Brief Original Article

Estimating the time period between infection and diagnosis based on $CD4^+$ counts at first diagnosis among HIV-1 antiretroviral naïve patients in Nigeria

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Abstract

Introduction: $CD4^+$ T-cell levels are an important criterion for categorizing HIV-related clinical conditions. Late diagnosis of infection contributes to poor medical outcomes and the continuation of viral transmission. This population-based cohort study in north central Nigeria reports the initial $CD4^+$ lymphocyte counts at the time of first HIV diagnosis and determines the approximate time interval when HIV infection was acquired..

Methodology: Confirmed HIV-1 infected individuals (n = 588) for whom the dates of first HIV diagnosis were known were enrolled in this study. $CD4^+$ lymphocyte counts were measured using a Fluorescence Activated Cell Sorter (FACS) platform that automatically quantifies $CD4^+$ lymphocytes as absolute numbers of lymphocytes per μL of blood. The estimated time interval between HIV infection and time of first HIV diagnosis was determined as a function of the $CD4^+$ lymphocytes' decay rate per calendar year.

Results: The results showed that 22.1% and 49.7% of HIV-infected individuals present late with advanced ($CD4^+$: 200-349 cells/μL) and severe ($CD4^+$: < 200 cells/μL) immunosuppression respectively, while only 12.1% present with $CD4^+ \geq 500$ cells/μL and 16.2%with $CD4^+$ between 350-499 cells/μL. Mean $CD4^+$ counts for females were higher when compared to those of males ($p > 0.05$), The time interval between HIV infection and first diagnosis was approximately 6.1 years for males and 7.3 years for females.

Conclusion: The majority of HIV-infected individuals in this study accessed health care at late stages of infection, suggesting many HIV-infected individuals in Nigeria are unaware of their HIV status. More efficient programs for early diagnosis of HIV to prevent transmission are urgently required.

Key words: HIV-1; delayed diagnosis; Nigeria

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Introduction

The human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is a pandemic that has affected millions of people globally. The 2009 AIDS epidemic update report from the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimate there are 33.4 million people living with HIV/AIDS worldwide, of which ~75% (22.4 million) reside in sub-Saharan Africa [1], a region facing profound socioeconomic, political, and infrastructural challenges to the expansion of HIV care and treatment programs. In 2008, an estimated 2.7 million new HIV infections occurred worldwide with sub-Saharan Africa accounting for 71% of all these new infections [1]. Africa remains the most heavily affected region, and Nigeria, with a population of over 140 million people, has the largest HIV/AIDS epidemic [2]. The government of Nigeria and other international agencies are vigorously instituting programs to increase awareness of HIV/AIDS in the country. Unfortunately, these efforts have not translated into a change in behavior as the rate of infection continues to expand [3,4,5].

HIV predominantly infects cells that express $CD4^+$ surface molecules. Infection causes shortened survival time and impaired production of $CD4^+$ T-cells, with a progressive decline of this cell population in the peripheral blood, resulting in immunosuppression [6,7]. The rate at which $CD4^+$ cell counts decline is one of the markers of disease progression in HIV infection. Current guidelines for the use of antiretroviral therapy in Nigeria place emphasis on the use of $CD4^+$ enumeration to determine when to initiate antiretroviral therapy and HIV disease monitoring [8,9,10]. Therefore, the extent of immunosuppression and the probability of developing AIDS-related complications in HIV-infected individuals are usually measured by the absolute number of $CD4^+$ T-cells [11]. The Centers

for Disease Control and Prevention's (CDC) disease staging system assesses the severity of HIV by determining $CD4^+$ cell counts and the presence of specific HIV-related conditions [12]. The definition of AIDS, for example, includes all HIV-infected individuals with $CD4^+$ counts of less than 200 cells/μL. In primary HIV infection (PHI), $CD4^+$ counts are usually greater than 500 cells/μL. This stage of infection lasts for a few weeks and is often accompanied by a short flu-like illness. In as many as 80% of people, no HIV symptoms are seen; as such, the diagnosis of HIV is frequently missed. A study of the natural history of HIV indicates that AIDS develops within 10 years after HIV infection and that death occurs within two years of its development [13]. However, the availability of antiretroviral therapy (ART) since 1996 and the rapid expansion of ART services in sub-Saharan Africa have made it possible for HIV-infected individuals to survive longer than 20 years [14,15].

Despite the large number of HIV cases in Nigeria, no study known to the authors has examined the average time from HIV infection to first diagnosis and the clinical staging at which most Nigerians present for HIV testing and management. This information is important for budgeting and planning practical and affordable HIV intervention programs. More than 80% of reported cases of HIV sero-positive individuals in developing countries, including Nigeria, are reported to be transmitted through heterosexual contact [1,16]. There is very little information with which to predict the time of HIV infection, unlike blood transfusion or vertical transmission.

This study sought to gain insight into the immunological status at which HIV patients in Nigeria are first diagnosed and, based on these $CD4^+$ counts, to estimate the amount of time that has elapsed since infection. The findings demonstrate that a majority of HIV patients in Nigeria are diagnosed when advanced to severe immunosuppression has set in, based on CDC/WHO staging criteria. The individual and public health challenges that accompany delayed diagnosis of HIV infection are discussed.

Methodology

Study Population

This study, which was conducted between July 2005 and February 2008, involved western blot confirmed HIV-1 positive patients who attended our facility (Virology Laboratory, Innovative Biotech, Keffi, Nasarawa State, Nigeria) for HIV counselling and testing, or for other health needs. All individuals tested for HIV infection were subjected to pre- and post-test counseling. The laboratory, which is located in north central Nigeria, is a complete diagnostic and research virology facility that performs testing for a full range of human pathogens of viral origin, including HIV. The catchment population of the laboratory is north central Nigeria, although the laboratory receives clinical specimens from the whole country. The patients enrolled in this study were anti-retroviral naïve and at their first seropositive visit. Patients were excluded if they were younger than 18 years of age or were pregnant. Patients who indicated that they had prior HIV testing for HIV infection were also excluded from the study. A total of 588 HIV-seropositive individuals were enrolled. This group consisted of 274 males and 314 females, ranging from 18-64 years. The study protocol was approved by the Innovative Biotech Research Committee and informed consent was obtained from all patients prior to blood collection.

$CD4^+$ T-lymphocyte profile

$CD4^+$ values were measured in the laboratory using a Fluorescence Activated Cell Sorter (FACS) system (Becton Dickenson FACSCount, San Jose, California, USA). Briefly, this system quantifies $CD4^+$ T lymphocytes as absolute numbers of lymphocytes per μL of blood. The $CD4^+$ T lymphocyte absolute values were automatically recorded using the manufacturer's protocol and reagents. $CD4^+$ test results were further recorded anonymously in the laboratory in a computer database.

Data analysis

All the data in this study was analyzed using SPSS version 15.0 for windows (SPSS Inc, Chicago, IL). Proportions were calculated using either the chi-square test or the student t test (as appropriate) at 95% confidence intervals. P-values of less than 0.05 were considered statistically significant. The association between the initial $CD4^+$ cell count and gender of patients was analyzed. Based on the 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults by the CDC [12] and the interim WHO clinical staging of HIV/AIDS for the African region based on severity of immunosuppression [17], data was classified into four categories of $CD4^+$ cell counts: Category 1: ≥

500 cells/μL, not significant immunosuppression; Category 2: 350−499 cells/μL, mild immunosuppression; Category 3: 200−349 cells/μL, advanced immunosuppression; Category 4: < 200 cells/μL Severe immunosuppression.

Time period after infection

Descriptive statistics were used to characterize the study group. The $CD4^+$ count level at time of diagnosis was used to provide an indication of the time delay between HIV infection and diagnosis among Nigerians as a function of normal $CD4^+$ decay per calendar year in drug naïve individuals. The normal reference values of $CD4^+$ counts in healthy Nigerians have been established to range from 365-1571 cells/μL [18]. This reference value is supported by another study of healthy Nigerians that showed the specific mean reference $CD4^+$ among men to be 717 cells/μL and 869 cells/μL among non-pregnant females [19]. Considering the latter, 80 cells/μL was subtracted from these reference $CD4^+$ values per calendar year period within the male and female group average $CD4^+$ counts until the overall mean $CD4^+$ counts determined in this study were reached. The time period for this to happen was considered to be the estimated period between infection and diagnosis of the infection. Without antiviral intervention, ~80cells/μL are naturally lost annually [20]. A recent study showed similarly declining rates in HIV-1 subtype A individuals, which is the predominant type in Nigeria [21]. A comparison of time intervals between infection and diagnosis in males and females was done using the student t-test at a 95% confidence interval.

The following formula was used to determine the approximate time (t) when HIV was acquired: t = N-n/80 and N = Reference $CD4^+$ count among healthy Nigerians, where n = Mean $CD4^+$ count level at time of diagnosis and 80 = represents the approximate number of $CD4^+$ cells naturally lost annually.

Results

A total of 588 adults who were diagnosed with HIV infection between July 2005 and December 2007 and who had records of $CD4^+$ counts with date of diagnosis were included in this study. In total, 274 males (mean age = 38.5 years) and 314 females (mean age = 31.3 years) participated. The distribution of $CD4^+$ values following WHO/CDC categorization and gender classification are used in Table 1 to show the clinical state at which patients in this study presented for the first time for HIV diagnosis. As shown, 22.1% of the patients presented for their first HIV test when they were in clinical stage 3 of HIV infection, and 49.7% of the patients presented for their first HIV test when they were in clinical stage 4. These stages indicate advanced to severe immunosuppression, respectively. A small number of patients, however, presented at clinical stages 1 (12.1%) and 2 (16.2%) of HIV infection (Table 1). Also, females in this study tended to have higher $CD4^+$ values than their male counterparts ($p = 0.83$) regardless of the clinical staging of the HIV infection (Table 1).

The overall mean $CD4^+$ value among males in this study was 231 cells/μL and 286 cells/μL for females. Considering an annual decrease of ~80 cells/μL among HIV-infected individuals and known reference values for males and females, the time from infection to first diagnosis was 6.1 years for males and 7.3 years for females ($p > 0.05$). This finding suggests that there is a delayed period from infection to diagnosis among Nigerians similar to that found in the study population.

Table 1. Distribution of $CD4^+$ values by gender based on CDC/WHO classification of HIV disease status

Clinical stage of HIV infection	**$CD4^+$ values in cells/μL**	**HIV associated symptoms**	**Gender**		**Total**	**%**
			Male	**Female**		
1	$CD4^+$>500	Asymptomatic	27	44	71	12.1
2	$CD4^+$= 350-499	Mild symptoms	41	54	95	16.2
3	$CD4^+$=200-349	Advanced symptoms	64	66	130	22.1
4	$CD4^+$<200	Severe symptoms	142	150	292	49.7
Total ---------->			274	314	588	

Discussion

The $CD4^+$ count is considered to be the best marker for HIV-1 disease and is currently used as a guide for antiretroviral therapy and disease monitoring since it is useful in staging HIV infection [22]. The $CD4^+$ lymphocyte levels were evaluated as a marker of HIV-1 disease because they are associated with clinical progression [6]. The results of the study showed that the majority of patients infected with HIV present for their first diagnosis at a health facility either at stage 3 or 4 according to WHO/CDC HIV disease classifications (Table 1). This phenomenon means that many individuals in Nigeria remain unaware of their positive HIV status until AIDS-defining illness occurs. This finding is consistent with those of Porter *et al*. [23]. From a private and public point of view, failure to diagnose HIV in a timely manner contributes to poor medical outcomes and sustains the opportunity for further HIV transmission [24]. HIV transmission rates are about 3.5 times higher among individuals who are unaware of their HIV status compared to those who have been diagnosed [25]. The overall low mean $CD4^+$ levels at first diagnosis also support this finding. Presenting with low $CD4^+$ cell count, especially less than 200cells/μL, is associated with a greater number of visits to a health care facility for mood, anxiety, and sexual disorders, thereby overwhelming the health care system that is already overburdened [26]. In addition, the results, although not statistically significant, showed that women had higher $CD4^+$ values than men, which maybe because women had higher $CD4^+$ counts to begin with probably due to the fact that women are likely to be tested earlier than men during the course of HIV infection. One could argue, therefore, that HIV-infected women should experience a more favourable course of disease than men, and is corroborated by earlier studies showing that women tend to have higher $CD4^+$ lymphocyte counts than men [27,28].

In this study, only a few individuals (12.1%) presented for HIV diagnosis during the primary stage of HIV infection (Table 1). The advantages of diagnosing primary HIV infection are many [25]. With mounting evidence that early initiation of antiretroviral therapy may result in improved survival [29], and further evidence suggesting that routine HIV screening is a cost-effective strategy in the era of highly active antiretroviral therapy [30], clinician and laboratory personnel should begin to screen for HIV infection in patients who present with flu-like symptoms as a first step in detecting primary HIV infections. The H5N1 and H1N1 pandemic has led to high rates of individuals with flu-like symptoms attending health facilities. Nigeria, and indeed Africa in general, could use this opportunity to expand its HIV screening programs by offering HIV tests to these groups of individuals. In the United Kingdom, for example, cases of HIV infection have been reported in patients suspected of H1N1 [31]. Primary HIV infection is accompanied by a short flu-like illness that resembles that of patients who have respiratory illness. Targeting this subgroup of individuals is important for case management, counseling, monitoring, health care planning, allocation of HIV/AIDS resources, and a general understanding of how the epidemic evolves in Nigeria.

Calculations revealed that the estimated time interval between HIV infection and first diagnosis of infection among Nigerians was 6.1 years for males and 7.3 years for females. This finding reinforces our observation that there is a substantial delay between HIV infection and diagnosis. This analysis also reveals that women actually have their first diagnosis later than males, which is contrary to popular opinion. Consequently, it is very important to understand the circumstances that prevent women in this part of the world from attaining early HIV diagnosis and health care. The factors that contribute to this problem remain largely unknown, but they may be attributable to the fact that with higher $CD4^+$ levels, women generally feel healthy and do not seek medical attention. The male dominance and large-scale financial dependence on men by women in Nigeria could also be contributing factors.

Due to the late entry of infected individuals into HIV diagnosis programs, the authors hypothesize that the very high number of AIDS deaths and the very short survival time for individuals after HIV infection in Nigeria and in most of sub-Saharan Africa could be attributed to the fact that the majority of these patients access health care late during the course of natural HIV infection. The median time from seroconversion to AIDS in industrialized countries is far longer than is suggested in this study and other studies from Africa [32,33,34,35], which in the past has been taken as evidence of rapid progression of the disease in Africa, as a high proportion of Africans infected with HIV-1 die sooner after HIV diagnosis than their counterparts in industrialized countries. This, however, does not seem to be the case. In the cohort, it was found that a majority of HIV-1 infected adults developed AIDS and broadly comparable

levels of immunosuppression as measured by $CD4^+$ cell count (Table 1), which is similar to outcomes seen in patients in industrialized countries. The shorter median time from seroconversion to death in HIV patients seen in this study is probably as a result of the delayed presentation for HIV management and care. This result is also supported by studies from Uganda and Tanzania [36,37,38].

It is difficult to exclude the possibility that individuals who were diagnosed for the first time in our laboratory may not have attended another health facility for HIV diagnosis. It is unlikely that the above have serious bias on our results due to the very stringent inclusion criteria used in this study and the fact that the facility is located in a setting with very limited capacity for HIV testing. Despite this possible limitation, this finding reflects the health-seeking behaviors of many Nigerians. To begin to overcome the problem of late or delayed HIV diagnosis, it is recommended that Nigeria should begin to implement the 2006 revised CDC recommendation [39], and not to depend on patient-elicited information on risky behaviors as the principal triggers for HIV testing. Clinicians should provide HIV testing routinely to all patients seen in health care facilities and also organize intensified free HIV testing in schools, churches, other institutions, and marketplaces to the general public across the entire Nigerian territory. These actions would contribute to an essential public health initiative that would lead to a better understanding of the HIV/AIDs epidemic in this region.

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