Immune Reconstitution Inflammatory Syndrome (IRIS) is atypical inflammatory disorders associated with immune recovery after antiretroviral therapy. Qualitative and quantitative recovery of pathogen-specific cellular and humoral responses to opportunistic pathogens is thought to be responsible for the development of IRIS. The target of the inflammatory response may be viable or dead microbial pathogens, host antigens or tumor antigens. The most frequently reported IRIS are with tuberculosis, MAC and cryptococcal meningitis. The interval from antiretroviral therapy to the development of IRIS is usually less than 60 days (range 3 to 658 days). IRIS occurs in 2 forms; ‘paradoxical IRIS’ i.e., a worsening of a treated OI, and ‘unmasking IRIS’ a new expression of a dormant, previously unrecognized OI. Most IRIS in HIV/TB disease occurs within 8 weeks of antiretroviral therapy. Delaying of the start of antiretroviral therapy may reduce the incidence and severity of IRIS. However, it must be weighed against the potential benefit of earlier antiretroviral therapy in improving immune function and preventing progression of HIV disease and mortality.

In this case discussion, the differential diagnosis, when to start antiretroviral therapy and management of IRIS will be discussed.

Managing adverse reactions to antiretroviral therapy in HIV patients

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Combination antiretroviral therapy (cART) has significantly improved the survival and reduced the morbidities of patients with HIV infection. An increasing number of drug classes targeting different phases of the HIV life cycle have been developed and more than 20 different drugs are available, thus increasing flexibility to the clinicians in tailoring the regimen to the individual patient. However, drug adherence remains an important factor for efficacy and durability of cART and adverse reaction to medications is an important reason for non-adherence. Cross resistance within drug classes and the need for 2 and preferably 3 active drugs to construct an effective regimen mean that patients have limited options for second- and third-line regimen should the first one fail. In addition, there is still limited access to the full range of antiretroviral drugs in resource limited settings. It is therefore important that adverse reactions to antiretroviral drugs are proactively managed to maximize their clinical benefit.

Individual antiretroviral agents have different profile of adverse reactions. Some such as rash, anaemia and hepatotoxicity present relatively early after treatment, in the time frame of weeks to months. Others especially metabolic side effects such as lipodystrophy and hyperlipidaemia are more insidious in onset, appearing after months to years. It is important to recognize that patients might discontinue their antiretroviral drugs if they perceive discomfort or that they have deterioration in their quality of life after starting treatment. HIV treatment services should incorporate active monitoring and management of the adverse reactions to cART so as to maintain the patients on treatment.

The initial cART regimen is the most crucial in determining the treatment outcome and a potent and well tolerated combination should be selected. The choice should be guided by the clinical and psychosocial profile of the patient taking into consideration the likelihood for adverse reaction and interaction with other medications that the patient is taking. These include the...
age and gender of the patient as well as co-morbidities such as chronic hepatitis infection or tuberculosis. Pre-existing or predisposition to marrow suppression, renal or liver impairment would deter the use of zidovudine, tenofovir and nevirapine respectively while abacavir, didanosine and certain protease inhibitors should be avoided in patients with high cardiovascular risk profile. Guidelines are now available on the CD4 level as well as lead-in dose escalation for safer prescription of nevirapine while test for HLA-B*5701 can be performed to avoid hypersensitivity reaction to abacavir.

The patient should be primed about the possible adverse reactions prior to initiation of treatment. In addition, the possibility of aggravation of pre-existing symptoms due to immune reconstitution syndrome should be explained. They should understand the symptoms that may occur, the option of switch in case of intolerance, as well as the appropriate method of safely discontinuing the medications if necessary. When the antiretroviral regimen contains drugs with different half-lives, simultaneous discontinuation of all drugs may result in functional monotherapy with the drug with the longest half-life. This might lead to development of drug resistance and is most relevant for the non-nucleoside reverse transcriptase inhibitor (NNRTI) class which has a low genetic barrier to resistance. To overcome this possibility, other than in the context of severe or life-threatening side effect, the nucleoside reverse transcriptase inhibitor (NRTI) backbone can be maintained for about a week after stopping the NNRTI. The alternative is to directly substitute the NNRTI with a protease inhibitor (PI).

During follow up, apart from noting symptoms of intolerance, blood pressure, body weight and laboratory monitoring should be performed on a regular basis for any adverse reaction that the patient may not be aware of. These include blood counts, renal and liver function tests, fasting glucose and lipid profile and urinalysis. The patients should be actively engaged in identifying and managing the adverse effect of cART to ensure sustainability of the benefit.

Appendix:

Adverse reaction to individual antiretroviral drugs:

1. Nucleoside reverse transcriptase inhibitor (NRTI):
   Lactic acidosis and hepatic steatosis (higher incidence with stavudine)
   Lipodystrophy (higher incidence with stavudine)
   Abacavir - hypersensitivity reaction
   Didanosine - pancreatitis, peripheral neuropathy
   Stavudine – peripheral neuropathy, pancreatitis

2. Non-nucleoside reverse transcriptase inhibitor (NNRTI):
   Nevirapine – hepatotoxicity, rash including Stevens-Johnson syndrome
   Efavirenz – neuropsychiatric symptoms, tenosynovitis

3. Protease inhibitor (PI)
   Atazanavir - hyperbilirubinaemia
   Darunavir - gastrointestinal intolerance, rash
   Indinavir - nephrolithiasis, gastrointestinal intolerance
   Lopinavir - diarrhoea
   Nelfinavir - diarrhoea
   Ritonavir - gastrointestinal intolerance, hepatitis
   Tipranavir – gastrointestinal intolerance, rash, liver toxicity, intracranial haemorrhage

4. Long term metabolic effect:
   Central fat accumulation, lipodystrophy over face and limbs
   Hyperlipidaemia
   Mitochondrial toxicity
   Osteopaenia
   Glucose intolerance and insulin resistance
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   - Lipodystrophy (higher incidence with stavudine)
   - Abacavir - hypersensitivity reaction
   - Didanosine - pancreatitis, peripheral neuropathy
   - Stavudine – peripheral neuropathy, pancreatitis

   Tenofovir - renal impairment
   - Zidovudine - headache, gastrointestinal intolerance, bone marrow suppression
   - TDF (Tenofovir disoproxil fumarate): bone marrow suppression

2. Non-nucleoside reverse transcriptase inhibitor (NNRTIs):
   - Nevirapine – hepatotoxicity, rash including Stevens-Johnson syndrome
   - Delavirdine – neurotoxicity, pregnancy
   - Efavirenz – neurotoxicity, hepatitis

3. Protease inhibitor (PI):
   - Atazanavir - hyperbilirubinemia
   - Darunavir - gastrointestinal intolerance, rash
   - Indinavir - nephrolithiasis, gastrointestinal intolerance
   - Lopinavir - diarrhea
   - Nelfinavir - diarrhea
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