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HIV-related skin disease in the era of antiretroviral therapy: recognition and management

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Abstract

Anti-retroviral therapy (ART) has revolutionized the treatment and prognosis of people living with HIV (PLHIV). With increased survival and improved overall health, PLHIV are experiencing dermatologic issues both specific to HIV and common to the general population. In this new era of ART, it is crucial for dermatologists to have a strong understanding of the broad range of cutaneous disease and treatment options in this unique population. In this review, we outline the most common skin diseases in PLHIV, including HIV-associated malignancies, inflammatory conditions, and infections, and focus on the role of ART in altering epidemiology, clinical features, diagnosis, and treatment of cutaneous conditions.

Introduction

The life expectancy, epidemiological makeup, diagnostic challenges, and treatment algorithms affecting people living with HIV (PLHIV) have changed drastically in the era of combined anti-retroviral therapy (ART). The population of PLHIV is increasingly diverse

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and older. The management of PLHIV increasingly includes common noninfectious entities like psoriasis in addition to rare opportunistic infections and infection-associated malignancies. This review serves as a practical guide for the modern dermatologist to the recognition and management of common HIV-associated skin conditions in the era of ART. We review those entities that are common in HIV, have a changing clinical context, and/or have innovations in management.

1. HIV-associated Malignancies

1.1 Kaposi sarcoma

AIDS-related Kaposi sarcoma (KS) is an epidemiologic variant of an angiogenic malignancy associated with the human herpes virus 8 (HHV8) (1–3). The ART-era drastically changed the epidemiology and prognosis of AIDS-related KS (4, 5). The United States has seen an 80% reduction in the incidence of KS since the ART era, from 1282 to 190 per 100,000 person-years (5, 6). However, despite significant reduction in incidence, KS remains one of the most common cancers in resource-poor settings such as sub-Saharan Africa. As of 2018, KS was still the leading cause of cancer incidence and cancer mortality in Malawi, Mozambique, Uganda, and Zambia. (7) Even in the ART era, 1 in 25 people living with HIV were likely to develop KS (5). The risk of KS is thought to be inversely related to CD4+ count, though KS is increasingly being discovered in patients with CD4+ counts over 350. In addition, a novel group of patients who are already virally suppressed on ART has been noted to develop new KS, possibly related to immunoscenesence (8–10).

KS typically presents with oral lesions, and/or multifocal cutaneous violaceous macules that may develop into papules and tumors, but may also present as patches and plaques (11). The disease has a predilection for the lower extremities, and lymphadenopathy with downstream lymphedema of the legs and/or genitals being common. Visceral involvement of the airway and gastrointestinal system can be fatal. In children, lymphadenopathy, rather than lymphedema, may be prominent (12).

Unfortunately, KS presents a diagnostic challenge using clinical features alone. (Figure 1). The myriad of presentations make room for multiple KS mimickers, including bacillary angiomatosis, syphilis, post inflammatory hyperpigmentation, lichen planus and melanoma, among others (11, 13). These lesions may also coexist (14). The results of empiric treatment without histopathological differentiation can be devastating. For example: bacillary angiomatosis, while readily responsive to antibiotics, can disseminate if empirically treated with chemotherapy for presumed KS (15). Therefore, the World Health Organization (WHO) recommends biopsy with histopathological examination for diagnosis (16). There are several new, novel point of care diagnostic strategies currently being explored for point of care diagnosis, including PCR and portable confocal microscopy (17).

The merits of staging disease to determine prognosis are debated in the literature. The AIDS Clinical Trials Group (ACTG) Staging System for KS was developed and validated during the pre-ART era (18, 19). The system’s prognostic value has been debated since the advent of ART (20–22). The staging criteria consider the extent of disease (T0 or T1), the degree of immunosuppression (I0 or I1) and the severity of AIDS (S0 or S1) (Table 1).

Treatment with ART is virtually universally recommended, though an initial clinical deterioration of KS may be seen as a manifestation of immune reconstitution inflammatory syndrome (23). The question of which patients might benefit from chemotherapy in addition to ART in the setting of AIDS-related KS is an area of active research (24, 25). At present, the WHO recommends starting chemotherapy at the same time as ART in patients with severe disease, which includes symptomatic visceral disease, lymphedema, or oral lesions that interfere with function such as walking or swallowing (Table 1) (16). It is not yet clear if there is a subset of patients with more mild disease that might benefit from early addition to chemotherapy.

The recommended systemic chemotherapy for the treatment of AIDS-related KS are pegylated anthracyclines: pegylated-liposomal doxorubicin or liposomal daunorubicin (16, 26). This regimen is preferred over bleomycin and vincristine (BV) combinations for better efficacy and side effect profile; however, in resource poor settings, BV is still most commonly used due to expense and transportation issues (27–30), though recent advocacy efforts are addressing this access disparity. Paclitaxel is a plausible second-line agent; a clinical trial demonstrated 56% of patients had a complete or partial response on the regimen after failing pegylated anthracycline or another chemotherapy regimen (31). Local treatments may also be used if control of specific lesions is desired. Alitretinoin, radiation therapy, imiquimod,(32, 33) and intralesional vinblastine have been used for this purpose (34, 35). Overall, the prognosis for KS has improved in the ART era with a 6% annual decline in hazard rate (CI −8% to −4%) (6).

1.2 Cutaneous Lymphoma

Cutaneous lymphomas are a diverse group of diseases in PLHIV. In PLHIV, cutaneous lymphomas include both lymphoproliferative disorders typically associated with the skin, such as mycosis fungoides, anaplastic large cell lymphoma, and plasmablastic lymphoma, as well as disorders not typically associated with the skin, like Burkitt lymphoma (36–38). Although mycosis fungoides is a common type of cutaneous lymphoma in the general population, it is less common in PLHIV (39).

PLHIV are at significant risk for cutaneous lymphomas. PLHIV are at least 2.4 times more likely to develop cutaneous lymphoma than the general population (40). Lymphoproliferative disorders are far more common in patients with AIDS, and may be the first presentation thereof (36, 39, 41).

Infectious agents are strongly associated with some types of cutaneous lymphoma in PLHIV. For example, the majority of plasmablastic lymphoma cases reported have been associated with EBV and/or HHV-8 infection (41, 42). EBV has also been associated with other B-cell lymphomas in PLHIV, as well as with non-lymphoma HIV-associated cancers like smooth muscle tumors (36, 43). HHV-8 is strongly associated with cutaneous anaplastic large cell lymphomas in PLHIV (44). HTLV-II RNA was detected in one report of a HIV+ patient with cutaneous T-cell lymphoma (45). The relationship between HIV and these viruses in malignant transformation is not completely understood.

There are many reported clinical presentations of cutaneous lymphomas, ranging from a single nodule to erythroderma (46). Notably, plasmablastic lymphomas commonly occur as nodules in the oral cavity (42). Lymphomas are defined primarily by histologic criteria. Therefore, a biopsy is required for diagnosis. After histopathological examination, clinicians should consider secondary syphilis in the differential diagnosis of cutaneous T-cell lymphoma, which may appear with large atypical-appearing CD8+ cells (47). Imaging should be pursued for staging and differentiation between primary cutaneous and systemic lymphomas.

The clinical course of primary cutaneous lymphoma may be more or less aggressive than its systemic counterpart depending on the type of lymphoma. For example, while systemic plasmablastic lymphomas are known to be aggressive, resulting in death within 6 months of diagnosis, primary cutaneous plasmablastic lymphomas generally have a more indolent course (42). The opposite has been reported regarding primary cutaneous anaplastic large T-cell lymphomas, which are more aggressive than their systemic counterpart (48). Regardless, when death occurs in PLHIV with cutaneous lymphoma, complications of immunocompromise, rather than lymphoma itself, are usually the cause (49, 50).

Because of this, treatment strategies are focused on optimizing immune status by initiating or continuing ART. Lymphoma may clear with ART alone (42, 48, 50, 51). Singular, obstructive, or disfiguring lesions may be irradiated or excised (48). Systemic chemotherapy should be targeted to the type of lymphoma, and success with systemic chemotherapy for the treatment of plasmablastic lymphoma has been reported (37).

1.3 Melanoma

The relationship between HIV infection and the development of melanoma is poorly understood. There is conflicting data regarding the association between these diseases. Because ART regimens and HIV itself are photosensitizing, and the risk of melanoma is strongly related to the degree of sun exposure, it would seem to follow that HIV increases the risk of melanoma (52–56). Studies alternatingly support moderately increased or moderately decreased risk of melanoma in PLHIV compared to the general population (6, 40, 52, 57–59).

Regardless, melanoma has an aggressive course with increased mortality when it does occur in PLHIV (6, 13, 60). The mechanism for the poor prognosis is not elucidated, but may be related to decreased antitumor activity of CD4+ cells in PLHIV (57, 61). Two biologic therapies that promote CD4+ antitumor activity, ipilimumab, a CTLA-4 inhibitor, and pembrolizumab, a programmed-death receptor 1 inhibitor, are being explored for the treatment of melanoma in PLHIV (62, 63). To date, use of these therapies has only been documented in case reports.

Recommendations for management of melanoma in PLHIV are otherwise not different from the management of melanoma in the general population. ART should be continued, but will not necessarily affect the clinical course of melanoma (64).

1.4 Keratinocyte Cancer

Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are among the most common cancers in both the general population and PLHIV (65, 66). In PLHIV, these cancers are both more common and have unique clinical and epidemiological features.

Among PLHIV, men, particularly MSM, have a 2.1-fold increased incidence of BCC compared to the general population; both men and women with HIV have a 2.6 fold higher incidence rate of SCC (66). Advanced degree of immunosuppression has been associated with increased incidence of SCC but not BCC (66). This observation is likely due to the association between SCC and HPV (see section on HPV-associated SCC below). PLHIV with BCC are more likely to be older, male, with higher household income (66). Some authors have implicated increased sun exposure in this population as a possible reason for the increased incidence of BCC (66, 67). Both malignancies are detected at a younger age than in the HIV negative population (66).

Clinically, in PLHIV BCC is more common on the extremities than the head and neck region, compared to the general population (6, 66). PLHIV have similar clinical presentations of keratinocyte cancer by invasiveness and differentiation, compared to the general population (66).

Diagnosis of keratinocyte cancers is made by biopsy (Figure 2). Treatment of keratinocyte cancers in PLHIV is similar to treatment in the general population (68). However, clinicians should be aware that hesitance to use surgery when appropriate may contribute to an extremely high rate of recurrence of keratinocyte cancers in this population (69).

1.4.1 HPV-associated SCC—While the prevalence of HIV-associated cancers like KS and NHL has decreased in the ART era, the prevalence of HPV-associated cancers has not (59). The rate of mucosal HPV infection in PLHIV is high, as is the prevalence of HPV-related cytological abnormalities. In one study, the prevalence of HPV-related anal dysplasia was as high as 43% in HIV+ men (70). The relative risk of HPV-associated anal cancer in HIV-infected men compared to HIV-uninfected men is 37.9, and in HIV-infected women compared to uninfected women is 6.8 (71). In women with HIV, the relative risk of invasive cervical cancer is also increased (5.8) (71). HPV infection in more than one mucosal area in the same patient is common (70).

The bivalent, quadrivalent, and nonavalent HPV vaccines are safe, immunogenic, and recommended for HIV-infected males and females aged 9 to 26 years old (72). The bivalent and quadrivalent vaccines protect against HPV types 16 and 18, which cause approximately 66% of cervical cancers and the majority of other HPV-associated cancers (73). The nonavalent vaccine protects against an additional 5 virus types collectively responsible for 15% of cervical cancers (73). The quadrivalent and nonavalent vaccines also protect against HPV types 6 and 11, which cause anogenital warts (73).

In addition, anal and cervical cancer screening are recommended for HIV positive patients. Dermatologists should ask about symptoms like pain, bleeding and itching, and perform a visual inspection of the area. The New York State Department of Health AIDS Institute

recommends annual anal cytology in all HIV+ MSM, any HIV patient with a history of anogenital condyloma/warts, and HIV+ women with a history of abnormal cervical or vulvar histology (74). The Infectious Disease Society of America (IDSA) guidelines add that HIV+ women with a history of receptive anal intercourse should also be screened (75). However, there are no universally accepted guidelines (76).

The presence of genital warts in an HIV patient should encourage the dermatologist to refer for cervical and anal cancer screening, as discussed above. Dermatologists should also have a low threshold to biopsy atypical-appearing warts given that warts may mimic and can rapidly progress to malignancy in this population. See the below section on HPV for further information.

Non-invasive therapies such as chemotherapy, radiation therapy and topical imiquimod can be used for the treatment of HPV-associated anal cancer (77, 78). Dermatologists may also refer appropriate patients for surgical intervention, which may lower the risk of recurrence (79).

2. Inflammatory Conditions

2.1 Psoriasis

There has been debate in the literature on the prevalence of HIV-associated psoriasis (80). The largest study on this subject to date found no association when compared to the prevalence of psoriasis in the general population but other smaller studies have noted an increased rate of psoriasis in HIV patients (81–83).

The clinical features of HIV-related psoriasis are different than psoriasis in the general population. Although plaque psoriasis is still the most common manifestation, unusual forms like rupoid psoriasis, sebopsoriasis, annular psoriasis, palmoplantar keratoderma are more prevalent in patients with HIV (80, 84–86). Psoriasis with multiple morphologies, acute onset of psoriasis, acutely worsening psoriasis, and erythroderma are also concerning for possible underlying immunosuppression (80, 85). Psoriasis has been noted to worsen or emerge with increased immunosuppression and progression towards AIDS (80, 85).

HIV-associated psoriasis can be difficult to recognize because of unusual clinical morphologies and HIV-associated comorbidities that act as clinical mimickers. Tinea, crusted scabies, cutaneous lymphoma and secondary syphilis may all mimic or coexist with psoriasis (87, 88). A low threshold to biopsy is recommended for diagnostic clarification.

Current recommendations for treatment of HIV-associated mild-to-moderate psoriasis are similar to treatment of psoriasis in the general population; similar side effects can also be expected (89). Topical medications (steroids, vitamin A derivatives, and vitamin D analogs), oral acitretin, as well as phototherapy are recommended (89, 90). Topical steroids should be used cautiously in patients on ritonavir or cobicistat given the risk of iatrogenic Cushing’s syndrome(91, 92). Phototherapy can be particularly helpful for PLHIV with severe psoriasis, given that many other medications used for psoriasis can interfere with ART. Because psoriasis may be worsened or exacerbated in the context of HIV, ART monotherapy is also

first-line. Patients should be followed closely as severe exacerbations may occur as part of IRIS (93).

Patients with moderate-to-severe and refractory disease may be treated with cyclosporine, methotrexate or hydroxyurea (80, 89). Although data is limited, apremilast has demonstrated efficacy in the treatment of HIV-associated psoriasis and may be a promising option that avoids further immunosuppression(94). Biologic therapy with TNF-alpha inhibitors should be used cautiously, and all patients should be screened for tuberculosis prior to drug initiation and regularly monitored for infections due to immunosuppression. Infectious complications commonly occur with use. Therapy is recommended only in patients taking ART with stable CD4+ counts (95). Newer biologics, such as IL-17 and IL-12/23 inhibitors have not yet been studied in this population (96).

2.2 Seborrheic dermatitis (SD)

SD is significantly more common in the HIV-infected population than in the general population. In the pre-ART era, prevalence among HIV patients was as high as 60–80% (97, 98). In the era of ART, the prevalence has decreased; studies report 2–25% of patients are affected (53, 99, 100).

HIV-associated SD ranges from typical presentations to those that are extensive and severe. The severe distribution moves beyond the typical seborrheic areas like the extremities, groin and axillae; patients may become erythrodermic (101). Scale is greasier and thicker.

Severe HIV-associated SD may be refractory to traditional topical antifungal therapy (101). Treatment may require additional systemic antifungal therapy, with or without topical corticosteroids or topical calcineurin inhibitors. There is also evidence that ART alone is superior to oral azoles for the treatment of HIV-associated SD (100). For refractory or recurrent disease despite the aforementioned treatments, oral anti-staphylococcal agents could be considered if superimposed bacterial infection is suspected(101).

2.3 Papular Pruritic Eruption (PPE)

PPE is an HIV-associated skin condition with prevalence ranges from 11–46%; the disease is significantly more common at increased levels of immunosuppression (102– 106).

The primary lesion of PPE is a firm, flesh-colored or pink, papule on the trunk and extremities and face (107). The distribution favors the distal extremities (in contrast to eosinophilic folliculitis, below). Diagnosis may be made clinically, though biopsy can be helpful to distinguish PPE from other pruritic rashes (106). Histopathological examination will show a dense eosinophilic infiltrate without necessary serological correlation. Lesions may mimic acne if not for intense, uncomfortable and often refractory pruritus. Acne, eosinophilic folliculitis (EF), dermatophyte folliculitis, and scabies should be considered in the differential. ART is first-line therapy for PPE according to WHO guidelines (16, 108). Symptomatic relief of pruritus may be achieved with antihistamines and topical steroids with evidence leaning in favor of antihistamine therapy (16, 109). Cases of HIV-associated PPE have been successfully treated with narrowband UVB light therapy; this therapy may be of

benefit on refractory cases (110, 111). A novel approach to treatment has been suggested with thalidomide (112).

2.4 Eosinophilic Folliculitis (EF)

Like PPE, EF is a pruritic inflammatory condition associated with high levels of immunosuppression. CD4+ count is typically less than 300 cells/mL (113–115).

Diagnosis may be made clinically and is based on the presence of multiple pruritic, urticarial, follicular papules and pustules distributed on the upper part of the body and the face, usually favoring the midline (in contrast to PPE) (Figure 3) (114). These lesions are often excoriated and therefore may be confused with acne, PPE, or other dermatoses; biopsy is recommended for diagnostic clarification (114).

Histopathological examination reveals perifollicular infiltrates of lymphocytes and eosinophils with spongiosis of the follicular epithelium (116, 117). Mild-to-moderate eosinophilia may be seen on serologic testing, though serology is not necessary for diagnosis (115).

First-line therapy for EF includes the use of ART, though EF may flare in the setting of IRIS following the initiation of ART (118). Moderate potency topical steroids may be used in conjunction with ART to improve inflammation, but ART does not need to be discontinued even in the setting of IRIS. Phototherapy is an effective second-line treatment (119, 120). Third-line treatments include oral itraconazole, oral isotretinoin, and macrolides (120).

2.5 Severe Cutaneous Adverse Drug Reactions

Due to polypharmacy and immune dysregulation, SJS/TEN and other drug-associated cutaneous conditions are extremely common in PLHIV (121–123). For comparison, in the general population the incidence of SJS and TEN is between 1–6 and 0.4–1.2 per one million people, respectively (124–126). In the pre-ART era, SJS/TEN were much more common in PLHIV (950–1000 per million people per year) (127). However, since the advent of ART, incidence is even greater at 1000–2000 per million people (128). Mortality rates for SJS and TEN are between 1–5% and 25–35%, respectively (129). Mortality rates correlate with body surface area affected and are similar in PLHIV and the general population (130). In pregnant HIV+ women, SJS/TEN is associated with poor fetal outcomes (131).

The clinician’s challenge is to determine the etiology of SJS/TEN. Extensive literature has implicated nevirapine as a common culprit, possibly because of an HLA association (128, 132–134). SJS secondary to use of stavudine, indinavir, amprenavir, efavirenz, trimethoprim/sulfamethoxazole, and clarithromycin has also been reported (128, 135, 136). Importantly, SJS/TEN may occur in HIV+ patients who are not on ART.

The management of SJS/TEN in PLHIV is controversial (16). Discontinuing the offending medication and initiating supportive therapy is recommended. Supportive therapy includes fluid and electrolyte repletion, nutritional support, wound care and physiotherapy (16). Drugs started in the 2–3 weeks prior to presentation should be most cautiously considered as

etiologies. Systemic steroids are sometimes used, but evidence for their use is poor (16, 137).

In addition to SJS/TEN, drug reaction with eosinophilia and systemic symptoms (DRESS) has also described in PLHIV most commonly taking abacavir and nevirapine(138). Although data is scarce in these settings, systemic steroids are frequently used and efficacious once the culprit medication has been discontinued (139).

3. Infections

3. 1 Bacterial

3.1.1 Community-Acquired Methicillin-resistant *Staphylococcus aureus* (CA-MRSA)—As in the general population, CA-MRSA skin and soft tissue infections (SSTIs) in the HIV-infected population have increased over the past twenty years, but evidence suggests that the rising annual cumulative incidence of CA-MRSA in HIV-infected patients may have started to stabilize (140). The incidence rate of CA-MRSA SSTIs in HIV-infected individuals has been shown to be six-fold higher than in non-HIV-infected individuals over one year and eighteen fold higher over three years (141, 142). Diagnosis is based on the clinical presentation of carbuncles, furuncles, folliculitis, or cellulitis in combination with wound cultures (Figure 4). In particular, abscesses in these patients are more likely to be located on the buttocks or scrotum(142). SSTIs in this population are also more likely to be recurrent, with a recurrence rate as high as 27% in a 6 month period (143).

First-line treatment of uncomplicated soft tissue abscesses is incision and drainage. However, antibiotics may be warranted in a small subset of patients if MRSA is suspected as antibiotics after incision and drainage have been shown to improve cure rates in abscesses caused by MRSA (144, 145). As in many bacterial infections, local resistance patterns should inform antibiotic choice. Reassuringly, MRSA strains causing abscesses in HIV-infected patients have shown low resistance to trimethoprim-sulfamethoxazole (146). In addition to trimethoprim-sulfamethoxazole, the Infectious Diseases Society of America recommends clindamycin, doxycycline, minocycline, and linezolid for oral antibiotic coverage of CA-MRSA in SSTIs (147). Although the majority of CA-MRSA strains are sensitive to these antibiotics, multidrug-resistance has been noted in USA300 MRSA strains, which typically demonstrate only β-lactam resistance (148, 149). Multidrug-resistant USA300 are especially prevalent among men who have sex with men and is associated with high-risk behaviors such as use of illicit drugs, multiple sex partners, and history of sexually transmitted diseases. The emergence of multidrug-resistant strains in this population is thought to be due to the use of antibiotics such as clindamycin and mupirocin and travel between coastal cities by men who have sex with multiple men (150). More recently and with the overall decline in MRSA globally, USA300 MRSA also appears to be decreasing in prevalence (151). Whether this decline is present in the HIV population specifically remains to be shown.

3.1.2 Atypical mycobacteria—The most common cutaneous atypical mycobacterial infections in HIV-infected patients are due to *Mycobacterium avium-intracellulare* complex (MAC), *Mycobacterium kansasii,* and *Mycobacterium haemophilum.* In the ART era of

2004– 2007, the incidence rates of atypical mycobacterial infections declined more than 10-fold as compared to the pre-ART era of 1994–1997 (152). Nevertheless, disseminated MAC with skin involvement continues to be a problem in advanced immunosuppression, and recurrent MAC infections in patients on ART have been reported (153). MAC-associated skin lesions can be polymorphous, presenting most commonly as subcutaneous nodules, but also as scaly plaques, crusted ulcers, ecthyma-like lesions, and draining sinuses (154– 156). Localized or primary cutaneous infections have also been reported as sporotrichoid eruptions and abscesses (157–159). *Mycobacterium kansasii* rarely primarily inoculates the skin but has been reported as pustules, papules, nodules, abscesses, and ulcers (160– 163). In patients with arthritis and painful purulent cutaneous lesions, *Mycobacterium haemophilum* should be considered. If *M. haemophilum* is suspected, culture media should be heme-enriched as the organism requires heme for growth (164–166).

Although skin biopsy should be performed in all patients with suspicion for atypical mycobacterial infection, granulomas may not be seen on routine hematoxylin and eosin staining in patients with decreased cell-mediated immunity. Thus, AFB staining and tissue culture should also be performed. Treatment of atypical mycobacterial cutaneous infections should be guided by susceptibility testing and infectious disease specialists when available.

3.1.3 Syphilis—Reported cases of syphilis have been rising since 2000, and a significant number of cases are associated with HIV co-infection (167). Reasons for this epidemiologic change are unclear. Some have postulated that with the advent of ART and increased longevity, individuals may be more willing to engage in risky sexual behavior while others suggest that antiretroviral therapy may impede both innate and acquired immunity to *Treponema pallidum* (168, 169). In general, HIV-infected individuals with primary or secondary syphilis have similar clinical presentations to HIV-noninfected individuals. However, HIV-infected patients may have larger, more numerous, and more slowly-resolving chancres (170, 171). Secondary syphilis in patients with or without HIV is characterized by condyloma lata or nonpruritic red-brown macules and papules over the trunk and extremities, often involving the palms and soles. Patients with HIV can present with less common findings of secondary syphilis, such as split papules on the oral labial commissures, annular plaques with central hypopigmentation, granulomatous lesions, and necrotic plaques with scale and crust. Very rarely, ulcerating nodules with peripheral lamellar crusting are noted as a manifestation of secondary syphilis, also known as lues maligna. A high index of suspicion is required for this diagnosis as without treatment, lesions can rapidly progress and become destructive (172). HIV-infected individuals are more likely to present initially with concomitant primary and secondary syphilis and undergo early progression to tertiary syphilis (170, 173). Importantly, ocular syphilis is of rising significance in the HIV-infected population, and because up to 85% of ocular syphilis occurs with neurosyphilis, a work-up for neurosyphilis including lumbar puncture should be considered in these patients (174, 175).

For any stage of syphilis, the Center for Disease Control and Prevention recommends screening with rapid plasma regain (RPR) and if reactive, subsequent confirmation with *Treponema pallidum* particle agglutination (TP-PA) should be performed. Screening can also be performed by the “reverse screening algorithm” with initial enzyme immunoassay

(EIA) or chemiluminescence immunoassay (CIA), followed by confirmatory quantitative RPR, and final reconfirmation with TP-PA (176). Importantly, the prozone effect should be considered if clinical suspicion for syphilis is high despite a negative nontreponemal test. The prozone effect describes falsely negative nontreponemal results that occur in cases of high antibody titers which prevent the formation of antigen-antibody complexes required for detection of a positive result. This effect is postulated to be more common in HIV co-infection because of excessive B-cell activity and resultant antibody production (177). If the prozone effect is suspected, serum should be diluted and testing repeated.

Diagnosis can alternatively be reached by skin biopsy. Skin biopsy of primary syphilis commonly demonstrates ulceration, endothelial swelling, a dermal infiltrate consisting of lymphocytes, histiocytes, and plasma cells, and the presence of spirochetes with immunohistochemistry. Histopathology of secondary syphilis varies based on the clinical appearance of the lesion. The epidermis of secondary syphilis lesions represents this, ranging from psoriasiform hyperplasia to ulceration. While a mixed dermal infiltrate and spirochetes can also be seen in both primary and secondary syphilis, chronic secondary syphilis lesions may be granulomatous.

Syphilis in HIV-infected adults is treated with benzathine penicillin G 2.4 million units intramuscularly. Primary, secondary, and early-latent syphilis require only a single dose, while late-latent and tertiary syphilis require weekly injections for three doses. Neurosyphilis and ocular disease treatment consists of aqueous crystalline penicillin G 18–24 million units per day intravenously over 10–14 days (72).

3.2 Viral

3.2.1 HSV—Herpes simplex virus (HSV) is one of the most common concomitant infections in HIV. Herpes simplex virus type 2 (HSV-2) seroprevalence in the HIV population is estimated to be three times as high as the seroprevalence in the U.S. general population (178). HSV-2 seropositivity at least doubles the risk of HIV transmission by providing a cutaneous inoculation site for HIV and synergistically promoting viral replication (179– 181). Despite the known increased risk of HIV acquisition in the setting of HSV coinfection, suppressive therapy with acyclovir 400 mg or valacyclovir 500mg twice daily for up to two years in patients with HIV-1 and HSV-2 coinfection has not been shown to reduce transmission of HIV-1 to serodiscordant couples. However, HSV suppressive therapy has been shown to decrease plasma HIV-1 viral load. Although the exact mechanism is unclear, acyclovir and valacyclovir are thought to directly inhibit HIV-1 replication. (182–186). Similarly, despite use of ART in HIV-1 and HSV-2 co-infected patients, HSV-2 DNA and mucosal HSV shedding can be detected, suggesting that treatment of HIV does not prevent HSV-2 reactivation or shedding (187, 188).

Classically, HSV infections present as vesicles in the oral or anogenital regions, but in those coinfected with HIV and particularly, in those with low CD4+ counts, lesions can be persistent, painful, ulcerative, verrucous, hypertrophic, and more frequently reactivated (189). This population is at risk for herpes vegetans, which can clinically be mistaken for a neoplasm, and is often acyclovir-resistant (190).

Given the atypical nature of HSV lesions in the HIV-infected patient, laboratory diagnostic techniques should be performed. Although previously HSV culture was the preferred testing modality, HSV DNA polymerase chain reaction (PCR) has been shown to be more sensitive and should be performed in any HIV-infected person with genital ulcers (191). Direct fluorescent antibody staining is another effective diagnostic modality. Tzanck smears can be performed at the bedside. While inferior to PCR, the equipment to perform a Tzanck smear is often readily available and results are timely. A study comparing PCR to Tzanck smear for HSV and VZV lesions demonstrated that positivity rates for Tzanck smear were highest for earlier lesions (blisters, pustules, lesion duration of 1–3 days) and lower for older lesions (erosions, crusted lesions, lesion duration of 4 days or more) (192).

Primary herpetic lesions can be treated with oral acyclovir, valacyclovir, or famciclovir until symptoms have resolved (193). In primary disease with severe mucocutaneous lesions or central neurologic involvement, intravenous acyclovir is recommended until no new lesions have formed, at which point oral therapy can be started (194). For recurrent disease, either episodic treatment or suppressive therapy are effective in decreasing symptoms of HSV (195–197). Episodic treatment consists of oral acyclovir, valacyclovir, or famciclovir started by the patient at the onset of prodromal symptoms. HIV-infected individuals generally require longer courses of therapy than HIV-uninfected individuals and treatment should be continued until lesions have resolved. Suppressive therapy consists of daily antiviral treatment and has been shown to decrease HSV recurrences and duration of lesions in patients treated with and without ART (198, 199). In patients who do not improve over the course of seven to ten days on antiviral therapy, HSV resistance should be considered. Acyclovir and other nucleoside analogue drugs, such as valacyclovir and famciclovir rely on thymidine kinase to be activated, and thus, a deficiency or mutation in thymidine kinase will cause HSV resistance. If antiviral therapy has been appropriately dosed and no clinical improvement has been noted, HSV susceptibility testing should be performed and topical, intralesional, or intravenous cidofovir or intravenous foscarnet should be considered (72, 200–202).

3.2.2 VZV—Although the relative risk of varicella zoster virus (VZV) infection in HIV-seropositive individuals is 15–17 fold higher than in HIV-seronegative individuals, ART has decreased the incidence rates of herpes zoster in the HIV-infected adult and pediatric population by restoring cell-mediated immunity (203–206). Despite an overall decline in incidence rates of zoster with ART and immune reconstitution, there are important populations for whom incidence rates may increase as a result of IRIS, including those with low CD4+ cell counts and high plasma HIV RNA levels (205, 206) (207–209).

In HIV-seropositive individuals, herpes zoster most commonly presents as typical vesicles in a dermatomal distribution but may also present as chronic, ulcerative, bullous, or verrucous lesions. Complications of zoster infection are predominantly seen in patients with low CD4+ cell counts and include post-herpetic neuralgia, superinfection, herpes zoster ophthalmicus, motor neuropathy, and central nervous system involvement (210, 211). Antiretroviral therapy has been suggested to have a protective effect against zoster complications (OR 0.46, 95% CI: 0.23 to 0.92)(211).

Less common than herpes zoster, primary varicella in the HIV-infected individual can present in a classic manner with lesions of varying stages of development including erythematous macules, papules, and vesicles or in an atypical manner with hemorrhagic lesions (Figure 5). If visceral dissemination of primary varicella, particularly if the lungs are involved, mortality rates can be as high as 43% even when antivirals are initiated (212).

The diagnosis of varicella or herpes zoster can be made clinically, and confirmatory laboratory tests include direct fluorescent antigen staining, polymerase chain reaction, viral culture, and Tzanck smear. When VZV infection is being considered, treatment should be initiated promptly. If lesions are disseminated or visceral involvement is present, hospitalization and intravenous acyclovir are required until clinical improvement is noted at which point oral antiviral therapy can be initiated. Oral acyclovir, valacyclovir, or famciclovir can be used for therapy in uncomplicated varicella. Unlike the immunocompetent population, HIV-infected individuals should be treated for herpes zoster with oral acyclovir, valacyclovir, or famciclovir even if symptom onset is greater than 72 hours from presentation (72). Acyclovir resistance can occur and in these cases, intravenous foscarnet is recommended (72).

Prevention is a key component of reducing incidence rates of VZV infection in HIV-infected individuals. HIV-infected children with CD4+ cell percentage greater than 15% should receive the live attenuated varicella vaccine (72, 213). Although data on the use of the varicella vaccine in HIV-seropositive/VZV-seronegative adults is limited, the Advisory Committee on Immunization Practices and the Infectious Disease Society of America (IDSA) recommend vaccination in this population if CD4+ cell count is greater than 200 (214, 215). According to the IDSA, the live attenuated zoster vaccine may be considered in adults over the age of 60 years with CD4+ cell count > 200cells/uL, but no formal recommendations exist for use of the recombinant zoster vaccine in PLHIV(75).

3.2.3 Molluscum—Molluscum contagiosum (MC) is a cutaneous poxvirus infection that classically manifests as skin-colored dome-shaped umbilicated papules. As compared to HIV-seronegative individuals, HIV-infected individuals have larger and more numerous lesions predominantly over the genital region and the face (216, 217). It is well documented that HIV-infected individuals with low CD4+ cell counts are especially susceptible to MC infection, correlating with loss of cell-mediated immunity (218, 219).

Given the characteristic appearance of MC lesions, diagnosis is generally based on the clinical presentation with careful consideration of morphologic mimics including basal cell carcinoma and dimorphic fungi such as *Cryptococcus*, *Coccidioides*, *Histoplasma*, and *Penicillium*. A KOH stain from a MC or MC-like lesion can help distinguish MC from fungal infections. MC will demonstrate characteristic Henderson-Patterson bodies (Figure 6).

In general, immune restoration with ART results in lesion resolution although MC has been seen as a manifestation of IRIS (220–226). ART should be continued even if IRIS-related MC is present. When lesions persist despite initiation of ART and are disfiguring, treatment may be pursued with cryotherapy or curettage of a few discrete lesions.

3.2.4 HPV—HPV infection is more common in the HIV-infected population than in the HIV-uninfected population as a result of both concomitant sexual transmission, and because HIV has been suggested to aid in HPV viral replication and tumor formation through upregulation of p27 expression and induction of cell proliferation (227, 228). Immune system reconstitution has had an effect on nonmalignant and precursor lesions, including decreased size and number of plantar warts and decreased incidence rate of genital warts (229, 230). However, with prolonged ART-associated survival and increased time allowed for oncogenic transformation, incidence rates of HPV-associated malignancy such as anal cancer, penile cancer, and periungual squamous cell carcinoma have increased (71, 231–233). (Please see keratinocyte carcinomas above). Additionally, genital warts in PLHIV on ART should not be assumed to behave like those in HIV-noninfected individuals as having an HPV infection at the time of a low CD4+ count increases the risk of malignant transformation (234).

Cutaneous HPV infection in the HIV-infected patient can present as benign lesions such as condyloma acuminata, premalignant conditions such as Bowen's disease, and malignant lesions including anal carcinoma and vulvar carcinoma. Of these presentations, condyloma acuminata, or genital warts, are the most common in this population and are reported to be the second most common dermatologic diagnosis in a population of HIV-infected individuals on ART (235). Successful treatment may require multiple treatment modalities and a prolonged treatment course. Patient-applied methods include imiquimod, podofilox, cidofovir, and sinecatechins. Provider-administered methods include cryotherapy, tricholoroacetic acid, surgical excision, and laser surgery (72). Recalcitrant genital warts should be biopsied to exclude the possibility of unrecognized squamous cell carcinoma.

An important but rare nongenital manifestation of HPV is acquired epidermodysplasia verruciformis (EV), which manifests as diffuse flat-topped papules that resemble flat warts or pityriasis versicolor-like macules. Unlike flat warts which are caused by alpha-HPV types, acquired EV is caused by beta-HPV-5 and −8 among others (236–238). Unfortunately, acquired EV remains difficult to treat and the effect of immune reconstitution with ART is equivocal (239, 240). As in the genetic form of EV, mainstays of treatment include interferon, topical and systemic retinoids, and topical imiquimod.

3.3 Fungal

3.3.1 Candida—*Candida albicans* commonly presents in HIV-infected individuals with low CD4+ cell counts as thrush, or non-adherent white plaques on the tongue or oropharyngeal mucosa (241). Treatment of mild oropharyngeal candidiasis consists of nystatin suspension four times daily or clotrimazole troches five times daily for 7–14 days. Treatment of moderate to severe disease is oral fluconazole for 7–14 days. Evaluation for esophageal candidiasis should be performed, as duration of treatment with fluconazole is longer in this case. Cutaneous candidiasis can also manifest as angular cheilitis, vaginitis, and acute or chronic paronychia. The introduction of antiretroviral therapy has been shown to decrease the incidence rate of oropharyngeal candidiasis, but an associated fluconazole resistance has been noted (242, 243).

Systemic candidiasis can present with disseminated papules and pustules on the skin. A KOH stain or India ink stain of a pustule will demonstrate pseudohyphae and will aid in distinguishing this from a cryptococcal lesion (Figure 7). Of note, the presence of disseminated cutaneous candidal lesions implies a systemic infection, rather than a solely cutaneous infection. Evaluation for systemic disease involvement, in particular central nervous system and liver, should be performed. Echinocandins, including caspofungin, micafungin, and anidulafungin, are used in the treatment of systemic candidiasis. If the patient is not critically ill and has not had prior exposure to azoles, fluconazole or voriconazole can also be used. Amphotericin B was once the first-line treatment for systemic candidiasis but is now generally avoided given its toxicity profile (244).

3.3.2 Dermatophyte—Dermatophyte infections in individuals with HIV are more likely to be atypical, disseminated, and severe. The most common presentation is tinea corporis, but tinea cruris, tinea pedis, and onychomycosis can all occur. Although many dermatophytes can cause cutaneous disease, *Trichophyton rubrum* is the most frequently isolated species in this population (245). Tinea cruris presenting as annular scaly plaques over the medial thighs should be differentiated from candidal intertrigo, which has a beefy-red color and associated satellite papules and pustules. Given that the differential of cutaneous dermatophyte infection includes psoriasis, seborrheic dermatitis, eczema, and pityriasis rotunda, work-up should include potassium hydroxide evaluation of scale from a leading edge and periodic acid-Schiff stain if biopsy is obtained (246). Use of a topical azole is recommended for treatment of tinea cruris, tinea corporis, and tinea pedis, and prolonged therapy may be necessary to ensure clearance in patients with low CD4+ counts. If disseminated disease is present, systemic antifungal treatment with terbinafine, itraconazole, or fluconazole is preferred. Onychomycosis is difficult to treat and the risks of liver toxicity and potential drug interactions with ART often outweigh the benefits of treatment.

3.3.3 Endemic fungal infections—Endemic fungal infections are commonly seen in patients with CD4+ counts less than 50cells/ml, and cutaneous disease is often a marker of disseminated infection (247). Endemic fungi can present with a wide range of skin manifestations. In particular, endemic fungal infection should be considered in any HIV-infected patient with molluscum contagiosum-like papules.

Disseminated cryptococcosis commonly presents as meningitis and cutaneous papules, nodules, or ulcers (248–250). Although cryptococcosis can be fatal, patients diagnosed with cryptococcosis more recently in the era of ART show better overall survival than those diagnosed pre-ART (251). Coccidioidomycosis is most commonly seen in endemic areas, including the southwestern United States, Central America, and South America but can be seen in any immunosuppressed HIV-infected individual regardless of geographic location. Polymorphous skin lesions accompany systemic disease as manifested by focal or diffuse pulmonary infiltrates, meningitis, or lymph node involvement (252). Cutaneous lesions of histoplasmosis are also nonspecific and may be macular, papular, nodular, ulcerative, acneiform, herpetiform, or vegetative (253). Mucosal erosions and ulcers are often seen in disseminated histoplasmosis. Mucocutaneous involvement is commonly associated with fever, dyspnea, and cough, indicative of pulmonary disease. Penicilliosis is endemic to

Southeast Asia and should be on the differential in a traveler or immigrant from this area with molluscum contagiosum-like lesions on the face, fever, or splenomegaly (254).

Diagnosis of systemic fungal infections should be made on the basis of KOH preparation, histopathology, and fungal tissue culture. If a dermatologic diagnosis of disseminated cryptococcosis is made, a lumbar puncture should be performed to evaluate for associated meningitis regardless of whether meningismus is present. Treatment of choice in cryptococcosis is amphotericin B in combination with flucytosine. Amphotericin B can also be used in severe disseminated coccidioidomycosis, histoplasmosis, and penicilliosis, while oral triazole antifungals are often sufficient for mild disease. Endemic fungal infections have been associated with IRIS (251, 255).

4. Conclusions

Even in the ART era, there is a substantial burden of skin disease experienced by PLHIV. Morbidity and mortality can be high from HIV associated skin disease, and therefore familiarity with conditions specific to HIV and also those that change course or management with HIV is critical to the practicing dermatologist.

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Key Points

- In the era of ART, PLHIV are living longer and healthier lives: PLHIV are affected by skin diseases that are common and chronic as much as those that are life-threatening and rare.
- PLHIV should be frequently screened for common skin conditions.
- ART is an important component of the management of almost all HIV-associated skin diseases.

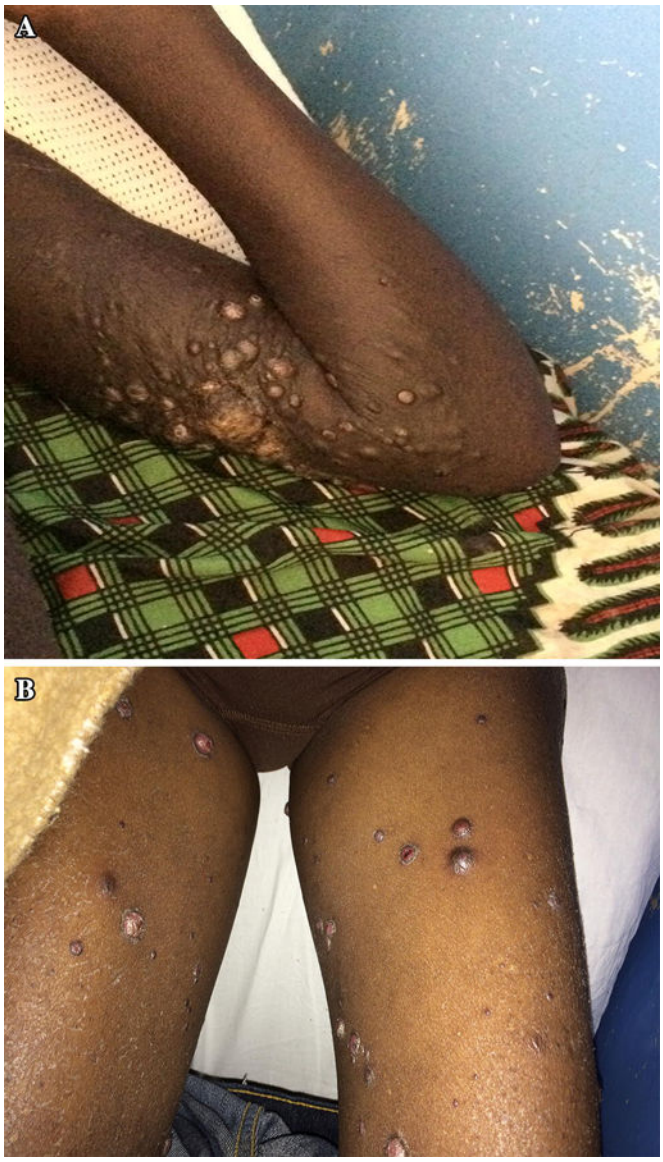

Fig. 1.

A) HIV associated KS. A 25-year old male with HIV (CD4+ count 350, VL 25) presented with nodules and tumors, which started nine months prior. His lesions progressed despite antiretroviral therapy (ART). He presented with severe respiratory distress secondary to pulmonary KS. Given his progressive disease despite ART and symptomatic visceral involvement, systemic chemotherapy was added to his ART. B) Bacillary angiomatosis is a clinical mimicker of KS that can be distinguished on histopathology.

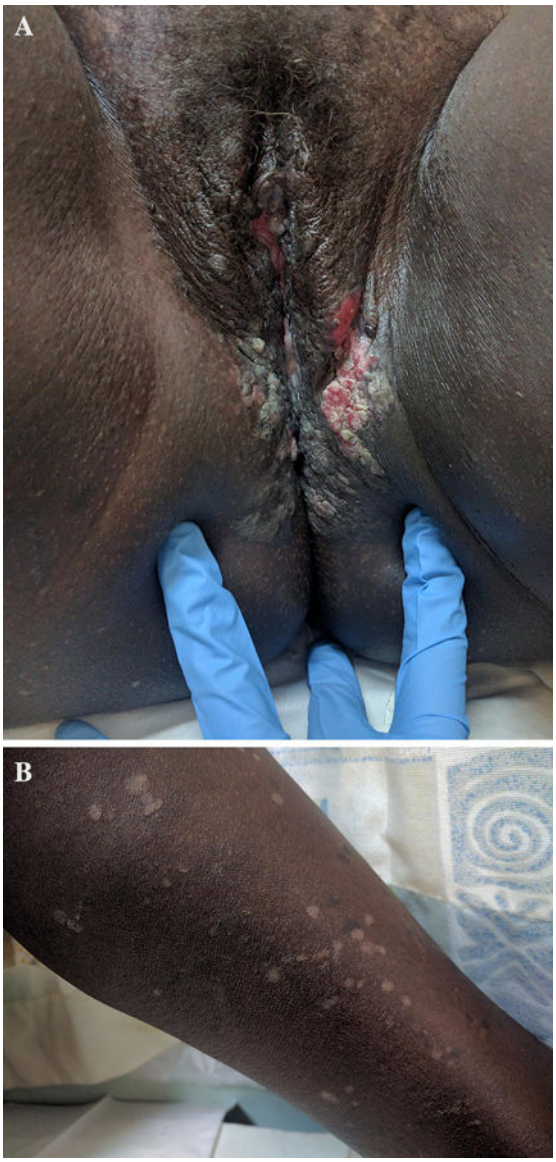

Fig. 2.

A) HPV-associated SCC. A 48-year old woman with HIV (CD4+ count 560, VL 0) presented with a long-standing history of small lesions on buttocks and legs and two-week history of painful wound on the vulva. Hypopigmented thin papules were scattered on the legs and buttocks. B) Vulva, perineum, and perianal region had multiple exophytic, hyperpigmented and eroded plaques, .Biopsy at the border of an exophytic plaque demonstrated squamous cell carcinoma

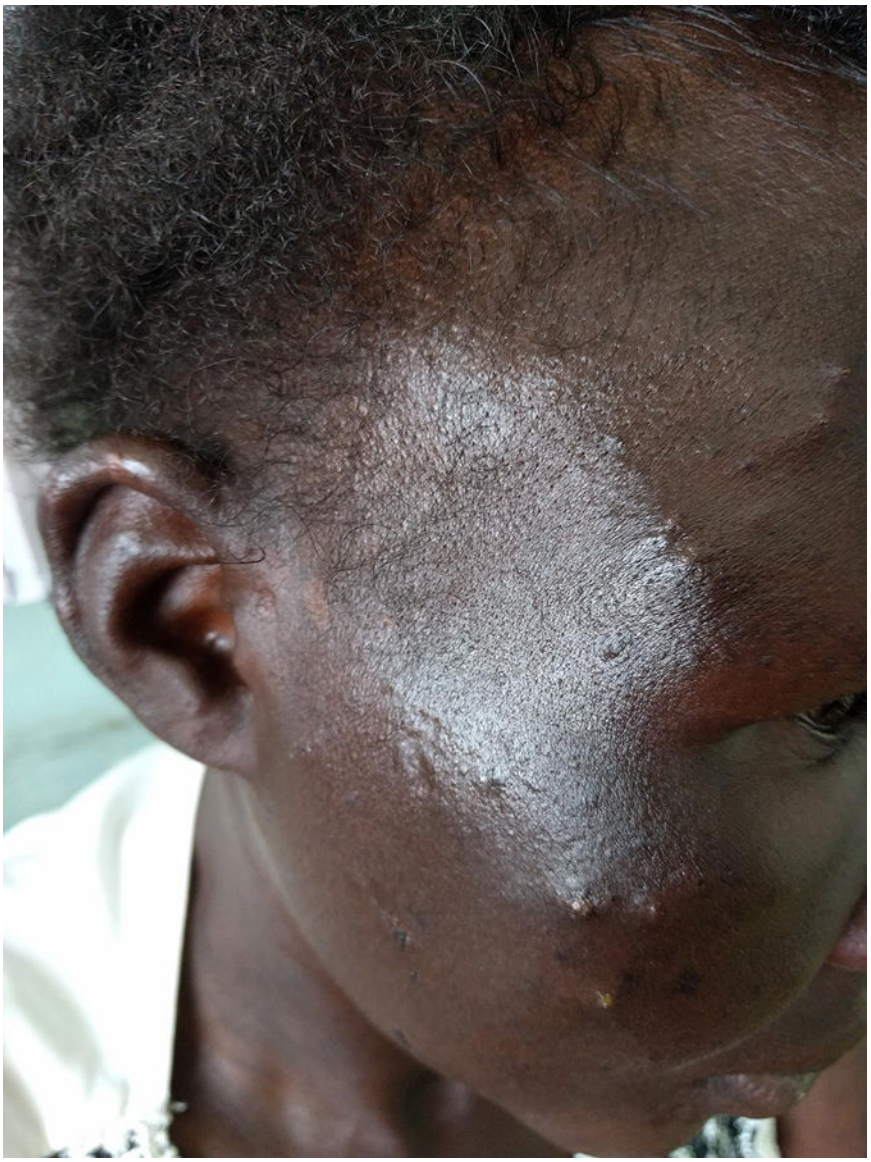

Fig. 3.

Eosinophilic folliculitis. A 30-year old woman with HIV (CD4+ count 12, VL 140,000) presented for new onset pruritic papules and pustules on the face and ears of three weeks duration. She has been on ART intermittently since her HIV diagnosis two years ago and initiated second-line ART three weeks prior.

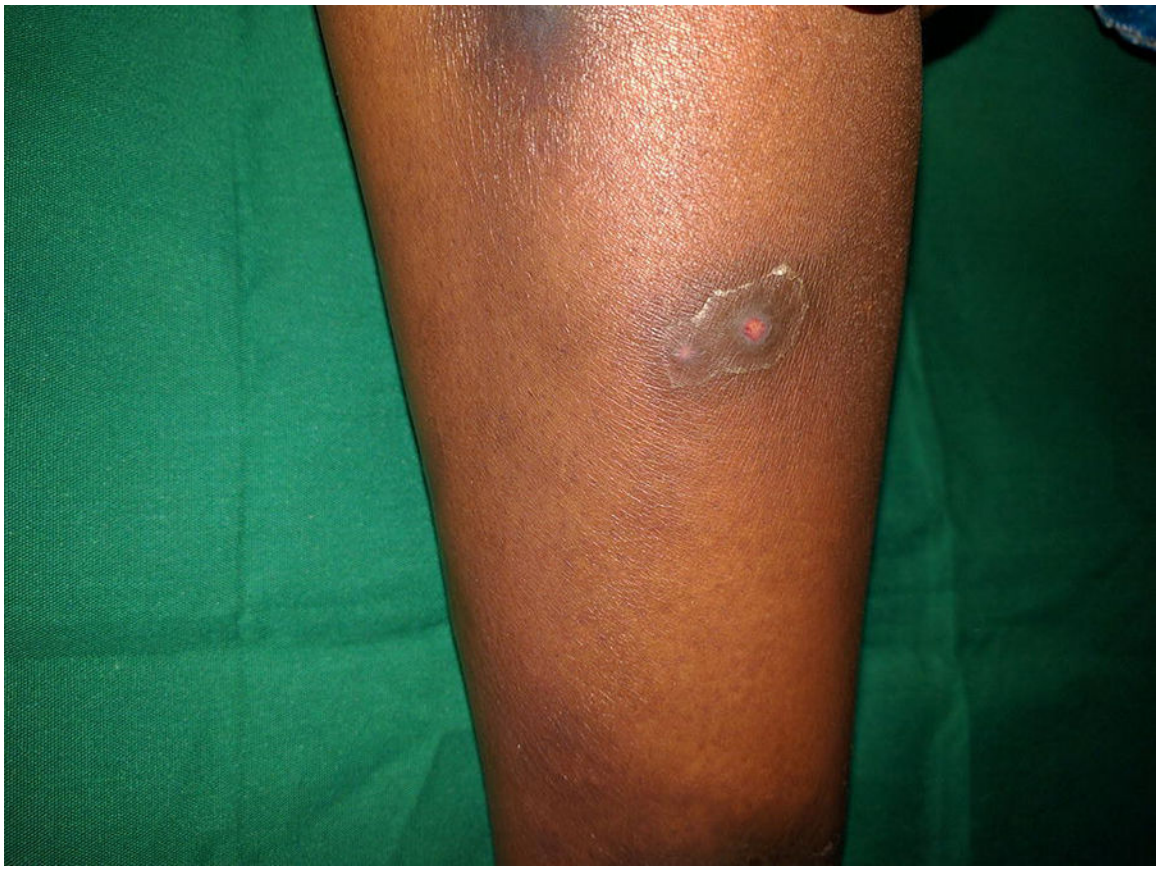

Fig. 4.

Community acquired MRSA. A 17-year old woman with HIV (CD4+ count 10, VL 680,000) on second-line ART presented with a 2 year history of intermittent pustules, crusted plaques, and scars on the feet and legs. Some healed spontaneously and others healed with oral medications (unknown what kind). She was started on doxycycline with improvement.

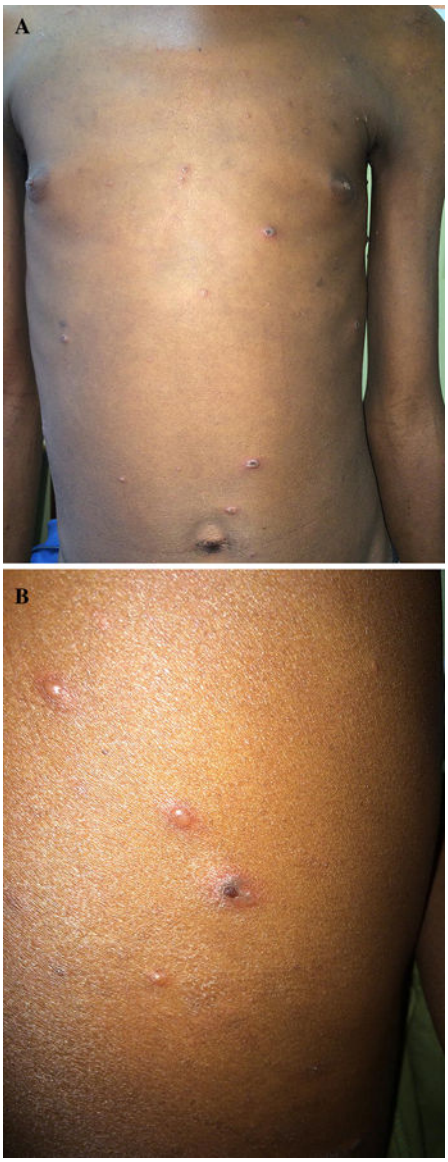

Fig. 5.

VZV. An 18-year old man with HIV (CD4+ count 24, VL 550,000), not on ART, presented with one week of scattered vesicles, some umbilicated and crusted, in the setting of new shortness of breath and increased liver function enzymes. Tzanck smear demonstrated multinucleated giant cells. He was started on empiric IV acyclovir for possible disseminated VZV.

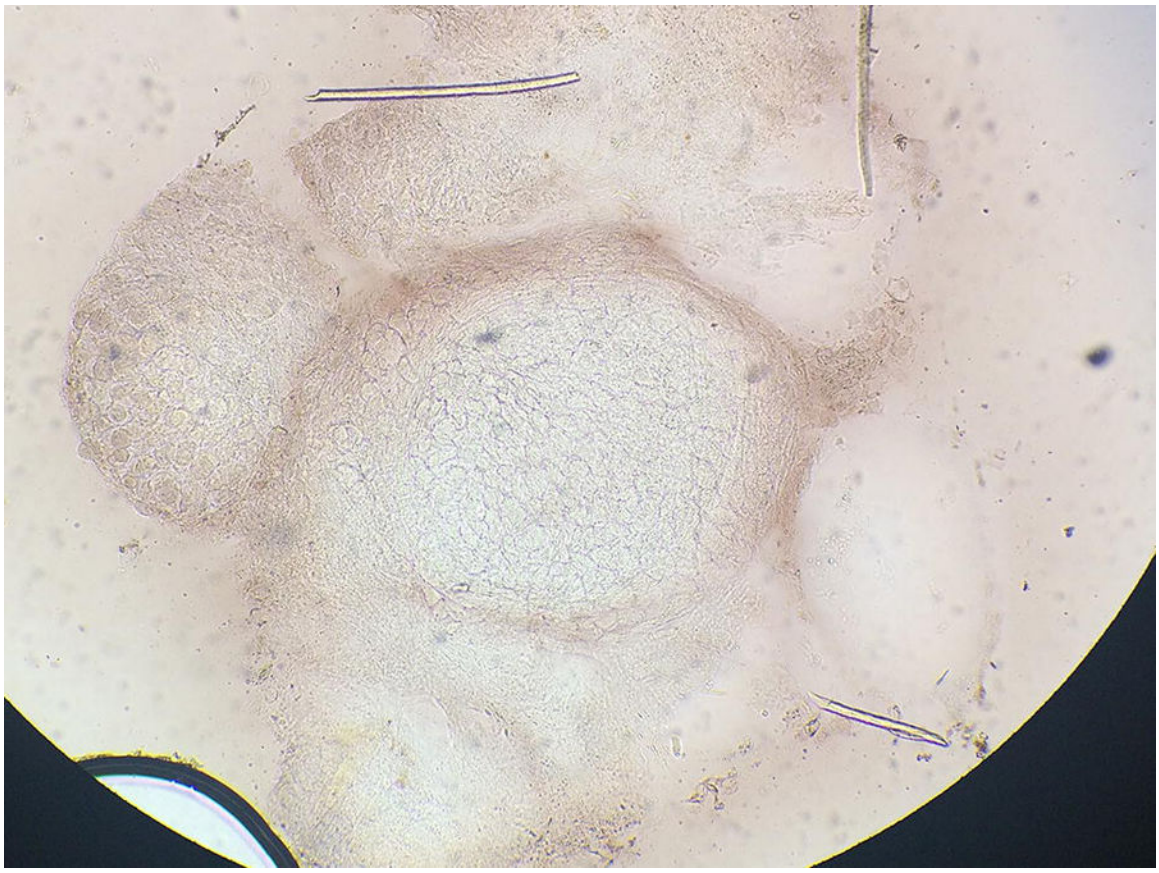

Fig. 6.
Molluscum. Henderson-Patterson bodies.

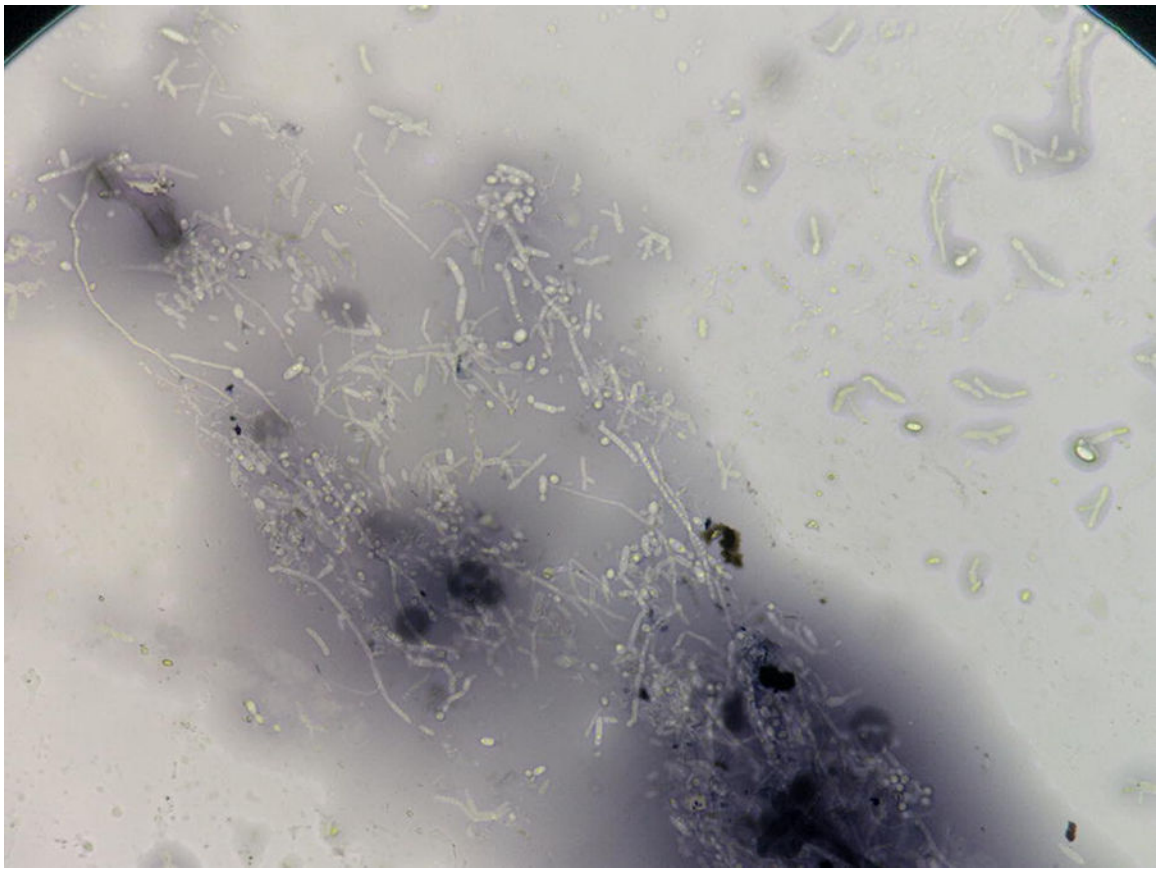

Fig. 7.
Candida. Pseudohyphae are present.

Table 1.

Staging and treatment guidelines for Kaposi sarcoma

ACTG Staging Classification[19]		
Characteristic	**Good Risk (all of the following)**	**Poor Risk (any of the following)**
Tumor (T)	Tumor confined to skin and/or lymph nodes and/or minimal oral disease	Tumor associated edema or ulceration; extensive oral KS; GI KS; KS in other non-nodal viscera
Immune system (I)	CD4+ cells >=150/microL	CD4+ cells <150microL
Systemic illness	No history of opportunistic infection or thrush; no systemic B symptoms; performance status >= 70 Karnofsky Performance Status	History of opportunistic infection and/or thrush; B symptom; performance status <70 Karnofsky Performance Status; other HIV-related illness (eg, neurologic disease, lymphoma)

WHO KS Treatment Guidelines[16]	
Mild/moderate Kaposi sarcoma: ART alone	**Severe symptomatic Kaposi sarcoma: ART plus systemic chemotherapy**
• Confined to skin and/or lymph nodes • No symptomatic visceral disease • No significant oral disease (does not interfere with chewing or swallowing) • No significant edema affecting function • Not functionally disabling or immediately life-threatening	• Symptomatic visceral disease • Extensive KS lesions which interfere with chewing or swallowing • Painful or disabling tumor-associated facial/gential/peripheral edema or ulcerated tumors • Life threatening or functionally disabling disease • Progressive or persistent KS despite ART