

Safety of Antiretroviral Drug Therapy in Jamaican Children with HIV/AIDS

C Pryce^{1,2}, RB Pierre¹⁻³, J Steel-Duncan¹⁻³, T Evans-Gilbert^{3,4}, P Palmer¹⁻³, J Moore¹⁻³, B Rodriguez^{3,5}, CDC Christie¹⁻³

ABSTRACT

Background: HIV has been a leading cause of death in Jamaican children aged \leq five years. Antiretroviral drugs (ARVs) are increasingly available in Jamaica through the Global Fund. Adverse effects of ARVs are a major cause for non-adherence to medications. Knowledge of the use and side effects of these drugs are crucial in the management of HIV-infected children as we scale-up the use of antiretroviral therapy, islandwide. We evaluated the adverse events and safety of antiretroviral therapy in children attending four Infectious Disease Clinics in Kingston, Jamaica, a resource limited setting.

Methods: Data for children prospectively enrolled in the Kingston Paediatric and Perinatal HIV/AIDS Programme during September 2002 to April 2005 were analyzed.

Results: Among 121 HIV-infected children, 77 (64%) were on ARVs, 90% had CDC class C disease, 60% were males and perinatal transmission predominated. AZT/3TC based regime was utilized in 93%, trimethoprim/sulphamethoxazole prophylaxis was used in 100% and five were completing anti-tuberculous drugs. Anaemia occurred in all patients, with increased severity in those on ARVs. Macrocytosis occurred in 83% and thrombocytopenia in 8% of those on ARVs. Elevation of bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT) levels and reversed albumin to globulin ratio prior to commencing ARVs, with significantly lower prevalence following use of ARVs emphasized the severity of HIV disease at time of ARV initiation. Clinical adverse reactions were uncommon and included nail discoloration (8%), vomiting (7%), nausea (3%), peripheral lipodystrophy (4%) and abnormal dreams (1%). Ten children required change of ARV medication because of severe adverse effects: three for severe anaemia with repeat blood transfusions, three for severe nevirapine-associated rash and four for indinavir-associated haematuria.

Conclusions: ARVs are being successfully initiated in HIV-infected Jamaican children using the public health model. The excellent safety profile, good tolerance and few reported significant adverse effects augur well as antiretroviral therapy is scaled-up islandwide.

Seguridad de la Terapia con Medicamento Antiretroviral en Niños Jamaicanos con VIH/SIDA

C Pryce^{1,2}, RB Pierre¹⁻³, J Steel-Duncan¹⁻³, T Evans-Gilbert^{3,4}, P Palmer¹⁻³, J Moore¹⁻³, B Rodriguez^{3,5}, CDC Christie¹⁻³

RESUMEN

Antecedentes: EL VIH ha sido la principal causa de muerte en los niños jamaicanos de \leq cinco años de edad. Las drogas antiretrovirales (ARVs) se hallan cada vez más a disposición en Jamaica a través del Fondo Global. Los efectos adversos de los ARVs constituyen una causa fundamental para la no adherencia a los medicamentos. El conocimiento del uso y los efectos colaterales de estos medicamentos son cruciales para el tratamiento de los niños infectados por VIH en la medida en que escalamos el uso de la terapia antiretroviral a lo largo de toda la isla. Evaluamos los eventos adversos y la seguridad

From: ¹Department of Obstetrics, Gynaecology and Paediatrics, The University of the West Indies, ²University Hospital of the West Indies, ³Kingston Paediatric and Perinatal HIV/AIDS Programme, ⁴Bustamante Hospital for Children, ⁵Spanish Town Hospital, Jamaica.

Submitted in partial fulfillment for the Doctor in Medicine Paediatrics degree, University of the West Indies.

Presented in part, *E-Journal of the International AIDS Society*. 16th International HIV/AIDS Conference, Toronto, Canada, Aug 13–16, 2006, Abstract # CDB 0724.

Funded in part by an Elizabeth Glaser Paediatric AIDS Foundation International Leadership Award (1-ILA-11-01) and Pfizer Foundation Fellowship (to CDCC); the Global Fund for AIDS, Tuberculosis and Malaria; University of the West Indies and the Ministry of Health in Jamaica.

Correspondence: Professor CDC Christie, Department of Obstetrics, Gynaecology and Paediatrics, The University of the West Indies, Kingston 7, Jamaica. E-mail: celia.christiesamuels@uwimona.edu.jm.

de la terapia antiretroviral en niños que asisten a cuatro clínicas de enfermedades infecciosas en Kingston, Jamaica, las cuales constituyen un escenario limitado en recursos.

Métodos: Se analizaron los datos de niños prospectivamente alistados en el Programa VIH/SIDA Prenatal y Pediátrico de Kingston, Jamaica, durante septiembre de 2002 hasta abril de 2005.

Resultados: Entre los 121 niños infectados con VIH, 77 (64%) estaban bajo medicación con ARVs, 90% tenían enfermedades del subgrupo C según la clasificación de CDC, 60% eran varones y predominó la transmisión perinatal. El régimen basado en AZT/3TC fue utilizado en 93%, trimetoprima/sulfametoxazol se usó en el 100%, y cinco estaban completando medicamentos antituberculosos. La anemia estaba presente en todos los pacientes, con mayor severidad en aquellos bajo ARVs. Se observó macrocitosis en el 83% y trombocitopenia en un 8% de los que se hallaban bajo ARVs. La elevación de los niveles de bilirrubina, aspartato transaminasa (AST) y alanina transaminasa (ALT) y la relación albúmina/globulina invertida antes de comenzar con los ARVs, con una prevalencia significativamente menor tras el uso de los ARVs, enfatizaron la severidad de la enfermedad del VIH al momento de la iniciación del ARV. Las reacciones clínicas adversas fueron poco común e incluyeron decoloración de las uñas (8%), vómitos (7%), náuseas (3%), lipodistrofia periférica (4%) y sueños anormales (1%). Diez de los niños necesitaron cambio de medicación ARV debido a los severos efectos adversos: tres a causa de una anemia severa con repetidas transfusiones de sangre, tres debido a una severa erupción asociada con la nevirapina, y cuatro a causa de hematuria asociada con indinavir.

Conclusiones: Los medicamentos ARVs han comenzado a ser administrados exitosamente en niños jamaicanos infectados por el VIH, usando el modelo de salud pública. El excelente perfil de seguridad, la buena tolerancia y el pequeño número de efectos adversos significativos reportados, auguran un buen futuro a la escalada de la terapia antiretroviral en toda la isla.

West Indian Med J 2008; 57 (3): 239

BACKGROUND

HIV has been a leading cause of death in Jamaican children aged less than five years (1, 2). Antiretroviral drugs have been accessible to the public in Jamaica through a grant from the Global Fund for AIDS/Tuberculosis and Malaria (2). The appropriate use of these drugs has significantly reduced the morbidity and mortality of patients suffering from HIV/AIDS. Once highly active antiretroviral drugs (HAART) are commenced, there has to be a long-term commitment and vigilance on the part of patients, parents and attending physicians. This is necessary to prevent the emergence of drug resistant virus that will occasion more expensive second and third line HAART therapy. Knowledge of the use and side effects of these drugs is therefore crucial, because this can contribute to adherence, which is necessary to significantly extend the life span of infants and children living with HIV/AIDS.

The Kingston Paediatric and Perinatal HIV/AIDS Programme (KPAIDS) is a joint collaborative initiative between The University of the West Indies (UWI) and the Ministry of Health (MOH), Jamaica, with their participating hospitals and clinics. The mission of the programme was the prevention of mother-to-child transmission (MTCT) of HIV and treatment of women, children and families with HIV/AIDS in four ambulatory clinics in Greater Kingston and others throughout Jamaica (3–14). The initial clinical description of these children using the criteria developed by the Centers for Disease Control and Prevention and use of ARVs in this population have been documented (7, 8). Except for a few initial case reports from Jamaica, there have been no

reports of adverse events to paediatric antiretroviral drugs from the English-speaking Caribbean (14).

Paediatric ARV Therapy and Adherence

The WHO guidelines were modified, the principles of paediatric ARV were summarized and guidelines for antiretroviral therapy recently developed for Jamaica and the Caribbean were implemented (15, 16). Children differ from adults in the progression and sequelae of HIV/AIDS. Almost 50% of adults with HIV will develop AIDS by 10 years. On the contrary, 25% of children will develop AIDS by one year and 50% by three years. Because of this and other factors (eg taste of drugs, liquid formulations, weight-adjusted dosing and adherence factors), children differ from adults in administration of antiretrovirals. In principle, antiretroviral therapy is to be delayed if the patient was stable, if there were unresolved issues of non-compliance or if non-adherence is expected to jeopardize success of treatment. Family and caregivers were assessed and prepared for adherence to therapeutic regimens. Major causes of treatment failure were a combination of non-adherence and intolerance. Comprehensive evaluation usually included nursing, social and enquiries into behavioural and psychological issues. Assessment of prior adherence should be sought noting all phases of medication administration including obtaining, storage and administration.

Adverse events of Paediatric HAART – internationally

Outside of the Caribbean, many recent studies have been reported analyzing the various side effects of antiretrovirals and their effects on treatment outcomes (17–31). These

studies have shown that HAART in HIV-infected children is feasible and accessible in developed and in some developing countries, improving long-term survival in children, with reduction of serious infections and death. Although adverse drug reactions to HAART sometimes occurred, most were minor and infrequent. Clinical effects of HAART therapy included rashes, vomiting, nausea and peripheral lipodystrophy, with laboratory abnormalities affecting the haematologic, renal and hepatic systems. Some instances of immune reconstitution syndrome were recorded. Overall, paediatric ARV therapy was thus deemed to be safe and well-tolerated.

Adverse events of Paediatric HAART in Jamaica

Initially, an observational prospective study was performed on antiretroviral therapy in 37 HIV-infected Jamaican children in the KPAIDS Programme (8). First line drugs usually comprised zidovudine/lamivudine and nevirapine or nelfinavir whereas second line drugs included stavudine, didanoside and nelfinavir or nevirapine (15, 16). Antiretroviral therapy in this study was shown to significantly reduce the number of admissions to hospital and length of stay and to improve weight gain and height. Of the 37 children studied, five required second line therapy; two of three in this group had issues of ARV compliance resulting in clinical signs of ART failure. However, it was not stated whether there were issues regarding side effects of medication used. Further, adverse events, whether minor or major, were not specifically enunciated as an outcome measure in this study.

Hypothesis

We hypothesized that HAART was being successfully initiated in Jamaican children with excellent safety profile, minimal intolerance and other adverse effects.

SUBJECTS AND METHODS

We designed a descriptive observational cohort study which sought to characterize the use of antiretroviral therapy (safety profile and adverse events) in children and adolescents attending the Infectious Disease Clinics in Greater Kingston, Jamaica. Specifically, we examined clinical and laboratory effects of ARVs in paediatric patients, including severity of adverse effects, symptom/signs: nausea, vomiting, nail discoloration, peripheral lipodystrophy; haematological parameters (such as anaemia, leukopenia, thrombocytopenia), biochemical profile (such as abnormal liver function, lipid profile and nephrolithiasis).

Data for children enrolled in the KPAIDS Programme during September 2002 to April 2005 were utilized. These children were all confirmed as infected with HIV and attended ambulatory Paediatric Infectious Disease Clinics at three main centres in Kingston and the Metropolitan Area: University Hospital of the West Indies (UHWI), Bustamante

Hospital for Children (BHC) and Spanish Town Hospital (STH). Five hospital charts at the BHC could not be located.

Standardized management protocols had been established for clinical care, laboratory monitoring and documentation (3, 7, 8). Trained paediatricians and registered nurses specifically trained in HIV/AIDS management were involved in the management of these patients. The infected children were managed by scheduling monthly visits for monitoring initially, then every 2–3 months as determined by the clinical status. Monitoring methods included history, nutrition, growth and developmental assessment, physical examination and adherence to prophylaxis and antiretroviral agents and evaluation of adverse events. Investigations included complete blood count, total lymphocyte count, serological tests for co-infection (*eg* hepatitis, syphilis, toxoplasmosis, cytomegalovirus and herpes viruses) and CD4 counts by non-flow technique, as available. Laboratory investigations were performed at baseline and three-monthly thereafter while on ART. The children in the before ART group usually had laboratory investigations collected immediately preceding ART. Abnormal laboratory values were repeated as frequently needed to guide clinical management. Standardized forms were used to record the relevant demographic, historical, clinical and laboratory data for each child before uploading to a database maintained to track the clinicopathological progress of the cohort. Records kept were confidential and are available only to the staff involved in the day to day care of the patients. Microsoft Access, Excel and SPSS were used where appropriate for analyses. Information was entered on Excel files and analyzed using SPSS. Here percentages of total for the different parameters were obtained with statistical means in the analysis of the data.

Adverse events and side effects

Clinical and laboratory effects evaluated included: drug reactions, nausea, vomiting, nail discoloration, lipodystrophy, central nervous system abnormalities, hypersensitivity reactions, anaemia, macrocytosis, deranged liver function tests, hypercholesterolaemia and hypertriglyceridaemia. Deranged liver function tests were determined for age appropriate groups using international reference values (32).

Guidelines for establishing antiretroviral drug toxicity in infants, children and adolescents, as established by the National Institutes of Health (NIH), National Institutes for Child Health and Human Development (NICHD) were used (33). These guidelines were developed specifically for use in clinical trials of ARVs in infants and children. The guidelines are as follows: Grade 1 – grading severity of paediatric (< 3 months of age) adverse experiences, November, 1993; Grade 2 – grading severity of paediatric (> 3 months of age) adverse experiences, September, 1993; Grade 3 – supplemental toxicity: grading severity of paediatric cutaneous/skin rash/dermatitis adverse reaction.

Variables

We examined and recorded the following parameters: socio-demographic data, address and healthcare institution, CDC clinical and immunological diagnostic criteria, where available, virological monitoring, where available, combinations of ARVs used; commencement and duration of therapy, other co-medications, *eg* trimethoprim/sulfamethoxazole, anti-tuberculosis medications; types of adverse events, monitoring of adverse events, continuation, discontinuation or changing of ARVs, interventions *eg* blood transfusion and suggested appropriate recommendations.

RESULTS

Demography

We report on a total 121 children with HIV/AIDS, 77 (64%) of whom were on ARVs. The demographic data for these children are presented (Table 1). Most patients (69%)

Table 1: Sociodemographic and clinical factors

Characteristic	Total	On ARVs	Not on ARVs
Total with HIV/AIDS	121	77 (64%)	44 (36%)
Site of care			
UHWI	83 (69%)	51 (60%)	32 (40%)
BHC	29 (23%)	20 (69%)	3 (33%)
STH	9 (7%)	6 (67%)	9 (31%)
Age, median(range)	7 (1–20) yrs	7 (1–18) yrs	8 (1–20) yrs
Sex	70 (58%) M	46 (59%) M	24 (54%) M
Residential institution	32 (26%)	24 (75%)	8 (25%)
Mode of transmission			
Perinatal	101 (83%)	66 (65%)	35 (35%)
Sexual	14 (12%)	6 (43%)	8 (57%)
Transfusion	2 (2%)	2 (100%)	–
Unknown	4 (3%)	3 (75%)	1 (25%)
Clinical staging of HIV/AIDS			
CDC – N	6 (5%)	2 (34%)	4 (66%)
CDC – A	27 (22%)	12 (44%)	15 (56%)
CDC – B	29 (24%)	10 (34%)	19 (66%)
CDC – C	59 (49%)	53 (90%)	10 (10%)
CD4 count cells/ μ L			
Median		51	45
Range		39 – 2 150	11 – 2 150

BHC = Bustamante Hospital for Children

STH = Spanish Town Hospital

UHWI = University Hospital of the West Indies

accessed treatment and care at UHWI and between 60 and 69% of patients initiated ARVs at clinic sites. The ages of the patients ranged from 1–20 years with a median age of seven years for patients on ARVs. There was a predominance of males in the subgroup of patients (58%) who were also on ARVs (59%). Twenty-six per cent were in residential institutions and the rest were receiving family-based care. There are three residential institutions caring for children, with HIV/AIDS, who receive comprehensive and standardized treatment and care through the KPAIDS programme. The

mode of transmission of HIV was primarily *via* the perinatal route (83%) but sexual (12%) and transfusion (2%) transmission modes were identified.

Clinical and immunologic criteria

The CDC categories for the patients are shown (Table 1). Most (49%) patients had severe disease (CDC-C), 22% had moderate disease (CDC-B) and 22% had mild (CDC-A) AIDS-defining signs. The median CD₄ count for patients on HAART was 51 (range 39–2150) cells/ml. None of the patients in the study had viral loads done as these became available after the period of study. Children commenced HAART based on the modified WHO guidelines.

Current medications

Current drug regimens by the patients comprised HAART in 64% (77), trimethoprim/sulfamethoxazole prophylaxis in 100% (121) and completion of antituberculous therapy in 6% (5). Eighty-seven per cent (67) were on a regime of zidovudine/lamivudine/nevirapine and 93% were receiving zidovudine/lamivudine based regimes; five were taking abacavir with zidovudine and nevirapine and five were on other HAART regimens. All patients were on trimethoprim/sulfamethoxazole prophylaxis and 6% of patients were completing therapy for TB. Standard antituberculous therapy is usually commenced in accordance with the WHO's guidelines.

Haematologic abnormalities

Severity of anaemia was classified according to the NIH guidelines for disease severity in HIV-infected children. We examined three groups of patients: those not on ARVs, those prior to starting ARVs and those on ARVs (Table 2). The children in the "prior to ART" and the children "on ART" represent a before and after comparison. There is some overlap between the populations of children prior to starting HAART and after starting HAART. The populations represent a cross-section of subjects who were on ART as compared to those who were not on ART.

Anaemia was found in all three groups with no marked difference between the groups with respect to mild and moderate. Only patients on ARVs and those prior to starting ARVs had severe anaemia (Hb < 7 g/dl). Of the patients with severe anaemia, three required change of regime due to symptomatic anaemia, as well as blood transfusions; all patients were on zidovudine-based regime and responded to withdrawal of zidovudine and commencement of new antiretroviral regimens. There were no deaths due to zidovudine-associated anaemia. Other haematological parameters evaluated included macrocytosis and thrombocytopenia (Table 2). Macrocytosis was identified in a significant number of patients on ARVs compared to the other two groups. Mean Corpuscular volume (MCV) >100 fl was found only in patients on ARVs. Importantly, there was no clinical consequence of macrocytosis in these patients.

Table 2: Haematological and biochemical abnormalities

Characteristic	Not on ARVs	Baseline before ARVs	After placed on ARVs	Statistical tests p-value
Total with anaemia	10/30 (33%)	22/50 (44%)	36/77 (47%)	0.29
Hb 9–9.9 gm/dl	5/30 (16%)	11/50 (22%)	14/77 (18%)	0.59
Hb 7–8.9 gm/dl	5/30 (16%)	5/50 (10%)	10/77 (13%)	0.61
Hb < 7 gm/dl	–	6/50 (12%)	12/77 (16%)	0.57
Macrocytosis	6/33 (18%)	2/30 (7%)	61/73 (83%)	< 0.01
Thrombocytopenia < 150,000	1/27 (4%)	5/49 (10%)	7/85 (8%)	0.7
High bilirubin	1/10 (10%)	3/19 (16%)	2/64 (3%)	0.04*
High AST	2/13 (15%)	36/49 (73%)	21/84 (25%)	< 0.01*
High ALT	None	2/10 (20%)	1/16 (6%)	0.29
High GGT	2/9 (22%)	7/26 (26%)	15/55 (27%)	0.97
Reversed albumin/globulin ratio	7/12 (58%)	27/37 (73%)	25/52 (48%)	0.01*
High cholesterol	5/10 (50%)	None	3/27 (11%)	–
High triglycerides	None	3/5 (60%)	15/24 (62%)	0.91

Thrombocytopenia was found in few patients in the different groups. The difference between patient groups was not significant. None of the patients was symptomatic for thrombocytopenia and did not require change of regime.

Biochemical abnormalities

Biochemical abnormalities included hyper-bilirubinaemia which occurred infrequently in all three groups (Table 2). Age appropriate elevated AST by international standards was found in a significantly higher proportion of patients just prior to starting ARVs (73%) compared to those on ARVs and those not on ARVs. A similar trend was observed for ALT levels. There was no marked difference between groups by proportion of children with elevated GGT levels. For patients on ARVs identified with elevated liver function tests, none required change of antiretroviral regime, since the abnormalities were mild (grade 1–2 toxicity– National Institute of Health guidelines, 2005). These patients have been continually monitored to track progress. Other biochemical abnormalities are also shown (Table 2). A reversed albumin to globulin (A/G) ratio was identified in 73% of patients just prior to starting ARVs. This proportion decreased after initiation of ARVs. Lipid profiles were not readily available in all instances. A higher proportion of ARV – naïve patients had elevated cholesterol levels compared to those initiated on ARVs. There was no marked difference in proportion of patients with elevated triglyceride levels according to international standards.

Clinical adverse events

Gastrointestinal (GI) abnormalities, primarily vomiting and nausea, were documented in 7% (5) and 3% (2) of patients, respectively. In all cases, the problems were mild and did not affect patient adherence to medications. Caregivers reported that the effects resolved within 5–7 days and did not require intervention. Nail discolouration was documented in 8% (6) of patients and was a likely complication of zidovudine ther-

apy. These consisted of linear hyperpigmented bands. None of the affected patients or caregivers was particularly perturbed by this problem.

Nevirapine-associated rash (hypersensitivity) was found in four per cent (3) of patients. In all instances, the rash was moderate to severe (*ie* grade 3 or 4, NIH, Division of AIDS grading of severity of paediatric adverse experiences) and required a change in regime. The diagnosis was confirmed following a marked response to nevirapine withdrawal. Minor rashes associated with nevirapine use were not documented. Peripheral lipodystrophy was noted in four per cent (3) of patients. These were all male adolescents who were on ARVs for a prolonged period (> 3 years). No metabolic characteristics (*ie* insulin resistance and glucose intolerance, and dislipidaemia) were identified in these affected children. They never expressed concern about their abnormal body image and in all instances the effect was recognized by the attending physician. One patient on an efavirenz-based regime had florid nightmares which affected quality of sleep for a brief period after starting medication. Other central nervous system abnormalities namely headache, visual problem and hallucination were not documented.

Interval to adverse event after HAART

The median interval to detection of adverse effects following initiation of ARVs are summarized (Table 3). Anaemia and elevated GGT were detected approximately 4–5 months after

Table 3: Interval between ARV initiation and adverse event

Characteristic	Median (weeks)	Interquartile range (weeks)
Anaemia	20	5–51
Macrocytosis	56	31–75
High AST	34	13–117
High ALT	16	na
High GGT	23	5–63

initiation of ARVs. The other abnormalities became apparent after a longer interval (8–14 months). Nevirapine-associated rash developed between 3–4 weeks after commencement of ARVs.

Interventions

Severe anaemia required blood transfusion and withdrawal of the offending agent (zidovudine) in three subjects. Children with nevirapine-associated rash were monitored in hospital and favourable response to withdrawal of nevirapine was observed in three subjects. Four children had gross haematuria while on indinavir-based regimes. This occurred against the background of inadequate daily fluid intake and sometimes inadvertent administration of the adult dose, although caregivers were continually advised on the specific requirements for indinavir use. These children were admitted to hospital and were carefully evaluated for haematuria. The episodes of haematuria did not recur after withdrawal of the drug.

DISCUSSION

Adverse effects of ARVs have been shown to be a major cause for non-adherence to medications. Knowledge of the use and side effects of these drugs are therefore crucial in managing HIV-infected children. This is particularly so in Jamaica and other developing countries as the use of anti-retroviral therapy is scaled-up. This prospective study shows that ARVs are being introduced in Jamaican children with an excellent safety profile and few adverse events. Even with proper monitoring, few children with clinically significant adverse effects are being identified and the appropriate interventions instituted.

Nevirapine-associated rash was the most important clinical abnormality requiring therapeutic intervention. Severe anaemia and gross haematuria were the other laboratory abnormalities that required therapeutic intervention. Most adverse effects were mild and were monitored in the ambulatory setting without the need for intervention.

Anaemia was common in the cohort of children identified in this study. This probably reflected the multifactorial causes involved in the pathogenesis of anaemia in HIV-infected children. For patients not on ARVs, causative factors were not fully explored in this study. These factors likely involved a direct toxic effect of HIV on the bone marrow and erythroid progenitor cells and could account for the higher percentage of patients with anaemia prior to starting ARVs. Most patients in this group had severe CDC (C) disease. Severe anaemia only occurred in patients on ARVs and in those prior to starting ARVs. It is important to note that HIV-associated anaemia, even though low in prevalence, can be severe and life-threatening when it occurs. Close monitoring and vigilance is therefore critical for early detection and intervention in a timely manner. Knowledge of the specific idiosyncratic effects of specific ARVs is critical. This would promote timely intervention in management of

clinically significant adverse effects. Fischl *et al* 1990, demonstrated that ARV-related anaemia due to zidovudine, which was mostly macrocytic, occurred with a prevalence of 30–40% (23). In this study, the prevalence was similar.

Macrocytosis occurred at a significantly higher frequency in patients on primarily zidovudine-based regimes. This is a known adverse event associated with zidovudine therapy. A few patients on zidovudine did not demonstrate this phenomenon but they were mainly patients with poor adherence to ARVs during the intervening period. This documented reaction of red cell progenitors to zidovudine use could probably be utilized as a surrogate means of monitoring for adherence with therapy (similar to use of haemoglobin A1C in monitoring diabetes mellitus) in a resource-limited setting (34). This is an interesting finding that may be worth further study in our setting. Thrombocytopenia occurred in eight per cent of the children on ARVs compared to four per cent in previously reported series (23). In most cases, thrombocytopenia was detected on routine laboratory monitoring and resolved spontaneously.

Biochemical abnormalities can occur in up to 58% of patients on ARVs (23). The finding that some patients have markedly elevated AST prior to starting ARVs in the present study may possibly reflect direct or indirect toxic effects of HIV on the liver in patients presenting with advanced disease, co-morbid opportunistic infections could contribute to abnormal liver function tests in patients with severe disease. Elevation of cholesterol and triglycerides may be seen in patients with HIV as a primary occurrence independent of ARV use. This was documented in the study where hypercholesterolaemia was found in significantly more patients not on ARVs. The cause of such elevation in these patients is still being elucidated but could be related to abnormal hepatic metabolism.

Clinical adverse events mainly GI intolerance can occur in up to 33% of patients (33). There was a lower prevalence of intolerance and this is encouraging since it would enhance adherence in the early phase of initiation of ARVs. It is possible that under-reporting could have resulted in this lower prevalence.

Nevirapine-associated rash occurred less frequently than previously reported (33). At least 90% of our patients are on a nevirapine-based regime, part of the recommended first line therapy in Jamaica. The low prevalence of nevirapine-hypersensitivity substantiates the continued use of this regime for ARV initiation.

Central nervous system abnormalities were rare, however only one patient (a male adolescent) was actually commenced on an efavirenz-based regime. Efavirenz-based regimes are known to be highly efficacious as initial therapy in ARV-naïve individuals but the use can be associated with bizarre central nervous system adverse effects. Although the World Health Organization guidelines recommends the use in resource-limited settings as first line therapy in children over the age of three years, the possibility of adverse central ner-

vous system effects makes it less favourable for use in affected children.

Teenagers and adults tend to be more concerned about issues of body image abnormalities associated with ARV use. Peripheral lipodystrophy has a reported prevalence of 38% (35). This abnormality is a longterm sequel to ARV use and the low prevalence in the present study is reflective of the few patients on ARVs for greater than three years duration. With time and increasing ARV use, more patients may present with this syndrome and other metabolic problems.

Limitations

The introduction and use of ARVs in HIV-infected Jamaican children has been based on a Public Health Approach (not a controlled clinical trial) related primarily and initially on guidelines for clinical management by the Ministry of Health, Jamaica, and utilizing the existing resources for clinical and laboratory monitoring. Hence patients were initiated on ARVs primarily on clinical criteria, as previously outlined. Laboratory monitoring capacity was not optimal throughout the period of study nor was it uniformly implemented at the various clinical sites and hence a number of children did not have appropriate investigations in a timely fashion. This may have affected the interpretation of some of the presented data. Notwithstanding, we were able to institute good uptake and monitoring of ARVs in children with minimal side effects.

CONCLUSION

We found that ARV use was generally safe and well tolerated with few significant adverse effects in HIV-infected Jamaican children. The most serious clinical adverse reaction was related to generalized rash with nevirapine use which occurred in few patients. Few patients developed severe anaemia requiring blood transfusion and withdrawal of zidovudine. The occurrence of macrocytosis following at least 6 months of zidovudine-based regime could well be utilized as a surrogate indicator of adherence. Although some patients had elevation of liver enzymes, none was severe enough to require a change in regime. The occurrence of haematuria in children who commenced on indinavir-based regimes may not make it a favoured option for children in our setting.

Recommendations

We recommend the institution of a detailed questionnaire to elicit pertinent adverse effects of medications, to ensure that all cases are reported, even if not volunteered. Close laboratory monitoring should be instituted prior to and post initiation of therapy in a timely manner and subsequently, if no abnormalities are detected. There should be continued training of staff in ARV use and side effects. Indinavir should be used in children only in situations where no alternative is available.

REFERENCES

1. Jamaican Ministry of Health, Jamaica AIDS report 2002, Facts and figures. http://www.nacjamaica.com/aids_hiv/facts_figures.htm
2. Figueroa JP. An overview of HIV/AIDS in Jamaica: strengthening the response. *West Indian Med J* 2004; **53**: 277–82.
3. Christie CDC. A paediatric and perinatal HIV/AIDS leadership initiative in Kingston, Jamaica. *West Indian Med J* 2004; **53**: 283–92.
4. Johnson N, Mullings A., Harvey K, Alexander G, McDonald D, Smikle M et al. HIV sero-prevalence, uptake of interventions to reduce mother to child transmission and birth outcomes in Greater Kingston, Jamaica. *West Indian Med J* 2004; **53**: 297–302.
5. Rodriguez B, Steel-Duncan JC, Pierre R, Evans-Gilbert T, Hambleton I, Palmer P et al. Socio-demographic factors of HIV-exposed and HIV-infected Jamaican children. *West Indian Med J* 2004; **53**: 303–7.
6. Steel-Duncan J, Pierre R, Evans-Gilbert T, Rodriguez B, Smikle M, Palmer P et al. Uptake of interventions, outcomes and challenges in caring for HIV-exposed infants in Kingston, Jamaica. *West Indian Med J* 2004; **53**: 308–14.
7. Pierre R, Steel-Duncan J, Evans-Gilbert T, Rodriguez B, Palmer P, Smikle M et al. CDC-defined diseases and opportunistic infections in Jamaican children with HIV/AIDS. *West Indian Med J* 2004; **53**: 315–21.
8. Evans-Gilbert T, Pierre R, Steel-Duncan J, Rodriguez B, Whorms S, Palmer P et al. Anti-retroviral drug therapy in HIV-infected Jamaican children. *West Indian Med J* 2004; **53**: 322–6.
9. Palmer P, Anderson-Allen MM, Billings CC, Moore JT, McDonald-Kerr C, Steel-Duncan JC et al. Nursing interventions in the Kingston Paediatric and Perinatal HIV/AIDS Programme. *West Indian Med J* 2004; **53**: 327–31.
10. Walker E, Mayes B, Ramsay H, Hewitt H, Bain B, Christie CDC. Socio-demographic and clinical characteristics of Jamaican adolescents with HIV/AIDS. *West Indian Med J* 2004; **53**: 332–8.
11. Geoghagen M, Farr JA, Hambleton I, Pierre R, Christie CDC. HIV and TB Co-infections in Jamaican Children. *West Indian Med J* 2004; **53**: 339–45.
12. Geoghagen M, Pierre R, Evans-Gilbert T, Rodriguez B, Christie CDC. TB, Scabies and Chicken pox Outbreaks in an Orphanage for Children with HIV/AIDS in Jamaica. *West Indian Med J* 2004; **53**: 346–51.
13. Steel-Duncan JC, Pierre R, Evans-Gilbert T, Rodriguez B, Christie CDC. HIV/AIDS following sexual Assault in Jamaican children and adolescents – A case for post exposure prophylaxis for HIV. *West Indian Med J* 2004; **53**: 352–5.
14. Steel-Duncan J, Pierre R, Gabay L, Christie CDC. Nevirapine-associated rash in a Jamaican child. *West Indian Med J* 2004; **53**: 356–8.
15. Brown-Tomlinson J, Harvey K, Christie CDC, Figueroa P. Clinical management of HIV Disease: Jamaican Guidelines for Health Care Providers. Ministry of Health, National HIV/AIDS Prevention and Control Programme, 2004.
16. Christie CDC, et al. Paediatric Antiretroviral Drug Formulary 2004 for the Caribbean, Center For HIV/AIDS Research and Training (CHART) website, Dec. 2005.
17. Wells CJ, Sharland M, Smith CJ, Du Mont G, Ball CS, Riordan FAI et al. Triple nucleoside analogue therapy with zidovudine, lamivudine and abacavir in the paediatric HIV in London South cohort, a 72 week update. Access For All 2004: Proceedings of the fifteenth international conference on AIDS; 2004 July 11–16; Bangkok Thailand: 2004. p. 325
18. Sirithansana V, Puthanakit T, Oberdorfer A, Akarantham N, Sirithansana T. Immune reconstitution syndrome in Thai HIV infected children after initiation of HAART. Access For All, 15th Proceedings of the International AIDS Conference, Bangkok, Thailand, J Inter AIDS Society, July 11–16, 2004, 325.
19. Alleandro V, Vigano A, Mora S, Brambilla P, Schneider L, Merlo M et al. Impaired Growth Hormone Secretion Correlates with Visceral Adiposity in HAART Treated HIV infected Adolescents. *AIDS* 2003; **17**: 1435–41.
20. Anaky MF, Laguida R, Kouakoussui KA, Wemin ML, Fassinou P, Rouet F et al. Follow-up of a cohort of HIV-infected children in

- Abidjan, Cote d'Ivoire (ANRS 1278). Access For All 2004: Proceedings of the Fifteenth International Conference on AIDS, 2004 July 11–16; Bangkok, Thailand: 2004. 330
21. Ananworanich J, Apateerapong W, Siripong A, Chuamchaitrakooi A, Cheunyam T, Thisyakorn U et al. Uptake and characteristics of children in the Thai Ministry of Public Health Paediatric Access to Care Programme at the HIV-NAT/ Chulalongkorn Paediatric Infectious Disease Clinic. Access For All 2004: Proceedings of the Fifteenth International Conference on AIDS; 2004 July 11–16; Bangkok Thailand: 2004. 326.
 22. Eley BS, Nuttall J, Davis MA, Smith L, Cowburn C, Buys H, et al. Initial experience of a public sector antiretroviral treatment programme for HIV-infected children in Cape Town, South Africa. Access. Access For All 2004: Proceedings of the fifteenth international conference on AIDS 2004 July 11–16 ; Bangkok Thailand: 2004. 325.
 23. Fischl MA, Parker CB, Pettinelli C, Wulfsohn M, Hirsch MS, Collier AC et al. A randomized controlled trial of a reduced daily dose of Zidovudine in patients with the Acquired Immunodeficiency Syndrome. *N Engl J Med* 1990; **323**: 1009–14.
 24. Levine AM, Berhane K, Masri-Lavine L, Sanchez M, Young M, Augenbraun M. Prevalence and correlates of anaemia in a large cohort of HIV infected patients. *J Acquir Immune Defic Syndr* 2001; **26**: 28–35.
 25. Luzuriaga K, Bryson Y, Krogstad P, Robinsson J, Stechenberg B, Lamson M et al. Combination treatment with zidovudine and nevirapine in infants with human immunodeficiency virus type 1. *N Engl J Med* 1997; **336**: 1343–49.
 26. McComsey G, Leonard E. Metabolic complications of HIV therapy in children. *AIDS* 2004; **18**: 1753–68.
 27. Nuttall N, Eley B, Davies M, Smith L, Buys H, Cowburn C et al. Serious medical events in children during the first six months of HAART. Access For All, 15th Proceedings of the International AIDS Conference, Bangkok, Thailand, Journal of International AIDS Society, July 11–16, 2004, pgs 328.
 28. Petdachai W, Estur A, Koen F, Wilson D. Antiretroviral therapy for children in Thailand. Access For All, 2004: Proceedings of the Fifteenth international conference on AIDS; 2004 July 11–16; Bangkok, Thailand: 2004. 325.
 29. Rhoads M. Effects of Combination Antiretroviral Therapy on Paediatric Metabolite Levels. In: Wainberg M, Badaro R, Biberfeld G, Cahn P, Chan R, editors. Access For All 2004: Proceedings of the fifteenth international conference on AIDS; 2004 July 11–16; Bangkok Thailand: 2004. 326.
 30. Temple ME, Koranyi KI, Nahata MC. The safety and antiviral effect of protease inhibitors in children. *Pharmacotherapy* 2001; **21**: 287–94.
 31. Woldetsadik EA, Anabwani GM, Bowman D, Evans DL, Kostova E, Kurup S et al. Adverse drug reactions (ADR) among antiretroviral drug naïve children in Botswana. Access For All 2004: Proceedings of the fifteenth international conference on AIDS 2004 July 11–16 ; Bangkok Thailand: 2004. 328.
 32. The Harriett Lane Handbook, Johns Hopkins Hospital. Seventeenth Edition. Editors, Jason Robertson and Nicole Shilkofski. Elsevier and Mosby. Blood Chemistries and Body Fluids. 662–3.
 33. Sleaseman J. Paediatrics HIV AIDS Florida 2004 (textbook), chapter 20, section 3, 264–5.
 34. Steele RH, Keogh GL, Quin J, Fernando SL, Stojkova V. Mean cell volume (MCV) changes in HIV-positive patients taking nucleoside reverse transcriptase inhibitors (NRTIs): a surrogate marker for adherence. *Int J STD AIDS* 2002; **13**: 748–54.
 35. Newell L, Thorne C. Retroviruses and opportunistic infections. Proceedings of the 12th conference on retroviruses and opportunistic infections 2004.