CLINICAL MANAGEMENT

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Cutaneous Manifestations of HIV: A Primer

CME CATEGORY 1
1 Hour

ANCC/AACN
2.5 Contact Hours

PHARMACOLOGY
.5 Hour

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The authors disclose that the following drugs have not been approved by the US Food and Drug Administration for use in the treatment of the following diseases: anticonvulsants, postherpetic neuralgia; tricyclic antidepressants, postherpetic neuralgia; acyclovir, orolabial herpes and Epstein-Barr virus; famciclovir, genital herpes and varicella; valacyclovir, orolabial herpes and varicella; tretinoin, Epstein-Barr virus and molluscum contagiosum; podophyllin, Epstein-Barr virus and molluscum contagiosum; zidovudine, Epstein-Barr virus, molluscum contagiosum, and psoriasis; vitamin A, Epstein-Barr virus; ganciclovir, Epstein-Barr virus; foscarnet, Epstein-Barr virus; imiquimod, molluscum contagiosum; trichloroacetic acid, molluscum contagiosum; interferon, molluscum contagiosum; bleomycin, human papillomavirus; fluorouracil, human papillomavirus; doxycycline, bacillary angiomatosis and *Mycobacterium marinum;* cotrimoxazole, bacillary angiomatosis and *M marinum;* tetracycline, bacillary angiomatosis and *M marinum;* rifampin, bacillary angiomatosis, *M marinum*, and *M avium-intracellulare;* isoniazid, bacillary angiomatosis; erythromycin, bacillary angiomatosis; azithromycin, bacillary angiomatosis; ethambutol, *M marinum* and *M avium-intracellulare;* clarithromycin, *M marinum;* itraconazole, *candida;* fluconazole, histoplasmosis; azoles, coccidioidomycosis; ivermectin, scabies; immunoglobulin, toxic epidermal necrolysis; vinblastine, Kaposi sarcoma; steroids, eosinophilic folliculitis; pentoxifylline, pruritic papular eruption; and acitretin, ichthyosis/xerosis.

PURPOSE:
To provide physicians and nurses with an overview of the characteristics and treatments for skin lesions associated with HIV/AIDS.

TARGET AUDIENCE:
This continuing education activity is intended for physicians and nurses with an interest in identifying and managing skin lesions in patients with HIV/AIDS.

OBJECTIVES:
After reading the article and taking the test, the participant will be able to: 1. Identify the characteristics of skin lesions associated with HIV/AIDS. 2. Identify treatment options for skin lesions associated with HIV/AIDS.

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Since its emergence in the early 1980s, human immunodeficiency virus (HIV) infection has had a major impact on the field of dermatology.[1] Skin diseases that were once rare have become commonplace. Because skin is among the organs where HIV disease and immunosuppression typically manifest, accurate diagnosis of skin eruptions is critical.

Cutaneous lesions may be the first sign of HIV infection or acquired immunodeficiency syndrome (AIDS). In patients with known HIV disease, skin diseases and skin-related signs of internal disease may be associated with significant morbidity and even mortality. Because certain skin manifestations of HIV infection are associated with levels of immune suppression, immune deterioration can be detected by monitoring skin disease[2] (Table 1).

HIV is associated with a variety of infectious and noninfectious diseases. The purpose of this article is to discuss a cross-section of these conditions and their cutaneous manifestations.

VIRAL INFECTION

Human herpesvirus 1 and 2

Classic human herpesvirus (HHV) 1 and 2, known as herpes simplex virus (HSV) types 1 and 2 (HSV-1, HSV-2), lead to orolabial and genital herpes, respectively.[2,3] However, significant crossover and novel areas of presentation have increased over the years. This is, in part, a result of a change in sexual practices. Transmission of HSV can occur via direct sexual contact. In addition to the morbidity of these conditions, early recognition, education, and treatment are critical because HSV facilitates infection with HIV, as well as activates and promotes replication of HIV.[3,4]

Clinically, HSV presents as grouped vesicles on a red base that may progress to deep ulcerations and necrosis.[1-6] In patients with HIV, HSV lesions occur more often, are more frequently atypical, and have a prolonged and recalcitrant course;[2,4] they may even become chronic. Lesions commonly appear in the mouth and esophagus and on genitalia, perianal areas, and distal fingers.

Diagnosis can be made based on histopathology, which reveals epidermal balloon degeneration with intraepidermal vesicles and eosinophilic intranuclear inclusion bodies. It can be confirmed with Tzanck smear, by visualization of multinucleated epidermal (giant) cells, viral culture, and serum antigen detection.[1-6]

The mainstay of treatment for HIV-associated HSV has been acyclovir.[1-6] Patients with HIV are usually treated with higher doses, for longer periods, and with lifelong suppressive therapy. Patients with HIV and orolabial herpes can be treated with acyclovir, 400 mg orally 5 times a day or 5 mg/kg intravenously (IV) every 8 hours for 7 days. Patients who need suppressive therapy can take 400 mg of oral acyclovir twice a day. Patients with HIV and their first episode of genital herpes can be treated with 200 mg of acyclovir orally 5 times a day for 10 days, and recurrent herpes can be treated with 200 mg of acyclovir orally 5 times a day for 5 days. If IV acyclovir is needed, it can be given at 5 mg/kg every 8 hours for 7 days. Suppressive therapy includes 400 mg of acyclovir orally twice daily. Patients on suppressive therapy have been shown to have lower viral loads and a survival advantage.

Table 1.
CD4 CELL COUNTS ASSOCIATED WITH SKIN LESIONS

	CD4 Cell Count (cells/mm^3)
Viral infection	
Herpes simplex virus	Any
Varicella-zoster virus	Any
Epstein-Barr virus	Any, but commonly <200
Cytomegalovirus	<100
Molluscum contagiosum	<100
Human papillomavirus	Any, but commonly <500
Bacterial infection	
Staphylococcus aureus	Any
Bacillary angiomatosis	<500
Mycobacterium tuberculosis	Any, but commonly <200
Atypical mycobacteria	<50
Syphilis	Any
Fungal infection	
Candida	Any, but commonly <200
Histoplasmosis	<100
Cryptococcosis	<50
Coccidioidomycosis	<100
Parasitic infection	
Scabies	Any
Pneumocystosis	<200
Drug reaction	Any
Neoplastic infection	
Kaposi sarcoma	Any, but commonly <200
Lymphoma	Any
Noninfectious disease	
Psoriasis	Any
Eosinophilic folliculitis	<200
Pruritic papular eruption	<50
Seborrheic dermatitis	Any, but commonly <200
Xerosis	Any, but commonly <200
Acquired ichthyosis	Any, but commonly <200
Atopic dermatitis	Any, but commonly <200

A high prevalence (6.4%) of acyclovir resistance is seen among patients with HIV disease. This occurs via a mutation in

thymidine kinase, necessitating the use of IV foscarnet, 40 mg/kg every 8 to 12 hours for 2 to 3 weeks, along with topically applied cidofovir 1% used once a day.[4]

Patients with HIV-associated HSV have also been effectively treated with valacyclovir and famciclovir. For orolabial herpes, the typical oral valacyclovir dosage is 1 gram 3 times a day for 7 days. Famciclovir may be given orally at 500 mg twice a day for 7 days for treatment or 500 mg twice a day for suppression. Genital herpes can also be treated with oral valacyclovir: 1 gram twice a day for 10 days for primary HSV-2 infection, 500 mg twice a day for 5 days for recurrent lesions, or 1 gram daily for suppression. Oral famciclovir may be used for genital herpes, at dosages of 500 mg twice a day for 7 days or 250 mg twice daily for suppression.

Varicella-zoster virus

Varicella-zoster virus (HHV-3) affects about 25% of patients with HIV.[3] Transmission can occur via respiratory droplets and direct contact. Primary varicella infection presents with successive crops of vesicles on red base, which start on the head and face and subsequently spread to the rest of the body. In patients with HIV, the lesions may be more painful, severe, and prolonged. After lying dormant within the dorsal root ganglions, reactivation may occur and present as zoster or shingles, which is characterized by dermatomal distribution of vesicles on a red base.[1] Patients with HIV experience numerous episodes that last longer, disseminate more frequently, and are more painful. The vesicles often become chronic ulcerative, necrotic, or verrucous.[1-3,5,6] Progressive neuronal inflammation and necrosis leads to severe pain (postherpetic neuralgia), which increases as the infection travels down the nerve.

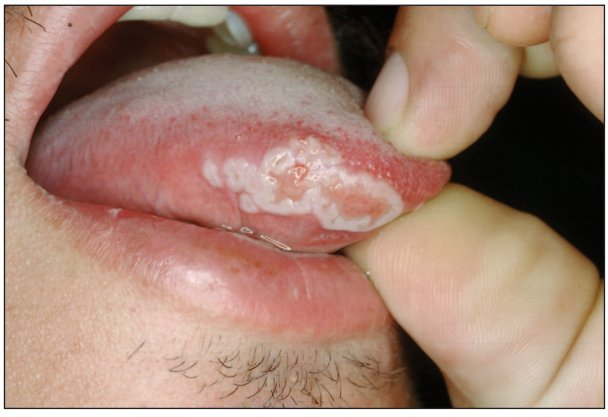
Diagnosis can be made on histopathology, which is indistinguishable from HSV infection. It is confirmed with Tzanck smear, also by visualization of multinucleated giant cells, viral culture, and antigen detection.[1-3,5,6]

Similar to HSV, varicella-zoster can be treated with acyclovir, famciclovir, and valacyclovir, but at higher dosages.[1-3,5,6] The oral acyclovir dosage is 800 mg 4 times a day for 5 days; oral valacyclovir is given at 1 gram 3 times a day for 7 days; and the dosage for oral famciclovir is 500 mg 3 times a day for 7 days. Zoster can be treated with acyclovir, either an oral dosage of 800 mg 5 times a day for 7 to 10 days or an IV dosage of 10 mg/kg every 8 hours for 7 days. Other options for treating zoster are oral valacyclovir, 1 gram 3 times a day for 7 days, and oral famciclovir, 500 mg 3 times a day for 7 days.

Postherpetic neuralgia is often difficult to treat. Some success has been achieved with nonsteroidal anti-inflammatory agents, opioid analgesics, anticonvulsants, and tricyclic antidepressants.

Figure 1.
ORAL HAIRY LEUKOPLAKIA

Patient has white corrugated plaques on lateral aspect of tongue due to infection with Epstein-Barr virus.



Epstein-Barr virus

Most adults have been infected with Epstein-Barr virus (EBV), which lays dormant within B cells.[5] Once HIV causes immunosuppression, EBV most frequently manifests as oral hairy leukoplakia (OHL), and less commonly as Burkitt's lymphoma and/or large-cell lymphoma. Up to 25% of patients with HIV can develop OHL.[3]

Lesions of OHL are characterized by white corrugated plaques on the lateral aspects of the tongue, dorsal and ventral surfaces of the tongue, buccal mucosa, and soft palate[1-3,5,6] (Figure 1). Generally, OHL is asymptomatic; however, some patients may complain of dysphagia. The distribution of the lesions is related to the presence of the EBV receptors in that distribution.

Diagnosis can be made clinically and histopathologically.[1-3,5,6] Swollen, pale keratinocytes; hyperkeratosis; and parakeratosis can be seen on histology; neutrophils are seen in the stratum corneum. OHL can be differentiated from thrush by the fact that OHL cannot be easily scraped off with a tongue blade.[3]

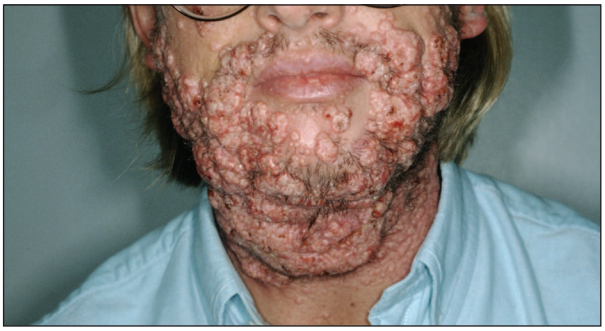
Because they are asymptomatic, most lesions do not need to be treated.[5,6] Lesions that cause dysphagia or are cosmetically displeasing to the patient can be treated topically with tretinoin, podophyllin, or vitamin A or with surgical excision.[1-3,5,6] OHL has been treated successfully with a variety of drugs: oral zidovudine, 300 mg 3 times a day; oral acyclovir, 200 to 400 mg 5 times a day; oral ganciclovir, 1 gram 3 times a day; and IV foscarnet, 40 mg/kg every 8 to 12 hours.

Cytomegalovirus

Cytomegalovirus (CMV) infection is the most common viral

Figure 2.
MOLLUSCUM CONTAGIOSUM

Patient has numerous large pink umbilicated papules and nodules on his face.



infection in patients with HIV whose CD4 cell counts are below 100/mm^3.[2,3] However, CMV does not commonly manifest in the skin; only a few reports in the literature discuss CMV-induced skin lesions, such as perianal and oral ulcerations that may occur as an extension of preexisting CMV-induced gastrointestinal disease.[2,3,5] In addition, macular purpura and leukocytoclastic vasculitis on the lower extremities and small keratotic verrucous lesions on the trunk, face, and extremities can be present.[6]

Diagnosis can be made from histopathology with immunohistochemical stains. Dilated dermal vessels, polymorphous inflammatory infiltrate, and large hyperchromatic intranuclear inclusion bodies can be seen.

Foscarnet, 40 mg/kg IV every 8 to 12 hours; oral ganciclovir, 1 gram 3 times a day; and topical anesthetics for pain are the main treatment options.[1-3,5,6]

Molluscum contagiosum

As CD4 cell counts drop below 100/mm^3, 10% to 20% of patients with HIV will develop molluscum contagiosum (MC) lesions.[1,3,6] These lesions are spread through direct and sexual contact. They predominate on the face and genital areas as firm, pearly pink papules with central umbilication. In patients with HIV, however, they may be more numerous, more verrucous, and larger[3,6] (Figure 2). With progression, they become quite disfiguring. Because the differential diagnosis for MC lesions includes histoplasmosis, cryptococcosis, and penicillium marneffei, accurate diagnosis is critical. Distinguishing MC from these conditions may have important considerations regarding diagnostic workup and therapy.

Although histopathology is useful, a simple molluscum preparation, performed by placing the content of the central umbilication onto a slide and applying Giemsa stain, will demonstrate the Henderson-Patterson bodies, or molluscum bodies, that are manifestations of the poxvirus.[3] Large intracytoplasmic inclusion bodies (molluscum bodies) and epidermal acanthosis are seen on histology.

Treatments for MC include cryotherapy, electrodesiccation, curettage, tretinoin, imiquimod, trichloroacetic acid, carbon dioxide laser, podophyllin, intralesional interferon (1 million units once a week for 4 weeks), and zidovudine (300 mg orally 3 times a day).[1,3,6]

Human papillomavirus

The prevalence of human papillomavirus (HPV) infection is increasing among HIV patients, and HPV has emerged as the most frequently occurring viral sexually transmitted disease.[7] Although HPV may present at any CD4 cell count, extensive involvement does not arise until the count falls below 500/mm^3.[3] These patients have more refractory disease.[5] Transmission occurs via skin-to-skin contact through breaks in the stratum corneum. As with HSV, HPV infection may facilitate HIV infection.[3]

Verruca vulgaris (common warts) appear as small, firm, tan papules on any skin surface; verruca plana are flat-topped, skin-colored papules on the face and dorsal hands. Verruca plantaris are hyperkeratotic papules and plaques on the soles of the feet.[3,6] Condyloma acuminata (genital warts) are characterized by soft, skin-colored cauliflower papules on the genital areas[3] (Figure 3). These lesions may progress to squamous cell carcinoma.[7] Also associated with HPV is cervical dysplasia and invasive carcinoma or bowenoid papulosis of the penis.

Diagnosis can be made clinically and histologically.[1-3] Acanthosis, papillomatosis, hyperkeratosis, elongated rete ridges, and vacuolated cells (koilocytotic cells) are seen.

These lesions can be difficult to treat and patients frequently have relapses. Treatment options include cryotherapy, electrodesiccation, carbon dioxide laser, podophyllin, imiquimod, intralesional interferon and bleomycin, trichloroacetic acid, fluorouracil, and salicylic acid.[1-3,5-7]

BACTERIAL INFECTION

Staphylococcus aureus

Staphylococcus aureus is the most common bacterial pathogen, affecting about 85% of patients with HIV.[6] Approximately 50% of patients with HIV harbor *S aureus* within their nares.[6,8] *S aureus* may manifest in a variety of ways, including folliculitis, impetigo, cellulitis, furuncles/carbuncles, and necrotizing fasciitis (NF).[1,3,6,8-10] Folliculitis presents as widely distributed, pruritic, acneiform papules and pustules. Impetigo is characterized

by red macules and vesicles that can rupture with purulent exudates. Honey-colored crusts will form as satellite lesions appear. Furuncles are deep, tender nodules on hair-bearing areas that develop from the coalescence of several infected follicles, just as carbuncles are a collection of several furuncles. NF is a life-threatening condition usually presenting with extreme pain and areas of erythema, which develop into ulcerations, necrosis, and sometimes hemorrhagic bullae.[10]

Wound cultures, tissue cultures, and blood cultures can be useful diagnostic tests.[1,3,6,8-10] Patients with NF may need radiographic evaluation with either plain films, computed tomography scans, or magnetic resonance imaging to aid in diagnosis.

Histologic examination may also help with the diagnosis.[11] On histology, vesicopustule appears above, within, or below the granular layer, with numerous neutrophils, Gram-positive cocci, and acantholytic cells. Folliculitis presents with a subcorneal pustule in the opening of a hair follicle, with surrounding neutrophilic infiltrate. Furuncles have perifollicular necrosis with numerous neutrophils; a large abscess is seen within the subcutaneous tissue, with Gram-positive cocci in the center of the abscess. The histologic picture of NF and cellulitis are similar. NF reveals acute and chronic inflammation of the subcutaneous fat, muscle, and fascia with necrosis, thrombosis of vessels, and, rarely, organisms. Acute and chronic inflammation may be seen with cellulitis, but the inflammation is more superficial.

Treatment with dicloxacillin or cephalexin is usually sufficient, except in cases of NF, where the combination of penicillin, third-generation cephalosporin, and clindamycin are necessary.[1,3,6,8-10] In patients with NF, adjuvant care with prompt extensive surgical debridement is critical to survival. Furuncles and carbuncles also benefit from incision and drainage on a smaller scale.[3] Topical mupirocin can be applied to nares twice a day the first week of every month to decrease nasal carriage.[6]

Bacillary angiomatosis

Bacillary angiomatosis (BA) is caused by infection with Gram-negative *Bacillus Bartonella henselae*, or *B quintana*, which usually manifests in HIV-infected patients whose CD4 cell count is below 100/mm^3.[3] Although skin is the most commonly involved organ, BA may occur in any organ system.[1,3,6,8] Cutaneous lesions present as firm, red-violaceous papules or nodules that may ulcerate and form a hyperkeratotic crust. Individual lesions may appear clinically similar to a pyogenic granuloma, but the generalized nature and fever, night sweats, chills, and malaise distinguish BA.

Diagnosis can be made on histopathology with a Warthin-Starry silver stain demonstrating the bacillus. Proliferations of capillaries with neutrophilic and mononuclear infiltrates and edema are seen on histology. Other diagnostic tests include serum fluorescent antibody tests and enzyme linked immunosorbent assays.[1,3,6,8] Tissue culture may also be helpful.

Figure 3.
CONDYLOMA ACUMINATA

Patient has multiple pink-brown verrucous papules coalescing into large plaques encasing his penis and scrotum and on his thighs due to human papillomavirus.

Treatment with erythromycin or doxycycline is effective.[1,3,6,8] Relapses may require prophylaxis with either of these agents. Other drugs used to treat BA include cotrimoxazole (trimethoprim and sulfamethoxazole), ciprofloxacin, rifampin, isoniazid, tetracycline, and azithromycin.[1,6]

Mycobacteria infections

Patients with HIV are susceptible to infections with various mycobacteria, including typical mycobacteria, such as *Mycobacterium tuberculosis*, and atypical mycobacteria, such as *M avium-intracellulare* (MAI) *complex* and *M marinum*.[1,3,6,8] Cutaneous *M tuberculosis* infection may be present from cutaneous inoculation of a nonimmune host (tuberculous chancre or tuberculosis cutis miliaris disseminata), in a patient with immunity (tuberculosis verrucosa cutis), or from dissemination in an immune naive or competent host (lupus vulgaris).[3]

The tuberculosis chancre begins as a firm, painless nodule that erodes and forms a tender ulcer.[3,6] Miliary tuberculosis appears as small, red-violaceous papules on which small vesicles form, subsequently forming crusts. Lupus vulgaris first appears as soft red-brown papules that develop into plaques. Other forms exist, such as hypertrophic, vegetative, ulcerative, papular, or nodular. Tuberculosis verrucosa cutis is character-

ized by papules or papulopustules that form in areas of repeated trauma and progress to hyperkeratotic plaques with fissures. Scrofuloderma appears as an extension from underlying suppurative lymph nodes, usually on the neck, and presents as ulcerated nodules with multiple sinus tracts.

Nontuberculous mycobacterial infections appear as erythematous papules and nodules that become keratotic or suppurate and form ulcerations.[3,6] *M marinum* usually presents with verrucous, ulcerated or bullous lesions on the dominant hand arranged in a sporotrichotic pattern; MAI infections are characterized by hemorrhagic or papulonecrotic lesions on the extremities.

Diagnosis can be made by histopathology with acid-fast stains, tissue cultures, and wound cultures.[1,3,6,8,11] The chancre appears as an ulcer with neutrophilic infiltrates and necrosis with numerous bacilli, which later develops epithelioid cells and giant-cell granulomas, then caseation necrosis. Tuberculosis verrucosa cutis has hyperkeratosis, acanthosis, abscesses within the epidermis, tuberculoid granulomas, and numerous bacilli. Histology of lupus vulgaris reveals tuberculoid granulomas, giant cells, caseation necrosis, and, often, fibrosis in long-standing lesions. Scrofuloderma appears as an ulceration or abscess with peripheral tuberculoid granulomas and necrosis. Histology of MAI shows granulomatous inflammation, macrophages containing bacilli, and spindle cell transformation of the macrophages. *M marinum* infection appears with multinucleated giant cells, epithelioid cell granulomas with central necrosis, ulceration, or hyperkeratosis.

Treatment with a multidrug combination, such as isoniazid, rifampin, ethambutol, streptomycin, or pyrazinamide, is quite effective.[1,3,6,8] Atypical infections with *M marinum* can be treated with minocycline, doxycycline, tetracycline, cotrimoxazale, rifampin and ethambutol, or clarithromycin. MAI requires multidrug treatment with ethambutol, rifabutin, and clarithromycin or azithromycin. Treatment options should be carefully considered because many of these drugs interact with highly active antiretroviral therapy (HAART).[3]

Syphilis

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum*, which affects 25% of patients with HIV.[1,3,6] In fact, syphilis is often the presenting disease that leads to a diagnosis of HIV. Syphilis, as with other types of genital ulcers, can facilitate the transmission and acquisition of HIV.[3]

Primary syphilis presents as a painless genital chancre 3 weeks after exposure.[1,3,6,8] Half of the patients progress to secondary syphilis; the other half remain in the latent phase. Secondary syphilis is characterized by diffusely distributed papulosquamous, maculopapular, vesicular, pustular, or hyperkeratotic lesions (Figure 4). Oral ulcerations, patchy alopecia, lymphadenopathy, and condyloma lata (moist flat or wart-like genital lesions) may also be present. Many patients advance to tertiary syphilis with cardiac, neurologic, and cutaneous gummas, which are painless nodules, asymmetrically distributed in groups on the face and trunk.

Diagnosis can be made with treponemal (microhemagglutination-Treponema pallidum [MHA-TB] and fluorescent treponemal antibody-absorption [FTA-ABS]) and nontreponemal (venereal disease research laboratory [VDRL] and rapid plasma reagin [RPR]) serologic tests.[3,8] Often, serologies are atypical in patients with HIV and require darkfield examination or direct fluorescent antibody testing. The nontreponemal tests usually have a higher titer; serologies are rarely impaired or delayed in patients with HIV. *T pallidum* cannot be cultured or gram stained.

In many cases, syphilis is the presenting disease that leads to a diagnosis of HIV infection.

Histopathologic analysis is helpful in making the diagnosis.[11] Histology of primary chancre reveals ulceration, dense plasma cell infiltrate, and necrotizing vasculitis. In secondary syphilis, psoriasiform hyperplasia with dense bandlike lymphocytic and plasma cell infiltrate appear at the dermal-epidermal junction. Tertiary syphilis is characterized by granulomas, multinucleated giant cells, and plasma cells in the dermis.

Treatment of choice is penicillin; the dosage depends of the stage of syphilis.[1,3,6,8] Primary and latent syphilis can be treated with penicillin G benzathine, 2.4 million units intramuscularly (IM) weekly for 3 weeks. Secondary syphilis can be treated with penicillin G procaine, 2.4 million units IM daily for 10 to 14 days, with probenecid, 500 mg orally 4 times a day for 10 to 14 days, followed by penicillin G benzathine, 2.4 million units weekly for 3 weeks. Tertiary syphilis or neurosyphilis should be treated with penicillin G sodium, 3 million units IV every 4 hours for 10 to 14 days, followed by penicillin G benzathine, 2.4 million units IM weekly for 3 weeks. Patients who are allergic to penicillin should be desensitized, then treated with penicillin.

FUNGAL INFECTION

Candida

Candida is the most common fungal infection in patients with HIV, developing in 30% to 50% of patients.[3] It is an ubiquitous organism that is part of the normal flora of the oropharynx and gastrointestinal tract.[3,8] *Candida* may affect the mucosa, nails, and skin.

Oral candidiasis (thrush) may present in several forms, such as pseudomembranous, erythematous, hyperplastic, or angular cheilitis.[3] It is characterized by white plaques on the tongue or buccal mucosa that can be easily scraped off with a tongue blade, producing bleeding or red macular atrophic patches on the buccal mucosa. The presence of thrush in a patient without known risk factors should raise the suspicion for HIV infection.[1] It may coexist with esophageal candidiasis, leading to odynophagia and dysphagia. Esophageal candidiasis is an AIDS-defining illness, occurring when CD4 cell counts fall below 100/mm^3.[8] In addition, vulvovaginal involvement consists of burning/irritation followed by odorous white cottage-cheese discharge from the vagina. Cutaneous candidiasis appears in intertriginous areas as erythematous patches with satellite pustules. Occasionally, *Candida* may invade the bloodstream, leading to life-threatening fungemia.[3] *Candida* onychomycosis typically affects the proximal nail, turning it white.

Immediate diagnosis can be made on microscopic examination of a scraping to which potassium hydroxide is added.[1,3,8] This allows for the visualization of pseudohyphae characteristic of *Candida*. Tissue cultures will show growth of moist, white colonies; blood cultures can be performed if fungemia is suspected. Histologic examination may reveal a subcorneal pustule, as well as pseudohyphae and spores in the stratum corneum.[11]

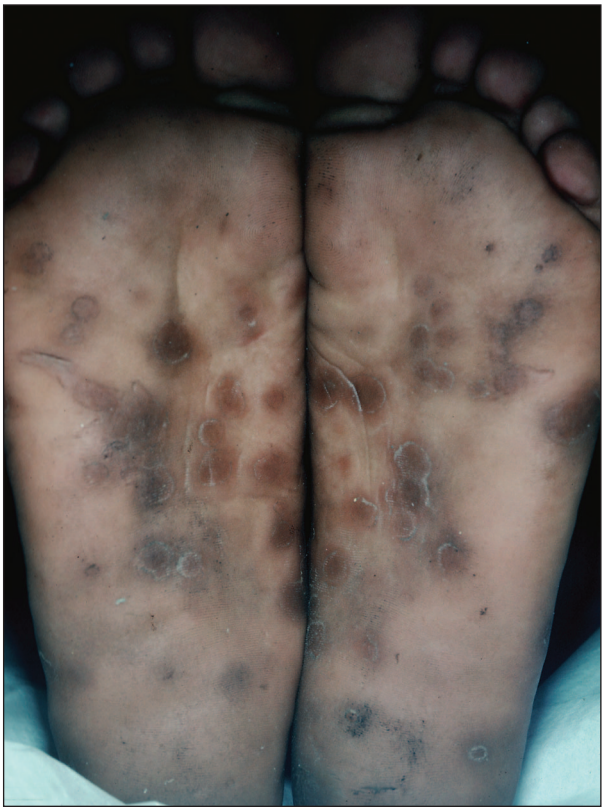
Effective treatment of oropharyngeal candidiasis is accomplished with topical nystatin or clotrimazole; however, patients with AIDS may need fluconazole, 100 mg orally or IV daily for 2 weeks, or 10 mL of oral itraconazole daily for 1 to 2 weeks.[1,3,8] Vulvovaginal candidiasis can be treated with topical azoles or polyenes. Fungemia must be treated with IV fluconazole, 400 mg daily, or amphotericin B, 0.5 to 0.5 mg/kg IV daily.[3] Onychomycosis should be treated with 200 mg of oral itraconazole daily for 12 weeks.[3]

Histoplasmosis

Infection with *Histoplasma capsulatum* rarely causes disease in immunocompetent patients.[8] Inhalation of spores within the soil may lead to disseminated infection, ultimately affecting the skin in 10% to 20% of patients with HIV.[1,3,6,8] Mucocutaneous ulcerations, erythematous macules and papules, pustules, and psoriasiform lesions appear diffusely on the face, trunk, and extremities. Primary cutaneous histoplasmosis is extremely rare.

Figure 4.
SYPHILIS

Patient has multiple brown macules on bilateral plantar aspects of his feet due to infection with *Treponema pallidum*.



Diagnosis is made with tissue culture or on histopathology with Wright-Giemsa or methenamine silver stains, which show the disease's characteristic budding yeast with its fruiting body.[1,3,6,8] Treatment consists of amphotericin B, itraconazole, or fluconazole, with lifelong maintenance with any of the above mentioned agents.[1,3,6,8]

Cryptococcosis

Much like histoplasmosis, cryptococcosis is caused by inhalation of contaminated soil or bird droppings, which subsequently disseminates to other organ systems in patients with HIV.[1,3,6,8] Disseminated cutaneous involvement occurs in 10% to 20% of patients. Primary cutaneous disease is also very rare. Lesions consist of erythematous papules, nodules, pustules, verrucous, or granulomatous lesions. Ulcerations appear predominantly on the head and neck, and also appear on the

trunk and extremities.[1,3,6,8]

Biopsy for histopathology can be stained with India ink or mucicarmine to aid in diagnosis by visualizing the wide, round polysaccharide capsule and budding cells.[1,3,6,8] Tissue cultures, touch preps, and serum antigens are also helpful. Treatment includes fluconazole, flucytosine, or amphotericin B, with lifelong maintenance with fluconazole.[1,3,6,8]

Coccidioidomycosis

Reactivation of pulmonary coccidioidomycosis occurs in patients with HIV, leading to disseminated cutaneous involvement.[1,3,6,8] Normally, these papules, pustules, and plaques are initially asymptomatic, but later coalesce into large verrucous plaques with ulcerations and draining sinuses. Mucosal ulcerations are not present. Erythema nodosum and erythema multiforme may occur as well.

Diagnosis is made by histopathology, which shows spherules free and within giant cells, and tissue culture.[1,3,6,8] Treatment with oral azoles or amphotericin B, followed by lifelong maintenance with oral azoles, is necessary.[1,3,6,8]

PARASITIC INFECTION

Scabies

Scabies infection with *Sarcoptes scabiei* is the most common parasitic infection in patients with HIV, affecting 20% of patients.[6] It is extremely contagious in patients with HIV and has resulted in several institutional epidemics. Patients with HIV are more likely to be infected with crusted (Norwegian) scabies, characterized by hyperkeratotic, diffusely distributed plaques and hyperkeratotic palms and soles.[8] This form is also seen in patients with neurologic disease. Typical burrows are often difficult to visualize in this form. Secondary bacterial infection with resultant fatal septicemia can occur.[6]

Scabies infection with *Sarcoptes scabiei* is the most common parasitic infection in patients with HIV, affecting 20% of patients.

Misdiagnosis of scabies is common.[3] It is generally diagnosed by finding scabies mites, eggs, or feces on microscopic visualization with the aid of mineral oil and through biopsy for histopathology.[1,3,6,8] On histology, mites are rarely seen; eosinophils are more commonly in the dermis.

Two topical treatments with 5% permethrin, 1 week apart, or a single dose of ivermectin, 200 mcg/kg orally, are both effective.[1,3,6,8] Lindane should be used cautiously because it may cause neurotoxicity.[3] Keratolytic agents may increase the efficacy of treatment by removing some of the thick scales, allowing improved penetration.[6] Clothing, bed linens, and towels should be carefully washed to prevent reinfection.

Pneumocystosis

Cutaneous dissemination of *Pneumocystis carinii* infection is rare, mostly affecting patients with HIV who take aerosolized pentamidine prophylactically.[1,6,8] This aerosolized treatment is believed to protect the lungs, but it allows *P carinii* to escape and present in other organ systems. Friable red-blue papules and nodules appear within the external auditory canals and nares.[1,6,8] Diagnosis is made with histopathology.[1,6,8] Treatment with IV pentamidine or cotrimoxazole is curative.[1,6,8]

DRUG REACTIONS

Drug eruptions occur more frequently in patients with HIV.[12,13] This observation has been attributed to several factors. First, patients with HIV take more medications than the general population, exposing them to greater risk.[13] Second, medications prescribed for these patients carry a greater relative risk of causing drug reactions, such as cotrimoxazole and other sulfa medications.[13] Third, patients with HIV have been found to have glutathione deficiency, with subsequently reduced ability to detoxify active drug metabolites.[13] Other associations include the coinfection with cytomegalovirus, toxoplasmosis, and Epstein-Barr virus and CD4 cell counts below 200/mm^3.[13]

The most common drug eruption in patients with HIV is the generalized morbilliform exanthem, which develops 7 to 10 days after the patient has taken the culprit medication and resolves after the medication is discontinued.[12] Vasculitis, urticaria, and anaphylaxis can occur as well. Erythema multiforme is characterized by target lesions in an acral distribution; they may also be present in the oral cavity. More severe drug reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN), which is characterized by varying degrees of bulla formation and subsequent epidermal detachment with mucosal erosions.

On histology, the morbilliform eruption is characterized by sparse perivascular infiltrate of eosinophils and lymphocytes, with vacuolization of the dermal-epidermal junction.[19] Erythema migrans, which is at the opposite end of the spectrum with TEN, displays keratinocyte necrosis with subepidermal bullae and eosinophilic infiltrate. Histologic examination

can be helpful in distinguishing TEN from the more superficial staphylococcal scalded skin syndrome; TEN is characterized by full-thickness epidermal necrosis and staphylococcal scalded skin syndrome remains in the granular layer. A frozen section of the blister roof is often necessary for rapid determination of where the separation lies.

Drug reactions can be treated with IV antihistamines and IV or topical steroids, as well as immediate withdrawal of the medication causing the reaction.[1,3,12] One exception is TEN, which should be treated with IV immunoglobulin, supportive care in the intensive care unit, and aggressive wound care.[13-15] In the authors' experience, steroids are contraindicated for TEN.

NEOPLASTIC INFECTION

Kaposi sarcoma

Kaposi sarcoma (KS) is a vascular neoplastic condition linked to infection with human herpesvirus 8 (HHV-8).[1,2,5] The 4 different types of KS include classic, endemic, epidemic, and idiopathic.[5] The epidemic, or AIDS-associated type, is characterized by more aggressive and widespread mucocutaneous lesions. Several contributing factors have been associated with the development of KS, such as immune factors, coexisting viral infections, and genetics. Patients with CD4 cell counts greater than 300/mm^3 and who have no other opportunistic infections have the best prognosis.[5]

KS may present as red or brown-violaceous macules, patches, plaques, or nodules in areas of trauma[1,2,5] (Figure 5). One-third of the lesions appear on the extremities. Lesions may be distributed singly or in groups; the grouped lesions may coalesce into large areas of involvement. These lesions often ulcerate and become secondarily infected.

KS can be diagnosed based on histopathology.[1,2,5] Macular lesions show atypical, ectatic vessels in the upper dermis associated with an inflammatory infiltrate containing plasma cells. Plaque lesions show collections of small vessels and endothelial cells in the upper dermis. Tumors show a spindle cell neoplasm with prominent extravasation.

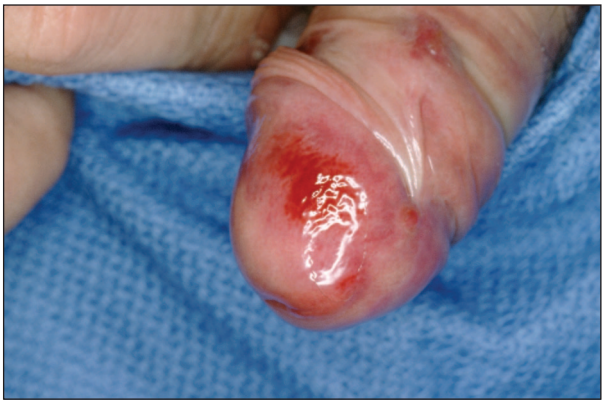
Treatment includes topical alitretinoin, cryotherapy, radiation, intralesional vinblastine or interferon alpha, or IV doxorubicin or daunorubicin.[1,2,5] Improvement in CD4 cell counts with HAART also leads to resolution of lesions.

Lymphoma

The development of lymphoma is associated with immunosuppression. Partly through this mechanism, patients with HIV develop lymphoma at a greater rate than the general population. The most commonly associated lymphomas are Hodgkin, non-Hodgkin (NHL), cutaneous T cell (CTCL), and human T-lymphotropic virus type I (HTLV-1).[1,2,5] Hodgkin lymphoma and NHL lesions usually present as red-violaceous nodules on the head and neck that may ulcerate. CTCL may present as large diffuse erythematous patches or plaques, which can progress to erythroderma or tumor formation. HTLV-1 may mimic a viral exanthem with morbilliform papules and fine vesicles.

Figure 5.
KAPOSI SARCOMA

Patient has red-violaceous eroded plaques on his glans penis due to infection with human herpesvirus 8.



Diagnosis can be made on histopathology, gene rearrangement, flow cytometry, and immunophenotyping.[1,5] Patch stage CTCL is characterized by epidermotropism of lymphocytes, with some hyperplasia and dermal fibrosis. In the plaque stage, there is a diffuse infiltrate of lymphocytes in the dermis, also with dermal fibrosis and epidermotropism. In the tumor stage, dense dermal neoplasms consisting of lymphocytes predominate. Sézary syndrome is similar to patch stage on histology, but peripheral smears reveal characteristic Sézary cells, which are large lymphocytes with cerebriform nuclei. Hodgkin lymphoma is characterized by the presence of Reed-Sternberg cells, which are large binucleate cells with irregular cell membranes.

Treatment for these lymphomas in patients with HIV does not differ from the treatment for uninfected patients.[1,5] Regimens consisting of combinations of chemotherapy, such as methotrexate, prednisone, bleomycin, doxorubicin, cyclophosphamide, and vincristine, can be given to patients with Hodgkin lymphoma, NHL, and HTVL-1. CTCL responds to standard treatments, including psoralen and ultraviolet A (PUVA) light therapy, total body electron beam, topical nitrogen mustard, and retinoids; however, some of these options are immunosuppressive, which may lead to rapid death.

Figure 6.
PSORIASIS

Patient has multiple small pink-violaceous plaques with white scale on his trunk.

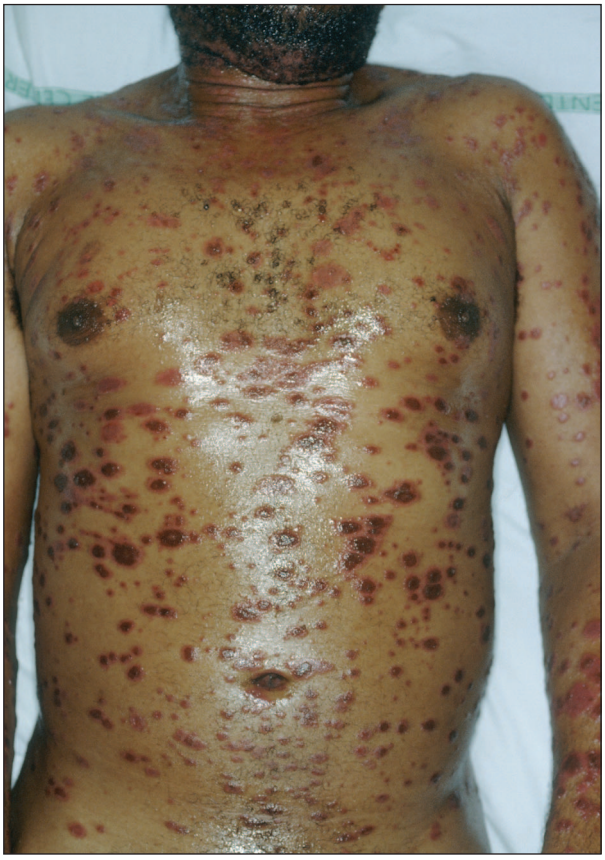
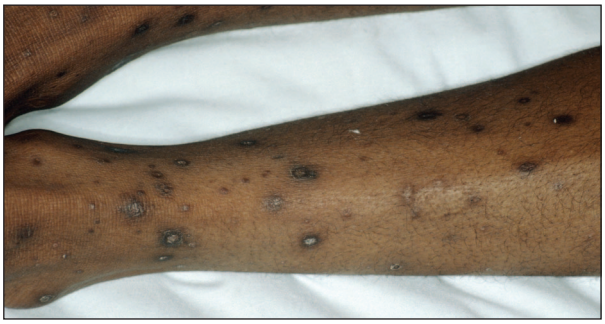


Figure 7.
PRURITIC PAPULAR ERUPTION OF HIV

Patient has many excoriated brown papules and nodules on bilateral legs.



NONINFECTIOUS DISEASE

Psoriasis

Psoriasis affects up of 2% of the HIV population, which is comparable to the percentage in the general population.[3,8] Psoriasis may occur before or after infection with HIV; however, in either case, it presents more severely, often with 2 coexisting patterns at the same time.[3] Patients with psoriasis vulgaris usually have large pink plaques with thick white scales involving a significant amount of body surface area.[1,3,8] Pustular psoriasis presents with large erythematous plaques with multiple small sterile pustules, which coalesce into large lakes of pus. Erythrodermic psoriasis is characterized by erythema, encompassing 100% of body surface area with extensive exfoliation. Guttate psoriasis usually occurs after a streptococcal throat infection and may appear as multiple small pink plaques with white scales.

On histology, there are mounds of parakeratosis, acanthosis, and dilated vessels at the tips of the dermal papillae and a thin granular layer.[11] Psoriasis is usually refractory to treatment. Avoidance of immunosuppressive treatment options, such as cyclosporin and methotrexate, in patients with HIV is recommended.[1,3,8] Although potentially immunosuppressive, phototherapy has been used uneventfully in patients with HIV.[1,3,8] Other treatment options include topical steroids or retinoids, acitretin, or zidovudine.

Eosinophilic folliculitis

Eosinophilic folliculitis is a rare pruritic eruption characterized by multiple sterile follicular pustules and urticarial papules on the face, trunk, and extremities.[1,3,8] It is usually diagnosed on biopsy. The involved follicles show spongiotic changes with eosinophilic and lymphocyte infiltration of the epidermis with eosinophilic pustules.[11]

Characteristically, patients have been treated empirically as having bacterial folliculitis and subsequently failed several courses of antibiotics.[1] The cultures of the pustules have grown nothing. Eosinophilia, leukocytosis, and elevated IgE levels are often present.[1,3,8] Ultraviolet B (UVB) light therapy and topical steroids are the mainstay of treatment.

Pruritic papular eruption of HIV

Pruritic papular eruption (PPE) was discovered in 1985 by James et al.[16] Its etiology is unclear, but PPE seems to be one of the earliest manifestations of HIV.[17,18] In fact, it may be the initial manifestation of HIV in 25% of patients. PPE is regarded as a cutaneous marker of advanced HIV (CD4 <50/mm^3). It can affect up to 50% of patients with HIV, depending on the geographic area.[17]

PPE is characterized by multiple, chronic, pruritic, hyperpigmented papules distributed symmetrically on the trunk and extremities. Eosinophilia and elevated IgE levels have been found in these patients. PPE is primarily a clinical diagnosis, but on histology, mixed perivascular lymphocytic infiltrate with eosinophils can be seen.[19] PPE is normally recalcitrant to most conventional antipruritic therapies. Success has been reported with UVB with or without oral sedating antipruritics, as well as pentoxifylline.[19]

Seborrheic dermatitis

Seborrheic dermatitis can affect 4% of the general population and 85% of the HIV-positive population.[3] It may present at any CD4 cell count, but usually becomes extensive and refractory as CD4 cell counts decline. HAART therapy has decreased the number of refractory cases. Some believe that infection with Pityrosporum may be associated with seborrheic dermatitis.

Seborrheic dermatitis usually affects sebaceous areas on the face, scalp, chest, back, and intertriginous areas as yellow-white greasy scales on erythematous patches.[1,3,8] It may even progress to erythroderma.[3] Diagnosis is made clinically as well as on histopathology, which reveals spongiotic dermatitis, parakeratosis, elongation of the rete ridges, dermal plasma cells, and lymphocytes.[11] Treatment options include UVB light therapy, ketoconazole shampoo or cream, topical steroids, sulfur, coal tar, and salicylic acid.[1,3,8]

Xerosis/acquired ichthyosis

Xerosis/acquired ichthyosis may be present in 30% of patients with HIV.[3] The exact pathogenesis of xerosis is unknown, but poor nutrition, immunosuppression, and chronic illness play a role.[1,3,8] Disease severity does not correlate with the level of immunosuppression; however, the lower the CD4 cell counts, the more severe and unremitting the disease is in these cases. Patients with xerosis present with fine white scales diffusely distributed, which may lead to fissuring and secondary bacterial infections. Acquired ichthyosis is usually more severe, with the presence of skin thickening and fish-like scales that may lead to fissuring and bacterial infection as well.[8]

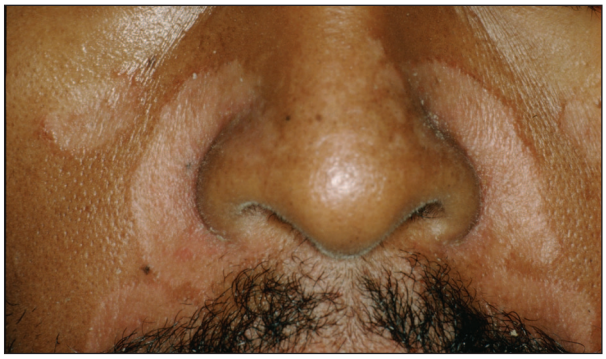
On histology, hyperkeratosis with a normal dermis can be seen.[11] Emollients, topical steroids, and oral antihistamines may be of some benefit.[1,3,8] Acquired ichthyosis usually requires the use of keratolytics or low-dose acitretin.[8]

Atopic dermatitis

Patients with atopic dermatitis (AD) may present with the triad of allergic rhinitis, asthma, and AD.[3] Patients with AD have a TH1 cytokine profile, which is similar to the cytokine profile seen in HIV disease. The TH1 cytokine profile is characterized by elevated IgE levels, increased eosinophils, and increased interleukin 4 and 5. Therefore, patients who are HIV-positive commonly manifest AD and often have severe disease that is recalcitrant to therapy.[1,3]

Figure 8.
SEBORRHEIC DERMATITIS

Patient has hypopigmented patches with greasy white scales on his cheeks, nose, and nasolabial folds.



AD manifests as erythematous patches and plaques with fine scaling. Over time, scratching leads to lichenification or lichen simplex chronicus, as well as secondary bacterial infection. Other cutaneous manifestations of AD include dennie morgan lines, hyperlinear palms, follicular accentuation, and pityriasis alba. Frequently, AD may progress to erythroderma.[3]

Diagnosis can be made on histopathology or with careful history and a physical.[1,3] Histology reveals spongiosis, exocytosis of lymphocytes, elongated rete ridges, hyperkeratosis, and parakeratosis.[11] Treatment options include emollients, oral antihistamines, topical steroids, and avoidance of irritants. Immunosuppressant medications should be avoided, but phototherapy has been used with success.[1,3]

CONCLUSION

Skin disease caused by opportunistic and other infections and inflammatory conditions of the skin can result in serious complications in patients with HIV. Because cutaneous manifestations are often the presenting sign of HIV, the management of skin-related diseases has increasingly become important for prompt and accurate diagnosis of historically rare conditions. Clinicians need to be cognizant of the differences inherent in treating patients with HIV to deliver prompt and sometimes life-saving interventions. ●

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- Take the test, recording your answers in the test answers section (Section B) of the CE enrollment form. Each question has only one correct answer.
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Cutaneous Manifestations of HIV: A Primer

CME CATEGORY 1 1 Hour | ce ANCC/AACN 2.5 Contact Hours | Rx PHARMACOLOGY .5 Hour

Jennifer T. Trent, MD, and Robert S. Kirsner, MD

PURPOSE: To provide physicians and nurses with an overview of the characteristics and treatments for skin lesions associated with HIV/AIDS.

TARGET AUDIENCE: This continuing education activity is intended for physicians and nurses with an interest in identifying and managing skin lesions in patients with HIV/AIDS.

OBJECTIVES: After reading the article and taking the test, the participant will be able to:

1. Identify the characteristics of skin lesions associated with HIV/AIDS.
2. Identify treatment options for skin lesions associated with HIV/AIDS.

1. Herpes simplex virus presents as

a. large diffuse erythematous patches or plaques.
b. firm, red-violaceous papules or nodules that may ulcerate and form hyperkeratotic crust.
c. small, firm, tan papules on any surface.
d. grouped vesicles on a red base that may progress to deep ulcerations and necrosis.

2. The mainstay of treatment for herpes simplex virus associated with HIV is

a. itraconazole.
b. clindamycin.
c. acyclovir.
d. amphotericin B.

3. HIV-infected patients with acyclovir resistance may receive

a. foscarnet.
b. interferon alpha.
c. ketoconazole.
d. amphotericin B.

4. The vesicles associated with primary varicella infection are initially seen on the

a. chest.
b. head and face.
c. lower extremities.
d. neck.

ENROLLMENT FORM: *Advances in Skin & Wound Care*, April 2004
Cutaneous Manifestations of HIV: A Primer

A. Registration Information:

Last name _____ First name _____ MI ___

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Registration Deadline: March 31, 2005
Contact hours (nurses): 2.5 Pharmacology hours .5 Fee: $14.95 for nurses
Category 1 credit (physicians): 1 hour $20 for physicians

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3.	❍	❍	❍	❍
4.	❍	❍	❍	❍
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23.	❍	❍	❍	❍
24.	❍	❍	❍	❍

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5. Did you perceive any evidence of bias for or against any commercial products? If yes, please explain. ❑ Yes _____ ❑ No
6. Please state 1 or 2 topics that you would like to see addressed in future issues. _____
7. It took ___(hr) ___(min) to read and review the article and take the test.

*In accordance with the Iowa Board of Nursing administrative rules governing grievances, a copy of your evaluation of the CE offering may be submitted directly to the Iowa Board of Nursing.

5. The lesions associated with zoster or shingles are characterized by
a. firm, pearly pink papules with central umbilication.
b. grouped vesicles on a red base that may progress to deep ulcerations and necrosis.
c. dermatomal distribution of vesicles on a red base.
d. red macules and vesicles that can rupture with purulent exudate.

6. Treatment for varicella-zoster is similar to herpes simplex except that
a. acyclovir is contraindicated for varicella-zoster.
b. the drug dosages are typically higher for varicella-zoster.
c. the drug dosages are typically lower for varicella-zoster.
d. foscarnet is preferred over acyclovir for varicella-zoster.

7. Lesions associated with oral hairy leukoplakia are characterized by
a. soft, skin-colored cauliflower papules.
b. hyperkeratotic papules and plaques.
c. flat-topped, skin-colored papules.
d. white corrugated plaques.

8. When lesions associated with oral hairy leukoplakia cause dysphasia, the patient may be treated with
a. ketoconazole.
b. tretinoin.
c. vinblastine.
d. famciclovir.

9. Lesions associated with molluscum contagiosum appear as
a. firm, pearly pink papules with central umbilication.
b. large diffuse erythematous patches or plaques.
c. hemorrhagic bullae.
d. red-brown papules that develop into plaques.

10. Lesions associated with molluscum contagiosum may be treated with
a. cryotherapy.
b. foscarnet.
c. salicylic acid.
d. acyclovir.

11. Hemorrhagic bullae may occur with
a. folliculitis.
b. cellulitis.
c. necrotizing fasciitis.
d. molluscum contagiosum.

12. Treatment for necrotizing fasciitis may include
a. amphotericin B.
b. penicillin.
c. valacyclovir.
d. itraconazole.

13. Which mycobacteria infection manifests as small, red-violaceous papules?
a. lupus vulgaris
b. tuberculosis verrucosa
c. scrofuloderma
d. miliary tuberculosis

14. Treatment of lesions associated with *Mycobacterium tuberculosis* may include
a. minocycline.
b. clarithromycin.
c. rifampin.
d. azithromycin.

15. Oral candidiasis
a. does not raise suspicion of HIV infection.
b. cannot be scraped off with a tongue blade.
c. rarely coexists with esophageal candidiasis.
d. is characterized by white plaques on the tongue or buccal mucosa.

16. Patients with AIDS and oropharyngeal candidiasis may need treatment with
a. fluconazole.
b. rifampin.
c. penicillin.
d. tetracycline.

17. In patients with HIV infection, scabies is typically characterized by
a. friable red-blue papules and nodules.
b. large diffuse erythematous patches or plaques.
c. large pink plaques with thick white scales.
d. hyperkeratotic, diffusely distributed plaques.

18. Treatment for scabies may include
a. pentamidine
b. flucytosine.
c. permethrin.
d. tetracycline.

19. The most common skin reaction to medications in patients with HIV is
a. toxic epidermal necrolysis.
b. generalized morbilliform exanthem.
c. urticaria.
d. erythema multiforme.

20. Toxic epidermal necrolysis is treated with IV
a. foscarnet.
b. steroids.
c. fluconazole.
d. immunoglobulin.

21. Lesions associated with Kaposi sarcoma
a. may appear singly or in groups.
b. do not ulcerate.
c. rarely appear on the extremities.
d. are always grouped.

22. Kaposi sarcoma lesions may be treated with
a. alitretinoin.
b. ultraviolet light therapy.
c. curettage.
d. trichloracetic acid.

23. Atopic dermatitis manifests as
a. large diffuse erythematous patches or plaques.
b. erythematous patches and plaques with fine scaling.
c. large pink plaques with thick white scales.
d. hyperkeratotic, diffusely distributed plaques.

24. Treatment for atopic dermatitis may include
a. topical retinoids.
b. topical steroids.
c. zidovudine.
d. keratolytics.