

## Case Report

# Bilateral pedal edema in an HIV patient: Lopinavir/Ritonavir-containing treatment regimen as a potential cause?

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### Abstract

A large number of patients are switched to second-line antiretroviral therapy, especially in resource limited settings. Lopinavir/Ritonavir is the main drug used in second-line treatment regimens. We describe a patient attending an HIV treatment centre in Kampala, Uganda, who presented with bilateral non-tender pitting inflammatory edema two weeks after switching to a Lopinavir/Ritonavir-containing second-line treatment regimen. The lack of an alternate explanation led us to suspect that Lopinavir/Ritonavir was potentially responsible for the edema.

**Key words:** edema, Lopinavir/Ritonavir, resource-limited setting

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### Introduction

A large number of patients are switched to second-line antiretroviral therapy due to development of resistance against the first-line medications. Lopinavir/Ritonavir with two nucleoside analogues or with Tenofovir and Lamivudine or Emtricitabine is the second-line regimen recommended by the World Health Organization [1]. It is imperative that physicians are familiar with the adverse effects of medications used as the second-line regimen, especially in resource-limited settings.

### Case Report

The patient, a 37-year-old Ugandan male infected with HIV-1, who had started antiretroviral therapy four years earlier when his CD4 count was 50 cells/mm<sup>3</sup>, presented to the Infectious Diseases Institute. Previously, his antiretroviral regimen had been switched three times because he developed peripheral neuropathy subsequent to Stavudine use. His treatment was also interrupted several times because of financial constraints. During this period, the patient took Stavudine, Zidovudine, Lamivudine, Efavirenz, and Nevirapine as different combinations. His CD4 count rose initially to 82 cells/mm<sup>3</sup> in the first year but then dropped to 20 cells/mm<sup>3</sup>. The viral

load rose to 124,059 copies/ml. The patient was started on the second-line antiretroviral regime comprised of Lopinavir/Ritonavir soft-gel capsules (400/100) mg twice daily, Zidovudine 300 mg twice daily, and Didanosine 400 mg once daily.

The patient reported a mild bout of self-resolving diarrhoea that lasted three days. Two weeks later, he complained of “heavy” but non-painful legs. He had non-tender pitting bilateral pedal edema up to the mid-shin level. He did not report any fever or malaise. The clinical presentation was atypical for Kaposi’s sarcoma or erysipelas. He did not have any symptoms or signs suggestive of a drug reaction. Specifically, he did not report itching or difficulty in breathing, and did not have any oral lesions, skin rash, or conjunctivitis. The patient was evaluated for cellulitis, renal failure, and cardiac failure through a comprehensive clinical examination and laboratory work-up. Renal function tests, serum albumin, liver function tests, complete blood count, and urinalysis were all found to be within the normal limits. The patient was started on 50 mg of Diclofenac Sodium three times daily and 40 mg of Furosemide once daily. He completely recovered in two weeks despite the maintenance of the same antiretroviral regimen.

## Discussion

Multiple factors can cause pedal edema in patients with HIV infection, including pulmonary hypertension, cardiomyopathy, deep venous thrombosis, nephritic syndrome, and myxoedema. In an analytic review of 131 HIV patients with pulmonary hypertension, pedal edema was the second most common symptom [2], the most common being shortness of breath. Our patient did not have any difficulty breathing or effort intolerance. Excluding the pedal edema, he did not have any other clinical symptoms or signs of heart failure, deep venous thrombosis, or renal disease. Although we were not able to measure the level of thyroid-stimulating hormone to rule out myxoedema as a sign of thyroid dysfunction, he did not have any symptoms or signs of thyroid disease.

The patient developed edema subsequent to switching to a second-line antiretroviral regimen which comprised of Lopinavir/Ritonavir, Zidovudine, Didanosine, and Stavudine. It is unlikely that the edema was caused by Zidovudine because the patient had been taking this drug before without any adverse effects. Didanosine may have been the cause of the edema but such a side effect has never been described for this drug. Stavudine has also been associated with pedal edema, particularly with high blood flow of the common femoral arteries [3]; however, the patient described in our report did not develop edema when he had previously been on Stavudine.

Frequent side effects associated with the use of Lopinavir/Ritonavir include diarrhoea, dyslipidemia, and lipodystrophy. Facial or pedal edema is not listed as one of the adverse effects in patient package inserts of Lopinavir/Ritonavir (Patient Package Insert of Kaletra® Abbott Laboratories, North Chicago, IL 60064. USA September 15, 2000); however, inflammatory edema of the legs in association with a Lopinavir/Ritonavir-containing Highly Active Antiretroviral Therapy (HAART) regimen has been reported in two patients in France [4] and four patients in Brazil [5,6]. A patient who developed edema during Ritonavir treatment without Lopinavir has also been reported [7].

Bilateral pedal edema that resolves when the offending agent is withdrawn has been previously attributed to drug use [8]. Psychiatric drugs reported to cause bilateral pedal edema include Olanzapine [9-11] and Lithium [12]. Acitretin, a retinoid used in psoriasis, has also been shown to cause bilateral pedal edema [13]. Our patient was neither on any

psychiatric medication nor on a retinoid. The pedal edema subsequent to the use of Olanzapine, Lithium, and Acitretin resolved only after the offending medications were withdrawn in the patients reported. Interestingly, in our patient and for the other case reports of pedal edema subsequent to the use of Lopinavir/Ritonavir [4-6], the edema resolved with supportive therapy despite the maintenance of Lopinavir/Ritonavir.

To the best of our knowledge, this is the first time a case of bilateral pedal edema secondary to the initiation of a Lopinavir/Ritonavir antiretroviral regimen in a patient has been reported from Africa. While it is difficult to prove that the edema was caused by Lopinavir/Ritonavir, the lack of an alternate cause led us to clinically suspect the edema as a side effect of the regimen. This clinical anecdote, therefore, should be considered with great caution and it is necessary that all important causes of edema in HIV patients are ruled out before Lopinavir/Ritonavir is labeled as a cause of edema. It is important for clinicians to be cognizant of this potential side effect of Lopinavir/Ritonavir.

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