Journal of Medicine and Medical Sciences Vol. 2(11) pp. 1221-1224, November 2011
Available online@ http://www.interesjournals.org/JMMS


*Full Length Research Paper*

# Efavirenz-induced gynaecomastia in HIV-infected Nigerian men: A report of six cases

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Accepted 04 November, 2011

**Highly active antiretroviral therapy (HAART) has revolutionized the treatment of HIV-infected patients. However, numerous adverse effects and limitations regarding tolerability remain a concern. We report six patients presenting in our treatment program with varying degrees of gynaecomastia following the use of efavirenz-based highly active antiretroviral therapy, despite adequate immunologic and virologic response. The time interval between commencement of treatment and appearance of gynaecomastia ranged from 8-16 months with a mean period of 10±3 months. Five of the patients experienced complete regression of gynaecomastia following efavirenz withdrawal within 6-10 weeks. One patient experienced partial regression and subsequently required bilateral mastectomy; he is without recurrence one year post surgery. Gynaecomastia is not uncommon in HIV-infected men receiving efavirenz-based highly active antiretroviral therapy. Careful attention need to be paid to the evaluation of these patients in order to institute appropriate therapy and effectively manage other co-morbid conditions that could also cause gynaecomastia.**

**Keywords:** HIV, efavirenz, gynaecomastia, Nigeria, ART toxicity.

## INTRODUCTION

Highly active antiretroviral therapy (HAART) has revolutionized the treatment of HIV infected individuals, with reductions in morbidity and mortality. However, multiple adverse effects have been described and serious limitations concerning tolerability and adherence to these drugs exist (Qazi et al., 2002; Jover et al., 2004)

Since the introduction of HAART, a number of cases of gynaecomastia have been reported in HIV-infected men on treatment (Manfredi et al., 2001; Paech et al., 2002; Arranz et al., 2001; Toma and Therrien, 1998). The incidence of gynaecomastia in this patient group was 0.8/100 patients /year with a prevalence of 2.8 in those treated longer than 2 years in one study (Piroth et al., 2001).

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True gynaecomastia in HIV-infected patients is usually unilateral with focal findings. When bilateral, it is asymmetric and can develop rapidly. However, gynaecomastia may initially present unilaterally and progress to both breasts (Garcia-Benayas et al., 2003; Qazi et al., 2000a, b; Qazi et al., 2002).

There are very few reports of HAART-induced gynaecomastia in resource-limited settings. We hereby report six cases of gynaecomastia associated with efavirenz-based HAART seen in our HIV treatment program at the Jos University Teaching Hospital, Jos, Nigeria with a review of available literature.

## METHODS AND INVESTIGATIONS

We followed-up patients diagnosed with gynaecomastia between November 2008 and November 2010 at the Jos

**Table 1.** Patient clinical features and treatment characteristics

| Parameter | Patient 1* | Patient 2 | Patient 3 | Patient4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Age (yrs) | 34 | 44 | 51 | 42 | 38 | 40 |
| Year of diagnosis | 2007 | 2008 | 2008 | 2007 | 2006 | 2007 |
| CDC stage | A3 | A2 | C2 | A3 | C3 | A3 |
| HIV transmission risk | Heterosexual | Heterosexual | Heterosexual | Heterosexual | Heterosexual | Heterosexual |
| HBV & HCV co-infection | Negative | Negative | HBsAg positive | HCVab positive | Negative | HBsAg & HCVab positive |
| Median Baseline CD4 count(cells/mm$^3$) | 48 | 12 | 220 | 162 | 57 | 107 |
| Median baseline HIV RNA (copies/ml) | 566,798 | 132,728 | 181,056 | 1,045,213 | 65,302 | 232,214 |
| Previous HAART | No | No | No | No | No | No |
| Date of HAART commencement | October 2007 | March 2008 | March 2008 | January 2008 | October 2008 | August 2007 |
| Regimen received | TDF/FTC/EFV | AZT/3TC+EFV | TDF/3TC/EFV | TDF/3TC/EFV | AZT/3TC+EFV | AZT/3TC+EFV |
| Gynaecomastia/ grading | Bilateral/IV | Bilateral/II | Right breast/II | Right breast/I | Bilateral/III | Bilateral/III |
| Lipodystrophy | No | No | No | No | No | No |
| Diagnostic method | Mammography /ultrasonography | Mammography | Mammography | Mammography | Mammography | Mammography |
| Hormone levels | Normal | Normal | Normal | Normal | Normal | Normal |
| Serum chemistry | Normal | Normal | Normal | Normal | Normal | Normal |

*Index patient, HBV-hepatitis B virus, HCV-hepatitis C virus, HAART- highly active antiretroviral therapy, AZT-zidovudine, TDF-tenofovir disoproxil fumarate, FTC-emtricitabine, 3TC-lamivudine, EFV-efavirenz

University teaching hospital ARV treatment program. All patients were HAART-naïve at enrollment. Mammography and/or ultrasonography confirmed gynaecomastia. Hepatitis virus co-infection was determined by HBsAg and HCVab assays (Dia Pro Diagnostic Bioprobes, Milano, Italy). Liver function tests, serum lipids and glucose levels were assayed. CD4+ cell counts were enumerated using flow cytometry (Partec, Munster, Germany) and viral load assays were performed by nucleic acid amplification (Roche-Amplicor HIV-1 Monitor Test, version 1.5; Roche Diagnostics, Branchburg, NJ, USA). Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), prolactin, testosterone, and estradiol were evaluated using commercial hormonal assay (Syntron Bio Research, Inc, USA). Other possible causes of gynaecomastia including medications were excluded. The Jos University Teaching Hospital Human Research Ethics Committee (HREC) and the Harvard School of Public Health Institutional Review Board (IRB) approved the study.

## RESULTS

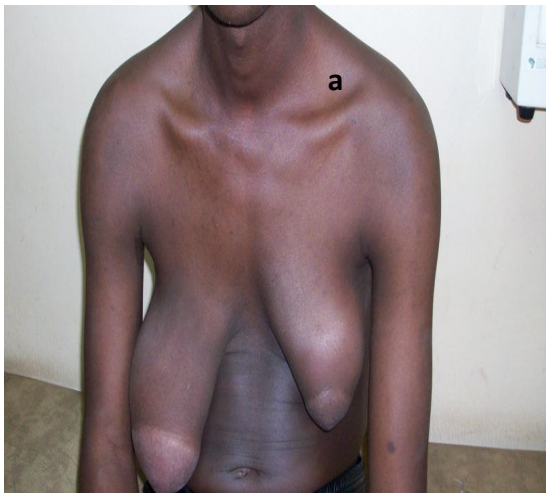
The characteristics and clinical features of our patients are presented in Table 1. Their mean age was 41±5 years. Two of the six patients were HBsAg positive and one of the six was HCV antibody positive. None of the patients co-infected with hepatitis B/C had clinical liver cirrhosis. At baseline, the median CD4+cell count was 82cells/mm$^3$ while the median baseline viral load was 206,635copies/ml (Table 1). All the patients had efavirenz withdrawn from their regimens, with complete resolution of gynaecomastia (Table 2) in five of them. The one patient with partial regression after six months of efavirenz withdrawal subsequently had bilateral mastectomy (Figure 1a and b) and was without recurrence after one year of follow-up.

## DISCUSSION

Breast enlargement in the HIV-infected population was first described in 1987 (Couderc and Clauvel, 1987). Since then there has been an increasing number of reports in medical literature, suggesting that breast enlargement could present as a side effect of HAART (Jover et al., 2004; Peyriere et al., 1999; Schürmann et al., 1998; Mastroianni and Cancellieri; 2000). The incidence of gynaecomastia in this patient group was 0.8/100 patients /year with a prevalence of 2.8 in those treated longer than 2 years in one study (Piroth et al., 2001). For our study population we obtained an incidence of 1.4/1000 population for effavirenz- induced gynaecomastia.

**Table 2.** Follow-up and outcome of six patients with efavirenz-induced gynaecomastia

| Parameter | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Current CD4 count(cells/mm$^3$) | 367 | 205 | 363 | 297 | 154 | 203 |
| Current HIV RNA (copies/ml) | 625 | 200 | 200 | 200 | 200 | 200 |
| Latent period (months) | 11 | 8 | 8 | 9 | 13 | 16 |
| Resolution after withdrawal | Partial | Complete | Complete | Complete | Complete | Complete |
| Time to resolution (weeks) | - | 6 | 4 | 8 | 6 | 10 |
| Definitive treatment | Bilateral mastectomy | - | - | - | - | - |



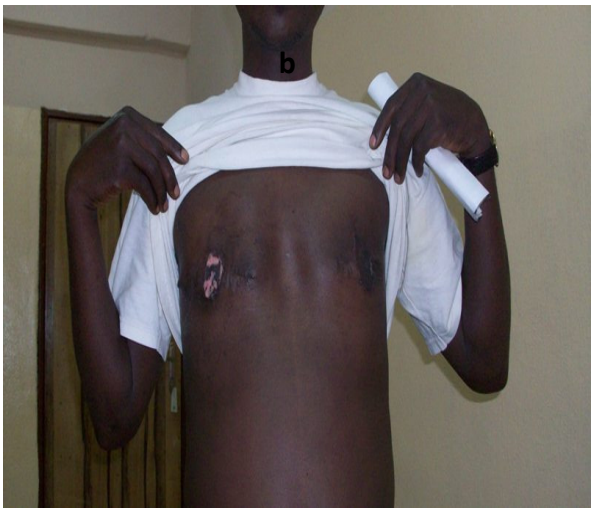




**Figure 1a.** Bilateral efavirenz-induced grade IV gynaecomastia at diagnosis; **Figure 1b.** 12 weeks post mastectomy

This study has shown that gynaecomastia occurs in HIV-positive men on HAART. It is thought to be associated with a decreased ratio of free androgens to free estrogens (Collazos et al., 2002). In this study, the concentrations of these hormones were within normal limits in all our patients. Gynaecomastia has also been linked to Protease inhibitor (PI) containing HAART as well as some nucleoside analogues (Donovan et al., 1999); giving rise to the hypothesis that gynaecomastia in patients receiving HAART may occur as part of the lipodystrophy syndrome. None of our patients had other clinical features of lipodystrophy. Three of our patients were on zidovudine containing regimens, but zidovudine has been reported to have a protective effect against gynaecomastia (Mira et al., 2004).

The majority of our patients (4 of 6) presented with bilateral asymptomatic gynaecomastia ranging in severity from grade II to IV, using the American Society of Plastic Surgeons (ASPS) staging (ASPS, 2001). In line with previous reports (Jover et al., 2004; Qazi et al., 2002), all our patients had adequate virologic and immunologic response to HAART (Qazi et al., 2002). The delay in onset of gynaecomastia in our patients ranged from 8-16 months. This range is similar to latency periods reported by other studies (Manfredi et al., 2001; Qazi et al., 2002). One patient with grade IV gynaecomastia needed bilateral mastectomy to definitively treat his gynaecomastia. Surgical treatment of HAART-induced gynaecomastia has been previously reported (Dzwonek et al., 2006).

The mechanisms underlying the development of HAART-induced gynaecomastia are not exactly clear. It has been suggested that improvements in T-cell cytokines, particularly interleukin-2 (IL-2) response may influence the growth of breast tissue after commencement of an effective HAART regimen. IL-2 has been shown to increase the proliferation of breast carcinoma cells in vitro. In addition, Interleukin-6 (IL-6) increases the availability of estrogen and stimulates breast growth, thus raising the possibility of an immune restoration process (Qazi et al., 2002).

Antiretroviral agents inhibit cytochrome P-450 which

may elevate the estrogen-androgen ratio. Decreased estrogen metabolism, displacement from estrogen-binding globulin, and diminished testosterone biosynthesis has also been postulated as possible mechanisms leading to gynaecomastia. Efavirenz levels increase by 37% in the area under the curve (AUC) when co-administered with ethynil estradiol, due to inhibition of cytochrome P-450 (Manfredi et al 2001). Unusually high levels of estradiol as measured by enzyme-linked immunosorbent assay (ELISA) were found in blood samples of patients receiving efavirenz (Sinicco et al 2000). However, estradiol levels in our patients were not elevated.

## CONCLUSION

In conclusion, gynaecomastia is not uncommon in HIV-infected men receiving efavirenz-based HAART and careful attention should be paid to the long-term follow-up of these patients.

## ACKNOWLEDGEMENTS

The authors are thankful to the staff and patients of the HIV clinic at the Jos University Teaching Hospital, Jos for their cooperation and support during this study. We wish to thank the Northwestern University Fogarty Program (Grant number 5D43TWOO7995-02) for assisting with the writing of the manuscript.

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