IJLSR (2015), Vol. 1, Issue 1 **Research Article**

IJLSR INTERNATIONAL JOURNAL OF LIFE SCIENCES AND REVIEW

Received on 29 April 2014; received in revised form, 18 July 2014; accepted, 04 December 2014; published 01 January 2015

RATIONALE FOR CHANGING INITIAL HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) REGIMEN AMONG HIV/AIDS PATIENTS IN WEST ETHIOPIA

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ABSTRACT: Background: Antiretroviral therapy (ART) is not a cure but it dramatically reduces the rate of morbidity and mortality, and it improves quality of life to people living with HIV/AIDS and it also now considered a manageable chronic disease. **Objective:** The main objective of this study is to determine the reason for treatment and regimen changes, types of regimen changes, and duration of first initiated antiretroviral regimen among patients on ART. **Methods and Materials:** The study was conducted retrospectively by reviewing the documentary source of patient and by self-administer questionnaire to health care providers. A sample size of 174 patient records was selected by using systematic sampling. **Result:** Out of 174 patients' medical records, the majority were females 112(64.4%). The initial ART regimens used were: Stavudine/ Lamivudine/Nevirapine 78 (44.8%) and Stavudine/Lamivudine/Efavirenz 33(19%). Drug toxicity was the first reason for treatment changes 123(70.7%), followed by Tuberculosis 20(11.5%). The most common toxicities observed were Skin Rash 28(16.1%), Peripheral neuropathy 25(14.4%), Fat change 25(14.4%) and Anemia 18(10.3%). **Conclusion:** ART regimens are effective in decreasing disease progression and AIDS-related death. However, they were associated with a high rate of drug toxicities, and unnecessary switching tends to aggravate the challenges.

Keywords: HIV/AIDS, Switch, HAART, Initial regimen, Nekemte

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INTRODUCTION: The primary goal of ARTs are maximal and sustained suppression of viral replication, restoration of immunologic function, reduction of HIV related morbidity and mortality, improvement of quality of life and prolong survival, because of such use ART has become an integral part of the continuum of HIV care [1]. In Ethiopia, ART service began in August 2003, and free ART was launched in January 2005.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.IJLSR.1(1).13-19

The article can be accessed online on www.ijlsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJLSR.1(1).13-19

Currently, 511 health facilities (142 hospital and 369 health centers) provide ART service throughout the country [2]. Free ART provision gives new hope to thousands of people who require this treatment to reduce morbidity levels and premature death. However, this decision brings with it a new set of challenges. This includes overcoming capacity, constraints within the public health sector, and issues of treatment literacy for patients to ensure treatment compliance and avoidance of the emergence and spread of drug resistant strain of the virus [3].

Generally, the average life expectancy of an HIV-infected person who is treated with ARV approximately increased from 10.5 years in 1996 to 22.5 years in 2005 and reduced AIDS-related

mortality rate by 19% and 84% in developing and developed country respectively. Currently, 5.25 million people eligible for ART in resource-limited countries and selection of ART for an individual is based on efficiency, convenience, toxicity, drug resistance, accessibility, availability, co-morbidity, patient-adherence and cost [4, 5]. Factors to be considered when changing regimen are, national guideline, prior ARVs history, ARVs resistance, side effects, number of drugs need to replace, barriers to adherence, patient lifestyle, and preference, ability to follow up in the clinic, drug interaction, cost, and sustainability. ART regimen is not changed unless necessary. The rationale for changing ART may be treatment failure (Clinical failure, Immunological failure or Virological failure), toxicity or intolerance, Co-morbid conditions, and non-adherence or compromised quality of life [6]. Despite high prevalence rate of HIV/AIDS and a high number of people who have been started ART service in the area, little is known about the underlying cause for switching and duration of first initiated ARVs regimen which are basic criteria for measuring the effectiveness of treatment. The aim of this study is, therefore, to assess the reason and cause of initial highly active antiretroviral therapy (HAART) regimen changes among HIV/AIDS patients on ART in West Ethiopia.

METHODS:

Ethical Consideration: An official letter was written from Wollega University, faculty of medical and health science to Nekemte Hospital and Nekemte health center for permission, and was accepted. The data that was collected confidentially and safekeeping of medical records was assured.

Study Setting: The study was conducted from May 20 to August 25, 2012, at two ART service providing facilities in West Ethiopia; Nekemte Hospital and Nekemte health center. The two facilities were staffed with professionals trained with ART treatment and adherence.

Study Design: The study was conducted retrospectively by reviewing patient's information which has been recorded from March 1, 2009, to March 21, 2011, in both settings and by administered self-administer questionnaire to a health care provider in both ART clinics for assessing the cause for changing first initiated ART regimen.

Data Collection: Data were collected by trained data collectors by using documentary sources from patient medical records. Finally, the data was handled appropriately for further analysis.

Data Analysis: The collected data were categorized and summarized on the data master sheet. All data collected were then analyzed using the Statistical Package for the Social Sciences (SPSS), version 16.0 software. The estimated prevalence of HAART modification was reported as a percentage, and the data was presented as a percentage, table, and bar graph.

RESULTS: 174 patient's medical records were reviewed from both facilities. Out of this, 112(64.4%), patients were females, and 62(35.6%) were males. The highest age group were young adults (26-49 years) with 114(65.5%) followed by teenagers (15-25 years) with 37(21.3%) and adults (50-70 years) with 18(10.3%) **Table 1.**

86(49.4%) of the patients at the initiation of treatment were at clinical stage III, 56(32.2%) were at clinical stage II, while 20(11.5%) patients were at clinical stage I and 8(4.6%) were at clinical stage IV. Clinical stages of 4(2.3%) patients were not recorded.

Majority of patients,78(44.8%), were on regimen D4T+3TC+NVP, followed by those that were on regimen D4T+3TC+EFV with 33(19%) of patients. 21(12.1%) of patients were on AZT+3TC+NVP regimen. RegimenAZT+3TC+EFV, TDF+3TC+ NVP andTDF+3TC+EFV accounts for 16(9.2%), 12(6.9%) and 11(6.3%) of patient s respectively. The remaining 3(1.7%) were treated on others regimen at the beginning of the ARV treatment. The major reason for modification of regimen was toxicity among 123(70.7%) of participants, out of this 81(65.9%) were females, and 42(34.1%) were males. Tuberculosis accounted for the second rank with 20(11.5%) of patients. 11(6.4%) patients changed their regimen because of the occurrence of pregnancy. New drug availability also contributed to 8(4.6%) of patients. The least contributing factors were poor adherence and treatment failure, which accounts for 2(1.1%) for each **Table 2**.

TABLE 1: DEMOGRAPHIC VARIABLES AND LEVEL OF ADHERENCE AMONG HIV/AIDS PATIENT IN NEKEMTE TOWN, ETHIOPIA

Variables	Categories	Frequency	Percentage
Gender	Male	62	35.6
	Female	112	64.4
Age	<15	5	2.9
	15-25	37	21.3
	26-49	114	65.5
	50-70	18	10.3
Educational	No Schooling	35	20.1
	Primary(1-8)	68	39.1
	Secondary(9-12)	43	24.7
	Tertiary(College &University)	28	16.1
Level of Adherence	Very Good	26	14.9
	Good	107	61.5
	Poor	26	14.9
	Missing	15	8.7
Patients Source	Patients	12	6.9
	In Patients	140	80.5
	PMTCT	22	12.6
ART Site	Nekemte Hospital	122	70.0
	Nekemte Health Center	52	30.0

TABLE 2: TOTAL INDICATED REASON FOR MODIFICATION OF REGIMEN AMONG HIV/AIDS PATIENTS IN NEKEMTE TOWN, ETHIOPIA

Reasons for ARV changes	Gender		Total Number	Percentage
	Female	Male		
Toxicity	81	42	123	70.7
Tuberculosis	12	8	20	11.5
Pregnancy	11	0	11	6.4
Because of new drug available	3	5	8	4.6
Because of drug out stock	1	4	5	2.9
Hospitalization	1	2	3	1.7
Poor adherence	2	0	2	1.1
Treatment failure	1	1	2	1.1
Total	112	62	174	100%

Skin rash was the most commonly observed toxicity with 28(22.8%) patients, followed by peripheral neuropathy and fat change each accounts for 25(20.3%) of patients. Anemia and CNS toxicity account for 18(14.6%) and 14(11.4%) of patients, respectively. According to this study, females 81(65.9%) and young adult (26-49 years old) 87(70.7%) were the most vulnerable group for toxicities **Table 3**.

TABLE 3: DISTRIBUTION OF AGE, GENDER AND REPORTED TOXICITIES AMONG HIV/AIDS PATIENTS IN NEKEMTE TOWN, ETHIOPIA

Variable		Reported Toxicity									
		Rash	Peripheral Neuropathy	Fat Change	Anemia	CNS Problem	Nausea	Head Ache	Jaundice	Fatigue	Diarrhea
SEX	Male	9	9	9	5	5	1	1	1	1	1
	Female	19	16	16	13	9	1	3	2	1	1
AGE	15-25	6	2	3	6	3	0	1	0	0	1
	26-49	21	19	18	12	10	2	3	1	0	1
	50-70	1	4	4	0	1	0	0	0	0	0
Total		28	25	25	18	14	2	4	3	2	2

Regimen D4T+3TC+NVP was the first cause of toxicity among 59(48%) of the patients followed by regimen D4T+3TC+EFV in 22(17.9%) of patients. The reaming 16(13%),12(9.8%),6(4.9%),5(4.1%) and 3(2.4%) were due to regimen AZT+3TC+NVP, AZT +3TC+EFV, TDF+3TC+NVP, TDF +3TC+ EFV and other regimens respectively.

According to the result of the study, skin rash accounts for 28(22.8%) cases out of the total observed toxicities. Nevirapine containing regimen (D4T+3TC+NVP, TDF+3TC+NVP, and AZT+ 3TC+NVP) was the major cause for skin rash in 19 (67.9%), 6(21.4%) and 3(10.7%) of patients respectively. Peripheral neuropathy and fat change were the second most observed toxicities in 25 (20.3%) for each.

In general, the result of the study describes regimen D4T+3TC+NVP associated with a high risk of toxicities among 59 (33.9%) of the study population followed by regimen D4T+3TC+EFV in 22 (12.6%) of the sample. Regimen AZT+3TC+NVP and AZT +3TC+EFV also accounts for 16(9.2%) and 12 (6.9%) of the study population, respectively. Regimen TDF +3TC+EFV is the minor group for inducing toxicities, which accounts for 5(2.9%) of the participants.

In this study, 70(40.2%) of patients changed their initial regimen after 168 days (24 weeks) while 35(20.1%) of patients had stayed for 28-56 days on their initial regimen. 23(13.2%) of patients changed their initial regimen between 84-168 days of duration. Only 8(4.6%) patients changed their initial regimen within 2 weeks.

Regimen D4T+3TC+NVPhavethe longest duration of initial therapy followed by regimen D4T+3TC+EFV. All of the patients on regimen TDF+3TC+NVP switched before 168 days. Regimen TDF+3TC+EFV is the most common regimen which has a high rate to be changed during the first two weeks of therapy. Regardless of the regimen majority of the patients, 70(40.2%), were changed after 168 days.

Regimen D4T+3TC+NVP was the most prescribed regimen during initiation of treatment with 78(44.8%) of patients followed by regimen D4T+3TC+EFV among 33(19%) patients. On switching, regimen TDF+3TC+NVP with 55(31.6%) and regimen TDF +3TC+EFV among 35(20.2%) patients account the first and the second figures respectively.

DISCUSSION: In this study rationale for treatment switch includes risk of acute and long term toxicity, poor adherence, a desire for pregnancy, treatment failure, and comorbidity which is consistent with other studies [8, 9, 10, 11, 12, 13, 14, 16]. However, the study done at Tercha Hospital has shown 95.8% of the study population had optimal adherence to ARV medications [15]. Toxicity or ADR is creating an adherence problem and affects the patient's willingness to take drugs. A study done in California showed that a greater percentage of pilot pharmacy patients were adherent to their ART medication regimens compared with patients using nonpilot pharmacies, with the difference being greater than 20 percentage points each year [14].

According to the result of the study, 64.4% of the study populations were females and 35.6% were males. Majority 44.8% of the patients were on regimen D4T+3TC+NVP, and 19% were on regimen D4T+3TC+EFV followed by regimen AZT+3TC+NVP (AZT+3TC+NVP) and AZT +3TC+EFV on 12.1% and 9.2% of the study population, respectively. The rest were on regimen TDF+3TC+NVP with 6.9% of patients and regimen TDF +3TC+EFV with 6.3% of patients.

This study is consistency with the research done in southern India when D4T+3TC+NVP accounts for 63 % [7] and research did at Hawassa and Shashemene referral hospital in which regimen D4T+3TC+NVP accounts for 54.7 % [12]. The probable reason for this similarity can be regimen D4T+3TC+NVP found in a single triple fixed dose as a result it enhances patients adherence, and it is relatively cheap than another regimen.

In this study D4T containing regimen accounts for 111(63.8%) of patients which is similar to research conducted in Abidjan Cote d'Ivoire in which D4T containing regimen accounts for 58% of the study population [8] and similarly the study conducted at eight hospitals located in South Nations, Nationalities and Peoples Region showed the most common prescribed ARV regimen at baseline was a combination of Stavudine + Lamivudine + Nevirapine (d4t-3TC-NVP) which accounted for 55.5 % of the initiation regimens [13]. However; the result contrasted with the study conducted at Zewditu memorial hospital was regimen AZT+3TC+NVP was the most initially prescribed regimen among 179(34%) of patients [11].

This may be as a result of the difference in drug-related information, availability of laboratory equipment and professional quality and competency towards prescribing laboratory tests, interpreting its results, and selecting specific drugs for each patient.

Gender distribution of the study which was 64.4% were females was consistent with the study conducted in Abidjan Cote d'Ivoire in which females accounts for 73% [8] and research conducted in South Africa and at Hawassa and Shashemene referral hospital in which they account for 210(69.8%) [10] and 69.29% [12] respectively. The study done at Tikur Anbessa has shown that females experienced a higher mortality rate than males [16]. This similarity may be due to regional similarity because in Sub Sahara Africa region, females are highly vulnerable to HIV infection.

According to the result of this study, the reason for changing the first initiated regimen was toxicity among 123(70.7%) of the study population.

This result is similar with study conducted in Southern India which accounts for 64% and research done in South Africa, at Zewditu memorial hospital and at Hawassa and Shashemene referral hospital in which it accounts among 134(44.8%) of patients, 97(81%) patients and 230(67.65%) of the study population respectively [7, 10, 11, 12]. Tuberculosis and pregnancy were the second and third cause for changing regimen as similar to a study conducted at Hawassa and Shashemene referral hospital. But this figure contrasted with other studies. The probable reason for this difference is tuberculosis accounts the first disease load in Nekemte town and gender distribution variation among the study population.

Despite the study conducted in India, Cote d'Ivoire, Malawi, and Brazil in this study cost, resistance, treatment failur, and intolerance are not a major problem for modification of first initiated regimen. This may be due to free ART provision since 2005 by American presidential fund, lack of continuous patient monitoring, and lack of viral load measuring device.

The most common toxicity observed during the study was skin rash in 28(22.8%) followed by peripheral Neuropathy and fat change each accounts for 25 (20.3%) of the study population. Anemia was the fourth reason for changing regimen. This result is consistent with the study conducted in southern India in which skin rash account for 66% of patients [7]. But in contrast to this study, the study conducted at Zawditu memorial hospital showed that anemia was the first types of observed toxicities in 42 (33.9%) patient [11].

The other studies conducted at Hawasa and Shashamne referral hospital showed peripheral neuropathy was the major type of toxicity among 84(36.52%) of patient [12]. The probable reason for this deference is most 179(34%) of patients at Zewditu memorial hospital were on AZT containing regimen which is cause for anemia [11] and deference in professional quality and competency on monitoring and reporting ADR and also majority 111(63.8.5%) of patients at Nekemte Hospital and Nekemte Health Center were on NVP contain regimen (D4T+3TC+NVP, AZT + 3TC+ NVP and TDF+3TC+NVP) which is the cause for skin rash. Skin rash was commonly seen in females, which accounts for 19(67.9%) of the figures.

Those participant aged between 26-49 years were highly vulnerable for this toxicity with 21(75%) of the figures. Regimen D4T+3TC+NVP contributes the highest proportion which 19 (67.9%) for skin rash toxicity followed by regimen TDF+3TC+NVP for 6(21.4%) of the participant because of their components NVP. Due to skin rash 19(69.7%) patients switched D4T+3TC+NVP to TDF +3TC+EFV and D4T+3TC+EFV and 6(21.4%) patients changed their regimen from TDF+3TC+ NVP to TDF +3TC+EFV.

Peripheral neuropathy was the second major observed toxicity and patients aged between 26-49 years, and females are highly vulnerable to these toxicities. D4T containing regimen D4T+3TC+ NVP and D4T+3TC+EFV contributes for all figures. Regimen D4T+3TC+NVP with 18(72%) and D4T+3TC+EFV with 7(28%) of patients. 25(14.4%) of study population changed their regimen from D4T containing to TDF containing regimen because of peripheral neuropathy.

Tuberculosis was the second reason for switching first initiated regimen next to toxicity. It was

observed on 20(11.5%) of the study population. Regimen D4T+3TC+NVP accounts for 11(55%) of the total figures followed by regimen AZT+3TC+NVP with 5(25%) of patients. A total of 20 (11.5%) of study population changed their regimen from NVP containing regimen to EFV containing regimen to reduce overlapping drug toxicity effect of NVP and anti-tuberculosis drug.

Prescribers in both health facility only focus changing NVP by EFV during the occurrence of tuberculosis cases but not seen other alternative provided by the national ART provisions guideline of the county this condition may aggravate irrational drug use and the chance of drug resistance. The occurrence of new pregnancy was the third leading cause for regimen and treatment modification. During the study, it accounts for 11 (6.4%) of the study population which is consistent with the study conducted at Zewditu hospital in which pregnancy account for 4(3%) of study population and study conducted at Hawasa and Shashemene referral hospital which accounts for (10.59%) of patients [11, 12]. But it contrasted with the study conducted in Abidjan, Cote d'Ivoire, and South Africa in which it accounts the second leading cause for regimen modification among 4.5% and 16 (5.4%) of patients respectively.

The probable reason for this difference may be the difference in proportions of female's patients at a stage of childbearing age and marital status of the patients. Because of teratogenicity effects of EFV 11 (6.3%) of the study population modified there regimen to non-EFV contains regimen during the study due to the occurrence of pregnancy.

According to the result of study duration of initial regimen was 188.4 days these result contrasted with research done in Malawi which was 16.3 month (489 days) [9] differences might be in professional competency in selecting appropriate drug type for specific patient during initiation of the regimen, patient level of adherence and availability and cost of the drug.

CONCLUSION: The major reason for regimen modification was toxicity, comorbidity (Tuberculosis) and pregnancy. From all toxicities reported, skin rash was the most common reason for modification of first initiated regimen. Majority of patients were on regimen D4T+3TC+NVP (D4T+3TC+NVP) even if it is highly associated with toxicity and it has longest duration of initial therapy.

ACKNOWLEDGEMENT: The authors would like to express due appreciation for all staffs of both ART clinics of Nekemte town for their cooperation and Wollega University for financial support.

CONFLICT OF INTEREST: Nil

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How to cite this article:
Birhanu S, Bussa Z, Gebre M and Addisu N: Rationale for changing initial highly active antiretroviral therapy (HAART) regimen among HIV/AIDS patients in West Ethiopia. Int J Life Sci & Rev 2015; 1(1): 13-19. doi: 10.13040/IJPSR.0975-8232.IJLSR.1(1).13-19.