World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Original Article

Reasons for modification of initial antiretroviral therapy regimens among patients with HIV/AIDS in Adama Hospital Medical College, Adama, Ethiopia

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Received: 27-10-2014 / Revised: 29-11-2014 / Accepted: 30-11-2014

ABSTRACT

Highly active antiretroviral therapy (HAART) has markedly decreased the morbidity and mortality due to HIV/AIDS. A switch in the antiretroviral regimen is often necessary because of both acute and chronic toxicities, concomitant clinical conditions, and development of virological failure. The aim of this study was to assess the causes of initial HAART regimen changes among patients on ART in Adama Hospital Medical College (AHMC), Adama, Ethiopia. A retrospective cross-sectional study was done by reviewing patient information cards recorded from June 1, 2010 to June 1, 2014. Patients who changed their regimen were included in the study to identify the reasons for change. Data from patients below 18 years and those who did not switch HAART regimen were excluded. Out of 150 patients, 60% were females and 65.3% were in the age 18 to 32. Most of the patients (63.3%) were under the WHO clinical stage III patients and 35.3% of patients had a CD4 count in the range of 101-200 cells/mm^3. The most common first regimen before first switch was D4T/3TC/NVP (32%), D4T/3TC/EFV (24.7%) and AZT/3TC/NVP (15.3%). The main reasons for modification of regimen were toxicity (70%), co-morbidity (12.7%), pregnancy (10%) and treatment failure (7.3%). The main types of toxicities observed were peripheral neuropathy (30.5%), lipoatrophy (18.1%) and anemia (17.1%). The result of this study indicated toxicity as the main reason for modification of initial ARV drugs among the study population.

Key words:- HIV/AIDS, HAART, Switching, Initial regimen, Drug toxicity, ARV, WHO clinical stage

INTRODUCTION

The emergence of the HIV epidemic is one of the biggest public health challenges the world has ever seen in recent history. In the last three decades HIV has spread rapidly and affected all sectors of society- young people and adults, men and women, and the rich and the poor. Sub-Saharan Africa is at the epicenter of the epidemic and continues to carry the full brunt of its health and socioeconomic impact. Ethiopia is among the countries most affected by the HIV epidemic. With an estimated adult prevalence of 1.5%, it has a large number of people living with HIV (approximately 800,000); and about 1 million AIDS orphans.

These concerted efforts have yielded encouraging results in reversing the rate of new infections and in mitigating the multi-faceted impacts of the epidemic. In fact, recent reports show that Ethiopia is one of the sub-Saharan countries demonstrating more than a 25% decline in new HIV infections. ANC sentinel surveillance data show that prevalence of new infections among pregnant women 15-24 years of age has declined from 5.6% in 2005, to 3.5% in 2007, and 2.6% in 2011. [1, 2]

Once ART is initiated, patients generally remain on medications indefinitely. A switch in the ARV regimen is often necessary because of both acute and chronic toxicities, concomitant clinical conditions, and development of virological failure. The approach to patients who need to switch ART may be different depending on several issues, including the reason for change, the amount of previous ART experience, and the available treatment options. At opposite end of the spectrum are patient with advanced HIV disease, who have experienced toxicities, virological failure, and drug resistance during multiple past treatment regimens and thus require a new treatment regimen. [3]

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METHODS

Study design: A retrospective cross-sectional study was utilized by reviewing patients' cards to assess initial ART regimen change.

Study area and period: This study was conducted in AHMC which is found in Adama town, 100 km away from east of Addis Ababa, Ethiopia. This study was conducted from 17/06/14 to 17/08/14.
Cards of all PLWHA below age of 18 yrs and who did not switch ART regimen and/or those having experiences of switching regimen more than one time have been excluded. Cards of all PLWHA who have been switched ART regimen earlier than June, 2010 have been excluded. From the total of 200 PLWHA who switched the first therapy, all the 150 patients meeting the inclusion criteria were included.

Data collection method: The data collection format & the whole method were pre-tested on randomly selected patients' clinical information records to ensure their completeness. A possible correction was made on the data collection format through in depth discussion within experienced pharmacists and related professionals. Data collection format containing socio-demographic variables and patient information, clinical information and antiretroviral treatment information such as CD_4 count on the start (CD_4 count/mm^3, WHO clinical staging at the start of initial ART regimen, initial regimen, date of treatment started, ARV drug regimen switch made, duration on initial ARV therapy before first switch, regimen switched to, and reason for changing regimen was included.

Ethical consideration: An approval letter was obtained from Institutional Research Ethics Review Committee of Rift Valley University and delivered to AHMC. The consent of the patients was maintained after explaining the significance of the study to them. The confidentiality of the patients was also secured by not using their names and card number in the data collection tools during data collection.

RESULTS

Demographic Characteristics: Records of 150 patients who had changed their initial ART regimen at AHMC ware assessed. Majority, 98 (65.3%) were between the ages of 18-32 years. Female accounted for the largest proportion (60%).

Table 1: Demographic Characteristics of HIV/AIDS who changed their initial ART regimen in AHMC, June 1, 2010 to June 1, 2014

Age Group	**N (%)**
18-32	98(65.3)
33-49	45(30)
≥50	7(4.7)
Sex	
Female	90(60)
Male	60(40)
Marital Status	
Single	61(40.6)
Married	72(48)
Widowed	10(6.7)
Divorced	7(4.7)
Educational Status	
Illiterate	25(16.7)
Primary education	44(29.3)
Secondary education	50(33.3)
Higher institute education	31(20.7)

WHO clinical stages, CD4 count and initial ART regimen upon initiation of ART: Majority of the patients 95(63.3%) had started their initiation of treatment at WHO clinical stage III while 31(20.7%) had started at WHO clinical stage IV, 12(8%) at stage II, and 9(6%) at stage I. for 2% of the patients, the clinical stage was not recorded.53(35.3%) had baseline CD4 count in the range of 101-200 cells/mm^3, 40(26.7%) had CD4 count in the range of 51-100, and 34(22.7%) had CD4 <50. For 5.3% of the patients the initial CD4 count was not recorded .A majority of the patients (32%) were on D4 T/3TC /NVP at the beginning of the ARV treatment and the rest were on D4T/3TC/EFV (24.7%), AZT/3TC/NVP (15.3%), AZT/3TC/EFV (9.3%), TDF/3TC/EFV (9.3%) and TDF/ 3TC/NVP (9.3%).

Table 2: Baseline CD4 count, initial WHO clinical stage and starting regimens in AHMC, June 1, 2010 to June 1, 2014

Baseline CD4 cells/mm3	**Frequency (%)**
<50	34(22.7)
51-100	40(26.7)
101-200	53(35.3)
>200	15(10)
Missing data	8(5.3)
Initial WHO clinical stage	
Stage I	9(6)
Stage II	12(8)
Stage III	95(63.3)
Stage IV	31(20.7)
Missing data	3(2)
Initial ART regimen	
D4T/3TC/NVP	48(32)
D4T/3TC/EFV	37(24.7)
AZT/3TC/NVP	23(15.3)
AZT/3TC/EFV	20(13.3)
TDF/3TC/EFV	11(7.3)
TDF/3TC/NVP	11(7.3)

Initial Antiretroviral treatment regimens and causes of change: The main reasons reported for modification of treatment regimen were toxicity/side effects (70%) new TB (12.7%), desire for pregnancy (10%) and treatment failure (7.3%) (**Table 3**). From all toxicities reported, peripheral neuropathy accounted for 32(30.5%) of the toxicities, was the most common followed by lipoatrophy 19(18.1%), Anemia 18(17.1%), CNS disturbances 17(16.2%), Rash 15(14.3%) and renal failure 4(3.8%), as shown in **Figure 1**. Peripheral neuropathy was due to stavudine containing regimens D4T/3TC/NVP 25(78.1%) and D4T/3TC/EFV 7(21.9%) lipoatrophy was due to stavudine containing regimens D4T/3TC/NVP 10(52.6%) and D4T/3TC/EFV 9(47.4%). Anemia was due to zidovudine containing regimens of AZT/3TC/NVP 10(55.6%) and AZT/3TC/EFV 8(44.4%) (**Table 4**). Efavirnez containing regimens were responsible for 100% of CNS disturbances; tenofovir based regimens accounted for 100% of incidence of renal failure .Rash was due to nevirapine containing regimens of D4T/3TC/NVP (46.7%) and AZT/3TC / NVP (53.3%) (**Table 4).**

Table 3: Common reasons for modification by first treatment regimen in AHMC, June 1, 2010 to June 1, 2014

Initial regimen	**Reasons for ART Regimen Change, N(%)**			
	Toxicity	**Pregnancy**	**TB**	**Treatment failure**
D4T/3TC/NVP	42(40)	-	5(26.3)	1(9.1)
D4T/3TC/EFV	26(24.8)	8(53.3)	-	3(27.3)
AZT/3TC/NVP	18(17.1)	-	5(26.3)	-
AZT/3TC/EFV	15(14.3)	3(20)	-	2(18.2)
TDF/3TC/EFV	3(2.9)	4(26.7)	-	4(36.4)
TDF/3TC/NVP	1(0.9)	-	9(47.4)	1(9.1)
TOTAL	105(70)	15(10)	19(12.7)	11(7.3)

Table 4: Toxicity reported as reason for initial treatment regime Per regimen in AHMC, June 1, 2010 to June 1, 2014 N (%)

	D4T/3TC/NVP	D4T/3TC/EFV	AZT/3TC/NVP	AZT/3TC/EFV	TDF/3TC/EFV	TDF/3TC/NVP	Total
Peripheral neuropathy	25(78.1)	7(21.9)	-	-	-	-	32
Lipoatrophy	10(52.6)	9(47.4)	-	-	-	-	19
Rash	7(46.7)	-	8(53.3)	-	-	-	15
Anemia	-	-	10(55.6)	8(44.4)	-	-	18
Renal Failure	-	-	-	-	3(75)	1(25)	4
CNS disturbances	-	10(58.3)	-	7(41.2)	-	-	17

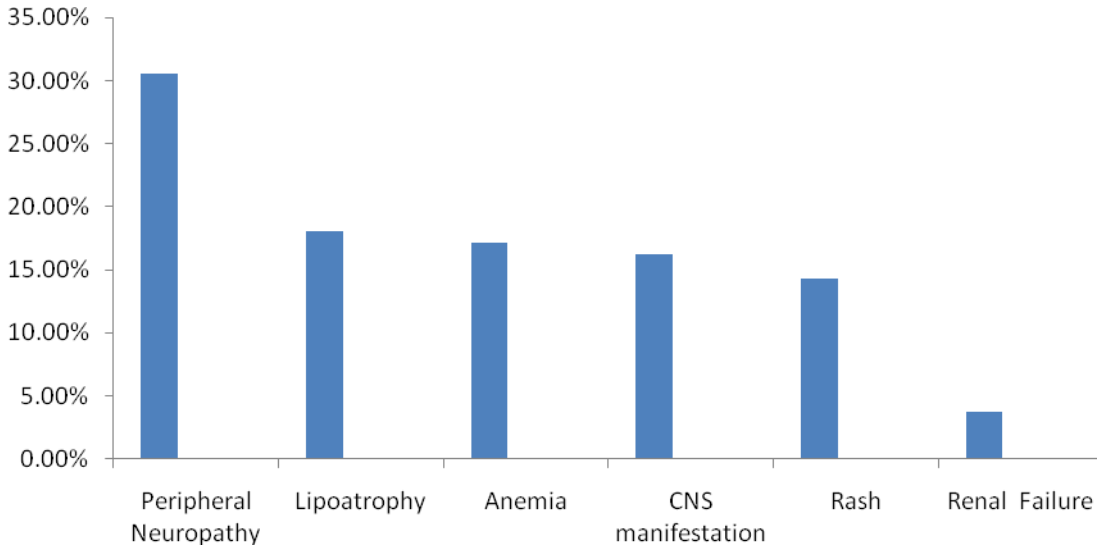

Figure 1: Toxicities reported as a reason for initial treatment regimen change in AHMC

Duration of initial antiretroviral treatment just before regimen change and reasons for modification of the regimen: From a total of 150 patients 36(24%) stayed on initial regimen for only 12 weeks followed by 34(22.72%) in more than 72 weeks, 27(18%) for 13 to 24 weeks and 26(17.3%) in 49 to 72 weeks (**Table 5**). From a total of 105(70%) patients whose initial regimen modification made due to toxicities, 32(30.5%) were in the first 12 weeks followed by 26(24.8%) in more than 72 weeks period. Similarly, from a total of 19(12.7%) patients whose initial regimen change was due to TB CO-infection, 14 (73.7%) were in the 13 to 24 weeks period (**Table 6**).

Table 5: Weeks of stay on initial antiretroviral treatment and treatment regimen in AHMC, June 1, 2010 to June 1, 2014

Initial regimen	Duration of ART before switch, N(%)					
	Start 12 weeks	13 -24 weeks	25-48 Weeks	49-72 weeks	>72 weeks	Total
D4T/3TC/NVP	7(14.6)	1(2.08)	11(22.9)	11(22.9)	18(37.5)	48
D4T/3TC/EFV	10(27.03)	8(21.6)	7(18.9)	8(21.6)	4(10.8)	37
AZT/3TC/NVP	8(34.8)	5(21.7)	4(17.4)	3(13)	3(13)	23
AZT/3TC/EFV	7(35)	3(15)	2(10)	3(15)	5(20)	20
TDF/3TC/EFV	-	1(9.1)	3(27.3)	4(36.4)	3(27.3)	11
TDF/3TC/NVP	-	9(81.8)	-	1(9.1)	1(9.1)	11
	32(21.3)	27(18)	27(18)	30(20)	34(22.7)	150

Table 6: weeks of stay on initial antiretroviral treatment versus reason for changing the regimen in AHMC, June 1, 2010 to June 1, 2014

Reason for change	Weeks of stay on initial therapy, N (%)					
	Start- 12 weeks	13-24 weeks	25-48 weeks	49-52 weeks	>72 weeks	Total
Toxicity	32(30.5)	-	22(21)	25(23.8)	26(24.8)	105(70)
New TB	-	14(73.7)	-	-	5(26.3)	19(12.7)
Treatment failure	-	2(18.2)	5(45.5)	1(9.1)	3(27.3)	11(7.3)
Pregnancy	-	11(73.3)	-	4(26.7)	-	15(10)
Total	**32(21.3)**	**27(18)**	**27(18)**	**30(20)**	**34(22.7)**	**150(100)**

DISCUSSIONS

Rationale for treatment switch could be due to risk of toxicity, poor adherence, a desire for pregnancy, treatment failure or co-morbidity.[4] More than half of the patients (56.7%) in this study were on D4T based regimens, D4T/3TC/NVP (32%) and D4T/3TC/EFV (24.7%) while the rest were on AZT/3TC/NVP (15.3%), AZT/3TC/EFV (13.3%), TDF/3TC/EFV (7.3%), and TDF/3TC/NVP (7.3%). The result of this study was not consistent with the studies done in southern India[5], cote divoire[6] and southern Ethiopia[7] where D4T/3TC/NVP alone accounts for 63%, 58% and 54.7% respectively. The probable reason could be the difference in patient conditions, co-morbid situation, or contraindications.

In the present study, toxicity/side effects was the most common cause of regimen switching in 70% of patients, which was similar to studies done in Southern India[5], Uganda[8], and Hospitals in southern Ethiopia.[7] The patients were with more advanced disease at baseline, which may necessitates higher rates of regimen change/ discontinuation due to adverse events.

Unlike in a study in Peru[9], peripheral neuropathy was the most common reason for modification in our study. This is most probable due to the reason that most of the patients in this study were on D4T–based regimen of D4T/3TC/NVP and D4T/3TC/EFV. Lipoatrophy was due to D4T containing regimen of D4T/3TC/NVP and D4T/3TC/EFV. anemia was due to AZT containing regimen AZT/3TC/NVP and AZT/3TC/EFV. Unlike the Peru's study[9], where the low rates of HAART change was due to anemia, in this study, was likely due to lack of adequate baseline anemia assessment and the fact that less close monitoring of anemia at the study site.

Co-morbidities in patients with advanced disease and concurrent treatments for opportunistic diseases may affect ARV tolerance and thereby increase risk of toxicities[10]. Co-morbidity was the other cause for HAART switch. 12.7% of the patients changed their regimen due to co-infection of tuberculosis and it was the only co-morbidity reported in this study. This is consistent with the study in the United Kingdom[11], Cote diviore[12] and hospitals in southern Ethiopia[7]. 47.4%, 26.3% and 26.3% of the patients on TDF/3TC/NVP, D4T/3TC/NVP and AZT/3TC/NVP respectively were switched. The most probable reason being over lapping drug toxicity of NVP with anti-TB drugs and potential for drug interaction as TB drug like rifampicin is 3A4 inducer.

Planning pregnancy or being pregnant was the third major reason for modifying ARV drugs in this study. 53.3%, 26.7%, and 20% of the patients on D4T/3TC/EFV, TDF/3TC/EFV, and AZT/3TC/EFV were switched, consistent with the study in Cote d'ivoire[6]. This switch was mainly due to the tetragenic effect of EFV which should mainly be avoided during the first trimester pregnancy according to recommendation of older treatment guideline of Ethiopia. However EFV is approved for its being safe in the first trimester based on current study[13] and it has been begin to use very recently for HIV infected pregnant women in our setting.

As expected and previously reported[5,14,15,16], patients were more likely to change therapy shortly after HAART initiation because of adverse events rather than statement failure. Treatment failure was given as the reason for change in 11(7.3%) of patients in current study, which occurred in patients on TDF/3TC/EFV (36.4%), D4T/3TC/EFV (27.3%), AZT/3TC/EFV (18.2%), D4T/3TC/NVP (9.1%) and TDF/3TC/NVP (9.1%). This may be explained by differences in primary resistance to NRTIs or NNRTIs containing regimens.[17] However, some studies have reported higher treatment failure as a reason or regimen switch. [5,6,8,18]

In the study in South Africa, treatment failure was observed in 12% patient[15] and according to the study in India, treatment failure accounts for 14% of the reasons for modifying therapy.[16] According to a study in Uganda[8], immunological failure alone predicted virological failure in 56% of patients. This may due to lack of continuous

monitoring of patients CD4 count, viral load and on occurrence of opportunistic infection in the setting of this study.

Contrary to studies in southern India[5] and Uganda[8] cost was not a major reason for ART regimen change due to cost free (free – fee) provision of ARV drugs for the patient in Ethiopia. As shown in table 3 and 4 of this study, a rough association was observed between common reasons for modifications of initial regimen and initial regimen even if significance of this relationship was not statistically tested. Similarly, toxicities like CNS disturbances, peripheral neuropathy, lipoatrophy and others were associated with respective initial regimen. Moreover, weeks of stay on initial regimen were correlated with respect to common reasons for regimen changes. Rash and CNS disturbances were reported in the first 12 weeks. All of peripheral neuropathy, lipoatrophy and anemia were seen after 25 weeks of stay on initial regimen. This was consistent with the findings reported in the United Kingdom[11] India[5] and Uganda.[8]

CONCLUSIONS

The result of this study indicated toxicity as the main reason for modification of initial ARV drugs among the study population. Peripheral neuropathy was the leading cause for modification of HAART. Tuberculosis was the only co-morbidity disease reported in this study and all patients who switched were due to occurrence of tuberculosis after starting ARV drugs on NVP-based regimen. Treatment failure was the least reasons for ARV regimen change.

Recommendation: There should be a wide use of viral load measuring device in AHMC to establish the extent of treatment failure even if the device is present in regional laboratory in AHMC. As much as possible, clinicians should stick to the national ARV drug use guidelines for management and follow up of patients receiving HAART. The national policy makers should up-date the guide lines as soon as possible. Switching should be based on a risk benefit ratio, especially for pregnant HIV patients. The factors associated with modification of HAART observed in this study should be investigated further in longitudinal studies of ART utilization.

Acknowledgement: Finally, we would like to thank Rift Valley University for giving us such a chance to carry out the research work and the administration and all staff members of antiretroviral therapy unit in AHMC.

Competing interests: The authors declare that they have no competing interests

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