Cutaneous toxicities of antiretroviral therapy for HIV

Part II. Nonnucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome

Camille E. Introcaso, MD,[a] Janet M. Hines, MD,[b] and Carrie L. Kovarik, MD[a,b]
Philadelphia, Pennsylvania

Cutaneous manifestations of antiretroviral medications for HIV are common and potentially dangerous conditions encountered by dermatologists. Part II of this two-part series on the cutaneous effects of antiretroviral medications for HIV will discuss the four most recent classes of medications that have been developed and immune reconstitution syndrome—an important diagnostic consideration when evaluating a dermatologic patient who is taking antiretroviral medications. (J Am Acad Dermatol 2010;63:563-9.)

Learning objectives: After completing this learning activity, participants should be able to recognize common and dangerous cutaneous adverse effects related to nonnucleoside reverse transcriptase inhibitors and entry and fusion inhibitors, determine which of these toxicities need further investigation or medication cessation, and understand the dermatologic manifestations of immune reconstitution syndrome and their importance in the differential diagnosis of a drug reaction in HIV-positive patients.

Key words: antiretroviral medications; cutaneous; drug eruption; HIV; immune reconstitution syndrome; toxicities.

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Key points

- **Nonnucleoside reverse transcriptase inhibitors are the most frequent class of antiretrovirals to cause morbilliform exanthems**
- **Morbilliform eruptions related to nevirapine may become severe and be associated with systemic hypersensitivity reactions; therefore, the introduction of nevirapine at a low dose with escalation over a 2-week period is recommended**

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) were the third class of antiretroviral medications to be developed. These medications bind at a site distant to the active site of the HIV reverse transcriptase enzyme and prevent conversion of RNA to DNA (Fig 1). Currently, there are four drugs in the NNRTI class that are approved by the US Food and Drug Administration (FDA) for combination treatment of HIV. At least one other NNRTI, rilpivirine, is currently undergoing clinical trials. In general, medications in this class are known to cause a high incidence of morbilliform eruptions during the first month of therapy. Many of these eruptions resolve despite continuation of therapy; however, a patient must be closely observed during an eruption because Stevens–Johnson syndrome (SJS) and systemic hypersensitivity syndromes have also been reported with NNRTIs. One report has associated a previous reaction to sulfa drugs with a higher likelihood of developing a morbilliform eruption when exposed to NNRTIs,[1] but this point remains controversial and is not the experience of most clinicians. However, because of the possibility of a morbilliform eruption occurring with either a sulfa drug or an NNRTI, the simultaneous initiation of both classes

From the Department of Dermatology[a] and the Division of Infectious Diseases,[b] Department of Internal Medicine, University of Pennsylvania, Philadelphia.

Funding sources: None.

Dr Hines has been on the advisory board for Abbot, Boehringer Ingelheim, Bristol Meyers, Gilead, and GlaxoSmithKline, and has been a speaker for Boehringer Ingelheim, Bristol Meyer, and GlaxoSmithKline. Drs Introcaso and Kovarik and the editors, planners, and peer reviewers have no relevant financial relationships.

Reprint requests: Carrie L. Kovarik, MD, Departments of Dermatology and Internal Medicine, Division of Infectious Disease, University of Pennsylvania School of Medicine, 2nd fl, Maloney Bldg, 3600 Spruce St, Philadelphia, PA 19104. E-mail: carrie.kovarik@uphs.upenn.edu.

0190-9622/$36.00

doi:10.1016/j.jaad.2010.02.059

can cause difficulty in isolating the single cause of the eruption.

Nevirapine

Approved by the FDA for HIV treatment in 1996, nevirapine was the first drug developed representing the NNRTI class. The most common and some of the most potentially dangerous side effects of nevirapine are skin toxicities; a morbilliform eruption has been described in 13% to 19% of patients and in as high as 28% in some populations.[2,3] In addition, a systemic hypersensitivity reaction or severe rash has been seen in as many as 8% of patients.[4] Nevirapine has a black box warning because of potentially fatal hepatitis, and one half of the patients who develop hepatitis do so in the setting of a rash and other signs of a hypersensitivity reaction.[5] Liver enzymes must be checked in any patient on nevirapine who develops skin findings, and if a morbilliform exanthem occurs in the setting of a fever, hepatitis, or other systemic symptoms, nevirapine must be discontinued immediately.

CAPSULE SUMMARY

- Multiple new classes of antiretroviral medications have been developed in the last 2 decades.
- Nonnucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, and integrase inhibitors have common and potentially serious skin manifestations.
- Immune reconstitution syndrome is an inflammatory condition that may occur when HIV patients are started on antiretroviral medications, and must be considered in the differential diagnosis of a patient with a skin complaint who is taking antiretroviral therapy.

Many studies have investigated the possible risk factors for development and treatment of nevirapine-associated exanthems and hypersensitivity reactions. There is evidence to suggest that patients with higher CD4 cell counts, including patients using nevirapine as postexposure prophylaxis, have a higher risk of systemic hypersensitivity reaction, and therefore nevirapine is not recommended as part of postexposure prophylaxis regimens.[6-10] Some studies also show an association between female sex and development of a morbilliform eruption without a systemic hypersensitivity reaction.[3,8,11,12]

Other adverse effects of nevirapine have included case reports of oral ulcers (Fig 2) and cases of acute generalized exanthematous pustulosis, both of which resolved with discontinuation of nevirapine, and a patient with the development of a white plaque on the buccal mucosa associated with xerostomia and a burning sensation that resolved following cessation of nevirapine.[13-15] SJS has also been reported in association with nevirapine, and nevirapine is one of the more common causes of SJS in the developing world, where nevirapine is frequently used[2,4,16,17] (Fig 3).

Although oral glucocorticoids and cetirizine have been shown to be ineffective in preventing nevirapine-associated hypersensitivity, an escalating dose scale for nevirapine has been established that decreases the risk of systemic hypersensitivity reaction.[18,19] It is now recommended that adult doses of nevirapine are started at 200 mg per day for 2 weeks, and that the dose is only increased to the standard 400 mg per day if there is no rash (or if a rash is not worsening) at the end of the 2-week trial period.[19] As mentioned, the development of fever in the presence of a rash during the first several weeks of nevirapine treatment should prompt discontinuation of the drug and indicate monitoring for systemic hypersensitivity.

Delavirdine

Delavirdine was approved for combination therapy of HIV in 1997; however, because of its lower efficacy than other medications and its dosing schedule of three times per day, it is not indicated for initial treatment. It also has a complex set of drug interactions related to its metabolism by the cytochrome P450 system, and for all of these reasons delavirdine is rarely used in clinical practice at this time. In clinical trials, between 18% and 50% of patients taking delavirdine were reported to have a diffuse, pruritic rash, usually in the first 2 months of therapy.[20-22] Therapies included topical and oral steroids and antihistamines, and a low percentage of patients required treatment cessation. Oral ulcers have also been reported to be associated with delavirdine.[13]

Efavirenz

Efavirenz is an NNRTI that is currently recommended as part of initial therapy for treatment naïve patients, and is one of the medications that makes up a triple drug combination pill (with tenofovir and emtricitabine) that allows for an only one-pill, once per day dosing regimen. In the mid-2000s, efavirenz became the first-line backbone of treatment over protease inhibitors for adults and children and was a preferred component of postexposure prophylaxis regimens, making it one of the most commonly encountered antiretroviral drugs.[23-25] Common toxicities include neuropsychiatric effects, such as