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## 16.1 Approach to dermatological presentations

Dermatological conditions are common at all stages of HIV infection. Cutaneous manifestations of HIV can present as the initial sign of HIV, as another infection, or as an inflammatory, neoplastic or drug-related disease. Since the advent of combination antiretroviral therapy (cART), dermatological presentations are increasingly encountered in the setting of immune restoration diseases (IRDs).

Although a few skin conditions occur almost exclusively in people with HIV infection, in general, the spectrum of dermatological conditions (Table 16.1) is similar to that found in the general population. These general dermatological problems may present more frequently, may be atypical in presentation and are often less responsive to the usual therapies. Dermatological disease is a common presentation of IRDs and may be associated with other organ involvement. With the restoration of the immune system the prognosis for resolution of skin disease is generally good.

### 16.1.1 Physical examination and investigation

History taking is essential (Table 16.2). Note the distribution, type of rash and any other associated physical findings including: mucosal changes, hair and nail changes as well as musculoskeletal involvement, lymphadenopathy and organomegaly. If the patient is febrile, urine analysis, chest x-ray and blood cultures should be performed.

Swabs should be taken of pustular and vesicular lesions. Punch biopsy may also be useful for histopathology. Appropriate cultures or antigen - nucleic acid studies should be performed to detect opportunistic infections such as bacterial, atypical

mycobacterial, viral or fungal infections. Imaging may be helpful in evaluating extracutaneous involvement if it is suspected.

## 16.2 Viral infections

All viral infections are more common and, depending on the stage of HIV infection, the clinical presentation may vary

Table 16.2 History essentials in the setting of cutaneous presentations	
<b>HIV status</b>	CD4 cell count, and viral load assays
<b>History</b>	Medical and surgical history
<b>Medications</b>	Current and recent medical therapy, including complementary therapy and over-the-counter medications
<b>Contacts</b>	<ul style="list-style-type: none"> <li>With children and adults experiencing similar symptoms</li> <li>All sexual contacts</li> <li>With pets, animals, insects, wildlife</li> </ul>
<b>Occupation</b>	Associated exposure
<b>Travel</b>	Recent and past

from classical to atypical. Atypical presentations include multidermatomal zoster and chronic ulcers due to herpes simplex or disseminated cytomegalovirus (CMV). *Molluscum contagiosum* umbilicated papules may enlarge and extend down hair follicles.

### Herpesviridae infections

Cutaneous disease resulting from herpes virus infection includes:

Table 16.1 The spectrum of dermatological conditions affecting people with HIV infection	
Rash morphology	Differential diagnosis
Follicular	Bacterial, eosinophilic and pityrosporum folliculitis; follicular eczema
Eczematous	Psoriasis, dermatitis, Reiter's syndrome, drug eruptions
Papular	Molluscum contagiosum, human papillomavirus, scabies cryptococcosis, histoplasmosis and Kaposi's sarcoma
Macular / Maculopapular	Secondary syphilis, parvovirus B19, HBV, disseminated candidiasis, widespread scabies and drug reactions Consider opportunistic infections with skin manifestations, such as cryptococcosis, penicillinosis, histoplasmosis and coccidioidomycosis
Vesicular	Herpes zoster (varicella-zoster virus), herpes simplex virus and drug reactions.
Petechial / pustular	Bacterial causes such as disseminated gonococcal infection, pseudomonal or staphylococcal sepsis, infective endocarditis, listeriosis Viral causes such as parvovirus B19, cutaneous vasculitis and drug reactions.
Nodular	Prurigo nodules from persistent scratching, basal and squamous cell carcinoma, Kaposi's sarcoma, mycobacteria, bartonella, histoplasmosis and coccidioidomycosis

## 16 Dermatological manifestations

- Primary varicella zoster virus (VZV) infection
- Dermatomal herpes zoster (HZ) from endogenous latent VZV reactivation
- Chronic cutaneous and mucocutaneous ulcers caused by herpes simplex virus (HSV)
- Disseminated papules of CMV infection

Epstein-Barr virus has been implicated in the pathogenesis of oral hairy leukoplakia.

### 16.2.1 Varicella zoster virus: primary (varicella or chicken-pox) and secondary (herpes zoster or shingles) infections

#### Clinical presentation

The cutaneous presentation of primary and secondary VZV infection in patients with HIV follows a typical course with crops of pruritic vesicles that become generalised in primary varicella and remain unidermatomal in HZ. In the setting of HIV, varicella is often more florid with a pronounced systemic prodrome (malaise, headache, fever, myalgia), has a prolonged course, and has a greater incidence of complications such as encephalitis, pneumonitis and hepatitis. Although mortality from varicella infection is higher in adults with HIV infection, children with HIV infection have a significant mortality rate from primary varicella infection and may also develop severe complications.<sup>1</sup>

HZ generally presents as a vesicular eruption involving one or more dermatomes. Most patients have prodromal pain in the affected dermatome prior to vesicular eruption.<sup>2</sup> This pain may be initially confused with other aetiologies.<sup>3</sup>

The classical rash of HZ is grouped vesicles or bullae, evolving into pustular and haemorrhagic lesions within a few days. Subsequently, crusting occurs and the resultant scarring may produce hypo or hyperpigmentation. The ulceration is often deeper and more prolonged, and scarring more severe. The diagnosis of HZ in the distribution of the ophthalmic division of the trigeminal nerve is important, as it can cause uveitis and keratitis. Ophthalmological review is indicated to minimise ocular complications.<sup>4</sup> Disseminated cutaneous zoster has been defined as more than 20 vesicles outside the area of the primary and adjacent dermatomes, and is rare.<sup>1</sup>

Atypical, disseminated and chronic HZ infections usually occur in the setting of advanced HIV disease or IRDs. Chronic herpes zoster can present as indolent and chronic haemorrhagic, echthymatous or verrucous lesions.

The risk of HZ varies with the CD4 cell count. Increased rates of HZ occur in patients with a CD4 cell count of 50 to 200 cells/ $\mu\text{L}$ .<sup>5</sup> Children with HIV infection who develop chickenpox have a higher incidence of developing HZ and are more likely to have recurrent HZ. A lower CD4 cell count increases this risk.<sup>6</sup>

Despite the established use of cART, the incidence of HZ has not decreased and patients remain at higher risk of HZ compared with the general population, particularly with CD4 cell counts of 50 to 200 cells/ $\mu\text{L}$ .<sup>5</sup> IRDs-related HZ presentations are generally uncomplicated and can be managed with oral antivirals such as aciclovir, valaciclovir or famciclovir.<sup>7</sup> Isolated cases of transverse myelitis, keratitis, iritis and acute retinal necrosis in IRDs have been reported.<sup>8</sup> It is thought that the use of cART may be protective against complicated zoster.<sup>6</sup>

#### Diagnosis

The diagnosis of VZV infection is usually clinical. If the cutaneous presentation is atypical, or laboratory confirmation is required, VZV polymerase chain reaction (PCR) is used. In urgent cases, immunofluorescence can be performed within two hours. PCR for viral nucleic acid is highly sensitive and can also distinguish between HSV and VZV.<sup>9</sup> PCR is typically performed on vesicular fluid.<sup>10</sup> Antibody testing for VZV immunoglobulin (Ig)M and IgG detects either acute infection or past exposure. Measurement of VZV IgG can determine immunity to varicella, which is useful in determining if patients need zoster immunoglobulin after varicella exposure, or varicella vaccination. VZV IgM is detected in acute chickenpox and in about 70% of people with HZ.<sup>9</sup>

#### Management, prevention and vaccination

Varicella vaccine has been demonstrated to be safe and immunogenic in children with HIV infection with minimal symptoms and CD4 cell percentages of 25% or more.<sup>11</sup> A study evaluated the safety and efficacy of varicella vaccine in children with either moderate symptoms and CD4 cell percentages more than 15% or a history of severe immunosuppression who had achieved immune reconstitution. Regardless of immunological category, 79% of vaccine recipients with HIV infection developed VZV-specific antibody and/or cell-mediated immunity 60 days after the immunisation series.<sup>12</sup> In the USA in 2007, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention recommended that single-antigen varicella vaccine should be administered to children with HIV infection with a CD4 T lymphocyte percentage greater than 15%, whereas the Australian guidelines currently recommend vaccination at greater than 25%.<sup>13</sup> The ACIP also recommend that single-antigen varicella vaccine may be considered in VZV-seronegative adolescents or adults with HIV infection with a CD4 cell count greater than 200 cells/ $\mu\text{L}$ . Two doses should be administered three months apart.<sup>14</sup>

Zoster immunoglobulin is indicated for patients with HIV infection within 96 hours of significant first VZV exposure (e.g. household or classroom contact) or alternatively a thymidine kinase inhibitor can be given up to seven days post exposure.

#### Treatment of primary varicella zoster

Antiviral treatment for chicken pox is administered in children with severe, complicated disease, neonates, adults and immunocompromised patients including those with HIV. Treatment should begin within 24–48 hours of onset. Severe disease is treated with intravenous aciclovir.

#### Treatment of herpes zoster

Aciclovir, valaciclovir and famciclovir are efficacious in acute HZ and should be used in ophthalmic HZ and can ameliorate postherpetic neuralgia.<sup>15</sup> Ideally antiviral therapy should be commenced within 72 hours of rash onset.<sup>16</sup>

Oral aciclovir has been the mainstay of HZ treatment, but it has poor bioavailability and needs to be given frequently. Valaciclovir and famciclovir need less frequent dosing (Table 16.3)

#### Aciclovir-resistant varicella zoster infection

Aciclovir-resistant varicella zoster infection is rare, especially in the post cART era, but when it does occur it is associated with significant mortality and morbidity. These patients usually have

Table 16.3 Oral antiviral medications for herpes zoster

Medication	Dosage	Duration of treatment	Most common side effect	Precaution and contraindication
Aciclovir	800 mg, 5 times a day	7-10 days or until lesions heal	Nausea, gastrointestinal side-effects	Dose adjust for renal impairment if creatinine clearance <25mL/min
Valaciclovir	1000 mg 3 times a day	7 days or until lesions heal	Nausea	Dose adjust for renal insufficiency, if creatinine clearance <50mL/min. Thrombocytopenic purpura and haemolytic uraemic syndrome reported at 8000 mg doses in immunocompromised patients
Famciclovir	500 mg 3 times a day	7 days or until lesions heal	Nausea, headache	Dose adjust for renal insufficiency if creatinine clearance <60mL/min

Source : Adapted from Dworkin, R, Johnson RW, Breuer J, Guann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis 2007;44:51

advanced disease with CD4 cell counts below 20 cells/ $\mu$ L. The presence of atypical lesions or a failed clinical response should prompt evaluation for aciclovir susceptibility.

Foscarnet is recommended for the treatment of aciclovir-resistant zoster infection.<sup>16</sup>

## 16.2.2 Herpes simplex virus

### Clinical presentation

HSV types 1 and 2 are the causative agents of herpes labialis, herpes genitalis, herpes gladiatorum, herpes whitlow, herpetic keratoconjunctivitis, eczema herpeticum, herpes folliculitis (herpes sycosis), lumbosacral herpes, disseminated herpes, neonatal herpes and herpes encephalitis. They have also been linked to some cases of erythema multiforme.<sup>17</sup>

The onset of clinical illness is usually sudden, with the appearance of multiple characteristic vesicular lesions superimposed upon an inflammatory, erythematous base. Primary infection may also be associated with systemic symptoms such as fever and malaise. In the setting of HIV infection, HSV lesions may be chronic, larger, atypical, more widespread in distribution, and extend into deeper cutaneous layers resulting in necrotising ulcers. The presence of herpes ulcers for one month or more in patients with HIV infection is considered an AIDS-defining illness. Recurrent episodes are common in HIV. Mucocutaneous herpes can present as an IRD-like phenomenon in patients initiated on cART.<sup>18</sup>

Most people with sexually-acquired HIV have HSV-2 co-infection. Recently studies have shown an association between HSV-2 infection and HIV acquisition. HIV-1 is shed from genital ulcers caused by HSV-2.<sup>19</sup> In this setting, cART has little influence on frequency or level of mucosal HSV-2 shedding, with 85% of episodes being subclinical. Frequent subclinical episodes of HSV-2 reactivation are associated with both a higher frequency and a higher amount of HIV-1 in genital secretions. In addition, valaciclovir has activity against HIV replication.<sup>20</sup>

### Diagnosis

The diagnosis of mucocutaneous HSV is made by clinical observation in uncomplicated cases and by HSV PCR of lesion secretions. Viral cultures from swabbed vesicles are required for resistance testing.

### Management

Few randomised, controlled trials have been performed in patients with HIV infection. Aciclovir, famciclovir and valaciclovir have all been shown to be safe and effective as both intermittent and continuous therapy for HSV-2 clinical and subclinical infection in HIV-positive men and women.<sup>21</sup>

In the majority of situations, mucocutaneous HSV responds to oral therapy with aciclovir (400 mg three times a day); valaciclovir (1g twice a day); or famciclovir (250 mg three times a day). Primary episodes are treated for seven to 10 days, recurrent episodes are treated for five days.<sup>6</sup> If standard dosing fails, biopsy and culture should be performed to obtain viral sensitivities and to exclude alternative pathology. Higher doses may be useful with aciclovir 800 mg twice a day or valaciclovir 1 g three times a day.<sup>22</sup> Severe cases or clinically-unresponsive confirmed cases may require high doses of oral agents or, rarely, intravenous aciclovir. Treatment of aciclovir-resistant HSV includes non-thymidine kinase dependent therapies such as foscarnet or cidofovir.

### Prevention

Chronic antiviral suppressive therapy is suggested for HIV-seropositive people whose disease is poorly controlled on cART and who have frequent HSV reactivation.<sup>23</sup> Valaciclovir 500 mg twice a day or aciclovir 400 mg twice a day is recommended for suppressive therapy.<sup>21</sup> In addition, people with HIV and HSV-2 co-infection who are sexually active should be advised of the association between HSV-2 reactivation and mucosal HIV-1 shedding.

## 16.2.3 Human papilloma virus (warts)

### Clinical presentation

HPV infection results in common warts (verruca vulgaris), plantar warts, filiform, condylomata accuminata and mucocutaneous warts, which can occur in the oral, ocular and anogenital mucosa.<sup>24</sup> Although they may be larger, multiple, recalcitrant to therapy and disfiguring, with a significant psychological burden, most commonly the warts look like those found in the general population.

In general, HPV infections are considered benign. Genital warts due to HPV are commonly due to types 6 and 11. There is also an association of HPV infection with squamous cell carcinoma.

## 16 Dermatological manifestations

Neoplastic transformation can occur to squamous cell carcinoma, Bowen's disease, cervical carcinoma and anogenital cancer in men.<sup>25</sup> HPV types 16, 18 and several others have oncogenic potential and have been shown to be associated with malignant transformation.<sup>26</sup>

### Diagnosis

The diagnosis of HPV warts is usually clinical. It can be confirmed by whitening of the mucosa when acetic acid is applied. The clinical presentation is closely correlated with the typical histopathology of acanthosis, compact hyperkeratosis, papillomatosis, hypergranulosis and koilocytosis.<sup>27</sup> Perianal, anal and penile intraepithelial neoplasia classically presents as a velvety erythematous plaque or as a hyperpigmented well-defined plaque. A biopsy is helpful in establishing a diagnosis, particularly in verrucal lesions unresponsive to therapy.

### Management

Treatment centres on the alleviation of signs and symptoms with traditional treatment modalities focusing on the destruction of infected tissue. This includes podophyllin resin, podophyllotoxin, salicylic acid, trichloroacetic acid, bichloroacetic acid, cryotherapy, laser and surgical techniques. Immunomodulatory compounds with antiviral properties have demonstrated superior efficacy with clearance rates up to 77% and low recurrence rates in some recent studies.<sup>27</sup> Topical imiquimod 5% has however been proven to be safe and effective and is recommended for those with CD4 cell counts of more than 200 cells/ $\mu$ L or who are on cART. Best outcomes have been with application three times a week for six-10 hours until visible inflammation occurs and the warts disappear. Side-effects can be controlled by decreasing the frequency of application.<sup>28</sup>

The management and monitoring of cervical intraepithelial neoplasia and anal intraepithelial neoplasia are described in Chapter 17.4 and 17.5.

### 16.2.4 Molluscum contagiosum

Molluscum contagiosum (MC) virus is a poxvirus that causes a chronic localised infection most often seen in immunocompromised patients. The severity of MC is inversely related to the CD4 cell count. MC is spread by direct skin-to-skin contact, occurring anywhere on the body except the palms of the hands and soles of the feet.

#### Clinical presentation

The classic lesions of MC consist of dome shaped, flesh-coloured 2-6 mm papules with central umbilication containing caseous material. The papules can be pruritic. Molluscum altered by the immunosuppression of HIV are often larger and more numerous; persistent lesions may occur. Most commonly, MC is on the face, neck, genitals, creases and folds or sites of friction e.g. axilla and groin.

#### Diagnosis

The diagnosis of MC is clinical although a biopsy of the papules demonstrate molluscum bodies on Giemsa staining. When multiple lesions are present, vulvar syringoma and condyloma acuminatum should be considered. Cutaneous *Cryptococcus* infection manifesting as a molluscum-like eruption has been reported in patients with AIDS.

### Management

MC is usually self-limiting and spontaneously resolves after a few months in immunocompetent hosts. In the setting of advanced HIV immunodeficiency, the recalcitrant lesions often improve with immune reconstitution on cART. Genital lesions should be definitively treated to prevent spread by sexual contact. Topical therapies include: cantharidin (single application that may need to be repeated); tretinoin cream (0.1%) or gel (0.025%) daily; podophyllin; trichloroacetic acid; imiquimod applied under occlusion; silver nitrate or phenol. Topical cidofovir, although expensive, may be useful in recalcitrant disease.<sup>29</sup> Most common alternatives are curettage, cryotherapy after deroofting the lesions, or laser therapies to remove individual lesions.

New lesions or inflammation of existing MC lesions may appear in the context of IRDs before disappearing with restored immune function.<sup>30</sup>

## 16.3 Fungal infections

Cutaneous presentations of fungal infections in HIV in Australasia include tinea, *candida*, malassezia, cryptococcosis, penicillinosis and pneumocystis.

### 16.3.1 Dermatophyte infections

#### Clinical presentation

Dermatophytosis is most commonly due to *Trichophyton rubrum*, frequently causing tinea cruris, corporis and onychomycosis. Despite cART and fluconazole prophylaxis, superficial dermatophyte infections can be atypical, widespread and refractory in this setting. Dermatophyte infections may also have deep dermal morphologies. These present as multiple fluctuant erythematous ulcerative nodules on the extremities and often are in areas of chronic superficial dermatophytosis. Atypical presentations of *T. rubrum* also include firm violaceous nodules and papules due to nodular granulomatous perifolliculitis usually with co-existing onychomycosis and/or tinea pedis. Proximal nail white onychomycosis is also a marker of HIV infection.<sup>31</sup>

#### Diagnosis

A clinical diagnosis can be confirmed by microscopic examination of a scraping with a potassium hydroxide (KOH) preparation.

#### Management

Superficial disease can be initially treated topically. However, if this fails or if there is widespread or dermal disease, systemic antifungal therapy for 12 weeks is recommended. Treatments of choice include fluconazole and itraconazole. Onychomycosis can be treated with terbinafine.

### 16.3.2 Candida infections

#### Clinical presentation

Candidiasis affects the oral, vaginal and gastrointestinal tract mucosae. Oral candidiasis is the most common, usually presenting as white, exudative, mucosal plaques on the tongue, and oral mucosa. It can also present as the erythematous/atrophic erythematous form without white plaques which is often missed. Alternative presentations include angular cheilitis with erythema and white scale, and chronic hyperplastic candidiasis with discrete leukoplakia. Recurrent episodes of vulvovaginal candidiasis are also common in HIV.

## Diagnosis

The diagnosis of candidiasis is usually made clinically.

## Management

Topical therapies are often used initially. Systemic antifungal therapy is often required; fluconazole is the agent of choice. Itraconazole and voriconazole are alternative agents for disease that is not responsive to fluconazole. Secondary prophylaxis with fluconazole is not normally recommended but may be used for recurrent disease.<sup>32</sup>

### 16.3.3 *Malassezia furfur*

#### Clinical presentation

*Malassezia furfur* can present in the setting of HIV as pruritic pustules, macules or papules on the face, chest, back and shoulders. Due to its morphology and distribution it may be confused with acne vulgaris. *Malassezia* has seven different subspecies that cause or contribute to a spectrum of conditions including Pityriasis versicolor, *Malassezia* folliculitis, seborrhoeic dermatitis, atopic dermatitis and infantile acne.<sup>32</sup>

#### Diagnosis

The diagnosis relies on a KOH preparation test from skin scrapings. Small, round yeast cells and short, hyphal filaments are seen on microscopy.

#### Treatment

Topical clotrimazole can be used initially but systemic fluconazole may be used if topical therapy fails.

### 16.3.4 *Cryptococcosis*

*Cryptococcus neoformans* is the most common invasive fungal infection in patients with HIV infection. Cutaneous disease due to dissemination is an AIDS-defining illness.

#### Clinical presentation

Approximately 10–20% of patients with HIV infection and cryptococcal infection have cutaneous lesions, which usually represent haematogenous spread. These lesions can have varying morphologies including: umbilicated papules and nodules similar to molluscum, erythematous papules, nodules, pustules, ulcers, herpetiform vesicles and infiltrated plaques or subcutaneous swelling. The differential is broad and therefore the lesions should be biopsied and cultured.<sup>1</sup>

#### Diagnosis

The diagnosis of cutaneous cryptococcal infection requires investigation for systemic disease. Biopsies may demonstrate granulomas, which may be absent in the immunocompromised state. Cryptococcal antigen can be measured in blood and body fluids or the organisms demonstrated in cerebrospinal fluid (CSF) by India ink staining.<sup>33</sup> Blood cultures should be taken.

#### Management and prevention

Cutaneous cryptococcosis without evidence of central nervous system invasion can be treated with fluconazole 200–400 mg/day. If extracutaneous disease is found then the recommended treatment is amphotericin B 0.7 mg/kg/day and flucytosine 100 mg/kg/day followed by fluconazole 400 mg daily.

Primary prophylaxis is not recommended, however secondary prophylaxis is the standard of care with either fluconazole 200–400 mg/day or itraconazole 400 mg daily. It can be discontinued with immune reconstitution of CD4 cell counts over 200 cells/ $\mu$ L for 6 months.<sup>34</sup> (see Chapter 13)

### 16.3.5 *Penicilliosis*

*Penicillium marneffe* is a fungus that can cause a fatal systemic mycosis in patients with HIV infection. It is endemic in tropical Asia where it is the third most common opportunistic infection in patients with AIDS after tuberculosis and cryptococcosis.

#### Clinical presentation

Disseminated *P. marneffe* infection in HIV presents as fever, anaemia, weight loss, lymphadenopathy, hepatosplenomegaly, respiratory signs and cutaneous lesions. Cutaneous lesions are of particular importance, appearing in 75% of patients who have penicilliosis, and are specific for the disease. The typical cutaneous lesions are umbilicated papules with central necrotic core. Other morphologies include: ecthyma-like lesions, folliculitis, subcutaneous nodules and morbilliform eruptions.<sup>1</sup> The distribution is on the face and neck and less commonly on the limbs and torso. The differential diagnosis of these lesions includes molluscum contagiosum, histoplasma and cryptococcus.<sup>35</sup>

Cutaneous ulcerations due to *P. marneffe* in the context of cART have been anecdotally reported (personal communication: Rachel Burdon, Vietnam), however, IRDs has not been described in association with this organism in the literature to date. (Personal communication: Rachel Burdon, Vietnam).

#### Diagnosis

Microscopic diagnosis by identification of *P. marneffe* in clinical specimens can be made before cultures are positive, by demonstration of intracellular *P. marneffe* yeast cells in the infected tissue.

#### Management and prophylaxis

There is a poor prognosis with a high mortality rate in the setting of delayed diagnosis and antifungal therapy. Standard primary treatment is two weeks of parenteral amphotericin B at a dose of 0.6 mg/kg/day, followed by 400 mg of itraconazole per day orally in two divided doses for 10 weeks.<sup>36</sup> Prolonged secondary suppressive therapy with oral itraconazole (200 mg once daily) is required to prevent relapse.<sup>37</sup>

### 16.3.6 *Pneumocystis jirovecii* (carinii)

#### Clinical presentation

Infrequently skin lesions of *Pneumocystis jirovecii* have been reported with a variety of morphologies. They may present as friable, reddish papules or nodules in the nares or external auditory meatus or resemble molluscum contagiosum lesions. The skin lesions are due to disseminated disease (see Chapter 13.1).

#### Diagnosis

Lesional biopsy with staining for microscopy stains with Gomori's methenamine silver or Steiner stains to show foamy-appearing cells with a teacup and saucer appearance<sup>38</sup>

## 16.4 Parasitic infections

### 16.4.1 Scabies

Scabies is caused by *Sarcoptes scabiei* var *humanus* and commonly presents in patients with HIV infection in a similar manner to the immunocompetent population.<sup>1</sup>

#### Clinical presentation

In patients with HIV infection, both the classic form and crusted Norwegian scabies (named because of its initial description in Norwegian patients with leprosy) can occur. The classic form can occur at any CD4 cell count, while Norwegian scabies is usually seen in patients with a CD4 cell count below 150 cells/ $\mu$ L. Classic scabies presents as papulovesicular lesions. The distribution varies, favouring the wrists, interdigital web spaces, elbows, axillae, breasts and genitals. Due to the associated pruritis, excoriation of the lesions often occurs. Bacterial superinfection may occur with impetigo, cellulitis and, in some cases, fatal sepsis. In patients with neurological disorders or immunosuppression, the number of mites can increase unchecked due to the impaired immunity, absence of pruritus or the patient's physical inability to scratch. Clinically, the eruption is suspected when there is marked thickening, often psoriasisiform plaques, papules and crusting of the skin. It occurs primarily on the hands, although the entire body including the face and scalp is often involved.<sup>39</sup>

#### Diagnosis

The diagnosis is usually clinical. Definitive diagnosis of scabies is by microscopic examination of the scrapings in potassium hydroxide 10% solution, demonstrating mites, ova or faeces. The skin is scraped with a sterile blade and the skin sample is placed in mineral oil for transport.<sup>1</sup> A standard skin biopsy may make the diagnosis.

#### Management

People with a CD4 cell count over 200 cells/ $\mu$ L respond to a single total body application of topical permethrin (5%) left on for eight to 14 hours. Treatment also involves hot water washing and drying of clothing and linen harbouring the mite. The mite can not survive longer than four days without epidermal contact. Skin lesions and pruritus usually resolve within six weeks, the time-frame given before treatment failure is diagnosed.<sup>40</sup> After that time, re-evaluation of causes of persistent itch should be explored. They include cutaneous irritation secondary to over-treatment (this responds to topical steroids), contact dermatitis from scabicide, treatment failure from low compliance, resistance or relapse (possibly secondary to poor scalp treatment), or delusions. Treatment failure is also related to degree of immunosuppression, and high mite burden. Repeated applications may be required, especially for patients with crusted scabies. Often, topical treatment does not penetrate the lesions of crusted scabies sufficiently for eradication. In adults, systemic therapy of oral ivermectin 200  $\mu$ g/kg in two doses two weeks apart can be given. Prophylactic treatment should be given for all household members and sexual contacts.<sup>40</sup>

## 16.5 Non-infectious disease

### 16.5.1 Seborrhoeic dermatitis

Seborrhoeic dermatitis is a very common non-infectious cutaneous presentation of HIV and is observed in 85% of patients

with AIDS.<sup>41</sup> In some instances it may be the initial cutaneous manifestation of HIV disease. Although it can present at any CD4 cell count, increased severity and extent of involvement with poorer response to treatment occurs with worsening immunosuppression. *Malassezia furfur* may have a role in the pathogenesis of this disease.<sup>42</sup>

#### Clinical presentation

Patients have erythema and yellow-white greasy scaling of the sebaceous areas of the scalp, nasolabial folds, chest, back and intertriginous zone. The eruption is characterised by widespread hyperkeratotic, greasy, inflammatory lesions and may progress to erythroderma.<sup>41</sup> This entity, similar to the immunocompetent population can have a clinical overlap with psoriasis. Examination of the patient for co-existing psoriasis should also occur.

#### Diagnosis

The diagnosis is made clinically. Histological assessment may reveal marked hyperkeratosis, confluent parakeratosis, follicular plugging, acanthosis, spongiosis with lymphocyte, and neutrophil exocytosis with keratinocyte necrosis and dyskeratosis.<sup>41</sup>

#### Management

Initial therapy includes anti-dandruff shampoo for mild disease with addition of ketoconazole shampoo and cream, topical steroids, sulfur, salicylic acid and tars for advanced disease. Ultraviolet B (UVB) light therapy is another modality in addition to topical therapies.<sup>41-43</sup> Pilot studies have demonstrated the benefit of topical pimecrolimus cream 1% twice daily in adults with facial seborrhoeic dermatitis who had not responded satisfactorily to conventional topical corticosteroids and antifungals.<sup>44</sup>

### 16.5.2 Xerosis

The underlying cause of xerosis in HIV is unknown; it may in part be linked to poor nutritional status, chronic illness and immunosuppression. It is cited as affecting approximately 30% of patients with HIV infection.<sup>41</sup>

#### Clinical presentation

There are varying degrees of xerosis, but it is generally characterised by diffuse dryness of the skin with hyperpigmented scales and focal crusting. If secondary fissuring occurs, superinfection from breaches in the protective skin barrier can complicate the clinical picture.

#### Diagnosis

Diagnosis is based on the clinical presentation.

#### Management and prevention

Adequate nutrition is important. Dry skin care regimens are effective in the management of this condition, with emollients, including those with urea, lactic acid or salicylic acid.

### 16.5.3 Psoriasis

Psoriasis affects 2-5% of the population with HIV infection compared to a prevalence of 1-2% in the general population.<sup>41,42</sup> Patients often present with more severe disease. It has been suggested that the immunodysregulation from HIV infection can trigger psoriasis in those genetically predisposed to it.<sup>45</sup>

## Clinical presentation

Psoriasis may present for the first time at progression to AIDS. There are reports of improvement of psoriasis in the setting of immune reconstitution with cART, after initial flares.<sup>44</sup> HIV infection may alter the course of psoriasis in individual patients with some patients having co-existing patterns of psoriasis such as both guttate psoriasis and psoriasis vulgaris.<sup>42</sup> Severe exfoliative erythroderma may also occur.<sup>40</sup> Patients with HIV infection are more likely to have arthritis associated with psoriasis.<sup>46</sup>

## Diagnosis

The diagnosis of psoriasis is clinical and can be confirmed on a biopsy.

## Management and prevention

Spontaneous remission to complete unresponsiveness to all therapy has been described for HIV-related psoriasis. Topical therapy includes tar products, emollients, salicylic acid, corticosteroids and retinoids. Traditional systemic therapies such as acitretin (0.5-1 mg/kg) are also used. Methotrexate, although commonly used in the non-HIV psoriatic population, is not commonly used because of its immune modulating effects and increased toxicity in the folate metabolic pathway with diminished renal excretion in many HIV patients also taking trimethoprim/sulfamethoxazole. The use of UV light therapy is debated.<sup>40</sup> Biologics are being increasingly used for psoriasis and, although there are limited reports, anti-tumour necrosis factor therapy has been used with success in patients with HIV infection with progressive psoriatic arthritis.<sup>47</sup>

### 16.5.4 Eosinophilic folliculitis, pruritic papular eruption and other inflammatory folliculitides

Eosinophilic folliculitis is a common intensely pruritic condition often occurring in advanced disease or IRDs, three to six months post commencement of cART.<sup>48</sup> There is significant associated morbidity and disfigurement.<sup>40</sup> The role of usually non-pathogenic commensals of the skin including *Pityrosporum* yeasts (*Malassezia*), *Demodex* mites, *Corynebacterium* and *Staphylococcus* is debated.<sup>8</sup> Pruritic papular eruption is an incompletely understood entity in HIV with symmetrical papular eruptions on the trunk and limbs in the absence of other definable causes of itching.<sup>49</sup> It is most likely that eosinophilic folliculitis and pruritic papular eruption are part of the same disease spectrum.

## Clinical presentation

Eosinophilic folliculitis presents as intensely pruritic 2-3mm erythematous oedematous urticarial papules centred around follicles and may have pustules. The distribution is over the forehead, neck, shoulders, trunk and upper arms. Occasionally it can become generalised. Due to the associated pruritus, secondary change with time is common. This includes excoriations with secondary staphylococcal infection, prurigo nodularis, lichen simplex chronicus and post-inflammatory pigmentary changes.<sup>8,40</sup>

## Diagnosis

The differential diagnosis is difficult and includes the common causes found in patients without HIV infection such as insect bite reactions, scabies, dermatitis herpetiformis, drug reactions, atopic dermatitis and bacterial folliculitis. Differential diagnoses and their management are listed in Table 16.4.

## Management

Depending on the cause, management varies, particularly if an infective cause such as scabies is found. The difficulty arises in the diagnosis of eosinophilic folliculitis and pruritic papular eruption (Table 16.4). Eosinophilic folliculitis and pruritic papular eruption can be difficult to manage with the pruritus often unresponsive to traditional therapies. Treatment options for eosinophilic folliculitis and pruritic papular eruption are similar with potent topical corticosteroids, oral antihistamines, oral antibiotics, emollients, antifungals, antiscabies and phototherapy treatments all being recommended.<sup>48</sup>

## 16.6 Serious adverse drug eruptions including Stevens-Johnson syndrome and toxic epidermal necrolysis

Cutaneous drug eruptions are reported more frequently in people with HIV infection.<sup>50</sup> The majority of adverse cutaneous reactions to medications have a low morbidity and mortality and are self limited. Of note, sulfonamide-induced drug reactions occur in as many as 29-65% of patients with HIV compared with 2-4% of other patients. Often patients with HIV have morbilliform (maculopapular), nonpruritic, nonblistering rashes, as can patients without HIV.

Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) belong to a spectrum of serious disorders with Stevens-Johnson syndrome at one end and TEN at the other. Both disorders are rare, and virtually always represent an idiosyncratic, adverse drug reaction. The incidence is higher in patients with HIV infection than in the general population. There have been well documented case reports of Stevens-Johnson syndrome and TEN in the setting of HIV treatment with protease inhibitors and, most commonly, nevirapine.<sup>51</sup> Stevens-Johnson syndrome and TEN are also seen in the context of HIV treatment with sulfonamides, and are thought to be attributable to reactive metabolites.<sup>52</sup>

### 16.6.1 Clinical presentation

Patients may present with a prodrome of fever, stinging eyes, painful swallowing, followed by the development of dusky erythematous macules that progress to flaccid blisters. Two or more mucous membranes are usually involved, with erythema and erosions of the buccal, genital and ocular mucosa. Severe ophthalmic involvement may lead to permanent scarring and blindness. Epidermal detachment is common, which may lead to massive fluid loss and electrolyte imbalance.

Although several classification systems for Stevens-Johnson syndrome and TEN exist, the most widely accepted divides the spectrum into five categories (Table 16.5).<sup>53</sup>

Table 16.4. Differential diagnosis of pruritic papular eruptions

	Pruritic papular eruption	Eosinophilic folliculitis	<i>Demodex folliculorum</i>	Scabies	Folliculitis: Bacterial (B) Pityrosporum (P)
<b>Clinical findings</b>	Skin-coloured papules Excoriations Pustules rare Postinflammatory hyperpigmentation Prurigo-like nodules Scarring	Oedematous papules Pustules not predominant Postinflammatory hyperpigmentation Prurigo-like nodules Scarring	Rosacea-like erythematous papules with background erythema	Papules/plaques with crust or excoriations Burrows Vesicles Nodules Eczematous changes especially in crusted Norwegian scabies	Pustules predominate Follicular pattern Perifollicular papules
<b>Distribution</b>	Symmetrical Extremities, face, trunk Rare on palms, soles, digital web spaces	Forehead, eyelids, cheeks, neck, postauricular, upper arms and trunk	Head, neck	Hands, wrists, interdigital, ankles, ears face, scalp	B: head, neck, upper trunk, axillae, groin, buttocks P: back, chest, shoulders
<b>Histopathology</b>	Dermal perivascular and interstitial lymphocytes, eosinophils Epidermal hyperplasia Follicular damage?	Follicular spongiosis Folliculocentric infiltrate rich in eosinophils Flames figures Eosinophilic abscesses	Spongiotic, infundibular folliculitis	Scabies mite faeces or eggs in epidermis Eosinophils in reticular dermis	B: <i>Staphylococcus aureus</i> : suppurative folliculitis, gram stain P: yeast forms
<b>Investigations</b>	Increase IgE Eosinophilia CD4 <100/ $\mu$ L increase CD8 T cells increase IgG ? Antibodies to bullous pemphigoid antigen?	increase IgE Eosinophilia CD4 <300/ $\mu$ L	Skin scraping	Skin scraping PCR from scale	Skin swab P: KOH yeast forms
<b>Treatment</b>	Potent topical steroids Emollients Antipruritic lotions Antifungal creams Antiscabies therapy Antihistamines Oral antibiotics Pentoxifylline Anti-retrovirals UVB phototherapy	Potent topical steroids Antihistamines Prednisone Metronidazole Itraconazole Permethrin/ivermectin Isotretinoin Dapsone UVB 1% tacrolimus ointment	Permethrin Oral/topical metronidazole Ivermectin	Permethrin Malathion Sulphur ointment Ivermectin	B: intranasal mupirocin ointment Topical benzoyl peroxide Topical or oral antibiotics Antibacterial washes P: topical antifungals Selenium sulphide shampoo 50% propylene glycol in water Fluconazole Itraconazole
KOH = potassium hydroxide; PCR = polymerase chain reaction; Ig = immunoglobulin, UVB = ultraviolet B light.					
Source Eisman S. Pruritic Papular Eruption in HIV. <i>Dermatol Clin</i> 2006;24(4):449-57.					

### 16.6.2 Diagnosis

The patient history and clinical presentation usually make the diagnosis of TEN obvious, however a skin biopsy is used for a definitive diagnosis.

### 16.6.3 Management

Stevens-Johnson syndrome has an attributable mortality of 5% and TEN an overall mortality of 30%. Discontinuation of the offending drug is essential. Stevens-Johnson syndrome and TEN should be managed by an experienced physician. Supportive

measures include identification and removal of the offending medication, admission to a burn unit if necessary, intravenous fluid administration, maintenance of electrolyte and temperature homeostasis, and ophthalmological assessment in case of ocular involvement. Skin care consists of proper wound dressings, oral hygiene (i.e. chlorhexidine rinses), antihistamine and topical corticosteroid therapy for pruritus, and antimicrobial therapy in cases of superinfection due to skin-barrier breakdown. Some units use high doses of immunoglobulin intravenously as mainstay therapy for TEN; however, more evidence of its effectiveness is needed.<sup>54</sup>

**Table 16.5. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme**

1. Bullous erythema multiforme: epidermal detachment involving <10% of the body surface, couple with localised typical target or raised atypical targets
2. Stevens-Johnson syndrome (SJS): epidermal detachment of <10% of the body surface in association with widespread erythematous or purpuric macules or flat atypical targets, haemorrhagic erosions of the lips
3. SJS and toxic epidermal necrolysis (TEN) overlap: epidermal detachment of 10-30% of the body surface plus widespread purpuric macules or flat atypical targets
4. TEN with spots: epidermal detachment of >30% of the body surface coupled with widespread purpuric macules or flat atypical targets
5. TEN without spots: large sheets of epidermal detachment involving >10% of the body surface without purpuric macules or target lesions

## References

- Hogan MT. Cutaneous infections associated with HIV/AIDS. *Dermatol Clin* 2006;24:473-95.
- Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis* 2007;44(Suppl 1):S1-26.
- Wareham DW, Breuer J. Herpes zoster. *Br Med J* 2007;334:1211-15.
- King J. Ophthalmologic complications of systemic disease. *Emerg Med Clin Nth Am* 2008;26(1):217-31.
- Gebo KA, Kalyani R, Moore RD, Polydefkis MJ. The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. *J Acquir Immune Defic Syndr* 2005;40:169-74.
- Gershon AA, Mervish N, La Russa P, Steinberg S, Lo SH, Hodes D, et al. Varicella-zoster virus infection in children with underlying human immunodeficiency virus infection. *J Infect Dis* 1997;176:1496-500.
- Martinez E, Gatell J, Moran Y, Aznar E, Buira E, Guelar A, et al. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. *Clin Infect Dis* 1998;27:1510-3.
- Lehloeny R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. *Dermatol Clin* 2006;24(4):549-70.
- Dwyer DE, Cunningham AL. Herpes simplex and varicella-zoster virus infections. *Med J Aust* 2002;177(5):267-3.
- Gershon AA. Prevention and treatment of VZV infections in patients with HIV. *Herpes* 2001;8:32-6.
- American Academy of Pediatrics. Committee on Infectious Diseases. Varicella vaccine update. Updated May 16, 2006. *Pediatrics* 2006;(1 Pt 1):136-41.
- Bekker V, Westerlaken GH, Scherpbier H, Alders S, Zaaijer H, van Baarle D, et al. Varicella vaccination in HIV-1-infected children after immune reconstitution. *AIDS* 2006;20:2321-9.
- National Health and Medical Research Council. The Australian Immunisation Handbook. 9th Ed. 2008. Chapter 2.3 Groups with Special Vaccination Requirements. Available at: <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home> (cited February 2009)
- Smith L. Practice Guidelines ACIP Recommendations for prevention of varicella. *Am Fam Physician* 2007;76(9):1396-402.
- Johnson RW, Whitton TL. Management of herpes zoster (shingles) and postherpetic neuralgia. *Expert Opin Pharmacother* 2004;5:551-9.
- Shafran SD, Tyring SK, Ashton R, Decroix J, Forszpaniak C, Wade A, et al. Once, twice, or three times daily famciclovir compared with aciclovir for the oral treatment of herpes zoster in immunocompetent adults: a randomized, multicenter, double-blind clinical trial. *J Clin Virol* 2004;29:248-53.
- Ng PP, Sun YJ, Tan HH, Tan SH. Detection of herpes simplex virus genomic DNA in various subsets of Erythema multiforme by polymerase chain reaction. *Dermatology* 2003;207:349-53.
- French MA, Price P, Stone SF. Immune restoration after antiretroviral therapy. *AIDS* 2004;18(12):1615-27.
- Nagot N, Ouedraogo A, Foulongne V, Konaté I, Weiss HA, Vergne L, et al; ANRS 1285 Study Group. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med* 2007;356:790-9.
- Wilkinson E. Herpes treatment may limit HIV transmission and progression. *Lancet Infect Dis* 2007;7(4) 249.
- Sizemore JM, Lakeman F, Whitley R, Hughes A, Hook EW. The spectrum of genital herpes simplex virus infection in men attending a sexually transmitted disease clinic. *J Infect Dis* 2006;193:905-11.
- Van Vranken M. Prevention and treatment of sexually transmitted diseases; an update. *Am F Physician* 2007;6(12) 1827-32.
- Strick LB, Wald A. Diagnosis for herpes simplex virus: is PCR the new gold standard? *Mol Diagn Ther* 2006;10(1):17-28.
- Rucco E, Donnarumma G, Baroni A, Tufano M. Bacterial and viral skin diseases. *Dermatol Clin* 2007;25(4):663-76.
- Madkan VK, Cook-Norris RH, Steadman MC, Arora A, Mendoza N, Tyring SK. The oncogenic potential of human papillomaviruses: a review on the role of host genetics and environmental cofactors. *Br J Dermatol* 2007;157(2): 228-41.
- Schöfer H. Evaluation of imiquimod for the therapy of external genital and anal warts in comparison with destructive therapies. *Br J Dermatol* 2007;157(2): 52-5.
- Hagensee ME, Cameron JE, Leigh JE, Clark RA. Human Papillomavirus infection and disease in HIV-infected individuals. Complications of HIV disease or treatment. *Am J Med Sciences* 2004;28(1):57-63.
- Hengge UR, Cusini M. Topical immunomodulators for the treatment of external genital warts, cutaneous warts and molluscum contagiosum. *Br J Dermatol* 2003;149(66):15-19.
- Toro JR, Wood LV, Patel NK, Turner ML. Topical cidofovir. A novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus-1. *Arch Dermatol* 2000;136:983-5.
- Lehloeny R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. *Dermatol Clin* 2006;24(4):549-70.
- Venkatesan P, Perfect J, Myers S. Evaluation and management of fungal infections in immunocompromised patients. *Dermatol Ther* 2005;18:44-57.
- Van der Wouden JC, Menke J, Gajadin S, Koning S, Tasche MJ, van Suijlekom-Smit LW, et al. Interventions for cutaneous molluscum contagiosum. *Cochrane Database Syst Rev* 2006;(2):CD004767.

## 16 Dermatological manifestations

- 33 Mehrabi M, Bagheria S, Leonard MK, Perciaccante VJ. Mucocutaneous manifestation of cryptococcal infection: report of a case and review of the literature. *J Oral Maxillofac Surg* 2005;63:1543-9.
- 34 Ruhnke M. Mucosal and systemic fungal infection in patients with AIDS. Prophylaxis and treatment. *Drugs* 2004;64(11):1163-80.
- 35 Varghese GM, Pise G, Michael S, Jacob M, George R. Disseminated *Penicillium marneffei* infection in a Human Immunodeficiency Virus-infected individual. *J Postgrad Med* 2004;50:235-6.
- 36 Taramelli D, Tognazioli C, Ravagnani F, Leopardi O, Giannulis G, Boelaert JR. Inhibition of intramacrophage growth of *Penicillium marneffei* by 4-aminoquinolines. *Antimicrob Agents Chemother* 2001;45:1450-5.
- 37 Vanittanakom N, Cooper CR, Fisher MC, Sirisanthana T. *Penicillium marneffei* Infection and recent advances in the epidemiology and molecular biology aspects. *Clin Microbiol Rev* 2006;19(1):95-110.
- 38 Hennessey NP, Parro EL, Cockerell CJ. Cutaneous *Pneumocystis carinii* infection in patients with acquired immunodeficiency syndrome. *Arch Dermatol* 1991;127(11):1699-1701.
- 39 Johnston G. Scabies: diagnosis and treatment. *Br Med J* 2005;331(7517):619-22.
- 40 Jacobson C, Abel E. Parasitic Infection. *J Am Acad Dermatol* 2007;56(6):1026-43.
- 41 Garman ME, Tyring SK. The cutaneous manifestations of HIV infection. *Dermatol Clin* 2002;20:193-208.
- 42 Dlova NC, Mosam A. Inflammatory noninfectious dermatoses of HIV. *Dermatol Clin* 2006;24(4):439-48.
- 43 Aftergut K, Cockerell CJ. Update on the cutaneous manifestations of HIV infection. *Dermatol Clin* 1999;17:445-71.
- 44 De NMoraes AP. An open-label efficacy pilot study with pimecrolimus cream 1% in adults with facial seborrhoeic dermatitis infected with HIV. *J Eur Acad Dermatol Venereol* 2007;21(5):596-601.
- 45 Mamkin I, Mamkin A, Ramanan S. HIV-associated psoriasis. *Lancet Infect Dis* 2007;7(7):496.
- 46 Medina F, Perez-Saleme L, Moreno J. Rheumatic manifestation of human immunodeficiency virus infection. *Infect Dis Clin North Am* 2006;20(4):891-912.
- 47 Saketkoo L, Espinoza L. Impact of biologic agents on infectious diseases. *Infect Dis Clin North Am* 2006;20(4): 931-61.
- 48 Rajendran PM, Dolev JC, Heaphy MR Jr, Maurer T. Eosinophilic folliculitis: before and after the introduction of antiretroviral therapy. *Arch Dermatol* 2005;141:1227-31.
- 49 Eisman S. Pruritic papular eruption in HIV. *Dermatol Clin* 2006;24(4):449-57.
- 50 Todd G. Adverse cutaneous drug eruptions and HIV: a clinician's global perspective. *Dermatol Clin* 2006;24(4):459-72.
- 51 Ward H, Russo G, Shrum J. Cutaneous manifestations of antiretroviral therapy. *J Am Acad Derm* 2002;46(2):284-93.
- 52 Greenberger P. Drug Allergy. *J Allergy Clin Immunol* 2006;117(2):S464-70.
- 53 Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme. *Arch Dermatol* 1993;129:92-6.
- 54 Freiman A, Borsuk D, Sasseville D. Dermatologic emergencies. *Can Med Assoc J* 2005;173(11):1317-9.