ANTIRETROVIRAL TOXICITY IN CHILDREN

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Antiretroviral (ARV) toxicity is an important issue that must be fully appreciated by prescribing doctors. While the benefits of therapy are well documented, toxicity is of concern and may be extremely serious, occasionally resulting in fatality. However, most side-effects are not serious and are reversible.

There are two ways in which children may be exposed to ARVs. One is *in utero* or postnatal exposure as a result of vertical transmission prophylaxis (VTP), and the other is treatment for symptomatic HIV infection.

SYMPTOMATIC INFECTION

Castelli-Gattinara *et al.*[1] presented a comprehensive review of ARV toxicity at the XIV International AIDS Congress in Barcelona in July 2002. As this is, to my knowledge, the largest review of ART toxicity in children, it is worth close attention. The Italian Multicentric Collaborative Study[1] was conducted between 1998 and 2000 and included 29 institutions.

Four hundred and eighty-four patients were enrolled in the study (male/female ratio 0.9). The median age was 6.4 years (range 1 month - 18 years). The median follow-up was 709 days, but again there was a wide range (8 - 1 381 days). The clinical and immunological profile (Fig. 1) suggested less severe disease than is commonly seen in South Africa. In the Italian group 71% of patients were either asymptomatic (N) or mildly symptomatic (A). In contrast, 68% of children first presenting at the Tygerberg Family Clinic are either stage B (moderate) or C (severe). The importance of this observation is that the adverse drug reaction (ADR) profile may be different in South Africa, perhaps due to a more severe disease profile.

ADRs were graded from 1 (mild) through 4 (severe) according to a World Health Organisation (WHO) classification. ADRs were experienced by 190 children, representing 39.3% of the total. There were 289 reactions, of which 42 were grade 3 or 4 (14.5%). The grade 3 and 4 ADRs are shown in Table I. Two persistently reported adverse reactions were diarrhoea and raised creatinine. There was only 1 death attributed to the ARV medication.

TABLE I. GRADE 3 AND 4 ADVERSE EVENTS SEEN IN HIV-POSITIVE CHILDREN IN THE ITALIAN COLLABORATIVE MULTICENTRIC STUDY

Adverse reaction	No.	Incidence rate ($X10^3$ patient-years)
Bone marrow	6	6.6
Renal stones	5	5.5
Elevated AST/ALT	4	4.4
Rash	4	4.4
Lipodystrophy	2	2.2
Dyslipidosis	2	2.2
Heart	2	2.2
Neuropathy	2	2.2
Pancreatitis	2	2.2
Diarrhoea	1	1.1

The four most common ADRs are shown in Fig. 2. They were lipid abnormalities (20%), bone marrow toxicity, liver function abnormalities (elevated aspartate aminotransferase/alanine aminotransferase (AST/ALT) and skin rashes

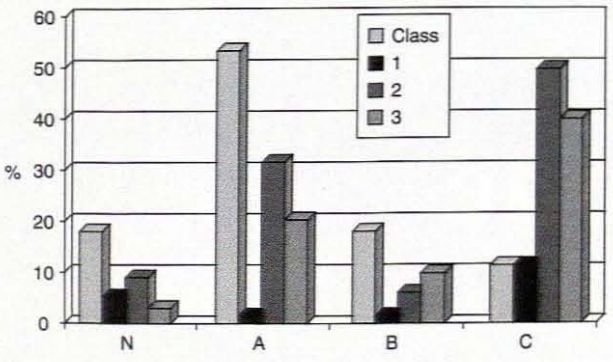

Fig. 1. Disease profile of HIV-positive children in the Italian Collaborative Multicentric Study.

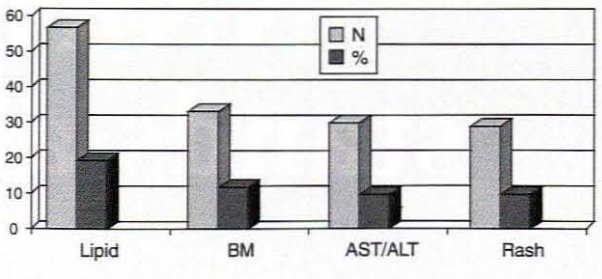

Fig. 2. Number and percentage of four most common adverse drug reactions in the Italian Collaborative Multicentric Study (BM = bone marrow toxicity).

(< 10%). Less frequent side-effects were renal stones, lipodystrophy and gastrointestinal disturbances, including nausea and vomiting (N/V).

Lipodystrophy and lipid abnormalities were more common in children over 10 years of age, and there was a marginally higher incidence in females. This observation is of importance as these abnormalities, currently rare in children in South Africa, will become more important with longer use of ARVs.

Another important observation was that the relative risk of ADRs increased quite significantly when more than three drugs were used simultaneously (Fig. 3).

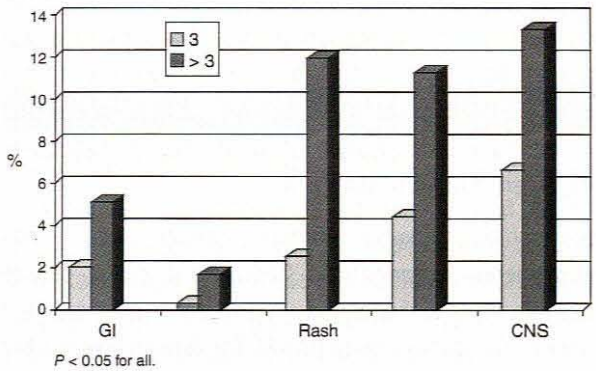

Fig. 3. Increased relative risk of toxicity when more than three antiretroviral drugs are used simultaneously (GI = gastrointestinal; CNS = central nervous system).

Many ADRs can be linked to specific ARVs. Examples are listed in Table II.

The Southern African HIV Clinicians Society's Paediatric Discussion Group, led by Paediatric Sub-committee Chairman, Dr Leon Levin, was recently informed by Dr Tammy Meyers that a toddler being treated with didanosine (ddI) + stavudine (d4T) + nevirapine (NVP) had died of lactic acidosis and hepatic steatosis.

TABLE II. SIDE-EFFECTS LINKED TO SPECIFIC ANTIRETROVIRAL AGENTS

Drug	Class	Side-effect
Ritonavir (RTV)	PI	Unpleasant taste may lead to drug failure
Zidovudine (ZDV)	NRTI	Bone marrow suppression
Lamivudine (3TC), didanosine (ddI)	NRTI	Pancreatitis
Stavudine (d4T)	NRTI All PIs	Peripheral neuritis Hyperlipidaemia
Abacavir (ABC)	NRTI	Fatal hypersensitivity reactions: gastrointestinal and respiratory symptoms, skin eruptions, fever and elevated liver enzymes (AST or ALT)
Nevirapine (NVP)	NNRTI	Skin rash and hepatotoxicity

PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor.

VERTICAL TRANSMISSION – THE ANTIRETROVIRAL-EXPOSED INFANT

In the antiretroviral-exposed infant mitochondrial toxicity may occur more frequently than in older children. ARVs have an affinity for mitochondrial gamma-polymerase which depletes mitochondrial deoxyribonucleic acid (DNA) and causes dysfunction. Mitochondrial dysfunction is generally associated with long-term use of NRTIs and usually resolves when the drugs are discontinued.

In 1999 Blanche *et al.*[2] reported on 8 patients with mitochondrial dysfunction following perinatal exposure to the nucleoside analogues. Four had been exposed to zidovudine (ZDV) alone and 4 to ZDV plus lamivudine. Two infants died. These data have not been replicated elsewhere. For example, no excess mortality was reported in follow-up of infants receiving ZDV after the landmark 076 study. In a large database of over 20 000 infants and 223 infant deaths in several cohorts followed up in the USA, no deaths suggestive of mitochondrial toxicity were reported. However, the majority of infants were exposed to ZDV alone.[3]

In the PETRA trial[4] involving 1 798 children, the majority of whom were exposed to ZDV and lamivudine, there was no excess mortality. However, a single case of severe transient neonatal lactic acidosis with prophylactic ZDV was reported in Switzerland by Scalfaro *et al.*[5] in 1998. It resolved when the drug was discontinued. This report suggests the need for continuing vigilance.

In conclusion, ARV toxicity is of concern, especially when wider access to these drugs is becoming possible. It would be very helpful to have a mechanism for multi-centre data collection in order to monitor toxicity and efficacy. This could possibly be coordinated through a national body such as the Medical Research Council or a university-based department of pharmacology.

REFERENCES

1. Castelli-Gattinaras G, Mannino S, Villa M, *et al.* Italian Multicentric Collaborative Study. 14th International AIDS Congress, Barcelona, July 2002.
2. Blanche S, Tardieu M, Rustin P, *et al.* Mitochondrial dysfunction and perinatal exposure to the nucleoside analogues. *Lancet* 1999; **354:** 1084-1089.
3. The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence of mitochondrial disease in children who died under 5 years of age in 5 United States cohorts. *J Acquir Immune Defic Syndr* 2000; **15:** 261-268.
4. The PETRA study team. The efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomized, double-blind, placebo-controlled trial. *Lancet* 2002; **359:** 1178-1186.
5. Scalfaro P, Chessaux J, Buchwalder P, Biollaz J, Micheli JL. Severe transient neonatal lactic acidosis with prophylactic ZDV. *Intensive Care Med* 1998; **24:** 247-250.