Perspective

The Skin and HIV: No Superficial Matter

The vast majority of HIV-infected patients experience some type of skin disorder; these may broadly be categorized as infectious, neoplastic, or inflammatory. Additionally, primary pruritus afflicts a considerable percentage of HIV-infected individuals, and an attempt should be made to identify potential underlying triggers. Chronic itch, whether related to an underlying cutaneous, systemic, or psychiatric illness, can have a profound effect on quality of life. Therapy for inflammatory skin disorders may involve initiation of antiretroviral therapy in those who have not yet started such treatment, oral antihistamines, topical corticosteroids, topical antipruritic agents, and skin moisturizers. Because topical corticosteroids are often a necessary component of the therapeutic armamentarium for skin diseases, practitioners are encouraged to become familiar with the appropriate indications, strengths, and formulations of available preparations. In some instances, psychiatric medications or phototherapy may be necessary for the treatment of HIV-associated skin disorders, particularly for patients experiencing refractory itch. Although psoriasis is not more frequent among HIV-infected patients than in the general population, it can be more severe and debilitating for those who are HIV infected. Our understanding of psoriasis in the setting of HIV infection has evolved and new therapies for psoriasis have recently become available. This article summarizes a presentation by Sareeta R. S. Parker, MD, at the IAS–USA continuing education program held in Atlanta, Georgia, in April 2014.

Keywords: HIV, skin, pruritus, psoriasis, antiretroviral therapy, topical steroids, itch, Merkel cell carcinoma, scabies

Approximately 90% of HIV-infected patients develop some type of skin disease.[1] Indeed, skin disease may be the only overt sign of HIV infection and can be a major cause of morbidity despite stable HIV disease. HIV-infected patients have impaired systemic and local immunity and are thus at increased risk for skin infections, malignancies, and worsening of existing dermatoses.

Skin conditions frequently encountered in those with HIV infection are listed in Table 1 and include infections, infestations, neoplasms, and inflammatory conditions. Scabies in those with advanced or poorly controlled HIV disease is notable for possible absence of associated itch; it should be considered when a patient presents with genital skin lesions. Topical steroids are not an effective treatment for scabies. Appropriate scabies treatment may include the topical scabicide permethrin or oral ivermectin.

Among neoplasms, Merkel cell carcinoma (MCC) deserves particular attention because it has been a generally underrecognized entity. MCC, a neuroendocrine-derived neoplasm observed more commonly in immunosuppressed persons, has recently been shown to be associated with polyomavirus infection. It is nodular or nodulocystic in appearance and is more commonly encountered in fair-complected individuals. The biologic behavior of MCC parallels that of melanoma in that both malignancies are potentially lethal; once MCC grows to larger than 2 cm in diameter, the likelihood of survival is approximately 50%.[2] With regard to other conditions encountered in the outpatient setting, drug eruptions occur up to 10 times more frequently among HIV-infected patients than in the general population, even after adjustment for increased drug exposure among HIV-infected patients.[3]

Topical Corticosteroids

Topical corticosteroids, frequently referred to as topical steroids, are the foundation for treatment for many of the noninfectious skin diseases encountered in HIV disease. Effective therapy with topical steroids requires knowledge of the various potencies and formulations available, as well as knowledge of potential adverse effects.

Table 1. Selected Skin Conditions in HIV Infection

Infections	Infestations	Neoplasms	Inflammatory Conditions	Other
▪ Cutaneous fungal, bacterial – Candida, tinea, staphylococcus ▪ Syphilis ▪ Systemic fungal – Cryptococcosis, histoplasmosis ▪ Herpes simplex virus and varicella-zoster virus ▪ Human papillomavirus, epidermodysplasia verruciformis–like phenotype ▪ Molluscum contagiosum	▪ Scabies	▪ Kaposi sarcoma ▪ Basal cell carcinoma ▪ Squamous cell carcinoma ▪ Merkel cell carcinoma ▪ Melanoma	▪ Seborrheic dermatitis ▪ Prurigo nodularis ▪ Eosinophilic folliculitis ▪ Pruritic papular eruption	▪ Drug eruptions ▪ Itch ▪ Xerosis ▪ Lipoatrophy ▪ Photosensitivity ▪ Psoriasis ▪ Postinflammatory hyperpigmentation ▪ Immune reconstitution inflammatory syndrome (IRIS)-related flare of skin disease or infection

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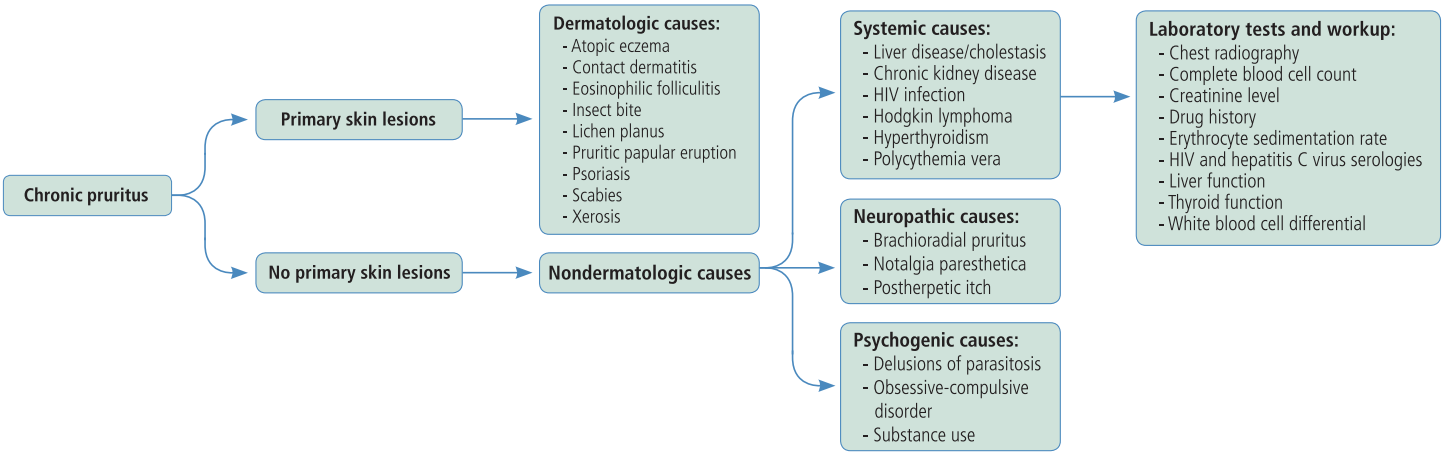

Figure 1. Diagnostic workup for chronic pruritus. Adapted from Yosipovitch and Bernhard.[5]

Topical steroids are divided into classes based on potency. It is helpful to become familiar with several distinct formulations (eg, ointment, gel, cream, or lotion), as this may affect patient adherence and effectiveness. For example, prescribing an ointment to be applied to a dense hair–bearing area is likely to result in poor adherence and outcome. Adverse effects of topical steroids should be considered; these include glaucoma if used around eyes or eyelids, striae or skin atrophy, acneiform eruptions, and bruising or purpura.

From lower to higher potency, commonly used topical steroids include hydrocortisone 2.5% cream or ointment; alclometasone cream or ointment; triamcinolone 0.1% cream or ointment (available in a 1-lb jar or in smaller quantities); fluocinonide 0.05% cream or ointment; and clobetasol cream, ointment, or solution. Generic formulations of many of these medications are available at lower cost than brand-name formulations.

Because they are the least potent of the topical steroids, hydrocortisone and alclometasone preparations are generally safe for long-term use on the face. For patients with seborrheic dermatitis, for example, it is helpful to supply several refills, enabling the patient to resume application if dermatitis recurs.

Dermatologists frequently prescribe triamcinolone 0.1% for widespread inflammatory skin diseases because it is available in a 1-lb jar. However, smaller quantities are also available and may be more appropriate for patients with limited skin involvement. Caution should be used when prescribing triamcinolone, as the 0.5% formulation is far more potent, and its use should be limited owing to greater potential for adverse effects.

Higher potency topical steroids, such as fluocinonide and clobetasol, are generally not recommended for use on the face, genitals, or body folds. Patients should be advised to limit use to lesional skin only. These stronger agents are useful when lesions are thick, as with psoriatic lesions, or heavily lichenified, as there is less concern of potential atrophy.

Approximately 30 g of cream is required to cover the surface of an average-size body once; this number should be considered when selecting the quantity of topical steroid to prescribe.

Itch

Itching is defined as an unpleasant cutaneous sensation that induces the desire to scratch, and it serves as a physiologic self-protective mechanism. The mediators of itch are not entirely known. Histamine is one but not the sole mediator. In recent years, there have been advances in the understanding of the mechanisms of itch. For many years it was thought that itch sensation, similar to pain sensation, was transmitted only or primarily through unmyelinated C fibers. It is now known that several nerve fibers, including thinly myelinated Aβ (fast) and Aδ (slow) fibers, transmit itch. It was also thought that nerve receptors did not penetrate the epidermis, whereas it is now recognized that neurofibrils do reach into the epidermis.

Itching is a serious problem for many HIV-infected individuals. A recent study of 200 HIV-infected patients in the southeast United States showed an itching prevalence of approximately 45%, with more than half of these patients reporting that itching had a statistically significant negative impact on their quality of life.[4]

The evaluation for an HIV-infected patient presenting with itch is fairly straightforward: examine for skin disease, evaluate the patient for systemic disease, and consider any underlying psychiatric conditions. With regard to the latter, itch perception may be amplified for those with psychiatric diseases, and the ability to control the impulse to scratch may be impaired, resulting in severe self-induced skin damage.

A diagnostic approach for chronic pruritus was proposed by Yosipovitch and Bernhard, and an adapted version is presented in Figure 1.[5] The patient should be evaluated for the presence or absence of primary lesions. If primary lesions are present and infestation (ie, scabies) is excluded, the condition can

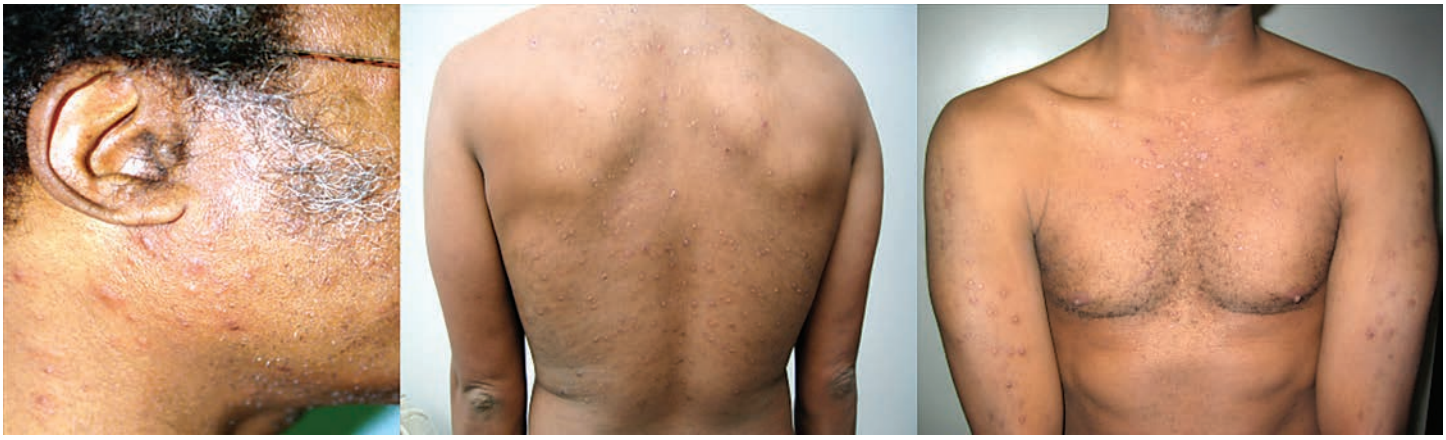

Figure 2. Examples of eosinophilic folliculitis.

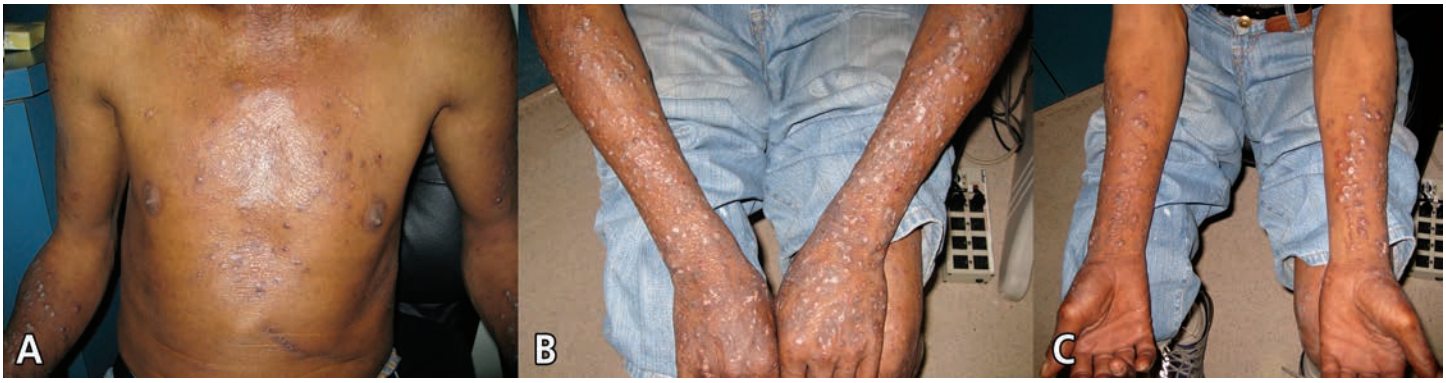

Figure 3. Pruritic papular eruption associated with HIV infection, manifesting as hyperpigmented papules in the mid chest (A) and lichenified papules on the distal arms (B and C).

usually be treated with topical steroids. HIV-associated eosinophilic folliculitis and pruritic papular eruption have been added to the list of dermatologic causes of itch because they are commonly encountered among HIV-infected patients. With regard to nondermatologic causes, most components of the workup for systemic causes of itch are already part of routine evaluation of HIV-infected patients. Of note, both lymphoma and hepatitis C virus infection can be underlying causes of chronic itch.

Examples of primary lesions are shown in Figure 2. The patient shown in Figure 2 has urticarial red papules on his neck and excoriations on the entire back and the anterior aspect of his trunk. This condition is eosinophilic folliculitis, a hallmark of which is the absence of lesions below the nipple line on the chest and the absence of lower-body involvement. The patient shown in Figure 3 has central chest lesions and lesions on the distal arms, and thus does not have eosinophilic folliculitis but rather pruritic papular eruption associated with HIV. Characteristic of this condition, the complete systemic workup for itch revealed nothing aside from HIV infection. Some of the lesions on this patient are primary lesions, while others are lichenified papules; the hemorrhagic, crusted excoriations attest to the severity of the itch associated with this condition. The patient shown in Figure 4 does not have a primary lesion and no papules, pustules, or blisters are evident. Linear excoriations, old scars, and some angular ulcerations in reachable areas are visible. The only identifiable underlying source of this patient's itch was HIV infection.

Treatment for itch includes oral agents such as the antihistamines diphenhydramine, hydroxyzine (10 mg to 50 mg up to 4 times daily), and doxepin (10 mg to 25 mg up to 4 times daily); the anticonvulsants gabapentin and pregabalin; and the serotonin-norepinephrine reuptake inhibitor mirtazapine (15 mg to 30 mg). Other therapeutic options include psychiatric medications (eg, the selective serotonin reuptake inhibitors paroxetine and sertraline); behavioral modification; antiretroviral therapy; topical treatments such as corticosteroids or antipruritic agents (eg, calamine or pramoxine-containing creams); treatment of dry skin with moisturizers and avoidance of harsh soaps; and phototherapy.

Antihistamine dosage can be self-titrated by patients. Doxepin is more potent than hydroxyzine or diphenhydramine, and some antihistamines have anxiolytic effects. For refractory itch, the anticonvulsants gabapentin and pregabalin can be added. Gabapentin and pregabalin produce excellent

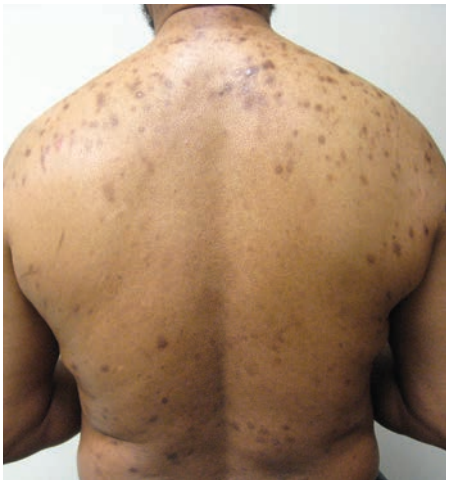

Figure 4. Pruritus with no primary lesions in the context of HIV-related itch; note sparing of the mid back in a region that is difficult for the patient to reach.

responses in some patients, and the dosing is similar to that for postherpetic neuralgia.[5] Although expensive, the antidepressant mirtazapine may be beneficial for intractable itch; paroxetine and sertraline may also help with the psychiatric component of perceived itch.

In patients with HIV-related inflammatory skin disease who have not yet started antiretroviral treatment, initiation of such treatment can result in resolution of the cutaneous disease as well as the associated itch.

Topical therapies may help relieve a component of the itch for patients suffering from chronic pruritus, particularly if they cannot resist touching their skin. Numerous over-the-counter antipruritic agents are soothing, and pramoxine-containing creams provide an anesthetic effect for some. Dry skin must be treated correctly. Patients often employ measures that make their condition worse. Owing to its antimicrobial effect, some patients apply alcohol to the skin, and others take numerous daily showers for the soothing effect of the hot water, without realizing that these measures dry the skin and worsen the underlying condition. Thus, use of moisturizers is an important component of itch or dermatitis therapy.

Phototherapy is extremely effective for intractable itch and is also very safe in the absence of prior history of melanoma or squamous cell carcinoma. It is, however, not always practical, requiring patients to visit a dermatologist's office to use a phototherapy unit 3 times a week for up to several months.

Psoriasis

Psoriasis, unlike many of the aforementioned conditions, is not more common among HIV-infected patients than HIV-uninfected patients. It is often, however, more severe in the setting of advanced HIV infection.

Numerous studies in the dermatology literature, and now also in the general medical literature, strongly support that psoriasis in and of itself is an independent risk factor for myocardial infarction, and is associated with elevated risk for metabolic syndrome, stroke, and peripheral vascular disease.[6,7] The risk of cardiovascular disease is especially high in younger patients with psoriasis. HIV-infected patients with psoriasis should be evaluated for cardiovascular disease risk factors.

Psoriasis is an immune-mediated chronic inflammatory disorder that manifests not only in the skin and joints but also as systemic inflammation. It occurs in genetically predisposed individuals and is estimated to affect approximately 3% of the US population. The disorder is mediated by T cells, and therapies that target T cells, such as cyclosporine, are effective in resolving psoriasis.

The classic presentations of psoriasis on the elbow, knee, trunk, hands, and feet are shown in Figure 5. The patient shown in Figure 5 (F and G) has psoriatic arthritis manifesting as inflamed, edematous fingers and near complete obliteration of the nails.

Why psoriasis worsens in the context of HIV disease is unclear. Psoriasis was once thought to be a T helper 1 (T_H1) cell–mediated disease, whereas inflammation in advanced HIV disease is characterized by predominance of T_H2 cell cytokines. The presence of or exacerbation of psoriasis in advanced HIV infection, when CD4+ helper cells are diminished, would seem paradoxical. In the past several years, however, it has become clear that CD8+ cells are prominently involved in psoriasis.[8] CD8+ cells in psoriatic skin produce inflammatory cytokines such as interleukin 17 (IL-17) and IL-22, and a number of novel IL-17 inhibitors have been found to be highly active in

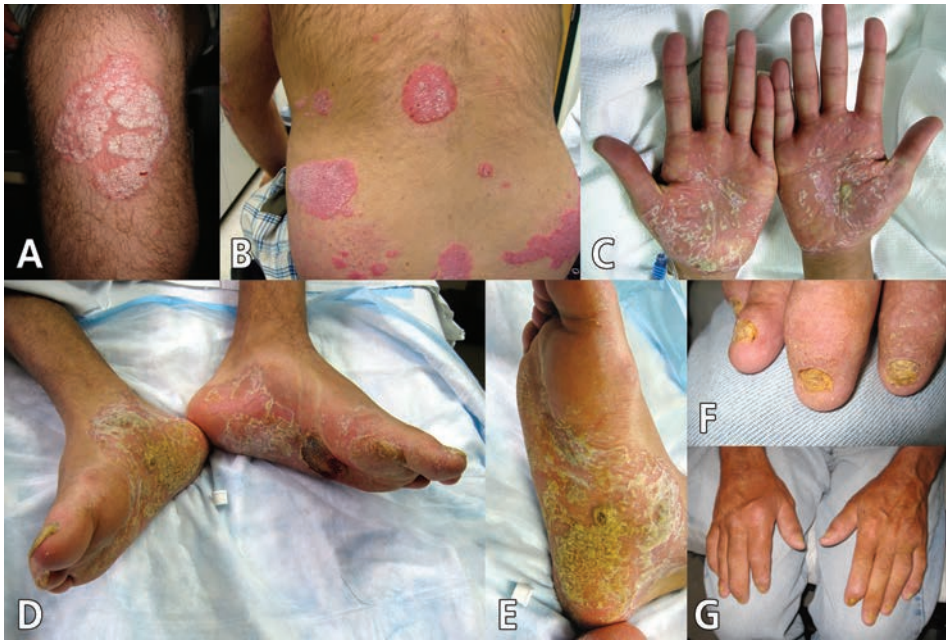

Figure 5. Classic, pink, psoriatic plaques on the knee (A), trunk (B), bilateral palms (C), and feet (D and E). Psoriatic nail dystrophy and psoriatic arthritis affecting several joints in the hands (F and G).

treating psoriasis.[9] As our understanding of the pathophysiology of psoriasis improves, there is thus hope for safer, more targeted, and more effective psoriasis therapies, including for patients with HIV infection.

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Financial affiliations in the past 12 months: Dr Parker has no relevant financial affiliations to disclose.

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