

# Efavirenz Induced Gynecomastia: An Uncommon Forgotten Adverse Effect and Review of Literature

Satish Swain<sup>1</sup>, Neeraj Nischal<sup>2</sup>, Naveet Wig<sup>3</sup>

<sup>1,3</sup>Department of Medicine, All India Institute of Medical Sciences, New Delhi-110029, India

<sup>2</sup>Additional Professor, Department of Medicine, All India Institute of Medical Sciences, 3<sup>rd</sup> Floor Teaching Block, Ansari Nagar, New Delhi 110029, India

Corresponding Email: [neerajnischal\[at\]gmail.com](mailto:neerajnischal[at]gmail.com)

**Abstract:** *Gynecomastia is defined as benign proliferation of the glandular tissue of the male breast. It is usually palpated as a glandular mass of tissue (>0.5 cm) which is symmetrical and located centrally just beneath nipple-areolar complex. Gynecomastia has been recognized as an uncommon adverse effect of few anti-retroviral (ARV) drugs. Among the currently used ARV drugs, efavirenz has been documented in literature to cause the same. Although the exact pathogenesis is unknown, two possible mechanisms implicated are immune restoration following treatment and direct stimulation of estrogen receptors present in the breasts. Lipomastia (pseudogynecomastia) is a benign breast enlargement, which occurs as a part of fat re-distribution syndrome associated with highly active antiretroviral therapy (HAART), it must be differentiated from true gynecomastia. We here in describe a case of 24 year old retro-positive individual who develop gynecomastia following efavirenz based anti-retroviral therapy. We also did a review of literature, enumerating the frequency of the ARV drug induced gynecomastia, various investigation needed and available treatment option for the same.*

**Keywords:** HIV, Highly active antiretroviral therapy, Anti-retroviral drugs, Gynecomastia, Efavirenz

## 1. Introduction

The term “gynecomastia” is derived from the Greek word *gynec* (female) and *mastos* (breast) and was first coined by Galen way back in the second century. Gynecomastia is defined as benign proliferation of the glandular tissue of the male breast. It is common in infancy, puberty, and in middle-aged to older men. Multiple etiologies has been implicated to persistent gynecomastia, common causes included drugs, hypogonadism (primary or secondary), persistent pubertal gynecomastia, cirrhosis or malnutrition, chronic kidney disease, hyperthyroidism or testicular tumors. Even after extensive evaluation the etiology remains unclear in 25 percent of cases. Gynecomastia is seen in individuals with human immunodeficiency virus (HIV) receiving highly active antiretroviral therapy (HAART). (1) True gynecomastia in must be differentiated from pseudogynecomastia or lipomastia, which occurs as a part of a fat redistribution syndrome (lipodystrophy) seen in HIV individuals on HAART. True gynecomastia in HIV individuals has also been described due to adverse effect of anti-retroviral (ARV) drugs like efavirenz, stavudine and didanosine. (2)

## 2. Case Report

A 24 year male, known retro-viral disease, presented to our infectious disease clinic with complain of bilateral breast enlargement since 6 months. The patient was diagnosed with human immunodeficiency virus 1 (HIV-1) disease in 2017 (WHO clinical stage III) with a baseline CD<sub>4</sub><sup>+</sup> count 280 /microL and was put on first line anti-retroviral therapy (ART)-tenofovir (TDF) 300 mg daily, lamivudine (3TC) 300 mg daily and efavirenz (EFV) 600 mg daily since then. The patient was doing well with no complications until now, when he noticed gradual onset breast enlargement which was painless and was not associated with any discharge from

nipples. On local examination, both breasts were symmetrical with no apparent skin changes, elastic and rubbery in consistency with glandular tissue centred beneath the nipple-areolae complex. There was no discrete swelling nor any tenderness present. The gynecomastia was graded 2a on the Simon’s classification and grade II on Rohrich’s classification. On general examination, the patient had average built and height with well-developed secondary sexual characters. There was no loss of axillary or pubic hairs, both testes normally descended and normal in size with no associated testicular mass. Penis also found to be normal with no history of loss of libido. There was also no history of intake of any other over the counter medication/herbal products apart from ART. There was no history or signs suggestive of chronic kidney or liver disease or hypothyroidism. Routine blood investigations (complete blood count, liver function test and kidney function test) along with thyroid function test was normal. Biochemical workup for gynecomastia revealed normal serum levels of testosterone, luteinizing hormone, estradiol (E2) and human chorionic gonadotropin (hCG) ruling out malignancy and central and peripheral endocrine cause. Ultrasonography of breast showed retro-areolar fan-shaped / triangular hypoechoic mass confirming true gynecomastia. After ruling out multiple etiology the gynecomastia was finally attributed to be drug induced with efavirenz being the culprit drug. Efavirenz was stopped and the ART regimen was changed. Efavirenz was replaced by integrase strand transfer inhibitor (INSTI) dolutegravir. After 6 month follow up in our infectious disease clinic, patient was found to be doing well with some reduction in the size of breasts.

## 3. Discussion

Gynecomastia is defined as benign proliferation of glandular tissue of male breast. It can be clinically appreciated by the presence of a firm or rubbery mass extending

Volume 11 Issue 3, March 2022

[www.ijsr.net](http://www.ijsr.net)

Licensed Under Creative Commons Attribution CC BY

concentrically away from the nipple (s). (3) It may be unilateral or bilateral and can present at any age. An imbalance in estrogen to androgen activity is primarily responsible for gynecomastia, although the etiology may be many. (4) Many drug have been associated with gynecomastia, among anti-retroviral drugs, efavirenz (EFV) has been often implicated for it. Although exact mechanism is not known, Matthew et al in an in-vitro study using estrogen receptor-positive breast cancer cell lines (MCF-7, T47D and ZR-75-1) found, efavirenz directly binds and activates the ER-alpha receptor in the breast tissue, promoting glandular proliferation. (5) Apart from efavirenz other anti-retroviral drugs like stavudine and didanosine has also been remotely linked to cause gynecomastia (6) in past, although these agents are not currently in use due to availability of better drugs. Qazi et al had also put forward a hypothesis for gynecomastia. Immune restoration in HIV patients (those with low CD4+) after starting ART may be responsible for development of gynecomastia. Although underlying mechanism is unclear they had postulated that an increase in T helper cells cytokine response leading to increase in IL-2 and IL-6 levels may be responsible for breast tissue estrogen availability causing gynecomastia (7).

The incidence of efavirenz induced gynecomastia has ranges between 2.8-6 % in various studies. In a recent study done by Sandra et al in Zimbabwe the incidence was 22.1/1000 person-years; with 73 of 1432 (5%) adult men on efavirenz-containing ART regimen, had developed gynecomastia (8). Similarly, in other prospective studies the prevalence was found to be 6% in Malawi (2017) in a study by Victor Singano et al (9); 2.8% in France (2009) by L. Piroth et al (10); 2.8% in Spain (2004) by José A Mira et al (citation). In all the cases of efavirenz induced gynecomastia more than half were bilateral (roughly 60%) and around 80% had developed it within first 2 year of starting efavirenz based ART. (8) Other associated symptoms like pain, nipple discharge were also seen although not commonly. No significant associations were observed between confirmed gynecomastia and age, body mass index, CD4 count and WHO disease stage at ART initiation, duration on ART, history of tuberculosis and presence of lipodystrophy. (9)

It becomes very important to differentiate between true gynecomastia from lipomastia (lipodystrophy syndrome) in the backdrop the HIV infection. Other differential to be consider are dermoid cysts, lipomas, sebaceous cysts, ductal ectasia, lymphoplasmacytic inflammation, hematomas and fat necrosis. A simple USG can differentiate between them. Mammography is to be consider if there is suspicion of malignancy, which has a high sensitivity for the same. (11) All retro-positive patient coming with gynecomastia must be thoroughly evaluated. A proper detailed clinical examination including that of gonads, past medical history and drug history must be taken. Other important investigation includes complete hormone profile

(testosterone, luteinizing hormone, estradiol), tumor markers (bHCG), thyroid function test, biochemical profiles, serum cholesterol, triglyceride and other tumor markers which can provide some diagnostic clue. Common causes of gynecomastia (Table 1), should be ruled out before attributing the etiology to drugs. (12)

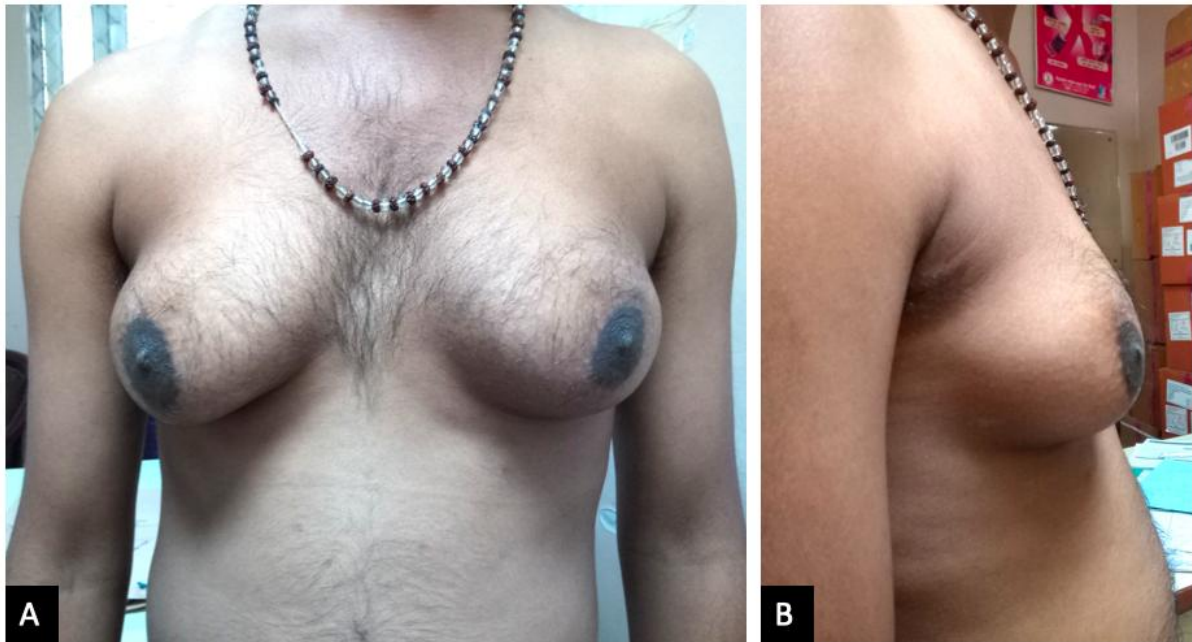
Stopping efavirenz and replacing it with other anti-retroviral drug is the most effective and commonly tried treatment option. Efavirenz can be replaced by nevirapine, protease inhibitors or newer drugs like dolutegravir (INSTI). In Sandra et al cohort, resolution was seen in 84% of the patients after stopping efavirenz with a median time to resolution being around 3 month. (8) Other treatment modalities may be tried if drug substitution fails or it becomes cosmetically/aesthetically unacceptable for the patient. Tamoxifen (a selective estrogen receptor modulator) has been used in very few cases with success at a dose of 10-20 mg daily. (13) Surgery is the last resort if medical therapy fails, reduction mammoplasty with free nipple graft can be done. (14) All cases of partial resolution or non-resolution must be re-evaluated at least once to look for any alternative etiology. Addressing the psycho-social issue is another pivotal component in management, many individuals with gynecomastia may have embarrassment in public and low-self-esteem and similarly many of the do not report this adverse effect to their health care provider.

#### 4. Conclusion

Although World Health Organization (WHO) its recent update has recommended INSTI (dolutegravir) based combination as the first line therapy in HIV treatment, efavirenz is still being used in many low income countries. It becomes essential to differentiate between true and pseudo gynecomastia, as further management would depend on it. All male patients on ART (especially on efavirenz based regimen) should be monitored for gynecomastia during therapy. Prompt withdrawal of the offending drug (efavirenz) while substituting it with other ARV drugs remains the most effective treatment.

**Table 1:** Pathological causes of gynecomastia

Chronic liver disease (cirrhosis)
Chronic Kidney Disease (CKD)
Male hypogonadism-primary or secondary
Hyperthyroidism
Drugs (common-Spironolactone, Ketoconazole, cimetidine, Chorionic gonadotropin, Tricyclic antidepressants, HAART, Estrogen etc)
Idiopathic
Testicular neoplasms-germ cell, Leydig cell, Sertoli cell, sex cord
Other rare causes-Feminizing adrenal tumors, ectopic beta human chorionic gonadotropin, Aromatase excess syndrome, Enzymatic defects of testosterone production



**Figure 1 (A, B):** Images of the patient showing enlarged breast /gynecomastia (Efavirenz induced)

## References

- [1] Pantanowitz L, Sen S, Crisi GM, Makari-Judson G, Garb J, Skiect D. Spectrum of breast disease encountered in HIV-positive patients at a community teaching hospital. *Breast Edinb Scotl.*2011 Aug; 20 (4): 303–8.
- [2] Jover F, Cuadrado JM, Roig P, Rodríguez M, Andreu L, Merino J. Efavirenz-associated gynecomastia: report of five cases and review of the literature. *Breast J.*2004 Jun; 10 (3): 244–6.
- [3] Braunstein GD. Gynecomastia [Internet]. <http://dx.doi.org/10.1056/NEJMcp070677>. Massachusetts Medical Society; 2009 [cited 2021 Jul 31]. Available from: <https://www.nejm.org/doi/10.1056/NEJMcp070677>
- [4] Gynecomastia: Pathophysiology, Evaluation, and Management [Internet]. [cited 2021 Jul 31]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2770912/>
- [5] Sikora MJ, Rae JM, Johnson MD, Desta Z. Efavirenz directly modulates estrogen receptor and induces breast cancer cell growth. *HIV Med.*2010 Oct 1; 11 (9): 603–7.
- [6] Gynaecomastia in a male patient during stavudine and didanosine treatment for HIV infection. *Int J STD AIDS.*2001 Jul 1; 12 (7): 481–2.
- [7] Qazi NA, Morlese JF, King DM, Ahmad RS, Gazzard BG, Nelson MR. Gynaecomastia without lipodystrophy in HIV-1-seropositive patients on efavirenz: an alternative hypothesis. *AIDS.*2002 Feb 15; 16 (3): 506–7.
- [8] Shwarira-Bote S, Shamu T, Chimbetete C. Gynecomastia in HIV-positive adult men receiving efavirenz-based antiretroviral therapy at Newlands clinic, Harare, Zimbabwe. *BMC Infect Dis.*2019 Aug 13; 19: 715.
- [9] Singano V, Amberbir A, Garone D, Kandionamaso C, Msonko J, van Lettow M, et al. The burden of gynecomastia among men on antiretroviral therapy in Zomba, Malawi. *PLoS ONE.*2017 Nov 20; 12 (11): e0188379.
- [10] L. Piroth HP M Grappin, JM Petit, M Buisson, M Duong, P Chavanet. Incidence of Gynecomastia in Men Infected with HIV and Treated with Highly Active Antiretroviral Therapy. *Scand J Infect Dis.*2001 Jan 1; 33 (7): 559–60.
- [11] Draghi F, Tarantino CC, Madonia L, Ferrozzi G. Ultrasonography of the male breast. *J Ultrasound.*2011 Jun 25; 14 (3): 122–9.
- [12] Cuhaci N, Polat SB, Evranos B, Ersoy R, Cakir B. Gynecomastia: Clinical evaluation and management. *Indian J Endocrinol Metab.*2014; 18 (2): 150–8.
- [13] Tamoxifen in antiretroviral-associated gynaecomastia. *Int J STD AIDS.*2002 Aug 1; 13 (8): 582–3.
- [14] Aурpibul L, Oberdorfer P. Gigantomastia in perinatally HIV-infected female adolescent on efavirenz including antiretroviral treatment. *Curr Pediatr Res [Internet].*2016 [cited 2021 Jul 24]; Available from: <http://www.currentpediatrics.com/articles/abstract/gigantomastia-in-perinatally-hivinfected-female-adolescent-on-efavirenz-including-antiretroviral-treatment-6100.html>

Volume 11 Issue 3, March 2022

[www.ijsr.net](http://www.ijsr.net)

Licensed Under Creative Commons Attribution CC BY