Perspective

Dermatologic Manifestations of HIV Infection

Although some dermatologic diseases have decreased markedly in frequency in the potent antiretroviral therapy era, other conditions remain common. Among patients with low CD4+ cell counts who are not on or not adherent to antiretroviral therapy, notable conditions include psoriasis, photodermatitis, prurigo nodularis, molluscum, and adverse drug reactions. Conditions that remain relatively common despite adequate antiretroviral therapy include eczema, xerosis, warts, and Kaposi's sarcoma. Disorders that are associated with immune reconstitution under potent antiretroviral therapy include acne, staphylococcal infections, and erythema nodosum. In addition, HIV and hepatitis C virus (HCV) coinfection is associated with a number of skin disorders. This article summarizes a presentation on dermatologic manifestations of HIV disease by Toby A. Maurer, MD, at the 8th Annual Clinical Conference for Ryan White CARE Act clinicians in New Orleans in June 2005.

In many locales in the United States, the frequency of dermatologic diseases in HIV-infected patients—including seborrheic dermatitis, fungal diseases, psoriasis, and opportunistic infections with skin manifestations—has declined with the use of potent antiretroviral therapy. However, dermatologic disorders remain common in the HIV-infected population.

Conditions in Patients With CD4+ Cell Counts Below 200/µL Who Are Not on Antiretroviral Therapy

Common conditions in patients with CD4+ cell counts less than 200/µL who are not on antiretroviral therapy include severe psoriasis (usually affecting more than 50% of the body), extreme photodermatitis, prurigo nodularis, molluscum, and recurrent drug reactions.

Psoriasis

With the institution of antiretroviral therapy, psoriasis can be controlled with topical treatments, such as clobetasol and calcipotriene and ultraviolet light. Before adequate immune reconstitution under antiretroviral therapy occurs or in cases of complex or more severe psoriasis, treatment with the retinoid agent acitretin at 10 to 25 mg/d can be considered; it should be noted that this agent is associated with increases in triglycerides and cholesterol. Psoriasis in HIV disease can have unusual presentations. Figure 1 shows inverse psoriasis of the feet and underarm, differing from the common presentation of psoriasis on extensor surfaces.

Photodermatitis

Figure 2 shows photodermatitis of the face, the "vee" of the neck, and the arm and hand, with the typical darkening of skin that is exposed to sun. Persons with background pigment of the skin (ie, people of color) are more photosensitive than persons without background pigment in the skin. HIV infection itself is photosensitizing, and patients with low CD4+ cell counts may be receiving photosensitizing drugs such as trimethoprim/sulfamethoxazole (TMP/SMX). Antiretroviral therapy allows patients to go off photosensitizing drugs and also decreases the reaction through immune reconstitution. Treatment includes sunscreen, potent topical steroids (eg, clobetasol), lubricants, and antihistamines. The tricyclic doxepin (25 mg qhs) is useful for its strong antihistamine effects.

Prurigo nodularis

Figure 3 shows prurigo nodularis ("itchy bumps") of the arms and trunk. The disorder, which may have a photocomponent, is more frequently seen in patients with CD4+ cell counts below 50/µL and is more common in persons of color. Patients are consumed by itching, which is not relieved with antihistamines. Institution of antiretroviral therapy is helpful in resolving the condition. Potent topical steroids should be used, and thalidomide is effective when it is started at a dose of 50 mg/d and titrated for response (rarely above 100 mg/d). Careful monitoring for development of peripheral neuropathies is suggested. In addition, thalidomide is a teratogen and special precautions need to be taken in women of childbearing potential.

Figure 4 shows a condition characterized by numerous papules smaller than those typically seen in prurigo nodularis; for years, this condition has been unhelpfully described as "pruritic eruption of HIV." This is a common condition in areas of Africa, and a study was recently performed in Ugandan patients to determine the cause of the disorder (Resneck, *JAMA*, 2004). Of 102 lesion biopsies, 86 showed evidence of bug bites. A lower CD4+ cell count was significantly associated with greater severity of eruption, and the condition appeared to improve in patients started on antiretroviral therapy. The condition may thus represent hypersensitivity to bug bites secondary to immune deficiency.

Molluscum

Figure 5 shows severe facial molluscum. Molluscum is frequently seen in HIV-infected young women and men of any age who are not on antiretroviral therapy or are not adherent to their regimen. Its appearance fairly assures

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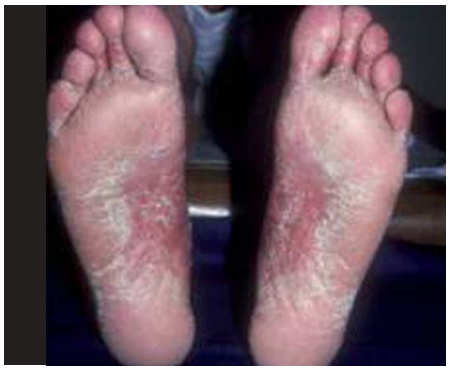


Figure **1a**. Inverse psoriasis of the feet.

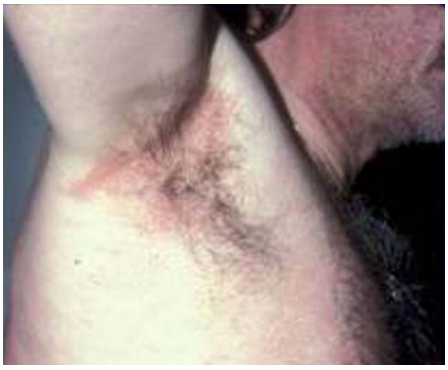


Figure **1b**. Inverse psoriasis of the underarm (underarm psoriasis is also bilateral).

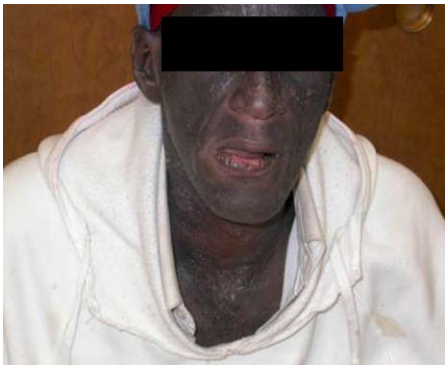


Figure **2a**. Photodermatitis of the face and "vee" of the neck.

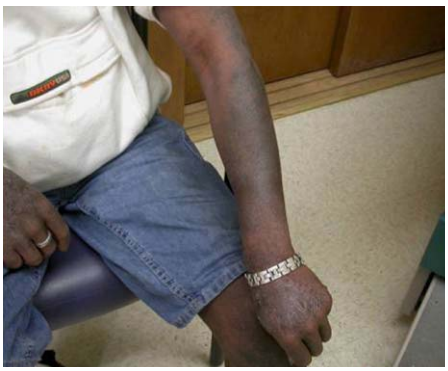


Figure **2b**. Photodermatitis of the arm and hand.

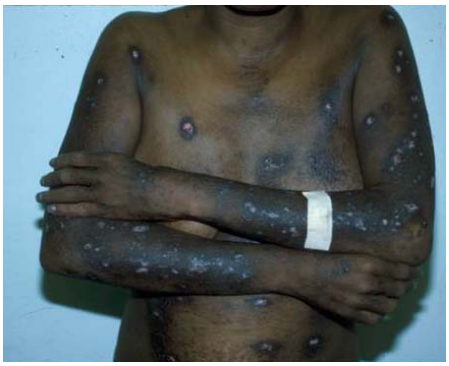


Figure **3**. Prurigo nodularis.

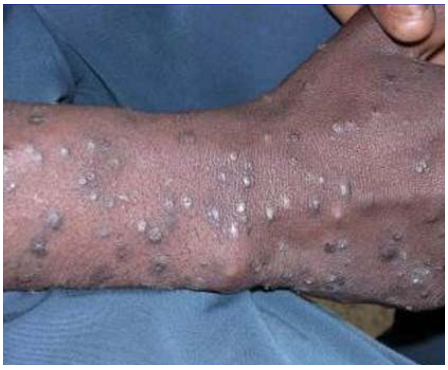


Figure **4**. Pruritic papular eruption that appears to be due to hypersensitivity to bug bites.

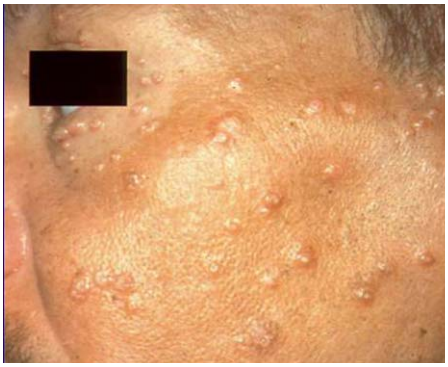


Figure **5**. Severe facial molluscum.

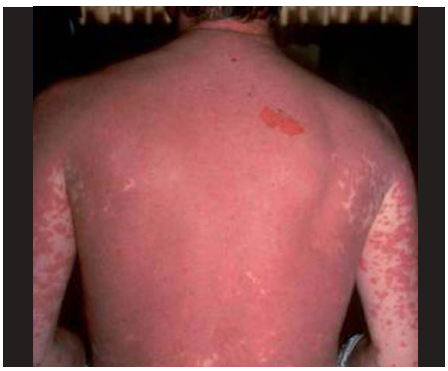


Figure **6**. Drug reaction producing full-body erythema.

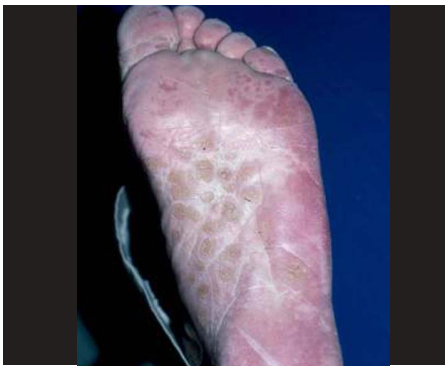


Figure **7**. Mosaic warts.

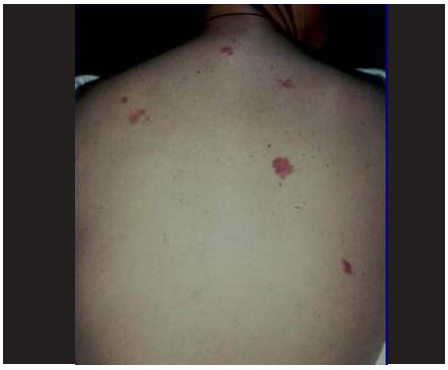


Figure **8**. Kaposi's sarcoma as it characteristically appears in the potent antiretroviral therapy era.

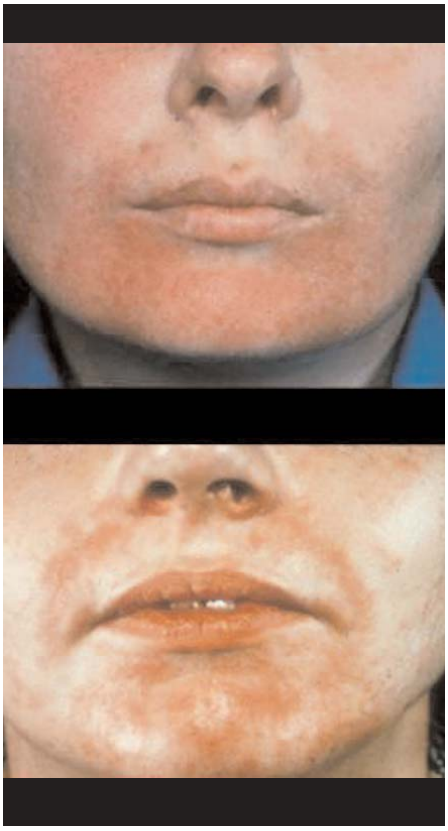


Figure **9**. Perioral dermatitis.

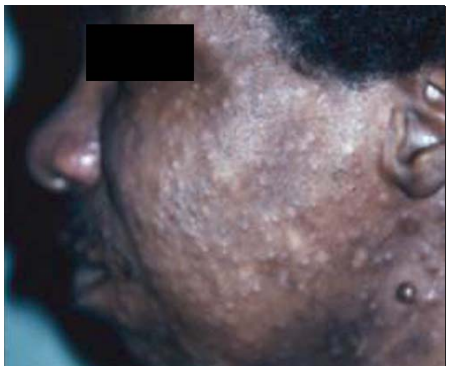


Figure **10**. Eosinophilic folliculitis.

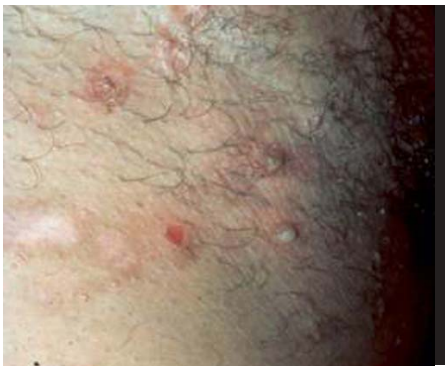


Figure **11a**. Staphylococcal infection can occur as abscesses.

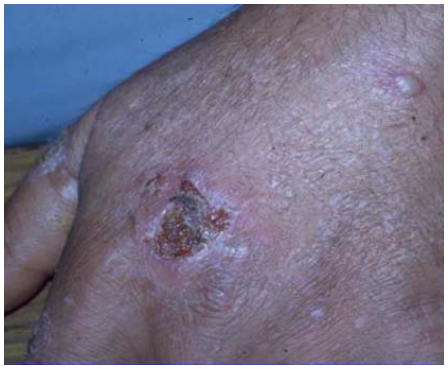


Figure **11b**. Staphylococcal infection can occur as ulcers.

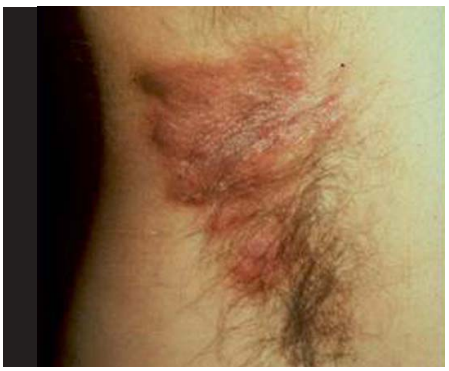


Figure **11c**. Staphylococcal infection can occur as folliculitis.

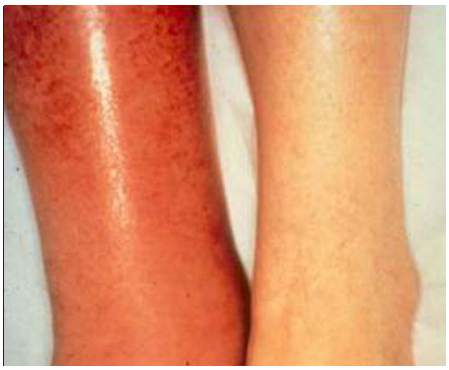


Figure **11d**. Staphylococcal infection can occur as cellulitis.

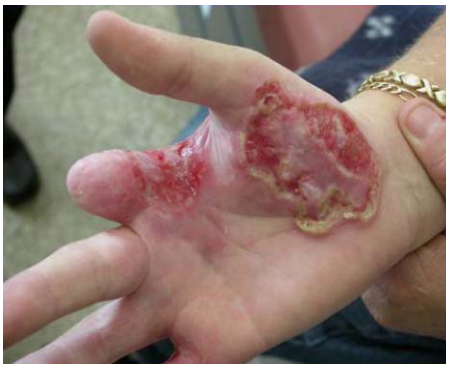


Figure **12**. HSV infection that was initially mistaken for staphylococcal infection.

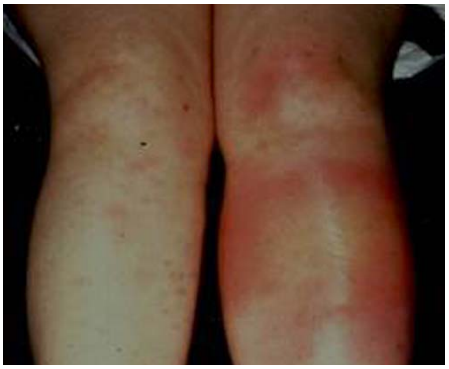


Figure **13a**. Erythema nodosum.

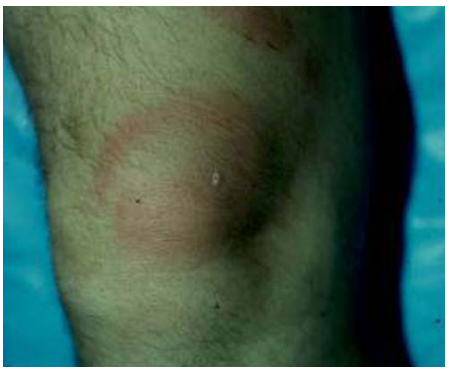


Figure **13c**. Infection due to *Helicobacter cinaedi* can mimic erythema nodosum in appearance.

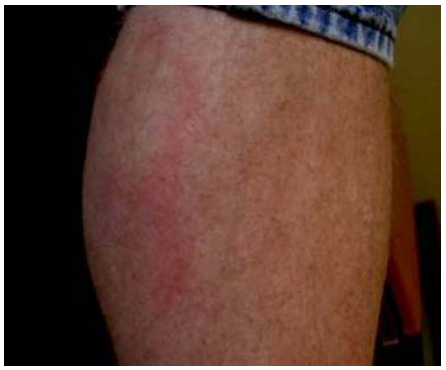
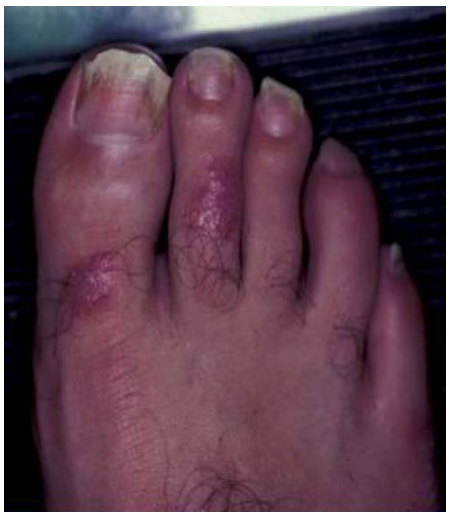


Figure **13c**. Infection due to *Campylobacter species* can mimic erythema nodosum in appearance. Reprinted from Rajendran et al, *Arch Dermatol*, 2005.



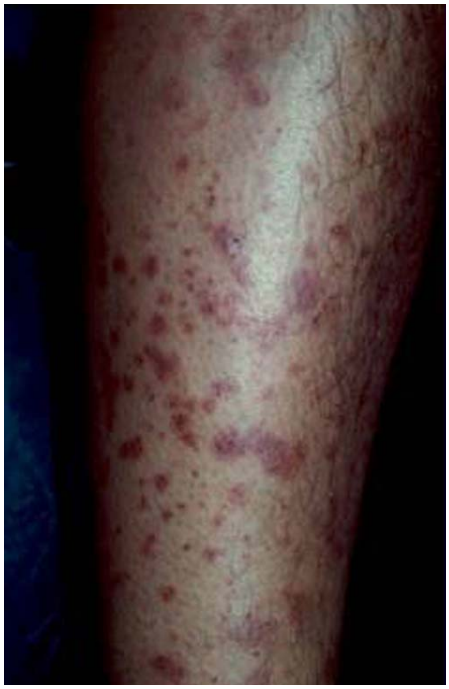


Figure **14**. HIV and hepatitis C virus coinfection-associated lichen planus (A) and vasculitis (B).

that the patient has a CD4 + cell count of less than 100/µL. First-line treatment is antiretroviral therapy. Liquid nitrogen provides only temporary treatment for the condition. We have found that curettage is successful in removing larger lesions and can be done without scarring.

Drug reactions

Figure 6 shows full-body erythema in a patient after starting a new drug. There is a group of patients with very low CD4 + cell counts (usually <50) who exhibit reactions to virtually every drug they are given, including antibiotics and antiretrovirals. Because of their low CD4 + cell counts, these are the very patients who require antiretrovirals and prophylactic antibiotics and are therefore at higher risk for drug reactions. A successful approach to reinstituting drug treatment has been to put these patients on prednisone with a slow taper over 12 weeks while other drugs are individually added (Dolev, *Arch Derm*, 2004). In cases of drug reaction apart from such chronic reactions, steroids should be used only if the patient has a hypersensitivity reaction marked by elevated liver function test results or increased creatinine levels. Even in cases of erythema multiforme, Stevens-Johnson syndrome, or when urticaria is present, the best approach is simply to remove the offending drug and wait until the reaction resolves. Drug clearance may take time for some drugs used in HIV-infected patients (eg, TMP/SMX). Doxepin can be used for itching.

Diseases That Do Not Go Away Even With Antiretroviral Therapy

Some HIV-related dermatologic conditions occur and recur even with appropriate antiretroviral therapy.

Eczema and xerosis

Eczema and xerosis are common conditions, particularly in patients in whom the CD4 + cell count nadir was less than 200/µL. Treatment consists of mid-potency steroids (ointment is better than cream, since it contains lubricant) and antihistamines. Tacrolimus and pimecrolimus, newer topical steroid formulations for eczema, have black box warnings regarding use in patients with altered immune function, although no specific degrees of immune deficiency are cited as contraindications for use.

Human papilloma virus-associated warts

Human papilloma virus (HPV)-associated warts are also highly recurrent despite adequate antiretroviral therapy, with some evidence indicating that eradication is difficult if the CD4 + cell count nadir was below 50/µL. Figure 7 shows mosaic warts on the bottom of the foot. No matter which is tried, treatment is only successful about 50 % of the time. Treatments include liquid nitrogen, podophyllin, laser treatment, and surgery. A recent study suggests that once genital warts are removed by cryotherapy or surgery, imiquimod is often successful at preventing recurrence. Some patients report that application of duct tape is successful at removing warts, although this approach has not yet been formally studied in HIV-infected patients. Whatever eradicative treatment is used, it should be repeated every 3 weeks, with successful treatment usually requiring an average of 12 treatments. We currently are investigating CD38 as a functionality marker of T cells in patients who have warts despite immune reconstitution under antiretroviral therapy.

Kaposi's sarcoma

Kaposi's sarcoma (KS) occurs throughout the course of HIV infection at CD4 + cell counts of anywhere from 0 to 800/µL. It remains an open question whether antiretroviral therapy, the first-line therapy for KS, should be started in a patient with KS but higher CD4 + cell counts than those counts currently serving as indicators for starting antiretroviral therapy. KS occurs even in patients with profound suppression of HIV replication. As with HPV-associated warts, it may be the case that alterations in functionality of T cells in HIV disease inhibit immune response to human herpesvirus 8, the causative agent of KS. Currently, KS tends to present as subtle purple patches (Figure 8) rather than the large fixed plaques characteristic of the disease in the pre-potent antiretroviral therapy era. From a dermatologic perspective, treatment usually is considered to consist in careful monitoring of CD4 + cell count and plasma HIV RNA levels, and topical treatment (eg, aliretinoin) in patients with CD4 + cell counts greater than 400/µL and plasma HIV RNA levels below detection limits. Potent antiretroviral therapy should be started in patients with CD4 + cell counts less than 400/µL. Liposomal doxorubicin or paclitaxel infusions should be given in patients with eruptive KS or lymphedema who are on antiretroviral therapy.

Conditions Emerging With Immune Reconstitution Under Antiretroviral Therapy

Diseases that are now being seen with immune reconstitution under antiretroviral therapy include: acne, which must be differentiated from eosinophilic folliculitis; staphylococcal infections (frequently methicillin-resistant strains), which need to be differentiated from herpes simplex virus (HSV) and fungal diseases; and erythema nodosum, which needs to be differentiated from *Helicobacter cinaedi* infection.

Acne

Acne is seen as acne vulgaris, acne rosacea, and perioral or periorbital dermatitis in HIV-infected patients. Treatment consists of tetracycline or minocycline, and isotretinoin for cystic acne. Acne rosacea is characterized by redness, papules, and broken blood vessels. Figure 9 shows perioral dermatitis, with characteristic scaliness

and acneiform papules around the mouth.

Acne is to be differentiated from eosinophilic folliculitis, shown in Figure 10. This condition consists of multiple extremely itchy urticarial bumps that can be found on the face, neck, scalp, chest, and back. Although the condition was once typically seen in patients with CD4+ cell counts less than 200/µL, it has become common during immune reconstitution in the first 3 to 6 months of antiretroviral therapy. Treatment consists of the antifungal itraconazole 200 to 400 mg/d, not because the condition is fungal but because of the antieosinophilic effect of this agent. Permethrin can be used from the waist up every other day to dry the papules. Patients can also simply be observed to determine if the condition resolves after the initial 3 to 6 months of antiretroviral therapy.

Staphylococcal infection

There has been an increased frequency of staph infections with the decreased need for prophylaxis with TMP/SMX or other antibiotics during the antiretroviral therapy era. Staph infections can manifest as abscesses, ulcers, folliculitis, or cellulitis, as shown in Figure 11. It is important to obtain a culture from pus when possible. First-line treatment for abscesses is incision and drainage; antibiotic treatment is not required. If there is no pus available and the infection is not recurrent, treatment should first be attempted with an antibiotic active against methicillin-susceptible staph strains, with the patient returning during treatment for an evaluation of their response. If the infection is recurrent, treatment should be started with an antibiotic active against methicillin-resistant strains: TMP/SMX, doxycycline, and clindamycin still have activity against such strains; resistance is an ever-expanding problem with ciprofloxacin and levofloxacin. The addition of rifampin (600 mg every day for 5 days) can also be considered; potential drug-drug interactions with protease inhibitors need to be considered if this drug is to be used. Mupirocin ointment is also effective. In recurrent disease, it is important to look for and treat underlying skin disorders that could provide a portal of entry for staph, including dry skin, eczema, tinea, and psoriasis. If there is no response to treatment, the sufficiency of treatment duration should be considered. Prolonged treatment usually is required when hair structures or deep tissues are involved in infection. A 3-week course of treatment should be considered in cases of folliculitis.

Care must be taken to distinguish staph infection from HSV infection, which can mimic several types of skin conditions. HSV culture, direct fluorescence antibody testing, or skin biopsy for histology should be performed for suspicious lesions. HSV infection can present as scaly, impetiginized lesions, as shown in Figure 12. HSV infection should be treated with appropriate antiviral medication. Similarly, suspicious lesions or nonresponding infection should prompt skin biopsy for histology and tissue culture for fungal or mycobacterial infection.

Erythema nodosum

Erythema nodosum is frequently confused with cellulitis (Figure 13). The condition can occur during immune reconstitution in patients with a diagnosis of sarcoidosis. It can also be associated with other etiologies, including streptococcal or *Yersinia species* infection or inflammatory bowel disease. Diagnosis is made by biopsy. Treatment includes bed rest, prednisone, and potassium iodide.

Infection with *Helicobacter cinaedi* mimics erythema nodosum (Figure 13). This gram-negative infection can be characterized by fever, bacteremia, and diarrhea. However, blood culture can be positive in the absence of fever. Stool can also produce positive culture. Skin biopsy shows a suppurative process. Treatment consists of 8 weeks of doxycycline or erythromycin. A recent report indicates that a similar presentation (Figure 13) can be caused by *Campylobacter species* infection. Diagnosis is made by blood culture. Treatment consists of ciprofloxacin.

HIV and HCV Coinfection

Coinfection with HIV and HCV is fairly common and is associated with a number of skin conditions, including lichen planus (Figure 14), xerosis, leukocytoclastic vasculitis (Figure 14), and itch without rash. Lubricants and steroid treatment should be used for xerosis. In cases of vasculitis, it is important to first rule out other potential causes, including: drug reactions; other infections (including streptococcal infection, endocarditis, and hepatitis A and B virus); collagen vascular disease and cryoglobulinemia; and leukemia and lymphoma. HCV viral load and liver function test results are not necessarily elevated in cases of active cutaneous vasculitis due to HIV and HCV coinfection. Treatment of vasculitis with colchicine has been helpful, and treatment of the HCV infection should be considered. The role of systemic steroids in treatment is not clear and may exacerbate the liver disease. The itch in HIV and HCV coinfection appears to be a central nervous system itch. Use of the opioid antagonist naltrexone (starting at 50 mg qhs) may be helpful. Neither antihistamines nor ultraviolet light have proved helpful in treatment. Treatment for HCV infection is also helpful.

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Suggested Reading

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