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CD4 Decay Rate as an Indicator of the Time Interval between Initial Infection and First Diagnosis among Drug-Naïve Human Immunodeficiency Virus Seropositive Individuals in Lagos, Nigeria

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Key Words
Human immunodeficiency virus · CD4 decay · Nigeria

Abstract
Objective: The aim of this study was to determine the time interval between human immunodeficiency virus (HIV) infection and the first diagnosis among drug-naïve individuals in Badagry, Nigeria. ***Subjects and Methods:*** A sample of 213 subjects who tested HIV positive for the first time were enrolled in this study. The HIV diagnosis was performed using Startpak® and Determine® kits, and a CD4 count was carried out using a FACS Count® flow cytometer. The mean CD4 values were determined by gender and age groups. The time interval between initial HIV infection and first testing was calculated based on the average CD4 decay rate per calendar year, and data analysis was performed using SPSS software. ***Results:*** At diagnosis, the mean CD4 values showed that females recorded 270 cells/μl and males 244 cells/μl. By age range, individuals <25 years recorded 437 cells/μl, those between 25 and 40 years of age had 237 cells/μl, and those aged ≥41 years had 192 cells/μl. There was a significant difference between CD4 cell categorization and age range ($p < 0.001$). Subjects aged between 25 and 40 years recorded the highest distribution of all CD4 cell counts. The time interval between infection and testing for females was 8.1 years and for males 6.7 years. Within the age group <25 years the interval was 5.1 years, whilst it was 8.1 years for those aged ≥41 years. ***Conclusion:*** Most of the population presented for testing during the advanced stages of infection. We suggest an upscaling of HIV voluntary counseling and testing to encourage early detection and better treatment outcomes.

Introduction

The human immunodeficiency virus (HIV) was first reported in Nigeria in the year 1985 [1]. A recent report by the United Nations Acquired Immunodeficiency Syn-

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drome program (UNAIDS) put global HIV infections at about 38 million people [2]. The adult working population was reported to be the most affected group, with sub-Saharan Africa being the worst hit region, with an average of about 1 in 20 adults being affected [2]. In Nigeria, however, the latest data from the National HIV/AIDS and Reproductive Health Survey (NARS Plus) puts the national prevalence rate at about 3.4% [3].

HIV infects a diverse population of cells, including glial and dendritic cells, and tissue macrophages [4]. However, during the acute and asymptomatic latent stages, the cell population most depleted by infecting virions is the CD4+ T lymphocytes, thus causing a progressive decline in the number of these cells, leading to severe immune compromise and immunosuppression [4–6]. Hence, staging of HIV disease is based on the number of circulating CD4+ T cells. In Nigeria, current treatment guidelines are based on estimated CD4+ cell counts, and clients are enrolled for antiretroviral (ARV) therapy (ART) if and when their mean CD4 count is ≤250 cells/μl [7, 8]. Previous studies have shown that the therapeutic outcome and CD4 T cell recovery can be influenced by the time at which care and treatment is initiated [8–10]. There is an ongoing debate on the need to review the current enrolment criteria into the ARV program in Nigeria, as has been done in other parts of the world [8].

Therefore, the aim of this study was to investigate the average time between the first detection of HIV antibodies and time of initial infection of HIV based on the annual CD4 decay rate among subjects in Badagry, a populous border city in southwest Nigeria with access to ART. The study also aimed to identify at what stage immunologically HIV-infected subpopulation groups presented for care and therapy in Badagry.

Materials and Methods

Study Area and Study Population

The study was conducted at the Heart to Heart Center, a HIV/AIDS care and treatment center located within the General Hospital Badagry, Lagos, Nigeria. Badagry is an international border town between Nigeria and the Republic of Benin. It is an old slave trade port town and a fishing hub with lots of commercial activity. The two major ethnic groups residing in the area are the Egun and the Yoruba, although other ethnic groups like Hausa and Igbos also reside and trade within the town.

Study Design

The study was a cross-sectional study of 213 (70 males and 143 females, age range 1–68 years) drug-naïve subjects enrolled into the ARV program at the General Hospital Badagry between October 2007 and May 2008. Ethical approval was obtained from the Institutional Ethics Committee. Written informed consent was sought from study participants before sample collection; where written consent could not be provided, oral informed consent was sought and obtained. Consecutive sampling was adopted for this study. The inclusion criteria were age ≥16 years and no previous history of ART.

Laboratory Analysis

Serological diagnosis was performed using a double enzyme immunoassay rapid screening protocol using Startpack® (Chenmio, Medford, N.Y., USA) and Determine® (Abbot Labs, Abbott Park, Ill., USA) according to the manufacturer's instructions. A flow cytometer (FACS Count®; Becton Dickinson, San Jose, Calif., USA) was used to count P4T lymphocytes. Briefly, whole blood was collected through venipuncture from the forearm. Samples were then stained and incubated with anti-CD4 and CD8 monoclonal fluorescent antibodies according to the manufacturer's instructions, specific for identifying populations of CD4- and CD8-expressing lymphocytes.

Grouping of the CD4 data was done according to the WHO-recommended criteria for ART enrollment [6], using the individual CD4 count values. The CD4 count at the time of initial enrolment was used as an indicator of the time delay between HIV infection and diagnosis, based on the average CD4 decay per calendar year among all 213 drug-naïve participants, as previously described [7]. The formula used to determine the approximate time when HIV was acquired based on CD4 values is $t = N - n/80$, where t is the approximate time of initial HIV infection, n is the mean CD4 count at initial diagnosis, 80 represents the approximate annual CD4 decay rate [11], and N is the average reference CD4 count among Nigerians, which is given as 782 cells/μl for males and 920 cells/μl for non-pregnant females, and 847 cells/μl for both genders combined, including pregnant women [12]. The grouping of CD4 cell values was done in accordance with WHO criteria [13]. A factor of approximately 3 cells/μl per 10-year increase in age was subtracted from the reference value to make an allowance for age-related CD4 variation following the model reported in the COHERE study [13, 14].

Statistical Analysis

A descriptive statistical analysis was used to initially analyze the characteristics of the study population. The statistical analysis was performed using SPSS version 20.0 (SPSS, Chicago, Ill., USA), with analysis of variance (ANOVA) used to test for significance between mean values and $p < 0.05$ considered as significant.

Results

The median age of the subjects was 33 years (range 1–68). The CD4+ cell count among the population ranged from 2 to 1,143 cells/μl, with a median value of 188 cells/μl. The percentile (0–25, 25–50, 50–75 and 75–100%) CD4+ cell values were 86, 188, 333 and 2,000 cells/μl, respectively. Females had a higher mean CD4 value than males (270 vs. 244 cells/μl). The highest mean CD4+ value of 437 cells/μl was recorded in the age group <25 years, while the lowest mean value (192 cells/μl) was recorded

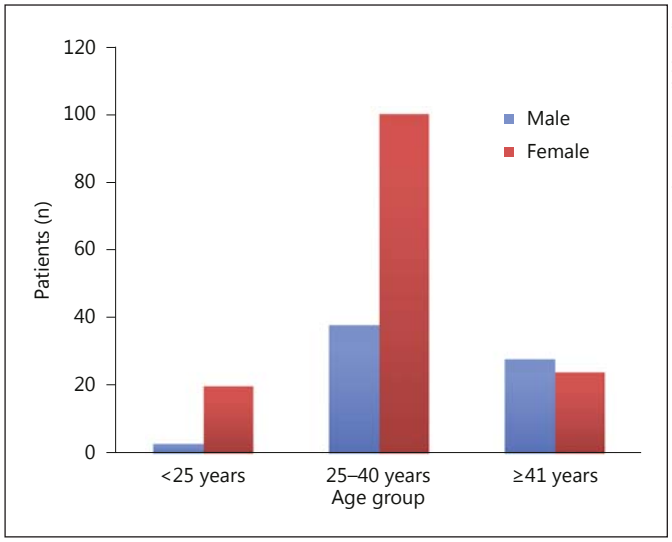

Fig. 1. Gender distribution across age groups. The differences observed between the groups were significant ($p < 0.0001$). Of the study population, 67% were female and 64% were aged between 25 and 40 years, with females constituting 74% of this age group.

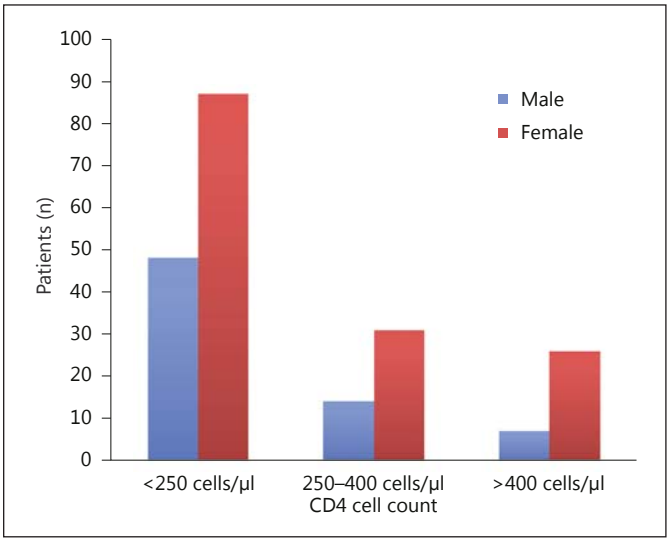

Fig. 2. Gender distribution of CD4 cell counts.

in the age group ≥41 years. The distribution of the study population based on age and gender is shown in figure 1.

Categorical Distribution of CD4 values

The gender distribution of the CD4 cell counts based on the WHO enrolment criteria is depicted in figure 2, showing that females had a higher number of CD4 cells among the 3 different groups. The distribution of CD4 cells by age group revealed that CD4 values <250 cells/µl were recorded by 86 (63.7%) participants aged between 25 and 40 years, 29 (28.9%) patients aged ≥41 years and 10 (7.4%) patients aged <25 years. A similar trend was observed for CD4 cell counts organized by age group, with 33 patients (73.3%) within the age range of 25–40 years having a cell count of 250–400 cells/µl, followed by 10 patients (22.2%) aged ≥41 years and only 2 patients (4%) aged <25 years, as shown in figure 3.

Average Time between First Diagnosis and Initial HIV Infection

The time between initial HIV infection and diagnosis for females was longer than for males (8.1 vs. 6.7 years; fig. 4). Calculations based on the age categories revealed that those aged ≥41 years experienced the highest time interval between infection and diagnosis (8.1 years), followed by those aged 25–40 years (7.6 years) and finally those aged <25 years (5.1 years).

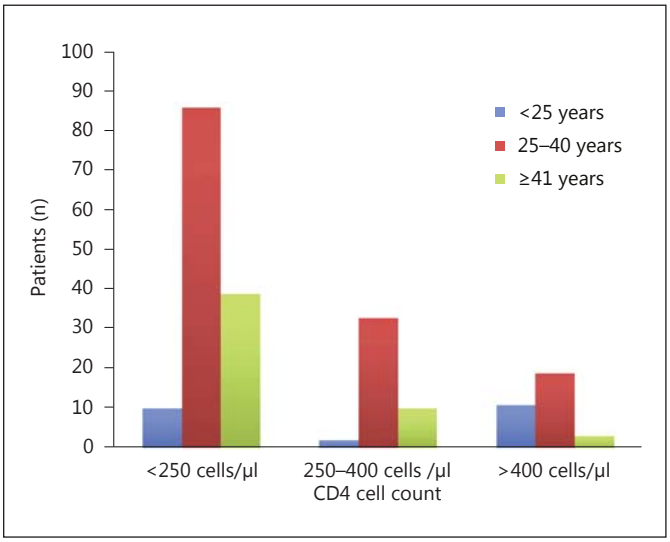

Fig. 3. Distribution of CD4 cells among age groups. The differences observed were significant ($p < 0.0001$).

Discussion

Our study showed that over 60% of patients presented for HIV treatment with a CD4 count <250 cells/µl. We also showed that patients aged between 25 and 40 years, representing the most productive age group, are the most affected with regards to the level of CD4 deterioration, constituting 63.7% of the study population. This study helps to identify the stage of the disease at which the ma-

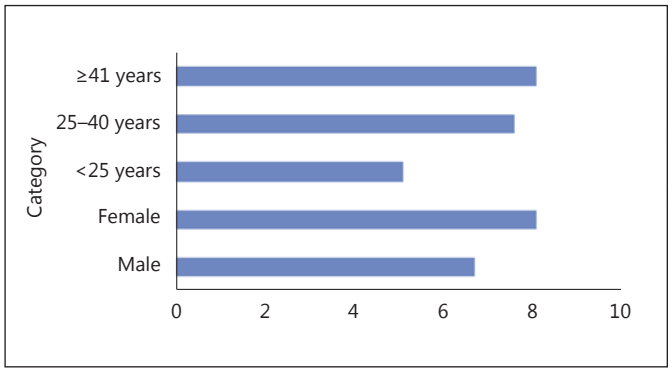

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Fig. 4. Bar graph showing the distribution of average intervals between infection and diagnosis according to age and gender among ARV drug-naïve HIV-seropositive individuals in Badagry, Nigeria.

jority of HIV individuals present voluntarily for care and treatment. Previous studies have highlighted the significance of baseline CD4 levels in predicting immune recovery and clinical outcome [8]. Studies investigating normal lymphocyte ranges including CD4+ cells have also been used to guide HIV treatment protocols in countries such as Turkey and Nigeria [12, 15]. Our findings reveal a higher mean CD4 lymphocyte value for females than for males, although the difference was not statistically significant. This is in agreement with several studies which also recorded a higher CD4 lymphocyte count in females than in males [16–18]. This has been attributed to the fact that women are more likely to test at an earlier stage than men [7], most likely as a result of antenatal HIV screening or HIV screening as a result of any other gynecological checkups. Age range and CD4 count categorization revealed that the 25- to 40-year age group contained the highest number of participants within the 3 CD4 categories, while the group <25 years of age recorded the lowest number of patients. This was expected because the age category between 25 and 40 years contains the group whose mean CD4 count is high because of a faster rate of cell development and proliferation [19, 20].

Our data (fig. 2, 3) show that a large number of female participants actually presented for HIV testing at a late stage of infection. The slightly higher mean CD4 value observed in this group (270 cells/μl for females vs. 244 cells/μl for males) might actually be a result of the higher number of females recruited into the study as a result of the sampling method adopted and the mandatory antenatal HIV screening of pregnant women, and not an indication of a better immunological status of HIV-infected women. The data presented in this study indicate that, despite the high level of media publicity and public health enlightenment, the majority of the population in our study setting do not present for screening until AIDS-defining illnesses begin to appear. This observation is supported by the findings of Forbi et al. [7], who reported that 12.1% of their subjects presented for screening during the early phase of infection, and Adewunmi et al. [18], who reported that the majority of individual's commencing HAART (highly active ARV treatment) were enrolled with a CD4 count of <250 cells/μl. Hence, the majority in this group had poor immune restoration and higher chances of therapeutic failure after commencing ART, as reported previously [21–23].

The time interval between the first diagnosis and initial HIV infection among our study population was 6.7 years for males and 8.1 years for females. This observation seems to support a contrary opinion that females present late for testing when compared with males, despite the fact that males recorded a lower mean CD4 cell count. This observation seems to show that females have a slower disease progression compared to males. The reason for this is not yet clear, but could be attributed to the fact that women with a higher CD4 value stay healthier for a longer period than their male counterparts and may not be willing to seek medical care, as has been previously reported [7]. The time intervals between first diagnosis and HIV infection between the age groups were 5.1 years for the younger age group, 7.6 years for those aged 25–40 years, and 8.1 years for the older age group (fig. 4). This observation was expected because the age group <25 years also consists of pediatric subjects, whose average survival time is shorter and immune deterioration faster compared with adults [19, 20].

A significant limitation of this study was the inability to verify information given by those who might have tested positive for HIV at another center before coming to retest at our study center. We had to blindly rely on all information provided by participants at our center during the course of the study. This is an indication of the need for an integrated national HIV database network between all testing centers that would enable national and local HIV data to be shared.

Conclusion

In this study there was a high level of immune deterioration based on CD4 cell counts among individuals presenting for HIV testing for the first time in Lagos, Nigeria. The results presented show a picture of the immune status of a representative urban Nigerian population at the

time of first voluntarily HIV testing. We therefore recommend an upward revision of the ART enrolment criteria from the 250 cells/μl to at least 350 cells/μl, which is currently being advocated [7, 8]. Also, community engagement should be intensified in order to encourage regular and universal counseling and testing across gender and age groups in order to enable early HIV detection and to facilitate better immune recovery among HIV-positive Nigerians.

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Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Mohammed I, Nasidi A, Chikwem JO, et al: HIV infection in Nigeria. AIDS 1988;2:61–62.
2 UNAIDS: Report on the global AIDS epidemic 2012. www.unaids.org/sites/default/files/media_asset/20121120_UNAIDS_Global_Report_2012.
3 Federal Ministry of Health Nigeria: National HIV/AIDS and Reproductive Health and Serological Survey (NARHS Plus), 2012. Abuja, Federal Ministry of Health, 2013, pp 1–57.
4 Clapham PR, McKnight A: HIV 1 receptors and cell tropism. Br Med Bull 2001;58:43–49.
5 Lawn SD: AIDS in Africa: the impact of coinfection on the pathogenesis of HIV-1 infection. J Infect Dis 2004;48:1–12.
6 Gallo RC: Human retroviruses after 20 years: a perspective from the past and prospects for their future control. Immunol Rev 2002;185:236–265.
7 Forbi JC, Forbi TD, Agawale SM: Estimating the time period between infection and diagnosis based on CD4 counts at first diagnosis among HIV 1 antiretroviral naive patients in Nigeria. J Infect Dev Ctries 2010;4:662–667.
8 Adewunmi OM, Odiabo GN, Olaleye OD: Baseline CD4 cell level predicts recovery rate after initiation of ART in HIV infected Nigerians. J Immunoassay Immunochem 2016;37:109–118.
9 Lahuerta M, Lima J, Nuwagaba-Biribonhowa H, et al: Fctors associated with late antiretroviral therapy initiation among adults in Mozambique. PLoS One 2012;7:e37125,
10 Lauretha M, Ue F, Hoffman F, et al: The problem of late ART initiation in sub-Saharan Africa: a transient aspect of scale-up or long-term phenomenon. J Health Care Poor Underserved 2013;24:359–338.
11 Saag MS: Natural history of HIV disease; in Broader S, Merigan TC Jr, Bolognesi D (eds): Textbook of AIDS Medicine. Baltimore, Williams & Wilkin 1994, pp 45–53.
12 Oladepo DK, Idigbe EO, Audu RA, et al: Establishment of reference values of CD4 and CD8 lymphocyte subsets in healthy Nigerian adults. Clin Vaccine Immunol 2009;16:1374–1377.
13 WHO: Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance, African region. 2005. http://www.who.int/hiv/pub/guidelines/clinicalstaging.pdf.
14 Natural History Project Working Group for the Collaboration of Observational HIV Epidemilogical Research Europe (COHERE): Factors associated with short-term changes in HIV viral load and CD4+ cell count in antiretroviral-naïve individuals. AIDS 2014;28:1351–1356.
15 Yaman A, Setiner S, Kibar F, et al: Reference ranges of lymphocyte subsets of healthy adults in Turkey. Med Princ Pract 2005;14:189–193.
16 Delmas MC, Jadand C, de Vincenzi I, et al: Gender difference in CD4+ cell counts persist after HIV-1 infection. AIDS 1997;11:1071–1073.
17 Camara M, Dieye TN, Seydi M, et al: Low-level CD4+ T cell activation in HIV-exposed seronegative subjects: influence of gender and condom use. J Infect 2010;201:835–842.
18 Adewunmi MO, Odiabo GN, Olaleye OD: Efficay of generic highly active retroviral therapy in HIV 1 infected individuals in Nigeria. J Immunoassay Immunochem 2015;36:464–477.
19 Ssewanyana I, Baker CA, Ruel T, et al: The distribution and immune profile of T cell subsets in HIV infected children from Uganda. AIDS Res Hum Retroviruses 2009;25:65–71.
20 Toblin NH, Aldrovandi GM: Immunology of pediatric HIV infection. Immunol Rev 2013;254:143–169.
21 Florence E, Lundgren J, Dreezen C, et al: Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. HIV Med 2003;4:255–262.
22 Battegay M, Nuesch, R, Hirschel B, et al: Immunological recovery and antiretroviral therapy in HIV-1 infection. Lancet Infect Dis 2006;6:280–287.
23 Aiuti F, Mezzaroma I: Failure to reconstitute CD4+ T-cells despite suppression of HIV replication under HAART. AIDS Rev 2006;8:88–97.