Cutaneous toxicities of antiretroviral therapy for HIV

Part I. Lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors

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Antiretroviral medications for the treatment of HIV are common drugs with diverse and frequent skin manifestations. Multiple new cutaneous effects have been recognized in the past decade. Dermatologists play an important role in accurately diagnosing and managing the cutaneous toxicities of these medications, thereby ensuring that a patient has as many therapeutic options as possible for life-long viral suppression. Part I of this two-part series on the cutaneous adverse effects of antiretroviral medications will discuss HIV-associated lipodystrophy syndrome, which can be seen as a result of many antiretroviral medications for HIV, and the specific cutaneous effects of the nucleoside reverse transcriptase inhibitors and protease inhibitors. (J Am Acad Dermatol 2010;63:549-61.)

Learning objectives: After completing this learning activity, participants should be able to recognize common and dangerous cutaneous adverse effects related to nucleoside reverse transcriptase inhibitors and protease inhibitors, including lipodystrophy syndrome, determine which of these toxicities need further investigation or medication cessation, and manage the treatment of these cutaneous toxicities.

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

Over the past 2 decades, multidrug antiretroviral therapy for patients infected with HIV has become the standard of care. Long-term viral suppression, increases in CD4 cell counts, decreases in opportunistic infections, and improvement in mortality have all resulted from combination antiretroviral therapy. Dermatologists must be familiar with the toxicities associated with antiretrovirals for multiple reasons. First, the epidemic continues to be far-reaching, with 1.2 million Americans estimated to be infected in 2007 and new infections outnumbering deaths.[1] A large proportion of the affected population is taking antiretrovirals, making them commonly prescribed drugs. Second, current therapy is not curative and requires multiple agents, so most patients will need to take several drugs for much or all of their lives. Third, the severity of the HIV epidemic continues to pressure the US Food and Drug Administration (FDA) to approve medications quickly, possibly without as much investigation into or caution regarding adverse events. Clinicians may encounter toxicities that were absent or underrepresented in preapproval clinical trials, so that the drug prescribing information may not be the most reliable source of information about adverse effects. Fourth, there are approximately 30 medications that fall into six classes for treatment of HIV, resulting in protean combinations of drugs, each with its own interactions and toxicities (Table I).

Cutaneous adverse effects are one of the most common toxicities of antiretroviral medications in patients of all ages, all races, and with all of the various combinations of therapies available.[2-9] In addition to the inherent risk of cutaneous side effects from the medications themselves, patients with HIV are at increased risk for immune-mediated cutaneous reactions to medications of any type, likely

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because of immune dysregulation. Morbilliform exanthems, systemic hypersensitivity reactions, lipodystrophy, pigmentation changes, and injection site reactions are examples of some of the frequently seen skin manifestations. These toxicities range from the serious and life threatening to cosmetic or annoyances; however, it has been shown that concerns about cosmetic skin-related side effects can lead to medication noncompliance with devastating results: loss of virologic control, development of resistance, and loss of efficacy of multiple drugs because of cross-resistance.[10] Dermatologists can recognize and treat these toxicities, and we can work with infectious disease specialists to determine if a medication needs to be discontinued. Because of the frequent development of resistance and the need to preserve as many medications as possible for patients' future use, it is imperative to make an accurate assessment about which drug is causing a cutaneous toxicity and to withhold the drug only if necessary.

CAPSULE SUMMARY

- Nuceloside reverse transcriptase inhibitors and protease inhibitors are classes of antiretroviral medications that are widely used and have diverse and frequent skin manifestations.
- Lipodystrophy syndrome is a common adverse effect of many of the classes of antiretrovirals and consists of metabolic and cutaneous abnormalities.
- Dermatologists play an important role in accurately diagnosing cutaneous toxicities of antiretroviral medications, ensuring that a patient has as many therapeutic options as possible for lifelong viral suppression.

ANTIRETROVIRAL-ASSOCIATED LIPODYSTROPHY SYNDROME

Key points

- **Antiretroviral-associated lipodystrophy syndrome can have a combination of lipoatrophy, lipohypertrophy, and metabolic abnormalities**
- **Lipodystrophy is most strongly associated with certain protease inhibitors and nucleoside reverse transcriptase inhibitors**
- **Poly-L-lactic acid and calcium hydroxylapatite are injectable fillers approved by the US Food and Drug Administration for restoration of facial fat loss in patients with HIV**

Antiretroviral-associated lipodystrophy syndrome is one of the most common cutaneous toxicities of antiretroviral medications. Members of the nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes of medications—and, less commonly, nonnucleoside reverse transcriptase inhibitors (NNRTIs)—have been implicated in causing this syndrome. Lipodystrophy syndrome consists of changes in body fat composition and is often seen in association with metabolic abnormalities.[11] The characteristic changes include a loss of fat in the face, limbs, and buttocks and the accumulation of dorsocervical and abdominal visceral fat and gynecomastia[12,13] (Fig 1). Lipohypertrophy or lipoatrophy is sometimes seen alone, but these changes often appear together and result in patients with a Cushingoid appearance. The metabolic abnormalities that may occur include insulin resistance, hyperinsulinemia and a resulting hyperglycemia, and dyslipidemia. These changes can put patients at risk for pancreatitis at any point during therapy and increase their risk of atherosclerotic disease over years of treatment. In addition, the recognizable facial appearance of temporal and buccal fat pad wasting creates an opportunity for stigmatization of the patient by the public[10] (Fig 2). Although this constellation of signs and metabolic abnormalities was first associated with PI therapy, it is now recognized as a side effect of NRTIs, particularly stavudine and the combination of stavudine and didanosine with or without PI therapy, and NNRTIs, specifically efavirenz.[14-17] The time course for development of lipodystrophy ranges from several months to 2 years, with changes in limb and waist circumference apparent in up to 35% of patients after 2 years of therapy.[12]

Management of the metabolic abnormalities of the lipodystrophy syndrome includes a balanced diet, regular exercise and, when appropriate, lipid- and glucose-lowering medications. Dermatologists should ensure that patients who present with appearance-related effects of lipodystrophy syndrome are adequately screened for metabolic disease by their primary care doctors or other appropriate specialists. It is unclear whether or not the risks of stopping or switching antiviral therapy are balanced by the potential cardiovascular and metabolic benefits, and such changes are not generally recommended.[12] Although a variety of studies have shown fractional long-term improvements in some of the appearance-related parameters of lipodystrophy when regimens are changed, these improvements are modest and often not perceived as significant by the patient.[18] Dermatologists play a significant role in the treatment of facial lipoatrophy