HIV Skin Complications in the Age of HAART

An Interview with Toby Maurer, MD

Bruce Mirken

Various dermatological conditions have been associated with HIV disease since the beginning of the AIDS epidemic. The purple lesions characteristic of Kaposi's sarcoma (KS) became a symbol for this modern plague. Other skin complications—such as herpes zoster (shingles), herpes simplex, and molluscum contagiosum—were so common that they sometimes were regarded as informal markers of immune deficiency.

While seborrheic dermatitis (discussed later) often appeared with only moderate immune system impairment, other conditions characteristically appeared in the wake of more severe immune depletion and at relatively predictable points. Molluscum contagiosum, for example, was commonly seen when a person's CD4 cell count dropped below 100 cells/mm³, and certain types of fungal infections almost always appeared with a CD4 cell count lower than 50 cells/mm³.

Though generally not lethal, many skin complications are painful, disfiguring, and devastating to a person's self-image and sense of well-being. Like so much in the HIV epidemic, the incidence and occurrence of dermatological conditions have changed dramatically since widespread use of highly active antiretroviral therapy (HAART) began in 1996. Many, but not all, of the common skin problems associated with HIV disease are seen far less frequently now than they were just a few years ago. On the other hand, dermatological manifestations of toxicities associated with drug therapy have emerged as a new problem.

Recently, BETA sat down with Toby Maurer, MD, Assistant Professor of Medicine at the University of California at San Francisco (UCSF) and Chief of Dermatology at San Francisco General Hospital (SFGH), for an update on dermatological issues in the age of HAART.
The Pre-HAART Era

Dr. Maurer noted that changes were occurring in the patterns of HIV-related skin problems she was seeing well before the HAART era. Such changes were most likely due to the widespread adoption of TMP-SMX (Bactrim, Septra) as the first-line *Pneumocystis carinii* pneumonia (PCP) prophylaxis drug at the beginning of the 1990s. Before that time, "the majority of [dermatological] illnesses had to do with staphylococcal (or staph) infection," she explained. "There were a lot of different presentations of staph at the time," including folliculitis—inflammation of the hair follicles—and "conditions that we called staph plaques: large, itchy areas of staph infection on the skin."

Like most HIV-associated skin conditions, staph infections are not unknown among HIV negative people. However, Dr. Maurer and her colleagues saw them far more commonly in people with HIV-damaged immune systems, in whom the conditions were generally more severe and more resistant to treatment. During this period, staph infections, more than any other HIV-associated skin condition, brought people seeking relief to the Dermatology Clinic.

Unlike other dermatological complications that remained quite common until the HAART era, bacterial skin infections began to recede from prominence in the early 1990s. Dr. Maurer claimed that staph infection levels fell considerably because TMP-SMX suppressed them at the same time that it prevented PCP.

Other skin problems started to materialize. "We began seeing things like eosinophilic folliculitis, a type of folliculitis specific to HIV infection," she explained. This red, itchy, acne-like skin eruption appears similar to staph folliculitis. The condition, which Dr. Maurer noted was "really bothersome to patients," is not caused by bacteria or fungi; in fact, the exact cause remains unknown. Eosinophilic folliculitis is most often seen in persons with a CD4 cell count below 200 cells/mm³. By 1995 it had become one of the most common HIV-related skin conditions Dr. Maurer was seeing.

Most likely, Dr. Maurer observed, these non-staph-related conditions were becoming more noticeable because the staph infections were no longer obscuring or masking them—that is, they were increasingly identified rather than increasing in incidence. She and her colleagues were likewise becoming more aware of a variety of other complications, including an outbreak of molluscum contagiosum. This viral skin infection is characterized by smooth, waxy bumps with navel-like indentations that can grow as large as a pea but are often smaller. While not considered as unpleasant as some
dermatological problems—the bumps generally are not painful or itchy—molluscum contagiosum can be a significant annoyance and were very difficult to treat.

Other skin conditions common prior to HAART included herpes simplex and herpes zoster. Herpes simplex type I primarily produces "fever blisters" or "cold sores" on the lips, while herpes simplex type II preferentially infects and causes recurrent sores on the genital or anal areas. Occasionally, either virus produces symptoms in other parts of the body as well. Persons with HIV-damaged immune systems generally experience more severe and prolonged herpes outbreaks than HIV negative people do; outbreaks of both types of herpes simplex can be painful and quite unpleasant.

Herpes zoster, the virus that causes chicken pox in childhood, can be reactivated to produce an itchy skin eruption often called "shingles." It occurs in a stripe or patch distribution on one side of the body. Inflammation of the affected nerves can make this extremely painful, even after the rash has resolved. In persons not taking HAART, the appearance of shingles is often an early warning sign of possible HIV infection and immune system damage.

Psoriasis is one skin disorder that seemed to decrease in frequency by the mid-90s even without HAART, Dr. Maurer noted. Characterized by pink, scaly, itchy patches, psoriasis in people with HIV tended to be more treatment-resistant than in HIV negative individuals. Dr. Maurer believes that the reduction in staphylococcus again can be credited for influencing the change in psoriasis incidence, since "staph, we know, definitely exacerbates psoriasis."

As for KS, doctors at SFGH were seeing it frequently while the rest of the country was reporting a gradual decline in incidence, even prior to HAART. "Even when they were reporting decreases in KS elsewhere, we were still seeing plenty of it," Dr. Maurer said. "That may have to do with the epidemiology of KS in gay males, which was primarily the group that we were seeing." KS is caused by another sexually transmitted herpesvirus called KSHV or HHV-8.

Seborrheic dermatitis, a red, itchy, flaky rash most often seen on the face, was also common before HAART. Incidence of photodermatitis, or sun sensitivity, also continued and even increased slightly. Although photodermatitis is usually caused by drugs, including TMP-SMX and dapsone, which are used for PCP prophylaxis, Dr. Maurer added that "HIV itself makes people photosensitive."

Somewhat surprisingly, dark-skinned people tend to experience more sun sensitivity than light-skinned individuals. "You would expect people with more
pigment in their skin to be protected from the sun, but among those with HIV who were taking these certain drugs, more pigment often meant more photosensitivity. African-Americans, for instance, are more photosensitive."

The HAART Era

By the summer of 1996, the use of HAART, most commonly in the form of two nucleoside drugs plus a protease inhibitor, had become common at SFGH-and the dermatological changes were swift and dramatic. "KS certainly turned the corner," Dr. Maurer recalled. "For about an 18-month period we had no [new cases of] KS, whereas previously we had been diagnosing it three to five times a week." Those who had KS prior to beginning HAART generally saw their lesions fade away with no treatment other than their antiretroviral therapy.

Other changes were equally dramatic, according to Dr. Maurer. "We also found molluscum disappearing. People for whom treatment never worked & suddenly were receiving HAART and the molluscum was resolving." Many other dermatologic complications, like opportunistic infections (OIs) in general, have been seen less frequently in the presence of HAART-induced immune recovery.

Some skin problems, however, seem unaffected by HAART. "Interestingly enough, warts seem prevalent. I don't know if they're more widespread or not, but we are seeing many cases of warts, genital warts as well as those on the hands and feet, and we're trying to figure out why this is so. Is it because we've gotten rid of other diseases and warts are remaining? There are people who believe that perhaps with higher CD4 cell counts and low HIV viral loads, certain cytokines are being released that stimulate warts. Or do the antiretroviral drugs stimulate them?"

One hopeful sign, though, is that "as CD4 cell counts are increasing to greater than 400 cells/mm³, some of those warts seem to disappear." It is too early to tell if this is a meaningful trend, however. In a study of HIV positive women, Deborah Greenspan, DSc (Doctor of Science), FDS (Fellow in Dental Surgery), from UCSF has reported a definite increased incidence of oral warts in the HAART era, compared with the pre-HAART era.

Another important dermatologic issue in HIV disease relates to adverse reactions to drugs, such as rashes and photosensitivity, which also began to change as HAART came into use. However, these changes have come in somewhat unexpected and confusing patterns-some people experience new or worsened drug reactions while others have drug allergies that seem to disappear. "Drug reactions were always prevalent," Dr. Maurer explained.
"In 1991, you'd see people with low CD4 cell counts who had a lot of drug reactions. They'd say, I'm allergic to this drug, that drug, and that drug and they were allergic to those drugs, and more."

Such a scenario seems counterintuitive: a weakened immune system ought to be less able to react to foreign irritants. But according to Dr. Maurer, when CD4 cell counts are low, people seem to develop a host of drug allergies. This increase may be related (as with warts) to altered cytokines or increased CD8 cell counts. At the same time, an elevation in antibody production triggers increased allergic reactions.

"What about drug allergies in the era of HAART? They didn't entirely disappear, but with people's CD4 cell counts rising [there were] maybe not as many, although we're looking at that data now."

Sometimes things seem to get worse before improving. "What can happen, I think, is that with the initial boost of CD4 cells, people are suddenly able to mount an immune response. So sometimes there will be a drug reaction when starting antiretrovirals. And I'm not sure if it's a real drug reaction or a rapid [immune] reconstitution" that generates inflammatory responses that fade over time. For example, studies have shown an increased risk of herpes zoster (shingles) within the first six months after starting HAART.

Dr. Maurer said she often hears from primary care physicians about someone who has started taking antiretroviral drugs and has "begun to turn red and somewhat itchy within the first few weeks of therapy, although not enough to stop therapy. Most health-care providers will continue treatment unless there are other signs and symptoms such as fever, blisters, and body aches." It is important for people experiencing drug reactions to consult their doctors at once. Initial drug reactions commonly fade as time passes, however, and Dr. Maurer emphasized, "That's an important message: not to stop therapy, because this in fact may be a reaction to starting medication and not a true drug allergy. With the protease inhibitors and most nucleoside analogs, there really aren't that many [dermatologic] drug reactions."

There are exceptions, though, and some drugs produce characteristic skin reactions that require careful attention. "Nevirapine (Viramune) and delavirdine (Rescriptor) [non-nucleoside reverse transcriptase inhibitors] are a little different in that people on either of those two drugs sometimes turn red—not necessarily itchy, but beet red." This is most likely a true drug reaction, she explained. With these drugs, "if the person can't be treated through (continue therapy) with regard to their redness, you usually have to stop the drug."
Another drug that may produce significant skin reactions is abacavir (Ziagen), a nucleoside analog drug. "Hives and all kinds of severe skin reactions have been associated with it," Dr. Maurer said. Abacavir can cause a rash that is always preceded by a fever and sometimes by flu-like symptoms. This type of hypersensitivity reaction can be life-threatening. "Nevirapine, delavirdine, and abacavir-those are the ones to watch in terms of drug reactions for dermatologic concerns."

Some people experience allergic reactions as their CD4 cell counts rebound, even though they had no drug allergies when their immune systems were suppressed. After stabilizing on HAART and improving clinically, some people "suddenly mount an immune response to some of the antibiotic medicines they had been on for some time, like TMP-SMX or clarithromycin (Biaxin). They've been fine, their CD4 cell counts are increasing, their viral loads are decreasing, and suddenly they get what looks exactly like a TMP-SMX reaction, even though they've been taking the drug for years. I think it's because they can now mount an immune response."

This may require the primary care provider to review all the drugs a person is taking and consider what might be causing the allergy. Reviewing these prescriptions with a pharmacist or dermatologist may be helpful. "I will often stop the antibiotics before stopping HAART," Dr. Maurer said. "That's the key question: is there also something else that could be causing this allergic reaction besides HAART? The answer is usually yes."

TMP-SMX photosensitivity "has not gone away with the [increasing] CD4 cell counts," she added. "People notice darkening of their skin." For that problem, Dr. Maurer recommends "plenty of sunscreen-and certainly don't stop HAART." Long pants, long-sleeved shirts, and wide-brimmed hats are also helpful. People may assume that their HAART drugs are causing the problem, but often the reason is simply too much sun-which may only have become an issue as improved health allows them to go outside more often.

So, Dr. Maurer explained, the overall picture regarding drug reactions is mixed and "very odd." Inconsistent patterns can be confusing as well for people with HIV, who may be unsure when or if they should call their doctor about a skin reaction that might be drug-related.

Dr. Maurer's advice: when in doubt, check with a health-care provider. "People should definitely call about any drug rash they have & when they start new medications." When talking to providers, people "should bring in all the medications that they are taking and discuss them. It may not be the HAART that's causing [the rash]; it may be something else."
It is necessary to consult a health-care provider, she emphasized, because "there are some kinds of drug rashes you can treat through and other drug rashes [for] which you must stop all the medications." For those that can be treated, an antihistamine often provides relief until the reaction subsides. Again, some drug reactions that begin as a skin rash can be serious or even life-threatening, so instead of guessing, consult a health-care provider as well as a pharmacist.

**Skin Problems Caused by HAART Itself**

Although protease inhibitors usually do not produce allergic reactions, some people experience a variety of annoying skin conditions that seem related to their antiretroviral therapy, including dry or itchy skin. "Certainly indinavir (Crixivan) has been implicated in dryness," Dr. Maurer observed. "People have noted dryness around their mouths and at the corners of the lips, and dryness of their skin in general." Another commonly reported symptom, ingrown toenails, may be related to dryness or to other effects of indinavir.

"Do you need to stop the drug? No. There are many ways of getting around dryness. If indinavir [as part of combination therapy] is working for you, I'd say don't stop the drug." The treatment for indinavir-induced dry skin is similar to other conditions involving dryness: use of lotions and moisturizers. "Excessive washing or showering can aggravate dryness," she added. "I saw somebody yesterday who was on indinavir and taking three showers a day. That's going to dry out your skin even if you don't have indinavir on board."

Dryness may also be the key factor in a recent report suggesting an association between 3TC (Epivir) and paronychia, an infection of the skin around a fingernail or toenail (for more information, see the *Lancet* 351(9111): 1256, April 25, 1998). Yet Dr. Maurer and her colleagues have seen paronychia in people experiencing dry skin no matter which drug regimen they were following. "I'm not convinced that it's the 3TC," Dr. Maurer said. "Maybe it's the dryness."

One treatment-associated problem not always thought of as a dermatological condition but that has been much on the minds of Dr. Maurer and her colleagues is body fat redistribution (BFR) or lipodystrophy (see *BETA*, January 1999, pages 23-32). "Nobody knows why people are experiencing fat redistribution," she said, "but many people are coming to the Dermatology Department with fat loss in the cheek area.

"We don't know what the fat redistribution is related to. Along with others, we are looking into the drugs that people are taking. Not everybody who's had this has
been on a protease inhibitor. We're looking into duration of treatment and length of survival—it's probably seen more in persons who are long-term survivors."

Health-care providers and people with HIV and BFR have experimented with different treatment approaches to fat redistribution, but thus far they have little data to guide them. Several treatments are purely cosmetic. In an attempt to counteract the gaunt or emaciated look, for example, "people have transferred fat [surgically] from one area to another," Dr. Maurer explained, "but it disappears after a time, probably for the same reason the original fat disappeared." People have had prosthetic (device) implants in the cheeks, with mixed results; some have reported severe complications. "People also have had collagen injections, with variable effects. Collagen too disappears after a certain period of time. You can have it reinjected, and some people are happy with that."

While such approaches address the appearances and not the underlying-and as yet unidentified-causes, Dr. Maurer said she sees value in treating symptoms that, for some people, are extremely stigmatizing. In considering treatments, she added, "I would be careful and want to know what good and bad outcomes have been seen with a particular treatment. I'd really question it."

The Endocrinology Department at SFGH is conducting trials of various drugs being considered for systemic treatment for lipodystrophy. "I would hope that people would enroll in those kinds of studies, so that we can understand what is occurring rather than just offering treatment [outside of the research setting]," Dr. Maurer said. Meanwhile, the hospital's Dermatology Department is beginning a protocol that involves measuring people's loss of facial fat and then following them during and after treatment. "We're scanning people to see how much fat has been lost, observing what happens if they have implants put in, observing them over time, and then scanning them again." [Ed. note: The Dermatology Department is studying whether computed tomography (CT) or magnetic resonance imaging (MRI) gives the best information.] Above all, Dr. Maurer stressed the need to look at BFR from a clinical perspective. "We don't do cosmetic stuff here; I'm interested in making sure people are followed."

For information about studies being conducted by the Dermatology Department at SFGH, call 415-206-8680.

Bruce Mirken is a freelance writer based in San Francisco.