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### DETECTION OF HUMAN IMMUNODEFICIENCY VIRUS AMONG INDIVIDUALS PRESENTING WITH FEBRILE ILLNESS IN LAGOS, NIGERIA

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#### RUNNING TITLE: DETECTION OF HIV IN FEBRILE INDIVIDUALS

#### ABSTRACT

**Introduction:** The Human Immunodeficiency Virus (HIV) is the aetiological agent of Acquired Immunodeficiency Syndrome (AIDS), which is a chronic and potentially life-threatening condition. Fever is mostly associated with the early stage of virus replication known as acute HIV infection or syndrome; as such, determination of HIV status during this critical period is a good means of improving clinical outcome in those infected. Thus, this study aimed to determine the prevalence of HIV among febrile individuals in Lagos, Nigeria.

**Materials and Methods:** A cross sectional study of 250 febrile individuals attending General Hospitals at Isolo, Mushin and Surulere, Lagos, Nigeria. Analysis was carried out at the Virology Research Laboratory, Central Research Laboratory, College of Medicine of the University of Lagos from July to October 2017. Sample analysis was done according to the Nigerian National Testing Algorithm to determine HIV status using Enzyme Immunoassay (EIA) and data analyzed using Statistical Package for Social Sciences (SPSS) version 20.

**Results:** Out of the 250 febrile participants, 8 were positive for HIV, with an overall prevalence of 3.2%. Further analysis however showed that 90% of the HIV positive participants had four or more episodes of fever in a month. HIV infection was still majorly among the ages 15-24 and 25-34 for male and ages 25-34, 35-44 and 45-54 for females.

**Conclusion:** This findings showed that different cohorts are significantly at risk of HIV infection. Hence, policies and all efforts to reduce the burden of HIV are paramount for a HIV free future for Nigeria.

**Keywords:** Acute Retroviral Syndrome (ARS), Fever, Asymptomatic and Enzyme-Linked Immunosorbent Assay (ELISA).

### La DÉTECTION DES VIRUS DE L'IMMUNODÉFICIENCE HUMAINE CHEZ LES PERSONNES PRÉSENTANT UNE MALADIE FÉBRILE À LAGOS, NIGERIA

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#### TITRE : DÉTECTION DU VIH DANS LES INDIVIDUS FÉBRILES

#### Résumé

**Introduction :** Le virus de l'immunodéficience humaine (VIH) est l'agent causal du syndrome d'immunodéficience acquise (SIDA), qui est une maladie chronique et potentiellement mortel. La fièvre est le plus souvent associé avec le début de la réplication des virus connus sous le nom de l'infection à VIH aiguë ou un syndrome ; à ce titre, la détermination du statut VIH durant cette période critique est un bon moyen d'améliorer les résultats cliniques dans les personnes infectées. Ainsi, cette étude visait à déterminer la prévalence du VIH parmi les personnes fébriles à Lagos, Nigeria.

**Matériels et méthodes :** Une étude transversale de 250 individus fébriles qui fréquentent les hôpitaux généraux à Dubuque, Mushin et Surulere, Lagos, Nigeria.

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L'analyse a été effectuée à la virologie, Laboratoire de recherche Laboratoire Central de recherche, Collège de médecine de l'Université de Lagos, de juillet à octobre 2017. L'analyse des échantillons a été faite selon le test national nigérian algorithmique pour déterminer le statut sérologique à l'aide de dosage immunoenzymatique (EIA) et les données analysées en utilisant le progiciel de statistiques pour les sciences sociales (SPSS), version 20.

Résultats : Sur les 250 participants fébriles, 8 étaient positifs pour le VIH, avec une prévalence globale de 3,2 %. Cependant d'autres analyses ont montré que 90 % des séropositifs les participants avaient quatre épisodes ou plus d'une fièvre dans un mois. L'infection à VIH est encore plus parmi les 15-24 ans et 25-34 ans pour les hommes et de l'âge 25-34, 35-44 et 45-54 pour les femmes.

Conclusion : Cette conclusions ont montré que différentes cohortes sont grandement à risque d'infection à VIH. Par conséquent, les politiques et tous les efforts visant à réduire le fardeau du VIH sont primordiales pour un avenir sans VIH pour le Nigeria.

Mots-clés : syndrome rétroviral aigu (EI), de la fièvre, asymptomatiques et de dosage immuno-enzymatique (ELISA).

## INTRODUCTION

The Human Immunodeficiency Virus (HIV) is a retrovirus known to cause human immunodeficiency infection, with sequel advancement to Acquired Immunodeficiency Syndrome (AIDS) if proper management is not instituted[1]. Since the initial recognition of AIDS as a distinct syndrome with associated severe and life-threatening clinical conditions, HIV/AIDS remains one of the world's most significant public health challenge[2],[3]. The pandemic proportion of HIV is further reflected in an estimated 36.7 million people living with HIV-1 infection with 1.0 million deaths from HIV-related causes globally in 2016[3]. Furthermore, current estimates demonstrate very heterogeneous spread of HIV-1, but with Sub-Saharan Africa more affected, as 70% of the global total of new HIV infections has been reported from the region.[4] An estimated 60% of new HIV infections in Western and Central Africa in 2015 occurred in Nigeria, which is designated to have the second largest HIV epidemic in the world. Although HIV prevalence among adults is remarkably low (3.1%) compared to other Sub-Saharan African countries such as South Africa (19.2%) and Zambia (12.9%), the size of Nigeria's population means 3.5 million people were living with HIV in 2015[4]. The sustained pandemicity of HIV is due to the multi route of transmission of the virus, with its chronicity perpetuated by the gradual depletion of primary cells of the immune defence; which among others include monocytes, macrophages and dendritic cells[5]. The sequel undermined immune response from these cells play a significant role in HIV pathogenesis, as there is a direct killing and increased apoptosis of these infected cells, which progresses to a total decline of CD4+ T cells if there is no appropriate treatment intervention[6].

During the first few weeks following HIV-1 acquisition, many people develop an acute retroviral syndrome (ARS), which is a set of nonspecific symptoms and signs that includes fever, body pain, fatigue among other symptoms[7]. There is a steep rise in the HIV-1 viral load during this period that coincides with a spurt of inflammatory cytokines which is elicited as a febrile response in the individual[8]. Febrile illness or fever is a term for elevated body

temperature, which is due to the body's natural reaction to invasion by an infectious pathogen. It is clinically established when an individual has a temperature  $\geq 38$  °C and is one of the leading causes of visit to the hospital[9]. In Nigeria, major agents of febrile illnesses include *Plasmodium falciparum* responsible for malaria, *Salmonella typhi* (typhoid fever) plus a number of parasitic and viral infections[10]. While a number of persons can be positive for HIV but remain asymptomatic, fever is a common feature in HIV infected adults and may be a presenting sign of acute HIV-1 infection or indeed HIV infection at any stage[10].

The association of fever with ARS has been shown by studies reporting up to 75% of individuals experiencing an acute 'malaria-like' illness approximately 2 weeks after infection[11],[12]. Furthermore, Bebell *et al.* reported in 2010, that 1-3% of adults who sought care for suspected malaria in Uganda actually had acute or early HIV infection[13]. Considering the surge in HIV-1 replication and viral load in individuals with ARS, who are highly contagious and the fact that such persons may not be aware of their status. Coupled with the fact that their febrile illness is often thought to be caused by malaria and typhoid fever in Nigeria; HIV status determination among these cohorts is clinically important for referral for early treatment, which promotes good clinical outcome for persons positive to HIV. Early detection is also significant for deterring spread of the virus by identifying persons at risk of HIV spread. Hence, the objective of this study was to detect HIV infection among febrile individuals presenting to the hospital for treatment, so as to determine the prevalence of HIV among febrile individuals, while promptly referring positive persons to a HIV treatment centre.

## SUBJECTS AND METHODS

**Study Centre/Site:** A cross sectional study of febrile individuals at selected General Hospitals in Lagos State, Nigeria. Laboratory analysis was carried out at the Virology Research Laboratory, Central Research Laboratory, College of Medicine of the University of Lagos.

**Study Population:** Study participants were 250 individuals  $\geq 15$  years of age who sort health care

for febrile illness at General Hospitals (Isolo, Mushin, and Surulere) in Lagos State. Study population was calculated by the minimum sample size (N), determined using the equation as described by Pourhoseingholi *et al* in 2013[14]:

$$n = \frac{Z^2 P(1-P)}{d^2} \quad n = \frac{Z^2 P(1-P)}{d^2}$$

Where n= sample size, Z=statistics for a level of 95% confidence interval=1.96, d= precision (allowable error) =5%=0.05. P=prevalence rate (3.17%) as reported by NACA[15]. The population of Isolo, Mushin, and Surulere are reported as 837,300, 841,100 and 669,400 persons respectively[16]. Meanwhile, a minimum of 48 participants were calculated for the study, but was marked up to 250 for improved quality of data.

**Ethical Consideration:** Ethical approval with reference number CMUL/HREC/06/17/188 was obtained from the Health Research Ethics Committee (HREC), College of the Medicine of the University of Lagos. Duly informed consent was obtained from the participants that met criteria for the study.

**Inclusion criteria:** Febrile individuals who do not have previous history of chronic illness and do not know their HIV status as at the time of presentation at the hospitals.

**Exclusion criteria:** Acutely ill febrile individuals, those who declined participation and individuals less than 15 years of age were excluded from the study.

**Data/ Sample Collection and Storage:** Socio-demographic data was obtained by Health Research Ethics Committee validated structured interviewer administered questionnaires. Participants designated as febrile after seeing the Clinician proceeded to sample collection for laboratory testing. Three to five millilitres (ml) of whole blood samples was collected into an EDTA bottle labelled with unique code for confidentiality and transported in cold chain using triple level packaging system to the laboratory. Samples were spun in the centrifuge

(Eppendorf, Germany) at 300 rpm for 10 minutes and plasma separated into labelled cryovials and stored at in a freezer at -20 °C until analysis.

**Sample Analysis using Enzyme Immunoassay**

**(EIA):** Analysis of all samples to determine HIV status were done according to the Nigerian National Testing Algorithm (serial testing)[17] and according to the manufacturer's instructions (Alere Determine HIV-1/2: Catalog number 7D2342/7D2343; Trinity Biotech Uni-Gold: Catalog number 1206502; SD-Bioline HIV 1/2 3.0: Catalogue number: 03FK10CE. The test kits were rapid test based on the principle of Enzyme Immunoassay (EIA)[17]. All kits were checked before use to ascertain that they were not expired or damaged and all procedures were carried out using universal safety precautions.

**Statistical Analysis:** Analysis was done using Statistical Package for Social Sciences (SPSS) version 20 to compute descriptive data and prevalences, which were recorded as simple percentages. Associations between non-parametric variables were tested using Fishers's exact test. The level of significance was set at 0.05.

**RESULTS**

Two hundred and fifty (250) febrile individuals were recruited for this study. There were 80 (32%) males and 170 (68%) females, giving a male/female ratio of 1:2.1. The mean age of the participants was 36.5 years, with a range of ≥15 - 84 years. The demographic features of the febrile individuals are as shown in table 1, with no significant associations found among the demographic variables collated from the participants.

Out of the two hundred and fifty (250) samples analysed, 8 samples were positive for HIV, with an overall prevalence of 3.2% in these febrile individuals. Of these, 5 (62.5%) and 3 (37.5%) were females and males respectively without any statistical significant difference ( $p = 0.32$ ) as shown in table 2.

TABLE 1: SOCIO-DEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

VARIABLES	CHARACTER	NUMBER OF PARTICIPANTS (%)	<i>p-values</i>
<b>Marital Status</b>	Single	140 (56.0)	<b>0.76</b>
	Married	103 (41.2)	
	Divorced	5 (2.0)	
	Widow	10 (0.8)	
<b>Religion Belief</b>	Christianity	110 (44.0)	<b>0.83</b>
	Islam	125 (50.0)	
	Traditional	10 (4.0)	
	Others	5 (2.0)	
<b>Tribe</b>	Yoruba	168 (67.2)	<b>0.09</b>
	Igbo	48 (19.2)	
	Hausa	23 (9.2)	
	Others	11 (4.4)	
<b>Educational Level</b>	Primary	82 (32.8)	<b>0.63</b>
	Secondary	102 (40.8)	
	Tertiary	61 (24.4)	
	None	5 (2.0)	
<b>Occupation:</b>	Civil Servant	35 (14.0)	<b>0.74</b>
	Business	41 (16.4)	
	Artisan	123 (49.2)	
	Farmer	4 (1.6)	
	Unemployed	47 (18.8)	
<b>Fever Episodes in a Month</b>	Once	49 (19.6)	<b>0.81</b>
	Twice	95 (38.0)	
	Thrice	85 (34.0)	
	≥Four Times	21 (8.4)	

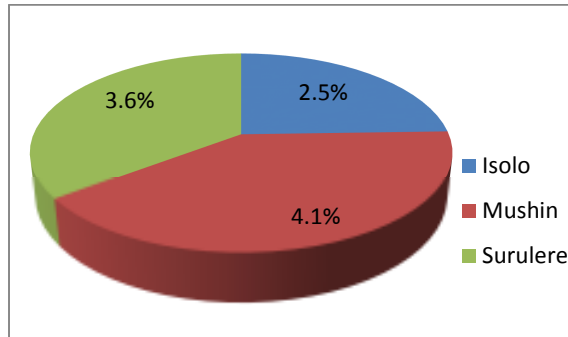
TABLE 2: PREVALENCE OF HIV AMONG FEBRILE INDIVIDUALS

SEX DISTRIBUTION	NUMBER (%)	NUMBER POSITIVE (%)	NUMBER NEGATIVE (%)	<i>p-values</i>
Male	80 (32)	3 (37.5)	77 (96.2)	<b>0.32</b>
Female	170 (68)	5 (62.5)	165 (97.1)	
<b>Grand Total</b>	<b>250 (100)</b>	<b>8 (3.2)</b>	<b>242 (96.8)</b>	

Further analysis however showed that 90% of the positive participants had four or more episodes of fever in a month and HIV positive participants fell

into the 15 to 54 years age range. Distribution and comparison of HIV positivity among the three general hospitals in Isolo, Mushin and Surulere

used for this study showed no statistical significant difference. HIV-1 detection among the 8 positive individuals from the study sites (Isolo, Mushin and Surulere) taking into consideration the numbers of samples collected from the sites were 2.5%, 4.1% and 3.6% respectively (figure 1).



**FIGURE 1: THE PERCENTAGE DISTRIBUTION OF POSITIVE SAMPLES FROM THE STUDY SITE**

#### DISCUSSION

Febrile illness or fever is a common reason for presenting and seeking healthcare in low and middle-income countries. Among patients with febrile illness requiring admission, case fatality ratios are high, sometimes exceeding 20%[18]. The many etiologies of fever are difficult to distinguish clinically and laboratory services may be limited or absent in such settings. Consequently, presumptive treatment significantly affects the proper management of febrile illnesses and HIV positive persons[18],[19]. These positive febrile individuals may probably be at the acute HIV-1 infection stage, remain asymptomatic, highly contagious and account for a large number of new HIV-1 infections. Thus, diagnosis and prompt initiation of Anti-retroviral drugs (ARTs) for these and other cases of HIV infection should be identified as a 'top priority' for HIV prevention, particularly in Nigeria.

The prevalence of 3.2% of HIV-1 among febrile individuals in this study falls within the overall range prevalence of 3.17% in Nigeria[15]. This finding shows that the burden of HIV infection in Nigeria is still a cause for concern particularly among febrile individuals seeking healthcare at various hospitals. Our finding among these febrile participants was similar to the study by Bebell *et al.*[13] who reported a similar prevalence of HIV among adults who sought care for suspected malaria in Uganda. Likewise, and also in 2010, Serna-Bolea *et al.*[20] reported that 3.3% of patients who sought care for fever at a district hospital in Southern Mozambique had acute HIV infection. However, the prevalence detected from this study was lower than respective 4.1%, 9%, 4.88% and

11.4% reported from Oyo,[21] six geopolitical zones,[22] Plateau,[23] and Ogun States in Nigeria.[24]

Our study also shows that positive samples were detected in the three locations, which are densely populated and are representative of most areas in Lagos. Corresponding variations in the prevalence's in several reports from different parts of the country is majorly attributed to the different population samples, geographic locations, testing platforms and other socio-economic factors related to the population and site studied.

In this study, more females presented at the hospitals seeking healthcare for febrile illnesses and were found to be more infected than males. Although, the percentage of positivity among males and females was not statistically significant. This findings was similar to the study of Omoniyi *et al.*[22] who also reported a higher prevalence in females than in males. The larger area of exposure in females (vagina/ compared to the penis) has been known to put females at greater risk of HIV infection.

A high prevalence of HIV infection was more prominent in age group < 54 years, also similar to the study by Omoniyi *et al.*[22] who reported high HIV prevalence within same age range. This is clearly indicative of the association of HIV with a more sexually active age group in our society; although, all gender and age groups are still at risk of HIV infection.

While febrile patients should be encouraged for HIV testing, a provider-initiated HIV-1 testing and counseling (PITC) programme should be instituted for all patients visiting health facilities. Unfortunately the uptake of PITC has been low in sub-Saharan Africa[25]. Frequently mentioned reasons for the low uptake documented in literature include patient burden, absence of test kits, patients' perceived HIV-1-negative status following a previous HIV-1 test, added costs for patients accessing care at private facilities and weak health systems in general[26]. However, focusing PITC efforts on patients with signs of acute infection (e.g. fever, sexually transmitted diseases, and diarrhea) may greatly reduce the number of patients requiring testing, while still allowing the identification of a large number of patients with undiagnosed prevalent HIV-1. Early detection through screening at the point of presentation for patients with febrile illness should be advocated for as a policy towards management. This would be significant for improved clinical care and reduction in HIV transmission in our environment.

#### CONCLUSION

The findings in this study shows that HIV was detected in individuals with febrile illnesses and was detected more in the sexually active age. It is important to put up a policy that will promote

identification and monitoring of patients presenting in Nigerian clinics with febrile conditions and engage them in voluntary HIV counselling and testing. Thus, the government at all levels should further support HIV prevention programmes in population at risk, particularly as identified in this study.

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**CONFLICTS OF INTEREST:** There are no conflicts of interest.

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#### AUTHORS' CONTRIBUTIONS

S.O.B., N.F.O. and B.T.E. conceptualized the study and were responsible for the experimental and project design, analysis of data and writing the manuscript. O.B.O. and J.A.B. made conceptual contributions, performed experimental analysis and assisted in preparing the manuscript. While O.S.A was the laboratory director, team lead of the Virology Research Group and was responsible for the experimental and project design, analysis of data and writing the manuscript. All authors read and approved the manuscript.

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