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Skin manifestations in HIV positive patients

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Abbreviations:

5-FU: 5-fluorouracil

AIDS: acquired immunodeficiency syndrome

ART: antiretroviral therapy

BA: bacillary angiomatosis

BCC: basal cell carcinoma

CBCL: cutaneous B-cell lymphomas

CDC: center for disease control and prevention

CL: cutaneous leishmaniasis

CMV: cytomegalovirus

CNS: central nervous system

CSF: cerebrospinal fluid

DCL: diffuse cutaneous leishmaniasis

DNA: deoxyribo nucleic acid

EBV: Epstein Barr virus

ECP: extracorporeal photopheresis

EF: eosinophilic folliculitis

ELISA: enzyme-linked immunosorbent assay

EORTC: European organization for research and treatment of cancer

FTA-ABS: fluorescent treponemal antibody absorption assay

HAART: highly active antiretroviral therapy

HCV: hepatitis C virus

HHV8: human herpes virus 8

HIV: human immunodeficiency virus

HPV: human papillomavirus

HSIL: high-grade squamous intraepithelial lesion

HSV: herpes simplex virus

IF: infectious folliculitis

IgE: immunoglobulin-E

IV: intravenous

KOH: potassium hydroxide

KS: Kaposi sarcoma

LSIL: low-grade squamous intraepithelial lesion

MC: molluscum contagiosum

MCL: mucocutaneous leishmaniasis

MF: mycosis fungoides

ML: mucocutaneous leishmaniasis

MRI: magnetic resonance image

MRSA: methicillin-resistant Staphylococcus aureus

MSM: men who have sex with men

NADCs: non-AIDS-defining cancers

NATs: nucleic acid tests

NHL: non Hodgkin lymphoma

NMSC: nonmelanoma skin cancer

NRTIs: nucleoside reverse transcriptase inhibitors

NSAID: nonsteroidal anti-inflammatory drugs

NTP: non treponemal test

OHL: oral hairy leukoplakia

PAS: periodic acid–Schiff

PCP: pneumocystic pneumonia

PCR: polymerase chain reaction

PCT: porphyria cutanea tarda

PIs: protease inhibitors

PUVA: psoralen and ultraviolet A

ReA: reactive arthritis

RNA: ribo-nucleic Acid

RT: reverse transcriptase

SCC: squamous cell carcinoma

SD: seborrheic dermatitis

SIV: Simian immunodeficiency virus

SS: Sezary syndrome

STD: sexually transmitted disease

TCIs: topical calcineurin inhibitors

TCR: T-cell receptor

TEN: toxic epidermal necrolysis

TK: thymidine kinase

TMP-SMX: trimethoprim-sulfamethoxazole

TNM: tumour, node and metastasis

TT: treponemal test

UV: ultraviolet

VC: visceral leismaniasis

VDRL: venereal disease research laboratory test

VZV: varicella zoster virus

WHO: world health organization

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Summary

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The HIV epidemic is a global health challenge and the epidemic is still growing nowadays. This disease doesn't affect only individuals, but entire households, communities, and carry an economic burden at the level of economic development and growth of a nation. Unfortunately, most of the people that are at risk of the HIV infection or are already seropositive, live in the developing world where prevention, care, and treatment are still not in line with the severity of the problem. The HIV infection can be the source of a tremendous number of health issues related to the immunodeficiency that it confers to the persons affected. Dermatologic manifestation in HIV positive individuals, are part of the wide spectrum of illnesses that go along this retroviral infection. Virtually, all skin conditions that the general population is susceptible to develop can affect the HIV positive population with greater concern, in terms of therapeutic measures and probable complications.

A variety of neoplastic, infectious, and noninfectious diseases can produce cutaneous manifestations throughout the course of HIV disease. These manifestations may occur more frequently than in persons without HIV infection and may be less responsive to usual treatment modalities.

Although no cure is still available, a wide range of therapy exist to treat the various disease and complications, and improve the quality of life of HIV patients.

Key words: HIV, AIDS, infections, neoplasm, treatment

Sažetak

KOŽNE PROMJENE U HIV POZITIVNIH BOLESNIKA
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Epidemija HIV-a je globalni zdravstveni izazov, a epidemija je i dalje u porastu. Ta bolest ne utječe samo na pojedince, već na sva domaćinstva, zajednice i nosi ekonomski teret na razini gospodarskog razvoja i rasta neke nacije. Nažalost, većina ljudi koji su u opasnosti od HIV infekcije ili su već seropozitivni, žive u zemljama u razvoju gdje prevencija, skrb i liječenje još uvijek nisu u skladu s težinom problema. HIV infekcija može biti izvor velikog broja zdravstvenih problema povezanih s imunodeficijencijom osobama koje su s njom inficirane.
Kožne promjene kod HIV pozitivnih osoba dio je širokog spektra bolesti koje idu uz ovu retrovirusnu infekciju. Gotovo, svim kožnim bolestima koje se mogu javiti u općoj populaciji podložne su i osobe koje su HIV pozitivne, ali tu je potreban oprez zbog eventualnih terapijskih pristupa i mogućih komplikacija.

Brojne neoplastičke bolesti, infektivne i neinfektivne bolesti mogu uzrokovati kožne promjene u svim stadijima HIV bolesti. Te kožne promjene se kod njih češće pojavljuju nego u osoba koje nisu HIV pozitivne i imaju slabiji odgovor na uobičajenu terapiju.

Iako još uvijek nije dostupan lijek, postoji širok spektar terapije za liječenje različitih bolesti i komplikacija, te poboljšanje kvalitete života pacijenata s HIV-om.

Ključne riječi: HIV, AIDS, infekcije, neoplazma, liječenje

1 Introduction

The Human Immunodeficiency virus (HIV) is said to have originated in Africa, Congo in the late 1900's early 1920's (1). Chimpanzee were identified as the source of HIV infection in humans. The primate version of the HIV is the so called Simian immunodeficiency virus or SIV. It most likely was transmitted to mankind and mutated into HIV when humans hunted these chimpanzees for meat and came into contact with their infected blood (1). In 1981, the United States (U.S.) Centers for Disease Control and Prevention (CDC) first described the symptoms of this unknown disease in one of their publication (2). HIV disease was first described in 1981 among 2 groups, one in San Francisco and the other in New York City (2). Numerous young homosexual men presented with opportunistic infections that, at the time, were typically associated with severe immune deficiency: *Pneumocystis pneumonia* (PCP) and aggressive Kaposi sarcoma (2, 3). In 1982, public health officials began to use the term "acquired immunodeficiency syndrome," or AIDS, to describe the occurrences of opportunistic infections (3). Formal tracking (surveillance) of AIDS cases began that year in the U.S. (3).

HIV infection is a worldwide phenomenon, more than 70 million of people have been infected since the beginning of the epidemic and about 35 million have died (2). Sub-Saharan Africa is the most affected region, with 25.6 (23.1–28.5) million people living with HIV in 2015 (3). Also, sub-Saharan Africa accounts for two-thirds of the global total of new HIV infections more than 10 million have already died and 3 to 4 new infections occur annually (3). The challenges that are brought up by the epidemic are numerous and differ from one geographical place to another. In developing countries, the socio-economic situation, lack of education and funding are huge obstacles to an appropriate prevention and stopping the spread of the virus.

Groups affected are not the same; in the developing world HIV infection is equally common in males and females and the primary route of HIV transmission is heterosexual contact. Children may become infected by transplacental transmission or by breastfeeding (4). In developed countries, men who have sex with men and intravenous drug abusers are still the most affected category but a rise of infection in the heterosexual population is noted. Young adults tend to have more chance of acquiring HIV, typically through high-risk behaviors.

HIV screening and testing is possible worldwide and there are three types of HIV diagnostic

tests: antibody tests, combination or fourth-generation tests, and nucleic acid tests (NATs) (5). The antibody test, hence the name, do not detect the HIV but the antibodies made by the host. Most rapid and home test are the antibody tests. Fourth generation tests look for both HIV antibodies and antigens. NATs detect HIV the fastest by looking for HIV in the blood, they are very expensive. The initial HIV test is either an antibody test or combination test. It may involve obtaining blood or oral fluid for a rapid test or sending blood or oral fluid to a laboratory. If it is positive, the individual will be directed to get follow-up testing. If the initial HIV test is a laboratory test and is positive, the laboratory will usually conduct follow-up testing on the same blood specimen as the initial test (5).

Individuals that obtain a positive test result can be managed with Highly Active Anti Retro-viral Therapy (HAART). HAART has been the standard treatment since 1997(4). A combination or "cocktail" of minimum three drugs is used in order to reduce the likelihood of resistance appearance. This doesn't not represent a cure, since there is not yet a cure to HIV but compliance to the treatment dramatically reduces the chances of death by AIDS and permits a better quality of life.

HIV is a retrovirus, which uses the reverse transcriptase (RT) enzyme to incorporate his genetic material (RNA) into the DNA of the infected host's cells. The DNA undergoes incorporation into the host cell chromosome. Then, when the retrovirus integrates its genetic material with the host's, it becomes part of the host's genome for life (6). Antigen presenting cell (in the mucosa of the genital tract) are the first targets of the virus. They then transport HIV into lymph nodes, where the virus infects lymphocytes. The receptors for HIV are CD4 molecules on the surface of T lymphocytes. The CD4+ lymphocytes whose T-cell receptors specific for HIV proteins proliferate and are preferentially infected. Viruses produced by the newly HIV-infected lymphocytes flood the blood and are transported into all tissues within days and viremia reaches high levels.

During this time, many patients become symptomatic with fever, skin lesions, pharyngitis, and lymphadenopathy. This "primary HIV infection" (seroconversion syndrome) usually lasts for a few days up to a few weeks and then resolves spontaneously (4).When the immune response rises, antibodies against HIV appear in the blood and cytotoxic T cells specific for infected cells proliferate. This permit a somewhat partial control of the infection and viremia levels decrease, the infection then reaches the "*plateau level*". This period can last up to 10 years in average. However, the higher the level of viremia is the faster the development of

AIDS is possible.

A progressive reduction in the level of CD4+ T cells is the hallmark of HIV-induced immune deficiency. During the chronic phase of HIV infection, a progressive annual loss of about 70 cells per cubic millimeter occurs (4). When the number of CD4+ cells declines below a critical level of about 200/m^3, the "AIDS defining diseases" start to appear (4).

Among others, skin disease is a very common clinical manifestation of HIV infection. It is estimated that 90% (6) of HIV positive individuals will present with a skin disorder during the course of the infection, from the maculopapular rash during primary infection to the Kaposi sarcoma or prurigo in full-blown AIDS. Some of these diseases appear at a certain T cell count, and are marker of the stage of the infection (7).

Skin manifestations can also be associated to antiretroviral therapy, weather the therapy helps to cure it or contribute to its appearance.

2 Infectious HIV-related cutaneous disorders

2.1 Skin manifestations associated with viral infections

Many other viruses often coexist in the HIV positive patient. In the immunocompromised host, those common viruses often disseminate and can cause serious and difficult to treat illnesses. They can behave as opportunistic agents. The common co infecting viruses include herpes simplex virus (HSV) 1 and 2, human cytomegalovirus (CMV), human herpesvirus 8 (HHV8), Epstein-Barr virus (EBV), Varicella Zoster virus (VZV), and human papillomavirus (HPV). They behave as opportunistic agents and cause various diseases in immunocompromised hosts. The increased frequency and severity of diseases caused by these viruses in HIV-infected individuals is due mainly to dysfunction of both the adaptive and innate immune responses to viral pathogens. In addition, molecular interactions between HIV and these opportunistic viruses are likely to play critical roles in the progression of disease, including neoplasia (8).

2.1.1 Herpes simplex virus infections

Recurrent oral and anogenital HSV infection is common in patients infected with HIV, and it may lead to chronic ulcerations (9). HSV exists in two different form HSV-1 and HSV-2. The HSV-1 type causes mostly orolabial lesions, whereas HSV-2 provokes genital lesions. More than 90% of adults worldwide exhibit serologic evidence of infection with HSV-1 (10). The prevalence of HSV-2 infection is considerably lower, but ranges from at least 10% to as high as 80% depending on the population studied (4, 10). Transmission of HSV usually occurs person-to-person, by direct contact with infected secretions or mucosal surfaces. As sexual activity increases the likelihood of HSV-2 infection also increases.

The diagnosis of HSV infection is mainly clinical, and in suspected cases, scraping of the ulcer's edge for a Tzanck smear can be done, but polymerase chain reaction (PCR) methods represent the diagnostic test of choice. The culture of the vesicular fluid is a very specific and sensitive test but is very rarely performed. Other methods such as direct fluorescent antibody assay or direct staining for HSV antigens can also be used to diagnose the infection (4).

HSV lesions present clinically as painful vesicles and ulcers of various sizes and number. These lesions may be coinfected with other pathogens. In the immunocompromised patients these lesions can be atypical, more severe, larger, and slower to heal than in the immunocompetent population (4, 11). In the patients with a low CD4+ count, giant ulcers have been described (up to 20 cm in diameter) as well as atypical verrucous lesions resembling condyloma (12). Patients with a CD4+ count inferior to 100 cells/mm^3 may develop disseminated infection and more frequent recurrences are observed. Chronic herpetic lesions lasting more than 1 month are a CDC classified as AIDS-defining illness (11).

Concerning the treatment of this condition, various antiviral drugs are used such as acyclovir, valacyclovir or famciclovir. Clinicians should consider the possibility of antiviral resistance if herpetic lesions fail to heal with standard antiviral therapy. Non-adherence and poor absorption should also be considered. The clinician should refer the patient to an HIV or infectologist when acyclovir-resistant HSV is suspected (11). In general, treatment is oral, well-tolerated, and effective. Systemic antiviral therapy has been shown to improve and shorten the duration of clinical symptoms and signs; however, treatment does not eliminate the virus. Topical antiviral therapy for genital herpes has a very limited efficacy. Intravenous therapy is necessary for severe mucocutaneous progressive disease, or in case of visceral involvement (e.g., esophageal or hepatic), or antiviral resistance.

Clinicians should obtain HSV drug-susceptibility tests, if available, when patients receiving antiviral treatment have persistent or recurrent HSV lesions. Most resistant viral isolates are thymidine kinase (TK) deficient and are therefore resistant to acyclovir, valacyclovir, famciclovir, penciclovir, and ganciclovir. If available, drug susceptibility testing should be obtained when patients receiving antiviral treatment have persistent or recurrent HSV lesions. Treatment options for resistant HSV include the use of several topical drugs such as cidofovir gel, imiquimod cream, trifluridine solution as well as systemic drugs such as iv foscarnet or cidofovir for a few weeks (11). After resolution of the primary symptoms, HSV becomes latent in the patient's cranial nerve or dorsal root sensory ganglia. The chronic immunodeficiency in the HIV patients put them at increased risk for HSV reactivation (4,13).

Subclinical reactivation, or viral shedding, of HSV infection is common in HIV-positive and in seronegative patients; however HSV-2 reactivation is more frequent in HIV-infected patients. Chronic suppressive therapy may be advisable in patient with frequent symptomatic recurrences. Suppressive antiviral therapy has been shown to decrease the frequency of recurrences, to decrease but not eliminate HSV shedding, and to decrease transmission of HSV to non-HSV-infected partners in immunocompetent hosts (13). There is evidence that HSV reactivation is associated with increased of HIV RNA levels and that chronic daily HSV antiviral therapy decreases HIV RNA drastically in patients not receiving HAART(13, 14). Thus, HSV suppressive therapy may be considered in HIV-infected patients who are not receiving effective antiretroviral therapy.

2.1.2 Varicella zoster virus infections

Varicella zoster virus (VZV) is a part of the α-herpesvirus family and is an exclusively human pathogen. This virus is present worldwide and is highly infectious (15). Primary infection leads to acute varicella or "chickenpox", usually from exposure either through direct contact with a skin lesion or through airborne spread from respiratory droplets (15, 4) VZV establishes lifelong latent infection in the dorsal root ganglia. Reactivation of VZV can result in herpes zoster, also known as "shingles". Herpes zoster presents as a localized eruption along the course of one or more dermatomes, most commonly the thoracic or lumbar. The rash, which is often preceded by localized pain, begins as erythematous papules that evolve into vesicles (15). The vesicles may coalesce into large, confluent blisters with a hemorrhagic component. Healing occurs over the course of 2 weeks, although permanent skin changes such as discoloration and scarring may occur (15, 17).

Herpes zoster caused by reactivation of varicella virus occurs almost 20 times more frequently in HIV-positive individuals than in HIV-negative individuals of the same age, and the condition can present at any stage of immunosuppression. In the severely immunosuppressed patient, herpes zoster may extend beyond one or two dermatomes, causing atypical, ulcerated, and painful lesions that are difficult to treat. In cases in which the skin lesions are atypical, biopsy with direct immunofluorescence or the use of PCR establishes the diagnosis (17).

The suggested treatment for herpes zoster in patients with severe immune deficiency consist of iv administration of acyclovir 10–15 mg/kg every 8 hours (4, 18). Patients should be treated until complete healing which correspond to a period of 10 to 14 days to decrease relapse rates (18). HIV positive patients whose level of immunosuppression is not dramatic can be treated orally with acyclovir taken at the dose of 800mg five times per day, or with 1g of valacyclovir three times per day, famciclovir 500 mg three times per day is also an option (18). In 2006, a varicella zoster vaccine was approved for use in patients over 60 years of age who have not previously had herpes zoster (4). The vaccine achieved an approximately 50% (4) reduction of the incidence and a 67% reduction of postherpetic neuralgia, suggesting that the vaccine may lessen the likelihood of complications even if herpes zoster occurs (4). Varicella-zoster immune globulin is effective in preventing disease in susceptible individuals when administered within 96 hours of exposure. Its use should be considered in all immunocompromised patients and in susceptible pregnant women who have been exposed.

2.1.3 Epstein Barr virus infections

Epstein Barr virus (EBV) is spread by oral secretions and it is estimated that 95% of adults carry this virus (4). Oral hairy leukoplakia (OHL) is a disease of the mucosa first described in 1984 (19). This pathology is associated with EBV and occurs mostly in people with HIV, both immunocompromised and immunocompetent (21). When associated with HIV or AIDS, oral hairy leukoplakia may be one of the first signs of infection with HIV (20-22). EBV is able to stay dormant in B cell of the host, establishing a latent lifelong infection, but persistent EBV infection remain asymptomatic in immunocompetent patients, whereas the lytic infection in the oropharynx of the immunosuppressed patient (21, 22). The majority of patients with OHL tend to have significant immunosuppression at the time of diagnosis which is usually made on clinical grounds (20). The definitive diagnosis of OHL is established thanks to histopathological studies of tissue, demonstration of the presence of

EBV DNA or RNA through *in situ* hybridization techniques, or biopsy in case of atypical and confusing lesions (20, 23). The main characteristics of the histopathological exam in OHL include hyperkeratosis, parakeratosis, acanthosis, while the basal epithelial layer is preserved and normal (20). It has also been noted an important decrease or absence of the Langerhans cells antigen presenting immune cells (22). In the biopsies of hairy cell leukoplakia tissues, a severe decrease or even absence of Langerhans cells has been noted. Langerhans cells are the antigen-presenting immune cells that are required for an immune system response to the viral infection and their deficiency may permit EBV to persistently replicate and escape immune recognition (22).

The clinical presentation and signs consists of unpainful white patches or plaques on the lateral borders of the tongue and rarely on other sites in the oral cavity. If lesions appear on the ventral tongue, buccal mucosa or on the gingiva they may lack the characteristic hairy appearance and look more smooth and flat (24). The plaques resemble the oral thrush encountered in candida infection. When scrapping is done to OHL lesions, they cannot be moved or dislodged totally (20, 25). Lesions may frequently appear and disappear spontaneously, they can also change the appearance daily, and this is probably why many patients are not aware of the fact that they are affected (20). The possible complication associated with OHL is candidal superinfection, which often results in glossopyrosis. Altered taste sensation is rare but might happen (20). Antifungal agent such as nystatin can be used to reduce the risk of candida superinfection (20).

OHL is a medically benign condition with low morbidity. The reason to seek treatment is mainly cosmetic and the presence of oral lesions has a significant impact on health-related quality of life (20, 26).

High doses of oral acyclovir or newer agents like valacyclovir and famciclovir can temporarily reverse the lesions (4, 20). Foscarnet is used in acyclovir-resistant case (20). However, nucleoside analogs are not efficient on persistent, latent EBV infection, lytic EBV replication and OHL frequently recur after therapy withdrawal (20). It is also possible to use topical agents like podophyllin and retinoic acids but this also not a conclusive treatment, since OHL can recurred several weeks after therapy (20).

2.1.4 Cytomegalovirus infections

Cytomegalovirus (CMV), a member of the Herpesviridae family, is an opportunistic infection which can have a benign course in the immunocompetent host but has a more severe course in the immunocompromised patients (27). Infection to human CMV is a common worldwide but its prevalence varies greatly according to socioeconomic factors. Person-to-person contamination can occur by contact with several body fluid or substance like blood, urine, saliva, cervical secretions, feces, breast milk, and semen (4, 9). Most CMV infection are considered subclinical and benign in the immunocompetent host. On the contrary, in the immunocompromised host, infection with CMV produces severe disease in multiple organs, causing retinitis, hepatitis, pneumonitis, gastrointestinal disease (gastric and esophageal ulcers and colitis), and polyradiculopathy (4).

Cutaneous CMV is considered rare, and it is mostly affecting HIV patients who developed AIDS. It has been also beem reported in immunosuppressed patient who are transplant recipient (27). Nevertheless, the skin might be the first site of CMV manifestation so it is still necessary to suspect and detect infection to provide the right treatment (27). Cutaneous CMV has a variety of clinical presentations ranging from localized ulcers to maculopapular rashes and vesiculobullous eruptions that can mimic herpetic infections (27). In the immunocompetent host, infection by CMV can be either asymptomatic or can mimic mononucleosis. On the contrary in the immunocompromised host is usually symptomatic, presenting with fever, malaise, leukopenia, and sometimes rash. The skin lesions can appear under multiple forms as nodules, crusted lesions, papules, oral ulceration. They can be presented as localized or generalized eruptions of papulopustules, crusted papules, nodules and urticaria-like lesions. In the HIV patients, often cutaneous manifestations of CMV present as ulcers located in the perineal region (9). Other pathogens, notably HSV may be found in the same lesion which can lead to confusion concerning the pathological role of CMV. HSV might be the initiating infective agent which causes the ulcer formation, and CMV localize secondary in the granulation tissue (9). Skin involvement with CMV can portend a disseminated infection and is associated with a high mortality estimated at 85% in six months in the immunodeficient patient (28). As already mentioned CMV infection can mimic or co-exist with other viral infection and suspicion of misdiagnosis should be high when lesions attributed to HSV or VZV don't improve under treatment. Several drugs are available for treating cutaneous CMV, including ganciclovir which is the drug of choice, foscarnet, cidofovir, and valganciclovir (4, 27, 29). Immunocompromised patients may

require an indefinite course to reduce the risk of reactivation of the disease.

2.1.5 Pox virus infections

Molluscum contagiosum (MC) is a condition resulting from the infection with a DNA virus from the Poxviridae family. It replicates in the cytoplasm of epidermal cells. MC infection is, in general, seen in children and it is a common viral disease, which in healthy individual is self-limiting. Adolescent can also present with MC in the genital area, as an STD (30). In young HIV positive individuals who are not on antiretroviral therapy or the ones who are not compliant, MC infection is frequently seen and might indicate a low CD4+ count (under 100/μL) (31). The clinical presentation is small painless flesh colored papules with central umbilication (4,9). As regards specificity to HIV patients, MC can be widespread and present on unusual sites like the face, scalp neck. The morphology and the size of the lesion is also atypical. The lesions can be solitary or aggregated, inflamed and giant. MCs can present like giant condyloma accuminata or ecthyma, comedones, abscesses, furuncles, syringomas, keratoacanthomas (9, 32). The lesions of molluscum in patients of HIV can appear verrucous, pruritic or eczematous (33). In immunosuppressed patients, they can persist for months and become extremely numerous.

The diagnostic is mostly clinical and can be confirmed by histopathological examination. (4). The lesions can be destroyed by curettage, electrocoagulation, or cryotherapy (4). But, the numerous lesions associated with immunocompromised host make it hard to use physical destruction methods like cryotherapy, extraction and curettage or topical treatment such as imiquimod and topical cidofovir (30). Cidofovir may be effective in the most severe cases (4) Diphencyprone contact immunotherapy might be another option in the treatment of widespread molluscum contagiosum in immunocompromised patients (30).

2.1.6 Human papillomavirus infections

Human papillomaviruses (HPV) are members of the Papovaviridae family of double-stranded DNA viruses (4). Currently about 200 types of HPV have been identified, with more than 30 types infectious for the lower genital tract, of which around 15 or them are oncogenic (34) The “low-risk” types (6, 11, 42, 43, 44) are primarily associated with genital warts and respiratory papillomatosis, and the “high-risk” types (16, 18, 31, 33, 35, 39, 45, 51, 52), are associated with low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL) and invasive cancer(36).

Diagnosis of genital warts is generally based on clinical observation. Subclinical infections occur more frequently than visible genital warts in both men and women. The application of acetic acid solution (5%) for 3 to 5 minutes can help in diagnosing cases in which lesions are very small or flattened. Biopsy and molecular detection of HPV genotypes may be necessary to confirm the diagnosis (37). Genital warts, or condylomata acuminata, are one the most common viral STD. Although the most common mode of transmission is through sexual contact, nonsexual routes of transmission via fomites and nonsexual contact are possible (37). Widespread or recalcitrant warts may be observed on the oral mucosa, the face, the perianal region, and the female genital tract in patients infected with HIV.

Lesions should be treated due to the high chances of contagion, and risk of squamous cell carcinoma development. In some cases they can undergo spontaneous resolution but this is rare in the immunocompromised patient. The lesions might also increase in size and number or remain unchanged. HPV lesions, especially in anogenital region may often be difficult to treat. Treatment of HPV lesions consist of the use of topical chemical agents such as podophyllin, bichloracetic acid trichloroacetic acid, chemotherapeutic agents. Immune response modifiers such as imiquimod or podofilox (gel or solution) are also an alternative and can be used in the treatment of external anogenital warts (37). Cytotoxic agents are also part of the HPV treatment, like for example 5-Fluorouracil (5-FU). Ablative therapy is also a mean of treating HPV associated lesions with the use of cryotherapy, electrodesiccation, surgical excision and CO_2 laser (37).

Unfortunately, the current medical pharmacologic treatment against HPV is neither highly specific neither highly efficient, therefore the primary mean for treating warts remains the surgical removal of symptomatic lesions. Lesion removal can induce a rapid improvement, followed by a "wart-free period". Patients who are immunosuppressed may not respond as well as immunocompetent persons to therapy for genital warts, and their lesions may be widespread and may recur more frequently after treatment (37). It has been shown that application of imiquimod 5% cream can result in complete resolution of genital warts in up to 50% of patients but recurrence rates range from 19-23% at 6 months (38). Prophylaxis is also available through the use of HPV vaccines which have been proven efficient in some cases (39).

2.2 Bacterial skin disease in HIV infections

2.2.1 Staphylococcus aureus infection

About 50% of HIV positive individuals are nasal carriers of *Staphylococcus aureus* (*S. aureus*) (40). *S. aureus* is the most frequent bacterial infection in HIV positive patients (41). Different pattern of infection can be present such as bullous impetigo, ecthyma, folliculitis, hidradenitis-like plaques, abscesses, cellulitis, and many more.

2.2.1.1 Bullous Impetigo

Impetigo usually affects children with a preponderance for males, but it also affects adults with decreased immunocompetence, like patient with HIV (42). Impetigo is a very superficial vesiculopustular skin infection that present mainly on exposed areas of the face and extremities but also in the groin, perineum and axilla (41). The infection is more frequent in warm, humid weather (4, 42). Bullous impetigo is 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 (41) and ulcerated impetigo is called ecthyma, which is considered a deep form of impetigo, as the same bacteria causing the infection are involved (42). Bullous impetigo is due to staphylococcal exfoliative toxins, which target desmoglein 1 (a desmosomal adhesion glycoprotein), and cleave off the superficial epidermis through the granular layer. No trauma is required as the bacteria can infect intact skin (42). The diagnosis of bullous impetigo is mainly clinical but microscopic examination of bacterial swabs can be done for confirmation (42).

To treat impetigo, it is important to clean the wounds to remove the crusts and apply antiseptic products, and or topical antibiotics ointments such as topical mupirocin or mucopurine. (42 ,43). The patient is treated topically unless multiple lesions are present, in which case, it is preferred to use a systemic oral antibiotic therapy mostly amoxicillin-clavulanate, dicloxacillin, flucloxacillin (4, 42,43). Prevention is important because the condition is contagious and can recur, therefore it is important that patients keep a high level of hygiene and avoid close contact and sharing laundry, towels, the patients should change linen and clothes daily (42).

2.2.1.2 Folliculitis

Folliculitis is a pyoderma of the hair follicles (4) The inflammation of hair follicules can be superficial or deep. Consequently, folliculitis can be present anywhere in hairy regions of the body, including chest, back, buttocks, arms and legs (4, 44). Immunosuppression, nasal carriage of *S. aureus* and other factors acts as predisposition to folliculitis. Folliculitis has been shown to occur predominantly when CD4+ lymphocyte counts fall below 200 cells/mm, (45). The lesions are small, erythematous, tender, and multiple, a pustule is often present at the "peak of the lesion". Drainage of the lesions may be spontaneous (4, 44). If the follicular lesions extend deeper they might forming abscesses. The infected follicles can also coalesce and form large purple "hidradenitis-like plaques" (41). Pyomyositis is another very rare complication of folliculitis in HIV positive patients; it is a bacterial infection of the skeletal muscles which results in a pus-filled abscess (41). The HIV-associated itchy folliculitis can be either eosinophilic folliculitis (EF) or infectious folliculitis (IF). It is not possible to differentiate between the two conditions on clinical grounds. As both condition have different treatment of choice, it is important to perform Gram's stain and culture to confirm the diagnosis (45). Often the follicular lesions of the trunk are intensely pruritic and may be mistaken for other pruritic dermatoses, such as scabies (7). About 50% (41) of HIV-infected patients with scabies have coexistent *S. aureus* folliculitis. Concerning treatment, hygiene and cleaning the lesions with an antiseptic is needed. Topical antibiotic can also be applied as the first-line of the treatment agents (44). In case of widespread, deep or difficult to treat lesion, systemic antibiotics may then be indicated. The drug of choice must cover penicillin-resistant *S. aureus* or, in some situations, methicillin-resistant *S. aureus* (MRSA) (46). Oral antibiotic therapy with dicloxacillin or cephalexin can be prescribed in the case of *S. aureus* folliculitis (41). For the prevention, once per month for a course of five days, patients can apply, mupirocin ointment on both nares, to reduce relapse of folliculitis (4 ,41).

2.2.2 Bacillary angiomatosis

Bacillary angiomatosis (BA) is caused by two species of Bartonella: *Bartonella quintana* and *Bartonella henselae*. Bacillary angiomatosis resulting from infection to *Bartonella henselae* is transmitted by cats (reservoir of the bacteria) through contact and scratches, and it is therefore considered as zoonotic infection (47). Today, the majority of the cases occurs in AIDS patients (or other immunosuppressed patients). It may also be a complication of cat-scratch disease in immunocompetent patients, which is a benign condition with persistent adenopathy (47-49). The size and number of lesions is widely variable. The lesions can be

superficial, and present as erythematous papules or nodules, and they can ulcerate and bleed (49). Deeper lesions can appear like cellulitis. Beside the skin other organs can be affected like bones, liver, lymph nodes spleen and mucoses. Sometimes, fever and bacteremia are the only sign of infection (49), in which case the diagnosis cannot be based on clinical grounds than with laboratory tests (49,50). On microscopic histologic exam, vascular growth with epithelioid endothelial cells and granulocytes are observed (48). The differential diagnosis includes Kaposi sarcoma and "Verruca peruana" as the lesions from bacillary angiomatosis look very similar. But unlike bacillary angiomatosis, microscopic examination of Kaposi sarcoma the bacilli in the granulomas lesions are lacking and the lesion are not painful (47, 49).

For the treatment, mostly macrolides are used. Oral erythromycin is the first choice of therapy (500mg is taken four times a day for three months in the immunosuppressed patient). Tetracycline can be used as second line treatments with the use of doxycycline 200 mg twice a day. IV administration of the antibiotic should be considered in severe cases and rifampin should be added (49). Erythromycin is the most potent drug in the treatment of BA. Its high efficacy appears to be due to an antiangiogenic effect of the molecule, not dependent on its bacteriostatic properties according to the results of an *in vitro* study in which it was observed that erythromycin provokes also regression of previous proliferative lesion due to *B. quintana* (51). Duration of the treatment should be strictly respected as relapses can occur; usually the lesions resolve after a few weeks but antibiotics should be taken up to several months (three or four) if visceral lesions are present(41, 47, 49). Patients should maintain hydrated and they are adviced to use analgesic for pain and fever as well as use of moist compresses on the nodes and if they have large pus filled lesions, drainage may be appropriate (47). As prevention, HIV infected individual should avoid contact with cats (49, 50).

2.2.3 Syphilis

Syphilis is a disease resulting from infection with the spirochete *Treponema pallidum (T. pallidum*) which is a long and slender bacteria (4, 52). Transmission occurs in majority of cases during unprotected sexual intercourse. Other mode of transmission include blood transfusion and transplacental infection (4, 52). Men who have sex with men (MSM), sexually active heterosexual with multiple partner and risky behavior are particular groups at risk of contracting the condition (4, 52-54). Individual affected with syphilis are twice to five times likely to acquire HIV due to the lesions are present in the genital mucosa and if they are

bleeding, which also increase the possibility of transmission of both conditions (53, 55). Clinically syphilis is described in four stages: primary, secondary, latent, and tertiary. During the primary stage, *T. pallidum* penetrates the skin and proliferate in the subcutaneous tissue. The infection by this organism is followed by an inflammatory response which leads to the formation of skin papules which become painless ulcers called chancre (4). The chancre is most of the time solitary but might also be multiple. These lesions appear about three weeks after exposure to *T. pallidum*, which correspond to the incubation period average of 21 days but can vary between 10 to 90 days (4, 54, 55). Healing occur in about one to two month without treatment (54).

The secondary stage is highly infectious period and can present differently (4, 54, 55). Secondary stage of syphilis has been known as "the great imitator" as it may cause symptoms similar to many other disease. Usually, a skin rash appear and it can be localized or widespread. In general the eruption is non pruritic. The exanthem may be macular, papular, pustular, or mixed. Lymphadenopathy is also present, and non-painful (55). This can go unnoticed in many patients but in other constitutional symptoms like fever, fatigue, muscle and joint pain can manifest. Patchy alopecia as well as *condylomata lata* can accompaigned this stage of the disease.

The latent phase refers to a silent period where the infection is under control by the host immune system. It can last up from a few years up to 25 years (55). During this phase, the patient appear normal and asymptomatic although in the early latent phase they are still infectious (4, 54, 55). Diagnosis is still possible during this period through the fluorescent treponemal antibody absorption assay (FTA-ABS) or by hemagglutinin tests (4).

The last phase is called tertiary or late syphilis. Patients with syphilis who remain untreated have a 40% risk of developing late syphilis (56). This disease causes three major syndromes: cardiovascular syphilis, neurosyphilis, and gummas (4). Gummas are granulomatous lesions of the skin, bone and mucous membranes. They form circles with peripheral hyperpigmentations. Skin gummas can break down into chronic ulcers, but usually they are "indurated nodular papulosquamous lesions " (4, 55).

The diagnosis of syphilis is not so simple. Several options are available but as in every medical procedure it should be cost effective. The most common diagnostic method is serologic testing. The Venereal Disease Research Laboratory test (VDRL) and the Rapid

Plasma Reagin (RPL) test are called non treponemal test (NTP) because they detect non treponemal antibodies directed against cardiolipin antigenic substance. NTP tests can be useful to monitor a response to therapy. On the other hand, treponemal tests (TT) detect antibodies directed against *T. pallidum*. The antibodies persist for a lifetime so the TT are not used to verify disease activity but rather confirm a positive VDRL or RPR test (4). The sensitivity and specificity of all these test is not identical and depend as well on the stage of the infection (4,57). Another diagnostic option is the use of darkfield microscopy for cutaneous lesion samples from the chancre, or *condyloma lata* scrapings. This is not always available and immunofluorescence staining of the smears can be used as well but is technically demanding but more sensitive (4, 54, 55).

Concerning the treatment of syphilis, the WHO established guidelines are the following: for the early syphilis a single intramuscular injection of benzathine penicillin G 2.4 million units should be given (55, 58). Late syphilis or unknown stage of syphilis, use intramuscular injection benzathine penicillin G 2.4 million units once per week for three consecutive weeks (55, 58). If the patients have a known penicillin allergy and desensitization is not an option, doxycycline at the dose of 100 mg twice per day, taken orally for a month should be used (55, 58).

Careful monitoring after therapy is required, as patients with HIV infection are at higher risk for reinfection and have a slower serologic response than patients without HIV infection (59).

It is important to note that there is a possibility of Jarisch-Herxheimer reaction after initiation of syphilis treatment (4). Jarisch-Herxheimer reaction is an inflammatory reaction due to the death of treponemes. Skin exacerbation of already present lesions like chancre or rash can also be part of the numerous symptoms of the reaction for example: fever, myalgias headaches, tachycardia 84, 55). The treatment is symptomatic and the reaction subsides in general 24h after its onset (4, 55).

Syphilis is a curable STD, so patient education about symptoms is important to encourage them for seeking medical help for treatment (53).

2.2.4 Atypical mycobacterial infection

The species the most commonly accountable for skin infections are: *Mycobacterium (M.) ulcerans, M. marinum*, *M. fortuitum* and *M. chelonae*. They are acquired from the environment and identification of reservoir is often challenging. The diagnosis of skin and soft tissue infection due to atypical mycobacteria is established by culture of drainage material or by tissue biopsy and histologic examination (60, 61). The treatment consists of a single antimicrobial or a regimen of several drugs acting synergistically, for at least several weeks to months (60, 61).

2.2.4.1 Mycobacterium ulcerans; Buruli's ulcer

This condition is endemic in tropical regions of Central Africa, hence the name Buruli, an Ougandese region. The infection is also present in Central and South America as well as South East Asia (62). The mechanism of infection is not well established but skin inoculation of the microorganism is probably the cause of the infection even though the initial wound is not present at the time of diagnosis (63). Clinically the lesion is in general solitary and painless, although an itchy nodule could also develop one to two weeks after the infection. This nodule is likely to evolve into a shallow ulcer one to two months later and spread over up to 15% of the patient's skin surface (61). Complication can involve destruction of blood vessels nerves and bone (61, 62). Surgical treatment consists of wide debridement followed by skin grafting. Medical treatment with sulfonamides, and clofazimine is less effective, especially if advanced lesions are present (60). Immunocompromised patients are at higher risk of developing severe form of the disease.

2.2.4.2 Mycobacterium chelonae and M. fortuitum

M. chelonae and *M. fortuitum* are distributed worldwide and the reservoir is water (tap, sources, sewage). They both affect multiple organs and skin. The infection occurs through skin traumas, and puncture wounds (61, 62). The lesions can represent nodules or abscesses. In patient with immunosuppression the infection can become widespread, disseminated and difficult to heal (61,62). Treatment may include amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, sulfonamides, and imipenem for the *M. fortuitum* group, whereas only amikacin, cefoxitin, imipenem, and clarithromycin or only amikacin, imipenem, tobramycin, and clarithromycin have activity against *M. abscessus* and *M. chelonae*, respectively. The duration of treatment vary between four to six month (60-62).

2.2.4.3 Mycobacterium marinum

Another condition called "swimming pool" or "fish tank" granuloma (61) is caused by the *M. marinum.* Skin lesions appear approximately two or three weeks after contact with water contaminated with *M. marinum*. Purple papules that can evolve into ulcers and scars are mostly present on the upper limbs, most often the small violet papules are present on the hands and arms and may progress to shallow crusty ulcerations which will cause scarring. (61,62). The medical treatment consists of simultaneous use of rifampin and ethambutol or single drug treatment with either doxycycline, minocycline, clarithromycin or TMP-SMX. The duration of therapy is minimum of three months (62). Rifampicin cannot be used in HIV treated patient due to interaction with protease inhibitors, the alternative is the use of rifabutin (60).

2.3 Fungal infections in HIV positive patients

Fungal infections are extremely common in the HIV positive patients. It is estimated that 90% (64) of HIV infected individuals have a form of candidiasis (oral or anogenital). Concerning systemic fungal infections, cryptococcosis is the most frequent one but aspergillosis, zygomycosis, phaeohyphomycosis, hyalohyphomycosis, coccidiomycosis, blastomycosis and penicillosis might also be encountered (65, 66). Fungal diseases can be present at any stage of the disease but the lower the CD4+ count the higher the chances of being infected (67).

2.3.1 Superficial fungal infections

Candida genus of yeast is a part of the normal human flora but if the host defense are lowered like in a immunocompromised patient, the infection can develop under different manifestations. *Candida albicans* is the most common species responsible for mucocutaneous infections.

The diagnosis of the condition is clinical but microscopic examinations of smears with potassium hydroxide and culture of swabs can be used for confirmation. The culture is not always relevant as a diagnosis tool because candida can be a normal part of the flora in a individual carrier, although it can aid in the differentiation of species (64, 68). On histological examination, under Periodic acid–Schiff (PAS) staining, candida hyphae in the superficial epithelium are observed. In immunodeficient patients, the inflammatory component of the

candida infection might be absent (64).

Oral candidiasis can be present in a variety of forms, the most common presentations being pseudomembranous, erythematous candidiasis, and angular cheilitis. Some of these conditions impair the quality of life of the patient as the symptoms interfere with eating like for example dysgeusia, burning mouth sensation. Moreover, oral candidiasis is often associated with esophagitis and dysphagia (64, 69). Pseudomembranous candidiasis, also known as thrush, usually presents with yellowish-white plaques on the oral mucosa (4). Plaques detach easily when scrapped, and removal of these plaques uncover a red mucosa. Erythematous candidiasis are red shiny spots which can be observed on the tongue (dorsal region) and/or palate. The erythematous form of candidiasis consists of brilliant spots or patches that can have different size. This infection is underdiagnosed due to its discrete appearance (4, 70). Candidiasis can also present as angular cheilitis. The clinical picture consist of redness, fissures, ulcers, bleeding and crusting at the corner of the mouth bilaterally. This condition can persist for a long time (71).

Systemic and topical drugs are used in the management of candidiasis. Nystatin or clotrimazole are mostly used for topical treatment. The topical agent needs to stay in contact with the mucosa for at least 20 minutes, the medication can be found as pastille or troches (72). Several drugs from the azole class can be used for systemic oral therapy. For example , 200 mg of ketoconazole can be taken once daily, or 100 mg of fluconazole 100 mg once per day for two weeks. Other drugs include itraconazole, voriconazole and ravuconazole (4, 64, 70). Intravenous therapy with amphotericin B is also used at the dose of 3-5 mg/kg per day. Newer agents such as the echinocandins can also be an option (4, 64). Unfortunately, relapses are common and can become more and more frequent with time. The management of the disease is then difficult. Patients with CD4+ counts <50 cells/µL (4) may be affected by refractory candidiasis, the condition becomes unresponsive to treatments and management becomes difficult. HAART is also an important component in the treatment and prevention of candidiasis by reversing the immunosuppressive state, patients can become candidiasis-free for a while (4). Prophylactic therapy is also used; the patient then takes drugs once weekly or monthly. However, continuous use of antifungals has to be avoided or used cautiously in cases where it is needed to prevent the emergence of drug resistance (4).

Vulvovaginal candidiasis is characterized with pruritus and burning sensation of the mucosa accompanied by white discharged. It is the common presentation of genital candidiasis in

women (67). Patients with lower immunity status have more severe symptoms and more frequent episodes (67, 73). This candida infection in anogenital region is like oral candidiasis diagnosed on clinical and microscopical examination of vaginal secretions with potassium hydroxide (KOH) slide preparation. Culture can confirm the diagnosis but is not necessarily done (67). The treatment consists of short courses of azoles drugs (oral fluconazole at the dose of 150 mg once), topical butoconazole cream for three days, or clotrimazole suppositories for seven days (67). In the case of chronic recurrent vulvovaginal candidiasis, long term and prophylactic oral azole therapy should be implemented. Patients should be put on a regimen including the use of fluconazole at the dose of 150 mg every other day for a total of three doses, then weekly fluconazole 150-200 mg for six months (74).

2.3.2 Deep fungal infections

2.3.2.1 Cryptococcal disease

Cryptococcus is an encapsulated yeast that exist in two variants: the neoforlant variant and gatti variant. This fungus is widespread around the world and is present in bird droppings (pigeon especially), dust and soil. The infection usually start in the lungs but the disseminated form of the disease is quite common and various organs including the skin are then affected. Disease attributed to the neoformans variant is more common in the immunosuppressed patients, hence the HIV population, as cell mediated immunity plays an important role in the evolution of the disease (75). In AIDS patients, cryptococcal disease affects the CNS and patients present with meningitis. Skin may be affected before or at the same time. The lesions are commonly located on the head or neck but can also be present elsewhere on the body. Approximately 6% (75) of patients with HIV disease and cryptococcosis have skin lesions. The lesions can have several aspects: papules or pustules, nodules that can become ulcers, plaques, or even masses (41, 75). Enzyme-linked immunosorbent assay, latex agglutination tests or microscopic examination of slides containing exudate from a lesion are used for detecting the condition. Skin biopsy and culture confirm the diagnosis (75). Lumbar puncture for cerebrospinal fluid (CSF) examination should also be performed in case of skin manifestations as it can indicate disseminated disease (75).

Concerning the treatment of non CNS cryptococcal disease, the use of amphotericin B formulations is recommended and should be combined with flucytosine followed by fluconazole at the dose of 400 mg daily (67, 75, 76). Fluconazole in doses ranging from 400-800 mg per day plus flucytosine is another option in patients unable to tolerate amphotericin

B (67, 75, 76). However, the combination of fluconazole plus flucytosine is clinically inferior to amphotericin B–based therapy. Moreover, fluconazole therapy is recommended for life in immunocompromised patient but it is possible to discontinue this treatment after 1-2 years if the patient is on HAART and has maintained a CD4+ >200/μL for at least 6 months (75), a non detectable viral load, and a negative serum *Cryptococcus* antigen test result (75). Other therapeutic alternatives in cutaneous cryptococal disease include surgical treatment, cryotherapy or excision of the lesions (75).

2.3.3 Dermatophytes infections

Dermatophytosis represent the infection by a group of three types of filamentous fungi that are common all around the world both in the healthy general population and immunosupressed individuals. Dermatophyte are the most common cause of fungal infections of skin, hair and nails presenting clinically with various tinea: *capitis, corporis, cruris, pedis, unguium* and Majocchi's granuloma (77). Infection of the nails by fungi is called onychomycosis and is considered responsible for about 50-60% of "abnormal-looking nails"(78). In HIV patients with lower CD4+ counts the prevalence is higher than in the general population and treatment is more difficult with higher recurrence rates and treatment failure (79-81). Diagnosis can be made with a KOH preparation of the skin or nail scrapings. Cultures and skin biopsy can also be performed. A periodic acid-Schiff stain can be used to identify fungus on the biopsy (82).

Tinea pedis or "athlete's foot" is the infection located on the feet and is the most common dermatophyte infection (83). The lesions are in general interdigital, and present as an hyperkeratotic or vesiculobullous eruption. Pruritus going along this infection is relieved by treatment which also decrease the development of secondary bacterial infection and risk of spread to other body parts (83). *Tinea pedis* frequently is accompanied by *tinea unguium*, *tinea cruris*, or *tinea manuum*. For these conditions, antifungal therapy is the treatment of choice for most patients. Systemic antifungal agents are primarily reserved for patients who fail topical therapy. In this case terbinafine at the dose of 250 mg per day for two weeks, or itraconazole 200 mg twice daily for one week (cannot be used with protease inhibitors) (83, 84). The use of fluconazole at the dose of 150 mg once weekly for two to six weeks is an alternative (83, 84).

Tinea of the nail or *tinea unguium* involves primarily the nail plate, and is most likely present

on the toes rather than fingernails. Nails look opaque and thickened, splitting and crumbling of the nails might happen. Onychomycosis requires a long-term therapy so it is important to confirm the diagnosis with microscopic examination and culture as not all ill-looking nails are infected by fungus. Relapse is common and constant use of topical antifungals is required. An associated tinea infection of the soles or toe webs is common, manifested by chronic maceration, scaling, blistering, and/or thickening of the skin. Occasionally, the palms are involved in a similar manner. Tinea is especially likely if two feet and one hand are affected in immunocompetent host whereas in HIV patients, both feet and hands are usually affected. Occasionally, tinea will spread to hairy areas, especially the face and lower legs, causing a chronic plaque-like folliculitis that can be confused with chronic bacterial infection. Previous use of topical steroids may induce this pattern and mask the correct diagnosis.

Tinea corporis is a cutaneous dermatophyte infection occurring in trunk legs or arms, and Trichophyton (*T.) rubrum* is the most common cause of tinea corporis. Clinically, pruritic circular or oval erythematous patches or plaques can be observed. The lesion spread centrifugally and central clearing occur, the border of the lesions are usually raised and take the appearance of an annular plaque also called ringworm (83). Multiple plaques can unite and pustules can be present. In HIV patients *tinea corporis* can be very extensive and is usually an expansion to the trunk that originated from *tinea cruris* (72).

Tinea cruris is mostly caused by *T. rubrum.* This infection is more common in men than women. The infection can be caused by the spread of *tinea pedis* in the same individual. Immunodeficiency is considered as a predisposing factor as well as obesity and profuse sweating, and diabetes. Clinically, an erythematous patch can be observed on the proximal medial thigh. As for tinea corporis the infection spreads centrifugally, and the lesion becomes clear in the center with and a slightly elevated, erythematous demarcated border. Tinea cruris can extend to the perineum and perianal areas, gluteal cleft, and to the buttocks (83, 84). Recurrence of *tinea cruris* is common. If concomitant *tinea pedis* is present it should be treated to reduce risk for recurrence of *tinea cruris*. Treatment of onychomycosis may also reduce recurrences. Other measures that may be helpful include daily use of desiccant powders in the inguinal area and avoidance of tight-fitting clothing and non-cotton underwear (82, 83).

Treatment of *tinea corporis* and *cruris* is very similar. Topical therapy with antifungal agents such as azoles, allylamines, butenafine, ciclopirox, and tolnaftate is used (83). Topical

antifungal treatment is generally administered once or twice per day for one to three weeks or till resolution. In the case of topical treatment failure, systemic treatment with terbinafine and itraconazole is started (84). Treatment may be of a duration of 1 week per month to reduce cost. Once treated, fingernail infection has a long disease-free period. Toenail infection is common and chronic and does not require therapy unless it causes discomfort. Fluconazole and itraconazole are effective but expensive. Toenail infection is probably more likely than fingernail infection to relapse therefore, constant use of topical antifungals is often necessary, although their efficiency is doubtful (41, 84). Majocchi's granuloma is treated with oral itraconazole or terbinafine. HIV-positive patients are also more susceptible to the development of invasive fungal infections, including systemic fungal infections, which can present with cutaneous manifestations (8). Intravenous therapy is frequently required in these cases, usually with the use of amphotericin B (77). Caspofungin, a newer potent iv antifungal therapy with less drug interactions and fewer side effects than amphotericin B, is also effective against invasive fungal infections (83). However, its spectrum of activity is narrower than that of amphotericin B but does include *Candida* and *Aspergillus* (77, 83). Often, HIV patients are already taking an oral antifungal medication for the treatment of systemic fungal infections, which provides prophylaxis and treatment for tinea and onychomycosis (77). HAART is also helpful in treating superficial fungal infections. One counterpart of the repeated and chronic use of antifungal drugs in HIV patients is that they might induce resistance. Drug interactions should also be taken into consideration (77).

2.4 Parasitic infections

2.4.1 Leishmaniasis

Leishmaniasis is a disease caused by parasitic protozoa of the leishmania species and is now endemic in eighty-eight countries (86). The condition is transmitted by sand flies infected with the protozoa *Leishmania (L.)* (86). It presents in two main forms: visceral and cutaneous. Visceral leismaniasis (VL) is caused by *L. donovani* and runs a fatal course without treatment while cutaneous leishmaniasis (CL) is caused by *L. major* (a range of species) (86-88).

Leishmaniasis has several recognized clinical forms and their manifestation depends upon the species inoculated and the host’s immune response. The most important distinction is between American and non-American species of *Leishmania*, as the *Viannia* subspecies

found in the Americas, can result in mucocutaneous leishmaniasis. Human leishmaniases are classified according to the sites of involvement: CL, mucocutaneous leishmaniasis (MCL), diffuse cutaneous leishmaniasis (DCL) (86,89, 90). CL can become disseminated (DCL) especially in immunosuppressed persons. The illness can go on for years and does not heal spontaneously. Patients with HIV/AIDS are particularly susceptible (89-91). Leishmaniasis can be categorized by geographic areas of occurrence with a division of the world into 2 parts: the so called "old world" designating African, middle eastern, Asian and Mediterranean species: *L. major, L. tropica, L. infantum, L. donovani* (87, 89). New World leishmaniasis characterize disease caused by *Leishmania* species found in Central and South America including *L. mexicana, L. braziliensis, L. amazonensis* (89) wich cause CL. American species of Leishmania and more particularly *Viannia* subspecies can provoke MCL, which is a virulent and destructive disease. Cutaneous leishmaniasis is limited to certain geographical areas, mainly the old world (Sudan, Ethiopia, Kenya, India, Middle East) and the new world namely Brazil, Mexico and the United States of America but is spreading fast because of improved travel and migration. It is spread by sand flies although human to human transmission is possible (87). HIV patients which present with solely CL form are usually in initial stage of the infection and do not have severe immunosuppression. Ultimately, all HIV patients infected with *Leishmania* are likely to develop VL at some point (88). In some HIV-infected patients, CL develops as isolated papules or plaques on exposed areas. In localized CL, the patients can present with crusted papules and or ulcerated lesions (88, 89). The first lesion is in general a small sized erythematous papule which enlarge gradually up to 2 centimeters in diameter. The exposed areas of the skin are usually affected by these painless sores. In the immunocompetent subjects, the lesions resolve in general in a few months but in immunodeficient patients the conditions usually become chronic (87). Diffuse CL, is the fruit of a decreased response to the infection due to a reduced cell mediated immunity, the number of lesions is high and papules and nodules are widespread and can resemble the one found in leprosy. Diffuse CL is a chronic condition that is difficult to treat and relapse rates are high (88). Hypopigmented macules or erythematous papules and nodules or plaques can appear several months or even years after patients recovery from VL. This condition is called Post-kala-azar (86, 87). Mucocutaneous leishmaniasis is a painful condition that can be very destructive especially in the naso-oral region with possible destruction of the cartilage, palate pharynx leading to disfigurement. Patients with MCL are also prone to infections (86).

Diagnosis of CL is usually based on the history and clinical appearance of the lesion. If the

patients present in a non-endemic area, it is important to take a thorough history of the past week and months, paying particular attention to travel regions (89). The diagnosis is confirmed by identifying the parasite on biopsy or split skin smear (90). Culture and PCR may also be used to confirm the diagnosis and identify the species of Leishmania, which is important when there is a risk of MCL (89). Serology is used to confirm the diagnosis in cases of visceral leishmaniasis (87). Histology shows intradermal and subcutaneous aggregates of lymphocytes and plasma cells as well as many free small cells, ovoid to round shape identified as leishmania amastigotes with a diameter of 2-4 micrometers (88). Hyperkeratosis and acanthosis can be observed in the epidermis, and in older lesions, pseudo epitheliomatous hyperplasia is noted (89).

Co infection of Leishmania and HIV is correlated to the level of immunosuppression of the individual. Thanks to the advent of HAART, and the fact that it reduces the viral load and degree of immunosuppression, Leishmania infection in HIV patients can decrease (87, 89). Prevention of insect bites by avoidance of infested sand fly regions, the use of covering clothing, use of DEET (N,N-diethylmetatoluamide) insect repellent (89, 90). Most cases of simple CL will resolve spontaneously without treatment but this may take many months and can result in scarring. Systemic antimonial use is the classical treatment for complex CL lesions, MCL and VL. These drugs cannot be given orally and the length of treatment may be up to 28 days for mucosal lesions. Treatment requires hospital admission and there is a risk of side effects including cardiotoxicity (87). Decisions about whether and how to treat should be individualized. The treatment approach depends in part on the *Leishmania* species/strain and the geographic area in which infection was acquired; the natural history of infection, the risk for mucosal dissemination/disease, and the drug susceptibilities in the pertinent setting; and the number, size, location, evolution, and other clinical characteristics of the patient's skin lesions (88). The goals of leishmaniasis therapy are multiples. First of all, therapy may accelerate the rate of healing of skin lesions and decrease the risk of relapses and mucosal dissemination. The morbidity of severe lesion is thus reduced and patient quality of life might be improved. Lastly, therapy might have a protective and preventive effect in areas with anthroponotic transmissions by decreasing the reservoir hosts of infection. This is particularly relevant concerning regions where *L. tropica* is endemic such as in Afghanistan (88, 90). Systemic parenteral treatment include pentavalent antimonial, amphotericin B deoxycholate therapy, or lipid formulations of amphotericin B, pentamidine or less often isethionate (87). Oral systemic therapy with miltefosine has been administered and its effectiveness has been

variable in different geographic regions. Antifungal azoles such as ketoconazole, itraconazole and fluconazole have been used as well (90). Local therapy is feasible in some cases of CL that are quite limited and not at risk for mucosal dissemination/disease. Examples of local therapies include cryotherapy with liquid nitrogen, thermotherapy, intralesional administration of sodium stibogluconate or meglumine antimoniate, and topical application of paromomycin which has been shown to be effective against cutaneous leishmaniasis caused by *L. major* and *L. Mexicana* (87, 90). In general, the first sign of a therapeutic response to adequate treatment is decreasing induration or lesion flattening. The healing process for large, ulcerative lesions often continues after the end of therapy. Relapse takes place typically at the margin of the lesion (90).

2.4.2 Strongyloidiasis

Strongyloides stercoralis is an intestinal nematode that are able to multiply in human beings, that are the principal hosts to this parasite(93). About 70 million people worldwide are affected by strongyloidiasis (94). This infection is common in warm and humid climate, in the tropics and subtropics and is acquired via skin penetration by infectious filariform larvae. Usually the infection by the larvae occurs by contact with soil contaminated with human feces and sewage especially if walking barefoot (94, 95). Strongyloidiasis occurs only sporadically in temperate areas such as Appalachia and southern Europe (96). Two stages of the disease are noted: an acute stage and a chronic one. During the acute phase, it is possible to miss the first sign of the infection, which correspond to the site of the larva penetration and presents as a localized pruritic erythematous rash (97). Then larvae migrates into the pulmonary circulation via the lymphatic system and venules an patients can feel an irritation in the trachea and cough while larvae migrate from the lungs through the trachea. Following swallowing of larvae, nonspecific gastro intestinal symptoms are usually present and include diarrhea, constipation and pain (95, 98). In chronic strongyloidiasis, cutaneous and gastrointestinal manifestations are the most encountered, although the condition can also be asymptomatic. The most frequent gastrointestinal complaints are: epigastric pain, postprandial fullness, heartburn, and brief episodes of intermittent diarrhea and constipation (98). The typical cutaneous manifestations of strongyloidiasis is *larva currens*. It is a linear lesions or can adopt a serpiginous shape. The lesion is very pruritic and is surrounded by a moving flare. Most of the time, the trunk, groin and buttocks are the area mostly affected but thighs face and arms could also, although rarely, present the lesion.

The diagnosis is difficult because of the short duration of symptoms that the patients experience before being symptom free for the next weeks or months. Other times, patient present with several "spurs of attack" that last longer or are continuous (93).

In immunocompromised hosts, dissemination is probable and extensive migration of filariform larvae occur. A petechial and purpuric rash appear at the sites of migration. The rate of migration has been estimated form five to 10 centimeters per hour (95).

Strongyloidiasis is associated with chronic urticaria on the waist or buttocks in the shape of wheels that can last a few days(95).

The diagnostic gold standard for strongyloidiasis is serial stool examination for larvae. Specialized stool exams are needed and they include Baermann concentration, Horadi-Mori filter paper culture, quantitative acetate concentration technique, and nutrient agar plate cultures (95). Duodenal aspirate and biopsy are very sensitive exams (95). Serologic tests such as ELISA for IgG and IgE can be used as well. Up to 75% of people with chronic strongyloidiasis present with mild peripheral eosinophilia or elevated IgE levels (95). If patients are affected by dissemination of the infection, larvae can be found in body fluids as well. In cases of dissemination, larvae may be found in a wide variety of body fluids. Larvae may also be seen in lesional skin biopsies (97).

Treatment of the condition should start with the use of ivermectin at the dose of 200 μg/kg, two doses for one or two consecutive days (95, 97). Therapy with albendazole at the dose of 400 mg two times per day for a period of 3 to 7 days is an alternative to ivermectin but cure rates have been reported to be lower. In immunocompromised patients who have a disseminated form of the disease, raising level of immunocompetence and multiple doses of ivermectin should be implemented until resolution of the symptoms and or stool examination are negative for two weeks (95). Serious complications can appear due to strongyloidiasis, for example neurological, nephrological and vascular complication with the hyperinfection syndrome which is a bacteremia (98). Patients with strongyloides hyperinfection syndrome are at risk of lethal and fatal gram-negative sepsis. It is important recognize this condition and perform blood cultures and start the use empiric broad spectrum antibiotics if needed. If therapy fails, longer or repeated courses of ivermectin with 10 to 14 days interval in between should be tried. Monitoring the result of the treatment is possible with stool examinations and eosinophilic count use (94, 95, 98).

2.5 Ectoparasitic infections

2.5.1 Scabies

Scabies is a dermatosis which appears after infection with the mite *Sarcoptes scabiei* (99). The condition is very itchy and extremely contagious. Scabies is transmitted by contact via the skin between individuals, even if the contact is brief. Overcrowded places such as prisons, home care, low socioeconomic status, immunodeficiency play in favor in the development of this condition. The symptoms of scabies, the rash and pruritus, have been attributed to a host immune reaction to the burrowed mites and their products (100). The most common presenting lesions are papules, vesicles, pustules, and nodules (99, 101). A burrow is a present at the surface of the skin and resemble a grey line, scaly and wavy (99). These burrows are considered a pathognomonic sign of the infection and are most of the time present on the hands and feet, particularly in the finger web spaces, thenar and hypothenar eminences, and on the wrists. It is possible not to see burrows if the skin is excoriated due to itching and intense scratching that it provokes. Secondary infections can also mask these burrows (99). The pruritus typically worsens at night and interfere with sleep. In women itching of the nipples and widespread pruritic papular eruption is characteristic whereas in men pruritic papules can be present on the scrotum and are characteristics of the infection (99). A high index of suspicion is needed to diagnose scabies correctly because of the wide range of symptoms and presentations (99).

Patients with HIV infection or AIDS are more prone to develop crusted scabies (99). In patients with neurological disorders or immunosuppression the number of mites can multiply very fast. This may be due to the impaired immune response, the lack of pruritus, or the patient's physical inability to scratch. This condition can be confused with psoriasis or seborrheic dermatitis (101). Clinically, scabies is then suspected when there is marked hyperkeratosis and crusting of the skin, especially on the hands, and often can involve the scalp which is usually spared in immunocompetent persons.

Scabies is usually diagnosed on history and examination. On dermatoscopy, the mites can be seen at the end of burrows (99, 101). Definitive diagnosis relies on microscopic identification of mites or eggs from skin scrapings of a burrow.

However, treatment should be started if scabies is suspected clinically, even if it cannot be confirmed by microscopy (99, 101). Non medical measures should be taken such as

decontamination of bedding and clothing (102). Therapy requires the sequential use of scabicides, usually over a longer period than is required to clear an ordinary case of scabies. Compliance is a concern, and the scabicides are best administered under supervision whenever possible. Isolating the patient and treating the environment of patients with crusted or atypical scabies is much more significant than in ordinary scabies (99, 103). Permethrin 5% cream is the treatment of choice for scabies. It is the most effective topical agent, and is well tolerated, and has low toxicity. Malathion should be used as second choice of treatment (99, 102, 104). Permethrin cream can be used on all the body from the neck to the feet, web spaces of fingers and toes, the genitalia, and under the nails and should be washed off after a period of 8 to 14h (102). This cream should be applied twice in total for a therapeutic course. Immunocompromised people should apply the cream also on the to the scalp, face, and ears (99, 102, 105). Oral therapy with ivermectin at the dose of 200μg/kg taken once only, with a second dose taken two weeks later (104). Permethrin is effective and safe and less expensive than ivermectin (105, 106). Lindane cream or lotion can be applied in a thin layer and washed after eight hours. This therapy is not a first choice as toxicity is limiting its use (105). Compliance of the patients and careful application of the cream is important for a satisfying therapeutic outcome (102). Clear instructions and information should be given by the physician which should warn the patients that pruritus and rash often persist for 2 weeks or more after the treatment, especially in patient presenting with crusted scabies, which is more resistant to topical treatment due to the hyperkeratosis of the skin (102). Treatment failure should not be diagnosed before six weeks have elapsed (99). If resistance or relapse present, treatment should be started again and patient should be monitored carefully and attention should be focused on compliance. Bedding and clothing should be decontaminated (102).

3 Non-infectious HIV-related cutaneous disorders

3.1 Papulosquamous disorders

3.1.1 Seborrheic dermatitis

Seborrheic dermatitis (SD) is often encountered in the general population, with a prevalence ranging between 3-5% (107). In the HIV population, the prevalence of this papulosquamous disorder increase markedly from 30% up to 85% (107, 108). SD can either appear in early stages of HIV disease and may be an initial clinical marker of the infection (107), or can

develop during the later stages of HIV infection with the decrease in CD4+ count (108). It has been also shown that SD represent a cutaneous marker of HIV infection but might as well be an indicator of a more severe prognosis (109).

The etiology of adult SD is not completely understood, but the condition is multifactorial (110). There are three main reason for the development of the condition: increased sebum level secretion by the sebaceous glands, hence the name of the disorder; activation of the alternative complement pathway and an individual factors and host response to a normal component of the cutaneous flora: the yeast *Malassezia*. These factors, with concomitant T cell depression promote the appearance of the disease (110), SD can also be drug induced or preexisting SD can be exacerbated by drugs (111, 112).

The clinical presentation involves different area of the body such as the scalp, face, chest. Widespread involvement can be present in HIV patients on the back, axilla and groin (77, 110). The lesions are greasy scaly patches or thicker and more adherent crusts. Usually present on a erythematous inflamed skin. Annular petaloid SD is a more common for than pityriasiform type. The latter can be confused with pityriasis rosea (110).

In the vast majority of cases, the diagnosis of SD is clinical and takes into account the history of the disease which presents with active phases and inactive phases followed again by relapses. If the diagnosis is still uncertain, biopsy can be performed and on histological examination, hyperkeratosis, parakeratosis, focal spongiosis and acanthosis can be found.

The goals of the therapy are to improve symptoms esthetically, relieve pruritus and prevent complications such as superinfection of the lesions (111). The effective treatment for scalp SD are anti dandruff shampoo with 2% ketoconazole twice per week for about a month (111). Other types of shampoo containing diverse substance can be used: salicylic acid, selenium, sulfur, or zinc. Coal tar keratolytic shampoo is a good alternative as well (110, 111). Patients are advised to avoid the use of regular commercial creams as *Malassezia* is a very lipophilic yeast (110, 112). Low-potency topical corticosteroids, such as hydrocortisone, desonide, mometasone furoate, and betamethasone have shown to be efficacious on the face but it is recommended for short term use only as side effects such as steroid (perioral) dermatitis appear with their prolonged usage (110, 111). The topical calcineurin inhibitors (TCIs) such as pimecrolimus 1% cream and tacrolimus 0.03% and 0.1% ointment decreases skin inflammation by inhibiting T lymphocyte cytokine production (113). They can be used for a

short period of time and with caution (110). Non-steroidal topical therapies are also proved to be effective: topical metronidazole or azelaic gels can be used for facial SD (111, 114). In severe cases of the disease, oral systemic low dose isotretinoin can be used (115). Several courses of these treatment might need to be used by the patient over time, as SD has a high tendency to relapse (108, 116).

3.1.2 Psoriasis

Psoriasis is a chronic common inflammatory papulosquamous skin condition. This autoimmune disorder is believed to be T cell induced proliferation of keratinocytes (117). The prevalence of psoriasis in HIV positive patients is similar to the one of the general population, between 5-6% (118). Different types of psoriasis exist with chronic stationary psoriasis or psoriasis vulgaris being the most common. Other types include plaque, guttate, pustular, erythrodermic, scalp and palmoplantar psoriasis (119). HIV positive individuals when compared to seronegative patients affected by psoriasis, have a more severe clinical picture and symptoms. An existing psoriasis usually exacerbate in HIV, while in other cases psoriasis appear with progression of the course HIV induced immunodeficiency (118).

Etiology of psoriasis is still not clear and appear to be multifactorial including a direct implication of HIV itself, autoimmunity acquired by retroviruses, genetic components, immunological dysregulation (120, 121).

On clinical examination, patients present with patches or scaly plaques with well-defined contours. The plaques can also be erythematous and itchy which can lead to lichenification with time. The usual location of the lesions are the scalp, elbows, knees, back, gluteal cleft, but can be present in all body parts. The scale is silvery white or shiny depending on the site (119, 122).

The diagnosis of psoriasis is clinical, and the type of psoriasis present affects the physical examination findings (119). HIV-associated psoriasis can be clinically confusing because several comorbid skin disorders in patients with HIV can mimic psoriasis (118).

The treatment of psoriasis is a challenge in HIV patients as the disease is more severe and often resistant to conventional treatments. Unfortunately, the classical treatment in HIV negative patients is often based on immunosuppressive drugs which are dangerous to use in the HIV population due to exacerbation of already existing immunodeficiency and exposing

the patient to increased opportunistic diseases (123). Mild to moderate disease are treated with topical treatments such as corticosteroids, tar, vitamin D3 analogs (calcipotriol), calcipotriene , anthralin (124). In the case of moderate and severe HIV-associated psoriasis patients typically improve with highly active antiretroviral therapy. Conventional systemic therapies are still an option as long as close monitoring is performed, as well as evaluation of risk to benefice in the concerned patient. Phototherapy with UV radiation is also used. Oral retinoid as considered second line treatment (123). If the disease is still refractory and severe, immunosuppressive drugs, such as cyclosporine, methotrexate tumor necrosis factor-alpha inhibitors can be used with extreme precaution (125).

3.1.3 Reactive arthritis

Reactive arthritis (ReA), formerly termed Reiter syndrome, is an autoimmune condition that develops in response to an infection. It has been associated with gastrointestinal infections with Shigella, Salmonella, Campylobacter, and other organisms, as well as with genitourinary infections (especially with *Chlamydia trachomatis*). It is a rheumatologic disorder whose etiology is not completely known. The prevalence of ReA in HIV positive persons, has been estimated to be largely superior to the one of the general population with 4.6% (126). This autoimmune disease which appear to be linked to previous gastrointestinal or genitourinary infections and might involve cross reactivity of antigens. Immunologic factors also play a role in ReA. Individuals possessing the class I histocompatibility complex glycoprotein HLA-B27 positive have 50 times more chances to develop ReA and the course of their disease is typically more severe, longer and involving the whole body systems (127, 128). HLA-B27 positivity is also correlated to with more frequent skin lesions and possibly with more weight loss (129). It has been estimated that about 60% to 80% of ReA patients are HLA-B27 positive, compared with 10% in the general population (130, 131). In one third of the patient, the clinical presentation comprise a lassic triad of conjunctivitis, arthritis and urethritis (132). ReA is a multi-organ disease involving notably the gastrointestinal and genitourinary tract, the eyes, the musculoskeletal system (several joints and the axial skeleton), as well as the skin and nails (132). *Keratoderma blennorrhagicum* is a typical association to ReA, and is present in about 10% of patients (133). *Keratoderma blennorrhagicum* is a manifestation on the skin that appears in patients diagnosed with ReA. The condition manifests itself by lesions that appear on the skin, initially on the palm of the hands and soles of the feet and have the tendency to spread, affecting other parts of the body,

such as the scrotum, scalp or trunk. This condition can be confused with pustular psoriasis as the lesions look alike (134). Abnormal nail changes might be present in 20-30% of patients (132,135) such as onychodistrophy, pustules in the periungual region, and sometimes Tery nails (136). The skin of the sole of the feet can present hyperkeratotic changes as well (134, 135). Urogenital mucocutaneous manifestations include ulcerative vulvitis and circinate balanitis which is encountered very often in ReA (in up to 50% of patients) (132, 134, 137).

The diagnosis of ReA is clinical, based on the history and physical examination findings (132, 138). A high index of suspicion is required because no laboratory tests, markers or imaging finding allow diagnosing of ReA. The most important is proper cooperation between a rheumatologist and a dermatologist (139).

The goals of ReA therapy are to improve the quality of life by relieving painful symptoms and skin lesions, as well as prevent joint damage, as there is no cure for this condition. The disease can be self-limited but in general in HIV patients, the course of the illness is severe and the condition evolve to become chronic (129). Among pharmacologic agents that may be used in treating ReA, NSAIDs, which are the mainstay of the therapy are the first line. These include ibuprofen, naproxen, indomethacin. They do not affect the course of the illness but ameliorate symptoms and may facilitate physical therapy by making it less painful procedure (140). ReA in patients with HIV/AIDS is more resistant to therapy and requires careful management, and can be the source of disagreement and incertitude (141). Systemic corticosteroids and other immunosuppressive drugs are usually not advisable to be used for ReA in AIDS patients compared to individuals that are seronegative. Methotrexate has been shown to provoke leukopenia and Kaposi sarcoma(KS) in these patients (142). However,, articular and extra articular manifestations in HIV patients can present with such a great intensity that immunosuppressive drugs might be needed and they are used with a lot of precaution. Other medication such as hydroxychloroquine, and sulfasalazine may be a safe and effective option (141). The tumor necrosis factor alpha inhibitor (etanercept) was shown to be efficient in AIDS patients on HAART with unresponsive to traditional drug modifying disease treatment of ReA (144).

3.1.4 Eosinophilic folliculitis

Eosinophilic folliculitis (EF) is one of the most common skin manifestations in HIV patients. It has been reported to be present in approximately 5–18% of HIV positive patients (145, 146). The disease in HIV population is characterized by extremely pruritic erythematous papular lesions, localized at the hair follicle. Pustules and urticarial lesions can be present as well. The lesions are excoriated due to intense itching from the patients, and crusts can be seen. EF has been associated with $CD4^+$ cell counts of 200-250 cells/µl (146).

The diagnosis of EF is established after skin biopsy and histological examination because the clinical pictures resemble infectious folliculitis (147, 149). The biopsy should be taken from an unexcoriated fresh lesion which is usually hard to find due to the severity of the pruritus of the condition. An inflammatory infiltrate consisting of lymphocytes and eosinophils at the level of the follicular isthmus, sebaceous duct and sebaceous glands (147, 149). Cultures from bacterial swabs taken from skin should be negative in HIV-related EF (41). Blood tests show an increase in eosinophil cell count and immunoglobulin-E (IgE), and diminished IgG and IgA levels (41).

The differential diagnosis comprise scabies, drug induced rashes, papular urticaria and eczema (148).

For the treatment of EF, several options are available. Topical corticosteroids are the first-line treatment option for EF. These drugs offer a relative quick but temporary relief of the pruritus. Topical tacrolimus can also be used in the initial stage of the disease (149). Non-steroidal anti-inflammatory drugs such as oral indomethacin are effective but the gastrointestinal side effects outweigh the benefits in the long term. The antihistaminic drug cetirizine used at higher dosage (20-40 mg/day) can relieve itching symptoms (149). Antibiotic such as metronidazole, minocycline and to a lesser extent dapson, have shown efficacy. Other medications such as the antifungal itraconazole, isotretinoin, a synthetic retinoid, and immunosuppressive drugs can be tried with caution, including cyclosporine, interferon alpha and gamma (149). Phototherapy with UVB three times per week for a month and a half, have been used with success, and can offer a cure (149). PUVA photochemotherapy therapy has also been use and shown to be effective but the risk benefits ratio is lower. HAART has been shown to improve symptoms of EF in treated HIV patients due to the partial reconstitution of the CD4+ cell count (148, 149).

3.2 Vasculitis

Vasculitis is an inflammatory condition of the blood vessel's wall (150). Vasculitis can appear at any stage of the HIV infection and this condition have multiple clinical presentations and wide array of etiological factors: infectious agents, HIV antigens, autoantibodies, cell mediated inflammation, or drugs. In other instances, the cause remains unknown (151). Vasculitis is classified according to the size of the vessel affected: from capillaries, small vessel vasculitis, medium vessel vasculitis to large vessel vasculitis (152). In general, the disease presents as a palpable purpura, or an erythema with infiltration characteristic of small vessel vasculitis. Ulcers, nodules and *livedo racemosa* can also be present although they are more rare manifestations (153). HAART might have an implication in vessel injury and endothelial dysfunctions, especially the following drugs: zidovudine, efavirenz and protease inhibitors (154). Drug induced hypersensitivity vasculitis typically involves small vessels and its pathologic mechanisms include T-cell recognition of proteins or deposition of immune complexes in blood-vessel walls. Hypersensitivity reactions should be considered as a possible etiology of vasculitis in HIV-infected patients on HAART (155). A great variety of inflammatory vascular diseases can develop in HIV patients. These comprise of polyarteritis nodosa, Henoch-Schonlein purpura and drug induced hypersensitivity vasculitis. Kawasaki-like syndrome and Takayasu's arteritis can also occurred (152). In HIV positive patients, the disease can progress faster compared to seronegative individuals affected with vasculitis. This is due to monocyte-macrophage stimulation of atherogenesis and this might be due to altered leukocyte adhesion (156, 157).

Cutaneous vasculitis can be diagnosed clinically and skin biopsy confirms it. The histopathological study of the sample is the gold standard for diagnosis of vasculitis (155). Screening test, blood and urine examination as well as imaging modalities can also be carried out to intend to find the etiology or check for systemic involvement (158). Sometimes, the clinical presentation can be similar to the one of lupus erythematosus, with patients presenting with arthralgia, myalgia, in addition to vasculitis. Positive antinuclear antibodies, and lupus anticoagulant can be also shown in these patients, as well as thrombocytopenic purpura and hemolytic anemia (156, 157).

Patients should avoid triggers (like standing for a long time), rest and use analgesics including NSAIDs. Topical treatment includes steroid creams and ointment and appropriate dressing of the skin in case of presence of ulcers (159).

Cutaneous vasculitis is in most cases a self-limiting disorder. In the case of persistence of the disease, the first line therapy is with dapsone and colchicine (159). As for severe presentation of cutaneous vasculitis, patients should be treated with systemic corticosteroids or immunosuppressive drugs like methotrexate and cyclophosphamide. In the case of recurrence treatment failure, or systemic disease, other options should be tried like: plasmapheresis, intravenous immunoglobulins, infliximab and rituximab. Those therapies have been beneficial in some cases (153).

3.3 Photosensitivity reactions

Photosensitivity is caused by an abnormal reaction to some component of the electromagnetic spectrum of sunlight and reactive substances present in the skin. The electromagnetic spectrum ranges from cosmic rays, ultraviolet (UV) radiation, through visible light, to infrared, microwaves and radio waves. UV radiation has 3 portions : UV-A, UV-B and UV-C (160). Individuals can be sensitive to one kind of sunlight or to a wider range of radiation. The most common photosensitivity is to UVA (160, 161). In general, photo dermatoses are located on sun exposed areas of the the skin such as face, neck and hands. These reaction can also ensue after indoor exposure to artificial UV light radiation.

3.3.1 Drug induced UV light hypersensitivity

Some class of drugs are particularly photoactive. Among the most susceptible to elicit a reaction are the antibacterial: tetracyclines, fluoroquinolones and sulfonamides. Adverse photosensitivity responses to drugs occur predominantly as a phototoxic reaction which is more immediate than photoallergy, and can be reversed by withdrawal or substitution of the drug (161,162). Photoallergic reactions are cell-mediated immune responses to a light-activated compound. Phototoxic reactions develop in most individuals if they are exposed to sufficient amounts of light and drug (161).

Prevention of photosensitivity involves adequate sun protection with clothing and adapted sunscreens. Moreover, diet supplementation with antioxidants might be beneficial in increasing the minimum erythemal UV radiation dose (161).

The initial manifestations that patients report is in general a burning or stinging sensation,

erythema usually appears the next day on sun exposed areas (forehead, nose, lips and hands) and can even involve, in severe cases, sun protected areas (161). The range of skin damage may vary from mild redness to swelling to bullae formation in more severe cases. The rash from this photosensitivity reaction usually resolves with desquamation after a few days (160).

HIV patients are more susceptible to develop adverse reactions to drugs then other patients. In the general population low incidence of sulfonamide hypersensitivity reactions have been reported against approximately 60% of patients with AIDS presenting with adverse symptoms with the use of sulfonamides (163,164). Moreover the HIV positive population is more exposed to the use of sulfa drugs for example or prevention and treatment of some opportunistic disease such as *Pneumocystis carinii* pneumonia (PCP) which has led to exploration into the utility of sulfamethoxazole desensitization in HIV patients (165, 166).

The classic sulfamethoxazole hypersensitivity syndrome is characterized by fever, a generalized maculopapular rash, and toxicity of one or more internal organs. This syndrome usually develops 7 to 14 days after the initiation of sulfamethoxazole therapy (164 ,167). A morbilliform rash, exfoliative dermatitis as well as pruritus are other possible manifestations of sulfa hypersensitivity reactions (165). More rare reaction but possible comprise toxic epidermal necrolysis (TEN) ,Steven's Johnson and erythema multiforme.

Photosensitivity in HIV-infected individuals usually appears in advanced disease. Most patients are sensitive to UVB but the most severely affected individuals are both UVB and UVA sensitive, and may show reactions to visible light (168, 169). The action spectrum of sulfonamides lies within both the UV-B range and the UV-A wavelengths. Photoallergic and, less frequently, phototoxic reactions are common adverse effects seen among patients treated with various "sulfa" drugs such as sulfacetamide, sulfadiazine, sulfaguanidine, and sulfapyridine (170). In the mild cases with no severe signs or symptoms and a relevant and precise history of the exposition to UV light and a particular drug, as well as careful observation of clinical presentation and morphologic pattern of skin lesions, the diagnosis can be made. In fact, absolute histological or immuno-histological criteria for the diagnosis of drug-induced maculo-papular exanthem have not been established. Biopsy is not always necessary nor conclusive since a significant overlap of features exist in other conditions. On the other hand, in the sever and complicated cases, biopsy can still provide help to find clues to the diagnosis (171).

Therapeutic choices of sulfonamide hypersensitivity reactions, should match the severity of the clinical presentation. If patients present solely with a mild rash , the discontinuation of the drug responsible for the reaction can be a satisfying measure. Serious reactions may require the use of oral antihistamines and corticosteroid therapy. Hospitalization is necessary if Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN) is present (165). Several studies have shown that patients who have been through oral desensitization protocols could tolerate trimethoprim/sulfamethoxazole (TMP/SMX) afterwards, as a prophylactic drug or treatment (165, 172, 173).

3.3.2 Porphyria cutanea tarda

Porphyrias are a group of metabolic disorder in the biosynthesis of heme complex by red blood cells due to the partial deficiency of uroporphyrinogen decarboxylase which is a poprhyrin precursor (174). This condition can be inherited or acquired and is classified in four types: the type I acquired hereditary form of porphyria cutanea tarda (PCT), is a sporadic form; type II is a hereditary form, due to the genetic mutation of the UROD gene, this is an dominant autosomal condition .Type III is as type I presents sporadically and is also called the toxic form of PCT. The homozygotic UROD gene defect causes Type IV, which is also named the hepatoerythropoietic form of porphyria (175). Common known risk factors or triggers are: alcohol, iron, estrogen, hepatitis C virus (HCV), polychlorinated hydrocarbons, chronic renal failure and age superior to forty (176, 177).

It has been proposed that HIV infection associated with cofactors might trigger the development of PCT (175). The physiopathology of PCT and HIV association is not totally understood, however HIV carriers might have altered steroid metabolism, which increases the production of endogenous estrogen and, consequently, interferes in the synthesis of heme, causing PCT (174). In addition, HIV infection is the cause of abnormal excretion of porphyrins, even with no clinical evidence of PCT (174). Conflicting information regarding the effect of antiretroviral therapy (ART) on PCT is present: it has been suggested that PCT may be caused by HAART, but also improvement of patients after the start of ART have been reported in other cases (175, 178). The damaging mechanism appear to be the deposition of porphyrins in the skin causing cutaneous photo-sensitization, and because they are unable to store energy from light, which is released to the skin as a photochemical reaction, causing cutaneous damage (175).

The first symptoms appear to be blistering of the skins of the hands and forearms , in some cases the lesions can be on the face or feet. The skin of the patient appears fragile (174). After healing, scarring of the crusted erosions, the leasions lead to hypopigmentation, and bullae leaves hyperpigmented areas (174). Hypertrichosis is a common feature usually present on temporal and malar facial areas and may also involve arms and legs. Pigmentary changes include melasma-like hyperpigmentation of the face. An erythematous suffusion or plethora of the central face, neck, upper chest, and shoulders may be present. Scarring alopecia and separation of nail plates from their beds (photo-onycholysis) can be seen in more severely affected patients (179).

Some preventive measures should be initiated by the patient such as avoidance of sunlight to protect the skin against photosensitivity, alcohol consumption should be totally stopped and patients should quit tobacco smoking as well (179).

Phlebotomy is performed to reduce serum iron level to 50-60g/dl and it should be performed weekly (175). If the patient is unsuitable for phlebotomy weather the procedure is contra indicated or the iron overload is still considered mild, oral chloroquine phosphate at the dose of 125-250 mg twice weekly or hydroxychloroquine sulfate can be used twice per week (175). Cimetidine, or deferoxamine, a chelating agent is also an alternative (175). Another measure can be taken in PCT anemic patients such as the use of humane recombinant erythropoietin to stimulate erythropoiesis (180).

3.4 Metabolic changes

3.4.1 HIV and ART associated lipodystrophy

Lipodystrophy in HIV disease represents a disturbance in the localization and repartition of subcutaneous fat. Three different disorders are noted: lipoatrophy, lipohypertrophy and a mixed type (181). The prevalence of lipodystrophy in HIV positive individuals vary according to the country but it is estimated between 10 to 80% worldwide in the year 2014 (182, 183). This condition progress slowly and the severity increase in a linear manner with age, duration of the disease and duration of protease inhibitor and or nucleoside reverse transcriptase inhibitor treatment (181).

On physical examination of a patient presenting with lipohypertrophy abnormal fat accumulation is noted in specific locations: breast enlargement, dorsocervical fat pad size

increases, central truncal adiposity or obesity, which is a sign of visceral abdominal fat accumulation, as well as suprapubic fat pads (pubic lipomas) are quite common as they present in about 10% of patients with lipodystrophy (181,184). In the case of lipoatrophy, patients present with an emaciated face due to wasting of fat from the temporal areas, cheek and perioral region, making nasolabial creases very noticeable (181). Other part of the body are concerned with fat depletion, especially arms, shoulders, thighs and buttocks; this is called peripheral wasting (181).

The task of determining a clear etiology and pathogenesis for the disorder hasn't been easy and straightforward, as patients are under regimen of several drugs, and it has been difficult to identify a culprit class of drugs. Nevertheless, certain hypothesis has been proposed following *in vitro* and *in vivo* studies and protease inhibitors as well as nucleoside reverse transcriptase inhibitors (NRTIs), in particular stavudine and zidovudine, as they appeared to be the cause of lipodystrophy and other significant metabolic side effects in HIV treated patients (181, 185).

Several risk factors are linked to HIV associated lipodystrophy including genetic diversity in the individuals that may give them increased susceptibility (186). Concerning gender differences, it appears that women tend to develop lipohypertrophy or mixed syndromes in about 40% of the cases whereas men have similar chances of developing any of the three disorders (187). Body fat at onset of HAART is also a risk factor: patients tend to develop lipohypertrophy, if body mass index was already high or lipoatrophy if they had lower BMI when starting the therapy. Other known risk factors comprise older age, higher duration of ART and lower CD4+ count (188).

The diagnosis of lipodystrophy is difficult because no consensus exists on diagnostic methods. Currently used diagnostic tools are first of all, clinical examination and patient complaint, anthropometric studies, bioelectrical impedance analysis and imaging such as dual-energy X-ray absorptiometry, MRI and CT (182). Clinically, lipodystrophy associated with HAART, especially NRTIs and protease inhibitors (PIs), is linked with a wide range of serious metabolic disorders such as dyslipidemias, diabetes, lactic acidemia as well as disorder in bone metabolism (182). Hyperlipidemia has also been noted in the absence of lipodystrophy and depends on PIs exposure in HAART therapies (185).

In addition to metabolic disturbances lipodystrophy can have an important psychological

impact on HIV positive patients, due to the esthetic alteration of the face and body. Patients might fear that their appearance reveals their diagnosis to the society and stigmatization that can ensue. They often report a reduced quality of life and even show less adherence to ART or in extreme cases complete cessation (189, 190). In these cases, it might be worth proposing to the patient switching therapies to prevent them from stopping the treatment. For example, in some studies, it has been shown that removal of thymidine analogues could reverse lipoatrophy, in this cases, efavirenz was used to replace PIs (191). Pharmacologic treatments such as the use man growth hormone, anabolic steroids, or a growth hormone releasing factor analog, naltrexone and growth hormone–releasing factor analog tesamorelin can be tried (181). Besides pharmacologic options, several plastic surgery procedures have been studied for the treatment of HIV-associated lipodystrophy such as liposuccion, lipotransfer and fat grafting (181).

4 Neoplastic HIV-related cutaneous disorders

The HIV positive population is more likely higher risk of developing some types of skin cancers than the general population (192). In fact, non-AIDS defining cancers like squamous (SCC) or basal cell carcinomas (BCC) are commonest cutaneous malignancies encountered in the HIV patients (193). Other neoplastic disorders for instance cutaneous lymphomas although rarer, should be kept into consideration when dealing with HIV infected patients as non Hodgkin lymphomas (NHL) are considered AIDS defining cancers. Kaposi sarcoma is also and AIDS defining cancer although its incidence has been considerably reduced in patient receiving HAART (194, 195).

4.1 Squamous and basal cell carcinomas

HIV positive subjects have a double incidence rate of Non-Melanoma Skin Cancers (NMSCs) compared with seronegative subjects. As the HIV population keeps on aging thanks to the advent of HAART, the burden of non-AIDS defining cancers and especially NMSCs will keep on increasing with time (196).

4.1.1 Basal cell carcinoma

Basal cell carcinoma is the most frequent cutaneous malignancy. Cutaneous non-AIDS-defining cancers (NADCs) were not associated with immune status or receipt of HAART, but most related to traditional risk factors such as aging and skin color (193). BCC is a locally invasive skin tumor and is also named basalioma. It is presented with a pink plaque or nodule. The size of the lesion is variable, from a few millimeters to centimeters of diameter and nodules can bleed and ulcerate (197). Patients can present with several primary lesions with time. Most BCC has slow growth rates some might invade skin deeply and even, although rarely it can metastasize (198). Different subtypes of BCC exist: nodular, superficial, pigmented, morphoeic, micronodular, basosquamous and infiltrative (198). Genetic predisposition, exposure to ultraviolet radiation are the most important risk factors, notably sun exposure during childhood. In fact, sun exposed areas are the most common site of localization of BCC lesions, typically the head and neck. Caucasians, individuals with skin type I and II as well as the elderly and the immunocompromised are the most susceptible to develop BCC (193, 199).

BCC is diagnosed clinically and confirmation of the diagnosis by biopsy sample histopathological examination.

Several surgical methods are available, and excision with established margins of normal tissue, Mohs micrographic surgery, curettage and cautery as well as cryosurgery are some of the traditional treatments. More rarely used carbon dioxide laser technique is an option. Photodynamic therapy offers good cosmetic results and is suitable for superficial disease. Topical treatment in the form of cream with the immune response modifier imiquimod or the cytotoxic agent fluorouracil can be used for superficial disease, for a period of several weeks. Radiotherapy or X-ray treatment can be used to treat primary BCCs or as adjunctive treatment if margins are incomplete and patients cannot be candidate to surgery. Despite many treatment options available local recurrences rates are possible, so follow up should be maintained. Preventive methods are important and involve mainly skin protection using proper clothing, sunscreen and overall avoidance of exposure at sun peak hours and not practicing indoor tanning in solariums (198).

4.1.2 Squamous cell carcinoma

Squamous Cell Carcinoma is the second most common skin cancer after BCC. It is more common in transplant recipients on immunosuppressive drugs and in immunosuppressed individuals due to HIV infection. Main established risk factors are similar to BCC's ones: fair skin types, UV exposition of the skin, especially the head and neck regions, aging, outdoor occupation, previous skin injuries and male gender (197, 199). Co-infection with HPV is another risk factor that is frequent in HIV positive patient and appears to play a major role in developing a certain type of SCC (anal SCC). HIV patients without HPV infection have lower incidence of anal SCC (200, 201). SCC originates from the keratinizing cells of the epidermis forming scaly or crusted lumps. They usually arise within actinic keratosis which are known as precancerous lesions. The lesions are nodular and keratinizing SCC presents with an indurated, nodular, crusted or keratinizing nodule or tumor that may ulcerate. It could also presents as a non keratinizing ulcer but this is rare. SCC is usually located on chronically sun exposed anatomic sites, particularly the head and neck, hands and lower legs. It may be both spontaneously painful and/or tender (201).

The diagnosis of cutaneous SCC is first based on clinical grounds. Confirmation is obtained through histopathological exam of the biopsy sample after excision. This examination reveals atypical epidermal keratinocytes that infiltrates the dermis. Some typical morphological features of differentiation are the horn pearl formation, parakeratosis and individual cell dyskeratosis (201). Tumour, node and metastasis (TNM) staging system is available for SCC and patient who present with advanced lesions should be checked for lymph node involvement and metastasis. Imaging studies such as US, X-rays, CT scans and MRI (201).

According to the European Dermatology Forum treatment guidelines, the first line therapy of cutaneous SCC is complete surgical excision with histopathological control of excision margins. Curettage and cautery are used when surgical excision is not suitable. Great cure rates have been reported in several studies concerning treatment of small tumors that are well differentiated (201).This technique can also be helpful in reducing the size of tumor before using another type of therapy. Other modalities like radiotherapy, cryotherapy, excision or Mohs'micrographique surgery are used like for BCC treatment. Radiotherapy should be used for non resectable SCCs or in large tumors where margins are poorly defined (198). Prevention and follow up are two main components of the management of SCC as for other skin malignancies (201).

4.2 Cutaneous Lymphomas

Cutaneous lymphomas are part of Non Hodgkin lymphomas (NHL) which are frequent malignancies in HIV-infected individuals and which have a 60% to 100% greater risk of developing NHLs than the general population (202, 203). The risk of contracting the disease increases with the immunosuppression level (202, 203). Non-Hodgkin's lymphoma presents in general at CD4+ counts under 200/mm^3, and can reveal itself with the usual constitutional symptoms like fevers, weight loss, and night sweats (204). In comparison to seronegative individuals, HIV infected patients have higher stage and higher grade disease and the response to chemotherapy is decreased (202).

4.2.1 B cell cutaneous lymphomas

More than 90% of HIV-associated NHL is derived from B cells and the majority is high grade. Extranodal presentation is most frequent in HIV-seropositive patients than in general population and occurs in 70% to 80% of the cases (205). The classification of B cell cutaneous lymphomas according to the lymphoma research foundation are primary cutaneous follicle center lymphoma, primary cutaneous diffuse large B-cell lymphoma, primary cutaneous diffuse large B Cell lymphoma-leg-type primary cutaneous diffuse large B-cell lymphoma (206).

The most common type of CL is primary cutaneous follicle center lymphoma which develops over periods from months to years with red brown "pimply" rash or nodules mainly on the trunk, head and neck. The second most common type of lymphoma is called primary cutaneous diffuse large B-cell lymphoma and presents on the trunk and arms with red lesions, nodules or tumors. Its progression is slow as well. The third type of cutaneous B-cell lymphoma (CBCL) is less common and is called primary cutaneous diffuse large B-cell lymphoma- leg-type. The course of this disease is more aggressive and develops over weeks or months. Solitary or multiple nodules and or tumors may appear on the legs and or the trunk of the patients. The lesions can ulcerate and spread, become large and invade deeply the body. Lastly, the primary cutaneous diffuse large B-cell lymphoma is a very rare disorder and the lesion also appear on head trunk and limbs (206).

Cutaneous NHL is diagnosed with biopsy skin lesions and histopathological examination of the samples. It is possible to determine immunophenotype of the lymphoma by performing immunostaining of biopsy smears with monoclonal antibodies (205).

CL has no cure. The aim of treatment is reducing and controlling patient symptoms as well as improving the quality of life. As for all treatment the choice of therapy should consider safety parameters, cost and effectiveness (207). The different therapies available include chemotherapy, radiotherapy, rituximab use, surgery. Concerning local therapy, surgical excision a first choice if the patients is presenting with a single or small number of lesions. Unfortunately, relapse and/or recurrence occur in a considerable proportion of patients (208). In HIV positive patients, combination chemotherapy with HAART is the gold standard to improve the prognosis and survival rates of cutaneous lymphoma patients (209). HAART can be used as a single therapy in patients presenting with a strictly cutaneous disease with a single or very few skin lesions. The good clinical response is probably attributed to the partial immune system reconstitution (210). In a comparative study, AIDS patients who received HAART and chemotherapy had survival similar to NHL patients without AIDS which represent an improvement from the pre-HAART era (209). The number of lesions presented is a prognostic factor in CBCL (211).

However, lymphomas with cutaneous compromise are uncommon in HIV-infected patients. The most important diagnosis elucidation is to determine whether the cutaneous tumor is a primary cutaneous lymphoma or when it represents cutaneous metastases of an aggressive systemic AIDS-related NHL (205).

4.2.2 T cell cutaneous lymphomas

The classification of primary cutaneous lymphomas is made by the WHO and the European organization for research and treatment of cancer (EORTC) is the origin of many debates and was confusing and difficult to establish (212). Lymphomas considered to be lower grade is the mycosis fungoides (MF) which is the most common cutaneous T cell lymphoma and represents more than 50% of primary cutaneous lymphomas (212). The next group of disorder is named MF variants and subtypes and comprise the folliculotropic MF, pagetoid reticulosis and granulomatous slack skin (212). The primary cutaneous CD30+ lymphoproliferative disorders group is the second most common cutaneous T cell lymphoma accounting for about 30% of the cases of CTCL. Finally, the two other slow growing type of CTCL are called subcutaneous panniculitis-like T cell lymphoma and primary cutaneous CD'+ small/medium pleomorphic T cell lymphoma which in general comprise only one lesion (212).

In a study involving 25 patients with both HIV infection and cutaneous presentations of lymphoma several types were noted: manifestations resembling mycosis fungoides or Sézary syndrome or CD30+ T-cell lymphoma (213).

4.2.2.1 Mycosis fungoides

Mycosis fungoides is more common in men than women. The disease presents with several stages: patch, plaque and tumor stages respectively. The skin lesions from the patch stage are flat oval or annular shaped pink dry patches mostly located in sun protected areas of the body like the buttocks. As MF has a typically indolent course, patients might stay in the patch stage for several years without progressing to the plaque stage. The lesions can either stay identical, disappear or slowly enlarge. MF patch stage differential diagnosis encompass some common skin conditions like psoriasis and discoid eczema (212). If the patient evolves to plaque stage of MF, the initial thin patches become thickened and are even more difficult to distinguish from psoriasis. This stage present with itching at the lesions sites (212). During the tumor stage, plaques evolves into large lumps with irregular border and the patient presents generally with lesions from the two other stages as well. Ulceration of the lesions and spread to other organs can occur (212).

The diagnosis sometimes requires repeated skin biopsies to confirm a diagnosis of CTCL. Histology, immunophenotypic and preferably T-cell receptor (TCR) gene analysis should be performed on all tissue samples. Initial staging CT scans are required in all patients except in those with early stages of MF (stage IA/IB) and lymphomatoid papulosis (214).

Patient presenting solely with patch stage MF can be treated with topical steroid or bexarotene gel which is a topical retinoid. Topical mechlorethamine also called nitrogen mustard can be also used (212,214). PUVA photochemotherapy alone or combined with alpha interferon therapy can be effective for patients with resistant early-stage disease. Radiotherapy is good option as CTCL is a radiosensitive disease. If the tumor stage of disease is advanced and doesn't respond to skin therapies or if systemic involvement is present, multi drug chemotherapy with should be used (214, 215).

4.2.2.2 Sezary syndrome

Sezary syndrome (SS) is a condition that affects the skin of the whole body, it has also been called the "red man syndrome". The skin is thick, dry and scaly and usually pruritic. Hyperkeratosis of the palms and soles is also a typical sign. Alopecia and onychodystrophy are also common features (212). SS is characterized by the triad of generalized lymphadenopathy, erythroderma, and the presence of neoplastic T cells or Sézary cells in the skin, lymph nodes and peripheral blood (217).

The diagnosis of SS is based on clinical findings, histopathology studies, immunophenotyping, molecular and cytogenetic method.

The treatment is similar to MF's treatment with the combined used of several agents. In most cases chemotherapy is necessary for the management of condition. Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities (eg, interferon alpha) is used with a variable rate of response depending on the patients. Interferon alpha in combination with PUVA therapy, prolonged treatment with a combination of low-dose chlorambucil and prednisone or with methotrexate have also been used. Topical steroid can be added as a complementary therapy. Some positive effects of bexarotene and monoclonal antibody antineoplastic like alemtuzumab (anti-CD52) has been shown but the long-term effects of these therapies is still unknown (212, 214, 216, 218). Palliative treatment should also be considered in severely ill patients as prognosis of SS is unfortunately quite poor, immunosuppression, opportunistic infections contribute to the high mortality rates (212).

4.3 Kaposi Sarcoma

Kaposi's sarcoma (KS) is a " multifocal vascular tumor" involving skin and other organs (219) and it is the most common neoplasm in patients with AIDS (220). Before the AIDS epidemic, KS was rare in the Western world. It was one of the earliest clinical presentations seen in the AIDS epidemic. In the mid-1990s, approximately 1 in 4 homosexual men contracted the disease. The number of new cases has decreased significantly with the advent of safer sexual practices in the early 1990s and accelerated with the introduction of HAART due to improved immune reconstitution (221). In the United States, the risk of KS among sexually active homosexual men is much greater than among others infected with HIV (222). Prior to the advent of HIV, the disease was common in central Africa and prevalent in

Mediterranean countries and the Middle East (222). In Africa and developing regions, epidemic AIDS-related KS is common in heterosexual adults and occurs less often in children (222). Endemic African KS occurs in HIV seronegative men in Africa (223) Classic KS typically occurs in elderly men of Mediterranean and Eastern European background and with a male-to-female ratio of 10-15:1 (222).

The exact etiology of KS is still controversial, but the role of multiple genetic and environmental factors, as well as infective agents has been proposed. (224). The possibility that the HHV 8 is the inciting factor in KS pathogenesis was considered because of the presence of virus in pathological lesions (222). Seroconversion to HHV8 positivity appears to precede to the development of epidemic KS by 5-10 years (225). Less than one-sixth of HIV-infected patients have CD4+ count of over 500 per microliter (226), and the disease usually develops in HIV infected patients with severe immunodeficiency (226). KS is a multifocal, systemic tumor of endothelial origin with stage dependent characteristic histopathology.

It has four clinical variants: classical KS, endemic African KS, KS associated with immunosuppressive therapy, and KS associated with AIDS. KS is the most common cancer occurring in persons with HIV. The lesions of KS are macules, papules, or nodules of characteristic purple color. Preferred locations are the extremities, the tip of the nose, and the palate. KS often starts as flat patches one or both lower legs, often in association with lymphoedema. The patches evolve into plaques, nodule or scaly tumors (19). Often, the lesions are only slowly progressive and do not cause pain. In rare cases, KS may run an aggressive course with nodular, ulcerated lesions; limb edema; and gastrointestinal and pulmonary involvement. Kaposi’s sarcoma is easy to recognize (4).

The clinical differential diagnosis includes bacillary angiomatosis, lichen planus, drug eruptions, coccidioidomycosis, pyogenic granuloma, angiodermatitis or pseudo-KS, and hemangioma (224).

Histopathology usually confirms the diagnosis and is characterized by profuse vascular proliferation showing slit-like spaces with presence of solid cords and fascicles of spindle cell arranged between vascular channels. Immunohistological detection of CD31, CD34 antigens, FVIII-Rag, and sialic acid expression are important for correct diagnosis of KS (4, 222)

Cutaneous KS lesions may be cosmetically disfiguring and often generate significant

psychologic distress for individuals infected with AIDS. The goals of pharmacotherapy for KS are to eradicate the tumors, reduce morbidity, and prevent complications (222). The introduction of HAART has significantly reduced the incidence of KS and changed its clinical course. Optimal control of HIV infection using HAART is an integral part of successful Kaposi sarcoma therapy. It should be the first step in therapy. Response to such therapy can be anywhere from 20-80% based on stage of disease and the amount of pretreatment (25). For reasons of relative lack of side effects and good efficacy, liposomal preparations of doxorubicin, are used at a dose of 40 mg/m2 every 2 to 3 weeks. The combination of bleomycin and vincristine is also effective, as is high-dose intravenous interferon in patients with a CD4+ count above 200/m3 (4, 9). These agents can achieve rapid tumor regression and palliation of tumor-related symptoms but at a cost of myelosuppression and risk of opportunistic infections. Growth factor support can help to counter act those side effects (9). Local therapy is preferred for patients who need palliation of locally advanced symptomatic disease (eg, radiation) or for individuals who have cosmetically unacceptable lesions. Radiation therapy is the most widely used local therapy. Cryotherapy and laser photocoagulation can be an option for small and superficial lesions. Surgery is reserved for patients with deep painful lesions, bleeding or obstruction. This therapy is also well suited for individuals with significant comorbidities and disease refractory to systemic modalities. It can provide better control of the bulky lesions that cause bleeding, pain or, edema, and treat extensive skin disease. Unfortunately, local therapy fails to halt the development of lesions (227). The efficiency of all these treatments vary widely and recurrence is often a problem in KS affection.

5 Conclusion

Dermatological manifestations are seen at every stage of HIV/AIDS, and are often earliest and the only sign of HIV/AIDS. Skin manifestation in HIV infections are numerous and any cutaneous disorder that affects the general population is potentially affecting the HIV positive individuals, weather it has an infectious, immunologic or neoplastic trigger. Other skin condition encountered during the course of HIV infection are more specific and more characteristic of the HIV population. Among these condition, are Kaposi Sarcoma and others such as disseminated histoplasmosis or chronic herplex simplex ulcers. Thus the

dermatological aspect of the HIV infection can aid in the diagnosis of the condition, prompt the start of a therapy and may also carry a prognostic value in other cases. Skin conditions in HIV patients can be more challenging when it comes to treatment and the response to classic or more specific therapies is variable. Thankfully, the advent of HAART, although it can raises skin problems on its own, in the majority of cases, by decreasing the level of immunodeficiency, is very helpful in reducing symptoms and even clearing skin conditions in the HIV patients.

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7 Biography

I was born on the 25th of March 1989 in Algiers but was raised in France. I completed my high school degree in the Lycée de la Méditerranée in La Ciotat. After that I enrolled in the university of Marseille in the PCEM program. In 2009 I moved to Norway to participate in the Agder Folkehøgskole program.In 2010 I enrolled in the university of Zagreb, school of medicine.

I am currently in the sixth year of the medical program in English and I am hoping to complete "internship " and pass my license exam in Croatia.