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A Comparison of Effectiveness of Efavirenz and Nevirapine - Based First-Line HIV Treatment in Patients Attending Coast Provincial General Hospital, Kenya

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Abstract

The objective of this study was to compare the effectiveness of Efavirenz and Nevirapine based First-line HIV treatment in patients attending comprehensive care centre in Mombasa. This was a prospective comparative study. The target population was HIV positive adult patients eligible for HAART. A total of 251 patients were enrolled in the study and followed up for 12 months. All ARV naive patients with CD4 count < 350/ul with WHO stage 3 or 4 and eligible for HAART were randomly into Efavirenz and Nevirapine based regimens (D4T/3TC/EFV and D4T/3TC/NVP) and followed up for a period of twelve months. Laboratory tests were done for each patient every three months by testing for Haemoglobin, Liver enzyme test (ALT), Creatinine and CD4 cell count. The study showed that first-line regimens of Efavirenz and Nevirapine were effective in suppressing HIV/AIDS infection with improvement in CD4 count (P<0.05). There was also improvement in haemoglobin levels and body weight among the patients on both regimens in the study. However, elevation of ALT and Creatinine were noted in both treatment groups, but this did not warrant drug discontinuation (P>0.05). Efavirenz based regimen appeared to be superior to Nevirapine based regimen on CD4+ profiles and renal function (P<0.05). There was no significant difference in haemoglobin levels, body weight and ALT enzyme for patients on both treatment groups.The findings demonstrated that D4TC/3TC/EFV and D4TC/3TC/NVP combinations were safe, well tolerated and effective in suppressing HIV progression in advanced HIV infected patients.

Acronyms and abbreviations

AE	**:**	Adverse Event
AIDS	**:**	Acquired Immune Deficiency Syndrome
ALT	**:**	Alanine aminotransferase
ART	**:**	Antiretroviral therapy
ARV	**:**	Antiretroviral
CCC	**:**	Comprehensive Care Centre
CD4+	**:**	Cluster of Differentiation
CPGH	**:**	Coast Province General Hospital
CNS	**:**	Central Nervous System

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CRF	**:**	Case Record Form
D4T	**:**	Stavudine
DNA	**:**	Deoxyribonucleic acid
EDTA	**:**	Ethyline diamine tetraacetic acid
EFV	**:**	Efavirenz
ELISA	**:**	Enzyme-Linked Immunosorbent Assay
FHI	**:**	Family Health International
FSC	**:**	Forward Scatter
HAART	**:**	Highly Active Antiretroviral Therapy
HIV-1	**:**	Human immunodeficiency virus (type- 1)
Hb	**:**	Hemoglobin
KAPR	**:**	Kenya AIDS Progress Report
KDHS	**:**	Kenya Demographic Health Survey
KNBS	**:**	Kenya National Bureau of Statistics
LFT's	**:**	Liver Function Tests
3TC	**:**	Lamivudine
MOH	**:**	Ministry Of Health
MTCT	**:**	Mother to Child Transmission
NASC OP	**:**	National AIDS and STI Control Program
NCST	**:**	National Council for Science and Technology
NRTI	**:**	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	**:**	Non- Nucleoside Reverse Transcriptase Inhibitor
NVP	**:**	Nevirapine
OI	**:**	Opportunistic Infection
PI	**:**	Protease Inhibitor
PMCT	**:**	Prevention of Mother –to – Child – Transmission
SAE	**:**	Severe Adverse Effects
SDI	**:**	Standard Deviation
SGPT	**:**	Serum Glutamate Pyruvate Transaminase
SSC	**:**	Side Scatter
STI	**:**	Sexual Transmitted Infection
UKNE QAS	**:**	United Kingdom National External Quality Assurance Scheme
ULN	**:**	Upper Limit of Normal
UNAIDS	**:**	United Nations Program on AIDS

VCT : Voluntary Counselling and Testing (for HIV)
WHO : World Health Organization.
WBC : White Blood Cell Count

Introduction

Background information

Antiretroviral have been widely used in developing countries, yet little has been done to find out the treatment outcome of these drugs by assessing the immunological and virological parameters of an individual's immune system in relation to the clinical response. Hence, it is important to follow the progression of HIV/AIDS patients through laboratory monitoring, as well as to review the acceptability and tolerability of ARV's which contribute to adherence, as this will help in treatment decisions by vclinicians as they can decide to continue treatment, change a particular regimen or discontinue therapy at the appropriate time. This decision will often be based on the occurrence of side effects, or increased toxicity or non-adherence to antiretroviral drugs. ART has significant toxicity that requires monitoring. Laboratory tests performed on a regular basis are usually used to detect severe toxicity, before it becomes clinically apparent and harmful. These tests, however, are costly and require patient visits, phlebotomy and appropriate infrastructure and equipment.

Limitations

The most important limitation in the study was the exclusion of co-morbidities and opportunistic infections like tuberculosis, which can induce important selection bias.

Secondly, lack of viral load testing was also another limitation of the study considering that viral load detection in blood is a good indicator of viral suppression and drug effectiveness. Thirdly, another limitation was the lack of calculation of body mass index (BMI) as an important anthropometric measurement to assess nutrition status of patients on HAART.

Materials and methods

Study site

The study was carried out in Mombasa County at the Coast Provincial General Hospital (CPGH). The County has approximately 939,370 people (KNBS, 2009) and is a Cosmopolitan Centre with a balanced population of both the youth and older people. The Centre was selected because it offered free services sponsored by Family Health International (FHI) and Ministry of Health (MOH) to all willing clients for Voluntary Counseling and Testing Services, and also that it formed the bulk of population of Mombasa District.

Research design

A Prospective longitudinal cohort study of HAART regimens given to ARV naïve HIV infected adult patients at Coast Provincial General Hospital. Clients were randomised into Efavirenz and Nevirapine based regimens (D4T /3TC / EFV and D4T /3TC / NVP) and followed up for a period of twelve months. Screening of patients was done at the Comprehensive Care Centre (CCC) after being refered from VCT clinics, outpatient clinics and the wards. Patients were then screened for eligibility criteria which included laboratory examination for liver enzymes, hemoglobin, renal function, CD4 Cell count and clinical assessments by the clinician. Patients who were eligible for HAART based on their CD4 count as per eligibility criteria were selected to be part of the study and followed up to one year (12 months).

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Data collection technique

Laboratory measurements

Ten (10) mls of blood were obtained for Haemoglobin, CD4 count and also for Liver enzyme assay (ALT) and Creatinine at baseline, 3 months, 6 months, 9 months and 12 months duration. Enzyme Linked Immunosorbent Assay (ELISA) test for HIV was used to confirm HIV positive status. Whole blood sample drawn in EDTA containing tubes was used to determine T-helper cells (CD4 count). Absolute numbers of CD4 was calculated as well as white blood cell count using the coulter counter as per manufacturer's instructions. Biochemical parameters which include Liver enzyme test (ALT) were used to assess the liver response in patients treated with ARV's by determining the values of these parameters at baseline and at intervals of three (3) months after commencement of ARV therapy for up to one year.

Statistical analysis

Data analysis was done using SPSS Version 11.0 statistical software. Basic characteristics of the study samples were summarised using simple proportions and means, median and inter quartile ranges. Further analysis was done to perform one way ANOVA comparing more than two means followed by Post hoc Student Newman Keul for multiple comparisons . Independent t-test was used to calculate if there was any significant difference between the two treatments. Study subjects were followed from HAART initiation to the earliest of death, loss to follow up, development of toxicity or end of twelve months.

Results

Analysis of Patients body weight

Body weight increased for both of the two treatment groups after initiating antiretroviral therapy for the first six months (Table 4.1) and tapered over time between 6 months and 9 months period for the two treatment groups. The mean weight increased between 9th month and 12th month (1 year) period with a mean of 62.1 kg 95% CI (60.6 - 63.5) compared to baseline which was 55.6 kg (95% CI 54.1- 57.1. The average increase in body weight for patients on EFV over the 12 months period was 2.2 kg whereas for patients on NVP was less than 2 kg. There was no significant difference on the body weight for both patients on EFV and NVP groups $p > 0.05$ as measured at 6 months. However, patients in both treatment groups experienced slight increase in weight between the 9th month and 12th month follow up period respectively.

Table 4.1. Body weight in kilograms of patients in the EFV and NVP study groups

Time in months	**Efavirenz**	**Nevirapine**	***p* - value**
0 months	56.21±12.59	54.75±10.38	0.347
3 months	57.49±12.29	56.48±10.18	0.504
6 months	59.18±12.31	58.80±10.00	0.797
9 months	59.49±12.29	58.30±10.29	0.432
12 months	62.49±12.29	61.30±10.29	0.432

Immunological changes

Immunological variables were measured on a maximum of 5 occasions. There were significant differences in CD4 lymphocyte subsets between patients on EFV and patients on NVP treatment arm ($p < 0.01$) at the 6th, 9th and 12th month respectively.

The profiles of these values showed that EFV based regimen was superior in improvement of CD4+ count compared to NVP based regimen as shown in Table 4.2 below.

Table 4.2. Mean CD4 + cells for patients in the study CD4 + Cells/mm3

Time in months	Efavirenz	Nevirapine	*p*-value
0 months	133.75±91.98	165.11±61.33	0.001
3 months	171.32±103.38	139.74±63.65	0.003
6 months	200.07±114.28	161.39±68.33	0.001
9 months	270.07±114.28	231.39±68.33	0.001
12 months	365.07±114.28	326.39±68.33	0.001

The comparison of differences in immunological parameters between the baseline period, 3 months, 6 months, 9 months and 12 months for both EFV and NVP patients are well illustrated in table 4.2 above. The means of the differences between changes for EFV and NVP were significantly different ($p < 0.001$). The data on CD4 count confirm that patients at enrolment had lower levels of CD4 cell count at the onset of the study for both groups. In addition, the data indicate that the mean absolute numbers of CD4 count were slightly higher for the patients on NVP regimen compared to EFV regimen at the baseline with means of 165.11 (103.78 – 226.44) and 133.75 (41.77 – 225.73) respectively. The mean absolute CD4 cell count for patients on both regimens increased to the 12th month period suggesting positive immune response following HAART therapy. During the first 6 months of ART, the number of CD4+ T cells typically increased by 30 cells to 60 cells/mm^3 of blood. This burst was then followed by a second, faster phase of T cell repopulation with an average rate increase of 70 cells / mm^3 in the 9th month of ART.

Hemoglobin levels during the study period

Hemoglobin levels increased for patients in both arms of treatment (EFV and NVP) group up to the 6th month. However, there was a sudden decline of hemoglobin levels towards the 9th month. Hemoglobin levels increased further from 9th month to 12th month during the study. There was no significant difference in haemoglobin levels of patients on EFV and NVP regimens throughout the study ($p > 0.05$) (Table 4.3).

Table 4.3. Mean of hemoglobin (g/dl) during the 12 months study period

Time in months	Efavirenz	Nevirapine	*p*-value
0 months	10.49±2.40	10.03±2.29	0.135
3 months	11.18±2.39	10.92±2.30	0.406
6 months	11.88±2.52	11.82±2.39	0.858
9 months	11.58±2.39	11.33±2.33	0.145
12 months	11.98±2.39	11.73±2.35	0.420

Reference ranges for Hemoglobin: Adult Male: 13.0g/dl – 18.0 g/dl and Adult Female: 12.0g/dl – 15.0g/dl

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Liver enzymes (ALT) before and after initiation of HAART

The monitoring of patients through the two ARV regimens allowed the analysis to be done for toxicity. There was no significant difference in the mean values of ALT enzymes for patients on EFV based regimen and NVP based regimen from baseline to the 12th month ($p > 0.05$). Nevertheless, the hepatic biological tolerance during EFV or NVP based regimen was generally good in months 3 and 6. The majority of the mean values of ALT enzymes studied were above normal ranges except for those at baseline (Table 4.4).

Table 4.4. Mean liver enzymes alt (U/L) for patients during the study

Time in months	Efavirenz	Nevirapine	*p*-value
0 months	49.81±3.48	44.83±4.40	0.379
3 months	67.86±5.13	62.39±5.29	0.485
6 months	85.80±9.21	90.38±14.55	0.780
9 months	126.57±12.13	137.89±21.40	0.620
12 months	165.99±18.30	183.32±31.09	0.608

Reference ranges for ALT enzyme: Adult Male and Female: 7 U/L – 55 U/L.

The comparison of ALT enzymes after initiation of HAART has shown that changes in these parameters were similar in both HAART regimens. The early hepatic biological tolerance during EFV or NVP based regimen was generally good and similar. However, significant increases in the enzyme values for ALT were observed with the NVP based regimen when compared with EFV regimen. There were also 16 cases of clinical toxicities which later resolved. Ten were associated with Stavudine and Nevirapine with mainly peripheral neuropathy, lipodostrophy and CNS symptoms.

Creatinine trends of patients in the study

The Creatinine levels increased minimally for all patients from onset of ARV's up to a maximum of 154 umol / L at the end of the follow up**.** There was significant difference of Creatinine levels for the two regimens with Nevirapine giving higher values than Efavirenz regimen ($p < 0.001$). (Table 4.5).At endpoint patients on EFV regimen had Creatinine mean of 135.61±0.89 compared to NVP mean of 151.04±3.30. However, none of the patients reached a Creatinine level of >300 umol / L to warrant drug discontinuation or regimen change.

Table 4.5. Mean creatinine levels (umol/L) for patients on EFV and NVP

Time in months	Efavirenz	Nevirapine	*p* -value
0	74.16±2.60	75.19±3.37	0.808
3	91.47±1.51	94.49±3.29	0.405
6	115.83±1.21	123.15±3.23	0.036

9	128.81±1.02	137.08±3.11	0.003
12	135.61±0.89	151.04±3.30	< 0.001

Reference ranges for Creatinine: Adult Male: 80.0 U/L – 115.0 U/L and Adult Female: 53.0 U/L – 97.0 U/L

Discussion

Effect of HAART on CD4 profiles

The study has demonstrated clinical benefits in terms of CD4 cell count and weight increase well into the end of first year of follow up. The finding of a rapid rise in CD4 cell counts during the initial few weeks of therapy followed by a slower rise for the patients in the current study are consistent with earlier reports on CD4 cell kinetics conducted in the USA. In addition, the mean CD4 cell increase seen in patients in this study at one year after antiretroviral therapy initiation is similar to the response seen in studies conducted in Europe (Lifson *et al.,* 2011). As such, the mean CD4 cell increase seen at later time periods reflect responses to both primary and secondary regimens (about 10% of the patients in the study switched to second line therapy). Alternatively, individuals in the current study may have different hepatic regeneration capacities at the initiation of ART. For this study population, $CD4^+$ cells had continued to increase up to 12th month period.

In fact, even among highly advanced patients in our study who initiated HAART with CD4 cell counts below 200 cells/mm3, subsequent increase in CD4 cell count was most strongly predicted following treatment with HAART. Previous studies showing that CD4 cell counts <350 cells/mm3 may preclude a CD4 cell count response may have been confounded by patient non adherence (Kenneth *et al*., 2013).

The main immunologic outcome observed was the change in CD4 cell count over time. A switch in therapy occurred if the ART regimen recorded at follow up was different from the regimen initially started. Any individual drug substitution or regimen change was considered a switch. Dose reduction however, was not considered an ART switch. The time of the first switch defined the time of reaching the outcome. If the physician recorded a symptom during a clinic visit believed to be attributed to ART, a toxicity event was considered to have occurred.

Deaths were recorded based on physicians or family notification on the discontinuation. Official records such as death certificates were not usually available. The primary end point was mortality from all cases in the 12 months after starting HAART. Changes in CD4+ cell counts in the first 3, 6, 9 and 12 months were secondary end point measurements used in this analysis. Time was measured from the start of HAART and ended at the earliest of the date of death, the date of the last follow up visit or month 12 after starting HAART.

Effect of HAART on body weight changes

The current study found that mean body weight gains mirrored CD4 cell increase immediately following antiretroviral therapy initiation and this correlated with the findings of Barnejee *et al.* (2010) which showed that HAART had a positive effect on growth in HIV 1 infected individuals. HAART had modestly favourable effects on body composition, particularly in patients with greater pretreatment immunosuppression and virological suppression. In a previous study HIV-1 infected individuals and especially children experienced a continued gain in body weight after starting HAART (Denue *et al.,* 2013). However, body weight was found to have subject variability with consistent mean body weight increases among the NVP based and EFV based treatment arms in the study period.

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Effect of HAART on liver enzyme (ALT)

All HAART drugs have a potential of causing severe hepatotoxicity (Adikwu *et al*., 2013). The results of this study tie with those obtained by another study by Lucien *et al.* (2010) which showed that HAART was associated with low level hepatotoxicity at therapy initiation, regardless of drug class. The lack of significant difference in the proportion of patients who experienced an increased enzyme activity between these two ARVs regimens could be due to the fact that Stavudine toxicity present on both arms of treatment could have masked the actual toxicity experienced by NVP. In another related study, patients who have been on HAART had significantly elevated ALT and AST levels but mild toxicity (Shakirat *et al*., 2014). Our study was also comparable with that of Kalyesubula *et al.* (2011) who in their retrospective cohort study determined the incidence of hepatotoxicity associated with (NNRTI) in a group of HIV infected patients who received EFV and NVP and the rate was similar among the treatment groups.

The findings in the current study were also comparable to those of Emily *et al*. 2010 who showed in a study on liver injury after receiving Nevirapine; that elevated liver enzymes was observed in their cohort. Other studies that showed similar results with our study are those on early hepatotoxicity during the first 12 weeks of treatment (Adikwu *et al*., 2013). In their analysis, the frequency of hepatotoxicity was 17% in the group receiving NVP and 0% in the EFV group. In another related study, data confirmed an increased risk of early hepatotoxicity associated with the use of NVP (Shakirat *et al*., 2014). The proportion of patients who had elevated ALT activity had tripled with each ARV therapy from month 3 to month 6. The increased activity of ALT was reported as a potential side effect of most ARVs used in the treatment of HIV infection. Kalyesubula *et al.* (2011) concluded in their study that hepatotoxicity occurs during HAART therapy and was more common in patients receiving NVP than those using EFV which is consistent with results of this study.

It has been reported in another study by Lucien *et al.*, (2010) that some patients who experienced serious liver toxicity with NVP did not develop hepatotoxicity during subsequent treatment with EFV, suggesting that toxicity was related to ARV and not to specific class (Lucien *et al.*, 2010). The high incidence rate of severe hepatotoxicity in the first 3 months of initiating ART necessitates the need for more frequent and careful monitoring of ALT levels early during therapy.

Effect of HAART on renal function

In our study, none of the patients had renal failure but the study showed that closer monitoring of renal function is essential in all HIV patients on HAART. This result is consistent with the study of Mainasara *et al.* (2014) which showed that HAART of Stavudine, Lamivudine and Nevirapine improve renal creatinine clearance functions among the HIV positive patients. Similar results were also obtained by Robert *et al*. (2015) on the study of predictors of renal outcome in HIV associated nephropathy.

HAART and other medical therapies for HIV related infections have been associated with both short and long term toxicities including nephrotoxicity.

Effect of HAART on haemoglobin levels

The present findings show that there is an association between anemia, decreased survival, and increased disease progression in patients with HIV infection. In our study, low platelets counts resolved in patients on ART and were probably not drug related. Thus monitoring of hemoglobin would have been enough to detect nearly all of the significant cases of anaemia. Metabolic abnormality associated with potent antiretroviral regimens including NVP may revert at least partially with time and after replacing NVP by EFV as observed in this study. In a different study haemoglobin changes following HAART varied by sex and age, but remained significantly associated with prognosis in both sexes (Florence *et al.*, 2011). Also studies from other developed countries suggest that use of HAART reduces the risk of anemia in patients with HIV infection and improves hemoglobin values in many patients who are already anemic at the time of HAART initiation (Simbarashe *et al.*, 2013). Our study showed decreased anemia

with HAART use, which supports data from prior studies which showed that patients on HAART had improved hemoglobin levels and less incidence of anaemia (Chauhan *et al*., 2011). Similarly, studies by Zelalem *et al*. (2014) found that HAART was an effective treatment for anemia of HIV infection, and the potential mechanisms that might be involved included a reduction in opportunistic infections and the anemia of chronic disease, and an improvement in nutritional status. Lower body mass index was also associated with a high risk of anemia.

Conclusions

The results from this study demonstrated that D4TC/ 3TC/ EFV and D4TC/ 3TC/ NVP combinations were safe, well tolerated and effective in increasing CD4 Cell counts and suppressing HIV progression in advanced HIV infected patients.

Recommendations for future steps

Patients with HIV should have their CD4 cell count monitored regularly before and after commencement of HAART before they reach immunological failure. The findings support the ongoing feasibility of early ART roll out in the country. Therapeutic monitoring may be a useful tool for the administration of HAART in the future. In the future, closer monitoring of renal function and adverse effects of HAART should be enhanced as these parameters appear elevated with time as patients continue to use the drugs. Renal function and Liver function should therefore be monitored on a regular basis in patients with HIV receiving any antiretroviral agent.

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