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ORIGINAL PAPER

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Serosurvey and Cellular Immune Status of HTLV-1/2 and HIV Co-infections in Bauchi State, Nigeria

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ABSTRACT

Introduction. Human T-cell lymphotropic virus types 1 and 2 (HTLV-1 & 2) are frequent co-pathogens among immunosuppressed individuals, particularly HIV/AIDS infected persons. Dual infected persons usually present with false normal or high CD4+ T cells count as a result of the ability of HTLV to induce clonal proliferation of CD4+ T lymphocytes. There is paucity of information on this clinical entity in Nigeria.

Aim. This study aimed to determine the seroprevalence of HTLV-1/2 and associated cellular immune response among antiretroviral naïve and experienced HIV infected persons at Bauchi State, Nigeria.

Material and methods. One hundred and eighty two (182) HIV seropositive patients' blood samples were analyzed for anti HTLV-1/2 IgM and IgG antibodies using ELISA while CD4+ T cells were counted using Flow cytometry technique. Socio-demographic data of the subjects and clinical history were obtained via questionnaire and medical records, respectively.

Results. The seroprevalence of anti-HTLV-1/2 was 14%. This comprised 76 (41.8%) males and 106 (58.2%) females. Six (3%) were seropositive for both ant-HTLV -1&2 IgM and IgG. Of the total positive for anti-HTLV-1/2, 20 (25%) ART-naïve and 6(5.9%) ART-experience subjects. Whole blood CD4+ T cell count was significantly high in HTLV-1/-2 IgG/IgM seropositive subjects compared to their HTLV-1/-2 negative counterpart.

Conclusion. All subjects (100%) who were HTLV-1/-2/HIV co-infected had normal to higher CD4+ T cell counts. It is suggested to be very careful in using only CD4+ counts to monitor HIV progression or as indicators for ART.

Keywords. HTLV**,** cellular Immunity, HIV co-infections, antiretroviral therapy

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Introduction

Human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2) are members of the deltaretrovirus genus in the Retroviridae family.[1,2] HTLVs likely originated from cross-species transmission of simian T cell lymphotropic virus (STLVs). Combined, this group of viruses are referred to as Primate T-lymphotropic viruses (PTLVs). While the close phylogenetic relationships of HTLV-1 and STLV-1 indicate simian origin for HTLV-1, HTLV-2 and (STLV-2) are only distantly related, so the exact simian origin of HTLV-2 is unknown. Recently, two novel HTLVs were identified in hunters in Cameroon and were called HTLV-3 and HTLV-4.[3]

HTLV-1 is related to adult T cell leukemia (ATL) and a neurologic syndrome called HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP).[3-10] HTLV-2 has not been categorically linked to any disease, but has been associated with several cases of myelopathy/tropical spastic paraparesis (HAM/TSP) like neurological disease.[11-14]

Human T-cell lymphotropic virus, type 2 (HTLV-2) generally causes no signs or symptoms. However, scientists suspect that some infected people may later develop neurological symptoms, such as sensory neuropathies, gait abnormalities, bladder dysfunction, mild cognitive impairment, motor abnormalities and erectile dysfunction.[15] Although evidence to these is limited. HTLVs has a world-wide distribution, with higher prevalence in some areas including Central and south America, Central Africa, south west of Japan, and Iran.[16]

Since HTLV-1, HTLV-2, and HIV share common modes of transmission, it is not surprising that co-infection are frequently reported, especially among people with high risk behaviors, such as injectable drug users, those who practice unprotected sexual intercourse; transfusion of contaminated blood and transplantation of infected organs and tissues.[17,18] Although, human retroviruses have worldwide distribution, HTLV/HIV co-infected have relatively higher prevalence in large metropolitan area and endemic regions.[18]

Epidemiologically, areas are characterized as endemic when the prevalence of HTLVs falls within 0.5%–20% of the total population and characterized as non-endemic when the prevalence is ≤ 0.1%, since it has been identified in all five continents with an estimate of 15 to 20 million infected people.[18-20] The sero-prevalence rates tend to increase with age, and they are higher in females than males.[20] Areas of high prevalence for HTLVs include Japan, Sub-Saharan Africa, Caribbean basin, South America, Melanesia, and the Middle East.[20] HTLV-1 has been widely studied in different subjects, especially, blood donors, injection drug users, thalassemia patients, and HIV-infected individuals.[21-23] Despite the clinical significance of HTLV/HIV co-infection, there is paucity of information on this clinical entity in Nigeria.

Aim

This study aimed to determine the seroprevalence of HTLV-1/2 and associated cellular immune response among antiretroviral naïve and experienced HIV infected persons at Bauchi State, Nigeria.

Material and methods

Study area and population

This hospital based, cross-sectional study consisted of 182 (76 males and 106 females) HIV infected subjects (ART-Naïve and Experienced) of different age groups (mean±SD: 31.2±12.9 years) attending the General Hospital Ningi, Bauchi State, North-Eastern Nigeria. The subjects were divided into two study groups. Viz; Eighty (44.0%) ART-naïve and 102 (56.0%) ART-experienced.

Ethical consideration

The study was conducted in accordance with the Declaration of the Helsinki and had its ethical aspects evaluated and approved (Reference Number MOH/GEN/S/1409/I) by the Human Ethical Research Committee of the Ministry of Health, Bauchi State, Nigeria. All subjects have signed a written informed consent.

Clinical History of the subjects

With the permission of the physicians, subjects' clinical information was obtained from their hospital record files. Only confirmed HIV sero-positive subjects (ART-Naïve/Experienced), voluntarily willing to participate were purposively enrolled in the study.

Sample collection and preparation

Five milliliter (5ml) of whole blood samples were collected aseptically. Two milliliters of ethylenediaminetetraacetic acid-preserved blood samples were used for CD4+ cell counts. The remaining were spun at 12000/g for 10 mins to harvest their serum samples for HTLV-1/2 serological tests. Samples were collected between from 7th May to 10th October 2018. Blood samples were analyzed consecutively within 1 hour of collection.

Laboratory analytical procedures

Flow Cytometry Assay for Lymphocyte Population

Partec ™ CD4 reagents were used in a closed system based on the manufacturer's instructions. The CD4+ cell counts in the whole blood were analyzed using a Partec™ CyFlow Analyzer (Sysmex, Norderstedt, Germany) Model SL3. The normal range for CD4+ T cell count was 500- 1500 cells/mm^3. This device used the principle of light scattering property (based on dissimilarity in cell size or granularity) and the fluorescence of cells following staining with monoclonal antibodies to markers on the cell surface bound to fluorescent dyes. Flow cytometry data was analyzed using FlowJo v.7.6.5 software. Cell

populations of interest were then gated after identification. The generated percentages were multiplied by the total number of lymphocytes in the hemogram to derive absolute values for circulating lymphocytes. Absolute CD4+ cell counts were subsequently analyzed using a single-platform technique.

Enzyme-linked Immunosorbent Assay for Anti-HTLV IgM and IgG antibodies

Indirect anti-HTLV-1/2 IgM (product code: SL-2422Hu) and IgG (product code: SL2421Hu) ELISA were carried out according description and instructions by kits' manufacturer (Sunlong Biotech®, China).

Statistical analysis

All generated data were analyzed using SPSS software version 26.0 (2016, IBM California, USA). The prevalence of HTLV-1 and -2 was expressed in simple proportions and percentages for the study groups. Chi-square contingency table was used to determine the associations between seroprevalence of HTLV-1/-2 infections and risk factors of infection. Then student T test was used to determine difference in mean CD4+ T cell counts of the 2 study groups. A confidence interval of 95%, p-values <0.05 were considered statistically significant.

Results

Twelve (7%) were anti-HTLV-1/2 IgG seropositive, while 26 (14%) were anti-HTLV-1/2 IgM seropositive. However, 6 (3%) had both anti-HTLV-1/2 IgG and IgM antibodies (Figure 1).

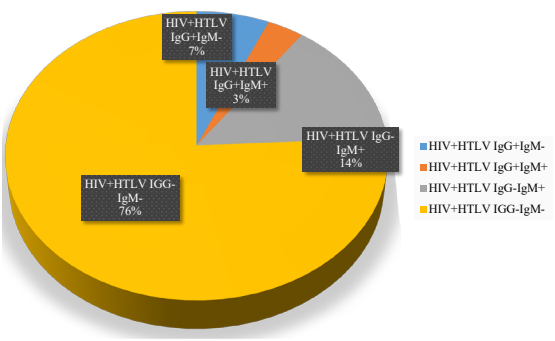

Fig. 1. Seroprevalence of anti- HTLV IgM and IgG in HIV infected subjects

In addition, 38 (21%) HIV infected persons tested seropositive to anti-HTLV-1/ 2 antibodies and 144 (79%) were negative for anti-HTLV 1/2 antibodies (Figure 2).

The HIV infected subjects who were anti- HTLV IgG positive and IgM positive had relatively higher CD4+ T cell count (681.7±191cells/mm3) and least in those had HTLV IgG positive and IgM negative results (554±274 cells/mm3). There was no significant difference between the CD4+ T-cells counts of subjects with varying serological responses to HTLV (p>0.05) (Table 1).

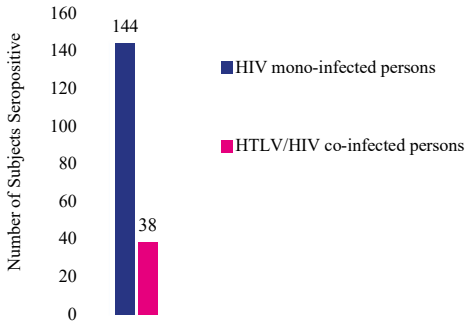

Fig. 2. Seroprevalence of anti-HTLV in HIV infected subjects

Of the 80 ART naïve HIV infected subjects tested, 20 (25%) were anti-HTLV-1/2 IgM seropositive and 14 (17.5%) were anti-HTLV-1/2 IgG seropositive. Conversely, of the 102 ART experienced HIV infected subjects tested, 6 (5.9%) had anti-HTLV-1/2 IgM, while 16 (15.7%) had anti-HTLV-1/2 IgG (Table 2).

Table 1. Comparison of CD4+ T-Cell Count of HIV-Infected Participants with and without HTLV Antibodies Enrolled for the Study

		CD4+ T-cell counts (cells/mm3)	
HTLV antibodies	**Frequency**	**Range**	**Mean± SD**
HTLV IgG Positive	12	289 – 941	554 ± 274
HTLV IgG/IgM positive	6	537 – 927	681.7 ± 191
HTLV IgM Positive	26	220 – 1125	630 ± 290.9
HTLV IgG/IgM Negative	138	194 – 1794	610 ± 445.2
F-statistic value		-	0.1526
p-value		-	0.9279

Table 2. Distribution of HTLV Antibodies according to ART Status of Subjects

ART status	**Total**	**No positive for HTLV-1/2 antibody**	
	Tested	**IgG Positive**	**IgM Positive**
ART-Naïve	80	14(17.5)	20(25)
ART-Experienced	102	16 (15.7)	6(5.9)
P-value		**0.0023***	0.1174
Total	**182**	**30 (33.2)**	**26(14.3)**

Discussion

Human T-cell lymphotropic virus type 1 (HTLV-1) and type 2 (HTLV-2) are retroviruses with global distribu-

tion.[24-26] In this study, an overall prevalence of 14% anti-HTLV IgM seroprevalence was recorded among HIV seropositive patients. This shows that, HTLV-1 /-2 infections are significantly high among HIV patients in the study area and should be subject of concern due to associated immunosuppression this could exert in affected persons.

This findings corroborate with the study of Seaton who reported a similar 14% of HTLV-1 infection in Papua New Guinea.[27] This may be due to the fact that the inhabitants of those areas share similar low economic statuses and high risk social life that have exposed them to these infections However, this findings did not corroborate with that of Nasir et al [28] reported a 4.9% among HIV patients attending University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria. In another study conducted by Yuguda et al., a lower prevalence of 3.2% among blood donors in Jos, Nigeria was reported, while Mohammed et al. documented a prevalence of 6.3% among blood donors in Gombe, Nigeria.[29,30] This disparity could be due to the variations in the subjects, and living conditions as well socio-demographic status of the study population. Conversely, a study by Brites et al. reported a relatively high prevalence of 31.8%.[31] This difference may be due to the persistent exposure of the high transmission rate of HTLV infections in their study area.[32]

This study evaluated CD4 counts of HIV subjects in relation to HTLV-1 and -2 infections. It was found that individuals with lower CD4 counts within the 0-200cells/μl range, had no detectable anti-HTLV-1/-2 antibodies, while those with CD4 counts greater than 200 cells/μl had 7% seroprevalence of anti-HTLV-1/2 IgG and 14% anti-HTLV-1/2 IgM antibodies However, Individuals with higher CD4 >500cells/μl had 3% prevalence of both anti-HTLV-1/-2 IgG and IgM, respectively.

CD4+ cell count is the most used as clinical criterion for ART eligibility in most HIV-infected individuals of low and middle income countries. However, HTLV/HIV coinfection makes persons have pseudu-normal or high CD4+ T cell counts. This may represent a serious problem, especially for clinicians that rely of CD4+ T cell counts for initiation and selection of ART combinations. This is common in settings where there is no availability laboratory reagents/equipment for HIV viral load tests. These findings are in consonance with those of Schechter et al., Fantry et al., Nadler et al., Casseb et al., Scapellato et al., Van Veldhuisen et al. and Gudo et al.[33-39] These studies reported that HTLV/HIV co-infected patients often progress to AIDS irrespective of high and stable CD4+ cell counts. These contrast the depletion of CD4+ cell counts observed in HIV mono-infected patients with AIDS. In cases of HTLV/HIV coinfection, it has been suggested that HIV viral load alongside clinical presentation, rather than CD4+ cell counts, should be used to monitor HIV disease progression.[40]

The predictive value of CD4+ cell count as a marker of HIV-related immunosuppression and disease stage for persons co-infected with HIV and HTLV is not similar with individuals infected with only HIV. HTLV promotes the clonal expansion of CD4-infected T-lymphocytes causing an elevation of less competent CD4+ T-cells in co-infected persons.[41] When compared to HIV-infected patients with CD4+ cell counts greater than 200 cells/mm^3, HIV/HTLV co-infected individuals with similar CD4+ cell counts are at higher risk of developing opportunistic infections.[41,42] ART status indicates a higher HTLV burden in ART-naïve (25%) subjects compare to those whom were ART-experienced (5.9%). This shows that HTLV-1 and -2 tastings/ screening in HIV patients would probably gain more importance in choice of ART combinations.

Conclusions

All subjects (100%) who were HTLV-1/-2/HIV co-infected had normal to higher CD4+ T cell counts. It is suggested to be very careful in using only CD4+ counts to monitor HIV progression or as indicators for ART.

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