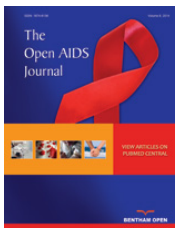

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RESEARCH ARTICLE

Reasons for Antiretroviral Treatment Change Among Adult HIVAIDS Patients at Nedjo General Hospital, Western Ethiopia

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Abstract:

Background:

Frequent change of Antiretroviral Treatment (ART) regimen is a challenging problem especially in a resource-limited setting like Ethiopia where treatment options are limited. This study was aimed to identify reasons for ART regimen change among adult HIV patients at Nedjo General Hospital (NGH).

Methods:

An institutional-based retrospective cross-sectional study was conducted at NGH by reviewing patient information cards from 2006 to 2016.

Results:

From a total of 117 included patients, 50.4% were females and the median (IQR) age of the patients was 28 (24-47) years. Majority of patients, 63 (53.9%) started their treatment at world health organization (WHO) clinical stage III (53.9%) and CD4 count of between 200-350 cells/mm3 (44.54%). At the beginning of ART, 56 (47.9%) patients were on a fixed-dose combination of stavudine-lamivudine-nevirapine (D4T/3TC/NVP). The single-drug substitutions were D4T (n = 63), NVP (n = 34), AZT (n =5), EFV (n = 2), and TDF (n = 1). Majority of the patients, 35(29.9%) switched their initial ART regimen after 3 years of regimen commencement. The common reasons reported for initial regimen change was availability of new drug 46 (39.3%) followed by toxicity/side effects 34 (29.2%). From all toxicities, peripheral neuropathy (47.1%) was the most common toxicity followed by rash (20.6%). After regimen change, 47 (40.2%) were received AZT+3TC+NVP.

Conclusion:

Availability of new drug and toxicity were the common reasons for regimen modifications. There should be updated guidelines, sustainable supply of affordable ART drugs, and effective laboratory materials to increase treatment success and minimize the toxicity of the drugs.

Keywords: ART, Regimen, ART change, HIV, Treatment modification, Nedjo, Ethiopia.

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1. INTRODUCTION

Human Immunodeficiency Virus (HIV) is an ongoing major global public health problem causing high morbidity and mortality [1, 2]. It is believed to kill more than 34 million lives so far, a huge percentage being in sub-Saharan Africa [2]. Antiretroviral therapies (ART) are the drugs for HIV AIDS treatment with no known cure yet today [3]. But markedly decreased the morbidity and mortality due to the virus which requires tolerable, affordable, and virologically potent regimens [1, 4]. ART has fundamentally changed the treatment of HIV and transformed this infection from a disease of high mortality to a chronic and medically managed disease [2]. The choice of first-line regimen should take into account not only international knowledge of the efficacy and tolerance of HIV drugs but also local specification of HIV disease (frequency of Tuberculosis (TB), HIV-2, and hepatitis B co-infection), drug tolerance, and pregnancy conditions [5]. Despite ARTs being of much help to the health of HIV AIDS patients, the issues of drug toxicities and complexities of current ART regimens has remained of great concern [2, 6]. Since, ART does not eradicate the virus, once started, patients generally remain on

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medications indefinitely [1, 3, 4].

The primary goals of ART are to maintain maximum suppression of the viral load as much as possible, which is achieved through properly regulated ART and rational treatment regimen switch [7]. Even though these medications inhibit viral replication, they may cause a number of adverse effects, which may end with treatment failure and/or regimen changes [3]. ART brings a complex series of choices; when to initiate therapy, what regimen to use, which class of drugs to use, when to change therapy, and which alternative drugs to use [8]. A switch in the antiretroviral regimen is often necessary [4, 9]. The rationale for treatment switch may be because of both acute and chronic toxicities, a sub-optimal regimen, concomitant clinical conditions, a desire for pregnancy, poor adherence, stock out of drugs, and treatment failure which includes when virological suppression is usually retained or reactive to virological rebound [4, 9 - 11]. Changes of multiple medications in ART regimen is commonly required simultaneously [2, 4]. Regimen change is also a major challenge for the sustainability of HIV treatment program [12]. Sometimes it may lead to ineffectiveness of ART medications [9] and diminish the clinical and immunological benefits of treatment [13].

In the past, different types of adverse drug reaction (ADR) or toxicities were the most common causes of initial regimen change [9, 10]. Toxicities starting from simple rash up to life-threatening adverse effects like hepatotoxicity, mitochondrial damage, and bone marrow toxicity create adherence and compliance problems [14]. When an adverse reaction occurs, the agent most likely to be responsible is usually deduced based on known toxic-effect profiles and clinical judgment [15].

Interactions between HIV and TB medications, overlapping medication toxicities and Immune Reconstitution Inflammatory Syndrome (IRIS) complicate the co-treatment of HIV and TB [16, 17]. There is a great concern regarding drug malabsorption and complex drug-drug interaction between anti-retroviral drugs and rifamycin, the key class of drugs in short-course TB treatment [18 - 20]. Because the rifamycin derivatives mostly rifampicin, can induce the hepatic Cytochrome P450 enzyme system, this results in decreased serum levels of ART drugs [21 - 23]. Pregnant women also experience serious toxic effects with more prolonged use of combinations of these drug regimens [24]. Increasing use of complex and potent ART combinations raises questions on the effect of exposure on pregnancy outcome [25]. A concern about these negative effects has led to a more conservative approach to the timing of initiation and monitoring of therapy to decrease the total exposure to drugs over time [8].

Frequent need for a change of ART regimens is a challenging problem especially in a resource-limited setting where treatment options are limited [1, 12]. Designing strategies to increase the durability of original regimen, improving the long term access and sustainability of HIV treatment program by optimizing the limited available combined anti-retroviral regimen is necessary [12, 26, 27]. In Ethiopia, nowadays there are a number of HIV infected patients [28]. Most patients tolerate their initial treatment regimens well after initiation. However, a significant number of patients' treatment regimens are modified for various reason; including drug toxicities, poor drug tolerability, drug-drug interactions, pregnancy, HIV-co morbidities especially TB, and treatment failure [29].

Data on causes and factors associated with ART drug regimen change are limited among HIV AIDS patients in Ethiopia. Thus this study was aimed to identify causes for ART regimen change among adult HIV patients at NGH.

2. MATERIALS AND METHODS

An institutional-based retrospective cross-sectional study was conducted by reviewing patient's information cards from 2006 to 2016 to assess reasons for ART regimen change. The study was carried out during the period of March to April, 2016 at NGH, western Ethiopia located 518 km from Addis Ababa. All adult information record cards of HIV/AIDS patients on ART were source population and all adult information record cards of HIV AIDS patients to whom the regimens were changed were study population.

2.1. Eligibility Criteria

Inclusion Criteria: All HIV adult patients (>15years) who had been on any ART for at least one year and have switched from their initial regimen due to different reasons were included in the study.

Exclusion Criteria HIV infected adults who had changed their regimen more than one time, incomplete patient cards, and deceased patients were excluded.

2.2. Sample Size and Sampling Technique

A total of 1,036 patients were on treatment at the ART clinic of NGH from 2006 to 2016. Out of these, 117 patients who remained on ART for at least one year had switched their initial regimen. So conveniently, all the 117 patient information cards that had undergone switching their ART regimen were included in the final analysis.

2.3. Data Collection Tools and Process

The available information on the patient's cards had been first identified and appropriate data extraction format was developed based on the objectives of the study. Then the data was collected by two nurses and one pharmacist by reviewing patient's charts which was retrieved using the patient registration number found in the database of the electronic system. The Pretested data collection format contains socio-demographic data as well as clinical information such as unique ART numbers, date when treatment started, baseline CD-4 count, WHO clinical stage, medications at start, causes for regimen change, duration of initial therapy, types of toxicities, type of treatment failure, and changed regimen. Reason for initial regimen change was the independent variable or outcome of the study.

2.4. Data Quality Control and Management

The clarity and completeness checkup of the data collection format and the whole method was pre-tested on

randomly selected patients' before the actual data collection was started. Possible corrections and modification were carried out on the data collection format based on available data and review of previous literature. Quality of data was maintained by giving intensive training for data collectors regarding the objective of the study and how to retrieve as well as extract data from patient's records. Completed data collection tools were checked regularly for completeness of information.

2.5. Data Processing and Analysis

After the data was collected, the finding was analyzed using SPSS version 20. Descriptive statistics of the findings like sociodemographic variables, WHO clinical stage, initial CD4 count, ART regimen at ART initiation, reasons for ART regimen change, and duration of initial therapy were presented by tables.

2.6. Operational Definitions

Functional status: Classified into the following categories [30]:

- *Working:* the ability to perform usual work in and out of the house.
- *Ambulatory*: the ability to perform activities of daily living.
- *Bedridden:* not able to perform activities of daily living.

Initial regimen change: a switch or substitution of at least one drug from the original ART regimen [12].

Regimen change: an event, through the follow-up period was ascertained retrospectively when the patients recorded as changed their regimen and started other ART drugs [12].

3. RESULTS

3.1. Baseline Socio-Demographic Characteristics

From a total of 117 patients, 50.4% were females and the median (IQR) age was 28 (24-47) years. Majority of the patients 56(47.9%) were below the age of 30 years and only 13.7% were illiterate (Table **1**).

3.2. Baseline Clinical and Immunological Characteristics

From the patients changed their regimen, majority of the patient's weight was less than 45 kg consisting of 43 (36.8%) at the start and at regimen change, most of the patient weight was from 45 to 60 kg comprising 50 (42.7%) patients. Majority of patients, 63 (53.9%) started their treatment at WHO clinical stage III (53.9%) and CD4 count of between 200-350 cells/mm3 (44.54%). At the time of regimen change, majority of the patients were in working functional status, increased CD4 count, and lower WHO clinical stage (Table **2**).

3.3. Initial Regimen and Duration on Initial ART before Regimen Change

At the beginning of ART, all 117 patients initiated with two nucleoside reverse transcriptase inhibitors (NRTI) plus one Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI). Majority of (47.9%) patients were on D4T/3TC/NVP followed by 16 (13.7%) were on D4T/3TC/EFV, 30 (25.6%) were on AZT/ 3TC/NVP, 6 (5.1%) were on AZT+3TC+EFV, 6 (5.1%) were on TDF+3TC+NVP, and 3 (2.6%) were on TDF+3TC+EFV. Majority of ART modifications were with single-drug substitutions. The single-drug substitutions were D4T (n = 63), NVP (n = 34), AZT (n =5), EFV (n = 2), and TDF (n = 1).

Table 1. Baseline Socio-demographic characteristics of patients on ART follow up at NGH from 2006 to 2016.

Variables	Classification	Frequency (%)
Gender	Female	59 (50.4%)
	Male	58 (49.6%)
Age (years)	15-30	56 (47.9%)
	31-45	52 (44.4%)
	>45	9 (7.7%)
Educational Status	Illiterate	16 (13.7%)
	Primary	45 (38.5%)
	Secondary	39 (33.3%)
	College or above	17 (14.5%)
Marital Status	Single	17 (14.5%)
	Married	87 (74.4%)
	Divorced	12 (10.3%)
	Widowed	1 (0.8%)

Majority of the patients, 35(29.9%) switched their initial ART regimen 3 years (156 weeks) after start of initial regimen. Out of the 56 patients who were on D4T+3TC+NVP, most of them (71.4%) remained on the initial treatment for more than 156 weeks (Table **3**).

3.4. Reasons for Regimen Change and Effect of Toxicity

The common reason reported for modification of initial regimens was availability of new drug 46 (39.3%), followed by toxicity/side effects 34 (29.2%), tuberculosis 21 (17.9%), treatment failure 12 (10.3%), pregnancy 3 (2.6%), and drug stock out 1(0.9%). From the fixed-dose combination of D4T+3TC+NVP, modification was made due to new drug available in place of D4T 46(39.3%) and toxicity of D4T comprising 16 (13.7%) patients. Drug out of stock or drug unavailability was the reason for initial regimen change in one patient due to AZT+3TC+NVP. The rates of TB-related drug substitutions were very high (seen in 20 patient) for nevirapine and occurred in one patient for stavudine containing regimen. The rate of ART modification due to the initiation of a rifampicin-based anti-tuberculosis treatment in the overall population was 20(17.09%) due to drug interaction with nevirapine (Table **4**).

From 34 patients changed regimen due to toxicity, the majority of them were due to stavudine containing regimen 16 (47.1%) followed by nevirapine containing regimen 10 (29.4%). From all toxicities, peripheral neuropathy (47.1%) was the most common followed by rash (20.6%) and anemia (14.7%). Stavudine containing regimens accounted for 100% of the peripheral neuropathy observed in this study, while EFV containing regimens accounted for 100% of the CNS disturbances (Table **5**).

Table 2. Baseline and at regimen change of clinical and immunological characteristics of patients on follow up at NGH from 2006 to 2016.

Characteristics	Variable	Baseline n(%)	At Regimen Change n (%)
Weight (kg)	<45	43 (36.8%)	31 (26.5%)
	46-60	41 (35%)	50 (42.7%)
	>60	33 (28.2%)	36 (30.8%)
Functional status	working	75 (64.1%)	101 (86.3%)
	Ambulatory	35 (29.9%)	10 (8.6%)
	Bed ridden	7 (6%)	6 (5.1%)
CD4 count (Cells/mm^3)	<50	8 (6.8%)	6 (5.1%0
	50-200	48 (41.1%)	25 (21.4%)
	200-350	52 (44.4%)	30 (25.6%)
	350-500	9 (7.7%)	13 (11.1%)
	>500	-	29 (24.8%)
	Refused	-	3 (2.6%)
	Machine problem	-	11 (9.4%)
WHO clinical stage	I	21 (17.9%)	39 (33.3%)
-	II	25 (21.4%)	34(29.1%)
-	III	63 (53.9%)	41 (35.0%)
-	IV	8(6.8%)	3 (2.6%)

Table 3. Initial ART regimen and duration on initial ART before switch at NGH, ART department from 2006 to 2016.

Initial Regimen	<12 Weeks	12-26 Weeks	26-52 Weeks	52-104 Weeks	104-156 Weeks	Above 156 Weeks	Total
D4T+3TC+NVP	3 (18.8%)	6 (42.9%)	4 (26.7%)	4 (44.4%)	14 (50%)	25 (71.4%)	56 (47.9%)
AZT+3TC+NVP	10 (62.5%)	5 (35.7%)	5 (33.3%)	2 (22.2%)	6 (21.4%)	2 (5.7%)	30 (25.6%)
D4T+3TC+EFV	-	-	2 (13.3%)	1 (11.1%)	7 (25%)	6 (17.1%)	16 (13.7%)
AZT+3TC+EFV	1 (6.2%)	1 (7.1%)	1 (6.7%)	1 (11.1%	1 (3.6%)	1 (2.9%)	6 (5.1%)
TDF+3TC+NVP	0 (0%)	2 (14.3%)	2 (13.3%)	1 (11.1%)	-	1 (2.9%)	6 (5.1%)
TDF+3TC+EFV	2 (12.5%)	-	1 (6.7%)	-	-	-	3 (2.6%)
Total	16 (13.7%)	14 (12.0%)	15 (12.8%)	9 (7.7%)	28 (23.9%)	35 (29.9%)	117 (100%)

Table 4. Types of drug and reason for initial ART regimen change at NGH from 2006 to 2016.

Start Regimen	Toxicity	Treatment Failure	Tuberculosis	Pregnancy	New Drug Available	Drug Out of Stock	Total
D4T+3TC+NVP	13 (11.1%)	3 (2.6%)	4 (3.4%)	-	36 (30.8%)	-	56 (47.9%)
D4T+3TC+EFV	3 (2.6%)	2 (1.7%)	1 (0.9%)	-	10 (8.5%)	-	30 (25.6%)
AZT+3TC+NVP	14 (12%)	2 (1.7%)	11 (9.4%)	2 (1.7%)	0 (0%)	1 (0.9%)	16 (13.7%)
AZT+3TC+EFV	1 (0.9%)	5 (4.3%)	-	-	-	-	6 (5.1%)
TDF+3TC+EFV	3 (2.6%)	-	-	-	-	-	6 (5.1%)
TDF+3TC+NVP	0 (0%)	0 (0%)	5 (4.2%)	1 (0.9%)	-	-	3 (2.6%)
Total	34 (29.2%)	12 (10.3%	21 (17.9%)	3 (2.6%)	46 (39.3%	1 (0.9%	117(100%)

Table 5. Toxicities reported as a reason for initial ART change at NGH from 2006 to 2016.

Toxicity	Start Regimen in which Toxicity Occurred	Responsible Medication	Frequency	Percentage (%)
Peripheral neuropathy	D4T+3TC+NVP	DT4	13	47.1%
	D4T+3TC+EFV	D4T	3	
Severe rash	AZT+3TC+NVP	NVP	7	20.6%
Anemia	AZT+3TC+NVP	AZT	4	14.7%
	AZT+3TC+EFV	AZT	1	

(Table 5) contd.....

Toxicity	Start Regimen in which Toxicity Occurred	Responsible Medication	Frequency	Percentage (%)
Hepatotoxicity	AZT+3TC+NVP	NVP	3	8.8%
CNS complication	TDF+3TC+EFV	EFV	2	5.9%
Nephrotoxicity	TDF+3TC+EFV	TDF	1	2.9%

3.5. Patterns of ART Switch

After treatment change, 47 (40.2%) received AZT+3TC+NVP and 35 (29.9%) patients received AZT+3TC+EFV regimen due to new guideline launched. For 20 patients nevirapine was changed to efavirenz due to the initiation of a rifampicin-based anti-tuberculosis treatment. The number of patients whose ART medications changed to TDF+3TC+EFV was 14 (12.0%) (Table **6**).

Table 6. Patterns of ART switch of HIVAIDS patients who changed their ART regimen in NGH from 2006 to 2016.

Current regimen after switch	Frequency (n)	Percentage (%)
D4T+3TC+NVP	3	2.6%
D4T+3TC+EFV	1	0.9%
AZT+3TC+NVP	47	40.2%
AZT+3TC+EFV	35	29.9%
TDF+3TC+EFV	14	12.0%
TDF+3TC+NVP	5	4.3%
TDF+3TC+Kaletra (Lopinavir/ritonavir)	12	10.3%

The rate of treatment modification due to pregnancy was 2.6%. From these 4 pregnant patients; 2 were on D4T+3TC+EFV and became pregnant after 98 weeks of treatment (changed from D4T+3TC+EFV to AZT+3TC+EFV due to new drug available) and (changed from D4T+3TC+EFV to TDF+3TC+EFV due to the toxicity of stavudine). The other one which was on AZT+3TC+NVP and 24 weeks switched to AZT+3TC+EFV due to anti TB drug-drug interaction. Finally the fourth one, due to peripheral neuropathy of D4T at 24 weeks of treatment, D4T+3TC+NVP regimen was changed to TDF+3TC+EFV.

4. DISCUSSION

This study finding focused on treatment modification of 117 patients who have started combined ART as a part of routine clinical, immunological and virological care, was almost comparable number of female and male patients have changed their regimen. The median (IQR) age was 28 (24-47) years and majority of the patients (47.9%) were below the age of 30 years that complies with previous finding by Meseret Wube *et al*. in Nekemte, Ethiopia [8]. Majority of patients, (53.9%) started their treatment at WHO clinical stage III and CD4 count of between 200-350 cells/mm3 (44.54%). This correlates with previous studies reporting that at initial majority of the patients where at WHO clinical stage III and CD4 count below 350 cells/mm3 [8, 12].

Majority of the patients, (47.9%) were on D4T/3TC/NVP at the beginning of ART which complies with previous studies [3, 4, 8, 26, 31]. But a study by Anlay *et al*. at the University of Gondar referral hospital reported that the predominant ART regimen initially prescribed for the patients was combination of zidovudine, lamivudine, and nevirapine (AZT-3TC-NVP) [12]. The difference was due to launching of new guideline by WHO favoring AZT and TDF in place of D4T.

Toxicity (29.2%) was one of the common reason for regimen modification next to the new drug available. However, the rate was lower as compared to previous studies reported in other areas like Mbabane government hospital in Swaziland (76.6%) [32], Kenya (66.3%) [26], North-western Tanzania 48.18%) [1], two hospitals and one health center Addis Ababa (65%) [23], Mekele (75.8%) [31], Fiche hospital (72.73%) [3], southern Ethiopia (67.65%) [33], south-west Ethiopia (58.96%) [30] and Nekemte (80.3%) [8].

Stavudine, accounted for the majority of toxicity (peripheral neuropathy with numbness) until it was phased out from the market. Previous studies also reported that peripheral neuropathy was the main reason for toxicity responsible for initial regimen change [2, 4, 34]. But according to a study by Assefa Desta *et al*. in Fitche reported that lipoatrophy [3], as well as a study by Mekonnen *et al*., fat changes were the common toxicity 82 (61.19%) [30]. Stavudine is associated with high toxicity profile mainly as acute lactic acidosis and long term mitochondrial toxicities with risk increasing with time on treatment [26]. Unlike previous studies majority of patients those changed or switched their regimen with stavudine containing regimen was due to the availability of the new drug. But this availability of new guideline by itself was due to stavudine severe toxicity. This has consequently led to the recent WHO guidelines recommending D4T to be phase-out of market and the subsequent replacement by either TDF or AZT which have better safety profiles [35].

In this study, the patterns of switch to TDF in the first-line regimen was observed to have a greater reduction in the risk of toxicity. This is an indication of its better safety profile as has been reported in Mekele referral hospital in which majority of patients were on TDF (48.7%) based regimens [31]. Additionally, initial efavirenz-based regimens were less likely to be changed because of relatively the lowest toxicity for change. However, the increased risk for change of efavirenz-based regimens was pronounced due to central nervous system complication.

ART treatment regimen modification due to failure was labeled 10.3% of the studied population which was higher as compared to studies at two hospitals in Addis Ababa (3%) [23], southern Ethiopia (2.65%) [33], and Nekemte referral hospital (2.8%) [8]. This might suggest that a moderate efficacy of first-line drugs or treatment failure in our finding at start period or the lack of proper management to monitor treatment failure. But, it was relatively low as compared to a study done in fiche hospital 14.2% [3] due to lack of adequate viral load laboratory determination in Fitche hospital during the study period.

TB accounted for 17.95% patient's treatment modification which was relatively close to the studies in Mbabane

government hospital in Swaziland (13.1%) [32], two hospitals and one health center in Addis Ababa 25% [4], Northwestern Tanzania 44(20.0%) [1], Mekele referral hospital (14%) [31], and two hospitals in southern Ethiopia (19.11%) [33]. But it higher as compared to studies in Coitedevoir 2.5% [36] and in Nekemte by Wube *et al*. 5.6% [8]. But the rate of TB was extremely low as compared to a study at Nekemte by Bokore *et al*. (57%) [2]. The reason for such ART treatment modification due to TB was due to NVP potential drug interaction with rifampicin. Rifampicin decreases the therapeutic level of NVP up to 20-55% by inducing liver enzyme (CYP3A4) which made situation preferable for the use of EFV in place of it during combined use of NVP and anti TB regimen containing rifampicin [2, 37 - 39].

In addition to NVP, D4T was relatively associated with risk of combined ART modification in one patient due to rifampicin based anti TB medication. This was due to the reported increased risk of peripheral neuropathy when both isoniazid used together with stavudine [40]. But none of the discussed literature; those in Coitedevoir [37], Kenya [26], Addis Ababa [4], southern Ethiopia [33], and Nekemte [8] indicated the extent at which D4T was changed due to anti-TB and ART drugs overlapping toxicity. Rates for treatment modification was highest, (61.5%) among persons initiating D4T combined regimen which was higher than the study done in Mekele referral hospital (45.4%) [31]. From the non-nucleoside reverse transcriptase inhibitors (NNRTI's), the rate of combined ART modification was higher with NVP, 33(28.2%) as compared to EFV, 2(1.7%) which was comparable with the study in Mekele where NVP change comprised of (24.1%) and EFV change accounted (5.1%) [31].

Treatment failure was given as the reason for the change in 12 (10.33%) of patients in our study finding. This occurred mainly due to D4T and AZT containing regimens, similar to previous studies in Ethiopia by Jima *et al*. in Addis Ababa and Mekonnen *et al*. in southwest Ethiopia [4, 30]. But higher rate of treatment failure as reason of initial regimen change was reported in northwestern Tanzania by Daniel *et al*. accounting 70(31.82%) [1]. The treatment failure was confirmed based on clinical, immunological and virological data's. Change of the entire regimen from first-line to second-line is required in case of treatment failure. With this case, 12(10.3%) patients initial regimen was switched to TDF+3TC+Kaletra. In order to increase likelihood of treatment success as well as to reduce the risk of cross-resistance the new second-line treatment selected should involve drugs that keep activity against the patient's virus strain and should preferably include at least three new drugs, one or more from new classes of drugs [2, 41].

There was 2.6% change due to pregnancy=related factors (planning pregnancy or being pregnant), which was somewhat close finding to study in Coitedevoir (4.5%) [36], southwest Ethiopia (3.96%) [30], Mbabane government (6.6%) [32], and Nekemte (6.3%) [8]. But it was lower than the study in southern Ethiopia (10.59%) [33] and relatively higher when compared to study done in Mekele referral hospital (0.6%) [31]. Different results of literature discussed that the substitution of Nevirapine (NVP) in the place of Efavirenz (EFV) especially in the first trimester is necessary [4, 31 - 33, 36]. This implies that the above studies were done by using previously written guidelines which described the issue of teratogenicity of EFV in the first trimester. But, today a further updated analysis and different established guidelines showed that the safety of EFV and there was concern about the high risk of NVP as compared to EFV especially in pregnant women with CD4 > 250 cell/mm^3 [35, 39].

The ART regimen of the majority of the patients 82(70.1%) was changed to AZT based regimens. This was unlike the study by Bokore *et al*. [2] in Nekemte where majority of the patients 168(69.14%) changed to TDF based regimen. This was due to the availability of the drug associated with the modified guideline.

The result of this study has a lot of contribution to the care of People Living With HIV (PLWH). Common reasons to consider switching antiretroviral therapy in the setting of virologic suppression include managing or preventing short-term or long-term adverse effects, high pill burden, difficulties with food requirements, or problematic drug interactions as well as improved convenience or tolerability than for drug resistance. This helps to strengthen adherence level, proper suppression of the virus and adopt benchmarking programs such as a linkage-case-management to enhance ART linkage and retention. New drugs that combine excellent potency with greater convenience, safety, and tolerability make lifelong viral suppression achievable and reduce the risk of viral resistance. Regimen change could be an option for management of toxicities and reduce the risk of treatment failure; however, it should be undertaken considering the risk of loss of future treatment options. Some regimen changes were attributable to failure of either hospital supply system or patient-related factors which would have been prevented considering limited treatment options we currently have. This is motivational messaging focusing on the known long-term health, longevity, and prevention benefits of achieving viral suppression through adherence and practical strategies.

4.1. Limitation of the Study

The findings of this study were associated with some limitations. The cross-sectional study design might not allow for a direct investigation of causal relationship between the factors studied and the outcome of interest. Additionally, lack of appropriately filled patient information card, small sample size and limited number of variables again may limit interpretation of the factors related to regimen change. Some of previously studied variables such as prevalence of hepatitis B virus co-infection were missing and may have acted as confounding factors. Additionally, this study was limited only to one site, which might be difficult to generalize for majority of the communities. In another case, the longtime of enrolment as ART has changed dramatically over the last few years, including reasons for discontinuation. This has major implications as there might be clusters of reasons for discontinuation within the timeframe and some of the results like availability of the new drug might not be applicable to today's situation anymore. Another weakness of the study was the cumulative analysis of patients who discontinued for actual reasons like side effects versus those who were changed

because of new guidelines. Clinically, that was two completely different situations unless the patient changed for guideline updates or new drug availability also suffered from side effects. But since our study was retrospective study, we received the recorded data on the patient's history chart. Finally, the study did not consider patients who have changed their regimen more than one time. Since our aim was single shot study, to avoid overestimation of reasons for regimen change which may cause potential bias.

CONCLUSION

In conclusion, the result of this study indicated the common reason for modification of initial regimens was new drug available followed by the toxicity of the drugs. Peripheral neuropathy was the leading toxicity reported as the cause for ART initial regimen modification. The highest rate of regimen switching was carried out among patients initiating treatment with a fixed-dose combination of D4T/3TC/NVP. Nevirapine was associated with toxicity in pregnant women's and drug-drug interaction with anti-TB drugs which obligate pregnant women on NVP containing regimen and patient on anti TB containing rifampicin regimen to change to EFV containing regimens. Tuberculosis was the only co-morbidity disease reported in this study and all patients who switched were due to occurrence of tuberculosis after starting ART drugs. Based on the above result and discussion done, to increase treatment success and minimize toxicity of the drugs the following recommendations were forwarded:

- Since, pharmacotherapy is dynamic for any modification to be done by prescribers there should be updated guideline and followed properly. As much as possible, prescribers should stick to the national antiretroviral drug use guidelines for the management and follow up of patients. Additionally, they should know initial ART regimen, reason for change, and select the correct regimen for the patients (*For all trained and responsible health professionals*).
- There should be a sustainable supply of affordable ART drugs and basic essential drugs to treat opportunistic infection as well as enough, good and well effective laboratory equipment and laboratory results at the time of start and change of regimen. As well as the national policymakers should update the guidelines timely (*For Nedjo General Hospital and Ethiopian Ministry of health).*
- There should be cooperated well-trained health professionals from different sectors and specialties including clinical pharmacists in order to select the right medication for the right patient at a right time by identifying the first and alternative drugs to prevent any occurrence of side effects, non-adherence, and wrong prescription for the patient *(for Nedjo General Hospital).*
- To increase adherence, proper suppression of the virus, and prevention of adverse drug reaction, the patient with the virus should use the drugs properly according to the advice given by trained health professionals. Additionally, patient should be evaluated regularly after a treatment change to assess for potential concerns with the new regimen, medication tolerance and to assess the effectiveness *(for patients).*
- At the national level, vast longitudinal studies of ART utilization and reasons for regimen change should be carried out to help drug suppliers and policymakers to improve and solve the problem (*for researchers*).

LIST OF ABBREVIATIONS

3TC	=	Lamivudine
AIDS	=	Acquired Immune Deficiency Syndrome
ART	=	Anti-Retroviral Treatment
D4T	=	Stavudine
CYP450	=	Cytochrome p450
EFV	=	Efavirenz; HIV: Human Immune Deficiency Virus
NGH	=	Nedjo General Hospital
NNRTI	=	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	=	Nucleoside Reverse Transcriptase Inhibitor
NVP	=	Nevirapine
PI	=	Protease Inhibitor
TDF	=	Tenofovir
TB	=	Tuberculosis
WHO	=	World Health Organization
ZDV/AZT	=	Zidovudine

AUTHORS' CONTRIBUTIONS

GF contributed to the design of the study, analysis, interpretation, and write up of the manuscript. LB made the supervision of the study, manuscript writing, and interpretation of the data. HG contributed to the design of the study and edition of the manuscript. All authors critically revised the manuscript and have approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical clearance was obtained from the Institutional Review Board (IRB) of Wollega University, Ethiopia with reference number of WUPharm96/2016.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that supports the findings of this study are available from the corresponding author upon [GF] reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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