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**Case Report**

# Gynecomastia caused by efavirenz: Two cases with different severity

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**Abstract** Gynecomastia is the proliferation of mammary glands in men due to physiological changes, systemic diseases, tumours, and certain medications. Drug-induced gynecomastia is rare. Efavirenz is the most frequently reported ARV in several studies and case reports as a cause of gynecomastia. ***Case:*** Two HIV-infected men complained of enlarged breasts with pain without nipple discharge. Complaints arose after the initiation of efavirenz-based ARVs. Breast examination revealed bilateral swelling in the form of a mass of soft consistency, supple, concentric on the nipple-areola, well-defined, movable, and painful to palpation. Ultrasound examination supports the appearance of gynecomastia. Examination of liver function, kidney, thyroid hormone, testosterone, β-hCG, and estradiol was within normal limits. ***Discussion:*** HIV-associated gynecomastia involves pathophysiological changes such as hypogonadism, increased prolactin production, and the presence of HIV-associated cirrhosis, as well as the effects of antiretroviral drugs. Gynecomastia diagnosis is based on clinical, hormonal, and ultrasound examinations. Assessment of causal drug causes using the Naranjo algorithm. Regression of drug-associated gynecomastia occurs 1-5 months after the drug is discontinued. ***Conclusion:*** Two cases of EFV-associated gynecomastia have been reported. Efavirenz substitution should be investigated to avoid a drop in medication adherence due to gynecomastia-related distress.

***Key words***
Gynecomastia, efavirenz, Naranjo, antiretroviral, HIV.

## Introduction

Drug-induced gynecomastia is rare.[1,2] Some cases of gynecomastia have been reported in association with antiretroviral (ARV) therapy. Efavirenz (EFV) is the most frequently reported ARV in several studies as a cause of bilateral or unilateral gynecomastia. The study results in Malawi from a total of 1,027 HIV patients who had received ARVs for 57 months, the prevalence of gynecomastia was 6%. There was 88.2% of patients used EFV. Most of the patients (85.5%) had bilateral gynecomastia.[3] Another study in Zimbabwe in 1,432 men receiving antiretroviral therapy containing EFV found the incidence of gynecomastia to be 2.2%. Regression of gynecomastia occurs in 85% of cases after three months of discontinuation of EFV.[4] This paper reports two cases of gynecomastia in HIV-infected men following EFV-based ARV therapy.

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## Case Report

***Case 1*** A 23-year-old man was diagnosed with HIV and treated with the fixed drug combination (FDC) regimen (Tenofovir + Lamivudine + Efavirenz) for nine months. He presented with a chief complaint of pain in both breasts. He complained of an enlarged right and then the left breast for eight days, associated with pain. He

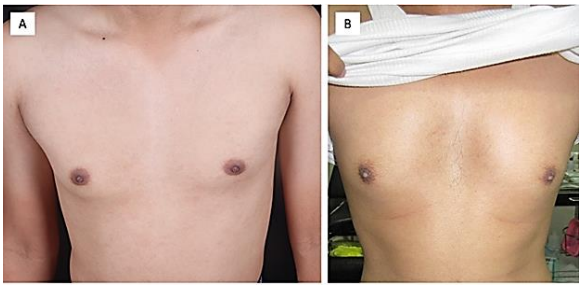


**Figure 1** Gynecomastia in case 1. (A) before (B) after 2 months of continuing ARV.

denies any nipple discharge.

There was no family history of breast cancer. The patient was diagnosed with herpes zoster and late latent syphilis in the fifth month after being diagnosed with HIV. The patient has received therapy for both diseases. The patient denied any history of thyroid disease, liver and kidney disorders, atopy, hypertension, diabetes mellitus, and testicular malignancies. The patient also denied any use of other drugs besides ARVs.

Physical examination of the patient showed consciously, nourished, and no enlarged lymph nodes. Local examination revealed concentric and bilateral breast swelling, with palpable nodules 2x1 cm in the right breast and 1x1 cm in the left breast, soft, elastic, well defined, and can be moved in all directions, tenderness on palpation, no fluid or ulceration (**Figure 1**). The visual analogue scale (VAS) for pain was 3. There was no hepatosplenomegaly, ascites, spider telangiectasia, testicular mass, normal thyroid, and secondary hair growth.

The hepatic, renal, thyroid function, sex hormones, and tumor markers are within normal limits. Ultrasonography (USG) of the breast revealed bilateral hypoechoic subareolar soft tissue lesions that were not well-defined. A causality assessment using the Naranjo scale obtained a total score of 4 (possible) and indicated that EFV might cause gynecomastia in patients.

The diagnosis, in this case, was gynecomastia grade I related to EFV in HIV patients. The patient received diclofenac sodium 2x50mg to reduce pain. Because of the efficacy of his current ARVs medication, the patient chose against other antiretrovirals. The results of the evaluation after two months of breasts are no longer increasing, and there are no other disturbing complaints related to breast enlargement.

***Case 2*** A man of 28 years is an HIV patient who has received FDC ARVs since three years ago and comes with the chief complaint of pain and enlargement in both breasts. He complained of enlarged breasts and felt a lump around the nipple with pain three months ago. He denies nipple discharge. The left breast was getting bigger one week before the examination.

There was no family history of breast cancer. The patient was diagnosed with intratesticular cellulitis, epididymitis orchitis, and urethrocutaneous fistula with a history of therapy with cefixime 2x100mg, diclofenac sodium 2x50mg, and gentamicin ointment. He had a routine check-up with the urology department. The continued therapy was only with topical gentamicin because the clinical condition had improved. The patient denied any history of thyroid disease, liver and kidney disorders, atopy, hypertension, diabetes mellitus, and testicular malignancies. The patient also denied any current use of drugs other than ARVs and topical gentamicin.

Physical examination of the patient showed consciously, nourished, and no enlarged lymph nodes. Local examination revealed concentric and bilateral breast swelling, with palpable nodules 2x2 cm in the right breast and 3x3 cm in the left breast, soft, elastic, well defined, and mobile, tenderness to palpation, no fluid or ulceration (**Figure 2**). The VAS for pain was 5.

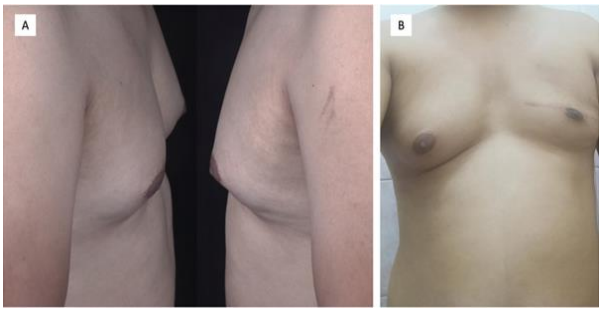


**Figure 2** Gynecomastia in case 2. (A) preoperative (B) postoperative of left breast

There was no hepatosplenomegaly, ascites, or spider telangiectasia, testicular swelling and mass, and normal thyroid.

The hepatic, renal, thyroid function, sex hormones, and tumor markers were within normal limits, but there was an increase in luteinizing hormone (LH) levels. The mammary ultrasound revealed a small, simple cyst in the right breast and supported gynecomastia in the left breast. A causality assessment using the Naranjo scale obtained a total score of 5 (probable) and indicated that EFV was more likely to cause gynecomastia in patients.

The diagnosis, in this case, was gynecomastia grade II related to EFV in HIV patients. He referred to the surgical oncology department, and he is currently undergoing an excision and biopsy of the left breast. Histopathological examination showed breast tissue with partially cystic dilated ductules. No malignant cells were found. The ARV regimen was replaced with tenofovir, lamivudine, and dolutegravir (DTG). Evaluation of treatment with the ARV regimen (TDF+3TC+DTG) after two months showed no progression of gynecomastia degree.

## Discussion

The clinical diagnosis of both patients in this study was gynecomastia. History taking includes age, duration, the onset of breast enlargement, pain, use of drugs, and psychological and social effects.[5] History of systemic disease should include signs and symptoms of liver disease, hyper or hypothyroidism, weight gain or loss, adrenal disease, alcoholism, heart failure, kidney, and malignancy. Mammae enlargement is generally slow and can be bilateral or unilateral, symmetrical or asymmetrical with varying sizes. Nipple discharge is very rare.[1,5,6]

Physical examination of the breast includes assessment of glandular or fat predominance (by pinch test), degree of gland ptosis, excess skin, nodules/ masses, and nipple discharge. The typical male breast has a flat shape with a nipple-areola complex 2 to 4 cm in diameter (mean 2.8 cm) and is located above the fourth intercostal space. Gynecomastia examination reveals a soft, elastic, or hard disk-shaped mass concentric with the nipple-areola complex.[5,6] The general physical examination that should be evaluated is testicular enlargement/ atrophy and asymmetry, thyromegaly, pulmonary abnormalities, hepatomegaly, and abdominal mass.[5]

The two patients, in this case, showed differences in the size of the breast enlargement. The second patient had a more prominent breast shape than the first patient. This is due to a history of epididymitis experienced by the second patient. Gynecomastia shows a gradation of clinical types ranging from simple areolar protrusions to breasts with a female appearance. According to Cordova and Moschella, the morphological classification of gynecomastia is clinically divided into four categories.[7] This classification classifies gynecomastia into four degrees of severity that increase from I to IV.[6,7]

Based on this classification, the patient in the first case showed a slight bulge limited to the areolar area, corresponding to grade 1 gynecomastia. The patient in the second case showed enlargement of both breasts with a

nipple-areola complex ratio of less than 1 cm below the inframammary fold. This corresponds to grade 2 gynecomastia.

Investigations in gynecomastia include imaging and laboratory. This examination rules out a differential diagnosis or assesses the cause.[8] Ultrasonography is essential for recognizing various patterns of gynecomastia. Typical findings include a hypoechoic retro areolar mass (nodular, indistinct, or flame-shaped) with an increased anteroposterior depth of the nipple.[6,9] Breast cysts in men are often associated with gynecomastia and are generally solitary lesions.[9] Laboratory investigations were performed in cases of indistinct gynecomastia. Liver, kidney, and thyroid function tests are required to exclude systemic causes. The hormonal test measures the total and bioavailability of testosterone, estradiol, prolactin, luteinizing hormone, and human chorionic gonadotropin (hCG). The results of these hormone tests can lead to endocrinopathy and pituitary, gonadal, and extragonadal neoplasms.[8] Histopathological examination of gynecomastia shows dense fibrous stroma and dilated ducts without lobules.[6]

The two main categories of causes of gynecomastia are physiological and pathological. Physiological gynecomastia occurs in newborns, adolescents, and the elderly. Pathological causes can be further divided into three subcategories: testosterone deficiency, increased estrogen production, and drug-induced breast enlargement. Testosterone deficiency can occur with HIV infection. Causes of estrogen excess include β-hCG-producing tumors (especially testicular cancer), chronic liver disease, and malnutrition.[10,11] Drug-induced gynecomastia comprises about 10%-20% of all types of gynecomastia and generally improves after discontinuation of treatment.[11,12] Antiretroviral drugs such as Stavudine, Didanosine, Efavirenz, Nevirapine, and protease inhibitors have been reported to cause gynecomastia.[13] Efavirenz has been reported to cause more bilateral or unilateral gynecomastia.[14,15]

The Naranjo algorithm is a questionnaire designed by Naranjo *et al*.[16] to determine whether an adverse drug reaction is caused by the drug or due to other factors. Probability is given through a definite, probable, possible, or doubtful score. This algorithm is also known as the Naranjo scale or Naranjo score.[17] Based on the Naranjo score to assess the causality of drug side effects, EFV may be the cause of gynecomastia in both cases (score 4-5).

The period for gynecomastia in the first case was nine months after the initiation of ARVs. One case showed a similar case where unilateral gynecomastia occurred in a patient after receiving EFV for nine months.[18] Another study reported that gynecomastia occurred after the patient received therapy for more than two years.[19] This is similar to the second case.

The mechanism of induction of gynecomastia by EFV is not known with certainty. There are several hypotheses about the mechanism of induction of gynecomastia by EFV: 1) The direct estrogenic effect of EFV has been shown that EFV stimulates the growth of the breast cancer MCF-7 and ZR-75-1 through the estrogen receptors of both cell lines. The study also proved that EFV binds to the estrogen-alpha receptor (ER-α2). Increased response of cytokines interleukin-2 and 6 (IL-2 and IL-6) mediated by helper T cells. Increased levels of IL-2 are associated with in vitro proliferation of mammary carcinoma cells, and IL-6 is associated with aromatase activity which causes increased levels of estrogen that stimulate mammary enlargement, and 3) Inhibition of

cytochrome P-450 enzymes can cause an increase in the estrogen-androgen ratio.[20]

Regression of EFV-induced gynecomastia can occur after four weeks of drug discontinuation.[18] Another study reported that regression of gynecomastia occurred an average of 5 months after EFV therapy was discontinued.[21] In cases where ARV therapy is still effective, an increase in breast mass can be observed every three months to six months because it tends to resolve spontaneously.[20] Qazi *et al*.[22] reported that 12 cases of EFV-associated gynecomastia experienced complete resolution after two months without specific therapy because ARVs were still immunologically and virologically effective. Kenji *et al*.[23] reported a similar case where the breast mass returned spontaneously over time and was painless. This is explained because gynecomastia in HIV is caused not only by indirect factors such as EFV drugs but also by direct factors due to pathophysiological changes due to HIV.[20,22]

Drug-induced gynecomastia can be treated with Tamoxifen 10-20mg/day, which is used for the prophylaxis and management of anti-androgen-induced gynecomastia. Other estrogen receptor inhibitors Raloxifene at a dose of 60 mg/day, and Anastrazole, an aromatase enzyme inhibitor, have been used to manage gynecomastia. Therapy is given for 3-9 months.[8,20,24]

Gynecomastia that persists for more than 1-2 years requires surgical management. Approaches to surgery include surgical excision via the Webster method. Newly available methods such as radiofrequency assisted liposuction remove fat and glandular tissue. Other techniques associated with less invasion include guided ultrasound using an 8-gauge mammotomy biopsy system.[8,20,24]

## Conclusion

Two cases of antiretroviral-associated gynecomastia have been reported with different degrees of severity due to EFV based on the Naranjo score. Identifying and evaluating the exact cause and grading will determine the therapeutic intervention. EFV substitution is considered to avoid non-adherence and discontinuation of ARVs due to cosmetic disturbances and psychological stress caused by gynecomastia.

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