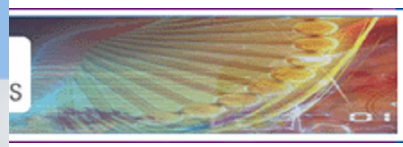

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The Reason for Regimen Change Among HIV/AIDS Patients Initiated on First Line Highly Active Antiretroviral Therapy in Southern Ethiopia

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Abstract

Background:

Highly active antiretroviral therapy (HAART) has markedly decreased the morbidity and mortality due to HIV disease. However, toxicities, comorbidity, pregnancy, and treatment failure, among others, would result in frequent initial HAART regimen change.

Aim:

The study was designed to assess the causes of initial highly active antiretroviral therapeutic regimen changes among patients on HAART.

Materials and Methods:

The study was conducted using a retrospective institution-based study, by reviewing the patient information sheet and physician diagnosis cards. Patient cards that showed a change in the initial treatment regimen were assessed and analyzed, to identify the common reason that resulted in a change from the initial treatment regimen. The data was analyzed using SPSS version 16.0.

Results:

A total of 340 patient cards were assessed. The majority of the patients (69.29%) were females. The most common first regimen, before the first switch, was stavudine / lamivudine / nevirapine (D4T/3TC/NVP) (54.70%) and stavudine / lamivudine / Efavirenz (D4T/3TC/EFV) (20.88%). The main reasons for modification were toxicity, comorbidity, pregnancy, and treatment failure. The main types of toxicities observed were peripheral neuropathy (36.52%), rash (17.83%), and anemia (17.39%).

Conclusion:

Toxicity was the main reason for the modification of initial HAART among the study population. Efavirenz-based regimens had the lowest hazard for change relatively, except in pregnancy-related cases.

Keywords: Ethiopia, HAART, Initial regimen, Switch, Toxicity

killed more than 25 million people since the first
f anti retroviral therapy (ART), the overall acquired
orbidity and mortality have been markedly decreased.
However, it is still high in sub-Saharan Africa,[4,5] including Ethiopia.[6]

There are now more than 16 approved therapeutic agents for infection with HIV. Approved antiretroviral (ARV) drugs include the nucleoside analogs (NRTIs), a nucleotide analog, the non-nucleoside analogs (NNRTIs), and protease inhibitors (PIs). Entry inhibitors and integrase inhibitors are also currently in use.[7–9] However, these advances have not been without their cost in terms of drug-resistance and side effects.[7]

The first-line antiretroviral regimen in Ethiopia included a triple therapy, including either two NRTIs and one PI or an NNRTI, or a triple therapy included three NRTIs. These were D4T plus 3TC plus EFV, or D4T plus 3Tc plus NVP, or zidovudine (ZDV) plus 3TC plus EFV or ZDV plus 3TC plus NVP.[10,11] A treatment switch, may be either because of the risk of long-term toxicity, poor adherence, a desire for pregnancy, a sub-optimal regimen, comorbidity with other chronic diseases or virological failure[12–14]

With the scaling up access to ART in Ethiopia, there is an opportunity to better understand the benefits and drawbacks of these regimens. Data on the modification of the initial highly active antiretroviral therapy are scarce among Ethiopia patients. The aim of this study is, therefore, to assess the causes of the initial highly active antiretroviral therapeutic regimen changes among patients on ART in Ethiopia.

Materials and Methods

The study was approved by the Ethics Committee of the Jimma University. The confidentiality of the data obtained was assured and no disclosure was made of any name of the patients, the healthcare provider or drug product in relation to the finding.

Study setting

The study was conducted from January 15 to March 5, 2010, at two hospitals in South Ethiopia; the Hawassa Referral Hospital and the Shashemene Referral Hospital. The ART Clinics in both the study areas were one of the ART sites in Ethiopia, which started providing ART service from 2006, and were staffed with health professionals trained in ART treatment and adherence counseling services.

Study design

A retrospective institution-based cross-sectional study by reviewing the patient information sheet and physician diagnosis cards was conducted, to assess the initial HAART regimen changes. A data collection format was used to collect data on the demographic conditions, the starting and changing regimens, duration of the initial therapy, CD4 count, World Health Organization (WHO) stage of the disease, and reasons for changing the regimen.

Data collection

Prior to the start of actual data collection, the data collection format and the whole method was pre-tested on randomly selected patient clinical records, at the ART Clinic of the Jimma University Specialized Hospital, to ensure their completeness. The data was collected using a questionnaire containing sociodemographic variables and patient information, and clinical information and ART information, such as, the CD4 count at the start (CD4 cell count/NL), WHO stage at the start of treatment, initial (starting) regimen, date on which treatment was started, date of the initial ARV drug regimen switch, duration of the initial ARV therapy before first switch, regimen switched to, and reason

failure was included.

e of new opportunistic infection (TB, candidacies, pneumonia, herpes simplex, toxoplasmosis, etc,), immunological failure (a drop of CD4 cell count below baseline pretreatment level) or virology failure (a virological rebound after complete suppression). Toxicity is defined as the occurrence of adverse events such as diarrhea, nausea, vomiting, anemia, rash, fatigue, peripheral neuropathy, lipidostrophy, metabolic disturbances or any other related to HAART.

Data analysis

The collected data was cleared, categorized, and coded and were entered in Epi Info Version 6.0. All data collected were then analyzed using the Statistical Package for the Social Sciences (SPSS), version 16.0 software.

Results

Sociodemographic distribution of the study population

Records of 340 patients who had changed their initial antiretroviral treatment regimen at Hawassa Referral Hospital and Shashemene Referral Hospital were assessed. The mean age of the patients was 38.6±7 (SD=±7) years. Over half (54.11%) of them were single. Orthodox Christianity (47.06%) was the most common religion found in patients who were on ART followed by Muslims (20.88%). With regard to the educational background, a majority of the patients (37.06%) was illiterate [Table 1].

A majority of the patients (53.53%) had their initiation of treatment at clinical WHO stage III, while (18.53%) at stage II, (16.47%) at stage IV, and (6.18%) at stage I. For 5.29% of the patients, the clinical stage was not recorded. One hundred and nineteen (35%) of them had CD_4 count in the range of 101-200 cells/mm^3 , 20.89% had a CD_4 count greater than 200 cells/mm^3 , 20.30% were in the range of 51-100 cells/mm^3 , 19.11% were less than 50 cells/mm3, and for 4.70% of the patients the initial CD_4 count was not recorded. A majority of the patients (54.70%) were on D4T/3TC/NVP at the beginning of the antiretroviral treatment and the rest were on D4T/3TC/EFV (20.88%), AZT/3TC/NVP (16.17%) and AZT/3TC/EFV (8.25%).

The main reason reported for modification of treatment regimen was toxicity among 230(67.65%) of the patients, comorbidity in 65(19.11%), pregnancy in 36(10.59), and treatment failure in nine (2.65%). From all the toxicities reported, peripheral neuropathy, which accounted for 36.5% of the toxicities, was the most common, followed by rash (17.90%) and anemia (17.40%) [Table 2]. Peripheral neuropathy was due to stavudine (D4T)-containing regimens of D4T/3TC/NVP (77.38%) and D4T/3TC/EFV (22.62%), whereas, rash was due to nevirapine (NVP)-containing regimens of D4T/3TC/NVP, in 70.73% of the patients, and due to AZT/3TC/NVP in 29.27% of them. Anemia was reported due to zidovidine (AZT) containing regimens of AZT/3TC/NVP (57.5%) and AZT/3TC/EFV (42.5%). The central nervous system (CNS) toxicities observed were dizziness, nightmare, and sleep disturbance, which were all reported due to efavirenz (EFV)-containing regimens of D4T/3TC/EFV (81.58%) and AZT/3TC/EFV (18.42%). Lipodystrophy was due to stavudine (D4T)-containing regimens of D4T/3TC/NVP (75%) and D4T/3TC/EFV (25%). The other toxicities observed were nausea and vomiting (G1 toxicities) due to zidovidine (AZT)-containing regimens of AZT/3TC/NVP (36.36%) and AZT/3TC/EFV (27.27%), and hepatoxicity mainly due to nevarapine (NVP)-containing regimens of

D4T/3TC/NVP and the remaining due to D4T/3TC/EFV, AZT/3TC/NVP, and hows weeks of stay on the initial antiretroviral treatment versus treatment regimen and reasons for modification. The majority of the patients (67.0%) modified their initial treatment regimen within six months of the start of taking medications. Among 230 patients who had modified due to toxicity, 63(27.40%) patients switched in the first three months (start–12 weeks), 87(37.83%) switched in the 12–26 week range, and 47(20.43%) switched in the 26-52 week range [Table 4].

Discussion

The rationale for treatment switch can be due to risk of toxicity, poor adherence, a desire for pregnancy, treatment failure, or comorbidity.[15] A majority of the patients were on the D4T-based regime of D4T/3TC/NVP (54.70%). Another study reported 63%.[16] However, the study was not in agreement with the other study,[12] where the AZT/3TC/EFV (44%) regimen accounted for a majority of the patients' initial HAART regimen. The probable reason was the difference in patient conditions, comorbid situations or contraindications.

Similar to several other studies,[12,16,17–22] the most predictable cause for ARV switching, in the present study, was toxicity (67.65%), with significant heterogeneity in the distribution of adverse events. The patients were with a more advanced disease at the baseline, which could necessitate higher rates of regimen change/discontinuation due to adverse events. From all the toxicities reported, peripheral neuropathy was the most common reason for modification, unlike the research done in Peru.[22] This was most probably the reason why most of the patients in this study were on a D4T-based regimen of D4T/3TC/NVP and D4T/3TC/EFV, and were initially with advanced HIV infection.

A study done in Peru reported anemia as a main reason for discontinuation (68%), and associated this finding with the use of standard 600 mg ZDV in low-weight patients.[23] In the current study, the distribution of change in regimen due to skin rash and anemia were the second and third most common reasons for modification, respectively. Rash was mainly due to the NVP-containing regimen and anemia was due to the AZT-containing regimen. Unlike the other study,[23] the low rates of HAART change due to anemia, in this study, could be due to the lack of adequate baseline anemia assessment and the fact that no close monitoring of anemia was done at the study site.

Comorbidities in patients with advanced disease and concurrent treatments for opportunistic diseases could affect antiretroviral tolerance and thereby increase the risk of toxicities.[22] Comorbidity was the other cause for HAART switch. Tuberculosis (19.1%) was the only comorbidity disease reported in this study. This was consistent with the study in UK[12] and Coite d'lvoire.[24] Due to Tuberculosis, (17.3%) a switch was made from D4T/3TC/NVP to D4T/3TC/EFV and 1.8% of the patients switched from the NVP-based regimen to an EFV-based regimen. The probable suggestion for this NVP switch to EFV was the overlapping drug toxicity of NVP with anti-TB drugs, which was hepatotoxicity, and the potential for drug interaction, as NVP was a CYP 3A4 enzyme inducer.

Efavirenz-based regimens had the lowest hazard for change relatively. However, the increased hazard for change of efavirenz-based regimens was pronounced during pregnancy or when planning pregnancy. Planning pregnancy or being pregnant was the third major

study. This replicated the other to the teratogenic effect of EFV, which ster of pregnancy.

ients were more likely to change the therapy shortly after HAART initiation, because of adverse events, rather than treatment failure. Treatment failure was given as the reason for change in 2.6% of the patients in the current study. Some studies,[12,16,17,24] however, reported higher treatment failure as the reason for a regimen switch. In the study in Coite d'IVoure, treatment failure was observed in 12.4% of the patients[24] and according to the study in India, treatment failure accounted for 14% of the reasons for modifying therapy.[16] According to the study in Uganda,[17] immunological failure alone predicated virological failure in 56% 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, and on the occurrence of opportunistic infection in the study setting of this study.

Cost was one of the major reasons for discontinuation and modification of ARV drugs according to the study conducted in India (64%)[16] and Uganda (23%).[17] However, it was not a reason for modification of ARV drugs in this study, due to the cost-free (fee-free) provision of ARV drugs for the patients in Ethiopia.

Conclusion

The result of this study indicated toxicity as the main reason for modification of the initial medications, and treatment failure as the smallest reason for ARV regimen change. However, there had to be sufficient qualitative and well-effective laboratory equipment and proper guidelines for switching the regimen, in Ethiopia.

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Footnotes

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Conflict of Interest: None declared.

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Figures and Tables

	N (%)
	7 (2.05)
11–30	151 (44.40)
31–45	142 (41.80)
46–65	38 (11.17)
>65	2 (0.58)
Sex	
Male	135 (39.71)
Female	205 (69.29)
Marital status	
Single	184 (54.11)
Married	121 (35.55)
Divorced	8 (2.40)
Widowed	27 (7.94)
Education	
Illiterate	126 (37.06)
Primary	106 (31.18)
Secondary	65 (19.12)
Tertiary	43 (12.64)
Religion	
Orthodox	160 (47.06)
Muslim	71 (20.88)
Protestant	58 (17.06)
Catholic	38 (11.18)
Others*	13 (3.82)

*pagan, jova witness, atheist

Sociodemographic distribution of the study population on HAART

	N (%)
	65 (19.11)
51–100	69 (20.30)
101–200	180 (35)
>200	71 (20.89)
Information missing	16 (4.70)
Initial HAART regimen	
D4T/3TC/NVP	186 (54.70)
D4T/3TC/EFV	71 (20.88)
AZT/3TC/NVP	55 (16.17)
AZT/3TC/EFV	28 (8.25)
Common reasons for modification	
Toxicity	230 (67.65)
Comorbidity	65 (19.11)
Pregnancy	36 (10.59)
Treatment failure	9 (2.65)
Toxicities reported as a reason for treatment change	
Peripheral neuropathy	84 (36.52)
Rash	41 (17.83)
Anemia	40 (17.39)
Lipidostrophy	15 (6.52)
CNS manifestation	38 (16.52)
Others*	12 (5.22)

*Hepatoxicity, GIT symptoms

Overall patterns of the HIV / AIDS patients on HAART

				AZT / 3TC / EFV
Peripheral neuropathy	65 (77.38)	19 (22.62)	-	-
Rash	29 (70.73)	-	12 (29.27)	-
Anemia	-	-	23 (57.5)	17 (42.5)
CNS toxicities	-	31 (81.58)	-	7 (18.42)
Lipodystrophy	12 (75)	4 (25)	-	-
Others	3 (27.27)	1 (9.10)	4 (36.36)	3 (27.27)
Total	109 (47.31)	55 (23.91)	39 (16.96)	27 (11.74)

Toxicities reported as a reason for initial treatment change

Toxicity	63 (27.40)	87 (37.83)	47 (20.43)	24 (10.43)	9 (3.91)
Comorbidity with tuberculosis	34 (52.31)	18 (27.69)	9 (13.85)	3 (4.61)	1 (1.54)
Pregnancy	9 (25)	17 (47.22)	10 (27.78)	-	-
Treatment failure	-	-	3 (33.33)	5 (55.56)	1 (11.11)

Weeks of stay on initial antiretroviral treatment versus treatment regimen and reasons for modification