

ANDROGENIC PROFILES IN HIV-INFECTED MALE PATIENTS ON HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY: COULD THIS BE A THREAT TO FERTILITY? SHORT COMMUNICATION

Ahmed, A.Y.¹, Gamde S.M.², Abubakar S.D.³, Muhammad Y.⁴, Saeed, S.A.¹, Rimi M.I.¹, Umar, M.⁵, Aiyelabegan, F.⁵

¹Department of Medical Laboratory Science, Faculty Allied Health Science, Kaduna State University, Kaduna-Nigeria

²Hospital Services Management Board Sokoto, Nigeria

³Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Ahmadu Bello University, Zaria-Nigeria

⁴Chemical Pathology Unit, Medical Laboratory Department, Rasheed Shekoni Teaching Hospital Dutse, Jigawa-Nigeria.

⁵School of Medical Laboratory Sciences, Usmanu Danfodiyo University, Sokoto-Nigeria.

Correspondence: E-mail: ahmedarmiyau@gmail.com; +2348069447174

ABSTRACT

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

Materials and Methods: One hundred and thirty-five HIV-infected male patients were evaluated in the Department of Medicine, Specialist Hospital Sokoto Nigeria from July 2017 to March 2018 using history, baseline investigations, and CD4 counts. 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 analysed using ANOVA and Chi-square tests and $p \leq 0.05$ was considered statistically significant.

Results: The serum testosterone and CD4 counts were reduced in 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 Therapy may pose threat to male fertility.

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

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection disrupts almost all endocrine systems of the human body, especially in advanced immune suppression (Renato *et al.*, 2013). Male hypogonadism is 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 cells (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-specific for 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° and 7° East and latitude 10° , and 14° North of the equator with a total mass of about 32,000 square kilometres and a population of about 4,602,298 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 estimated using competitive enzyme immunoassay technique (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 fluoresce at characteristic color of emission. The fluorescent signals are then displayed and analyzed in histograms.

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 LH was 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.

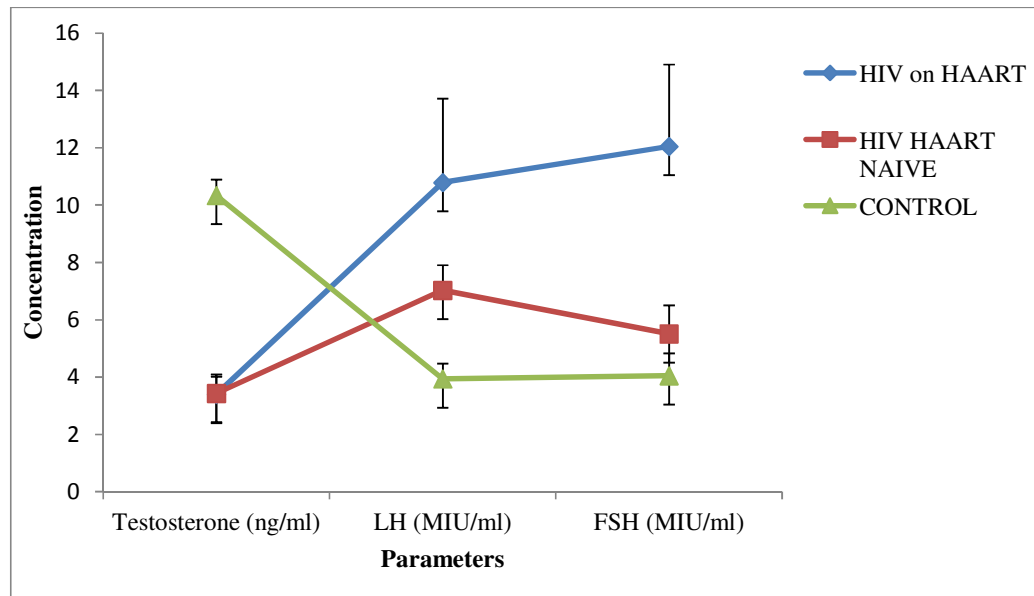


Figure 1: Comparison of Androgenic profiles in HIV-infected male patients

DISCUSSION

The study showed reduced serum 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 LH was reduced in HIV-infected male patients treatment naive compared to the HIV-negative controls (Table 1). This finding is consistent with previous study that reported secondary 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 ketsamathiet *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

REFERENCE

- Aggarwal, J., Taneja, R.S., Gupta, P.K., Wali, M., Chitkara, A. and Jamal, A. (2018). Sex hormone profile in human immunodeficiency virus-infected men and the correlation with CD4 cell counts. *Indian Journal of Endocrinology and Metabolism*, 22:328-334.
- Bremner, W.J., Vitiello, M.V. and Prinz, P.N. (1983). Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *Journal of Clinical Endocrinology and Metabolism*, 56:1278-1288.
- Crum-Cianflone, N.F., Bavaro, M., Hale, B., Amling, C., Truett, A. and

modifications of serum SHBG have been described (Rietschelet *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 decrease in 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 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

Brandt, C. (2007). Erectile dysfunction and hypogonadism among men with HIV. *AIDS Patient Care: Sexually Transmitted Diseases*, 21:9-19.

Dobs, A.S., Dempsey, M.A., Ladenson, P.W, and Polk, B.F. (1988). Endocrine disorders in men infected with human immunodeficiency virus. *American Journal of Medicine*, 84:611-616.

Dohle, G.R., Arver, C., Bettocchi, T.H., Jones, S., Kliesch, M. and Punab, S. (2015). Guidelines on male Hypogonadism. *European Association of Urology*, 1-24.

- Ketsamathi, C., Jongiaroenprasert, W. and Stenger, R.J. (2006). Prevalence of thyroid dysfunction in Thai HIV infected patients. *Current HIV Research*;4:463- 467.
- Lamba, H.,Goldmeier, D., Mackie, N.E. andScullard, G. (2004). Antiretroviral therapy is associated with sexual dysfunction and with increased serum estradiol levels in men. *International Journal of STD & AIDS*; 15:234–237.
- Meena, LP., Rai, M., Singh, S.K., Chakravarty, J., Singh, A. and Goel, R. (2011). Endocrine changes in male HIV patients. *JAPI*. 59; 231-234
- Moreno-Pérez, O., Corina, E., Carmen, S.C., Antonio, P., Rocio, A., Esperanza, M., Sergio, R.V.,Boix, J., Sanchez-Paya, M.,and Joaquin, P. (2010). Risk factors for sexual and erectile dysfunction in HIV-infected men: the role of protease inhibitors. *AIDS*; 24; 255–264.
- Nicholas, W., Miles,L., Iain, S. (2017). Hypogonadism in the HIV-Infected Man.*Current Treatments Options in Infectious Diseases*. DOI 10.1007/s40506-017-0110-3.
- Renato, F., Daniel, S., Zylberstejn, S. and Esteves. C. (2013). Hypogonadotropic Hypogonadism Revisited. *CLINICS* , 68(S1):81-88.
- Rietschel, P., Corcoran, C., Stanley, T., Basgoz, N. andKlibanski, A, (2000). Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. *Clinical Infectious Disease* 31: 1240–1244
- Rochira, V., Zirilli, L., Orlando, G., Santi, D. andBrigante, G. (2011). Premature Decline of Serum Total Testosterone in HIV-Infected Men in the HAART Era. *PLoS ONE* 6(12): e28512. doi:10.1371/journal.pone.0028512
- Tietz, N.W. A clinical guide to laboratory tests. Testosterone kits book. (1995). 3rd ed. Philadelphia, PA: WB Saunders Co.; 1995:186-188.
- United Nations Population Fund (UNPF). Annual report. 605 Third Avenue New York, NY, 10158; 2013:1-56.