Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20140201

Research Article

Factors determinant for change of initial antiretroviral treatment regimen among patients on ART follow-up clinic of Mekelle Hospital, Mekelle, Ethiopia

Tigist Bayou[1], Minyahil Woldu[2]*, Gebrehiwot G. Meskel[1], Haftay Mezgebe[1]

[1]Department of Pharmacy, College of Health Sciences, Mekelle University, Mekelle, Ethiopia
[2]Department of Pharmacy, College of Health Sciences, Ambo University, Ambo, Ethiopia

Received: 30 October 2013
Accepted: 13 November 2013

***Correspondence to:**
Minyahil Woldu,
Email: minwoldu@gmail.com

ABSTRACT

Background: Treatment interruption and switch to a new Highly Active Antiretroviral Therapy (HAART) regimen act as competing risks for patient on HAART.
Methods: The study was conducted in Mekelle hospital. A case-control study was conducted. Socio-demographic, immunologic and clinical characteristics were components of the checklist. Data was compiled, processed, and analyzed using Statistical Package for Social Sciences (SPSS) for windows version 16. Ethical consideration was obtained from Mekelle University.
Results: 105 patients' records were sampled and studied. Twenty one (20%) of the patients had changed their initial ART regimen and about three-fourth 15 (71.4%) of the reasons for change was attributable to toxicity while 3 and 2 were due to treatment failure and pregnancy respectively. The odds of Adverse Drug Reactions (ADRs) who had one initial ART change (cases) were 2.37 times greater than the odds who did not change (controls) Patients, initiated ZDV based ART regimen had 9.93 times greater chance of changing their initial ART regimen compared to those initiated with D4T based ART regimen and patient on ART for treatment duration of 12-36 months were relatively at higher risk compared to patients with lesser duration of treatment. Patients who's ART had 99.94% lesser chance of changing their baseline ART regimen compared to those who did take other medications
Conclusions: The main factor determining the change of initial ART regimen in our study was the occurrence of adverse drug reactions, with ZDV being the most dominant drug.

Keywords: Antiretroviral therapy, Case-control, ART follow up, Determinant factors, ART regimen change

INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) has dramatically reduced the morbidity and mortality associated with Human Immunodeficiency Virus (HIV) infection, and has improved the prognosis of People Living with HIV/AIDS (PLWHA).[1-5] Since 2001, the World Health Organization (WHO) has advocated a "public health approach" to HAART to rapidly improve HIV related problems in a resource limited settings.[6]This approach focuses on maximizing survival at the population level through standardized sequencing of available antiretroviral drugs, delivered to patients by means of simplified approaches to clinical decision making and basic laboratory monitoring.[7]

As with initiation of antiretroviral therapy (ART), the decision to change treatment regimens should be approached with careful consideration of several complex factors.[8] These factors include: recent clinical history and physical examination, plasma HIV-RNA levels measured on two separate occasions, absolute CD4+ T lymphocyte count and changes in these counts, assessment of adherence to medications, remaining treatment options, potential resistance patterns from prior antiretroviral therapies; and preparation of the patient for the implications of the new regimen which include side

effects, drug interactions, dietary requirements and possible need to alter concomitant medications.[1]

The discovery of HAART and its introduction in the developed countries is considered by many to be one of the greatest success stories of modern medicine.[9] Besides, long-term administration HAART is also associated with poor adherence,[10] an increased risk for developing drug resistance,[11] and undesirable side effects.[12] Because of these complications associated with the long-term use of HAART, an increasing number of subjects interrupt and change treatment.[13-14]

Treatment interruption and switch to a new HAART regimen act as competing risks for patient starting ART, and ignoring this fact may lead to overestimated event incidence and to biased effect estimates.[15-16] Long term ARV toxicity is recognized as a major threat to long term life prognosis and immediate quality of life of ARV patients.[17]

Though the arrival of ARVs was a breakthrough for the PLWHA in Africa, it also brought a different challenge of dealing with numerous side effects of the drugs which may vary from one person to the next and range from mild and manageable to severe side effects.[17] Knowing the determinant factors for ART change may help to minimize the risk factors. These leads to decrease the regimen change, treatment failure, drug resistance, and increase quality life of the patient. Treatment failure and toxicity are the commonest reasons to discontinue ART.[18]

Health authorities and healthcare providers should then rely on the pharmacovigilance system to obtain the required epidemiological data and manage insights required to deal with long term toxicity.[17] This study was aimed at determining the factors responsible for the change of ART regimen in the study place.

METHODS

Study area

The study was conducted in Mekelle hospital, Mekelle city, Tigray regional state, Northern Ethiopia, 786 km away from the capital city Addis Ababa towards north.

Study design

A case-control study was conducted. 'Cases' were those who changed their initial ART while 'controls' were those who didn't change their initial ART regimen.

Data collection instrument

A prepared and pretested checklist was used to collect data for the study. Socio-demographic, immunologic and clinical characteristics were components of the checklist.

Data organization and analysis

Data was compiled, processed, and analyzed using Statistical Package for Social Sciences (SPSS) for windows version 16. Descriptive statistics was used to summarize data and statistical analysis using logistic regression was carried out to determine whether there was any association between the dependent and independent variables. A 95% CI and p-value of <0.05 was considered to be statistically significant.

Ethical consideration

A formal permission letter was obtained from Mekelle University to Mekelle Hospital to access medical records and charts.

RESULTS

Socio-demographic characteristics of the study subjects

In this study, 105 patient records were sampled and studied. The mean age of the study subjects was 33.5+ 8years. More than half of the study subjects 59 (56.2%) were females and similar figure of 59 (56.2%) were married. Moreover, more than threefold 79 (75.2%) of the patients were Orthodox Christians. About 47 (44.85%) of the study subjects had completed their primary school while only 6.7% were attended their college study (Table 1).

Table 1: Socio-demographic characteristics of patients on ART follow-up clinic of Mekelle hospital, Mekelle-Ethiopia, 2013.

Variables	Classification	Frequency (%)
Sex	Male	46 (43.8)
	Female	59 (56.2)
Age	15-30 years	45 (42.9)
	30-45 years	53 (50.5)
	>45 years	7 (6.7)
Educational status	illiterate	31 (29.5)
	primary	47 (44.8)
	secondary	20 (19)
	Tertiary	7 (6.7)
Religion	Orthodox	79 (75.2)
	Muslim	25 (23.8)
	Others	1 (1)
Marital status	Single	31 (29.5)
	Married	59 (56.2)
	Divorced	15 (14.3)

Clinical and immunological characteristics of the study subjects

The mean CD4 count was 188 cells/µl ranging from the lowest count of 2 cells/µl to the highest recorded count of 568 cells/µl. Nearly, two-third of the patients 67 (63.8%)

had a CD4 count less than 200 cells/µl. Additionally, the mean weight and ART treatment duration were 52.49±9.1kg and 26.94±15.2 months respectively. Of all study subjects, majority 57 (54.3%) were initiated ZDV/3TC/NVP followed by 13 (12.4) TDF/3TC/ NVP and 12 (11.4%) TDF/3TC/EFV. Hence, ZDV based regimen was the dominant type of treatment regimen initiated (Table 2).

Twenty one (20 %) of the study subjects had changed their initial ART regimen. About three-fourth 15 (71.4%) of the reason for the change was attributable to toxicity while 3 (14.3%) and 2 (9.5%) of the reasons for the change were due to treatment failure and pregnancy respectively. About 12 (57.1%) of those patients who changed their initial ART regimen changed to TDF based regimen (TDF/3TC/NVP or TDF/3TC/EFV). Furthermore, 30 (41.67%) of the patients who developed Adverse Drug Reaction (ADR) used other drugs to treat the problem (Table 2).

Among all study subjects, 72 (68.6%) patients had recorded ADR of which rash (31.9%; n=23), anemia (12.5%; n=9) and nausea (12.5%; n=9) were the commonest for more than half of the overall drug reactions experienced by the patients (Figure 1).

Table 2: The clinical and immunologic characteristics of the patients on follow-up clinic of Mekelle hospital, Mekelle, Ethiopia, 2013.

Variables		Frequency (%)
CD4 count	<200 cells/µl	67 (63.8)
	200-350 cells/µl	33 (31.4)
Weight in kg	≤45 kg	37 (35.2)
	46-55 kg	39 (37.1)
	>55 kg	27 (25.7)
Initial ART regimen	D4T/3TC/NVP	10 (9.5)
	ZDV/3TC/NVP	57 (54.3)
	D4T/3TC/EFV	9 (8.6)
	ZDV/3TC/EFV	4 (3.8)
	TDF/3TC\EFV	12 (11.4)
	TDF/3TC/NVP	13 (12.4)
Patient changed initial ART regimen	Yes	21 (20)
	No	84(80)
Reason for initial ART regimen change	Toxicity	15 (71.4)
	Treatment failure	3 (14.3)
	Pregnancy	2 (9.5)
	Poor Adherence	1 (4.8)
Developed adverse drug reaction	Yes	72 (68.6)
	No	33 (31.4)
Used other drugs when ADR developed	Yes	30 (41.67)
	No	42 (58.33)
Number of drugs other than ART	1-2 drugs	26 (65)
	3-4 drugs	6 (15)
	≥ 5 drugs	8 (20)
Cotrimoxazole prophylaxis	Yes	101 (96.2)
	No	4 (3.8)
INH prophylaxis	Yes	17 (16.2)
	No	88 (83.8)
TB treatment	Yes	18 (17.1)
	No	87 (82.9)
Duration of ART treatment	<=12 months	40 (38.1)
	12-36 months	50 (47.6)
	>36 months	15 (14.3)
WHO stage	Stage I & II	45 (42.9)
	Stage III & IV	52 (49.5)

Determinants of initial art regimen change

The odds of ADR among cases were 2.37 times greater than the odds among the controls (AOR=2.37, p=0.002). Similarly, 17 (99.4 %) patients who did not use concurrent drugs up on ART treatment had lesser chance to change their initial ART regimen compared to those who did use (AOR=0.06, p=0.011*)*. The result shows that not to use additional drugs up on the ART regimen have a protective effect for treatment regimen change (Table 3).

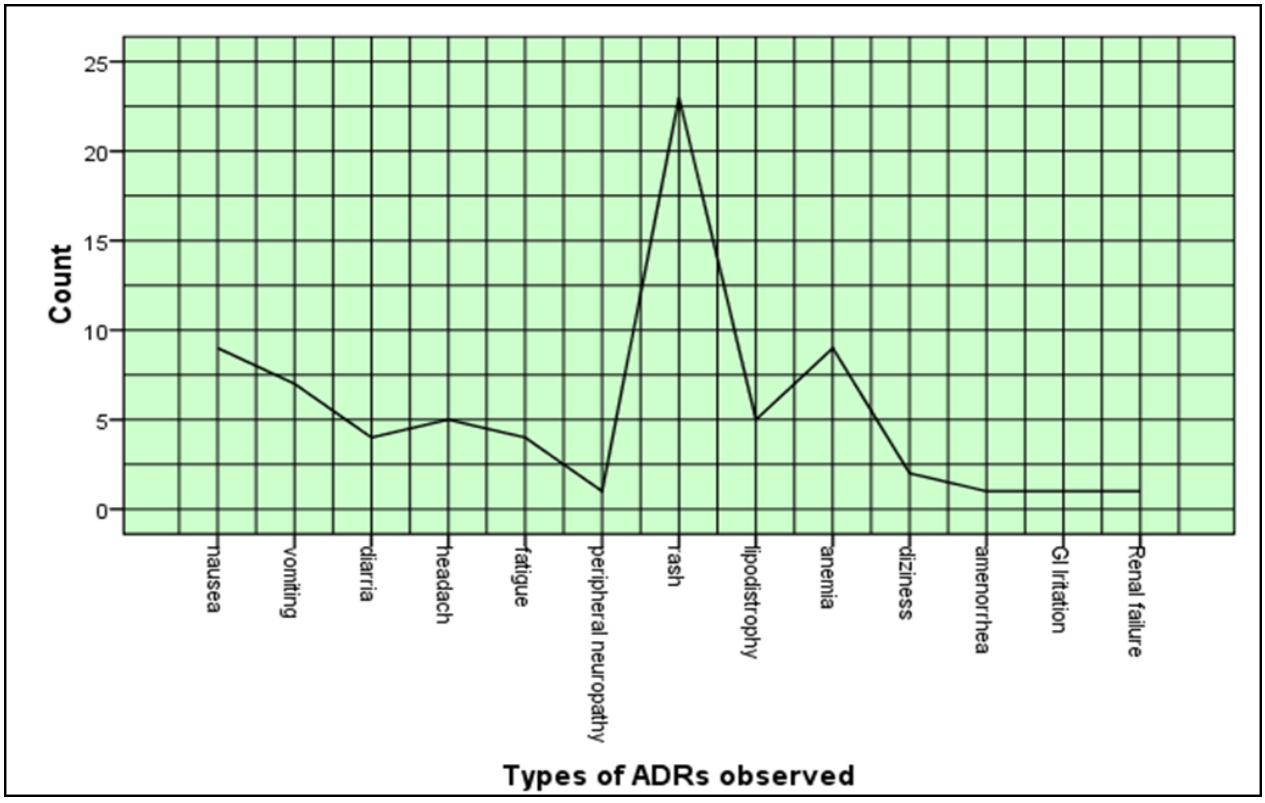

Figure 1: The different types of ADRs Developed on patients who were on RT follow-up clinic of Mekelle hospital, Mekelle, Ethiopia, 2013.

DISCUSSION

The magnitude of initial ART regimen change in our study was 21 (20%) which is similar in percentage to the study conducted in Brazil 68 (22.1%) in 2012.[19] Similarly in a study conducted in South Africa 28% were changed their ART regimen at least once in the first three years of their treatment.[20] In a study conducted in southern India a relatively higher rate of regimen change was reported 91 (39.6%).[21] In another study conducted in South Africa the number of patients that changed their initial treatment regimen were 175 (58.9%).[22] In another retrospective study of 345 randomly selected antiretroviral-naive patients, 61% had showed change or discontinuation of their initial ART regimen.[23]

All of these findings showed that there were comprehensive records of change in initial ART regimen. However, compared to these studies, the magnitude of initial ART regimen change in our study was relatively lower in percentage. The reasons could be due to the difference in the type of study design used, study time conducted and patient disease magnitude and management difference among the different studies.

About three-fourth 15 (71.4%) of the reason for the change of initial ART regimen in our study was attributable to toxicity while 3 (14.3%) and 2 (9.5%) of the reasons for the change was due to treatment failure and pregnancy respectively. In line with this study, the study from South Africa showed that the major reasons for ART regimen change were drug toxicity 134 (44.8%) followed by change due to pregnancy 18 (5.4%).[22] Similar studies conducted in India showed that drug toxicity was the reason for treatment change 62 (27%) [21]. In another study 24% of change in initial ART regimen was also due to an adverse events.[23] Contrary to these findings a report from South Africa in 2007 showed that contraindications were more common than treatment-limiting toxicities.[20]

Table 3: Crude and AOR of variables obtained from patients records Mekelle hospital, 2013.

Variables		Cases (No)	Control (No)	Crude OR (95% CI)	Adjusted OR (95% CI)	*p*-value
Sex	Male	11	35	1.00		
	Female	10	49	1.54 (0.59, 4.02)	1.83 (0.41, 8.25)	0.433
Education	Illiterate	9	26	1.00		
	Literate	12	58	1.67 (0.63, 4.46)	5.90 (0.96, 36.11)	0.055
Age	15-30 years	10	35	1.00		
	30-45 years	8	45	1.61(0.57,4.50)	4.01(0.74, 21.67)	0.107
	>45 years	3	4	0.38 (0.07, 1.99)	2.12 (0.07, 62.15)	0.663
Marital status	Single	6	25	1.00		
	Married	15	44	0.70 (0.24, 2.05)	10.83 (0.99, 118.61)	0.051
WHO stage	Stage 1 & II	13	40	1.00		
	Stage III & IV	8	44	1.79 (0.67, 4.76)	3.01 (0.73, 12.48)	0.129
ADR	No	3	30	1.00		
	Yes	18	54	1.67 (0.63, 4.46)	2.37 (4.73, 22.74)	0.002**
Other drugs	Yes	4	26	1.00		
	No	17	58	0.53 (0.16, 1.71)	0.06 (0.01, 0.52)	0.011**
TB treatment	Yes	5	13	1.00		
	No	16	71	1.71 (0.53, 5.47)	7.49 (0.80, 70.26)	0.078
CD4 count	<200 cells/µl	17	50	1.00		
	≥200 cells/µl	4	29	2.47 (0.76, 8.03)	4.29 (0. 80, 23.05)	0.090
Weight	≤45 kg	6	31	1.00		
	46-55 kg	9	30	0.65 (0.21, 2.03)	1.03 (0.20, 5.32)	0.971
	>55 kg	5	22	0.85 (0.23, 3.15)	4.52 (0.50, 40.91)	0.180
Initial ART regimen	D4T based	6	22	1.00		
	ZDV based	10	44	1.2 (0.39,3.73)	9.93 (1.31, 75.36)	0.026**
	TDF based	5	18	0.98 (0.26, 3.75)	10.83 (0.99, 118.61)	0.051
Duration on ART	1-12months	8	32	1.00		
	13-36months	9	41	1.14 (0.40, 3.28)	6.59 (1.01, 42.94)	0.049**
	>36months	4	11	0.69 (0.17, 2.74)	1.05 (0.13, 8.77)	0.965

** Shows statistically significant association

Poor adherence was the least reason responsible for initial ART regimen change unlike of most studies which depicted factors associated with non-adherence as the major reason. In our study this adherence problem was found to be lower may be due to the advancement in drug information system in recent time globally and the strict follow up trend in the study area.[20] In our study, ZDV based regimen was the dominant regimen to cause initial ART regimen change due to its hematological toxicity and this finding was harmonized with a number of different studies.[19-20, 22]

The odds of not exposed to other drugs other than ART among cases were 99.4% (AOR=0.06, *p*=0.011), which resulted in lesser chance to change ART. This implies that those who did not take medications other than ART had 99.94% lesser chance of changing their baseline ART regimen compared to those who did take other medications up on their ART regimen. This could probably be due to drug-drug interactions and/or drug toxicity with their corresponding ART regimen. On the other hand, this might also be due to polypharmacy which could lead to poor adherence due to pill burden which in turn resulted in poor effect of the ART regimens. The finally mentioned possible pathway justification could then lead to treatment failure and the event of ART regimen change.

CONCLUSIONS

The main factor determining the change of initial ART regimen in our study was the occurrence of adverse drug reactions, with ZDV being the most dominant drug, and anemia and rash were the most commonly reported ADR events.

ACKNOWLEDGEMENTS

We would like to thank Mekelle University, College of Health Sciences, Department of Pharmacy and Mekelle Hospital academic, medical and administrative staffs.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Permission obtained

REFERENCES

1. UNAIDS. Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDS epidemic update 2007.
2. Palella FJ DK, Moorman AC. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.
3. Hamer SM SK, Hughes MD. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimetre or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med 1997;337:725-33.
4. Jahn A FS, Crampin AC, Mwaungulu F, Mvula H, Munthali F. Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. Lancet 2008;371(9624):1603–11.
5. Bhaskaran K HO, Sannes M, Boufassa F, Johnson AM, Lambert PC. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. Jama 2008;300:51–59.
6. Gilks CF CS, Ekpini R, Gove S, Perriens J, Souteyrand Y. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet 2006;368(4):505-10.
7. WHO. Anti Retroviral Therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access: recommendations for a public health approach In: Programme HA, ed. Geneva: WHO; 2006.
8. Olawale Ajose SM, Edward J. Mills, Andrew Boulled and Nathan Fordd. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. AIDS 2012;26:929–38.
9. Ajith S AO, Priscilla R, Susanne A, Joyce R, Rajkumar S. High Rates of Regimen Change due to Drug Toxicity among a Cohort of South Indian Adults with HIV Infection Initiated on Generic, First-Line Antiretroviral Treatment 2009.
10. Paterson D SS, Mohr J. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection Ann Intern Med 2000;133:21-30.
11. The UK Collaborative Group on HIV Drug Resistance UCSG. Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. AIDS 2005;19:487-94.
12. Carr A CD. Adverse effects of antiretroviral therapy. Lancet 2000;356:1423-30.
13. Taffe P RM, Hirschel B. Impact of occasional short interruptions of HAART on the progression of HIV infection: results from a cohort study. AIDS 2002;16:747-55.
14. Park-Willie LY SA, Tseng A. High rate of discontinuation of highly active antiretroviral therapy as a results of antiretroviral intolerance in clinic practice: missed opportunities for adherence support AIDS. 2002;16:1084-86.
15. Kalbfleisch J PR. The statistical analysis of failure time data. New York: Wiley. 1980:163-78.
16. Fine JP GR. A proportional hazards model for the subdistribution of a competing risk J Am Stat Assoc 1999;94:496-509.
17. Boule A OC, Kaplan R, Cutsem G, Mcnally M, Hilderbrand K, London Myer, Matthias Egger, David Coetzee, Gary Maartens and Robin Wood. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. Antiviral therapy 2007;12:753-60.
18. Organization WH. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV infection 2005.
19. Lima D, Arruda E, Lima A, Oliveira B, FonteLes M. Factors determining changes in initial antiretroviral therapy. Medical Bras 2012;58 (2):222-28.
20. Boule A, Orrell C, Kaplan R, et al. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. Antivrial Therapy 2007;12:753-60.
21. Sivadasan 28. A AO, Rupali P, Pulimood SA, Rajan J, Rajkumar S, . High rates of regimen change due to drug toxicity among a cohort of South Indian adults with HIV infection initiated on generic, first-line antiretroviral treatment. J Assoc Physicians India 2009;57:384-88.
22. Moeketsi N, Supa P. Treatment and regimen change in a cohort of HIV positive patients on Anti-Retroviral Treatment Tshepang Wellness Clinic, Dr George Mukhari Hospital.: School of Public Health University of Limpopo;2010.
23. O'brien ME CR, besch CL, Myers L, Kissinger P. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. J Acquir Immune Defic Syndr 2003;34(407-14).

doi:10.5455/2319-2003.ijbcp20140201
Cite this article as: Bayou T, Woldu M, Meskel GG, Mezgebe H. Factors determinant for change of initial antiretroviral treatment regimen among patients on ART follow-up clinic of Mekelle Hospital, Mekelle, Ethiopia. Int J Basic Clin Pharmacol 2014;3:44-9.