changes tend to occur. It is found to be teratogenic in animal studies; contraindicated during the first trimester of pregnancy and for use by women of child bearing age group. Elevations in liver function tests and Hyperlipidemia help detect toxicity.

Delaviridine (DLV)
The adverse effects include fatigue, elevations in liver function tests, hepatitis,Nausea, diarrhea. This drug is seldom used; and is less potent than other NNRTIs.

Etravirine [2nd line NNRTI]
This drug causes elevations in liver function tests and has significant interactions with many other drugs (may differ from those of first generation NNRTIs) therefore it is important to screen carefully for drug interactions before prescribing. It does not interact with methadone.

Rilpivirine [2nd line NNRTI]
Adverse effects include Insomnia, Depression, Elevations in liver function tests and elevations in serum creatinine.

PROTEASE INHIBITORS [PI]
All PIs are associated with metabolic abnormalities including dyslipidemia, hyperglycemia, insulin resistance, and lipodystrophy. (Atazanavir is less likely to cause dyslipidemia). They may increase the risk of bleeding in hemophiliacs. PIs may have significant interactions with other drugs; dosage adjustment of interacting agents may be required.

Atazanavir (ATV)
This drug causes hyperbilirubinemia and jaundice, however indirect hyperbilirubinemia does not require discontinuation of Atazanavir. Elevations in liver function tests, PR interval prolongation can also occur. Proton pump inhibitors interfere with atazanavir absorption and are contraindicated for use by patients receiving atazanavir.

Other antacid medications and H2 blockers also interfere with absorption of atazanavir and should be used with caution by patients receiving atazanavir.

Ritonavir (RTV)
The adverse effects include nausea, vomiting, diarrhea, abdominal pain, elevations in liver function tests, fatigue, circumoral or peripheral numbness, taste perversion i.e. metallic taste,

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hyperuricemia[11]. We must avoid combining oral solution with metronidazole or disulfiram as alcohol in the oral solution may cause disulfiram-like reaction.

Lopinavir/ ritonavir
The adverse effects include diarrhea, nausea, vomiting, dyslipidemia, elevations in liver function tests, taste perversion. The Oral solution contains 42% alcohol therefore we must avoid combining oral solution with metronidazole or disulfiram as it may cause disulfiram-like reaction.

Darunavir (DRV)
Adverse reactions include rash, elevations in liver function tests.

Indinavir (IDV)
The adverse effects include Nephrolithiasis and flank pain, therefore to reduce risk of nephrolithiasis, patients should drink at least 1.5 liters of fluid daily. Other side effects include hyperbilirubinemia, elevations in liver function tests, retinoid-like manifestations, alopecia, dry skin, ingrown nails, insomnia, taste perversion, acute porphyria, Stevens–Johnson syndrome, hypersensitivity reaction.

When used as sole PI, it should be taken on an empty stomach, 1 hour before or 2 hours after a meal, and should be taken every 8 hours (not 3 times per day).

Nelfinavir (NFV)
The adverse effects include diarrhea, nausea, vomiting, elevations in liver function tests and fatigue.

Saquinavir (SQV)
The adverse effects include nausea, vomiting, diarrhea, elevations in liver function tests, headache, oral ulcerations.

Amprenavir (APV) is not available in India and is known to cause Morbilliform rash, Stevens–Johnson syndrome.

Fosamprenavir (FPV) is not available in India and is known to cause diarrhea, nausea, vomiting, elevations in liver function tests, rash. It may cause rash in patients sensitive to or intolerant of sulfonamides, hyperlipidemia.

Tipranavir (TPV) is not available in India and causes nausea, vomiting, diarrhea, elevations in liver function tests, increased total cholesterol and triglycerides, rash, intracranial hemorrhage and should never be used without ritonavir boosting. It should be taken with food and may cause rash in patients sensitive to or intolerant of sulfonamides. Case reports of intracranial hemorrhage; association between tipranavir and intracranial hemorrhage is not clear. Many drug-drug interactions occur and certain drug combinations should be avoided.

FUSION INHIBITORS
Enfuvirtide (ENF, T20) is not available in India and is known to cause injection site reactions; erythema, cysts, and nodules at injection sites, neutropenia, hypersensitivity reaction in less than 1% of patients. There is possible increased frequency of pneumonia.

CHEMOKINE CORECEPTOR CCR5 ANTAGONISTS
Maraviroc (MVC)
The adverse effects include diarrhoea, nausea, elevations in liver function tests, hepatitis, upper respiratory tract infections, cough, fatigue, dizziness, headache, joint pain, muscle pain.

INTEGRASE INHIBITORS
Raltegravir (RAL)
They cause nausea, diarrhea, flatulence, elevations in amylase and liver function tests, headache, dizziness, abnormal dreams, pruritus, rash, fatigue, muscle pain.

Miscellaneous cutaneous side effects during retroviral therapy
Acute generalized exanthematous pustulosis, Angiolipomas, Fixed toxic drug reaction, Hypertrichosis of the eyelashes, Allergic contact dermatitis, Photoallergic contact dermatitis, Whisker hair, Oral ulcerations, Esophageal ulcerations, Striae, Urticaria, Leucocytoclastic vasculitis are other side effects.

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