

# Nevirapine induced Stevens Johnson Syndrome

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## Abstract

Date Received: 05/10/2020 Date Revised: 20/11/2020 Date Accepted: 24/11/2020	A 56-year-old male patient presented with a complaint of lesions all over the body with a burning sensation for 4 days. He was on an ART regimen, containing zidovudine, lamivudine, and efavirenz combination for 4 years. But patient accidentally started nevirapine and after 10 days he developed maculopapular lesions which were diagnosed as SJS syndrome. There was a history of rash with nevirapine when ART was started initially in 2012. This incident of an adverse event could be assigned a term "probable" according to the WHO-UMC scale for causality assessment as the re-challenge was found positive. Severe and life-threatening SJS is more common with nevirapine than with other NNRTIs. Physicians and patients must be aware of this adverse effect on early diagnosis and treatment.
<b>Keywords</b> Stevens johnson syndrome, antiretroviral therapy, generalized erythematous eruption, nevirapine	
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## Introduction

Anti-retroviral therapy that is being used to treat HIV includes nucleoside/ nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors (FI), CCR5 antagonists & integrase inhibitors. Highly active antiretroviral therapy' (HAART) having a combination of three or more drugs is the standard of care for HIV and has an advantage in reducing HIV-RNA level successfully. NRTIs such as tenofovir, emtricitabine, lamivudine, zidovudine, and abacavir are often given in combination with either NNRTIs such as efavirenz, nevirapine, and etravirine, Protease inhibitors (PI), or integrase inhibitors (Usach *et al.*, 2013). Apart from this protease inhibitors and integrase inhibitors are also combined.

Nevirapine is an antiretroviral drug that comes under the category of non-nucleoside reverse transcriptase inhibitors (NNRTs). It is used for the treatment of HIV because of its high efficacy, good tolerability, and comparatively low cost. DNA polymerase activity gets blocked by nevirapine as it binds directly to the reverse transcriptase enzyme. This destroys the catalytic site of the enzyme. The NNRTI's were reported to have reducing HIV-RNA levels but it has certain side effects like skin rashes, nausea, headache, fever, and hepatotoxicity (Pau *et al.*, 2014). Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are potential noxious skin disorders that commonly result from a drug reaction in which symptoms

may occur within hours to weeks of exposure due to triggering agent. The mechanism involved in drug-induced SJS is cytotoxic T cells, that express and release perforin and granzyme B, and Fas-FasL interaction, which leads to apoptosis by either caspase-dependent or caspase-independent means (Su *et al.*, 2014). The risk factors for this include older age, systemic lupus erythematosus (SLE), acquired immune deficiency syndrome (AIDS), and bone marrow transplantation.

In SJS, skin lesions are initially erythematous macules that rapidly develop central necrosis with vesicles, bullae, and denudation on the face, trunk, and extremities (Reddy *et al.*, 2013). Mucosal erosions typically occur in at least two sites, including conjunctivae, mucous membranes of the nares, mouth, anorectal junction, and genital mucosa. Other clinical features include pneumonitis, productive cough, fever, headache, and malaise. The major pathologic change observed in SJS is an acute lymphohistiocytic inflammatory infiltrate around blood vessels and degenerative changes in the endothelial cells of capillaries (Alsaad *et al.*, 2005). Marked epidermal edema and epidermal necrosis and an immune complex process with hypocomplementic vasculitis are also evident. With pressure, the epidermis is easily separated from the dermis.

## Case Study

A 56-year-old male patient with a bodyweight of 62 kg was admitted to the dermatology department with complaints of lesions all over the body with a burning

sensation for 4 days. He was a nonsmoker and nonalcoholic and had a history of antitubercular treatment. The patient was on an antiretroviral regimen containing zidovudine, lamivudine, and efavirenz combination for 4 years. But patient accidentally started nevirapine and after 10 days of nevirapine use, he developed maculopapular lesions which were diagnosed as SJS syndrome.

When ART was given to the same patient in 2012 he was started on the fixed-dose combination of zidovudine 300 mg/lamivudine 150 mg /nevirapine 200 mg. At the start of the treatment itself, he had developed rashes and tablet nevirapine was stopped. He recovered from the adverse event and the patient was advised to avoid tab nevirapine in the future. So this time after 4 years patient accidentally started tablet nevirapine for which he was admitted to the Department of Dermatology and was diagnosed with Steven Johnson Syndrome. This is presented in **Figure 1**.



**Figure 1:** Skin lesions in a patient recovering from SJS

Ophthalmological examination showed B/L eyelid edema, conjunctival edema, dryness of cornea. Laboratory evaluation showed disarranged Liver function test; Alanine aminotransferase and Aspartate aminotransferase levels were raised more than three times of normal. Hemoglobin 10.2 g/dl, Red Blood Cell count ( $3.67 \times 10^6/\text{mm}^3$ ), and packed cell volume 31.7 % were reduced. Total leucocyte count, lymphocytes, and platelet counts were within the normal range. Serum biochemistry and Urinalysis was normal.

The patient was managed with supportive treatment and steroids. Dexoren-S (chloramphenicol + dexamethasone) for the oculo-cutaneous syndrome, fluconazole for oral candidiasis was given. After 1 week of treatment, the patient recovered. No recurrence of rash and impairment of hepatic functions were recorded in the subsequent follow-up. Causality assessment was performed as per the

WHO causality scale and probable association of the event with nevirapine was found.

### Discussion

SJS is an immune complex hypersensitivity reaction characterized by extensive necrosis and detachment of the epidermis and erosions of the mucous membrane. The intake of antibiotics, analgesics, cough, and cold medication, nonsteroidal anti-inflammatory drugs (NSAID), and psycho-epileptics drugs are the most common cause of SJS (Philip *et al.*, 2020). There may be a genetic predisposition to SJS. Patients with human leukocyte antigen Bw44, HLA-B12, and HLADQB1\* 0601 seem to be more susceptible to SJS (Namayanja *et al.*, 2005). The reasons why HIV-infected patients are at increased risk of severe cutaneous reactions are unclear but the literature supports the mechanism that probably involves drug-specific cytotoxic lymphocytes (Adler *et al.*, 2017).

It affects all ages and both genders but females are more prone to SJS as compared to males (Budamakuntla *et al.*, 2014). Unlike nucleoside analog reverse transcriptase inhibitors, nevirapine does not require phosphorylation to an active metabolite. Marked plasma HIV viral load suppression has been shown to occur shortly after initiation of nevirapine-containing antiretroviral regimens (Sinha *et al.*, 2013). Symptomatic hepatotoxicity, occur in approximately 3% of HIV-infected individuals who receive long course nevirapine-containing HAART regimens, with higher rates being noted among women and individuals with higher CD4 lymphocyte counts (McKoy *et al.*, 2009). The most frequent adverse events associated with nevirapine are rash (in ~ 16% of patients) and pruritus. The risk of severe mucocutaneous adverse reactions associated with nevirapine in HIV-1-infected people appears to be among the highest reported for any drug. SJS (reported in 0.3% of patients on nevirapine) is an acute, self-limited disease, with high morbidity, that is potentially life-threatening. Mortality rates are 5%. There are different scoring systems for vital prognosis estimation, simplified acute physiology score (SAPS core), which are not specific. A specific score like (SCORTEN) has been developed and validated. (Rapsang *et al.*, 2014). Treatment of SJS is primarily supportive and symptomatic. Studies report that most cases of SJS in HIV patients were due to antibacterial sulphonamides in western countries and thiacetazone in Africa (Namayanja *et al.*, 2005). Known risk factors for SJS include female gender, previous history of drug allergy, low body weight, high nevirapine plasma concentration, and CD4 counts > 250 cells/mm<sup>3</sup> in women and > 400 cells/mm<sup>3</sup> in men

(Knobel *et al.*, 2008). While our patient had a low CD4 cell count. Moreover, HIV-infected patients are at higher risk of developing SJS because of decreased antioxidant levels due to infection.

### Conclusions

With the increasing use of nevirapine, the incidence of SJS increases which presents a major challenge to physicians while treating HIV patients so physicians should consider these adverse events while prescribing HAART. The risk should not outweigh the benefit of the drug. The reported case is aimed to aware of the patient as well as a physician while dealing with the drug nevirapine. Physicians must have a high index of suspicion to be able to diagnose and treat patients with SJS in time. This could be beneficial in terms of patient safety. One must be careful and suspect SJS if a patient on an ART regimen containing NVP, presents with symptoms of irritation of the skin and mucous membranes.

### Conflict of interest

The authors declare that they have no conflicts of interest that are directly relevant to the content of the case report.

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