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Case Report

Dolutegravir induced Stevens-Johnson syndrome in a newly diagnosed person living with HIV

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Abstract

Hypersensitivity reactions are notably more frequent among people living with HIV, ranging from benign cutaneous eruptions to severe conditions like Stevens–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). These reactions arise from multifactorial mechanisms; altered drug metabolism, immune dysregulation, viral co-infections, and genetic susceptibility. Frequently implicated agents include abacavir, nevirapine, and medications for opportunistic infections. Though uncommon, integrase inhibitor associated hypersensitivity has been reported. This case describes the first documented occurrence of SJS in Sri Lanka related to the fixed-dose regimen of Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate (TLD).

A 42-year-old male developed SJS after initiating TLD and cotrimoxazole. Following recovery, re-exposure to TLD without cotrimoxazole reproduced hypersensitivity symptoms, suggesting dolutegravir as the causative agent. A Darunavir-based second line regimen was subsequently successfully introduced.

This report reinforces the need for early recognition, diagnostic caution, and enhanced pharmacovigilance even for newer antiretroviral therapies with favourable safety profile.

Key words: People living with HIV(PLHIV), Stevens-Johnson syndrome (SJS), Dolutegravir (DTG), Antiretroviral treatment (ART)

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Introduction

Hypersensitivity reactions to medications are 100 times commoner among PLHIV compared to general population. (1) These can range from mild skin reactions to life threatening conditions such as erythema multiforme, Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Identification of specific agents and management of these hypersensitivity reactions are difficult and challenging due to prescription

of multiple medications specially among patients presenting with advanced HIV infection. Understanding of predisposing factors, clinical vigilance, identification of the causative agent, prompt and appropriate medical interventions are crucial in management of drug hypersensitivity reactions among PLHIV.

Common causes of drug hypersensitivity among PLHIV are treatments of opportunistic infections, such as cotrimoxazole, anti-TB, antifungal and anti-toxoplasma medications. Among antiretroviral therapies (ART) hypersensitivity reactions were frequent among older compared to newer agents, such as abacavir and non-nucleotide reverse transcriptase inhibitors (NNRTIs), particularly nevirapine. Cross-reactivity between Darunavir and sulphonamide hypersensitivity has also been described, Hypersensitivity to integrase strand transfer inhibitors (INSTI) is relatively uncommon, occurring in fewer than 1% of individuals. (2)

Pathophysiology of drug hypersensitivity among PLHIV could be multifactorial such changes in drug metabolism, immune dysregulation, oxidase stress, genetic predisposition and viral infections. Low CD4 count, old age, presence of other skin conditions and coinfection with EBV and CMV infections are factors which could lead to increase likelihood of drug hypersensitivity among PLHIV. (3)

Clinical features of drug hypersensitivity among PLHIV are like the general population. Hypersensitivity can be classified as cutaneous drug reactions, anaphylaxis-like drug reactions, fever, drug induced liver injury and drug induces neutropenia, thrombocytopaenia and anaemia. Cutaneous drug eruptions are the commonest form of drug hypersensitivity reaction commonly presenting as an erythematous maculopapular rash with or without constitutional symptoms. They can also involve internal organs causing hepatitis, pneumonitis, pericarditis and nephritis. Lifetime risk of SJS and TEN in the general population is less than 0.5% and is marked by extensive keratinocyte apoptosis, leading to complete epidermal and mucosal loss, which significantly increases the patient's vulnerability to septic complications, with an associated mortality rate of 30%.(4) SJS and TEN are classified based on the extent of epidermal detachment, with SJS involving less than 10% of total body surface area and TEN affecting more than 30%.(4) According to the review of Peter et al, immune-mediated adverse drug reactions, particularly the delayed hypersensitivity variants, occur up to 100 times more frequently in individuals living with HIV. (5)

In 2021, WHO recommended Tenofovir Disoproxil Fumarate, Lamivudine and Dolutegravir (TLD) as first line therapy for ART-naive patients. Dolutegravir, a relatively new ART, belongs to the INSTI class with high efficacy, good tolerability, and minimal drug interactions. Findings from randomized controlled trials indicate that the most reported adverse effects include headache, nausea, diarrhoea, insomnia, and fatigue. These side effects are generally mild and do not necessitate discontinuation of treatment. Weight gain with INSTI remains controversial. Rare cases of dolutegravir, hypersensitivity reactions and liver toxicity have been reported. (6,7)

Case presentation

A 42-year-old male was diagnosed with HIV infection while being evaluated for unintentional weight loss and a pruritic rash affecting both arms and the chest for three months. His baseline HIV viral load was 94,900 HIV RNA copies/mL plasma, and CD4 count was 252 cells/µl. He was HLA-B*57:01 negative.

Anaphylaxis to oral cloxacillin several years prior had been documented. He had Type 2 diabetes mellitus, hypertension and dyslipidaemia managed with insulin, losartan, and atorvastatin respectively and an asymptomatic atrial septal defect (left-to-right shunting).

Notable physical examination findings were low BMI (17.62 kg/m^2), papular pruritic eruptions over the arms and torso, an ejection systolic murmur at the upper left sternal border, and blood pressure was160/100mmHg.

Cotrimoxazole prophylaxis for Pneumocystis Jirovecii pneumonia was commenced (prior to CD4 count) with no adverse events reported. Following the exclusion of active tuberculosis, he was initiated on single-tablet fixed dose combination TLD as per WHO guidelines 13 days

later. During the first few days of ART, he experienced mild nausea and abdominal discomfort. By the end of the first week, he developed a generalized erythematous pruritic rash, facial swelling, oral and lip ulcers which significantly restricted his oral intake. He did not report fever, breathing difficulties, abdominal pain, yellowish conjunctiva or symptoms suggestive of genital mucosal involvement.

Clinical examination revealed generalized erythematous maculopapular eruptions, redness in both conjunctiva, ulcerative oral mucosal lesions, mildly oedematous, cracked and eroded lips, and angioedema, His blood pressure was 90/60 mmHg. Investigations revealed a normal full blood count, hepatic transaminases and renal function. Based on these findings, drug-induced Stevens-Johnson syndrome was diagnosed, and all medications were immediately discontinued. The SCORTEN score was 1, correlating with a 3.2% mortality rate.

The patient was managed with short course of intravenous hydrocortisone, oral chlorpheniramine, and symptomatic topical treatments including aqueous cream with 1% hydrocortisone (face) and betamethasone cream (body),10% cetrimide shampoo for the scalp, prednisolone and metronidazole solution for oral mucosal lesions. Complete clinical resolution occurred within 10 days.

Assuming cotrimoxazole to be the culprit, TLD was restarted without cotrimoxazole, after 20 days under close supervision. Within 2 hours, the patient developed moderate fever (101°F), and within 12 hours, he experienced generalized body itching. No signs of anaphylaxis were observed. TLD was discontinued and symptoms resolved within 24 hours without treatment.

Following extensive literature review and expert input, dolutegravir was now suspected as the most likely culprit. Although it was contraindicated, due to limited ART options and their essential role in disease control, a revised second-line regimen again comprising Tenofovir disoproxil fumarate, Emtricitabine, and Ritonavir-boosted Darunavir was initiated 15 days after the second hypersensitivity episode, under informed consent and close inpatient monitoring.

The patient remained clinically stable, with no observed adverse effects. He was discharged on day 5 and scheduled for outpatient follow-up every two weeks for the first month, followed by monthly visits thereafter. At three months post-switch, he was tolerating the new antiretroviral therapy regimen well, with sustained viral suppression and normal biochemical parameters. However, 4 months later due to the unavailability of the Tenofovir disoproxil fumarate/emtricitabine combination, the regime was switched to a Tenofovir disoproxil fumarate, Lamivudine, Ritonavir boosted Darunavir regimen under close observation. He continues to tolerate this regimen without any reported adverse effects.

Discussion

Stevens–Johnson syndrome (SJS) is a rare but severe mucocutaneous reaction, often triggered by medications, including antiretroviral therapy (ART) and treatment for opportunistic infections. Among ART agents, Nevirapine has the highest SJS incidence (0.3%–1%), particularly in individuals with high CD4 counts at treatment initiation. (8) Fatal abacavir associated hypersensitivity has been reported, predominantly in HLA-B*57:01 positive individuals, especially following re-challenge (which is contra-indicated), reinforcing the importance of genetic screening before therapy initiation. (9) Both therapies are now rarely initiated so these problems will become less common. While lamivudine and zidovudine-induced SJS cases exist, they are exceedingly rare and often complicated by polypharmacy. (10,11).

This case illustrates the difficulties of managing suspected HIV infection following a severe drug hypersensitivity reaction. The primary suspect was co-trimoxazole, a known cause of SJS. The absence of adverse effects during the initial exposure period, combined with the onset of hypersensitivity shortly after rechallenging with the same ART regimen in the absence of cotrimoxazole, supports the conclusion that ART was the likely trigger. Though it is uncommon, hypersensitivity to either lamivudine or dolutegravir was suspected.

In Phase III clinical trials, adverse drug reactions (ADRs) associated with DTG were reported in 1% to 4% of participants and were generally mild. (6) Hypersensitivity reactions leading to therapy discontinuation occurred in less than 1% of cases, typically presenting as rash, systemic symptoms, or, in some instances, organ dysfunction, including liver injury. These hypersensitivity reactions most often emerged early after treatment initiation. (6)

Lamivudine (3TC) induced hypersensitivity reactions have been reported in approximately 0.7% of HIV-positive patients. (12) The chemical structure of lamivudine and emtricitabine are very similar, and cross-reactive hypersensitivity has been reported (including skin tests). (13) In this case, the absence of hypersensitivity to emtricitabine (FTC) during the third attempt, and no adverse reaction following the switch to 3TC, collectively reinforces the pharmacological and structural equivalence of FTC and 3TC in antiretroviral therapy and suggest dolutegravir as the offending agent.

Additionally, the 2nd line therapy is based around Ritonavir-boosted Darunavir. Drug hypersensitivity with Darunavir is very common, but fortunately usually mild. Although hypersensitivity to sulphonamides had been excluded, carefully monitoring was still important, particularly given the evidence of hypersensitivity on more than one occasion. (14)

Conclusion

In the final analysis, we conclude that this person, living with HIV, with immune dysfunction, developed SJS due to dolutegravir – a first report from Sri Lanka.

Identification of the causative agent responsible for drug hypersensitivity in people living with HIV is often complex due to polypharmacy and

lack of specific diagnostic tools. However, through better knowledge, clinical vigilance and following available scientific evidence, patients could be managed with minimum morbidity and mortality even in limited resource settings. This case highlights the importance of making clinicians practicing in resource-limited settings aware about the rare but potential adverse drug reactions of ART including generic fixed-dose combination ART like TLD which are generally considered as safe with minimal side effects.

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