ADVERSE DRUG REACTIONS (ADR) DUE TO ANTI-RETROVIRALS (ARV) : ISSUES AND CHALLENGES

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‘LETS RESOLVE OURSELVES TO FIGHT THE WORST, SELF-MADE DISASTER – HIV/AIDS’

INTRODUCTION

Entry of HIV into body leads to continuous high-level viral replication, immunosuppression, resistance (due to mutation) and persistence (due to entry of HIV in sanctuary sites and resting memory T-cells) making HIV an incurable condition. Thus, life long multi-drug therapy is required for near complete suppression of HIV-1 replication.

There are now 20 drugs available in 4 drug classes and choosing between many of these combinations is therefore increasingly dependent upon knowledge of anti-retroviral toxicities.

In a review of over 1000 patients in a Swiss cohort that received combination ARV therapy, 47% and 27% of the patients were reported to have clinical and laboratory adverse events, respectively.1

Cutaneous manifestations of ADR can serve as surrogate marker of internal involvement. Thus, dermatovenereologists can play a crucial role in identifying and managing ADR.

CLASSIFICATION OF ARV

1. Nucleoside Reverse Transcriptase Inhibitor (NRTI) - Zidovudine, Lamivudine, Stavudine, Didanosine, Zalcitabine, Abacavir, Emtricitabine

2. Non - Nucleoside Reverse Transcriptase Inhibitors (NNRTI) - Nevirapine, Delavirdine, Efavirenz.

3. Protease inhibitor (PI) - Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir & Ritonavir, Atazanavir, Fosamprenavir

4. Fusion Inhibitors – Enfuvirtide

ANTIRETROVIRAL ISSUES

Pharmacoeconomic issue: Access

Though the access to ARV is increasing because of reducing cost only 5-10% of patients in need for ARV are on ARV.

Gender Discrimination

The recommendation of when to start ARV is same for HIV infected adult male and female patients and the sex specific differences in CD4 counts, viral load and rate of disease progression2 are same but the number of females who actually take ARV are very few.

Adherence

HIV viral suppression, reduced rates of resistance and improved survival have been correlated with high rates of adherence to ARV. Hira et al reported adherence of more than 95% in 50-60% of cases and the most important factor resulting in non-adherence is toxicity.3

Drug-Drug Interaction

E.g. Oxidative metabolism of nevirapine is in the liver by cytochrome P450 isoforms CYP3A4 and...
CYP2B6. Rifampicin induces the synthesis of CYP3A4 and thus decreases nevirapine levels by 20-58%. Thus use of this combination is not recommended; however if used, co-administration should be done with careful monitoring.4

**Drug-Food Interaction**

The oral bioavailability of certain ARV is affected if administered with food.

**Other issues**

While designing the regimen along with toxicities other issues to be kept in mind are resistance, treatment failure and consideration for future options.

**FACTORS DECIDING ADR**

**Pharmacogenomics** – One of the most fashionable field of medical science these days is pharmacogenomics. This is the study of how people with different genetic make up respond differently to particular drugs. The hope is that it will lead to high precision prescription, with fewer side effects & better outcomes.

**Sex** – Female patients have a higher propensity of developing SJ Syndrome and symptomatic hepatic events from Nevirapine.5

**Stage of HIV** – Viral load and CD4 count e.g., HIV infected women with CD4 counts > 250 cells/mm3 are at a 12-fold increased risk and men with CD4 counts > 400 cells/mm3 have a 3-fold greater risk for Nevirapine associated over toxicity than with CD4 counts below this threshold. It is for this reason Nevirapine should never be used for post-exposure prophylaxis.6

**Co-administration of other drugs**

**Co-existing infection / opportunistic infections**

**ADVERSE DRUG REACTIONS**

Anti-retroviral can lead to short-term toxicities or long-term side effects.

**Short-term toxicities:**

1. Organ: Liver, kidney, bone marrow
2. Cutaneous Reactions: SJ syndrome, hypersensitivity

**Long term side effects:**

1. Morphologic complications
   - Lipoaccumulation / lipohypertrophy, visceral adiposity
   - Breast enlargement
   - Dorso-ventral fat pad
   - Lipomas
   - Cosmetic disfigurement
2. Metabolic Abnormalities
   - Dyslipidimias
   - Abnormalities of glucose metabolism
   - Insulin resistance
   - Lactic acidosis
   - Hepatosteatosis
   - Osteonecrosis, osteopenia, osteoporosis
   - Increasing bleeding in hemophiliacs

**MITOCHONDRIAL TOXICITIES**

The medium and long-term side effects are due to inhibition of mitochondrial DNA polymerase resulting in impaired synthesis of mitochondrial enzymes that generate ATP by oxidative phosphorylation.

Myopathy – Zidovudine

Neuropathy – Stavudine, Didanosine, Zalcitabine

Hepatic-steatosis and lactic academia – Stavudine, Didanosine, Zidovudine

Peripheral neuropathy – All NRTIs predominantly Stavudine
Pancreatitis - Didanosine

Most serious mitochondrial toxicities are lactic acidosis and pancreatitis. Mortality was 80% when lactate concentration was greater than 10 mmol/L.

Lactic acidemia is far more common (about 15%) and is often associated with mild constitutional symptoms, mild increase in liver enzymes and peripheral lipoatrophy.²

**Muscle:** Fatigue, myalgia, proximal weakness, wasting

**Heart:** Dilated cardiomyopathy

**Nerve:** Distal pain, numbness, paraesthesia, reduced reflexes/power

**Liver:** Hepatomegaly, nausea, ascites, edema, dyspnoea, encephalopathy

**Pancreas:** Abdominal pain

**Fat:**

- Peripheral lipoatrophy
- Lipomata

Management of mitochondrial toxicities is generally limited to cessation of causative drug. Given that toxicity can be of late onset, clinical screening for drug toxicity should be done throughout therapy.

**HYPERSENSITIVITY**

Drug hypersensitivity in HIV-1 infected patients is about 100 times more common than in general population.

Drug hypersensitivity typically manifests as erythematous maculopapular, pruritic and confluent rash with or without fever. Rash is most prominent on body and arms and begins after 1-2 weeks of therapy. Constitutional features are often prominent and can precede rash (with abacavir) or occur without rash. SJ syndrome or Toxic Epidermal Necrolysis (TEN) develops in less than 0.3% of patients.⁸

All NNRTI (Nevirapine, Delavirdine, Efavirenz), NRTI (Abacavir) and PI (Amprenavir) are common ARV that cause hypersensitivity.

**Clinical Features**

**Principal Features**

- Morbilliform / maculopapular rash
- Fever (often precedes rash)
- Myalgias, fatigue
- Mucosal ulceration

**Less common features (< 5%)**

- SJ syndrome/TEN
- Anicteric hepatitis
- Hypotension
- Acute interstitial nephritis
- Acute interstitial pneumonitis

About 50% of ARV hypersensitivity resolves spontaneously despite continuation of therapy. Therapy should be stopped if there is mucosal involvement, blistering, exfoliation, clinically significant hepatic dysfunction (e.g. tender hepatomegaly, aminotransferase concentrations greater than five times baseline), fever (> 39°C or intolerable pruritus).⁹

Glucocorticosteroids are ineffective for the prevention of nevirapine hypersensitivity.

Rechallenge is possible for mild to moderate NNRTI hypersensitivity but not for abacavir, since several deaths have been attributed to abacavir rechallenges.

**LIPODYSTROPHY SYNDROME**

Main clinical features are peripheral fat loss (presumed lipoatrophy with loss of buccal fat and thinning of extremities and buttocks) and central fat accumulation within abdomen (crix –belly or protease paunch), breasts (gynecomastia) and over dorsocervical spine (buffalo hump) and other peripheral lipomatosis.

The overall prevalence is about 50% after 12-18 months of therapy.
In adult males, there is an overall fat loss although fat accumulation may predominate in women.

**Metabolic Features**
- Hypetriglyceridemia
- Hypercholesterolemia
- Insulin resistance
  (increased insulin, C-peptides)
- Type-2 diabetes mellitus / impaired glucose tolerance
- Lactic academia

Lipodystrophy should not be diagnosed if patient has had a recent severe illness associated with weight loss.

Risk factors for lipodystrophy are genetic factors, low body weight before therapy, raised C-peptides and triglyceride concentrations after about 1 year, use of dual PI combination ritonavir-saquinavir and use of nucleotide analogue, stavudine.

**Clinical Significance**
- Adherence to ARV could be compromised because of cosmetic effects, leading to virological and then clinical failure.
- Metabolic effects could lead to increase in cardiovascular disease.
- Severe hypertriglyceridemia seen with PI therapy may be due to pancreatitis.
- Patients with diabetes mellitus or impaired glucose tolerance are at increased risk of micro-vascular diabetic disease such as retinopathy, neuropathy and nephropathy.

**Evaluation**
Patient perception, physical examination, serial photography, waist – hip ratio (>0.85 for women, >0.95 for men), DEXA scan, ultrasound, CT scan and MRI.10

**Management**
- Low fat diet and aerobic exercise – may exacerbate lipoatrophy
- Testosterone replacement therapy (in hypogonadal men) or anabolic steroids (eugonadal men)
- Growth hormone – Subcutaneous or intralesional growth hormone can reduce intraabdominal adiposity and size of buffalo hump respectively.
- Thiazolidinediones
- Metformin – improves insulin sensitivity, results in weight loss and decreased intra-abdominal fat
- Gemfibrozil and Atorvastatin might be safe and have some efficacy in lowering lipids. A trial of fibrate for hypertriglyceridemia and either Pravastatin or Atorvastatin for hypercholesterolemia has been recommended.
- Anabolic steroids are anabolic for muscle not fat, although increased muscle mass may partly disguise fat loss.
- Restorative surgery (excision or liposuction) has been done on some patients with severe fat accumulation.
- Withdrawal or substitution of ARV: McComsey GA et al reported improvement in lipodystrophy associated with ARV in patients who were switched from Stavudine to Abacavir or Zidovudine.11

**CUTANEOUS MANIFESTATIONS OF ANTIRETROVIRAL THERAPY**

Patients have been associated with lipodystrophy syndrome, hypersensitivity reactions, urticaria, morbilliform eruptions and a large number of drug interactions. NNRTIs have resulted in various cutaneous eruptions, as well as a hypersensitivity syndrome. NRTIs have resulted in alterations of the nails, nail and mucocutaneous pigmentation, hair changes, vasculitis, and morbilliform eruptions.12
<table>
<thead>
<tr>
<th>DRUG</th>
<th>CUTANEOUS REACTIONS</th>
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| Protease inhibitors (in general) | 1. Lipodystrophy  
2. Hypersensitivity reaction  
3. Acute generalized exanthematous pustulosis |
| Indinavir                   | 1. Acute porphyria  
2. Stevens-Johnson syndrome  
3. Drug eruption  
4. Gynecomastia  
5. Alopecia  
6. Paronychia with nailfold pyogenic granuloma-like lesions |
| Ritonavir                   | 1. IgA-mediated hypersensitivity reaction  
2. Drug reaction  
3. Hematoma formation |
| Nelfinavir                  | 1. Morbilliform eruption  
2. Generalized urticaria |
| Saquinavir                  | 1. Gynecomastia  
2. Fixed drug reaction  
3. Stevens-Johnson syndrome  
4. Hypersensitivity syndrome (DRESS) |
| Delavirdine                 | 1. Drug eruption |
| Zidovudine                  | 1. Nail hyperpigmentation  
2. Mucocutaneous hyperpigmentation  
3. Hypertrichosis  
4. Eyelash hypertrichosis  
5. Hypersensitivity syndrome  
6. Leukocytoclastic vasculitis  
7. Heightened reaction to mosquito bites  
8. Paronychia with lateral nailfold pyogenic granuloma-like lesions |
| Didanosine                  | 1. Leukocytoclastic vasculitis  
2. Stevens-Johnson syndrome  
3. Papuloerythroderma of Ofuji  
4. Acute gouty arthritis  
5. Alopecia |
| Lamivudine                  | 1. Allergic contact dermatitis  
2. Paronychia with lateral nailfold pyogenic granuloma-like lesions |
| Zalcitabine                 | 1. Morbilliform eruption  
2. Hypersensitivity syndrome |
GASTROINTESTINAL EFFECTS
All ARV can cause transient nausea, vomiting or diarrhoea early in therapy.

Among NRTI nausea is more common with Zidovudine and Didanosine (partly because of latter’s antacid buffer).

Indinavir is also associated with esophageal reflux (about 3%) but should not be given with antacid because salts in the antacids can bind to Indinavir and prevent its absorption. H2 blockers and proton pump inhibitors are acceptable options.

IS HAART (Highly Active Antiretroviral Therapy) BAD FOR HEART?
Many epidemiological studies suggest that the risk of myocardial infarction increases with duration of exposure to combination antiretroviral therapy containing NNRTI / PI which are known to cause metabolic complications like hyperlipidemia and insulin resistance.\textsuperscript{13, 14}

PI / NNRTIs may be substituted by abacavir (3 NRTI regimen).

Newer PI Atazanavir is less likely to cause elevation in total and LDL cholesterol and triglyceride level.

HEPATITIS
NRTIs can cause hepatic steatosis, generally after more than 6 months of therapy, probably via mitochondrial toxicity.

NNRTIs can cause hepatitis in the first 2-3 months of therapy, sometimes as a part of hypersensitivity reaction.

Protease inhibitors can also cause hepatitis by an unknown mechanism, particularly in patients co-infected with hepatitis B or C, raised hepatic aminotransferase concentrations and alcoholism.

Some cases of hepatitis with antiviral seem to represent a side effects of an improved immune response, where immune restoration leads to recognition of hepatitis B or C in chronic carriers, and results in a clinical episode of hepatitis with seroconversion.\textsuperscript{15}

Withdrawal of lamivudine may result in a hepatic flare in 25% of chronic hepatitis B carriers.

OSTEOPENIA/OSTEOPOROSIS AND OSTEONECROSIS/AVASCULAR NECROSIS
The most common site is the femoral head; many patients have other risk factors, including alcohol abuse, hyperlipidemia, lipid lowering agents, testosterone therapy, corticosteroid use, and hypercoagulability. X-rays are not sensitive for detecting avascular necrosis. Bone density studies using DEXA scan shows osteopenia and osteoporosis. Screening of asymptomatic patients is not recommended. CT scan or MRI should be considered in patients with symptoms and risk.

COMMONLY USED DRUGS AND THEIR TOXICITIES
1. AZT (ZDV, ZIDOVUDINE)
Common side effects: Anemia, low white blood cell count, nausea, fatigue, headache, myopathy
Dermatological: Nail and skin pigmentation
Drug interactions: Antagonistic with D4T (never co-administer)
Notes: Contraindicated if significant anemia or neutropenia

2. 3TC (LAMIVUDINE) Minimal toxicities

3. D4T (STAVUDINE)
Common side effects: Usually well tolerated
Nausea, peripheral neuropathy, pancreatitis (especially if with DDI), lipoatrophy Drug interactions: Antagonistic with AZT (never co-administer)
Notes: Avoid co-administration with DDI, particularly during pregnancy

4. NEVIRAPINE (NVP)
Should always be started in lead-in dose (200mg OD for the first 14 days and then make 200mg BD)
Rash: usually in first 2-8 weeks, higher in women, more if higher CD4 count
Can progress to severe rash or SJ syndrome
Hepatotoxicity: Often mild to moderate but can be severe (potentially fatal)

2 weekly monitoring of enzymes for first 8 weeks. Alternative is efavirenz.

Drug interactions: should not be given with rifampicin and can decrease levels (and efficacy) of estrogen-containing oral contraception.

Not recommended for PEP.

5. EFAVIRENZ (EFV)

Common side effects: CNS (nightmares, dizziness, others) rash (usually mild), Hepatotoxicity, lipid abnormalities.

A study confirms multiple EEG abnormalities in Efavirenz treated patients with difficulty in sleeping and correlated with serum drug levels.16

Note: Teratogenic do not use in pregnancy or in women of child-bearing potential who are not using any forms of birth control.

CYTOCHROME P450 INTERACTIONS

Many protease inhibitors and the NNRTIs interact with cytochrome P450 isoforms, perhaps the most significant being CYP3A4 and CYP2D6. Common potential interactions and outcomes before starting therapy includes decreased concentrations of oral contraceptives (leading to pregnancy) and increased concentrations of some non-sedating antihistamines, macrolides and cisapride (torsade de point arrhythmias); rifabutin and rifampicin (polyarthritis and hepatitis); benzodiazepines and opiates (sedation); ergot derivatives (vasospasm); sildenafil (hypotension).

Pharmacologic boosting

One positive side effect of ritonavir is the inhibition of cytochrome P450 mediated metabolism of other protease inhibitors. This inhibition allows for fewer and less frequent doses of other protease inhibitors. Since this inhibition occurs at very low ritonavir doses (as low as 100 mg twice daily), dual protease inhibitor regimens including ritonavir and saquinavir, indinavir, lopinavir or amprenavir are common although not licensed.

PREGNANCY

No antiretroviral has been rated by the Food and Drug Administration as category A (well demonstrated lack of risk to human fetuses in the first trimester). 17

Drugs rated as categories B (safe in animal studies) are didanosine, saquinavir, ritonavir and neffinavir.

Drugs rated as category C (animal toxicity proven or not studied) are delavirdine, zalcitabine, nevirapine, lamivudine, stavudine and zidovudine.

Efavirenz has caused cranial malformations in monkey fetuses and so is contraindicated in pregnancy or when pregnancy is possible.

INJECTING DRUG USERS

Several drugs can interfere with the metabolism of methadone. This effect may lead to an increase (delavirdine) or decrease (nevirapine, efavirenz) in plasma concentrations of methadone and so to sedation or withdrawal, respectively.

IMMUNE RECONSTITUTION SYNDROME (IRIS)

A subgroup of HAART treated patients will exhibit paradoxical deterioration in their clinical status, despite satisfactory control of viral replication and improvements in CD4 counts. This clinical deterioration, known as the immune restoration syndrome or immune reconstitution inflammatory syndrome (IRIS) is a result of an exuberant inflammatory response towards previously diagnosed or incubating opportunistic pathogens, as well as response towards other as yet undefined antigens.18

A study reported IRIS in 21% cases within 12 weeks of starting therapy (EACS, 2003).

This includes paradoxical exacerbation of pulmonary and CNS mycobacterium tuberculosis infection, cytomegalovirus retinitis, toxoplasmosis, cryptococcus neoformans meningitis, chronic active hepatitis, reiters disease, herpes zoster and psoriasis. Jenny-Avital reported illness occurring after ARV initiation that likely represented
an immune reconstitution MAC lymphadenitis, an entity that occurs in patients who begin ARV when they have advanced immunosuppression presumably in the setting of pre-existing occult MAC infection. Treatment for this disorder includes continuation of primary therapy, continuation of effective HAART, judicious use of anti-inflammatory agents.

GENERAL PRINCIPLES OF MANAGEMENT OF ANTIRETROVIRAL DRUG TOXICITY

Drug Initiation
- Start drugs with non-overlapping toxicities and small risk of interaction with existing therapy
- Consider clinical setting:
  - Pregnancy/ Pediatric age group
  - Injecting drug user
  - Chronic hepatitis B or C
  - Hemophilia
  - Post exposure prophylaxis

Adverse reaction
- Dose reductions not advised because of potential for drug resistance
- In patients with good control of viral replication: If possible, immediately switch to drug with different toxicity profile (if etiology certain)
  - Stop all drugs, particularly if severe reaction, then consider new regimen with different toxicity profile (if etiology uncertain)
- In patients with uncontrollable viral replication: Stop responsible drug; initiate new agent with different toxicity profile (but if possible aim for new regimen with improved antiviral activity).

Post adverse reaction
- Rechallenge should be medically supervised but is contraindicated with hypersensitivity to: Abacavir / Mucosal involvement / Grade 3-4 rashes.

Desensitization probably inappropriate because of potential for induction of viral resistance.

HOW TO MONITOR ANTIRETROVIRAL THERAPY

It is advisable for patients on triple therapy to be seen monthly; particularly at the start of treatment. Once stabilized, patients may then be seen every three months. At each visit side effects and adherence to the treatment should be discussed in depth. At the start of treatment, routine hematological and biochemical tests should be done monthly to detect potential side effects. Careful monitoring is needed particularly in patients who abuse alcohol or are infected with hepatitis B or C, who have abnormal liver function and in patients with abnormal renal function.

CD4 count should be measured regularly, preferably every 3-6 months.

In developing countries where CD4 counts or viral loads are not routinely available, clinical indicators such as weight and absolute lymphocyte count will give some indication of disease progression and treatment response.

TABLE II - LABORATORY MONITORING DURING ANTIRETROVIRAL TREATMENT

<table>
<thead>
<tr>
<th>Tritherapy (including a protease inhibitor)</th>
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<tbody>
<tr>
<td>Hematocrit / hemoglobin</td>
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<td>White blood cell count + differential counts</td>
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<td>Platelets</td>
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<td>Bilirubin</td>
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<td>Transaminases</td>
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<td>Amylase</td>
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<td>Creatinine / Urea / Urine protein analysis</td>
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<td>Creatinine phosphokinase</td>
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<td>Glucose / Glucose urine analysis</td>
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<td>Triglycerides</td>
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<td>CD4 lymphocyte count</td>
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<td>Viral load</td>
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** Highly recommended, but not essential
FUTURE DIRECTIONS

Type and timing of ARV therapy will be influenced by their potential toxicities, which have an impact on tolerability and adherence and thus resistance. This will require phenotypic and genotypic testing for resistance.

There is a need for assays that predict drug induced toxicity. Therapeutic drug monitoring of Protease inhibitors is one possibility.

Improving awareness of ADR will continue the impetus to development of improved 2nd and 3rd generation ARV.

HAART IS AN ART: CHOOSE AND USE WISELY

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FIGURE - 1:
FLOW CHART FOR NON-ITCHY SKIN RASH

Patient complains of non-itchy bilateral skin rash

Yes

Take History

Past History of Unprotected sexual contact and / or genital ulcer within one year

No

Refer to Dermatology Department

Yes

Examine Clinically

Ulcer (s) present in genital area

Yes

Use genital ulcer flow chart

No

Bilateral non-itchy non-vesicular skin rash with/without oral mucosal, perianal perigenital lesion(s)

No

Educate
Counsel
Provide Condom & Promote use

Yes

-Treat SY.II
-Educate
-Counsel
-Provide Condom & promote use
-Do VDRL / RPR if facility available
-Come Back after two weeks