

## Case Series

# Efavirenz induced gynecomastia, hidden reality: a case series

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### ABSTRACT

The prognosis of HIV infection has considerably improved following the introduction of highly active anti-retroviral therapy by reducing AIDS related morbidity and mortality. At the same time, ART drugs are well known for their side effects. Gynaecomastia is a lesser known side effect of a commonly used anti-retroviral drug efavirenz. There are very few reports of HAART-induced gynaecomastia in resource-limited settings. The current study presents a series of three cases that developed ultrasound confirmed gynaecomastia following efavirenz containing HAART. Initial reports of gynaecomastia related to HAART were in HIV patients with lipodystrophy, they were termed as pseudogynaecomastia. Gradually, few reports of efavirenz related gynaecomastia were published wherein other causes of gynaecomastia were ruled out. Several hypothesis have been suggested for the pathophysiology of development of gynaecomastia related to efavirenz consumption. All other causes were ruled out in our patients too. The incidence of gynaecomastia is increasing in men with HIV on HAART therapy, proper identification and management will promote better drug adherence.

**Keywords:** HIV, Efavirenz, HAART, gynaecomastia, AIDS

### INTRODUCTION

The prognosis of human immunodeficiency virus (HIV) infection has considerably improved following the introduction of highly active anti-retroviral therapy (HAART) by reducing AIDS related morbidity and mortality. All agencies across the globe have now accepted the “treat all” policy i.e. initiation of ART in all patients, irrespective of CD4+ count in accordance with WHO.<sup>1</sup>

According to the standard recommendations, first line ART for treatment naive adult should consist of triple drug regimen; nucleoside reverse-transcriptase inhibitors (NRTIs) backbone (2 drugs), and one non-nucleoside

reverse-transcriptase inhibitor (NNRTI). Based on the efficacy and fewer side effects, tenofovir + lamivudine + efavirenz (TLE) as a fixed dose combination is preferred.<sup>2</sup> Efavirenz in a dose of 600 mg is given per day in this regimen.

Antiretroviral drugs have a broad range of toxicities ranging from low grade intolerance which may be self limiting to life threatening side effects. Efavirenz, which is the preferred NNRTI, has most of the adverse effects limited to central nervous system for example drowsiness, dizziness, confusion, vivid dreams etc.<sup>3</sup> Gynaecomastia is one of the lesser known and under reported adverse effects associated with efavirenz based therapy.

Gynaecomastia is benign enlargement of male breast tissue caused by proliferation of glandular breast tissue.<sup>4</sup> It has been observed in a small number of people taking efavirenz. Drug induced gynaecomastia is rare. Efavirenz induced gynaecomastia still remains an underreported fact. Piroth et al reported in a study on men with HIV on HAART, that the incidence of gynaecomastia in the patients on efavirenz was about 0.8/100 patients/year with a prevalence of 2.8% in those treated for longer than 2 years.<sup>5</sup>

Gynaecomastia may either be unilateral or bilateral and may also be associated with pain. Onset of gynaecomastia is slow, occurring after several months on ART. There are very few reports of HAART induced gynaecomastia in resource limited settings.

Here we report three male patients on efavirenz based HAART who were diagnosed with gynaecomastia.

### CASE SERIES

#### Case 1

50 year old male, seropositive, presented with bilateral breast swelling. Patient was a known case of HIV since 2 years and on treatment since 17 months. Patient was on TLE based regimen. Patient had bilateral breast swelling since 2 months, associated with pain. There was no history of fever, sexual dysfunction, and discharge from nipples.

Clinically, patient had bilateral breast swelling measuring 11 cm x 4 cm on right side and 9 cm x 10 cm on left side. Ultrasonography confirmed the diagnosis. Detailed history was taken and medications that could have caused gynaecomastia were ruled out. Other possible causes of disease-induced gynaecomastia were ruled out. Liver and renal function test were within normal limits. Routine endocrinologic evaluation; serum prolactin, testosterone, estradiol, and TSH were within normal limits. Diagnosis of efavirenz induced gynaecomastia was made. efavirenz was substituted by Nevirapine. On follow up, pain had reduced and size of swelling reduced significantly (Figure 1).



**Figure 1: Case 1 A) before and B) after withdrawal of efavirenz.**

#### Case 2

A 19 year old male, known case of HIV, presented with bilateral breast swelling since 3 months. The swelling was insidious in onset, associated with pain and had increased in size over 1 month. There was no history of fever, sexual dysfunction, and discharge from nipples. Patient was a known case of HIV since 1 year. He was on TLE since 6 months.

Clinically, patient had bilateral breast swelling measuring 12 cm x 9 cm on right side and 11cm x 10 cm on left side. Ultrasonography confirmed the diagnosis. Medications and diseases that could have induced gynaecomastia were ruled out. Hormonal work up was within normal limits. A diagnosis of drug induced gynaecomastia probably secondary to efavirenz was made and efavirenz was stopped. There was regression in size of swelling after 8 weeks and symptoms had subsided (Figure 2).



**Figure 2: Case 2 A) before and B) after withdrawal of efavirenz.**

#### Case 3

A 40 year old male known case of HIV presented with bilateral breast swelling since 5 months, insidious in onset, and was associated with pain on the left side. The patient was on TLE since 1 year. There was no history of discharge from the nipple. No history of sexual dysfunction.

USG showed bilateral hypoechoic subareolar illdefined soft tissue lesions. Size of swelling was 11 cm x 10 cm on the right side and 12 cm x 10 cm on the left side. Through history, physical examination and laboratory tests, other causes of gynaecomastia were ruled out. Hormone levels were within normal limit. After excluding other causes, diagnosis of gynaecomastia probably due to efavirenz was made. The drug was withdrawn and replaced with nevirapine. Regression of the breast swelling occurred during the follow up after withdrawal of efavirenz. Nevirapine was chosen due to easy availability and unaffordability for other second line drugs in all three cases.

All three cases are summarised in (Table 1).

**Table 1: Summary and comparison of the three cases.**

Parameter	Case report 1 Male patient	Case report 2 Male patient	Case report 3 Male patient
Age (years)	50	19	40
Date of diagnosis	26/9/2014	16/5/2016	30/2/2015
CD4 count before HAART	286	516	480
Date of initiation of HAART	March 2015	October 2016	March 2015
Regimen of HAART	TLE	TLE	TLE
USG breast	Bilateral hypoechoic subareolar illdefined soft tissue lesions, gynaecomastia	Bilateral hypoechoic subareolar illdefined soft tissue lesions, gynaecomastia	Bilateral hypoechoic subareolar illdefined soft tissue lesions, gynaecomastia
Gynaecomastia	21/11/2016 Bilateral Right side: 11x14 cms Left side : 9x10 cms with well defined margins firm in consistency and freely mobile	03/04/2017 Bilateral Right side: 12x9 cms Left side: 11x10 cms with well-defined margins, firm in consistency and freely mobile	08/4/2016 Bilateral Right side: 11x10 cms Left side: 12x10 cms with well-defined margins , firm in consistency and freely mobile
Duration of treatment	One and half year	6 months	13 months
Hormonal study			
Estradiol	20.3 pg/ml	19.0 pg/ml	17.0 pg/ml
Prolactin	13.4 ng/ml	12.2 ng/ml	8.2 ng/ml
Testosterone	4.0 ng/ml	5.4 ng/ml	6.4 ng/ml
TSH	3.1 mIU/ml	1.4 mIU/ml	3.4 mIU/ml
Regression after drug stoppage	17/02/2017	29/06/2017	10/7/2016
Alternate regimen	Nevirapine	Nevirapine	Nevirapine

## DISCUSSION

Mercie et al reported the first few cases of efavirenz induced gynaecomastia in patients with lipodystrophy on HAART.<sup>6</sup> They reported an incidence of 8.1% in their cohort. There have been increasing reports in literature since then, associating HAART with breast enlargement as its adverse effect. Mira et al reported 2.3% incidence of efavirenz associated gynaecomastia, theirs being a bigger cohort of 1304 men with HIV on potent ART.<sup>7</sup> Qazi et al in an extensive series reported efavirenz induced gynaecomastia in HIV affected men without lipodystrophy syndrome. In 12 out of 15 cases, there was complete resolution after a mean period of 2 months without any specific therapy.<sup>8</sup> Various reports have shown that 1.8-8.4% of the males on efavirenz therapy develop gynaecomastia.<sup>6-11</sup>

Gynaecomastia in an HIV positive individual can be attributed to hypogonadism, increased prolactin production, HIV associated cirrhosis or indirect factors such as use of protease inhibitors, anti-fungal agents like

ketoconazole.<sup>4,12</sup> The underlying mechanism of efavirenz induced gynaecomastia is not completely understood but various hypothesis exist in literature. In an experimental study by Sikora et al, direct estrogenic effect of efavirenz was explained. In their study, it was proved that efavirenz can induce the growth of breast cancer cell lines MCF-7 and ZR-75-1 which have estrogen receptor (ER) positivity. It was also proved that efavirenz can directly bind to ER-alpha (ER-a). These effects were observed in the cell model at the dose of 600 mg of daily administration of efavirenz.<sup>13</sup>

Qazi et al raised the possibility of an immune restoration disease. After initiation of HAART, there is an improvement in the helper T cell cytokine response, specifically increased interleukin-2 (IL-2) production. IL-2 has been shown to increase proliferation of human breast carcinoma cells in vitro. In addition, IL-6 increases the availability of estrogen and stimulates breast growth. Overall, immune restoration may increase breast tissue estrogen availability, which ultimately causes true gynecomastia.<sup>8,14</sup>

Cytochrome P450 inhibition induced by HAART can result in elevation of the estrogen-androgen ratio. Decreased estrogen metabolism, displacement from estrogen binding globulin, and diminished testosterone biosynthesis have been described as possible explanations.<sup>15</sup>

In the three cases we have reported, patients experienced symptoms after being treated with TLE regimen. Out of the other two existing drugs in the current regimen, efavirenz is likely to cause gynecomastia as reported in other studies by Oche et al and Ishwar et al.<sup>16,17</sup> Resolution of gynecomastia is slow and may take several weeks. In current study there was regression of symptoms in all three patients after 6 to 12 weeks of drug withdrawal.

## CONCLUSION

The incidence of gynecomastia is increasing in men with HIV on HAART therapy. The patient also has agony to reveal his symptoms. High suspicion should be kept in men receiving efavirenz containing regimen. Proper identification and management will promote better drug adherence.

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