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ORIGINAL ARTICLE

Immuno-virological Response to HAART in Human Immunodeficiency Virus -1 positive Patients Diagnosed at Age 50 or more in North Eastern Nigeria

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ABSTRACT

The aim of the present study is to document immunological and virological response to HAART in older patients in our environment. Patients were included in two age groups. Group 1 (G1) consisted of HIV-infected people 50 years or older (n = 133), and Group 2 (G2) were patients aged 17 – 40 years (n =94). Participant's immunological and virological parameters were determined using standardized techniques outlined in the body of the work at baseline, 6, 12, 24 and 30 months and evaluated. Three outcomes were considered for the study: 1. Immunological success (IS): defined as T lymphocytes CD4+ cell count >200cells/µl at the end of the follow-up; 2. Virological success (VS) defined as a HIV viral load undetectable (≤200 copies/ml) at the end of the follow-up; 3. Viroimmunological success (VIS) defined as undetectable HIV viral load (≤200 copies/ml) and CD4+ T cell count ≥ 200 cells/ul at the end of the follow-up. Group 1 (G1), older patients showed higher proportion of men than Group 2 (G2). The baseline mean of CD4+ T count and viral load log 10 was similar in both groups. There was a progressive linear enhancement of CD4 +T count and viral suppression in both groups at assessment period throughout the follow-up. IS was observed in 115 (86.7%) of the G1 and 85 (90.4%) of the G2 (p = 0.67).VS was observed in 104 (78.2%) of G1 and 77 (81.9%) of G2 (p = 0.606). VIS was observed in 107 (80.45%) of G1 and 76 (80.85%) of G2 (p = 0.757). Older patients tend to have initial blunted immunologic response; while younger have a higher probability of achieving reduction in HIV-RNA viral load level. However, both elderly and younger naive patients on HAART display similar virological and immunological success and outcome.

Key words: *HIV, AIDS, VS,IS, VIS*

INTRODUCTION

The widespread use since 1996 of combination antiretroviral therapy (ART) has substantially improved the prognosis of human immunodeficiency virus (HIV)-infected patients [1-3]. In the era of highly active antiretroviral therapies (HAART), the magnitude of immunological and virological responses to treatment constitute strong predictors of disease progression and death among HIV-1-infected patients [4,5]. Published data regarding immunologic and virologic response by age to HAART has been mixed. Some studies have demonstrated a smaller increase in CD4 cell count in older compared with younger adults, [6-12] whereas others have been equivocal [13-17]. Some studies have demonstrated increased virologic suppression in older compared with younger adults[6-12,18] (which was hypothesized to be adherence-driven [7,19], whereas a study reported the reverse,[20] and many other studies have reported no differences [10,12,15,17,18,21]. Recent studies have suggested that all-cause mortality in patients successfully treated with ART might approach that of the general population, and that in many patients mortality rates are comparable with other chronic conditions, such as diabetes [22-26]. In the past, there was little attention to older people with HIV infection due to the little number of them. Over the last years, the proportion of old individuals infected with HIV is increasing. Thus, HIV-infected people grow older and live longer. Antimicrobial therapy and chemoprophylaxis have also allowed the increase survival of people living with HIV infection [27]. The aim of the present study is to document immunological and virological response to HAART in older patients in our environment.

METHODS

Study Area: The study was conducted in the Department of Medicine, University of Maiduguri Teaching Hospital, Borno State. This is a 500 bedded hospital designated as a Centre of Excellence for infectious diseases and provides primary, secondary and tertiary services for the North Eastern part of Nigeria. It also caters for the neighbouring Countries such as Cameroon, Niger and Chad Republics. Maiduguri the capital of Borno State is situated in the North Eastern Nigeria and the largest settlement near the Lake Chad.

Study design

Retrospective cohort study (2007- 2010)

Ethical consideration: Permission was obtained from the University of Maiduguri Teaching Hospital (UMTH) Ethical Committee; Written Informed consent (signed or thumb print) was obtained from patients.

Study population: Two hundred and twenty seven HAART eligible patients consisting of 133 patients aged 50 years and above and 94 patients aged 17-40 years who had complete data were considered for this study. Using a structured, pre-evaluated questionnaire, information was obtained on demographic characteristics, clinical manifestation, medication used, blood transfusion, sexual and drug use behaviour from their records. Participants received their free monthly HAART supply and drugs for opportunistic infection(s) where necessary from the Harvard PEPFAR assisted ARV programme including adherence counselling. All participants considered for this study had a documented adherence of at least 80%.

Participants were classified according to the CDC 1993 revised classification system for HIV infection and expanded AIDS surveillance case definition for Adolescent and Adult [28]. Two groups were defined taking into account the age at the time of diagnosis. Patients were included in two age groups. Group 1 (G1) consisted of HIV-infected people 50 years or older (n = 133), whereas Group 2 (G2) consisted of patients aged 17 – 40 years (n = 94). Similar to previous studies [9,11,13,17,29,30], patients aged between G1 and G2 groups were excluded in order to separate both groups. It was decided that the cut off would be 50 years old considering many previously HIV-infection studies data as well as most significant immunological change take place around this age. The time of the beginning of HAART was considered as baseline in the analysis. All subjects underwent periodical clinical evaluations including determination of CD4+ T cells and HIV viral load every six months. Adherence was defined through a self-reported evaluation by the patient and registered as percentage by the physician. An evaluation higher than 80% was classified as "adherent", whereas lower as 80% was considered as "non-adherent" and were excluded from this study.

Three outcomes were considered for the study: 1. Immunological success (IS): defined as T lymphocytes CD4+ cell count >200cells/µl at the end of the follow-up; 2. Virological success (VS) defined as a HIV viral load undetectable (≤200 copies/ml) at study end point; 3. Viro-immunological success (VIS) defined as either undetectable HIV viral load (≤200 copies/ml) and CD4+ T cell count ≥ 200 cells/ul at study end point.

Blood samples Analysis

Data obtained from analysed blood sample obtained from each participant at baseline, 6, 12, 18, 24 and 30 months were subjected for analysis. Sample for CD4+ T cell count was collected between 9:00-10:00am and assayed within 6 hours of collection of whole blood and analysed using standardized flow cytometricCyflow machine (manufactured by Cytec, Partec, Germany 2005. While plasma HIV RNA levels was measured using freshly frozen specimen separated within 6 hours of phlebotomy utilizing the Amplicor HIV-1 Monitor Test, version 1.5 Manufactured by Roche® Germany, with a minimum cut off value of 200 copies per ml.

Statistical analysis

Software program SPSS 11.5 (SPSS Inc, Chicago IL) was used. Group comparisons were performed using Chi-squared test. However, if a cell of the table had few expected cases (< 5), Fisher exact test was used. The mean increase in the CD4 cell count and the mean decrease in viral load over time were studied using a mixed ANOVA procedure. Two-Way ANOVA from random factors were used where age group, and time were fixed factors, and patient was random factor. This model studies effect of age, time and interaction between age and time, on CD4 cell count or viral load. $P < 0.05$ was considered significant.

RESULTS

From a database of 950 HAART naive but eligible HIV-1 patients studied for part II (West African of Physician) Dissertation, 122 (12.8%) subjects aged ≥ 50 years that had HAART for 30 months were identified and evaluated, their data analyzed for virological and immunological outcome. Data was available for 94 younger patients aged between 13-40 years. At the enrolment, the mean time between HIV diagnosis and therapy initiation was 20.6 ±12 (14-58) days. The mean age of G1 and G2 group 57.50 ±6.70 (52-79) and 33.86±5.59 (17-40) P=0.000, respectively.

Baseline characteristics

Table 1 shows the demographic and baseline clinical, immunological and of the study participants. Group 1 (G1), older patients had more males (70%), where as Group 2 (G2) showed a female preponderance (74.5%). Taking AIDS criteria into account, there were similar proportion of participants advanced disease (AIDS) in both group (p=0.189). Heterosexual routes of transmission was the presumed risk factors for HIV infection in the two groups, but twenty nine (21.8 %) cases in G1 reported unknown risk factor compared to 4 (4.3%) in G2 (p =0.000). The baseline mean of CD4+ T cells in G1 compared to G2 (179.98±131.59 cells/µl vs. 208.82 ± 161.87; (p=0.140). Mean of HIV viral load log was similar in the two groups (5.08 ± 2.37 vs. 5.23 ± 2.65 copies/ml; p = 0.655). The prevalence of HBsAg positivity was not significantly higher in either group, no participant tested positive for HCVab.

HAART related immunoreconstitution

Comparing the mean values obtained at baseline in both group with those obtained at the end of the follow-up, a statistically significant increase in CD4+cell count was observed. The CD4+ cell count determined at 6month increased from 208.92 ± 161.87 to 281.77 ± 166.21 for G1 (p =0.625), and from 179.98 ± 131.60 to 291.61 ± 181.88 for G2 (p = 0.000). After 6 month of HAART There was a progressive linear enhancement in both groups at any individual time of the follow-up. The increase in CD4 count at 6 month in G1 was not significant at baseline (p=0.625), in contrast to G2 (p=0.000) in comparison to baseline. After 6 month the enhancement in CD4 count became significant in both arm, this trend persisted until the end of the follow-up. The increasing value of T CD4+ cell count every six months in respect to baseline was comparable in the two groups (Table 2). According to the above mentioned outcome definition, IS was observed in 115 (86.7%) of the G1 and 85 (90.4%) of the G2 (p = 0.67) at the end of the study (Figure 1). The following variables were significantly associated with IS at univariate analysis: CDC stage A (p = 0.01), CD4+ T cell count at the beginning and at 6,12,18,24,30,36 months of HAART (p = 0.03), months to achieve CD4+ T cell >200 cells/µl (p = 0.01), enhancement of CD4+ T cell count in the first six months (p 0=0.01) undetectable HIV viraemia at 30 months (p = 0.01).

HAART related viral suppression

A statistically significant reduction of HIV viral load was observed in both groups when comparing baseline with the study end point values. In particular, means of HIV-RNA viral load log10 decreased in 6 months from 5.08 ± 2.37 to 4.78 ± 1.37 copies/ml in G1 (p =0.207) and from 5.32 ± 2.65 to 4.52 ± 1.02 copies/ml in G2 group (p =0.016). HIV viral load reduced under antiretroviral therapy in both groups in a comparable manner. In fact, despite significant difference in viral suppression after 18 month, there was no statistically significant difference in proportion of G1 and G2 group that achieve viral suppression. (Figure 3). According to the above mentioned outcome definition, VS was observed in 104 (78.2%) of G1 and 77 (81.9%) of G2 (p = 0.606) as depicted in Figure 2. The following variables were significantly associated with VS at univariate analysis: CDC stage A (p = 0.02), undetectable HIV viral load at 6 (p = 0.03) and 24 months (p = 0.02).

HAART related virological and immunological outcome

According to our definition of the outcome, VIS was observed in 107 (80.45%) of G1 and 76 (80.85%) of G2 (p = 0.757). The following variables were significantly associated with VIS at univariate analysis: CDC stage A (p < 0.01), CD4+ T cell number at baseline and at 6,12,18,24,30,36 months of HAART (p < 0.01), enhancement of CD4+ T cell count in the first six months (p = 0.01), undetectable HIV viral load at 6 (p = 0.04) and 30 months (p = 0.01). No statistical difference in immuno-virological outcome was found between G1 and G2 in this study.

Table 1. Characteristics of the sample and its subgroups at first visit.

Characteristics	Total sample	Group 1 (G1)	Group 2 (G2)	p-value
Sample size (n)	227	133	94	
Age (years)		57.50±6.70(52-79)	33.86±5.59(17-40)	
Sex n (%)				
Male	117(51.5)	93(70)	24(25.5)	0.000
Female	110(48.5)	40(30)	70(74.5)	0.000
HIV risk factor				
Heterosexual	194	104(53.6)	90(46.4)	0.230
Unkown	33	29(87.9)	04(12.1)	0.000
Blood transfusion				
IDU	0	0	0	
MSM	0	0	0	
AIDS criteria n (%)				
Yes	136(72)	71(74.7)	65(69.2)	0.446
No	53(28)	24(25.3)	29(30.8)	0.446
CD4 count (cells/µl)	196.93±150.45	208.82±161.87	179.98±131.59	0.141
Viral load (log10)	5.15±5.53	5.08±2.13	5.15±3.40	0.860
HBsAg: n (%)				
positive	28(14.2)	14(12.8)	14 (14.9)	0.797
Negative	169 (85.8)	95(87.2)	74 (78.7)	0.127
Anti-HCV: n (%)				
positive	0 (0)	0 (0)	0 (0)	
Negative	183(100)	95(100)	88(100)	

Table 2. CD4 + T count in patients on Highly Active Anti Retroviral Therapy (HAART)

Treatment duration (month)	Group 1 (G1)	Statistical significance[a]	Group 2 (G2)	Statistical significance[a]	Statistical significance[b]
Sample size (n)	133		94		
0(Baseline)	208.92±161.87	-	179.98±131.60	-	0.140
6	281.77±166.21	0.625	291.61±181.88	0.000	0.002
12	341.59±206.80	0.000	350.40±196.01	0.000	0.746
18	357.15±190.64	0.000	383.44±181.42	0.000	0.298
24	431.28±258.22	0.000	431.30±219.23	0.000	1.000
30	432.18±242.85	0.000	533.30±376.08	0.000	0.004

Data presented as mean ± SD (cells/µl).

[a]Statistical significance versus baseline; least-squares difference of one way analysis of variance.

[b]Statistical significance of CD4 count group 1 (G1) versus group 2 (G2); least-squares difference of one way analysis of variance.

Table 3. Viral load in patients on Highly Active Antiretroviral Therapy (HAART)

Treatment duration (month)	Group 1 (G1)	Statistical significance[a]	Group 2 (G2)	Statistical significance[a]	Statistical significance[b]
Sample size(n)	133		94		
0 (Baseline)	5.08±2.37	-	5.23±2.65	-	0.065
6	4.78±1.37	0.207	4.52±1.02	0.016	0.120
12	4.34±1.88	0.005	4.34±1.17	0.003	1.000
18	4.39±1.39	0.005	3.91±1.47	0.000	0.013
24	4.31±2.25	0.007	3.36±1.32	0.000	0.000
30	3.91±1.65	0.000	3.23±1.75	0.000	0.000

Viral load expressed as log10.

Data presented as mean ± SD.

[a]Statistical significance versus baseline; least-squares difference of one way analysis of variance.

[b]Statistical significance of viral load log^{10} between Group 1(G1) versus Group 2 (G2); least-squares difference of one way analysis of variance.

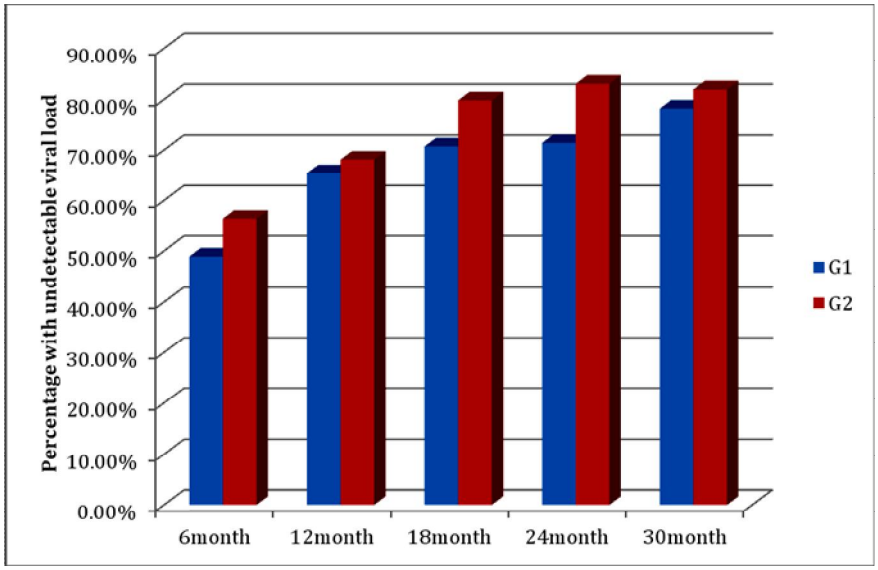

Figure 1. Proportion of patients by age group who achieved undetectable viral suppression

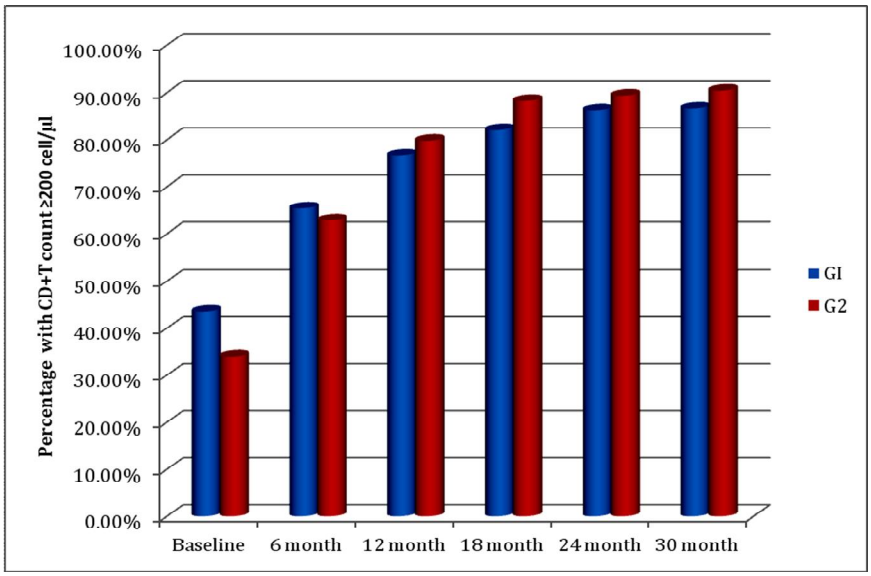

Figure 2. Proportion of patients by age group with CD4+Tcount ≥200cells/µl

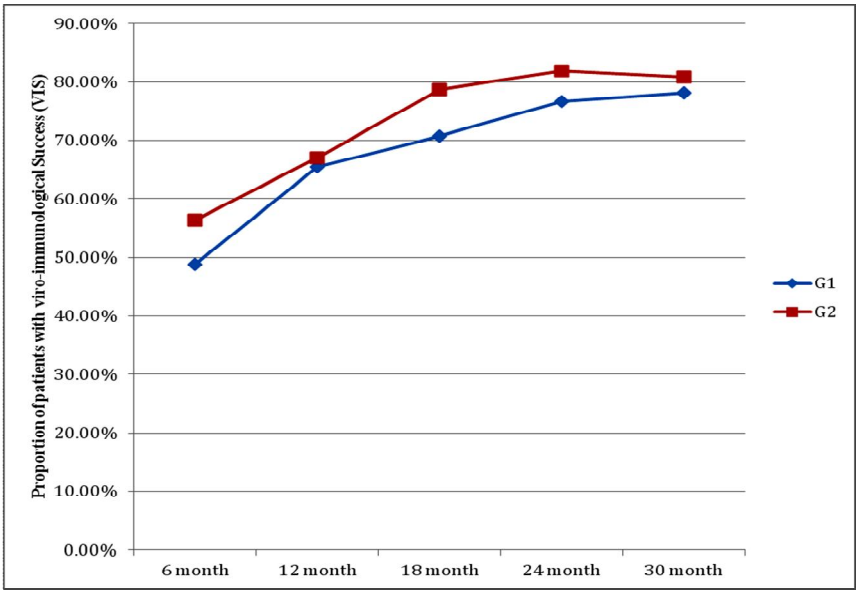

Figure 3.Viro-Immunological Success (VIS) by group in response to HAART

DISCUSSION

Highly active antiretroviral therapy (HAART) therapy entails treatment with a combination of two nucleoside reverse transcriptase inhibitors and a potent protease or non-nucleoside reverse transcriptase inhibitors, and has generally been taken as the gold standard for management of HIV patients [31], its use is effective in increasing CD4 cell counts, decreasing the virus load, morbidity and mortality in HIV positive patients. Since 1996, when HAART became widely available, elderly patients infected with HIV are a growing population [31, 32]. Therefore, HIV-infected individuals have prolonged survival and they enjoy good life conditions for longer [32]. Few data have been published concerning the specific response of older patients to new HIV antiretroviral treatments, and currently there are no guidelines for specific antiretroviral treatment modalities for patients>50 years of age.

Regarding HIV-risk behaviour, our data indicate the heterosexual route as the most frequent in patients, followed by unknown risk, no homosexual contacts or intravenous drug abuse was observed. In particular, our data confirm recent reports [33,34] indicating an increased incidence of HIV subjects with no risk reported. Remarkably, the number of older individuals whose risk behaviour was unknown was much higher than the number of younger patients. The HBV seropositivity was similar in both groups, while prevalence of antibodies against Hepatitis C virus was not detected in any participant. This finding could be due to rare practice of injected drugs an important mode of Hepatitis C spread in our cohort.

Our study demonstrates that despite modest differences in initial immunological and and late virological parameters, there was no difference in proportion of participants in both group with respect to virological and immunological success and outcome. Research from previously published studies fails to present a consistent association between age and CD4 T cell count and HIV RNA level responses to HAART. This may be due in part to small sample sizes or to lack of multivariate adjustment for key factors. Few studies [6,32] have included more than 100 patients 50 years or older; few studies [13,17,29,33] have adjusted for adherence. Despite similar high adherence in our cohort, we determined that patients 50 years or older and younger patients have similar virological success in responses to HAART. We found that patients 50 years or older had a blunted immune recovery in the first 6 month after HAART initiation, which may be due to immune senescence because no other factors examined explained this finding. Subsequent recovery of immune function was however faster among younger patients, so that by 30 month, there were significant age group differences in the mean CD4 T-cell counts. Prior studies looking at the effect of age on immune response to HAART have shown mixed results. Some studies [6,10,11,27,34,35] demonstrate a blunted immune recovery among older patients, while other studies [9,13,16,17.30,36] demonstrate no differences in CD4 T-cell count change by age, and a study(14) among women indicated a greater immunological response with older age. The age has been associated to deficiencies in the immune system, with a progressive depletion of lymphocytes [34,37, 38]. Moreover, thymic volume, which decreases with age, is associated with recovery of CD4 T cells [20, 39]. Previous study suggest substantial output of CD4 cells can be maintained in advanced age, even with less thymic function. Thus, HAART therapy contributes to immune recovery in older patients, too [13]. Nevertheless, there are controversies with respect to immune-virological response between older and younger patients. Some studies show that older patients have poorer immune response [34,35]. In contrast, some surveys seem to demonstrate that virological and immune response in older HIV infected people receiving HAART is similar to that of younger patients [9,16,17,32]. For instance, Perez et al. observed older patients have a great benefit associated with HAART, suggesting lower survival in older people was due to late diagnosis [40]. Tumbarello et al. have demonstrated that older patients under HAART therapy can achieve the same response, although they present a more severe HIV infection [17]. According to our results, it is felt that our analysis agrees with similar virologic and immunologic success and outcome. Older patients constituting higher proportion and higher but non significant CD4 count achieved a similar virologic -immunologic success at each stage of assessment in our cohort. This may imply that faster progression to AIDS and shorter survival in older patients may be due to other factors such as delayed diagnosis and thus a smaller chance of having received antiretrovirals. Our study is in agreement with previous work that showed a similar virological and immunological outcome in older and younger HIV-positive subjects [9,16]. This 30 month

observational study not only confirms this observation but indicates that older patients under HAART experienced a successful virologic and immunological response in line with preliminary reports [17,41,42].

CONCLUSION

Older patients tend to have initial blunted immunologic response, while younger have a higher probability of achieving reduction in HIV-RNA viral load level. However, both elderly and younger naive patients on HAART display similar virological and immunological success and outcome.

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