Anti-retro viral therapy adverse drug reaction and associated factors among human immuno deficiency virus infected adult patients at Nigist Eleni Mohammed Memorial hospital, South Ethiopia

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Abstract

Background: Recent increases in access to HAART have made the management of drug toxicities an increasingly crucial component of HIV care in developing countries. The aim of this study was to determine prevalence of antiretroviral therapy adverse drug reactions and associated factors among HIV-infected adult patients at Nigist Eleni Mohammed memorial hospital.

Methods: A cross sectional study was conducted by retrospective review of patients' medical records. From a total 721 adult patient records, 231 patients record were selected by simple random sampling technique. The study was conducted April15-25, 2015.The association between dependent and independent variables was measured by using OR at 95% CI. P-value <0.05 was considered as statistically significant.

Result: About 53(22.9%) patients developed ADRs (adverse drug reactions). Female (AOR=2.72, CI=1.177-6.30), patients with WHO stage III and IV (AOR= 13.06, CI=4.17- 40.90) were found more likely to develop ADRs. Commonly identified ADRs were fatigue (18.1%), diarrhea (7.7%), nausea (6.5%), headache (3.6%) and anemia (2%).

Conclusion: Nearly one in five patients develop ADRs. Sex of respondents, WHO stage and functional status were associated with ADRs. The health care providers should give due attention to ambulatory, bedridden, and WHO stage III and IV patients.

Keywords: ART; HIV; AIDS; Ethiopia.

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Background

Human immune deficiency virus (HIV) has created an enormous challenge[1]. Globally, an estimated 35.3 million people were living with HIV in 2012[2]. An estimated 0.8% of adults aged 15-49 years are living with HIV[3]. Sub-Saharan Africa remains the most severely affected region, with nearly 1 in every 20 adults living with HIV. This accounted for 69% of the people living with HIV worldwide[3]. In Ethiopia, the overall prevalence of HIV among adults aged 15-49 was 1.5% in 2011[4]. Ethiopia is among the selected countries that had shown changes in the incidence rate of HIV infection among adults (15–49years old)[3].

Antiretroviral therapy (ART) prevents people living with HIV from dying from the acquired immune deficiency syndrome (AIDS) and from developing tuberculosis, becoming ill and transmitting tuberculosis and HIV. Emerging science indicates that people should start HIV treatment earlier to realize these benefits[2]. Since 1995, ART has saved 14 million life-years in low and middle-income countries, including 9 million in sub-Saharan Africa[3]. As of December 2012, an estimated 9.7 million people in low and middle-income countries were receiving ART, an increase of 1.6 million over 20112.

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The massive scale up of ART is saving more lives[5]. In 2013, an additional 2.3 million people gained access to the life-saving medicines. This brings the global number of people accessing ART to nearly 13 million by the end of 2013[6]. The number of people receiving ART in eastern and southern Africa increased from 625 000 in 2005 to approximately 6.3 million in 2012[7]. The region accounts for about 84% of the estimated 7.5 million people who received ART in Africa and 65% of the estimated 9.7 million people who received ART globally in 2012[8]. The number of people receiving ART in Ethiopia increased from less than 9,000 in 2005 to more than 439,000 in 2013[9].

There are different types of ant retro viral (ARV) regimens in Ethiopia. First-line ARV regimens for adults and adolescents in Ethiopia include the following. One of the following should be used unless there are contraindications: The preferred ones include tenofovir disoproxil fumarate (TDF) +emtricitabine (FTC) +efavirenz (EFV) = triple FDC (fixed drug combination). It also comprises ZDV (zidovudine) + 3TC (lamivudine) +EFV = combivir + EFV. The other preferred options are ZDV+3TC+NVP (nevirapine) = triple FDC.AlternativesincludeD4T (stavudine)/3TC/EFV = double FDC (d4T/3TC) + EFV, TDF/3TC/NVP, D4T/3TC/NVP = triple FDC, ABC (abacavir) /3TC/EFV, ABC/3TC/NVP, ABC/3TC/ZDV = combivir + ABC[10].

Like most medicines, ARV drugs can cause side effects. These unwanted effects are often mild, but sometimes they are more serious and can have a major impact on health and quality of life[11]. Recent increases in access to highly active antiretroviral therapy (HAART) have made the management of drug toxicities an increasingly crucial component of HIV care in developing countries. The spectrum of adverse effects related to HAART in developing countries may differ from that in developed countries because of the high prevalence of other conditions such as anemia, malnutrition, and tuberculosis and frequent initial presentation with advanced HIV disease[12]. ART adverse reaction prevalence varies from region to region, country to country[1,13,14]. The severity and profile of ART drug reaction also varies from patient to patients, from drug regimen to regimen[14-17].
Different studies depicted the ARV regimens and their side effects. Study conducted in Cameron showed that among those who reported ADRs, 29.6% were on D4T-3TC-EFV, 29.3% on D4T-3TC-NVP, 16% on AZT-3TC-EFV and 10.8% on AZT-3TC-NVP[18]. Another study done in India conveyed that ZDV+3TC+NVP regimen use reported majority of ADRs[19]. In Ethiopia, one study displayed that D4T/3TC/NVP was the most commonly used regimen and mostly causes side effects like toxicity[20].

Continuous evaluation and reporting of unusual effects of ADRs (adverse drug reaction) of ART drug is important for those people receiving ART to get all the help they need to minimize the impact of ADRs. In Ethiopia, there is an ADRs monitoring center. The ADRs monitoring center is responsible for collecting, compiling and analyzing any ADRs information reported by health professionals. Based on this information, risk-benefit evaluations are made and safety measures are taken to protect the public from unnecessary harm. Nevertheless, information on the types and severity of ADRs of ART is inadequate in the study area. Therefore, the aim of this study was to determine the prevalence of ADRs of ART and associated factors among HIV infected adult patients, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment.

Methods

Study setting

The study was conducted in Nigist Eleni Mohamed memorial hospital (NEMMH). NEMMH is found in Hosanna Town, southern Ethiopia. It is located 230kilometers and 194kilometersfrom Addis Ababa and Hawassa, respectively. It renders comprehensive HIV/ AIDS related services including, voluntary counseling and testing (VCT), provider initiated testing and counseling (PITC), prevention mother to child transmission (PMTCT) and ART program. There were721 HIV/AIDS adult patients attending ART in the hospital between 2005 and 2014.

The patients were initiated on ART based on CD4 cell counts <200/ mm. However, lack of CD4 count could not preclude ART initiation in patients clinically eligible for treatment. To ensure patient safety, treatment must not be delayed until CD4 count falls below 200. The optimum time to initiate ART is when a patient's CD4 count is 200-350. CD4 count levels do not determine treatment initiation in stage IV patients; regardless of CD4 count, stage IV patients are promptly started on ART. In stages I and II, immunological assessment is important to initiate ART; in stage III, treatment can be considered under certain clinical conditions with CD4 count of 350 and below. This is a rule in Ethiopia dur-

ing study period. But currently some modifications are being introduced.

After the 12th week of initiation of ART, patients are scheduled to return every eight weeks. At each visit ARV, drugs and co-trimoxazole preventative therapy for two months are given, counselling of positive living, safe sexual practice, adherence assessment and support are done. Lab tests including alanine aminotransferaseare requested when indicated. CD4 is repeated every 6 months. The ART treatment is given by trained health professional on ART and management of opportunistic infections. The treatment is given in separate ART treatment room.

Study design

Cross sectional study was done by using retrospective review of 10 years (2005 to 2014) patients' medical record.

Study population and period

All randomly selected adult patients (>15 years) who were on ART between 2005 and 2014. The study was conducted April 15-25, 2015.

Sample size determination and sampling technique

Sample size was determined by using a single population proportion formula; considering 5% margin of error, 95% , level of confidence and 65.5%, prevalence of ADRs among Adult HIV/AIDS(acquired immune deficiency syndrome) patients on ART at the ART clinic of Jimma University Specialized Hospital in 2012[14]. After correcting for finite population, 231 samples were included. About 721 registered patients who fulfilled the inclusion criteria were identified, then sampling frame was arranged (1 to 721), finally by applying simple random sampling technique (computer generated method), 231 records were selected.

Data collection, measurements and definitions

The data were collected using a checklist. Records review covered patients' information from beginning of ART service to their last visit. Data were collected by 3 trained data collectors. The principal investigator and supervisors made a day to day on site supervision during the period of data collection and checked each checklist daily for its completeness and consistency. Both the data collectors and supervisors were trained on the objective, methodology and data collection approach. Data collection format/check list was checked and necessary modification was done before data collection.

Data collected on socio-demographic factors included age, marital status, sex, religion, occupational status, educational status, and initial weight. On clinical and behavioral state; drinking history, khat chewing, WHO stage, initial CD4 count, and functional status were collected. Data on the ART regimen, initial regimen and regimen change; types and frequency of ARVdrugs and ADRs were also collected.

ADRs were defined as unintended and noxious (harmful) response that occurs at normal doses of the drug used for prophylaxis, diagnosis and treatment of diseases. Symptoms reported by the participants, as well as laboratory abnormalities were defined as ADRs while patients are on ART after 6th months follow up[12,14].

A side effect is the weak form of the adverse effect, which is unpleasant but generally acceptable. The marked changes in dosage schedule or drug withdrawal are usually not necessary[12,14,21].

Severity of ADRs: those individuals with one drug changed and regimen changed are considered due to the severity of ADRs. Severity can cause life threatening hospitalization result permanent harm/disability or discontinuation of regimen or change in regimen.

Prevalence of ADRs: indicates cumulative prevalence, which indicates patient whoever had an ADR in the past, and switched.

Data processing and analysis

Data were checked, cleaned, and entered in to Epi data version 3.1, then exported to SPSS version 16 for analysis. The prevalence of ADRs was estimated by using simple descriptive summary statistics such as frequency and proportion. Tables and graphs were used to present the result of the analyzed data. Bivariate analysis was employed to identify candidate variables for further analysis in multivariable analysis. Variables with P-value <0.25 in bivariate analysis were transferred to multivariable logistic regression. The association between dependent and independent variables was measured by using OR at 95% CI. P-value<0.05 was considered as statistically significant.

Ethical approval and consent to participant

Ethical clearance was obtained from Jimma University, College of public health and medical sciences ethical review committee. Permission was obtained first from Hadiya zone health department and NEMMH medical director office. Data were handled confidentially during all phases of research activities.

Result

Socio-demographic characteristics

In this study, a total of 231patients 'records were reviewed. Of the 231 records, 82(35.5%) were males and 149(64.5%) were females. The age range was 15-49yearswith mean of 31(SD 7.63). Concerning marital status, 173(74.9%) were married and 16(6.9%) were divorced. Majority, 104(45%) of the females were housewives. About, 96(41.6%) patients attended primary school. Most of respondents, 104(45%) were "protestant religion "followers. For 113 (48.9%) patients, the initial weight was greater than 50 kg (Table 1).

Table 1: Socio-demographic characteristics of the respondents in NEMMH, Hosanna.

Variables	Total	%
Age(n=231)		
15-19	6	2.6
20-24	30	12.99
25-29	60	25.98
30-34	64	27.7
35-39	32	13.86
40-44	23	9.95
45-49	16	6.92
Marital status(n=231)		
Single	23	10
Married	173	74.9
Divorced	16	6.9
Widowed	19	8.2
Sex(n=231)		
Males	82	35.5
Females	149	64.5
Religion(n=231)		
Orthodox	88	38.1
Muslim	36	15.6
Protestant	104	45
Catholic	2	0.9
Others	1	0.4
Occupation(n=231)		
Housewives	104	45
Merchants	31	13.4
Government employee	39	16.9
Self employed	20	8.7
Farmers	21	9.1
Students	15	6.5
Unemployed	1	0.4
Educational status(n=231)		
No formal education	69	29.9
Primary education	96	41.6
Secondary education	57	24.7
Tertiary education	9	3.9
Initial weight in KG(n=231)		
<40kg	27	11.7
40-45kg	45	19.5
46-50kg	46	19.9
>50kg	113	48.9

Clinical and behavioral state at the beginning of ART

Among the selected patients, more than 50 % had started ARV at WHO stage III. Regarding initial CD4 count, more than 94% patients started ARV with less than or equal to 350 CD4 count. About, 17 (7.4%) patients had alcohol drinking and khat chewing history. Only 1 person (0.4%) had history of cigarettes smoking. The functional status showed that 104(45 %) of patients were able to work (Table 2).

Table 2: Clinical and behavioral state at the beginning at NEMMH, Hosanna.

Variables	Total	%
Alcohol drinking history		
Yes	17	7.4
No	214	92.6
Khat chewing history		
Yes	17	7.4
No	214	92.6
Cigarettes smoking history		
Yes	1	0.4
No	230	99.6
WHO		
I	13	5.6
II	76	32.9
III	120	51.9
IV	22	9.5
Initial CD4 count		
=<350	219	94.8
>350	12	5.2
Functional status(n=231		
Working	104	45
Ambulatory	76	32.9
Bed ridden	51	22.1

ART drug regimens

The initial regimen was D4T/3TC/NVP for 123(53.2 %), AZT/3TC/NVP for 49(21.2 %), AZT/3TC/EFV for 10(4.4 %) and other ART for 49(21.2 %) patients. However, only 81(35.1%) patients were on initial regimen during study period but 150(64.9%) were not. From those who had changed the regimen, total replaced by other regimen was147 (63.6%) and only one drug changed was 3 (1.3%).

Drugs used other than ART

Only 31(23.4%) patients did not have history of taking drugs other than ART. From those who took drug other drugs other than ART, 196(84.8 %) patients were on cotrimoxazole and 9(3.9) % patients were on isoniazid prophylaxis.

Types and frequencies of ADRs

About 53(22.9%) patients developed ADRs. Therefore, the prevalence of ADRs in NEMMH was 22.9%. For the total ADRs, starting with D4T/3TC/NVP contributed 57.4%. About 20% of the patients changed the regimen due to AZT/3TC/EFV. Fatigue was common ADRs among initial drug regimen and regimen changed patients (Table 3).

Table 3: Types of adverse drug reactions and regimens at NEMMH, Hossana.

	Initial regimens					**Current regimens**				
Variable	D4T/3TC/NVP	AZT/3TC/NVP	AZT/3TC/EFV	Other	Total (%) N=108	AZT/3TC/NVP	ZDV/3TC/NVP	AZT/3TC/EFV	Others	Total (%) N=40
ADRs										
Fatigue	35	6	1	3	45(41.7)	0	13	6	4	23(57.5)
Diarrhea	8	4	3	4	19(17.6)	1	3	0	3	7(17.5)
Nausea	9	3	1	3	16(14.8)	2	1	0	2	5(12.5)
Headache	4	4	0	1	9(8.3)	0	0	1	1	2(5.0)
Rash	2	2	4	0	8(7.4)	0	0	0	0	1(2.5)
Vomiting	2	0	1	1	4(3.7)	0	0	0	0	0.0
Anemia	1	1	1	2	5(4.6)	0	0	1	1	2(5.0)
Peripheral neuropathy	1	1	0	0	2(1.8)	0	0	0	0	0.0
Total no (%)	62(57.4)	21(19.4)	11(10.2)	14(13)	108(100)	3(7.5)	17(42.5)	8(2)	11(27.5)	40(100)

Factors associated with adverse drug reaction

Variables that were significantly associated at bivariate analysis with P-value< 0.25 were further examined in multivariable logistic regression to see their relative effect on ADRs.Variables that had an association on bivariate association was transferred to multivariable logistic regression. In multivariable logistic regression analysis sex, functional status of patients and WHO stage were significantly associated with ADRs.

The finding from multivariable analysis revealed that females were 3 times more likely to develop ADRs than males (AOR=2.72, CI=1.18-6.29). Regarding clinical and immunological factors, WHO stage and functional status of patients were significantly associated with ADRs. Patients with WHO stage III&IV were 13 times more likely to develop ADRs than WHO stage I &II(AOR=13.06,CI=4.17-40.90). Ambulatory patients were 3 times more likely to develop ADRs than patients who can work (AOR= 3.06, CI=1.29-7.29). Bedridden patients were 18 times more likely to develop ADRs than patients who can work (AOR=18.00, CI=6.07-53.43) (Table 4).

Table 4: Factors associate with adverse drug reaction in NEMMH, Hossana.

Variables	ADRs				
			Bivariate	Multivariable	
Sex	Yes (%)	No (%)	COR at 95% CI	AOR at 95%CI	P-value
Female	42(79.2)	107(60.1)	2.53(1.22-5.25)	2.72(1.18-6.29)	0.019
Male	11(20.8)	71(39.9)	1	1	
WHO stage					
III&IV	49(92.5)	93(52.2)	11.19(3.88, 32.34)	13.06(4.17-40.90)	0.000
I&II	4(7.5)	85(47.8)	1	1	
Functional status					
Bedridden	26(47.2)	26(14.6)	15.71(5.83-42.28)	18.00(6.07-53.43)	0.000
Ambulatory	22(41.5)	54(30.3)	2.36(1.13-4.94)	3.06(1.29-7.29)	0.011
Working	6(11.3)	98(55.1)	1	1	

Discussion

The prevalence of ADRs among adult HIV/AIDS patients was 22.9%. This is similar to findings of a study done in Zewditu Memorial Hospital, which showed a prevalence of 24%[21]. However, it is higher than figures from a study in Ghana, which showed the prevalence of ADRs9.4%[22]. The difference may be due to differences in recruiting study subjects, as the former study included all patients who were on ART. This can decrease the prevalence of ADRs. The prevalence of ADRs in the current study is also higher than that of a study from Cameroon, which depicted 19.5 % on HAART patients, reported ADRs 18.ADRs in the current study is three fold higher than the systematic review studies, which showed that the overall incidence of ADRs 6.7%[23-24].

The ADRs in current study is lower than the finding of Guwahati hospital, India, which was 31% 19. It is also lower than studies of DebraMarkos and Jimma, which showed 51.4%and 65.5% of ADRs cases, respectively[14,25]. The lower prevalence of ADRs in the current study might be due to our smaller sample size of long period reviews (2005-2014) and using patient data after 6 months follow up. Using data from the 6th months of enrolment created a chance to incorporate the whole history of ADRs of patients and this might have compromised prevalence of ADRs. The reason for the difference could also be certain ADRs are common at the beginning of treatment, and in addition, ADRs can differ based on toxicity of regimens used.

Regarding socio-demographic variables, only sex of patients showed significant association with the development ADRs. The finding of the current study revealed that females were 3 times more likely to develop ADRs than males. This is consistent with the studies from Tanzania[26], and Ghana[27]. The reason for sex difference in ADRs might be difference in body mass index and fat composition between males and females.

Regarding clinical and immunological factors, WHO stages and functional status of the patients were significantly associated with ADRs. Patients with baseline WHO stages III and IV were found more likely to develop ADRs than patients of stage I and II. This is similar to findings from an Indian study, which showed that clinical stage III and IV were more likely to develop

ADRs than clinical stage I and II[28]. Baseline WHO stage III/IV indicated poor clinical status of the patients in Ahmadabad, Gujarat, India[29]. Nevertheless, the study conducted in Ghana reported that WHO stages were not significantly associated with the development of ADRs[22]. Poor clinical status of the patients might be the leading factor to ADRs, due to patient's drug intolerance, physiological disturbance, and using drugs other than ARVs to treat other opportunistic infections.

Functional status at initiation of treatment showed significant association with the development of ADRs. Ambulatory and bedridden patients during initiation of treatment were found to have higher risk of developing ADRs than patients who could work. The movement of patients might enhance drug distribution. As a result, the ADRs might decrease.

This study has the following limitations: Wide confidence intervals were observed seen, and this might be due to the small sample size. There was lack of clear-cut differences between side effects and ADRs largely because of missing data.

The results of biochemical studies, including the blood PH, bicarbonate and Co_2 are essential to establish the diagnosis and determine the cause of ADRs. However, biochemical variables were missed and were not included in this study. Recording quality was poor (poor hand writing, incomplete records). Hence, the interpretation of the finding should be taken into account all these factors.

Conclusion

The prevalence of ADRs was high. Sex of the patients, functional status and WHO stages of HIV/ AIDS showed significant association with ADRs. Females were more likely develop ADRs than males. WHO stage III and IV patients were more likely to develop ADRs than those with WHO stage I and II. Ambulatory and bedridden patients were more risky to develop ADRs than patents who could work. Commonly identified ADRs included fatigue, diarrhea, nausea and headache. The health care providers should give due attention to ambulatory and bedridden patients, and those in WHO stage III and IV since they are more risky to develop ADRs.

List of abbreviations

ABC: abacavir; ADRs: Adverse Drug Reactions; AIDS: Acquired Immune deficiency syndrome; 3TC: Lamivudine; ART: Anti-Retroviral Therapy; ARV: Antiretroviral drugs used for the treatment of HIV infection; BMI :Body mass index; D4T: stavudine; EDHS: Ethiopian demographic health survey; HAART: highly active antiretroviral therapy; EFV; efavirent, FDC: fixed drug combination; FTC : emtricitabine; HIV :Human immune virus; MOH: ministry of health ;NEMMH :Nigist Eleni Mohamed Memorial Hospital ;NFV: Nelfinavir; NVP : nevirapine; ,PLWHA: People living with HIV and manifestations of AIDS; PMTCT: prevention of mother to child transmission; TDF: tenofovir disoproxil fumarate; SNNPR: South nation nationality and people region; D4T: Stavudine; WHO: World health organization; VCT: Voluntary Counselling and Testing; ZDV; zidovudine.

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