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Magnitude of Antiretroviral Drug Toxicity in Adult HIV Patients in Ethiopia: A cohort study at seven teaching hospitals

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ABSTRACT

Background: The introduction of antiretroviral therapy (ART) has resulted in significant mortality reduction and improvement in the quality of life. However, this has come at a cost of increased drug toxicity. The objective of this study was to assess the patterns and predictors of ART toxicity in adult HIV patients in Ethiopia.
Methods: This is a prospective cohort study conducted at seven teaching hospitals between September 2009 and December 2013 involving 3921 HIV patients on ART. Adverse drug reactions (ADR) due to ART were identified based on clinical assessment and/or laboratory parameters. Multivariable random effects Poisson regression analysis was used to identify factors independently associated with toxicity.
Result: ADR due to ART drugs was reported in 867 (22.1 %) of the participants; 374 (9.5%) had severe forms. About 87% of reported toxicities were limited to three organ systems – the skin, nervous system and blood. The overall incidence of ADR was 9 per 100 person years. About a third of toxicities occurred during the first six months after ART initiation with the incidence rate of 22.4 per 100 person years. Concomitant anti-tuberculosis treatment was the strongest independent predictor of toxicity.
Conclusion: ADR was found to be highly prevalent in HIV patients on ART at tertiary hospitals in Ethiopia. Most of these conditions occurred early after ART initiation and in those with concomitant anti-tuberculosis treatment. Thus, routine monitoring of patients on ART should be strengthened with particular emphasis in the first 6 months. Strategies should also be devised to replace older and more toxic agents with newer and safer drugs available.
Key words: HIV, ART, adverse drug reaction, incidence rate, ACM, Ethiopia

INTRODUCTION

Human immunodeficiency Virus (HIV) has caused significant socioeconomic crisis for the last few decades in sub-Saharan Africa (1). The discovery of antiretroviral therapy (ART) was the breakthrough in care and treatment of people living with HIV, resulting in reduction in mortality and improvement in the quality of life. This has transformed HIV from untreatable condition into a chronic manageable disease (2). However use of ART and other drugs used in HIV care has resulted in an increment in serious adverse drug reactions (ADR) some of which are life-threatening conditions (3, 4).

Adverse drug reaction is a response to a drug which is noxious and unintended. It is drug toxicity which occurs at doses normally used for prophylaxis, diagnosis, or treatment (5). Among HIV patients, the possible causes for drug toxicity are antiretroviral (ARV) drugs themselves; drug used for prophylaxis and treatment of opportunistic infections (OI) and other concomitant medications (6, 7). Adverse reactions occur with all ARV drugs and are among the major reasons for switching or discontinuing therapy as well as for medication non-adherence (8-10). ADRs have thus become one of the most important limiting factors to the successful treatment of HIV (11-13).

The magnitude of the problem significantly differs between developed and developing world due to various reasons (7). Toxicities related to ART in the developing world, in sub-Saharan Africa in particular, are more prevalent because the regimens contain older and more toxic agents like stavudin (d4t), zidovudin (AZT) and nevirapin (NVP). In addition to these, patients late presentation with advanced disease state, occurrence of opportunistic infections and comorbid medical conditions like malnutrition have made the problem even worse (6, 7, 14). Lack of laboratory monitoring and skilled professionals may also result in failure or delay in diagnosing specific toxicities and hence increasing their severity (6, 7, 12).

In the year 2013, about 790,000 people were estimated to live with HIV in Ethiopia; with adult prevalence of 1.2% and 45,000 deaths annually (15). Routine HIV care and free antiretroviral therapy (ART) services started in the country in 2005 (16). This has resulted in a marked decrement in morbidities and mortalities related to the disease and improvement in quality of life. There are currently about 320,000 adults receiving ART in Ethiopia (17). Few studies in the country have shown that ARV drug toxicity in Ethiopia is a common occurrence and major reason for ART regiment change or modification (9, 18, 19). However, most of the studies lack generalizability due to small sample size focusing on limited facility in central Ethiopia. The aim of this study was thus to assess the magnitude and patterns of ARV drug toxicity in adult HIV patients at major tertiary hospitals in Ethiopia.

METHODS

Study design and setting: This study is part of Advanced Clinical Monitoring (ACM) multi-center cohort. The ACM cohort was conducted in Ethiopia at seven teaching Hospitals located at various parts of the country (Addis Ababa, Hawassa, Jimma, Haramaya, Mekelle, Gondar and Army forces hospital). The cohort included both ART naïve and ART experienced adult and pediatric HIV positive patients.

This article presents findings of adverse drug reaction in adult HIV patients on ART. To involve all patients who were started on ART since the beginning of HIV care in Ethiopia, both retrospective and prospective cohort study designs were used. In the retrospective design, data was obtained from medical records of ART experienced patients since initiation of ART which covers the period of January 2005 to August 2009. The other group consisted of ART naïve patients who were enrolled since 2009. ART experienced patients who were still alive and on follow-up at the beginning of the prospective design were followed in the same way as prospective group.

Baseline data collected from participants included socio-demographic profile, general medical conditions, laboratory parameters and components of HIV care given to them (ART regimen, treatment for OI and prophylaxis given). Participants were subsequently followed for occurrence of adverse reactions related to ART

using clinical parameters and laboratory data where applicable. A particular emphasis was given to the first 6 months after ART initiation as most of the toxicities tend to occur during this time (7). These data were obtained from medical records for patients who were started on ART before 2009 (before recruitment started).

Assessment for ADR was done by physician working at ART clinics at respective hospitals. Patients were assessed on each visit using checklists prepared for routine follow-up evaluation. National guidelines (and WHO recommendations if applicable) for timing of hematologic and blood chemistry evaluation were followed. In patients with suspected ADR, all necessary laboratory tests were done as needed.

Inclusion and Exclusion Criteria: To assess ART related adverse drug reactions, this study included all adult ACM cohort participants who were either ART naïve or ART experienced HIV positive patients at the start of the cohort. Only participants of age 18 years or older at enrollment were included in this study. Accordingly, a total of 3921 adult HIV positive patients from seven teaching hospitals in Ethiopia were included in this study for analysis of ART drug toxicity. Large proportion of the participants, 2304 (58.8%) belonged to ART experienced group.

Patients who died or were transferred out within a week of ART initiation and those who were on ART for the same duration at the last recruitment were not included in this study.

Definition of outcome variables: The outcome of interest in this study was drug toxicities. An algorithm was developed to identify drug toxicities meeting the operational definition based on World Health Organization (WHO) criteria for ADR (5) (Annex 1).

Adverse drug reactions in patients on ART were identified based on clinical and/or laboratory data. Only clinical conditions known to arise from potential agent, in the absence of other compelling medical conditions, were attributable to ADR. Mild medical conditions which commonly occur in the general public but can be attributable to the drugs were excluded from this list unless specified and there was clear evidence for direct contribution by the agent. In most cases this refers to gastrointestinal disturbances (dyspeptic symptoms) which in most of the patients have been reported before or after ART initiation. Major gastrointestinal upset reported by patient to be worsened after these medication or has resulted in their discontinuation due to these conditions were considered as evident drug toxicity.

Severe or life threatening toxicity was defined based on clinical or laboratory evidences classified as grade 3 or 4 by WHO criteria (Annex – 1). All forms of toxicities resulting in hospitalization, major disability, changing or discontinuation of the culprit agent were categorized in this group.

In cases of multiple occurrences of toxicities in a single patient, the count was based on the systems involved and time of occurrence. Multisystem complications that were due to single mechanism were counted as one (e.g lactic acidosis and pancreatitis due to stavudin were considered as related toxicities if occurred within one week of each other). However, if the pathophysiologic mechanisms were different, they were counted separately (e.g., anemia and lactic acidosis in zidovudin were considered as separate forms of toxicities). Similar toxicities, toxicities of similar pathophysiology or of the same spectrum occurring within one week of each other and non-resolving ones were counted as one type of toxicity.

All forms of toxicity were classified based on their severity and body system affected.

Data quality assurance: Data collectors were trained and regularly supervised by Johns Hopkins Technical Support for the Ethiopian HIV/AIDS Initiative (TSEHAI). Refresher trainings were given to sites based on gaps identified. Standard reporting formats were used to minimize interpersonal variation and Variation between sites. All incoming staffs (physicians and nurse) were trained on entry.

Data management and Data analysis: The data was initially computerized using Microsoft access. This data was exported to SPSS version 20 and STATA version 12 for analysis. Tableau version 8 was also used to portray the trends in toxicity.

Because toxicities are more likely to occur during the initial period of exposure to ART, we calculated the six-month incidence of drug toxicity as a probability of a participant experiencing one or more drug toxicities during the first six months from initiation of ART. The crude incidence rates

of toxicity per 100 person-years on ART was calculated by summing the total number of occurrences of toxicity and dividing this total by the summed person-time of each participant from ART start to either the time patient left the study or study terminated.

Incidence of toxicity was estimated using random effects multivariable Poisson regression analysis. Potential risk factors to be included in multivariable model were selected if p-value in the bivariate analysis was less than 20%. Clustering at site level was adjusted both in univariate and multivariable analysis.

We also calculated stratified incidence rates for each year that patients took ART. It was acknowledge that each participant might have one or more incidence of toxicity. The six-month incidence and incidence rates of all toxicities combined and of each severity category was calculated separately. Homogeneity of the 6-month incidence across sites was assessed using the Breslow-Day test and homogeneity of the incidence rates across sites was assessed using a chi-square test.

Ethical considerations: Ethical clearance of the study was obtained from Ethiopian Public Health Institute, Minister of Science and Technology of Ethiopia and Center for Diseases Control and prevention (CDC), Atlanta, USA.   Written informed consent was obtained from all participants before recruitment. Data was collected using numerical codes and will remain anonymous.

RESULTS

Baseline characteristics: ACM cohort of 3921 adult HIV patients who were on ART were assessed for the occurrence of ART drug toxicity; 62% of them were women. The mean age at ART initiation was 34.5 years (SD =9.2) and 75% were between 25 and 44 years of age. More than 60% of the participants had baseline body weight of less than 55 kilograms. Nearly 60% of the participants reported use of some form of substance; 6.7% have used hard drugs including morphine and cocaine. The majority of the participants were at advanced staged of their HIV at initiation of ART; 65.9% had WHO stage ≥ 3 disease and 69.7% had CD4 count of <200. In terms of functional status, 4.4% of the patients were bedridden at baseline (Table 1).

Table 1: Baseline characteristics of adult HIV patients at initiation of ART in HIV patients at tertiary hospitals in Ethiopia.

	Total participant		Toxicity			
			Yes		No	
Age category (N=3921)	Number	%	Number	%	Number	%
<25	399	10.2	92	23.1	307	76.9
25-34	1761	44.9	386	21.9	1375	78.1
35-44	1181	30.1	248	21.0	933	79.0
>=45	580	14.8	141	24.3	439	75.7
Gender (N=3921)						
Female	2426	61.9	609	25.1	1817	74.9
Male	1495	38.1	258	17.3	1237	82.7
Baseline body weight, Kg (N=3738)						
<45	802	20.5	209	26.1	593	73.9
45-54	1547	39.5	359	23.2	1188	76.8
55-64	970	24.7	197	20.3	773	79.7
≥ 65	419	10.7	69	16.5	2350	83.5
ART history (N=3921)						
ART experienced	2304	58.8	642	27.9	1662	72.1
ART naïve	1617	41.2	225	13.9	1392	86.1

Table 1. continued…

Educational status (N=3843)						
No education	723	18.4	189	26.1	534	73.9
Primary	1393	35.5	304	21.8	1089	78.2
Secondary	1310	33.4	276	21.1	1034	78.9
Tertiary	417	10.6	78	18.7	339	81.3
Employment status (N=3285)						
Unemployed	1571	40.1	374	23.8	1197	76.2
Too sick to work	385	9.8	92	23.9	293	76.1
Working part-time	91	2.3	20	22.0	71	78
Working full time	1225	31.2	230	18.8	995	81.2
Other	13	0.3	3	23.1	10	76.9
Marital status (N=3870)						
Never married	663	16.9	122	18.4	541	81.6
Married(Inc. de facto)	1834	46.8	358	19.5	1476	80.5
Separated or Divorced	803	20.5	218	27.1	585	72.9
Widow/Widower	570	14.5	151	26.5	419	73.5
Facility (Hospital) (N=3921)						
Tikur Anbessa	566	14.4	165	29.2	401	70.8
Army	557	14.2	53	9.5	504	90.5
Gondar	610	15.6	155	25.4	455	74.6
Jimma	540	13.8	83	15.4	457	84.6
Mekelle	582	14.8	178	30.6	404	69.4
Haramaya	530	13.5	129	24.3	401	75.7
Hawassa	536	13.7	104	19.4	432	80.6
WHO staging (N=3852)						
1 and 2	1265	32.8	253	20.0	1012	80.0
3 and 4	2587	67.2	598	23.1	1989	76.9
CD4 count category (N=3789)						
<200	2735	72.2	581	21.2	2154	78.8
200-349	983	25.9	232	23.6	751	76.4
≥350	71	1.9	17	23.9	54	76.1
Functional status (N=3840)						
Working	2796	71.3	631	22.6	2165	77.4
Ambulatory	872	22.2	199	22.8	673	77.2
Bedridden	172	4.4	23	13.4	149	86.6
ART regiment at initiation (N=3918)						
AZT+3TC+EFV	434	11.1	87	20.0	347	80.0
AZT+3TC+NVP	1053	26.9	237	22.5	816	77.5
D4T+3TC+EFV	344	8.8	93	27.0	251	73.0
D4T+3TC+NVP	951	24.3	289	30.4	662	69.6
TDF+3TC+EFV	920	23.5	122	13.3	798	86.7
TDF+3TC+NVP	209	5.3	39	18.7	170	81.3
Others	7	0.18	0	0	7	100.0

The initial ART regimen in all patients was a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). The most commonly prescribed NRTIs were AZT (38%) and d4t (33.1%). However, this trend changed after the introduction of tenofovir (TDF) in 2009 which was used as an initial NRTI in 53.6% of the cases since then. Efavirinez (EFV) and NVP were the only NNRTs prescribed; the

latter was used in 56.5% of the patients. All but one patient took lamivudine (3TC) as the backbone of the entire regimen.

Over 90% (3585) of them were on cotrimoxazole prophylactic treatment (CPT) while only 4.1% (160) were prescribed isoniazid (INH) preventive therapy (IPT) at time of ART initiation; 15.4% (604) were taking anti-tuberculosis treatment.

The mean follow-up period of patients on ART was 43.7 (SD =28.7) months with median follow-up of 41.6 months. There was significant difference in the mean follow-up of patients in Experienced group (mean = 60.3; SD = 24.5;

median = 64.8 months) and Naïve group (mean = 19.2; SD =13.1; median 18.5 months).

Patterns of adverse drug reaction: Overall, there were 1253 incidents of ADR reported during the follow-up period. Of these, 542 (43.3%) were severe or life threatening toxicities. The rate of toxicity was the highest in the first 6 months after ART initiation; 31.8% occurred during this period with the trend gradually decreasing overtime (Fig 1). In general, ADR was reported in 867 (22.1 %) of the participants over the follow-up period; 374 (9.5%) had severe forms. Of those with ADR, 240 (27.7%) had more than one incident.
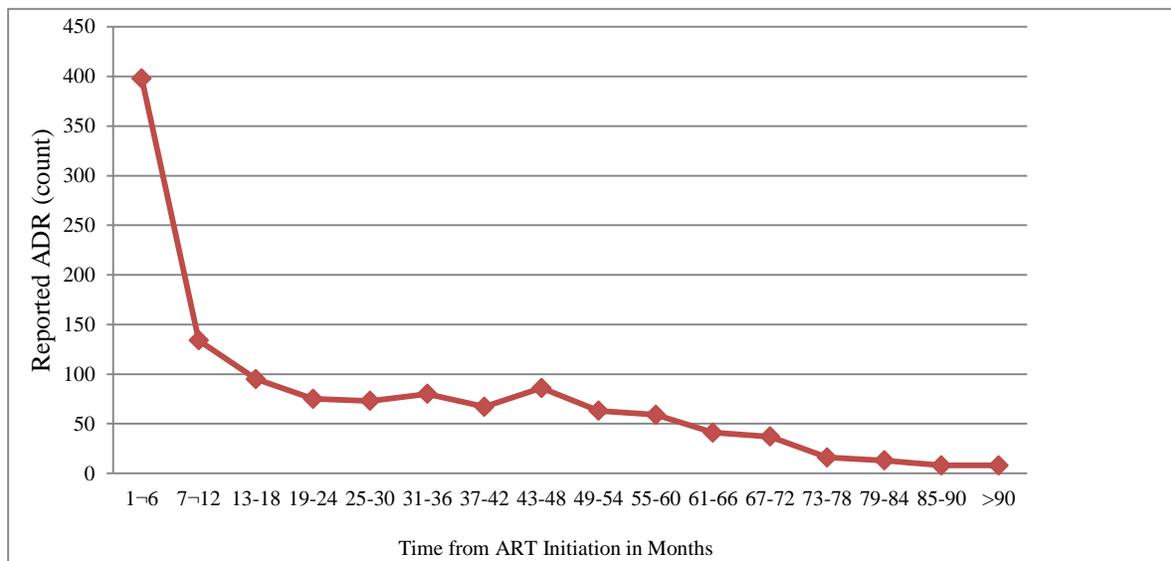

Figure 1: Trends in occurrence of ADR in adult HIV patients on ART at tertiary hospitals in Ethiopia

The incidence rate of ADR over follow-up time was 9 per 100 person years. The incidence of toxicities was highest in the first 6 months of ART initiation with incidence rate of 22.4 per 100 person years.

About 87% of reported toxicities were limited to three organ systems – the skin (36.6%), nervous system (35.4%) and blood (14.9%). While most of dermatologic ADR were milder forms, about

67.0% of severe forms of adverse events were neurologic (Fig 2). Moreover, over 80% of neurologic toxicities were classified as severe forms which have resulted in either disabilities or hospitalization or regimen change. Most of the patients with neurologic toxicities and all with severe forms were taking d4t at the time of the toxicity incidence.
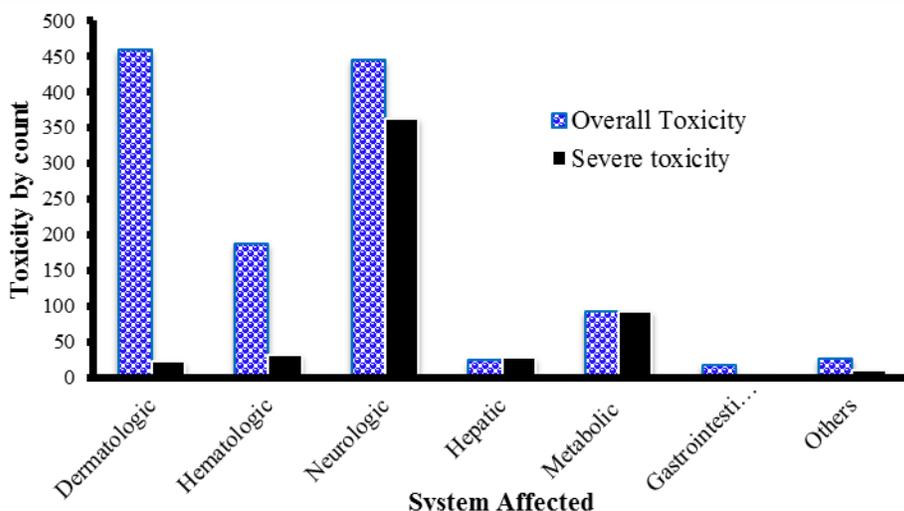
Figure 2: Types of ADR by system affected in HIV patients on ART at tertiary hospitals in Ethiopia

The incidence rate of adverse events in the first six months by year of ART start (2005 – 2013) ranged from 11.9 to 36.8 per 100 person year. In general, the 6 months and overall incidence rate of ADR were higher in patients who started on ART since the 2009 as compared those who started earlier (Table 2).

Table 2: Incident Rate of Toxicity by Year of ART Start at six month and over all follow-up period in HIV patients at tertiary hospitals in Ethiopia.

ART start year	Within 6 month			Overall		
	Follow Up Time (in days	No. of Toxicity	Incident rate (Per 100 Person-Year)	Follow Up Time	No. of Toxicity	Incident rate (Per 100 Person-Year)
2005	41378	21	18.5	586067	103	6.4
2006	110812	36	11.9	1380500	277	7.3
2007	92257	52	20.6	993457	256	9.4
2008	79201	49	22.6	718597	174	8.8
2009	85133	58	24.9	584458	168	10.5
2010	114886	88	28.0	555865	152	10.0
2011	58475	59	36.8	193012	84	15.9
2012	52531	29	20.2	101332	33	11.9
2013	14670	6	14.9	15669	6	14.0

Predictors of adverse drug reaction: Multivariable random effect Poisson regression analysis was done to find predictors for occurrences of ADR in the first six months of HAART initiation. Patients who started ART in 2009 and after had higher rates of ADR as compared to those who started treatment prior to that; AIRR 1.38, 95% CI 1.017 - 1.87 and 1.49, 95% CI 1.03 - 2.15 for 2009-2010 and 2011-2013 respectively as compared to ART start year of 2005-2008. Similarly, lower literacy status, marital inconvenience (being divorced or separated), and concomitant anti-TB treatment were independent predictors of ADR in the first 6 months (Table 3).

Similar analysis for patients started on HAART since 2009 (prospectively recruited patients) showed that lower educational status, lower CD4 count (<200), and concomitant TB treatment were independent predictors of ADR (Table 4).

Table 3: Predictors of Toxicity within 6 months of ART initiation in HIV patients at tertiary hospitals in Ethiopia: *both ART naïve and experienced groups.*

Characteristics		Uni-variable analysis		Multivariable analysis	
		IRR (95% CI)	P-value	IRR (95% CI)	P -Value
Sex	Female	1		1	
	Male	0.803(0.640 - 1.007)	0.057	0.825(0.630 - 1.079)	0.160
Age at ART start	18 -24	1			
	25 -34	1.159(0.795 - 1.688)	0.443		
	35 -44	1.047(0.703 - 1.559)	0.823	NS	
	45+	1.245(0.809 - 1.915)	0.319		
ART Start Year	2005-2008	1		1	
	2009-2010	1.524(1.202 - 1.932)	0.000	1.378(1.017 - 1.868)	0.039*
	2011-2013	1.533(1.173 - 2.003)	0.002	1.487(1.029 - 2.151)	0.035*
Educational status	No education	1		1	
	Primary	0.724(0.545 - 0.961)	0.025	0.729(0.543 - 0.980)	0.036*
	Secondary	0.867(0.656 - 1.145)	0.314	0.851(0.633 - 1.144)	0.284
	Tertiary	0.807(0.545 - 1.194)	0.283	0.866(0.573 - 1.309)	0.495
Marital Status	Never married	1		1	
	Married(Inc. de facto)	1.145(0.827 - 1.585)	0.416	1.093(0.778 - 1.537)	0.608
	Separated or Divorced	1.663(1.181 - 2.340)	0.004	1.545(1.070 - 2.230)	0.020*
	Widow/Widower	1.027(0.687 - 1.534)	0.898	1.100(0.719 - 1.683)	0.659
Weight at ART Start	<=45	1		1	
	46 -51	0.973(0.726 - 1.304)	0.855	1.075(0.791 - 1.460)	0.645
	52 -58	0.935(0.693 - 1.263)	0.663	1.011(0.732 - 1.397)	0.947
	59+	1.224(0.905 - 1.655)	0.190	1.323(0.936 - 1.869)	0.113
Base WHO Stage	I	1			
	II	1.291(0.870 - 1.915)	0.205		
	III	1.034(0.721 - 1.482)	0.858	NS	
	IV	1.107(0.723 - 1.694)	0.640		
Base Functional Status	Working	1		1	
	Ambulatory	0.935(0.715 - 1.221)	0.621	1.019(0.759 - 1.370)	0.899
	Bedridden	0.535(0.254 - 1.128)	0.100	0.539(0.221 - 1.314)	0.174
Base CD4 Count	<=50	1			
	51 - 100	0.958(0.659 - 1.393)	0.823		
	101 - 200	0.905(0.646 - 1.266)	0.559	NS	
	201 - 350	1.240(0.879 - 1.750)	0.220		
	350+	1.433(0.674 - 3.049)	0.350		
Base Regimen	TDF-NVP	1		1	
	TDF-EFV	0.745(0.500 - 1.111)	0.149	0.650(0.428 - 0.986)	0.043*
	ZDV-EFV	0.649(0.418 - 1.008)	0.054	0.687(0.426 - 1.107)	0.123
	ZDV-NVP	0.559(0.380 - 0.821)	0.003	0.596(0.396 - 0.897)	0.013*
	d4T-EFV	0.443(0.260 - 0.756)	0.003	0.551(0.304 - 0.997)	0.049*
	d4T-NVP	0.487(0.323 - 0.736)	0.001	0.573(0.351 - 0.935)	0.026*
CPT	Yes	0.864(0.602 - 1.239)	0.426	NS	
	No	1			
IPT	Yes	0.853(0.466 - 1.561)	0.606	NS	
	No	1			
TB Treatment	Yes	1.439(1.124 - 1.843)	0.004	1.443(1.081 - 1.926)	0.013*
	No	1		1	

* Statistically significant, NS – not statistically significant (P was >0.25 in univariate analysis)
CPT – co-trimoxazole prophylactic therapy, IPT – Isoniazid prophylactic therapy, TB – tuberculosis

When severe forms of toxicity were analyzed separately, marital inconvenience (being divorced or separated) and concomitant TB treatment remained independent predictors. AZT-EVF containing regimen was also found to result in 71% decrement in severe toxicity as compared to TDF-NVP containing regimen (Table 5).

Table 4: Predictors of Toxicity within 6 months of ART initiation in HIV patients at tertiary hospitals in Ethiopia: *ART naïve group*.

Characteristics		Uni-variable analysis		Multivariable analysis	
		IRR (95% CI)	**P-Value**	**IRR (95% CI)**	**P-Value**
Sex	Female	1		1	
	Male	0.63 (0.446, 0.901)	0.011	0.71 (0.465, 1.077)	0.107
Age ART Start	18 -24	1			
	25 -34	1.38 (0.744, 2.577)	0.304		
	35 -44	1.08 (0.560, 2.063)	0.828		
	45+	1.22 (0.601, 2.492)	0.579		
ART Start Year	2013	1		1	
	2009	1.60 (0.548, 4.680)	0.389	1.20 (0.351, 4.126)	0.768
	2010	1.66 (0.719, 3.819)	0.235	1.51 (0.593, 3.849)	0.387
	2011	2.12 (0.907, 4.973)	0.083	2.15 (0.841, 5.511)	0.110
	2012	1.30 (0.537, 3.136)	0.563	0.96 (0.356, 2.591)	0.937
Education	No education	1		1	
	Primary	0.54(0.357, 0.839)	0.006	0.52 (0.326, 0.822)	0.005*
	Secondary	0.83 (0.555, 1.233)	0.351	0.83 (0.536, 1.290)	0.410
	Tertiary	0.71 (0.416, 1.206)	0.204	0.87 (0.500, 1.530)	0.639
Marital Status	Never married	1		1	
	Married(Inc. de facto)	1.32 (0.819, 2.130)	0.254	1.34 (0.797, 2.251)	0.270
	Separated or Divorced	1.72 (1.026, 2.881)	0.040	1.75 (0.995, 3.066)	0.052
	Widow/Widower	1.30 (0.704, 2.415)	0.399	1.24 (0.628, 2.450)	0.536
Weight at ART Start	<=45	1		1	
	46 -51	0.71 (0.452, 1.120)	0.141	0.77 (0.472, 1.260)	0.299
	52 -58	0.73 (0.471, 1.134)	0.162	0.91 (0.558, 1.478)	0.697
	59+	0.76 (0.486, 1.174)	0.212	0.93 (0.557, 1.478)	0.765
Base WHO Stage	I	1		1	
	II	1.67 (1.004, 2.770)	0.048	1.82 (1.056, 3.145)	0.031*
	III	1.48 (0.901, 2.417)	0.122	1.46 (0.830, 2.559)	0.189
	IV	1.68 (0.913, 3.109)	0.095	1.62 (0.785, 3.346)	0.191
Base Functional Status	Working	1			
	Ambulatory	0.99 (0.617, 1.589)	0.967		
	Bedridden	0.91 (0.288, 2.884)	0.875		
Base CD4 Count	<=50	1		1	
	51 - 100	0.79 (0.473, 1.311)	0.359	0.74 (0.425, 1.286)	0.285
	101 - 200	0.62 (0.389, 1.000)	0.050	0.57 (0.337, 0.972)	0.039*
	201 - 350	0.83 (0.520, 1.332)	0.443	0.82 (0.474, 1.406)	0.464
	350+	1.17 (0.474, 2.871)	0.738	1.20 (0.450, 3.196)	0.717
Base Regimen	TDF-NVP	1		1	
	TDF-EFV	0.72 (0.448, 1.155)	0.172	0.52 (0.318, 0.863)	0.011*
	ZDV-EFV	0.91 (0.502, 1.654)	0.760	0.78 (0.415, 1.466)	0.440
	ZDV-NVP	0.76 (0.458, 1.271)	0.299	0.69 (0.403, 1.174)	0.170
	d4T-EFV	0.74 (.169, 3.254)	0.692	0.25 (0.033, 1.955)	0.188
	d4T-NVP	0.83 (0.246, 2.790)	0.762	0.79 (0.229, 2.759)	0.719
CPT	Yes	0.87 (0.503, 1.505)	0.619		
	No	1			
IPT	Yes	0.48 (0.067, 3.413)	0.461		
	No	1			
TB Treatment	Yes	1.72 (1.179, 2.499)	0.005	1.67 (1.043, 2.677)	0.033*
	No	**1**		**1**	

* Statistically significant

Table 5: Predictors of Severe Adverse drug reactions within 6 months of ART initiation in HIV patients at tertiary hospitals in Ethiopia: *ART experienced group.*

Characteristics		Uni-variable analysis		Multivariable analysis	
		IRR (95% CI)	P Value	AIRR (95% CI)	P Value
Sex	Female	1		NS	
	Male	0.771(0.515 - 1.155)	0.207		
Age ART Start	18 -24	1		1	
	25 -34	1.125(0.550 - 2.303)	0.747	1.142(0.556 - 2.345)	0.717
	35 -44	1.011(0.475 - 2.154)	0.977	0.977(0.453 - 2.105)	0.953
	45+	2.147(1.013 - 4.550)	0.046	2.099(0.971 - 4.539)	0.059
ART Start Year	2005-2008	1		1	
	2009-2010	0.663(0.429 - 1.026)	0.065	0.785(0.454 - 1.356)	0.385
	2011-2013	0.661(0.393 - 1.113)	0.120	0.829(0.422 - 1.631)	0.588
Educational status	No education	1		1	
	Primary	0.526(0.316 - 0.873)	0.013	0.601(0.358 - 1.010)	0.054
	Secondary	0.714(0.445 - 1.146)	0.164	0.901(0.549 - 1.478)	0.681
	Tertiary	0.739(0.386 - 1.417)	0.363	0.975(0.501 - 1.897)	0.941
Marital Status	Never married	1		1	
	Married(Inc. de facto)	1.057(0.584 - 1.913)	0.855	1.073(0.587 - 1.962)	0.818
	Separated/Divorced	2.107(1.157 - 3.838)	0.015	2.110(1.141 - 3.901)	0.017*
	Widow/Widower	1.263(0.630 - 2.531)	0.511	1.217(0.591 - 2.503)	0.595
	<=45	1			
Weight at ART Start	46 -51	0.984(0.584 - 1.658)	0.952	NS	
	52 -58	0.936(0.545 - 1.608)	0.811		
	59+	1.120(0.649 - 1.932)	0.684		
Base WHO Stage	I	1			
	II	0.992(0.455 - 2.160)	0.984	NS	
	III	1.174(0.600 - 2.297)	0.639		
	IV	1.432(0.673 - 3.048)	0.351		
Base Functional Status	Working	1			
	Ambulatory	1.131(0.707 - 1.809)	0.607	NS	
	Bedridden	0.762(0.240 - 2.418)	0.645		
Base CD4 Count	<=50	1			
	51 - 100	0.866(0.445 - 1.685)	0.672		
	101 - 200	0.898(0.501 - 1.611)	0.718		
	201 - 350	1.290(0.712 - 2.337)	0.402		
	350+	0.472(0.062 - 3.559)	0.466		
Base Regimen	TDF-NVP	1		1	
	TDF-EFV	0.769(0.336 - 1.759)	0.534	0.544(0.232 - 1.277)	0.162
	ZDV-EFV	0.493(0.190 - 1.281)	0.147	0.285(0.104 - 0.779)	0.014*
	ZDV-NVP	0.741(0.340 - 1.615)	0.450	0.622(0.277 - 1.396)	0.249
	d4T-EFV	1.057(0.428 - 2.610)	0.905	0.537(0.196 - 1.473)	0.227
	d4T-NVP	1.217(0.557 - 2.656)	0.623	0.817(0.335 - 1.988)	0.655
CPT	Yes	1.350(0.675 - 2.701)	0.396		
	No	1			
IPT	Yes	1.619(0.705 - 3.719)	0.256		
	No	1			
TB Treatment	Yes	2.409(1.630 - 3.559)	0.000	2.817(1.847 - 4.298)	<0.0001*
	No	**1**		**1**	

*- Statistically significant

It is thus evident that anti-tuberculosis treatment in the first 6 months of HAART in initiation was found to be the strongest independent predictor of ADR; any form of ADR increased by 67% in those taking TB treatment (Table 3) while severe forms were found to be 3 times higher.

DISCUSSION

Toxicities related to ART drug were widely prevalent among HIV patients on follow-up in tertiary hospitals in Ethiopia; significant proportion of them resulted in serious morbidities. Toxicities were found to be highest in the first 6 months of ART initiation. Concomitant anti-tuberculosis treatment was found to be an independent predictor of adverse drug reaction due to ART.

All of the participants were started on combination of two NRTIs and NNRTI adhering to WHO's recommendation for resource limited settings (20). Most of patients taking d4t were shifted to TDF since 2009 after revision of national guidelines in 2008 (16). As a result, the proportion of patients starting on d4t containing regimen dropped from 70% in 2006 to 1% in 2013. However, the fact that some patients were still started on stavudin containing regimen (42 patients in 2010, 4 in 2011, 3 in 2012 and 2 in 2013) years after revision of the guideline should not pass unnoticed.

The overall prevalence of ADR of 22.1% in our study is comparable with findings from the developing world; 19.5% in Cameroon (21), 26.8% in India (22). However, the incidence rate is much higher than findings in Nigeria of 4.6 per 100 person years (23). Because of the very nature of occurrences of ADR due to ART, neither assessment of the total prevalence of the problem nor the overall incidence rate tell the exact magnitude of the problem. Longer exposure to the drugs may inflate the prevalence and overall incidence rate of ADR. However, more serious and common toxicities occur during the initial phase of ART (7). Hence, comparison between studies may not be straight forward.

Consistent with global data, incident toxicities in our study were found to be more common in the first 6 months of ART initiation (4, 7, 24). Patients with advanced disease at ART initiation in particular are at higher risk of ADR (25, 26). However, neither WHO stage of the disease nor CD_4 count at ART initiation was associated with occurrences of ADR in our study. This may be partly explained by the fact that most the study participants had advanced WHO stage and low CD_4 count at HAART initiation. Additionally, failure to detect and report milder forms of ADR may explain the absence of this relationship. Despite using standardized reporting format for any ADR, it is well documented that both highly trained professionals and patient underreport milder forms (27, 28). We thus believe that milder dermatologic manifestations and gastrointestinal symptoms might have been underreported by patients and overlooked by treating physician as non-life threatening event.

Early toxicities are also known to be worsened with concomitant OI treatment (29). Though INH and Cotrimoxazole prophylaxis for OIs were not associated with increased toxicities in our study, concomitant anti-tuberculosis admiration was found to be the strongest predictor of ADR. Overlapping toxicities between HAART and anti-TB drugs has been well documented and know to hamper success of the treatment (30). While this has been an issue, the benefit of addressing the two infections should take priority.

When years of ART initiation were compared, incident toxicity was found to be more common in those who started ART since 2009. This difference is mainly due to design effect. Data for patients who started ART before 2009 was obtained only retrospectively and incident toxicities could have been under reported. When only prospectively cohorts were analyzed separately, the effect of year of ART initiation disappears. We believe that the lowest incidence of toxicities in prior years was mainly due to underreporting than other reasons. Besides, as experience in HIV care has improved over the last many years in the country, detection rate of all forms of adverse reaction has expectedly improved resulting in the increment in the rate of reported ADR.

Even though this study is multicenter large scale cohort in Ethiopia, there are certain limitations worth mentioning. First of all, the data prior to 2009 were collected from medical records only. As a result, certain ADR, the non-life threatening ones, could have been underreported. Secondly, some of the adverse reactions diagnosed on clinical ground only were based on treating physician's diagnosis which might have also resulted inconsistence across sites and under-reporting. Last but most importantly, the study

was based in tertiary/university hospitals in the country with better laboratory facilities and more qualified professionals in HIV care. Hence, the findings may not be generalizable to all HIV patients in Ethiopia.

In conclusion, ADR due to ART drugs has been found to be highly prevalent in HIV patients on follow-up at tertiary hospitals in Ethiopia. A significant proportion was found to be serious adverse reactions resulting in admissions and/or regimen changes. ADRs were prominent during the first 6 months after ART initiation. Concomitant administration of full anti-tuberculosis regimen was the strongest independent predictor for the occurrence of these toxicities. Thus, routine clinical and laboratory monitoring of patients on ART should be strengthened with particular emphasis in the first 6 months. High risk patients (those with comorbidities, advanced immunosuppression and concomitant OIs) should be actively identified before ART initiation. These patients should be effectively treated for the OIs or comorbidities, if possible, before ART initiation. Selection of ART regimen should also put into consideration their other medical conditions. Strategies should also be devised to replace older and more toxic agents with newer and safer drugs available. All facilities rendering ART service should follow standard reporting method for incident ADR related to ART and OI treatment.

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