

Efavirenz-Induced Hypersensitivity Reaction Manifesting in Rash and Hepatitis in a Latino Male

Jennifer M Leung, John G O'Brien, Hing Ka Wong, and Dean L Winslow

The use of nonnucleoside reverse transcriptase inhibitors as first-line treatment in antiretroviral-naïve patients has become a preferred regimen. Such regimens generally have a lower pill burden and reduced adverse effects compared with most protease inhibitor-based regimens.¹ Efavirenz has demonstrated equally efficacious viral suppression when compared with nevirapine, with fewer severe adverse effects.^{1,2} In particular, clinical trials have demonstrated that the likelihood of severe hepatotoxicity is less frequent with the use of efavirenz (1–8%) than with nevirapine (4–18%).^{3,4} However, rare cases of severe hepatotoxicity have occurred with the use of efavirenz.

We report a hypersensitivity reaction manifesting in rash, fever, and severe hepatotoxicity with the initiation of efavirenz for HIV treatment.

Case Report

A 30-year-old, HIV-positive Latino male presented to the emergency department in October 2005 with persistent intense headache and fever. The patient had not been initiated on highly active antiretroviral therapy (HAART) prior to admission. His CD4 lymphocyte count was 20 cells/mm³ and his plasma HIV-1 RNA viral load was 32,388 copies/mL.

OBJECTIVE: To report a case of hypersensitivity manifesting in a rash, fever, and life-threatening hepatitis in a patient initiated on efavirenz therapy.

CASE SUMMARY: A 30-year-old Latino male newly diagnosed with HIV was started on efavirenz-based highly active antiretroviral therapy (HAART) using tenofovir 300 mg, emtricitabine 200 mg, and efavirenz 600 mg once daily. Eleven days after beginning therapy, he developed a hypersensitivity reaction manifesting in rash and fever preceding severe drug-induced hepatitis. Liver enzyme peak values were aspartate transaminase 3410 U/L and alanine transaminase 2132 U/L. Hepatitis resolved with discontinuation of the HAART. The patient was rechallenged with tenofovir and emtricitabine one year later; no adverse reactions occurred.

DISCUSSION: The Naranjo probability scale demonstrated a probable relationship between this adverse reaction and efavirenz. A MEDLINE search (2004 to September 2007) revealed 2 cases of rash preceding hepatitis with the initiation of efavirenz. Both cases were in women; there were no prior reported cases of efavirenz hypersensitivity in men. Although the mechanism of this reaction is unknown, a few factors may have contributed to this reaction. The half-life and the auto-induction of efavirenz may explain the continued rise in liver enzymes and severe hepatitis that continued to occur once the drug was discontinued. Another cause that may have contributed is the metabolism of the medication. CYP2B6 is responsible for almost 90% of the clearance of efavirenz. Data from a recent pharmacokinetic study showed that efavirenz concentrations were higher in both black and Latino patients when compared with those of white patients. In addition, it is highly probable that this patient's liver function was impaired when transaminase levels peaked, resulting in decreased clearance of efavirenz.

CONCLUSIONS: Although such a hypersensitivity reaction is rare, efavirenz is the most probable cause of the erythematous maculopapular rash and acute hepatitis in this patient. Monitoring of liver function in patients who present with a rash following initiation of efavirenz-based HAART is recommended. In addition, clinicians should exercise caution in patients presenting with rash, fever, and increased liver enzymes (>3 times the upper limit of normal or patient baseline). It is strongly recommended that efavirenz therapy be withheld in such cases and reevaluated once liver enzyme levels stabilize.

KEY WORDS: efavirenz, hepatitis, hypersensitivity, nonnucleoside reverse transcriptase inhibitors, rash.

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Based upon X-ray and clinical evidence, the patient was diagnosed with *Toxoplasma gondii* encephalitis (TE) and treated with pyrimethamine 75 mg daily and sulfadiazine 2 g 3 times daily. There was no documentation of other hepatotoxic agents such as alcohol or illicit drugs.

After one week of treatment the patient's encephalitis improved. He was discharged home on a regimen of pyrimethamine, sulfadiazine, azithromycin, and fluconazole. Four weeks after the initiation of TE treatment, the patient began HAART consisting of tenofovir 300 mg/emtricitabine 200 mg and efavirenz 600 mg, both taken once daily. Baseline transaminase levels at the initiation of treatment were slightly elevated (aspartate aminotransferase [AST] 28 U/L and alanine aminotransferase [ALT] 67 U/L). Total bilirubin and alkaline phosphatase (ALP) were normal (0.2 mg/dL and 82 U/L, respectively). Serologies for hepatitis A virus (HAV), hepatitis B virus, and hepatitis C virus (HCV) were all negative.

Eleven days after the initiation of HAART, the patient developed a generalized erythematous maculopapular rash which was prominent on his torso, neck, and proximal extremities. Hydroxyzine was prescribed for symptomatic treatment of the rash. In addition, fluconazole was discontinued, and the pyrimethamine and sulfadiazine doses were decreased by 50% to rule out possible involvement in the adverse reaction. Although the rash persisted, an attempt

was made to continue HAART treatment. The patient was instructed to continue efavirenz plus tenofovir/emtricitabine and return to the clinic if symptoms worsened.

The patient returned to the clinic 18 days after initiation of HAART, reporting burning epigastric pain accompanied by nausea, vomiting, and diarrhea. Laboratory studies revealed a marked increase in transaminase levels, with AST 455 U/L, ALT 699 U/L, total bilirubin 3.0 mg/dL, and ALP 1073 U/L (Figures 1 and 2). All medications were stopped immediately.

Upon discontinuation of efavirenz and tenofovir/emtricitabine, the patient's rash improved. However, he was admitted to the hospital 2 days later with nausea, vomiting, and diarrhea in addition to severe abdominal pain in the epigastric and peri-umbilical region. Liver enzymes had increased significantly, with AST 1162 U/L, ALT 1181 U/L, ALP 1362 U/L, and total bilirubin 4.2 mg/dL. The patient's temperature peaked at 39.5 °C on day 2 of hospitalization. He was diagnosed with drug-induced hepatitis and was treated with supportive therapy and aggressive intravascular repletion. Antiemetics were administered, and all other medications were withheld until further evaluation. Liver enzyme values peaked at AST 3410 U/L and ALT 2132 U/L 5 days after the discontinuation of HAART. The patient's international normalized ratio peaked at 2.6. The lactic acid level was normal at 10.8 mg/dL; however, both lactate dehydrogenase and

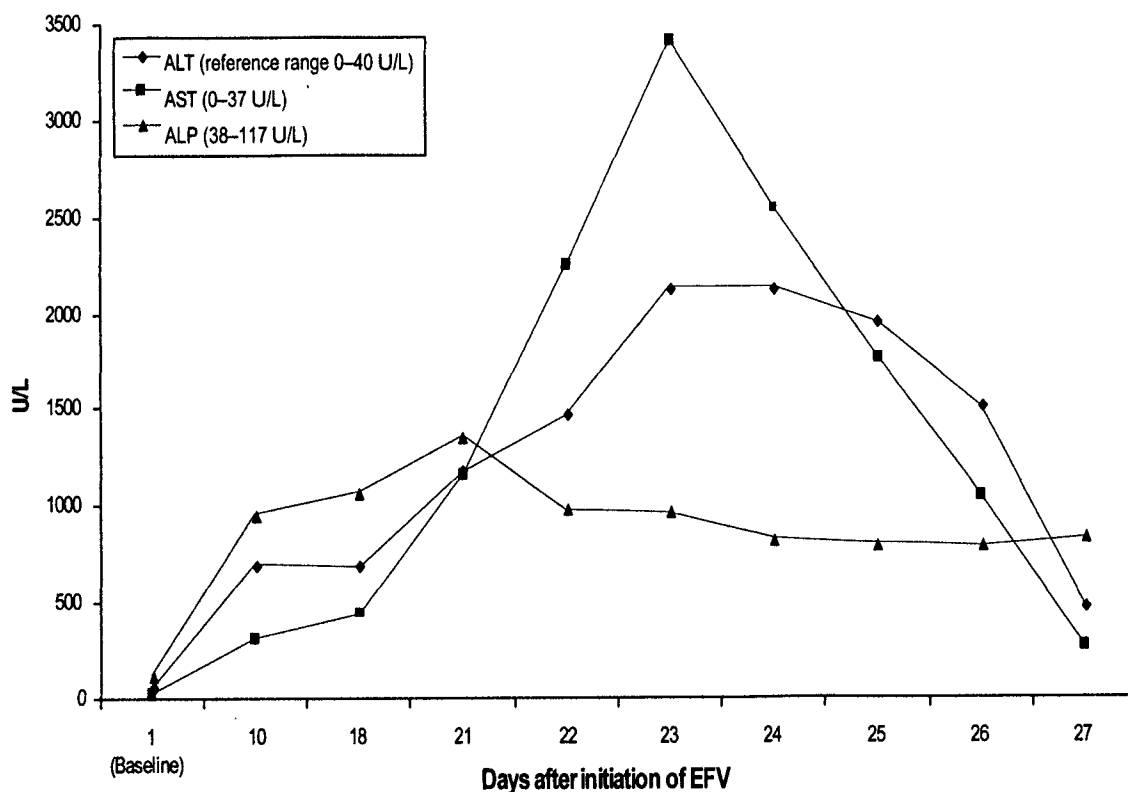


Figure 1. Changes in liver enzyme levels after initiation of EFV therapy. ALT = alanine aminotransferase, ALP = alkaline phosphatase, AST = aspartate aminotransferase; EFV = efavirenz.

blood ammonia were markedly elevated (644 U/L and 119 μ g/dL, respectively).

Upon the patient's discharge one week later, symptoms of hepatitis had largely resolved and transaminase levels had decreased (AST 271 U/L, ALT 488 U/L, ALP 840 U/L, total bilirubin 7.5 mg/dL). To rule out viral hepatitis, the patient underwent repeat testing for anti-HAV (immunoglobulin M) antibodies, hepatitis B surface antigen, anti-HCV antibodies, and a qualitative assay for HCV RNA. All results were negative. In addition, tests for antinuclear antibodies and serum ceruloplasmin were normal. The patient was subsequently lost to follow-up; however, he was readmitted to the hospital one year later with a TE exacerbation. At that time liver enzymes were within normal limits. The TE was treated with pyrimethamine and clindamycin. In addition, the patient was rechallenged with tenofovir/emtricitabine. Atazanavir 300 mg and ritonavir 100 mg were also added to complete the HAART regimen. All medications were tolerated without evidence of rash, fever, or hepatitis.

Discussion

Use of the Naranjo probability scale indicated a probable relationship between the hypersensitivity reaction con-

sisting of rash and hepatitis and efavirenz in our patient.⁵ Efavirenz treatment began 11 days prior to the onset of a rash and 18 days before the reported symptoms of acute hepatitis. However, other confounding factors make it difficult to prove unquestionable causality. One such variable is the concurrent initiation and discontinuation of tenofovir/emtricitabine and efavirenz 600 mg. The black box warning with tenofovir/emtricitabine describes lactic acidosis and severe hepatomegaly with steatosis.⁶ However, the patient's lactic acid levels were normal throughout the course of the adverse reaction. The onset of lactic acidosis secondary to mitochondrial toxicity rarely occurs during the initiation of treatment.⁷ In addition, the patient is currently being treated with tenofovir/emtricitabine and a boosted protease inhibitor regimen with no adverse effects. Although the time of initiation and discontinuation of both medications was the same, it is highly unlikely that the rash and hepatitis can be attributed to tenofovir/emtricitabine. Another confounding variable is treatment with sulfadiazine, which has been associated with hepatotoxicity, although it seems unlikely due to the timing of the reaction. However, it cannot be ruled out that sulfadiazine, which was initiated over one month before the onset of rash and acute hepatitis, may have contributed to the susceptibility of the efavirenz adverse event.

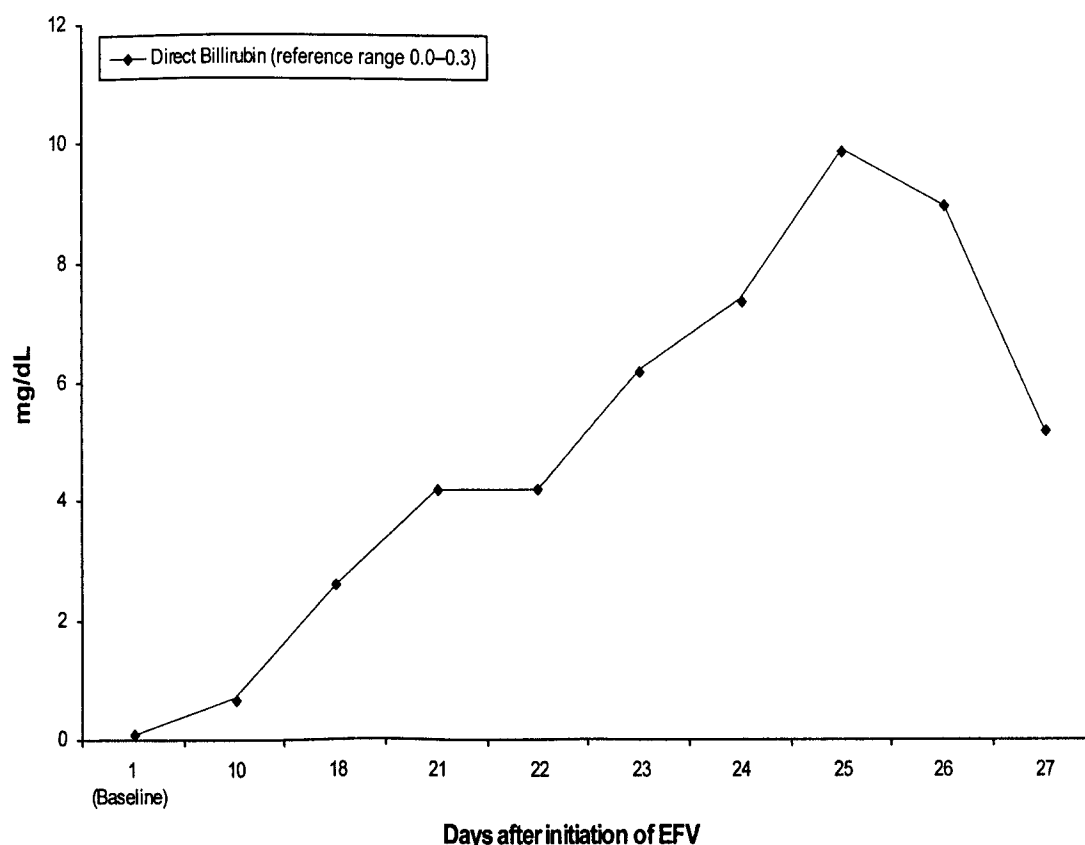


Figure 2. Changes in direct bilirubin after initiation of EFV therapy. EFV = efavirenz.

A review of the literature revealed 2 similar cases of hypersensitivity and hepatotoxicity associated with initiation of efavirenz therapy. The first case involved a 30-year-old HIV-positive woman (CD4 26 cells/mm³, viral load 5.7 log₁₀ copies/mL) who presented with a skin rash 7 days after the initiation of efavirenz, stavudine, and lamivudine.⁸ Three days later she developed jaundice and liver dysfunction, subsequently leading to liver failure. The patient's liver failure was complicated by disseminated intravascular coagulation, which ultimately led to her death.

The second case involved a 44-year-old HIV-positive woman from the Ivory Coast who presented with skin rash followed by acute hepatitis 20 days after beginning efavirenz, stavudine, and lamivudine.⁹ This patient was admitted to the hospital with fever, diffuse maculopapular rash, abdominal pain, jaundice, diarrhea, and dry cough. In addition, liver enzymes were elevated more than 5 times the upper limit of normal. Her symptoms resolved one week after discontinuation of all drugs and initiation of treatment with methylprednisolone. She had previously been treated for *T. gondii* encephalitis. However, she started sulfadiazine/pyrimethamine therapy 3 months prior to the first appearance of hypersensitivity; therefore, the reaction was attributed to efavirenz therapy.

An additional case of possible efavirenz-induced hepatotoxicity was reported in a study testing the concomitant use of efavirenz and the antimalarial drugs amodiaquine and artesunate.¹⁰ Five healthy HIV-negative individuals were enrolled. However, the study was discontinued prematurely when the first 2 participants experienced an increase in transaminase levels. The first subject, a 51-year-old African American man, had a peak AST of 78 U/L and ALT of 206 U/L. The second subject, a 26-year-old white woman, displayed a peak AST of 559 U/L and ALT of 868 U/L 42 days after completion of the trial. It is not clear whether she was symptomatic at the time that her transaminase levels were increased. Of note, this woman had ingested significant amounts of alcohol after the study was completed. The onset of increased transaminase levels occurred at a much later time course in this study than in our patient, as well as the other cases reported here. Furthermore, the participants in this study did not experience rash or fever.

The pharmacokinetic profile of efavirenz is consistent with the timing of this adverse drug reaction. The half-life of a single dose of efavirenz ranges from 52 to 76 hours.¹¹ In addition, efavirenz undergoes auto-induction of its metabolism, which usually occurs within 10 days of the initiation of treatment. Once autoinduction is complete, the half-life of efavirenz ranges between 40 and 55 hours. The extended half-life of efavirenz may explain the prolonged rise in liver enzymes and severe hepatitis that continued to occur in our patient once the drug was discontinued.

CYP2B6 is responsible for almost 90% of the clearance of efavirenz. Studies have demonstrated a significant in-

terindividual variability in the isoenzyme activity of CYP2B6, thereby altering the hepatic clearance of efavirenz.¹² Studies have also described a potential link between the homozygous recessive genotype and ethnicity.¹²⁻¹⁴ Data from a pharmacokinetic study showed that efavirenz concentrations were higher in both black and Latino patients compared with those in white patients.¹⁴ Patients with higher plasma concentrations of efavirenz have been shown to be at an increased risk of central nervous system adverse effects.¹⁵ Although concentration-dependent hepatotoxic adverse effects have not been studied with efavirenz, this cannot be ruled out. Unfortunately, we did not obtain pharmacogenomic or pharmacokinetic data on our patient. In addition, due to the drug-induced hepatitis, it is highly probable that this patient's liver was impaired when transaminase levels peaked, resulting in a decreased clearance of efavirenz.

Conclusions

Although such a hypersensitivity reaction is rare with efavirenz, the drug was the most probable cause of the erythematous maculopapular rash, fever, and acute hepatitis in our patient. In practice, clinicians have continued treatment with efavirenz in the presence of rash. However, based upon our case, if a patient has rash with the initiation of efavirenz, liver enzymes should be assessed, even if the patient is asymptomatic. Clinicians should exercise caution in patients presenting with rash, fever, and increased liver enzyme levels (>3 times the upper limit of normal or patient baseline). It is strongly recommended that efavirenz therapy be withheld in such cases and that its use be reevaluated once liver enzyme levels stabilize.

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Una Reacción de Hipersensibilidad Asociada con Efavirenz Manifestando en la Erupción y la Hepatitis de un Hombre Latino

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EXTRACTO

OBJETIVO: Informar un episodio de hipersensibilidad que se manifestó con erupción cutánea, fiebre y hepatitis severa en un paciente que comenzó tratamiento con efavirenz (EFV).

RESUMEN: El paciente descrito es un hombre latino de 30 años de edad, recién diagnosticado con infección por HIV. El paciente desarrolló una reacción de hipersensibilidad que se manifestó con una erupción cutánea y fiebre seguido por una hepatitis severa, once días luego de haber comenzado terapia antirretroviral altamente efectiva (HAART). Los valores de las enzimas hepáticas llegaron a alcanzar valores máximos de AST/ALT de 3410/2132 unidades/L. La hepatitis resolvió al discontinuarse la terapia antirretroviral.

DISCUSIÓN: Al utilizar la escala de probabilidad de efecto adverso de Naranjo, ésta demostró una relación probable entre la reacción adversa y el efavirenz. Una búsqueda que utilizó la base de datos de MEDLINE, reveló otros dos casos de reacción cutánea precediendo la hepatitis asociada con el uso de efavirenz. Ambos casos descritos fueron en mujeres, y no se encontraron casos previos de hipersensibilidad reportados en hombres. Aunque el mecanismo por el cual esta reacción ocurre no es conocido, algunos factores pudieron haber contribuido. La vida media ($t_{1/2}$) de autoinducción de efavirenz puede explicar el continuo aumento de los valores de las enzimas hepáticas y la hepatitis severa que continuó aún

después de haberse discontinuado la droga. Otro factor que puede haber contribuido es el metabolismo de efavirenz. Casi un 90% del metabolismo del fármaco ocurre mediante la isoenzima CYP2B6. Datos provenientes de un estudio farmacocinético reciente demostraron que las concentraciones de efavirenz eran mayores en pacientes negros y latinos en comparación con pacientes caucásicos.

CONCLUSIONES: El uso de efavirenz es la causa más probable de la reacción de hipersensibilidad con erupción cutánea maculopapular y hepatitis aguda en este paciente. Se recomienda el seguimiento de los valores de enzimas hepáticas en pacientes que se presentan con reacciones cutáneas luego de comenzar un régimen antirretroviral que contiene efavirenz. Además, los proveedores de cuidado de salud deben de ser cautelosos en pacientes que presentan con erupción cutánea, fiebre, y aumento en los valores de las enzimas hepáticas (más de 3 veces el valor normal o el valor base del paciente). Se recomienda que en estos casos se discontinue el efavirenz y que se evalúe el paciente una vez las enzimas hepáticas se estabilicen.

Traducido por Wanda T Maldonado

Une Réaction d'Hypersensibilité Associée à l'Éfavirenz se Manifestant par une Rougeur et une Hépatite Chez un Jeune Latino
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RÉSUMÉ

OBJECTIF: Signaler un cas d'hypersensibilité se manifestant par une rougeur, une fièvre, et une hépatite menaçante pour la vie après l'introduction de l'Éfavirenz (EFV) chez un patient.

PRÉSENTATION SOMMAIRE DU CAS: Le patient décrit est un jeune latino âgé de 30 ans chez qui on a récemment diagnostiqué une infection au VIH. Onze jours après l'introduction d'une thérapie antirétrovirale hautement active (TARHA) à base d'EFV, il a développé une réaction d'hypersensibilité se manifestant par une rougeur et une fièvre suivies d'une hépatite grave d'origine médicamenteuse. Les résultats des enzymes hépatiques AST/ALT ont culminé à 3410/2132 unités/L. L'hépatite s'est résolue avec l'arrêt de la TARHA.

DISCUSSION: Le résultat obtenu avec l'échelle d'imputabilité des effets indésirables de Naranjo a démontré un lien probable entre cet effet indésirable et l'EFV. Une recherche MEDLINE a révélé 2 cas de rougeurs ayant précédé une hépatite lors de l'introduction de l'EFV. Ces 2 cas se sont produits chez des femmes; aucun cas d'hypersensibilité associée à l'EFV n'a encore été signalé chez l'homme. Bien que le mécanisme de cette réaction soit inconnu, il y a quelques facteurs pouvant contribuer à cette réaction. La demi-vie et l'auto induction de l'EFV peuvent expliquer l'élévation continue des tests de la fonction hépatique, et l'hépatite grave survenue une fois le médicament cessé. Une autre cause pouvant avoir contribué est le métabolisme de la médication. Le cytochrome CYP2B6 est responsable pour presque 90% pour cent de la clairance de l'EFV. Les données d'une étude de pharmacocinétique récente ont démontré que les concentrations d'EFV sont plus élevées chez les patients noirs et chez les latino par rapport aux patients blancs. De plus, il est fort probable que le foie du patient se soit altéré lors de l'élévation culminante des transaminases, résultant en une diminution de la clairance de l'EFV.

CONCLUSIONS: L'EFV est la cause la plus probable de la réaction d'hypersensibilité s'étant manifesté par un érythème maculopapulaire et une hépatite aigue chez ce patient. Le suivi de la fonction hépatique chez les patients qui présentent une rougeur après l'introduction d'une TARHA à base d'EFV est recommandé. De plus, les cliniciens devraient user de prudence chez les patients présentant une rougeur, de la fièvre, et une augmentation des tests de la fonction hépatique (au-delà de 3 fois la limite supérieure de la normale ou des valeurs de base du patient). Il a été fortement recommandé que la thérapie à base d'EFV soit suspendue chez ce patient et qu'elle soit évaluée de nouveau lorsque les tests de la fonction hépatique seront stabilisés.

Traduit par Marie Larouche