Emergencies in HIV – Part 2

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Abstract
In a short span of two and a half decades, HIV/AIDS has emerged as second largest killer disease that has affected mankind. The triple drug antiretroviral therapy (ART) has ensured a reasonably good quality of life to HIV infected individuals. Human immunodeficiency virus (HIV) infection is associated with several opportunistic infections/malignancies that may be life threatening and need quick intervention by health care workers. These emergencies could be related to opportunistic infections that are seen at presentation or that occur as the immune system gets weaker, or may bede to HIV itself per se. The emergencies could also result from use of antiretroviral drugs like lactic acidosis, pancreatitis, bone marrow suppression and may include the immune reconstitution syndromes. The emergencies due to the opportunistic conditions and HIV per se had been dealt with in detail in the part 1, and this part describes various emergencies that could be encountered due to the administration of the anti retroviral treatment. Some patients may present due to emergencies as a result of co-administration of antiretroviral drugs with drugs used for treatment of some opportunistic infections like ATT etc. ©

INTRODUCTION
Emergencies that can occur over the complete spectrum of HIV illness can be related to the various opportunistic infections or even due to the medications that are used to mange the disease. The former was discussed in depth in the first part of the article. The present section deals with the emergencies that can be encountered due to the treatment of HIV.

EMERGENCIES DUE TO ANTI RETROVIRAL THERAPY
The advent of anti retro viral drugs has remarkably modified the course of the illness and HIV disease, particularly after the advent and use of HAART, after mid nineteen nineties. The anti retroviral drugs that are currently used belong to three classes. However, more classes have been identified and newer drugs are in the pipeline.¹

There have been several studies to document the spectrum of the ART related toxicities. One of the studies from South India² it was reported that among the patients with 1 year of follow-up, Nevirapine therapy was significantly associated with developing rash and d4T therapy with developing peripheral neuropathy. Anemia and hepatitis often occur within 12 weeks of initiating generic HAART. Frequent and early monitoring for these toxicities is warranted in developing countries where generic HAART is increasingly available. In resource-poor settings, where limited drug options are there, decision on when and how to change therapy are especially difficult problems.³

A review of literature in some of the studies⁴ have reported that current evidence, though limited, does suggest the existence of a sex disparity in antiretroviral pharmacokinetics, and such disparity has been shown to have pharmacodynamic implications for some drugs. Sex-mediated intracellular pharmaco-enhancement was associated with superior antiviral activities for the zidovudine and lamivudine members of the nucleoside reverse transcriptase inhibitor class. There appears to be divergent opinions about whether sex is a significant determinant of either nevirapine or efavirenz plasma concentrations. For certain protease inhibitors (PIs) (eg, saquinavir [SQV] and indinavir [IDV]), clinically significant relationships between sex differences in plasma drug concentrations and clinical outcomes have been observed. There appears to be a trend toward higher drug exposure in women than in men when PIs are boosted with ritonavir (RTV). Nelfinavir, the only PI that is currently administered

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unboosted with RTV, does not exhibit a sex difference in its plasma concentrations. Unboosted amprenavir exposure was lower in women compared with men. Sex differences in the pharmacokinetics of SQV and IDV were observed only in the setting of RTV boosting. However, most of these studies had a limitation that they had very few female subjects and most of these studies were retrospective, with lack of correlating pharmacokinetic studies.

Lactic Acidosis

The term “mitochondrial toxicity” describes a group of different clinical conditions that happen because of damage to the mitochondria. One possible cause of damage to mitochondria may be anti-HIV drugs known as nucleoside reverse transcriptase inhibitors (NRTIs).

The most serious condition that can result from such damage is lactic acidosis (an increase of lactic acid in the blood). Lactic acidosis has been reported in patients receiving NRTI regimens including combinations of Zidovudine (AZT) or stavudine (d4T) with didanosine (ddI), or rarely lamivudine (3TC). Lactic Acidosis is therefore an important class specific side effect for the NRTI group.

One of the studies\(^2\) have reported that women were significantly more likely to experience lactic acidosis, while men were significantly more likely to experience immune reconstitution syndrome \((p < 0.05)\).

The initial symptoms of lactic acidosis may include nausea, vomiting, abdominal pain, weight loss, malaise, fatigue (feeling tired), shortness of breath and occasionally fever. In addition, the patient may experience diarrhea, tachycardia and tachypnea.

Laboratory tests usually show a high amount of lactic acid in blood, somewhat abnormal liver function tests, and moderate to severe acidosis.

The management of lactic acidosis should include stopping anti-HIV drugs, and correction of these abnormalities. Patients may need to receive bicarbonate and glucose intravenously. Treatment with riboflavin might help in some cases. As many as 60\% of patients with lactic acidosis can die from it. Recovery, sometimes may take few months. Long term residual effects are common. Studies\(^5\) have reported that there is a lack of awareness about the risk factors for developing severe lactic acidosis and recognition of its onset with dire consequences.

Abacavir Hypersensitivity Reaction

The use of the NRTI abacavir can cause a serious hypersensitivity reaction in a small number of patients \((4.8\% \text{ range})\).\(^67\) Median onset 8 day of abacavir initiation, majority develop in first 6 weeks. A higher rate is noted in patients who were receiving once daily regime, those who were ART naive, in patients with a nevirapine allergy, and in acute HIV infection.\(^8\) Genetic predisposition is defined for some patients and possibly has a role in most.

The symptoms of abacavir hypersensitivity include fever, skin rash, nausea, vomiting, diarrhoea, abdominal pain, malaise, and lethargy (sleepiness). Usually a hypersensitivity reaction will start within the first six weeks of taking abacavir. If a patient develops these symptoms, the abacavir should be stopped immediately. Whether hypersensitivity is suspected or confirmed, abacavir should never be restarted, as it may cause a more severe hypersensitivity reaction along with hypotension (low blood pressure), tachycardia (fast heart beat), and even death.

It has been reported that serious adverse events associated with the use of abacavir can be avoided by appropriate recognition and management of the Hypersensitivity reaction. Screening patients for HLA-B*5701 prior to initiation of abacavir represents a tool to further decrease the risk of HSRs as well as unnecessary discontinuation of this drug.\(^9\) However, this may not be routinely possible in resource constrained settings.

Indinavir-Induced Nephrolithiasis

Indinavir belongs to the protease inhibitor group of anti retro viral drugs. It tends to form crystals in the kidneys. These crystals can form kidney stones made up almost completely of this protease inhibitor. This can happen in 5\% to 35\% of patients treated with the standard dose of indinavir \((800\text{mg three times a day})\). Patients with indinavir stones can feel like those with other kinds of kidney stones: pain on the sides, hematuria (blood in urine), nausea, and vomiting. There have been case reports of indinavir associated toxicity mimicking urinary tuberculosis in patients with AIDS.\(^10\)

The confirmation of kidney stones may be difficult because indinavir-containing stones are not visible using plain radiography or non-contrast CT scans. Most patients will respond to conservative treatment that includes intravenous fluids, pain control, monitoring kidney function, and discontinuation of indinavir. Most people replace indinavir with some other agent.

To prevent kidney stones caused by indinavir, patients should take more liquids — a minimum of 1.5 liters per day of non-caffeinated, non-alcoholic liquids. Wasmuth et al.\(^11\) have reported that dose reduction of IDV improved tolerability of IDV-containing highly active antiretroviral treatment (HAART) and sufficient IDV trough concentrations were maintained in all patients as was virologic control.

Marrow suppression by zidovudine

The Marrow suppression by zidovudine manifests as neutropenia and/or anemia after weeks or months of therapy. Anemia has been reported with 1-4\% and neutropenia with 2-8\% cases. Risk is said to be more with advanced stage of HIV disease.

Zidovudine should be discontinued immediately. Erythropoietin and granulocyte stimulating factor G-CSF may be needed for anemia and neutropenia respectively. Blood transfusions are often required.

Hepatic necrosis with Nevirapine

Elevation of the liver enzymes with ARV is not very uncommon, and severe hepatotoxicity has been reported
in up to 6% cases. However, the side effect depends on the drug class, agents used in regimen and the pre existing state of liver function. Nevirapine has been more commonly associated with liver toxicity, though cases have been reported for ritonavir as well. It has been reported in 1-2% of all receiving nevirapine can develop hepatotoxicity. It has been observed that the rate of symptomatic hepatitis is almost 11% in females with CD4 count more than 250/cmm and 6% in males with baseline CD4 count more than 400/cmm. Kondo et al studied the nevirapine induced toxicity in pregnant women, and they reported a high incidence of adverse events with nevirapine in this study, but most of them were cutaneous. There was no correlation between high CD4 counts and adverse events when analyzing both cutaneous and hepatic reactions. However, hepatotoxicity occurred only in pregnant women with CD4 counts > or =250 cells/microL. In another study, prior history of drug allergy, especially against sulfamethoxazole, and concurrent use of antitubercular drugs have been identified as predisposing factors for nevirapine toxicity. The incidence of NVP toxicity in this study was reported to be 1.09/100 person-months. And the median time of onset was 4 weeks post NVP initiation (2.57 weeks for skin toxicity and 12.43 weeks for hepatic toxicity).

The drug should be promptly discontinued. Role of anti histaminics and steroids is doubtful. The side effect may progress even after the discontinuation of the drug.

Rash by Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

The toxicities of NNRT, mainly nevirapine (more commonly) and efavirenz to some extent have been reported. In a French cohort of HIV positive patients, HLA-DRB101 allele plays an important role in susceptibility to cutaneous reactions associated with nevirapine and efavirenz in HIV patients.

Maculopapular rash

NNRTIs sometimes can cause a maculopapular rash (a rash made up of small, well-defined bumps on the skin). NNRTIs include delavirdine, nevirapine, and efavirenz. The rash can affect the trunk, face, arms, and legs. It usually appears within the first four to six weeks of taking the medication.

Stevens-Johnson syndrome

This is the most serious form of rash caused by NNRTIs. This severe and life-threatening rash can affect the skin but also mucosal surfaces (like inside the mouth or nose). It is sometimes known as toxic epidermal necrolysis. It is seen in 0.5 -1% patients on Nevirapine and 0.1% on efavirenz. The symptoms are a diffuse rash with peeling of large areas of the skin, blistering inside of the mouth, conjunctivitis (swelling and reddening of the eyes), bronchitis, and general symptoms including fever, myalgia (muscular pain), arthralgia (joint pain), and malaise. This condition is an extreme emergency and most of the time patients are treated in burn units where close medical observation is necessary. IV fluids, and antibiotics may be required. Role of steroids is controversial.

The S J syndrome is characterized by the severe cutaneous disorder characterized by skin lesions and mucosal involvement. Lesions may become bullous and later rupture. Mucosal involvement may include erythema, edema, sloughing, blistering, ulceration and necrosis.

Pancreatitis

Up to 7% of patients treated with didanosine suffer from pancreatitis. Occasionally, stavudine, lamivudine and zalcitabine cause pancreatitis too. The combinations of didanosine plus stavudine or didanosine plus tenofovir carry a particularly high risk for pancreatitis. Alcohol consumption and treatment with intra-venous pentamidine are further risk factors. A significant interaction between didanosine and tenofovir leads to a 40% rise in didanosine plasma concentration. Cases of severe, sometimes fatal, pancreatitis on concurrent didanosine and tenofovir therapy, have been reported. Didanosine and Tenofovir should therefore not be co-administered in patients weighing less than 60...
kg, who have renal dysfunction or who take lopinavir/ritonavir. Antiretroviral drug-induced pancreatitis is not distinguishable from pancreatitis of any other etiology, either clinically or in laboratory tests. Antiretroviral therapy should be stopped immediately. Treatment is the same as for pancreatitis of other etiologies. The symptoms and laboratory changes usually resolve rapidly. Drugs that have induced pancreatitis once, must never be given again. If patients have a history of pancreatitis of any origin, didanosine is contraindicated.

CNS Side Effects

Lochet et al. have reported that up to 40% of patients, treatment with efavirenz leads to CNS side effects such as dizziness, insomnia, nightmares; even mood fluctuations, depression, depersonalization, paranoid delusions, confusion and suicidal ideation.

These side effects are observed mainly during the first days and weeks of treatment. Discontinuation of therapy becomes necessary in only 3% of patients.

Higher plasma levels of Efavirenz have been associated with frequent occurrence of the CNS symptoms. Lorazepam can diminish the CNS side effects, and haloperidol can be given for panic attacks and nightmares, but both drugs should be restricted to severe cases, as these medications can also have side effects, and lorazepam can be addictive over time.

Haas et al. have suggested a genetic predilection to CNS effects of Efavirenz. CNS side effects are rarely seen with other NNRTIs. If they persist for more than six weeks, efavirenz should be replaced.

References