ORIGINAL ARTICLE

Cutaneous Manifestations in Patients Infected with Human Immunodeficiency Virus: An Audit in the Department of Dermatology Hospital Kuala Lumpur

Gin Peng Chan, *MRCP*, Meena Nithianandan, *MBBS*, Suganthi Thevarajah, *MMed,* Min Moon Tang, *AdvMDerm*

Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Abstract

Introduction

Patients with human immunodeficiency virus (HIV) may have significant cutaneous morbidities which can potentially affect their quality of life or be life-threatening. This study aimed to describe the demographic data and the pattern of cutaneous manifestations of patients infected with HIV.

Methods

This is a retrospective study on all HIV-infected patients who were referred to the Department of Dermatology Hospital Kuala Lumpur between 2016 and 2019. Patients' medical records were retrieved and reviewed.

Results

There were 424 patients infected with HIV referred to us between 2016 and 2019. The mean age was 31.74 years. The majority of them (50.4%) were in the age group of 20-29 years. About 96.0% (407 patients) were male. Homosexuality was the most common (52.3%) mode of HIV transmission in these patients. Two-hundred-and-ninety-six patients (69.8%) had their CD4 count available for analysis. Of these, about 39.5% of them had a CD4 count less than 200/mm^3. Less than half of the patients (189, 44.6%) were taking anti-retroviral therapy (ART) upon referral to us. There were a total of 638 cutaneous diagnoses made in this cohort with 152 patients had more than one cutaneous diagnosis. Ninety-four patients (22.2%) underwent skin biopsy with a total 98 biopsies performed. The most frequently encountered dermatosis was cutaneous infections (74.0%). These include genital warts, syphilis, genital herpes, talaromycosis and molluscum contagiosum. The most frequent non-infective inflammatory dermatoses observed in our cohort was eczematous dermatoses including papular eczema, seborrheic dermatitis, photodermatitis, contact dermatitis, nodular prurigo, discoid eczema and stasis eczema, contributing 8.4%. Cutaneous adverse drug reaction was diagnosed in 31 patients (7.3%). Fifteen patients (3.5%) had Kaposi sarcoma.

Conclusion

Our data showed that individuals with HIV infection may present with wide variety of skin disorders which included infective dermatoses, non-infective inflammatory dermatoses, cutaneous adverse drug reactions and tumours. About 35% of them had more than 1 dermatoses in our cohort. The most frequent dermatoses observed was cutaneous infections.

Key words: *Human immunodeficiency virus, retroviral disease, acquired immunodeficiency syndrome, Kaposi sarcoma, talaromycosis*

Introduction

Human immunodeficiency virus (HIV) is a retrovirus that causes immunosuppressive state,

which was first described in 1981 in Los Angeles and New York in homosexual men.[1] Based on World Health Organization (WHO) data, since the beginning of the epidemic, 75 million people have been infected with HIV virus and about 37.9 millions of people were living with HIV at the end of 2018.[2] About 0.8% of adults aged between 15 and 49 years worldwide were living with HIV.[2] In 2016, there were 115,263 cases reported to be infected with HIV in Malaysia[3], with an average of 3400 cases per year between 2010-2017.

HIV infection carries significant morbidity, reduces quality of life and causes mortality. With the development of antiviral therapy (ART) it has now significantly changed the perception of HIV/ Acquired immunodeficiency syndrome (AIDS) from a fatal to a chronic potentially manageable disease.[4] In 2018, 23.3 million people were receiving antiretroviral therapy worldwide.[2]

Individuals infected with HIV may present with various cutaneous manifestations, which may result from HIV infection or opportunistic disorders. Recognizing HIV-related skin changes may enable early diagnosis of HIV, thus allowing early initiation of ART. Since the advancement of ART, the incidence of drug reactions and non-infectious skin eruptions has also been enhanced.[5]

This study aimed to describe the demographic data and pattern of cutaneous manifestations of patients infected with HIV who were referred to the Department of Dermatology, Hospital Kuala Lumpur between 2016 and 2019.

Materials and Methods

This is a retrospective study on all newly referred HIV-infected patients to the Department of Dermatology in Hospital Kuala Lumpur between 2016 and 2019. Patients' case notes were retrieved and reviewed. Data collected included demographics, types of referrals, CD4 counts, treatment durations, types of mucocutaneous manifestations, numbers of skin biopsies done, co-morbidities and co-infections.

Results

There were a total of 424 patients infected with HIV referred to the department between 2016 and 2019. Their demographic characteristics are showed in Table 1. The youngest patient referred to us was 15 years old and the oldest was 74 years old. The mean age was 31.74 years old. More than half of the total

Corresponding Author
Dr Chan Gin Peng
Department of Dermatology,
Hospital Kuala Lumpur,
Jalan Pahang,
50586, Kuala Lumpur, Malaysia.
Email: gpncamel@gmail.com

patients, 214 (50.4%) referred were in the age group of 20 to 29 years, and a quarter of them were in the age group of 30 and 39 years (115, 27.1%). Among the Malaysian patients, Malays contributed to 65.7% of the referrals, followed by Chinese, 25.4%, Indians 7.2% and others, 1.7%. Seven (1.6%) of were foreigners, which includes Indonesians (2, 0.5%), Myanmarese (2, 0.5%), followed by Pakistani (1, 0.2%) and American (1,0.2%). Majority of patients referred were male, 407(96.0%).

Homosexuality was among the most common mode of transmission of HIV in these patients, (222, 52.3%), followed by heterosexual transmission (63,14.9%). As shown in Table 2, a third of the patients (143, 33.7%) had other concomitant medical illnesses which include extracutaneous tuberculosis (TB) (36.4%), extracutaneous fungal infection (11.2%), both extracutaneous tuberculosis and fungal infection occurring concurrently (2.8%), Hepatitis C infection (12.6%), Hepatitis B infection (7.7%), Pneumocystis jiroveci pneumonia (4.9%) etc. Excluding 128 patients whom their CD4 counts were unavailable upon referral, 39.5% (117 of 296 patients) had CD4 count less than 200/mm3. About a quarter (27.4%) had CD4 counts more than 500/mm3. Less than half of our cohort (189, 44.6%) were on ART. Of these, 72 patients (38.1%) received ART within 12 months before they were referred to the Department of Dermatology and most of them has CD4 counts less than 200/mm^3.

A total of 638 cutaneous diagnoses were made for the 424 patients as shown in Table 4. About 36% of the 424 patients had more than one dermatosis diagnosed after dermatology review. Ninety-four patients (22.2%) underwent skin biopsy with a total 98 biopsies performed. As shown in Table 4, the most common dermatoses encountered by our HIV infected patients was cutaneous viral infections, reported to occur in 263 of them (62.0%). These include genital warts, herpes labialis, extra genital wart, viral exanthem, oral leukoplakia, and genital herpes. About 31% of patients (n=131) had bacterial infection, and syphilis was the most common bacterial infection in this cohort (94 patients). This was followed by gonorrhea (15 patients), folliculitis (7 patients), and others such as abscess, cellulitis, furuncles, chancroid, carbuncle and rectal ulcers (Table 4). Seventy-two patients (17%) presented with cutaneous fungal infection, and talaromycosis (formerly known as penicilliosis) was the most common fungal infection (24 patients) encountered. This was followed by oral mucosal candidiasis (14 patients), histoplasmosis (11 patients), tinea corporis (10 patients) and onychomycosis. Five patients had scabies infestation as their first presentation to the clinic. Of these 72 patients (38.1%) received ART within 12 months before they were referred to the Department of Dermatology and most of them has CD4 counts less than 200/mm3. In the subgroup of patients who received ART for a duration of 12 months or less, infective dermatoses were again the most common dermatoses encountered, occurring at 2.3x the number of non-infective dermatoses.

Table 1. Demographic characteristics of 424 patients infected with human immunodeficiency virus (HIV) referred to the Department of Dermatology Hospital Kuala Lumpur between 2016-2019

Characteristics		**n=424(%)**
Mean age in years (range)		31.74 ± 9.94 (15-74)
Age group	<20	11 (2.6)
	20-29	214 (50.4)
	30-39	115 (27.1)
	40-49	52 (12.3)
	50-59	28 (6.6)
	60-69	2 (0.5)
	70-79	2 (0.5)
Gender	Male	407 (96.0)
	Female	17 (4.0)
Nationality	Malaysian	417 (98.4)
	Non-Malaysian Indonesian Myanmar Pakistan American Not available	7 (1.6) 2 (0.5) 2 (0.5) 1 (0.2) 1 (0.2) 1 (0.2)
Race (n=417)	Malay	274 (65.7)
	Chinese	106 (25.4)
	Indian	30 (7.2)
	Others	7 (1.7)
Possible mode of HIV transmission (n=339)	Heterosexual	63 (18.5)
	Homosexual	222 (65.4)
	IVDU	16 (4.7)
	Blood transfusion	2 (0.59)
	Bisexual	33 (9.7)
	Homosexual + IVDU	2 (0.59)
	Heterosexual + IVDU	1 (0.29)
	Not available	85
HAART treatment (n=405)	Yes	189 (46.7)
	No	216 (53.3)
	Not available	19
CD4 count (cell/mm^3) (n=296)	<200	117 (39.5)
	200-500	98 (33.1)
	>500	81 (27.4)
	Not available	128

About a third of our patient (132 patients, 31.1%) was noted to have non-infective dermatoses. The most common non-infective dermatoses diagnosed among the patients infected with HIV was eczematous dermatoses (including papular eczema, seborrheic dermatitis, photodermatitis,

contact dermatitis, nodular prurigo, discoid eczema and stasis eczema; a total of 36 patients or 8.4%). Pruritic papular eruption and eosinophilic folliculitis which are commonly described among the HIV infected individuals occurred in 4.0% and 1.2% in our cohort respectively. Psoriasis was diagnosed in 1.6% of our cohort. These patients were not known to have psoriasis before the HIV was diagnosed. There were 15 patients (3.5%) diagnosed to have Kaposi sarcoma in our cohort.

Table 2. Comorbidities and concomitant illness(s) among 424 patients infected with HIV referred to the Department of Dermatology between 2016 and 2019

Comorbids/Concommitant illness(s)	n (%)
Extracutaneous tuberculosis	52 (36.4)
Hepatitis C	18 (12.6)
Extracutaneous fungal infection	16 (11.2)
Hepatitis B	11 (7.7)
Pneumocystis jiroveci pneumonia	7 (4.9)
Anaemia	6 (4.2)
Both extracutaneous tuberculosis and fungal infection occurring concurrently	4 (2.8)
Diabetes Mellitus	4 (2.8)
Bronchial Asthma	3 (2.1)
Toxoplasmosis	3 (2.1)
Dyslipidemia	3 (2.1)
Mood disorders	2 (1.4)
Neurosyphilis	2 (1.4)
Hypertension	2 (1.4)
Deep vein thrombosis	1 (0.7)
Ischaemic Heart Disease	1 (0.7)
Renal Tubular Acidosis	1 (0.7)
Cytomegalovirus retinitis	1 (0.7)
Upper gastro-intestinal bleed	1 (0.7)
Autoimmune encephalitis	1 (0.7)
Cardiomegaly	1 (0.7)
Adrenal insufficiency	1 (0.7)
Cerebral vascular accident	1 (0.7)
Post ictal psychosis	1 (0.7)
Total	**143 (100)**

Table 3. Number of cutaneous diagnosis in 424 individuals with HIV referred to the Department of Dermatology Hospital Kuala Lumpur between 2016 and 2019

Number of Cutaneous Diagnosis in One Patient	Number of Patients				Total n=424
	CD4 <200 cells/m^3	CD4 200-500 cells/m^3	CD4 >500 cells/m^3	CD4 Not Available	
	n=117	n=98	n=81	n=128	
1	61 (52.1)	66 (67.3)	58 (71.6)	87 (68.0)	272
2	40 (34.2)	22 (22.4)	19 (23.5)	25 (19.5)	106
3	14 (12.0)	8 (8.2)	2 (2.5)	9 (7.0)	33
4	2 (1.7)	2 (2.0)	2 (2.5)	4 (3.1)	10
5	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.3)	3
Total Dermatoses	**191**	**142**	**110**	**195**	**638**

Table 4. Types of dermatoses detected among individuals with HIV between 2016 and 2019

Type of Dermatoses	Number				
	CD4 <200 cells/m³	CD4 200-500 cells/m³	CD4 >500 cells/m³	CD4 Not Available	Total
	n=117	n=98	n=81	n=128	n=424
Cutaenous Adverse Drug Reactions	**16**	**3**	**3**	**9**	**31**
Non life-threatening					
Maculopapular eruption	8	0	1	7	16
Erythema multiforme	1	1	1	0	3
Pruritus	0	0	0	1	1
Life threatening					
Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	4	1	1	0	6
Drug reaction with eosinophilia and systemic symptoms (DRESS)	3	1	0	1	5
Non Infective Dermatosis	**53**	**23**	**18**	**38**	**132**
Inflammatory					
Pruritic papular eruption	10	3	0	4	17
Papular eczema	3	1	4	2	10
Seborrhoeic dermatitis	3	4	0	3	10
Psoriasis	3	0	3	1	7
Acne vulgaris	2	1	2	1	6
Photodermatitis	1	3	0	1	5
Eosinophilic folliculitis	1	1	1	2	5
Contact dermatitis	2	1	0	2	5
Xerosis	2	0	1	1	4
Nodular prurigo	2	0	1	1	4
Proctitis	0	0	2	1	3
Chronic spontaneous urticaria	0	0	1	2	3
Papular urticaria	2	0	0	1	3
Anal fissure	0	1	0	1	2
Discoid eczema	0	1	0	0	1
Venous ulcer	1	0	0	0	1
Lichen planus	1	0	0	0	1
Icthyosis vulgaris	1	0	0	0	1
Alopecia	0	0	1	0	1
Neurogenic pruritis	0	0	0	1	1
Pityriasis lichenoides chronica	0	0	0	1	1
Post inflammatory hyperpigmentation	0	0	0	1	1
Stasis eczema	0	0	0	1	1
Viral exanthem	0	0	0	1	1
Milaria rubra	1	0	0	0	1
Eosinophilic dermatitis	1	0	0	0	1
Vasculitis	1	0	0	0	1
Sarcoidosis	1	0	0	0	1
Hidradenitis suppurativa	0	1	0	0	1
Vitiligo	1	0	0	0	1
Non inflammatory					
Benign growth					
Skin tag	0	2	2	2	6
Sebaceous cyst	1	2	0	1	4
Perianal cyst	1	1	0	0	2
Steatocytoma multiplex	0	0	0	2	2
Syringoma	0	0	0	1	1
Seborrhoiec keratosis	0	0	0	1	1
Lipoma	0	0	0	1	1
Malignant tumour					
Kaposi sarcoma	12	1	0	2	15
Infective Dermatoses/Infestation	**122**	**116**	**88**	**147**	**473**
Bacterial	28	28	25	50	131
Syphilis	16	22	18	38	94
Gonorrhea	4	3	2	6	15
Folliculitis	3	0	3	1	7
Abscess	1	1	1	0	3
Cellulitis	1	2	0	0	3

Furuncle	1	0	1	0	2
Chancroid	1	0	0	1	2
Carbuncle	0	0	0	1	1
Ecthyema	0	0	0	1	1
Rectal ulcer	0	0	0	1	1
Lymphogranuloma venereum	0	0	0	1	1
Chlamydia	1	0	0	0	1
Mycobacterial infection	0	1	1	0	2
Leprosy	0	0	1	0	1
Lupus vulgaris	0	1	0	0	1
Viral	59	74	59	71	263
Genital warts	27	47	48	43	165
Herpes genitalis	13	17	7	12	49
Molluscum contagiosum	7	2	1	9	19
Herpes zoster	4	3	0	1	8
Herpes labialis	3	1	1	2	7
Common warts	1	0	2	3	6
Viral exanthem	1	3	0	0	4
Leukoplakia	1	1	0	0	2
Herpes simplex	1	0	0	1	2
Plane wart	1	0	0	0	1
Fungal	33	11	3	25	72
Talaromycosis	13	1	0	10	24
Oral mucosal candidiasis	8	1	1	4	14
Histoplasmosis	7	0	0	4	11
Tinea corporis	3	4	1	2	10
Onychomycosis	1	2	0	2	5
Cryptococcus	1	0	0	1	2
Candida cheilitis	0	1	0	0	1
Chromoblastomycosis	0	1	0	0	1
Toe webs intertrigo	0	0	1	0	1
Candida balanitis	0	0	0	1	1
Sporotrichosis	0	0	0	1	1
Tinea cruris	0	1	0	0	1
Scabies infestation	2	2	0	1	5
Non Dermatological Diagnosis*	**0**	**0**	**1**	**1**	**2**
Total	191	142	110	195	638

Thirty-one patients were referred for cutaneous adverse drug reactions, of which majority was maculopapular eruption (51.6%) to the antibiotics received for their opportunistic infections (8 to bactrim, 3 to bactrim/anti-tuberculosis therapy, 1 to dapsone, 1 to efavirenz). Eleven patients (35.5%) suffered from severe cutaneous adverse drug reactions (SCARs) namely the Stevens Johnson Syndrome/Toxic epidermal necrolysis (metamphetamine (1), bactrim (1), Akurit-4 (1), carbamazepine (1)) and drug reaction eosinophilia with systemic symptoms (DRESS) due to fansidar (1), bactrim (2), anti-tuberculosis Akurit-4 (1), bactrim/pyrimethamine(1). Two patients developed erythema multiforme secondary to ART therapy and one to bactrim. There were two patients were found to have non dermatological disorders after assessment, which were reactive arthritis, and false positive rapid plasma reagin (RPR) test.

Based on the 1993 Centers for Disease Control and Prevention (CDC) case definition of AIDS,[6] we further analysed the type of dermatoses that were seen among patients with clinical category C (patients who have AIDS-defining conditions and/or CD4 count of less than 200cells//mm^3). As shown in Table 5, patients with AIDS were significantly more prevalent to suffer from cutaneous adverse drug reactions, non-infective dermatoses, viral and fungal infections. Cutaneous viral infections were the most frequent infections encountered in patients with AIDS and without AIDS. However, the rate was significantly higher among the patients without AIDS. The rate of cutaneous bacterial infections and scabies infestations were similar in patients with AIDS and without AIDS.

Table 5. Types of dermatoses in patients with and without AIDS

Types of Dermatoses		Patients with AIDS* n=144	Patients without AIDS n=167	*p* value
Cutaneous adverse drug reactions		21	5	*<0.05*
Non infective dermatoses		62	38	*<0.05*
Infective dermatoses	Bacterial infection	44	47	*0.64*
	Viral infection	72	126	*<0.05*
	Fungal infection	48	9	*<0.05*
	Scabies	2	2	*1.00*

**Clinical category C - patients who have AIDS-defining conditions and/or CD4 count of less than 200cells//mm^3*

Table 6. Literature review on the prevalence of skin disorders in HIV infected individuals

	Uthayakumar S et al.[39]	Coopman SA et al.[40]	Spira R et al.[18]	Spira R et al.[18]	Spira R et al.[18]
	Brighton	Boston	France	Dallas	Bangkok
Year	2017	1988-1991	1996	1989	2004
Total patients observed	151	684	450	100	120
Total patients with skin disorders	138 (91.4%)	540 (79%)	294 (65.2%)	92 (92%)	96 (80%)

Discussion

Cutaneous manifestations are very common in individuals infected with human immunodeficiency virus (HIV) and are associated with significant morbidity.[7] Our National Strategic Plan for Ending AIDS targets to end AIDS by 2030.[3] At the end of year 2018, it was estimated that 87,041 people were living with HIV in Malaysia and 41,430 (55%) of them are on antiviral therapy.[3] In this audit, only 46.7% of patients referred were on antiviral therapy, which is less than the national record. We are yet to achieve one of the main Global AIDS Monitoring indicators which is to have at least 90% of people who know their HIV-positive status are accessing ART by 2020.[8] More efforts are needed to screen and detect HIV infection early so that ART can be initiated early in order to improve the overall health of these group of patients and their quality of life.[9]

More than 75% of our patients were in the age group between 20 and 39 years. This is consistent with our national data[3] and another 2 studies, Halder et al in West Bengal, India[10] and Sanjay et al. in Maharashtra, India.[11] Our national data showed that 77% of individuals infected with HIV were 20-39 years old.[3] The trend of HIV epidemic in Malaysia has now shifted to sexual transmission since 2011. Men who have sex with men (MSM) was expected to become the main driver for the epidemic in the years to come beginning from 2018.[2] In our audit most patients contracted HIV via homosexual practice in males. This may also explain the reason of high prevalence in of genitourinary infections observed in our cohort.

The common denominator of the immunosuppressed state resulting from HIV infection is the destruction of T-helper cells that express CD4 receptors[12], causes profoundly impaired cellular immune response. The number of circulating CD4 T cells predicts the onset of overt immunodeficiency.[13] The suppression of HIV replication with ART improves the CD4 T-cell counts and was found to be able to reverse immunodeficiency.[14] The progression of disease is indicated by the detection of specifically defined opportunistic infections. CD4 count is a prognostic indicator and marker of stage of HIV-induced immunodeficiency and estimation of morbidity and mortality.[14] The classification system for HIV infection among adolescents and adults has been revised to include the CD4 + T-lymphocyte count into 3 categories i.e. CD4 counts <200, 200-499, >500. These categories reflect HIV-related immunosuppression, clinical status, risk of opportunistic infections and assist the clinicians in diagnostic decision-making.[6,15] A typical healthy, HIV negative individual has a CD4 count greater than 500cells/mm^3.[14] Individuals infected with HIV who have CD4 counts >500cells/mm^3 are expected to present with common non-infective skin conditions like normal healthy individuals. Patients with lower CD4 counts (<200cells/mm^3) may present with serious or fatal opportunistic infections with cutaneous manifestations.[14]

Immunodeficiency state is associated with a wide spectrum of clinical disorders that may range between asymptomatic to Acquired Immunodeficiency syndrome (AIDS).[12] Mucocutaneous eruptions associated with HIV infection are common and occur throughout the course of HIV infection.

Although mucocutaneous eruptions are not the direct result of HIV infection, most of these eruptions are resulted from immunosuppressive state or related to the HIV treatment.[12] These lesions may be the first manifestations of HIV infection. Pre-existing dermatoses may be aggravated or worsened when AIDS develops.[7,12] It was shown that greater than 90% of patients developed at least one skin or mucous membrane manifestation during the course of their infection in a study involving 100 patients done in Dallas (Table 6).[9,16] Another study in Bangkok in 1995 also showed that 95% of 248 observed patients had one or more skin disorders.[17] A cross sectional survey involving 450 patients in France done in 1996 observed 65.3% of them had at least one skin manifestation during the course of HIV infection.[18] Mucocutaneous eruptions in HIV can be classified according to its underlying aetiologies. Viral, fungal, and bacterial infections as well as inflammatory dermatoses have all been reported with an increased frequency in association with HIV infection.[7] It has been shown that herpes zoster infection is an early manifestation of HIV infection, whereas Kaposi sarcoma and cryptococcosis reflect more advanced immunosuppression. Hence certain skin conditions may guide the clinicians to stage the clinical progression of HIV infection.[7]

Traditionally lower CD4 counts are reported to be associated with infective dermatoses.[19-21] Unsurprisingly, infective dermatoses encountered among those with CD4 <500cells/m^3 in our cohort was 2.7x more that those with CD4 >500cells/m^3. Being the most common indication of referrals, viral infections in HIV infected patients contributed 41.2% of the total dermatology referrals. Genital warts contributed 62.7% of the total viral related dermatoses. This was higher than other studies done in South of Iran[22] and Maharashtra, India[11], whereby viral infections contributed about 17.9-27.3% of their total diagnosis. Genital warts caused by human papillomavirus (HPV) is the most common sexually transmitted infection in the United States of America. Common warts may occur in unusual locations, with unusual severity, and with high frequency in HIV-infected patients.[7]

The rising trend of primary and secondary syphilis worldwide has been primarily attributable to increased cases amongst men who have sex with men (MSM), highest among persons aged 25-29 years.[23] There is a higher rate of HIV coinfection among MSM with syphilis and the disease course is more aggressive.[24] Syphilis carries significant morbidities if left untreated as the infection can span decades and progresses through multiple stages of infection. In this audit, 94 patients presented with cutaneous manifestations of different stages of syphilis. Skin lesions in secondary syphilis can mimic many other diseases hence detailed workups are needed to exclude other bacterial or fungal infections in order to institute the appropriate treatment.

Malaysia is classified as a country with an intermediate TB burden, with less than 100 per 100,000 populations.[25] All patients who are diagnosed with tuberculosis will be screened for HIV. It was found that 1346 (6.3%) patients of a total of 21,296 new TB cases were infected with HIV (1234 pre TB diagnosis and 112 post TB diagnosis).[25] Systemic infections with *Mycobacterium tuberculosis* and non-tuberculous mycobacteria are common in HIV disease.[7] Despite tuberculosis being the most commonly reported opportunistic infection and the leading cause of death among people living with HIV, the prevalence remained below 6% since 2014. In our audit, 56 patients were infected with tuberculosis (pulmonary tuberculosis, tuberculosis meningitis and disseminated tuberculosis). We only encountered a case of cutaneous tuberculosis i.e. lupus vulgaris in our current cohort.

Interestingly, the number of non-infective dermatoses detected among those with CD4 counts <500cells/m^3 counts in our audit were 4 times more than those with CD4 counts >500cells/m^3. Most patients with non-inflammatory dermatoses were referred for pruritic papular eruptions (PPE), 14.9% followed by papular eczema and seborrhoiec dermatitis, 10%. However, Sivayathorn et al.[17] in 1993-1994 done in Bangkok involving 248 patients showed that there were 32.7% patients with PPE and 21.0% with seborrhoiec dermatitis. Another study in Shiraz, South Iran by Davarpanah et al.[22] also showed that 0.5% of the total 240 patients had eczema. About 19.6% of patients in that study had xerosis and pruritis. In our study only 4 patients (0.9%) patients had xerosis and 1 had neurogenic pruritis. Psoriasis affects 1% to 3% of patients with HIV infection in the United States of America, as compared with its prevalence of 1% in the general population.[26] In some studies patients infected with HIV had psoriasis as their first presentation to a clinician before the diagnosis of HIV, or at the late stage of HIV during the progression into AIDS.[27] A flare of psoriasis or worsening arthropathy can be seen in patients with pre-existing psoriasis following HIV infection.[28] Our audit showed that 7

(1.65%) patients had psoriasis diagnosed after they were confirmed to have HIV. This was comparable to an audit reported Davarpanah et al.[22], whereby 2.9% of the patients had psoriasis. Concomitant HIV infection with psoriasis complicates the management especially in patients who require systemic therapy owing the possibility of drug-to-drug interactions. Commonly used medications i.e. methotrexate or cyclosporin may predispose HIV patients to malignancies and opportunistic infections due to their immunocompromised state.

Human immunodeficiency virus (HIV)-infected patients have complex immunological alterations with higher risk of developing drug hypersensitivity to antiretroviral or multiple drugs that usually prescribed for prevention or treatment of opportunistic infections.[29] About 5% of the dermatoses among the HIV infected patients referred to us were cutaneous adverse drug reactions. About 82% of SCARs in our cohort developed in those with CD4 counts <500cells/m^3. Cutaneous ADRs increased as the immune system deteriorates with the apparent decreasing in CD4 T-cell count.[29] The pathophysiology of drug hypersensitivity in HIV is multifactorial and related to alterations in drug metabolism, dysregulation of the immune systems (immune hyperactivation, patient cytokine profile), oxidative stress, genetic predisposition, and also the viral factors.[28] Patients with HIV infections are at risk of developing severe adverse drug reactions (ADR) towards ART, anti-toxoplasmosis as well as co-trimoxazole (bactrim) used in PCP prophylaxis. Severe drug hypersensitivity reactions such as Stevens Johnson syndrome and toxic epidermal necrolysis develop more often in HIV-infected patients compared to other populations.29 Davarpanah et al.[22] also observed that 10.8% of their patients had drug reactions. ADR was commonly seen with the initiation of ART (regardless of the CD4 counts) as well as with the use of anti-toxoplasmosis/bactrim (in patients with low CD4).

As life expectancy of HIV infected individuals increases, cancer has become a predominant cause of morbidity and mortality in this group of patients.[26] Patients with HIV infection are at higher risk of acquiring a few types of malignancies. Kaposi sarcoma, which is the most commonly reported malignancy in HIV infected patients. It occurs at a rate of more than 1000 folds greater than general population. Most Kaposi sarcoma traditionally occurs in individuals with low CD4 (<200cells/mm^3), however cases have been reported to occur at individuals with higher CD4 counts (>350cells/mm^3).[30] In our cohort, 12 (80%) patients with Kaposi sarcoma had CD4 counts less than 200. Apart from that, Non-Hodgkin Lymphoma (NHL) is also being classified as AIDS defining malignancy.[31] There were however no other malignancies observed in our cohort.

The introduction of ART has been shown to have a huge impact on the spectrum and severity of skin disease. Studies have shown an overall decrease in the prevalence of mucocutaneous manifestations with ART.[9] Advancement in ARTs have led to improved quality of life and life expectancies in HIV patients. It significantly changes the perception of HIV/AIDS from a fatal to a potentially manageable chronic disease.[4] Immune reconstitution inflammatory syndrome(IRIS) represents wide range of immunopathologic reaction resulting in restoration of immune function in HIV-infected patients after receiving ARTs.[32] Mucocutaneous presentations accounted for 68% of IRIS.[30] There are large varieties of presenting signs and symptoms for IRIS depending on the underlying infection acquired after a rapid decrease in HIV viral load and most IRIS results in mild to moderate symptoms.[33,34] However non dermatological manifestation related to IRIS may result in significant morbidity and mortality.[34] It may occur as early as 2 to 6 weeks of initiation of ART, but some may present within days to months.[35] It was found that the incidence of developing IRIS is particularly higher in patients starting ART at CD4 counts below 50cells/microL.[36] Cutaneous IRIS, may varies from infective, inflammatory, neoplastic to autoimmune disorders.[37] Patients may presents with acne, cutaneous ulcerations due to Mycobacterium avium, eruptions of warts, varicella zoster, herpes viruses, genital ulcers and folliculitis.[31,37,38] In our audit, 38.1% received ART within 12 months before they were referred to us. The dermatoses presented in these group of patients could be the manifestations IRIS. Infective dermatoses were noted to be the most common dermatoses in this subgroup of patients. Due to the retrospective nature of this audit, we could not ascertain that all the dermatoses described in these patients were truly manifestations of IRIS as we could not demonstrate presence of rebound of CD4 counts in them.

Our data is limited by the retrospective nature of the audit. Further prospective studies are in need for better describing the mucocutaneous manifestations of the HIV infected individuals based on the CD4

counts categories, as well as to monitor the evolution of skin diseases through the different stages of HIV. Nevertheless, our data illustrated the wide range of dermatoses in this group of patients which may be encountered by the clinicians. Clinicians should have a high index of suspicion when we manage such patients so that their skin conditions could be managed accordingly.

Conclusion

Our data showed that individuals with HIV infection may present with wide variety of skin disorders which included infective dermatoses, non-infective inflammatory dermatoses, cutaneous adverse drug reactions and tumours. About 35% of them had more than 1 dermatoses in our cohort. The most frequent infective dermatoses encountered were genital warts, syphilis, genital herpes, talaromycosis and molluscum contagiosum. The most frequent non-infective inflammatory dermatoses observed in our cohort was eczematous dermatoses. Kaposi sarcoma was the most frequent malignant tumour encountered in our cohort especially in those with low CD4 counts. About 7.3% of them developed cutaneous adverse drug reactions to the medications used to treat the HIV and co-morbidities.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

Acknowledgement

We would like to thank the Director General of Health Malaysia for the permission to publish this article.

References

1. CDC. *Pneumocystis* pneumonia - Los Angeles. MMWR 1981;30:250--2.
2. Web Annex 1. Key data at a glance. In: Progress report on HIV, viral hepatitis and sexually transmitted infections 2019. Accountability for the global health sector strategies, 2016–2021. Geneva: World Health Organization; 2019 (WHO/CDS/HIV/19.22). Licence: CC BY-NC-SA 3.0 IGO.
3. Ministry of Health, Malaysia. Country Progress Report on HIV/AIDS 2019.
4. Oguntibeju OO. Quality of life of people living with HIV and AIDS and antiretroviral therapy. HIV AIDS (Auckl) 2012;4:117-24.
5. Garman ME, Tyring SK. The cutaneous manifestations of HIV infection. Dermatol Clin 2002;20:193-208.
6. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41(RR-17):1-19.
7. Tschachler E, Bergstresser PR, Stingl G. HIV-related skin diseases. Lancet 1996;348:659-63.
8. Joint United Nations Programme on HIV/AIDS. Global AIDS Monitoring 2020. Geneva: UNAIDS 2019.
9. Lowe S, Ferrand RA, Morris-Jones R, Salisbury J, Mangeya N, Dimairo M et al. Skin disease among human immunodeficiency virus-infected adolescents in Zimbabwe: a strong indicator of underlying HIV infection. Pediatr Infect Dis J 2010;29:346-51.
10. Halder S, Banerjee S, Halder A, Pal PR. Skin diseases in HIV-infected patients: Impact of immune status and histological correlation. Indian J Sex Transm Dis AIDS 2012;33:65-7.
11. Chawhan SM, Bhat DM, Solanke SM. Dermatological manifestations in human immunodeficiency virus infected patients: Morphological spectrum with CD4 correlation. Indian J Sex Transm Dis AIDS 2013;34:89-94.
12. Herbst JS, Resnick L. Mucocutaneous manifestations of HIV infection. Clin Dermatol 1989;7:56-64.
13. Okoye AA, Picker LJ. CD4 (+) T-cell depletion in HIV infection: mechanisms of immunological failure. Immunol Rev 2013;254:54-64.
14. Institute of Medicine (US) Committee on Social Security HIV Disability Criteria. HIV and Disability: Updating the Social Security Listings. Washington (DC): National Academies Press (US); 2010.
15. Ford N, Meintjes G, Vitoria M, Greene G, Chiller T. The evolving role of CD4 cell counts in HIV Care. Curr Opin HIV AIDS 2017;12:123-8.
16. Coldiron BM, Bergstresser PR. Prevalence and clinical spectrum of disease in patients infected with human immunodeficiency virus. Arch Dermatol 1989;125:357-61.
17. Sivayathorn A, Srihra B, Leesanguankul W. Prevalence of skin disease in patients infected with human immunodeficiency virus in Bangkok, Thailand. Ann Acad Med Singapore 1995;24:528-33.
18. Spira R, Mignard M, Doutre MS, Morlat P, Dabis F. Prevalence of Cutaneous Disorders in a Population of HIV-Infected Patients; Southwestern France, 1996. Arch Dermatol 1998;134:1208-1212
19. Huang XJ, Li HY, Chen DX, Wang XC, Li ZC, Wu YS et al. Clinical Analysis of Skin Lesions in 796 Chinese HIV-positive Patients. Acta Derm Venereol 2011;91:552-6
20. Chandrakala C, Parimalam K, Wahab AJ, Anand N. Correlating CD4 count with mucocutaneous manifestations in HIV-positive patients: A prospective study. Indian J Sex Transm Dis AIDS 2017;38:128-35.
21. Oninla OA. Mucocutaneous M anifestations of HIV and the Correlation with WHO Clinical Staging in a Tertiary Hospital in Nigeria. AIDS Res Treat 2014;2014:360970.
22. Davarpanah MA, Motazedian N, Jowkar F. Dermatological Manifestations of HIV/AIDS Individuals in Shiraz, South of Iran. J Glob Infect Dis 2018;10:80-3.
23. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64:1-137
24. Devkota AR, Ghimire R, Sam M, Aung O. Malignant Syphilis as an Initial Presentation of Underlying HIV Infection: A Case report. BJMP 2015 8:a816.
25. Ministry of Health Malaysia. National Strategic Plan for Tuberculosis Control (2016-2020). Accessed: 16th November 2020. Available from: http://www.moh.gov.my/index.php/pages/view/1917?mid=613.
26. Dlova NC, Mosam A. Inflammatory non-infectious dermatoses of HIV. Dermatol Clin 2006;24:439-8.
27. Wölfer LU, Djemadji-Oudjiel N, Hiletework M, Tebbe B, Husak R, Goerdt S et al. HIV-associated Psoriasis. Clinical

and Histological Observations in 36 Patients. Hautarzt 1998;49:197-202.
28. Nakamura M, Abrouk M, Farahnik B, Zhu TH, Bhutani T. Psoriasis Treatment in HIV-Positive Patients: A Systematic Review of Systemic Immunosuppressive Therapies. Cutis 2018;101:38-56.
29. Yunihastuti E, Widhani A, Karjadi TH. Drug hypersensitivity in human immunodeficiency virus-infected patient: challenging diagnosis and management. Asia Pac Allergy 2014;4:54-67.
30. Crum-Cianflone N, Hullsiek KH, Ganesan A, Weintrob A, Okulicz JF, Agan BK et al. Is Kaposi's Sarcoma occuring at higher CD4 counts over the course of the HIV epidemic? AIDS 2010;24:2881-3.
31. Crum-Cianflone N, Hullsiek KH, Satter E, Marconi V, Weintrob A, Ganesan A et al. Cutaneous malignancies among HIV-infected persons. Arch Intern Med 2009;169:1130-8.
32. Gopal R, Rapaka RR, Kolls JK. Immune reconstitution inflammatory syndrome associated with pulmonary pathogens. Eur Respir Rev 2017;26:160042.
33. Sharma SK, Soneja M. HIV & immune reconstitution inflammatory syndrome (IRIS). Indian J Med Res 2011;134:866-77.
34. Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. Dermatol Clin 2006;24:549-70.
35. Summers NA, Armstrong WS. Management of advanced human immunodeficienct virus disease. Infect Dis Clin North Am 2019;33:743-67.
36. Novak RM, Richardson JT, Bucxhacz K, Chmiel JS, Durham MD, Palella FJ et al. Immune reconstitution inflammatory syndrome: incidence and implications for mortality. AIDS 2012;26:721-30.
37. Huiras E, Preda V, Maurer T, Whitfeld M. Cutaneous manifestations of immune reconstitution inflammatory syndrome. Curr Opin HIV AIDS 2008;3:453-60.
38. Murdoch DM, Venter WD, Van Rie A, Feldman C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. AIDS Res Ther 2007;4:9.
39. Uthayakumar S, Nandwani R, Drinkwater T, Nayagam AT, Darley CR. The Prevalence of Skin Disease in HIV Infection and Its Relationship to the Degree of Immunosuppression. Br J Dermatol 1997;137:595-8.
40. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous Disease and Drug Reactions in HIV Infection. N Engl J Med 1993;328:1670-4.
41. Wiwanitkit V. Prevalence of Dermatological Disorders in Thai HIV-infected Patients Correlated with Different CD4 Lymphocyte Count Statuses: A Note on 120 Cases. Int J Dermatol 2004;43:265-8.