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Sexually Transmitted Diseases

Charles B. Whitlow, Lester Gottesman, and Mitchell A. Bernstein

Introduction

There are over 25 diseases primarily spread by sexual means with an annual incidence of approximately 15 million cases in the USA.[1] In 1994, the overall cost related to major sexually transmitted diseases (STDs) was estimated to be 17 billion dollars. In the UK, the incidence of STDs has substantially increased over the past 6 years and has led to a new government strategy to counteract these increases.[2,3]

Site and route of infection determine the symptoms caused by STDs. Infections of the distal anal canal, anoderm, and perianal skin are similar to lesions in other parts of the genitalia and perineum caused by the same organisms. These infections are typically the result of anal receptive intercourse but in some instances represent contiguous spread from genital infections. Proctitis from sexually transmitted organisms is almost always acquired from anal intercourse. Direct or indirect fecal–oral contact produces infection with organisms which cause proctocolitis or enteritis but which are generally thought of as food or waterborne diseases instead of STDs. Included in this group are *Entameba histolytica*, *Campylobacter*, *Shigella*, *Giardia lamblia*, and hepatitis A. While it appears that male homosexual activity and the use of the anorectum for sexual gratification is increasing, data regarding the frequency of these behaviors both past and present are limited. Current estimates are that less than 2% of adult males regularly practice anal receptive intercourse while between 2 and 10% participate in homosexual activity at any point in their life.[4] Between 5 and 10% of females engage in anal receptive intercourse "with some degree of regularity" and females appear to be more likely than men to have unprotected anal intercourse.[4]

Difficulty in correct diagnosis and appropriate treatment of STD of the anorectum is caused by several factors. (1) The signs and symptoms of infection are more organ related than organism related so that no symptom or symptom complex or physical finding is diagnostic for many STDs. (2) The presence of more than one organism is not uncommon, especially with anogenital ulcerations. (3) Determining true pathogen from colonizing organism may be difficult. (4) Lastly, there is a lack of rapid sensitive diagnostic tests for many STDs so that empiric treatment is frequently required.

This chapter discusses the STDs that are most commonly seen by colorectal surgeons. Entire texts are devoted to STDs; however, we confine most of our comments to the diagnosis, treatment, and prevention of the anorectal component of these infections. Infections, which manifest as one of the colitides, are covered in Chap. 34.

Overview of Anorectal Immunology

The optimal state of health of the anus requires the integrity of the skin, which acts as the primary protection against invasive pathogens. The mucosa shed from the rectum contains IgA, which traps foreign antigens and expels them with stool, preventing them from reaching the rectal crypt cells.[5] Cellular immunity is controlled by the Langerhan's, or dendritic cells which communicate with the T cells through a complicated mechanism and essentially prime the T cells to identify foreign cells.[6] This process allows the entire complement of cell-mediated immunity to destroy alien substances. Although study of anal immunology is still in its infancy, it appears that certain pathogens may alter the balance of cellular elements. It is known that while Human papillomavirus (HPV) increases Langerhan's cells, human immunodeficiency virus (HIV) may damage their effectiveness. In addition, pathogens like HPV and herpes simplex virus (HSV) invade into the host cell, combining with cellular elements or the genome, evading surveillance mechanisms. In addition, in the case of HPV, the identifying foreign antigens are placed onto the frame of the new virus near the epidermis, where the virus normally sheds and where an attack by the host has little value.[7]

HIV is known to impair cell-mediated immunity by depletion of T cells and destruction of Langerhan's cells. This process allows propagation of oncogenic processes such as HPV to become dysplastic. Although both exact switches and the

D.E. Beck et al. (eds.), *The ASCRS Textbook of Colon and Rectal Surgery: Second Edition*,
DOI 10.1007/978-1-4419-1584-9_17, © ASCRS (American Society of Colon and Rectal Surgeons) 2011

mechanism(s) have not yet been elucidated, they appear to be related to the coexistence of perhaps HSV and the highly active antiretroviral therapy (HAART) drugs.

Failure of the mucous complex to protect the rectum is seen in various diseases contracted through anal intercourse. The act of intercourse abrades the mucous lining and delivers pathogens directly to the crypt and columnar cells allowing for easy entry. Depending on their mechanism of action, they may burrow into the cells (ameba) or proliferate on the cells without damaging them (*G. neisseria*). Invasive pathogens (*LGV*) unleash nefarious cytokines which destroy the cell. The immune response is usually too late to contain an acute attack. In the case of recurrent viral attacks, it appears that the level of functioning T cells may have an impact on recurrence of warts or herpes outbreaks. The mechanics of anoreceptive intercourse, as compared to vaginal intercourse, almost demands denuding of the protecting cellular and mucous protection of the anus and rectum.

Latex allergies may also cause severe invasive and erosive proctitis and should be in the differential of a caustic burn to the rectum after protected sexual anoreceptive intercourse.

Diagnosis and Management of Bacterial Pathogens

Gonorrhea

Neisseria gonorrhea, the gram-negative diplococcus (Figure 17-1) responsible for gonorrhea was first described by Albert Neisser in 1879 from exudates from urethritis and cervicitis.[8] It is probably the most common bacterial STD affecting the anorectum. While gonorrhea rates decreased over the last several decades, in the mid-1990s the incidence slowly increased to the current rate of about 650,000 cases per year. Similar recent increases have been noted in Canada and the UK.[9] Peak incidence for all forms of gonorrhea is in the late teens for females and early 20s for males. African Americans have a 30-fold higher rate of infection than do white Americans.

Infection from *N. gonorrhoeae* occurs in columnar, cuboidal, or noncornified epithelial lined cells of the urethra, endocervix, rectum, and pharynx and is frequently asymptomatic. The incubation period ranges from 3 days to 2 weeks. Untreated infection may lead to disseminated gonococcal infection with transient bacteremia, arthritis, and dermatitis. Rare but severe sequelae include endocarditis and meningitis.

Anorectal transmission in homosexual males and in some females is by anoreceptive intercourse with an infected partner. Thirty-five to fifty percent of women with gonococcal cervicitis have concomitant rectal infection which is believed to be from contiguous spread from the genital infection.[10] Oral–anal sex has been suggested as another mode of anorectal gonococcal infection.[11] A large percentage of patients who culture positive for rectal gonorrhea are asymptomatic – up to 50% of males and 95% of females. Asymptomatic rectal infection constitutes the main reservoir of gonococcal disease in homosexual men.

Symptomatic anorectal gonococcal infection results in pruritis, tenesmus, bloody discharge, mucopurulent discharge, or severe pain. External inspection of the anus is generally unremarkable; however, nonspecific erythema and superficial ulceration may occur (Figure 17-2). Anoscopy reveals a thick purulent discharge, which classically is expressed from the anal crypts as pressure is applied externally on the anus. Nonspecific proctitis may be present with erythema, edema, friability, and pus. Diagnosis is confirmed by culture on selective media (Thayer-Martin or Modified New York City) incubated in a CO_2-rich environment and Gram's stain of directly visualized discharge.[12] The use of lubricants other than water may introduce antibacterial agents during anoscopy and decrease diagnostic yield. Nonculture detection of gonorrhea is being used more frequently especially in

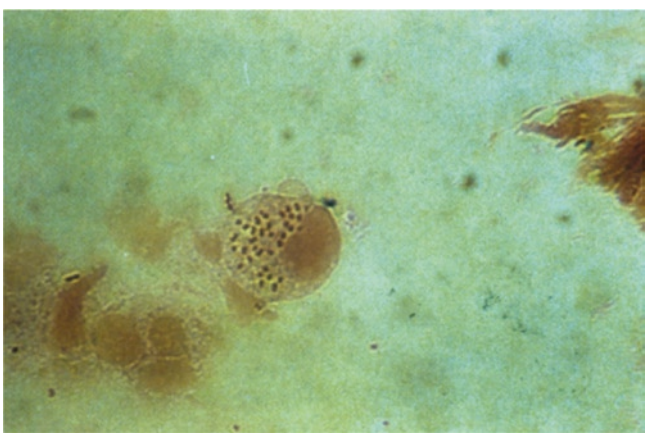

FIGURE 17-1. Gram-negative intracellular diplococcus.

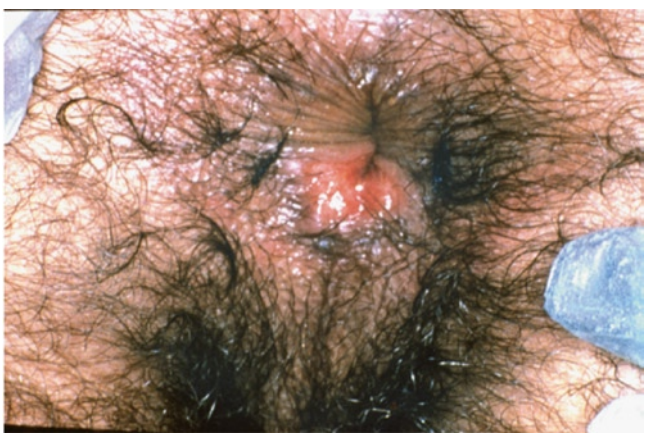

FIGURE 17-2. Anorectal gonorrhea.

TABLE 17-1. Treatment of anorectal gonococcal infection[14]

One of the following as a single dose:
Ceftriaxone – 125 mg IM
Ciprofloxacin – 500 mg orally
Ofloxacin – 400 mg orally
Levofloxacin – 250 mg orally
Cefixime – 400 mg orally

urethral and cervical infections. Nucleic acid amplification tests (NAATs), such as polymerase chain reaction (PCR), ligase chain reaction (LCR), and nonamplified DNA probes, provide sensitivities of greater than 95% but do not provide antibiotic susceptibility data. There are no NAATs currently licensed for the detection of rectal gonorrhea.[13]

Because of the prevalence of penicillinase-producing *N. gonorrhoeae* (PPNG) starting in the 1970s, penicillin G is no longer the drug of choice for gonorrhea. The most current recommended treatment regimen from the Centers for Disease Control (CDC) was published in 2002 and is listed in Table 17-1. Since publication of these guidelines cefixime has become unavailable in the US alternative regimens include spectinomycin (2 g as a single intramuscular injection), other cephalosporins (ceftizoxime, cefoxitin, and cefotaxime), and other quinolones. Only a few isolates reported by the Gonococcal Isolate Surveillance Report (GISP) in the past 10 years showed decreased susceptibility to the cephalosporins listed in Table 17-1.[15] Quinolone resistant *N. gonorrhea* (QRNG) have been detected in the past decade with increasing frequency in Asia and the Pacific. In the USA, this is particularly important in Hawaii (where QRNG may account for as much as 14% of gonorrhea isolates) and California. In the UK, the overall rate of QRNG was reported at 9.8% for 2002.[16] Concurrent HIV infection does not alter treatment for anorectal gonorrhea. Because of the high rate of concomitant infection with chlamydia, patients treated for gonococcal infections should be given appropriate treatment for chlamydia at the same visit or measures to exclude chlamydial infection should be taken.

Routine follow-up at 3 months is no longer necessary since current treatment provides near 100% efficacy. Patients with persistent symptoms after treatment should be followed and cultured as should those treated with nonstandard antibiotics. Sexual partners from the past 60 days should be treated and patient should abstain from intercourse until treatment is completed and symptoms resolved.

Chlamydia/Lymphogranuloma Venereum (LGV)

Chlamydia trachomatis is an obligate intracellular bacterium that is sexually transmitted and results in clinical infections that are similar to those caused by *N. gonorrhea*. Simultaneous infection with both organisms is common. Chlamydia is the most commonly reported STD in the USA with an annual incidence of about three million cases per year.[17] Aggressive screening programs have been credited with the decline of the Chlamydia infection rate from its peak of over four million per year in the early 1970s.

Anorectal transmission of chlamydia is through anoreceptive intercourse although secondary involvement can occur as a late manifestation of genital infection. Different serovars of *C. trachomatis* produce differing clinical illness. Serovars D through K (non-LGV) are responsible for proctitis and common genital infections. Lymphogranuloma venereum is caused by LGV serovars L1-L3. The incubation period for chlamydia is 5 days to 2 weeks. Non-LGV serovars are less invasive and cause mild proctitis (manifest by tenesmus, pain, and discharge) but asymptomatic infection is common. LGV serovars produce a much more aggressive infection with perianal, anal, and rectal ulceration. The proctitis produced can be difficult to distinguish from Crohn's disease (including microscopic findings of granulomas) with resulting rectal pain and discharge. Anoscopy and sigmoidoscopy demonstrate friable rectal mucosa, which is more severe in appearance (and extends above the rectum in some cases) in LGV strains.[18–20] Perianal abscesses, fistulas, and strictures may also occur. Lymphadenopathy develops in draining nodal basins, including the iliac, perirectal, inguinal, and femoral regions several weeks after initial infection. Large indurated matted nodes (Figure 17-3) and overlying erythema may produce a clinical picture similar to syphilis.

Diagnosis of chlamydia as the causative agent in proctitis can be difficult. Proper specimen collection increases diagnostic yield and consists of a cotton or Dacron swab with an inert shaft (plastic or metal). Specimen for tissue culture should be transported on specific medium and kept refrigerated or on ice until inoculated onto culture plates. Specimens that are to be tested by a nonculture technique are transported and stored in accordance with the test manufacturers guidelines. In patients with a clinical presentation consistent with chlamydia proctitis, rectal Gram's stain showing polymorphonuclear leukocytes without visible gonococci is presumptive for a diagnosis of chlamydia.[20]

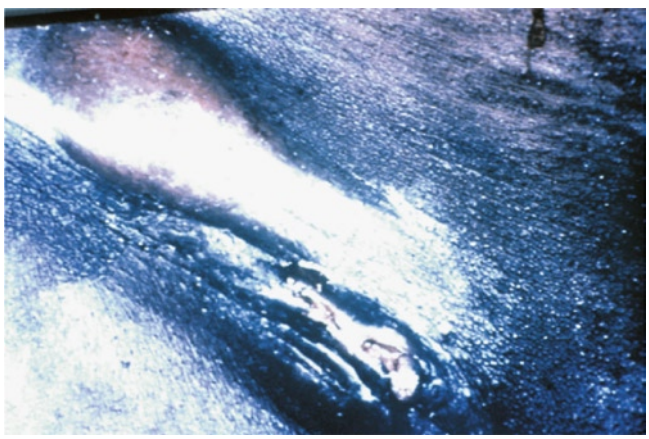

FIGURE 17-3. Inguinal adenopathy of LGV; *LGV* lymphogranuloma venereum.

Tissue culture for chlamydia is relatively insensitive and is not widely available because of cost and technical requirements.[21]

Antigen detection by direct fluorescent antibody (DFA) or enzyme immunoassay DFA is highly specific, widely available and does not require rapid transportation or refrigeration. A trained microscopist is needed for interpretation. As with gonorrhea, newer NAATs are available. Their use is increasing in genital infection but unproven for anorectal chlamydia. A pilot study using both PCR and LCR techniques showed that these techniques can be effective for making this diagnosis but there are little additional data on the use of NAATs in anorectal chlamydia.[22]

The two recommended treatment regimens for rectal chlamydia (non-LGV) are azithromycin, 1 g orally as a single dose or doxycycline, 100 mg orally, twice a day for 7 days.[14] Alternative regimens include erythromycin (less effective, more GI side effects), ofloxacin (7-day course, more expensive), or levofloxacin (7-day course, no data on efficacy). Treatment of lymphogranuloma venereum is with doxycycline or erythromycin for 21 days. In patients with HIV and LGV prolonged therapy may be required. Management of sexual contacts is the same as for gonorrhea. Abstinence from sexual intercourse should last until 7 days after treatment with azithromycin or completion of 7 days of doxycycline.

Syphilis

Syphilis is an STD caused by the spirochete *Treponema pallidum* that can present in one of several progressive stages – primary (chancre or proctitis), secondary (condyloma lata), or tertiary. The incidence of syphilis had its recent peak of 107 cases per 100,000 people in the USA in 1991, but decreased to 2.2 per 100,000 in 2001, meaning that only 6,103 cases were reported. A slight increase in primary and secondary syphilis cases reported occurred in 2002.[23] These low rates have led to a national plan for eliminating syphilis.[24]

The primary stage of anorectal syphilis appears within 2–10 weeks of exposure via anal intercourse. The chancre begins as a small papule that eventually ulcerates. Anal ulcers are frequently painful (in contrast to genital ulcers) and without exudates. They may be single or multiple (Figures 17-4 and 17-5) and located on the perianal skin, in the anal canal or distal rectum. Differentiation from idiopathic anal fissures may be difficult. Painless but prominent lymphadenopathy is common. Proctitis from syphilis may occur with or without chancres.[18] Untreated lesions in this stage usually heal in several weeks.

Hematogenous dissemination of untreated syphilis leads to a secondary stage that occurs 4–10 weeks after primary lesions appear. Nonspecific systemic symptoms from this infection include fever, malaise, arthralgias, weight loss, sore throat, and headache. A maculopapular rash is seen on the trunk and extremities. Condyloma lata, another secondary manifestation, are gray or whitish, wart-like lesions that appear adjacent to the primary chancre and are laden with spirochetes. Untreated, the symptoms of syphilis usually resolve after 3–12 weeks – of these patients, approximately one-fourth have a relapse of symptoms in the first year, a stage known as early latent syphilis.

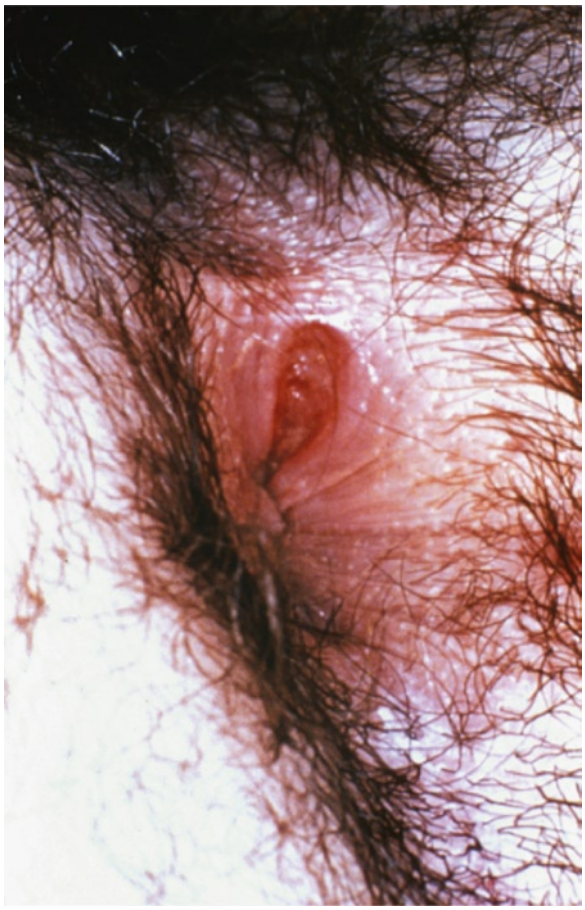

FIGURE 17-4. Solitary anal chancre.

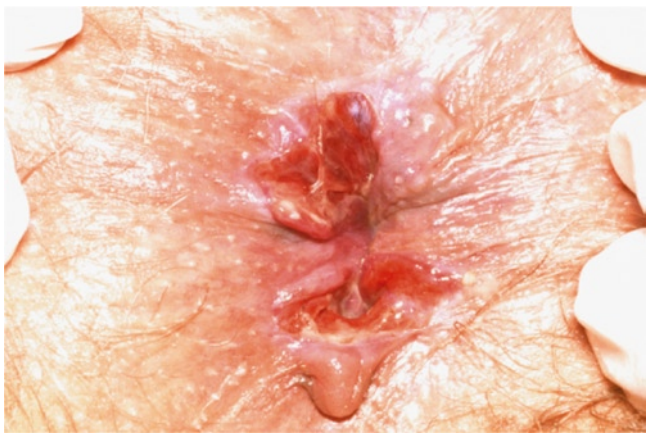

FIGURE 17-5. Multiple anal chancres.

Diagnosis in the primary or secondary stage is made by visualization of spirochetes on dark-field microscopic exam

FIGURE 17-6. Spirochetes demonstrated on dark-field microscopy.

of scrapings from chancres (Figure 17-6). Alternatively, spirochetes may be demonstrated on Warthin-Starry silver stain of biopsy specimens. A DFA test for *T. pallidum* (DFA-TP) is performed by some labs.[18,25] Serologic tests, rapid plasma regain (RPR) and Venereal Disease Research Laboratory (VDRL), have a false negative rate of up to 25% in primary syphilis and are called nontreponemal tests because they are not specific for *T. pallidum* infection. Positive nontreponemal tests should be confirmed by a treponemal test, such as the fluorescent treponemal antibody absorption test (FTA-ABS), which remains positive for life.

A single intramuscular injection of 2.4 million units of benzathine penicillin G is the treatment for primary and secondary syphilis. Penicillin-allergic patients are treated with doxycyline (100 mg orally, twice daily for 14 days) or tetracycline (500 mg orally, four times a day for 14 days). Follow-up serology (VDRL or RPR) should be checked at 6 months after therapy for HIV negative patients and every 3 months for HIV positive patients.[14] Treatment failures are retreated with the same dose of penicillin but at weekly intervals for a total of 3 weeks. Partner notification, testing, and treatment depends on stage at diagnosis of the index case. At-risk partners include sexual contacts (a) within the prior 3 months plus duration of symptoms for patients with primary syphilis; (b) within the prior 6 months plus duration of symptoms for patients with secondary syphilis and; (c) within the prior year for those with early latent syphilis.[26]

Chancroid

Chancroid is an ulcerating STD caused by the gram-negative, facultative anaerobic bacillus *Hemophilus ducreyi*. While there were approximately 5,000 cases reported per year in the late 1980s and early 1990s in the USA, there were fewer than 200 cases reported in 1999.[1] It is much more common in developing countries with a global incidence estimated at six million.[27]

Transmission of *H. ducreyi* is strictly via sexual contacts through breaks in the skin during intercourse and results in genital ulcers. The initial manifestation (hour to days after exposure) is as infected tender papules with erythema that subsequently develop into pustules and then (days to weeks) become ulcerated and eroded. Multiple ulcers are common and are generally painful, especially in males. While chancroid ulcers are most commonly located on the genitalia, perianal abscesses and ulceration may occur. Anal ulcerations in females may be the result of drainage from adjacent genital infections. Differentiation of other ulcerating STDs cannot be made on gross appearance in most cases.[28] Painful inguinal adenopathy accompanies half of cases in males and is usually unilateral. Females are less likely to develop adenopathy from *H. ducreyi* infection.[29] Abscess formation may result, necessitating drainage. Besides causing genital ulcers, *H. ducreyi* facilitates transmission of HIV and vice versa.

Diagnosis of chancroid is made by Gram stain and culture of *H. ducreyi* (on selective medium agar) from the base of ulcers. Gram stain is only 40–60% sensitive relative to culture and demonstrates nonmotile Gram-negative rods in small groups. *H. ducreyi* is difficult to culture and many labs in the USA are not equipped to perform this test. PCR is more sensitive than culture for detecting *H. ducreyi* but is not commercially available at this time.[30] Treatment for *H. ducreyi* is single dose treatment with azithromycin (1 g, orally) or ceftriaxone (250 mg, intramuscularly). Alternatively, regimens include ciprofloxacin, 500 mg orally twice a day for 3 days or erythromycin 500 mg three times a day for 1 week.[14]

Granuloma Inguinale (Donovanosis)

Donovanosis is an ulcerating infection of the genitalia and anus caused by *Calymmatobacterium granulomatis* (also called *Donovania granulomatis*). Transmission is believed to occur from both sexual and nonsexual contact. It is rarely seen in the USA but is common in parts of Africa, South America, and Australia. Morphologic manifestations include and ulcerogranulomatous form (nontender, fleshy, beefy red ulcers), hypertrophic or verrucous lesions, necrotic ulcers, or cicatrical. Genital involvement is most common but contiguous involvement of the anorectum occurs. Development of sclerotic lesions causes anal stenosis.[31]

C. granulomatis cannot be cultured by routine techniques. Diagnosis can be made by tissue smear or biopsy that reveals Donovan bodies (small inclusions) within macrophages. Several antibiotic regimens have been recommended, although the most recent CDC guidelines are doxycycline (100 mg orally, twice daily for 1 week) or trimethoprim-sulfamethoxazole (one 800 mg/160 mg tablet orally, twice a day for at least 3 weeks).[14] Alternative treatments include at least 3 weeks of ciprofloxacin, azithromycin, or erythromycin. Some authors believe azithromycin to be the preferred treatment.[31]

Diagnosis and Management of Viral Pathogens

Herpes Simplex Virus

HSV is a DNA virus of the family Herpesviridae that includes Varicella-Zoster virus, Epstein–Barr virus, and Cytomegalovirus (CMV). Herpes is the most prevalent STD in the USA with current the seroprevalence rate for HSV-2 estimated to be 20% for the general population.[32] Black females are the subgroup with the highest seroprevalence at 55%. Two serotypes of HSV are described. HSV-2 has been most associated with anogenital herpes infections. HSV-1 infection most commonly presents as labial oral or ocular lesions but accounts for about 30% of genital infections. Several recent reports have shown an increasing percentage of genital infections due to HSV-1;[33,34] asymptomatic infection with HSV is common.

Transmission is via close contact with an individual who is shedding the virus and infection results from penetration of mucosal surfaces or breaks in the skin. Productive infection causes viral replication within cells and cell death. Clinical infection presents first with systemic symptoms, such as fever, headache, and myalgias, followed by local symptoms, including pain and pruritis. Vesicles appear over the anogenital area, increase in number and size, and eventually ulcerate and coalesce (Figures 17-7 and 17-8). These vesicles and ulcerations generally heal over a mean time of 3 weeks.

Anorectal involvement by HSV-2 is acquired by anorectal intercourse and is second only to gonorrhea as a cause of proctitis in homosexual men. Herpetic infection of the anorectum results in severe anal pain, tenesmus, hematochezia, dysuria, and rectal discharge. The proctitis seen is typically limited to the distal 10 cm of the rectum with diffuse friability. Simultaneous with infection, HSV moves through peripheral sensory nerves to sensory or autonomic nerve root ganglia. Sacral radiculopathy of the lower sacral roots from this infection causes sacral paresthesias and neuralgias, urinary retention, constipation, and impotence. Tender inguinal adenopathy occurs in half of patients with HSV proctitis.[35]

Herpes has the ability to persist in their host because of latency – the viral genome maintained in a stable condition in host cell nuclei. For HSV, the site of latent infection is the sensory ganglia of nerves innervating the site of infection. Reactivation of latent virus results in recurrent infection but the stimuli for this process are poorly understood.[36] Recurrent attacks are generally milder, shorter in duration, and without the constitutional symptoms that occur with initial infection.

Diagnosis is frequently made by clinical evidence although cultures taken from ulcerations, rectal swabs, or biopsies confirm the diagnosis. Multinucleated giant cells with intranuclear inclusion bodies (ground-glass appearance) on Pap smear or Tzank prep are less sensitive than viral culture. Direct immunofluorescence has also been used for diagnosing HSV.[18] For cases in which cultures are not available, paired type-specific serology demonstrating seroconversion is diagnostic. In the past 5 years, the Food and Drug Administration (FDA) have approved several commercially available HSV serology tests. These tests have specificities and sensitivities greater than 90% and are sure to become more commonly used in the diagnosis of HSV.[37,38] It should be noted that seroconversion may take several weeks after initial infection and repeat testing intervals are dependent on the particular serology kit used.[39]

Treatment of patients with anorectal herpes includes comfort measures, such as warm soaks and oral analgesics. The only prospective randomized trial of antiviral treatment for herpes proctitis demonstrated a shortened duration of symptoms and period of viral shedding with oral acyclovir 400 mg, five times a day for 10 days.[40] A three times per day dosing has been shown to be effective for genital herpes but has not been evaluated for herpes proctitis.[41] Other antiviral agents, such as valacyclovir and famciclovir used for genital herpes, are most likely effective for HSV proctitis at

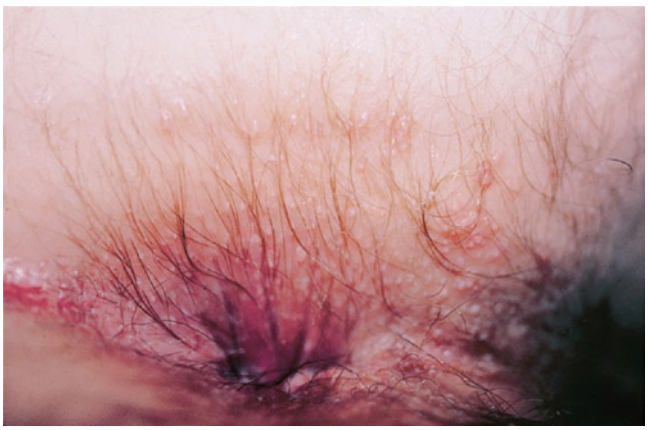

FIGURE 17-7. Perianal herpes.

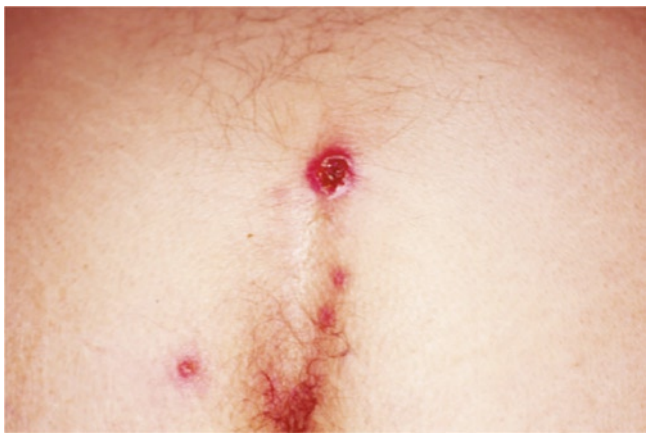

FIGURE 17-8. Perianal herpes.

the same doses used for genitourinary infection but clinical studies for this indication are lacking. Severe mucocutaneous HSV infection in which the patient cannot tolerate oral medication warrants intravenous acyclovir. Topical acyclovir has limited efficacy and is not recommended. Treatment of initial episodes of HSV do not prevent latency, asymptomatic viral shedding, or the course of subsequent episodes. Recurrent episodes may be treated with oral antiviral agents. Valacyclovir (500 mg twice a day) and acyclovir (200 mg five times a day) have demonstrated equal efficacy in treating genitourinary HSV recurrences.[42] Prompt initiation of treatment at the onset of symptoms of HSV recurrence reduces the duration of symptoms and healing times. Patients who experience more than five recurrences per year are considered for suppressive treatment. Valacyclovir, acyclovir, and famciclovir have all demonstrated 70% or greater reduction compared to placebo.

As with all STDs, counseling of patients with HSV is an important part of treatment and prevention.[41,42] Specific items that should be addressed are (1) infectivity is not isolated to symptomatic outbreaks; most sexual HSV transmission occurs during asymptomatic periods; (2) latent infection and the risk of recurrence; suppressive therapy does not eliminate latent infection or viral shedding; (3) abstinence is recommended while lesions are present. Condoms are advised for all other times although they most likely provide incomplete protection. Most recently, once-daily administration of valacyclovir has been shown to reduce the risk of HSV-2 transmission between HSV-2 seropositive patients and there seronegative sexual partners.[43]

Human Papilloma Virus

HPV is a DNA papovirus. It is the most common STD in the USA with an estimated incidence of over five million cases per year.[1] There are over 80 subtypes of HPV, almost one-third of which cause anogenital warts. Subtypes 6 and 11 are the most common of the low-risk HPV subtypes while subtypes 16 and 18 have the greatest associated risk of anal dysplasia and anal cancer. Transmission is vial sexual contact with infected individuals with or without gross lesions and asymptomatic infection is common. Perianal involvement can occur in the absence of receptive anal intercourse.

Presenting complaints of perianal or anal condyloma accuminata include the presence of a growth, pruritis, bleeding, chronic drainage, pain, and difficulty with hygiene. Physical examination is generally all that is required for diagnosis and shows the characteristic gray or pink fleshy, cauliflower-like growths of variable size in the perianal region (Figure 17-9). Anoscopy is an integral part of the evaluation. In the anal canal, the lesions tend to be small papules and involvement above the dentate line is rare. Examination should focus on the genitalia, including vaginal speculum exam and Pap smear, as well as evaluation of the perineum and groin folds.

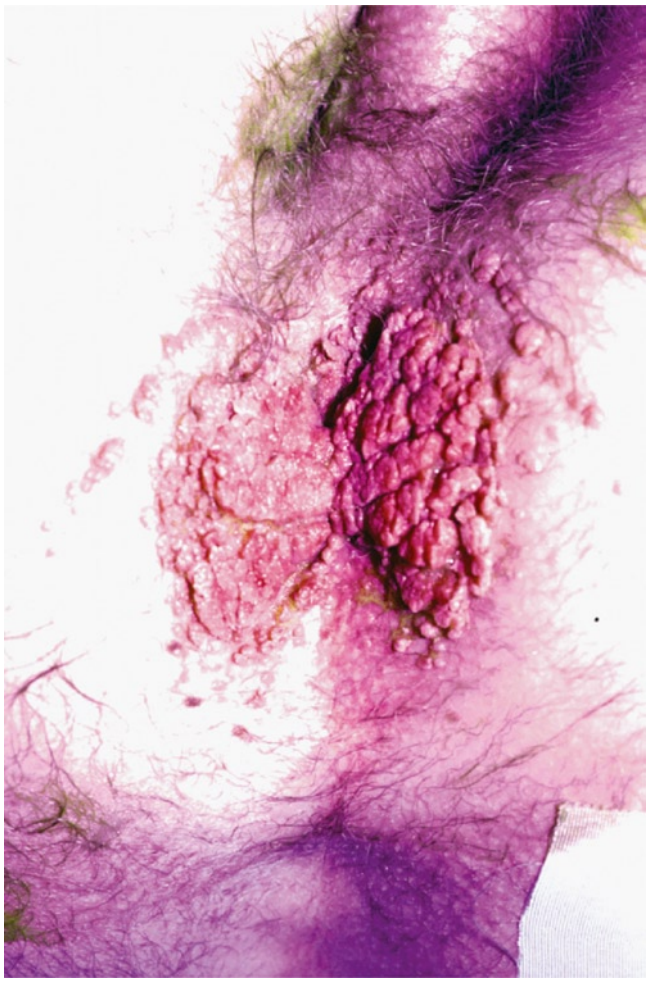

FIGURE 17-9. Perianal condyloma.

The goal of treatment of condyloma accuminata is destruction or removal of all obvious disease while minimizing morbidity, although this process does not ensure eradication of infection. Tangential excision, cryotherapy, or fulguration of small lesions can be performed as an office procedure with a local anesthetic, and causing little discomfort or inconvenience to the patient. Larger lesions are treated by electrodessication. The patient is placed in the lateral or prone jack-knife position. Depending on the size and number of lesions local, spinal, or general anesthesia is used. The superficial-most layer of the condyloma is fulgurated with the electrosurgery tip until the lesion takes on a gray–white appearance. This step is followed by curettage or simply abrading the fulgurated tissue with gauze. The process is repeated until the condylomas are completely removed without burning into the deep dermis or subcutaneous fat. Pedunculated warts are simply transected at their base. Tissue from HIV+ patients, recurrent lesions, flat lesions, or those suspicious lesions which may be ulcerated, friable, or hypervascular should be sent for histopathologic evaluation. Topical 5% lidocaine is helpful in decreasing postoperative pain. Oral analgesics

and daily cleansing with mild soap and water are all that is required for postoperative care in most patients. Silver sulfadiazine or mupirocin are applied in cases in which postoperative bacterial infection is suspected. Overall condyloma clearance rates for surgical techniques range from 60 to 90% with recurrence rates of 20–30%.[44]

The patient can apply topical agents like podofilox and imiquimod although neither agent is approved for use in the anal canal. Podofilox is the purified active component of the antimitotic plant resin podophyllin and is available as a 0.5% gel or solution. A treatment cycle consists of twice daily application for 3 days followed by no treatment for 4 days utilized for up to 1 month. Toxicity concerns are less than those issues with podophyllin while clearance rates for condyloma of 35–80% have been reported. Recurrence rates in patients treated with podofilox are 10–20%.[44–48] Imiquimod is an immune response modifier that increases local production of interferon. A complete response can be expected in 50% of patients treated with imiquimod with 11% of patients experiencing a recurrence.[44,49–51] It is applied at bedtime three times a week, left in place for 6–8 h and then removed by washing; treatment may take up to 16 weeks. One study demonstrated no benefit to increased dosing frequency from one to two or even three times daily.[52] Side effects of imiquimod include pain burning, itching, and ulceration which may require cessation of therapy. Imiquimod is used (1) as initial treatment with electrodessication reserved for those who have incomplete response or (2) following destructive treatment and epithelial healing to treat remaining disease or decrease recurrence (no randomized data to support this use). Currently, imiquimod is not approved for anal canal use but this application is being investigated.[53] Trichloracetic acid is applied topically and is useful for treating small lesions in the anal canal. Topical and intralesional interferon have been used to treat condyloma accuminata with mixed results. Other agents that have been used to treat anogenital condyloma but are not in widespread use include 5-FU cream, cidofovir and autologous vaccine.

Bushke and Loewenstein first described giant condyloma accuminata (GCA) in 1925.[54] They are most associated with HPV types 6 and 11 but histologically demonstrate some differences from ordinary condyloma – marked papillomatosis, acanthosis, thickened rete ridges, and increased mitotic activity. The substantial percentage of cases with in situ or invasive squamous cell cancers has lead to speculation that GCA represents part of a continuum from condyloma to invasive squamous cell cancer.

Wide local excision with a 1 cm margin is the treatment of choice for these lesions. Local tissue flaps or grafted skin may be required to repair surgical defects. Abdominal–perineal resection has been used for GCA involving the anal sphincters. Chemoradiation is also an option in the treatment of GCA, especially in those patients who are poor surgical candidates or in whom clear surgical margin are not attainable.[55] Complete regression of GCA with chemoradiation has been reported.[56]

HPV, Anal Intraepithelial Dysplasia, and Anal Cancer

While it is clear that HPV plays a significant role in the development of cervical cancer, its significance in the development of anal cancer (Figure 17-10) and its presumed precursor, anal intraepithelial dysplasia, is not as well defined. Parallels can be drawn between the anal canal and the cervical canal as they share embryologic and histologic features. Furthermore, both canals derive from the embryonic cloacal membrane and both are areas where ectodermal and endodermal tissues fuse to form a transition zone from columnar epithelium to squamous epithelium.

Epidemiologic parallels can be drawn as well. Studies prior to the HIV infection epidemic showed the incidence of anal cancer in homosexual males to be 12.5–37 per 100,000 in the USA[57] This incidence is similar to the incidence of cervical cancer prior routine Pap testing. The risk of anal cancer developing in an HIV+ homosexual male is estimated to be 38 times that of the general population and twice the risk of an HIV− homosexual male.[57,58] HPV infection has been reported in 93% of HIV+ homosexual males compared to 60% of HIV− homosexual males.[55]

Anal cytology has been suggested as a screening tool for detecting patients with anal dysplasia. Applying the current cervical cytology terminology specimens are designated normal, atypical squamous cells of indeterminate significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous intraepithelial lesions (HSIL). The benefit and best timing of this screening is undetermined. Evaluation and treatment algorithms as well as recommended testing schedules have been reported.[59,60] One such evaluation and treatment algorithm recommends high-resolution (with acetowhitening and staining with Lugol's solutions) anoscopy with biopsy.[60] Subsequent treatment is based on histologic findings which are typically reported as normal or anal epithelial neoplasia (AIN) I, II, or III. Options for treatment include local destruction (with topical agents,

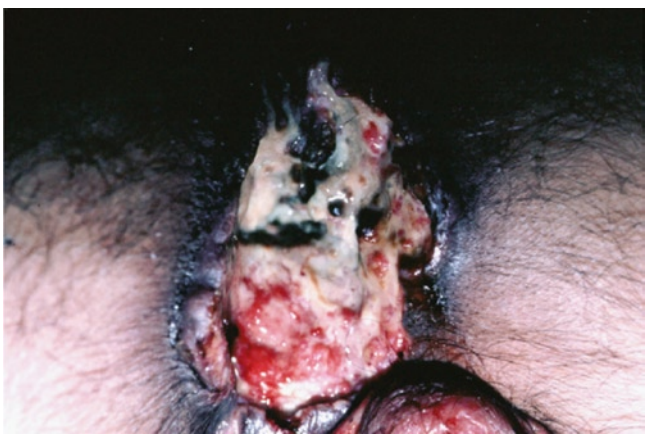

FIGURE 17-10. Anal cancer in HIV-positive patient; *HIV* human immunodeficiency virus.

cryotherapy, or fulguration), excision, or observation. However, there are limitations of our understanding of the relationship between HPV, AIN, and anal cancer that prevent the dogmatic recommendation and widespread acceptance of such an approach. First, the incidence and predictability of the progression of AIN to invasive cancer is unclear.[61,62] The lack of inter- and intraobserver agreement in the interpretation of AIN no doubt contributes to this lack of understanding.[63] Second, data demonstrating efficacy, which is defined as long-term removal of AIN and prevention of anal cancer of treatment is lacking. The absence of established benefit combined with the morbidity of treatment leads us and others to the recommendation that AIN, regardless of grade, be observed unless there are gross visual or palpable lesions or ulcerations present.

Two additional comments with regard to the association of HPV, HIV, and AIN should be made. First, the use of HAART (discussed further later in the section on HIV) does not reduce the incidence of AIN.[64] The clinical implications of this fact are: (a) anal cytology screening should not be stopped just because a patient is treated with HAART and (b) with HIV patients living longer secondary to HAART, the incidence of anal cancers may increase. Second, the prevalence of HPV and AIN is high in HIV positive males with CD4+ counts less than 500×10^6 cells/L even in the absence of a history of anal intercourse.[65] These patients should also be considered for cytologic screening.

Molluscum Contagiosum

The molluscum contagiosum virus is a member of the poxvirus family and causes a benign papular condition of the skin. Transmission is by sexual and nonsexual contact. The incubation period is 1–6 months, followed by the development of 2–6 mm flesh-colored, umbilicated papules.[66] Symptoms are uncommon though pruritis or tenderness may occur. Immunocompromised hosts, such as those with HIV, are more prone to infection with molluscum contagiosum (compared to HIV negative) and may have a more severe form of the disease with hundreds of lesions. Diagnosis is usually made on clinical grounds but excisional biopsy demonstrates enlarged epithelial cell with intracytoplasmic molluscum bodies. Treatment is generally through eradication with curettage, electrodessication or cryotherapy. Podophyllotoxin (0.5%) and imiquimod (5%) have both been used as self-applied topical preparations with success,[67,68] although neither compound is FDA approved for this use.

HIV and the Acquired Immunodeficiency Syndrome

Infection from the HIV (originally called human t-lymphotropic virus) related to acquired immunodeficiency syndrome (AIDS) was first described in 1983.[69] The most current data available show that in 2005 there were approximately 433,760 people in the USA with AIDS and another 215,653 with HIV infection not meeting the criteria for AIDS.[70] Cumulative totals showed a total of 984,155 cases of AIDS in the USA through 2005 and a death rate of 51% in this group. While the incidence of HIV infection has apparently stabilized, the numbers of new AIDS cases and deaths from AIDS have decreased. This fact is in large part due to HAART – combinations of potent anti-HIV drugs which are nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, or protease inhibitors. Table 17-2 shows the current classification system for patients who are HIV positive.

Table 17-2. Revised classification system for HIV and AIDS[72]

CD4+ T-lymphocyte categories
Category 1: greater than or equal to 500 cells/μL
Category 2: 200–499 cells/μL
Category 3: less than 200 cells/μL
Clinical categories
Category A: HIV positive; asymptomatic; persistent generalized lymphadenopathy
Category B: Symptomatic conditions not listed in clinical category C; are conditions that are attributed to HIV infection; or conditions that have a clinical course or require management that is complicated by HIV infection. Examples include: bacillary angiomatosis, oropharyngeal or vulvovaginal candidiasis, cervical dysplasia, diarrhea (greater than 1 month in duration), more than one episode of herpes zoster, pelvic inflammatory disease, peripheral neuropathy
Category C: Diagnoses included in the AIDS surveillance case definition – candidiasis (pulmonary or esophageal), invasive cervical cancer, Coccydiomycosis, extrapulmonary cryptococcosis, chronic intestinal Cryptosporidiosis, Cytomegalovirus disease (other than liver, spleen, nodes) or retinitis, HIV-encephalopathy, HSV (chronic ulcers, pulmonary or esophageal), Histoplasmosis (disseminated or extrapulmonary), Isosporiasis (chronic intestinal), Kaposi's sarcoma, Burkitt's lymphoma, immunoblastic lymphoma, primary brain lymphoma, Mycobacterium avium complex or any mycobacterium species other than M. tuberculosis (extrapulmonary or disseminated), Mycobacterium tuberculosis, Pneumocystis carinii pneumonia, progressive focal leukoencephalopathy, recurrent Salmonella speticemia, Toxoplasmosis of the brain, HIV wasting syndrome

	Clinical categories		
CD4+ categories	A1	B1	***C1***
	A2	B2	***C2***
	A3	***B3***	***C3***

Bold italic groups are defined as AIDS.

Surgery for anorectal diseases is the most common indication for surgery in HIV infected patients and in 5% of patients, their anorectal complaint is the presenting symptom of their HIV infection.[71] Most of the indications for surgery are common to the population at large but some are unique to AIDS patients. Several studies demonstrate poor wound healing and increased morbidity in the surgical treatment of anorectal disease in AIDS patients.[72–74] Delayed or failed wound healing has been associated with the presence of AIDS, decreased absolute leukocyte count, and decreased CD4 count. Morandi et al. found that at 32 weeks after hemorrhoidectomy, 50% of AIDS patients had incompletely healed wounds. The overall complication rate was significantly higher in the AIDS group than in HIV+ patients without AIDS.[73] Conversely, Lord reported decreased wound healing in HIV+ patients with T-lymphocyte count of less than 50.[75] Others have shown longer interval and decreased complete wound healing in HIV+ patients with CD4+ T-lymphocyte counts of less than 200.[74] The studies reviewed above describe patients who were not treated with HAART. There is a lack of data describing wound healing in anorectal surgery since the widespread use of HAART; however, the observation of the authors is that compensated HIV+ patients are at no significant risk of increased complications from anorectal surgery. Other factors to be considered in selecting appropriate treatment include any untreatable diarrheal conditions, degree of existing fecal incontinence, and the effect of the proposed surgical procedure on incontinence.

Anal fissures that occur in HIV+ patients must be distinguished from idiopathic AIDS-related anal ulcers (Figure 17-11) and ulcerating STDs, such as HSV or syphilis. Anal fissures in this patient population are indistinguishable from those in the general population and their treatment is similar – initial conservative management with surgery for treatment failures.[76,77] Treatment of fissures in HIV+ patients is modified by the factors described previously and include controlling diarrhea when possible and encouraging abstinence from anoreceptive intercourse.

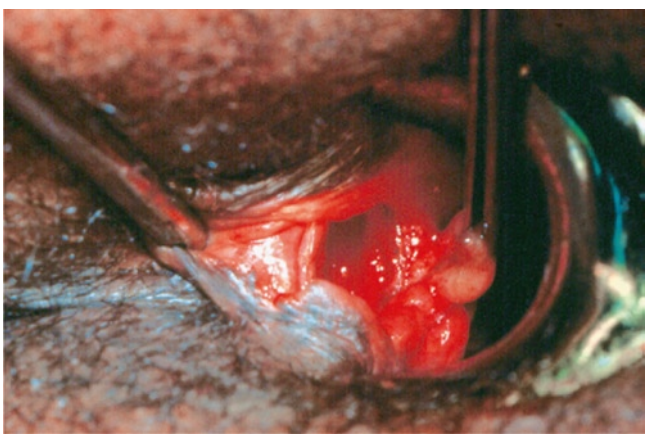

FIGURE 17-11. AIDS and ulcer.

While data on the incidence of AIDS-related anal ulcers is lacking, it appears that they are less common with HAART because the lesions are most frequently associated with clinical AIDS and lower CD4+ counts. These ulcers can be distinguished from typical anal fissures because they are more proximal in the anal canal (frequently above the dentate line or anorectal ring), broader based, deeply ulcerating with the destruction of sphincter planes, and may demonstrate mucosal bridging. Debilitating pain is a common presenting symptom of these ulcers. Surgical debridement allows for adequate drainage of feculent or purulent material trapped in the ulcer and removal of necrotic debris. Biopsy and culture identifies potentially treatable causes for ulceration – malignancy, acid-fast bacilli, HSV, *H. ducreyi*, *T. pallidum*. CMV has been cultured from these ulcers by some authors but is apparently not causal and therefore does not require treatment. Intralesional injection with steroids (methylprednisolone 80–160 mg, in 1 cc 0.25% bupivacaine) provides relief in the majority of patients but not healing.[78] Patients who have persistent pain are reinjected at their ulcer sites.

Perianal suppurative diseases are common conditions in AIDS patients. Abscesses should be drained using small incisions and the placement of a mushroom catheter lessens recurrent sepsis. Broad spectrum antibiotics should be given in immune compromised especially if cellulitis is present. Culture (to include mycobacterium) and histopathologic evaluation identifies infection from atypical organisms and malignancy.

Naldal et al. reported on fistulotomies performed in 31 HIV+ patients. Seven patients had failure of wound healing and all had clinical AIDS, CD4+ counts of less than 200, and absolute leukocyte counts of less than 3,000/mm^3.[74] Based on this, the authors treat anal fistulas in AIDS patients with high viral loads and low CD4+ counts similar to Crohn's patients. Draining setons are placed liberally with selective use of fistulotomy for low uncomplicated fistulas. Fistulotomy in HIV+ patients with AIDS and normal CD4+ counts is based on criteria similar to HIV− patients.

Thrombosed external hemorrhoids in patients with AIDS are treated the same as for HIV− patients. Acute thrombosis (24–48 h after onset of symptoms) is treated with excision. Subacute thrombosis (longer than 48 h from symptom onset) is treated conservatively with Sitz baths and oral analgesics.

Internal hemorrhoids present with symptoms of bleeding or prolapse. Initial treatment in patients with AIDS is with a high fiber diet and bulking agents. Proximal colonic sources of bleeding should be excluded via colonoscopy. Patients who fail initial conservative measures are treated with rubber band ligation or infrared coagulation. Other nonoperative techniques, such as bipolar coagulation, cryotherapy, or injection sclerotherapy, are acceptable. There are conflicting recommendations for operative treatment of hemorrhoids published within the last decade. In a retrospective study, Hewitt et al. found no difference in wound healing between HIV+ and HIV− patients.[79] The mean CD4+ count was 301 but they classified 81% of patients as having AIDS based on

symptoms or CD4 count less than 200. In the discussion, the authors comment that the majority of their patients were well nourished and otherwise healthy. They conclude that HIV status should not alter the indications for surgery in patients with symptomatic hemorrhoids. In contrast, as mentioned, Morandi et al. prospectively evaluated healing time after hemorrhoidectomy.[73] Functional status and the presence of AIDS were the two factors that correlated with poor wound healing. AIDS patients with nonhealing had a mean CD4+ count of 79. Unfortunately, they do not comment relief of hemorrhoid symptoms. It appears that asymptomatic HIV+ patients and who do not meet the clinical or CD4+ count diagnostic criteria for AIDS (Table 17-2) can be treated with hemorrhoidectomy with the expectation that they have good symptomatic relief and normal wound healing. AIDS patients with more advanced disease (clinical category C) or low CD4+ counts (especially less than 100) are at increased risk for wound healing problems. The benefit of symptomatic relief may still warrant performing surgical treatment in this group.[76]

References

1. Centers for Disease Control and Prevention. Tracking the hidden epidemics. Trends in STDs in the USA. Atlanta: Centers for Disease Control and Prevention; 2001. p. 1–26.
2. British Medical Association. Sexually transmitted infections. February 2002;1–25.
3. Kinghorn G. A sexual health and HIV strategy for England. Br Med J. 2001;323:243–4.
4. Halperin DT. Heterosexual anal intercourse: prevalence, cultural factors, and HIV infection and other health risks, Part 1. AIDS Patient Care STDs. 1999;13:717–30.
5. Kozlowski PA, Neutra MR. The role of mucosal immunity in prevention of HIV transmissions. Curr Mol Med. 2003;3:217–28.
6. Sobhani I, Walker F, Aparicio T, et al. Effect of anal epidermoid cancer-related viruses on the dendritic (Langerhans') cells of the human anal mucosa. Clin Cancer Res. 2002;8:2862–9.
7. Middleton K, Peh W, Southern S, et al. Organization of human papillomavirus productive cycle during neoplastic progression provide a basis for selection of diagnostic markers. J Virol. 2003;77:10186–201.
8. Kampmeier RH. Identification of the gonococcus by Albert Neisser. Sex Transm Dis. 1978;5:71.
9. Hansen L, Wong T, Perrin M. Gonorrhoea resurgence in Canada. Int J STD AIDS. 2003;14:727–31.
10. Hook III EW, Handsfield HH. Gonococcal infection in the adult. In: Holmes KK, Sparling PR, Mardh PA, et al., editors. Sexually transmitted diseases. New York: McGraw-Hill; 1999. p. 451–66.
11. McMillan A, Young H, Moyes A. Rectal gonorrhoea in homosexual men: source of infection. Int J STD AIDS. 2000;11:284–7.
12. Ison C, Martin D. Gonorrhea. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, editors. Atlas of sexually transmitted diseases and AIDS. Edinburgh: Mosby; 2003. p. 109–25.
13. Young H, Manavi K, McMillan A. Evaluation of ligase chain reaction for the non-cultural detection of rectal and pharyngeal gonrrhea in men who have sex with men. Sex Transm Infect. 2003;79:484–6.
14. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR. 2002; 51(RR-6):1–77.
15. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2002 supplement. Gonococcal isolate surveillance project annual report. Atlanta: US Department of Health and Human Services; 2003.
16. Fenton KA, Ison C, Johnson AP, et al. Ciprofloxacin resistance in *Neisseria gonorrhoeae* in England and Wales in 2002. Lancet. 2003;361:1867–8.
17. Cates W. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. Sex Transm Dis. 1999;26(Suppl):S2–7.
18. Rampalo AM. Diagnosis and treatment of sexually acquired proctitis and proctocolitis: an update. Clin Infect Dis. 1999;28 Suppl 1:S84–90.
19. Gregory A, Gottesman L. Sexually transmitted and infectious diseases. In: Beck DE, Wexner SD, editors. Fundamentals of anorectal surgery. London: WB Saunders; 1998. p. 414–31.
20. Stamm W. *Chlamydia trachomatis* infections of the adult. In: Holmes KK, Sparling PR, Mardh PA, et al., editors. Sexually transmitted diseases. New York: McGraw-Hill; 1999. p. 407–22.
21. Schacter J, Stephens R. Infections caused by *Chlamydia trachomatis*. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, editors. Atlas of sexually transmitted diseases and AIDS. Edinburgh: Mosby; 2003. p. 73–96.
22. Golden MR, Astet SG, Galvan R, et al. Pilot study of COBAS PCR and ligase chain reaction for detection of rectal infections due to *Chlamydia trachomatis*. J Clin Microbiol. 2003;41:2174–5.
23. Centers for Disease Control and Prevention. Primary and secondary syphilis – United States 2002. MMWR. 2003; 52:1117–20.
24. Centers for Disease Control and Prevention. The national plan to eliminate syphilis from the United States. Atlanta: US Department of Health and Human Services; 1999. p. 1–84. http://www.cdc.gov/stopsyphilis/plan.pdf.
25. Cox D, Liu H, Moreland A, Levine W. Syphilis. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, editors. Atlas of sexually transmitted diseases and AIDS. Edinburgh: Mosby; 2003. p. 23–51.
26. Kohl KS, Farley T, Ewell J, Scioneaux J. Usefulness of partner notification for syphilis control. Sex Transm Dis. 1999; 26:201–7.
27. Spinola SM, Bauer ME, Munson RS. Immunopathogenesis of *Haemophilus ducrei* infection (Chancroid). Infect Immun. 2002;70:1667–76.
28. DiCarlo RP, Martin DH. The clinical diagnosis of genital ulcer disease in men. Clin Infect Dis. 1997;25:292–8.
29. Ballard R, Morse S. Chancroid. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, editors. Atlas of sexually transmitted diseases and AIDS. Edinburgh: Mosby; 2003. p. 53–71.
30. Orle KA, Gates CA, Martin DH, et al. Simultaneous PCR detection of *Haemophilus ducreyi*, *Treponema pallidum*, and herpes simplex virus types 1 and 2 from genital ulcers. J Clin Microbiol. 1996;34:49–54.
31. O'Farrell N. Donovanosis. Sex Transm Dis. 2002;78:452–7.
32. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med. 1997;337:1105–11.

33. Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis. 2003;30:797–800.
34. Lafferty WE. The changing epidemiology of HSV-1 and HSV-2 and implications for serological testing. Herpes. 2002;9:51–5.
35. Goodell SE, Quinn TC, Mkrtichian E, et al. Herpes simplex virus proctitis in homosexual men. Clinical, sigmoidoscopic, and histopathological features. N Engl J Med. 1983;308:868–71.
36. Pertel PR, Spear PG. Biology of herpesviruses. In: Holmes KK, Sparling PR, Mardh PA, et al., editors. Sexually transmitted diseases. New York: McGraw-Hill; 1999. p. 269–83.
37. Wald A, Ashley-Morrow R. Serological testing for herpes simplex virus (HSV)-1 and HSV-2 infection. Clin Infect Dis. 2002;35 Suppl 2:S173–82.
38. Slomka MJ. Current diagnostic techniques in genital herpes: their role in controlling the epidemic. Clin Lab. 2000;46: 591–607.
39. Ashley RL. Performance and use of HSV type-specific serology test kits. Herpes. 2002;9:38–45.
40. Rompalo AM, Mertz GJ, Davis LG, et al. A double-blind study of oral acyclovir for the treatment of first episode herpes simplex virus proctitis in homosexual men. JAMA. 1988;259:2879–81.
41. Wald A. New therapies and prevention strategies for genital herpes. Clin Infect Dis. 1999;28(Suppl):S4–13.
42. Patel R. Progress in meeting today's demands in genital herpes: an overview of current management. J Infect Dis. 2002;186 Suppl 1:S47–56.
43. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11–20.
44. Wiley DJ, Douglas J, Beutner K, et al. External genital warts: diagnosis, treatment, and prevention. Clin Infect Dis. 2002;35 Suppl 2:S210–24.
45. von Krogh G, Longstaff E. Podophyllin office therapy against condyloma should be abandoned. Sex Transm Infect. 2001;77:409–12.
46. von Krogh G, Lacey CJN, Gross G, et al. European course on HPV associated pathology: guidelines for primary care physicians for the diagnosis and management of anogenital warts. Sex Transm Infect. 2000;76:162–8.
47. Greenberg MD, Rutledge LH, Reid R, et al. A double-blind, randomized trial of 0.5% podofilox and placebo for the treatment of genital warts in women. Obstet Gynecol. 1991;77:735–9.
48. Edwards L, Ferenczy A, Eron L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol. 1998;134:25–30.
49. Tyring S, Edwards L, Cherry LK, et al. Safety and efficacy of 0.5% podofilox gel in the treatment of anogenital warts. Arch Dermatol. 1998;134:33–8.
50. Maitland JE, Maw R. An audit of patients who have received imiquimod cream 5% for the treatment of anogenital warts. Int J STD AIDS. 2000;11:268–70.
51. Beutner K, Tyring SK, Trofatter Jr KF, et al. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. Antimicrob Agents Chemother. 1998;42:789–94.
52. Fife KH, Ferenczy A, Douglas JM, et al. Treatment of external warts in men using 5% imiquimod cream applied three times a week, once daily, twice daily, or three times a day. Sex Transm Dis. 2001;28:226–31.
53. Kaspari M, Gutzmer R, Kaspari T, et al. Application of imiquimod by suppositories (anal tampons) efficiently prevents recurrences after ablation of anal canal condyloma. Br J Dermatol. 2002;147:757–9.
54. Buschke A, Lowenstein L. Uber carcinomahnliche condylomata acuminata. Klin Wochenschr. 1925;4:1726.
55. Trombetta LJ, Place RJ. Giant condyloma acuminatum of the anorectum: trends in epidemiology and management. Report of a case and review of the literature. Dis Colon Rectum. 2001;44:1878–86.
56. Butler TW, Gefter J, Kleto D, et al. Squamous-cell carcinoma of the anus in condyloma acuminatum: successful treatment with pre-operative chemotherapy and radiation. Dis Colon Rectum. 1987;30:293–5.
57. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst. 2000;92:1500–10.
58. Goedert JJ, Cote TR, Virgo P, et al. Spectrum of AIDS-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. Lancet. 1998;351:1833–9.
59. Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. Clin Infect Dis. 2002;35:1127–34.
60. Palefsky JM. Anal human papillomavirus infection and anal cancer in HIV-positive individuals: an emerging problem. AIDS. 1994;8:293–5.
61. Cleary RK, Shaldebrand JD, Fowler JJ, et al. Perianal Bowen's disease and anal intraepithelial neoplasia. Dis Colon Rectum. 1999;42:945–51.
62. Caruso ML, Valentini AM. Different human papillomavirus genotypes in anogenital lesions. Anticancer Res. 1999;19:3049–53.
63. Colquhoun P, Nogeras JJ, Dipasquale B, et al. Interobserver and intraobserver bias exists in the interpretation of anal dysplasia. Dis Colon Rectum. 2003;46:1338.
64. Piketty C, Darragh TM, Heard I, et al. High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy. Sex Transm Dis. 2004;31:96–9.
65. Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. Ann Intern Med. 2003;183:453–9.
66. Douglas Jr JM. Molluscum contagiosum. In: Holmes KK, Sparling PR, Mardh PA, et al., editors. Sexually transmitted diseases. New York: McGraw-Hill; 1999. p. 385–9.
67. Skinner RB. Treatment of mollscum contagiosum with imiquimod 5% cream. J Am Acad Dermatol. 2002;47:S221–4.
68. Syed TA, Lundin S, Ahmad M. Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of molluscum contagiosum in males. A placebo-controlled, double-blind study. Dermatology. 1994;189:65–8.
69. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983;220:868–71.

70. Centers for Disease Control and Prevention. HIV/AIDS surveillance report 2005 (modified June, 2007);17:12.
71. Centers for Disease Control and Prevention. MMWR 1992; 41(RR-17)
72. Barrett WL, Callahan TD, Orkin BA. Perianal manifestations of human immunodeficiency virus infection. Experience with 260 patients. Dis Colon Rectum. 1998;41:606–12.
73. Morandi E, Merlini D, Salvaggio A, et al. Prospective study of healing time after hemorroidectomy. Influence of HIV infection, acquired immunodeficiency syndrome, and anal wound infection. Dis Colon Rectum. 1999;42:1140–4.
74. Nadal SR, Manzione CR, Galvao VM, et al. Healing after fistulotomy. Comparative study between HIV+ and HIV− patients. Dis Colon Rectum. 1998;41:177–9.
75. Lord RVN. Anorectal surgery in patients infected with human immunodeficiency virus. Factors associated with delayed wound healing. Ann Surg. 1997;226:92–9.
76. Brar HS, Gottesman L, Surawicz C. Anorectal pathology in AIDS. Gastrointest Endosc Clin N Am. 1998;8:913–31.
77. Bernstein M. Anal fissure and the human immunodeficiency virus. Semin Colon Rectal Surg. 1997;8:40–5.
78. Modesto VL, Gottesman L. Surgical debridement and intralesional steroid injection in the treatment of idiopathic AIDS-related anal ulcerations. Am J Surg. 1997;174: 439–41.
79. Hewitt WR, Sokol TP, Fleshner RP. Should HIV status alter indications for hemorrhoidectomy? Dis Colon Rectum. 1996; 39:615–8.