ANTIRETROVIRAL RELATED ADVERSE DRUG REACTIONS AMONG HIV-1 INFECTED CHILDREN ON FIRST LINE REGIMEN AT TIKUR ANBESA SPECIALIZED HOSPITAL, ADDIS ABABA-ETHIOPIA

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ABSTRACT

Background*: ART has brought significant change in morbidity and mortality among children on HAART. However, antiretroviral related adverse drug reactions are one of the leading causes of drug changes, poor adherence and treatment failure.*

Objective*: To determine the prevalence, severity and time of occurrence of antiretroviral adverse drug reactions among HIV-1 infected children taking HAART at Tikur Anbesa Specialized Hospital.*

Methodology*: This is a retrospective analytic cohort study conducted in the department of pediatrics and child health. A special questionnaire was designed to collect parameters from follow up charts of patients on HAART.*

Results*: A total of 1000 children were enrolled and 600 were eligible and started HAART between Jan 2005-Jan 2010. Out of 600 on ART, 25 (4.2%) died, 75 (12.5%) lost, 50 (8.33%) transferred out and 450 (75%) continued ART until the time of data collection. Fifty patients on HAART were having incompletely filled charts and excluded from the study. Total eligible group for the study were 400 children on HAART of which 212(53%) were males and 188(47%) were females. Majority (83%) had started ART with immune category III and most of them were WHO grade III (50%) and IV (32%). The age at the beginning of ART ranges from 8-180 months and 50% of them were in the range of 60-120 months. There was a total of 12% (48/400) of drug changes due to various reasons. ARV related adverse drug reactions were the leading cause of drug change constituting 41.7% (20/48) of total drug changes. Treatment failure 31.25% (15/48), shifting regimen to FDC 16.7% (8/48) and TB treatment 10.4% (5/48) were other common reasons of drug changes. The prevalence of severe anemia (HCT<21%) was 3.13% (10/320) which occurred exclusively among children taking AZT containing regimen. The prevalence of NVP induced skin rash and hepatitis was 3.34% (6/177) and 1.7% (3/177) respectively. Three cases of neuropathy 3.8% (3/79) and two cases of lipo-dystrophy 2.5% (2/79) were recorded in d4T containing regimen. Chronic illness with concomitant non-ARV drug use had strong association with the development of anemia and hepatitis (P-value <0.005). No other predictive factor was found to have statistically significant association with commonly encountered adverse drug reactions.*

Conclusion*: ARV related adverse drug reactions are the leading causes of drug changes among children on HAART at Tikur Anbesa Specialized Hospital. Skin rash, anemia, hepatitis, neuropathy and dystrophy are the major adverse drug reactions which required drug changes. Severe skin rash ascribed to nevirapine use appeared early in the course of antiretroviral therapy while neuropathy and lipo-dystrophy due to stavudine administration developed late in the course of treatment. In addition, moderate to severe anemia and hepatitis occurred in patients with chronic illness and concomitant non-ARV medications.*

Recommendation*: Patient counseling regarding signs and symptoms of ARV related adverse drug reaction and time of occurrence is paramount. Early recognition of side effects and timely intervention could lead to reduction of morbidity and poor adherence. Due attention should be paid for children who have chronic illness and concomitant non-ARV medications. Finally, I recommend prospective trial to demonstrate all types of ARV related adverse drug reactions, grade severity, determine time of occurrence and identify risk factors.*

Introduction

HIV/AIDS created enormous challenge to mankind since it's recognition in 1981. Close to 60 million people are infected out of which about 40 million are living with HIV/AIDS. There are more than 2.1 million under 15 children living with HIV/AIDS of which 90% live in sub-Saharan African countries **(1, 2).**

Ethiopia has an estimated population of 77 million people of whom 44% are children below 15 years. The adult prevalence of HIV is 7.7% in urban and 0.9% in rural with average population prevalence of HIV around 2.1%. The prevalence of HIV in children is unknown but there are 134,586 children living with HIV/AID and out of whom more than 67,000 are estimated to be eligible for ART but only 4863 were taking HAART as of March 2008 **(3, 4).**

More than 90% of children acquire the infection through mother to child HIV transmission (MTCT). Despite this, only 10% of HIV infected pregnant ladies are offered any form of prevention of mother to child HIV transmission (PMTCT) in sub-Saharan countries **(5).**

In resource rich settings HAART has changed the face of Pediatrics AIDS. HIV infected children now survive to adolescents and adult hood. In developed and some areas of developing nations which have already implemented pediatrics ART, witnessed significant reduction of HIV associated childhood morbidity and mortality **(6, 7).**

Despite this, antiretroviral therapy has brought its own challenge which is observed in different age groups since the time of initiation. Lifelong drug use, pill burden, stigma and discrimination, adverse drug reaction and treatment failure are the leading challenges of HAART. By and large antiretroviral adverse drug reactions are major causes of drug discontinuation, drug changes, poor adherence, dropouts and treatment failure **(8).**

There are no data regarding the prevalence of antiretroviral adverse drug reactions among children on HAART in Ethiopia. Some data from developed nations are very limited and were done in few children **(9).** Most data are from adult HIV/AIDS patients but extrapolation to children is difficult as the two groups have different drug dynamics **(10)**.

The Federal HAPCO of Ethiopia has developed pediatric ART guide line. Combinations of NNRTIs and NRTIs are used as a first line antiretroviral therapy in ART naïve children throughout the country. AZT, D4T and 3TC are drugs used in NRTI group while NVP and EFV are drugs in NNRTI group. Second line options are combinations of ABC, DDI, boosted LPV/R and other PIs.

Among first line antiretroviral drugs, several side effects have been observed in children taking HAART. NVP taking children have developed skin rashes of variable degree within few weeks of therapy while those on AZT manifested with moderate to severe anemia. GIT upsets are also frequent and develop almost in all types of antiretroviral therapy. In addition, longer duration of antiretroviral therapy particularly stavudine (d4T) leads to the development of peripheral neuropathy and lypodystrophy syndromes in adolescents **(11).**

Both adults and children on first line agents are observed to develop anemia, skin rashes, hepatitis and peripheral neuropathy. The occurrence of neuropathy, lipodystrophy and lactic acidosis are higher in adults than children (**12**). Commonly encountered ART related adverse drug reactions are analyzed in this study but adverse drug reactions which are difficult neither to document clinically nor require expensive laboratory test and imaging are left unstudied such as lactic acidosis, hyperlipidemia and other metabolic complications.

Objectives

General objectives

- To determine the prevalence of antiretroviral adverse drug reactions among children on first line regimen between Jan 2005- Jan 2010 at Tikur Anbesa Specialized hospital, department of Pediatrics and child health, AAU-MF.

Specific objectives

1. To determine the **prevalence** of different types of antiretroviral adverse drug reactions among children on first line antiretroviral therapy.

2. To assess the **severity** of adverse drug reactions by determining the rate of drug change due to HAART related severe toxicity.

3. To estimate the **average time of occurrence of specific adverse drug reactions** in children taking HAART.

4. To determine factors associated with the development of **ARV** related adverse drug reactions among children taking **HAART**.

Operational definitions

Adverse drug reactions: WHO definitions of an adverse drug reaction is stated as ‘’any response to the drug that is noxious or unintended and which occurs at doses used in man for the purpose of prophylaxis, diagnosis or treatment’’.

Drug interaction: Any unwanted drug side effect resulting from the opposing or additive effect of two or more drugs taken together.

Drug change: Drug changes are made for treatment failure, severe adverse drug reactions, and drug interactions or due to other reasons. Drug change in the context of ART consists of drug substitution or switching. Total regimen switching from first line to second line ART is made during treatment failure. In case of drug substitution only the offending drug will be replaced by better alternative especially when severe adverse effect is observed.

Anemia: A decrement in red blood cell mass or packed cell volume apparent clinically as palmar pallor, fatigue, dizziness, dyspnea and even over congestive heart failure. It is confirmed by doing HB or HCT level which is also helpful for grading of severity. Mild –grade 1 (**10-8.5mg/dl**), Moderate of grade 2(**7.5- <8.5 mg/dl**), Severe-grade 3(**6.5-<7.5 mg/dl**) and life threatening –grade 4**(<6.5mg/dl**). The grading is defined based on PACTG.

Peripheral neuropathy: It is clinically apparent as tingling sensation, pricking pain over the extremities and even progressive weakness. Depressed reflexes and loss of deep sensations can be elicited in late complication. Electromyography may illicit axonal degeneration or demylination as a cause of the peripheral neuropathy.

Hepatitis: It may manifest as unicteric or icteric hepatitis. Children often have anorexia, vomiting and right upper quadrant pain. On physical examination tender hepatomegaly, jaundice and bleeding diathesis. Severity is assessed by laboratory tests especially liver function tests comprising AST, ALT, BIL, TSP, and PT/PTT. Based on **PACTG** grading system **ALT** and **AST** values between **1.25-2.5 X** ULN is mild (grade 1); **2.6-5.0** X UNL moderate(grade 2);**5.1-10.0** X UNL severe (grade 3) and >**10 X UNL** life threatening (grade 4). Hepatitis can occur along with skin rash as a hypersensitivity syndrome in early phase of ART or it may occur along with lactic acidosis as hepatic steatosis in late stages of ART due to mitochondrial toxicity.

Skin rash: It is the appearance of urticarial, maculopapular or vesicular generalized itchy lesions on the average within 8 weeks of ART initiation. The rash is also graded for

management purpose as follow as. **Grade 1** (mild) cases are localized macular or urticarial rash, **Grade 2**(moderate) lesions are diffuse macular, maculopapular or morbilli form rashes or target lesions, **Grade 3** (severe) lesions characterized by diffuse macular, maculopapular or morbilli form rash accompanied with limited number of vesicles or bullae or superficial ulcerations, **Grade 4** life threatening bulous lesions like **SJS** and **TEN.**

Toxicity Management: - Management depends on the degree of toxicity. In general **Grade 1** and **Grade 2** toxicities are managed with supportive care. **Grade 3** toxicities require substitution of the offending drug whereas **Grade 4** toxicities necessitate whole regimen discontinuation and re- initiation of adjusted regimen after the acute toxicity has subsided.

Prevalence of ARV related adverse reaction: is defined as the proportion of specific ARV adverse drug reactions developed among children taking ART regimen containing the incriminated ARV drug.

Chronic illness: An illness which has occurred more than three months prior to the time of data collection and includes Tuberculosis, cardiac, renal, neurologic, endocrine and other organic disorders.

Treatment failure: Based on WHO guide line, it is the development of new opportunistic infection with a decline in CD4 count after 24 weeks of HAART considering clinical and immunologic criteria.

Malnutrition: Based on NCHS, it is defined as moderate (-3< Z score <-2) and severe (Z score < -3). Wasting (Wt/Ht), stunting (HT/age) and underweight (Wt/age) are graded based on NCHS classification.

Materials and Methods

Study area: The study was conducted in the department of pediatrics and child health, Addis Ababa University –Medical faculty. The department has three outpatient pediatric clinics, one emergency room, one pediatric ICU, one neonatal ICU, three in patient wards comprising 120 beds and more than eight subspecialty clinics. Pediatric infectious disease clinic is one of the leading overburden subspeicalilty clinics where HIV/AIDS children are enrolled and followed regularly. There are nearly 1000 HIV-1 infected children enrolled since 2004 out of which more than 600 children were eligible and started on HAART by the end of 2009.

Source population: There were a total of 1000 cases of children registered in pediatrics ART clinic. Out of which 600 cases have been eligible and started on ART between Jan 2005-Jan 2010. Among six hundred cases, 450 children were still taking HAART, 25 died, 75 lost to follow up, 50 transferred out by the time of data collection.

Study subjects: Charts of 400 patients on HAART were eligible in the study as it contains completely filled documents.

Study design: A retrospective analytic study was made from follow up charts of children taking HAART of variable period in pediatrics ART clinic. Data were collected from each patient record chart using a questionnaire which contains important parameters. Important variables recorded include: age, sex, CD4 count, weight, height, ART regimen, treatment for TB, chronic illness, immune status, concomitant drug use and WHO clinical stage. Documented HAART related adverse drug reactions including the time of occurrence, degree of severity and requirement for drug changes were also included in the record format.

Assessment was made for prevalence, severity, time of occurrence and associated factors for the development of HAART related side effects over a period of treatment. Results were compared with each antiretroviral regimen group. In addition analysis was made to evaluate statistical

significance of independent variables on the occurrence of adverse drug reaction.

Inclusion criteria: A total of 400 cases on ART were included in the study as all bear completely filled parameters in the record format.

Exclusion criteria: Exclusion was made for cases whose charts were incompletely filled, died, lost to follow up, transferred in and transferred out to other facilities.

Data entry and processing: EPI info soft ware was used for data entry and analysis of anthropometry pre and post HAART. Data was directly transferred to **SPSS** version 17 for calculations of important parameters, significance testing and data output in graphs and tables.

Ethical consideration: The research was approved by the department of pediatrics research committee and institutional review board of medical faculty **(IRB),** AAU-MF.

Variables of the study: ***Dependant variables*** include anemia, skin rash, hepatitis, neuropathy and lipodystrophy. ***Independent/predictor variables*** include: base line age, sex, immune category, WHO clinical stage, chronic illness, base line CD4 count and duration of therapy.

Statistical methods: Risk factor determinations for association of predictors and dependant variables have been compared using logistic regression and chi-square tests. Relative risk, odds ratio and paired-t tests were also used to compare statistically significant associations (**P-value <0.05**).

Results

continued ART until the time of data collection (Jan 2010). A total of 400 children on ART whose charts had complete data were included in the study while 50 cases dropped due to incomplete data. Males constitute 53% (212/400) while females contribute 47% (188/400).

The minimum age at the start of ART was 8 months and the highest being 180 months (inter quartile range 60-120 years). Those who were started at the age of less than 12 months constitute the least number 4% (16/400) and those who started treatment between 60-120 months were by far the largest 46.5% (186/400).

The average duration of antiretroviral therapy was 37 months and ranged from 2-68 months. Majority of patients took ART for a longer period (60% took ART for more than 36 months) and there was a drop in rate of ART initiation in recent years. For instance proportion of children who took ART < 12 months, 12-24 months, 24-36

There were a total of 1000 children enrolled since 2004 in pediatrics ART clinic out of whom 600 started on HAART between Jan 2005-Jan 2010. Out of 600 children on HAART, 25 died (4.2%), 75 lost to follow up (12.5%), 50 transferred out to other facilities (8.3%) and 450 (75%) months, 36-48 months and > 48 months were 6.8% (28/400), 13% (53/400), 19.8% (81/400), 31.1% (127/400) and 29% (120/400) respectively.

Majority of patients (83.25%), were immune category III at base line, 15.25% were immune category II and 1.5% had immune category I. In addition, base line WHO clinical stages II, III and IV were 15.5%, 50.5% and 32.25% respectively. Base line CD4 count ranged from 2-2203 c/ml with inter quartile range of 129-370 c/ml and average CD4 count of 275 c/ml.

After an average of 37 months of HAART, 82.25% were immune category I, 12.5% immune category II and 5.25% were immune category III. The CD4 count has also increased to average count of 645 c/ml and ranged from 42-2309 c/ml with inter quartile range of 429-804 c/ml.

Using paired t-test the mean of CD4 count pre and post HAART was compared. The result is a statistically significant value with

mean CD4 count difference of 365, 95% CI (334.46-396.88); P-value <0.005.

Tuberculosis diagnosis and treatment was made in 48% (193/400) of children before the initiation of HAART. However, after antiretroviral therapy was initiated only 3.5% (14/400) cases diagnosed and treated for tuberculosis showing a 92% decline in rate of infection.

Majority have been on cotrimoxazole prophylaxis 98% (398/400) at base line which was discontinued in 30% of cases (120/400) after adequate immune reconstitution (CD4>25%) following ART. There were four (1%) recorded cases of severe cotrimoxazole allergy and the drug was substituted by doxycycline.

NRTI group proportion at base line revealed that AZT containing regimen was prescribed for 317 children (79.25%) and d4T containing regimen constitute 19.75% (79/400). Four cases, 1% were taking boosted lopinavir (LPV/r) containing regimen due to prior PMTCT exposure. NNRTIs group at base line showed that 44.25% (177/400) were taking NVP containing regimen while 54.75% (219/400) were on EFV containing regimen.

There were a total of 33 (8.25%) cases with documented chronic illness including new development of tuberculosis. New onset tuberculosis, acquired cardiac illnesses, chronic kidney disease, seizure disorder, developmental delay and chronic otitis media were among the frequently registered chronic illnesses.

Table 1: Base line values of children before HAART initiation; department of Pediatrics, AAU-MF, Jan 2010

Base line value	Category	Male	Female	TOTAL	Percentage
Sex		212	188	400	
Base line Age	<12 months	6	10	16	4%
	12-60 months	72	48	120	30%
	60-120 months	93	93	186	46.5%
	>120 months	41	37	78	19.5%
	Total	**212**	188	**400**	**100%**
Immune Category (CD4 Percentage)	>25% (Category I)	4	2	6	1.5%
	15-25% (Category II)	33	28	61	15.3%
	<15% (Category III)	175	158	333	83.3%
	Total	**212**	**188**	**400**	**100%**
CD4 count in c/ml	<200	99	89	188	47%
	200-350	53	49	102	25.5%
	350-500	37	27	64	16%
	=>500	23	23	46	11.5%
	Total	**212**	**188**	**400**	**100%**

Stunting	**Moderate to severe**	**120**	**113**	**233**	**56.7%**
Wasted	**Moderate to severe**	**21**	**15**	**37**	**9.25%**
Underweight	**Moderate to severe**	**114**	**90**	**204**	**51%**
ART regimen	D4T +3TC+NVP	29	24	53	13.3%
	D4T+3TC+EFV	14	12	26	6.4%
	AZT+3TC+NVP	58	66	124	31%
	AZT+3TC+EFV	110	83	193	48.3%
	LPV/r+3TC+D4T/AZT	1	3	4	1%
	Total	**212**	**188**	**400**	**100%**
TB before HAART	YES	104	89	193	48.2%
	NO	108	99	207	51.8%
	Total	**212**	**188**	**400**	**100%**
Cotrimoxazole prophylaxis	Yes	205	187	392	98%
	No	7	1	8	2%
	Total	**212**	**188**	**400**	**100%**
Chronic illness	Yes	15	18	33	8.2%
	No	197	170	367	91.8%
	Total	**212**	**188**	**400**	**100%**

Base line anthropometric data showed that total cases wasted were 9.25%, moderate and severe wasting being 6.25% and 2.75% respectively. In addition moderate stunting at base line was 26.1% (107/400) and severe stunting was 30.6% (126/400) with total of stunting being 56.7%. In general 51% (204/400) were underweight before the start of antiretroviral therapy. The average base line Z score value of underweight, stunting and wasting was -1.88, -2.17 and 0.94 respectively.

After the initiation of antiretroviral therapy, there was a decrement in the rate of malnutrition. Moderate wasting was 4% (16/400) and no severe wasting recorded. The overall underweight rate was 38.5% (157/400). Total cases stunted were 45.1%, moderate and severe stunting being 18.5% and 26.6% respectively. Moreover, the average Z score value of underweight, stunting and wasting has increased to -1.51, -1.73 and 4.33 respectively.

The improvement of underweight, stunting and wasting after antiretroviral therapy showed statistically significant changes using paired T-test. For instance the average wasting pre and post HAART showed statistically significant improvements with the average mean difference of wasting being 3.39, 95% CI (2.89-3.88), P-value < 0.005. Likewise average mean difference of stunting was 0.44, 95% CI (0.25-0.63), P-value <0.005 and average mean difference of underweight was 0.38 95% CI (0.245-0.522), P-value <0.005.

Paired t-test comparing pre and post HAART stunting

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	haz_cur - haz_base	.44320	1.95789	.09669	.25312	.63327	4.584	409	.000

There were a total of 15 (3.5%) treatment failures out of 4OO children on HAART. The large proportion of children who failed antiretroviral therapy were Males 80% (12/15) while (20% 3/15) were Females. Rate of treatment failure in NVP containing The average time of drug switch to second line regimen due to treatment failure was 49 months and ranged from 30-59 months. No significant antiretroviral related adverse drug reactions occurred prior to the diagnosis of first line treatment failure. Moreover, there were no reasonable prior drug changes made in patients who failed first line antiretroviral therapy. There were more cases of treatment failure 9.1% (3/33) among patients who have concomitant chronic illness compared with 3.3% regimen was 5.65% (10/177) while on EFV containing regimen was 1.8% (4/219). Moreover, treatment failure in AZT group was 4.3% (14/319) while in d4T regimen was 1.3% (1/79).

(12/367) patients without accompanying chronic illness though statistically significant association is lacking. Otherwise, there was equal proportion of treatment failure in different age groups except infants in whom no failure was recorded. Moreover, no marked difference was noted between the development of treatment failure and WHO clinical staging or immune category at baseline.

Table 2: Profile of children after antiretroviral therapy, department of Pediatrics, Jan 2010					
Profile after ART	**Category**	**Male**	**Female**	**Total**	**Percentage**
CD4 count	<200	9	9	18	4.5%
	200-350	29	21	50	12.5%
	350-500	42	33	75	18.8%
	>500	132	125	257	64.3%
	Total	**212**	**188**	**400**	**100%**
Immune category	Category I	174	155	329	82.25%
	Category II	26	24	50	12.5%
	Category III	12	9	21	5.5%
	Total	**212**	**188**	**400**	**100%**
Stunting	**Moderate to severe**	**95**	**90**	**185**	**45.1%**
Wasted	**Moderate to severe**	**12**	**4**	**16**	**4%**
Underweight	**Moderate to severe**	**93**	**61**	**154**	**38.5%**
Treatment failure	Yes	12	3	15	3.75%
	No	200	185	385	96.25%
	Total	**212**	**188**	**400**	**100%**
Cotrimoxazole prophylaxis discontinued	yes	62	58	120	30%
	No	150	130	280	70%
	Total	**212**	**188**	**400**	**100%**
Drug change	Yes	27	21	48	12%
	No	185	167	352	88%
	Total	**212**	**188**	**400**	**100%**
Duration of ART therapy	<12 months	13	15	28	6.8%
	12-24 months	27	26	53	13%
	24-36 months	44	37	81	19.8%
	36-48 months	73	54	127	31.1%
	>48 months	58	62	120	29.3%
	Total	**212**	**188**	**400**	**100%**

There were a total of 48 drug changes (12%) among 400 cases on first line antiretroviral regimen. Antiretroviral related adverse drug reactions are the leading cause of drug changes constituting 41.65% of all drug Anemia occurred almost exclusively in AZT containing regimen. There were a total of changes followed by treatment failure 31.25%, switching to fixed dose combination (FDC) 16.7% and due to tuberculosis treatment 10.4%.

Table 3:Profile of drug changes among children on HAART, department of Pediatrics, Jan 2010

Reason of drug change	**Frequency**	**Percentage**
Antiretroviral Side effects total	20	42.%
1. Anemia	10	20.8%
2. Rash	5	10.4%
3. Hepatitis	2	4.3%
4. Neuritis	1	2.2%
5. Dystrophy	2	4.3%
Shift to fixed dose combination	8	16.6%
Tuberculosis treatment	5	10.2%
Treatment failure	15	31.2%
Total drug changes	**48**	**100%**

11 severe cases of anemia with hematocrit level of less than 21%. Anemia occurred in 3.125% of AZT regimen (10/320) and 1.25% (1/80) from d4T taking group. The hematocrit level ranged from 6-21% with average count of 13.7% (inter quartile range 12-16%). All except anemia in d4Tarm, required blood transfusion and drug change from AZT to d4T. The average level of MCV at the occurrence of anemia was 101fl and ranged from 92-110 fl. The average time of anemia detection was 23 weeks but anemia developed as early as 8 weeks and as late as 48 weeks.

Chronic illness with concomitant non-ARV medications had statistically significant association with the development of AZT related anemia using Fischer exact test (P-value=0.019) and binomial logistic regression (OR: 7.03, 95% CI 1.95- 25.37, P=0.003). There were 4 cases of severe anemia developed in 33 (12.12%) patients who had chronic illness compared to 7 cases of

anemia among 367 (1.9%) patients without associated chronic illness (RR=6.4). Chronic illness found to have association with development of anemia were tuberculosis, seizure disorder and chronic kidney therapy. Otherwise, the occurrence of anemia was not affected by other predictor factor factors.

diseases. Moreover, anticonvulsants and antituberculosis medications have been used in these patients who developed anemia in addition to antiretroviral

Logistic regression showing chronic illness as a factor in the development of AZT induced anemia

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	chronic(1)	1.942	.655	8.791	1	.003	6.971	1.931	25.165
	Constant	-3.957	.382	107.533	1	.000	.019		

a. Variable(s) entered on step 1: chronic.

Skin rash developed mainly in NVP containing regimen. There were a total of five severe skin rashes (grade III &IV) which warrant NVP discontinuation and substitution with EFV. NVP taking children were 177 (44.25%) out of which 6 developed severe skin rash (3.4%). EFV taking children were 219(54.75%) out of which only one moderate rash recorded (0.45%). The average time of skin rash occurrence was 4 weeks and ranged as early as 2 weeks up to 8 weeks. All except EFV related moderate rash, required drug change from NVP to EFV. Five females and two males developed severe skin rash. Mild to moderate rashes which didn't require drug withholding or substitution were not found recorded in the follow up charts of patients.

The occurrence of rash was compared if it is affected by predictor variables like sex, WHO, base line CD4 and chronic illness but none were found to have statistically significantly associations. The effect of cotrimoxazole on skin rash development has no significant association. Chemo-prophylaxis in children prior to ART initiation showed the occurrence of severe skin reaction in four cases who took cotrimoxazole (1%) and required drug switching to doxycycline. Children who developed NVP induced rash while on cotrimoxazole prophylaxis didn't show recurrence or aggravation of rash despite continuation of the prophylaxis.

Hepatitis cases were observed in 3 patients taking NVP containing regimen (1.7%). The minimum time to develop clinical hepatitis was 28 weeks and occurred as late as 128 weeks. A liver function test during the occurrence of hepatitis was above 10X UNL in two cases and 5-10X UNL in one case who didn't require drug change. There was no concomitant HBV or HCV co-infection in patients who developed NVP related hepatitis. However, two of severe hepatitis cases have been taking anticonvulsant concomitantly for seizure disorder and required substitution of NVP with EFV. The use of these drugs has strong association with the development of hepatitis using Fischer exact test. No other independent variable had strong association with the development of hepatitis which was tested using multinomial logistic regression.

There were two cases of peripheral neuritis (2.5%) among 79 children taking d4T regimen, one of which required drug change to AZT. Peripheral neuropathy was observed in adolescents after longer period of d4T therapy. The time of occurrence of peripheral neuropathy ranged from 128-192 weeks after HAART initiation.

Two (2.5%) patients developed clinically observed lipodystrohy among 79 children on d4T containing regimen. Both cases required drug substitution from d4T to ABC. The time of occurrence of dystrophy was 192 weeks for the first case and 200 weeks for the second case after ART initiation and both were adolescents.

Table 4: Profile of Antiretroviral adverse drug reaction among 400 children on HAART from Jan 2005- Jan 2010

Major Side effects	**Frequency**	**Associated ARV drug**	**Percentage per regimen**	**Changes made**	**Average time of occurrence**	**Time in range**
Anemia	11	AZT(10)	10/317=3.13%	10 (3.13%)	23 weeks	8-48 **weeks**
Skin rash	7	NVP(6)	6/177=3.4%	5 (2.8%)	4 weeks	2-8 **weeks**
Hepatitis	3	NVP(3)	3/177=1.7%	2(1.1%)	64 weeks	28-128 **weeks**

Peripheral neuropathy	3	D4T(3)	3/79=3.8%	2(2.5%)	169 weeks	128-192 **weeks**
Lipo-dystrophy	2	D4T(2)	2/79=2.5%	2(2.5%)	196 weeks	192-200 **weeks**

Discussion

Morbidities and mortalities due to HIV/AIDS have been extremely reduced worldwide when appropriate ART initiated timely. In this study anthropometry, clinical and immunological evidences witnessed the efficacy of HAART in children. Similar studies in Vietnam and Burkinafaso elaborates the efficacy of ART **(13, 14)**. For Anthropometry data also revealed the advantage of antiretroviral therapy in making a significant improvement of malnutrition in HIV-1 infected children. A similar study in Kenya also confirmed the use of HAART as a potent tool to alleviate malnutrition in HIV-1 infected children **(15).**

Moreover, immune restoration is the basic mechanism that ART could do in fighting HIV infection. This is reflected very well in

on first line therapy followed for more than three years showed marked increment in immune status and reduction of viral load **(17).**

The reduction of new opportunistic infection following HAART has been evidenced by the rate of tuberculosis development pre and post HAART in this study. Similar studies also showed significant improvement in HIV morbidities and mortalities merely due to a reduction in the rate of AIDS defining illnesses (**17**).

There were a total of 20/400 (5%) severe drug reactions warranting substitution of offending drug in this study (Table-4). A similar study done in Jamaica where 77 children enrolled from Sep 2002 up to Apr 2005 in Kingston pediatric ART clinic and followed prospectively showed a total of ten drug changes among 77 children on HAART due to antiretroviral related severe toxicity (12.9%). Three cases were severe anemia

instance a study done in Vietnam where 252 children were started on first line ART regimen and followed for 12 months period showed CD4 percentage increment by 10%, reduction of new opportunistic infection by 50% and a marked improvement of weight for age and Height for age Z scores.

After adequate antiretroviral therapy in this study, the prevalence of malnutrition HIV-1 infected children is equivalent to the rate of malnutrition in the general population (under 5 children) described in the Ethiopian demographic and health survey 2005 report (**16**).

this study and similar study in Cambodia where children

Despite improvements in morbidities and mortalities after administration of antiretroviral therapy, there are emerging issues related to HIV/AIDS treatment. Several ARV related adverse drug reactions, drug switches and treatment failures have been observed in this study (Table-3). A similar study in Rwanda showed a total of 46(14.6%) drug changes out of 315 children on HAART mainly due o drug reactions 28 (60%) of total drug changes followed by changes due to tuberculosis treatment(**18**).

related to AZT (3.9%), three were due to NVP induced severe skin rash (3.9%) and four cases were due to indinavir related hematuria (**19**).

As high as 19% (31/160) drug changes due to ARV related adverse drug reactions have been observed in Uzbekistan study among 160 children on HAART for two years (**20**). The marked Variability in the difference of adverse drug reactions among children

taking HAART in different countries could be genetic makeup of an individual, study Anemia related to AZT administration is said to occur due to bone marrow suppression, evidenced by progressive decline in hemoglobin, macrocytosis and physical symptoms of anemia around 3-4 months after HAART initiation (**21**). The occurrence of anemia is highly associated with AZT administration than d4T regimen in this study (10/320 vs. 1/80, RR=2.5). Moreover, majority of children in this study developed anemia on average 23 weeks after ART and ranged from 8-48 weeks. In other studies the occurrence of AZT related anemia is earlier than this study **(22).** The Chronic diseases including HIV infection and non-ARV medications which suppress bone marrow brings about anemia and could aggravate AZT induced anemia (**23**). The occurrence of AZT associated anemia in four patients with chronic illness in this study speaks for the above statement. Overall the development of anemia is comparable to other studies (**24**) but significantly lower than reported in adults (**25**).

The prevalence of mild to moderate anemia (HB level between 8-10gm/dl) is less prevalent in this study than other studies among patients taking HAART (**26**). The lower prevalence rate could be failure to detect mild to moderate anemia due to infrequent laboratory monitoring or inconsistent recording of the result.

In this study, severe skin rash has occurred mainly in NVP containing regimen than EFV group (7/177 vs.1/219, RR=8.6). Rash is due to a hypersensitivity reaction principally due to NVP administration. It ranges from simple macular rash to severe toxic epidermal necrolyis and SJS (**27**). In this study, severe cases of skin rash happened in 2-8 weeks of ART initiation with average time of occurrence being four weeks which is the usual trend in other studies as well (**27**).

design, type and doses of antiretroviral drugs and duration of therapy.

relative late occurrence anemia in this study could be due to late detection of the signs and symptoms related to anemia and infrequent laboratory monitoring. Moreover two cases of anemia were detected very late at 48 weeks and both cases were taking anticonvulsants (phenobarbitone) which could aggravate AZT toxicity.

This study also showed macrocytosis (MCV>95 fl) in 81% (9/11) of AZT related anemia which is a feature of AZT reaction in the bone marrow as it is witnessed in other study **(22).**

The prevalence of skin rash in children could reach as high as 20% but severe cases requiring drug discontinuation is nearly 3-5% among NVP regimen as it is revealed in this study and other studies **(28).** The prevalence of mild to moderate skin rash in this study is significantly lower than other studies where the reverse is true **(28).** The reason could be either there is failure to report mild and moderate cases or failure of detection or documentation of grade I and II skin rashes**.** Besides, the variability in rate of NVP related skin rash depends on genetic makeup, gender, base line CD4, dosage of nevirapine and concomitant non-ARV drug use **(29)**.

Peripheral neuropathy and lypo-dystrophy are said to occur due antiretroviral related mitochondrial toxicity especially marked effect on adipocytes (**30**). Nucleoside reverse transcriptase inhibitors are more potent than non nucleoside reverse transcriptase inhibitors as a cause of mitochondrial DNA polymerase gamma inhibitor. Zalcitabine, didanosine, stavudine, zidovudine, lamivudine, abacavir and tenofivir are known potent inhibitors of mitochondrial DNA synthesis in decreasing order of potency (**31**). A study confirmed progressive adipocyte atrophy using tissue

biopsy in patients taking NRTIs for more than a year (32).

In this study, lipodystrophy and peripheral neuropathy occurred in adolescents and after longer duration of therapy (>160 weeks). Similar study has also reflected the importance of age, duration of therapy and type of ARV regimen as a risk of developing neuropathy and dystrophy (33). More over a study done in Burkinafaso where 52 HIV-1 infected children started on daily DDI decreased rate of reporting from caregivers or there is failure to detect and document the occurrence of side effects as it was witnessed in other forms of adverse drug Hepatitis in children is often times witnessed in NVP containing regimen. It may be clinically evident or confirmed by laboratory as an isolated liver function test elevation. Liver function tests 5-10X above the normal range are classified as grade III toxicity while LFT above 10x of normal are grade IV hepatotoxicity. ARV related hepatitis develop in two phases. The acute form of hepatitis develop along with skin rash due to NVP related liver toxicity and manifesting in the range of 6-18 weeks (36) while the late form of hepatitis appears with lactic acidosis due to NRTIs on average after 3-4 months of antiretroviral therapy (37).

In this study hepatitis occurred relatively longer than from actually expected period. This could be due to the effect of concomitant hepatotoxic non-ARV drug use which has aggravated the development of hepatitis later than the expected period. Moreover no hepatitis cases were identified along with skin reactions due to NVP related reaction in this study which was supposed to happen early. This study showed three cases of clinically apparent hepatitis among children taking NVP regimen. Both hepatitis B and C viral markers were negative in patients with hepatitis which is a common factor in aggravating drug related hepatitis (38). In this stud, Liver function tests were elevated 10X above normal range in two patients who required NVP discontinuation and substitution with EFV.

Asymptomatic elevation of liver function tests and mild to moderate hepatits which doesn't require drug change is relatively common in other studies (39). However, the prevalence of mild to moderate hepatitis and asymptomatic liver function test elevation are few in number. This could be due to infrequent laboratory monitoring or probably failure of reporting of mild symptoms and inconsistent recording of non severe drug reactions by attending physicians.

Chronic illness with concomitant drug use had statistically significant association with the development of hepatitis. Two patients who developed hepatitis were taking anticonvulsants, namely phenobarbitone and valproic acid respectively in this study. Concomitant hepatotoxic drug administration with NVP based ART like aniconvuslants and antituberculosis brings about profound effect on rate of liver toxicity **(40).**

Conclusion

This study showed that antiretroviral side effects are the leading cause of drug substitution and regimen changes followed by treatment failure as it is witnessed in similar studies. The prevalence of severe antiretroviral drug reaction is comparable to based regimen and followed for two years manifested neither lipodystrophy nor peripheral neuropathy clearly depicting the importance of duration of therapy in the manifestation of adverse drug reactions (34). Due to few numbers of cases who developed neuropathy and dystrophy, comparison didn't show any statistically significant correlations with predictor variables. This could be either there is reactions. Otherwise children do have lower rate of developing both neuropathy and lipodystrophy compared to the rate of development in adults (35).

other studies. However, the prevalence of mild to moderate adverse drug reactions is significantly lower in this study. Severe skin rash is an earlier noticed drug reaction while neuropathy and dystrophy appeared late in the course of antiretroviral therapy. Chronic illnesses and concomitant medications have aggravated the development of ARV related adverse drug reactions like anemia and hepatitis.

Recommendation

Timely identification and appropriate intervention of antiretroviral related adverse drug reaction is paramount. This can be accomplished by repeated counseling of parents on the sign and symptoms of commonly encountered adverse drug reactions. Physicians caring for children should anticipate the time of occurrence of each ARV related adverse drug reactions and request appropriate laboratory tests in relation to the type of regimen. Non-ARV drugs and diseases which will worsen adverse drug reaction should also be given due attention. The overall management of adverse drug reactions requires WHO grading system. Besides, unnecessary and premature drug switches could lead to shortage of options of first line ART regimen. In conclusion, prospective study should be done to determine all types of adverse drug reactions and determinant factors, magnitude of severity and impact of ARV related adverse drug reaction on adherence and treatment failure.

Limitation of the study

As a retrospective study, it is dependent on the quality of secondary data. The overall prevalence of adverse drug reaction depends on thorough reporting, detection and documentation of events. Failure of reporting, inconsistent detection and documentation may be reasons for lower prevalence of mild to moderate adverse drug reactions in this study. Moreover, infrequent laboratory monitoring could miss asymptomatic and mild cases of anemia and hepatitis.

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