International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Assessment of Pharmacoepidemiology of Antiretroviral Drugs in a University Hospital of Enugu State

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Abstract—
Background of study*: Potent combinations of antiretroviral drugs have altered the progression of HIV infection, and significantly improved patient's quality of life. As a result, the number of AIDS-related opportunistic infections and death has declined. Limited documented data exist that addressed the effects and the pattern of antiretroviral drugs usage in a specified population.*
Objective*: To assess the pharmacoepidemiology of antiretroviral drugs in a tertiary hospital in Enugu state, Nigeria.*
Methods: *This was a retrospective study carried out at the University of Nigeria Teaching Hospital, Ituku-ozalla, Enugu state. A total of 600 patients' medical records were randomly selected and pharmacoepidemiology of antiretrovirals used over a period of 6 years in the teaching hospital was evaluated. The patients'demographics, pattern of antiretroviral (ARV) drugs combination prescribed, adverse drug events (ADEs), level of adherence and some haematological parameters were extracted from their case files. Analysis was done with descriptive statistics using Statistical Package for Social Sciences (SPSS) version 16.*
Results*: A total of 8 antiretroviral combinations were commonly prescribed. Tenofovir-Emtricitabine-Efavirenz was the most frequently prescribed combination both at baseline (50%) and at follow up (51.2%). Greater percentage adhered to their medications (55.5%). Over 750 ADEs were reported with headache and cough having the highest occurrence at baseline (13.6%) and follow up (32.5%) respectively.*
Conclusion*: The pharmacoepidemiology of the antiretrovirals used in the hospital was assessed. Tenofovir-Emtricitabine-Efavirenz was the most frequently prescribed combination. The result revealed a rational drug prescription pattern. Headache and cough were the most frequently reported ADEs. There is need to improve the level of adherence of the ARV medications.*

Keywords— *Antiretroviral drugs; Enugu; HIV; Pharmacoepidemiology; Tertiary hospital.*

I. INTRODUCTION

HIV infection has spread over the last 35 years and has a great impact on health, welfare, employment and criminal justice sectors; affecting all social and ethnic groups throughout the world. Recent epidemiological data indicated that HIV remains a public health issue that persistently drains our economic sector having claimed more than 35 million lives so far. In fact, a total of 1 million people die of HIV-related causes in 2016 [1]. The estimated overall number of People Living with HIV (PLWHIV) in 2016 globally, was 36.7 million. About 6.1 million of these reside in the western and central Africa and only about 35% of these population (i.e. 2.1 million) were accessing antiretroviral medications [2].

The use of highly active antiretroviral therapy (HAART) has resulted in a significant reduction in the morbidity and mortality related to AIDS. HAART is defined as the concurrent use of a combination of three or more ARV drugs to suppress HIV replication. It represents the current standard of care for HIV-infected patients [3,4]. Antiretroviral therapy use has been associated with numerous problems, among these problems is drug-drug interaction which is often a serious complication of taking multiple medications and account for 3% to 5% of all in-hospital medication errors [5]. The consequences of drug interactions vary, ranging from drug toxicities to therapeutic failures. These consequences can result in suboptimal treatment of the targeted disease states, damage to vital organ systems, or death. Drug interactions are of particular concern in patients infected with HIV who are receiving highly active antiretroviral therapy (HAART). ARVs used in the treatment of HIV are often prone to this because many of them are metabolized through the cytochrome P450 (CYP450) system. Of the CYP450 isoenzymes, CYP3A4, CYP2D, and CYP2C9/19 are considered the primary isoenzymes involved in the drugs' metabolism [3]. Adherence to ART is central to therapeutic success. Although there is no gold standard for assessing adherence [4], properly implemented validated tools and assessment strategies can prove valuable in most clinical settings. Viral load suppression and increase in CD4 counts are among the most reliable indicators of adherence and can be used as positive reinforcement to encourage continuous adherence [6–13].

Some patients may selectively adhere to components of a regimen believed to have the fewest side effects or the lowest dosing frequency or pill burden while others may not adhere due to the following reasons: adverse effects of the drug, failure to understand dosing instructions, depression, drug and alcohol use, cost-related issues, complexity of regimen, pill

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fatigue, stigma etc. Other problems such as adverse reactions, drug resistance, intolerance and toxicities have been greatly implicated in the use of antiretroviral drugs.

Pharmacoepidemiology has been defined as the study of the use and effects of drugs in large numbers of people[14]. It is the bridge between pharmacology and epidemiology. In Nigeria, limited data exist on the utilization pattern as well as the adverse drug reactions of antiretroviral medications among the HIV-infected persons [15–18]. This study, therefore aimed to evaluate the pharmacoepidemiology of antiretroviral therapy among people living with HIV/AIDS and receiving medication from of a tertiary hospital in south eastern Nigeria.

II. Materials and Methods

Study Design

A retrospective analysis of clinical records of HIV infected adults who received treatments from the year 2011 to 2016 was carried out. The study assessed the pharmacoepidemiology of antiretroviral drugs used in the hospital within these years.

Study Setting

This study was carried out at the University of Nigeria Teaching Hospital (UNTH) Ituku-Ozalla, Enugu State which is located 21 kilometres from Enugu Capital City along Enugu – Port Harcourt express road. The Hospital was equipped under the Federal Government assisted Engineering Equipment Programme which elevated it and some other Teaching Hospitals in the country to an international standard. There were 41 main departments in the hospital.

Among the various units in the hospital is the HIV/AIDS unit where the research was carried out which is qualified to cater and provide intensive care and free antiretroviral drugs to HIV patients. Clinic visits are usually Tuesdays and Thursdays every week except on public holidays.

Sample Size

The total number of HIV/AIDS patients' records who had been enrolled for treatment from 2011-2016 were about 5000. The actual number of patients whose hospital records were used in the study within the duration of study was 600.

Sample Selection and Technique

The hospital records of patients were secured with the help of the medical personnel in charge of the Medical Records unit. Sampling was done randomly and each folder was picked after every other folder. Confidentiality of the patients' data was maintained throughout the study by use of numbers for identification, their names were not taken. The participants whose folders were used were the ones that met the inclusion criteria for the study.

Study Instrument and Data Collection

Required information from the medical records of eligible participants was extracted using a data collection form. The form was face validated by a team of clinical experts working in the hospital's HIV/AIDS clinic. Relevant data extracted included socio-demographic data, level of adherence, ART regimens, adverse drug reactions, and hematological parameters such as CD4+ count, packed cell volume, and white blood cell count.

Data Analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS), Version 16.0. Descriptive statistics such as frequencies (percentages) and mean ± standard deviation were used to summarize data. The major outcomes analyzed were adherence to treatment, drug utilization pattern, frequency of adverse reactions to ARV drugs, and socio-demographics of patients.

Eligibility Criteria

- Inclusion criteria

The subjects whose data were collected were adult HIV/AIDS patients (18 years and above) and had been on HAART for at least 3 month before the commencement of the study.

- Exclusive criteria

Special population groups like pregnant women and children were excluded.

Ethical Consideration

The research protocol was reviewed and approval was obtained from the Research and Ethics committee of UNTH. Information obtained from the patient folders were kept with utmost confidentiality.

III. Results

Demographic Data of the Respondents

This showed that there were 28.5 and 71.5 percent male and female HIV-infected persons, respectively. Results also revealed that the age range of 35-44 which showed the highest percentage at 39.0 percent was the dominated age group. Most of the respondents had secondary education or more and greater percentage of the enrollees was employed (Table 1).

TABLE 1. Socio-demographic profile of the respondents. N=600

Variables	Frequency	Percentage
Age (years)		
18-24	49	8.2
25-34	173	28.8
35-44	234	39.0
45-54	92	15.3
>55	52	8.7
Gender		
Male	171	28.5
Female	429	71.5
Marital status		
Single	160	26.7
Married	247	41.2
Widowed	134	22.3
Divorced	21	3.5
Separated	38	6.4
Educational status		
Below primary	80	13.3
Primary	125	20.8
Secondary	186	31.0
Tertiary	209	34.9
Employment status		
Employed	335	55.8
Unemployed	265	44.2

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Utilization of Antiretroviral Drugs

The study reveals that AZT-3TC-NVP and TDF-FTC-EFV combinations were the most frequent regimens prescribed, both at base line and during the follow – up visits (Table 2a).

TABLE 2a. Antiretroviral regimens at baseline.

ART regimen	Frequency	Percentage
TDF-FTC-EFV	300	50.2
TDF-3TC-NVP	3	.5
AZT-3TC-EFV	3	.5
ABC-3TC-NVP	19	3.2
AZT-3TC-ATV/r	1	.2
ABC-3TC-EFV	2	.3
TDF-3TC-EFV	9	1.5
Total	598	100

TABLE 2b. ART regimens during follow-up

ART regimen	Frequency	Percentage
AZT-3TC-NVP	239	40.0
TDF-FTC-EFV	306	51.2
TDF-FTC-NVP	4	.7
TDF-3TC-ATV/r	11	1.8
AZT-3TC-EFV	1	.2
AZT-3TC-ATV/r	9	1.5
ABC-3TC-NVP	12	2.0
ABC-3TC-EFV	4	.7
TDF-3TC-EFV	12	2.0
Total	598	100

Adherence to Antiretroviral Medications

Almost half of the patients' folders assessed showed poor adherence to their medications (44.5%). This was extracted from the patients' medical records and was based on their current CD4+ count. It was graded thus:

CD4+ count >500 cells/mm^3 =Good

CD4+ count between 400 and 500 cells/mm^3 =Fair

CD4+ count <400 cells/mm^3 =Poor

TABLE 3. Level of adherence to ART

Adherence level	Frequency	Percentage
Good	284	47.3
Fair	49	8.2
Poor	267	44.5
Total	600	100.0

TABLE 4. Some hematological characteristics of the respondents

Variables	No of valid variables	Missing variables	Mean (SD)
CD4+ (cells/mm^3)			
At baseline	598	2	228.60 (168.35)
After 6 months	478	122	318.98 (197.97)
After 12 months	510	90	380.43 (191.30)
Most recent	577	23	529.45 (256.03)
PCV (mg/dl)			
At baseline	414	186	11.92 (52.43)
After 6 months	338	262	9.47 (2.24)
After 12 months	327	273	9.81 (2.11)
Most recent	368	232	10.96 (2.10)
WBC (/ul)			
At baseline	415	185	6063.16 (2113.28)
After 6 months	343	257	5724.96 (1830.00)
After 12 months	325	275	5502.12 (1661.01)
Most recent	370	230	5227.16 (1735.86)

Distribution of Adverse Drug Reactions (ADRs)

The study results showed that headache, fatigue and cough were the most frequent ADRs experienced by the respondents, both at baseline and at follow-up (Tables 5a & 5b).

TABLE 5a. Adverse drug reactions of respondents at baseline

ADEs	Frequency	Percentage
Internal heat	11	1.40
Cough	84	10.73
Chest pain	28	3.58
Malaise	13	1.66
Abdominal pain	26	3.32
Dizziness	56	7.15
Headache	103	13.16
Fatigue	87	11.11
Diarrhea	18	2.30
Night sweat	13	1.66
Fever	47	6.00
Joint pain	21	2.68
Anemia	41	5.24
Rash	25	3.19
Itching	45	5.75
Edema	8	1.02
Vomiting	16	2.04
Loss of appetite	33	4.21
Weakness	10	1.28
Weight loss	10	1.28
Aches	14	1.79
Insomnia	8	1.02
Other ADEs(23 of them)	66	8.43
Total	783	100

TABLE 5b. Adverse drug reactions during follow-up

ADEs	Frequency	Percentage
Fatigue	29	8.73
Dizziness	14	4.21
Fever	22	6.62
Cough	73	21.98
Itching	15	4.52
Chest pain	24	7.33
Rash	18	5.42
Anorexia	12	3.62
Headache	33	9.94
Other ADEs(24 of them)	92	27.71
Total	332	100

Non- ART Drugs

The findings from this study showed that Cotrimoxazole and Paracetamol were the most commonly non- antiretroviral drugs prescribed both at the basaline and at follow-up (Table 6a). However, Cotrimoxazole was the most popular non-ART drug prescribed during the follow-up visits (64.1%) (Table 6b).

TABLE 6a. Non-ART regimen at baseline

Drugs	Frequency	Percentage
Metronidazole	50	5.65
Cotrimoxazole	93	10.51
Ciprofloxacin	24	2.11
Astymin	22	2.49
Pyrazinamide	33	3.73
Rifampicin	31	3.51
Isoniazid	30	3.39
Ibuprofen	20	2.26
Eleron/fesolate	88	9.94
Loratadine	45	5.09

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Fluconazole	52	5.88
Antimalarials	56	6,32
Paracetamol	126	14.24
Multivite	36	4.07
Albendazole	14	1.58
Nystatin	12	1.36
Vitamin B. complex	12	1.36
Oral rehydration salt	12	1.36
Folic acid	13	1.47
Omeprazole	8	0.90
Ampiclox	11	1.24
Clarithromycin	9	1.02
Amoxicillin	8	0.90
Loperamide	6	0.68
Chemiron	9	1.02
Clotrimazole	10	1.13
Others (about 25 drugs)	55	6.22
Total	885	100

TABLE 6b. Non- ART regimens during follow-up

Drugs	Frequency	Percentage
Clotrimoxazole	584	64.11
Paracetamol	47	5.12
Fesolate/eleron	30	3.29
Isoniazid	10	1.10
Pyrazinamide	13	1.43
Fluconazole	16	1.76
Metronidazole	25	2.74
Multivite	10	1.10
Loratadine	28	3.07
Rifampicin	10	1.10
Astymin	16	1.76
Others(about 39 drugs)	122	13.39
Total	911	99.97

IV. DISCUSSION

The study assessed the utilization pattern, adherence level, and adverse effects of these drugs on HIV/AIDS patients.

Patients with age range of 35 to 44 years appeared to be the group with the highest frequency of the disease. This may be due to high sexual activity among people within this age bracket. Gender was also among the factors considered and it appeared that females were more pre-disposed to the disease than males. Women are twice as likely to acquire HIV as their male counterparts [19]. HIV disproportionately affects women and adolescent girls because of their unequal cultural, social and economic status in society [20]. Sometimes, women are faced with significant barriers to accessing health care services and may take many forms including denial of access of services that only women require, discrimination from service providers stemming from views around female sexuality, and poor quality services. The marital status of these patients was equally analyzed and the married ones turned out to be the highest in frequency of occurrence. It is important to note that prevalence of HIV among people that were formally married is more than double that of those who were currently married or cohabitating with a sexual partner and more than three times those that were never married [20]. Therefore, the result of this research was in line with this fact.

The study also revealed the utilization pattern of the antiretrovirals used in the hospital. According to the 2013 WHO guideline, the first-line ART should consist of two Nucleoside Reverse Transcriptase Inhibitors (NRTI) and one Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) example TDF+3TC (FTC) +EFV as a fixed dose combination. If it is contraindicated or not available, one of the following options is recommended: AZT+3TC+EFV/AZT+3TC+NVP. Therefore, the drug utilization pattern in the hospital was in line with this guideline as these WHO standard regimens were the most frequently prescribed. TDF+FTC+EFV had the highest frequency of prescription followed by AZT+3TC+NVP. Other ART regimens (about six in number) were not frequently prescribed. Thus one could say that there was rational drug use within these given years. Similar study carried out at Lagos University Teaching Hospital (LUTH) by Oregba IA, et al. revealed a total of 23 ARTs being prescribed in the hospital [15]. This could mean irrational drug use and can lead to increased morbidity and mortality, waste of resources leading to reduced availability of other vital drugs and increased cost, increased risk of unwanted effects such as adverse drug reactions.

Adherence to ART is central to therapeutic success. It is simply the patient's ability to take his medication as directed. Poor adherence to medication may be due to pill burden, stigma, complexity of the regimen, cost of drug and adverse drug events associated with the drug. In this study, the adherence of patients to antiretroviral drugs was determined. Although there is no gold standard for assessing adherence, increased CD4+ count and low viral load are good indicators of proper adherence to antiretroviral drugs. As regards to this study, CD4+ count was used as indicator of adherence. It was rated good when it fell above 500cells/mm^3, fair when it was between 400 and 500cell/mm^3 and poor when it was below 400cells/mm^3. The mean CD4+ count increased progressively from the baseline to the most current; this showed that there was an improvement in the therapy. Other hematological parameters like WBC and PCV were used to determine adherence. WBC count in acute infection disease state is always high as the body, in that state, is trying to combat the organism causing the infection, thus, there is proliferation of these cells in infectious state. In this study, at the baseline, mean WBC count was found to be high but decreased as the therapy continued. In general, there was significant adherence to medication by the patients. Those that adhered properly to their medication were higher in frequency and percentage than those that poorly adhered. Non-adherence may be as a result of adverse events associated with the ART regimen used in the hospital. For instance, efavirenz- based combination is well known for its CNS effects which include hallucination, headache, dizziness, delirium, among others. Those on this regimen might have withdrawn from it when it became unbearable without the consent of the doctors. Also, zidovudine-based combination is associated with anemia, this might have equally led to their non –adherence. Other factors that might have caused the non-adherence to medication are stigmatization from people, cost of travelling to this hospital for drug collection, occasional industrial action and public holidays observed by the hospital.

Antiretroviral drugs are associated with several side effects and complications. As with any medication, adverse reactions occur with antiretroviral agents that can range from life

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threatening to minor intolerances. A broad spectrum of complication usually associated with aging appears to occur in HIV-infected patients in the ART [21,22]. These complications include osteoporosis and osteopenia, renal insufficiency, metabolic syndrome, neurocognitive decline, atherosclerotic disease, frailty, and malignancy. Tenofovir has been associated with renal tubulopathy as well as osteopenia[19]. Protease inhibitors (PIs) and zidovudine-lamivudine have also been associated with osteopenia, although the precise mechanism for these effects is not clear [23,24]. On the other hand, efavirenz has been associated with neuropsychiatric disorder while zidovudine causes anemia. Nevirapine has been associated with hypersensitivity reactions such as skin rashes. In this study, adverse drug events experienced by the patients placed on these antiretrovirals was assessed. While some of the events were managed with palliative therapy such as paracetamol tablet given to take care of the headache caused by efavirenz-base combination, others required dose adjustment, switching to another class of antiretrovirals, temporary or permanent discontinuation of the drug. The most frequent adverse drug reaction experienced by the patients at the start of the therapy was headache. This adverse effect may be due to efavirenz-base antiretroviral they received. Other reactions such as dizziness, fatigue, fever, chest pain were very significant while reactions like insomnia, indigestion, back pain, pain during swallowing occur less frequently. After the initiation of the baseline drug, the patients appeared to have more of cough while headache significantly reduced. In general, over seven hundred and fifty adverse drug reactions were recorded with headache and cough being the frequently occurred ones at baseline and follow-up respectively. These adverse drug events were well managed with other non-ARV drugs such cotrimoxazole and paracetamol.

Limitations of study

This study was carried out at the HIV/AIDS unit in the University of Nigeria Teaching Hospital Ituku-Ozalla, an outskirt of Enugu state. Due to the remote and isolated nature of the environment, the unit closed for the day by 2.30pm. This was a very big challenge as not good number of patients' folders was assessed at the time of study; cost of transportation to this area was also a limiting factor. The time it took to get ethical approval from the Research and Ethics committee of the hospital was very long and this delayed the commencement of the research.

V. CONCLUSION

The pharmacoepidemiology of the antiretrovirals used in University of Nigeria Teaching Hospital was assessed. Tenofovir-Emtricitabine-Efavirenz was the most frequently prescribed combination. The result of the research revealed a rational drug prescription pattern. Headache and cough were the most frequently reported ADEs. The level of adherence to ARVs should be improved.

Recommendation

In order to avoid the draw- backs associated with antiretroviral drug use, proper sensitization of people placed on HAART is recommended. This can be achieved by conduction of seminars on proper antiretroviral drug use, creation of awareness. It is also recommended that the health professionals especially the physicians prescribing the ART regimens should be well informed of the recommended standard ART regimens. This will ensure avoidance of irrational drug prescribing and emergence of drug resistance. Efforts and interventions geared towards improving adherence to ARVs are essential in the management of HIV infection.

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