Important Predictors of Cytomegalovirus Infection in the Setting of Human Immunodeficiency Virus Infection, in Makurdi, North Central Nigeria

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ABSTRACT

Background: Replication of cytomegalovirus (CMV) in the absence of an effective immune response is central to the pathogenesis and complications of CMV disease. Interplay of biological, social, economic and demographic factors have been variously described to provide fertile ground for CMV in HIV infection. **Objectives:** This study was to determine the predictors of CMV in the setting of HIV infection at two major treatment centres in Makurdi, North Central Nigeria. **Materials and Methods:** Semi-structured, pre-tested questionnaires were used to obtain relevant socio-demographic information from 268 confirmed HIV patients. Blood samples collected were analyzed with enzyme-linked immunosorbent assay (ELISA) for CMV IgG and IgM. Data were analyzed using Statistical Package for Social Sciences (SPSS). Bivariate and multivariate logistic regression analyses were used to determine the predictors of CMV by estimating odds ratios and their 95% confidence intervals (CI) at a significance level of $p < 0.05$. Only variables which showed significant association in the bivariate analysis were included in the multivariate analysis to obtain the most significant predictors of CMV in HIV. **Results:** Of the total of 268, 199 were males while 69 were females. Their mean age $\pm$ SD, was 38.8 $\pm$ 11.9 years. Age group ($\chi2=13.363$, $df=3$, $P=0.004$) and Type of apartment ($\chi2=9.581$, $df=3$, $P=0.022$), all showed significant association with CMV IgG Age group ($\chi2=10.438$, $df=3$, $P=0.015$), Marital Status ($\chi2=8.823$, $df=3$, $P=0.032$) and blood transfusion ($\chi2=10.091$, $df=1$, $P=0.001$) all showed significant association with CMV IgM. Multivariate analysis revealed the strongest predictors of CMV in the setting of HIV infection to be the Type of apartment; [*Two bedrooms flat*: ($aOR=0.223$, 95% $CI=0.052-0.965$, $P=0.045$)] and Blood transfusion [*No blood transfusion:* ($aOR=0.317$, 95% $CI=0.165-0.609$, $P=0.001$)]. **Conclusion:** The strongest predictors of CMV in HIV were type of living apartment and blood transfusion. We recommend improved living conditions and blood transfusion practice for these patients in addition to the current interventions to minimize CMV transmission and its complications in HIV patients.

Keywords: Determinants, Predictors, Cytomegalovirus, Human immunodeficiency virus

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INTRODUCTION

Cytomegalovirus (CMV) infections are known to be endemic throughout human population, prevalence rate ranges from 30% to 60% in developed countries of the world to nearly 100% in Africa and Asia [1]. It remains a global public health challenge especially in immunocompromised individuals like pregnant women, neonates, organ transplant recipients on immunosuppressive drugs and HIV patients. Infections by CMV may be transmitted from a variety of sources, including saliva, urine, blood, cervical secretions, semen, breast milk etc. Although primary CMV infection usually remains dormant in healthy individuals, it causes serious health challenge in immunocompromised persons.

Despite the introduction of highly active antiretroviral therapy (HAART) that has greatly reduced the frequency of secondary infection in advanced AIDS patients, CMV is still responsible for a significant morbidity and mortality rate among patients who begin treatment with low $CD4^+$ T-cell counts [2]. Several CMV cases are as a result of reactivation of a latent infection and may lead to an increased chance of formation of a new CMV strain. Serious complications such as retinitis, esophagitis, and colitis, are common in HIV patients infected with CMV [1],[2].

Factors such as age, gender, living conditions, occupation, parity and marital status have been found to be associated with CMV transmission in HIV infection, increasing the likelihood of CMV infection in people with HIV. Understanding these factors helps to identify HIV patients at higher risk and tailor prevention and treatment strategies accordingly. One of the most significant risk factors for CMV infection in HIV is a low Cd4 cell count. A CD4 cell count of less than 50 cells/μL is strongly associated with an increased risk of CMV infection [3]. Other risk factors include co-infection with other opportunistic pathogens and high HIV viral load.

This study aimed to determine the predictors of CMV in the setting of HIV infection at two major treatment centres in Makurdi, North Central Nigeria.

MATERIALS AND METHODS

Study Area

Makurdi the capital city of Benue State is located on Latitude: $7^0$43` 50``N and Longitude: $8^0$32` 10``E, it has an estimated population of 422,000 as at the year 2020. Temperature range is between 23^0C and 35^0C 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.

Study Population

A cross sectional study was carried out among HIV positive patients attending clinic at the Benue State University Teaching Hospital (BSUTH) and General Hospital North Bank Makurdi, Tertiary and secondary healthcare centres respectively. Both hospitals also serve patients from neighboring states of Nasarawa, Taraba, Kogi etc. A Consecutive sampling technique was employed, a non-probability sampling method which involves taking every subject who meets the inclusion criteria.

Ethical considerations

Permission to carry out the study was sought from the research ethics committee of Benue State Ministry of Health Makurdi. A written informed consent was obtained from each patient.

Inclusion criteria: These include **c**onsenting, HIV patients and attending clinics at BSUTH and General Hospital North Bank Makurdi.

Exclusion criteria: Failure to meet inclusion criteria.

Sample Size: The sample size was calculated using the formular; $n = \frac{Z^2P(1-P)}{d^2}$ [4]

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 [13]

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

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

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

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

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

$$= 244.017366912,$$

approximately 244.

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

Sample collection

Blood samples (5mls) were collected from 268 consenting HIV patients attending these clinics Socio-demographic data were collected with the aid of well-structured and pre-tested questionnaires.

Serological test with ELISA for IgG and IgM

Blood samples were collected by venipuncture and centrifuged at 3000 revolution per minutes for 10 minutes. The serum was subsequently stored at -20^{0}C until ready for use. Serum samples were tested for the presence of CMV IgG and IgM antibodies using commercially available Enzyme Linked Immunosorbent Assay (ELISA) kit E-CVG-K01 Cytomegalovirus IgG/IgM kit according to the kit's manufacturer instructions.

Absorbance of the solution in the wells was read within 30 minutes using a microplate reader set at 450nm. Samples with a concentration higher than 0.5 WHO IU/ml were considered positive for CMV IgG whilst samples with concentration below the cut-off were regarded as negative results. In all, a total of 248 (92.5%) of HIV patients in this study tested positive for IgG. All IgG reactive samples numbering 248 were subjected to IgM test using similar procedure as IgG according to the manufacturer's instructions. A total of 57 (21.3%) samples were positive for IgM.

Data analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS). Frequencies and proportions were generated for categorical variables. Chi-square test was used to test the association between the variables and CMV infection status (CMV IgG/IgM). Bivariate and multivariate logistic regression analyses were used to determine the predictors of CMV infection by estimating odds ratios and their 95% confidence intervals (CI) at a significance level of $p < 0.05$. Only variables which showed significant association in the bivariate analysis were included in the multivariate analysis to obtain the strongest predictors of CMV in HIV infection. The results were then presented in tables.

RESULTS

Age group ($\chi 2=13.363$, $df=3$, $P=0.004$) and Type of apartment ($\chi 2=9.581$, $df=3$, $P=0.022$), all showed significant association with CMV IgG (Table 1).

Table 1: Association Between the Study Variables and CMV IgG Status in HIV Co-infection.

Variable	CMV IgG Status		χ2	df	p-value
	Positive n(%)	Negative n(%)			
Age Group (Years)			**13.363**	**3**	**0.004***
0-19	13 (72.2)	6 (27.8)			
20-39	114 (95.0)	6 (5.0)			
40-59	110 (94.0)	7 (6.0)			
60-79	11 (84.6)	2 (16.4)			
Sex			**0.006**	**1**	**0.937**
Male	184 (92.5)	15 (7.5)			
Female	64 (92.8)	5 (7.2)			
Occupation			**Fisher's Exact Test = 3.417**		**0.696**
Civil Servant	22 (95.7)	1 (4.3)			
Traders	108 (91.5)	10 (8.5)			
Health Workers	6 (100.0)	0 (0.0)			
Students	22 (84.6)	4 (15.4)			
Unemployed	81 (94.2)	5 (5.8)			
Artesans	2 (100.0)	0 (0.0)			
Professionals	7 (100.0)	0 (0.0)			
Marital Status			**3.137**	**3**	**0.371**
Single	40 (87.0)	6 (13.0)			
Married	147 (93.0)	11 (7.0)			
Divorced	8 (100.0)	0 (0.0)			
Widowed	53 (94.6)	3 (6.4)			
Educational Status			**6.423**	**3**	**0.093**
Informal	80 (93.0)	6 (7.0)			
Primary	44 (84.6)	8 (15.4)			
Secondary	74 (96.1)	3 (3.9)			
Tertiary	50 (94.3)	3 (5.7)			
No of Children			**6.352**	**5**	**0.273**
One	40 (95.2)	2 (4.8)			
Two	31 (100.0)	0 (0.0)			
Three	30 (93.8)	2 (6.2)			
Four	24 (96.0)	1 (4.0)			
More than 4	84 (90.3)	9 (9.7)			
None	39 (86.7)	6 (13.3)			
Blood Transfusion			**0.083**	**1**	**0.773**
Yes	67 (91.8)	6 (8.2)			
No	181 (92.8)	14 (7.2)			
Type of Apartment			**9.581**	**3**	**0.022***
One room	124 (92.5)	10 (7.5)			
Room and Parlor	73 (96.1)	3 (3.9)			
Two bedroom flat	20 (100.0)	0 (0.0)			
More than two bedroom flat	31 (81.6)	7 (18.4)			
HAART Exposure			**1.986**	**1**	**0.159**
Exposed	205 (93.6)	14 (6.4)			
Not Exposed	43 (87.8)	6 (12.2)			
Length of Follow up			**0.668**	**3**	**0.881**
Every three months	162 (92.6)	13 (7.4)			
Every Month	40 (93.0)	3 (7.0)			
Twice monthly	6 (100.0)	0 (0.0)			
Every two months	40 (90.9)	4 (9.1)			

* = P<0.05

Age group ($\chi^2 = 10.438$, $df=3$, $P=0.015$), Marital Status ($\chi^2=8.823$, $df=3$, $P=0.032$) and blood transfusion ($\chi^2=10.091$, $df=1$, $P=0.001$) all showed significant association with CMV IgM (Table 2).

Table 2: Association between the Study Variables and CMV IgM Status in HIV Co-infection.

Variable	CMV IgM Status		χ2	df	p-value
	Positive n (%)	Negative n (%)			
Age Group (Years)			**10.438**	**3**	**0.015***
0-19	7 (38.9)	11 (61.1)			
20-39	32 (26.7)	88 (73.3)			
40-59	15 (12.8)	102 (87.2)			
60-79	3 (23.1)	10 (76.9)			
Sex			**3.305**	**1**	**0.069**
Male	37 (18.6)	162 (81.4)			
Female	20 (29.0)	49 (71.0)			
Occupation			**Fisher's Exact Test= 8.256**		**0.180**
Civil Servant	7 (30.4)	16 (69.6)			
Traders	21 (17.8)	97 (82.2)			
Health Workers	0 (0.0)	6 (100.0)			
Students	8 (30.8)	18 (69.2)			
Unemployed	17 (19.8)	69 (80.2)			
Artesans	1 (50.0)	1 (50.0)			
Professionals	3 (42.9)	4 (57.1)			
Marital Status			**8.823**	**3**	**0.032***
Single	16 (34.8)	30 (65.2)			
Married	33 (20.9)	125 (79.1)			
Divorced	2 (25.0)	6 (75.0)			
Widowed	6 (10.7)	50 (89.3)			
Educational Status			**5.370**	**3**	**0.147**
Informal	14 (16.3)	72 (83.7)			
Primary	13 (25.0)	39 (75.0)			
Secondary	22 (28.6)	55 (71.4)			
Tertiary	8 (15.1)	45 (84.9)			
No of Children			**5.193**	**5**	**0.393**
One	9 (21.4)	32 (78.6)			
Two	4 (12.9)	27 (87.1)			
Three	6 (18.8)	26 (81.2)			
Four	8 (32.0)	17 (68.0)			
More than 4	17 (18.3)	76 (81.7)			
None	13 (28.9)	32 (71.1)			
Blood Transfusion			**10.091**	**1**	**0.001***
Yes	25 (34.2)	48 (65.8)			
No	32 (16.4)	163 (83.6)			
Type of Apartment			**0.967**	**3**	**0.809**
One room	27 (20.1)	107 (79.9)			
Room and Parlor	18 (23.7)	58 (76.3)			
Two bedroom flat	3 (15.0)	17 (87.0)			
More than two bedroom flat	9 (23.7)	29 (76.3)			
HAART Exposure			**0.992**	**1**	**0.319**
Exposed	44 (20.1)	175 (79.9)			
Not Exposed	13 (26.5)	36 (73.5)			
Length of Follow up			**2.566**	**3**	**0.463**
Every three months	36 (20.6)	139 (79.4)			
Every Month	7 (16.3)	36 (83.7)			
Twice monthly	1 (16.7)	5 (83.3)			
Every two months	13 (29.5)	31 (70.5)			

* = P<0.05

Age, Marital Status, blood transfusion and type of living apartment which showed significant association with CMV infection in the bivariate analysis were included in the multivariate analysis, and this showed that the strong predictors of CMV infection in HIV were Type of apartment; [*Two bedrooms flat* (*aOR=0.223, 95% CI=0.052-0.965, P=0.045*)] and Blood transfusion [*No blood transfusion* (*aOR=0.317, 95% CI=0.165-0.609, P=0.001*)] (Tables 3 and 4).

Table 3: Predictors of CMV IgG infection on Multivariate Logistic Regression Analysis

Variable	aOR	95% CI	p-value
Age			
0-19	Reference		
20-39	3.007	0.162-55.981	0.460
40-59	0.350	0.054-2.280	0.272
60-79	0.413	0.070-2.452	0.330
Marital Status			
Single	Reference		
Married	0.952	0.076-11.865	0.970
Divorced	1.485	0.350-6.307	0.592
Widowed	0.000	0.000-	0.999
Blood transfusion			
Yes	Reference		
No	1.359	0.470-3.935	0.571
Type of Apartment			
One room	Reference		
Room and Parlor	0.369	0.119-1.151	0.086
Two bedroom flat	0.223	0.052-0.965	0.045*
More than two bedroom flat	0.000	0.000-	0.998

Omnibus Tests $\chi 2=18.861$, df=10, p=0.042, Hosmer and Lemeshow Test $\chi 2=5.193$, df=7, p=0.636, Nagelkerke $R^2=0.165$

Table 4: Predictors of CMV IgM infection on Multivariate Logistic Regression Analysis

Variable	aOR	95% CI	p-value
Age			
0-19	Reference		
20-39	0.788	0.114-5.460	0.810
40-59	1.156	0.262-5.099	0.848
60-79	2.361	0.538-10.356	0.255
Marital Status			
Single	Reference		
Married	0.328	0.087-1.239	0.100
Divorced	0.505	0.178-1.434	0.200
Widowed	0.421	0.065-2.734	0.365
Blood transfusion			
Yes	Reference		
No	0.317	0.165-0.609	0.001*
Type of Apartment			
One room	Reference		
Room and Parlor	1.219	0.475-3.130	0.680
Two bedroom flat	0.961	0.355-2.601	0.937
More than two bedroom flat	1.612	0.354-7.329	0.537

Omnibus Tests $\chi 2=25.640$, df=10, P=0.004, Hosmer and Lemeshow Test $\chi 2=11.170$, df=8, P=0.192, Nagelkerke $R^2=0.142$

***Key**: aOR=Estimated Odd Ratio, CI=Confidence Interval; IgG: Immunoglobulin G; HIV: Human Immunodeficiency Virus; IgM: Immunoglobulin M; * = P<0.05*

DISCUSSION

Cytomegalovirus (CMV) is a common opportunistic infection that affects people living with HIV. Many risk factors have been identified to increase the likelihood of CMV infection in people with HIV. These risk factors or predictors, vary depending on geographical location, individual patient characteristics, study populations etc.

A good example of this interplay between CMV and demographic context was in the work on some American adults [5]. They also employed Logistic regression modeling, to reveal that persons born outside the US and those with less than 20 years of residency in the US showed significantly higher percentages of positive CMV IgG compared to individuals born in the US [5]. This provides further insights into some underlying demographic risk factors for CMV infection.

Our study meticulously assessed a number of variables: age, sex, marital status, occupation, and educational level, type of living apartment, parity, blood transfusion and HAART status, documented in literatures, to be associated or potentiate CMV transmission in populations with impaired immunity. In our setting, this study was able to establish the association of CMV transmission with age, marital status, type of living apartment, and blood transfusion on bivariate analysis, however, subjecting these to further multivariate analysis showed that type of living apartment, and blood transfusion were the strongest predictors of CMV infection in the HIV population.

A study, though in children, by Aristizabal *et al*., in latin America, using similar bivariate and multivariate analytical method was able to establish strong association of high viremia post haemtopoietic stem cell transplantation but that the remaining demographic characteristics were not predictors of infection [6].

The age groups in our study showed a significant association with CMV infection on bivariate analysis though not a significant predictor on multivariate analysis.

Age group as a risk factor for CMV as seen in the initial analysis could be explained by the higher risky behaviours of young adults and the vulnerability of the elderly, predisposing to CMV infection. Cumulative nature of the infection due to virus latency with potentials for reactivation and a life-long infection has been described in the elderly population [7].

Risk of CMV transmission through blood transfusion has significantly decreased in recent years due to improved screening techniques and advances in blood safety measures. In HIV patients, especially those with advanced immunosuppression, receiving CMV-seronegative blood products (blood from donors who are CMV negative) can help reduce the risk of CMV transmission through transfusion. This is particularly important for individuals who have not been previously exposed to CMV or who are at a higher risk of developing CMV-related complications.

From this study, both bivariate and multivariate analysis confirmed blood transfusion to be a significant predictor of CMV infection in HIV patients. This agrees with a previous report on CMV and blood transfusion by Onoja *et al*., [8]. Result from this study was also in agreement with those of Akinbami *et al.,* [2] where a higher CMV IgG positivity rate was recorded among pregnant women with past history of blood transfusion in Lagos, Nigeria. Also, a recent study in Mashhad, Iran showed a higher CMV antibody prevalence of 99.2% among transplant recipients with history of blood transfusion [9].

Living in crowded or communal settings, such as homeless shelters, correctional facilities, or shared housing with inadequate sanitation or hygiene facilities, can increase the risk of

exposure to infectious agents, including CMV. A study reported a strong association between low income earners and CMV infection [10]. The type of living condition can be a function of ones earnings, and thus supporting our finding of type of apartment as a strong predictor of CMV infection..

The type of living apartment could create close contact and limits personal space which have been known to facilitate the transmission of CMV and other infections. Inadequate hygiene practices, such as poor hand hygiene or sharing personal items that may come into contact with bodily fluids, have also been reported to increase the risk of CMV transmission. These could be relevant in any housing environment where proper hygiene practices are not followed consistently. Aljumaili *et al.,* reported a higher CMV infection among rural dwellers compared to urban dwellers [11].

Marital status was found to be associated with increased serological evidence of CMV, but not a strong predictor in our multivariate analysis. Though closely related, Lanzieri *et al*., found strong association between CMV in women with higher number of children compare to those with fewer, [12]. Thus, multi-parity was a significant determinant of CMV infection but this was contrary to the finding of this study,

Factors predisposing to CMV transmission may vary across different populations and geographical locations. Local studies and surveillance are essential for the establishment of place specific risk factors associated with CMV in the setting of HIV infection.

CONCLUSION

The strongest predictors of CMV in the setting of HIV infection in our environment were the type of living apartment and blood transfusion. We recommend improved living condition and blood transfusion practice for this category of patients in addition to the current interventions to minimize CMV transmission and its complications in HIV patients.

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Author contribution

This paper and idea was conceptualized and written by Onoja A. Theresa, including the design, data analysis and the final draft. It was reviewed and supervised (PhD thesis) by Prof Umeh EU, Prof Gberikon GM and Dr Ogbonna IO. Dr. Onoja A. Michael, an Associate professor and consultant Haematologist edited, did part of data analysis and proofread the final draft with emphasis on the clinical contents and interpretations.

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