THE ONE-YEAR IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON QUALITY OF LIFE OF HIV-INFECTED NIGERIANS

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ABSTRACT

Objective: The availability of highly active antiretroviral therapy (HAART) has resulted in a number of achievements as well as challenges. The aim of this study was to assess the influence of 48 weeks HAART of stavudine, lamivudine and nevirapine on the quality of life of HIV-infected Nigerians.

Materials and Method: Quality of life indices of hemoglobin, platelet count, CD4 lymphocyte count, body weight, body mass index as well as questionnaire based outcome of adverse clinical events, general health perception and emotional effect of pill burden were assessed at baseline and compared with the 48 weeks therapy.

Result: There was a HAART-dependent improvement in the hemoglobin (2.48g/dl), platelet count (55.87 x 10^9/L), CD4 lymphocyte count (122 cells/µl) body weight (13.26kg) and body mass index (1.32) ($p < 0.005$). Current positive health perception increased from 53% at baseline to 87.3% after 48 weeks HAART. Body weight correlated with changes in CD4 count ($r = 0.4$, $p < 0.0001$). Emotional dimension of HAART related quality of life deteriorated within the 48 weeks of therapy due to long-term HAART-related incidence of overweight and truncal obesity, adverse clinical event of Steven Johnson's syndrome and high pill burden thus producing a negative effect on quality of life.

Conclusion: The study emphasizes the importance of HAART related quality of life survey particularly in resource poor settings in sub-Saharan Africa when there is desperate need for antiretrovirals. Efforts must be made towards simplifying the therapeutic regimen to reduce the number of daily doses and substitution with treatment combinations and strategies that minimize negative adverse effect to ensure that mortality and morbidity are minimize and quality life optimized.

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction of AIDS-related morbidity and mortality and HIV-disease has become one of relative chronicity for most HIV-infected patients [1-3].

Highly active antiretroviral therapy would thus be expected to have a positive effect on quality of life. Unfortunately however, up to 25% of patients discontinue their initial regimen because of treatment failure (inability to suppress HIV viral replication to below the current limit of defection- 50 viral RNA copies/ml), tolerability and concern related to drug toxicities [4,5].

Several studies both cross-sectional and longitudinal have focused on the HAART related quality of life (HRQL) of HIV-positive individuals in different stage of HIV-infection and under different antiretroviral regimens. The results have varied but in general HIV-infection has been shown to affect several physical, psychological, clinical and social dimension of HRQL and patients with symptomatic disease or an AIDS-defining complication are more severely affected than those with asymptomatic or other comparable disease [6,7]. HAART related quality of life has been shown to be related to the CD4 value, viral load and symptoms with patient with a more advanced state of HIV infection reporting poorer HRQL [8,9]. Moreover symptoms, physical functioning, role functioning and sexual function deteriorated over time [10] . Few studies have investigated the influence of long-term HAART on the quality of life of HIV-infected in the West. Nieuwkerk *et al* [11], compared the development of HRQL during 3 different protease inhibitor based regimens and concluded that in terms of HRQL, patient with higher CD4 values at start of therapy experience less benefit from treatment, Burgoyne *et al* [12] followed HRQL in 41 HIV-infected patients over a period of 4 years and found no overall change of HRQL and that HRQL has less sensitive to CD4 changes than to symptoms.

The Nigerian government subsidized antiretroviral therapy programme was initiated in June 2002. There is paucity of data on highly active antiretroviral therapy related quality of life of HIV-infected Nigerians on antiretroviral. The aim of this present research effort was to investigate HRQL indices of body weight, BMI, CD4, mortality and adverse clinical events within 48 weeks of HAART of two nucleoside analogues (stavudine and lamivudine) and one non-nucleoside (nevirapine).

SUBJECTS AND METHODS

This case study was conducted in the Hematology Department of the University of Port Harcourt Teaching Hospital. The hospital is a 500 bed hospital and in the cosmopolitan oil rich Rivers State in the heart of Niger Delta of Nigeria and one of the designated center for the

Nigerian government- assisted antiretroviral therapy program. Patients included in the longitudinal case study included 100 previously antiretroviral naive HIV-infected individuals (91 symptomatic and 9 asymptomatic) recruited into the Nigerian government sponsored antiretroviral therapy programme in the University of Port Harcourt Teaching Hospital. Inclusion criteria included age >18 years, HIV-positivity, previous antiretroviral naivity, non pregnant (for females) and willingness to give informed consent. Patients were placed on a fixed antiretroviral therapy combination of stavudine (40mg) lamivudine (15mg) and nevirapine (200mg) orally twice daily for a 48 weeks observation period. The study was conducted between March 2004 to April 2005). A pre-tested interviewer-administered questionnaire regarding demographics (age, sex) and quality of life indices of; perception of negative effect, adverse clinical events, physical ability and general health perception were obtained at baseline before the initiation of HAART and 48 weeks post.

METHOD

Ten milliliters of venous blood was collected from each participant into EDTA anticoagulated tubes (5 milliliters) and non-anticoagulated tubes (5 milliliters). Blood samples were analyzed within four hours of collection. Hemoglobin was determined using the Cyanmethaemoglobin method while platelet count was determined using the Breecher and Cronkite method of manual platelet count. Manual methods as described by Dacie and Lewis [13] were used for hematological analysis.

HIV SEROLOGY

HIV infection was documented by at least two laboratory test (two repeated ELISA test) of WHO approved Immunocomb HIV 1 and 2 kits (Orgenics, Israel) a rapid enzyme immunoassay test for the qualitative and differential diagnosis of antibody of HIV in human serum and Genscreen HIV 1 and 2 kits (Bio Rad, France).

CD4 T-CELL ENUMERATION

The CD4 T-cell enumeration was carried out using the Dynabeads technique (Dynal Asa Oslo, Noway). This is an alternative method to flow cytometry. It uses paramagnetic polymer beads with anti-CD4 monoclonal antibodies (mAbs) to capture and isolate CD4 T-lymphocyte from whole blood. Previous study by Diagbouga *et al* [14] suggested that CD4 values from Dynabeads techniques correlated positively with that from flow cytometry (r = 0.90).

BODY WEIGHT AND BODY MASS INDEX MEASUREMENT

Subjects were measured for height without shoes standing erect on a flat surface with a horizontal gaze and measurement taken to the nearest centimeter. Weight was recorded in kilograms (to the nearest 0.5kg) with subject

clad in minimum clothing using a flat scale on a firm horizontal surface [15]. Body mass index (Queletex index) was calculated by dividing the weight in kilograms (kg) by the square of the height (m2). The method is suggested as a diagnostics tool in monitoring disease associated with body wasting [16] .The WHO guideline classification of BMI defined underweight as BMI < 20; ideal weight as BMI of ≥ 20 but ≤ 25, over weight as BMI > 25 but ≤ 30, obesity as BMI > 30 but ≤ 35 and morbidity obese as BMI > 35 [17].Quelelet observed empirically that in adults this index is minimally correlated with fat mass measured densitometrically and adjusted for height (r = 0.9) for both men and women [18].

HAART RELATED QUALITY OF LIFE QUESTIONNAIRE

All subjects completed an interviewed-administered HAART-related quality of life questionnaire at baseline and 48 weeks follow-up visit. The questionnaire, which was designed to measure HRQL, consisted of indices such as physical functioning caloric intake, general health perception emotional dimension of high pill burden and adverse clinical events.

STUDY DESIGN

This is a case study involving 100 HIV-infected patients who were antiretroviral naive at entry randomized to take HAART of two nucleoside analogue, stavudine (40mg) and lamivudine (150 mg) and one non nucleoside analogue nevirapine (200mg) orally twice daily for 48 weeks. Indices of quality of life outcomes of CD4 lymphocyte count Hemoglobin value, platelet count, occurrence of adverse clinical events, general health perception were collected at baseline and compared with post 48 weeks values.

RESULTS

At baseline, the mean age was 34 ± 8.45, range 18-56 years) made up of 91 symptomatic and 9 asymptomatic patients. Baseline characteristics of subjects are shown in table 1. Mean of indices of health related quality of life of Hemoglobin (9.86 ± 1.76), platelet count (169.80± 61.43 $x10^9$/L), body weight (5 7.26 ± 11.76 kg), BMI (20.75 ± 4.55). The proportion of other outcomes like underweight (BMI < 20) was (46%), overweight (BMI greater than 25 but less than or equal to 30 was (12%) while 2.0% had obesity (BMI > 30). Analysis of pre-HAART questionnaire indicates that 47% of subject had a negative current health perception associated with low caloric intake while 53% indicated a current positive health perception.

Changes from Pre HAART to 48 Follow Up

From the Pre-HAART to the follow –up the CD4 lymphocyte count of surviving patients increased from a median of 235.60 (range 123 – 348.2 cell/μl) at baseline to 357.94 (288.21 -

427.67 cell/µl), hemoglobin from 9.86 (range 8.1 – 11.62 g/dl) to 12.34 (11.37 -13.3g/dl), platelet count from 169.80 (range 108.37 – 231 .23) to 225.67(180.47-270.87), Body weight 57.26 (range 45.5 -69.02) to 70.52 (range 61.74 – 79.3 g/dl), body mass index 20.75 (range 16.2 – 25.3) to 25.88 (range 22.02 – 29.74) ($P< 0.001$). The proportion of underweight (BMI < 20) declined from a pre – HAART value of 46.0% to 1.0% after 48 weeks, overweight (BMI > 30) increased from 2.0 to 11.3%. Analysis of 48 weeks post HAART questionnaire indicated that 87% of subjects attested to an increased daily caloric intake and a current positive health perception while 13% indicated a negative current health perception. Fifteen percent of subjects had evidence of Steven Johnson's syndrome. The incidence of cytopenia (anemia, leucopenia, thrombocytopenia and neutropenia) declined from baseline values of 94, 20, 36 and 40% respectively to 57.7%, 1%, 3.1% and 32% after 48 weeks of HAART. Evidence of lipodystrophy associated with truncal obesity was evident in 11% of subjects after 48 weeks HAART. Subjective experience of adverse effect of Steven Johnson's syndrome (rash) was observed in 15% of subject during the 48 weeks observational period. Mortality was observed in 3% of the study population. Mortality was found clustered among subjects who initiated therapy at a pre-HAART CD4 lymphocyte count of < 200 cells/µl, body weight of < 45kg and BMI of < 20. Body weight changes correlated positively with changes in the CD4 lymphocyte count ($r = 0.64$, $p < 0.001$).

CD4 lymphocyte response was compared based on pre-HAART CD4 lymphocyte count; < 200, 200 – 350 and > 350 cells/µl. On the average CD4 cell count had increased by at least 122 cells/µl irrespective of the pre- HAART CD4 count. CD4 lymphocyte response appear significantly higher in patients initiating HAART with lower baseline CD4 Count <200 cells/µl (163 cells/µl) compared to 118 cells/µl and 50 cells/µl respectively for those initiating at a pre-HAART CD4 count of 200-300 and > 350 cells/µl ($\chi^2 = 1.80$, $P< 0.05$).

Analysis of 48 weeks post HAART questionnaire indicated that 80% of subject developed an emotional negative effect to high pill burden of antiretrovirals while 20% felt otherwise while 87% indicated a current positive health perception and increased caloric intake indicating a negative effect on emotional HRQL. Table 2 shows the 48 weeks post HRQL indices of subject.

Figure I: Trend in the incidence of cytopenia among subjects

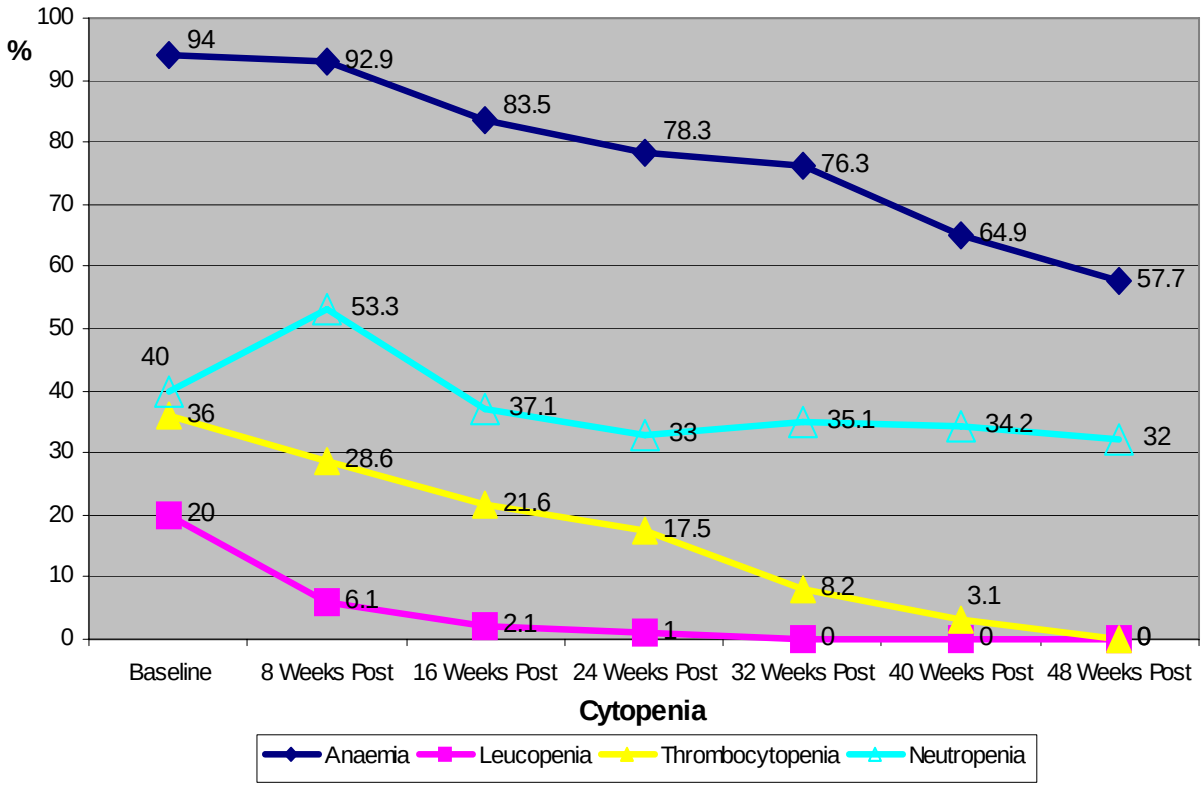

Table 1: Characteristics of study population at baseline

Parameter	Mean	SD	Range
HB (g/dl)	9.86	1.76	8.10 – 11.62
Platelet (x 10^9/L)	169.80	61.43	108.37 – 231.23
Body Weight (Kg)	57.26	11.76	45.5 – 69.00
BM	20.75	4.55	16.2 –25.3
CD4 (cells/µl)	235.60	112.59	123.01 –348.19
CD4 threshold <200	142.50	28.2	114.3 – 170.7
200 –350	273.06	45.47	227.57 – 318.53
>350	430.63	68.5	362.13 – 499.13

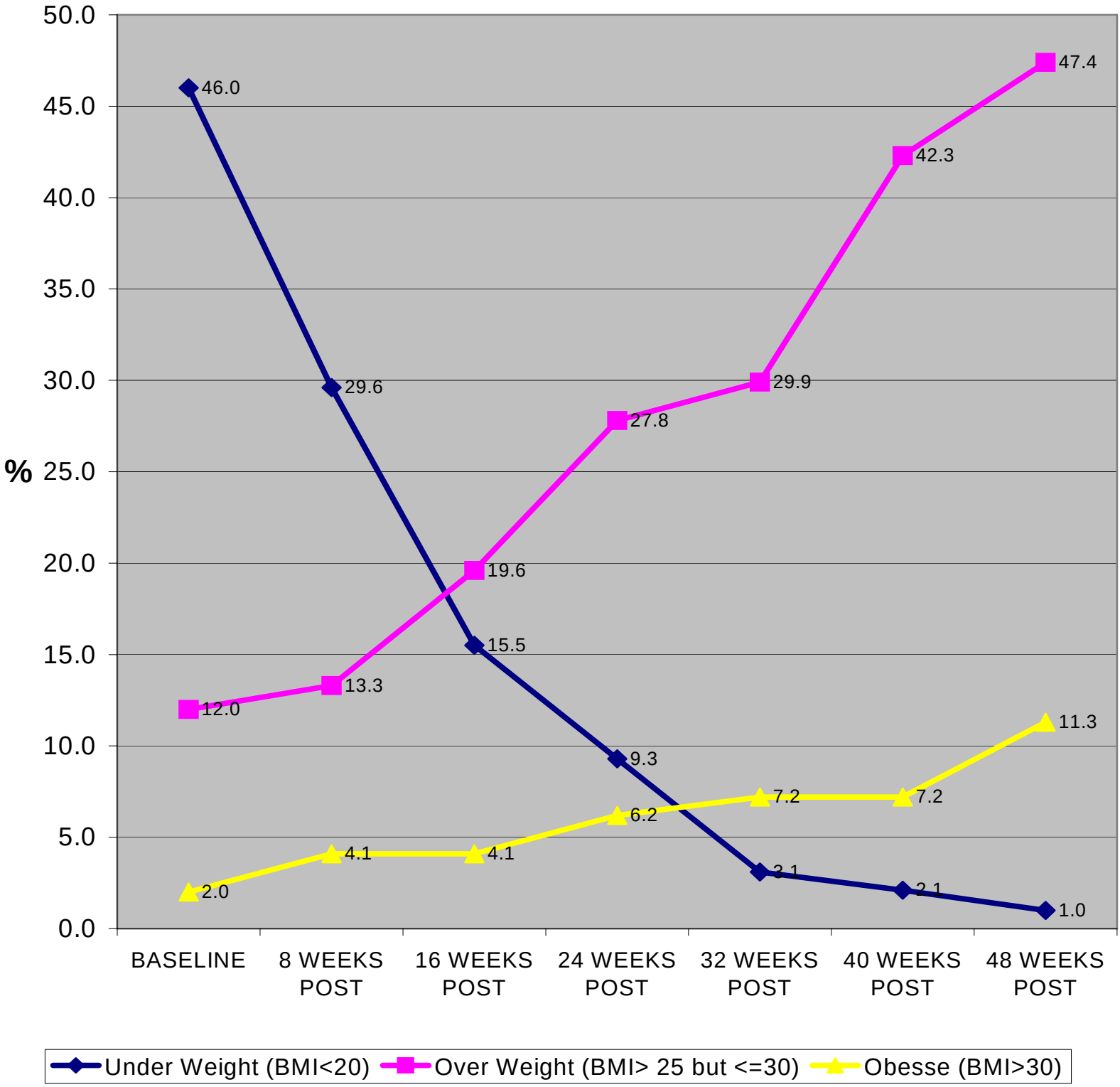

Figure II: Trend in incidence of underweight, overweight and obesity

Table 2: Characteristic of study population after 48 week HAART

Parameter	Mean	SD
HB (g/dl)	12.34	0.97
Platelet (x 10^9/L	225.67	45.20
Body Weight (Kg)	70.52	8.78
BM	22.07	3.65
CD4 (cells/µl)	357.94	69.73
CD4 threshold (cells/µl)		
< 200	305.22	12.95
200 -350	391.14	31.60
>350	480.63	58.20
Emotional HRQL outcome	**N**	**%**
Negative perception to pill burden	78	80
Increase caloric intake	87	87
Current positive health perception	87	87
Adverse clinical event	15	15
Lipodystrophy (overweight truncal obesity)	11	11.0
Steven Johnson's syndrome	15	15.0
Mortality	3	3%

DISCUSSION

In this study we have investigated the HRQL of 91 symptomatic and 9 asymptomatic patients before and after 48 weeks of HAART of two nucleoside analogues (stavudine and lamivudine) and one non-nucleoside (nevirapine). We have studied the patient's immunological, hematological outcome, experience of adverse clinical events, mortality and outcome of physical well being as indices of accessing the HAART related quality of life.

Anemia observed in HIV – infected patients at baseline in this study had a characteristic of anemia of chronic disease with hemoglobin of 10g/dl as previously suggested [19]. Many factors have been incriminated in the etiology of anemia associated with HIV infection, the secondary effect of drug therapy and other pre-existing or co-existing medical problem. Other compounding factors responsible for the high incidence of anemia may be malnutrition, malaria and other tropical parasitic infections.

The incidence of underweight defined as BMI (<20) at baseline was 46%. This observation is consistent with previous report [20] which found body wasting and weight loss significantly associated with HIV positivity. The high incidence of underweight observed in this study may have been attributable to the fact that 19% of subjects included in this study who initiated therapy with a pre-HAART CD4 count of <200 cells/µl presented with watery diarrhea. Weight loss in HIV – infected seems more severely associated with watery diarrhoea. Three sometimes overlapping process cause body

wasting in HIV- infected; reduction of food intake due to physical or physiological factors affecting appetite, economic factors affecting food availability, and nutritional quality, the side effect of drugs, nutrient malabsorption due to frequent diarrhoea and damage to intestinal cell by the virus.

Our study indicated a stable improvement in CD4 lymphocyte count (mean increase of 122 cells/µl). There was no immunological advantage in initiating HAART at a pre – HAART CD4 count > 350 rather than at 200 -350 or < 200 cell/µl (mean increase of 163, 118 and 50 cells/µl respectively) ($p<0.05$). This observation is consistent with previous report [21] which indicated that there is no immunological advantage in initiating ART at a CD4 count of > 350 rather than at 200-350 cells/µl.

Body weight and body mass index measured longitudinally increased consistently and significantly from baseline values (13.6 kg and 5.13) respectively. The weight gain correlated positively with increase in CD4 lymphocyte count. This finding is consistent with previous report [18] involving 19 patients with AIDS and AIDS related complex treated with zidovudine in which patients gained 2.2 kg during 8 weeks of therapy. Other studies [22, 23] observed an initial weight gain followed by a decline in patients treated with nucleoside analogue such as zidovudine and didanosine alone or in combination. Several hypotheses have been proposed to explain the mechanism of weight gain following HAART. The current explanation is that increased CD4 cell count following HAART may restore a cytokine balance that favors weights gain [24] or that HAART might help eradicate opportunistic pathogens that induce body-wasting [25].

Our study indicated a significant HAART- dependent decline in the incidence of underweight (BMI <20) from 46% at baseline to 1% after 48 week HAART and an increase in the incidence of overweight and obesity from baseline values of (1.2 and 20%) respectively to (47.4% and 12.3%) after 48 weeks HAART ($p < 0.05$). Adults HIV -1 infected receiving protease inhibitors (PI) therapy have developed a syndrome of lipodystrophy associated with overweight and truncal obesity [26]. Our report is consistent with previous suggestion [27] that protease inhibitor may not be the sole factor associated with body fat changes and that evidence of lipodystrophy (overweight and truncal obesity) may occur in HIV-infected on long-term HAART of two nucleoside analogue (stavudine and lamivudine) and one non-nucleoside (nevirapine). Lipodystrophy associated with overweight and truncal obesity can cause physical discomfort leading to reduced self-esteem and self-confidence, resulting in poor social functioning and social isolation thus negatively affecting the HRQL of HIV – infected.

Steven Johnson's syndrome was a common adverse clinical event observed in 15% of HIV-infected in this study. Adverse events can contribute a lot to deterioration in the emotional HRQL. Erlen *et al* [28] observed in previous study that side effects were one of the major problems associated with HAART. It is imperative that in order to improve the HRQL and adherence to HAART in HIV-infected, if may be crucial to find treatment combinations and strategies that minimize these negative effects and to individualize treatment.

Our 48 weeks post HAART questionnaire indicated that 80% of HIV-infected subjects developed a negative emotional effect to the high pill burden taken. Efforts must be made towards simplifying the therapeutic regimen to reduce the number of daily doses and substituting with regimens that are accompanied by fewer adverse effects wherever possible as previously suggested [29,30]. Emphasis on instruction of patients to take the medication is fundamental coupled with patient's participation in treatment decisions [31].

The effect of the number of pills has been studied. Taking a larger number of pills is likely to affect adherence due to greater difficulty involved. Difficulty in taking large number of pills can drastically affect adherence producing negative effect on HRQL of HIV-infected patient [32].

Our study indicated an AIDS-related mortality in 3% of subjects in this study. Mortality was found clustered among HIV-infected who initiated HAART at a baseline CD4 lymphocyte count, body weight and BMI of < 200 cells/μl, < 45kg and < 20 respectively. This observation has a negative effect on HRQL of HIV-infected and is consistent with previous reports [20] that mortality in HIV-infected can be predicted by the amount of weight loss in HIV-infected person and that mortality in HIV-infected initiating HAART are clustered in subjects initiating HAART with a pre-therapeutic CD4 count of < 200 cells/μl [33]. Nevertheless, it seems that a reasonable conclusion would be to focus primarily on CD4 lymphocyte count in determining the optimal time to initiate therapy in many HIV-infected patients. A CD4 count of < 200 cells/μl in peripheral blood appears to be the critical level and it would seem prudent to initiate therapy before CD4 cell count decreases below this level.

The result of this present study show the importance of HRQL survey particularly in sub-Saharan Africa with the highest disease burden and greatest need for antiretrovirals but with less than 8% of them having access .Our study has indicated that although HAART of stavudine lamivudine and nevirapine improves the hematological, immunological indices and the indices of physical well being on short term basis, its long – term use is associated with overweight and truncal obesity, producing a negative effect on physical HRQL. Subjective

experience of HAART related adverse effect could contribute to a negative emotional HRQL of HIV-infected. Finding treatment combination and strategies with the least negative long-term influence on HRQL is essential particularly at a time where there is promised price reduction in cost of antiretroviral to improve access in resource limited settings. There is also need for further short –term and long-term investigation of HRQL in patients receiving antiretroviral therapy. Findings from this study will help physicians gain a working knowledge of the adverse effects of HAART with the ultimate goal of improving the tolerability and effectiveness of treatment, promoting early recognition and reversal of potentially serious adverse effect

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