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Association of Adverse Drug Reactions to HAART with Alcohol Consumption, Herbal Medication and Co-Trimoxazole Prophylaxis among Patients Living with HIV/AIDS in FMC Makurdi, Nigeria

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ABSTRACT: The use of HAART for the treatment of HIV/AIDS infection, despite its success, has been reported to be accompanied by increased number of adverse drug reactions (ADRs) for which some risk factors such as age, gender, co-morbidities have been implicated. The association between alcohol consumption, herbal drug intake and use of co-trimoxazole and ADRs to HAART has not been documented much. The main objective of this study is to determine the association between alcohol consumption, herbal drug intake, use of co-trimoxazole and presentation of ADRs to HAART in HIV/AIDS patients in Makurdi where there's high HIV infection, alcohol consumption and herbal use. It was a combination of prospective and retrospective study at FMC, Makurdi. We used clinical records of the patients and questionnaires for patients enrolled from January to October, 2019 and followed up for six months. The biodata, drug history including herbal medications and social life (use of alcohol) history were retrieved. A total number of three hundred and three (303) patients were recruited during the study period out of which two hundred and ten (210) patients were used. From a total of 210 patients, 144 (68. 6%) were females while sixty-six, 66 (31.4 %) were males. Of these, only 68(32.4%) patients took alcohol while 89 (42.4%) patients used herbal medications together with HAART regimen and 185(88.1) were on co-trimoxazole prophylaxis. 22 patients presented with ADR with peripheral neuropathy and insomnia being the commonest ADRs. 54.5% (majority) of the patients with ADRs took alcohol while 81.8% (majority) of the patients who developed ADRs were actually on herbal medications or co-trimoxazole. The p-value>0.05. Alcohol consumption, herbal medication use and co-trimoxazole prophylaxis in HIV/AIDS positive patients while on ARVs may increase ADRs to ARVs. Thus, HIV/AIDS patients should be discouraged from use of alcohol and herbal medication while on HAART.

KEYWORD: HAART, ADRs, Alcohol, Herbal Medication

INTRODUCTION

HIV/AIDS was first reported in Nigeria in 1986 and since then there had been increase in the disease burden worldwide (Sharp and Hahn, 2011). Nigeria now has the 4th highest burden of HIV globally (The World Factbook) and findings by Nigeria Aids Indicator and Impact Survey (NAIIS) showed a current national prevalence of HIV estimate at 1.4% (15 – 49 years), with a total estimated 1.9 million PLWHA in Nigeria. Prevalence among females is significantly higher, estimated at 1.9% while male prevalence was estimated at 0.9%. Out of the seven states considered to have a high prevalence of 2.0% and above, Benue state (4.9%) is the second after Akwaibom state (5.6%) in the new prevalence estimates by state. Others include Abia, Taraba, Enugu, Anambra, and Rivers state. Kastina and Jigawa states have the least prevalence (0.3%) (NACA,2019).

Treatment of HIV infection was a major public health concern until the discovery and introduction of antiretroviral drugs (ARVs) for treating HIV/AIDS patients in the 1990s. This brought hope to the affected people, reducing mortality and improving the quality

of life of People Living with HIV/AIDS, [PLWHA] (WHO, 2002). At first, these drugs (e.g nevirapine) were used as single agents for treatment (monotherapy) to interfere with HIV-related production of DNA needed for cell replication. However, this was associated with likelihood of developing drug resistance within weeks or months of treatment (Rabkin *et al*., 2002), hence, the international treatment guidelines now indicate that optimal treatment for HIV infection should involve a drug combination consisting of different kinds of ARVs, which attack the virus in different ways. This combination is referred to Highly Active Antiretroviral Therapy (HAART). It is highly effective at interfering with HIV replication in both early and late stages in the viral replication cycle. However, the advantages of using HAART are not without challenges. It has been reported to be accompanied with increase in the number of Adverse Drug Reactions (ADRs), including minor and serious ADRs (Calmy *et al*., 2009).

ADR is a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function (WHO, 2013). ADRs are the single most common reasons for poor adherence to treatment (Charles *et al.*, 2006; Lut *et al*., 2012, p. 411). Evidences showed that up to 25% of patients discontinue their initial highly active antiretroviral therapy (HAART) regimen because of toxic effects [ADRs] (Bhuvana, Hema and Sangeetha, 2014, pg.381). ADRs to ARVs and other drugs have also been shown to be among top 10 leading causes of mortality despite the fact that most ADRs are preventable (Florence, 2011).

Variable reports have be shown on the prevalence and incidence of ADRs from different studies done, ranging from 65.5% and 83% in Ethiopia and Zimbabwe respectively to 75.4% in central India (Nemaura*et al.*,2013, p. 203; Bhatnagar, Sharma and Sharma, 2013, p. 122). Another study done in India showed that almost 37.70% and 30% of PLWHA developed ADRs within 0-6 months and 6–12 months duration of treatment respectively (Lut*et al*., 2012, p. 411). Some risk factors have been associated with the development of ADRs such as age (Chang *et al*., 2012)), gender (Harugeri *et al.*, 2010), polypharmacy (Adebayo and Hussain, 2010) and co-morbidities (FMoH, 2010). However, much have not been documented on the effects of alcohol intake, use of herbal drug and prophylactic co-trimoxazole on the presentation of ADRs associated with HAART, especially in this part of the world despite high intake of alcohol and herbal medications, hence, the need for such a study in Makurdi, Benue State, Nigeria, for proper education and management of HIV/AIDS who are into alcohol and herbal drug use while on ARVs.

METHODOLOGY

Study Area

The study was done at Federal Medical Centre (FMC), Makurdi, Benue State, Nigeria. The hospital boasts of a good number patient and has not less than 100 bed spaces. It currently offers HIV care services to not less than 11,000 patients across the state as at the study period.

Study Population

The study population included all adult individuals between age 15 and 65years that were confirmed to be HIV positive for the HIV antibody by western blotting and were receiving ARVs in the hospital within the study period.

Inclusion Criteria

This includes all adult treatment naive HIV positive patients who were taking ARVs during the study period and gave their consent to participate in the study.

Exclusion Criteria

Patients who for any other reason were not able to communicate, thus, failing to be interviewed for example due to memory loss, separation from the usual caregiver or patients who were not willing to participate in the study. Patients who had other medical conditions whose medications can interfere with the presentations of the ARV adverse effects. Patients who were pregnant during the study period and children below 15years

Study Design

It was a combination of retrospective and prospective study conducted from October, 2019 till March 2020 among 210 adult HIV positive patients. All adult treatment naïve HIV patients that meet the selection criteria, enrolled for treatment from January-October, 2019 were followed up (using their medical records and computer data base) for a period of six months each. Their medical records and APIN computer database contained the HIV patients' demographic, social life (alcohol and traditional medicine intake), clinical, laboratory and treatment information; time of commencement of HAART, various HAART regimen the patients were taking; number, type and nature of ADRs developed by patients, co-morbidities of the patients, e.t.c collected by the clinicians who were trained to detect and record these information using the pharmacovigilance forms. In addition, the collected data were validated and missing information completed (using structured questionnaire and oral interview) during their clinic visits.

Sample size determination

The sample size was calculated using the formula described by Dahiru, Aliyu and Kene(2006) for determining sample size when the population is greater than 10 000.The confidence interval was 95% and a margin error of 5%.

$$N = \frac{Z_{\frac{\alpha}{2}}^{2} P(1-P)}{d^2}$$

Where:
N = The desired sample size when population is more than 10 000.
Z = Standard normal distribution at 95% confidence interval = 1.96
Using the above formula and the prevalence rate 'P' of 70.8% from the previous study on prevalence of adverse drug reactions conducted by Ramanjireddy and Yitagesu (2014)
d = error margin taken to be 5% for this study = 0.05
Therefore, N = ?, Z = 1.96, P = 0.708, d = 0.05

$$N = \frac{1.96 \times 0.708\ (1 - 0.708)}{0.05^2}$$

$$N = \frac{1.38768\ (0.292)}{0.05\ x\ 0.05}$$

$$N = \frac{1.38768 \times 0.292}{0.0025}$$

$$N = \frac{0.40520256}{0.0025}$$

$$N = 162.081024$$

The calculated minimum sample size (N)$= 162.$
A sample size (N) of two hundred (200) -approximation to the nearest hundred.

Study Variables
Dependent variable: adverse drug reactions
Independent variable: sex, age, weight, marital status, occupation, religion, education level, type of ADRs, time of ADRs.

Sampling Technique
FMC, Makurdi, Benue state, Nigeria was selected because it had the highest number of HIV patients under care and treatment compared to other public health facilities within the state. Patients on anti-retroviral interviewed were selected by convenient sampling. Informed consent was obtained from the patient or the caregiver before the interview was conducted.

Ethical Consideration
The approval for this study was obtained from the Health research and Ethical Review committee of the FMC, Makurdi where the study was carried out. Patients' clinical records were reviewed anonymously and all information obtained from clinical records was kept confidential.

Data Collection Procedure
Data of the respondents which included patients' demographic, clinical, prescription and social life (alcohol and traditional medicine intake) records maintained in an electronic data base of the Harvard/APIN program were retrieved while oral interview was conducted using structured questionnaires among the patients during their clinic visits to ascertain the documented information especially on their use of alcohol, herbal medications and co-trimoxazole. Quantitative data collected included respondents' information about age, sex, weight, occupation and HAART regimen. Data was also collected from Health Care Provider (HCP) on detection of ADRs using the pharmcovigilance form. Structured questionnaire provided data that was objective, scientific, and reliable for hypothesis testing.

Data Quality Control
The research instrument, the structured questionnaire, was presented at FMC and checked for applicability and accuracy. In the hospital, an overlap of patients was unlikely to occur. The research assistants who had some clinical knowledge were trained in data collection. Regular crosschecking, inspection and scrutinizing of information on the research instruments were used to ensure accuracy, completeness, consistency and uniformity of the data collected.

Data Management and Analysis
Completed questionnaires were examined for any inconsistencies in data recording. Data obtained from the patients' medical records, computer database and completed questionnaires were entered, sorted and coded using Microsoft excel sheet. It was analyzed using descriptive statistics, Chi-square test of independence and binary logistic regression. The analysis was done with the help of Statistical Package for Social Sciences (SPSS) software version 23.

RESULTS AND DISCUSSION
A total number of three hundred and three (303) patients were recruited during the study period out of which two hundred and ten (210) patients were used for the study based on the inclusion criteria. From a total of two hundred and ten (210), one hundred and forty-four patients, 144 (68. 6%) were females while sixty-six, 66 (31.4 %) of them were males, 175 (83.3%) were aged 44 years or less and 17(8.1%) were aged 65years or more (fig.1 & 2).

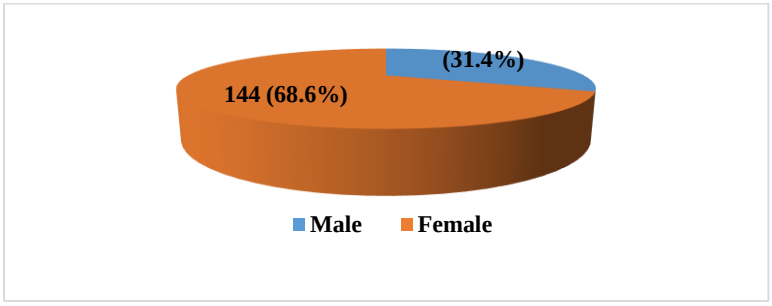

Figure 1: Gender of Adult HIV Patients on HAART

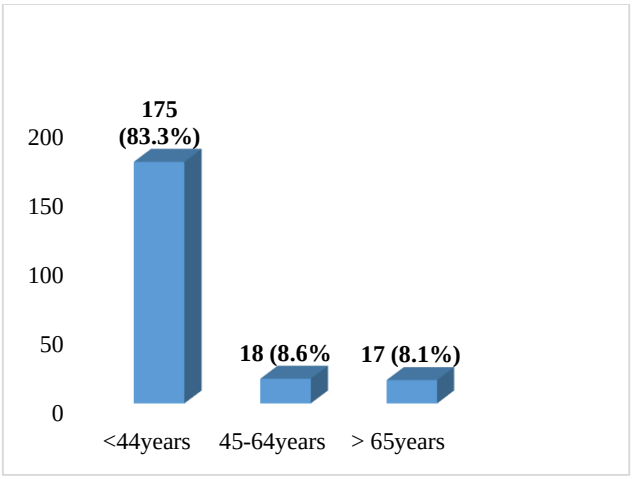

Figure 2: Age of Adult HIV Patients on HAART

Table 1: Socio-demographic Characteristics of Adult HIV Patients on HAART at FMC, Makurdi

Variables	Frequency	Percentage(%)
Marital Status		
Single	90	42.9
Married	85	40.5
Widowed	20	9.5
Separated	15	7.1
Total	**210**	**100**
Occupation		
Salaried (Employed)	53	25.3
Waged labour (Casual)	37	17.6
Petty trade (Hawker)	38	18.1
Merchant/Trader	27	12.9
Peasant farmer	12	5.7
Housewife	3	1.4
Unemployed	40	19.0
Total	**210**	**100**
Religion		
Christianity	200	95.2
Muslim	6	2.9
Not Indicated	4	1.9
Total	**210**	**100**
Education		
Primary	33	15.7
Secondary	77	36.7
Post-Secondary	63	30.0
Never Been to School	27	12.9
Not Indicated	10	4.8
Total	**210**	**100**

90(42.9%) of them were single while 15(7.1%) had their marriage separated. Majority of the patients were non-salary earners, 157(74.7%) while only 53 (25.3%) patients were government employed salary earners. Most of the respondents were Christians, 200(95.2%) while 77(36.7%) had secondary education. Table 1 shows the socio-demographic features of the respondents.

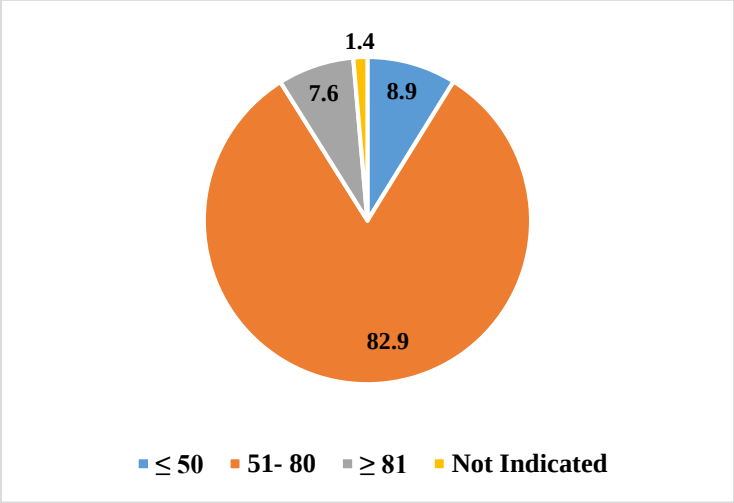

Figure 3: Weight of Adult HIV Patients on HAART

The weights of majority, 174(82.9%) of the respondents were within 51-80kg

Table 2: Alcohol Consumption, Herbal Medication and Cotrimoxazole use Among Adult HIV patients on HAART at FMC, Makurdi.

Variable	Male	Female	Frequency
(Alcohol)			
Yes	26 (39.4)	42(29.2)	68 (32.4)
No	40 (60.6)	102 (70.8)	142 (67.6)
Total	**66 (100)**	**144 (100)**	**210 (100)**
(Herbal drugs)			
Yes	19 (28.8)	70 (48.6)	89 (42.4)
No	47 (71.2)	74 (51.4)	114 (54.3)
Total	**66 (100)**	**144 (100)**	**210 (100)**
(Co-trimoxazole)			
Yes	52(78.8)	133(92.4)	185(88.1)
	52(78.8)	133(92.4)	185(88.1)
No	14(21.2)	11(7.6)	25(11.9)
Total	**66(100)**	**144(100)**	**210(100)**

Numbers in brackets are in percentage

Table 2 shows the use of alcohol, herbal medication and co-trimoxazole among the respondents. 32.4% of the respondents used alcohol concomittantly with ARVs, 42.4% of them were using one form of herbal medication or the other while on ARVs while 88.1% were taking the co-trimoxazole prophylactic.

Table 3: Types of ADRs and Prevalence among Adult HIV Patients on HAART at FMC, Makurdi

ADRs	Frequency (%)
Peripheral neuropathy	4 (18.18)
Heart burn	1 (4.55)
Diarrhea	2 (9.09)
Palpitation	3 (13.64)
Vomiting	1 (4.55)
Depression	1 (4.55)
Hallucination	1 (4.55)
Drowsiness	1 (4.55)

Skin rash	1 (4.55)
Insomnia	4 (18.18)
Anemia	3 (13.64)
TOTAL	**22 (100)**

Table 3 shows the various types and pattern of ADRs presented by the patients while on ARVs. A total of 22 patients presented with one ADR or the other while peripheral neuropathy and insomnia were the commonest ADRs with each accounting for 18.18%.

Table 4: Relationship of ADRs with Alcohol Consumption, Herbal Medication and Cotrimoxazole prophylaxis

Variable	ADR Occurred		Total	P-value
	Yes	No		
Alcohol Consumption	12 (54.5)	10 (45.5)	**22 (100)**	0.069
Herbal Medication	18 (81.8)	4 (18.2)	**22 (100)**	0.108
Co-trimoxazole	18 (81.8)	4 (18.2)	**22 (100)**	0.264

Table 4 shows the association between the presentation of ADRs and alcohol intake, herbal drug use and co-trimoxazole prophylaxis among the patients that presented with ADRs.

The study showed that only 68(32.4%) patients were taking alcohol in one form or the other. This disagrees with a study by Braithwaite *et al.* (2007) who found that alcohol use is higher among People Living with HIV and AIDS (PLWA) than in the general population. The difference may be due to underreporting of alcohol use among our respondents since this may create additional stigma in them. This was similar to finding in a study Hahn *et al*., (2010) where alcohol was under-reported among the HIV patients. Majority of the patients who presented with ADRs took alcohol in one form or the other. This represents 54.5% of patients with ADRs. This can be explained by the findings made by Schneider *et al*. (2011) that alcohol consumption weakens the immune system, both innate and adaptive; reduces adherence of HIV patients to HAART and increases the likelihood of viral replication and ADRs. The liver also metabolizes both alcohol and ARVs and alcohol-related liver toxicity results in compromised liver function with ARVs not working optimally and an increased risk of serious toxicity from antiretroviral therapy. All these may explain the higher percentage of ADRs found among respondents taking alcohol. However, this study shows that the association between alcohol and presentation of ADRs was not statistically significant (p-value >0.05).

Although this study showed no significant association between alcohol and ARV adverse effect, it should be noted that comparing studies and drawing definitive conclusion on this subject matter has been very difficult because of diverse measures of alcohol consumption used in studies on interactions between alcohol and HIV. It is essential to acquire clear evidence-based guidelines on alcohol consumption for HIV-positive patients and their health-care providers.

The variables alcohol, HIV and ART and their myriad interactions have not been clearly delineated. The multiple effects from HIV, alcohol and ART may compound each other, making it difficult to disentangle presenting adverse reactions and specifically the associations with alcohol (Schneider *et al*., 2011).

About 89(42.4%) patients were found in this study to be taking at least one form of herbal medications together with HAART regimen. A study done by Tinashe *et al.* (2012) in Zimbabwe showed that about 98.2% of the respondent concomitantly used at least one indigenous herbal medication with ART regimen. The higher percentage noticed in study conducted in Zimbabwe may be due to differences in the study setting and cultural beliefs. Most of the patients in Zimbabwe were using herbal medications to alleviate the side effects of ARVs while in this study, the patients used the herbal drugs to treat other disease conditions and not really HIV infection. It was found in this study that 81.8% of the patients who developed ADRs were actually on herbal medications. This is consistent with a study done by Nyasha *et al.* (2011) in which some traditional herbal remedies used in Zimbabwe were found to be associated with occurrence of abdominal pain and rash when used in combination with antiretroviral drugs.

The relationship between ARV and herbal medications can be explained by drug-herbal interaction. Herbs contain naturally occurring phytochemicals which may be substrates for enzymes or transporters that act on drugs, potentially inhibiting the drugs' metabolism or transportation, which can result in altered drug absorption, distribution, metabolism and/or elimination. This will result in altered drug plasma levels, hence a different ADR profile due to altered drug/herb concentrations.

Toxicity or sub-therapeutic drug concentrations, pathogen resistance, and treatment failure are also possible outcomes (Nyasha*et al.*, 2011). Monera *et al*. (2008) found moringa to have significant inhibitory effects on CYP3A4, which results in the elevation of plasma levels of drugs metabolized by this pathway like Nevirapine and Efavirenz. Thus a potential interaction exists between the NNRTIs with moringa. This study, however, did not show any statistically significant relationship between herbal drugs and presentation of ADRs (p-value >0.05). Similarly, Nyasha *et al.* (2011) also reported that there was no significant association between some ARV adverse events and improvement in quality of life with the use herbal medications in combination with antiretroviral

therapy. Therefore, majority of the patients that had ADRs took alcohol concomitantly with HAART regimen. This is also applicable to herbal drug consumption and use of cotrimoxazole prophylaxis. However, these associations were not statistically significant for alcohol (p-value >0.05), herbal medication (p-value >0.05) and cotrimoxazole (p-value >0.05).

CONCLUSION

The study tends to investigate the association between ADRs to HAART and alcohol consumption, herbal medication and co-trimoxazole prophylaxis among HIV positive patients living in Makurdi, Benue state, Nigeria. Such study has not been done previously in the study area. ADRs pose a lot of problems and challenges to HIV patients. Some disfigure the patients while others cause treatment failure by reducing the adherence of patients to the ARVs. The detection, reporting and management of these ADRs are real challenges to both the patients and health providers. HIV/AIDS health care providers should be conversant with drug regimen with minimal adverse effects such DTG containing regimen and use them on the patients especially the elderly patients. Alcohol consumption, herbal medication use and co-trimoxazole prophylaxis in HIV/AIDS positive patients while on ARVs may affect the presentation of ADRs to ARVs. A study of pharmacovigilance is recommended not only for ARVs but for other drugs used in the treatment of the opportunistic infections and other classes of drugs since the knowledge and practice of pharmacovigilance is poor among HCPs. Further research should be done on the effects of specific alcohol and herbal medications and possibly their quantification on the presentation of ADRs associated with HAART in HIV/AIDS patients.

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