

HTLV-1/2 serodetection and predictors among HIV-positive individuals receiving combination antiretroviral therapy in Ogbomoso, Nigeria

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Abstract

Background: Human T-cell leukemia/lymphotropic virus (HTLV) coinfection with Human Immunodeficiency Virus (HIV) is common due to shared route of transmission and changes the course of acquired immunodeficiency syndrome (AIDS). Knowledge of the extent of coinfection and its predictors will aid in the prescription and implementation of appropriate preventive measures and better management of patients. This study aimed to determine the prevalence of HTLV-1/2 and associated risk factors in HIV/AIDS patients receiving antiretroviral treatment in Ogbomoso, Nigeria.

Methods: Blood samples were collected from a total of 200 HIV-infected persons, including 54 (27%) men and 146 (73%) women, all of whom were receiving combination antiretroviral treatment (cART) at Oyo State Hospital, Ogbomoso, Nigeria. Plasma from the blood was

tested for HTLV-1/2 antibodies using the linked immunosorbent assay (ELISA) technique. Chi-square test was used to determine predictors of infection ($p < 0.05$).

Results: The majority of the patients 71(35.5%) were within the age group 41-50, 164(82.0%) diagnosed of HIV more than 2 years ago, 143(71.5%) on cART for over 2 years, 113(56.5%) with CD4⁺ count of ≥ 200 cells/mm³, and 117(56.5%) at WHO clinical stage 1 of infection. Of these, 1 (0.50%) was HTLV-1/2 seropositive. Time on cART and CD4⁺ count were significantly ($p < 0.05$) associated with HIV/HTLV-1/2 coinfection.

Conclusion: Although a relatively low prevalence of HTLV-1/2 was reported, routine screening of all HIV-infected persons is advocated for early detection and appropriate choice of treatment regimen.

Keywords: HTLV-1/2, HIV, Co-infection, cART, Nigeria

Introduction

Human Immunodeficiency virus (HIV) and Human T-cell leukemia/lymphotropic virus (HTLV) are two distinct viruses that belong to the family retroviridae. There are two types of HIV: HIV-1 and -2 while four types of HTLV have been established so far with specific illnesses associated with only types 1 and 2. Infections with HTLV-1 are usually asymptomatic with minority of cases developing into symptoms of disease (Kaplan *et al.*, 1990; de The & Bomford, 1993). While HTLV-1 is reportedly linked with myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia/lymphoma (ATLL) (Brites *et al.*, 2009), HTLV-2 pathogenesis for humans remains undefined (Beilke *et al.*, 2004) although its infections have been associated with neurological disorders (Araujo & Hall, 2004). These viruses share similar routes of transmission including; sexual contact, breastfeeding, blood transfusion, and intravenous drug use (IDU). Furthermore, these two retroviruses have common *in vivo* tropism for CD4⁺ T-cells³. Because of the shared routes of transmission, coinfection of HIV and HTLV is common especially in areas endemic for HTLV (Galletto *et al.*, 2014; de Mendoza *et al.*, 2019). An estimated 15 to 20 million individuals are infected with HTLV-1/2 globally (Edlich *et al.*, 2000; Gessain & Cassar, 2012). HTLV-1 is highly prevalent in Africa, Japan, Caribbean islands and South America while HTLV-2 infections are frequently reported in specific populations such as American Indians (Ameridians), and IDUs in the US, Europe, Asia and South America (Araujo & Hall, 2004; Proietti *et al.*, 2005).

Although details are still sketchy, HIV/HTLV coinfection changes the course of acquired immunodeficiency syndrome (AIDS). Previous studies have suggested an accelerated progression to AIDS in HIV-1/HTLV-1 coinfecting persons than HIV-1 monoinfected persons (Casoli *et al.*, 2007; Gudo *et al.*, 2009; Bahia

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et al., 2011). Contrarily, the effect of HTLV-2 on HIV positive individuals is still largely unclear (Beilke, 2012) although some studies have suggested that co-infection of these two viruses decreases HIV-1 replication (Yazdani et al., 2018) leading to a delay of AIDS progression and death (Brites et al., 2011). Accelerated proliferation of CD4⁺ T lymphocytes has been observed in some HIV-1/HTLV-1 coinfecting individuals (Schechter et al., 1994; Araujo, 2020). HTLV-I-associated nonspecific lymphocyte proliferation and clonal expansion of the CD4⁺ infected lymphocytes has been suggested as the reason for this observation (Schechter et al., 1994). Consequently, most of these cells may be functionally impaired and may not necessarily provide immunological benefit to the infected person rather it hinders accurate diagnosis of AIDS (Beilke, 2012). This could result in delayed commencement of antiretroviral therapy (ART) and poor treatment especially in resource limited countries where commencement of antiretroviral treatment is largely dependent on CD4⁺ cell count of the patients.

Despite its significant contributions to morbidity and mortality, many developing countries including Nigeria are yet to commence routine screening for HTLV. Consequently, there is limited awareness and implementation of preventive measures against the infection. In Nigeria, few studies have been carried out on HTLV and focus have been mainly on blood donors and pregnant women (Oladipo et al., 2015; Okoye et al., 2015; Yuguda et al., 2017; Udeze et al., 2018a). HIV-infected individuals are among the high-risk groups for HTLV infection as a result of shared route of transmission and similar cellular tropism, yet there is knowledge gap in the prevalence and characteristics of HTLV 1/2 among this cohort in the country. This study was aimed at describing the prevalence of HTLV 1/2 and associated risk factors in HIV/AIDS patients receiving treatment in Ogbomoso, Nigeria.

Methods

Study design and population

This cross-sectional, hospital-based cohort study was conducted between October and December, 2020 in Ogbomoso, South-west Nigeria. The study participants included 200 (54 males and 146 females; age range 13-72 years) HIV-infected individuals who are receiving treatment at Oyo State Hospital, Ogbomoso, Nigeria. The participants were selected by simple random sampling technique. Determination of the sample size was done by Fischer's formula (Araoye, 2003).

$$N = z^2 (p)(q) / d^2$$

Where N = minimum sample size, z = statistic for the level of confidence at 95% is 1.96, p = expected prevalence, q = 1-p, d = standard error margin = 0.05.

Prevalence of 4.9% reported in Abuja among HIV patients (Nasir et al., 2015) was used to calculate the sample size. Hence the value p = 0.049 was used to calculate sample size for the study.

$$\text{Thus, } N = 1.96^2 \times 0.049 (1-0.049) / 0.05^2 = 72$$

For statistical credence, the sample size was increased to 200 HIV-infected patients.

Data and sample collection and preparation

Relevant socio-demographic and clinical information including age, gender, diagnosis time, time on cART, CD4⁺ cell count and WHO clinical stage were recorded using well-structured questionnaire forms. The information was obtained both directly from the patients and their clinical record books. About 5 mL of venous blood was collected from each participant by a trained phlebotomist. The plasma was separated by centrifugation at 3000 rpm for 20 minutes and stored at -20°C until ready for analysis.

Serology

Presence of antibodies against HTLV-1/2 were determined by Enzyme Linked Immunosorbent Assay (ELISA) kit (Sunlong Biotech Co., Ltd, China) for the qualitative determination of HTLV-1+2. The optical density (OD) was read spectrophotometrically at a wavelength of 450 nm within 15 minutes. Interpretation of the results followed the kit's manufacturer's instructions.

Ethical clearance

Ethical approval for the study was obtained from the University Ethical Review Committee (UERC) of University of Ilorin, Nigeria (UERC/ASN/2019/1983). Approval was also obtained from Research Ethics Review Committee of Oyo State Ministry of Health (AD13/479/1654^A). The ethical standards of the committees and

the Helsinki Declaration of 1975 (revised 2000) were strictly adhered to in carrying out the study. The study participants' anonymity was maintained throughout the study. Informed consent was obtained from each participant and from the parents/legal guardians (in case of participants who are less than 18 years old) before sampling. Those who did not wish to take part in the study were excluded.

Statistical analysis

Analyses of data were performed using SPSS version 22.0. The study variables were summarized using descriptive statistics. All variables were summarized using frequencies and proportions. Pearson's Chi-Square test was used to identify factors significantly associated with the prevalence of HTLV-1/2. A p-value ≤ 0.05 was considered to be statistically significant.

Results

Characteristic of the study participants

A total of 200 [54 (27.0%) male and 146 (73.0%) female; age range: 13-72 years] individuals were included in the study. About one-third (35.5%) of the study participants were in the age range 41-50 years followed by age range 31-40 (27.0%) while age range ≤ 20 had the least number of participants (3.5%). Clinical records showed that majority (82.0%, 164/200) of these patients have known their HIV status for more than two years, have been on cART for over a period of two years (71.5%, 143/200), had CD4⁺ T-cell count of ≥ 200 cells/mm³ (56.5%, 113/200), were in WHO clinical stage 1 of infection (58.5%, 117/200) (Table 1).

Table 1: Socio-demographic and clinical variables of HIV-positive individuals receiving treatment at Oyo State Hospital, Ogbomosho

Variable	Number	Frequency (%)
Gender		
Male	54	27.0
Female	146	73.0
Age group (years)		
≤ 20	7	3.5
21-30	21	10.5
31-40	54	27.0
41-50	71	35.5
51-60	31	15.5
> 60	16	8.0
HIV Diagnosis time (years)		
< 1	7	3.5
1-2	29	14.5
> 2	164	82.0
Time on cART (years)		
< 1	24	12.0
1-2	33	16.5
> 2	143	71.5
CD4⁺ count (cells/mm³)		
< 200	71	35.5
≥ 200	113	56.5
Unascertained	16	8.0
WHO clinical stage		
1	117	58.5
2	3	1.5
3	74	37.0
4	1	0.5
Unascertained	5	2.5

Among the population described above, 0.5% (1/200) was positive to anti-HTLV 1/2 antibodies (Figure 1). The infected person belonged to female gender, age group 51-60 years, have been diagnosed of HIV since 1-2

years, have been on cART for less than 1 year, had unascertained CD4⁺ cell count and in WHO clinical stage 3 of infection at the time of study. Of all the variables analysed, time on cART and CD4⁺ cell count were significantly ($p < 0.05$) associated with HTLV-1/2 infection among the study participants. There was no statistically significant association ($p > 0.05$) between HTLV-1/2 infection and other variables (Table 2).

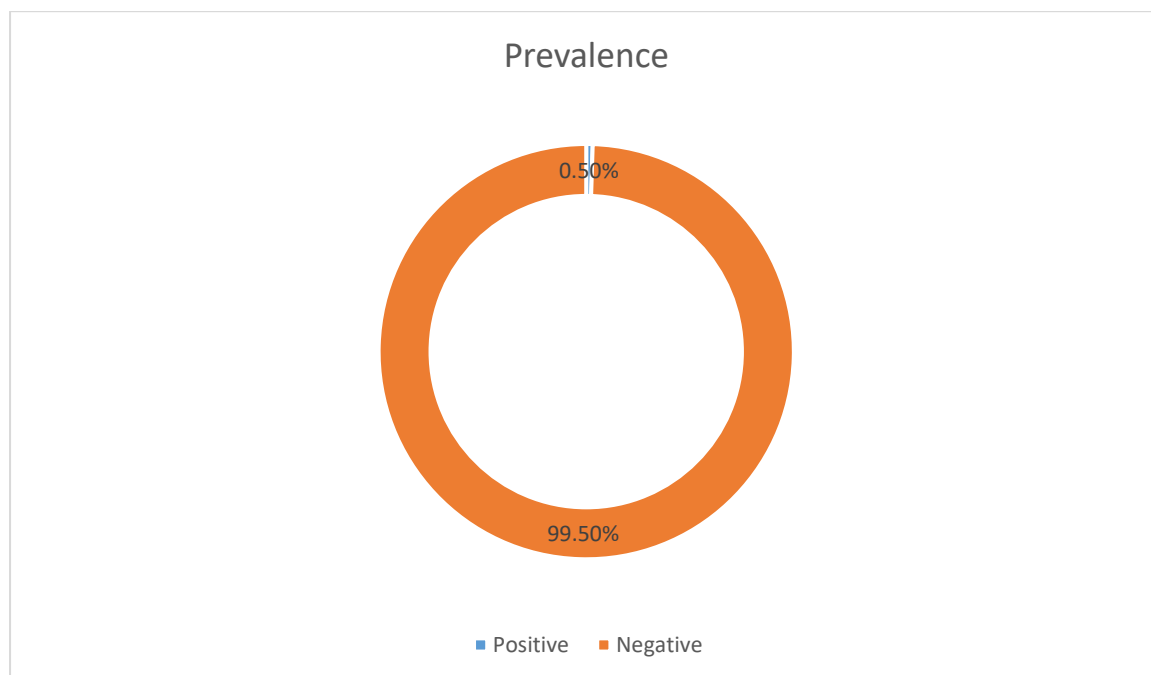


Figure 1: Pie chart of HTLV-1/2 seropositivity among HIV-positive individuals receiving treatment at Oyo State Hospital, Ogbomoso

Table 2: Bivariate analysis of HTLV-1/2 status and Socio-demographic and clinical variables of HIV-positive individuals receiving treatment at Oyo State Hospital, Ogbomoso

Variable	Number tested (%)	HTLV-1/2 Status		p-value
		Positive n (%)	Negative n (%)	
Gender				
Male	54 (100)	0 (0)	54 (100)	0.542
Female	146 (100)	1 (0.7)	145 (99.3)	
Age group (years)				
≤20	7	0 (0)	7 (100)	0.360
21-30	21	0 (0)	21 (100)	
31-40	54	0 (0)	54 (100)	
41-50	71	0 (0)	71 (100)	
51-60	31	1 (3.2)	30 (96.8)	
>60	16	0 (0)	16 (100)	
HIV Diagnosis time (years)				
<1	7	0 (0)	7 (100)	0.052
1-2	29	1 (3.4)	28 (96.6)	
>2	164	0 (0)	164 (100)	
Time on cART (years)				
<1	24	1 (4.2)	23 (95.8)	0.025
1-2	33	0 (0)	33 (100)	
>2	143	0 (0)	143 (100)	
CD4+ count (cells/mm³)				
<200	71	0 (0)	71 (100)	0.003
≥200	113	0 (0)	113 (100)	

Unascertained	16	1 (6.2)	15 (93.8)	
WHO clinical stage				
1	117	0 (0)	117 (100)	0.789
2	3	0 (0)	3 (100)	
3	74	1 (1.4)	73 (98.6)	
4	1	0 (0)	1 (100)	
Unascertained	5	0 (0)	5 (100)	

Discussion

Since its discovery over 4 decades ago (Poiesz *et al.*, 1981), HTLV infection has gradually gained global attention especially in regions of high endemicity as a significant contributor to morbidity and mortality. Previous studies of the infection in Nigeria focused mainly on blood donors and pregnant women (Oladipo *et al.*, 2015; Okoye *et al.*, 2015; Yuguda *et al.*, 2017; Udeze *et al.*, 2018a). We report here HTLV-1/2 infection among HIV-infected individuals who are receiving treatment at Oyo State Hospital, Ogbomosho, Nigeria. Prevalence of 0.5% was recorded in this study similar to 0.5% reported in a similar study in Brazil (Orletti *et al.*, 2021).

As a result of factors bordering on geographic location, peculiar regional endemicity, varied routes of exposure and risk behaviours, there are variations in the occurrence and distribution of HTLV (Caterino-de-Araujo *et al.*, 2015). Studies conducted in Gombe State among blood donors (Manga *et al.*, 2016) and Nigeria's federal capital (Abuja) involving HIV-uninfected individuals (Anyanwu *et al.*, 2019) each reported zero percent prevalence of the infection. Similarly, zero percent prevalence have been reported from other African countries including Benin Republic and Mali (Houinato *et al.*, 1996; Denis *et al.*, 1988).

The 0.5% prevalence recorded in this study is comparatively lower than 1.1% earlier reported among pregnant women in Ilorin, Nigeria (Udeze *et al.*, 2018a). Similarly, some earlier studies in Ibadan involving different cohorts including leukemia and STD patients, pregnant women and teenagers reported 11.5%, 16.7% and 5.1% of the infection respectively (Proietti *et al.*, 2005; Olaleye *et al.*, 1996; Forbi *et al.*, 2007). More recently also higher prevalence of 4.9% and 32.6% were reported from Abuja and Ilorin respectively among similar study population (Nasir *et al.*, 2015; Adeoye *et al.*, 2019). Various preventive measures targeted at HIV infection also reduces the infection of HTLV since they have common routes of transmission. The implementation of these measures may partly be responsible for the relatively low prevalence of HTLV-1/2 recorded in this study.

Of note in this present study is that most (73%) of the study participants belong to female gender. This may not necessarily mean that more females were infected by HIV rather a further affirmation of earlier observation that more Nigerian adult female patients seek medical care than men (Uneke *et al.*, 2005; Udeze *et al.*, 2019). Higher prevalence was recorded among the females than male participants in this study. This could be because of more efficient transmission of HTLV from men to women than women to men during sexual intercourse (Kajiyama *et al.*, 1986), hence more female predisposition to HIV/HTLV coinfection (Caterino-de-Araujo *et al.*, 2015). Similar finding was reported by Adeoye *et al.* (2019).

Furthermore, greater percentage of the study participants were in the age range 41-50 years. Although age was not a significant factor in the distribution of the infection in this study ($p > 0.05$), higher prevalence was recorded among participants of age range 51-60 years. This is not surprising since the burden of infection is known to accumulate with increasing age. Our finding is in agreement with previous study (Adeoye *et al.*, 2019).

Majority of the study participants have had their HIV diagnosis and started receiving cART for more than 2 years. In fact, most of the HIV infections could have occurred years back when the infection was at its peak. Implementation of the various HIV preventive measures however reduced the incidence rate of the infection (Udeze *et al.*, 2018b), hence the fewer number of respondents with more recent infections (diagnosed and started receiving treatment for < 1 year). While HIV diagnosis time was not associated with the occurrence, time on cART was significantly ($p < 0.05$) associated with the occurrence of HTLV infection in this study with those who have been receiving treatment for less than 1 year having higher prevalence of HTLV.

Greater percentage (56.5%) of the study participants had CD4⁺ count of ≥ 200 cell/mm³. Similarly, majority (58.5%) were in WHO clinical stage 1 of HIV infection. While the WHO clinical stage 1 status after

many years of infection could be attributed to the efficacy of the cART, the CD4⁺ cell count should not be misinterpreted as a sign of good prognosis as most of these lymphocytes may be functionally deficient and unable to offer the needed immunological protection to the infected persons instead could hinder accurate diagnosis of AIDS (Beilke, 2012; Mazanderani & Ebrahim, 2013; Ribeiro *et al.*, 2019). Enhanced CD4⁺ lymphocyte proliferation has been reported among HIV/HTLV-1 coinfecting individuals (Araujo, 2020). In this study, participants whose CD4⁺ count could not be ascertained at the time of sample collection and analyses were significantly ($p < 0.05$) more infected than the rest of the participants. Expectedly, patient with more advanced stage of HIV infection (WHO clinical stage 3) was the only patient infected by HTLV in this study suggesting its contribution to the advancement of HIV infection.

Limitations of the study

This study employed only a serological assay. This assay, in combination with more sensitive and specific assays such as PCR, would have eliminated cases of false positive and negative results, thereby giving a more accurate picture and true burden of the infection in this cohort.

Conclusion

Relatively low prevalence of HTLV was reported. Time on cART and CD4⁺ lymphocytes count were significant correlates of coinfection in this study. There is a need to conduct routine screening of all HIV infected persons for HTLV infection and administer an appropriate treatment regimen. There is also the need to apply caution in the interpretation of CD4⁺ results as a measure of prognosis among HIV/HTLV coinfecting patients.

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Competing interests

The author declares that he has no competing interests.

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