# Keratoconjunctivitis associated with nevirapine toxicity in HIV pregnant woman

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## Abstract

Highly active antiretroviral therapy (HAART) is the treatment of choice for human immunodeficiency virus - acquired immunodeficiency syndrome (HIV-AIDS) patients. Severe side effects of these drugs have been described that produce generalized autoimmune blistering diseases, such as Stevens-Johnson syndrome and toxic epidermal necrosis (TEN). These complications may seriously compromise the patient's life or cause disabling consequences such as blindness. We describe a case of 21-year old female HIV patient with a CD4 count of 126 cells/microliter. Ten days post elective caesarean delivery she restarted HAART with nevirapine and developed TEN after approximately two weeks. Nevirapine was discontinued, but despite this, ocular surface disorder persisted. She presented severe bilateral keratoconjunctivitis that was treated with free tear substitutes, moxifloxacyn, and prednisolone acethate eye drops. At 2-month follow up her visual acuity without correction was 20/160 in the right eye and 20/40 in the left. She had bilateral moderate cicatricial keratoconjunctivitis and a central corneal leukoma in the right eye.

Early treatment is important and should consist of preservative-free lubricants, and amniotic membrane transplantation to decrease the frequency of severe sequelae such as keratitis and corneal leukomas that will reduce the quality of life for these patients.

## Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are considered variants of a single disease. They are severe acute-onset epidermolytic adverse mucocutaneous drug reactions. The only difference between them is the extent of skin detachment.[1] Different studies have shown that HIV patients have a high incidence of TEN.[2,3]

The highly active antiretroviral therapy (HAART), which involves the combination of three or more antiretroviral drugs each with different pharmacological principles, reduces viral load in the blood to undetectable levels, leading to the patient's immune recovery and improving survival. In the case of pregnant women, the use of HAART prevents transmission of infection to the fetus. In Peru, HAART guidelines are given in the Technical Standard 124-2004-MINSA/DGSP-V.01 established by the Ministry of Health and include various antiretroviral drugs, one of which is nevirapine.[4,5]

Nevirapine (NVP) is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with a favorable pharmacokinetic profile that permits a simplified dosage and provides an inexpensive regimen to prevent perinatal transmission, especially in developing countries.[6] The two most common side effects of this drug are rash and hepatic toxicity.[7-9]

Approximately 16% of patients taking this agent experience a mild to moderate maculopapular rash.[10] Severe rash has been observed in several series with an incidence of 2.4% and 4.6%.[11,12] Life-threatening rashes occur in 2% of patients.[13] Studies from developed countries report an increased risk of severe hepatotoxicity and cutaneous rash in women with CD4 count over 250 cells/mm,[3,14-16] but other studies found no significant association between high levels of CD4 and these hypersensitivity reactions.[11,12,17,18]

We report the case of an HIV-infected pregnant woman undergoing HAART treatment including NVP who developed symptoms of TEN, presenting a severe bilateral keratoconjunctivitis.

## Case Report

A 21-year old HIV-infected pregnant woman undergoing HAART therapy (etavudina, lamivudine and nevirapine) was admitted to hospital after two days of progressive feet itching, a rash on both arms, a burning sensation in the eyes and a sore throat. She received outpatient treatment with intravenous dexamethasone and was told to suspend NVP. Given there was no improvement in the rash, and the presentation of edema of lips and vaginal mucosa lesions, she was admitted to hospital.

She had been diagnosed with HIV infection (HIV 1-2) three months earlier at the 7th month of pregnancy. She had initiated HAART therapy with etavudina, lamivudine and lopinavir/ritonavir.

Ten days post elective caesarean delivery she restarted HAART with a new regimen with NVP and presented symptoms of TEN approximately two weeks after. It was her third gestation. In her personal medical history, she had low myopia, and her mother and uncle had a history of tuberculosis.

Physical examination on admission showed a febrile-oriented patient with generalized hyperpigmented maculopapular, erythematous, confluent blisters with epidermal pigmentation that involved oral, genital and conjunctival mucosa and the soles of the feet.

Ophthalmic examination showed crusty and hemorrhagic lesions on the eyebrows and eyelids, mucopurulent discharge clumping on the eyelashes, conjunctival marked hyperemia, inferior fornix with membranes and a more severe keratitis in the right eye (Figure 1).

Laboratory data on admission showed CD4 count of 126 cells/microliter, total white blood cell (WBC) count $4.320\times10^9$/L, hemoglobin 10.4 g/dL and erythrocyte sedimentation rate 100 mm/h. Platelet count was $199\times10^9$/L and random blood glucose was 110.2 mg/dL. Hepatic, urinalysis and serum chemistry were within normal limits. Blood and urine cultures were negative. Chest X-ray did not show any active tuberculous lesion.

The patient was located in a restricted access area. She was treated with hydration and antibiotics, imipenem 500 mg every 6 h and vancomycin 900 mg every 12 h for two weeks. Ophthalmic treatment consisted in free tear substitutes, moxifloxacyn and prednisolone acethate eye drops. Warm compresses were indicated for cleaning eyelids with saline solution. The skin lesions were treated with Burrow's solution and mupirocin ointment.

Patient condition improved with fever peaks under control and skin lesions healed at twenty days. At this time point, laboratory tests showed total WBC count $3.170\times10^9$/L, hemoglobin 9.3 g/dL, and platelets $335\times10^9$/L.

Eye test revealed a visual acuity without correction of 20/80 in the right eye and 20/40 in the left. The conjunctiva of both eyes was hyperemic with areas of scarring in fornices. A stromal central erosion was observed In the right eye and an inferior superficial punctate keratitis in the left. The patient was put on a

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strict regimen of free tear substitute drops and gel, and referred to another Ophthalmological Center for transplantation of amniotic membrane; in the end, however, this was not performed.

At 2-month follow up, the patient had moderate photophobia in both eyes. Her visual acuity without correction was 20/160 in the right eye and 20/40 in the left. She had bilateral moderate cicatricial keratoconjunctivitis and a central corneal leukoma in the right eye (Figures 2 and 3).

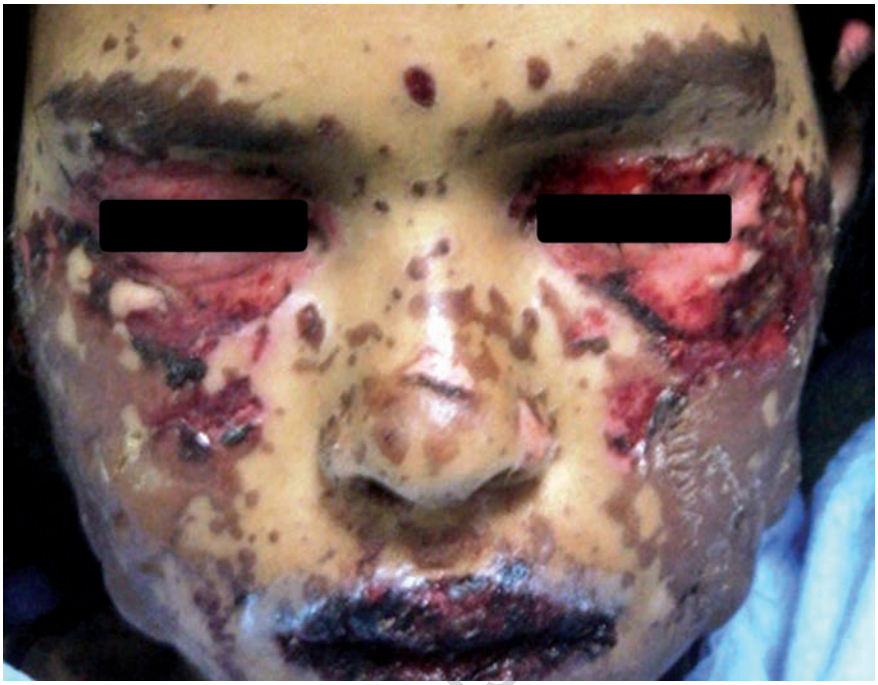

**Figure 1. Ulcers and hemorragic lesions on face.**

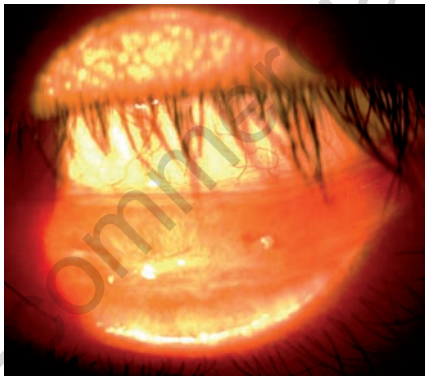

**Figure 2. Conjunctival inflammation and scarring.**

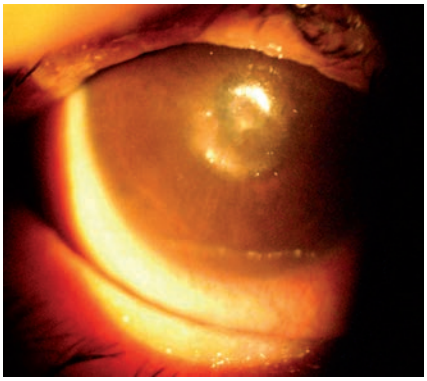

**Figure 3. Corneal central leukoma.**

## Discussion

In Peru, the use of antiretroviral drugs in pregnant women began in 1996 as part of a national policy to fight AIDS. The treatment regimens are consistent with World Health Organization guidelines, although with some variations in the time of administration of some antivirals.[4] The current use of HAART during pregnancy allows the possibility of infection in children to be reduced to below 2%.[5]

Rash and hepatotoxicity are the most frequent hypersensitivity reactions (HSR) associated with NVP.[11,19] High rates of rash in pregnant women from developed countries have been described.[12,14-16] Severe rash ranges between 2.4% and 4.6%.[11,19] NVP is the preferred NNRTI in first-line antiretroviral regimens in pregnancy because of a substantial clinical experience with pregnant women and its proven efficacy in reducing mother-to-child transmission.[6]

Studies from developed countries report an increased risk of severe toxicity of NVP administered during pregnancy to HIV-1-positive women with CD4 count over 250 cells/mm$^3$.[14-16] It relates especially to an increased risk of hepatotoxicity. These results remain questionable given that they are from studies of only a small number of women. However, research conducted by Marazzi *et al.*[11] and Kondo *et al.*[17] in pregnant women and Coffie *et al.*[12] among infected women (pregnant and non-pregnant) found no significant differences in CD4 cell counts.

A few studies have been carried out in Peru on HSRs secondary to HAART.[20-22] Astuvilca *et al.*[20] and Saldaña-Gastulo *et al.*[21] found an accumulated incidence of 66.7% adverse reactions to initial HAART. These results are similar to those obtained in Asian patients[23] but are high compared with those from research in Brazil.[17,24]

SJS and TEN are severe cutaneous disorders characterized by acute skin blisters and mucous membrane erosions. In TEN, necrosis of the epidermis and other epithelia are seen and the extent of skin involvement is over 30%.[1]

The reported incidence of ocular complications in SJS/TEN is 50-68%.[25] In the acute phase, SJS/TEN patients manifest severe conjunctivitis, conjunctival membrane or pseudomembrane formation or corneal erosion and, in severe cases, cicatrizing lesions, symblepharon, fornix foreshortening, and corneal ulceration.[26] In the chronic phase, corneal damage that can cause blindness is the most severe long-term complication for survivors of SJS/TEN.

There are few ocular complications from HSR by NVP described in the literature. The most frequent are conjunctivitis,[27] keratitis[28,29] and severe dry eye.[30] In a study conducted by Saka *et al.*[31] in Lomé, Togo, described 3 cases of blindness.

It has been recognized that meticulous skin and mucous membrane care is important in the acute phase, as with our patient. Amniotic membrane coverage of the ocular surface in its entirety coupled with the use of intensive short-term topical corticosteroids is associated with the preservation of good visual acuity and an intact ocular surface. In this procedure, criopreserved amniotic membrane transplantation modulates ocular surface wound healing by promoting epithelialization while suppressing stromal inflammation, angiogenesis and scarring during the acute stage of SJS/ TEN, thus preventing sight-threatening cicatricial complications.[31,32] This is the treatment of choice for the patient in the acute stage of ocular inflammation. The stromal corneal erosion described was sealed with free preservant lubricants but left a central leukoma that produces low vision in the right eye.

Management of the chronic stage of SJS/TEN requires recognition of the toxicity induced by drugs and reduction of the conjunctival inflammation; this may be related to trichiasis or severe dry eye and a recurrent endogenous inflammation. In these cases, use of systemic immunosuppression with corticosteroids and/or steroid-sparing agents must be considered. To treat severe dry eye, free tear substitutes, topic autologous serum, cyclosporine eye drops to 0.05% and conservative environmental measures (humidifiers, moist chamber spectacles) must be indicated.

Finally, our case highlights the risk of serious damage to the ocular surface in HIV patients treated with NVP who have TEN. Early treatment is important with preservative-free lubricants, and amniotic membrane transplantation to reduce the frequency of severe sequelae, such as cicatricial keratoconjunctivitis and corneal leukoma that will reduce the quality of life of these patients.

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