Less common complaints include gastrointestinal problems such as nausea, vomiting, and/or diarrhea, or neurologic symptoms such as headache. The duration of symptoms typically is less than 2 weeks; however, in rare instances it may persist for as long as 10 weeks.7

Cutaneous manifestations are seen in up to 75% of symptomatic patients and usually appear several days after the onset of symptoms. The most common is a morbilliform eruption with pink macules and papules up to 1 cm in diameter (1). The trunk is most commonly involved, followed by the face, lower limbs, and upper limbs.6 Vesicles, pustules, urticaria, alopecia, desquamation of the palms and soles, and Stevens-Johnson syndrome (SJS) have also been reported.10 It has been suggested that the exanthem could be secondary to infection of Langerhans cells in the epidermis. In approximately 25% of ARS, the exanthem is accompanied by painful erosions and ulcerations of the mucous membranes. Ulcers range in size from 5 mm to 10 mm in diameter, are round to oval, shallow with white bases surrounded by a red halo, and can involve the tonsils, palate, buccal, and/or esophageal mucosa. Although the oral cavity is most commonly involved, genital lesions have been reported rarely.11

The presentation of ARS is nonspecific and the differential diagnosis includes many infectious diseases including exanthems caused by primary cyto-megalovirus (CMV) infection, primary Epstein-Barr virus (EBV) infection, influenza, streptococcal infection, secondary syphilis, toxoplasmosis, rubella, brucellosis, and malaria.12 Drug reactions, early toxic shock syndrome, Rocky Mountain spotted fever, Lyme disease, herpesvirus infection, and viral hepatitis should also be considered.

**DIAGNOSIS**

It is unknown how many patients seek medical attention for ARS. It is likely that the initial visit is with a primary care clinician because the symptoms mimic those of more common illnesses.4 Because ARS may simulate many other conditions, awareness is requisite for diagnosis. It is also important that the condition be recognized for a number of reasons. First, several studies have demonstrated that patients with ARS have a more aggressive disease course and earlier onset of AIDS than those who do not develop the syndrome.13,14 It has also been observed that the severity of the seroconversion illness may predict the subsequent course of HIV infection. Among patients with illnesses lasting longer than 2 weeks, 78% had an AIDS-related diagnosis within 3 years versus 10% of those whose primary illness lasted less than 2 weeks.15 Furthermore, symptomatic primary HIV infection may be a period in which initiation of treatment allows immune reconstitution which may improve the subsequent clinical course and CD4+ count.16,17 as treatment with antiretroviral agents results in rapid remission of ARS in the majority of patients. Lastly, patients are highly infectious during primary HIV infection due to pronounced viremia.

The risk of acquiring HIV when exposed to an individual with symptomatic primary HIV infection may be 500-fold greater than when exposure occurs in the period of clinical latency.18 Thus, it is of prime importance to identify newly infected patients to prevent further spread of the disease.

The diagnosis of primary HIV infection is usually made by documentation of HIV seroconversion, the development of anti-HIV antibodies, with the enzyme linked immunosorbent assay (ELISA) technique confirmed by Western blot assays. In early disease, however, tests for viral antigen itself must be used as antibodies will not appear for a number of weeks. Established HIV infection can be confirmed by these serologic tests but can also be documented by isolation of HIV from blood or cerebrospinal fluid (CSF), or demonstration of p24 antigen.

In those with a morbilliform eruption, physicians can inquire about risk factors for acquisition of HIV including having unprotected intercourse with someone at risk, possible occupational exposure, and intravenous drug use. The absence of any HIV risk factors lessens the likelihood of ARS; however, it is important to appreciate that sexual and substance abuse histories may not be readily volunteered. Screening for other sexually transmitted diseases (STDs) including syphilis and hepatitis B infection should be performed.

**HISTOPATHOLOGY**

The histologic findings are nonspecific and resemble those of other acute viral exanthems.19 Pervascular lymphohistiocytic infiltrates in the superficial dermis with minimal epidermal alterations are most common (2). In some cases, there may be scattered individually necrotic keratinocytes in the epidermis as well as scattered plasma cells in the infiltrate in the dermis.

**MANAGEMENT**

Treatment protocols for ARS are similar to those used in patients with advanced AIDS although because relatively few cases have been treated, there is little data about which protocols may be optimal for this form of HIV infection. As noted previously, early treatment often leads to immune preservation and reconstitution. Treatment during primary infection also appears to restore the balance between naive and memory CD4+ T cells and improves lymphoproliferative responses to candidiasis and tetanus.20 Furthermore, neutralizing antibodies appear more rapidly in treated patients than in untreated patients. In some patients, however, by the time acute symptoms arise, treatment may already be too late to prevent the accumulation of a large pool of infectious virus in CD4+ T-lymphocytes.21 In addition, it has been suggested that removal of HIV antigen before the evolution of a complete immune response may impair future immune control. Because of the complexities of treating ARS, it is recommended that expert consultation be obtained as soon as the diagnosis of primary HIV infection is made. The availability of comprehensive services including social workers, pharmaceutical assistance, psychological and social counseling, and patient education is crucial to a successful management strategy.
MOLLUSCUM CONTAGIOSUM

Definition/overview
Molluscum contagiosum (MC) is a viral infection almost universally encountered in sexually active individuals with HIV. Although most lesions are self-limiting, patients with weakened immune systems have increased difficulty clearing lesions, which may persist for prolonged periods. The association between MC and HIV was first noticed in 1983 through an autopsy study of 10 patients with AIDS. MC has surfaced as one of the three most common nondermatology referrals in HIV patients to a university-based immunosuppression skin clinic. Molluscum contagiosum virus (MCV) is present worldwide and is passed by direct skin-to-skin contact to produce cutaneous, and rarely, mucosal lesions. It occurs predominately in preadolescent children, sexually active adults, participants in sports with skin-to-skin contact, and in individuals with impaired cellular immunity.

Pathogenesis/pathophysiology
The virus (genus *Molluscipoxvirus*) causing MC is a member of the family Poxviridae of which smallpox is also a member. MCV is a large double-stranded deoxyribonucleic acid (DNA) virus with a brick-shaped morphology. Four subtypes have been identified, all of which have a similar clinical presentation and are not localized to a particular region of the body. MCV type 1 (MCV-1) is the most common subtype, detected in 98% of infected patients, whereas MCV-3 and 4 are rarely observed. MCV-2 and 3 are slightly more prevalent in Europe, and significantly more prevalent in Australia and in patients with HIV. In HIV-infected patients, MC occurs most commonly when immune function has been dramatically reduced, especially when the CD4+ count falls below 200 × 10⁶/l. Several studies have documented that MC is a sign of HIV progression and very low CD4+ counts and is correlated with poor prognosis and a median survival time of 12 months. However, the presence of MC is not an independent prognostic indicator after accounting for immunosuppression. The development of MC in AIDS patients is believed to reflect reactivation of latent infection, although others propose that it is due to recently acquired infection complicating progressive immunosuppression. MCV commonly infects the general population with 23% of individuals having antibodies to the virus.

In adolescents and adults, MC is most commonly transmitted by sexual contact and is considered a STD. However, MCV may be transmitted by casual contact, fomites (e.g., underwear), or self-inoculation. The incubation time for MCV has not been well established; however, the average incubation period for MCV in humans ranges from 14 to 50 days.

Clinical features
In AIDS patients, the prevalence of MC skin lesions ranges from 5% to 18%. In sero-positive individuals, MC can occur at any time of HIV disease. They typically appear as white, pink, or skin-colored, umbilicated, raised papules (1–5 mm in diameter) or nodules (6–10 mm in diameter). MC may occur as single or multiple lesions. Although most patients are asymptomatic, they may present with a dermatitis surrounding lesions and may experience pruritus or tenderness due to host immune responses, so-called ‘molluscum dermatitis’. Gentle pressure on a MC lesion will often cause the central plug to be extruded. In children, the cutaneous lesions of MC are commonly located on the extremities, often as grouped lesions in the axillae, antecubital fossa, and less commonly the popliteal fossa, due to auto-inoculation. In adults, where they are often sexually transmitted, they are located in the genital region, lower abdomen, and thighs. In dark-skinned individuals, significant postinflammatory hyperpigmentation may occur after treatment.

Immunocompromised patients may present with atypical features of MC including unusual morphology and growth patterns (3–7). HIV-positive patients may develop giant (>1 cm) lesions or may have clusters of several hundred lesions. In young men and immunocompromised patients, facial involvement commonly occurs and is spread by shaving (auto-inoculation) which may result in a diffuse infection that simulates a beard. Rarely,
sexual transmission may also result in intraoral or perioral involvement, especially in immunocompromised patients. MC can also develop on the conjunctiva causing conjunctivitis.

The clinical differential diagnosis of MC includes flat warts, condylomata acuminata, vulvar syringomata, and sebaceous hyperplasia for multiple small MC lesions. Disseminated infections including Cryptococcus, histoplasmosis, penicilliosis, and pneumocystosis may also appear similar to MC. Larger lesions may appear similar to squamous or basal cell carcinoma, keratoacanthoma, and epidermoid cysts.

**Histopathology**

Studies evaluating the microscopic and ultrastructural features of MC identify no major differences between samples taken from healthy individuals and from AIDS patients. Direct microscopic examination of Giemsa-stained smears of the keratotic plug reveals ‘molluscum bodies’ (Henderson–Patterson bodies). Histologically, epidermal cells contain large inclusion bodies that appear as single, ovoid eosinophilic structures in the lower cells of the stratum malpighii. Each body contains large numbers of maturing virions. The epidermis invaginates into the dermis and infection involves the epithelium of the hair follicles which eventually coalesce producing a small cyst-like structure. Early transcription of MCV occurs within the basal cell layer, and MCV viral colonies first become visible by histology after destruction of the follicular epithelium, routine fixation produces an area of retraction artifact separating the one to three layers of CD34+ stromal cells that immediately surround the follicle. This feature may be obscured when the lesions are inflamed, usually after rupture, into the surrounding dermis. One study noted ultrastructural presence of viral particles in adjacent normal appearing skin adjacent to mollusca in HIV-positive patients. It has been suggested that this may partially explain the high rate of recrudescence after destructive treatment.

**Diagnosis**

Diagnosis of genital MC is generally made by clinical examination of the patient. However, because of the atypical nature of MC in the HIV-positive patient, diagnosis may be dependent on biopsy. Studies evaluating the microscopic and ultrastructural features of MC did not identify any major differences between samples taken from healthy patients as compared to patients with AIDS. One exception to this is that AIDS patients may lack the inflammation and lymphocytic infiltration seen in ruptured lesions. If genital MC lesions are identified, patients should be tested for other STDs as a precautionary measure.

**Management**

Preventative management includes avoidance of skin-to-skin contact with individuals infected with MV. HIV patients with MC in the beard area should also be advised to minimize shaving facial hair to grow a beard. MC in HIV patients is notoriously difficult to treat, and there is little evidence that lesions spontaneously resolve. Perhaps the most widely used methods are curettage and cryosurgery. Small mollusca may be removed with a small curette with minimal discomfort. Freezing lesions for 10–15 seconds is effective using either a cotton-tipped applicator or liquid nitrogen spray. For MC refractory to cryosurgery, especially in HIV-infected individuals, electrodesiccation or laser surgery is the treatment of choice. Large lesions typically require anesthesia either applied topically or intralesionally. Giant MC may require several cycles of electrodesiccation and curettage.

While destructive treatment is the mainstay, several topical agents have demonstrated efficacy in treating MC. Daily topical tretinoin application may serve as an adjunctive therapy to local destructive treatment and studies have also reported success with cantharidin with or without curettage for resistant lesions. Although tretinoin appears to diminish the appearance of new lesions and helps eliminate older lesions, its use is limited by local irritation. Trichloroacetic acid peels yielded an average reduction in MC lesion counts of 40.5% in seven HIV-infected individuals. Immune therapy with systemic and intravenous interferon (IFN) has been used with moderate success in treating AIDS patients with MC. Topical application of imiquimod enhances functional maturation of Langerhans cells and their migration to regional lymph nodes, thereby enhancing cutaneous adaptive responses, as well as innate and adaptive immunologic response. It has been studied for treatment of MC in AIDS patients and has shown moderate success although its use is limited by local irritation. Podophyllin is also effective but may be a poor choice in patients with HIV given their predisposition for development of cancer and its being mutagenic. If applied, it should be left on for only a minimal period (1–4 hours) and then thoroughly washed off. Because podophyllin is caustic and causes irritation, only a small area should be treated at one time. A nucleotide analog of deoxyxycytidine monophosphate, cidofovir, is an antiviral with activity against a broad variety of DNA viruses, including MCV. It is most commonly used for the treatment of CMV retinitis in AIDS patients, and is useful as topical or intravenous treatment for recurrent MC although it is quite expensive. Patients with concurrent MC and CMV treated with intravenous cidofovir have experienced clearance of MC lesions. Finally, several case reports have described the reduction in MC after beginning antiretroviral treatment.
HUMAN PAPOILLOMAVIRUS INFECTIONS

DEFINITION/OVERVIEW

Human papillomavirus (HPV) infections are extremely common in humans and cause a wide variety of clinical lesions of the skin and mucous membranes (9–12). HPV is a double-stranded DNA virus of the papovavirus class that induces hyperproliferative lesions of cutaneous and mucosal epithelia.34 Many viral strains play roles in oncogenesis of epithelial neoplasms including squamous cell carcinoma in situ (SCCIS) and invasive squamous cell carcinoma (SCC). More than 150 types of HPV have been identified and many are associated with distinct clinical syndromes. Transmission is by skin-to-skin contact and minor breaks in the stratum corneum facilitate epidermal infection.

PATHOGENESIS/PATHOPHYSIOLOGY

Three cutaneous HPV infections are encountered most frequently: common warts (verrucae vulgaris), plantar warts, and flat warts. While they may be of minimal consequence, they often cause significant cosmetic and functional abnormalities. Genital warts (condyloma acuminatum), although less common in the general population, are seen with higher frequency in HIV-infected individuals. Plantar warts located over pressure points of the feet, may be extremely painful and may limit normal daily activities. Common warts are firm papules 1–10 mm in diameter with a verrucous, hyperkeratotic surface. Characteristic red or brown dots, 1–10 mm in diameter with a verrucous, hyperkeratotic surface. These warts are often hard and painful, especially when walking. Flat warts are asymptomatic, smooth, and flat with a brownish color. They are usually found on the face, arms, and legs.

Management

Traditional treatment modalities include podophyllin, podophyllotoxin, salicylic acid, trichloroacetic acid, and surgical techniques.45 Recently, topical application of immunomodulatory compounds such as imiquimod have demonstrated good efficacy with clearance rates up to 77% and low recurrence rates. A vaccine to prevent acquisition of oncogenic HPV has also recently been released although it is unclear how useful this will be in those with established HPV infection. Unfortunately, in immunocompromised hosts, cutaneous HPV infections may be very resistant to all modalities of therapy.

HERPESVIRIDAE

DEFINITION/OVERVIEW

The herpesviridae are double-stranded DNA viruses that are somewhat arbitrarily classified into three subfamilies: the alpha, the beta, and the gamma subgroups.16 There are eight human herpesviruses. Members of alphaherpesviruses replicate rapidly in vitro and in vivo and lead to lytic destruction of infected cells. Herpes simplex virus (HSV–1, HSV–2 and varicella-zoster virus (VZV) belong to this group. Betaherpesvirus, on the other hand, has a relatively long reproductive cycle and grows slowly in culture. CMV is the only human pathogen in this group. CMV typically causes a chronic nonlytic cellular infection resulting in cytomegalic changes (cellular enlargement). The gamma herpesviruses of humans include four lymphotropic agents: EBV and herpesviruses 6, 7, and 8. Members of the herpesvirus family share a common structure. They all have an icosahedral nucleocapsid composed of 162 subunits called ‘capsomeres’.