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A Comparative Study of Pruritus Sine Materia in Haart Naive and Haart Experienced Patients in a Tertiary Hospital in Southern Nigeria

Roli C. Madubuko[1*] and Benson U. Okwara[1]

[1]Department of Medicine, University of Benin Teaching Hospital, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Author RCM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author RCM the analyses of the study. Author BUO managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Pruritus is one of the most common symptoms encountered in patients with HIV and it arises from a spectrum of dermatoses of diverse etiologies; a few are peculiar to patients with HIV while others are not. Pruritus without the presence of dermatoses (pruritus sine materia) is also common and may be severe enough to provoke sleep loss and significant psychological stress.
Aim: To compare pruritus sine materia 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 idiopathic pruritus. P value of < 0.05 was considered statistically significant.
Results: The mean age of the HAART experienced group and HAART naïve group were 42.39± 10.1 yrs and 39.9±11.2 yrs respectively. 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

**Corresponding author: E-mail: rolimadubuko@yahoo.com;*

female and 83 males) with a female to male ratio of 3:1. The median CD4 count of the HAART naive group was significantly lower than the HAART experienced group (275.5 vs 487 cells/μ *p<0.01)*. The prevalence of pruritus sine materia was 19(5.8%) in the HAART naïve group and 6(1.8%) in the HAART experienced group (p<0.01).
Conclusion: Pruritus sine materiae was more common in HAART naive HIV infected patients compared to HAART experienced patients.

Keywords: HAART; HIV; Pruritus sine material; HAART experienced; HAART naïve.

1. INTRODUCTION

Human immunodeficiency virus is associated with a spectrum of cutaneous morbidities of diverse aetiologies. Pruritus is a very common symptom which is usually encountered in patients with HIV. It can be defined as an unpleasant sensation of the skin that provokes the urge to scratch. Pruritus can be localized or generalized and can occur as an acute or a chronic condition [1-2]. The scope of skin diseases in these patients encompasses dermatologic disorders of diverse etiologies; a few are peculiar to patients with HIV while others are not [3-5]. Some of these conditions may cause severe and sometimes intractable pruritus that provokes scratching, picking, disfigurement, sleep loss, and significant psychological stress [6]. Furthermore, the cost of ongoing medical treatments can be daunting. Skin rash can sometimes be the initial presentation of HIV infection or serve as a harbinger of disease progression. Stander and colleagues [7] have proposed a classification for pruritus which is divided into three groups of conditions; pruritus on diseased (inflamed) skin (group I), pruritus on non-diseased (non-inflamed) skin (group II), and pruritus presenting with severe chronic secondary scratch lesions, such as prurigo nodularis (group III) [7].

Pruritus sine materia (group II) which is pruritus in the absence of skin lesions is not an unsual finding in the setting of HIV infection. It tends to impact negatively on the quality of life of these patients. Furthermore the financial cost of medical therapy can be quite enormous for them further contributing to the burden of the disease. Some studies have reported a prevalence of between 6-10% [8-9]. These studies were done outside the West African sub-region. Highly active antiretroviral therapy(HAART) which can be defined as antiretroviral therapy which acts in at least two target sites have been shown to reduce cutaneous morbidity in general in HIV infected patients. Our study sought to compare the prevalence of pruritus sine materia in HAART naïve (HIV infected patients yet to commence HAART) and HAART experienced (HIV infected patients who have been on HAART for at least 6 months) HIV infected patients in the university of Benin Teaching Hospital in Benin city, Nigeria.

2. METHODOLOGY

2.1 Study Site

The study was carried out in the University of Benin Teaching Hospital in Benin City Edo State, the South-South geopolitical region in Nigeria.

2.2 Study Design

Comparative cross-sectional study was utilized. The duration of study was from August to November 2013.

2.3 Study Population

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

2.4 Selection Criteria

The HAART experienced patients included all consenting HIV positive patients who had been on HAART for at least 6 months, while all HIV positive patients that were not on HAART and those who were less than 18 years were excluded from this group. Furthermore, all HIV positive patients with other immunosuppressive illnesses like malignancies and diabetes mellitus, those on immunosuppressive drugs, and those patients who failed to give written consent were also excluded.

The HAART naïve patients included all consenting HIV positive patients above 18 years of age that attended the HIV clinic, who were not on HAART. Patients on HAART, those less than 18 years, those with other immunosuppressive

conditions and those who failed to give a written consent were all excluded from the study.

2.5 Sample Size Determination

Minimum sample size for this study was calculated using the sample size formula, for two independent sample size proportions [10].

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

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 altrition 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.

2.6 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 gotten from the ethical committee of the University of Benin Teaching Hospital, Benin City, Nigeria; to ensure there was no violation of the above considerations.

2.7 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.

2.8 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.

2.9 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 pruritus sine materia in each study population was analysed by calculating the number of patients with skin disease relative to all patients participating in the study. Pruritus sine materia were represented in bar charts. The prevalence of pruritus sine materia 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 hypothesis. Mean age in the two groups were compared using t –test for 2 independent sample population groups.

3. 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).

Table 1. Sociodemographic characteristics of study population

Demographic item	Haart experienced (%)	Haart naive (%)	p-value
Mean age	42.39± 10.1 yrs	39.9±11.2 yrs	<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)	
Median CD4 count	487 cells/µl.	275.5 cells/µl	<0.01

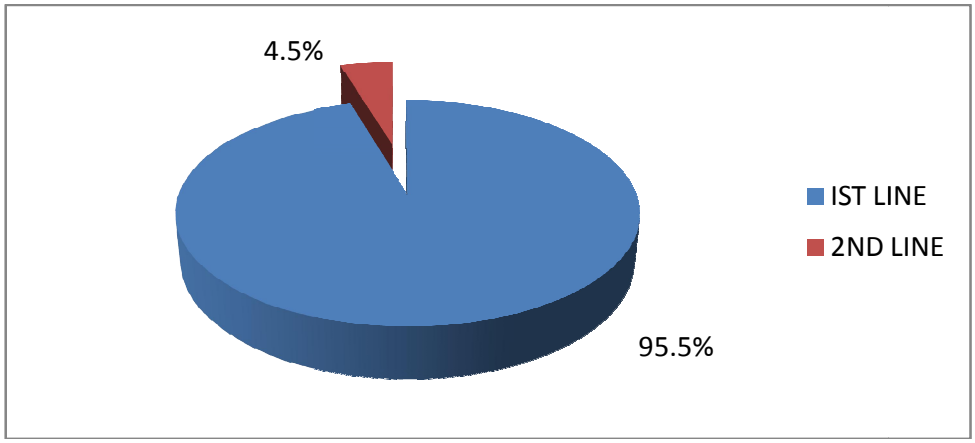

Fig. 1. Classifiaction of haart experienced group

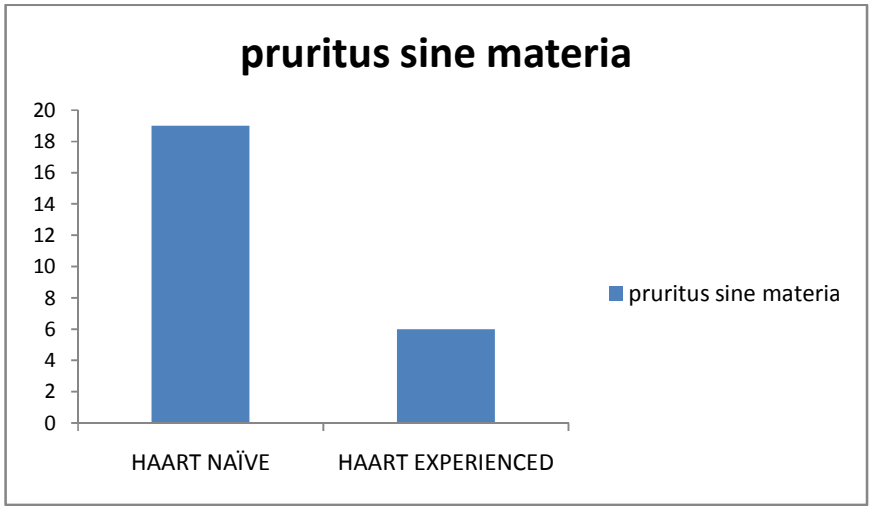

Fig. 2. Pruritus sine materia seen in the haart naive and haart experienced groups P=0.01 (chi square with yates correction

Pruritus sine materia occurred in 19(5.8%) and 6(1.8%) of the HAART naive and HAART experienced groups respectively *P<0.01.*

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

4. DISCUSSION

Pruritus is defined as an unpleasant sensation of the skin leading to the desire to scratch [11].

While many pruritic skin diseases can be diagnosed readily, this becomes more difficult for pruritus that occurs in apparently normal skin (Pruritus sine materia). The quality, intensity and diurnal rhythm of itch are important factors that currently have limited diagnostic value [11].

Pruritus sine materia featured in both groups in this study, constituting 6(1.8%) and 19(5.8%) in the HAART experienced and HAART naive study population respectively. This is in keeping with Zancanaro et al. [7] and Calista et al. [6] published works in which Idiopathic pruritus ranging between 6-10% [6,9] was said to be common in HIV patients resulting from hyperstimulation of humoral immunity [11]. This manifests as hyper IgE, hyper IgA, augmented IL4, augmented IL5 and subsequent activation of mast cells and release of histamine [11]. The prevalence was higher in the HAART naive group which was at variance with studies done outside Africa where idiopathic pruritus was commoner in the HAART experienced group. The probable explanation for this variance is that protease inhibitors which is associated with pruritus as one of its side effects was a constituent of the HAART regimen used by those studies as opposed to this study where protease inhibitors constituted only 4.5% of the HAART regimen. The median CD4 count was lower in the HAART naïve population (275.5 cells/µl) compared to the HAART experienced group (487 cells/µl) This is in keeping with published works that immune reconstitution continues for prolonged periods of time in those maintaining virological suppression with HAART [12]. CD4 molecules in skin cells are destroyed by HIV virus resulting in a marked impairment of antigen presentation, killer cell ability and cellular immunity [13]. This predisposes the patient to various types of cutaneous morbidities [14]. Our observation was in keeping with published reports by Josephine and colleagues who indicated that CD4 counts are low in patients with advanced HIV infection [15]. This is expected as the CD4 counts tend to drop by 35-50 cells/µl per year in treatment naïve patients [16].

Workup of pruritus should include a careful examination of the skin, hair, nails, and mucous membranes to establish a primary dermatologic diagnosis. Pruritus sine materia should warrant the search for a systemic cause or medication-related etiology. The management of HIV-associated pruritus should be directed at the underlying condition. Phototherapy has been found to be a useful treatment modality of several HIV-associated dermatoses and pruritus sine materia as well [6]. Unfortunately, some of the therapies that have been suggested for patients with HIV are anecdotal or based on small uncontrolled studies [6]. The last decade has seen a surge in the utilization of HAART which, to some degree, reconstitutes the immune system and ameliorates some dermatologic diseases. On the other hand, some skin diseases become more obvious temporarily when HAART is started. Unless frank medication reaction occurs, HAART does not need to be stopped [6].

5. CONCLUSION

Pruritus sine materiae occurred more commonly in HAART naive HIV infected patients compared to HAART experienced patients.

6. LIMITATION OF STUDY

Patients in this study had a onetime assessment for skin morbidities, studying them for longer periods would have been better. Furthermore patients were not investigated for systemic causes of pruritus, doing so would have contributed to the wealth of knowledge.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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