МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ

УЧРЕЖДЕНИЕ ОБРАЗОВАНИЯ
«ГОМЕЛЬСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ»

Кафедра поликлинической терапии и общеврачебной практики
с курсом дерматовенерологии

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ВИЧ: КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ НА КОЖЕ И СЛИЗИСТЫХ ОБОЛОЧКАХ

Учебно-методическое пособие
для студентов 4 и 6 курсов факультета по подготовке специалистов
для зарубежных стран медицинских вузов

CUTANEOUS MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS DISEASE

Teaching workbook for 4th and 6th year students
of the Faculty on preparation of experts for foreign countries
of medical higher educational institutions

Гомель
ГомГМУ
2017

УДК 616.97 (072)=111
ББК 55.8(2Англ)я7
П 59

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Порошина, Л.А.
П 59 ВИЧ: клинические проявления на коже и слизистых оболочках: учеб.-метод. пособие для студентов 4 и 6 курсов факультета по подготовке специалистов для зарубежных стран медицинских вузов = Cutaneous manifestations of human immunodeficiency virus disease: teaching work-book for 4th and 6th year students of the Faculty on preparation of experts for foreign countries of medical higher educational institutions / Л. А. Порошина. — Гомель: ГомГМУ, 2017. — 40 с.
ISBN 978-985-506-942-4

Учебно-методическое пособие содержит курс лекций по дерматологии, который составлен в соответствии с типовой учебной программой.

Предназначено для студентов 4 и 6 курсов факультета по подготовке специалистов для зарубежных стран медицинских вузов.

Утверждено и рекомендовано к изданию научно-методическим советом учреждения образования «Гомельский государственный медицинский университет» 29 декабря 2016 г., протокол № 6.

УДК 616.97 (072)=111
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ISBN 978-985-506-942-4

CONTENT

ABBREVIATIONS

HIV — human immunodeficiency virus

AIDS — acquired immune deficiency syndrome

ART — antiretroviral therapy

DRESS — drug rash with eosinophilia and systemic syndroms

SJS — Stevens — Johnson syndrome

EM — erythema miltiforme

AGEP — acute generalized exathematous pustulosis

NRTI — Nucleoside reverse transcriptase inhibitor

NNRTI — Non-nudeoside reverse transcriptase inhibitor

PI — Protease inhibitor

NHL — non-Hodgkin lymphoma

1. SYNOPSIS

- ***As of 2008, more than 30 million people were living with HIV infection/AIDS.***
- ***HIV-1 and HIV-2 are human lymphotropic retroviruses that principally infect CD4+ T lymphocytes and CD4+ cells of monocytic lineage.***
- ***An individual is deemed to have AIDS if he or she is HIV-seropositive with a CD4+ T cell count <200/μL, a CD4+ T cell percentage <14, or anyof several diseases deemed to be indicative of a severe defect in cell mediated immunity.***
- ***The broad and diverse spectrum ofdermatologic disease in HIV infection/AIDS includes inflammatory, infectious, neoplastic, and medication-related disorders.***
- ***Specific stages of HIV disease (acute HIV syndrome, immune reconstitution, clinically latent disease, and advanced disease) tend to be associated with different dermatologic disorders.***
- ***Dermatologic disease may help to estimate the level of immunosuppression in HIV infection/ AIDS, particularly in resource-limited settings.***
- ***As there are many dermatologic disorders thatare seen in HIV infection/ AIDS, this chapter focuses on those diseases that are the most closely associated.***

Since the original description in 1981 of an unusual cluster of cases of Pneumocystis carinii pneumonia and Kaposi's sarcoma in previously healthy men who have sex with men, substantial advances in our understanding of the acquired immune deficiency syndrome have been achieved. The identification of a cytopathic retrovirus in 1983 and development of a diagnostic serologic test for HIV in 1985 have served as the basis for developing improvements in diagnosis.

In addition, therapy was dramatically altered with the introduction of antiretroviral drugs in 1987 and revolutionized by combination antiretroviral therapy in 1996. In the three years following the introduction of ART, mortality, AIDS, AIDS-defining diagnoses, and hospitalizations all decreased 60 to 80 percent. The EuroSIDA study, comparing this early ART period to pre-ART and later ART (1998 to 2002) treatment periods, found a sustained decrease in mortality and progression to AIDS with ongoing ART. Despite the absence of a cure, the natural history of the disease was radically changed and patients with the HIV infection without other significant comorbidities who are treated appropriately can expect to have a life expectancy the same as the general population.

Despite these advances, it is still useful to review the natural history of HIV infection without antiretroviral therapy and the classification of disease.

2. ETIOLOGY

THE HUMAN IMMUNODEFICIENCY VIRUS is a lentivirus (a subgroup of retrovirus) that causes HIV infection and acquired immunodeficiency

syndrome. AIDS is a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells.

3. PATHOGENESIS

HIV infects vital cells in the human immune system such as helper T cells (specifically CD4+ T cells), macrophages, and dendritic cells. HIV infection leads to low levels of CD4+ T cells through a number of mechanisms, including apoptosis of uninfected bystander cells, direct viral killing of infected cells, and killing of infected CD4+ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When CD4+ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections.

Immunology. After the virus enters the body there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.

This response is accompanied by a marked drop in the numbers of circulating CD4+ T cells. This acute viremia is associated in virtually all people with the activation of CD8+ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts rebound. A good CD8+ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus.

During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

However, the symptoms of immune deficiency characteristic of AIDS do not appear for years after a person is infected, the bulk of CD4+ T cell loss occurs during the first weeks of infection, especially in the intestinal mucosa, which harbors the majority of the lymphocytes found in the body. The reason for the preferential loss of mucosal CD4+ T cells is that a majority of mucosal CD4+ T cells express the CCR5 coreceptor, whereas a small fraction of CD4+ T cells in the bloodstream do so.

HIV seeks out and destroys CCR5 expressing CD4+ cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase. However, CD4+ T cells in mucosal tissues remain depleted throughout the infection, although enough remain to initially ward off life-threatening infections.

Continuous HIV replication results in a state of generalized immune activation persisting throughout the chronic phase. Immune activation, which is reflected by the increased activation state of immune cells and release of proinflammatory cytokines, results from the activity of several HIV gene products and the immune response to ongoing HIV replication. Another cause is the breakdown of the immune surveillance system of the mucosal barrier caused by the depletion of mucosal CD4+ T cells during the acute phase of disease.

This results in the systemic exposure of the immune system to microbial components of the gut's normal flora, which in a healthy person is kept in check by the mucosal immune system. The activation and proliferation of T cells that results from immune activation provides fresh targets for HIV infection. However, direct killing by HIV alone cannot account for the observed depletion of CD4+ T cells since only 0.01–0.10 % of CD4+ T cells in the blood are infected.

A major cause of CD4+ T cell loss appears to result from their heightened susceptibility to apoptosis when the immune system remains activated. Although new T cells are continuously produced by the thymus to replace the ones lost, the regenerative capacity of the thymus is slowly destroyed by direct infection of its thymocytes by HIV. Eventually, the minimal number of CD4+ T cells necessary to maintain a sufficient immune response is lost, leading to AIDS.

CD4 T-cell Death and Inflammation. Recent studies employed an ex vivo human lymphoid aggregate culture (HLAC) system formed with fresh human tonsil or spleen tissue[8] to model molecular and cellular events in human tissues during in vivo HIV infection. These studies found that >95% of CD4 T cells die because of abortive HIV infection. These dying cells are resting and thus are nonpermissive for productive HIV infection. Full viral replication was limited to the ~5 % of activated CD4 T cells present in these tissues; these cells die by apoptosis. Abortive HIV infection occurs due to slowing of reverse transcription promoting cytosolic DNA accumulation. This viral DNA is sensed by gamma-interferon-inducible protein 16 (IFI16), which produces an innate immune response against the virus by activating caspase 1 in IFI16 inflammasomes and inducing pyroptosis, a highly inflammatory form of programmed cell death. These findings cast CD4 T-cell death during HIV infection in a different light. Rather than the virus playing a major role, it is the host response to viral DNA produced during abortive infection that triggers CD4 T-cell death. Further, these findings identify novel drug targets that may be exploited to both block CD4 T cell demise and the chronic inflammatory response generated during pyroptosis.

Cells affected. The virus, entering through which ever route, acts primarily on the following cells:

Lymphoreticular system:

CD4+ T-Helper cells (main target cell)

Macrophages

Monocytes

Certain endothelial cells

Central nervous system:

Microglia of the nervous system

Astrocytes

Oligodendrocytes

Neurones — indirectly by the action of cytokines and the gp-120

The effect. Although the virus has cytopathic effects in productively infected cells, this effect may not directly contribute to HIV pathogenesis (see above). Importantly, the virus can remain inactive (latent) in these productively infected cells for long periods.

CD4 T-cell depletion and chronic inflammation are the two signature events that drive HIV pathogenesis and progression to AIDS.

Infection of the cells of the CNS cause acute aseptic meningitis, subacute encephalitis, vacuolar myelopathy and peripheral neuropathy. Later it leads to even AIDS dementia complex.

The CD4-gp120 interaction (see above) is also permissive to other viruses like Cytomegalovirus, Hepatitis virus, Herpes simplex virus, etc. These viruses lead to further cell damage i.e. cytopathy.

4. TRANSMISSION

HIV transmission takes place through the following routes:

1. Sexual intercourse (vaginal/anal/oral): With an infected partner:

- Man with woman (heterosexual).
- Man with man (homosexual).
- Woman with woman (?).

2. Transfusion: With infected blood and blood products, transplantation of organ/tissue, andthrough artificial insemination.

3. Contaminated needles and syringes: Seenmost frequently in intravenous drug users(IDUs) when they share unsterilized needlesand syringes.

4. Vertical transmission: From an infected mother to child, i.e., perinatal transmission (before,during and after delivery).

5. Nosocomial infection: In hospital/health caresettings on account of accidental needle stickinjury or sharp instrument cuts, etc., whiletreating an HIV/AIDS patient, though rare, doesoccur.

HIV Risk Behaviors

The risk of getting HIV varies widely depending on the type of exposure or behavior (such as sharing needles or having sex without a condom). Some exposures to HIV carry a much higher risk of transmission than other exposures. For some exposures, while transmission is biologically possible, the risk is so low that it is not possible to put a precise number on it. But risks do add up over time. Even relatively small risks can add up over time and lead to a high lifetime risk of getting HIV. In other words, there may be a relatively small chance of acquiring HIV when engaging in a risk behavior with an infected partner only once; but, if repeated many times, the overall likelihood of becoming infected after repeated exposures is actually much higher.

The table 1 below lists the risk of transmission per 10,000 exposures for various types of exposures.

Table 1 — Estimated Per-Act Probability of Acquiring HIV from an Infected Source, by Exposure Act(according http://www.cdc.gov)

Type of Exposure	Risk per 10,000 Exposures
Parenteral	
Blood Transfusion	9,250
Needle-Sharing During Injection Drug Use	63
Percutaneous (Needle-Stick)	23
Sexual	
Receptive Anal Intercourse	138
Insertive Anal Intercourse	11
Receptive Penile-Vaginal Intercourse	8
Insertive Penile-Vaginal Intercourse	4
Receptive Oral Intercourse	Low
Insertive Oral Intercourse	Low
Other^	
Biting	Negligible
Spitting	Negligible
Throwing Body Fluids (Including Semen or Saliva)	Negligible
Sharing Sex Toys	Negligible

* Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and pre-exposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

^ HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

However, while all groups are affected by HIV, some are more vulnerable than others.

Anyone can contract HIV, and while intravenous drugsusersare at great risk because of practices related to their drug use, anyone who engages in unsafe sex (e.g., unprotected sex with an infected partner), could be exposed to HIV infec-

tion. Anyone who have another STIcould be exposed to HIV infection. Many sexually transmitted infections (STIs) produce open sores on your genitals. These sores act as doorways for HIV to enter your body.Studies indicate that lack of circumcision increases the risk of heterosexual transmission of HIV. Gay or bisexual MSM are the most severely affected population. MSM account for just a small fraction (2 percent) of the total U.S. population, yet nearly two-thirds of all new infections occurred within this group in 2009, and one-half of all people living with HIV in 2008 were MSM. MSM within ethnic minority populations are at greatest risk.

5. EPIDEMIOLOGY

United States statistics. According to the Centers for Disease Control and Prevention (CDC), in 2009 the estimated rate of diagnoses of HIV infection in the 40 states that have confidential name-based reporting was 17.4 per 100,000 population. From 2006 to 2009, the estimated number and rate of annual diagnoses of HIV infection in those states remained stable.

The CDC estimated that at the end of 2006, the most recent year for which national prevalence estimates are available, there were 1,106,400 adults and adolescents living with HIV infection in the United States. This represents an increase of approximately 11 % from the previous estimate in 2003; the increase may reflect a higher proportion of HIV-infected people knowing their status and seeking care, and/or increased survival among people infected with HIV.

In 2009, the estimated rate of AIDS diagnoses in the US was 11.2 per 100,000 population. More than 1 million persons were diagnosed with AIDS from 1981 to 2008, and more than 600,000 people died with AIDS (although reporting limitations mean that not every «death with AIDS» is directly attributable to AIDS itself).

US rates vary by state. See the latest CDC surveillance report for full details.

The overall figures may give a false impression that the HIV epidemic is relatively homogeneous. In fact, the HIV epidemic is best viewed as numerous separate epidemics among distinct risk groups, although the various epidemics clearly have some level of overlap. In any given area, the infection may be most prevalent among users of intravenous drugs who share needles. In another, the main risk group may be men who have sex with other men. And in yet another, the main risk group may be female sex workers.

These sub-epidemics each follow their own pattern, although there is some degree of interdependence. Early on, nearly all cases of HIV infection detected in the Western Hemisphere were in homosexual men, but the spread of the disease to female partners of bisexual men with HIV infection gave rise to an increased rate among heterosexual persons.

Contributing to the increased cross-prevalence were persons with hemophilia who had been infected with HIV from contaminated factor VIII concentrate

and persons who used intravenous drugs, an activity that transcends all sexual preferences. Currently, less than half of new HIV infections are reported in homosexual men, and infected heterosexual women outnumber infected heterosexual men nearly two to one.

One community-based study targeting areas where men who have sex with men (MSM) meet demonstrated that an average of 44 % of study participants appeared unaware of their HIV-positive status. High rates of positivity and unawareness of positive status were associated with younger participants, men of black non-Hispanic race, and lower education levels.

Healthcare visits in the preceding year were associated with a lower rate of unawareness (37 % vs 81 %) but a higher rate of HIV-positivity (21 % vs 12 %). Because this study targeted a high-risk group and may involve participation bias, the overall rate of HIV infection (19 %) cannot be easily extrapolated to the overall population.

Mortality from HIV disease has not been among the 15 leading causes of death in the US since 1997. The age-adjusted death rate for HIV disease peaked in 1995 at 16.3 per 100,000 populations, decreased 69.9 % through 1998, and then further decreased 30.2 % from 1999 through 2007, to 3.7 per 100,000 populations. In 2007, a total of 11,295 persons died from HIV disease. However, HIV disease has remained among the 5 leading causes of death for specific age groups for females, and in the black population.

Adolescents and young adults. CDC HIV surveillance statistics from 2010 report that 25.7 % (~12,200 individuals) of new HIV infections in the United States are in adolescents and young adults aged 13 to 24 years. Males accounted for 82.8 % of new HIV infections in youth. Of these, 7000 (57.4 %) were in African Americans, 2390 (19.6 %) in Hispanics, and 2380 (19.5 %) in whites. Male-to-male sexual contact accounted for 72.1 % (8800 individuals). The percentage of youths tested for HIV infection was 12.9 % in high- school students and 34.5% in individuals aged 18–24 years. Testing was lower in males than females. More than half (59.5 %) of youths with HIV are unaware of their infection.

International statistics. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), worldwide in 2008 approximately 33.4 million people (1 % of the global adult population aged 15–49 y) were infected with HIV, a decline from 2006 (39.5 million reported at that time). UNAIDS estimates that 2.7 million people were newly infected with HIV and that 2 million people died from AIDS in 2008, both statistics showing a slight decline over time.

The vast majority of infections remain in sub-Saharan Africa, where 5.2 % of the population is thought to be infected. Between 2004 and 2006, the prevalence of HIV infection in central and eastern Asia and Eastern Europe increased by 21 %. During this period, the number of new HIV infections in persons aged 15 to 64 years rose by 70 % in Eastern Europe and central Asia.

The infection rates in many developed countries remain stable, and some developing countries have achieved significant gains in controlling and even reversing the effects of the HIV epidemic. However, this is partially due to deaths in HIV-infected people, together with simultaneous prevention of new infections. India, for example, has used a national prevention campaign focusing on high-risk populations that may have prevented 100,000 new HIV infections over the 5 years it has been implemented, with increasing results seen in areas with higher levels of investment. These figures together show that global HIV infection is in a state of flux.

The mortality rate in some countries has greatly increased. In South Africa (a country that, despite having a relatively late-onset HIV epidemic, has developed one of the highest prevalence rates), the all-cause HIV-associated mortality rate increased by 79 % between 1997 and 2004. In women aged 25–34 years, mortality rates increased by 500 % during this period.

Swaziland has the highest overall prevalence of HIV infection (>26 % of all adults based on 2007 figures).

The Ministry of Health in Zambia predicts that, without therapy and assuming current levels of prevalence, young adults have a 50 % lifetime risk of dying from AIDS.

In developing nations, co-infection with HIV and tuberculosis is very common. The immunosuppressed state induced by HIV infection contributes not only to a higher rate of tuberculosis reactivation but also to an increased disease severity, as with many other opportunistic infections.

Further details of the global epidemic can be found in the Joint United Nations Programme on HIV/AIDS 2009 Epidemic Update.

Racial, sexual and age-related differences in incidence

In the United States, the rate of HIV infection is highest in blacks (83.7 cases per 100,000 populations). The prevalence is also high among Hispanic persons (29.3 per 100,000 populations). These increased rates are due to socioeconomic factors rather than genetic predisposition.

In the developed world, HIV infection is much more common in males. In 2009, males accounted for 76 % of all diagnoses of HIV infection among adults and adolescents in the US. Among heterosexuals, females are more likely to acquire HIV infection from an infected male than a male is from an infected female, but a large proportion of infections in males are due to homosexual contact, with or without injection drug use. Males are also more likely to acquire HIV infection from injection drug use alone.

Males were also more likely to acquire HIV infection through contaminated blood products for treatment of hemophilia before universal testing of the blood supply was instituted. The risk of HIV exposure from factor VIII concentrates has been virtually eliminated by viricidal treatment of plasma-derived fac-

tor VIII concentrates, as well as the introduction of recombinant factor VIII concentrates and the gradual elimination of albumin from the production process used for these products.

In the developing world, HIV infection is equally common in males and females. The primary route of HIV transmission in the developing world is heterosexual contact.

Young adults tend to be at higher risk of acquiring HIV, typically through high-risk activities such as unprotected sexual intercourse or intravenous drug use. In 2009 in the US, the largest percentage (15% of all diagnoses) and the highest rate (36.9 per 100,000 populations) were in persons aged 20–24 years.

Children may become infected by transplacental transmission or by breast-feeding. Rare cases of children infected after sexual abuse by HIV-infected adults have also been reported.

6. INTERNATIONAL CLASSIFICATION OF DISEASES, REVISION 10 (1990)

(B20-B24) Human immunodeficiency virus [HIV] disease

B20 Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases

B20.0 HIV disease resulting in mycobacterial infection

B20.1 HIV disease resulting in other bacterial infections

B20.2 HIV disease resulting in cytomegaloviral disease

B20.3 HIV disease resulting in other viral infections

B20.4 HIV disease resulting in candidiasis

B20.5 HIV disease resulting in other mycoses

B20.6 HIV disease resulting in Pneumocystis carinii pneumonia

B20.7 HIV disease resulting in multiple infections

B20.8 HIV disease resulting in other infectious and parasitic diseases

B20.9 HIV disease resulting in unspecified infectious or parasitic disease

B21 Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms

B21.0 HIV disease resulting in Kaposi's sarcoma

B21.1 HIV disease resulting in Burkitt's lymphoma

B21.2 HIV disease resulting in other types of non-Hodgkin's lymphoma

B21.3 HIV disease resulting in other malignant neoplasms of lymphoid, haematopoietic and related tissue

B21.7 HIV disease resulting in multiple malignant neoplasms

B21.8 HIV disease resulting in other malignant neoplasms

B21.9 HIV disease resulting in unspecified malignant neoplasm

B22 Human immunodeficiency virus [HIV] disease resulting in other specified diseases

B22.0 HIV disease resulting in encephalopathy

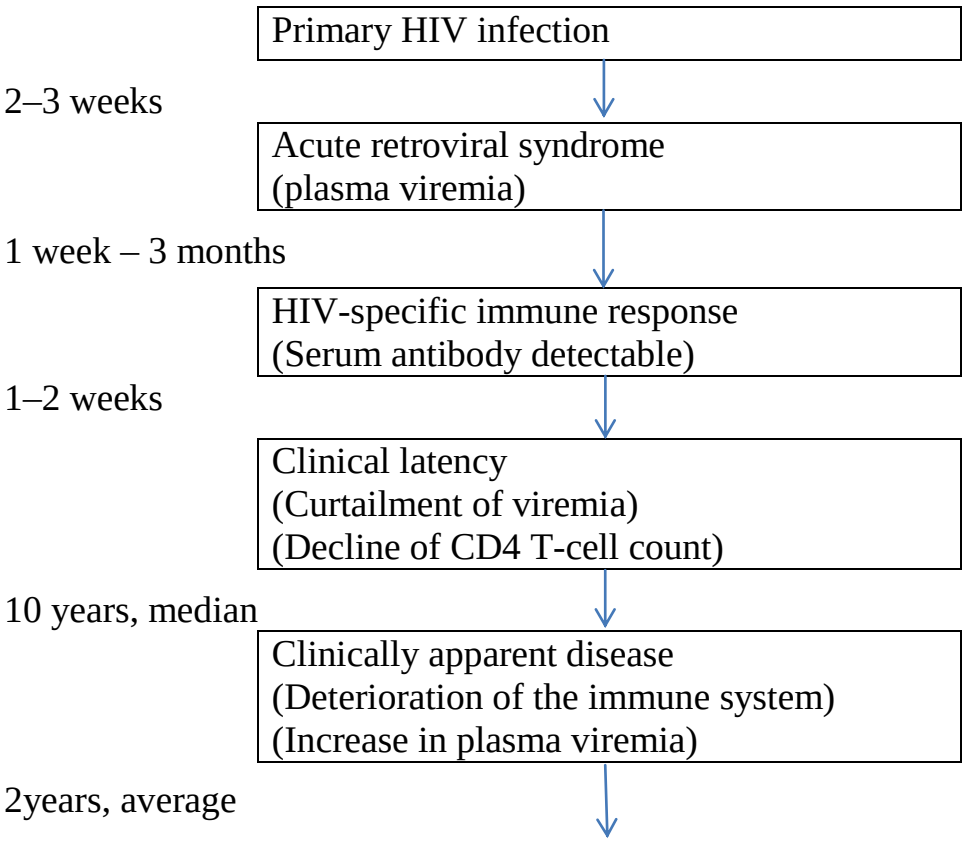
B22.1 HIV disease resulting in lymphoid interstitial pneumonitis
B22.2 HIV disease resulting in wasting syndrome
B22.7 HIV disease resulting in multiple diseases classified elsewhere
B23 Human immunodeficiency virus [HIV] disease resulting in other conditions
B23.0 Acute HIV infection syndrome
B23.1 HIV disease resulting in (persistent) generalised lymphadenopathy
B23.2 HIV disease resulting in haematological and immunological abnormalities, not elsewhere classified
B23.8 HIV disease resulting in other specified conditions
B24 Unspecified human immunodeficiency virus [HIV] disease

7. NATURAL HISTORY OF HIV INFECTION

The course of HIV infection from the time of initial infection to the development of full blown AIDS is divided into five stages

Incubation period — two to three weeks, though may be much longer.

The natural history of HIV disease is outlined below: from primary HIV infection, the acute HIV syndrome, and the HIV-specific immune response through a period of clinical (but not viral) latency (median duration ~10 years) to clinically apparent disease or AIDS-defining illness, and finally death from AIDS (figure 1).



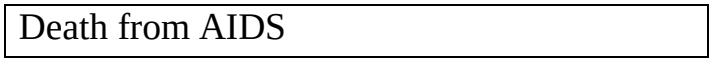


Figure 1 — Progression of HIV infection from Primary infection through acute HIV syndrome to clinical latency and then to clinically apparent disease or AIDS-defining illness

Of course, the duration of clinical latency following primary HIV infection varies widely among individual persons depending upon many factors, among them exposure categories (blood, sexual contact, mother-to-child) and portal of entry, viral pathogenicity and mutation, host resistance and intrinsic and specific immune responsiveness, and new treatment strategies with combinations of potent antiretroviral drug therapy.

There are also some HIV-seropositive, long-term «non-progressors» who have continued to be healthy without evidence of disease or immune defect for 10 or more years after primary HIV infection.

Acute retroviral syndrome

This mononucleosis-like syndrome develops in 40–70 % of patients at 3–6 weeks after primary HIV infection. The presenting symptoms may include fever, headache, sore throat, erythematous rash, diarrhea, and generalized lymphadenopathy. Laboratory tests may show leukopenia, anemia, thrombocytopenia, atypical lymphocytosis, elevated liver enzymes, and hypergammaglobulinemia. The peripheral blood CD4+ T-lymphocyte count (reference normal adult count is usually at least 800/cumm) and the CD4/CD8 ratio (reference normal ratio is about 2) both decline. The acute illness usually resolves spontaneously within 2–3 weeks.

HIV viremia, p24 antigenemia, and viral dissemination to, and replication in, the regional and other lymph nodes occur during this early stage of HIV infection.

An HIV-specific antibody and cellular immune response follows the primary infection. Serum testing for HIV antibody, by a screening test such as ELISA (enzyme-linked immunosorbent assay) and confirmatory Western blot (showing 2 or more bands of reactivity with Gag, Env, or Pol proteins), is positive in most individuals within 1 to 3 months after primary infection and in ~95 % within 6 months. (Potentially confounding, the serum of an uninfected (or infected) infant born to a seropositive mother may be expected to contain passively acquired maternal antibody).

The HIV-specific immune response is associated with a marked decline in plasma viremia, but HIV replication continues in lymph nodes or other tissue compartments or organs, such as genital tract or brain.

Clinical latency

This is an asymptomatic period of HIV infection and usually has a duration of several years (median duration of 10 years). The peripheral blood CD4 T-cell

count may return to normal, or stabilize at a somewhat lower level, or decline slowly over time.

The plasma level of HIV viremia tends to reach a steady state (termed 'viral set point') at the end of the acute phase following primary infection. The steady-state level of viremia (plasma viral load), as measured by assays for the number of copies of HIV-1 RNA per ml of plasma, is a prognostic indicator for the rate of HIV disease progression, high viral loads correlating with faster, low with slower, rates of disease progression to AIDS and death.

Latent, as well as productive, cellular infection by HIV is active in the lymphoid (cervical and axillary lymph nodes, tonsils, adenoids, etc.) and other tissue compartments during this variably prolonged period before the person becomes clinically ill.

Clinically apparent disease

This clinically apparent, symptomatic stage is a consequence (secondary manifestation) of the progressive and profound deterioration of the immune system that occurs over time in most patients with HIV infection. The CD4 T-cell count continues downward to the range of 200-400/ cubic mm. Plasma viremia and p24 antigenemia approach high levels such as seen in the primary infection. Some of the constitutional symptoms, opportunistic infections, and other manifestations of advanced symptomatic HIV disease are given in the following table 2.

Table 2 — Manifestations of Advanced Symptomatic Disease (CD4 T-cell count 200–400 / cubic mm.)

Constitutionalsymptoms:	Infections:	Other:
Fever	Oral or vaginal candidiasis	Cervical dysplasia
Weight loss	Oral hairy leukoplakia	Cervical carcinoma in situ
Fatigue	Herpes zoster (shingles)	Idiopathic thrombocytopenic purpura (ITP)
Night sweats	Herpes simplex	Neuropathy
Diarrhea	listeriosis	Seborrhea
Persistent generalized lymphadenopathy		

The CD4 T-cell count continues to fall, sometimes precipitiously, and reaches levels that define AIDS (CD4 T-cell count less than 200/cubic mm.)(Table 2) and predispose to AIDS-defining conditions, such as opportunistic infections caused by viruses, bacteria, fungi and protozoa, neoplastic disease, HIV encephalopathy, wasting syndrome, and progressive multifocal leukoencephalopathy that complicate the clinical course and are often the cause of death.

Table 2 — List of Conditions in the 1993 AIDS Surveillance Case Definition Issued by the Centers for Disease Control and Prevention

1. CD4 T-cell count < 200 / cubis mm.
2. Opportunistic Infection: • Candidiasis of bronchi, trachea, or lungs • Candidiasis, esophageal • Coccidioidomycosis, disseminated er extrapulminary • Cryptococcosis, extrapulmonary • Cryptosporidiosis, chronic intestinal (> 1 month duration) • Cytomegalovirus disease (other than liver, spleen, or nodes) • Cytomegalovirus retinitis (with loss of vision) • Herpes simplex: chronic ulcer (s) (1> month duration); or bronchitis, pneumonitis, or esophagitis • Histoplasmosis, disseminated or extrapulmonary • Isosporiasis, chronic intestinal (> 1 month duration) • Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary • Pneumocystis carinii pneumonia • Pneumonia, recurrent • Salmonella septicemia, recurrent
3. Neoplastic disease • Cervical carcinoma, invasive • Kaposi`s sarcoma • Lymphoma, Burkitt`s (or equivalent term) • Lymphoma, primary in brain • Lymphoma, immunoblastic (or equivalent term) • Lymphoma, primary in brain
4. HIV encephalopathy (AIDS dementia complex)
5. Wasting syndrome due to HIV
6. Progressive multifocal leukoencephalopathy (PML)

8. DERMATOLOGICAL MANIFESTATIONS OF HIV INFECTION

Cutaneous manifestations of human immunodeficiency virus disease may result from HIV infection itself or from opportunistic disorders secondary to the decline in immunocompetence from the disease. Cutaneous disorders may be the initial signs of HIV-related immunosuppression. Recognizing HIV-related skin changes may lead to the diagnosis of HIV infection in the early stages, allowing initiation of appropriate antiretroviral therapy. Many associated skin diseases are more severe in this group.

Although some dermatologic diseases have decreased markedly in frequency in the potent antiretroviral therapy era, other conditions remain common.

Among patients with low CD4+ cell counts who are not on or not adherent to antiretroviral therapy, notable conditions include psoriasis,photodermatitis, prurigo nodularis, molluscum, and adverse drug reactions. Conditions that remain relatively common despite adequate antiretroviral therapy include eczema, xerosis, warts, and Kaposi's sarcoma. Disorders that are associated with immune reconstitution under potent antiretroviral therapy include acne, staphylococcal infections, and erythema nodosum. In addition, HIV and hepatitis C virus (HCV) coinfection is associated with a number of skin disorders.

Common conditions in patients with CD4+ cell counts less than 200/μL who are not on antiretroviral therapy include severe psoriasis (usually affecting more than 50 % of the body), extreme photodermatitis, prurigo nodularis, molluscum, and recurrent drug reactions. Some HIV-related dermatologic conditions occur and recur even with appropriate antiretroviral therapy. There are Eczema and xerosis, Human papilloma virus-associated warts, Kaposi's sarcoma. Diseases that are now being seen with immune reconstitution under antiretroviral therapy include: acne, which must be differentiated from eosinophilic folliculitis; staphylococcal infections (frequentlymethicillin-resistant strains), which need to be differentiated from herpes simplex virus (HSV) and fungal diseases; and erythema nodosum, which needs to be differentiated from Helicobacter cinaedi infection (Table 3).

Table 3 — Mucocutaneous disorders stratified by CD-4 count

CD4 range (per ml)	Skin diseases
> 500	— acute retroviral syndrome — vaginal candidiasis — seborrheic dermatitis — psoriasis — Kaposi`s sarcoma
200–500	— oral thrush — herpes zoster — herpes simplex — refractory psoriasis — hypersensitivity to nevirapine — condyloma acuminatum — tinea infection — verruca vulgaris
100–200	— disseminated herpes simplex — refractory seborrhoeic dermatitis — eosinophili folliculitis — pruritic papular eruption — molluscum contagiosum — extensive Kaposi`s sarcoma

< 100	— cutaneous penialliosis — Baallary angiomatosis — herpes simplex: large @ unhealing — cutaneous Cryptococcus — giant Mollusca — disseminated cytomegalovirus — acquired ichthyosis

CLASSIFICATION OF DERMATOLOGICAL MANIFESTATIONS OF HIV INFECTION

- **Infectious**

Mycobacterial infection
Cytomegalovirus
Viral hepatitis
Varicella zoster virus
Herpes simplex virus
Human papillomavirus
Cryptococcosis
Histoplasmosis
Leishmaniasis

- **Inflammatory**

Sarcoidosis
Rheumatoid arthritis
Systemic lupus erythematosus
Tumid lupus
Dyshidrotic eczema
Eosinophilic folliculitis

- **Neoplastic**

Kaposi sarcoma
Dermatofibroma

8.1. Inflammatory dermatoses

Seborrheic dermatitis is one of the most common dermatologic manifestations of HIV disease, affecting as many as 83% of HIV-infected individuals during the course of their disease. Seborrheic dermatitis may occur during all stages of HIV disease, and frequently occurs early in HIV-infection (CD4+ T cell count >500/μL). As is the case in immunocompetent adults, HIVinfected individuals with seborrheic dermatitis typically present with erythema and greasy scale involving the scalp, eyebrows, nasolabial folds, and posterior auricular regions. Seborrheic dermatitis in HIV-infected individuals has a broad clinical spectrum, ranging from typical seborrheic dermatitis to a widespread form more like inverse psoriasis or sebopsoriasis.However, more disseminated formsof se-

borrheic dermatitis are often seen in advanced HIV disease. The forehead and malar areas, as well as the chest, back, axillae, and groin may be involved. In fact, erythroderma arising from seborrheic dermatitis may be an initial presenting sign of HIV infection.

A small percentage of patients present with the most severe form of seborrheic dermatitis, which consists of typical severe seborrheic dermatitis of the face and scalp, plus extensive involvement of the intertriginous areas. The axillae and groin are bright red and covered by a fine scale. The eruption moves out from the intertriginous areas onto the trunk and neck and may involve large areas of the body. Like classic seborrheic dermatitis, pruritus is generally mild. This severe form of seborrheic dermatitis may also be seen in non-HIV-infected persons, although it is quite unusual. This form may be called sebopsoriasis or inverse psoriasis — a cross between seborrheic dermatitis and psoriasis — and may be the presenting manifestation of HIV infection

Treatment. Mild seborrheic dermatitis in HIV-infected patients is managed in the same manner as in non-HIV-infected patients: mild topical steroids (e.g., 1 % hydrocortisone), tar shampoos, and often twice daily application of topical imidazole cream (clotrimazole or ketoconazole), which is used for its anti-inflammatory rather than its antifungal effects. Patients are very slow to respond to treatment with topical imidazoles alone.

Psoriasis Vulgaris. Although psoriasis may develop at any stage of HIV infection, the severity of psoriasis tends to correlate with worsening immune function. For some individuals, psoriasis may be the initial presenting symptom of HIV infection, and new onset psoriasis in an individual at risk for HIV is an indication for HIV testing. All clinical subtypes of psoriasis are observed in HIVinfected individuals, though guttate, inverse and erythrodermic psoriasis are the most common.The incidence of severe involvement of the axillae and groin (sebopsoriasis) is increased in HIV-infected patients. In addition, psoriatic erythroderma is not rare in these patients. Drug reactions and psoriasis are the first and second most common causes, respectively, of an erythroderma in patients with advanced HIV disease. As in routine psoriasis, pruritus may be a serious problem for the HIV-infected patient with psoriasis. With scratching, secondary infection of excoriated psoriatic plaques with S. aureus may occur. Erythrodermic psoriasis in HIV-infected patients may be a sign of S. aureus septicemia, and the psoriasis may improve dramatically with only intravenous antibiotics.

With the institution of antiretroviral therapy, psoriasis can be controlled with topical treatments, such as clobetasol and calcipotriene and ultraviolet light. Before adequate immune reconstitution under antiretroviral therapy occurs or in cases of complex or more severe psoriasis, treatment with the retinoid agent acitretin at 10 to 25mg/d can be considered; it should be noted that this agent is associated with increases in triglycerides and cholesterol. Psoriasis in HIV disease can have unusual presentations.

Pruritus is a common complaint in individuals with late symptomatic and advanced HIV disease. In the majority of cases, primary or secondary dermatoses rather than metabolic disorders are the cause of pruritus. An atopic-like diathesis may become manifest in individuals with advanced HIV disease and pruritus, even in the absence of a prior history of atopy. Changes secondary to chronic rubbing and scratching are often seen, including excoriations, lichen simplex chronicus, and prurigo nodularis. Secondary S. aureus infection (impetiginization, furunculosis, or cellulitis) may also occur in traumatized lesions. Ichthyosis vulgaris and xerosis are common in advanced HIV disease and may be associated with mild pruritus.

Eosinophilic folliculitis is a chronic pruritic dermatosis occurring in persons with advanced HIV disease. In one retrospective study of HIV-infected individuals, low CD4+ T-cell counts (< 200/μL) were associated with the development of eosinophilic folliculitis, independent of ART status. Clinically, eosinophilic folliculitis presents with extremely pruritic small pink to red edematous, folliculocentric papules, and less commonly pustules. Lesions tend to develop symmetrically above the nipple line on the chest, proximal arms, head, and neck. Secondary changes are common, and include excoriations, lichen simplex chronicus, and prurigo nodularis, as well as secondary infection with S. aureus. In individuals with darker skin, postinflammatory hyperpigmentation often produces significant cosmetic disfigurement. Treatment consists of the antifungal itraconazole 200 to 400 mg/d, not because the condition is fungal but because of the antieosinophilic effect of this agent. Permethrin can be used from the waist up every other day to dry the papules. Patients can also simply be observed to determine if the condition resolves after the initial 3 to 6 months of antiretroviral therapy.

Papular Pruritic Eruption of HIV has been considered to be within the spectrum of pruritic papular disorders in HIV, which includes eosinophilic folliculitis and nonspecific pruritus. The primary lesion is a firm urticarial papule, though sterile pustules have been described as well. The eruption is usually symmetric and distributed primarily on the extremities, and less commonly on the trunk and face. Lesions are occasionally but not always folliculocentric. Because the eruption is intensely itchy, the eruption is typically associated with multiple excoriations, marked postinflammatory hyperpigmentation, and scarring.

Prurigo nodularis — («itchy bumps») of the arms and trunk. The disorder, which may have a photocomponent, is more frequently seen in patients with CD4+ cell counts below 50/μL and is more common in persons of color. Patients are consumed by itching, which is not relieved with antihistamines. Institution of antiretroviral therapy is helpful in resolving the condition. Potent topical steroids should be used, and thalidomide is effective when it is started at a dose of 50 mg/d and titrated for response (rarely above100 mg/d). Careful monitoring for development of peripheral neuropathiesis suggested. In addition, tha-

lidomide is a teratogen and special precautions need to be taken in women of childbearing potential.

Can be a condition characterized by numerous papules smaller than those typically seen in prurigo nodularis; for years, this condition has been unhelpfully described as «pruritic eruption of HIV». This is a common condition in areas of Africa, and a study was recently performed in Ugandan patients to determine the cause of the disorder. A lowerCD4+ cell count was significantly associated with greater severity oferuption, and the condition appearedto improve in patients started onantiretroviral therapy. The conditionmay thus represent hypersensitivity tobug bites secondary to immune deficiency.

Photodermatitis is the typical darkening of skin that is exposed tosun. Persons with background pigment of the skin (ie, people of color) are more photosensitive than persons without background pigment in the skin. HIV infection itself is photosensitizing, and patients with low CD4+ cell counts may be receiving photosensitizing drugs such as trimethoprim/ sulfamethoxazole (TMP/SMX). Antiretroviral therapy allows patients to go off photosensitizing drugs and also decreases the reaction through immune reconstitution. Treatment includes sunscreen,potent topical steroids (eg, clobetasol), lubricants, and antihistamines. The tricyclic doxepin (25 mg qhs) is useful for its strong antihistamine effects.

Porphyria cutanea tarda (PCT). Porphyria cutanea tarda has been described in many HIV-infected persons, suggesting an association between the two. Some patients have the familial form and others the sporadic form of PCT. Many patients who are genetically susceptible to PCT develop the disease only after exposure to hepatotoxic agents (ethanol) or drugs that interfere with uroporphyrinogen decarboxylase (iron or estrogens, for example). Hepatitis may also precipitate clinical PCT. Hepatitis C has been associated with PCT. Why patients capable of developing PCT do so after HIV infection is unknown, but in many cases, patients have been exposed to one or more of the above mentioned precipitating factors.

Drug reactions. There is a group of patients with very low CD4+ cell counts (usually < 50) who exhibit reactions to virtually every drug they are given, including antibiotics and antiretrovirals. Because of their low CD4+ cell counts, these are the very patients who require antiretrovirals and prophylactic antibiotics and are therefore at higher risk for drug reactions. A successful approach to reinstituting drug treat ment has been to put these patients on prednisone with a slow taper over12 weeks while other drugs are individually added. In cases of drug reaction apart from such chronic reactions, steroids should be used only if the patient has a hypersensitivity reaction marked by elevated liver function test results or increased creatinine levels. Even in cases of erythema multiforme, Stevens- Johnson syndrome, or when urticaria is present, the best approach is simply to remove the offending drug and wait until the reaction re-

solves. Drug clearance may take time for some drugs used in HIV-infected patients (eg, TMP/SMX).

Eczema and xerosis are common conditions, particularly in patients in whomthe CD4+ cell count nadir was less than 200/μL. Treatment consists of midpotency steroids (ointment is better than cream, since it contains lubricant) andantihistamines. Tacrolimus and pimecrolimus, newer topical steroid formulations for eczema, have black box warnings regarding use in patients with altered immune function, although no specific degrees of immune deficiency are cited as contraindications for use.

Atopic Dermatitis. Atopic dermatitis may appear in both children and adults infected with HIV. In one series, 50% of infants with advanced HIV disease had atopic dermatitis. Hemophilic children infected by blood transfusion may have flare-ups of previously quiescent atopic dermatitis. Adults with a previous history of atopic disease may also note recurrence of atopy in advanced HIV disease. They may develop atopic dermatitis when previously they had only respiratory atopic symptoms. Treatment recommendations are the same as for non-HIV-infected patients: use of topical steroids and lubricants, sedating antihistamines, and avoidance of water and soap.

Erythroderma in HIV disease may be related to drug hypersensitivity, atopic dermatitis, psoriasis, seborrheic dermatitis, photosensitivity dermatitis, coexisting human T-cell lymphotrophic virus-1 infection, pityriasis rubra pilaris, or cutaneous T cell lymphoma.

8.2. Opportunistic infections

HPVinfections are commonly seen at all stages of HIV disease, and anogenital and oral HPV infections have been reported to occur at a higher rate in HIV-infected individuals compared to that in the general population.

Common Warts. Human papilloma virus (HPV)-associated warts are also highly recurrent despite adequate antiretroviral therapy, with some evidence indicating that eradication is difficult if the CD4+ cell count nadir was below 50/μL.As immunodeficiency progresses, common warts may become larger, more numerous, confluent, and more refractory to treatment. HPV-5 can cause an unusual pattern of extensive verruca plana and pityriasis (tinea) versicolor-like lesions, similar to that seen in epidermodysplasia verruciformis.

Anogenital Warts. Clinically, anogenital warts appear similar to those seen in immunocompetent individuals; however, condyloma may be more numerous or extensive, and are often less responsive to therapy. As in immunocompetent individuals, anogenital warts in HIV-infected individuals most commonly result from infection by HPV-6 and HPV-11. Although anogenital warts are commonly considered to be benign lesions, anogenital warts in HIV-infected individuals are morelikely to reflect infection with multiple HPV types, includ-

ing high-risk oncogenic types -16, -18, -31, -51,-53, -56, and -58 as well as low-risk types -6 and -11.

No matter which is tried, treatment is only successful about 50 % of the time.Treatments include liquid nitrogen, podophyllin, laser treatment, and surgery. A recent study suggests that once genital warts are removed by cryotherapy or surgery, imiquimod is often successful at preventing recurrence. Some patients report that application of duct tape is successful at removing warts, although this approach has not yet been formally studied in HIV-infected patients.

Oral HPV Infections. HPV-induced oropharyngeal lesions typically present as pink or white verrucous papules, resembling anogenital condyloma. If lesionsare extensive, they may coalesce to form multiple large plaques, which may transform to verrucous carcinoma (oral florid papillomatosis). Oral HPV infection has also been associated with a subset of oropharyngeal SCC, which sometimes arises from the base of the tongue and tonsils.

HPV-Induced Dysplasia and Invasive SCC. The risk of HPV-induced dysplasia and malignancy is significantly higher in HIV-infected individuals compared to that in the general population.

Herpes Simplex Virus 1 and 2 Infections is commonly associated with HIV disease. As long as the host immune system is still reasonably intact, the course of genital and orofacial HSV recurrences may be similar to the course in non-HIV-infected patients. Clinicians should consider HSV in evaluating all ulcerative lesions, particularly perirectal ulcers and nonhealing ulcers anywhere on the body.

Chronic herpetic ulcers of greater than 1 months' duration are an AIDS defining condition. HSV infection in HIV disease may present with severe, painful ulcerations of the perioral region, anogenital region, and digits. Atypical morphologies, such as hyperkeratotic, verrucous papules and nodules, are sometimes observed in advanced HIV disease. In more advanced HIV disease, lesions typically respond less promptly to oral antiviral therapy and recur more frequently.

HSV may rarely cause a necrotizing folliculitis that appears as 0.2- to 1.0-cm papules with firm central crusts. A biopsy is usually required to establish the diagnosis, because the site of infection is the epithelium along the hair shaft in the dermis.

Treatment. Oral acyclovir is extremely useful in managing HSV infections in HIV-infected patients. In the immunocompetent HIV-infected patient, either intermittent or chronic suppressive therapy may be used. The immunosuppressed patient with chronic ulcerative lesions should receive acyclovir (200 to 400 mg orally 5 times daily) until the ulcers heal, which may take several weeks. Then, chronic suppressive therapy should be instituted with acyclovir (400 mg orally twice daily) to reduce recurrences. The newer acyclovir analog antiviral agents are available with better absorption and higher bioavailability. Famciclovir (250 mg 3 times daily) and valaciclovir (100 mg twice daily) are alternatives.

Varicella Zoster Virus Infections. In HIV-infected individuals, varicella zoster virus infection (VZV) may present as severe varicella (primary VZV infection), persistent varicella, dermatomal herpes disseminated herpes zoster, and chronic or recurrent herpes zoster. In advanced HIV disease, herpes zoster may present atypically. Disseminated herpes zoster infection may manifest with scattered vesicles in the absence of dermatomal lesions. Persistent ecthymatous ulcerations and verrucous papules in the absence of a vesicular stage have also been described.

Patients with Previous Varicella. Varicella zoster virus (VZV) infection is commonly seen early in the course of HIV infection, particularly in healthy-appearing individuals, before the onset of other symptoms.Because most HIV-infected persons have had varicella previously, the initial manifestation of VZV infection is usually herpes zoster. During the course of HIV disease, herpes zoster often precedes thrush and oral **hairy leukoplakia** by about 1 year, making it an important early finding and raising suspicion of HIV infection in persons at risk.

Unlike zoster in individuals without HIV infection, this dermatomal eruption may be particularly bullous, hemorrhagic, necrotic, and painful in HIV-infected persons. The duration of blisters and crusts is usually 2 or 3 weeks. The approximate duration of significant pain is also 2 or 3 weeks. Necrotic lesions may last for up to 6 weeks and heal with severe scarring. This dermatomal scarring is characteristic of HIV-infected patients and should be sought when evaluating at-risk individuals. In severe cases, and occasionally in severe cases in non-HIV-infected persons, excruciating and disabling pain may last for many months.

Recurrences have been reported in up to 25 % of African HIV-infected persons with herpes zoster. This number is about 5 % higher than that seen in San Francisco. As immune suppression advances, recurrent episodes may increase in severity.

Dissemination of VZV in HIV infection is fortunately uncommon. VZV does disseminate more commonly in HIV-infected persons than does HSV, however, so all disseminated herpetiform eruptions should be considered VZV until proven otherwise, and high-dose acyclovir should be given. The clinical manifestations of disseminated VZV infection include typical widespread Tzanck-positive blisters with or without an associated dermatomal eruption. In addition, chronic disseminated VZV may present as widespread ecthymatous ulcers or hyperkeratotic verrucous lesions. This verrucous pattern often appears with prolonged infection that has been treated with acyclovir. VZV strains cultured from verrucous lesions in patients failing acyclovir therapy are often acyclovir-resistant, thymidine-kinase-negative mutants of VZV.

A less common manifestation of VZV infection in HIV infection is persistent, chronic, localized herpes zoster. Patients may develop typical herpes zoster that either fails to clear with acyclovir therapy or immediately recurs after therapy. Although dissemination does not occur, lesions fail to resolve with increasing doses of acyclovir, and patients eventually develop chronic localized zosteri-

form thymidine-kinase-negative VZV infection. Children with HIV infection may frequently develop primary, recurrent and persistent VZV infection.

Treatment. The use of corticosteroids in therapy for VZV infection in HIV-infected patients is somewhat controversial. Elderly patients without HIV infection are often given relatively high doses of oral corticosteroids for several weeks to prevent post-zoster neuralgia, although the efficacy of this treatment is debated. Systemic steroid therapy for VZV infection usually is not recommended for HIV-infected patients because of a theoretic risk of additional immunosuppression.

Because acyclovir reduces the initial pain, speeds healing, and reduces the risk of VZV dissemination, all VZV-infected patients with HIV disease should receive acyclovir treatment and their therapy should be initiated as soon as possible. The patient's immune status and pattern of zoster determines the method of administration.

Oral Acyclovir. If the patient has a reasonably intact immune system and does not have clinical features of disseminated or visceral infection, and if lesions are not near the eye (trigeminal nerve), then oral acyclovir is probably adequate and beneficial. Recommended doses for treating VZV are much higher than those for HSV because of the relative insensitivity of VZV to this medication. A dosage of 800 mg orally 5 times daily for 5 days is recommended. Therapy should continue at least 5 days beyond the last day of blister formation. Some authors believe that intravenous administration is more effective than oral. Fortunately, side effects from this drug are rare, even at these high doses. Famciclovir (500 mg) and valaciclovir (1000 mg) may be given only three times daily but must be dose adjusted in the setting of renal impairment.

Intravenous Acyclovir. Intravenous acyclovir (10 mg/kg 3 times daily) is indicated when the patient's immunosuppression is significant (CD4 < 200 plus additional immune repression, e.g., lymphoma), when disseminated or visceral lesions are present, and when VZV affects the ophthalmic branch of the trigeminal nerve (eyelid or tip of the nose especially). The possible increased risk for herpetic keratitis, retinal vasculitis, and uveitis supports intravenous treatment of persons with such VZV infections. Only intravenous acyclovir is guaranteed to reach plasma levels adequate to inhibit all VZV strains.

Treatment should continue until the lesions are well crusted (usually about 7 days), after which full doses of oral acyclovir may complete the therapy. Treatment should continue for 10 to 14 days. Early and vigorous treatment may prevent the severe necrotic forms of zoster and help relieve the terrible pain that can occur. Acyclovir treatment does not appear to reduce the risk of postherpetic neuralgia.

Other treatments for VZV consist mostly of analgesics and topical care of skin lesions. In mild cases, soap and water are adequate for bathing skin lesions, but in severe cases, compresses (2 or 3 times daily) help remove necrotic debris. Use of an antibiotic ointment after such treatment, such as silver sulfadiazine

(Silvadene; Marion Merrell Dow, Kansas City, MO) or bacitracin, keeps the scabs soft, helps prevent them from sticking to dressings, and may also prevent secondary infection. Capsaicin cream (Zostrix; Genderm, Lincolnshire, IL), a substance P depletor, may reduce both acute and chronic zoster pain. It may be applied to the lesions 5 times daily until the pain is controlled; rebound pain may occur when Zostrix use is discontinued.

Patients without previous varicella zoster virus infections. On initial exposure to VZV, a disseminated blistering eruption called varicella (chickenpox) usually occurs. This presentation is followed by lifelong immunity, but dormant virus can later reactivate dermatomally, causing herpes zoster. Not surprisingly, varicella occurs in HIV-infected persons. HIV-infected persons with no prior history of varicella may on exposure develop typical chickenpox. In HIV-infected children and adults, however, varicella may be severe, cause visceral disease, and be fatal.The predisposition for visceral disease seems greater in children than in adults with HIV disease. Prior VZV infection and the presence of anti-VZV antibodies do not protect the HIV-infected person from developing clinical lesions of varicella. Recurrences or persistence of varicella can occur despite acyclovir therapy. One possible explanation is the difficulty in achieving adequate blood levels of acyclovir during oral therapy.

Clinicians should give acyclovir to all HIV-infected persons with varicella. Adults who are feeling well, have normal chest radiographic findings, and have no evidence of visceral disease may be treated with oral acyclovir (800 mg 5 times daily for 10 to 14 days). For pediatric use, oral doses from 1,000 to 3,000 mg/m2 may be used in HIV-infected children with uncomplicated varicella. This therapeutic approach must be used with extreme caution, and intravenous acyclovir must be instituted if healing is not prompt. Oral therapy with acyclovir may predispose patients to subsequent chronic cutaneous VZV infection due to suboptimal blood levels of the drug. HIV-infected persons with varicella who are not given oral acyclovir should receive intravenous acyclovir (10 mg/kg every 8 hours). The clinical status of the patient determines the length of therapy. Acyclovir therapy should continue at least until the lesions are completely healed.

Molluscum contagiosum lesions are caused by poxvirus infection, and are a cutaneous marker for advanced HIV disease. Commonly seen in children, molluscum infections in HIV-infected individuals may bpresent with pearly skin-colored umbilicated papules characteristically seen in immunocompetent individuals. However, lesions that are large, confluent and predominantly facial are characteristic of advanced HIV disease. Atypical lesionsare also common, and may resemble folliculitis,abscesses, warts, furuncles, and cutaneous horns. In HIV-infected individuals, molluscum infections tend to be progressive and recurrent.

Molluscum is frequently seen in HIV-infected young women and men of any age who are not on antiretroviral therapy or are not adherent to their regimen. Its appearance fairly assuresMolluscum is frequently seen in HIV-infected

young women and men of any age who are not on antiretroviral therapy or are not adherent to their regimen. Its appearance fairly assures that the patient has a CD4+ cell count of less than 100/μL. First-line treatment is antiretroviral therapy. Liquid nitrogen provides only temporary treatment for the condition. Curettage is successful in removing larger lesions and can bedone without scarring.

Oral hairy leukoplakia is a benign infection of epithelial cells of oral mucosa with Epstein–Barr virus. A common oral manifestation of HIV disease, oral hairy leukoplakia is marker of moderate to advanced immunosuppression.

Clinically, oral hairy leukoplakia presents with asymptomatic hyperplastic, whitish plaques on the bilateral aspects of the lateral tongue. Lesions are typically asymmetric, and have corrugations accentuating the normal tongue ridges.

Staphylococcus aureus is a common bacterial pathogen causing cutaneous and systemic infections at all stages of HIV disease. No unique staphylococcal infections occur in HIV disease. Rather, HIV-infected individuals tend to present a wide range of primary skin and soft tissue infections that are normally seen in immunocompetent individuals. S. aureus infections in HIV-infected individuals are most commonly severe and recurrent.Infection with S. aureus may occur before any other signs or symptoms of HIV infection. Morphologic patterns that may occur include: bullous impetigo, ecthyma, folliculitis, hidradenitis-like plaques, abscesses, cellulitis, and pyomyositis.

Bullous Impetigo. Bullous impetigo is most common in hot, humid weather, presenting as very superficial blisters or erosions, most commonly seen in the groin or axilla. Because the blisters are flaccid, they are short-lived; often only erosions or yellow crusts are present. These lesions closely mimic cutaneous candidiasis.

Ecthyma. Ecthyma is an eroded or superficially ulcerated lesion with an adherent crust. Under this crust is often a plane of purulent material teeming with staphylococci. Removal of this crust is necessary to treat the lesion topically.

Folliculitis. Folliculitis due to S. aureus occurs most commonly in the hairy areas of the trunk, groin, axilla, or face, especially in men who shave. Follicular pustules are the primary lesion. Gram's stain and culture confirm the diagnosis and allow selection of appropriate antibiotic therapy, such as dicloxacillin (500 mg 4 times daily). Often the follicular lesions of the trunk are intensely pruritic and may be mistaken for other pruritic dermatoses, such as scabies. About 50 % of HIV-infected persons with scabies have coexistent S. aureus folliculitis. Occasionally, follicular lesions extend more deeply, forming abscesses. Rarely, all follicles across several square centimeters are infected, forming a large, violaceous, hidradenitis-like plaque. The plaque may be studded with pustules and have deep tracts connecting infected follicles. These plaques may mimic KS, but overlying pustules are quite unusual in KS. Rarely, abscess of the muscle (pyomyositis) may occur.

Treatment of Cutaneous Staphylococcal Lesions. The depth of the infection determines the treatment of cutaneous staphylococcal infections. Very superficial lesions, like bullous impetigo, often respond to a 7- to 10-day regimen of an

appropriate antistaphylococcal antibiotic, such as dicloxacillin (500 mg given orally 4 times daily). Deeper lesions often require courses of treatment lasting for months. In addition, combinations of antibiotics, especially a penicillinase-resistant penicillin or first-generation cephalosporin plus rifampin (600 mg once daily), are often necessary to clear the infection.

Adjunctive topical therapy is helpful in beginning treatment and reducing recurrences. Washing the infected area once daily or every other day with an antibacterial agent (Hibiclens, Betadine, or benzoyl peroxide wash) helps remove crusts, dries lesions, and decreases surface bacterial concentration. Topical antibiotics (clindamycin 1 % or erythromycin 2 % solutions) applied twice daily may be used in chronically infected areas.

Loculated abscesses must be incised and drained when fluctuant if antibiotics are to be effective. When cellulitis of any significance or symptoms of bacteremia are present, hospital admission for treatment with intravenous antibiotics is appropriate. Intranasal mupirocin may reduce carriage rate and prevent relapses. Chronic oral antibiotics may be required in some patients.

Infections due to Bartonella: bacillary angiomatosis

Bacillary angiomatosis, a treatable opportunistic infection, was initially reported as atypical subcutaneous infection in patients with advanced HIV disease and as epithelioid angiomatosis. The agents causing this infection, initially designated as Rochalimaea, have been reclassified as Bartonella. The term bacillary angiomatosis is being replaced by Bartonella infection because the infectious agents causing this condition have been identified as two species of Bartonella - B. henselae and B. quintana. These bacteria, closely related to rickettsiae, are extremely difficult to culture. As proposed initially by Le Boit, Koehler, and others at the University of California, San Francisco, one of the agents causing bacillary angiomatosis, B. henselae, is associated with most cases of cat scratch disease. One epidemiologic study has demonstrated cat exposure and cat scratches as risk factors for acquiring bacillary angiomatosis.

Bacillary angiomatosis initially was considered primarily a disorder of the skin, but systemic involvement is common. Visceral disease may include osseous lesions, hepatic and splenic involvement, lymph node disease, pulmonary lesions, brain lesions, and widespread fatal systemic involvement.

Clinical Features.The most characteristic cutaneous lesions of bacillary angiomatosis resemble pyogenic granulomas -- fleshy, friable, protuberant papules-to-nodules that tend to bleed very easily. In addition, deep cellulitic plaques and subcutaneous nodules may occur. Lesions number from a few to hundreds. Clinically, the skin lesions are frequently misdiagnosed as vascular tumors, especially KS. A prominent vascular proliferation that forms an elevated papule histologically characterizes the lesions. Neutrophilic leukocytes are prominent in the interstitium. Basophilic aggregates are found adjacent to the vascular lumina,

representing collections of the bacterium. Diagnosis is confirmed by identifying the causative organism in affected tissue using silver stains or electron microscopy.

Systemic findings such as fever, night sweats, weight loss, and anemia are common in patients with bacillary angiomatosis. Reports describe mucosal lesions of the conjunctiva and upper respiratory tract. Visceral lesions may be as or more common than cutaneous lesions. Involvement of the liver and spleen with or without skin lesions is the most commonly diagnosed form of visceral disease. These patients present with abdominal pain, fevers, elevated levels on liver function tests, and hepatosplenomegaly. Liver and spleen biopsies may show large ectatic vascular spaces, a pattern called peliosis. Abundant bacilli are adjacent to these vascular spaces. Osseous lesions manifest as bone pain and may precede the appearance of skin lesions. Routine radiographs reveal a lytic lesion at the site of pain. Bone scans rarely reveal additional asymptomatic lesions. Isolated lymph node enlargement is another presentation. The diagnosis of visceral disease is made on the basis of biopsy of the affected organ and examination with silver stains or electron microscopy. In the untreated patient, fatal widespread visceral disease may occur.

Treatment. Treating affected patients with erythromycin in full doses (500 mg orally 4 times daily) resolves the lesions, as does treatment with doxycycline (100 mg orally twice daily). Cutaneous lesions usually resolve in 3 to 4 weeks, but therapy should continue for at least 8 weeks. Patients with documented visceral disease should receive at least 4 months of therapy. Relapses can occur if treatment is not continued appropriately. In vitro sensitivities as currently performed do not correlate well with clinical response. Unlike KS, bacillary angiomatosis lesions do not respond to radiation therapy.

Cutaneous Tuberculosis is caused by Mycobacterium tuberculosis, Mycobacterium bovis, and the BCG vaccine. Various manifestations of cutaneous-tuberculosis have been described in HIV-infectedindividuals, including scrofuloderma, lichen scrofulosorum, disseminated miliary tuberculosis, gummatous tuberculosis, and tuberculous abscess. Cutaneous miliary tuberculosis — a previously rare form of cutaneous tuberculosis that arises from hematogenous spread of bacilli to the skin from an internal focus of infection. Clinically, cutaneous miliary tuberculosis may initially present with red–brown pinpoint macules, papules, and papulovesicles. Lesions often develop into small flat-topped papules that crust over centrally. The eruption tends to be asymmetrically distributed, and favors the buttocks, thighs, and extensor surfaces. The cutaneous findings of cutaneous military tuberculosis are nonspecific, and may resemble a bacterial folliculitis. Pulmonary symptoms may be present, though radiographic findings may be nonspecificas well.

Candidiasis. Candida colonization of the oropharynx is common in HIV-infected individuals, and has been reported in up to 90 % of individuals with advanced disease.

Oropharyngealcandidiasis typically presents in four different clinical patterns:

- pseudomembranous (thrush);
- hyperplastic;
- erythematous (atrophic);
- angular cheilitis.

Pseudomembranous candidiasis typically involves the tongue, and presents with yellow–white plaques that are removable by scraping.

Hyperplastic candidiasis usually involves the buccal mucosa, and consists of white plaques that are not removable by scraping.

Erythematous candidiasis commonly presents with erythematous patches of the palate and the dorsal tongue with associated depapillation.

Angular cheilitis manifests as erythema with curdlike flecks or painful fissures at the angles of the lips.

Intertriginous Infections. Either Candida or Tinea may cause intertriginous infection and may involve the groin, axillary vault, or inframammary areas. In these areas, candidiasis presents as a vivid red, slightly eroded eruption in the depths of the folds. The surface is wrinkled and a white membrane may coat the eroded surface. A hallmark of this rash is satellite pustules extending out centrifugally from the eroded areas. In males, the scrotum is often involved. Patient complaints of a burning pain may be as numerous as those related to pruritus.

Tinea in the groin is usually pruritic. The scrotum is spared. The depth of the folds may be clear, and a well-demarcated, annular patch expands down the upper thigh. In more extensive cases, the lesions may extend through the pubic hair onto the lower abdomen and buttocks. Rarely, tinea of the groin may extend to cover large areas of the body.

Both Candida and Tinea are diagnosed by potassium hydroxide examination of scales taken from the active border or a satellite pustule.

Topical treatment is usually adequate and involves the application twice daily of an imidazole cream (clotrimazole, miconazole, or ketoconazole). Candidal lesions may be moist, so drying soaks with Burow's solution 1:20 may be initially helpful. Eroded lesions in intertriginous areas are very tender, so topical solutions may burn. Treatment should be continued for 21 to 28 days. Because relapses are common, intermittent prophylactic treatment may be required. Addition of a topical imidazole is dramatically beneficial.

Candida Infection of the Nails. Both Candida and Tinea may infect the nails. Candida almost always affects the tissue around the fingernails, frequently presenting as a paronychia (inflammation of the tissues surrounding the nail). Findings include tenderness, erythema, and bogginess of the proximal nail fold. Pressure on the inflamed nail fold may express purulent material. Infection tends to be chronic, in which case the cuticle is lost and the nail plate may become ridged or dystrophic. Onycholysis (separation of the nail plate from the nail bed)

may also occur. The nail plate itself is usually not invaded, so nail thickening, opacity, and crumbling are unusual.

Topical imidazole in solution or 2 to 4% thymol in chloroform twice daily is the initial therapy. The onycholytic nail must also be trimmed away so that the medication can be applied at the most proximal area of onycholysis. In refractory cases, fluconazole (100 mg daily), itraconazole (200 to 400 mg daily), or ketoconazole in doses of 200 mg to 400 mg daily for 2 to 4 weeks is helpful.

A number of studies have documented a higher incidence of vulvovaginal candidiasis in HIV-infected women, particularly in those with advanced HIV disease.

Dermatophyte infections. As is the case for immunocompetent individuals, Trichophyton rubrum and Trichophyton mentagrophytes are the most common dermatophytes seen in HIV-infected individuals. In HIV disease, dermatophyte infections of the epidermis, commonly caused by T. rubrum may be more extensive, and are often asymptomatic. Disseminated disease may sometimes present atypically. Infectionsof the nails are also common. T. rubrum frequentlycauses distal and lateral subungual onychomycosis in both HIV-infected and immunocompetent individuals.However, T. rubrum also causes proximal subungualonychomycosis (infection of the undersurface of the proximal nail plate), which is seen almost exclusivelyin individuals infected with HIV. Unless immunocompetence is restored, dermatophyte infections are often chronic and recurrent.

Fingernail infection can be treated with fluconazole, or itraconazole (100 to 200 mg (fluconazole) and 200 to 400 mg (itraconazole) daily). Toenail infection is probably more likely than fingernail infection to relapse. Because relapse is common, constant use of topical antifungals is often necessary.

Invasive Fungal Infections. Disseminated fungal infections in advanced HIV disease may arise either by local invasion of the skin or mucosa with secondary lymphatic or hematogenous dissemination or reactivation of a latent pulmonary focus of infection. Cryptococcosis, Coccidioidomycosis, Histoplasmosis, Penicilliosis, Aspergillosis are most common life-threatening fungal infection associated with advanced HIV disease.

Scabies infection in adults and children is characterized by pruritic papular lesions and/or linear burrows found most commonly in the webs of the fingers and toes, folds of the wrist, antecubital area, axilla, and genitals. Infants may also have lesions on the palms and soles of the feet that often become pustular. Scrapings observed under the microscope may reveal the mite, eggs, or feces.

Treatment consists of an application of topical benzyl benzoate lotion, 25%, which is applied from the neck down, left on the skin overnight, and washed off in the morning; the process is repeated 1 week later. HIV-infected patients with advanced disease can experience a variant of scabies known as crusted scabies (Norwegian scabies), which is characterized by generalized scaling and enlarged, crusted plaques. After a patient is treated for scabies,the fami-

ly should be advised to wash all clothing and bedclothes in hot water and iron them to kill mites that may live in the cloth.

Sexually transmitted diseases. Given that the vast majority of HIV infections are sexually transmitted, individuals with HIV infection should also be screened for other sexually transmitted diseases such as Chlamydia, gonorrhea, and genital ulcerative diseases (e.g., syphilis, herpes, and chancroid).

STDs and HIV make a lethal combination and have several interactions:

• Presence of STDs amplifies the risk of transmission of HIV. The ulcerative STDs (syphilis, herpes genitalis, and chancroid) increase the transmission of HIV almost ten times, while the STDs associated with discharges (gonorrhea, chlamydial infection) amplify the transmissionof HIV by four to five times.

• In the early phase of HIV infection, the course of STDs is normal but as the immunosuppression nprogresses, the STDs may present atypically, run a fulminant course and may be resistant to conventional treatment.

• Presence of STDs may modify the course of HIV, e.g., human papilloma virus may have a higher oncogenic potential in presence of HIV infection.

Syphilis. Cutaneous presentations of primary and secondary syphilis in HIV-infected persons are usually similar to those in non-HIV-infected persons. The patients' HIV infection apparently delayed development of serologic evidence of Treponema pallidum, resulting in negative tests. Thus, in the HIV-infected person, a negative serologic test may not be adequate to rule out secondary syphilis.

CNS Manifestations. Syphilitic infection of the CNS may occur early, even in the primary or early secondary stage, among both non-HIV-infected and HIV-infected persons. Clinical CNS disease may be manifest as early as a few months after infection. Recommended therapies may not be adequate to treat or prevent this complication in non-HIV-infected persons. Early CNS relapse (even after standard treatment regimens) may be more common in HIV-infected individuals, possibly because of a combination of impaired cell-mediated immunity due to HIV and suboptimal CNS levels of medication. Clinicians should carefully follow HIV-infected patients who have been treated with standard therapies for early syphilis. If CNS signs or symptoms develop, clinicians should perform appropriate evaluation for early CNS relapse, including lumbar puncture and VDRL of the cerebrospinal fluid (CSF). The CDC recommends that a CSF examination precede and guide therapy in all HIV-infected patients with latent syphilis present for longer than 1 year or for unknown duration.

8.3. Opportunistic neoplasms

Individuals with HIV disease have been reported to have a higher prevalence of the AIDS-defining malignancies, Kaposi sarcoma, in situ and invasive cervical SCC, and non-Hodgkin lymphoma. However, HIV-infected individuals have also been noted to have an increased incidence of in situ and invasive anal

SCC, vulvar/vaginal SCC, Hodgkin lymphoma, primary liver cancer, lung cancer, melanoma, nonmelanoma skin cancers, oropharyngeal cancer, and leukemia. The etiology of the higherincidence of malignancy among HIV-infected individuals is likely multifactorial. Contributing factors may include diminished immune-mediated tumor surveillance, concomitant infection with oncogenic viruses (such as Epstein–Barr, HPV, and human herpesvirus-8), and associated behavior and lifestyle factors.

AIDS-related Kaposi's Sarcoma. Kaposi's sarcoma (KS) occurs throughout the course of HIV infection at CD4+ cell counts of anywhere from 0 to 800/μL. KS — rapidly progressive form in HIV-infected patients with early involvement of extracutaneous sites.

Clinically, AIDS KS differs from classical KS by its more rapid course and its rapid multifocal dissemination: early AIDS-KS lesions that appear as small oval violaceous macules develop rapidly into plaques and small nodules, which frequently are present at multiple locations at disease onset and have a tendency for rapid progression. In contrast to other variants of KS, the initial lesions in AIDS patients frequently develop on the face, especially on the nose, eyelids, ears, and on the trunk, where the lesions follow the relaxed skin tension lines. If untreated, disseminated AIDS-KS lesions may coalesce to form large plaques involving large parts of the face, the trunk, or the extremities leading to functional impairment. The oral mucosa is frequently involved and represents the initial site of a 10–15 % of AIDS KS. Involvement of the pharynx is not uncommon and may result in difficulty in eating, speaking, and breathing. The involvement of extracutaneous sites occurs more rapidly and more dramatically in patients with AIDS KS than those with classical KS. Besides the oral mucosa, KS lesions are most frequently found in the lymph nodes, the gastrointestinal tract, and the lungs. Although gastrointestinal KS is usually found when cutaneous lesions are present, exclusive gastrointestinal involvement is possible as is noted in transplantation-associated KS. KS lesions have a predilection for the stomach and duodenum and can cause bleeding and ileus. Although visible by gastroscopy, such lesions are under diagnosed histologically because they are located in the sub mucosa and may escape the biopsy forceps. Pulmonary KS can cause respiratory symptoms such as bronchospasm, coughing, and progressive respiratory insufficiency.

Potent antiretroviral therapy should be started inpatients with CD4+ cell counts less than 400/μL.

Non-Hodgkin lymphoma

HIV/AIDS-related NHL is the second most common cancer associated with HIV/AIDS, after Kaposi's sarcoma. There are many different subtypes of NHL. The most common subtypes of NHL in people with HIV/AIDS are primary central nervous system lymphoma (affecting the brain and spinal fluid), found in 20 % of all NHL cases in people with HIV/AIDS, primary effusion lymphoma (causing fluid to accumulate around the lungs or in the abdomen), or interme-

diate and high-grade lymphoma. More than 80 % of lymphomas in people with HIV/AIDS are high-grade B-cell lymphoma, while 10 to 15 % of lymphomas among people with cancer who do not have HIV/AIDS are of this type. It is estimated that between 4 and 10 % of people with HIV/AIDS develop NHL.

Other types of cancer. Other, less common types of cancer that may develop in people with HIV/AIDS are Hodgkin's lymphoma, angiosarcoma (a type of cancer that begins in the lining of the blood vessels), anal cancer, liver cancer, mouth cancer, throat cancer, lung cancer, testicular cancer, colorectal cancer, and multiple types of skin cancer including basal cell carcinoma, squamous cell carcinoma, and melanoma.

8.4. Cutaneous reactions to antiretroviral agents

The antiretroviral medications themselves can also have cutaneous effects. There are currently seven nucleoside reverse transcriptase inhibitors (NRTIs), one nucleotide reverse transcriptase inhibitor, four non-nucleoside reverse transcriptase inhibitors (NNRTIs), nine protease inhibitors (PIs), one fusion inhibitor, one chemokine receptor 5 (CCR5) inhibitor, one integrase inhibitor, and six combination medications that are currently approved by the FDA for the treatment of HIV and AIDS. Typically, patients are given a combination of three of these drugs from two or more classes (Table 3). While many of the drugs are well known to cause certain cutaneous reactions, it can also be challenging to determine which drug is the instigator when a patient is on multiple medications. In general, HIV patients are also ten-times more likely to develop reactions to medications than patients who do not have HIV.

Table 3 — Cutaneous reactions to antiretroviral agents

Nucleoside reverse transcriptase inhibitor	
Zidovudine	Mucocutaneous and nail hyperpigmentation, hypertrichosis, leucytodastic vasculitis, paronychia
Stavudine	Peripheral oedema
Didanosine	Leuocytoclastic vasculitis, SJS, papuloerythroderma of Ofuji, alopecia
Abacavir	Maculopapular eruption, urticaria, EM, Sweet`s syndrome
Lamivudine	Allergic contact dermatitis, paronychia
Emtricitabine	Palmoplantar hyperpigmentation
Zalcitabine	Mobilliform eruption, oral ulcer
Non – nudeoside reverse transcriptase inhibitor (NNRTI)	
Nevirapine	DRESS, SJS, AGEP
Efavirenz	Skin eruption (usually mild), leucocytoclastic vasculitis
Delavirdine	Diffuse erythema
Protease inhibitor (PI)	
PI (in general):	Lipodystrophy, hypersensitivity reaction, AGEP
Indinavir	Paronychia, porphyria,SJS,alopecia, curly hair, gynaecomastia
Nelfinavir	Morbilliform eruption, generalized urticaria
Saquinavir	Fixed drug eruption, SJS,DRESS, gynaecomastia

Ritonavir	Haematoma
Fusion inhibitor	
Enfuvirtide	Injection site reaction (induration, erythema, nodules, cysts)

Morbilliform Rash & Urticaria

The most common cutaneous reaction to antiviral drugs is a morbilliform rash that covers the trunk and proximal extremities. Usually the face is not involved. The rash presents as a pruritic erythematous maculopapular eruption approximately 2–10 days after initiation of the medication. Drugs used in the treatment of associated infections frequently cause this type of rash.

Urticarial drug reactions present as erythematous wheals due to dermal edema. Lesions may coalesce. They are often widespread, involving the face, trunk and extremities. Pruritus is frequently present. Acute urticaria is usually due to an IgE-mediated allergic reaction. Usually the reaction occurs shortly after the initiation of the antiviral medication. Most often, simply stopping the offending drug and administering systemic antihistamines will resolve the rash. If needed, oral corticosteroids can be used. Urticaria is also common during the first 8–10 days of treatment. Some success has been reported with a desensitization program.

Stevens–Johnson Syndrome & Toxic Epidermal Necrolysis. There is a great deal of debate over the definitions of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS manifests as diffuse erythematous macular target-like lesions with at least two mucosal sites of involvement. Less than 10 % of the body surface area (BSA) has epidermal detachment, which appears as flaccid bullae and erosions on examinations. There is often a prodrome of fever, malaise, headache, nausea and vomiting, and myalgias. TEN is defined as greater than 30 % of BSA involvement of epidermal detachment with diffuse erythematous macules. Epidermal detachment of 10–30 % with a macular rash is considered an overlap of SJS and TEN. A 30 % mortality rate with TEN makes early diagnosis imperative. TEN lesions often develop over 2–10 days, but an acute evolution over 24 h is also possible. Treatment, not surprisingly, includes stopping the suspected offending drug. Patients should be placed in the burn unit. Frequent culturing and monitoring for infection needs to be done since sepsis is a significant cause of mortality in these patients.

Drug Hypersensitivity Syndrome. Drug hypersensitivity syndrome consists of a rash, fever and eosinophilia. Visceral involvement of the liver, lungs, heart, kidney, thyroid and brain are possible. The rash starts as erythematous macules on the upper body and head and can lead to desquamation. The use of the offending drug should be immediately stopped.Topical and systemic corticosteroids are used in cases of DHS in non-HIV-infected patients.

Pigmentary Changes. Hyperpigmentation of the nails, mucosa, palms and soles is frequently observed with antiretroviral medications. Photosensitivity in HIV patients can also lead to hyperpigmentation, regardless of whether they are on HAART. The fingernails, toenails, or both can be affected. Zidovudine can lead to bluish nails in Hispanics and brownish-black nails in African–Americans

with transverse or longitudinal banding. Hyperpigmentation is dependent on the dose and is not permanent if the patient is taken off the drug. Emtricitabine can cause hyperpigmentation of the nail beds, palms and soles within weeks to months of starting therapy. Most commonly, this effect is seen in African–Americans. Hypertrichosis has also been reported with patients on zidovudine.

Injection Site Reaction. Enfuvirtide is administered as a subcutaneous injection, unlike miraviroc, which is taken orally. During trials, an injection site reaction occurred in 98 % of patients during the first week of treatment. Patients typically complain of some pain and may have erythema, induration, pruritus, nodules and cysts at the injection site. Having the patient rotate the sites of injection helps to decrease the injection site reaction.

Retinoid-like Reaction. Indinavir has been associated with multiple cutaneous manifestations such as SJS, DHS, EM, gynecomastia and acute porphyria, but it is probably best known for its retinoid-like manifestations. Paronychia with accompanying granulomatous lesions at the lateral nailfold, nonscarring alopecia, xerosis, cheilitis and ingrown toenails may be seen as manifestations of this. No risk factors for the development of retinoid-like manifestations have been found, however, the effects may be dose dependent.

Immune reconstitution syndrome (IRIS). Since the beginning of HAART, progressive flares of diseases associated with the immunodeficiency have been observed. These symptoms were provoked by recovering immune functions and are known as immune reconstitution inflammatory syndromes or IRIS. They start a few weeks after instituting antiretroviral therapy, after a decrease in HIV-RNA and a rise in the CD4 cell counts and are most pronounced when the CD4 counts are low at therapy onset (9). Dermatological manifestations can occur in an IRIS Kaposi's sarcoma, HSV/VZV infections, (HSV, herpes simplex virus; VZV, varicella zoster virus),in infections with human papilloma viruses (HPV), mollusca contagiosa, dermodicosis, mycobacterioses, sarcoidosis and eosinophilic folliculitis.Kaposi's sarcoma can spread rapidly in IRIS: an anogenital HSV infection can take asevere erosive course. The reactivation of herpes zoster occurs after 2 to 4 months withtypical clinical symptoms and in most cases is confined to one dermatome. Occasionally zoster sine herpete may develop. There is a risk of condylomata acuminata and Mollusca contagiosa spreading rapidly in immune reconstitution. Inflammatory demodex folliculitiscan develop shortly after the beginning of HAART (10). In subclinical atypicalmycobacteriosis, reactivation with granulomatous or necrotic cutaneous lesions occurs. Eosinophilic folliculitis may manifest with intolerable pruritus after HAART. Management of IRIS consists in treating the underlying disease and, where appropriate, providing adjuvant immunosuppressive therapy (body of evidence: B III). In individual cases HAART may have to be interrupted.

8.5. Clinical Considerations to prevention of dermatological manifestations of HIV infection

Patients should be encouraged to complete all medications as prescribed and to report any lesions that get worse or do not heal. Patients should be instructed to monitor for the development of bacterial super infection of lesions. Super infection, or secondary infection, occurs when a primary lesion becomes infected with a secondary organism, such as a varicella lesion that becomes infected with Staphylococcus aureus.

Patients should be instructed on how to maintain hygiene without producing dry skin. They should be instructed to avoid deodorant soaps and to use tepid water when bathing. Skin should be patted dry without rubbing, and moisturizer should be applied to the skin immediately after bathing. Bedridden patients should be turned every 2 h to avoid skin breakdown. Patients should keep their nails short and smooth and be discouraged from scratching lesions. Scratching can lead to open lesions and secondary infections. If open lesions are present, patients should be instructed to avoid contact with other areas of the skin to prevent spread of the infection.

9. INVESTIGATIONS

Laboratory tests in a patient suspected of having HIV infection.

- Tests for HIV-specific antibodies:

Screening tests

✓ *ELISA*
✓ *Rapid tests*
✓ *Supplemental tests*
✓ *Western Blot assay*
✓ Immunofluorescence test

- Tests to identify HIV (Confirmatory tests)

✓ *Viral isolation*
✓ *HIV-specific core antigen*
✓ *PCR for RNA copies*

10. SPECIFIC TREATMENT

Drugs available based on mechanism of action, two classes of antiretroviral drugs are available.

- Reverse transcriptase inhibitors: Which are of two types:

Nucleoside reverse transcriptase inhibitors (NRTIs).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs).

- Protease inhibitors.

Drug regimens

- Use of a single drug often results in resistance, so monotherapy should be avoided.
- Studies using two to three antiretroviral drugs have shown encouraging results (lowering of HIV-RNA to <50 copies/ml, i.e., not detectable).
- The use of highly active antiretroviral therapy (HAART) involves use of two NRTI along with one NNRTI or PI

Indications for antiretroviral therapy. Eradication of HIV infection cannot be achieved with currently available regimens because a pool of latently infected CD4+ cells is established very early in the infection and this persists in the body. However, antiretroviral therapy is helpful because it:

- Restores immune function.
- Reduces morbidity and mortality in HIV patients.
- Improves the quality of life.

THE PROGNOSIS in patients with untreated HIV infection is poor, with an overall mortality rate of more than 90 %. The average time from infection to death is 8–10 years, although individual variability ranges from less than 1 year to long-term non-progression. Many variables have been implicated in HIV's rate of progression, including CCR5-delta32 heterozygosity, mental health, concomitant drug or alcohol abuse, super infection with another HIV strain, nutrition, and age.

There is less evidence that treatment of HIV-2 infection slows progression, and certain antiretroviral medications (specifically the non-nucleoside–analogue

reverse-transcriptase inhibitors) are not effective against HIV-2. The HIV-1 viral-load assays are much less reliable at quantifying HIV-2, if they work at all. HIV-2 viral load assays have been developed, but none has been approved by the US Food and Drug Administration except as blood donor – screening tools.

Once infection has progressed to AIDS, the survival period is usually less than 2 years in untreated patients. Persons in whom the infection does not progress long-term may not develop AIDS for 15 years or longer, although many still exhibit laboratory evidence of CD4 T-cell decline or dysfunction.

The appropriate use of combination antiretroviral therapies and prophylaxis for opportunistic infections dramatically improves survival and greatly decreases the risk of secondary opportunistic infections. The risk of AIDS-associated lymphoma is not altered by antiviral therapy and, as such, has grown in prevalence among overall AIDS-defining conditions.

Sack off et al found that between 1999 and 2004, the HIV-related mortality rate in New York City decreased each year by approximately 50 deaths per 10,000 people with AIDS. The rate of non-HIV-related deaths also showed a decline, more modest but consistent, with about 7.5 fewer deaths per 10,000 people with AIDS per year.

Importantly, many researchers have consistently shown that the primary risk factor for infection affects mortality. For example, the mortality rate among intravenous drug users tends to be higher, whether related to HIV disease or non-HIV disease.

Overall, with the increasing use of antiretroviral therapy and the introduction of better antiviral regimens, survival with HIV infection has increased over time, although it is not yet equivalent to that in uninfected individuals.

In addition to the concern for new opportunistic infections, pre-existing infections can reactivate and cause significant disease in people with AIDS. The most important example on a global scale is that of tuberculosis, as reactivated tuberculosis can cause symptomatic disease with lower levels of reactivation.

Other important pathogens include cytomegalovirus, (which causes retinitis, pneumonitis, and colitis) and Pneumocystis jiroveci (formerly known as Pneumocystis carinii; the causative organism in Pneumocystis pneumonia). In immunocompetent hosts, these organisms are generally nonpathogenic, and asymptomatic infection is common (and in the case of cytomegalovirus infection, life-long).

Antiviral medications are associated with adverse effects and thus contribute to patient morbidity and mortality rates, especially because of the growing population of long-term survivors who are receiving combination antiviral therapy. In particular, protease inhibitors may cause lipid-profile abnormalities.

In a study of 6,036 HIV-infected patients who had achieved suppression of HIV with antiretroviral therapy, researchers found that the incidence of non-Hodgkin lymphoma remained high (171 per 100,000 person-years [PY]), far exceeding the rate of approximately 10 to 20 per 100,000 person-years reported in HIV-uninfected populations. The high incidence of NHL was observed even in patients with nadir CD4 cell count > 200 cells/μl (140 per 100,000 PY). After adjustment for older age, white race, male sex, HCV co infection, and time-varying CD4 cell count, the risk of NHL risk was higher when HIV viremia was above the limit of detection (50 copies/mL) in a dose-dependent manner.

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Учебное издание

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ВИЧ: КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ НА КОЖЕ И СЛИЗИСТЫХ ОБОЛОЧКАХ (на английской языке)

Учебно-методическое пособие для студентов 4 и 6 курсов факультета по подготовке специалистов для зарубежных стран медицинских вузов

Редактор ***Т. М. Кожемякина***
Компьютерная верстка ***С. Н. Козлович***

Подписано в печать 11.07.2017.
Формат 60×84$^{1}/_{16}$. Бумага офсетная 65 г/м^{2}. Гарнитура «Таймс».
Усл. печ. л. 2,33. Уч.-изд. л. 2,54. Тираж 90 экз. Заказ № 347.

Издатель и полиграфическое исполнение:
учреждение образования «Гомельский государственный медицинский университет».
Свидетельство о государственной регистрации издателя,
изготовителя, распространителя печатных изданий № 1/46 от 03.10.2013.
Ул. Ланге, 5, 246000, Гомель