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CUTANEOUS MEDICATION REACTIONS IN HAART EXPERIENCED AND HAART NAIVE PATIENTS IN A TERTIARY HOSPITAL IN SOUTHERN NIGERIA

Roli C. Madubuko* and Benson U. Okwara

University of Benin Teaching Hospital, Department of Medicine.

***Corresponding Author: Dr. Roli C. Madubuko**

University of Benin Teaching Hospital, Department of Medicine.

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ABSTRACT

Background: The use of highly active antiretroviral therapy (HAART) has improved patients' survival. There is however limited information in Nigeria on HAART associated cutaneous reactions which may lead to increased morbidity. **Aim:** To determine the prevalence and pattern of cutaneous medication reactions in HAART experienced and HAART naive patients in the University of Benin Teaching Hospital, Benin City, Nigeria. **Methods:** This was a comparative cross sectional study that involved 330 HAART experienced patients and 330 HAART naive patients. Patients were evaluated for cutaneous medication reactions. **Results**: The mean age of the HAART experienced group and HAART naïve group were 42.±10yrs and 40±11 years respectively. The male: female ratio of the HAART naïve and experienced population were 1.9:1 and 3:1 respectively. The median CD4 count of the HAART naive group was significantly lower than the HAART experienced group (275.5vs 487cells/µ p = < 0.01).Cutaneous medication reactions was present in 19(5.8%) of the HAART experienced patients and only 1(0.3%) of the HAART naïve group (P = < 0.01). Among the HAART experienced group, 14 (4.2%) had melanonychia, 3(0.9%) had zidovudine induced skin pigmentation and 2(0.6%) had lipodystrophy 2(0.6%). Lichenoid drug eruption 1(0.3%) was the only cutaneous medication reaction in the HAART naïve group. **Conclusion**: Cutaneous medication reactions was more common in the HAART experienced patients. Melanonychia was the most common cutaneous medication reactions among our patients with human immunodeficiency virus infection.

KEYWORDS: HAART, HIV, Cutaneous medication reaction.

INTRODUCTION

Human immunodeficiency virus is associated with a spectrum of cutaneous morbidities of diverse aetiologies. These dermatoses are quite common and may be uniquely associated with the disease, but more often represents common disorders, which may be more severe and recalcitrant to treatment.[1-3]

Medication related cutaneous eruptions are also common in HIV infection. The last decade has seen a surge in the utilization of HAART which, to some degree, reconstitutes the immune system and this has resulted in a change in the pattern of cutaneous morbidities seen. Some studies have reported a higher prevalence of cutaneous drug eruptions in the post-HAART era.[4] Although HAART has immensely impacted positively in the longevity of patients living with HIV, the post-HAART era has brought along with it its own challenges which includes an increase in medication reactions from these drugs resulting in an impaired quality of life.[4] There is limited information on cutaneous medication reactions among Nigerians with HIV infection.

This study therefore compared the prevalence and pattern of cutaneous medication reactions in the HAART experienced patients and HAART naïve patients in University of Benin Teaching Hospital (UBTH), Benin City, Edo State.

METHODOLOGY

Study Site

The study was carried out in the UBTH, Benin City Edo State, the South-South geopolitical region in Nigeria.

Study Design

This was a comparative cross-sectional study that was conducted between of study August 2013 to November 2013.

Study Population

They included 330 HIV positive patients who were on HAART for at least 6months and 330 HIV positive patients who were HAART naïve.

SELECTION CRITERIA

A. Study Population 1

I. Inclusion Criteria

- All consenting HIV positive patients above 18 years of age that attended the HIV clinic on HAART for at least 6months

II. Exclusion Criteria

- All HIV positive patients that were not on HAART.
- All HIV positive patients who were less than 18 years.
- All HIV positive patients with other immunosuppressive illnesses like malignancies and diabetes mellitus and those on immunosuppressive drugs.
- Patients who failed to give written consent.
- All pregnant patients.
- All patients with prior skin disorders before the diagnosis of HIV was made

B. STUDY POPULATION 2

I. Inclusion Criteria

- All consenting HIV positive patients above 18 years of age that attended the HIV clinic, not on HAART.

II. Exclusion Criteria

- All HIV positive patients on HAART.
- All HIV positive patients who failed to give written consent.
- All HIV positive patients less than 18 years
- All pregnant patients.
- All HIV positive patients with other immunosuppressive illnesses like malignancies, DM and those on immunosuppressive drugs like steroids
- All patients with prior skin disorders before the diagnosis of HIV was made

SAMPLE SIZE DETERMINATION

Minimum sample size for this study was calculated using the sample size formula, for two independent sample size proportions[5]

$$n = n_1+n_2 = \frac{4\{Z\alpha + Z(1-\beta)\}^2 \left(\frac{P1+P2}{2}\right)\left\{1-\frac{(P1+P2)}{2}\right\}}{(d = P1 - P2)^2}$$

Where $Z\alpha$ = Standard normal devite at 5% level of significance = 1.96

$Z_{(1-\beta)}$ = Standard normal devite for statistical power.(where β = type two error = 10%= 1.28

P_1= Prevalence in population 1= 53%(prevalence of cutaneous morbidity in patients on HAART)

P_2= Prevalence in population 2 = 66% (for prevalence of cutaneous morbidity in patients not on HAART)

Therefore, $n = n_1+n_2 = \frac{4(1.96 + 1.28)^2 (0.595 \times 0.405)}{0.13 \times 0.13}$

$$= \frac{10.121}{0.0169}$$

$$= 598.88$$

Therefore minimum sample size for each population was $\frac{598.88}{2}$

$$= 299.4$$

With expectation of attrition rate of 10% = 29.94

$$= 30$$

Minimum sample size was therefore = 329.4

$$= 329$$

For this study, a sample size of 330 for each of the population groups was used.

ETHICAL CONSIDERATION

Permission was gotten from all patients in whom this study was done, after explaining to them the purpose of the research, procedures involved, risks and benefits of the research. In addition information received was treated with utmost confidentiality. Furthermore, intellectual property rights were respected and plagiarism avoided. Approval was obtained from the ethical committee of UBTH.

SAMPLING TECHNIQUE

A systematic random sampling technique was utilized. Sampling interval was calculated. An initial work through survey was done. The HIV clinic was noted to run four days weekly excluding wednesdays. Approximately 150 HIV infected patients were seen on each clinic day. Of these, about 120 patients were on HAART. Among those patients, 90 of them had been on HAART for 6months and above. About 30 patients were yet to commence HAART (ie being worked up, yet to fulfill treatment criteria, etc).

On the average, 1440 patients who were on HAART for 6months and above were seen monthly while about 480 patients who were not on HAART were seen monthly.

Therefore the sampling interval for study population 1(patients on HAART for 6months and above) was = $\frac{N}{n}$

Where N= total number of HIV positive patients on HAART seen over a three months period

n= sample size

$$\frac{1440 \times 3}{330}$$

$$= \frac{4320}{330}$$

$$= 13.09$$

Therefore sampling interval = 13:1

On each consulting day, HIV positive patients who had been on HAART for 6months and above were selected from the list of patients expected for that day. The first patient was selected based on the balloting technique and successive patients were selected after the 13th person. If the patient selected did not meet the inclusion criteria, reballoting was done. Also if the patient had been previously selected, reballoting was done.

The sampling interval for study population 2 (HIV positive patients not on HAART) = $\frac{N}{n}$

Where N= total number of HIV positive patients not on HAART seen over a three months period

n= sample size

$$\frac{480 \times 3}{330} = 4.36$$

Sampling interval = 4:1

On each consulting day, HIV positive patients were selected from the list of patients expected for that day. The first patient was selected based on the balloting technique and successive patients were selected after the 9th person. If the patient selected did not meet the inclusion criteria, reballoting was done. Also if the patient had been previously selected, reballoting was done.

DATA MANAGEMENT

A standardized interviewer administered questionnaire was administered to clients to obtain demographic characteristics like gender, age, marital status, together with relevant clinical information such as commencement of HAART, duration of HAART therapy, names of combination drugs patient was on, adherence to HAART, presence of skin problems, type of skin problem such as rash, pruritus, ulcers, and swelling location, distribution and duration of skin disorder.

A full clinical examination was carried out on each patient. Diagnosis was made on clinical grounds. Dermatological tools like dermoscopy was used to boost diagnostic accuracy. Skin biopsy was done for confirmation of clinical diagnosis where applicable. Clinical pictures were taken of several skin lesions seen.

DATA ANALYSIS

All data generated was collated, checked and analyzed using computer based statistical package for social sciences (SPSS) IBM version 21.0. Percentages and proportions were used to describe categorical variables while means and standard deviation were used to summarize data. Prevalence of cutaneous medication reactions in each study population was analysed by calculating the number of patients with skin disease relative to all patients participating in the study. Types of cutaneous drug reaction seen in each study population were represented in frequency tables. The prevalence and types of cutaneous drug reactions were compared in both study population using chi square test (p value <0.05 was considered statistically significant). Chi square test with yates correction was used for comparisons with small sub-group size of 5 or less. Median was used to present skewed data (CD4 counts) and Mann-Whitney U test was used as a test of comparison. Mean age in the two groups were compared using t –test for 2 independent sample population groups.

RESULTS

There were two study population groups, the HAART experienced group and HAART naive group. The HAART naive population was 330 (218 females and 112 males) with a female to male ratio of 1.9:1.The HAART experienced population was 330 (247 females and 83 males) with a female to male ratio of 3:1.

Most of these patients had primary level of education, 196 (59.4%) for the HAART experienced group and 235(71.2%) for the HAART naive group. Those who had no level of education were the least observed in both groups.

The mean age for the HAART experienced group was 42.39± 10.1yrs with an age range of 18-79yrs while the mean age for the HAART naive group was 39.9±11.2yrs with an age range of 18- 75yrs.(p<0.01). (table1)

The HAART experienced group had (315) 95.5% of its respondents on first line HAART and (15) 4.5% on second line HAART. Amongst those on the first line HAART, (287) 91.1% were on zidovudine based first line therapy which were zidovudine, lamivudine and nevirapine or zidovudine, lamivudine and effavirenz. Twenty eight (8.9%) were on other first line combination therapy (these were tenofovir, emtricitabine and nevirapine combination and tenofovir, lamivudine and nevirapine combination. Another first line combination therapy observed was abacavir, lamivudine and nevirapine. All the respondents who were on second line therapy were on tenofovir, emtricitabine and lopinavir /ritonavir combination. All the HAART experienced patients observed in this study were adherent to medications. (Fig. 1)

A total of 19 (5.8%) medication reaction were observed in the HAART experienced group while the prevalence was 1(0.3%) in the HAART naive group. The difference was statistically significant (p<0.01). The medication reactions in HAART experienced group were melanonychia 14(4.2%), zidovudine induced skin pigmentation 3(0.9%) and lipodystrophy 2(0.6%) in decreasing order of frequency. Lichenoid drug eruption 1(0.3%) was observed in the HAART naïve population and did not occur in the HAART experienced category.

The median CD4 count for the HAART naive population was 275.5cells/µl while for the HAART experienced population, it was 487cells/µl. The difference was statistically significant *(p<0.01)*.

Table 1: Sociodemographic Data of Study Participants.

Demographic item	Haart Experienced (%)	Haart Naive (%)	p-value
Mean Age	42.39± 10.1yrs	39.9±11.2yrs	<0.01
Median Cd4 Cell Count	487cells/µl.	275.5cells/µl	<0.01
SEX			
Female	247 (74.8)	218(66.1)	0.01
Male	83 (25.2)	112(33.9)	
Marital Status			
Married	216 (65.5)	196(59.4)	0.01
Single	66 (20.0)	100(30.3)	
Widowed	34 (10.3)	26(7.9)	
Separated	14(4.2)	8(2.4)	
Level Of Education			
None	16 (4.8)	7 (2.1)	0.01
Primary	196 (59.4)	235(71.2)	
Secondary	68 (20.6)	52 (15.8)	
Tertiary	50 (15.2)	36 (10.9)	

Categories of Haart Experienced Patients

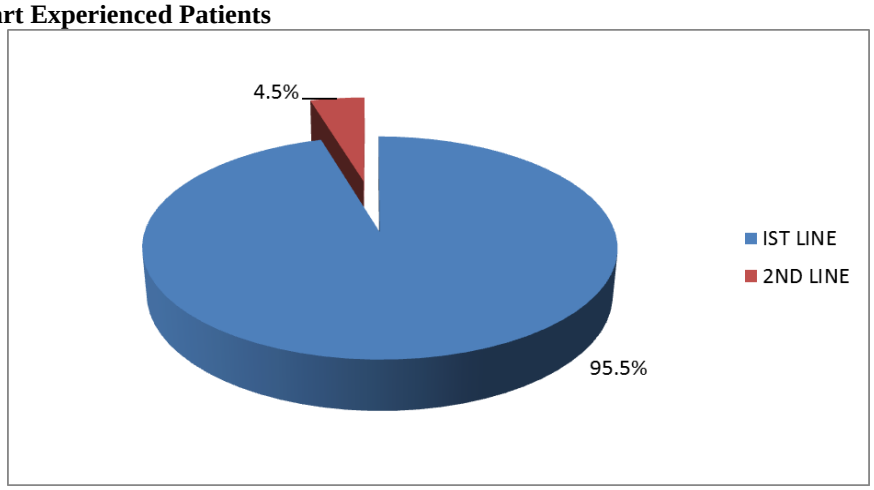


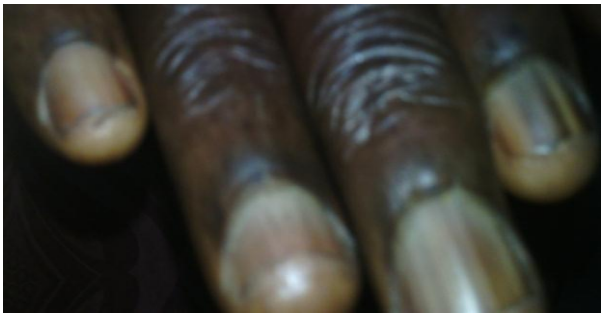
Figure 1: Categories of Haart Experienced Group.

Table 2: Cutaneous Medication Reaction And Pruritus Sine Materia Seen In The Haart Experienced And Haart Naive Groups.

**Cutaneous Morbidity	HAART Experienced n (%)	HAART Naive n (%)	p-value*
Melanonychia	14(4.2)	0(0)	<0.01*
Lichenoid eruption	1(0.3)	0(0)	1.00
Lipodystrophy	2(0.6)	0(0)	0.48
Azt pigmentation	3(0)	0(0)	0.25

Chi square with yates correction

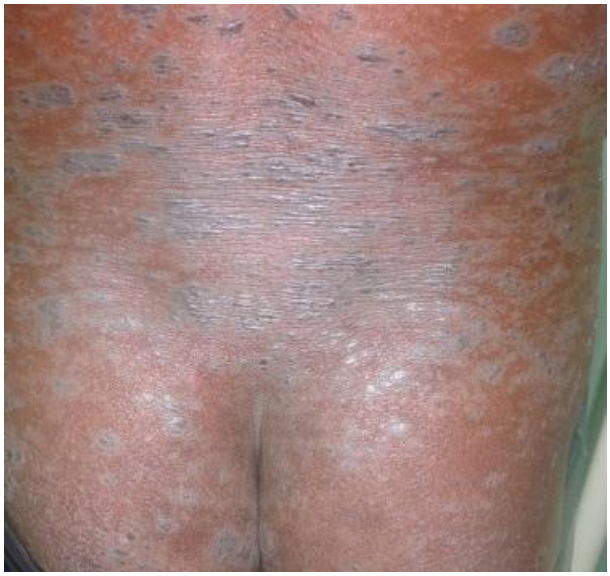
2a



2b

Figure 2: Melanonychia: observed in a patient who had been on zidovudine,lamivudine and nevirapine for 2yrs.

Noticed longitudinal black streaks within the nail plate of the fingers 6mths after commencement of HAART.



3b.

Figure 3: Lichenoid Drug Eruption Noted In One Of The Haart Naive Patient: These skin eruptions were observed in the back, buttocks following the use of trimethoprim/sulfamethoxazole. Histology confirmed the diagnosis of a lichenoid reaction.

DISCUSSION

Cutaneous medication reactions were more commonly observed in the HAART experienced patients in this study. The prevalence of cutaneous medication reactions in the HAART experienced group was 4.8% and melanonychia was the most commonly observed, accounting for 4.2% of these reactions. This is similar to previous reports where medication reactions have been found to contribute to cutaneous morbidity in the HAART experienced population.[4,6] On the other hand, lichenoid drug eruption was the only cutaneous medication reaction that occurred in 0.3% of the HAART naïve group.

The prevalence of cutaneous medication reaction in some previous studies ranged between 12.4-20%[7]. These prevalence rates are higher than 4.8% observed in our study. This variation may be a reflection of the different combinations of HAART used by the different study populations. Also, racial and genetic differences may also be contributory to the difference in prevalence rates because our study involved Nigerian subjects while the other studies with higher prevalent rates involved Asian subjects.

Melanonychia is a brown black pigmentation that arises from the nail plate due to the presence of melanin. Zidovudine is associated with melanonychia as one of its side effects.[8-9] In a study done by Launa et al[8] on melanonychia in HIV patients who were on zidovudine based HAART, longitudinal bands was commonly observed in patients who had been on zidovudine for about more than 6 months. This is comparable to the finding of our study where all the patients with melanonychia had been on zidovudine based triple therapy for six months and above. This is also similar to reports by Parvaneh et al[10] Melanonychia results from increase melanogenesis in areas of hyperpigmentation and not from drug deposition. In this study, melanonychia was the most common cutaneous drug reaction observed and this was associated with zidovudine as the major drug culprit in the HAART experienced group. This is at variance to reports by Salami et al[11], Calista et al[6] and Haung et al[7] where Steven Johnson syndrome and toxic epidermal necrolysis caused by cotrimoxazole and nevirapine were the major cutaneous medication reactions identified. This may be explained by the differences in methodology used in the various studies. Our study involved HAART experienced patients who have been on HAART for at least six months. This may possibly account for absence of cutaneous drug reactions like hypersensitivity reactions, Steven Johnsons syndrome and toxic epidermal necrolysis in our study since they commonly occur within the first six weeks of commencement of HAART therapy.[12]

HIV associated lipodystrophy is a syndrome that occurs in HIV patient being treated with antiretroviral drugs. It can be classified into lipohypertrophy which is central fat accumulation and lipoatrophy which is localized fat loss.[13-14] Most patients with lipodystrophy exhibits either lipohypertrophy or lipoatrophy. However, a subset of patients may present with both.[13-14]

In our study, lipohypertrophy, (characterized by enlargement of dorsocervical fat pad, expansion of the neck, abdominal fat accumulation and breast enlargement) occurred in 0.6% of the HAART experienced category and they were all on second line HAART medications that contained protease inhibitor. This finding is in keeping with previous report that showed that protease inhibitor is associated with biochemical derangement of glucose, lipids as well as localised accumulation of fat[15]. Protease inhibitors causes lipodystrophy through various mechanisms which include interruption of lipogenesis and adipocyte maturation, generation of reactive oxygen species, induction of inflammation, inhibition of glucose transport and alteration of expression of regulation genes such as *CHOP*, *ATF4* and *XBP* that alters lipid metabolism and autophagy.[16,17]

Lichenoid drug eruptions occurred in one of our patients in the HAART naïve group who had taken cotrimoxazole a few weeks before the eruption. It resembled lichen planus clinically with violaceous, papular, polygonal and pruritic lesions. This is however different from lichen planus, because it tends to have more confluent areas with an eczematous nature and less (if any) mucosal involvement.[18]

The limitation of this study was that the patients were assessed once for skin morbidities. Following them up for a longer period would have been better because more cutaneous medication reactions may be observed in both study groups

CONCLUSION

Cutaneous medication reactions were more common in the HAART experienced patients. Melanonychia was the most common cutaneous medication reactions among our patients with human immunodeficiency virus infection.

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