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Evaluation of tetanus antibody protection among HIV-infected patients in Ile-Ife, Nigeria

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Abstract

Introduction: Development of vaccine-mediated immunity in general population remains crucial in the fight against epidemics. This concept enabled successful eradication of diseases, such as smallpox and other infections of public health importance. The aim of this study was to evaluate the level of immunity against tetanus in human immunodeficiency virus (HIV)-positive individuals, and explore the relationship between antibody levels and CD4+ T cell counts.

Material and methods: This cross-sectional study was conducted at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria. Sixty people living with HIV (PLHIV) participated in the study. Clinical and laboratory data, including CD4+ count and tetanus antibodies, were analyzed using SPSS version 20.0.

Results: The average age of PLHIV enrolled in the study was 40.63 ± 6.15 years, and 88.3% were females. Tetanus antibodies were high among the participants, with 55.5% of them exhibiting high levels. One-half of the study cohort with CD4+ greater than 200 cells/ml had moderate (range, 0.1-1.0 IU/ml) levels of tetanus antibodies, while the other half had high (range, 1.0-5.0 IU/ml) levels. With CD4+ counts below 200 cells/ml, 75% of PLHIV showed high level of tetanus antibodies.

Conclusions: The course of HIV adversely affects humoral immunity, and may impede the progress made in eradicating vaccine-preventable diseases. The study suggests that increasing access to antiretroviral therapy improves PLHIV protection and prevents disruption of host immunity. Intensive case HIV finding, integration of vaccination, and HIV supporting programs will consolidate vaccine-mediated immunity.

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Key words: HIV, Nigeria, tetanus antibodies, vaccine, immunity.

Introduction

The advent of vaccination and the resulting induction of immunity have been used as a tool in the management of infectious diseases and related outbreaks. Vaccination has been integrated into primary healthcare in the majority of developing countries due to its low cost and effectiveness in diseases' prevention and morbidity reduction. Spreading of a number of vaccine-preventable diseases, including polio, rubella, and mumps, has substantially been halted

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by vaccinations [1]. Although it is desirous to achieve vaccine-mediated immunity and rapid prevention of the spread and severity of a disease, the population may lose acquired immunity over time due to the absence of sub-clinical infections, which are often required to stimulate the immune system and enhance the immune memory. This phenomenon established the need for vaccines' booster doses to achieve the desired protection.

The development of vaccine-mediated immunity among the population, as the main goal in the fight against epidemics, has been delayed [2]. The proportion of population required to be immunized for successful development of people's immunity varies within different pathogens.

The knowledge and understanding of this concept required the adoption of a vigorous vaccination campaign to eradicate diseases, such as smallpox, polio virus, and other infections of public health importance [3]. Smallpox was successfully eradicated after massive vaccinations, while the polio virus, is on the verge of being eradicated. Social and cultural factors, including false beliefs and myths about vaccines, impede the realization of the minimum vaccination level required to achieve the desired results [4].

Tetanus, a vaccine-preventable disease, is relatively common in the tropics, and is considered as one of the killer diseases of childhood in Nigeria, with poor prognosis in children and elders. Due to high morbidity and mortality associated with this disease, vaccination is incorporated into the national immunization scheme, where all children under the age of five are given the vaccine. Booster doses are also included as a part of routine antenatal care. Moreover, tetanus is commonly indicated in young adults presenting to emergency department with acute injuries. In view of the frequent occurrence of tetanus in tropical environment and the increased exposure to vaccines, the current study evaluated the level of vaccine-mediated immunity among people living with human immunodeficiency virus (PLHIV).

Nigeria was declared free of wild type polio virus in August 2020. However, a number of circulating vaccine-derived polio viruses was reported in 2021 [5]. Even though such development may be discouraging, funding organizations, such as World Health Organization (WHO), United Nations Children's Fund (UNICEF), non-governmental agencies, and the government of Nigeria, remain focused and continue to intensify efforts aiming at achieving the complete eradication of the virus.

Apart from social and cultural factors, host factors, including primary or acquired immunodeficiency states, can influence the outcomes of vaccination and compromise their expected benefits [1, 6]. While vaccine-preventable diseases are prevalent in developing countries, such as sub-Saharan Africa, the enthusiasm associated with faster eradication of the disease may not be achieved within the projected timeframe due to the advent of HIV/acquired immunodeficiency syndrome (AIDS).

HID/AIDS have vastly strained health budget. Resources that would have been available for implementing vaccination programs are diverted to stop the HIV epidemic [7]. Furthermore, HIV impacted social well-being of people in this region, and indirectly influenced their vaccine uptake rate. The influence of HIV may not be limited to the social issues associated with vaccination. HIV directly affects both the cellular and humoral components of the immune system. The virus infects CD4+ T cells within hours of infection, and rapidly infects and destroys many CD4+ T cells [8]. The progressive and steady depletion of T cells is responsible for the observed defect in cellular immunity.

Although the humoral immune system is not spared in the infection of HIV, cell-mediated immunity is the pathogen's main target [9]. The subsequent immunological suppression resulting from HIV infection undoubtedly impact the development and maintenance of vaccine-mediated immunity among this population [10].

As part of the efforts to improve well-being of PLHIV and to limit the impact of HIV on vaccine-preventable diseases, the Federal Government of Nigeria in collaboration with partners, including U.S. President's Emergency Plan for AIDS Relief (PEPFAR), Joint United Nations Programme on HIV/AIDS (UNAIDS), and the Global Fund, has expanded the access to antiretroviral drugs for people living with HIV in sub-Saharan Africa.

Even though a number of factors affecting the development and retention of vaccine-mediated immunity are known, several other elements remain a subject of speculation. Similarly, a high-rate of immunosuppression among the general population can affect vaccine-mediated immunity. Re-constitution of the immune system using antiretroviral medications produces a state where the effect on vaccine-mediated immunity requires investigation. Therefore, the purpose of the current research was to evaluate the level of immunity against tetanus in HIV-positive individuals, and explore the relationship between tetanus antibody level and CD4+ T cell counts.

Material and methods

Study location

This cross-sectional study was conducted between August 2020 and March 2021 at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife. It is a first-generation tertiary healthcare facility funded by the Federal Government of Nigeria, and accepts referrals from the entire South Western Nigeria, providing medical care to Osun State's population of about 4.7 million people [11].

Study population

The study was carried out among people living with HIV/AIDS, who are registered at a healthcare facility. Adults between 18 and 60 years old were considered and enrolled in the study. Patients with other evident causes of immune suppression, such as hematological malignancies or solid organ transplant patients, were excluded. The Obafemi Awolowo

University Teaching Hospital's Ethnic and Research Committee provided ethical consent (approval number: IRB/IEC/0004553 NHREC/27/02/2009a).

Sampling and sample size determination

Convenience sampling method was adopted and patients were recruited consecutively. Sixty PLHIV were enrolled. A sample size of 60 PLHIV was determined using Leslie Kish formula [12]. HIV prevalence rate of 3.5% in sub-Saharan Africa [13] was applied in calculating the sample size, while allowing for marginal error of 5% and a confidence interval of 95%. An average number of 2,500 PLHIV are using medical care from this facility. The calculated sample size of the study was 51, with an additional figure of 5, amounting to 10% attrition, and constituting 56 patients, which was rounded up to 60.

Data collection

Clinical informations, including socio-demographic characteristics, were obtained from the patients and corroborated by the medical records using a proforma. Relevant clinical signs were similarly obtained and documented while concealing identities of participants. Patients' latest CD4+ T cell counts done within the past six months were retrieved from patients' records, while those with no recent CD4+ T cell counts had a repeat CD4+ count performed. Patients' blood samples were taken, and separated serums were stored at –20°C until the designated number of samples was collected ($n = 60$). These were subsequently processed to determine the level of tetanus' antibodies using ELISA technique. In general, antibody level of < 0.1 IU/ml is considered low and basic immunization is recommended. Antibody levels between 0.1 and 1.0 IU/ml need to be controlled after 1-2 years, while antibody levels between 1.0 and 5.0 IU/ml should be measured after 2-4 years. Patients with antibody levels > 5.0 IU/ml have the best protection, and need to be controlled after 4-8 years [14].

Data were analyzed using SPSS version 20.0. The obtained variables were compared using χ^2 test and logistic regression model to define association and correlation. A p-value < 0.05 was considered statistically significant. Relevant tables were used to display the observed findings.

Table 1. Demographic characteristics of people living with HIV ($N = 60$)

Factor	
Age (years)	
Mean age	40.63
Standard deviation	6.153
Gender, *n* (%)	
Male	7 (11.7)
Female	53 (88.3)
Marital status, *n* (%)	
Married	57 (95.0)
Single	2 (3.3)
Widowed	1 (1.7)
Divorced	–
Ethnicity, *n* (%)	
Yoruba	53 (88.3)
Hausa	3 (5.0)
Igbo	3 (5.0)
Other	1 (1.7)
Antiretroviral therapy, *n* (%)	
Yes	60 (100)
No	–

Results

The average age of HIV-positive patients recruited for the study was 40.63 ± 6.15 years. Females constituted the larger proportion (88.3%) of HIV-positive patients. All PLHIV involved in the study were placed on antiretroviral medications. 45% of HIV-infected patients had moderate levels of antibodies, defined as levels between 0.1 and 1.0 IU/ml, while 55% of PLHIV had high levels of antibodies, defined as levels between 1.0 and 5.0 IU/ml (Table 1). Twelve participants had acquired immune deficiency syndrome (AIDS), with a CD4+ count of less than 200 cells/ml. Among this sub-population, 25% had moderate levels of tetanus antibodies, while the remaining 75% had high levels of tetanus antibodies. These distributions of tetanus antibodies among participants with a CD4+ count greater than 200 cells/ml were equal, being 50% moderate and 50% high. Low levels of tetanus antibodies (< 0.1 IU/ml) and very high levels (> 5 IU/ml) were not observed among the study cohort (Table 2). Although impressive levels of antibodies were noted among PLHIV, it did not show a significant variation after adjusting for confounders, such as gender and age (Table 3).

Discussion

HIV has ravaged the globe for the past four decades, evading numerous efforts to develop a cure or vaccine that could curtail the ensuing epidemic [15]. Several laudable attempts were made by numerous organizations to develop vaccines. Also, numerous trials were conducted with variable outcomes on the efficacy of HIV vaccine. Although a cure is yet to be discovered after four decades of intense research on the vaccine for HIV, significant advances were made, and the prospect of cure is brighter than what could be imagined a decade ago. Some of the trials conducted include VAX 003 and VAX 004, Step and Phambili studies,

Table 2. Immunological assessment of people living with HIV

CD4+ cells counts	Tetanus antibodies				χ^2	df	*p*-value
	Low, < 0.1 (IU/ml), *n* (%)	Moderate, 0.1-1.0 (IU/ml), *n* (%)	High, 1.0-5.0 (IU/ml), *n* (%)	Very high, > 5.0 (IU/ml), *n* (%)			
< 200 cells/ml (*n* = 12)	–	3 (25)	9 (75)	–	2.424	1	0.119
> 200 cells/ml (*n* = 48)	–	24 (50)	24 (50)	–			
Total (*n* = 60)	–	27 (45)	33 (55)	–			

Table 3. Tetanus antibody evaluation with adjustment for confounders

Variables	B	SE	Wald	df	95% CI for B		β	*p*-value
					Lower limit	Upper limit		
Age	0.000	0.046	0.000	1	0.914	1.094	1.000	0.998
Gender	–0.553	0.872	0.402	1	0.104	3.176	0.575	0.526
Constant	0.270	1.846	0.021	1			1.310	0.884

Omnibus test coefficients			
	χ^2	df	*p*-value
Model	0.470	2	0.791

Model summary		
–2log likelihood	Cox and Snell's R^2	Nagelkerke's R^2
82.107	0.008	0.010

RV144, and HVTN 505. These trials were based on different mechanisms, including broadly neutralizing antibodies [16].

As the world and medical community anxiously await a breakthrough in successful vaccine development for HIV, the challenge of declining immunity to vaccine-preventable diseases and infections persists. O'Connor *et al.* [10] reported a decrease in vaccine-mediated immunity among HIV-infected patients. Several other diseases, which have been controlled by vaccination, such as pulmonary tuberculosis, have resurged with the advent of HIV/AIDS [17]. Susceptibility to numerous other opportunistic infections observed among PLHIV has come to form the basis of the World Health Organization (WHO) clinical staging of HIV infection [18].

Despite the bleak outlook portrayed by earlier observation, our finding shows an impressive level of protection against tetanus among PLHIV. This observation is consistent with a preliminary report by Salawu *et al.* [19], where patients with HIV were found to produce a sufficient amount of tetanus antibodies. However, Alagapan *et al.* [20] in the US showed that a fraction of HIV-positive patients had low anti-tetanus antibody levels, particularly among individuals born outside of the United States.

The improvement observed in this study could be ascribed to a change in treatment protocol that allows all PLHIV to be placed on antiretroviral therapy irrespective of their clinical stage of disease, level of CD4+ T cell counts, or viral load. Until a few years ago, only a proportion of patients met the criteria for antiretroviral treatment in sub-Saharan Africa. Some of the requirements included a CD4+ count of less than 200 cells/ml and clinical stage 4 disease. However, as more evidence started to emerge with more funds available, these protocols evolved gradually to a stage where all HIV-positive patients are required to be placed on highly active antiretroviral therapy (HAART) without exception. Although the history of booster tetanus doses could not be recalled by most of the participants, it is possible that more females, which were dominant among the participants in the current study, are likely to receive booster doses as a routine component of antenatal care. This may contribute to the enhanced protection against tetanus observed in this study.

Significant advances have also been made regarding the use of antiretroviral therapy. The recent antiretroviral drugs appear to be more effective, and the regimens are less likely to encounter drug resistance [21]. This intervention enhanced viral suppression and prevented depletion of host immunity, thereby, contributing to vaccine-mediated immunity.

Establishing vaccine-mediated immunity in the population is critical for public healthcare and epidemic management [1]. While socio-cultural factors could prevent vaccination of the population's required proportion, immune suppression, such as HIV, could prevent the development of immune response and mitigate the establishment of vaccine-mediated immunity. It is gratifying to see improvement in this trajectory among PLHIV, who were involved in this

study. The presence of protective antibodies to diseases, e.g., tetanus, during pregnancy, may benefit maternal health and improve well-being of the infant by lowering the incidence and severity of neonatal and infantile tetanus.

Conclusion and recommendations

Vaccine-preventable diseases and the HIV epidemic are prevalent in sub-Saharan Africa. The course of HIV adversely affects vaccine-mediated immunity and reverses progress made in eradicating vaccine-preventable killer diseases. This increases vulnerability to vaccine-preventable diseases and worsens HIV-associated morbidity. This study shows that with increasing access to potent and effective antiretroviral regimens, there is improved protection of PLHIV against tetanus infection as well as suggests that HIV may not cause disruption in the acquired vaccine-mediated immunity. In view of these observations, intensive HIV case finding will contribute to the provision of vaccine-mediated immunity by facilitating early diagnosis and subsequent initiation of HAART. As the campaign for the prevention of the HIV epidemic and vaccination against killer diseases often involves advocacy and social awareness strategies, integrating both programs will maximize these efforts, ensuring an accelerated implementation and realization of the set objectives.

Disclosures

1. Institutional review board statement: This study was approved by the Ethnic and Research Committee of the Obafemi Awolowo University Teaching Hospital (approval number: IRB/IEC/0004553 NHREC/27/02/2009a.
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