ORIGINAL ARTICLE

AFRICAN JOURNAL OF CLINICAL AND EXPERIMENTAL MICROBIOLOGY JANUARY 2005 ISSN 1595-689X VOL 6 NO 1
AJCEM/2004007/2505

INFLUENCE OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON THE SURVIVAL OF HIV-INFECTED PATIENTS: PART REPORT OF THE ILORIN TRIAL CENTER

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This report is part of the ongoing highly active antiretroviral therapy (HAART) trial, 167 patients were enlisted, but current analysis was restricted to 107 patients that were about a year old on the programme. The baseline weight, CD4+ cell count and serum albumin of 59 males and 48 females age 15-60 years, were compared with values at 12 months of administration of HAART. Patients mean weight, CD4+ count and serum albumin increased significantly (p-value < 0.05) by 9.7kg, 127.4/uL and 9.1g/L over the enrolment values. Side effects of antiretroviral (ARV) drugs were mild and included; rashes 19.6%, jaundice 7.5% and reactive arthritis 3.5%. Fifty-eight patients (59%) were alive by the end of 1 year, 33 (30%) had died and 11 (10.8%) were lost to follow-up. The risk of death increased 3 times when baseline CD4+ count was less than 116.8/uL (RR= 3.36, 95%CI=1.86– 6.06, P-value = 0.000048). TB/HIV co-infection raised the chance of death twice (RR= 2.33, 95%CI=1.31-4.15, P- value=0.005). In conclusion, the use of triple-drug combination of HAART has led to improved CD4+ cell count and resolution of clinical symptoms in HIV/AIDS patients. These resulted in increased survival.

Keywords: HAART, AIDS, CD4+ cells count and survival.

INTRODUCTION

The scourge of HIV/AIDS is progressing and causing devastation to lives and health care system worldwide. Most people infected with this disease live in resource poor countries, especially Sub Saharan Africa. Since the discovery of ARV drugs, there has been tremendous amelioration in the previously fatal clinical course of AIDS, these reflected in improved survival, decreased frequency and severity of opportunistic infection and improved quality of life (1).

However, despite the availability of these drugs and the increasing awareness of the immense benefit from it use, less than 5% of those who require treatment with these drugs have access to it (2). It has been estimated that in the year 2001 half of the 230,000 people receiving ARV in the developing world live in Brazil (2), while in the whole of Africa, the continent that is hardest hit by the HIV/AIDS pandemic, less than 50,000 people are receiving ARV therapy (2). This is why the Government of Nigeria should be commended on the recent provision of access to ARV drugs at a highly subsidized rate to the ever-increasing number of HIV/AIDS patients in the country.

As at 2003 there were about halve a million people living with AIDS in Nigeria, giving a national prevalence rate of 5.8% (3). Only 10,000 of this number have access to antiretroviral drugs (3). Government can be encouraged further to make continuous supply of these drugs one of her priorities among other contending health problems, if local evidences on the effectiveness or otherwise of these drugs are seen in the end users. Hence, we chose to document, using the experience of the ARV drug trial programme in our center, the influence of

HAART drugs on the survival of HIV-infected patients.

MATERIALS AND METHODS

University of Ilorin Teaching Hospital is one of the pilot clinical trial centers for the ARV drugs in the country, utilizing triple-drug combinations (one non-nucleoside; nevirapine and two nucleoside reverse transcriptase inhibitors; starvudine and lamivudine. The programme is at the concluding stage of its phase 2.

Adults Nigerian diagnosed by 2 different serological methods to be HIV positive, are eligible for inclusion in the programme. Patients referred from other health facilities were retested in our center before receiving ARV drugs. Cohorts of those who were about a year old on the programme were evaluated. Their records were analyzed for demographic information like age and sex. The clinical details, laboratory profiles and side effects of the medications were noted. Patients serial weights, $CD4^+$ cell counts and serum albumin were compared at enrolment and at 12 months of HAART administration using three set points: (i) clinical and immunological improvement on medication, (ii) death during the course of treatment, either in the hospital or at home, but reported by the relatives and (iii) lost to follow-up, when final outcome was not known.

Statistical method

Response to ARV drugs was determined clinically and immunologically by linear rate of increase in weight, serum albumin and $CD4^+$ cells count over the enrolment values. Paired-samples T- test was then employed to compare the means of each of these variables. Difference between the means was considered significant when p-value was less than 0.05. Risk of death was estimated by Chi-square analysis.

RESULTS

One hundred and seven patients, 59 (55%) males and 48 (45%) females, aged 19-60 years with a mean age of 36.4 years were seen during this period (Table1).

Table 1: Demographic and clinical variables of patients on antiretroviral drugs

Sex	Frequency	Percent
M	59	55
F	48	45
Age group		
15-24	11	10.3
25-34	35	32.7
35-44	39	36.4
45-54	14	13.2
≥55	8	7.4
Clinical features		
Fever	76	71
Diarrhea	69	64.5
Weight loss	67	62.6
Oral thrush	64	59.8
Tuberculosis	41	38.3
Rashes	31	29
Pneumonia	14	13.1
Clinical severity		
Stage 1	5	4.7
Stage 2	9	8.4
Stage 3	27	25.2
Stage 4	66	61.7

About 70% of these cases were in the 25-44 years age group. The most frequent clinical features were; fever 71%, diarrhea 64.5%, weight loss 62.6%, oral thrush 59.8% and rashes 29%. Tuberculosis occurred in 38.3% of the patients and pneumonia in another 13.2%. Over 85% of the patients fell within stages 3 and 4 of the WHO clinical staging system for HIV infection and disease.

The mean value of $CD4^+$ at enrolment was 194.9/ul; with a range of 40/ul -540/ul the lowest value occurred in 2 cases of TB. The mean serum albumin was

28.8g/L (range 15– 43g/L). There was statistically significant increase in all the monitoring variables (P-value < 0.0 5). Mean weight increased by 9.7kg, from enrolment value of 48.24kg to 57.9kg during the 12 months period (Table 2), while the mean value of $CD4^+$ cell count increased by 127.4/uL; from enrolment value of 194.9/uL to 322.3/uL. The weight was moderately correlated with the increase in $CD4^+$ count (correlation coefficient 0.58 (0.41-0.54). Mean values of albumin and Packed Cell Volume increased by 9.1g/L and 8.8% from baseline values of 28.7g/L to 37.8g/L and 24.1% to 32.9% respectively (Table 3). Increase in serum albumin was only mildly correlated with $CD4^+$ change (correlation coefficient 0.42 (0.08-0.39).

Adverse drug reactions occurred in 29 patients (27%) on ARV drugs. Twenty-one (19.6%) of these were rashes, '8(7.5%) had jaundice and 4(3.5%) had reactive polyarthritis. All resolved spontaneously. Fifty-eight (59%) patients were alive and receiving care, while 11 (10.3%) were lost to follow-up and 5 patients (4.7%) refused ARV drugs because of the belief that AIDS is not curable. Thirty-three patients (30.8%) died; their mean enrolment $CD4^+$ cell count was 116.8/uL. Twenty-one (64%) of the deceased had $CD4^+$ count below this value and only 11 out of the total survivals had $CD4^+$ count below 116.8/uL. The relative risk of death increased more than 3 folds when the $CD4^+$ count was less than 116.8/uL (RR= 3.36, 95% CI =1.86 – 6.06, and p-value = 0.000048) (Table 4).

Table 2: Changes in variables used to monitor response to HAARTS therapy

Variable	Mean at inception	Mean at 9 months	Difference in mean	Standard error	95% CI difference	P-value
Weight	48.2	57.9	9.7	0.64	-10.9 to -8.4	0.000
$CD4^+$	194.9	322.3	127.4	13.2	-153 to -100.9	0.000
Serum albumin	28.7	37.8	9.1	0.8	-10.6 to -7.4	0.001
PCV	24.1	32.9	8.8	0.72	-10.2 to -7.3	0.008

Table 3: Adverse effects of HAART and outcome of the pilot study

Variable	Frequency	Percent
Drug reaction		
Rashes	21	63.6
Jaundice	8	24.3
Arthralgia	4	12.1
Outcome		
Alive	58	54.2
Dead	33	30.8
Lost to follow-up	11	10.3
Refused treatment	5	4.7

Table 4: Factors responsible for death in HIV/AIDS patients on ARVS drugs

Variables	Dead	Alive	RR	95% CI	p-value
CD4 <116.8/uL	21	12	3.3	1.86-6.06	0.00005
PTB/HIV co-infection	21	18	2.3	1.31-4.156	0.005
PTB/CD4<116.8/uL	16	3	3.4	1.54-7.38	0.0007

Forty-one patients (38.3%) had PTB/HIV co infection, 18(44%) were still on ARV and anti-TB drugs, 21 (51.2%) died and 2(4.8%) were lost to follow-up. The risk of death in patients with co-infection was twice that of those with HIV infection only (RR= 2.33, 95%CI=1.31-4.15, p-value=0.005), while the risk of death was more than 3 folds in those with TB/HIV infection and $CD4^+$ less than 116.8/uL (RR=3.37, 95% CI=1.54-7.38). Of the 21 patients who died of TB/HIV co-infection, 16 had $CD4^+$ count less than 116.8/uL while only 3 of those who are alive and on treatment for both condition had count less than 116.8/uL.

DISCUSSION

The mean age of the HIV/AIDS patients was 36.4years with a slight male preponderance, M: F= 1.2:1. Over 70% of them were in the 25-44 years age group. The group that is prone to high-risk sexual behaviour such as multiple sexual partners and unprotected heterosexual intercourse. An individual living with HIV virus could develop AIDS from continuous replication of the virus, which will target the $CD4^+$ lymphocytes and other immune mediating cells of the body thereby decreasing the immune capability of such individual (4).

Knowledge of the life cycle of the HIV virus has led to the development of ARV drugs that also target the reverse transcriptase and the protease enzymes of the virus (4). Therapeutic trial of a triple-drug combination of ARV in our center showed disappearance or improvement of the enrolment symptoms and signs with associated significant changes in the clinical and immunological status of the patients. This experience was shared with similar trial programme of combination ARV therapy earlier conducted within and outside the country (5-8).

In this report, the mean weight of patients at enrolment increased by 9.7kg during the 12 months of ARV therapy and the mean baseline $CD4^+$ cells count increased by 127.4/uL over the same period of time. Serum albumin and PCV also increased by 9.1kg and 8.8% over their baseline values. Resolution of clinical symptoms that followed improvement in the patients' immunological status was reflected in the correlation coefficient of about 60% between the changes in the baseline $CD4^+$ cell count and the observed weight gained. Increase in $CD4^+$ cell count has been known to follow administration of HAART (9). This increase was even more in those receiving protease inhibitor-containing regimen (10) or better still showed a decrease in the viral load upon commencing ARV drugs (11).

In Nigeria, cost is an important limiting factor against the inclusion of protease inhibitors in the current combination of ARV regimen. The same could be said of provision of facilities for accessing and monitoring patients' viral load while on ARV therapy. The observed effectiveness of HAART in delaying the clinical progression of AIDS was not without some drawbacks. Thirty-three patients (30.8%) developed one form of reaction or the other; majority of these (63.6%) were rashes that resolved without intervention. Hepatic reactions occurred in 8 patients (24.2%). Medications were stopped momentarily in two of them. Four other patients (12.1%) developed reactive polyarthritis; it was effusive in two of them. They all responded to NSAID.

Outcome of this trial revealed that by the 12th month of the programme over 50% of the patients were alive and receiving maintenance care, while 11 patients (10.8%) were lost to follow-up and 5 patients (4.7%) refused administration of ARV drugs on the ground of lack of hope for survival. Thirty-three patients (30.8%) died, TB contributed to death in 21 (64%) of them, raising the risk of death more than twice. The risk of death was also raised by a low $CD4^+$ count, especially when it was lower than 116.8/uL. The risk of death was increased more than three times in those with count less than this. Combination of HIV/TB co-infection and $CD4^+$ count of less than 116.8/uL did not raise the risk of death more than that of a low $CD4^+$ counts alone. This probably suggests that baseline $CD4^+$ count is a very strong predictor of survival or death in AIDS patients. Some studies had earlier confirmed this observation (12, 13).

In the industrialized nations, much lower count of less than 72 cells/uL was associated with poorer outcome (14). Disparity in the predictive value of $CD4^+$ count of this magnitude could be a reflection of the advance level of care in terms of potent ARV drugs and prophylaxis against AIDS-related opportunistic conditions that are available to patients in the developed world. High mortality amongst AIDS patients in the developing countries could therefore be attributed to limited access to adequate health care (15). This is partly because of social stigma attached to people living with HIV/AIDS (16) and partly because of poverty, high cost of ARV treatment and lack of sufficient international financial aid to fund ARV treatment programme (17). Solving the problems of HIV/AIDS in Nigeria therefore, requires multisectoral collaboration especially from the private individuals and the organized private sectors to expand the scope of patients access to ARV drugs as it is currently being done in some African countries (18, 19).

In conclusion ARV drug was effective, albeit with minimal side effects, in stopping the clinical progression of HIV disease, it improved immunological and general well being of the patients thereby prolonging survival of people living with HIV/AIDS. Therefore we suggest; (i.) Early commencement of ARV drugs in all symptomatic HIV/AIDS patients, (ii) Treatment points of these should be increased from the current 25 trial centers to include all the general hospitals in the federation so as allow easy access to the drugs, (iii) Government should continue to make ARV drugs available at cheap and affordable cost, with inclusion of protease inhibitors in the treatment regimen, (iv) Government should sustain the current public awareness campaign about HIV/AIDS and continue the political and financial supports shown so far to ameliorate the suffering of Nigerians living with the virus, (v) Private individuals and organized private sectors should be encouraged to help fund ARV treatment programme.

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