ANDROGENIC PROFILES INHIV-INFECTED MALE PATIENTS ON HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY: COULD THIS BE A THREAT TOFERTILITY?
SHORT COMMUNICATION

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ABSTRACT

Background: This study aimed to evaluate the Serum Androgenic Profilesof HIV-infected Male Patients on Highly Active Antiretroviral Therapy and those not onActive Antiretroviral Therapyin Specialist Hospital Sokoto, Nigeria.

Materials and Methods: One hundred and thirty-five HIV□infected male patients were evaluated in the Departmentof Medicine, Specialist Hospital Sokoto Nigeria from July 2017 to March 2018 using history, baseline investigations, and CD4counts. Free testosterone, luteinizing hormone (LH), and follicle□stimulating hormone (FSH) were measured using an overnight fasting serum sample. Patients were divided into three groups (n=45); Group A= HIV-infected male patients on HAART, Group B = HIV-infected male treatment naive patients, and Group C= HIV-negative control subjects. Data were analysedusing ANOVA and Chi□square tests and $p \leq 0.05$ was considered statistically significant

Results: The serum testosterone and CD4 counts were reducedin HIV-infected male patients on HAART and HAART naive compared to the negative control. The reduced testicular functions were substantiated by raised serum LH and FSH in HIV-infected male patients on HAART ($p < 0.05$) compared to the negative control.

Conclusions:HIV□infections associated with low CD4 counts even among patients on Highly Active Antiretroviral Therapymay pose threat to male fertility.

Keywords:HIV-infected Males, Hypogonadisms, Sokoto Nigeria.

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection disruptsalmost all endocrine systems ofthe human body,especially in advanced immune suppression (Renato *et al.,* 2013).Male hypogonadismis one of the most common endocrine disorders in HIV□infected men, a clinical syndrome resulting from the failure of the testes to produce sufficient testosterone (androgen deficiency) and reduced numbers of sperm cellscells (Dohle*et al.,* 2015).Although the emergence of highly active antiretroviral therapy (HAART) reduced the incidence of hypogonadism in HIV -infected males, the true prevalence remains poorly defined in different studies (Dobs *et al.,* 1988; Crum-Cianflone*et al.,* 2007).Clinical presentations such as decreased libido, impaired erectile function, muscle weakness, increased adiposity, depressed mood, and decreased vitality are non-specificfor male hypogonadism and attributed to a variety of causes, making the diagnosis challenging (Nicholas *et al.,* 2017).

The first-line investigation to confirm hypogonadism in an adult male is the measurement of early morning serum total testosterone(Bremner*et al.,* 1983).However, attempts to determine male hypogonadism in HIV-infections have yielded mixed results.Some of those differences were attributed to the diagnostic techniques and the variations in HIV-load(Dobs *et al.,* 1988; Crum-Cianflone*et al.,* 2007). Besides, interpretations of the laboratory-based immunoassays (biochemical results)are not straightforward and need to be considered in the context of the clinical presentations (Renato *et al*., 2013). We attempt to evaluate serum androgenic profiles in treated and untreated HIV -infected males in the Specialist Hospital Sokoto Nigeria.

MATERIALS AND METHODS

This study was approved in July, 2017 by the Research Committee of Specialist Hospital Sokoto Nigeria (SHS/SUB133/VOL.1).

Research design and study population

A cross□sectional laboratory-based study was conducted from July 2017 to March 2018 on 135 male participants (n=45); 45 were healthy, 45 HIV-infected patients on HAART, and 45 HIV- infected patients yet to commence HAART in the Specialist Hospital Sokoto Nigeria.

Data were analysed using ANOVA and Chi-square test, and $p \leq 0.05$ was statically significant.

Sokoto State is situated in the extreme part of North-Western Nigeria between longitude 3^o and 7^o East and latitude 10^o, and 14^o North of the equator with a total mass of about 32,000 square kilometres and a population of about 4,602298 million (UNPF, 2013).

The followings were inclusion criteria used;

1. HIV seropositive male aged 15-60 years presented with no clinical conditions likely to affect serum concentrations of sex hormones.
2.Healthy male subjects as negative controls.

The followings are exclusion criteria;

1. HIV-positive patients with a history of concomitant comorbidities such as diabetes mellitus, chronic kidney disease (serum creatinine > 1.5 mg %), chronic liver disease, history of meningitis, stroke, cryptococcal infection, and other related conditions.
2. HIV-positive patients with established cases of sexual dysfunction and/or infertility before the commencement of HAART therapy.
3. HIV-positive patients with substance abuse opiates (including heroin and methadone) or marijuana
4. HIV-positive patients who declined to give consent for inclusion

Laboratory investigations

Partec, Germany flow cytometer was used to determine the CD4 count while free testosterone and pituitary gonadotropins (LH and FSH) were estimatedusing competitive enzyme immunoassaytechnique(Tietz, 1995; Aggarwal *et al.,* 2018).

Principles of flow cytometer

Flow cytometer was used to obtain CD4 T cell count. In flow cytometry, cells are separated in aqueous suspension and stained with fluorescent dyes. Cells in flow cuvette are individually illuminated by excitation light source of the laser (488nm). This excitation causes dye molecules to fluorescence at characteristic color of emission. The fluorescent signals are then displayed and analyzed in histograms.13

Principles of enzyme immunoassay (determination of sex hormone profile)

Serum sex hormone was carried out using standard method of estimation of testosterone, estrogen, serum luteinizing hormone, and follicle stimulating hormone.15-18.

RESULTS

The serum testosterone and CD4 counts were reduced in HIV-infected male patients on HAART and HIV-infected male patients without HAART compared to the negative control. Serum LH and FSH were raised in HIV-infected male patients on HAART while LHwas reduced in HIV-infected male patients without HAART ($p< 0.05$) compared to the HIV negative control.

Table 1: Comparison of Androgenic profiles and CD4 counts in HIV-infected male patients

PARAMETERS	CD4(cell/mm^3)	Testosterone (ng/ml)	LH (MIU/ml)	FSH (MIU/ml)
Group A	**294.95± 40.38***	**0.43 ± 0.18***	10.43 ± 2.26	**10.01 ± 1.54***
Group B	**268.10± 45.34***	**0.38 ± 0.21***	5.26 ± 1.39	**5.05 ± 0.70***
Group C	**867.15± 45.09***	0.93 ± 0.10	10.34 ± 3.81	3.68 ± 0.63

Values are mean ± SEM and p values are statistically significant at $p < 0.05$ (*), Group A= HIV-infected male patients on HAART, Group B = HIV-infected male patients treatment naive, and Group C= HIV-negative controls.

Table 2: Correlation of CD4$^+$ count with androgenic profiles in HIV-infected male patients

Parameters	r-value	p-value	Remark
Testosterone(ng/ml)	**0.682****	**<0.001**	**SS**
LH(MIU/ml)	**-0.181**	**0.025**	**SS**
FSH(MIU/ml)	**-0.271***	**0.027**	**SS**

**=correlation is significant at 0.01 level (2-tailed), LH= Leutinizing hormone, FSH= Follicular stimulating hormone. A= HIV-infected male patients on HAART, Group B = HIV-infected male patients treatment naive, and Group C= HIV-negative controls.

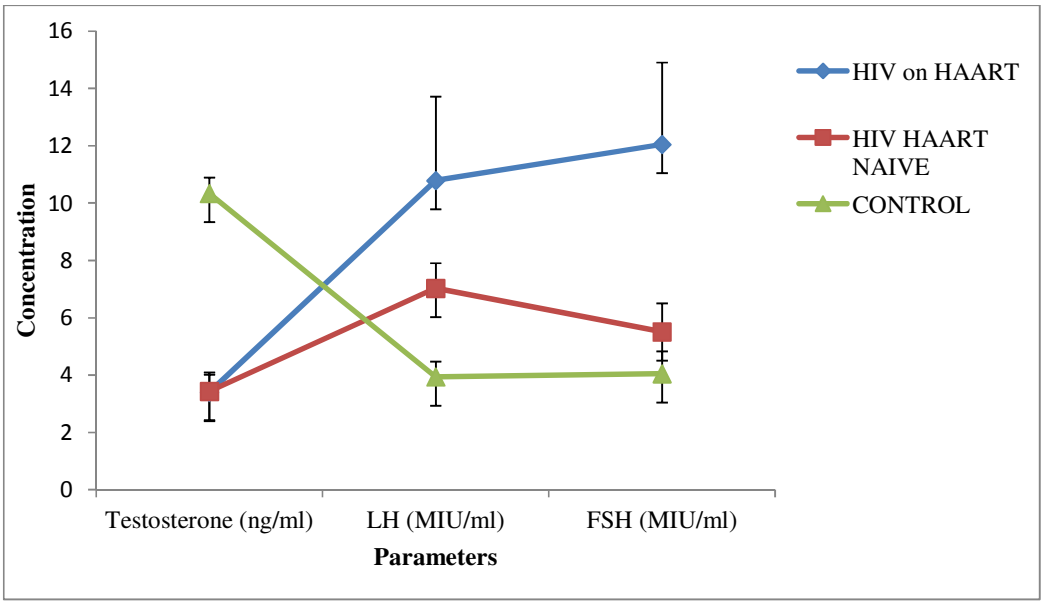

Figure 1:Comparison of Androgenic profiles in HIV-infected male patients

DISCUSSION

The study showed reducedserum testosterone and CD4 counts in HIV-infected male patients on HAART and HAART naive compared to the HIV-negative controls. The reduced testicular functions were substantiated by raised serum LH and FSH in HIV-infected male patients on HAART while the serum LHwas reduced in HIV-infected male patients treatment naïve compared to the HIV-negative controls(Table 1).This finding is consistent with previous studythat reportedsecondary hypogonadism among HIV-infected men(Aggarwal *et al.*, 2018).

Testosterone deficiency is more common in HIV-infected men than in the general population (Rochira*et al.,* 2011).Lamba*et al.*, (2004) observed that, decrease testosterone level was responsible for low libido and erectly dysfunction among HIV infected men on HAART, this pose a serious threat to fertility among HIV infected men.As most of the HIV-infected patients with testosterone deficiency had inappropriately low serum LH, a primary impairment of pituitary gonadotropin secretion could be postulated. Thus, the hypothalamic-pituitary axis should be regarded as the main element involved in the development of testosterone deficiency in HIV-infected patients, as previously suggested by ketsamathi*et al*., (2006).

The lack of the sex hormone binding globulin (SHBG) measurement and, therefore, of free serum testosterone represents a limitation of this study. The use of total serum testosterone alone may have resulted in an underestimation of the prevalence of biochemical hypogonadism since calculated free serum testosterone has been suggested as more appropriate in the context of HIV due to the possible rise in serum SHBG in these patients. Changes of SHBG levels in the HIV context remain, however, controversial, since increases in SHBG with concomitant weight loss, decreases in SHBG and no modifications of serum SHBGhave been described (Rietschel*et al.*, 2000).

Testosterone level is positively correlated with $CD4^+$ cell counts (r= **0.682**) while LH and FSH are negatively correlated to cd4 count. these finding is similar to the study by Meena *et al.*, (2011). The decreasein $CD4^+$count level is directly related to decrease testosterone level.

Moreno-perez*et al.,*(2010) noted that 53.4% of their study population had erectly dysfunction which was correlated to the the decrease level of total serum testosterone and $CD4^+$count.

CONCLUSION

This study has demonstrated significant decrease in the level of testosterone,This may contribute to decrease libido, erectly dysfunction, morbidity of the patients and have a bearing on quality of life of the HIV infected patients.HIV□infections are a threat to male fertility and are associated with low $CD4^+$ counts even in Highly Active Antiretroviral Therapy.

Recommendations:

Further studies to determine the prevalence of primary and secondary hypogonadisms in HIV□infected male patients in Sokoto, Nigeria is recommended.

Conflict of interest

None declared

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