Journal of AIDS and HIV Research Vol. 4(9), pp. 219-222, September 2012
Available online http://www.academicjournals.org/JAHR
DOI: 10.5897/JAHR12.006
ISSN 2141-2359 ©2012 Academic Journals

Full Length Research Paper

Are first line anti-retroviral therapies really toxic for children? A study from Eastern India

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Accepted 29 August, 2012

This research aims to study the incidence of drug induced toxicity during antiretroviral therapy (ART) among children from a tertiary care institute from Kolkata. This is a prospective study that consist of 100 children aged 2 to 14 years receiving first line ART [Stavudine (d4T), Lamivudine (3TC), Nevirapine (NVP)/Efavirenz (EFV)]; these children were followed up for 3 years (2007 to 2010). The results showed gastro-intestinal symptoms in 20% (n = 20), transient maculo-papular skin rashes in 10% (n = 10), clinical jaundice in 4% (n = 4) and peripheral neuropathy in 1% (n = 1). No death or life threatening conditions like Steven-Johnson syndrome, immune reconstitution syndrome (IRIS), acute fulminant hepatitis and pancreatitis were noted. d4T, 3TC and NVP/EFV are safe in HIV positive children even after 3 years of uninterrupted ART.

Key words: Human immunodeficiency virus (HIV), highly active anti retroviral therapy (HAART), fixed dose combination (FDC).

INTRODUCTION

India harbours the world's third highest number of HIV infected people of whom 3% are children (Joint United Nations program on HIV/AIDS (UNAIDS)/WHO, 2010). Paediatric HIV differs from adults regarding its treatment plan. Any child aged below 2 years irrespective of their CD4 status should be started on a combination of highly active antiretroviral therapy (HAART) at the earliest opportunity to avoid severe damage of their immature immune system (http: http://aidsinfo.nih.gov/.). Many studies have shown that HAART suppresses HIV replication to undetectable levels, which restricts selection of drug resistant mutants thus, delaying disease progression and prolonging life. But, high levels of adherence are needed for successful therapy (Paterson et al., 2000). Poor adherence to ART medication is the biggest barrier in treating paediatric HIV. High pill burden, difficult scheduling and food restrictions are important factors influencing adherence (Escobar et al., 2003). However, the introduction of HAART in the form of fixed dose combination (FDC) has helped to improve adherence. FDC consisting of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) is now the recommended first line of therapy against pediatric HIV infection. Most of the individual drugs in the FDC have some toxic effects and potential complex drug interact-tions with other concomitantly administered medicines, but their easy scheduling and reduced pill burden results into excellent drug adherence which is one of the big reasons of success behind FDC regimes (Laurent et al., 2004), particularly in resource-limited setting. HAART FDC for children with HIV in resource-limited setting has been shown to be feasible, but few data exist on outcomes and toxicity in pediatric population. Our main aim was to study this outcome of first line HAART FDC in children in resource-limited setting like eastern part of India.

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Table 1. Demographic profile and baseline investigations.

Age	2 - 5 years	5 - 10 years	>10 years
Number	58	30	12
M:F	27:31	12:18	7:5
Weight (kg)	8.4 ± 2.88	11.95 ± 3.4	19 ± 2.4
Height (cm)	82.1 ± 2.14	89.9 ± 3.2	103 ± 3.19
Hb%	10.9 ± 1.3	11.1 ± 2.1	11 ± 1.9
SGPT	38 ± 14	30 ± 17.8	28 ± 21.4
CD4	345.8 ± 243.9	301 ± 179.4	269 ± 240.3

n = 100.

Table 2. Improvement of clinical factors at 6 months following onset of ART.

Age	2 - 5 years	5 - 10 years	>10 years
Number	58	30	12
M:F	27:31	12:18	7:5
Weight before (kg)	8.4 ± 2.88	11.95 ± 3.4	19 ± 2.4
Weight after (kg)	9.2 ± 2.43	12.44 ± 2.82	20.4 ± 2.6
CD4 count before	345.8 ± 243.9	301 ± 179.4	269 ± 240.3
CD4 count after	415.4 ± 226.5	388.48 ± 211.92	356.33 ± 231.65

METHODOLOGY

To study the incidence of toxicity in children on first line ART, we conducted an open labelled, prospective study at Apex Clinic, Medical College, Kolkata over a time period of 3 years (2007 to 2010). The study was approved by the College Council Ethical Committee.

100 children (age group 2 to 14 years, 56% male) attending the Apex Clinic and receiving ART were included in the study following consent from their guardians. The HIV diagnosis of the children had been confirmed by three positive enzyme-linked immunosorbent assay (ELISA) tests according to World Health Organization (WHO) strategy III (Lodha et al., 2005). Base line investigations including complete hemogram, CD4 count, absolute lymphocyte count, alanine transaminase (ALT), chest x-ray (CXR) and Mantoux test were done at entry level in all patients prior to commencement of HAART. Clinical examination, routine anthropometry and nutritional assessment were also performed before HAART. The children were graded for protein energy malnutrition using weight for age (Gupta and Shah, 2004).

Tuberculosis (TB) treatment was commenced according to intra-abdominal pressure (IAP) consensus guidelines as soon as diagnosis was made based on criteria detailed by Osborne (1995) and Revised National Tuberculosis Control Programme (RNTPC, 2004). Each child was staged according to WHO clinical staging and Centers for Disease Control and Prevention (CDC) clinical and immunological staging. ART was started for children in WHO stage 3, CDC category B or C and/or immune category 2 or 3. Cotrimoxazole prophylaxis was started in all cases (USPHS/IDSA Report, 1997). Patients received ART in the form of FDC of Lamivudine (3TC) + Stavudine (d4T)+ Nevirapine (NVP)/ Efavirenz (EVZ) free of cost from the clinic. FDC are supplied in-distab (3TC = 30 mg / d4T = 6 mg / NVP = 50 mg). For bigger (older) children, adult FDC were scored and used as required. The doses of various drugs were 3TC = 4 mg/kg BD, d4T = 1 mg/kg BD, NVP = 120 – 200 mg/m^2 BD. Children with active TB were first started on 4 drug intensive anti tubercular therapy and ART started within 2 weeks to 2 months as soon as tolerance was noted. NVP was substituted by EFZ in TB patients taking Rifampicin to avoid drug interaction. However, due to unknown dosing schedule for EFZ in children below 3 years, the maximum dose of NVP (200 mg/m^2) was used in this group of children (World Health Organization, 2010).

Monitoring

After starting ART, follow up was advised on 2, 4, 8, 12 and 24 weeks and thereafter, every 6 months unless required in between. On every visit, a detailed history and clinical examination were done and any adverse drug reaction was recorded. Adverse reactions to medicines were recorded in a pre-formatted register.

RESULTS

Total of 100 children were treated and followed up for 3 years. Age and sex distribution of the children and their baseline investigations [weight, height, haemoglobin (Hb%), serum glutamic pyruvic transaminase (SGPT), CD4] are shown in Table 1. There was significant clinical, anthropometrical and immunological improvement in all the children (Table 2) at first 6 months of therapy. Increase in mean weight and CD4 count was observed.

Features of ART induced toxicities were maximal during the first 6 months. Twenty-eight percent (28%) of the patients reported adverse drug reactions during that time. Gastrointestinal (GI) abnormalities like diarrhoea, nausea and vomiting accounted for 12% (n = 12) of the

Table 3. Adverse reactions during 3TC + d4T = NVP/EFZ therapy over 3 years.

Toxicities over 3 years	First 6 months	Subsequent 2½ years
GI abnormalities (n = 20) 20%	N = 12 (12%)	N = 8 (8%)
Maculo-papular rash (n = 10) 10%	N = 10 (10%)	Nil
Nonfulminant Hepatitis (n = 4) 4%	N = 04 (4%)	Nil
Peripheral neuropathy (n = 1) 1%	Nil	N = 1 (1%)
Steven-Johnson	Nil	Nil
Lactic acidosis	Nil	Nil
Fulminant hepatic failure	Nil	Nil
Neuropsychiatric	nil	Nil

adverse events, of whom 4 were hospitalized, followed by transient maculo-papular rashes (10%, n = 10), hepatitis [elevation of serum glutamic oxaloacetic transaminase (SGOT)/SGPT in symptomatic patient] was seen in 4% (n = 4) of the patients. None of the hepatitis patient required hospital admission. In the subsequent period till 3 years, another 8 patients came with diarrhoea and 1 patient developed peripheral neuropathy. Not a single case of Steven-Johnson syndrome, lactic acidosis, neuropsychiatric disorder, fulminant liver failure or immune reconstitution syndrome (IRIS) was reported during 3 years of continuous therapy. No death was recorded nor was there any change of regime or case failure during the same duration (Table 3). Thirty-one (31) patients were diagnosed with concomitant TB, 10 of who were less than 3 years old.

DISCUSSION

Many studies worldwide proved the efficacy and safety of NVP based FDC of ART (Montaner et al., 1998; Raffi et al., 2000). A recent meta-analysis by Ciaranello et al. (2010) concluded that virological and immunological benefits after 12 months of ART in resource-limited settings were comparable with those observed among children in developed settings. Our study also showed the efficacy and safety of NVP based FDC by means of increasing CD4 count, improving anthropometric parameters, sense of well being, decreasing on-going infections, and low hospitalization. The recent guideline by WHO mentioned to avoid NVP based HAART in those patients who have been exposed to NVP previously as a measure of prevention of parental to child transmission (PPTCT) and to switch over to protease inhibitor based regimen (WHO, 2010). However, it was not possible to screen our patients on that basis due to non-availability of protease inhibitor based FDC in our set up. We used EFZ based regimen in the more than 3 years age group patients who were on concurrent acute tryptophan depletion (ATD), because of complex drug interaction of rifampicin with NVP. Leth Van et al. (2003) found EFZ based regimen as potent as NVP based regimen and that EFV had a good safety profile. Similarly, analysis of seven randomized controlled trials (1688 participants) by Mbuagbaw et al. (2011) concluded that both NVP and EFV have equivalent efficacies in initial treatment of HIV infection when combined with two NRTIs, but with different side effects.

Our finding of maximal drug toxicity occurrence within the first six months of commencing treatment was comparable to that of Pujari et al. (2004), where they found maximum adverse effect within first 8 weeks of treatment. They reported skin rashes (6.6%), hepatitis (3.2%), and GI side effect (15.5%). We had more incidences of skin rash most likely due, unlike Pujari et al. (2004), to our non-adherence to lead-in dose of NVP. We did not use a lead-in dose of NVP as this is costly in terms of the need for multiple FDCs.

Analysis of 43 HIV children by Shah (2006) found hepatotoxicity as commonest adverse effect (16%) followed by raised serum amylase without symptomatic pancreatitis (12%), anemia (12%) and skin rash (9%). Anemia and elevated serum amylase were both due to usage of zidovudine which was not used in our children. Incidence of skin rash was similar with our reports. But incidence of hapatotoxicity was much lower in our reports probably due to lack of routine liver enzymes measurement at regular intervals. We only carried out liver enzyme measurement in symptomatic patient.

Unlike similar studies done in India, we did not report any death or any life-threatening events (Lodha et al., 2005; Pujari et al., 2004; Kumarasamy et al., 2003) like IRIS, Steven-Johnson syndrome, pancreatitis, lactic acidosis and fulminant liver failure. The reason of absence of life threatening incidence in our study could be due to early presentation, routine availability of free medicines, good treatment adherence, nutritional rehabilitation and other supports from both government and non-governmental organizations (NGOs). Also, severe toxicities were significantly more frequently seen with Zidovudine than with d4T in African children of 12 to

59 months of age (Sauvageot et al., 2010). In our study, Zidovudine containing FDC was not used.

The limitation of our study was that we have not done viral load test which was very expensive and was not available in our centre. Improvement in CD4 count along clinical improvement was used to assess the response to ART therapy. We also did not report the type and frequency of adverse events attributable to backbone nucleoside in our study.

In conclusion, NVP/EFZ based FDC is extremely safe, well tolerated, easy to use first line regimen in treating pediatric HIV with encouraging clinical outcomes.

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