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CAUSE OF ANTIRETROVIRAL DRUG CHANGES AMONG PATIENTS ON ANTIRETROVIRAL THERAPY AT THE ART CENTER IN DESSEI REGIONAL REFERRAL HOSPITAL, ETHIOPIA

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ABSTRACT

Background: Beside the fact of poor adherence to antiretroviral drugs in resource limited country, serious adverse effects of the drugs and treatment failure complicate the whole management of antiretroviral therapy. Consequently, treatment modification and discontinuation of therapy has become a common phenomenon and hence limitation of treatment option has turn out the major concern of the future HAART. The aim of the study was to assess the factors responsible for modification of ARV regimen in patients taking ARV drugs.

Methods: A cross sectional descriptive study was conducted between January 2007 and December 2007 in Dessie regional referral hospital

Result: One hundred twenty two patients switch their first regimen in Dessie regional referral hospital within the study period. The most frequent prescribed first regimens before switch were AZT/3TC/EFV (36%), AZT/3TC/NVP (27%), D_4T/3TC/EFV (19%) and D_4T/3TC/NVP (18%). Toxicity (66%) followed by co-morbidity (14%) and planning pregnancy (11%) were the most common reasons for modification of antiretroviral therapy .The main toxicity was anemia (64 patients)and peripheral neuropathy (11 patients).

Conclusion: The proportions of patients who modify HAART in our resource constrained setting present a challenge to the limited treatment options that currently present.

INTRODUCTION: According to the latest figures published in the UNAIDS/WHO 2006 AIDS epidemic update, 39.5 million people were living with HIV (PLWHA), these figures included 4.3 million new infection HIV/AIDS. Meanwhile, 63% PLWHA were in sub-Saharan Africa where health coverage is poor [1].

Based on report of 2006 taken from VCT centers, blood banks and ART programs, the cumulative number of people living with HIV/AIDS (PLWHA) in Ethiopia were about 1.32 million (45% male and 55% female) . The estimated number of new adult AIDS cases was 137,499. The number of PLWHA on need of ART was 277,757 including 43,055 (15.5%) children aged 0-14 years [2].

The antiretroviral HIV drugs that are currently available can improve the quality of some one infected with HIV, helping them to stay well much longer than they otherwise would [3]. After the introduction of ART, the overall AIDS related morbidity and mortality have been markedly decreased [1, 3]. However, in resource limited country like Ethiopia even if the availability of ARV drugs have been cost free, there is still significant

HIV/AIDS related morbidity and mortality [4]. Besides the fact of poor adherence to ARV drug in resource limited country, serious adverse effect of the drug and treatment failure complicate the whole management of antiretroviral therapy [5, 6, 7].

Consequently, modification and discontinuation of therapy has become a common phenomenon and hence limitation of treatment option has turn out the major concern of the future HAART [8, 9, 10].

Several studies in both developed and developing country showed that ARV drug switch was considerably common event [8, 11, 12]. However, data on modification of highly active antiretroviral therapy are scarce among patients of Ethiopia, so, the data can potentially provide a long term strategic approach to initial and subsequent decisions regarding ART. With these rational, this study aimed in assessing the reasons for change of antiretroviral therapy.

METHODS AND MATERIALS: The study was conducted from January 1, 2007 to December 31, 2007 G.C., in ART Clinic, at Dessie Regional Referral Hospital, which is situated 400 km away from Addis Ababa in Northern of Ethiopia.

The study was conducted using a cross sectional descriptive study design. One hundred twenty two patient information cards of HIV- infected patients who switch Antiretroviral Therapy regimen from Jan. 1, 2007 to Dec. 31, 2007 were included in the study. Patients which were below 18 years of age and those patient information cards which had insufficient information for the study were exclude from the study.

From the patient information sheet; Demographic data; starting and changing regimen, duration on initial therapy, CD_4 count and reason for changing, etc were collected using check list.

After collecting data, it was cleared, categorized and analyzed. The chi-square test method (http: //faculty. vassar.edu/lowry/newcs.html) was conducted to observe the statistical significant association between causes of change of HAART with some variables.

Ethical approval to conduct this study was obtained from Jimma University Student Research Program and from Dessie Regional Referral Hospital. To be ethical patient card numbers were used instead of patient name. The quality of the study was improved through training of data collector on how and which data was collected from the patient information sheet, supervision and daily check up of filled questionnaire.

RESULT: In a study conducted in Dessie Regional Referral Hospital, 122 patient cards were assessed. From these, 59% were female. The median age was 32 (± 6). Most patients were receiving a starting regimen of AZT/3TC/EFV, 44 patients (36%), and AZT/3TC/NVP, D_4T/3TC/EFV, D_4T/3TC/NVP are 27%, 19% and 18%, respectively (**Table 1**).

TABLE 1: BASELINE CHARACTERISTICS OF STUDY POPULATION AT FIRST REGIMEN IN DESSIE REGIONAL REFERRAL HOSPITAL, FROM JAN. 1, 2007 TO DEC. 31, 2007

Characteristics		
Age, years mean (SD)		32 (±6)
Gender n (%)	Male	50 (41)
	Female	72 (59)
	Total	122
CD_4 cell/µl at baseline n (%)		
<50		26 (21)
51-100		24 (20)
101-200		37 (30)
>200		35 (29)
Total		122
First treatment combination n (%)		
D_4T/3TC/NVP		22 (18)
D_4T/3TC/EFV		23 (19)
AZT/ 3TC /NVP		33 (27)
AZT/3TC/EFV		44 (36)
Total		122

The main reasons reported for modification of both first regimen (66%) and second regimen (58%) was toxicity. Co-morbidity (14%) and planning pregnancy or being pregnant (11%) was the second and third most common cause for modification of first line regimen, respectively. Other reasons are treatment failure and adherence difficulty (**Table 2**).

TABLE 2: REASONS FOR MODIFICATION OF 1ST AND 2ND REGIMEN IN DESSIE REGIONAL REFERRAL HOSPITAL, FROM JAN. 1, 2007 TO DEC. 31, 2007

Reason	1st regimen	2nd regimen
	No (%)	No (%)
Toxicity	80 (66)	4 (58)
Treatment failure	8 (7)	1 (14)
Adherence difficulty	3 (2)	-
Planning pregnancy or being pregnant	14 (11)	1 (14)
Co morbidity	17 (14)	1 (14)
Total	**122**	**7**

From modification of ARV drug regimen due to toxicity, 50% were from AZT/3TC/EFV, and the remaining 28%, 11% and 7% were due to AZT/3TC/NVP, D_4T/3TC/EFV, and D_4T/3TC/NVP, respectively. D_4T/3TC/NVP (56%) and AZT/3TC/NVP (39%) were the first two regimens that the patient switched to another ARV regimen due to co morbidity (**Table 3**).

TABLE 3: COMMON REASON FOR MODIFICATION; BY FIRST ARV REGIMEN IN DESSIE REGIONAL REFERRAL HOSPITAL, FROM JAN 1, 2007 TO DEC 31, 2007

Reason	Treatment n (%)					
	D_4T/3TC/NVP	D_4T/3TC/EFV	AZT/3TC/NVP	AZT/3TC/EFV	Chi-square	p-value
Toxicity	5 (7)	10 (11)	25 (28)	44 (50)	43.91	0
Treatment failure	3 (40)	4 (50)	1 (10)	-	6.8	0.07855
Adherence difficulty	1 (25)	-	2 (75)	-	3.667	0.2997
Planning pregnancy	1 (7)	11 (73)	-	3 (20)	19.93	0.00018
co morbidity	10 (56)	-	7 (39)	1 (6)	15.33	0.00155

From all toxicity reported; anemia was the most common one that resulted from AZT/3TC/EFV, 53.5% (45 patients) and AZT/3TC/NVP, 23.6% (19 patients). Also lipotrophy, pancreatitis, Rash and CNS side effect (D_4T/3TC/EFV); recurrent vomiting and hepatitis (d_4T/3TC/NVP) were shown (**Table 4**).

TABLE 4: TOXICITIES REPORTED AS REASON FOR FIRST REGIMEN CHANGE; BY TREATMENT REGIMEN OF DESSIE REGIONAL REFERRAL HOSPITAL, FROM JAN. 1, 2007 TO DEC. 31, 2007

Reason	Treatment n (%)			
	D_4T/3TC /NVP	D_4T/3TC/ EFV	AZT/3TC/ EFV	AZT/3Tc/ NVP
Rash	-	1 (1.2)	-	3 (3.6)
Anemia	-	-	45 (53.5)	19 (22.6)
Peripheral neuropathy	3 (3.6)	8 (9.5)	-	-
other	1 (1.2)	1 (1.2)	-	2 (2.4)
total	4	10	45	24

Most of the patients (40%) were placed in their first regimen for 3 months since start. Thirty six percent of patients remain in their regimen from 12-26 weeks; whereas only 7 patients (6%) remain on first regimen for more than 104 weeks (**figure 2**).

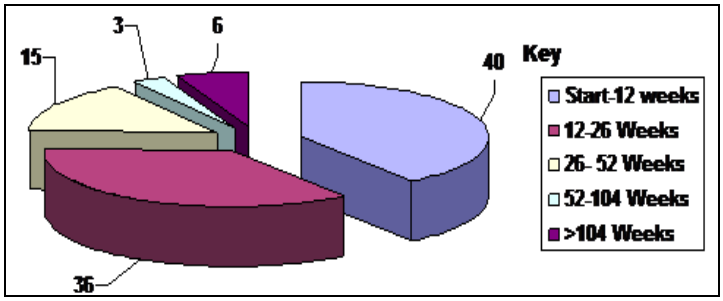

FIG. 1: WEEKS ON INITIAL ANTIRETROVIRAL TREATMENT BEFORE FIRST SWITCH OF STUDY POPULATION, IN DESSIE REGIONAL REFERRAL HOSPITAL, FROM JAN. 1, 2007 TO DEC. 31, 2007

From all those patients who took D_4T/3TC/NVP, 8 patients remain with there regimen for 4 months while three patients remain on their therapy for more than 2 years. Patients who placed on AZT/3TC/NVP (16 patients) were on there regimen for the first 3 months whereas there were 24 patients who were in AZT/3TC/ EFV regimen from 12-16 weeks since start (**table 5**).

From 84 patients who develop toxicity; 46% was within 12-26 weeks and 40% was in the first 3 month since start. From 8 patients who showed treatment failure 6 patients develop after 2 Years follow up on their first regimen (**table 6**).

TABLE 5: WEEKS ON INITIAL ANTIRETROVIRAL (ARV) THERAPY, BY FIRST REGIMEN IN DESSIE REGIONAL REFERRAL HOSPITAL, FROM JAN 1, 2007 TO DEC 31, 2007

1st-regimen	Week on initial therapy, n (%)				
	Start-12 weeks	12-16 weeks	26-52 weeks	52-104 weeks	>104 weeks
D_4T/ 3TC /NVP	8 (36)	1 (5)	8 (36)	2 (9)	3 (14)
D_4T/3TC/EFV	7 (30.5)	7 (30.5)	5 (22)	1 (4)	3 (13)
AZT/3TC/ NVP	16 (50)	13 (41)	1 (3)	1 (3)	1 (3)
AZT/3TC/ EFV	18 (38)	24 (51)	5 (11)	-	-
Total	49	45	19	4	7

TABLE 6: COMMON REASON FOR MODIFICATION; BY DURATION ON FIRST REGIMEN IN DESSIE REGIONAL REFERRAL HOSPITAL, FROM JAN 1, 2007 TO DEC 31, 2007

Reason	Week on initial therapy, n (%)					Chi- square	P-value
	Start-12 weeks	12-26 weeks	26-52 weeks	52-104 weeks	>104 weeks		
Toxicity	34 (40)	39 (46)	8 (9)	3 (4)	1 (1)	76.8	-
Treatment failure	-	-	1 (12.5)	1 (12.5)	6 (75)	15.75	0.00337
Adherence difficulty	-	1 (25)	2 (75)	-	-	5.33	0.255
Planning pregnancy or pregnant	6 (43)	3 (21)	5 (36)	-	-	11	0.0265
Co morbidity	9 (65)	2 (14)	3 (21)	-	-	19.57	0.000606
Total	49	45	19	4	7		

DISCUSSION: This cross sectional study showed that 122 patients switch there first regimen from Jan 1, 2007 to Dec 31, 2007. Most of the patients were on zidovudine based regimen; 36% on AZT/3TC/EFV, and 27% on AZT/3TC/NVP. This is consistent with that of the research conducted in UK, which is 44% on ZDV/3TC based regimen[11] and contrast with that of research done in Treat Asia HIV Observational Database, with 37% on D_4T/3TC/NVP regimen.[12] The probable reason for these differences is laboratory result variation and prescribing professional competency in relation with what to choose specific drug which again may be due to variation in ART drug related information.

The most known cause of ARV switching was toxicity (66%) which is consistent with study conducted in UK (60%) [11], South India (64%) [13], and Uganda (71.8%) [14]. Co morbidity and planning pregnancy were the second and third most cause for modification of ARV drug, which was not the main problem in the study conducted on UK. The probable reason for these is economical variation specially the amount they invest to health care and difference in know-how related to disease and medication. Unlike the study in UK, treatment failure was not the main problem in this study, these maybe due to lack of viral load measuring device and lack of continuous monitoring of patients especially on there CD4 count and on occurrence of opportunistic infection.

Study conducted in India and Uganda shows that cost was one of the most reasons for discontinuation (poor adherence) and modification of drug, but in this study, since the drug reach to the patient with free-fee, it may not be an important reason.

From toxicity reported, anemia was the most common reason, unlike research done in UK [11] and south India [13]. These may be due to poor nutrition habiting in addition to bone marrow depression effect of the drug they take like AZT and situational condition of patients like pregnancy and concomitant disease. From drug point of view, 50% toxicity was due to AZT /3TC/ EFV, from these anemia was the only adverse effect resulted from these regimen.

AZT /3TC/ NVP (28%) was the second most common cause of toxicity for switching, which resulted anemia (19 patient) due to zidovudine, rash (3 patients) due to neverapine, hepatitis (1 patient) due to neverapine, and recurrent vomiting (1 patient). The main zidovudine related effects are blood-disorders like anemia, leucopoenia and bone marrow suppression; GI-effects like vomiting, diarrhea and abdominal discomfort, insomnia, and parasthesia etc.

From these adverse effects, anemia was the most common side effect that cause modification of regimen from ZDV-based regimen taking patients in this and most other studies. Eleven percent of toxicity was due to D_4T/3TC/EFV which result peripheral neuropathy (8 patients) due to D_4T, rash (1 patient) due to efavirenz, pancreatitis (1 patient) due to 3TC. Seven percent toxicity was due to D_4T /3TC/ NVP which result peripheral neuropathy (3 patients) and lipoathrophy (1 patient) due to D_4T.

Tuberculosis (18 patients) was the only co morbid disease reported in this study, which is consistent with research done in UK, 6 out of 10 patients[11] with co morbidity switch due to TB. Due to Tuberculosis 56% (10 patients) switch D4T/3TC/ NVP to D_4T /3TC/EFV; 7 patents switch from AZT/3TC/NVP to AZT /3TC/EFV; and one patient switch from AZT/3TC/EFV to TDF/3TC/EFV since he develop Disseminated TB and start anti TB treatment. The probable suggestion for NVP switch to EFV is overlapping drug toxicity of NVP with anti-TB, which is hepatotoxicity, and drug interaction since NVP is CYP3A4 enzyme inducer.

Planning pregnancy & being pregnant was the third major reason for switching of drugs; 11 patients from D_4T/3TC/EFV, 3 patients from AZT/3TC/EFV which was mainly due to EFV teratogenic effect, and one patient switch from D_4T/3TC/NVP which may be due to higher risk of neverapine associated hepatic events and lactic acidosis associated with stavudine which is consistent with study in UK (one pregnant patient switched due to D_4T) [11].

Only 8 patients face treatment failure from there first regimen which occurred mainly from D_4T containing regimen (90%) and one from AZT/3TC/NVP. This is due to immunological failure (5 patients) and development of opportunistic infection (3 patients) reported as treatment failure. The research conducted in Malawi [15] showed that 75% (114 patients) immunological failure, 21% (32 patients) clinical failure and 45 (6 patients) both clinical and immunological failure. According to study in Uganda, immunological failure alone predicted virological failure in only 56 % of patients and may lead to unnecessary ART change in up to 44% of patients [16].

This study also showed the association of common cause of initial ARV regimen modification with duration of therapy before first switch and starting regimen type. Modification due to toxicity have statistical significance relation ship with starting regimen type (p=0, x2= 43.905).

The suggested reason for these is the toxicity effect of the drugs is mainly an inherent property of drugs which cause modification of ARV regimen and these was consistent with research done in UK [11], south India [13] and Uganda [14], in which the most known cause of ARV switch was toxicity.

Planning pregnancy or pregnant (P=0.000175, x2=19.933) and co morbidity (p=0.0155, x2=15.333) had also statistical significant relation with starting regimen type whereas treatment failure (p 0.0785) and adherence difficulty (p=0.2997) were statistically insignificant with starting regimen type. Development of toxicity that cause switching have statistically significant relation ship with duration of initial therapy (p=0, x2 76.8) which is in agreement with the research done in Uganda [14]. The probable reason is the longer exposed to antiretroviral drugs the more likely to experience long term adverse effects of the ARV drug.

The median time on therapy before substitution because of toxicity was 3 months. The median time on therapy before substation due to co morbidity and treatment failure was of 73 days and 771 days (2 years), respectively. Co morbidity (p= 0.00061, x2 = 19.571) and treatment failure (p=0.00337 x2 =15.75) have significant association whereas planning pregnancy or pregnant (p=0.0265), adherence difficulty (p=0.255) have insignificant association with duration of initial therapy. The limitation of these study were lack of appropriately and completely filled patient information sheet, the cross sectional study may not allow for a direct investigation of causal relation between the factors studied and the outcome of interest and we collected the main reason as reported by physician for modification of treatment, but reasons for modification are often interrelated.

CONCLUSION: In conclusion, the proportions of subjects who modify HAART in our resource constrained setting present a challenge to the limited treatment options that we currently have. Within these, the main reason for modifications are toxicity, planning pregnancy or pregnant and co morbidity are the top three. From all recorded toxicity, anemia is the leading one cause for modification of HAART. Furthermore, most of the toxicity and even most modification are incurred from ZDV-based regimen especially ZDV/3TC/EFV.

From study on developed country, Virological failure is the most common kind of treatment failure. However, there are no reports of virological failure in this study and as a result of these some patients wouldn't be beneficial from treatment they take. So, it is strongly recommended to have viral load measuring device. For any modification of antiretroviral drug regimen, there should be a Guideline for switching based on benefit - risk ratio, especially for pregnant HIV Patient.

Since, most of modification of ARV regimen require laboratory result monitoring, there should be enough, qualitative and well effective laboratory equipments and trained professionals in Dessie Regional Referral Hospital. The factors associated with modification of HAART observed in this cross sectional study should be investigated further in longitudinal studies of ART utilization.

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