Reasons for Regimen Change Among HIV/AIDS Patients Initiated on First Line Highly Active Antiretroviral Therapy in Fitche Hospital, Oromia, Ethiopia

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Abstracts
Background: Highly active antiretroviral therapies are the drugs of HIV/AIDS treatment with no cure. Even though they inhibit viral replication, they may cause a number of adverse effects; which may end with treatment failure and/or regimen changes. Objective: The study was aimed to determine the reasons for HAART regimen change among HIV/AIDS Patients on first line HAART during 12 months follow up in Fitche Hospital, ART Clinic. Methodology: Hospital based retrospective study was conducted at Fitche Hospital, ART Clinic from January 28 to February 12, 2013 by reviewing patients’ information sheets and physician diagnostic cards. The data was categorized and analyzed manually using calculator for statistical analysis. The results has been interpreted and presented by tables and graphs. Results: Majority of the patients 29(42.65%) were on D4T/3TC/NVP at the beginning of the Highly Active Antiretroviral Treatment. The main reason for regimen change was toxicity 56(72.73%) followed by, treatment failure 11 (14.23%), new drug available 7(9.09%), co morbidity 2(2.60%), and 1(1.30%) patient refused to took the drug. From all the toxicities reported, lipoatrophy, which accounted for 73.47% of the toxicities, was the most common. Conclusion: Results shows that majority of patients were initiated D4T/3TC/NVP compared to other regimens. Toxicity appears as the main reason for treatment and regimen change in this study. The other reasons include; treatment failure, new drug available, co morbidity and patient refused to took the drug respectively.

Keywords: HAART, Initial Regimen, Switch, Toxicity, Treatment Failure

1. Introduction

Human Immunodeficiency Virus is a retrovirus that causes AIDS and first diagnosed in 1981. According to the latest statistics from UNAIDS and WHO on AIDS day in 2012, globally 34.0(31.4-35.9million) people were living with HIV at the end of 2011. An estimated 0.8% of adults aged 15-49 years worldwide are living with HIV; although the burden of the epidemic continues to vary considerably between countries and regions. According to UNAIDS report on the global AIDS epidemic 2013, after discovery of the life-saving highly active antiretroviral therapy, even if Sub-Saharan Africa, such as Ethiopia remains most severely affected, the number of new HIV infections and AIDS related deaths has been declining. In 2011, among 84.3 million peoples of Ethiopia, the number of people living with HIV were 790,000 (720,000 - 870,000). Of them adults aged 15 and up (610,000 (560,000 - 680,000)), women aged 15 and up (390,000 (350,000 - 430,000)) and children aged 0 to 14 (180,000 (160,000 - 210,000)) were living with HIV. But, worldwide, the number of people newly infected and HIV/AIDS mortality continues to fall. The number of people (adults and children) acquiring HIV infection in 2011 (2.5 million (2.2 million -2.8 million)) was 20% lower than in 2001. In 2011, 1.7 million (1.5 million–1.9 million) people died from AIDS-related causes worldwide. In Ethiopia, the number of deaths due to AIDS were 54,000 (46,000 - 63,000) and orphans due to AIDS aged 0 to 17 were 950,000 (850,000 - 1,100,000) in 2011. (1-4)

Highly active antiretroviral drugs (HAART) are HIV/AIDS drugs that can substantially reduce HIV related deaths and complication. They stop viral replication and delay the development of AIDS; but don’t cure. There are different classes of HAART. They include; nucleoside analogs (NRTIs), non-nucleoside analogs (NNRTIs), protease inhibitors (PIs), entry inhibitors and integrase inhibitors. A combination of at least three drugs is recommended to suppress virus from replicating and boost immune system. The first-line antiretroviral regimen in Ethiopia included a triple therapy; including either two NRTIs and one PI or an NNRTI, or 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. (5, 6)

Expanding access to HAART can also reduce the HIV transmission at population level, impact hood and preserve families. However, these advances have not been without their cost in terms of drug-resistance and side effects that are rational for treatment switch and discontinuation. (7-9)

Rational for treatment switch and discontinuation may be;
long term toxicity, due to failure (includes virological, immunological and clinical failure), poor adherence, a desire for pregnancy and/or comorbidity with other chronic diseases. Adverse drug reactions are the most common cause for regimen change among HIV/AIDS patients. Some adverse effects are life threatening and need follow up and management. These adverse drug reactions include; decrease level of RBC (anemia), pancreatitis, hepatotoxicity, rash, gastrointestinal disturbance, hyperuricemia, diabetes, lipodystrophy, peripheral neuropathy and etc. Types of adverse reaction and duration of initial treatment can be affected by patient’s WHO HIV/AIDS stage and CD4-cell count during HAART initiation and drugs combination type. (10-24)

According to retrospective cross-sectional study conducted from January 1 to March 1, 2010 in two primary hospitals and one health centre in central Ethiopia; the most common first regimen before first switch was D4T/3TC/NVP (63%) and D4T/3TC/EFV (18%). The main reasons for modification were toxicity (65%), co-morbidity (25%), pregnancy (5%) and treatment failure (3%). The main types of toxicities observed were peripheral neuropathy (39%), rash (20%) and anaemia (13.33%). Drug toxicity was the main reason for modification of initial antiretroviral regimen and initial Efavirenz-based regimens are less likely to be changed. (25)

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 modification of highly active antiretroviral therapy are scarce among HIV patients in Ethiopia. The study is aimed at to determine the reasons for initial and subsequent decisions regarding ART.

2. Methods and Materials

2.1. Study Area and Period

The study was conducted in Fitche Hospital, ART Clinic. Fitche is found at central Ethiopia; 112km away from Addis Ababa in north direction. Fitche Hospital is zonal hospital with having different departments; i.e. gynecology, pediatrics, internal medicine, surgery, ophthalmology, laboratory, and etc. to deliver diversified health care activities. This hospital gives services for patients referred from primary health care sites and self-referred patients. The study was conducted from January 28 to February 12, 2013.

2.2. Study Design

Hospital based retrospective cross sectional study was done by reviewing patients’ information sheets and physician diagnostic cards to assess reasons for initial HAART regimen change.

2.3. Population

2.3.1. Source Population

All HIV/AIDS positive patients who were on HAART in Fitche Hospital, ART Clinic from September 12, 2011 to September 12, 2012 were included.

2.3.2. Study Population

Study Population was all HIV/AIDS positive patients who had undergone switching of the initial first line HAART regimen in Fitche Hospital, ART Clinic in between September 12, 2011 to September 12, 2012.

2.3.3. Exclusion Criteria

- Patients who didn’t switch HAART regimen in between September 12, 2011 to September 12, 2012.
- Under eighteen year old HIV/AIDS patients.

2.3.4. Inclusion Criteria

- All patients who had changed their HAART regimen in between September 12, 2012 to September 12, 2012 were included in the study.

2.3.5. Sample Size Determination

All HIV/AIDS positive patients who changed their HAART regimen in between September 12, 2011 to September 12, 2012 were included in the study.

2.4. Study Variables

2.4.1. Dependent Variables

- Regimen change
- Types of initial regimen
- Duration of initial therapy

2.4.2. Independent Variables

- Age
- Base line CD4 cell count
- Sex
- WHO stage of disease during HAART initiation
- Pregnancy
- Co morbidity
- Toxicity
- Opportunistic infection

2.5. Data Collection

Data was collected using data collection format. Before the start of the actual data collection, the data collection format and the whole method was pre-tested on randomly selected patients’ clinical information records to ensure their completeness. The data collection format contains; the socio demographic data (i.e. age, gender, weight (during initiation and switching HAART) and antiretroviral treatment related data (i.e. date of starting and changing regimen, CD4 count, reasons for regimen change, duration of initial regimen, WHO stage of HIV/AIDS).

2.6. Data Analysis and Presentation

The data was checked, categorized and analyzed manually.
using calculator for statistical analysis. The results have been interpreted and presented by tables and graphs.

2.7. Quality Assurance

The data was collected from patients’ information sheet and physician diagnostic cards carefully to assure quality and completeness.

2.8. Ethical Consideration

An official letter was written by Department of pharmacy, College of Public Health and Medical sciences, Jimma University to Fitche Hospital Administration to get permission. After permission to conduct the study was given, data has been collected in one of refilling rooms at ART Clinic by safe keeping of records. Only numerical identification was used as a reference, confidentiality and anonymity of subject was maintained by not recording identifying details, such as name or any other personal details.

2.9. Pilot Study

Before starting the actual data collection, the data collection format and the whole method was been pretested on patient information sheet to find out any errors, and correct them if present; so that effective work has been done.

2.10. Problem Encountered

- Illegibility of some information on patients’ information sheets and physician diagnostic cards
- Some unrecorded patient information such as initial CD4 count, reason/s for regimen change, initial WHO stage of HIV/AIDS.

3. Results

Table 1. Age-Sex Distribution of HIV/AIDS Patients Groups During HAART Initiation

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sex N (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>18-30</td>
<td>4(5.88)</td>
<td>16(23.53)</td>
</tr>
<tr>
<td>31-45</td>
<td>15(22.06)</td>
<td>23(33.82)</td>
</tr>
<tr>
<td>46-60</td>
<td>4(5.8)</td>
<td>5(7.35)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1(1.47)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>24(35.3)</td>
<td>44(64.7)</td>
</tr>
</tbody>
</table>

Total records of 1238 HIV/AIDS positive patients that were on HAART in between September 12, 2011 to September 12, 2012 were assessed. Sixty-eight patients had changed their initial highly active antiretroviral treatment regimen at Fitche Hospital, ART Clinic in between September 12, 2011 to September 12, 2012. Most of the patients were females 44 (64.7%) and 24(35.3%) were males. The mean age of the patients was 35.9 years (Table 1).

A majority of the patients had their initiation of treatment at clinical WHO stage III; while a few of them started at stage I, stage II, and stage IV, respectively. For 3(4.11%) of the patients, the clinical stage was not recorded. During HAART regimen initiation, most of the patients had a CD4 count greater than 200 cells/mm³ (figure 1 and 2).

Figure 1. Patient’s initial CD4 cells count /mm³ during HAART initiation

A majority of the patients, 29(42.65%), were on D4T/3TC/NVP at the beginning of the antiretroviral treatment and the rest were on D4T/3TC/EFV, AZT/3TC/EFV and AZT/3TC/NVP (Figure 2).

Figure 2. Initial HAART regimen the patient was taking in Fitche Hospital, ART Clinic, from September 12, 2011 to September 12, 2012

The main reason reported for modification of treatment regimen was toxicity. The other reasons include treatment failure, new drug available, co morbidity and a patient refused to take the drug. This means a significant association was found between changes in initial regimens and the report of adverse reactions (Table 2).
80 Reasons for Regimen Change Among HIV/AIDS Patients Initiated on First Line Highly Active Antiretroviral Therapy in Fitche Hospital, Oromia, Ethiopia

Table 2. Common Reasons for Modification of Haart Regimen

<table>
<thead>
<tr>
<th>Reasons</th>
<th>D4T/3TC/NVP</th>
<th>D4T/3TC/EFV</th>
<th>AZT/3TC/NVP</th>
<th>AZT/3TC/EFV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>29(33.72)</td>
<td>17(19.76)</td>
<td>6(6.98)</td>
<td>4(4.64)</td>
<td>56(72.73)</td>
</tr>
<tr>
<td>Co morbides i.e. TB</td>
<td>1(1.16)</td>
<td>-</td>
<td>1(1.16)</td>
<td>-</td>
<td>2(2.60)</td>
</tr>
<tr>
<td>New drug available</td>
<td>-</td>
<td>2(2.32)</td>
<td>3(3.49)</td>
<td>2(2.32)</td>
<td>7(9.09)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>3(3.39)</td>
<td>4(2.64)</td>
<td>3(3.49)</td>
<td>1(1.16)</td>
<td>11(14.23)</td>
</tr>
<tr>
<td>Others</td>
<td>-</td>
<td>1(1.16)</td>
<td>-</td>
<td>-</td>
<td>1(1.30)</td>
</tr>
</tbody>
</table>

Table 3. Toxicities Reported due to Initial Haart Regimen

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>D4T/3TC/NVP</th>
<th>D4T/3TC/EFV</th>
<th>AZT/3TC/NVP</th>
<th>AZT/3TC/EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1(50)</td>
<td>1(50)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>3(97.5)</td>
<td>-</td>
<td>1(2.5)</td>
<td>-</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td>22(57.9)</td>
<td>16(42.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>-</td>
<td>-</td>
<td>1(50)</td>
<td>1(50)</td>
</tr>
<tr>
<td>PNP</td>
<td>3(100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>-</td>
<td>-</td>
<td>1(100)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1(100)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>-</td>
<td>-</td>
<td>1(50)</td>
<td>1(50)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>-</td>
<td>-</td>
<td>1(50)</td>
<td>1(50)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-</td>
<td>-</td>
<td>1(100)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4. Weeks of Stay on Initial Haart Versus Treatment Regimen and Reasons for Modification

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Initial HAART Regimen</th>
<th>Start-12</th>
<th>13-26</th>
<th>27-52</th>
<th>53-104</th>
<th>105-156</th>
<th>&gt;156</th>
<th>REASONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D4T/3TC/NVP</td>
<td>-</td>
<td>-</td>
<td>2(7.14)</td>
<td>2(7.14)</td>
<td>5(17.86)</td>
<td>19(67.86)</td>
<td>Toxicity</td>
</tr>
<tr>
<td>2</td>
<td>D4T/3TC/EFV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1(4.17)</td>
<td>5(20.83)</td>
<td>18(75)</td>
<td>New drug available</td>
</tr>
<tr>
<td>3</td>
<td>AZT/3TC/NVP</td>
<td>1(10)</td>
<td>-</td>
<td>-</td>
<td>1(10)</td>
<td>1(10)</td>
<td>7(70)</td>
<td>Treatment failure</td>
</tr>
<tr>
<td>4</td>
<td>AZT/3TC/EFV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6(100)</td>
<td>Co morbides</td>
</tr>
</tbody>
</table>

From all the toxicities reported, lipoatrophy was the most common, followed by headache, peripheral neuropathy, nausea, rash, anemia, abdominal pain, jaundice, fatigue, and diarrhea, respectively. Lipoatrophy was due to stavudine (D4T)-containing regimens of D4T/3TC/NVP and D4T/3TC/EFV; whereas, rash was due to nevirapine (NVP)-containing regimens of AZT/3TC/NVP. Anemia was reported due to zidovudine (AZT) containing regimens of AZT/3TC/NVP and AZT/3TC/EFV. Headache was reported due to nevirapine containing regimens of D4T/3TC/NVP and AZT/3TC/NVP. Peripheral neuropathy was due to stavudine (D4T)-containing regimens of D4T/3TC/NVP. The other toxicities observed were nausea due to stavudine (D4T)-containing regimens of D4T/3TC/NVP and D4T/3TC/EFV, and hepatotoxicity (jaundice) mainly due to zidovudine-containing regimens of AZT/3TC/NVP and AZT/3TC/EFV.

Most toxicity was due to D4T/3TC/NVP and the remaining was due to D4T/3TC/EFV, AZT/3TC/NVP, and AZT/3TC/EFV regimens, respectively (Table 3).

The majority of the patients modified their initial treatment regimen after thirty-nine months of initiating medications (Table 4).

4. Discussion
There are many factors 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 (includes; virological, immunological and clinical failure), poor adherence, a desire for pregnancy, and/or co morbidity (8, 14). Majority of the patients were on the D4T-based regimen of D4T/3TC/NVP (41.17%) and 5.49% of patients changed their initial HAART regimen. The retrospective institution-based study done in 2012 in Southern Ethiopia reported 54.70% (22). However, this study was not in agreement with the descriptive and exploratory study done in AIDS Tertiary Care Hospital in Ceará, Brazil in 2008 (10), the AZT/3TC/EFV (44%) regimen accounted for a majority of the patients’ initial HAART regimen. The probable reason was the difference in patients’ conditions; i.e co morbidity situations, contraindications or initial HAART.

Of 1238 patients who were on HAART during a median follow-up of 12 months, 68 patients (5.49%) were modified their HAART regimen. This shows there was a high rate of modification and discontinuation of HAART regimens in the first 12 months, particularly due to toxicities. This result didn’t agree with that of research done in Italia (2000) and Royal Free Hospital London, UK (2001) (15, 16). 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 1238 HIV-positive patients who initiated HAART, 68 (5.49%) of patients changed their initial HAART regimen in between September 12, 2011 to September 12, 2012; 72.73 % did so because of an adverse events. The events most commonly cited as the cause for discontinuation were Lipoiatrophy, headache and peripheral neuropathy. A retrospective cohort study in New Orleans, L.A., USA in 2001 reported nausea, vomiting, and diarrhea were the most common cause (18). The probable reason was the difference in duration on HAART regimen.

Similar to several other studies (11,14,15,17,19,22,23,25), the most predictable cause for HAART switching, in this study, was toxicity (65.12%), 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, lipoatrophy was the most common reason for modification, unlike the research done in Peru in 2010 and Southern Ethiopia in 2012 (17, 22 and 23). 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 relative to that of Peru.

According to this study, rates of regimen change due to drug toxicity among 1238 adults with HIV infection initiated on generic, first-Line highly active antiretroviral treatment indicated, of sixty eight persons with HIV, most of them had advanced HIV infection (WHO clinical stage 3 or 4) (79.41%) and CD4+ T-lymphocyte counts below 200 cells/µL (55.88 %). The initial HAART regimens used were: Lamivudine (3TC) with Stavudine (D4T) (in 76.47%) and Nevirapine (NVP) (in 50%) or Efavirenz (EFV) (50%). It didn’t agree the study done in South India (2009).This may be due to more consideration is given to CD4+ T-lymphocyte counts than identifying HIV/AIDS stage and PIs were not prescribed as first line in this study area (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 (17). Co morbidity was the other cause for HAART switch. Tuberculosis (2.60%) was the only co morbidity disease reported in this study. This was consistent with the study in UK in 2007 (11) and Coite d’Ivoure in 2010 (20). Due to Tuberculosis, (1.16%) a switch was made from D4T/3TC/NVP to D4T/3TC/EFV. This means 1.16% 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.

As study in Italia on insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients in 2000 reported (15), patients were more likely to change the therapy shortly after HAART initiation, because of adverse events, rather than treatment failure. It agrees with this study.

Treatment failure was given as the reason for change in 11 (14.23%) of the patients in the current study. Some studies, (11, 20, and 21) however, reported highly treatment failure as the reason for a regimen switch. In the study in Coite d’Ivoure in 2010, treatment failure was observed in 12.4% of the patients (20). According to the study in Uganda on discontinuation and modification of highly active antiretroviral therapy in HIV-infected Ugandans and associated factors in 2007 (21), 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 the difference in the occurrence of opportunistic infection in the study area.

According to the result of this study, no patients change their regimen due to pregnancy. This did not agree with that of study done in Uganda (20) and Royal Free Hospital London, UK (2001) (16).The difference may be due to miss understanding about the HIV/AIDS patient pregnancy and fear of managing HIV transmission from mother to infant at study area.

Cost was one of the major reasons for discontinuation and modification of ARV drugs according to the study conducted in Uganda (23%) (20). 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 study collected the main reasons as reported by physician for modification of treatment, but
reasons for modification are often interrelated.

5. Conclusions

Majority of the patients were females, had their initiation of treatment at clinical WHO stage III, had a CD4 count greater than 200 cells/mm³ and were on D4T/3TC/NVP at the initiating of the antiretroviral treatment and the rest were on D4T/3TC/EFV, AZT/3TC/EFV and AZT/3TC/NVP, respectively.

Toxicity appears as the main reason of treatment and regimen change. Most of toxicities patients reported includes; lipoatrophy, headache, peripheral neuropathy, nausea, rash, anemia, abdominal pain, jaundice and fatigue, respectively.

Most toxicity was due to D4T/3TC/NVP and the remaining was due to D4T/3TC/EFV, AZT/3TC/NVP, and AZT/3TC/EFV regimens, respectively. This is due to nevirapine is less safe than efaviranz. The other reason includes; treatment failure, new drug available, co morbidity, and patients refused to took the drug.

The majority of the patients were modified their initial treatment regimen after thirty-nine months of the start of taking medications.

The HAART regimens used in this study were effective in decreasing disease progression and death. However, they were associated with high rates of drug toxicities, particularly those attributable to thymidine analogue NRTI, i.e. D4T. As efforts are made to improve access to ART, treatment regimens chosen should not only be potent, but also safe. Components of the initial and subsequent regimens must be individualized, particularly in the context of concurrent conditions. Patients receiving antiretroviral treatment should be monitored regularly; treatment failure should be detected and managed early.

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