

Adverse drug reactions of Highly Active Antiretroviral Therapy on adult patients at Debre Markos Referral Hospital, Ethiopia: A Retrospective study

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Abstract

Introduction: Highly Active Antiretroviral Therapy could suppress viral replication and stop progression of the disease. Data on adverse drug reactions related to antiretroviral uses are few. This study aimed at assessing antiretroviral adverse reactions and associated factors.

Objective: To assess major antiretroviral drug adverse reactions and associated factors among adult patients initiated highly active antiretroviral therapy from September 2005 to August 2010, at Debre Markos Hospital.

Methodology: Retrospective data was collected at Debre Markos Hospital. A total of 930 adult subjects' clinical records were selected using systematic random sampling technique. Chi-square and logistic regression were utilized to quantify magnitude and identify independently associated risk factors for adverse drug reactions of highly active antiretroviral therapy.

Results: Five hundred twelve (55.1%) of the participants were females. The median age was 34(IQR=28-40) years. The median CD4 T cell count was 116 (IQR, 59 -167) cells/ μ l. Three hundred fifty one (37.1%) patients were taking 3TC-d4t-NVP and 272(29.3%) were on 3TC-AZT-NVP. Two hundred fourteen (23.0%) patients had reported one or more adverse drug reactions. The most frequently reported adverse drug reactions were anemia, 65(25.0%), fat change, 45(17.2%), and skin rash, 42(16.1%). Patients with CD4 T cell count of 50-99 cells/ μ l (AOR=1.9, 95%CI [1.115-3.364]), 3TC-d4t-NVP (AOR=5.8, 95% CI [1.692-9.591]), 3TC- AZT-NVP (AOR=4.2, 95% CI [1.227-10.673]) were associated risk factors for adverse drug reactions.

Conclusion: Severe forms of adverse reactions were reported by the participants. Proper drug counseling to report on the adverse reaction should be implemented. Prospective cohort study is recommended to illustrate the impact of adverse drug reactions on the outcomes of Highly Active Antiretroviral Therapy (HAART).

Key words: HAART, adverse drug reactions, zidovudine based regimen, stavudine-based regimen

Introduction

Antiretroviral therapy has improved the quality of life of HIV-infected individuals. It decreases the HIV viral burden in the body, thus leading to improved immunity and clinical wellbeing. However, antiretroviral therapy has potential life threatening adverse drug reactions (ADRs). Like most chronically administered drugs, antiretroviral drugs (ARVs) have documented toxicities and ADRs range from mild to life threatening with short and long term effects (Hogg et al. 1999). The spectrum of adverse effects associated with ARVs may vary between developed and developing countries (Subbaraman et al. 2007). Studies in developing and developed countries showed that the incidence of ADR is between 11%–35.9% (Bonfanti et al. 2000, Severe et al. 2010). Incidence of severe ADR has been reported to be as high as 10% (Severe et al. 2010) with a study observing an incidence rate of 8 per 100 person years (Duval et al. 2004). The long term effects of highly active antiretroviral treatments (HAARTs) are largely unknown

but ongoing research provides insights into some ADRs of ARV (WHO 2007). These include peripheral neuropathy and lipodystrophy associated with stavudine (Duval et al. 2004; Palella et al. 1998), anemia associated with zidovudine (AZT) (Laurent et al. 2008; Pollard 1998), nevirapine (NVP) based hepatotoxicity and rash (Baylor and Johann-Liang 2004; De Maat et al. 2003; Dieterich et al. 2004; Martínez et al. 2003; Montessor et al. 2004; Phanuphak et al. 2007; Stern et al. 2003). Incidence of hepatotoxicity was observed to be 16% and 8% for patients on NVP and efavirenze (EFV); respectively (Sulkowski et al. 2003) while incidence of anemia ranged from 3–12% among patients on zidovudine in developing countries (Subbaraman et al. 2007). There are limited or no studies to the best of the authors' knowledge that provides reliable information on the adverse drug reactions to HAART in Ethiopia. The purpose of this study was to assess the prevalence of ADRs and to determine risk factors associated with ADRs among HIV positive patients on ARVs.

Materials and Methods

Study Design, Area and Period: A retrospective cohort study was conducted at Debre Markos Referral Hospital (300 Km Northwest of Addis Ababa) from December, 2011 to May, 2012.

Inclusion / Exclusion criteria: All adult patients who started HAART from September, 2005 to August, 2010 were included in the study. Excluded were medically incomplete records of WHO clinical stage or CD4 cell count and transferred in patients from other health facilities.

Sample Size Determination: The sample size was estimated by using Cox proportional hazards model (Sstpower cox) in STATA 11 menu (Stata Corp, College Station, Texas USA). Calculation was based on the assumption that $\alpha = 5\%$, power =80%. The significant predictors assessed from the different study were used to calculate the largest sample size. Data incompleteness was anticipated to be 10%, and then the total sample size was 930.

Data Collection and Data Source: The data was collected by advanced ART nurses from ART data base, ART intake form and ART follow-up form by using data extraction form prepared for this purpose. Anemia classification was modified as non-anemic if haemoglobin level ≥ 10 g/dL, and anemic if haemoglobin level < 10 g/dL (WHO 2001).

Study variable: The occurrence of ADRs was the outcome variable. The independent variables were age, sex, educational level, marital status, residence, WHO clinical stage, anemia, drug regimen, CD4 cell count, cotrimoxazole prophylaxis and TB co-infection.

Data Quality Assurance: Training was given to the data collectors on how to collect data by using the data extraction format for two consecutive days. The principal investigator closely supervised the data collector on a daily basis to ensure data accuracy and completeness. Every incomplete questionnaire had been sent back to the corresponding data collector for checkup under supervision. Ten percent of the collected data was randomly selected and re-entered and compared with the already entered to check the correct entry of the data.

Statistical analysis: Data analysis was conducted by STATA version 11.0 (Stata Corp, USA). Pearson chi-square was used to determine the association of the independent variable with the outcome variable. Multicollinearity was excluded using Spear-man's correlation coefficient with a cutoff at 0.5. Baseline

variables significant at $p < 0.2$ level in bivariate analysis were included in the multivariable logistic regression model. All tests were two-sided and level of significance was set at $P < 0.05$.

Ethical Considerations: The study was approved by the Health Research Ethics Review Committee of Mekele University, College of Health Sciences.

Results

Cohort Basic Characteristics at the initiation of HAART: Table 1 describes the characteristics of the study participants. Of the 930 patients, five hundred twelve (55.1%) were females. Half of the study participants were below age of 35 years and the median age was 34 (IQR=28 - 40) years. Two hundred ninety (31.2%) of the patients were illiterate and 41.6% of the patients were married.

Six hundred ninety nine (75%) of the participants were on WHO stage III. About 90 % of the study participants had CD4 count less than 200 cells/ μ L and the median CD4 count was 116 (IQR, 59 -167) cells/ μ L. The median hemoglobin value was 12.4 (IQR, 10.6-14.0)g/dL. Five hundred ninety three (63.8%) and 381 (41%) of patients had fever (> 1 month, unexplained) and recurrent upper respiratory tract infection, respectively. One hundred eighty two (19.6%) of study participants had TB co-infection. One hundred ninety one (20.5%) of the clients showed poor adherence. Three hundred fifty one (37.7%) of the patients were taking d4t-3TC-NVP and 272 (29.2) were taking AZT-3TC-NVP and 66 (7.1%) were taking TDF-based treatment (Table 1).

Adverse Drug Reactions: After initiation of HAART, 214 patients (23.0%) of the 930 study populations developed at least one adverse event during the follow-up periods. One hundred twenty three (57.8%) of those patients taking AZT 84 (39.3%) of those taking stavudine and 2.9% of those taking TDF based regimen showed ADRs. Among the 261 episodes of HAART adverse drug reactions, the most commonly observed adverse drug reactions by the patients were anemia 65(25.0%), fat change 45(17.2%), skin rash 42(16.1%), peripheral neuropathy 32 (12.3%) and abdominal pain 26(10%) (Table 2).

Peripheral neuropathy was common ADR among patients on stavudine-based regimen while anemia and fat change were common with patients on AZT based regimen (Table 2). Of the 214 patients who experienced at least one drug related adverse event, 52 (24.3%) substituted their regimens due to drug toxicity and skin rash.

Table 1: Baseline characteristics and associated adverse drug reactions among 930 HIV-infected patients starting ART at Debre Markos Hospital, 2012

		N (%)	Adverse effects (%)	Pearson χ^2 (p)
Sex of participants	Male	418(44.9)	93 (43.5)	0.25(0.618)
	Female	512(55.1)	121 (56.5)	
	3TC- d4t-NVP	351(37.7)	92(43.0)	
Regimen	3TC -d4t-EFV	165(17.7)	31(14.5)	10.73(0.030)*
	3TC -AZT-NVP	272(29.2)	69(32.2)	
	3TC- AZT-EFV	76(8.2)	15(7.0)	
	TDF-3TC- EFV	66(7.1)	7(3.3)	
	Unmarried	118(12.7)	29 (13.6)	
Marital Status	Married	387(41.6)	96 (44.9)	1.89(0.388)
	Separated	425(45.7)	89 (41.6)	
	Illiterate	290(31.5)	48 (22.5)	
Education	Primary	309(33.6)	71 (33.3)	13.72(0.001)*
	Secondary +	322(35.0)	94 (44.1)	
	Urban	673(73.6)	163 (76.9)	
Residence	Rural	242(26.4)	49 (23.1)	1.58(0.209)
	Yes	554(66.6)	130 (67.0)	
Past Cotrimoxazole	No	278(33.4)	64 (33.0)	0.02(0.886)
	No	431(51.7)	114 (58.8)	
Anemia	yes	402(48.3)	80 (41.2)	4.5(0.025)*
	Good	648(77.2)	156 (78.4)	
Adherence	Poor	191(22.8)	43 (21.6)	0.20(0.656)
	Stage I-III	815(87.6)	196 (91.6)	
WHO stage	Stage IV	115(12.4)	18 (8.4)	4.01(0.045)*
	≥ 200	95(10.2)	17 (7.9)	
	100-199	428(46.0)	121 (56.5)	
CD4 Cells/ μ l	50-99	212(22.8)	43 (20.1)	13.02(0.005)*
	<50	195(21.0)	33 (15.4)	
	15-24	94(10.1)	16 (7.5)	
Age (Years)	25-34	375(40.3)	89 (41.6)	3.42(0.332)
	35-44	304(32.7)	67 (31.3)	
	45+	157(16.9)	42 (19.6)	

Note: * = Significant, 3TC-d4T-NVP = Lamivudine, stavudine, and nevirapine; 3TC-AZT-NVP = lamivudine, zidovudine, and nevirapine; 3TC-d4T-EFV = lamivudine, stavudine, and efavirenz; 3TC-AZT-EFV = lamivudine, zidovudine, and efavirenz.

Factors associated with the occurrence of HAART

Adverse drug reactions: Pearson chi square measures of association showed that the occurrences of ADRs were associated with regimen type, base line hemoglobin level, WHO clinical stage, baseline CD4 count and educational level (Pearson chi square, $p < 0.05$) (Table 1). In the bivariate logistic regression analysis, sex, HAART regimen, marital status, occupation, residence, cotrimoxazole prophylaxis and

adherence were not associated with the occurrence of adverse drug reactions (Table 3). In multivariable analysis with CD4 ≥ 200 cells/ μ l as the reference, patients on CD4 50-99 cells/ μ l (AOR=1.9, 95%CI [1.115- 3.364]) were more likely to develop ADR. With TDF based regimen as the reference, patients on d4t-3TC-NVP (AOR=5.8, 95% CI [1.692-9.591]) and AZT-3TC-NVP (AOR= 4.2, 95% CI [1.227-10.673]) were more likely to develop an ADR.

Table 2: Adverse effects of HAART during the follow up periods of September, 2005 up to August, 2011 at Debre Markos Hospital, 2012

	AZT-based	d4t-based	TDF -based	Total (%)
	N (%)	N (%)	N (%)	
Abdominal pain	25(9.58)	-	1(0.38)	26(10.0)
Anemia	35(13.41)	26(10.0)	4(1.53)	65(25.0)
Diarrhoea	2(0.77)	3(1.15)	-	5(1.9)
Dizzy, anxiety, night mare	5(1.92)	1(0.38)	-	6(2.3)
Fat change	27(10.34)	17(6.51)	1(0.38)	45(17.2)
Fatigue	3(1.15)	1(0.38)	-	4(1.5)
Headache	1(0.38)	-	1(0.38)	2(0.8)
Jaundice	2(0.77)	14(5.36)	-	16(6.13)
Nausea	10(3.83)	4(1.53)	-	14(5.4)
Numbness/tingling	4(1.53)	-	-	4(1.5)
Peripheral neuropathy	12(4.60)	20(7.66)	-	32(12.3)
Skin rash	23(8.81)	18(6.90)	1(0.38)	42(16.1)
Total occurrence of adverse effects				261

Note: d4T = Stavudine-based; AZT = Zidovudine-based TDF-based = TDF-3TC- EFV

Table 3: Factors associated with the occurrence of adverse drug reactions of patients on HAART at Debre Markos Hospital, 2012

Covariates		COR	[95% CI]		p	AOR	[95% CI]		p
Sex	Female vs. male	1.081	0.795	1.471	0.618	0.918	0.626	1.347	0.662
Hemoglobin	<10g/dl	1.447	1.046	2.004	0.026	1.359	0.915	2.02	0.129
Adherence	Good vs. Poor	1.091	0.743	1.603	0.656	0.936	0.589	1.488	0.779
WHO clinical stage	I-III vs. IV	1.706	1.006	2.893	0.047	1.427	0.737	2.763	0.291
CD4 cells/ μ l	CD4 $\geq$ 200	1.00				1.00			
	CD4 100-199	1.07	0.562	2.038	0.837	1.285	0.575	2.871	0.542
	CD4 50-99	1.935	1.259	2.973	0.03	1.936	1.115	3.364	0.019
	CD4 <50	1.249	0.756	2.064	0.385	1.33	0.715	2.475	0.368
Educational level	Illiterate	1.00				1.00			
	Primary	0.481	0.325	0.712	< 0.001	0.449	0.276	0.73	0.001
	Secondary +	0.724	0.506	1.035	0.076	0.761	0.492	1.175	0.218
Residence	Urban vs. Rural	1.259	0.879	1.804	0.210	0.85	0.551	1.311	0.463
Cotrimoxazole	Yes vs. No	1.025	0.729	1.442	0.886	1.05	0.712	1.548	0.805
HAART Regimen	TDF-3TC- EFV	1.00				1.00			
	d4t-3TC-NVP	2.994	1.32	6.79	0.036	5.758	1.692	9.591	0.042
	d4t-3TC-EFV	1.95	0.812	4.68	0.875	3.291	0.906	11.95	0.490
	AZT-3TC-NVP	2.865	1.25	6.568	0.032	4.242	1.227	10.673	0.036
	AZT-3TC-EFV	2.073	0.789	5.445	0.752	3.327	0.857	8.909	0.489

COR=Crude Odds Ratio; AOR=Adjusted Odds Ratio, 3TC - d4T - NVP=Lamivudine, stavudine, and nevi-rapine; 3TC-AZT-NVP= lamivudine, zidovudine, and nevirapine; 3TC-d4T-EFV= lamivudine, stavudine, and efavirenz; 3TC-AZT-EFV= zidovudine, lamivudine, and efavirenz

Discussion

The occurrence of adverse drug reactions of ARVs among patients on HAART in this study is 23% which is in agreement with other studies which reported that the incidence of side effect ranges between 11.0%–35.9% (Asfaw 2010; Bonfanti *et al.* 2000, Severe *et al.* 2010). Only 24.3% of patients were substituted and no change their regimen due to the adverse effects of HAART. This suggests good tolerance level to ARVs in general.

The prevalence of anemia in this study was 25.0% (65). Among these, 13.4% (35) of anemia occurred in those patients taking zidovudine based regimen. This finding is in agreement with previous studies from Nigeria, Cote d'Ivoire, Haiti, and India found that a rate of zidovudine-related anemia is 3%–12% (Idoko *et al.* 2002; Kumarasam *et al.* 2008; Moh *et al.* 2005; Severe *et al.* 2005; Subbaraman *et al.* 2007). In this cohort, the incidence of fat change was 17.2%.

This is comparable to the study report in Southeast Asian cohorts (16.8%) and Thai cohort (17%); but lower than the report from Rwandan cohort (24.8%) (Puttawong *et al.* 2004; Tin *et al.* 2005; Van-Griensven *et al.* 2010). The prevalence of peripheral neuropathy was 12.3% which is higher than the Indian cohort (9%) and Rwandan cohort (8 %) (Kumarasam *et al.* 2008; Van-Griensven *et al.* 2010); but lower compared to the study in South Africa 17 % (Menezes *et al.* 2011). The occurrences of ADRs are the reason for poor adherence to treatment, counseling the patients on the expected ADRs are crucial to maximize the benefit of the HAART.

In this study patients with CD4 50-99 cells/ μ l (AOR=1.9, 95%CI [1.115- 3.364]), d4t-3TC-NVP (AOR=5.8, 95% CI [1.692-9.591]), AZT-3TC-NVP

(AOR= 4.2, 95% CI [1.227-10.673]) are more likely to develop the ADRs. Other studies show the association of low CD4 count and adverse drug reactions (Subbaraman *et al.* 2007). Eluwa *et al.* (2012) reported that patients on stavudine and zidovudine were less likely to develop ADR with TDF based regimen as the reference may be due to the different sample size and small patients on TDF based regimen (1.7%).

Our study showed no difference in adverse drug reactions with sex, age, adherence, hemoglobin and WHO clinical stage. Eluwa *et al.* (2012) also showed that age, gender and CD4 count were not significantly associated with developing ADRs. However, Bonfati *et al.* (2000) observed that women experienced significantly greater number of adverse effects compared to men and could be due to the large proportion of women in the study compared to our study. Knowledge of the risk factors of ADRs of the ARV regime can help focus scarce resources to managing ADRs in a resource limited countries. The study has the following strengths: First it is a six year cohort study and including large sample size, it reflects the reality in the ART follow up study thus may be applicable to other similar settings. The study has also several limitations: the data were collected retrospectively from patient files in a context of routine care and hence there might be a certain degree of under reporting of events. The study was confined to report on known adverse drug reactions only. Thus the specific ADRs in this study are most likely under reported. Finally, the reported adverse drug reactions do not have their complete details and graded. To conclude, adverse drug reactions are common with HAART in HIV-infected patients and thus regular screening for side effect is required. Prospective

cohort and randomized clinical trials will be required to confirm our findings and studies on the relationship of duration of therapy and ADRs should be conducted in the future to manage ADRs.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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