

Common Antiretroviral toxicities

The vast majority of HIV infected children tolerate ART extremely well. Increasing evidence suggests that antiretroviral therapy prolongs life and reduces AIDS and non-AIDS related morbidity. So the risk-benefit discussion is clearly now weighted in favour of early and appropriate ARV use. However, we who care for children on antiretroviral therapy must be aware of and identify appropriately adverse events related to treatment – both early and late effects, to provide safe and effective treatment.

We won't have time to cover all possible toxicities so today's talk will aim to cover:

- Adverse events associated with high mortality and hence important to avoid or identify early.
- Adverse events commonly seen in paediatric ARV clinics
- Discussion points on prevention and management of adverse events for us to relate to our own varied settings

Identification of ARV related toxicities can often be complicated by many possible differential diagnoses: HIV infection itself causes many of the known ARV related problems, opportunistic infections, underlying co-morbidities such as renal or hepatic impairment may increase a child's risk of toxicities, drug-drug interactions likewise.

Although individual drugs are known to cause specific toxicities interaction between ARV drugs or other drugs used in the management of HIV-infected children may alter pharmacodynamics and increase toxicity.

Knowledge of known toxicities and their possible differential diagnoses can help guide management of individual patients as well as provide sensible and safe guidelines at the level of a busy, often resource constrained, clinic.

Pathogenesis of antiretroviral related adverse events is complicated and not fully understood in many situations but experience has led to the recognition of the following distinct adverse drug events:

- Mitochondrial toxicity: lactic acidosis, peripheral neuropathy, hepatic toxicity and pancreatitis
- Metabolic abnormalities: fat maldistribution, dyslipidemia, insulin sensitivity, osteopenia, osteoporosis and osteonecrosis
- Haematological events: anaemia, neutropenia, thrombocytopenia
- Allergic reactions: rashes and hypersensitivity responses

To start our discussion, a clinical case:

Lactic acidosis

Lactic acidosis occurs less frequently in children than in adults but is important not to miss

Asymptomatic mild hyperlactatemia (defined as 2.1-5.0 mmol/l) is common in adults and children on ART. It occurs in 15-35% of adults on ARV for 6 months or longer. It has been reported to occur with similar frequency in paediatric patient groups. There is no clear risk between mild asymptomatic hyperlactatemia and progression to severe clinical lactic acidosis

Symptomatic severe hyperlactatemia (> 5.1 mmol/l) is much less common but has a high mortality rate - 33-57%. It is most commonly associated with the Non nucleoside reverse transcriptase inhibitors (NRTIs), stavudine and didanosine and risk is increased with underlying hepatic or renal impairment. The syndrome of lactic acidosis/hepatic steatosis is very rare.

Diagnosing lactic acidosis early is very important. The most difficult part of making a diagnosis is thinking of it in the first place. Lactic acidosis symptoms are very non specific, can occur acutely or sub-acutely (1-20 months after HAART initiation).

Symptoms include:

- general fatigue, weakness, myalgias, anorexia, nausea, vomiting, diarrhoea, abdominal pain, unexplained weight loss
- respiratory symptoms: dyspnoea, tachypnoea
- Neurological symptoms: weakness
- Hepatic dysfunction: hepatomegaly, ascites, encephalopathy. Modest elevations of transaminases. Jaundice is unusual.

Laboratory test:

Specimen for lactate must be taken correctly: uncuffed specimen, kept cool and processed within 4 hrs or alternatively a rapid site-of-care test.

Management of a child with suspected ARV associated hyperlactatemia

Laboratory result	Suggested Management
Lactate < 2mmol/l and normal HCO₃	Not lactic acidosis, continue antiretroviral therapy
Lactate 2.1-5.0 mmol/l (confirm with repeat specimen)	Consider replacing d4T or ddI, can continue ARVs
Lactate >5 mmol/l (confirm with repeat specimen) lactate >10 mmol/l	Stop all ARVs, supportive care. On resolution of clinical and laboratory symptoms resume alternative regimen: NRTI- ABC or TDF. Monitor closely.

Antiretroviral associated hepatic toxicity

Hepatic toxicity has been recorded to occur with all classes of ARV drugs. The differential diagnosis in HIV infected children with hepatic toxicity is broad: HIV itself, opportunistic infections, other drugs, drug-drug interactions, malignancies, underlying co-morbidities for example. The ARV related mechanism of injury is not clear but may be due to direct drug toxicity, hypersensitivity reactions as in the case of NVP and ABC, mitochondrial toxicity as hypothesised with the NRTIs or immune reconstitution in the presence of HCV/HBV. The most common event is mild to moderate asymptomatic rises in transaminases (<10 x ULN).

There is a high incidence of elevated transaminases in HIV infected children not on HAART. Amongst 598 HIV infected children attending paediatric clinic in Cape Town, 32% had Grade 1-2 ALT elevation at presentation. Of the 498 children who subsequently started HAART, only 19 (3.4%) of children developed severe hepatotoxicity, all of which resolved over time. This is similar to internationally reported incidences.

Suggested management of hepatic events

Children with mild asymptomatic elevations of transaminases should continue ART and only investigated further if they become symptomatic.

However in view of the fact that fulminate hepatic failure has been reported with all classes of ART, children with severe elevations or clinical hepatitis should be reviewed, investigated for alternative causes of hepatitis and consideration given to stopping medication.

Of note: Although rare the syndrome of NVP associated severe clinical hepatitis can progress rapidly to hepatic failure and death. Hence NVP should be permanently discontinued in children who develop severe NVP-associated hepatotoxicity

Mild asymptomatic elevations of transaminases (Grade 1-2)	Continue antiretroviral therapy and investigate only if becomes symptomatic
Clinical hepatitis or severe elevations of transaminases (Grade 3-4)	Investigate for alternative causes of hepatitis (HepA/B/C, CMV, drug interactions).

Lipodystrophy

There has been increased recognition of the importance of lipodystrophy in both children and adults with longer term use of HAART. Experience has also clarified the pathogenesis of the 'lipodystrophy syndrome'. Where the combination of lipodystrophy (or change in body habitus) and associated metabolic problems of insulin resistance and dyslipidemia were initially thought to occur together - and as a consequence most likely of the protease inhibitors - it now makes more sense, in view of the differing pathogenesis, to look at the lipodystrophy and metabolic problems separately. Of course they can and often do occur together but not exclusively.

Lipodystrophy is a common consequence of longterm ARV use, described in clinical groups in 1-33% of children on HAART. It can either occur as loss of subcutaneous fat or accumulation of subcutaneous or visceral fat OR a mixture of the two. Lipodystrophy occurs gradually, only becoming apparent months to years after initiation of therapy. In children lipoatrophy appears to be the commonest presentation of body shape change and is more specifically related to ARV use than is lipohypertrophy.

In our clinic a recent audit of children diagnosed with lipodystrophy over the past 18mths showed that over 71% had lipoatrophy alone, 20% had both lipoatrophy and lipohypertrophy and 9% lipohypertrophy. All the children were on a stavudine containing regimen. Mean time from starting HAART to developing lipodystrophy was 49 months.

Lipoatrophy presents typically as facial wasting with decreased subcutaneous fat in limbs and buttocks, making children look muscular with prominent veins. The NRTI induced alteration in mitochondrial function is thought to be partially responsible for

this, particular thymidine analogues, d4T and ddI, and to a lesser extent ZDV. ABC, TDF and 3TC seem to have minimal effect on body shape. Diagnosis is made by patient report and clinical examination by experienced clinician. Because this is very subjective and relies heavily on a familiar carer and clinician – we have started taking baseline and 6 monthly photographs to keep in our clinic folders to monitor development of lipodystrophy.

Expedient switch off d4T or ddI once body shape change is noted is supported by evidence that the shorter the exposure to the thymidine analogues the better the fat recovery.

Results of the SWEET study are represented here showing the fat recovery in different groups of adults switched from a tNRTI regimen, by time of exposure to the tNRTI. It demonstrates, the shorter the exposure the better the fat recovery, the longer the exposure the less the recovery. Numerous adult switch studies have showed a significant gain in mean limb fat after switch off tNRTI to alternative NRTI such as ABC or TDF.

Lipohypertrophy also known as ‘pseudo-Cushings’ has a stronger association with other metabolic complications such as insulin sensitivity and dyslipidemia. Visceral and limb fat can be measured using DEXA scanning and serial anthropometric measurements, but this is generally used only in research settings. Medication switch has less obvious improvement than with lipoatrophy, highlighting the likely interplay between genetic, developmental factors, diet, activity level and antiretroviral drugs. Children and adolescents with lipohypertrophy need to be screened for other metabolic problems, advised on healthy diet and exercise and consideration given to switching of medications.

This picture is not of ART induced lipohypertrophy but demonstrates many of the body shape changes. This is in fact a child who developed Cushing syndrome from Budesonide-Ritonavir interaction.

Dyslipidemia

HIV infection itself causes dyslipidemia: raised tot cholesterol, LDL –C, decreased HDL-chol and raised TG and it is for this reason that HIV-infected children are at increased risk of CVD. In addition lipid abnormalities occur in 20-50% of children on HAART, protease inhibitors being the most commonly associated. ARTs such as Stavudine also cause rises in lipids - tot chol and TG.

Ideally monitoring of non-fasting lipids should be at baseline and 6 – 12 monthly. If the results are high then repeat with fasting levels. Persistently raised results require diet and exercise modification. If LDL-cholesterol >5mmol/l in children at high risk for CVD (HIV infected children are considered high risk) medical management with statins such as pravastatin should be considered (AAP guidelines). Low levels of raised cholesterol and TG are very common in our clinics particularly in children on Kaletra. In view of the potential long-term cardiovascular risk associated with abnormal lipid profiles – this area is definitely going to need further research and discussion.

AAP Classification of Fasting Cholesterol levels in Children and Adolescents

Category	Total Cholesterol	LDL Cholesterol
High	>5.1mmol/l	>3.3mmol/l
Borderline	4.4-5mmol/l	2.8-3.2mmol/l
Acceptable	<4.4mmol/l	<2.8mmol/l
Triglyceride levels <5 are considered acceptable		

Haematological events

Haematological complications in HIV infected children can occur as a consequence of HIV infection itself – bone marrow suppression and autoimmune disease. These symptoms may actually improve on ARV therapy. Opportunistic infections and lymphoma can likewise cause haematological non-ARV events. ART drugs have been associated with cytopenia of all cell lines.

Anaemia (<7.5g/dl): most commonly ZDV

Neutropenia (<500cell/mm³): common (10-26% of children on HAART) and most often attributed to ZDV

Thrombocytopenia (<100 x10³ cells/mm³): more common in HIV infected children not on HAART than those treated with ARVs. As many as 30% of untreated children have thrombocytopenia.

Treatment depends on cause, symptoms and severity. In some cases Zidovudine may need to be switched.

Sin rashes

Another case

Although rashes can occur with NRTI regimens alone or in combination with PIs, these rashes are usually mild. Most rashes occur with NNRTIs particularly NVP. 21-27% of children on NVP develop rash, 6-15% severe rashes, 0.3% life threatening Steven-Johnson syndrome/toxic-epidermal necrolysis. Rash is typically maculopapular, erythematous, confluent rash on arms and trunk. It usually occurs 2-4 weeks after treatment initiation and not usually after 8 weeks.

Management is discontinuation of Nevirapine and supportive care. Rechallenge is contraindicated. The use of standard 14 day once daily lead-in period does decrease risk of rash developing.

Hypersensitivity reactions

Hypersensitivity reactions can occur with Abacavir and Nevirapine. Hypersensitivity with Abacavir occurs in 5% of patients. There are specific HLA markers associated with hypersensitivity. It presents as a systemic illness with fatigue, fever, nausea, vomiting, maculopapular rash, abdominal and flank pain, myalgia, arthralgia.

Respiratory symptoms such as dyspnoea, pharyngitis, cough may also occur. Other symptoms include adenopathy, mucositis, hepatitis, myocarditis. Hypersensitivity usually occurs within the first 6 weeks of treatment (median time 8 days). A similar

syndrome with severe life threatening hepatitis occurs with NVP, also early in treatment and more commonly in adults than in children.

Management is immediate discontinuation of drug and no re-challenge

I have not given an exhaustive list of possible toxicities but rather many of the events we identify and need to manage daily in our clinics. The thymidine analogues will remain part of our first line therapy for some time yet, this poses challenges for us in our clinics to be sure that toxicity is screened for and acted on even in resource limited settings. Knowledge of potential side effects should not lead to fear of using these life saving medications but rather we need to translate this knowledge into appropriate guidelines, practice and patient accessible information, bearing in mind that toxicities are so often the cause of poor adherence. It is also important to ensure that toxicities get reported so that this information can be used to lobby for safer medications for our children who are growing up with these medications and require them for LIFE.