Cytomegalovirus Infection Prevalence and Blood Transfusion in Patients with Human Immunodeficiency Virus attending some Retro-Viral Treatment Centers in, North-Central Nigeria

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ABSTRACT

Background: Cytomegalovirus (CMV) is a well-known leading cause of opportunistic viral infection in human immunodeficiency virus (HIV). Blood transfusion is a key component of anaemia treatment. Anaemia is often a common complication of HIV/AIDS. Blood transfusion, though useful in the treatment of anaemia which may result from complications of the lethal triad of CMV-HIV coinfection on highly active anti-retroviral therapy (HAART), It could pose a significant risk for transfusion transmissible CMV infection in HIV positive patients. **Objectives:** This study aimed to evaluate the relationship between CMV infection and blood transfusion amongst HIV Positive Patients on HAART attending selected Retro-Viral Treatment Centers. **Materials and Methods**: This was a cross-sectional, descriptive study of 268 confirmed HIV positive adults, registered and attending HIV clinics at a Tertiary and a Secondary health facility in Nigeria. Relevant biodata and blood samples were collected and analysed with enzyme-linked immunosorbent assay (ELISA) for CMV IgG and IgM antibodies. **Results:** CMV IgG and IgM sero-prevalence were 92.5% (248/268) and 21.3% (57/268) respectively. A total of 73 (60 males and 13 females) were transfused. Of the 73 transfused, 67 (91.8%) and 25 (34.2%) were IgG and IgM positive respectively. Of those transfused and positive, 56 (93.3%) were Males while 11 (84.6%) were females. This was however not statistically significant with a P=0.100. Circulating IgM was highest in younger age groups of 0-19 years with IgM of 7 (38.9%) and 20-39 years with IgM of 32 (26.7%) while IgG was highest in the older age groups 20-39 years with IgG of 114 (95.0%) and 40-59 years with IgG of 110 (94.0%); P=0.004 and 0.015 respectively. **Conclusion:** Age and blood transfusion were found to be significant risk factors for CMV seropositivity. CMV IgM was found to be significantly higher (recent infection) in younger respondents while IgG was higher (past infection) in the older respondents. While blood transfusion was a significant risk factor for Transfusion

Transmissible CMV Infection (TTCI), TTCI risk was not significantly gender biased. We recommend the provision of CMV negative blood for all cases of HIV patients that may require blood transfusion irrespective of their HAART status as part of measures to reduce CMV infection rate and its complications in immune incompetent populations.

Keywords: ELISA, CMV, IgG, IgM, HAART, Makurdi.

INTRODUCTION

Cytomegalovirus (CMV) is known to contribute significantly to the HIV disease pathogenesis in HIV patients and is believed to accelerate HIV progression to acquired immunodeficiency Syndrome (AIDS).

CMV, HIV/AIDS, blood transfusion and HAART are known to relate in a complex manner in overall disease pathogenesis. Blood transmits both HIV and CMV, HIV is a risk factor for lethal CMV which could worsen HIV and increases blood transfusion demand. The HAART alone or with HIV could lead to anaemia and blood transfusion risk, etc. A lot more research needs to be done to further explore this complex interplay (Jeanne et al., 2009).

In healthy individuals, CMV may remain dormant, but becomes life threatening in the immunocompromised such as pregnant women, transplant recipients, neonates and HIV patients. Infection with CMV could be transmitted through sexual activities, blood transfusion, delivery, organ transplant and contact with infected body fluid such as saliva, tears, blood and urine.

It's been reported in several other studies that nearly fifty percent of HIV infected patients will eventually develops any or all of these opportunistic CMV chorioretinitis, easophagitis, colitis, pneumonia, and central nervous system diseases. Autopsy reports of patients who died from HIV in Australia have revealed pathological evidence of CMV disease in up to about 76% of cases (Dore *et al.,* 1995).

In addition to these clinical impacts of CMV/HIV co-infection, there are also significant socio-economic implications on both the patients, families, caregivers as well as constituting serious strain on the national health resources.

The aim of this study was to determine Cytomegalovirus infection prevalence and blood transfusion rates amongst HIV Positive Patients on HAART attending selected Retro-Viral Treatment Centers in Makurdi, Benue State. The study hopes to determine wether or not CMV sero-status increased demand for blood and that blood transfusion was a significant risk factor for CMV infection in HIV patients on HAARTS. It hopes to also determine other factors in these patients that may increase transfusion risk. The findings of this study may guide policy on CMV/HIV co-infection control, safe, effective and efficient use of blood and transfusion services in the management of patients with CMV/HIV co-infection on HAARTS,

MATERIALS AND METHODS

Study design: This was cross sectional, descriptive study design. The subjects were selected for inclusion by consecutive sampling technique, this is a non probability sampling method which involves taking every subject who meets the inclusion criteria, and until the calculated sample size was met. The socio-demographic data was collected with the aid of well-structured questionnaires. These included the age, sex, HAART and blood transfusion history etc.

Study population: These were HIV positive patients attending antiretroviral treatment clinics at the Benue State University Teaching Hospital (BSUTH) and General Hospital North, Bank Makurdi, Nigeria

Study location: Makurdi is the state capital city of Benue State. It is located on Latitude: $7^0$43` 50``N and. Longitude: $8^0$ 32` 10``E, Makurdi and has an estimated population of 422,000 as at the year 2020. Temperature range is between 23^{0}C and 35^{0}C depending on the time of the year. The main inhabitants are Tiv, Idoma and Igede speaking people; however, there are settlers from other parts of the country.

Sample Size Determination: The sample size was calculated using the formula;

$n = \frac{Z^2P(1-P)}{d^2}$ (Daniel, 1999)

Where:

n = required sample size,

Z = level of confidence at 95% (standard value of 1.96)

P = known prevalence for CMV IgM is 19.8% or 0.198(Omosigho *et al*., 2019)

d = precision or margin of error at 5% (standard value of 0.05).

Therefore, sample size, $n = \frac{Z^2 P(1-P)}{d^2}$

$$n = \frac{1.96^2 * 0.198(1-0.198)}{0.05^2}$$

$$= \frac{3.84168 * 0.198 * 0.802}{0.0025}$$

$$= \frac{0.5816457187}{0.0025}$$

=244.017366912, approximately 244.

To make up for attrition, 10% of this was added to the total number of samples to give a final sample size of 268.

Serological Test (ELISA IgG/IgM): Blood samples (5ml) were collected from the 268 HIV patients by venipuncture into plain vacutainer bottles. The blood were allowed to stand till clot and centrifuged at 3000 revolution per minutes for 10 minutes. The supernatant serum were extracted stored at -20^{0}C until ready for use. The serum were later tested for IgG/IgM antibodies using enzyme-linked immunosorbent assay (ELISA), and results were recorded accordingly.

Inclusion Criteria: Criteria for inclusion in this study were consenting HIV patients attending clinics at BSUTH and General Hospital, North Bank, Makurdi.

Exclusion criteria: Failure to meet inclusion criteria.

Ethical clearance: The proposal was submitted, assessed and clearance for this study was issued by the ethics committee of the Benue State Ministry of Health Makurdi. Written informed consents were also obtained from each patient before the study.

Data analysis: Data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 20 (Armonk. NY:IBM Corp), using simple frequencies and cross-tabulations. Chi-square test was used to study relationships and associations between categorical variables and P-value of < 0.05 was considered significant at the 95% confidence interval. The final results were presented in figures and tables.

RESULTS

IgG and IgM sero-prevalence were 92.5% (248/268) and 21.3% (57/268) respectively (Table 1). Circulating IgM was highest in younger age groups of 0-19 years with IgM of 7 (38.9%) and 20-39 years with of IgM 32 (26.7%) while IgG was highest in the older age groups of 20-39 years with IgG of 114 (95.0%) and 40-59 years with IgG of 110 (94.0%); P=0.004 and 0.015 respectively (Table 2).

Age was therefore a significant risk factor for CMV seropositive IgG and IgM with P=0.004 and 0.015 respectively. Blood transfusion was a significant risk factor for CMV IgM in HIV infection with P=0.001. (Table 2). Sex was not a significant risk factor for both CMV IgG and IgM sero-positivity with P=0.937 and 0.069 respectively (Table 2). A total of 73 (60 males and 13 females) were transfused. Of the 73 transfused, 67 (91.8%) and 25 (34.2%) were IgG and IgM positive respectively.

Of those transfused and positive, 56 (93.3%) were Males while 11 (84.6%) were females. This was however not statistically significant with a P=0.100 (Table 3). While blood transfusion was a significant risk factor for the CMV IgM [Transfusion Transmissible CMV Infection (TTCI)] with a P=0.001, TTCI risk was not significantly gender biased P=0.100 (Table 3).

Table 1: CMV Seroprevalence (Ig G and Ig M) among HIV patients

	CMV IgG		CMV IgM	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Positive	248	92.5	57	21.3
Negative	20	7.5	211	78.7
Total	268	100.0	268	100.0

Table 2 Age, Sex and blood transfusion against CMV IgG and IgM antibodies in HIV Patients

	Ig G				Ig M			
	Positive n (%)	**Negative n (%)**	**Total**	***p-value***	**Positive n (%)**	**Negative n (%)**	**Total**	***p-value***
Age Group								
0-19	13 (72.2)	5 (27.8)	18 (100.0)		7 (38.9)	11 (61.1)	18 (100.0)	
20-39	114 (95.0)	6 (5.0)	120 (100.0)		32 (26.7)	88 (73.3)	120 (100.0)	
40-59	110 (94.0)	7 (6.0)	117 (100.0)		15 (12.8)	102 (87.2)	117 (100.0)	
60-79	11 (84.6)	2 (15.4)	13 (100.0)	0.004*	3 (23.1)	10 (76.9)	13 (100.0)	0.015*
Total	**284 (92.5)**	**20 (7.5)**	**268 (100.0)**		**57 (21.3)**	**211 (78.7)**	**268 (100.0)**	
Sex								
Male	184 (92.5)	15 (7.5)	199 (100.0)		37 (18.6)	162 (81.4)	199 (100.0)	
Female	64 (92.8)	5 (7.2)	69 (100.0)	0.937	20 (29.0)	49 (71.0)	69 (100.0)	0.069
Total	**248 (92.5)**	**20 (7.5)**	**268 (100.0)**		**57 (21.3)**	**211 (78.7)**	**268 (100.0)**	
Blood transfusion								
Yes	67(27.0)	6 (30.0)	73 (27.2)		25(43.9)	48 (22.7)	73 (27.2)	
No	181 (73.0)	14 (70.0)	195 (72.8)	0.773	32 (56.1)	163 (77.3)	195 (72.8)	0.001*
Total	**248(100.0)**	**20 (100.0)**	**268 (100.0)**		**57 (100.0)**	**211 (100.0)**	**268 (100.0)**	

Table 3: Sex and blood transfusion with CMV Ig G / Ig M status in HIV Positive patients on HAART

		Ig G				Ig M			
		Positive n (%)	**Negative n (%)**	**Total**	***p-value***	**Positive n (%)**	**Negative n (%)**	**Total**	***p-value***
Blood transfusion									
Yes	**Sex** M	56 (93.3)	4 (6.7)	60 (100.0)		18 (30.0)	42 (70.0)	60 (100.0)	
	F	11 (84.6)	2 (15.4)	13 (100.0)		7 (53.8)	6 (46.2)	13 (100.0)	
	Total	**67 (91.8)**	**6 (8.2)**	**73 (100.0)**	0.299	**25 (34.2)**	**48 (65.8)**	**73 (100.0)**	0.100
No	**Sex** M	128 (92.1)	11 (7.9)	139 (100.0)		19 (13.7)	120 (86.3)	139 (100.0)	
	F	53 (94.6)	3 (5.4)	56 (100.0)		13 (23.2)	43 (76.8)	56 (100.0)	
	Total	**181(92.8)**	**14 (7.2)**	**195 (100.0)**	0.532	**32 (16.4)**	**163 (83.6)**	**195 (100.0)**	0.103

DISCUSSION

The high prevalence IgG 92.5% and Ig M 21.3% found in this study amongst HIV patients was not uncommon as with other immune compromised states. This agrees with findings of Umeh *et al*, though among pregnant women, in Makudi Nigeria who reported IgG of 93.3% (Umeh *et al,* 2015).

High CMV seroprevalence rates in Nigeria and developing countries have been attributed to poor educational and low socio-economic status as compared to the more developed countries. Our finding is also in agreement with studies done in Lagos and Zaria, Nigeria where CMV IgG seroprevalence rates of 72.8% and 86% respectively were found among HIV patients (Adeiza *et al*., 2016). Though, the above two studies, including ours, from Makurdi, Benue State and that of Zaria which are North-central, seemed slightly higher than the 72.8% from Lagos South-West of Nigeria. This difference in the CMV IgG prevalence between North-central and South Western States could be explained by the difference in socio-economic status and living conditions, which are often better in the South than in the Northern part of Nigeria.

The CMV IgM class represents a valuable marker of active or recent primary infection, although majority of the AIDS patients who develop clinical signs and symptoms of CMV infection probably have reactivation of previous infection rather than primary infection (Akinbami *et al*., 2010). The CMV IgM prevalence rate of 57(21.3%) found in our study is higher than findings of Udeze *et al*, and Fowotade *et al*, where CMV IgM antibody rates of 7.0% and 11.7% respectively were reported among HIV patients in (Udeze *et al*., 2018; Fowotade *et al*., 2018). Findings of lower CMV IgM seroprevalence rates have also been reported in Asia and other developed world.

Anaemia requiring blood transfusion is a common complication of HIV and a risk factor for CMV transmission in HIV patients. It was therefore important to evaluate the relationship between blood transfusion and CMV positivity rate among the HIV positive respondents.

In one study on the haematological effects of CMV infection, though in pregnant women, it was reported that haemoglobin and platelets appeared lower in CMV infection, however, they were not significantly so (Onoja AM *et al*, 2017). Our study also agrees with this, even though these were done in two different population types but with some similarities in terms of immune compromised status (HIV and pregnancy).

In our study, blood transfusion was a significant risk factor for CMV IgM in HIV infection with P=0.001. This could further mean that transfusion transmitted CMV infection was a significant contributor to the high rate of CMV infection in these HIV patients. This is similar to report by Omosigho *et al* in Kwara State, Nigeria which reported a significant association between blood transfusion and CMV Infection (Omosigho *et al*., 2022). The study also reported a high CMV prevalence of 92% among HIV patients on HAART similar to this the finding of this study.

J.A.J. Barbara, and G.E. Tegtmeier in a write up on Cytomegalovirus and blood transfusion cited instance of lack of any association between the sex of respondents and blood transfusion in CMV (Mahmoud *et al*., 2016). We also found and reported in this study that while blood transfusion was a significant risk factor for Transfusion Transmitted CMV Infection, the risk was however not significantly gender biased P=0.100 (Table 3).

CMV infection has been reported worldwide, but sero-positivity rates vary widely and said to be highest in underdeveloped countries, rising with age and poor socio-economic status. In this study age of respondents has been associated with a significant rising prevalence rates. We found

rising prevalence of IgG with older age and IgM with younger age indicating more of past infections with development of immunity as against more recent infections in the younger respondents.

Ordinarily, in immune competent persons, a CMV positive blood poses no problems, but in immune incompetent persons, like in our case of HIV or others like transplant patients, low-birth weight infants or pregnancy, it could be fatal. Assessing the existence or otherwise of any association between CMV/HIV and blood transfusion could highlight the importance of early detection and management of anaemia to reduce the need for blood transfusion and the risk of CMV transmission. It could also help to optimize our transfusion practices in immunoincompetent persons.

CONCLUSION

Age and blood transfusion have been found to be significant risk factors for CMV seropositivity. We also found significant serological evidence of recent CMV infection to be more in our younger respondents and more evidence of past infection in the older respondents. While blood transfusion was a significant risk factor for Transfusion Transmitted CMV Infection, the risk was however not significantly gender biased. We recommend provision of CMV negative blood for all cases of HIV patients in need of blood transfusion irrespective of their HAART status as measures to reduce CMV infection and complications in immune incompetent populations.

Conflict of interest: The authors have no conflict of interest to declare.

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Author contribution: OAT conceptualized the study design and wrote it, including the final draft and data analysis. OAM edited, proofread and assisted with data analysisi. Professor UUE was the PhD supervisor of OAT and this work was a part of OAT's PhD work.

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