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Factors for Antiretroviral Regimen Change Among HIV/AIDS Patients Initiated First Line HAART at Assela Referal Hospital, Oromia Region, Ethiopia

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Abstract: *Background*: AIDS, which is acquired immune-deficiency syndrome, is treated by highly active antiretroviral therapy with ART agents including Nucleoside reverse transcriptase inhibitors, Non-Nucleoside reverse transcriptase inhibitors and protease inhibitors. Antiretroviral therapy (ART) has markedly decreased the morbidity and mortality due to HIV disease. However, toxicities, co-morbidities and treatment failures were seen among others. *Objective*: To determine the reasons for initial antiretroviral regimen change among adult patients on anti-retroviral therapy. Methods: A retrospective cross-sectional study was conducted by using patient information sheet record cards in Asella Referral Hospital ART clinic. *Results*: 229 patients that modified their first regimen in case of toxicity, 34(40.47%) were due to AZT/3TC/NVP and the remaining 6(54.54%), 12(22.22%) , 11(21.60%) and 7(33.33%) were due to AZT/3TC/NVP, D4T/3TC/NVP, TDF/3TC/NVP and AZT/3TC/NVP were respectively. From 11, 6(54.54%) patients were initially on AZT/3TC/NVP and the remaining 3(27.27%) and 2(18.18%), respectively on D4T/3TC/NVP and TDF/3TC/EFV modified due to co-morbid condition. *Conclusion*: The proportions of patients who modify HAART in our resource-constrained setting present a challenge to the limited treatment options that currently present. Within these, the main reasons for modifications in the study setting were toxicity, co morbidity and planning pregnancy or pregnant were the top three. Since, most of modification of ARV regimen requires laboratory result monitoring, there should be: enough, qualitative and well effective laboratory equipment and trained professionals in Asella Referral Hospital; Proper clinical recording; Improvements in pharmaceutical procurement and stock management systems at hospital or national level are recommended.

Key words: Antiretroviral therapy · Changes · Regimen · Factors · HIV/ADS · Patients · Assela

INTRODUCTION

Human Immune Virus (HIV) is responsible for a worldwide pandemic and it is the cause of Acquired Immune Deficiency Syndrome (AIDS) [1]. According to latest statistics 33.4 million individuals worldwide are living with HIV, of which 15.7 million (47%) are women and 2.1 million (6.3%) are children under 15 years. In addition, there are 2.7 million new infections and 2.0 million deaths from AIDS worldwide. Sub-Sahara Africa remains the region most heavily affected by HIV. About 1.9 million people living in Sub-Sahara Africa become newly infected with HIV, bringing the total number of people living with HIV to 22.4 million. Moreover, an estimated 1.4 million AIDS related deaths occur in Sub-Sahara Africa. But the rate of new HIV infections and death has slightly declined as a result of improved access to anti-retroviral therapy. The HIV/AIDS epidemic in Ethiopia continues to pose a threat to the lives of its people [2]. According to the single point estimate in 2007, 977, 394 people were living with the virus in Ethiopia; resulting, a prevalence rate of 2.1% (1.7% among males and 2.6% among females; 7.7% urban and 0.9% rural areas) for a total estimated population of 73 million. The number of new infections is 125, 528 including 14, 147 HIV positive births of which females' account 57.4% [3].

Since the beginning of Highly Active Antiretroviral Therapy (HAART) in 1996, there have been dramatic declines in morbidity and mortality due to HIV. But these advancements were not without a cost in terms of drug resistance and side effects. A concern about these negative effects has led to a more conservative approach to the timing of initiation of therapy and to clinical trials of

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intermittent therapy in an attempt to decrease the total exposure to drugs over time. Antiretroviral management brings a complex series of choices; when to initiate therapy, what regimen to use, which drugs within each class, when to change therapy and which alternative drugs to use [4]. According to Ethiopian guideline, criteria for initiating antiretroviral therapy in adults and adolescents with documented HIV infection are as follows: If CD4 Testing is Available, WHO Stage 4 disease irrespective of CD4 cell count, WHO stage 3 disease with CD4 cell count < 350/mm^3, if CD4 testing is Unavailable, WHO stage 3 and 4 disease irrespective of total lymphocyte count, WHO stage 2 disease with a total lymphocyte count < 1200/mm^3 [5].

Statement of the Problem: After the introduction of ART in all over Ethiopia, drug-related adverse reactions and other co-morbidity attributed to ART regimen switch. Among the major cause of ART regimen change, the most frequently encountering are; toxicity, co-morbidity and treatment failure [5]. Toxicity or adverse drug reaction (ADR) is creating adherence problem and affect patients' willingness to take drugs. Some studies showed that ADR starting from simple rash up to life threatening Steven Johnson's syndrome and other life threatening adverse effects like hepatotoxicity, mitochondrial damage and bone marrow toxicity create adherence and compliance difficulties [4].

Comorbidity and drug-drug interactions are the other reasons for ART regimen modification. This interaction makes Tuberculosis co-morbidity treatment difficult and challenging. The drug-drug interactions between rifampicin and antiretroviral groups, NNRTIs and PIs results in ineffectiveness of ARV drugs, ineffective TB treatment or an increased risk of drug toxicity. For example, rifampicin stimulates liver enzymes, which metabolize PIs and NNRTIs that can lead to decreased blood level of these drugs. PIs and NNRTIs can also enhance or inhibit this same enzyme system and lead to altered blood level of rifampicin [6].

Treatment failure is the other reason for ART regimen change which is defined as either clinical failure (New or recurrent WHO stage 4 condition like pneumocystis *cariniipneumonia*, toxoplasmosis of the brain and kaposissarcoma, extrapolmunary tuberculosis or immunological failure (50% fall from the on-treatment peak value (if known) or virologic failure (a biological rebound after complete suppression [5].

Significance of the Study: Since there are few studies done on the factors for regimen changes among HIV/AIDS whose were on ART in this country, it is believed that valuable information will be gained from the study. This result will be used as a base line data for future investigators in this area. For reasons of antiretroviral regimen change, for potentially providing strategic plan and decision making on ART drugs management, as general information for planning by policy maker. Therefore, the objectives of the study were to assess reasons for regimen change among patients on antiretroviral therapy in Assela Referal Hospital ART clinic. To assess adverse effects associated with ART that cause regimen change; to assess co- morbid condition that contributes to ART regimen change and to assess treatment failure associated with ART regimen switch

MATERIALS AND METHODS

Study Area: The study was conducted in Asella Referrals Hospital, which is located at 175 km from Addis Ababa. Asella is found in east Arsi Zone of Oromia region. The hospital delivers outpatient and inpatient services and has 16 specialists (surgeon, gynecologist/ obstetrician, internist, pediatrician and ophthalmologist), 85 general practitioners, 116 Nurses, 13 health officers, 10 laboratory technicians and 14 lab technologists and 6 pharmacists and 8 pharmacy technicians.

Study Design: A cross-sectional study on retrospective data was conducted by reviewing patient information sheet record cards.

Study Population: All adult patients' information sheet record cards of HIV/AIDS patients whose regimen were changed in Asella hospital ART clinic from were participated for this study.

Eligibility Criteria: All study populations whose regimen was changed within study period were included; however, all study populations whose regimens were not changed with in study period were excluded from this study.

Sample Size and Sampling Technique: The previous two years patient record cards for patients who visited Asella Referral Hospital ART clinic starting February 10/2013 to February 10/2015 were considered in this study.

Among a total of 1468 patients who visited the clinic, about 229 of them switched their initial regimen were included in the study.

Study Variables: Duration of initial therapy and Modification of HAART regimen were dependent variables. Age, Sex, Marital status, Religion, Educational status, Pregnancy, Toxicity and Co-morbidity were considered as independent variables.

Data Collection: Data collection instruments were developed by reviewing different relevant literatures. Then, it was used to collect patient information from patients' record cards as source of data. The data was collected by the principal investigator.

Data Processing and Analyzing: The collected data was checked, categorized and analyzed using MS excel and SPPS software. The rate of HAART modification and other relevant information were reported as percentage and the data was presented by using tables.

Ethical Consideration: An official and formal letter was received from Jimma University, CHMS research and ethics committee, then it was presented to Asella Referral Hospital to get permission to collect data from patient records.

Quality Assurance: Before starting actual data collection, pretest was undertaken to ensure the completeness of patient information cards and to evaluate the data collection instrument for its validity, reliability and consistency. Then, the possible correction of errors and addition of necessary information was made.

Disseminations of Results: The final finding of the study will be disseminated to concerned bodies such as: Department of Pharmacy, College of Health Science, Jimma University and CBE.

RESULTS

Two hundred twenty nine patients recode cards were revised in the study. More than half of patients were females (57.64%). Most of the patients (20.12%) were in the age group of 26-30 followed by age group of > 45 (17.5%) and age group of 36-40(15.3%). The majority of female patients (12.22%) were in the age group of 26-30 (Table 1).

Table 1: Age and sex distribution of patients for whom treatment modification was made, at Asella Referal Hospital, ART Clinic:

	Sex		
Age	Male n(%)	Female n(%)	Total n(%)
18-20	7(3.06)	10(4.40)	17(7.5)
21-25	8(3.50)	12(5.24)	20(8.74)
26-30	18(7.90)	28(12.22)	46(20.12)
31-35	16(6.98)	25(10.91)	31(17.87)
36-40	14(6.11)	21(9.17)	35(15.3)
41-45	19(8.3)	11(4.8)	30(13.1)
> 45	15(6.6)	25(10.91)	40(17.5)

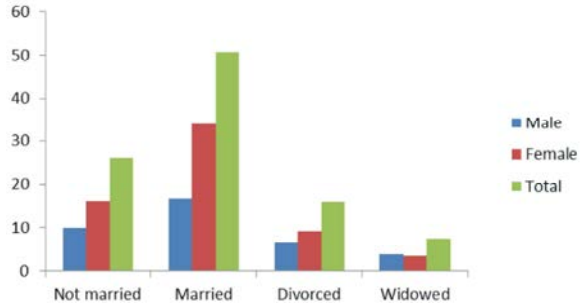

Fig. 1: Marital status of patients for whom treatment was made, at Asella Referal Hospital ART Clinic:

Table 2: CD4 count of patients whom treatment modification was made at initiation of therapy, at Asella Referal Hospital ART Clinic:

CD4 Count	Number	Percent
< 50	23	10.04
51-100	17	7.42
101-150	16	6.99
151-200	53	23.14
> 200	120	52.40

Table 3: Educational level of patients' for whom treatment modification was made at initiation of therapy, Asella Referal Hospital ART Clinic:

Educational Status	Number	Percentage
Illiterate	15	6.55
Primary 111	48.47	
Secondary	70	30.57
Tertiary 33	14.41	

Concerning marital status, the majorities of them 116 (50.7%) was married of which female accounts 78(34.04%). The least number of patients were window in both female and male accounting 3.5% and 3.93%, respectively (Figure 1).

Regarding CD4 count, about half of patients (52.40%) had initial CD4 count greater than 200. While only 10% of the patients had CD4 counts less than 50% Table 2.

In the case of educational status 111 (48.47%) of patients had primary school education and 70(30.57%) and 33(14.41%) were secondary school and tertiary school respectively.

Table 4: Common reason for modification of initial treatment regimen at Asella Referal Hospital ART Clinic

	Treatment Regimen Number					
Reasons	D4T/ 3TC/NPV	D4T/3TCEFV	AZT/3TC/ NVP	AZT/3TC/EFV	TDF/3TCNVP	TDF/3TCEFV
Drug Toxicity	11(13.09)	10(11.90)	34(40.47)	9(10.71)	7(8.33)	13(15.48)
Co-morbidity	3(27.27)	-	6(54.54)	-	2(18.18)	-
Treatment Failure	12(22.22)	9(16.70)	6(11.11)	11(20.37)	9(16.7)	7(12.96)
Poor Adherence	9(17.64)	8(15.69)	10(19.61)	8(15.69)	11(21.6)	5(9.8)
Pregnancy	3(14.26	5(23.8)	7(33.33)	4(19.04)	-	2(9.52)

Table 5: Toxicity reported as reason for modification of treatment regimen, Asella Hospital ART Clinic

	Treatment Regimen N (%)					
Reasons	D4T/3TC/NVP	D4T/3TC/EFV	AZT/3TC/ NVP	AZT/3TC/EFV	TDF/3TC/NVP	TDF/3TC/EFV
Nausea	2(2.38%)	7(8.33%)	7(8.33%)	2(2.38%)	2(2.38)	2(2.38%)
Anemia	-	-	15(17.85%)	4(4.76%)	-	3(3.57%)
Peripheral neuropathy	5(5.95%)	2(2.38%)	3(3.57%)	3(3.57%)	3(3.57%)	5(5.95%)
Rash	4(4.76%)	1(1.19%)	9(10.71%)	-	2(2.38%)	3(3.57%)

Table 6: Common reason for modification at different duration from initial treatment regimen, Asella Hospital ART Clinic

	Weeks Initial Therapy n%				
Reasons	Start-12	12-26	26-52	52-104	>104
Toxicity	27(32.1)	23(27.4)	15(17.9)	13(15.5)	6(7.14)
Co-morbidity	4(36.4)	3(27.27)	2(18.18)	1(9.09)	1(9.09)
Treatment failure	5(9.25)	10(18.52)	20(37.03)	12(22.22)	7(13)
Poor adherence	17(33.33)	11(21.6)	13(25.5)	6(11.8)	4(7.84)
Pregnancy	9(42.9)	5(23.8)	4(19.04)	2(9.52)	1(4.8)

Two hundred twenty nine patients modified their first regimen. Among these 36.68% changed their medications because of drugs toxicity. In 34(40.47%) of patients the medication change were due to AZT/3TC/NVP and the remaining patients 6(54.54%), 12(22.22%), 11(21.60%) and 7(33.33%) the change from first regimen were due to AZT/3TC/NVP, D4T/3TC/NVP, TDF/3TC/NVP and AZT/3TC/NVP toxicity, respectively. From eleven patients who modified their initial regimen owning to co-morbid condition, 6(54.54%) of them were initially on AZT/3TC/NVP and, the remaining 3(27.27%) and 2(18.18%) on D4T/3TC/NVP and TDF/3TC/EFV, respectively. Among 21 patients that modified their first regimen in case of pregnancy, the majority of patients 7(33.33%) were due to AZT/3TC/NVP. Similarly, eleven patients initially on AZT/3TC/EFV and another 9 patients on D4T/3TC/EFV and 6 patients on AZT/3TC/NVP were modified their first regimen due to treatment failure.

The major reason stated related to drug toxicity for changing initial treatment regimen was anemia which were 15(17.85%) and 4(4.76%) for AZT/3TC/NVP and AZT/3TC/EFV, respectively. The other reasons recorded for initial regimen change were nausea for D4T/3TC/EFV and AZT/3TC/NVP; rash for D4T/3TC/NVP and AZT/3TC/NVP; nausea for D4T/3TC/NVP and D4T/3TC/EFV (Table 5, 6).

Among patients who switched the regimen due to medication toxicity, majority of them (32.1%) shifted the regimen in the first 3 months and only 7.14% of patients continued their initial regimen for more than 104 weeks before first switch. Similarly in case of patients with co-morbid condition, poor adherence and pregnancy, most of them switched initial regimen in the first 3 months (the first 12 weeks) which were accounting for 36.4%, 33.33% and 42.9%, respectively. Moreover, 37.03% of patients switched first regimen in 26-52 weeks because of treatment failure.

DISCUSSION

There are many reasons that lead to ineffectiveness, change of HAART combination and discontinuation of HAART regimen. Rational for treatment switch and discontinuation may be long term toxicity, treatment failure (virological, immunological and clinical failure), poor adherence, a desire for pregnancy and/or co morbidity [7]. In the present study, the majority of patients who changed their initial medication were because of drug-related toxicity (36.68%). This finding is not consistent with the study done in Southern Ethiopia and in Tertiary Care Hospital in Ceará, Brazil which were reported to be 54.70% and 88.5%, respectively [8, 9].

The AZT/3TC/EFV (20.8%) regimen accounted for a majority of the patients' initial HAART regimen. The probable reason was the difference in patients' conditions; i.e. co morbid situations, contraindications. This shows there was a high rate of modification and discontinuation of HAART regimens in the first 24 months, particularly due to toxicities. This result is not in agreement with that of research done in Italia (2000) and Royal Free Hospital London, UK (2001), d'Arminio Monforte *et al.* [10]. This may be due to less consideration given to monitor HAART side effects by other methods than regimen change in this study area and difference with study population (white versus black) (heterogeneity).

Of 1468 HIV-positive patients who initiated HAART, 84(34%) of patients changed their initial HAART regimen in between February 10, 2013 to February 10, 2015. The most common cause for HAART switching in this study was toxicity (36.4%) and the most frequently cited toxicity related cause for modification of initial regimen were nausea, rash, anemia and peripheral neuropathy. Similarly, in another retrospective cohort study conducted in New Orleans, LA., USA it was reported that nausea, vomiting and diarrhea were the most common cause for modification of initial regimen which is similar with this study [11].

In this study, the rate of regimen change due to drug toxicity with HIV infection initiated on generic, first-line highly active antiretroviral treatment was indicated and most of them had advanced HIV infection (WHO clinical stage 3 or 4) (50.7%) and CD4 counts above 200. The initial HAART regimens used were: Lamivudine (3TC) with Stavudine (D4T) (in 20.52%) and Nevirapine (NVP) (in 37.6%) or Efavirenz (EFV) (29.26%). This result is in agreement with the study done in South India [12, 13].

Co-morbidities in patients with advanced disease and concurrent treatments for opportunistic diseases could affect antiretroviral tolerance and thereby increase the risk of toxicities (13). This was one of the main reasons for HAART switch. But, tuberculosis was the only co- morbidity diseases reported in this study. This finding is consistent with the study conducted in UK (13) and Cote d'Ivoire [14].

Treatment failure was also reported as the main reason for change regimen in 54(23.6%) of the patients in the current study. Similarly, in various studies highly treatment failure was reported as the reason for a regimen switch. In the study conducted in Cote d'Ivoire and Uganda, treatment failure was one of the main reasons for discontinuation and modification of initial regimen [15, 16].

Immunological failure alone predicated virological failure in 57% of the patients. This may be due to lack of the viral load measuring device, lack of continuous monitoring of patients with a CD4 count. According to the result of this study, 9.2% patients change their regimen due to pregnancy. This finding is consistent with that of study done in Uganda [15] and Royal Free Hospital London, UK (2001), Mocroft *et al.* [17].

Medication cost was one of the major reasons for discontinuation and modification of ARV drugs according to the study conducted in Uganda [15]. However, it was not a reason for modification of HAART drugs in this study area, due to the cost-free (fee-free) provision of HAART drugs for the patients in Ethiopia. The findings of this study should be interpreted with some limitations. These include, lack of appropriately filled patient information sheet. The data (reasons) was collected as reported by physician for modification of treatment, but the reasons for modification are often interrelated.

CONCLUSIONS

In conclusion, the proportions of subjects who modified HAART in this resource-constrained setting was high which could present a challenge to the limited treatment options currently available in the country. The main reasons for regimen modifications were toxicity, co morbidity, treatment failure and pregnancy. Moreover, peripheral neuropathy, nausea, anemia and rash were the main toxicities which caused modification of HAART. Furthermore, most of the toxicity and even most regimen modification were incurred from NVP-based regimen especially AZT/3TC/NVP. Base on the finding of this study the following recommendations were forwarded: As most of modification of ARV regimen requires laboratory result monitoring, there should been through, qualitative and well effective laboratory equipment and trained professionals in Asella Referral Hospital. Health providers working in the ART clinic should monitor patients both clinically and with the laboratory for the occurrence of side effects. The health system should develop ADR database so as to easily record and report adverse effects. This study results illustrate that the reason why the majority of patients changed their initial regimen is: drug toxicity, treatment failure and poor adherence. Therefore, careful follow-up and selection of appropriate antiretroviral regimen must be carried out to prevent drug toxicity and enhance patients' adherence to the treatment regimen.

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