HIV-AIDS

Prof. Dr. Gabor Ternak

Introduction

- The human immunodeficiency virus (HIV) was unknown until the early 1980's but since that time has infected millions of persons in a worldwide pandemic.
- The result of HIV infection is relentless destruction of the immune system leading to onset of the acquired immunodeficiency syndrome (AIDS).
- The AIDS epidemic has already resulted in the deaths of over half its victims.
- All HIV-infected persons are at risk for illness and death from opportunistic infectious and neoplastic complications because of the inevitable manifestations of AIDS.

Introduction

- The AIDS pandemic has evolved over time, with ***four main*** phases of evolution.
- In the initial phase, HIV emerged from endemic rural areas to spread among urban populations at an accelerating rate.
- In the second phase, dissemination occurred and involved definable risk groups.
- Behaviors in these risk groups, including sexual promiscuity and injection drug use, led to the third phase of escalation, which occurred through the 1980's.
- A fourth phase of stabilization has occurred in some regions such as western Europe, North America, and Australia, where control measures appear to be having a positive effect.

Introduction

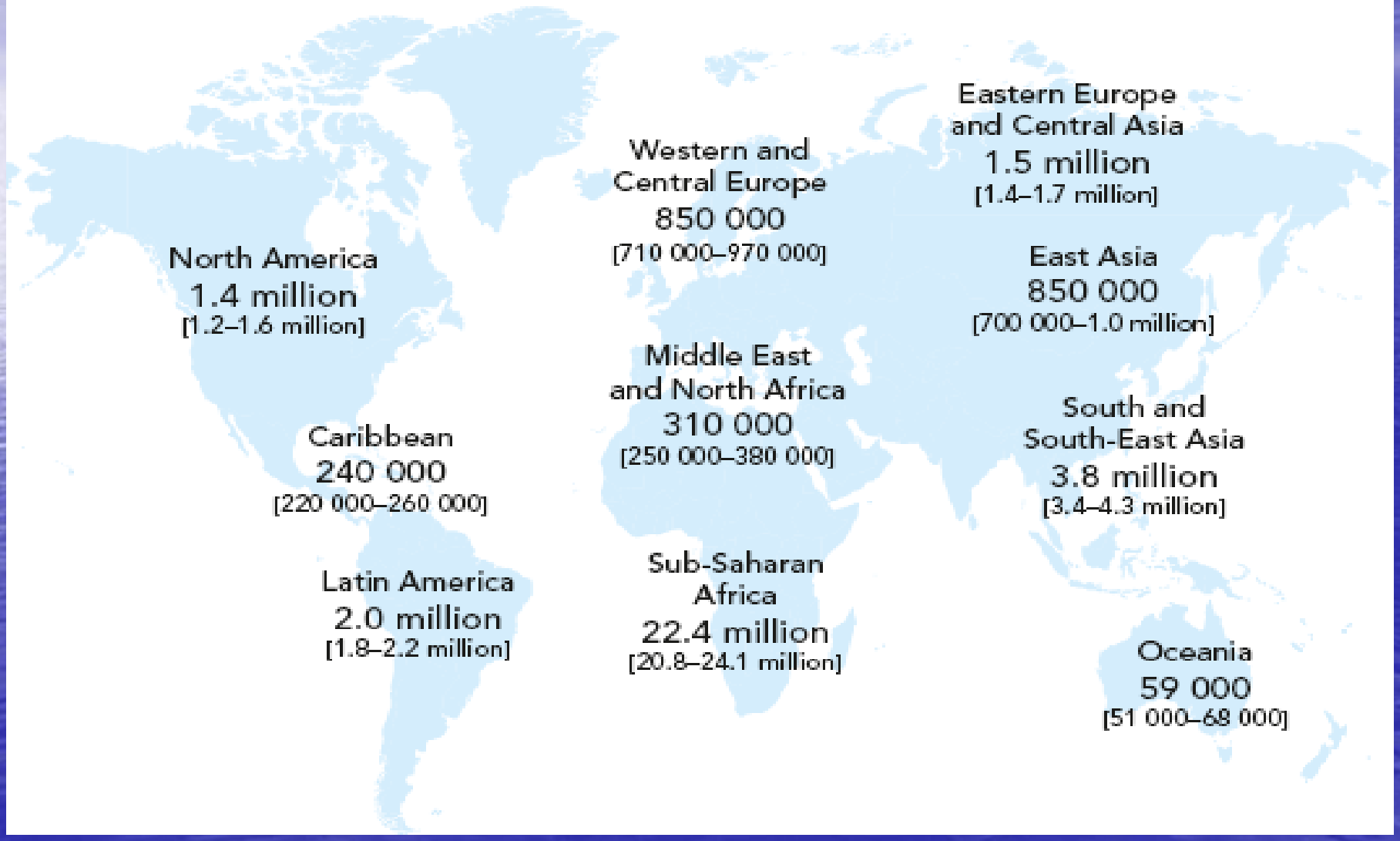
- The scope of the AIDS pandemic has already led to serious consequences, not only for health care systems of countries unable to cope with many AIDS victims, but also for the national economies of those countries because of the loss of young to middle aged who are economically most productive.
- At the start of the 21st century, 95% of new HIV infections and deaths occurred in developing nations, and two thirds of persons living with HIV infection resided in sub-Saharan Africa.
- The age group most affected, young persons from 15 to 24 years of age, accounted for 40% of new HIV infections.
- Worldwide, over half the victims of AIDS are women, and a consequence of this is perinatal infection resulting

Global summary of the AIDS epidemic

December 2008

Number of people living with HIV in 2008		
	Total	33.4 million [31.1 million–35.8 million]
	Adults	31.3 million [29.2 million–33.7 million]
	Women	15.7 million [14.2 million–17.2 million]
	Children under 15 years	2.1 million [1.2 million–2.9 million]
People newly infected with HIV in 2008		
	Total	2.7 million [2.4 million–3.0 million]
	Adults	2.3 million [2.0 million–2.5 million]
	Children under 15 years	430 000 [240 000–610 000]
AIDS-related deaths in 2008		
	Total	2.0 million [1.7 million–2.4 million]
	Adults	1.7 million [1.4 million–2.1 million]
	Children under 15 years	280 000 [150 000–410 000]

Adults and children estimated to be living with HIV, 2008



BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS 1.

- Human immunodeficiency virus (HIV) and its subtypes are ***retroviruses***, and they are the etiologic agents of AIDS.
- Human retroviruses were unknown until the 1980's, though animal retroviruses such as feline leukemia virus had been detected previously.
- HIV belongs to a large family of ribonucleic acid (RNA) lentiviruses that are characterized by association with diseases of immunosuppression or central nervous system involvement and with long incubation periods following infection before manifestations of illness become apparent.

BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS 2.

- Molecular epidemiologic data suggest that HIV type 1, the most common subtype of HIV that infects humans, has been derived from the simian immunodeficiency virus, called SIVcpz, of the *Pan troglodytes troglodytes subspecies of* chimpanzee.
- The lentivirus strain SIVcpz is highly homologous with HIV-1, and another form of simian immunodeficiency virus found in sooty mangabeys (SIVsm) has similarities as well and likely gave rise to HIV-2.
- There is molecular epidemiologic evidence for multiple crossspecies transmissions of SIV to humans occurring in the first half of the 20th century, probably through exposures to primate blood.

BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS 3.

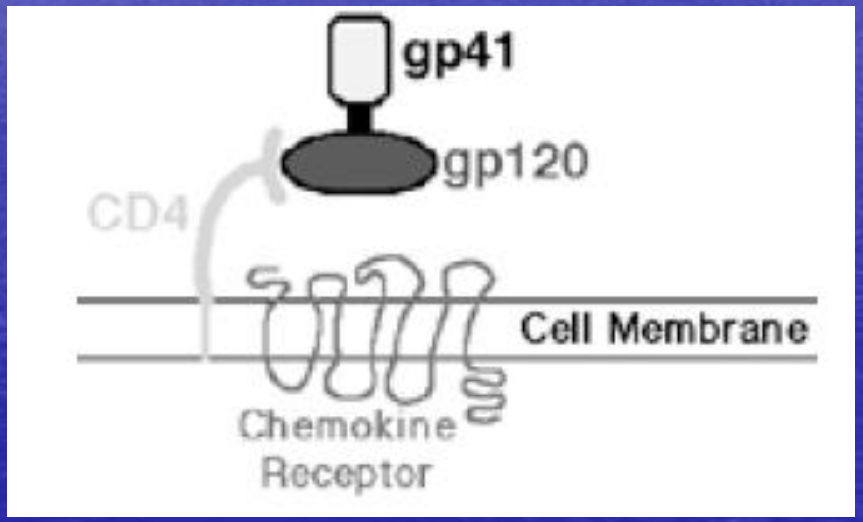
- The mature virus consists of a bar-shaped electron dense core containing the viral genome--two short strands of ribonucleic acid (RNA) about 9200 nucleotide bases long—along with the enzymes reverse transcriptase, protease, ribonuclease, and integrase, all encased in an outer lipid envelope derived from a host cell.
- This envelope has 72 surface projections, or spikes, containing an antigen, gp120 that aids in the binding of the virus to the target cells with CD4 receptors.
- A second glycoprotein, gp41, binds gp120 to the lipid envelope.
- By electron microscopy, the plasma membrane of an infected CD4+ lymphocyte exhibits budding virus particles approximately 100 nanometers in diameter.

BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS 4.

- The genome of HIV, similar to retroviruses in general, contains three major genes--*gag, pol, and env. These genes code for the major structural and functional components of HIV,*including envelope proteins and reverse transcriptase.
- The structural components encoded by *env include the envelope glycoproteins: outer envelope glycoprotein gp120 and transmembrane* glycoprotein gp41 derived from glycoprotein precursor gp160.
- Components encoded by the *gag* gene include core nucleocapsid proteins p55, p40, p24 (capsid, or "core" ntigen), p17 (matrix), and p7 (nucleocapsid); the important proteins encoded by *pol are the enzyme proteins p66 and* p51 (reverse transcriptase), p11 (protease), and p32 (integrase).

BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS 5.

- In addition to the CD4 receptor, a coreceptor known as a chemokine is required for HIV to infect cells.
- Chemokines are cell surface membrane-bound fusion-mediating molecules found on many cells.
- A diagrammatic representation of the relationship of the chemokine receptor to the CD4 receptor is shown below.



BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS 6.

- HIV entry into a host cell begins with gp120 binding to CD4 receptor, which induces a conformational change in gp120, exposing coreceptor binding sites.
- The V3 loop region of gp120 determines whether the host cell CCR5 or CXCR4 chemokine coreceptor will be engaged.
- After the chemokine coreceptor is engaged, the gp41 on the HIV surface undergoes a conformational change.
- The gp41 transmembrane coreceptor consists of HR1 and HR2 helical regions along with a fusion peptide.
- Conformational change in gp41 through HR1 and HR2 interaction leads to formation of a stable structure that allows fusion of HIV and host cell membranes, with a fusion pore through which the viral core enters the host cell.

BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS 7.

- The differences in chemokine coreceptors that are present on a cell also explain how different strains of HIV may infect cells selectively.
- There are strains of HIV known as T-tropic strains, which selectively interact with the CXCR4 ("X4") chemokine coreceptor to infect lymphocytes.
- The M-tropic strains of HIV interact with the CCR5 ("R5") chemokine coreceptor, and also CCR2 and CCR3, to infect macrophages and dendritic cells.
- CCR8 has been identified as a cofactor to permit infection by either T-cell tropic or by M-tropic strains of HIV.
- Dual tropic HIV strains have been identified that can use more than one chemokine coreceptor.

Epidemiology

- The transmission of HIV is a function of both where the virus appears in the body and how it is shed.
- HIV can be present in a variety of body fluids and secretions.
- The presence of HIV in genital secretions and in blood, and to a lesser extent breast milk, is significant for spread of HIV.
- However, the appearance of HIV in saliva, urine, tears, and sweat is of no major clinical or social importance, as transmission of HIV through these fluids does not routinely occur, primarily because of the low concentration of HIV in these fluids

Epidemiology

- Transmission of HIV can occur from male to male, male to female, and female to male.
- Female to female transmission remains extremely rare, though women with same-sex contact are also often bisexual and have additional risk factors for HIV infection.
- Even a partial modification of sexual behavior practices may help retard the rate and extent of HIV transmission.
- Amongst males having sex with males in the U.S. in the 1990's, the prevalence of HIV infection remained high at 7.2%, and the prevalence of unprotected anal intercourse over a prior 6 month period was 41%.

RISK GROUPS FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION

- Risk groups for HIV infection based upon behavior patterns that put persons at risk
- In countries such as the United States, through the first decade of the AIDS pandemic, about half of AIDS cases were reported in men having sex with men (homosexual or bisexual).
- The second largest risk group is comprised of injection drug users, accounting for 20% to 25% of reported AIDS cases in the United States.
- The percentage of HIV infections seen in heterosexual adults (marital sex, casual sex, commercial sex workers) has increased over time in developed nations.
- Pediatric AIDS in the United States and elsewhere is largely a function of maternal risk factors, particularly from injection drug use.
- In countries of sub-Saharan Africa and Asia, HIV infection is spread more widely in the population through heterosexually active urban adults.

NATURAL HISTORY OF HIV INFECTION

- On average, there is a period of 8 to 10 years from initial infection to clinical AIDS in adults, though AIDS may be manifested in less than two years or be delayed in onset beyond 10 years.
- About 10% of persons will rapidly progress to AIDS in 2 to 3 years following HIV infection, while about 10% have not progressed to AIDS even after 10 years.
- It is clear that the longer an individual is infected, the more likely the development of illness and subsequent death will be.
- Thus, HIV infection does not follow the pattern of more traditional viral diseases in which the risk of serious illness or death decreases with time.
- There has been no study to date that shows a failure of HIV-infected persons to evolve to clinical AIDS over time, though the speed at which this evolution occurs may vary, and a small number of HIV-infected persons will not progress to AIDS for many years.[

NATURAL HISTORY OF HIV INFECTION

- Primary HIV infection, also known as acute retroviral syndrome, may produce a mild and self-limited disease in 50 to 90% of persons infected with HIV, regardless of the mode of transmission.
- The time from mucosal infection to viremia is about 4 to 11 days.
- The time from exposure to development of symptoms averages 2 to 6 weeks.
- The symptoms may persist for 1 to 2 weeks, after which symptoms subside over 1 to 2 months.
- Prospective studies of acute HIV infections show that fever, fatigue, arthralgia or myalgia, lymphadenopathy, pharyngitis, diffuse erythematous macular or mixed maculopapular rash (often involving the trunk), diarrhea, nausea or vomiting, weight loss, night sweats, mucocutaneous ulcerations, and headache are the most common symptoms seen with acute HIV infection.

NATURAL HISTORY OF HIV INFECTION

- An acute meningoencephalitis may be seen in some recent infections and appear as an "aseptic meningitis."
- The symptoms of acute HIV infection resemble a flu-like or an infectious mononucleosis-like syndrome.
- Primary HIV infection is not life-threatening.
- Primary HIV infection in children is usually accompanied by one or more of the following: mononucleosis-like syndrome, dermatitis, or generalized lymphadenopathy

NATURAL HISTORY OF HIV INFECTION

- During this acute phase of HIV infection, there is active viral replication, particularly in CD4 lymphocytes, and a marked HIV viremia.
- This peripheral blood viremia is at least as high as 50,000 copies/mL and often in the range of 1,000,000 to 10,000,000 copies/mL of HIV-1 RNA.
- High titers of cytopathic HIV are detectable in the blood so that the p24 antigen test is usually (but not always) positive, while HIV antibody tests (such as enzyme immunoassay) are often negative in the first three weeks.
- The viremia is greater in persons whose primary HIV infection is symptomatic

NATURAL HISTORY OF HIV INFECTION

- The HIV infection then becomes clinically "latent."
- During this phase, there is little or no viral replication detectable in peripheral blood mononuclear cells and little or no culturable virus in peripheral blood.
- The CD4 lymphocyte count remains moderately decreased.
- However, the immune response to HIV is insufficient to prevent continued viral replication within lymphoid tissues.
- Though lymph nodes may not become enlarged and their architecture is maintained, active viral replication continues.
- Tests for HIV antibody will remain positive during this time but p24 antigen tests are usually negative.
- There is no evidence to suggest that seroreversion, or loss of antibody, occurs in HIV-infected persons.[

NATURAL HISTORY OF HIV INFECTION

- Though no clinical signs and symptoms are apparent, the immune system, primarily through depletion of CD4 lymphocytes, deteriorates.
- Not only CD4 cells are lost, but also cytotoxic CD8 cells, and the most avid ones in particular, leading to exhaustion of controlling T cell responses. Levels of cytokines driving lymphoid proliferation, such as IL-2, decrease.
- The virus continues to replicate in lymphoid organs, despite a low level or lack of viremia.
- HIV can be found trapped extracellularly in the follicular dendritic cell network of germinal centers in lymphoid tissues or intracellularly as either latent or replicating virus in mononuclear cells.
- The period of clinical latency with HIV infection, when infected persons appear in good health, can be variable--

NATURAL HISTORY OF HIV INFECTION

- Emergence of HIV infection from clinical latency is marked by a decline in the CD4 lymphocyte count and an increase in viremia.
- Replication of HIV increases as the infection progresses.
- There is loss of normal lymph node architecture as the immune system fails.
- Before serologic and immunologic markers for HIV infection became available, clinical criteria established emergence from latency by development of generalized lymphadenopathy.
- This condition, described by the term persistent generalized lymphadenopathy (PGL), is not life threatening.

NATURAL HISTORY OF HIV INFECTION

- Another phase of HIV infection described clinically but no longer commonly diagnosed in practice, is the condition known as AIDS-related complex (ARC), which is not necessarily preceded by PGL.
- ARC lacks only the opportunistic infections and neoplasms, which define AIDS.
- ARC patients usually show symptoms of fatigue, weight loss, and night sweats, along with superficial fungal infections of the mouth (oral thrush) and fingernails and toenails (onychomycosis).
- It is uncommon for HIV-infected persons to die at the stage of ARC.
- The staging of HIV disease progression through the use of CD4 lymphocyte counts and plasma HIV-1 RNA levels has made use of the terms PGL and ARC obsolete.

NATURAL HISTORY OF HIV INFECTION

- The stage of clinical AIDS that is reached years after initial infection is marked by the appearance of one or more of the typical opportunistic infections or neoplasms diagnostic of AIDS by definitional criteria.
- The progression to clinical AIDS is also marked by the appearance of syncytia-forming (SI) variants of HIV in about half of HIV-infected patients.
- These SI viral variants, derived from non-syncytia-forming (NSI) variants, have greater CD4+ cell tropism and are associated with more rapid CD4+ cell decline.
- The SI variants typically arise in association with a peripheral blood CD4 lymphocyte count between 400 and 500/μL, prior to the onset of clinical AIDS. However, appearance of the SI phenotype of HIV is a marker for progression to AIDS that is independent of CD4+ cell counts.

PROGRESSION OF HIV INFECTION

- The development of signs and symptoms of AIDS typically parallels laboratory testing for CD4 lymphocytes.
- A decrease in the total CD4 lymphocyte count below 500/µL presages the development of clinical AIDS, and a drop below 200/µL not only defines AIDS, but also indicates a high probability for the development of AIDS-related opportunistic infections and/or neoplasms.
- The risk for death from HIV infection above the 200/µL CD4 level is low.

PROGRESSION OF HIV INFECTION

- Persons with HIV infection can be categorized as typical progressors, rapid progressors, and nonprogressors toward AIDS.
- The typical progressors average 8 to 10 years of "latent" HIV infection before the appearance of clinical AIDS.
- These persons typically have a fall in HIV viremia following acute infection.
- They maintain nonsyncytium-inducing HIV variants that replicate slowly over time, until more rapidly replicating variants develop during progression to AIDS.
- About 10% of HIV-infected persons rapidly progress to AIDS in only 2 to 3 years following initial infection.
- These persons have a high viral load during acute HIV infection that does not fall to the levels seen with typical progressors.

Symptoms 1.

Major symptoms:

- **Slimming down, which exceeds the 10% of the original body weight**
- **Chronic diarrhea (over 1 month)**
- **Permanent fever (over 1 month)**

Minor symptoms

- **Permanent cough (over 1 month)**
- **Generalised pruritus**
- **Generalised lymphadenopathy**
- **Recurrent varicella-zoster**
- **Chronic, progressive herpes simplex infection**
- **Oropharyngeal candidiasis**

Nosocomial and coinfections, tumors 1.

Bacterial infections (multiplex, or recurrent)
Candidiasis: Bronhii, or (and) lungs
Candidiasis: oesophagus
Cervical carcinoma, invasiv +
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic, intestinal(> 1 month)
Cytomegalovirus infections (besides the liver, spleen, lymphglands involved)
Cytomegalovirus retinitis (blindness)
Encephalopathy, related to HIV infection

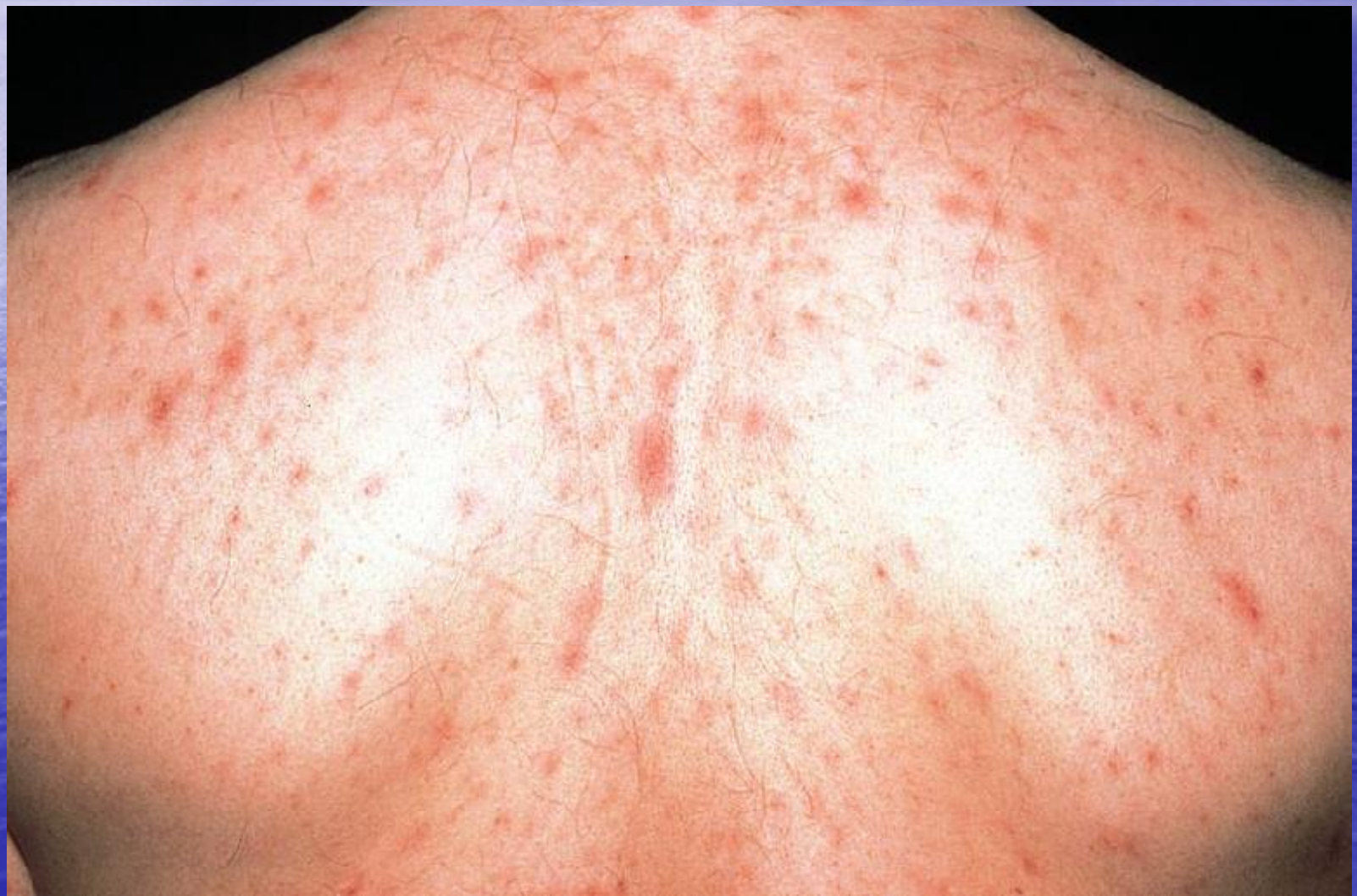
Nosocomial, and coinfections, tumors 2.

1. Herpes simplex infections, chronic ulcers(>1 month); vagy bronchitis, pneumonitis, oesophagitis
2. Histoplasmosis, disseminated, or extrapulmonary Isoporiasis, chronic, intestinal(> 1 month)
3. Kaposi's sarcoma
4. Lymphoid interstitial pneumonia and/or pneumonal lymphoid hyperplasia
5. Lymphoma, Burkitt's (or similar)
6. Lymphoma, immunoblastic (or similar)
7. Lymphoma, primer, cerebral manifestation
8. *Mycobacterium avium-intracellulare* complex,
9. *Myobacterium kansasii,* disseminated or extrapulmonary

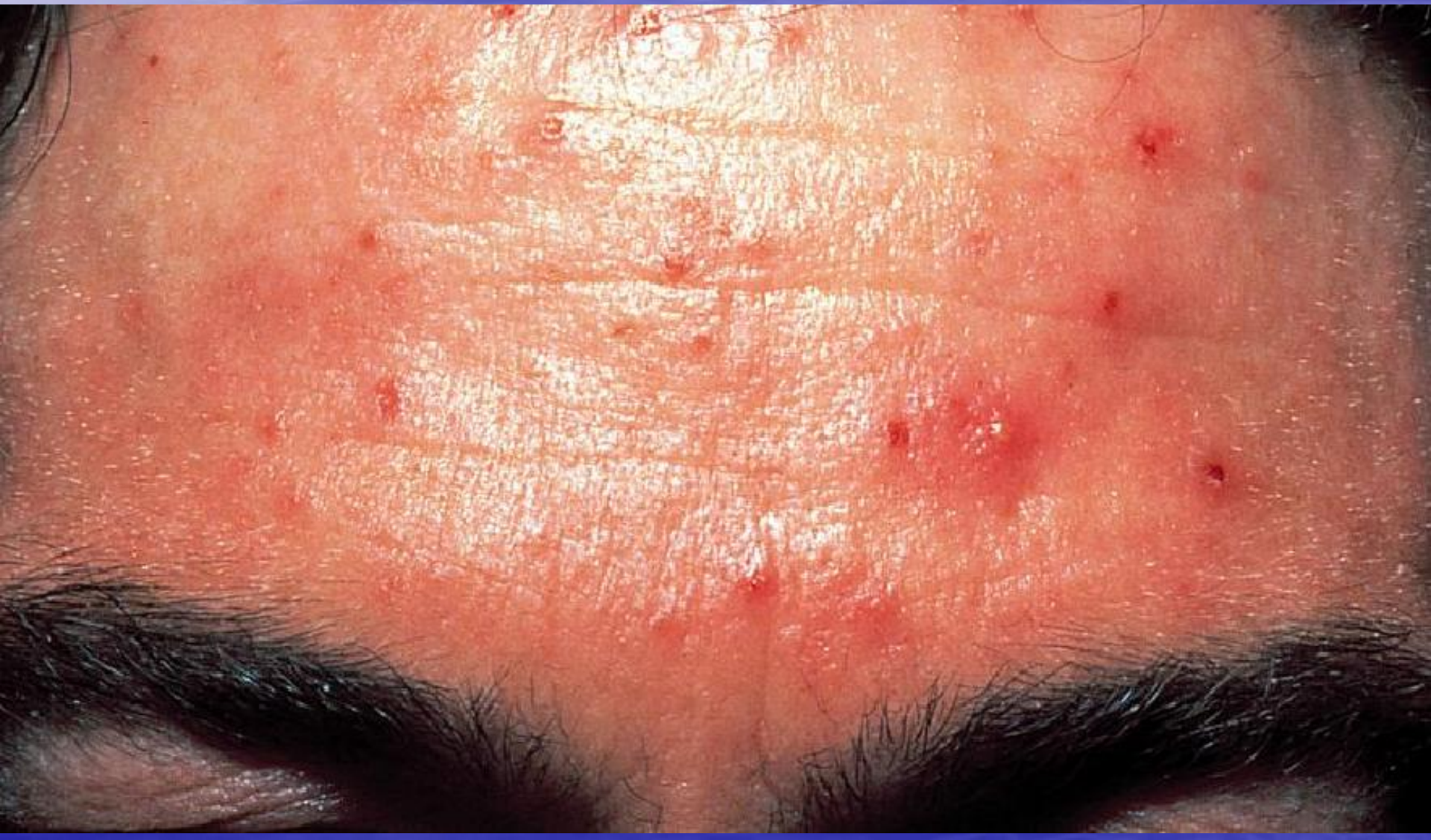
Nosocomial, and coinfections, tumors 3.

1. *Mycobacterium tuberculosis,* anywhere (pulomonary or extrapulmonary)
2. *Mycobacterium,* (other species), disseminated, orpulmonary)
3. *Pneumocystis carinii* pneumonia
4. Pneumonia, recurring
5. Progressive multifocal leukoencephalopathy
6. *Salmonella* septicemia, recurrent
7. Toxoplasmosis, cerebral manifestations
8. "Wasting syndrome"

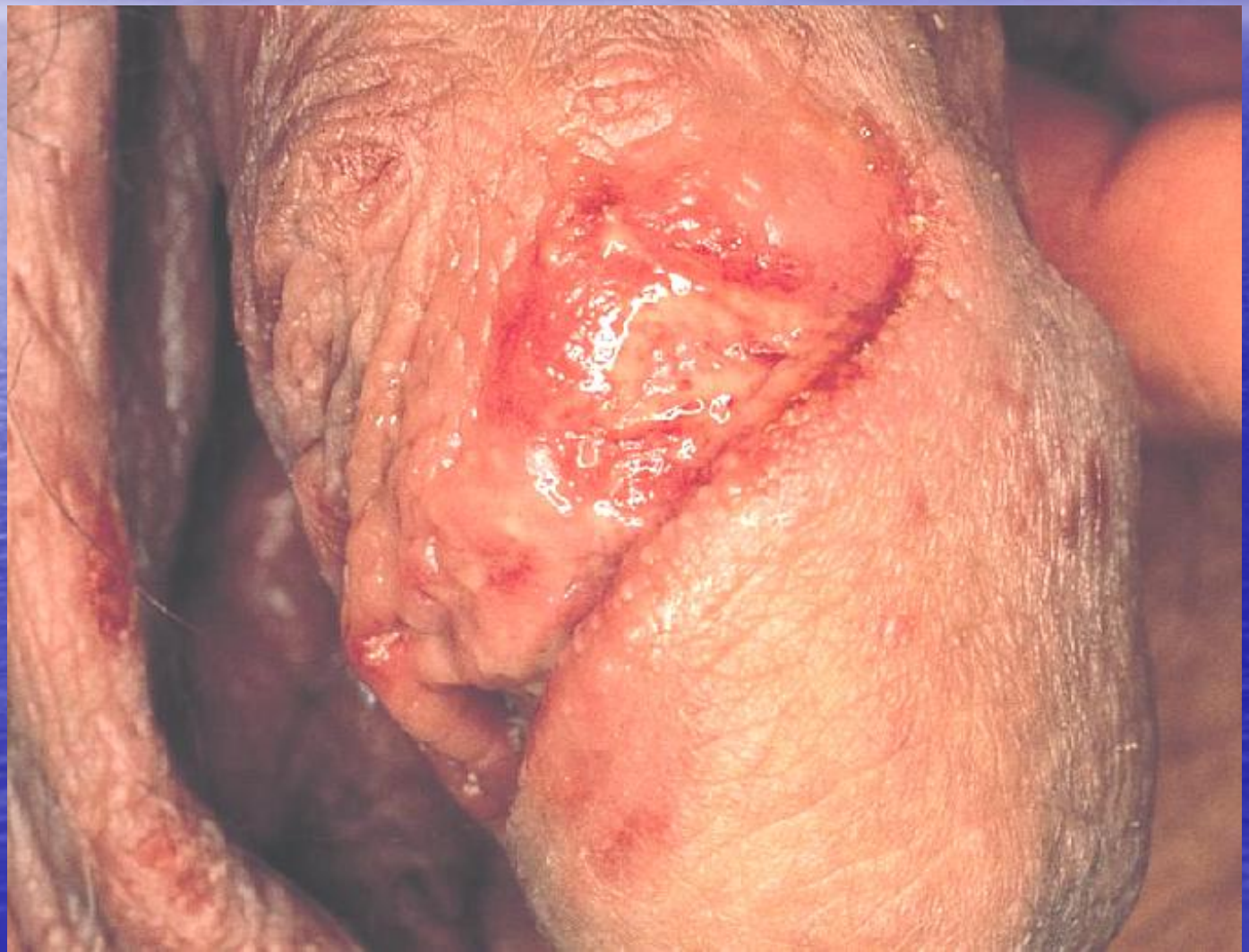
Maculopapular rash in acute HIV infection



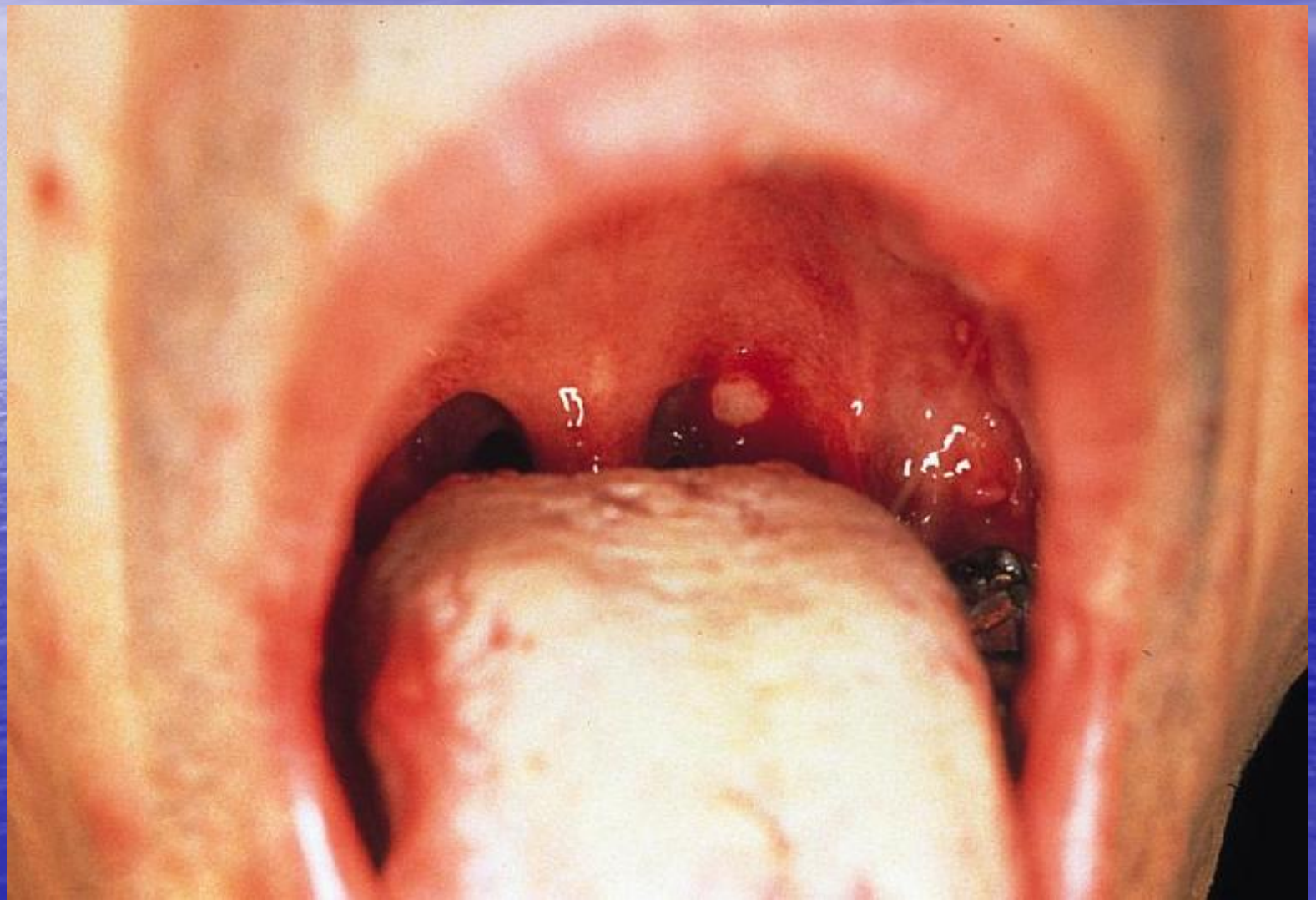
Acneiform skin lesion in HIV infection



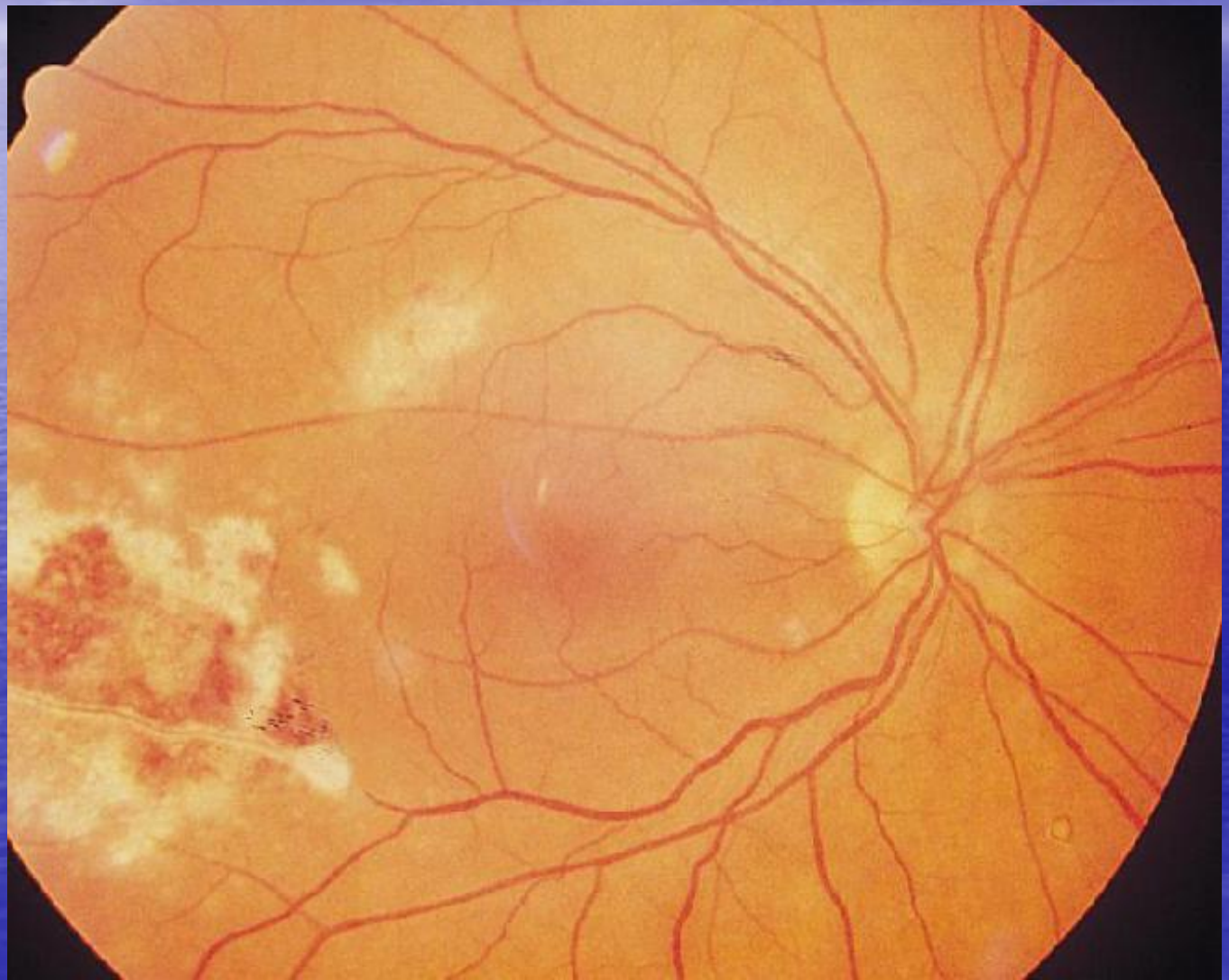
Penis ulcer in primary HIV infection



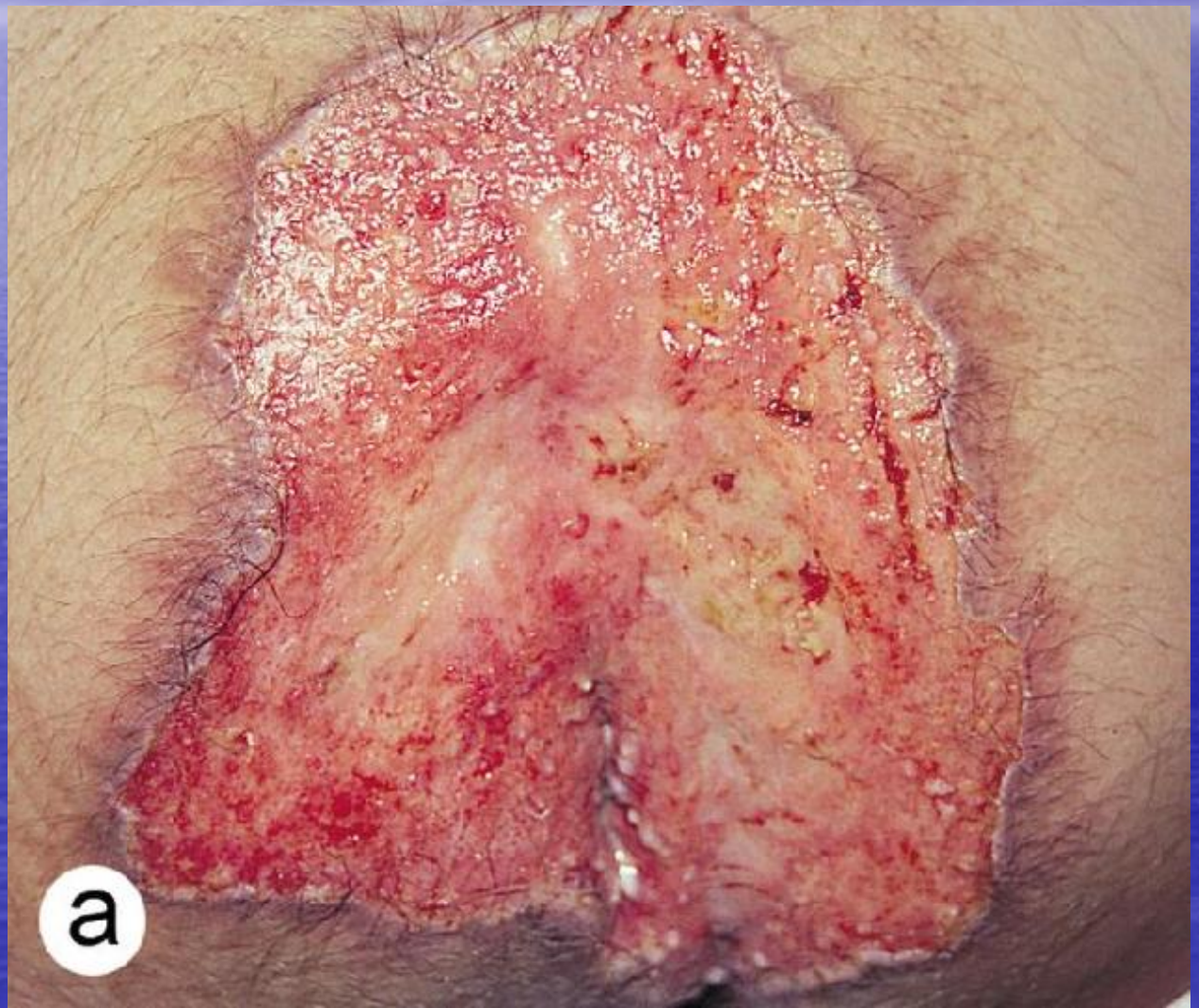
Mucosal ulceration in primary HIV infection



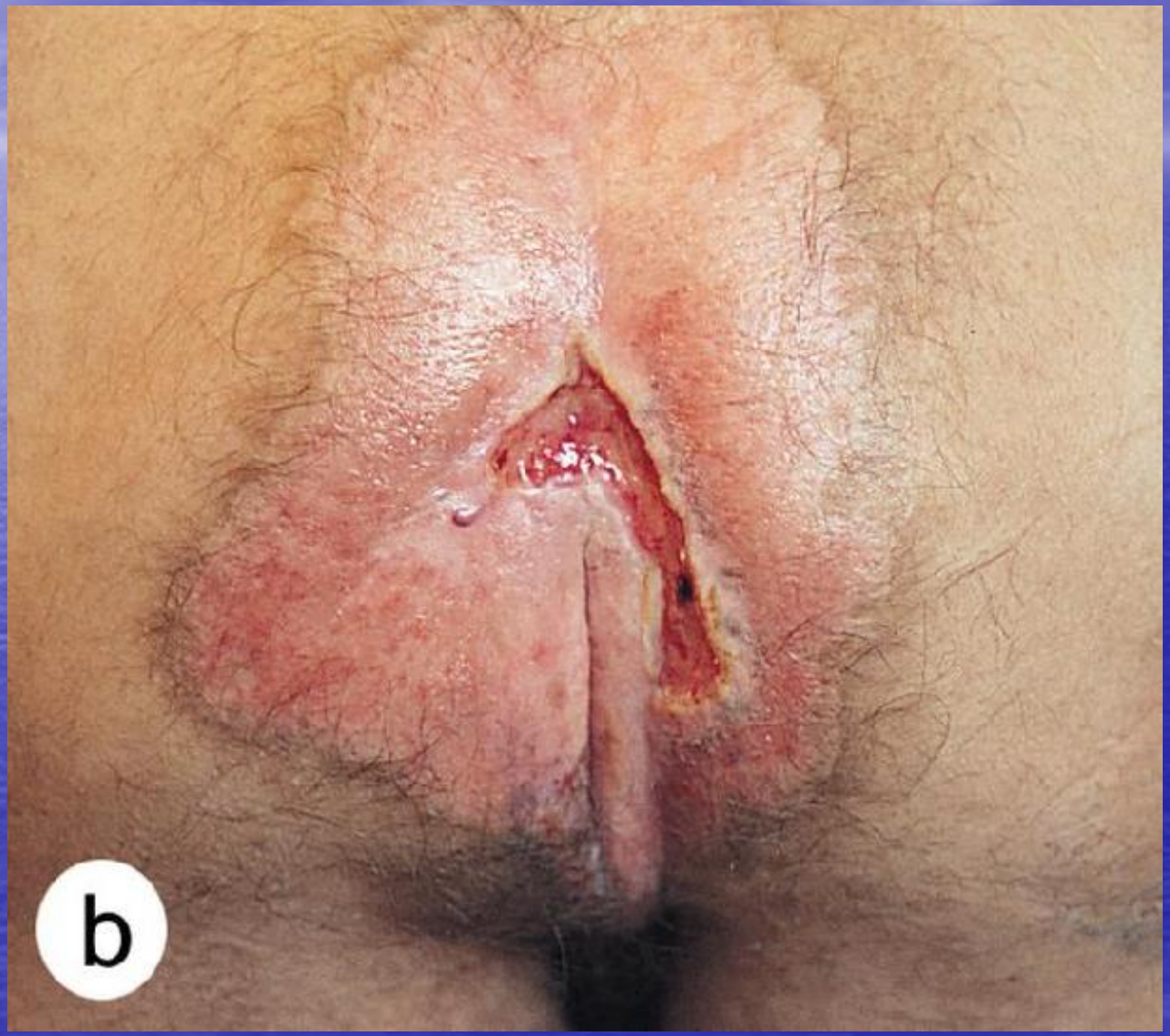
CMV retinitis



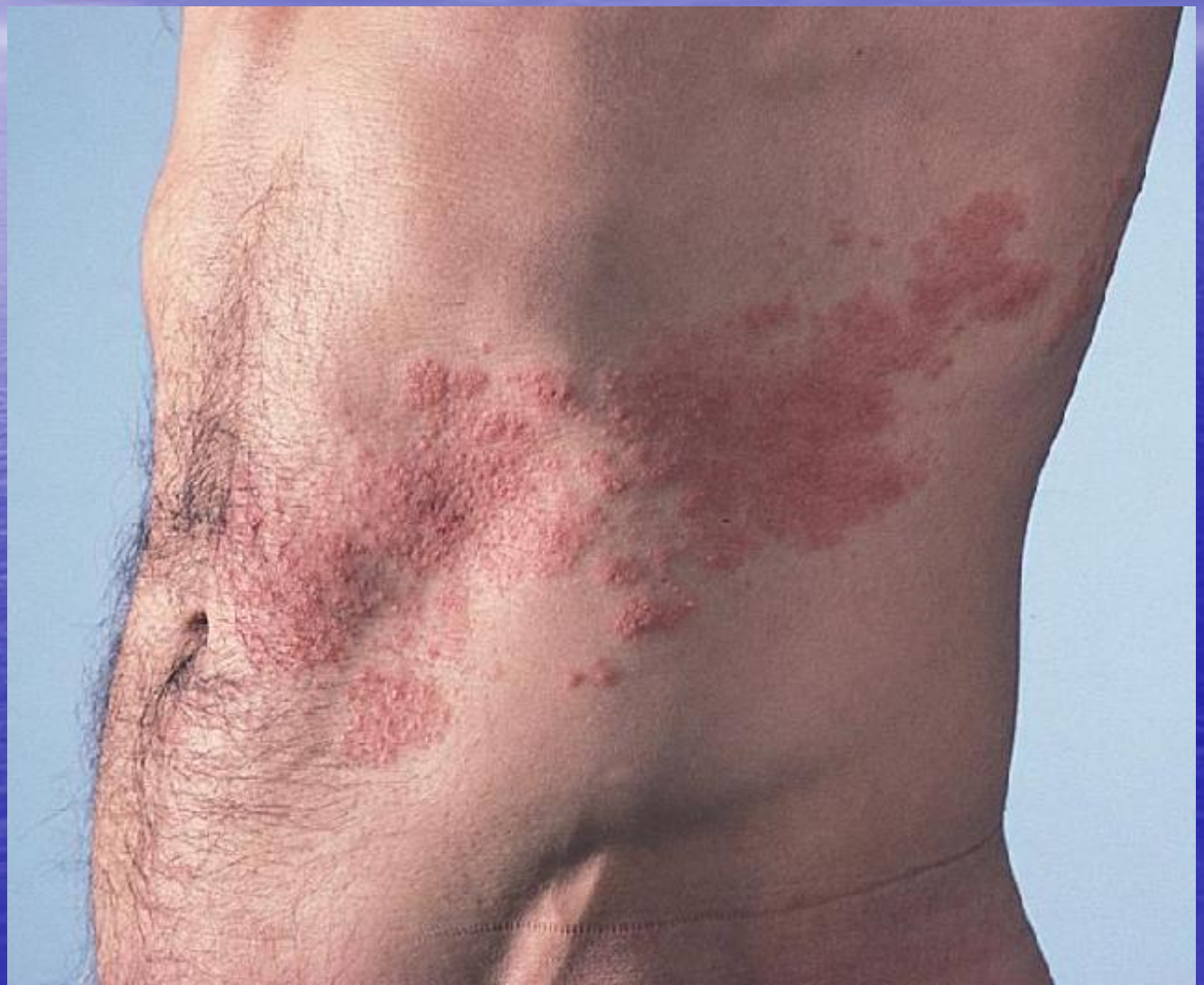
Perianal acyclovir resistent HSV2 infection



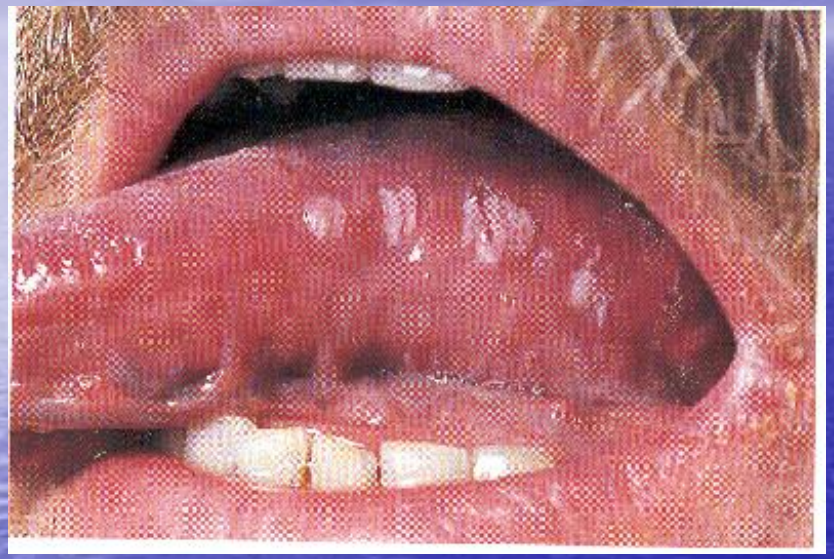
The healing of the previous infection after Foscarnet and HAART treatment

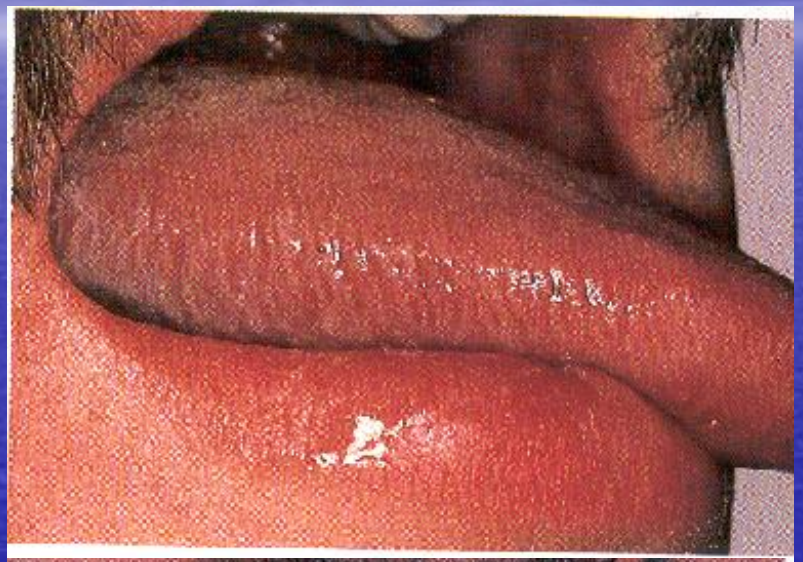


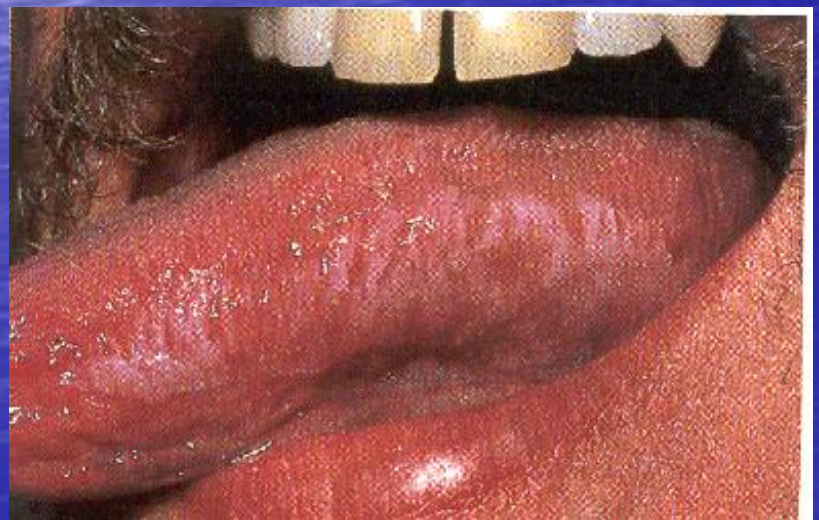
Zoster infection in AIDS

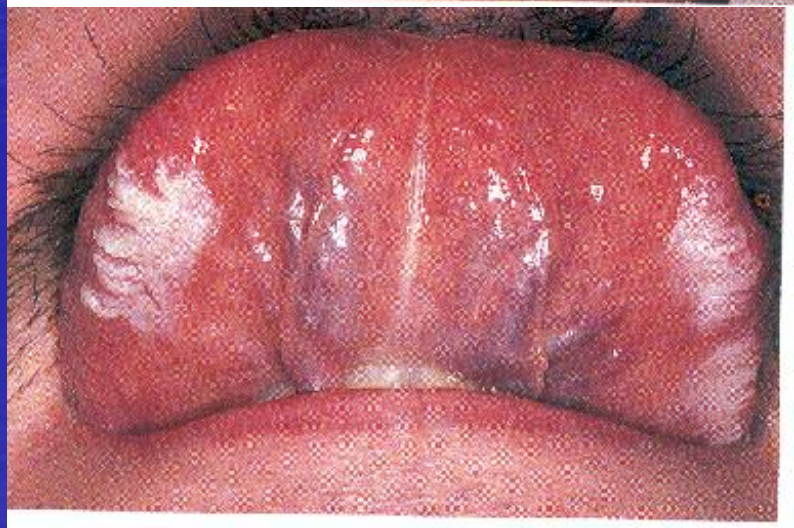


Hairy leukoplakia

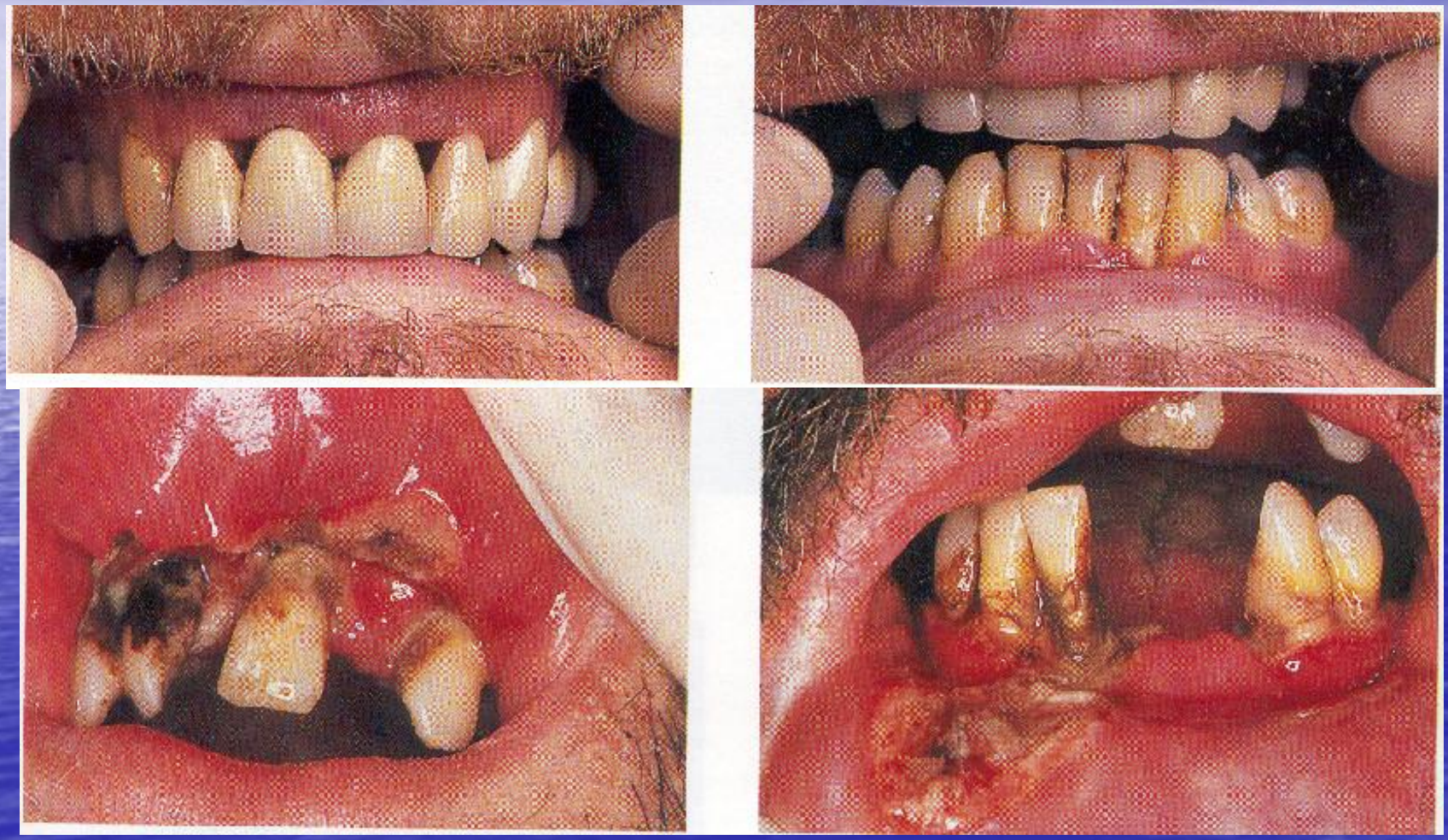




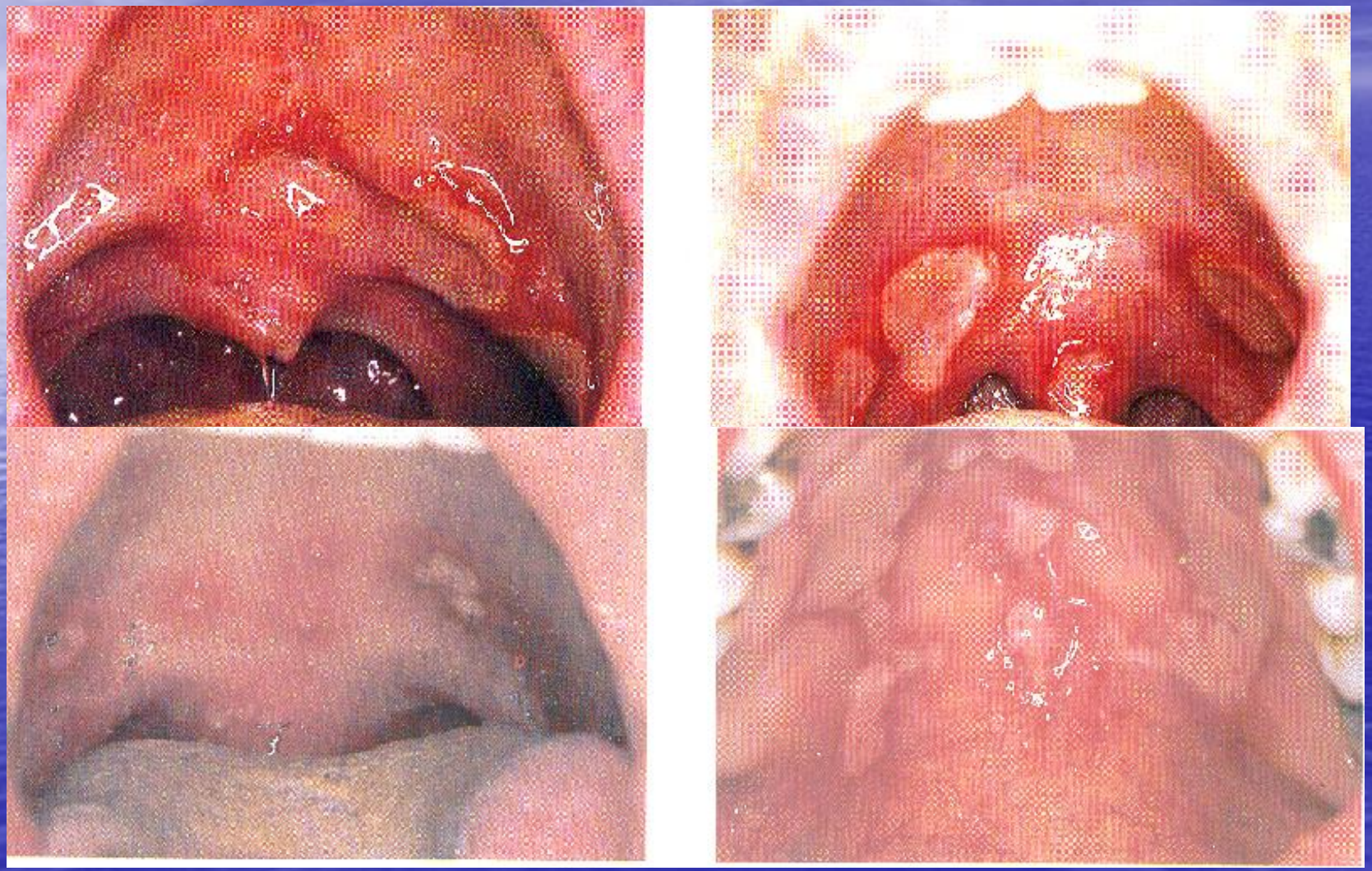




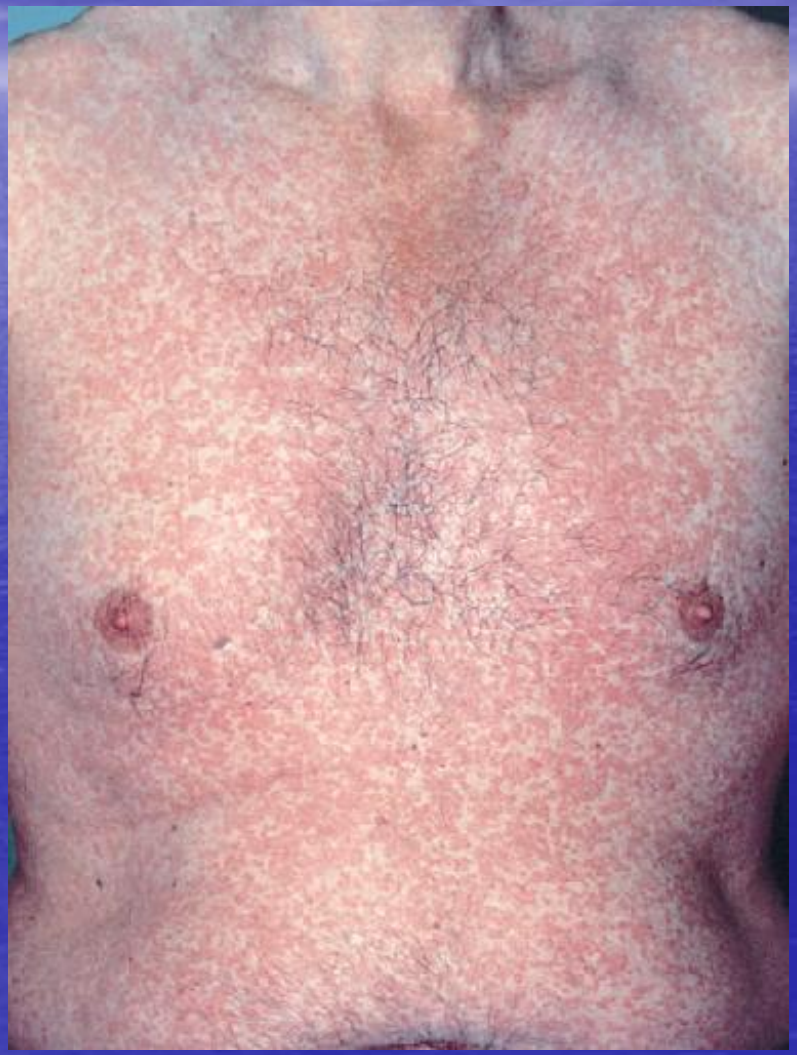
Gingivitis in AIDS



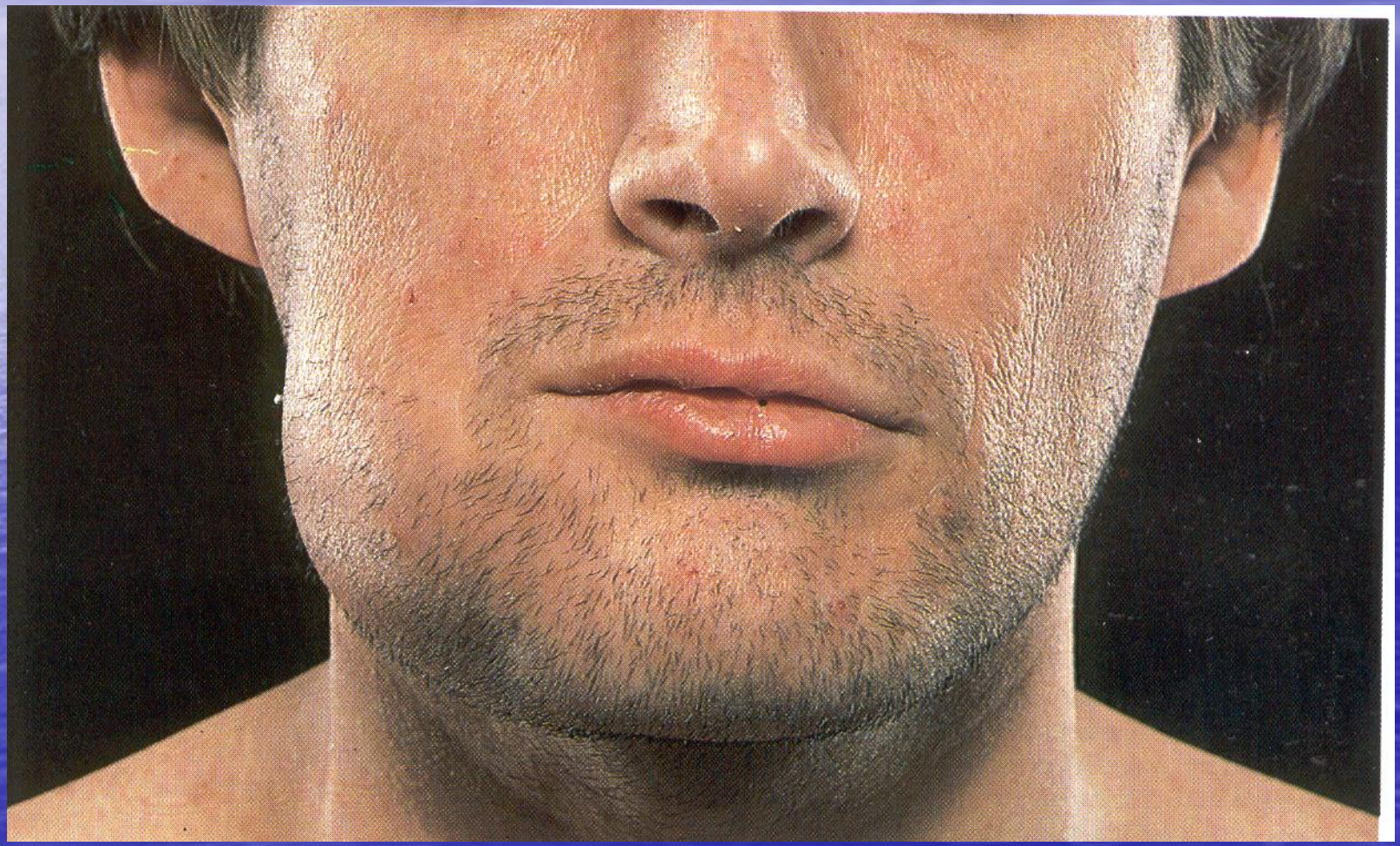
Pharyngeal ulceration in AIDS



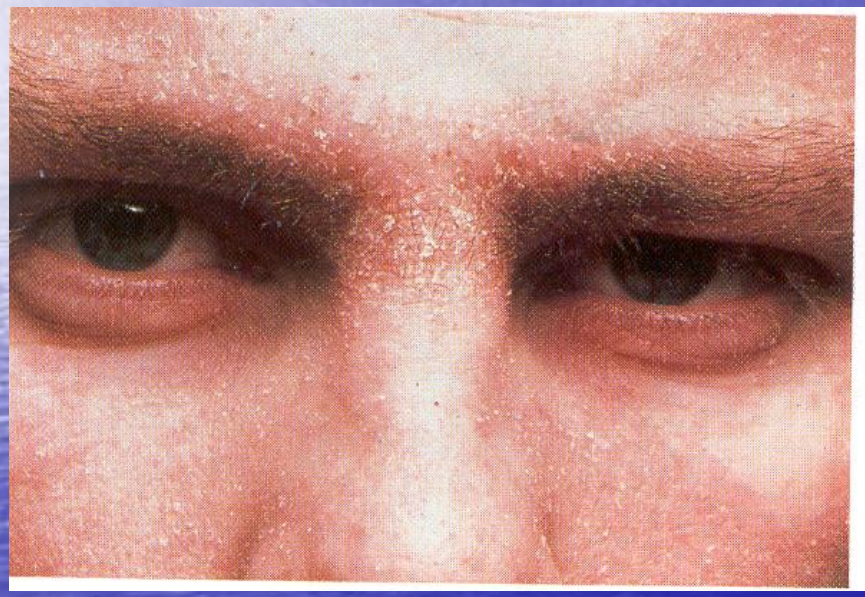
Morbilliform drug eruption in AIDS

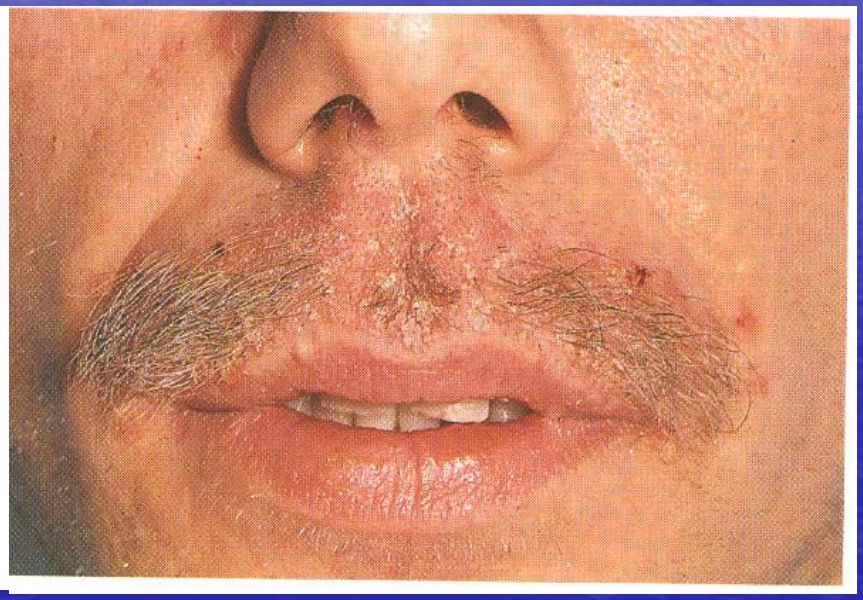


Dental abscess in AIDS

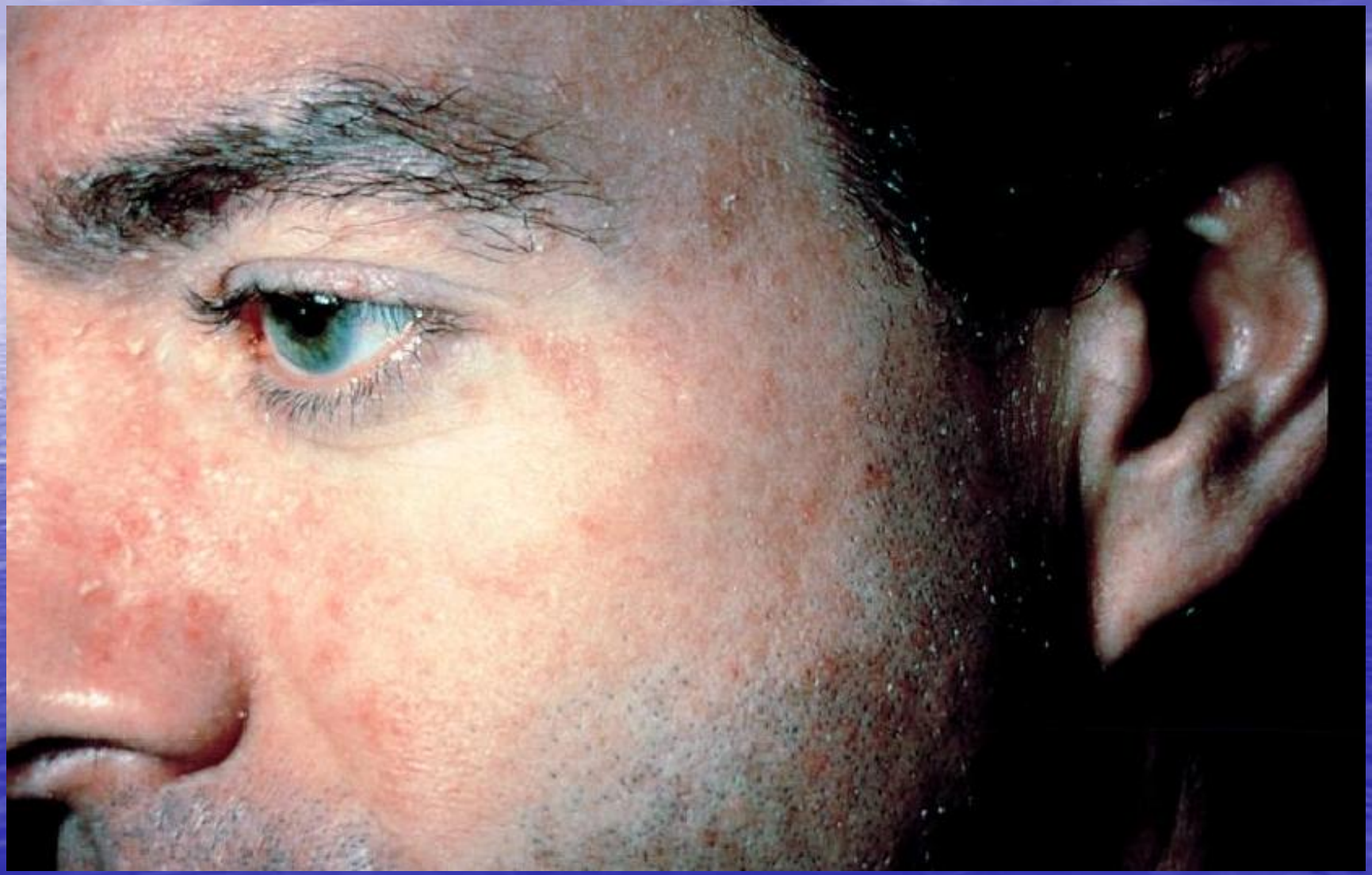


Seborrhoic skin changes in AIDS

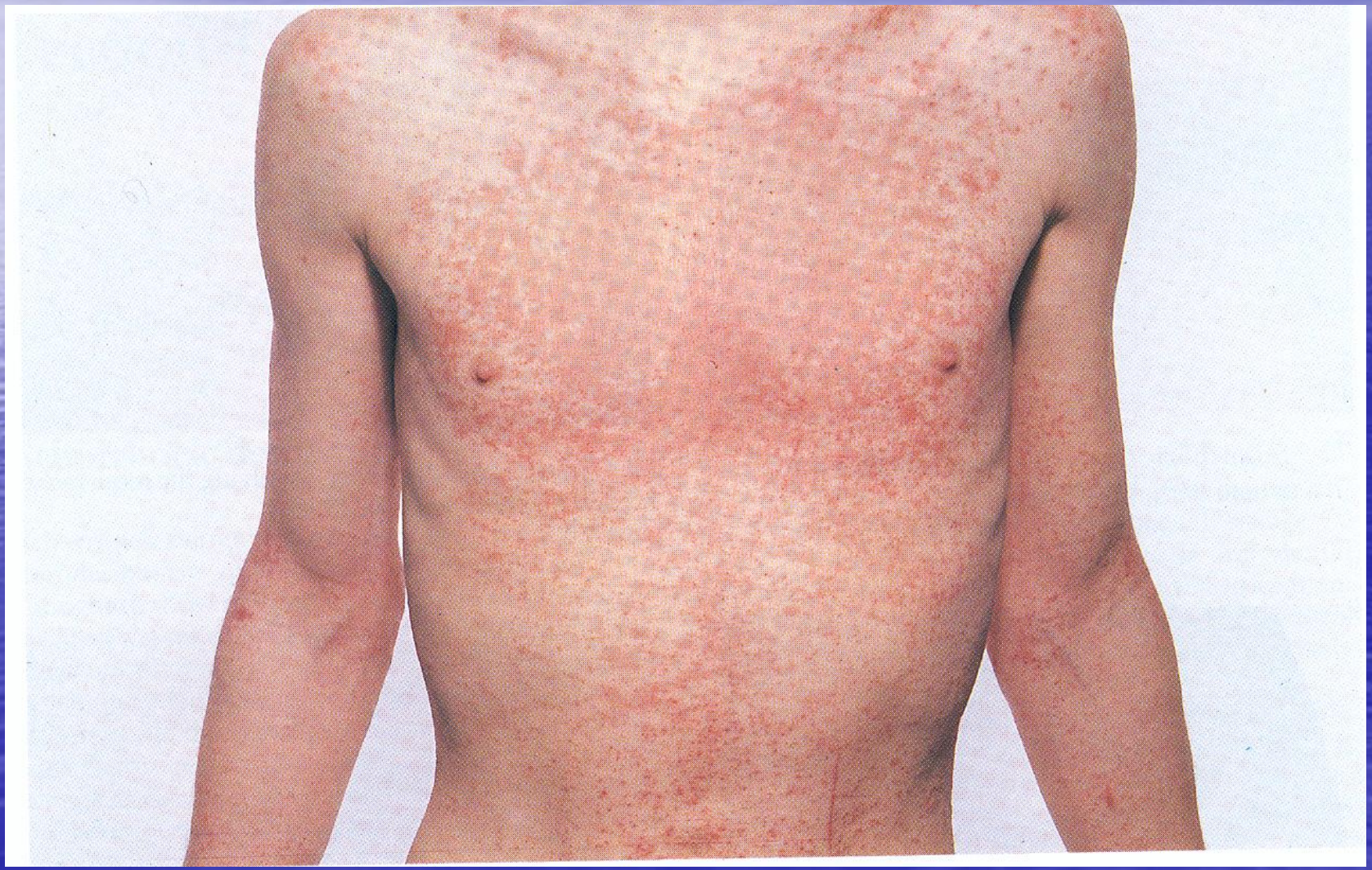




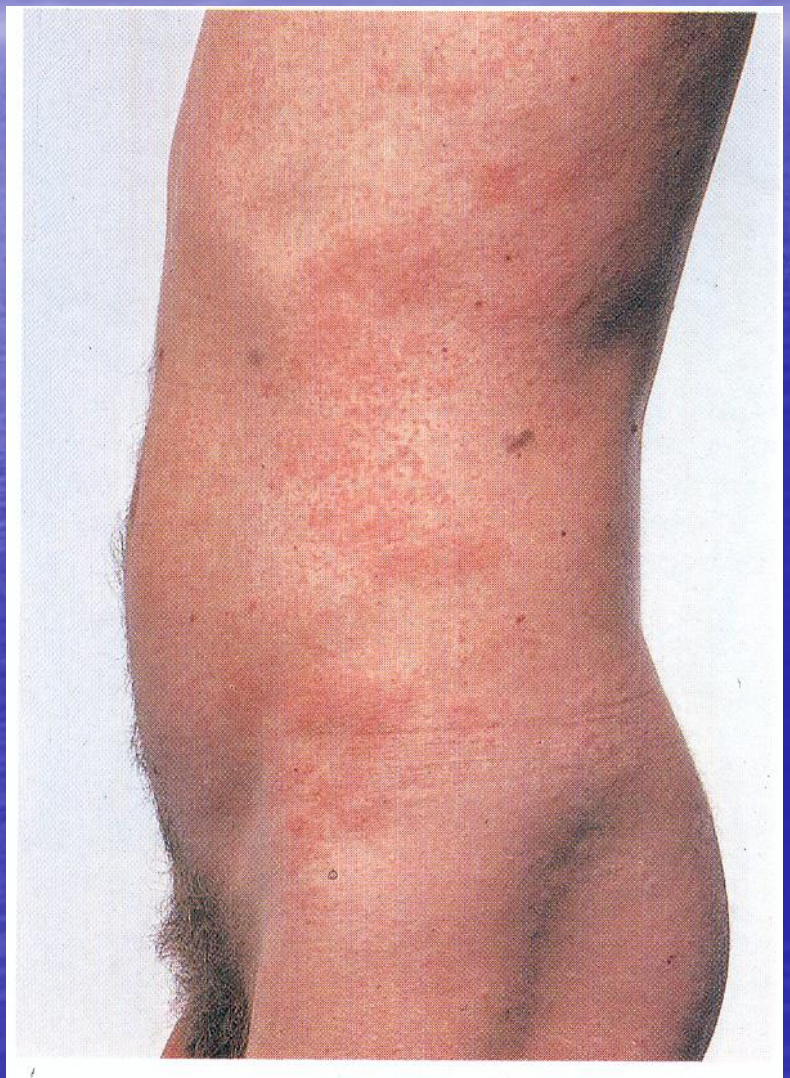
Seborrhoic dermatitis



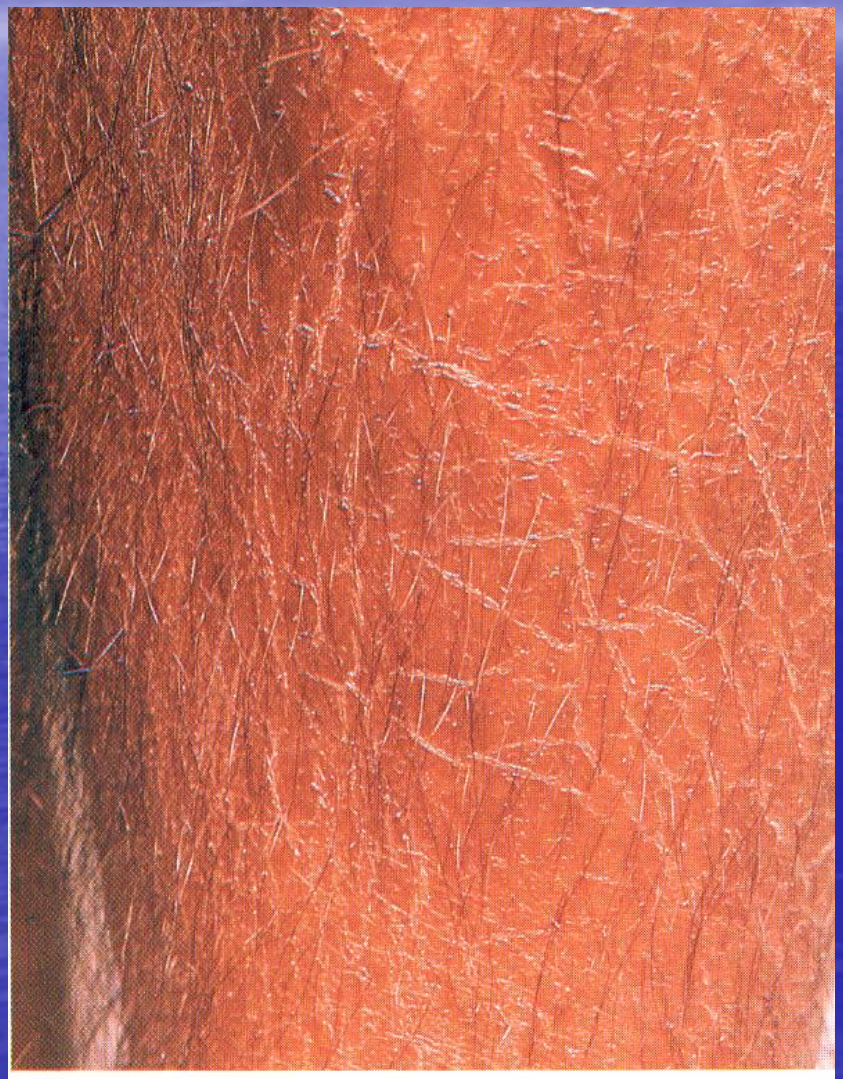
Seborrhoic skin changes in AIDS



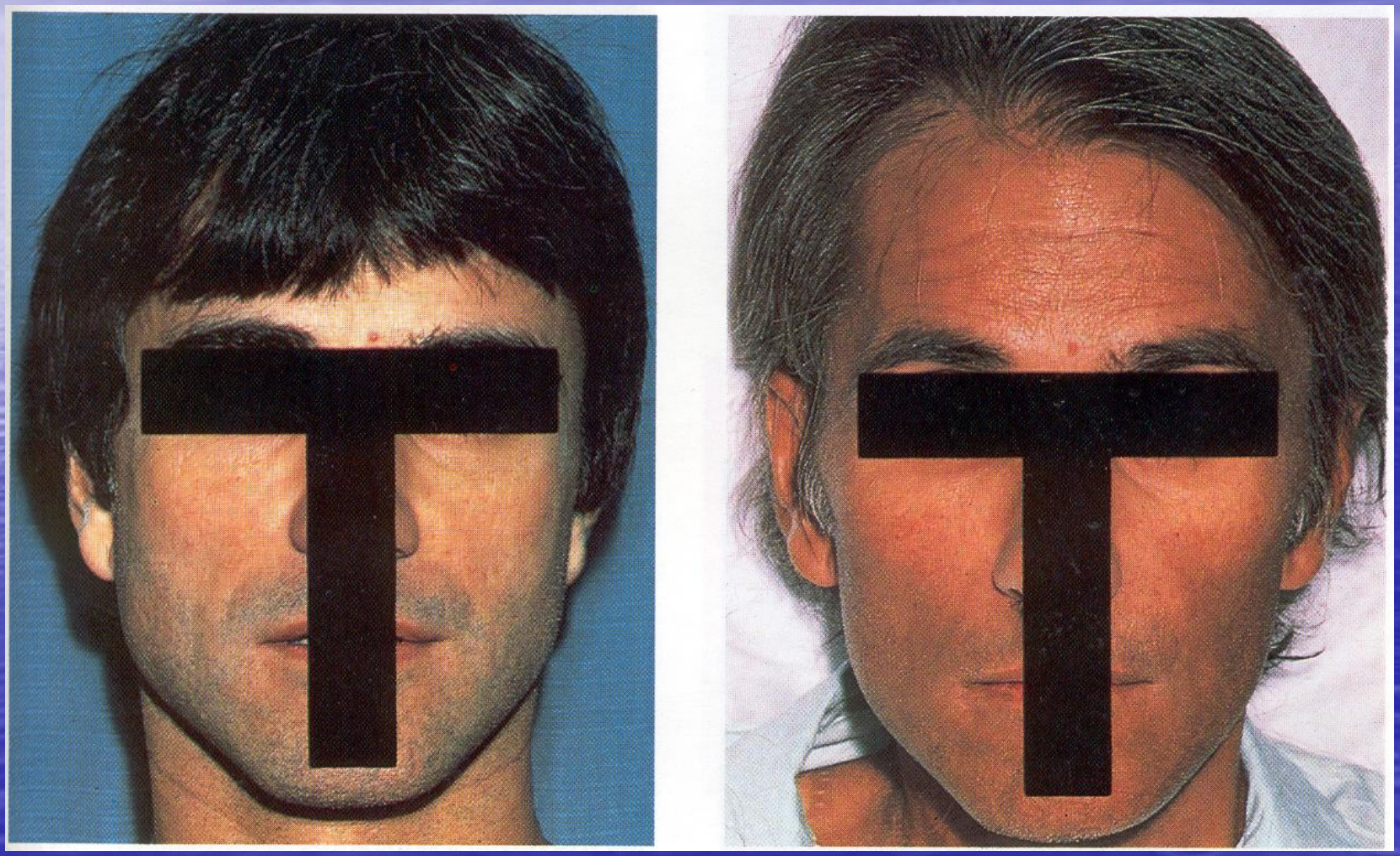
Follicular dermatitis and Kaposi sarcoma



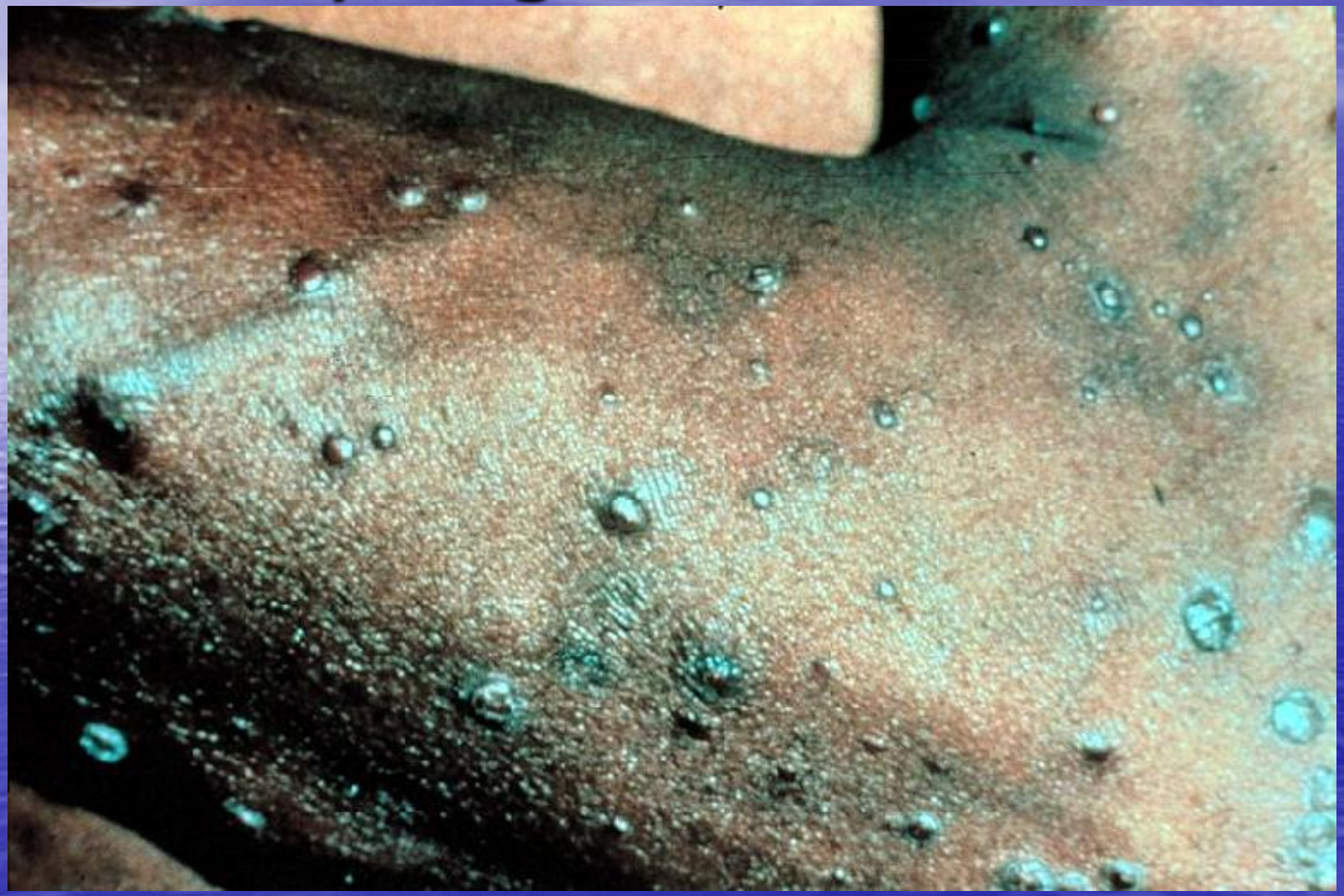
Xeroderma in AIDS



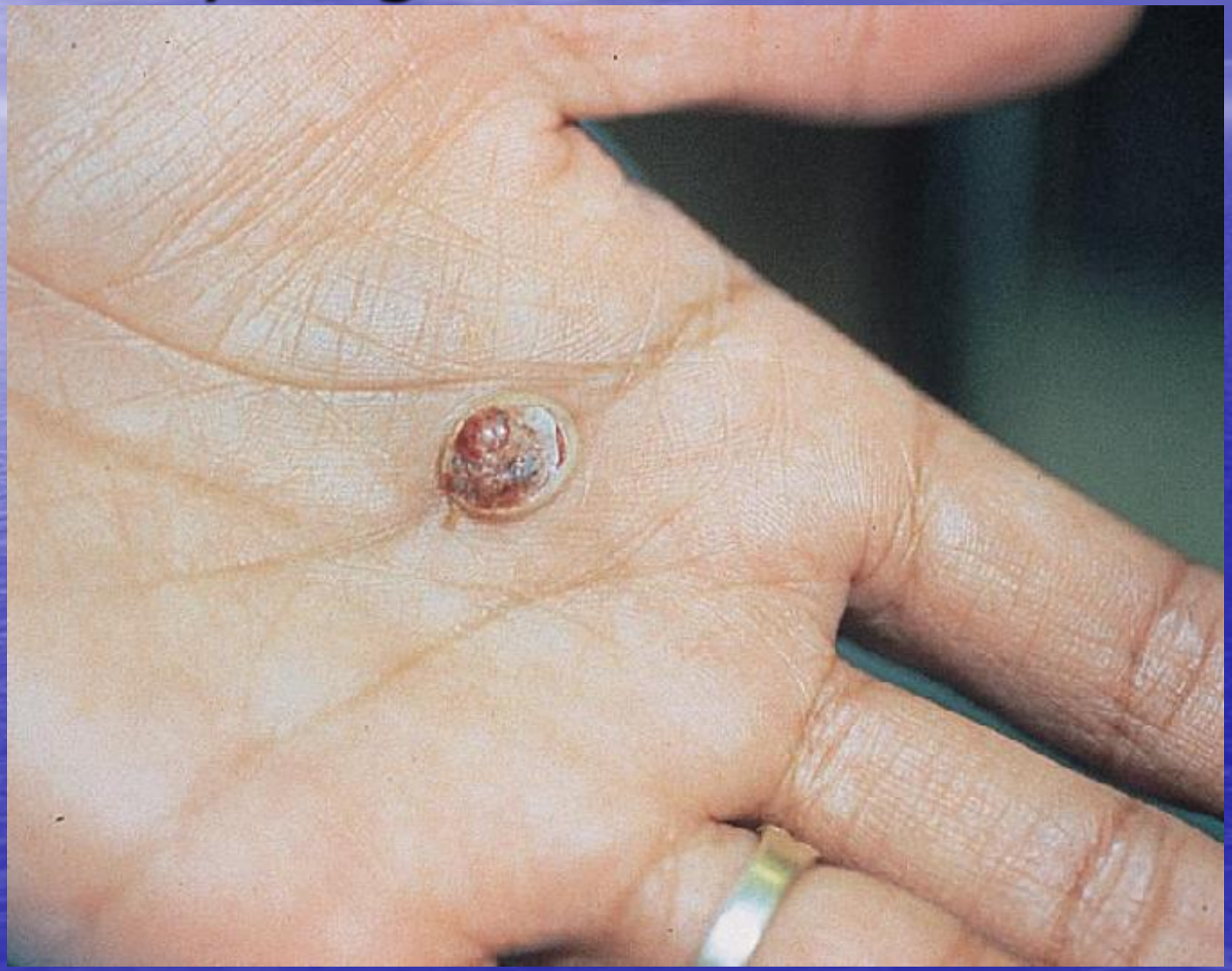
Early aging inAIDS



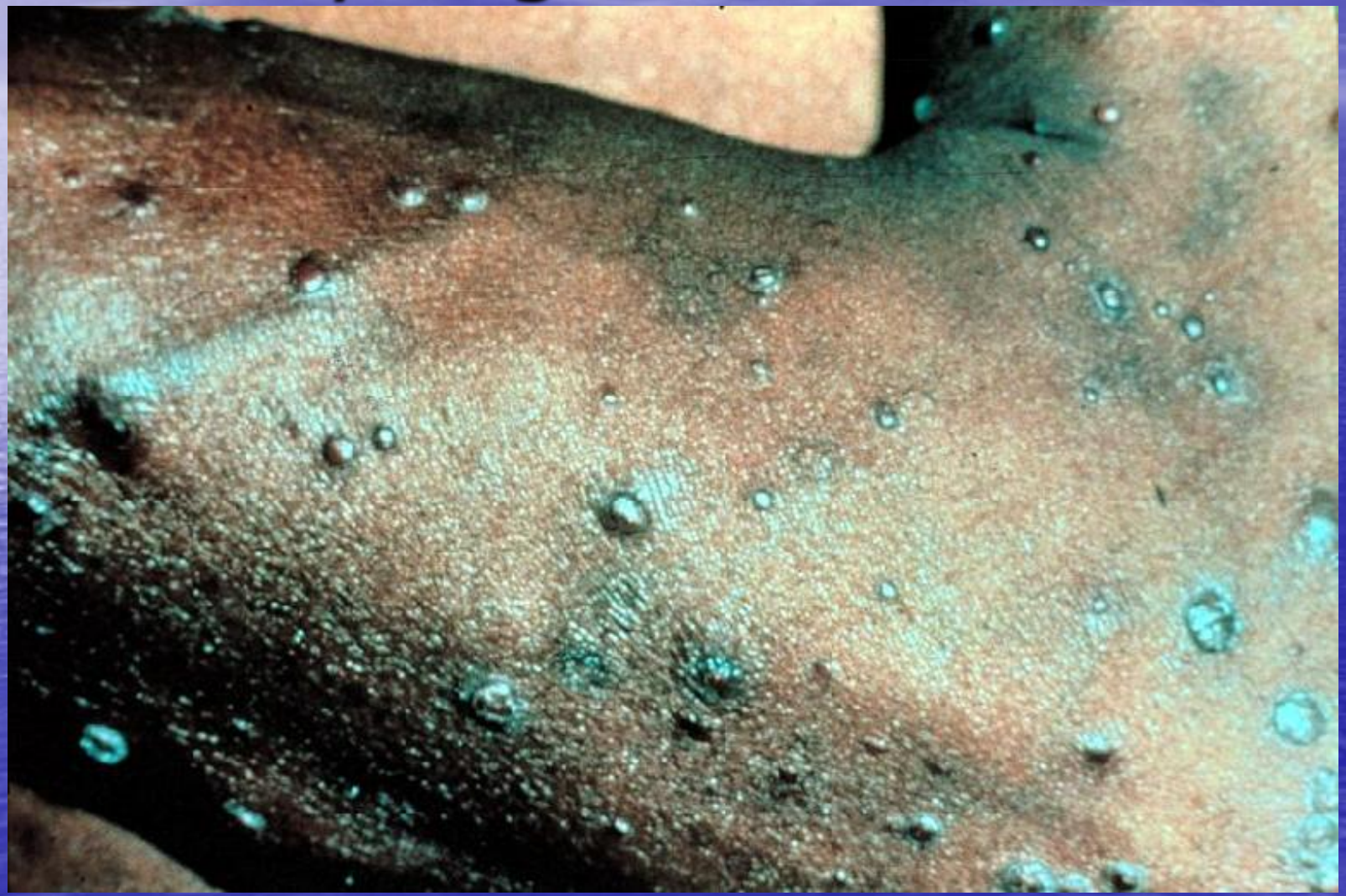
Bacillary angiomatosis



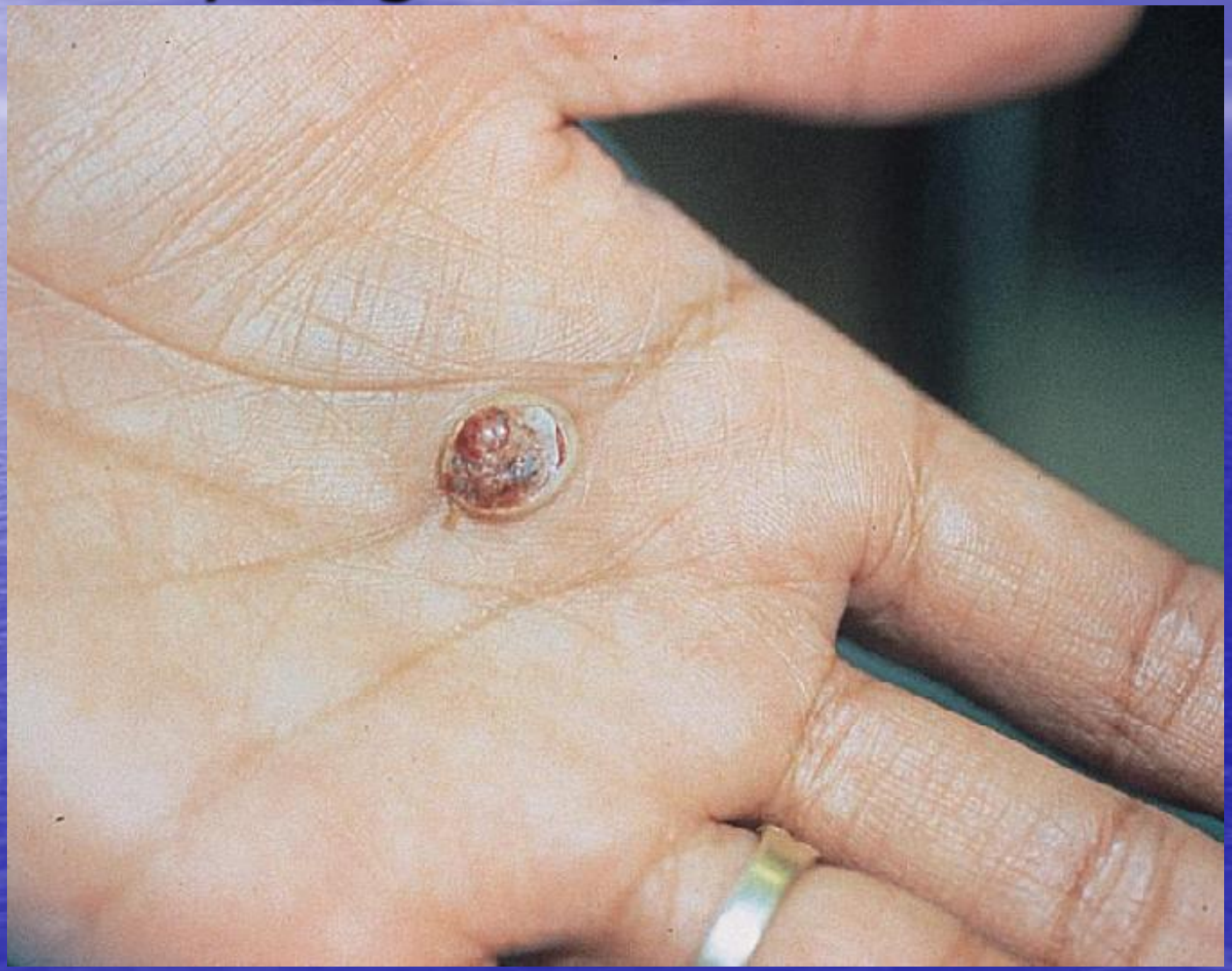
Bacillary angiomatosis



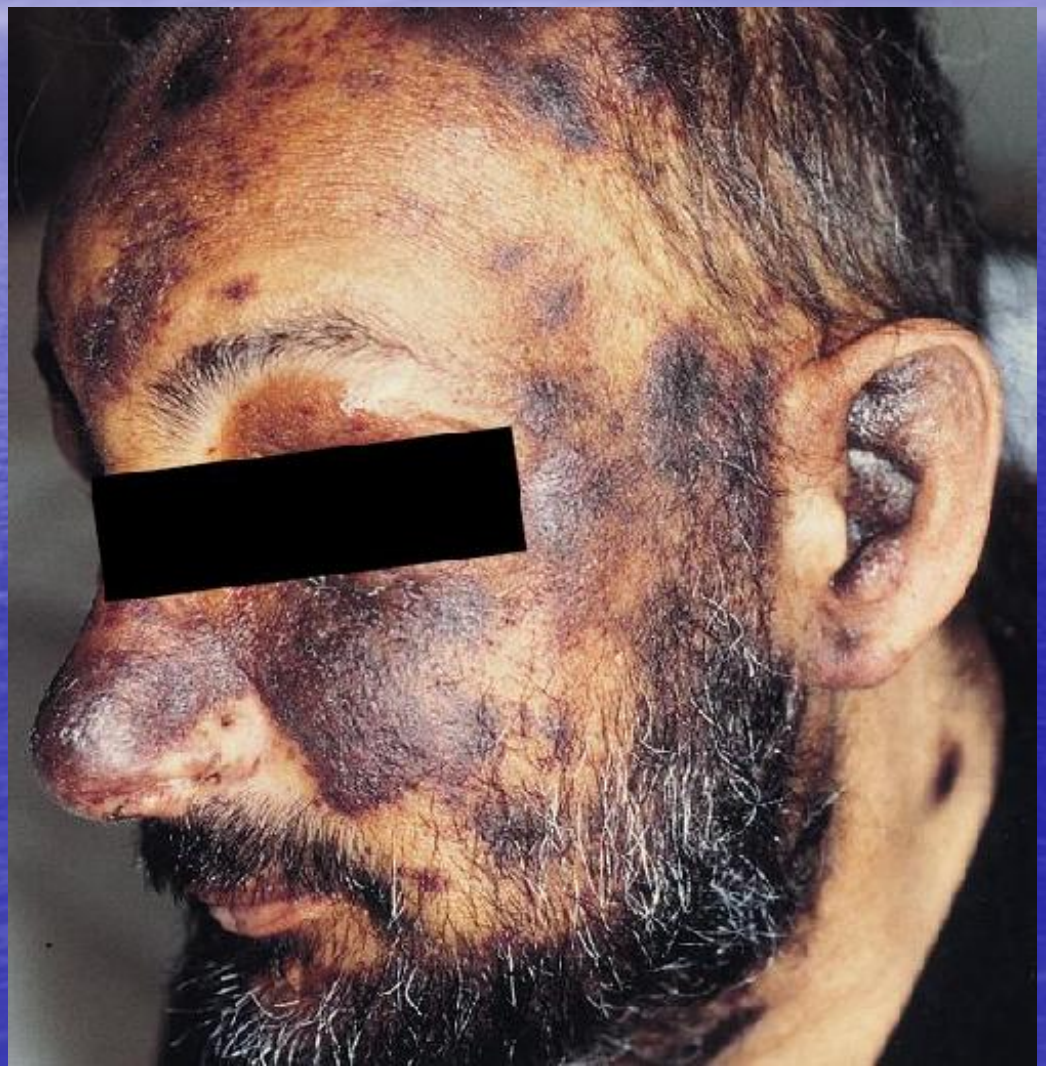
Bacillary angiomatosis



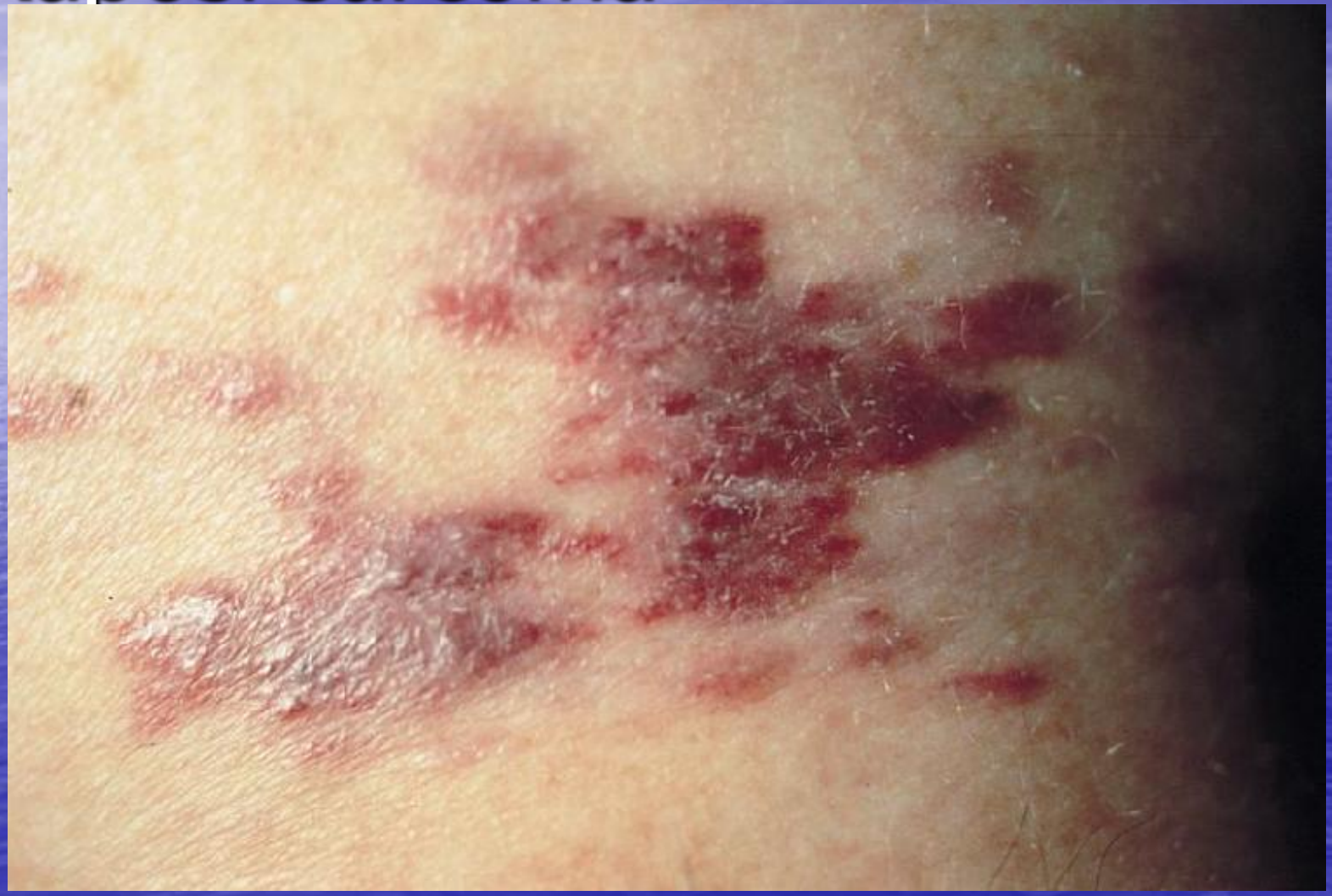
Bacillary angiomatosis



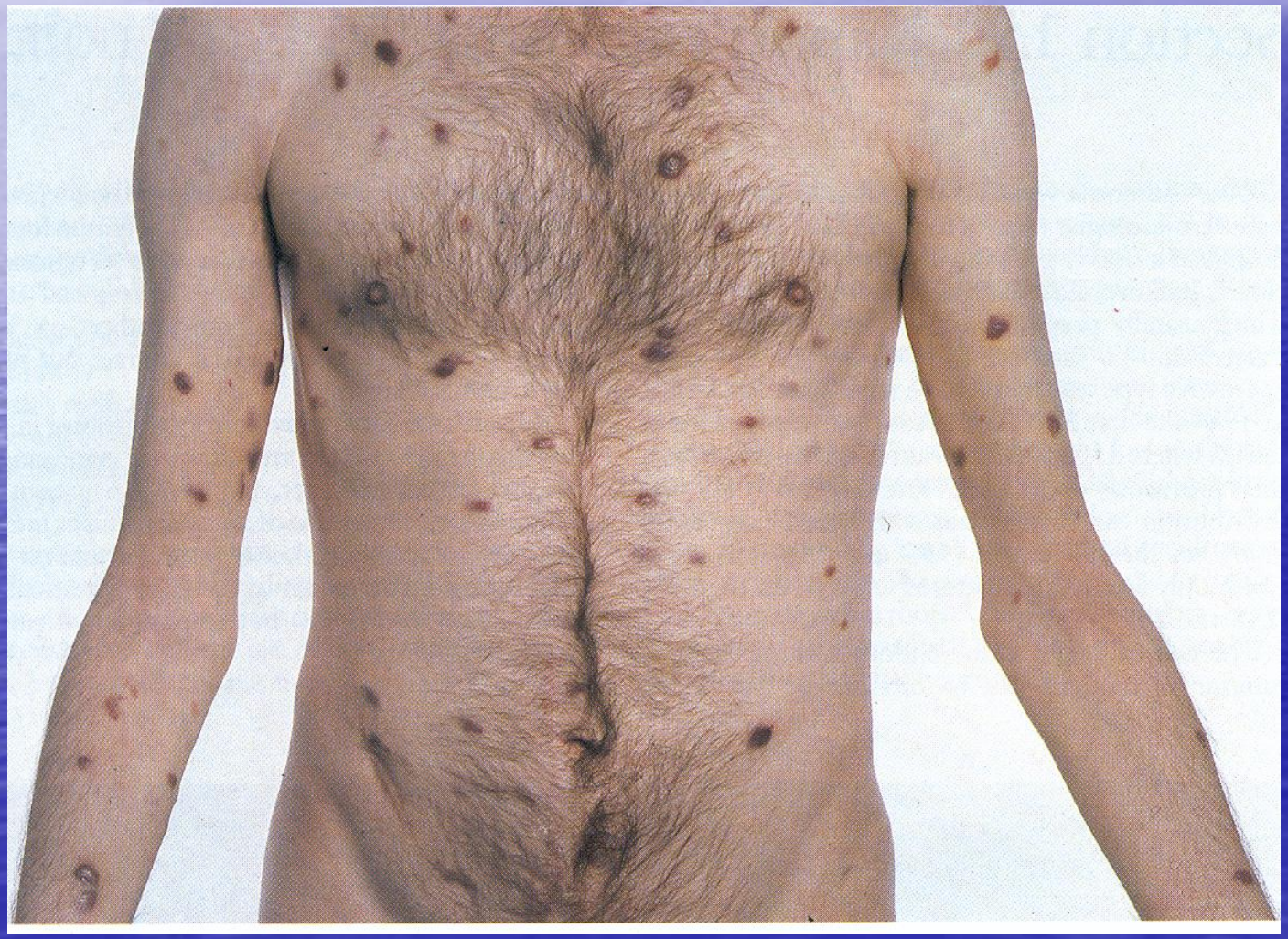
Kaposi sarcoma



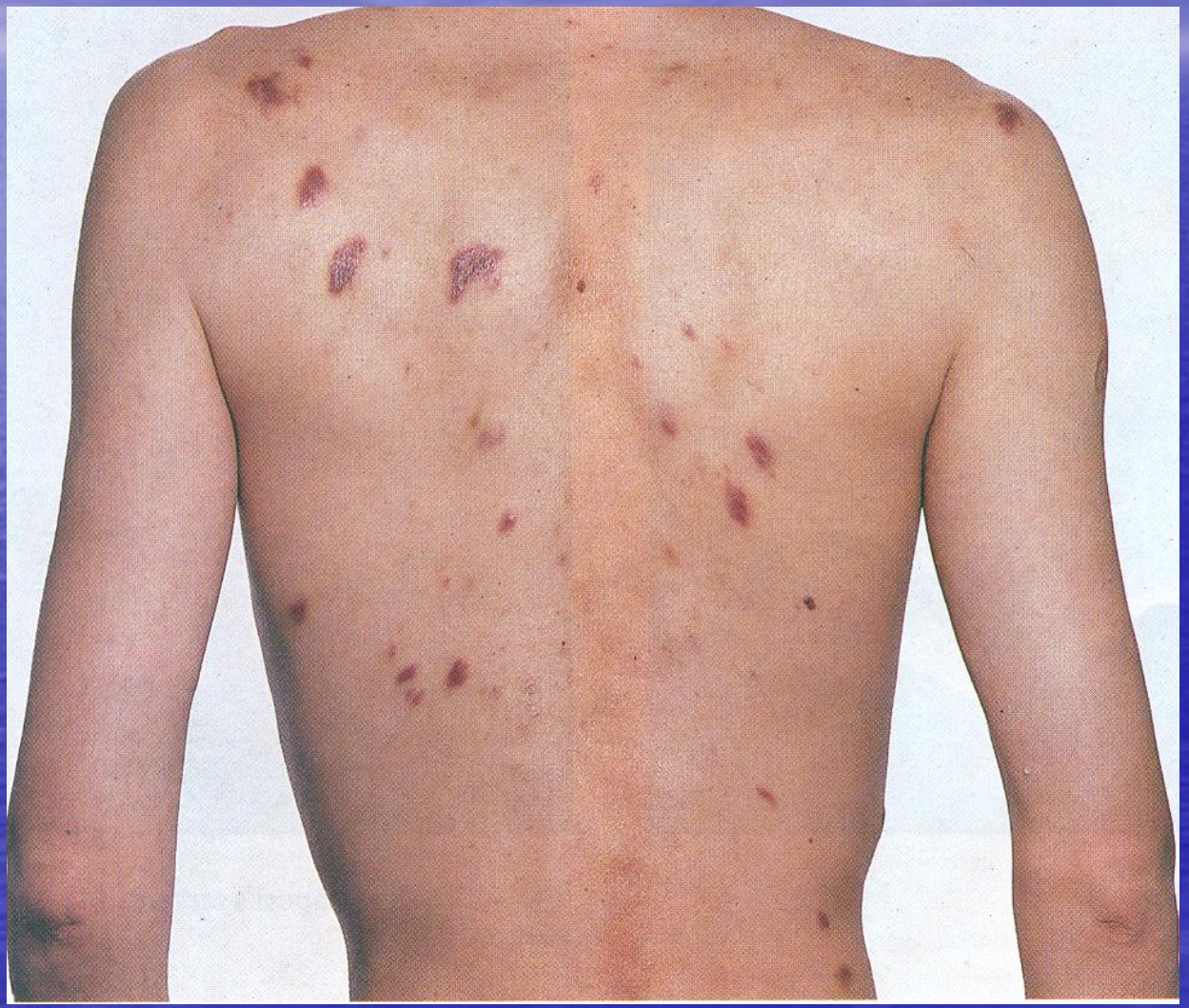
Kaposi sarcoma



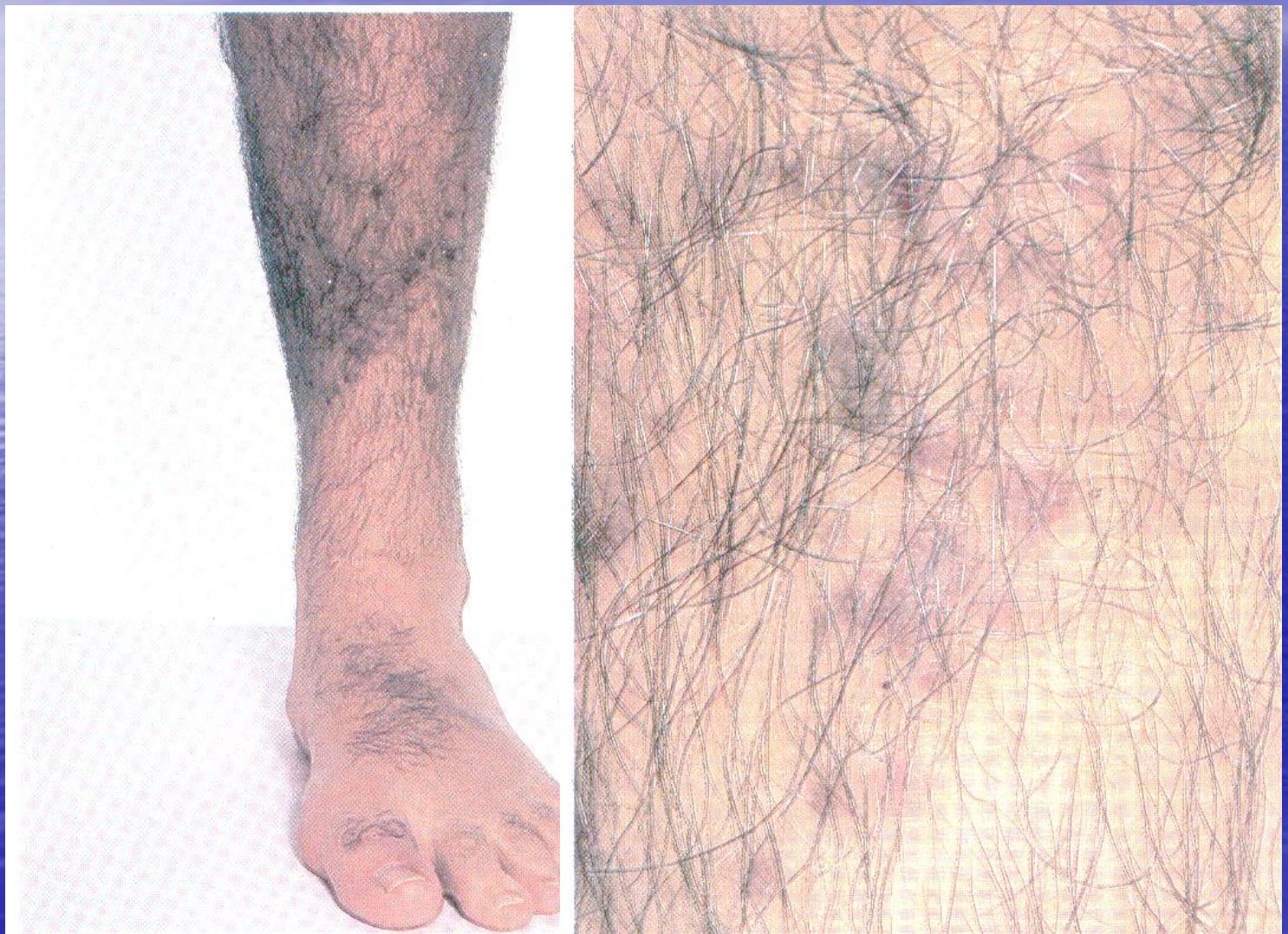
Kaposi sarcoma



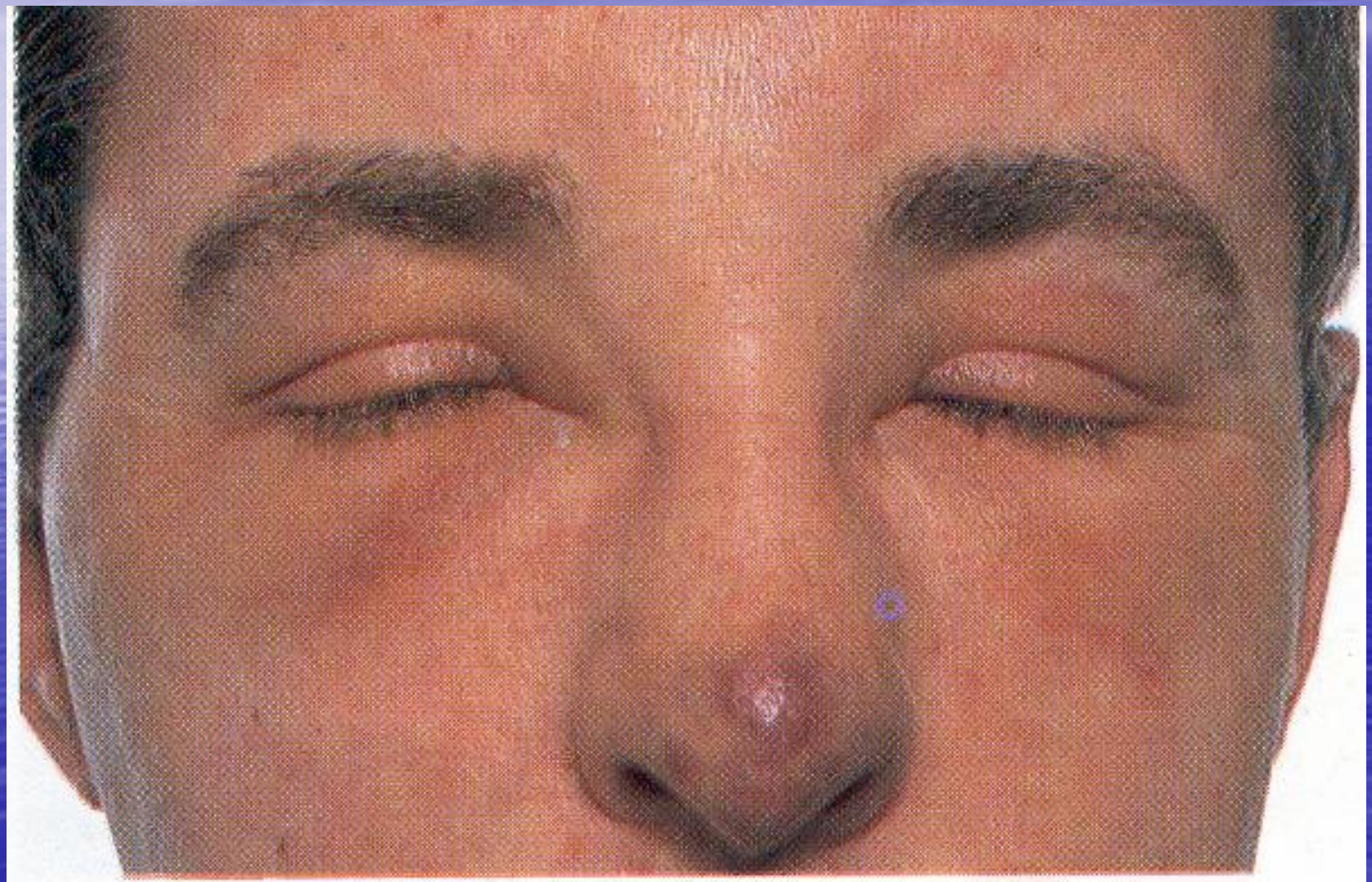
Kaposi sarcoma



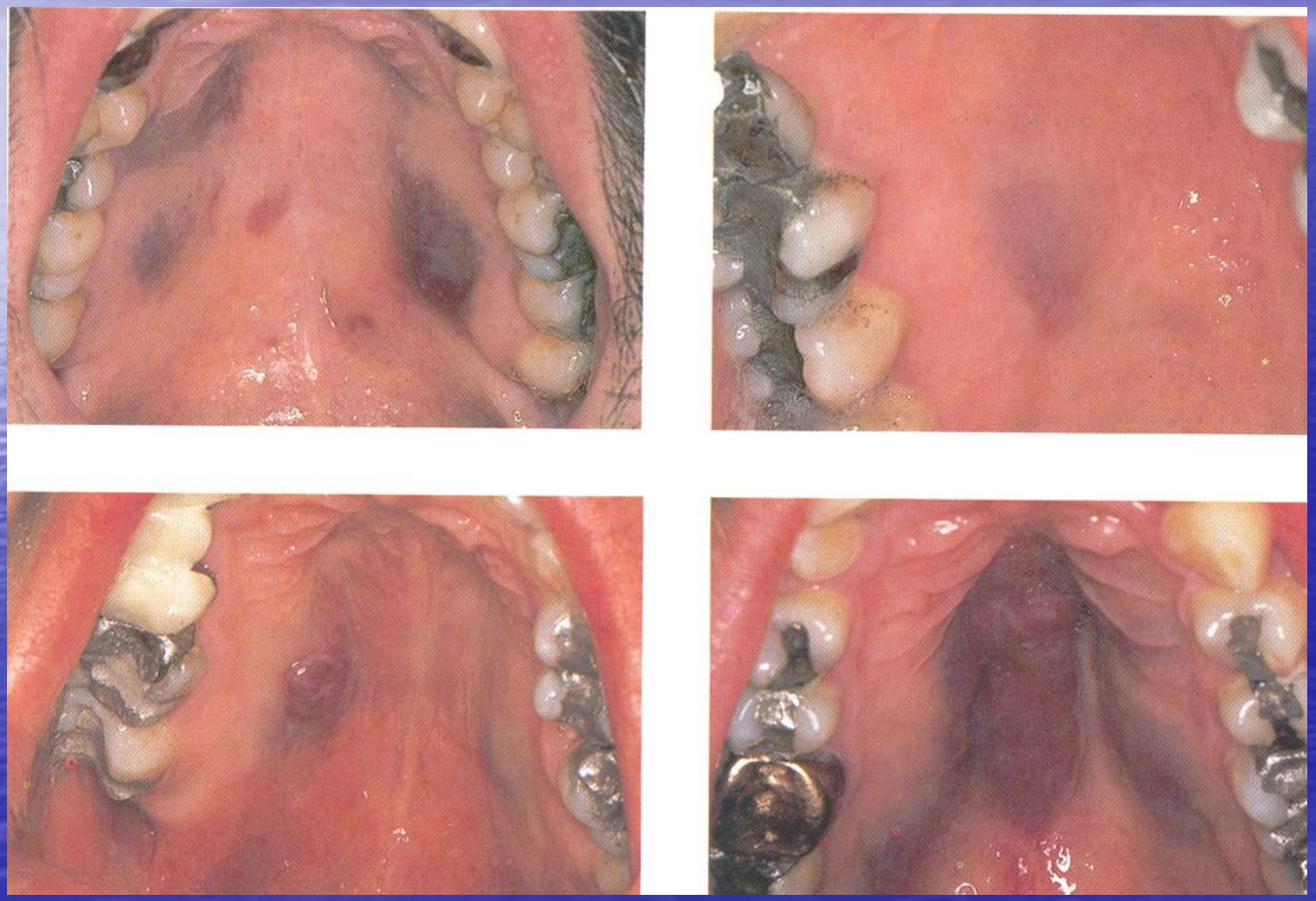
Kaposi sarcoma



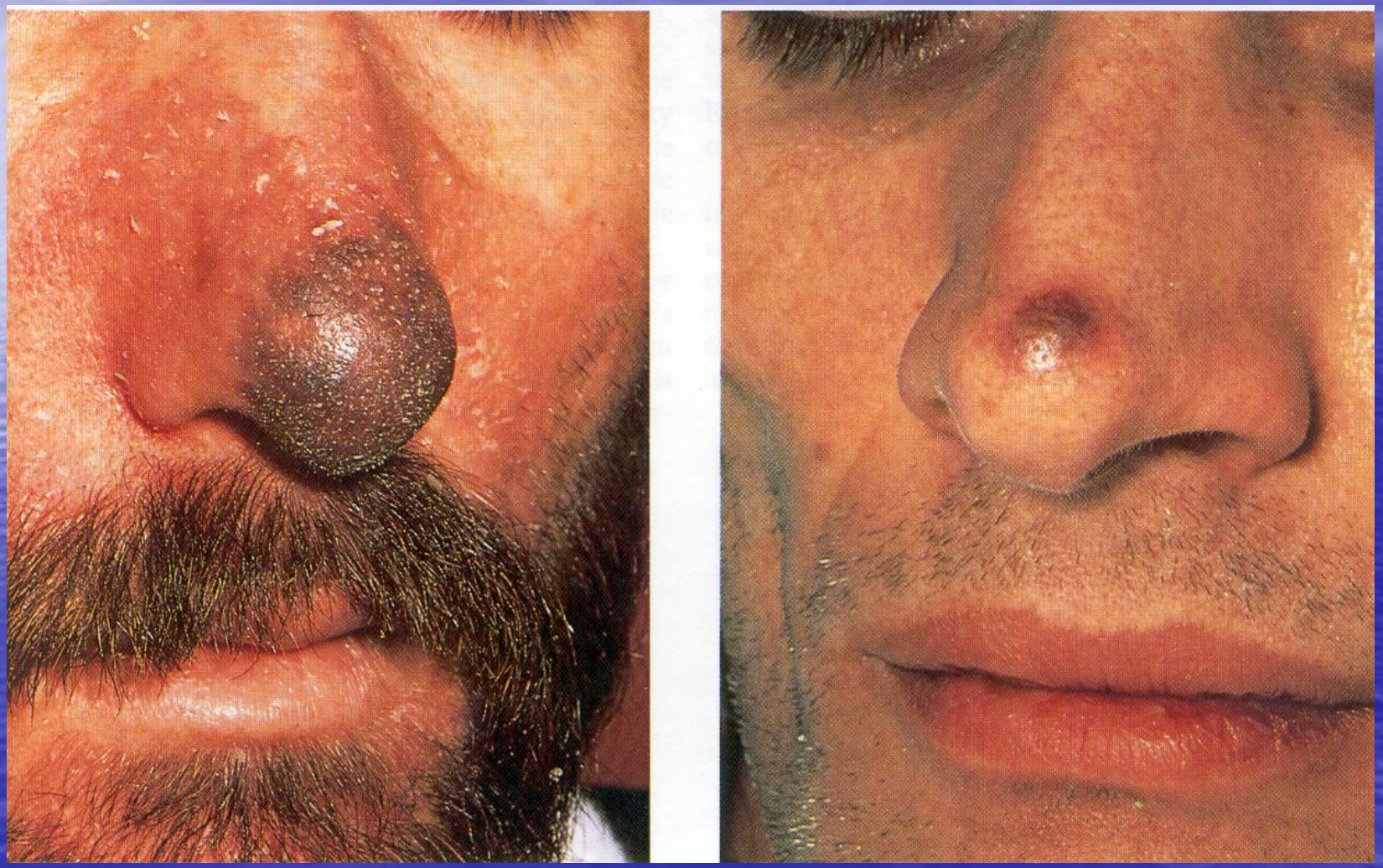
Kaposi sarcoma on the nose



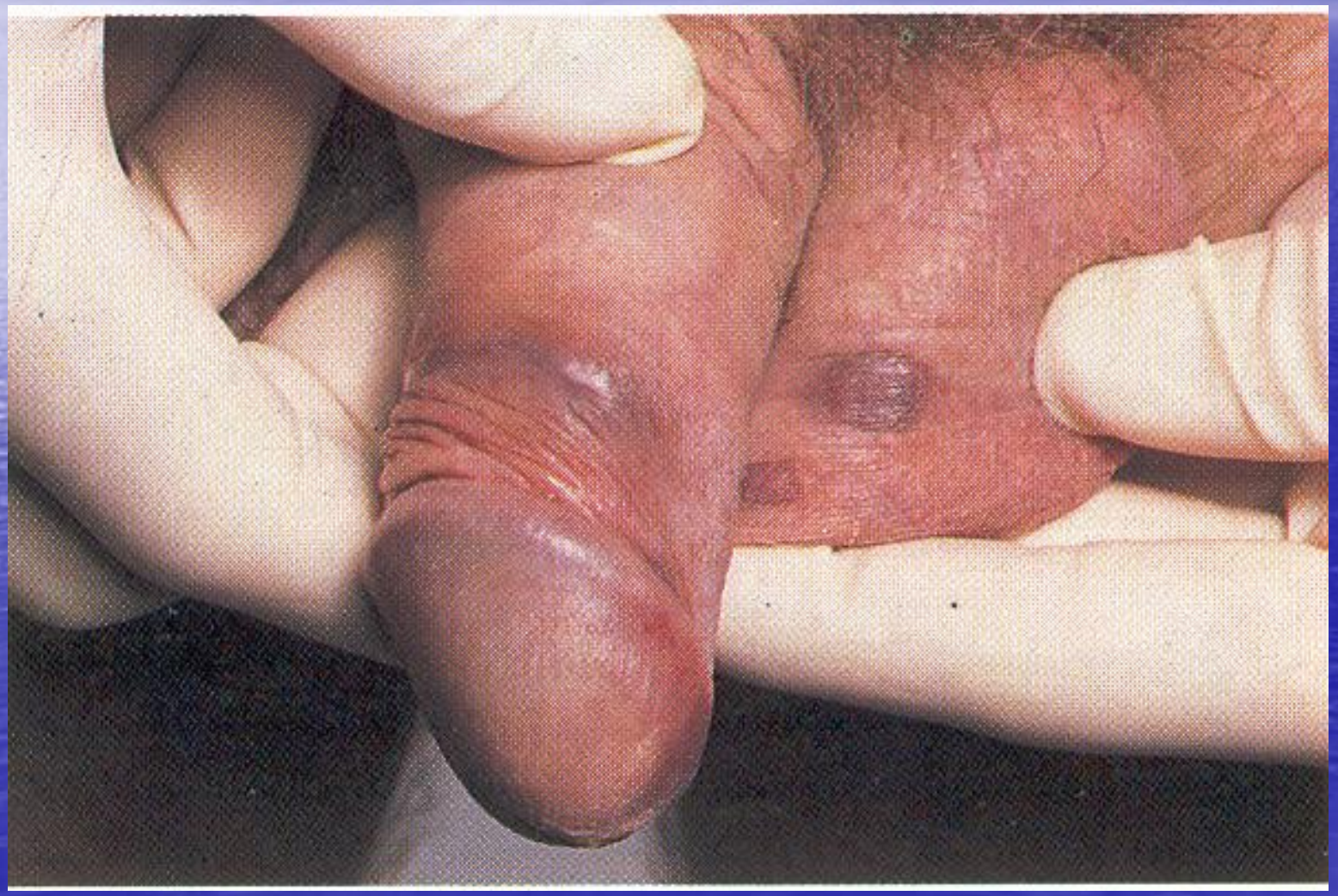
Kaposi sarcoma with oral localization



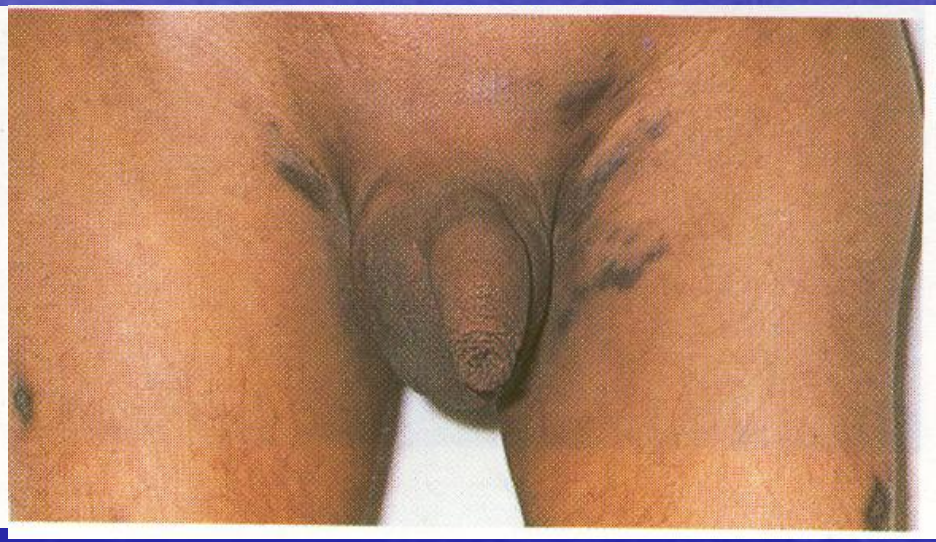
Kaposi sarcoma on the nose



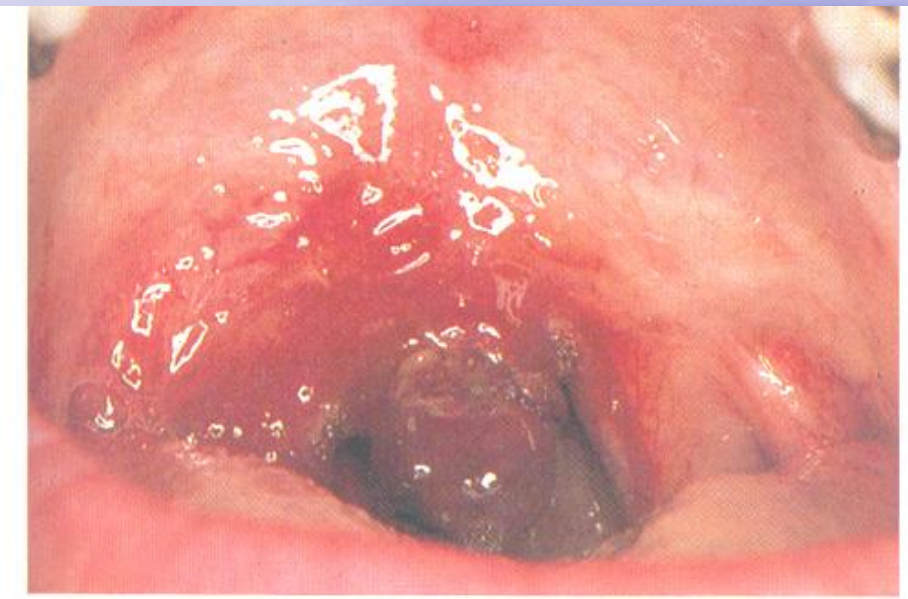
Kaposi sarcoma

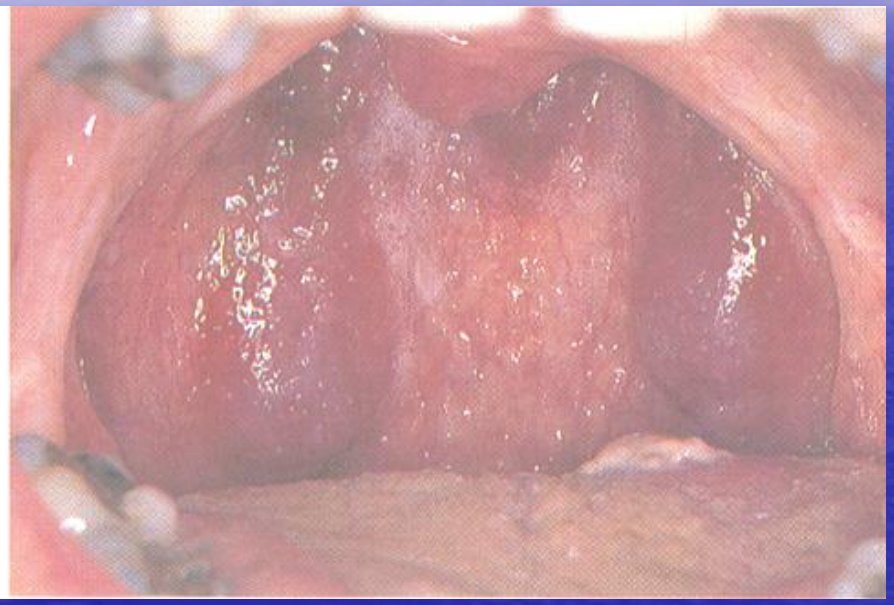


Kaposi sarcoma

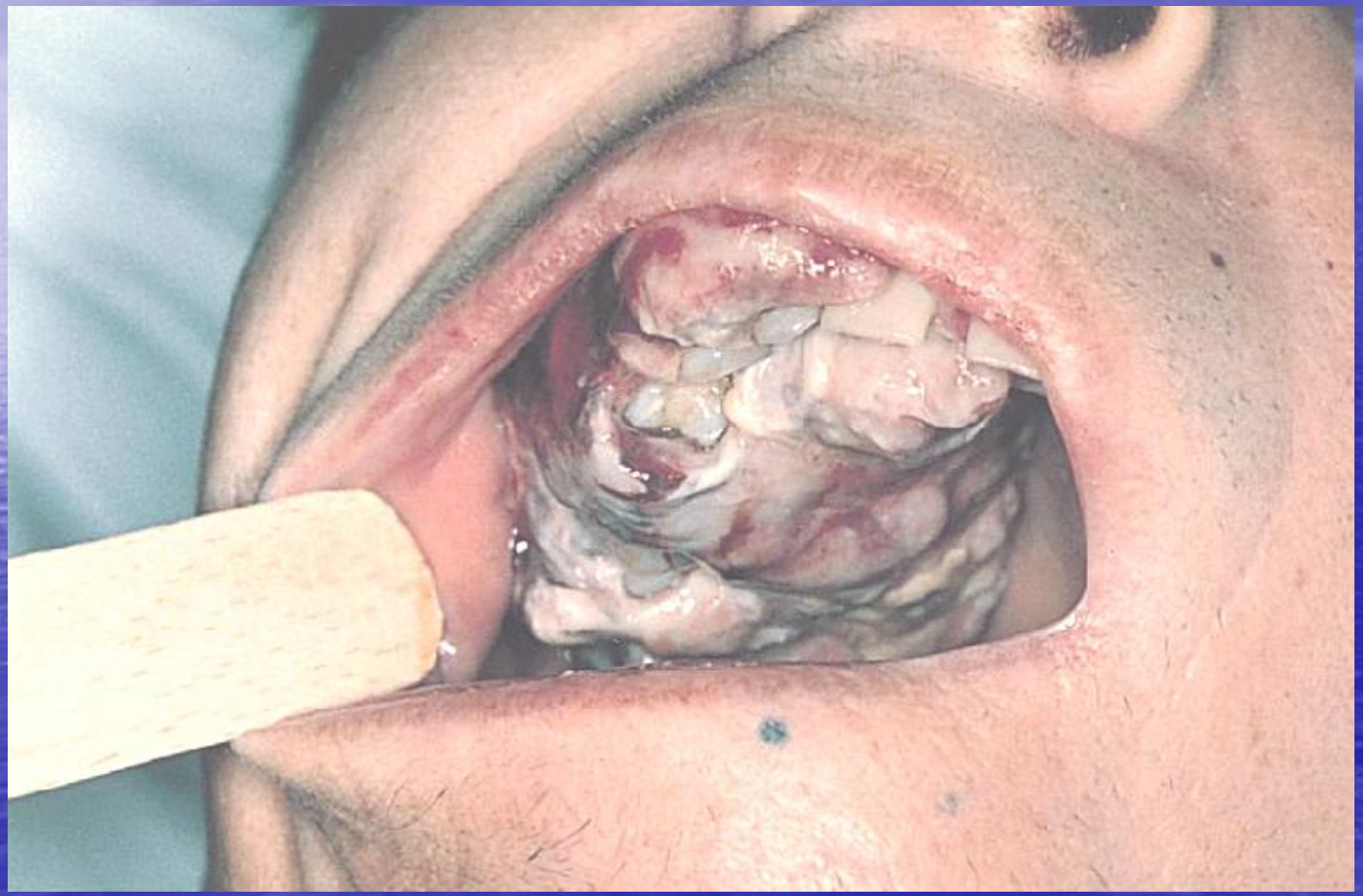


Kaposi sarcoma in the pharynx

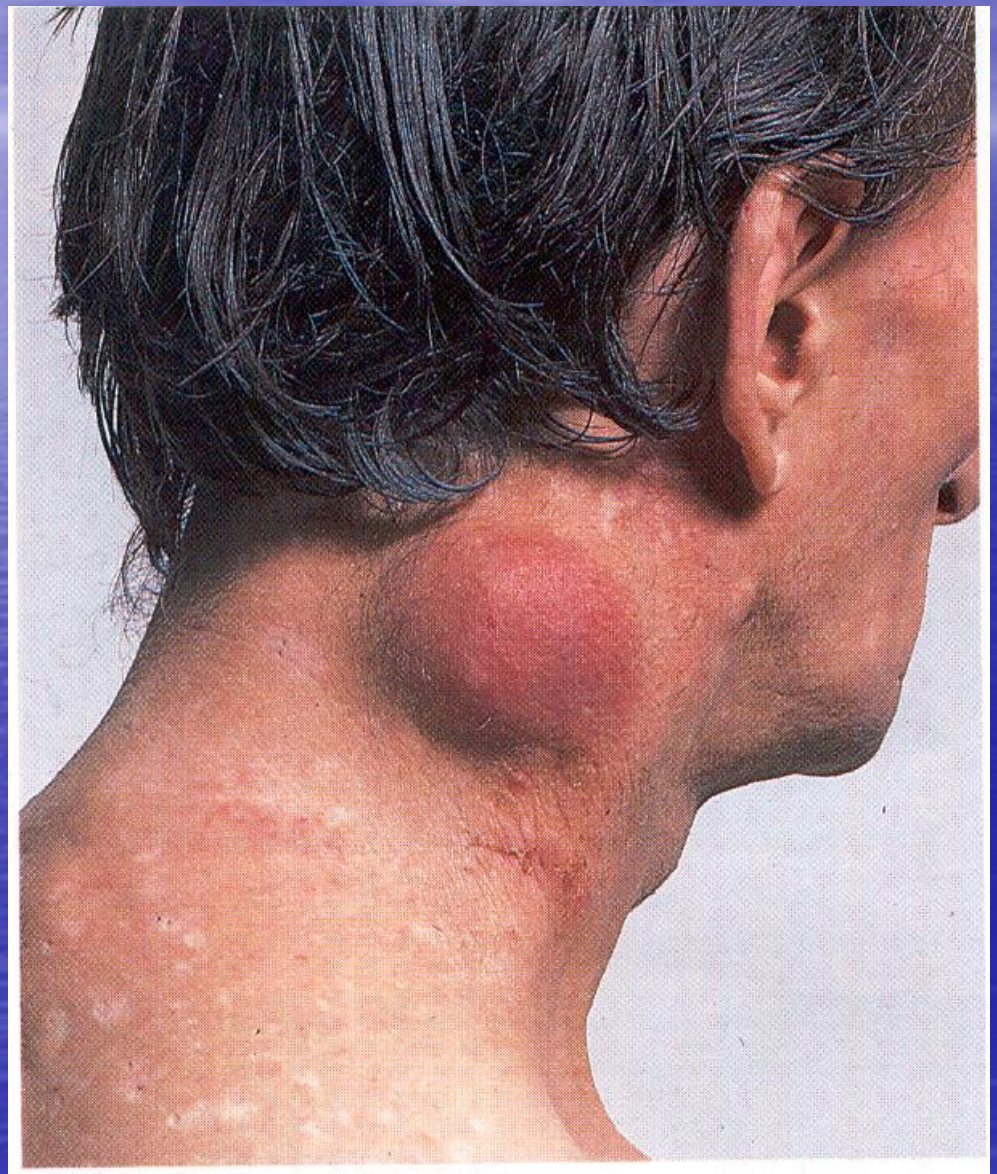




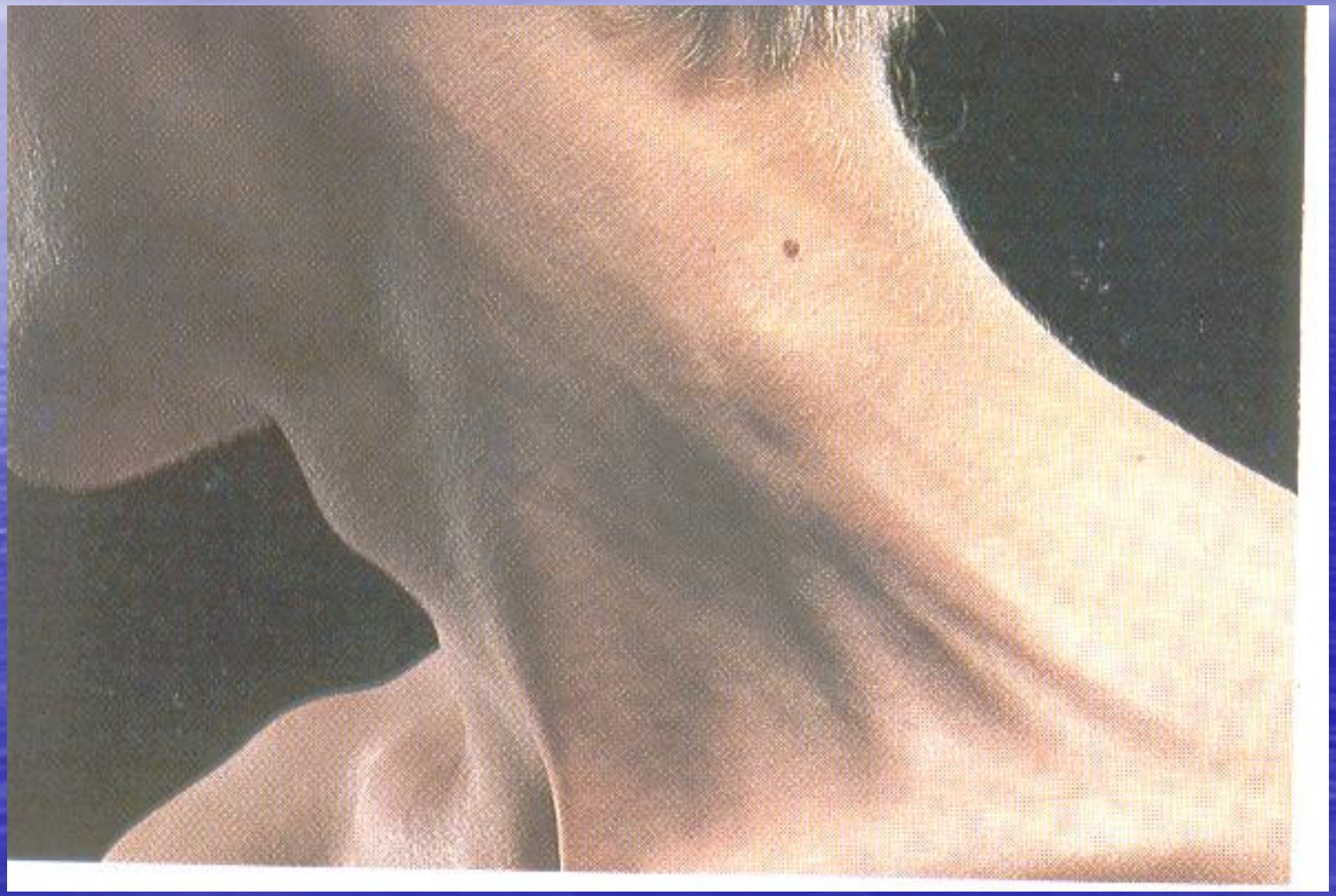
Non-Hodgkin lymphoma



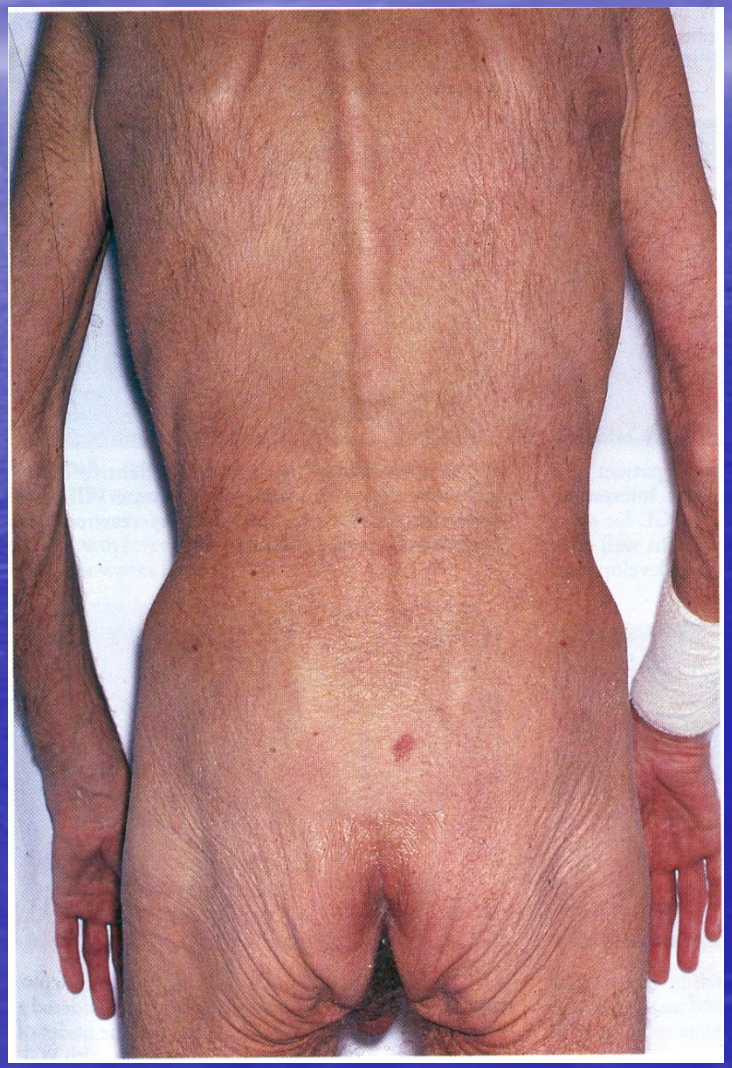
Cervical lymphadenopathy in AIDS

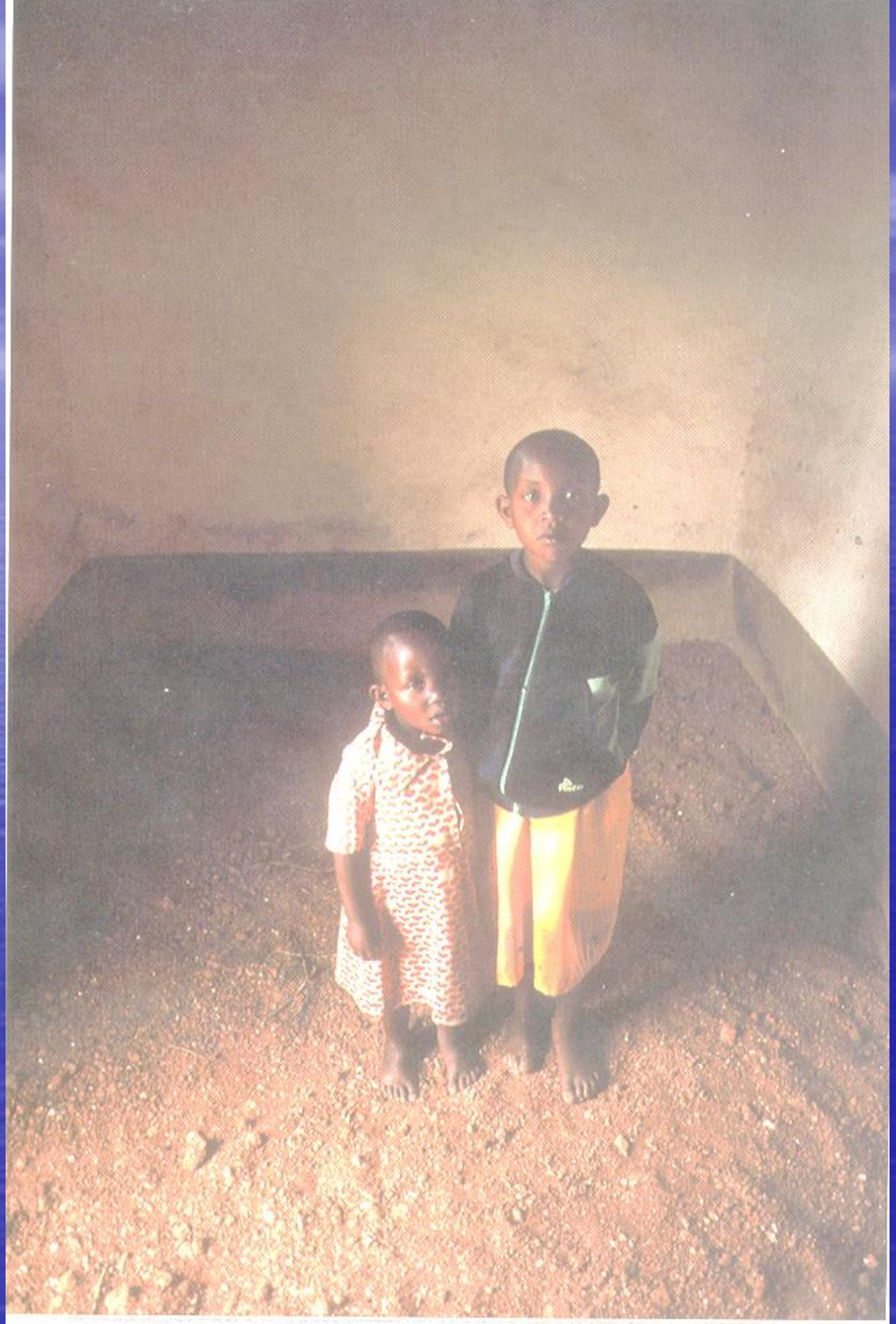


Cervical lymphadenopathy in AIDS



„Slim disease" in AIDS





Diagnosis

- ENZYME IMMUNOASSAY
- WESTERN BLOT
- LINE IMMUNOASSAY
- INDIRECT IMMUNOFLUORESCENCE ASSAY
- HIV-1 IGA ASSAY
- IMMUNOBLOT AND IMMUNOBINDING ANALYSIS
- POLYMERASE CHAIN REACTION
- HIV-1 RNA ASSAY
- NUCLEIC ACID TESTING
- IMMUNOHISTOCHEMISTRY
- *IN SITU HYBRIDIZATION*
- HIV-1 CULTURE
- IMMUNOLOGIC SURROGATE MARKERS

Pharmacologic Agents for Antiretroviral Therapy

Nucleoside Reverse Transcriptase Inhibitors (NRTI's)

- Abacavir (ABC)
- Didanosine (ddI)
- Lamivudine (3TC)
- Stavudine (d4T)
- Zalcitabine (ddC)
- Zidovudine (ZDV, or AZT)

Nucleotide Reverse Transcriptase Inhibitors

- Adefovir (ADV)
- Cidofovir (CDV)
- Emtricitabine (FTC)
- Tenofovir (PMPA)

Pharmacologic Agents for Antiretroviral Therapy

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's)

- Delavirdine (DLV)
- Efavirenz (EFV)
- Nevirapine (NVP)

Protease Inhibitors (PI)

- Atazanavir (ATV)
- Amprenavir (APV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV) – non-peptidic

Pharmacologic Agents for Antiretroviral Therapy

- Cell Fusion Inhibitors
  - Enfuvirtide
- CCR5 Inhibitor
  - Maraviroc
  - Vicriviroc
- Integrase Inhibitor
  - Raltegravir
- Maturation Inhibitor
  - Bevirimat

Therapies for Diseases Indicative of AIDS

Disease Process	Clinical Therapy
Candidiasis, oral	Clotrimazole troches, topical nystatin
Candidiasis, esophageal	Clotrimazole troches, topical nystatin, fluconazole, ketoconazole
Candidiasis, vulvovaginal	Miconazole, clotrimazole suppositories
Cervical cancer	Surgical therapy
Coccidioides immitis	*Amphotericin B*
Cryptococcus neoformans	*Amphotericin B with or without flucytosine; or fluconazole or itraconazole*

Therapies for Diseases Indicative of AIDS

Disease Process	Clinical Therapy
Cryptosporidium	Paromomycin
Cytomegalovirus	Ganciclovir, foscarnet
Herpes simplex or zoster	Acyclovir
Histoplasma capsulatum	*Amphotericin B, or itraconazole, or fluconazole*
Isosporiasis	Trimethoprim-sulfamethoxazole
Microsporidium	Albendazole (for *Septata intestinalis)*
Giardia lamblia	*Metronidazole*

Therapies for Diseases Indicative of AIDS

Disease process	Clinical therapy
Kaposi's sarcoma	Surgical therapy, chemotherapy, radiation therapy
LIP	None effective
Malignant Lymphoma	Chemotherapy, radiation therapy, surgical therapy
M tuberculosis	*Isoniazid, rifampin, pyrazinamide, plus ethambutol for resistance*
M avium complex	*Rifabutin, clarithromycin, ethambutol*
PML	Cytosine arabinoside
P jiroveci (carinii) pneumonia	*Trimethoprim-sulfamethoxazole, or pentamidine, trimetrexate*
Pneumonia, recurrent	Antibiotic therapy appropriate to sensitivity of bacteria cultured
Salmonellosis	Amoxicillin, trimethoprim-sulfamethoxazole, ciprofloxacin
Toxoplasma gondii	*Pyrimethamine with sulfadiazine and folinic acid*