EPIDEMIOLOGY OF PRURITIC PAPULAR ERUPTION AND MAJOR HIV RELATED SKIN DISEASES AFFECTING NEW PATIENTS IN RIFT VALLEY PROVINCIAL GENERAL HOSPITAL

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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ABSTRACT

Pruritic papular eruption (PPE) is a skin disease exclusively found in HIV seropositive individuals. It is characterised by eruption of extremely itchy papules, conspicuous blemishes and a profound negative impact on quality of life (QoL). Its prevalence ranges from 6.9% to 58% depending on geographical location. HIV related skin diseases affect up to 98% of HIV seropositive individuals. The epidemiology of PPE and major HIV related skin diseases among adults attending Comprehensive Care Centre (CCC) in Rift Valley Provincial General Hospital (RVPGH) has not been documented. The impact of PPE on QoL as well as the prevalence of major HIV related skin diseases among patients with various CD4 cell counts in RVPGH is also unknown. This study aimed at determining epidemiology of PPE, establishing its impact on QoL and determining the prevalence of major HIV related skin diseases and their relationship with CD4 cell counts. The study was conducted at the CCC in RVPGH in Nakuru County. New HIV-seropositive patients aged 18 years and above formed the target population. A cross-sectional study design was used to conduct this study. Sample size was determined using Daniel's formula (1999). 394 consecutive patients were studied. Consenting patients underwent a full skin examination conducted by two dermatologists. Patients with PPE were reviewed separately for further epidemiologic evaluation and QoL assessment. Data on QoL was collected using the Dermatology Life Quality Index (DLQI). Epidemiologic questionnaires and observational checklists were used to collect data on major HIV related skin diseases and CD4 cell counts. Descriptive statistics were used to describe qualitative data. Chi-square and logistic regression were used to evaluate associations. Student's *t* test was used to evaluate differences in means. A p-value < 0.05 was considered significant. The prevalence of PPE in this study was 5%. PPE affected more women (75%) than men. The mean DLQI score for QoL was 15.2. Prevalence of HIV related skin diseases was 42.1%. There was a significant association between PPE, oral candidiasis, seborrheic dermatitis and low CD4 cell counts. The burden of PPE and major HIV-related skin disease in RVPGH is substantial and significantly associated with low CD4 cell counts. Clinicians in RVPGH need to be updated on the burden and impact of PPE and the major HIV related skin diseases for proper and holistic management. More skin specialists are needed to cope with increased demand for care occasioned by patients with HIV related skin disease in RVPGH.

CHAPTER 1

INTRODUCTION

1.1 Background information

Pruritic Papular Eruption (PPE) is a unique skin disease characterised by an eruption of extremely itchy papules (Resneck *et al.,* 2004). It occurs exclusively among HIV infected individuals especially in those with advanced immunosuppression (Resneck *et al.,* 2004; Lakshmi *et al.,* 2008). The disease was described as a clinical entity for the first time by James *et al.,* (1985). It is considered the leading skin disease in HIV seropositive individuals in Africa (Colebunders *et al.*, 1987).

The epidemiology of PPE is dynamic; its prevalence, distribution, pattern and impact on quality of life are variable across populations: According to Resneck *et al.,* (2004), the prevalence and distribution of PPE differs from region to region and its pattern varies depending on the characteristics of affected individuals, state of their immunity and stage of their disease. While the epidemiology of the diseases has been documented in other countries, there is a dearth of information regarding the prevalence, distribution and pattern of PPE in Nakuru County and Kenya as a whole. The impact of the disease on QoL among newly diagnosed HIV infected adults attending CCC in RVPGH is also not known. This study was conducted in order to address this gap.

The exact cause of PPE is currently unknown. However, various aetiological associations have been hypothesised by various authors: Resneck *et al.,* (2004) have suggested that PPE is caused

by arthropod bites while Aires *et al.,* (2000) consider PPE to be a consequence of an abnormal hypersensitivity reaction to the human immunodeficiency virus. The controversies surrounding the aetiological theories of PPE reaffirm the indefinable nature of the disease.

The disease is characterised by a spontaneous, usually sudden occurrence of discrete, intensely pruritic skin coloured papules distributed predominantly on outer aspects of lower arms and legs of HIV seropositive patients (Bason *et al.,* 1993). With time, the papules, which are usually excoriated, transform into nodules and heal with hyperpigmented macules. The different stages of lesions observed in PPE signify a chronic disease typified by episodes of remissions and relapses (James *et al.,* 1985; Resneck *et al.,* 2004; Wiwanitkit 2004). Chronicity and recurrences are some of the factors which have contributed to the high prevalence of the disease reported in different communities (Banuls *et al.,* 1991).

Pruritic papular eruption is more common in tropical than in temperate countries and its distribution depends on time, place and person characteristics (Resneck *et al.,* 2004). Different countries have reported different prevalence estimates: According to Rosateli & Rosalino (2001), the prevalence of PPE in Brazil in the year 2001 was 11.7%. In Thailand the disease affected up to 51% of HIV infected individuals in the same year making it the most prevalent cutaneous disease among Thai HIV seropositive individuals (Supanaranond, *et al.,* 2001). According to Singh *et al.,* (2009), the prevalence of PPE in India range from 22% to 50% depending on the regions.

The prevalence of PPE in Africa ranges from 6.9% in South Africa to 58% in Tanzania (Budavari & Grayson 2007; Mgonda 2004). It occurs in 37.5% of patients with HIV infection in Togo and in 35% of patients with acquired immunodeficiency syndrome (AIDS) in Rwanda, Zaire, and Uganda (Resneck, *et al.,* 2004). Though the prevalence and distribution of PPE has been reported in East African countries, it is not known or is yet to be reported in Kenya. Besides, its distribution and pattern on newly diagnosed HIV seropositive patients seeking care at Rift Valley Provincial General Hospital (RVPGH) is not known.

Pruritic papular eruptions contribute significantly to patient morbidity in terms of quality of life (QoL) yet little is known about its effects among Kenyans. Quality of life assessments are epidemiological measures used to demonstrate the intangible yet significant effects of a disease or its treatment on the life of patients (Keibert *et al.,* 2002). If the cosmetic, psychological and emotional effects of PPE are not highlighted through QoL reports, the importance of the disease may not be appreciated and patients run a risk of being under treated (Keibert *et al.,* 2002; Muyinda *et al.,* 1997). Since patients with PPE do not appear ill, chances are high that their disease may be dismissed as mere rashes unless its negative effects on QoL are established and reported. The need to assess quality of life among newly diagnosed HIV seropositive patients with PPE in RVPGH cannot therefore be overemphasised.

HIV related skin diseases are a major cause of public health burden in the world (Uthayakumar *et al.,* 1997). Up to 90% of HIV seropositive patients suffer or will suffer one or more skin diseases in the course of their lives (Goh *et al.,* 2007). The distribution of HIV related skin

diseases differ by country: According to Boonchai *et al;* (1999) the major cutaneous disorders commonly associated with human immunodeficiency virus (HIV) infection in India include seborrheic dermatitis, oral hairy leukoplakia (OHL), herpes simplex virus infections, molluscum contagiosum, oral candidiasis, Kaposi's sarcoma, and pruritic papular eruption (PPE). However, according to Palangyo (1992), disease like Kaposi's sarcoma and oral hairy leukoplakia are either rare or have not been frequently reported in literature from East Africa.

There is paucity of data from Kenya regarding the burden and distribution of major HIV related skin diseases and the same is not known for Nakuru County. The prevalence, pattern and distribution of HIV related skin diseases and their association with CD4 cell counts among newly diagnosed HIV seropositive patients seeking care at the Comprehensive Care Centre (CCC) in RVPGH are currently unknown.

1.2 Statement of the Problem

The distribution, epidemiological pattern and prevalence of PPE are important components in the mangemnt of the disease yet little is known regarding these characteristics in patients attending RVPGH. Though the disease is routinely diagnosed among HIV-seropositive individuals in several Kenyan hospitals, the extent to which it affects newly diagnosed patients visiting Rift Valley Provincial General Hospital (RVPGH) is unknown. Lack of relevant epidemiological data regarding PPE has led to inconsistent approaches in the management of the disease and to disproportionate allocation of resources in the hospital.

The conspicuous lesions of PPE attract suspicious looks from the public thus subjecting patients to intense stigma, discrimination and ultimately make them withdraw from public life. The chronic nature of the disease causes financial losses while the intense itching lead to loss of sleep and interference with work and school. These factors contribute to the poor quality of life yet the degree with which PPE affects quality of life among newly diagnosed HIV seropositive patients in RVPGH is unknown or has not been documented.

The large number of patients seeking care at the RVPGH has increased the workload and outstretched the available resources. It is however unclear to what extent HIV related skin diseases have contributed to increased outpatient consultations in the CCC. Allocation of resources and formulation of policies pertaining to management and control of HIV related skin diseases in RVPGH cannot be done effectively without adequate data. Data on prevalence and distribution of PPE and major HIV related skin diseases in the population seeking care at the RVPGH is currently missing.

1.3 Objectives of the Study

1.3.1 Broad Objective:

To determine the epidemiology of PPE and its impact on quality of life and assess the prevalence of major HIV related skin diseases and their association with CD4 cell counts among newly diagnosed HIV seropositive patients aged 18 years and above consulting at the Comprehensive Care Centre in Rift Valley Provincial General Hospital (RVPGH).

1.3.2 Specific Objectives

1. To determine the distribution and pattern of PPE in newly diagnosed HIV patients attending RVPGH.
2. To assess quality of life of the newly diagnosed HIV patients with PPE in RVPGH.
3. To analyse association between major HIV related skin diseases and CD4 cell counts in the newly diagnosed HIV patients in RVPGH.
4. To establish the prevalence of HIV related skin diseases in the newly diagnosed HIV patients in RVPGH.

1.4 Research questions

1. What is the distribution and pattern of PPE in newly diagnosed HIV seropositive patients in RVPGH?
2. How does PPE impact on quality of life of newly diagnosed HIV seropositive patients?
3. Is there an association between major HIV related skin diseases and CD4 cell counts in newly diagnosed HIV seropositive?
4. What is the prevalence of HIV related skin diseases in newly diagnosed HIV patients in RVPGH?

1.5 Justification of the Study

Establishing the distribution and pattern of PPE among newly diagnosed HIV seropositive patients generates data that can be used in decision making regarding PPE interventions. Patients

with PPE are severely stigmatised and have poor quality of life (QoL). Assessing the impact of the disease on quality of life among newly diagnosed HIV seropositive patients reassures them that steps are being taken to minimise their suffering. Secondly, QoL studies help in sensitising authorities on the importance of PPE, thus attracting favourable policies regarding resource allocation for its management.

Estimating the prevalence of HIV related skin diseases among newly diagnosed patients provide data which may be used in surveillance, hypotheses formulation and decision making. Efficient utilisation of health resources is made more expedient when health care planners and policy makers take action with reference to available morbidity data. This study has provided the data on the burden occasioned by PPE and other HIV related skin diseases in RVPGH.

1.6 Limitations of the Study

Given that diagnosis of skin diseases were made on clinical grounds, there are chances that some misdiagnosis could have occurred. This was however minimised by utilising two dermatologists for diagnosis concurrence. The study site is a referral hospital where only patients with difficult or unresponsive skin diseases are referred. Some patients with common and easily treatable skin diseases may not therefore have reached the CCC because they were treated in peripheral health centres. Since this was a hospital based study, generalisation of study findings to all patients with HIV living in Nakuru County cannot therefore be made. This study only analyzed outpatients; consequently, HIV related skin diseases among hospitalized patients were not taken into consideration.

CHAPTER 2

LITERATURE REVIEW

2.1. Definition of Pruritic Papular Eruption (PPE)

The definition of PPE is controversial; the phrase 'pruritic papular eruption' is considered a descriptive term rather than a definite name of a disease (Lakshmi *et al.,* 2008). Although its definition is controversial, its clinical description is unequivocal; almost all authors describe PPE in a similar manner (Boonchai *et al.,* 1999). Despite the lack of a precise definition and a controversial nomenclature, PPE is universally recognised as a common, itchy skin disease occurring predominantly among patients with advanced human immunodeficiency virus (HIV) infection (Annam *et al.,* 2009). A brief but detailed description of the clinical features of PPE is currently accepted as a surrogate for a standard definition.

PPE is described as a unique, pruritic skin disease characterised by an eruption of extremely itchy papules occurring exclusively among HIV infected individuals with advanced immunodepression (James *et al.,* 1985; Berman *et al.,* 1998; Lakshmi *et al.,* 2008). The disease is typified by recurrent episodes of discrete, excoriated, skin-coloured papules averaging 2-5 mm in diameter distributed predominantly on the outward aspects of extremities (Annam *et al.,* 2009). The features of the disease appear consistent across age, race and gender but for unknown reasons its lesions are more profuse on outer legs and arms, especially among people residing in mosquito infested areas (Resneck *et al.,* 2004; Salim & Lawrence 2003). This characteristic distribution may provide clues on the aetiology of the disease.

2.2. Historical aspects of PPE:

During the early years of the HIV/AIDS, an unidentifiable skin disease characterised by extremely itchy discrete papules was described and recognised as a clinical entity for the first time in 1985 by James *et al.,* (1985). This entity was subsequently referred to as pruritic papular eruption. From the time the disease was initially described its prevalence has increased tremendously and surpassed that of Kaposi' sarcoma and herpes zoster to become the most prevalent HIV related skin disease in Africa (Palangyo 1992).

Early studies on PPE were predominantly descriptive studies which were aimed at generating hypotheses. However, as the disease became more prevalent, analytical studies were conducted to explain its aetio-pathogenesis, treatment and to assess its impact on quality of life. Hevia *et al.,* (1991) were the first to conduct a study on histologic features of PPE in the year 1991. They evaluated biopsies of thirty patients with PPE and described histological features which were subsequently used as reference for PPE histology. Goldstein *et al.,* (1997) and Ajithkumar *et al.,* (2001) investigated the relationship between immunedysregulation, CD4/CD8 cells and PPE to explain the pathogenesis of PPE.

In 2001 Kent *et al.,* (2001) did a study to evaluate the effect of PPE on the quality of life of patients with HIV and found that majority suffered poor quality of life. In 2004, Resneck *et al.,* (2004) investigated the role of arthropod bites in PPE in Ugandan patients and concluded that PPE could be a result of mosquito bites. Recently, Navarini *et al.,* (2010), did a comparative study on the efficacy of promethazine compared to topical hydrocortisone in the management of PPE to determine the best treatment option of the disease.

2.3 Significance of PPE in HIV infection

Pruritic papular eruption has several epidemiological and clinical uses in HIV disease (Resneck *et al.,* 2004). It can be used as an initial marker of HIV infection, a clinical indicator of stage of HIV disease, a predictor of the level of immunodepression and is used in monitoring efficacy of Highly Active Anti-Retroviral Therapy (HAART) in HIV treatment (Castelnuovo *et al.,* (2008):

2.3.1 Sign of HIV Infection

Approximately 90% of patients presenting in hospitals across Africa with PPE turn positive on HIV testing (Resneck *et al.,* 2004); this makes PPE a significant sign of HIV and its presence should always alert the clinician and the patient on the possibility of HIV infection (Rigopoulos *et al.,* 2004). Such awareness has motivated patients with PPE to spontaneously undertake early HIV testing (Singh *et al.,* 2009). Early diagnosis of HIV infection prevents complications usually associated with late diagnosis.

2.3.2 Monitoring HIV progression

HIV infection inexorably progresses to AIDS, however, the time when AIDS develops is unpredictable (Cedeno-Laurent *et al.,* 2011). This unpredictability reinforces the importance of monitoring HIV infection to avoid late diagnosis of AIDS. Conventionally, CD4 cell counts and viral load assessments have been used to assess disease progress, however, where the tests are unavailable especially in resource-poor countries HIV disease progress can be monitored by clinical means (Castelenuovo *et al.,* 2008).. Since PPE is consistently observed in patients whose CD4 cell counts have dropped to severe immunodepression levels, Aires *et al.,* (2000) and Kumarasamy *et al.,* (2000) suggests that the disease can be used as a tool to monitor HIV progression. According to Raju *et al.,* (2004) and Samanta *et al.,* (2009) occurrence of PPE in

patients with HIV should be regarded as an early warning of impending development of AIDS. PPE is therefore an important clinical sign of deteriorating immunity and immune restoration interventions should be instituted immediately the disease occurs (Lakshmi *et al.,* (2008).

2.3.3 Clinical staging of HIV

HIV disease is staged according to severity from stage 1 to 4. According to WHO (2006) guidelines, patients with PPE are categorised as being in second stage meaning they are significantly immunocompromised. Thus, patients presenting with PPE may be regarded as eligible for HAART in resource constrained settings where CD4 cell counts and viral loads cannot be determined routinely (WHO 2006).

2.3.4 Monitoring Effectiveness of HAART

In resource-limited settings where CD4 cell and viral load counts are unavailable, clinical outcomes of PPE can be used to predict the success or failure of HAART (Castelnuovo *et al.,* 2008). Chua & Maurer (2009) observed that patients treated with HAART for six consecutive months were healed of PPE but the disease recurred when the regime failed. Therefore, the clinical status of PPE in patients on HAART can be used to determine the efficacy of the regime (Castelnuovo *et al.,* 2008). Accordingly, if a patient on HAART developed PPE, the regime the patient is using should be changed because most likely it has invariably failed. However, if clearance of PPE occurs, the HAART regime should be considered a success and maintained.

2.4 Epidemiology of PPE

2.4.1 Prevalence, distribution and patterns of PPE

The frequency and distribution of PPE differ from country to country and varies according to geographic location (Resneck *et al.,* 2004). Any HIV infected individual of whatever age, race or gender is potentially at risk of developing PPE especially when they are severely immunodepressed (Bason *et al.,* 2007).

The estimated prevalence of PPE varies from 10% to 58% in Africa and its frequency rises tremendously in areas with high mosquito densities (Resneck *et al.,* 2004, Aires *et al.,* 2000). This type of distribution however has not been consistently observed in other countries and may in the meantime remain only fortuitous. The disease is more prevalent in developing than in developed countries and in tropical than in non-tropical countries (Lakshmi *et al.,* 2008). Majority of cases of PPE occur in sub-Saharan Africa, Haiti, Thailand, India and Brazil (Lakshmi *et al.,* 2008; Resneck *et al.,* 2004). However, PPE appears to be declining in some countries; recent estimates from South Africa demonstrate a prevalence of only 6.9% (Budavari & Grayson 2007). This is quite low compared to earlier reports from other African countries. The reasons for the decline are unknown.

The distribution of PPE is influenced by several factors including seasons, geographic locations and the characteristics of persons (Resneck *et al.,* 2004). The frequency of the disease therefore differs according to country and prevailing climatic conditions in those countries. Even in the same country PPE is distributed differently depending on the regions. Table 2.1 shows the different prevalence estimates reported from hospitals in different countries.

Table 2.1: Prevalence estimates of PPE in various countries.

Author/country/Year	*n/N*	Prevalence of PPE (%)	Sampling procedure	Remarks
Lowe *et al.*, /Zimbabwe/2010	59/139	42.45%	Convenience hospital sample	Small sample: Clinical diagnosis
Navarini *et al.*,/Tanzania/2010	105/852	12%	Convenience hospital sample	Adequate sample: Clinical diagnosis
Singh *et al.*,/India – Chattisgarh /2009	27/137	19.7%	Convenience hospital sample	Small sample size: clinical diagnosis
Yahya H./Nigeria/2007	108/258	41.9%	Patients records sample	Retrospective study
Goh *et al.*,/Singapore/2007	31/96	32.29%	Convenience hospital sample	Small sample: Clinical diagnosis
Budavari & Grayson/South Africa /2007	6/40 *	15%	Convenience hospital sample	Very small sample: Biopsy diagnosis
Sharma *et al.*,/India/2007	43/200	21.5%	Convenience hospital sample	Small sample: Clinical diagnosis
Wiwanitkit *et al*,./Thailand/2004	44/120	36.67%	Convenience hospital sample	Small sample: Clinical diagnosis
Mgonda A.Y./Tanzania/2004	204/354	58%	Convenience hospital sample	Average sample size: Clinical diagnosis
Colebunders *et al.*,/DRC/1987	52/284	18%	Convenience hospital sample	Small sample: Clinical diagnosis

Key: * considered among patients with pruritic skin disease in HIV

2.4.2 Continental distribution of PPE

Pruritic papular eruption is distributed in almost all the continents of the world albeit with varying prevalence (Rosateli *et al.*, 1997). However, for unknown reasons PPE is rare in North America and Europe and has not been reported in Australia. Africa is the leading continent in terms of the prevalence of PPE. The disease occurs most commonly in Sub-Saharan Africa especially in East and West Africa. The second leading continent regarding PPE prevalence is

Asia. In the continent of Asia the disease is more prevalent in South and Southeast Asia than in any other parts of the continent. The reasons for the unique distributions are currently unclear.

1. PPE in Asia

Pruritic papular eruption has been described as the most common HIV-related skin disease occurring in HIV seropositive patients residing in Asian nations: In India, the prevalence of PPE ranges from 22% to 50% according to provinces. For instance, the prevalence of PPE in the province of Jagalpur is 22.5% (Singh *et al.,* 2009). This differs significantly from that observed in the province of Baroda which is estimated to be 35.8% (Sharma *et al.,* 2007). The regional variations of prevalence estimates reported from one country emphasises the epidemiologic dynamism of PPE.

According to Lumbiganon *et al.,* (2009) the prevalence of PPE in Thailand by the year 2009 was 46.6% among the adult population while it was 5.5% among HIV infected children under 13 years (Wananukul & Thisyakorn 2002). Different prevalence estimates in adults compared to children has important connotations regarding causes of the disease. The recent estimates however, represent a decline because between 1995 and 1999 the prevalence of PPE in Thailand was 51.2% among HIV seropositive persons (Supanaranond *et al.,* 2001). The reasons for the decline are not presently known.

2. PPE in America and Europe

Few epidemiologic studies on PPE have been conducted in the United States of America (USA) probably because the disease is not very common there. Available literature documents one study done in 1997 by Goldstein *et al.,* (1997) in South Florida. The study estimated the prevalence of PPE to be 11.4% among HIV positive patients residing in that state. In Brazil, the prevalence of

PPE was 11.7% in 2001 (Rosateli & Roselino, 2001). The rarity of PPE in Europe raises many possibilities. It may mean that the disease is rare or has been successfully controlled by effective HAART in the different countries of Europe. However, PPE was not found during a recent study in Spain by Blanes *et al.,* (2010) although a number of their patients were not on HAART. The reasons for the absence of PPE in many European nations may not be entirely clear but it appears that the prevailing climatic conditions and the heterogeneity in genetic constitutions of populations in Europe may influence the disease occurrence.

3. PPE in Africa

The prevalence of PPE is highest in Africa than in any other continent; more than half of HIV infected patients in Sub-Saharan Africa have PPE (Aires *et al.,* 2000). Majority of them are found in East, Central, South and West African nations (Resneck *et al.,* 2004).

a. Prevalence of PPE West Africa

West African countries where reports of PPE prevalence are available include Togo, Cameroon and Nigeria: In Togo, PPE affected 37.5% of Togolese living with HIV in 1995 (Pitche *et al.,* 1995) and in Cameroon 39% of HIV positive patients have PPE (Josephine *et al.,* 2004). In both countries PPE is ranked as the leading HIV-related skin disease. The disease is also the most prevalent skin disease in Nigeria where it affected 41.9% of HIV seropositive individuals between 2000 and 2005 (Yahya 2007).

b. Prevalence of PPE in East Africa

The highest prevalence of PPE in the world was reported in Tanzania. According to by Mgonda (2004) PPE affected 58% of adults with HIV in the city of Dar es Salaam in 2003. However, Muhammad *et al.,* (2003) found a prevalence of only 7.1% among HIV infected police officers residing in Dar es Salaam between 1998 and 2000. These estimates contrasts sharply from one

another; the reasons for this is unclear. However, police officers reside in specified areas which may be significantly different from that of general population. In Hai, a rural district in Northern Tanzania, the prevalence of PPE was 12% in the year 2010 (Navarini *et al.,* 2010); this district has different climatic conditions compared with Dar es Salaam and this could explain the differences in prevalence estimates.

About half of Ugandans, Rwandese and Burundians with HIV present with PPE as the initial HIV manifestation (Resneck *et al,* 2004; Colebunders *et al;* 1987). This makes the disease the most prevalent HIV-related skin disease in those countries. Despite detailed literature search, data on the epidemiology of PPE in Kenya or any of its regions were not found. This scenario makes it difficult to make any meaningful comparisons between Kenya and other countries regarding the epidemiological variables of PPE.

c. Prevalence of PPE in South Africa

Compared to reports from East and Central Africa, the prevalence of PPE in South Africa is surprisingly low; in 2007, PPE was seen in only 6.9% of the HIV seropositive patients studied by Budavari & Grayson (2007). However, unlike in other studies where the diagnosis of PPE was made clinically, the South African investigators made their diagnosis by examining serial sections of biopsies. The prevalence of PPE was 42% in Zimbabwe in the year 2009 (Lowe *et al.,* 2010). The diagnosis of PPE in this study was made on clinical grounds.

2.4.3 Aetiology of PPE.

The cause of PPE has remained elusive since the disease was described in 1985. Nevertheless, several factors have been linked to its occurrence but none has been proved. The fact that PPE is

exclusively found among HIV seropositive individuals bring into high suspicion that PPE is caused by HIV infection (Annam *et al.,* 2009). However, this single agent theory has been disputed because not all patients with HIV infection develop PPE. According to Resneck *et al.,* (2004) and Lakshmi *et al.,* (2008) PPE results from multiplicity of factors including an interaction of HIV infection, advanced immunosuppression and arthropod bites especially mosquito bites.

According to Roberto (2000), PPE is an aberrant immune response occurring in patients with abnormal hypersensitivity to the human immunodeficiency virus. However, Ashack *et al.,* (1989), argues that PPE does not result from HIV but is a form of folliculitis which is caused by the direct infection of the hair follicle with *Demodex folliculorum* and *D. brevis.* However, Resneck *et al.,* (2004) did not find features consistent with microbial infection in sections of PPE biopsies. The exact cause of PPE therefore remains unconfirmed up to now.

2.4.4 Impact of PPE on Quality of Life (QoL)

Health related quality of life (QoL) is an epidemiologic measure of disease burden: It is defined as the subjective perception of the impact of disease and its treatment on the health status of an individual (Keibert *et al.,* 2002). Apart from the physical symptoms, skin diseases such as PPE affect patients spiritually, psychologically and socially (Keibert *et al.,* 2002). These are intangible attributes difficult to quantify by clinical observations only. Therefore assessment tools have been developed to objectively measure QoL.

Chronic skin diseases which alter patients' appearance lead to intense stigma, unemployment, discrimination and even suicide due to the constant frustrations endured by patients (Evers *et al.,* 2005; Ongenae *et al.,* 2006; Feldman *et al.,* 2004). Being a disease with conspicuous lesions, PPE alters patients' appearance and has capacity to affect patients psychologically, emotionally and physically (Kent *et al.,* 2001). Nearly all patients with PPE complain that the disease has altered their appearance and has lowered their self esteem. They are forced to change their dressing code in a bid to shield their altered skin from the public eye (Lakshmi *et al.,* 2008).

According to Annam *et al.,* (2009) PPE impacts negatively on quality of life (QoL) in various ways: it causes protracted itching which disrupts sleep, tires the patient and interferes with activities of daily living while the altered skin appearances subject patients to uninvited glances and gossip. When compared to other HIV related skin diseases PPE causes a much poorer QoL (Kent *et al.,* 2001). It is known that patients already on treatment develop coping skills and their QoL improves, however, it is not known, how PPE impacts on newly diagnosed HIV seropositive patients. QoL reports are important in epidemiology because they are used as reference points for prioritising interventions (Holm *et al.,* 2006; Heuring 2004).

Despite their significance, quality of life assessments among HIV seropositive patients with PPE have not been documented in Kenya nor have they been conducted among newly diagnosed HIV seropositive patients with PPE consulting at the RVPGH. This gap can contribute to the relegation of skin diseases often seen in various care centres.

2.5 Clinical features of PPE

Clinically, PPE mimics several other papulo-pruritic disorders of HIV: Since PPE is a descriptive term chances are high that the disease may be used as a "waste basket" diagnosis where any pruritic papular eruption occurring in HIV is erroneously diagnosed as PPE (Teofoli *et al.,* 2002). To reduce confusion and increase diagnostic precision, the clinical diagnosis of PPE should be made by following an established diagnostic criterion (Lakshmi *et al.,* 2008).

Patients with PPE typically complain of sudden eruption of numerous, extremely itchy papules which cannot be relieved even with intense scratching (Berman *et al.,* 1998). They also complain of sleeplessness due to night time scratching. Due to lack of sleep, patients suffer fatigue and irritability. The excoriations occasioned by frenzied scratching lead to pain, bleeding and secondary infection of the damaged skin.

2.5.1 Distributions and pattern of PPE lesions

The predominant lesions found in PPE include papules, nodules excoriations and macules (Resneck *et al.,* 2004). These are typically distributed on outer arms and legs, dorsa of hands and feet, thighs and ankles (Lakshmi *et al.,* 2008). The trunk and face are also involved but with relatively less intensity while the palms, genitalia and soles are conspicuously spared (Goldstein *et al.,* 1997; Lakshmi *et al.,* 2008). In some patients however, PPE lesions may be generalised as was found in 35% of Thai patients by Boonchai *et al.,* 1999; Kumarasamy *et al.,* (2000).

According to Liautand *et al.,* (1989) the disease usually starts on lower outer arms and extend to the outer upper arms, outer legs and then to the outer aspects of the thighs. Dorsa of hands and

feet are then affected in that order; however a haphazard occurrence is possible. Unlike in eosinophilic folliculitis PPE lesions are rarely observed in areas above the nipple line (Fiza & Rudikoft, 2003).

2.5.2 Diagnosis of PPE

Currently, biological means of confirming PPE are inexistent. Though histology has been used to identify PPE, the diagnosis of the disease is usually made on clinical grounds by following established criteria (Boonchai *et al.,* 1999). The making of a clinical diagnosis involves taking an inquisitive history and conducting a full skin examination (Garg *et al.,* 2008). While the clinical diagnosis of PPE may be suggested by typical skin lesions, some authors consider it a diagnosis of exclusion, that is, a diagnosis made only after ruling out other similar but definable diseases (Annam *et al.,* 2009). To exclude diseases which bear striking resemblance with PPE, relevant laboratory investigations are performed where appropriate (Toutous-Trellu *et al.,* 2005; Simpson-Dent *et al.*, (1999).

In order to standardise the diagnosis of PPE and minimise misdiagnosis, a clear epidemiological case definition should be made and a criterion established. Boonchai *et al.,* (1999) formulated a criterion to be used in epidemiologic studies and in dermatology clinics. The criterion requires that a patient with PPE must:

i. Be infected with HIV
ii. Have chronic, pruritic discrete papules on the trunk, extremities and face
iii. Have no other definable cause of the pruritus.

2.5.3 Differential diagnosis of PPE

The clinical picture of PPE is nonspecific; the disease can very easily be confused with most other itchy dermatoses affecting HIV infected individuals (Annam *et al.,* 2009). A disease such as eosinophilic folliculitis (EF) for example, is so identical to PPE that it is difficult to clinically distinguish the two. However, some salient clinical and epidemiological features of PPE are not found in EF (Resneck *et al.,* 2004).

Eosinophilic folliculitis presents as an eruption of pruritic papules occurring among individuals with HIV, however, unlike PPE, the lesions of EF are distributed more on the face. Histologically, EF demonstrates a characteristic follicular damage— a feature not found in PPE (Resneck *et al.,* 2004). Epidemiologically, the distribution and pattern of EF is different from PPE: EF is seen more commonly in Caucasians while PPE is more common in Africans especially those residing in mosquito infested areas (Resneck *et al.,* 2004). Compared to patients with EF, those with PPE are more severely immunocompromised (Rosenthal *et al.,* 1991).

Other skin diseases which closely resemble PPE include HIV associated infective folliculitis, papular urticaria, scabies, eczematous eruptions and drug eruptions (Singh *et al.,* 2009). Drug eruptions are ubiquitous in HIV due to the concoctions of drugs used by patients with HIV. They should always be suspected and ruled out whenever HIV patients present with pruriginous papules (Coopman & Stern 1991).

2.6 Prognosis and complications of PPE

Pruritic papular eruption runs a chronic course, uninterrupted, the disease waxes and wanes throughout the course of HIV. PPE is inevitably associated with psycho-social, cutaneous as well as multi-organ complications. The excoriated skin predisposes patients to both local and systemic infections which could lead to severe organ damage (Howard & Frieden, 1996).

Its conspicuous and disfiguring lesions cause profound stigma, frustrations and suicidal tendencies. The excoriated lesions cause bleeding which soil patients' clothes and beddings (Holm *et al.,* 2006). The protracted pruritus associated with PPE and its unresponsiveness to conventional therapy severely impairs quality of life of affected patients (Colebunders *et al.,* 1987; Holm *et al.,* 2006).

2.7 Role of epidemiology in the management of PPE

Several epidemiological studies have been conducted to evaluate treatment options for PPE but consensus on the best treatment approach is still lacking. The gold standard for proving efficacy of an intervention is through randomised controlled clinical trials but none has been conducted for PPE. Castelnuovo *et al.,* (2008) did a prospective study which lasted for 24 months and found that 86% of patients receiving an uninterrupted HAART regime obtain a meaningful remission of PPE. However, the sample size used for the study was low. In yet another cross-sectional study, Chua and Maurer, (2009) observed that PPE lesions resolve during active HAART but relapsed six months after discontinuation of treatment or following regime failure. Several other empirical treatments have been proposed including antihistaminic drugs, systemic and topical steroids, ultraviolet B phototherapy, pentoxifylline, and tacrolimus (Toutous-Trellu *et al.,* 2005).

However, these treatments only provide minimal symptomatic relief but do not alter the clinical course of the disease.

A descriptive study conducted in Tanzania by Navarini *et al.,* (2010) found oral promethazine to better control the pruritus of PPE compared with topical hydrocortisone. Conducting epidemiological studies on patients with PPE helps in generating hypothesis for future interventions.

2.8 Overview of HIV related Skin Diseases:

2.8.1 HIV and the skin

Besides PPE, other HIV related skin diseases are fairly widespread. Right from seroconversion and throughout the course of HIV infection, diverse skin diseases manifest in up to 90% of HIV seropositive individuals (Cedeno-Laurent *et al.,* 2011). The skin is the first and the most universally afflicted organ in the course of HIV infection (Singh *et al.,* 2009; Queiroz-Zancanaro *et al.*, 2006). The major HIV related skin diseases increase in frequency and severity as the populations of CD4 cells get depleted (Cedeno-Laurent *et al.,* 2011).

2.8.2 Major HIV related skin diseases

The major HIV related skin diseases are those skin diseases uniquely associated with advanced HIV. They are the most debilitating diseases among HIV seropositive patients (Wiwanitkit 2004). Majority of studies done to estimate the prevalence of skin diseases evaluated both old and new HIV individuals but only a limited number has been done exclusively on newly

diagnosed patients (Maurer *et al.,* 2004). Patients already on preventive therapy against opportunistic infections and those on HAART have different spectrum of skin disease compared to newly diagnosed HIV positive patients who are not on any care (Blanes *et al.,* 2010).

Specific skin disorders are most likely to occur when immune functions deteriorate below a certain level of CD4 cell counts. However, this relation is controversial and some of the diseases observed tend to differ from study to study (Singh et al., 2010). Despite the lack of consensus, major HIV-related skin disorders have been recognised as predictors for initial HIV infection and are sources of intractable morbidity.

Major HIV related skin diseases are used as clinical indicators of immune deterioration among HIV infected patients especially in resource poor nations (Ghate *et al.,* 2000; Goldstein *et al.,* 1997). The types, distribution and prevalence of the major HIV related skin diseases have not been adequately described in Kenya. Majority of HIV seropositive patients who seek care at the CCC in RVPGH present with diverse skin diseases but the relevant epidemiological data is lacking.

2.8.3 Public health implications of HIV related skin diseases

Determining the burden of skin diseases among HIV infected patients is important in the planning and management of HIV disease (Jung and Paauw 1998; Ghate *et al.,* 2000). Reports from Spain and India estimate prevalence of skin diseases in HIV to range from 80-90% (Blanes *et al.,* 2010; Wiwanitkit 2004). This makes skin diseases the highest source of morbidity among

HIV infected individuals. Even when patients are using HAART and their immune status appear to be restored, a significant number still suffer diverse skin disease albeit of a different spectrum. While HAART naïve patients present with severe opportunistic cutaneous infections those on HAART have more of drug related dermatoses (Blanes *et al.,* 2010). This means that skin disease will remain the biggest public health concern as far as HIV infection continues.

The high prevalence of skin diseases among HIV infected individuals, the longer survival duration of patients due to the success of HAART and the frequently changing disease patterns certainly overstretch the available public health resources (Hu *et al.,* 2011). Since the description of Kaposi's sarcoma as an AIDS-related condition, 56 other cutaneous disorders have been linked to HIV and AIDS (Cedeno-Laurent *et al.,* 2011). This number keeps rising as new HIV related skin diseases emerge. Frequent epidemiological surveillance of skin disease is therefore recommended as a long-term public health measure to monitor the trends of skin diseases in people living with HIV.

Majority of HIV patients live in Sub-Saharan Africa and almost all of them suffer or will suffer diverse skin problems (Maurer and Amerson, 2010). The high prevalence of HIV-related skin diseases encountered in Africa profoundly increases the public health burden that the continent is already facing (Hu *et al.,* 2011). Although it is generally accepted that the prevalence of HIV related skin diseases is high, the estimates differ depending on country and region. The spectrum and burden of skin diseases in HIV is therefore different in different countries and regions (Thompson 2008). Therefore every country needs to update its data on HIV related skin disease in order to facilitate proper planning in the public health sector. This endeavour can only be

achieved through conduction of regular epidemiological studies which ultimately lead to improved health service delivery.

The prevalence, distribution and spectrum of HIV-related skin diseases is not known in Kenya. This dearth of epidemiologic data has resulted in differing opinions on the importance of HIV-related skin diseases. Some AIDS defining skin illnesses have not been found in some countries yet scholars regularly use such diseases to describe AIDS in their country. In such situations a review of the existing HIV related skin diseases through epidemiologic studies will help countries to come up with their own AIDS defining skin diseases (Sharma *et al.* 2004).

The frequency of skin diseases increases with increasing prevalence of HIV infection in the population. The current HIV prevalence in Kenya is estimated to be 6.4% (6.1 - 6.9) with females (8%) outnumbering males (4%) by 2:1 (National AIDS Control Council of Kenya, 2009). Though the prevalence of HIV in Nakuru is known that of HIV-related skin diseases is lacking or unpublished. Estimating the burden of all HIV-related skin diseases and establishing the distribution of the major HIV related skin diseases among patients in RVPGH in Nakuru is therefore necessary since it will assist in health care planning and resource distribution.

CHAPTER 3

METHODOLOGY

3.1 Site of Study

The study was conducted at the Rift Valley Provincial General Hospital (RVPGH) which is situated about a kilometer from the main Nakuru municipal market. Nakuru, as shown in Figure 1 is a highway town along Nairobi - Eldoret - Kisumu road; it is approximately 150 kilometers from Nairobi. According to Global Positioning System (GPS), Nakuru town is located on Latitude 0.303098800000000000 and Longitude 36.080025999999975000 respectively.

RVPGH is the regional referral hospital which serves part of Rift Valley and Central regions. A Comprehensive Care Centre (CCC) housed in the hospital serves about 300 HIV seropositive patients on every clinic day and about 20 new patients every three clinic days in a week. A dermatology clinic situated in the centre attends to approximately 20 new HIV patients suffering various skin diseases on every clinic day in a week. Approximately 3,120 new patients visit the CCC per year and about 1,040 new HIV seropositive patients seek care at the dermatology clinic every year. HIV seropositive patients with diverse skin diseases are either referred or refer themselves to the dermatology clinic for specialised care. The large numbers of new patients visiting the CCC and the dermatology clinic provides an accessible population from which the required study sample size could be drawn. These, together with the fact that the hospital is located beside a major highway were some of the reasons the study site was selected.

Figure 3.1: Map of Kenya showing the GPS location of Nakuru town (*Latitude*: 0° 16' 32" S. *Longitude*: 36° 05' 03" E).

3.2 Study Population Characteristics

The target population included all HIV-seropositive men and women living in Nakuru County while the accessible population comprised patients who sought care at the Comprehensive Care

Centre (CCC) in the Rift Valley Provincial General Hospital (RVPGH). The study population comprised women and men aged 18 years and above who had been tested for HIV in the CCC and found positive.

3.3 Study Design

Descriptive study design was used in this study which was conducted in a hospital setting: A cross-sectional study design was used to determine the epidemiology of PPE and major HIV related skin diseases and to assess quality of life of patients with PPE. During this phase, patients were examined for skin disease and interviewed on their demographic characteristics. Only patient with PPE were interviewed on the effects of the disease on their QoL since the disease was the main focus for this aspect of study.

A resident consultant dermatologist, a dermatology officer and the principal researcher were involved in patients' examinations and diagnosis. All diagnoses were made on clinical grounds; however, where a diagnosis was in doubt basic laboratory investigations such as skin scrapings and syphilis tests were conducted. Due to financial reasons biopsies were not done, however, there were no compelling indications for a biopsy from any of the patients observed.

Consenting patients were examined one after another until the required number was reached: The examination was conducted in a room well lit with natural light. It involved a systematic evaluation of the whole skin and mucous membranes using various diagnostic aids such as hand

held lens, pen torches and picture charts. Patients found with skin diseases were treated and their diagnoses entered in a questionnaire. Those who did not have any skin disease were counseled and advised on good skin care. All patients' CD4 cell counts and demographic characteristics were recorded in relevant questionnaire.

The epidemiology of PPE was evaluated during this phase of the study: It involved estimating its prevalence, describing its epidemiological and lesional distribution, assessing its impact on quality of life and describing its distribution and pattern in relation to gender and age. The prevalence PPE was calculated by dividing the total number of patients with PPE by the total number of patients examined multiplied by 100. The total number of patients with all types of skin diseases including PPE divided by the total number of patients examined multiplied by 100 formed the overall prevalence of skin diseases among patients with HIV attending the CCC at RVPGH in one year.

Quality of life was assessed in patients with PPE using the Dermatology Life Quality Index (DLQI) questionnaire. Using a designated scoring system, each patient's report on the impact of the symptoms of PPE and its treatment on QoL was determined and graded according to their mean DLQI scores. The higher the mean DLQI scores the poor the quality of life.

3.4 Sample size determination

Daniel's formula (Daniel, 1999) for calculating sample size was used to determine the sample size for this study: In this formula $[n=z^2p\ (1-p)\ /d^2]$,

n = sample size

z = standard normal deviate at 95% confidence interval (1.96)

p = estimated proportion (if prevalence is in percentage, convert to a proportion of 1)

d = precision (in proportion of 1 i.e. if 5%, d = 0.05)

Daniel's formula for determining sample size was selected because of its wide application in prevalence studies. Since the prevalence of skin diseases and PPE in Kenya are unknown, estimates from other countries were used to estimate *p*. According to available literature the prevalence of skin diseases in HIV range from 10% to 90% and that of PPE from 5% to 51%. From these estimates a prevalence of 50% was chosen to represent *p* in this study. Consequently the selected *p* was (0.5). The confidence and significance level selected for this study were 95% and 5% (0.005) respectively. Using Daniel's formula and substituting the predetermined parameters with the symbols, the sample size was calculated as follows:

$n = (1.96)^2(.5)\ (.5)\ /\ 0.05^2 = 384.$

This formula gives the required minimum sample size. This means that any figure <384 is not considered adequate. It should be ≥ 384.

3.5 Sampling technique

All the new adults aged 18 years and above who were visiting the CCC underwent voluntary counseling and testing for HIV. Every new patient who turned positive was referred to the dermatology clinic by a research assistant. In the clinic, the researchers explained to each patient the purposes of the study and sought their consent. Those who consented were enrolled in the study one by one until the desired sample size was met. All patients approached accepted to participate in the study.

3.5.1 Case Definition

For purposes of this research, a case of PPE was defined as follows: An HIV positive adult (≥ 18 years) who presents with multiple unexplained pruritic papules and nodules. The lesions must be excoriated and must be seen on the lower and upper extremities. An HIV related skin disease was defined as an alteration of the appearance or function of the skin, mucous membranes or appendages.

3.5.2 Inclusion Criteria

Patients with PPE were considered eligible for the study if they met the following criteria:

1. Be HIV positive and attending the comprehensive care centre for the first time
2. Not using systemic steroids
3. Have not used HAART before the study
4. Be 18 years and above and willing to participate in the study.
5. Be in fair general health and able to communicate
6. Not suffering from debilitating medical illness

3.5.3 Exclusion Criteria

Patients were excluded from the study if they were

1. Extremely ill patients
2. Pregnant women
3. Aged below 18 years

3.5.4 Ethical Consideration

Before this study was conducted mandatory ethical issues were considered. An application for permission to carry out the study in RVPGH was made to the hospital's research ethics committee through the medical superintendant. After permission was granted to conduct the study in the hospital, clearance to carry out the research was sought from one of the bodies mandated to authorize research in Kenya. For this study the Kenyatta National Hospital working in conjunction with the University of Nairobi ethics and research committee (KNH/UoN ERC) was approached and granted permission for the study. Finally the study was approved and certified by the National Institute of Science and Technology (NIST).

Verbal and written consents were sought from eligible patients before they were recruited for the study. Prewritten consent forms were read and interpreted to patients unable to read English while the literate ones read the forms on their own. The forms explained in detail the process of the research, the benefits or risks that could occur during the research. If any procedure was to be done on any patient, it was explained exactly how it was to be done. As a proof of consent patients signed or thumb-printed the forms and the study was commenced.

To ensure confidentiality, the names of patients were omitted from all questionnaires and all patients' information in custody of the researchers was not shared with any parties not involved in the study. Voluntariness was ensured by allowing participants to enroll in their own free will and reassuring those who declined that they were not going to be victimized in any way. Participants who wished to withdraw from the study were allowed to do so at any stage of the study.

Permission was sought from every patient before a skin examination was performed and a gender equivalent chaperone was present during the entire examination. Photographs were only taken for didactic purposes and only after obtaining express permission from the patients. The images taken were limited to the affected parts and were taken only if deemed didactically important. Even when permission was granted, photographs that could reveal patients identity were censored accordingly.

3.6 Data collection techniques

3.6.1 Data collecting instruments

Three questionnaires were used to collect data— DLQI questionnaire and two observational checklists. DLQI is a dermatology specific quality of life assessment tool composed of 10 items. This tool was selected because of its conciseness and simplicity (Finlay & Khan, 1994; Halioua & Beaumont, 2000; Hongbo *et al.,* 2005). Moreover, it had been used to assess QoL among Kenyans with skin diseases in RVPGH and found to be relevant and appropriate (Mawenzi *et al.,*

2007, unpublished thesis). Both Swahili and English version of the DLQI were used to collect data on the impact of PPE on quality of life (QoL) in this research.

The items of the DLQI are divided into five themes: symptoms and feelings (questions 1 and 2); daily activities (3 and 4); leisure (5 and 6); work and study (7); personal relationships (8 and 9); and treatment (10). Patients' responses to the questions carry scores which range from 0 (meaning no effect) to 3 (extreme effect). The aggregate scores of each patient represent the degree of QoL impairment of that patient while the sum of all individual scores divided by the total number of patients give the mean DLQI score of that group. Mean DLQI scores of 0-5 indicate no effect on QoL; 6-10 moderate negative effect on QoL; and scores greater than 10 represent extreme negative effects on QoL.

Two observational checklists were used to collect data on PPE and major HIV related skin diseases: Observation checklist 'A' was used to record the types of skin diseases and patients' demographic profiles while observation checklist 'B' was used to record epidemiologic information on PPE pertaining to its distribution and pattern.

3.6.2 Administration techniques

Data collection instruments were pre-tested on 40 patients (10% of minimum sample size) who, though eligible for the study were not included in the real study. After results of the pilot study demonstrated suitability of the instruments, the three questionnaires were released for use. DLQI was administered by research assistants through face to face interviews: they read for every patient all items of the DLQI questionnaire and ticked on provided checkboxes according to

every patient's response. The interviews were conducted in either English or Kiswahili depending on the patients' preferences: Where barrier to the two languages existed, an interpreter from among patients' relatives was used. Observational checklist A and B were filled by the researchers.

3.7 Data analysis

All data were entered into a computer and analysed using Statistical Package for the Social Sciences (SPSS) version 12 software program. Chi square test of association was used to determine the strength of association between categorical data. The association between major HIV related skin diseases prevalence and CD4 cell count (above or below 200 cells/mm^3 was evaluated using logistic regression. Student's *t* test was used to analyse differences of mean DLQI scores between male and female patients. A *p*-value was considered significant when it was less than 0.05. Qualitative data were sumarised using frequency distribution tables while descriptive statistics were used to summarise quantitative data and to calculate proportions.

Quality of life among patients with PPE was analysed by summing up all DLQI scores and dividing them by the number of patients with PPE. Mean (±SD) scores and the range of score were analysed. The qualitative aspect of QoL was described according to the domain of life affected.

Prevalence of PPE was calculated by finding the average of the total number of patients with PPE divided by the total number of HIV positive patients multiplied by 100. Prevalence of major

HIV related skin diseases was calculated by finding the average of the total number of patients with a particular skin disease divided by the total number of HIV positive patients examined multiplied by 100. The overall prevalence of skin diseases among the newly diagnosed HIV seropositive patients was calculated by dividing the total number of patients with skin diseases by the total number of patients examined. All prevalence estimates were calculated on annual basis.

CHAPTER 4

RESULTS

4.1 Study Sample Demographic Characteristics

Of the 394 patients analysed, 258(65.5%) were females and 136 (34.5%) males. Their overall mean age was 36.5 (± 9.69) years: Mean age for female and male patients were 35 and 39.5years respectfully. Table 4.1 shows the distribution of age and gender of the sample. Marital status was observed as follows: 202 (51.3%) of them were married; 72 (18.3%) were single; 56 (12.4%) widowed; 44 (11.2%) divorced and 20 (5.1%) separated. By the time of the study, 328 (83%) patients were residents in the Municipal Council of Nakuru (MCN) while 66 (17%) came from outside MCN.

4.2 Epidemiology of PPE:

4.2.1 Prevalence, distribution and pattern

PPE was found in 20 patients giving it a prevalence of 5%. The disease was distributed as follows: 15 (75%) women and 5 (25%) men with PPE. The difference was statistically significant (*p*-value 0.03). 84% of the patients with PPE came from within MCN while 16% emanated from areas outside MCN. The ages of patients with PPE ranged from 23- 48 and the mean age was 35 (±.3). All patients had severe PPE.

The pattern of PPE lesions was as follows: Most lesions were located on the outer upper and lower arms, followed by legs and thighs, upper back and face in that order. Table 4.3 shows the lesional distribution of PPE. The mean duration of PPE among the patients was 3 months.

4.2.2 Quality of Life among Patients with PPE

The mean DLQI score was 15.2 (±3.26). The scores ranged from 3 to 24. Mean DLQI scores for women was 15.13(±3.40) and 15(±2.97) for men. The difference was not statistically significant. The domain of life mostly affected by the disease was the psychological and physical domains in that order. All patients reported that the disease caused them severe itching and made them feel embarrassed. 80% reported that the disease affected the choice of clothes they wear.

4.3 Association between major HIV related skin diseases and CD4 cell counts

Oral candidiasis, PPE and seborrheic dermatitis were found to be significantly associated with low CD4 cell counts. Table 4.5 summarises the association between the major HIV related skin diseases and CD cell count categories.

4.4 Prevalence and distribution of major HIV related skin diseases

166 of 394 patients had one or more skin diseases giving a prevalence of 42%. The distribution of observed skin diseases was as follows: 126 (75%) had one type of a skin disease each, 33 (19.9%) had two types, 5 (3%) had three, 1 (0.6%) patient had 4 while another one had 5 different types of skin diseases. The major HIV related skin diseases observed are as shown in Table 4.4. Table 4.5 shows the prevalence of major HIV related skin diseases and their relationship with CD4 cell counts respectively.

Table 4.1: Age and gender distribution of the study sample

Age group (years)	N (%)	F	M
18 — 27	76 (19.3%)	66 (86.8%)	10 (13.2%)
28 — 37	157 (39.8%)	104 (66.2%)	53 (33.8%)
38 — 47	101 (25.6%)	59 (58.4%)	42 (41.6%)
48 — 57	52 (13.2%)	24 (46.2%)	28 (53.8%)
≥ 58	8 (2%)	5 (62.5%)	3 (37.5%)
Total	394 (100%)	258 (65.5%)	136 (34.5%)

Table 4.2 CD4 cell distribution in relation to gender

CD4 cell count (/mm^3)	Female *n* 173	Male *n* 221	P-value
0-50	17(9.8%)	8(3.7%)	.019
51-100	14(8.1%)	6(2.7%)	.012
101-150	17(9.8%)	2(0.9%)	.001
151-250	12(6.9%)	5(2.3%)	.103
251-300	5(2.9%)	9(4.1%)	.140
301-350	5(2.9%)	6(2.7%)	.082
351-400	9(5.2%)	2(0.9%)	.101

Tab Table 4.3: Distribution and pattern of PPE lesions on body sites

Body site	Distribution Number (%)	Pattern & Morphology of Lesions
Scalp	1(5%)	E^{0}; P^{+}; N^{0}; HM^{0}; Ps^{0}
Face	1 5(%)	E^{0}; P^{+}; N^{0}; HM^{0}; Ps^{0}
Neck	0 (0%)	N/A
Arms	20(100%)	E^{+++}; P^{+++};N^{++};HM^{+++}; Ps^{+}
Chest	5(25%)	E^{+}; P^{+}; N^{0}; HM^{0}; Ps^{0}
Back	7(35%)	E^{++}; P^{++}; N^{++}; HM^{+++}; Ps^{0}
Legs	19(95%)	E^{+++}; P^{+++}; N^{++}; HM^{++}; Ps^{0}
Buttocks	3(15%)	E^{+}; P^{+}; N^{0}; HM^{+}; Ps^{+}
Thighs	17(85%)	E^{++}; P^{++}; N^{+}; HM^{++}; Ps^{+}
Genitalia	0 (0%)	N/A
Palms & Soles	0(0%)	N/A

Key:

- E = Excoriations; P= Papules; N= Nodules; HM= Hyperpigmented Macules; Ps= Pustules
- ^{0}= Nil; $^{+}$ = Few; $^{++}$ = Many; $^{+++}$ = Very Many
- N/A = Not applicable

Table 4.4: Prevalence of major HIV related skin diseases and corresponding mean CD4 cell count.

DISEASE	*n* (%)	Mean CD4 count (±SD)
Oral thrush	25(6.3%)	88.6(10.6)
Pruritic papular eruption (PPE)	20(5.0%)	46.6(6.5)
Seborrheic dermatitis	19(4.8%)	48(40.7)
Unclassifiable eczema	17(4.3%)	287.6(34.9)
Herpes zoster	14(3.6%)	318.6(22.7)
Xerosis	11(2.8%)	242.8(22.4)
Herpes genitalis	11(2.8%)	357(211.5)
Vaginal candidiasis	10(2.5%)	357(211.5)
Dermatophytosis	10(2.5%)	158.4(22.5)
Pruritus	7(1.8%)	313.0(202.3)

Table 4.5: Association between major HIV related skin diseases and CD4 cell count categories

DISEASE	CD4 COUNT ≤200 (*n* 173)	CD4 COUNT > 200 (*n* 221)	P-Value
Oral thrush	17(9.8%)	8(3.7%)	.019
Pruritic papular eruption	14(8.1%)	6(2.7%)	.012
Seborrheic dermatitis	17(9.8%)	2(0.9%)	.001
Eczema	12(6.9%)	5(2.3%)	.203
Herpes zoster	5(2.9%)	9(4.1%)	.072
Xerosis	5(2.9%)	6(2.7%)	.276
Herpes genitalis	9(5.2%)	2(0.9%)	.067
Vaginal candidiasis	1(0.6%)	9(4.1%)	.058
Dermatophytosis	7(4%)	3(1.4%)	.213
Pruritus	2(1.2%)	5(2.3%)	.463

CHAPTER 5

DISCUSSION

5.1 Demographic characteristics of study sample

In this study, women were more than men (65.5% Vs 35.5%); they were also significantly younger compared to men (35years Vs 39.5 years respectively). A similar observation was made in Cameroon where female patients were the majority (61.5%) and comparatively younger (Josephine *et al.,* 2004). However, in other studies, especially those done outside Africa a predominance of men was noted (Sen *et al.,* 2009). The reasons for these discrepancies may not be entirely clear, however, in the Kenyan context, the gender variance observed may reflect the national HIV prevalence where women are twice affected as men (National AIDS Control Council of Kenya 2009). Nevertheless, it may also mean that women are more skin health conscious and do seek treatment better than men as it has been observed in Cameroon by Josephine *et al.,* (2004).

5.2 Prevalence, distribution and pattern of PPE

Though PPE is described as the most common skin disease among HIV infected Africans with a prevalence reaching as high as 58% (Resneck *et al.,* 2004; Goldstein et al., 1997: Mgonda, 2004), this study found a PPE prevalence of only 5%. However, this study only looked at newly diagnosed HIV seropositive patients. Prevalence of PPE from other studies was based on populations composed of new and old HIV patients who were already on HAART. Patients on HAART have a different disease burdens compared to HAART naïve ones. This could therefore explain the large differences observed between this study and others. Nevertheless, the

apparently small prevalence estimate obtained in this study is comparable to the 6.9% reported from South Africa by Budavari and Grayson (2007).

The diagnosis of PPE in this study was based on the criteria formulated by Boonchai *et al* (1999). However, it is not known what criteria were used in the study by Mgonda (2004) which reported a PPE prevalence of 58% in Dar es Salaam. Different diagnostic criteria may lead to over- or under-diagnosis of PPE thus affecting prevalence estimates. Nevertheless, when trends of PPE are considered evidence abounds to the effect that the prevalence of PPE is declining. For example the prevalence of PPE was 58% in Dar es Salaam in 2003 (Mgonda 2004) and by 2010 it had declined to 12% in Hai district of Tanzania (Navarini *et al.,* 2010). Thus, the rather low prevalence reported in this study could actually represent the true prevalence of PPE which is declining. However, according to Resneck *et al.,* (2004) the prevalence of PPE is influenced by factors such as the time of study, the geographic location and the characteristics of the study population. The inconstancies of these epidemiological variables inevitably lead to the wide discrepancies observed in PPE prevalence across the world.

The distribution of PPE in this study indicates a preponderance of women (75%) compared to men with PPE. This observation was also made in Uganda where 81% of patients with PPE were women (Resneck *et al.,* 2004). The reasons for this female predominance with regard to PPE are currently unknown.

5.3 QoL among patients with PPE

Like many chronic skin diseases, PPE impacts negatively on QoL and untreated patients with PPE lead very disturbed lives (Kent *et al.,* 2001). This study also found a highly impaired QoL in patients with PPE (mean DLQI score of 15.2). According to Kent *et al.,* (2001) patients with PPE have poorer QoL compared to patients with seborrheic dermatitis and molluscum contagiosum. The extreme negative impact of PPE on QoL underscores the importance of the disease compared to other HIV related skin diseases.

All patients in this study complained that the appearance more than symptoms of PPE was the aspect of the disease that affected them the most. For this reason, future management of PPE should pay particular attention to the appearance of the skin. There was no difference in the QoL in women and men in this study. This observation dispels the belief that women get more affected by the psychological effects of skin diseases than men (Josephine *et al.,* 2004). Therefore, any planned PPE intervention should focus on alleviating psychological symptoms in both genders with equal vigour.

5.4 Association between major HIV related skin diseases and CD4 cell counts.

The mean CD4 cell count in this study was 251.5 cells/mm^3. The distributions of the CD4 cell counts were as follows: 71.3 % of the patients had a CD4 cell count $\leq$ 350 cells/mm^3 (the level at or below which HAART is given in Kenya); 53% had $\leq$ 200 cells/mm^3; 41% had $\leq$ 100 cells/mm^3 and 27% had $\leq$ 50 cells/mm^3. The implication here is that almost 70% of newly diagnosed HIV patients are severely immunocompromised and require HAART. A similar CD4

cell counts distribution was observed by Goh *et al.,* (2007): According to them, 63.5% of their patients had CD4 counts below 200cells/mm^3, 38.5% had counts below 50cells/mm^3.

In this study, the mean CD4 cell counts differed depending on the type of skin disease (Table 4.4). PPE had the least mean CD4 cell count among the major HIV related skin diseases. This is in keeping with the observation that PPE occurs commonly in those with severe immunodepression (Goh *et al.,* 2007). This level of immunodepression is usually associated with very severe forms of PPE (Annam *et al.*, (2009). This was corroborated in this study where all patients with PPE were severely immunodepressed and had severe forms of the disease. In a study by Castelnuovo *et al* (2008), the median CD4 cell count in a cohort of patients with PPE in Uganda was 15cells/mm^3. This observation together with what was observed in this study may imply that patients with PPE should be considered for HAART immediately they are seen.

The association between major HIV related skin diseases and CD4 cell counts has been established in several studies. In this study, oral candidiasis, seborrheic dermatitis and pruritic papular eruption were the leading major HIV related skin disease found to be associated with low CD4 cell counts. This observation is corroborated by Goldstein *et al.,* (1997) who found significant relationship between the three diseases and low CD4 cell counts. However, Singh *et al.,* (2009) did not establish a relationship between seborrheic dermatitis and low CD4 cell counts but observed that oral candidiasis was significantly associated with low CD4 cell counts.

Occurrence of one or more major HIV related skin diseases, especially when in their most severe or atypical form is an indication of advanced immunodepression (Sharma *et al.,* 2004). This has

been proved in this study where all patients diagnosed with one or more major HIV related skin disease had extremely low CD cell counts. This finding further supports the idea that major HIV related skin diseases be used to predict levels of immunodepression in resource constrained nations. According to World Health Organisation (WHO 2006), major HIV related skin diseases can be used instead of viral loads or CD4 cell counts in resource poor countries to monitor HIV disease progression. The ten leading HIV related skin diseases associated with severe immunodepression in this study are also recognised by WHO as clinical indicators of the stage of HIV disease (WHO 2006).

Oral candidiasis occurring in severely immunocompromised individuals is often florid and atypical (Sharma *et al.*, 2004). Such form of oral candidiasis was observed in the majority of patients examined in this study. Their candidiasis involved the whole buccal cavity and extended to the pharynx, larynx and oesophagus. Their mean CD4 cell count was 88cells/mm^3 indicating severe immunodepression. Such advanced immunodepression among patients with oral candidiasis was also found by Goh *et al.,* 2007; Sharma *et al.*, 2004; and Puttaiah *et al.,* 2010). The import of this observation is that oral candidiasis in HIV seropositive patients should be treated aggressively because of its potential to disseminate and cause sinister prognosis.

In this study, an association between seborrheic dermatitis and low CD4 cell counts was established; however, this appears to be at variance with what was observed by Sharma *et al.,* (2004). They did not find a relationship between seborrheic dermatitis and low CD4 counts, and on account of this finding, the authors suggest the disease should no longer be considered an AIDS defining illness. However, seborrheic dermatitis is a disease with a wide spectrum of

clinical severity ranging from simple dandruff to an erythroderma (Maurer and Amerson 2010). Whilst mild seborrheic dermatitis occur even in the immunocompetent, severe seborrheic dermatitis is seen more frequently among HIV patients with very low CD4 cell counts (Goldstein *et al.,* 1997; Altraide 2010; Rigopoulos 2004; Mathes and Douglas 1985). It will make more clinical logic therefore, to first categorise seborrheic dermatitis according to its clinical severity then evaluate whether its severe forms meet the AIDS defining criteria. According to the findings of this study, severe seborrheic dermatitis is universally associated with low CD4 cell counts and should therefore be regarded as an AIDS defining illnesses.

5.5 Prevalence and distribution of major HIV related skin diseases

The prevalence of skin diseases in this study was 42.1%: This figure compares well with that of Mohammad *et al.,* (2003) who reported a prevalence of 41.7% among HIV positive police officers in Dar es Salaam. However, when compared to other African countries, the prevalence reported in this study is proportionally low. In Zimbabwe, the prevalence of skin diseases in HIV was reported to be 88% while in Cameroon it was 68.8% as reported by Lowe *et al.,* (2010) and Josephine *et al.,* (2006) respectively. However, unlike in this study and that conducted in Tanzania, the Zimbabwe and the Cameroon study population included adolescents and children. The differences in the composition of study population could partly explain the notable variation in prevalence estimates. Nevertheless, other factors such as study design, geographic location and economic status of study population as well as season when studies were conducted do influence prevalence of skin diseases in HIV (Josephine *et al.,* 2006).

This study has shown oral candidiasis as the commonest skin disease followed by pruritic papular eruption (5%), seborrheic dermatitis (4.8%), unclassifiable eczema (3.6%), and herpes zoster (2.8%) in that order. A similar order of disease occurrence was observed in Thailand by Wiwanitkit, (2004) and in Tanzania by Mohammad *et al.,* (2003). According to Puttaiah *et al.,* (2010) oral candidiasis was the leading skin disease in the HIV cohort they studied. However, with exception of this study, oral candidiasis has not been ranked as the leading HIV related skin disease in other studies done in Africa. One of the reason could be that all patients examined in this study were new and HAART naïve. Patients continuing with care and on HAART have a reasonable immunity restoration and therefore suffer less skin infection and more of inflammatory skin diseases (Blanes *et al.,* 2010).

The major HIV related skin diseases identified in this study have universally been found among patients with advanced HIV infection. However, their presence or absence in any patient depends on the immune status of the patients. Interestingly, diseases such as psoriasis and oral hairy leukoplakia which are common in Europe and North America were not observed in this study. The reasons for these differences may include availability of health care, use of HAART, degree of immunosuppression, and genetic factors (Goh *et al.,* 2007). However, compared to countries such as India and Thailand the spectrum of HIV skin diseases observed in this study is comparable to what they found in their country (Singh *et al.,* 2009; Wiwanitkit 2004).

The prevalence of herpes zoster (HZ) in this study compares well that observed by Sharma et al., (2004) but is much lower compared to estimates from Tanzania and Cameroon where prevalence of HZ were 11% and 28% respectively (Mohammad *et al.,* 2003; and Josephine *et al.,* 2006). This could have occurred because in those studies people with HZ scars were considered as cases

of HZ. Though cases of HZ scars were found in some patients, they were not diagnosed as HZ because this study regarded only active cases of HZ. Since HZ is usually easily recognised, many patients with the disease could have been treated in the periphery health centres before they reached RVPGH. These could be some of the reasons the prevalence of HZ was comparatively low in this study.

Unclassifiable eczema has not commonly been listed among the leading HIV-related skin disease in Africa; however, in this study, it was among the top ten HIV-related skin diseases. 70% of patients with unclassifiable eczema had severe, atypical and recalcitrant eczema and CD4 cell counts of less than 200cells/mm^3. Despite extensive literature search, unclassifiable eczema was not listed among the most common HIV-related skin disease in Africa. The reason(s) for this discrepancy is currently unknown; more research is required to address this gap. However, unclassifiable eczema is listed among the leading HIV-related skin disease in countries outside Africa: Supanaranond *et al.,* (2001) and Goh *et al.,* (2007) reported unclassifiable eczema among the top ten skin diseases in Thai HIV positive patients. Entry of unclassifiable eczema into the list of top ten HIV related skin diseases means that the disease, especially when severe and unresponsive to treatment can be used as a predictor of HIV infection and decreased immunity.

5.6 Other important observations

5.6.1 *Severely immunodepressed individuals*

Three women with extremely low CD4 counts who did not have any medical or skin disease were seen during this study: The first was a 27 year old married woman (CD4 count 1 cell/mm^3); the second was 32 years old, (CD4 count of 3cells/mm^3). It is extremely unusual for

humans with such advanced immunodepression to be disease free and physically fit. This observation could mean that there are other factors that play vital roles in the preservation of human immunity besides CD4 cells.

5.6.2 Kaposi's sarcoma

There was only 1 (0.25%) patient with cutaneous Kaposi's sarcoma (KS) in this study. He was 35 years old, married heterosexual man with a CD4 count of 28cells/mm^3. Although KS is rare in Africa, its prevalence (0.25%) in this study appears to be extremely low compared to 1.6% in Tanzania (Mohammad *et al.,* 2003) and 9.9% in Cameroon (Josephine *et al.,* 2006). KS occur more frequently in male homosexuals and among those infected with human herpes virus type-8 (Josephine *et al.,* 2006; Puttaiah *et al.,* 2010). While the prevalence of HHV-8 infection and males who engage in sex with other males has not been reported in Kenya, it is probably negligible and this may explain the rarity of KS observed in this study.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 Summary

Pruritic papular eruption is a skin disease exclusively found in HIV infected individuals. It is characterised by sudden eruption of extremely itchy rashes predominantly distributed on outer aspects of limbs. The epidemiology of pruritic papular eruption is dynamic. Its prevalence, distribution and pattern differ by country and person. It is more prevalent in Sub-Saharan Africa and South Asia where it is commonly associated with late HIV disease. The disease has significance in assessing the clinical status of HIV disease and treatment. The distribution of the disease on exposed parts of the body makes it easy to see leading to stigmatisation and poor quality of life. HIV infected individuals suffer diverse skin diseases and the major HIV-related skin diseases affecting them are universally associated with severe immunodepression. These diseases cause significant morbidity and are a source of immense public health burden.

6.2 Conclusions

Distribution and pattern of PPE: There is a preponderance of women (75%) than men with PPE. The disease has however been established to be declining in RVPGH compared to other hospitals in other countries. The quality of life of patients with PPE has been shown to have no bearing to gender though its effect is profound on patients suffering from the disease compared to the other ski disease.

Association between major HIV related skin diseases with CD-4 cell count: PPE was found to be associated with low CD4 cell count (immunocompromised) status. The same was established

for major HIV - related skin diseases such as candidiasis and seborrheic dermatitis both of which are categorised as AIDS- defining skin diseases.

Prevalence of HIV -related skin diseases: Prevalence of HIV-related skin diseases was found to be moderately high in RVPGH while that of herpes zoster and Kaposi's sarcoma was very low. Unclassified eczema was also found to be common.

6.3 Recommendations

6.3.1 Clinical practice

Major HIV - related skin disease ought to be used to predict HIV infection and estimate CD4 cell levels in affected patients. Since QoL has been shown to have no relationship with gender, clinical interventions need not be geared toward any gender. It is recommended that care givers be trained to make prompt and correct diagnosis of PPE and treat the disease holistically since it severely impairs QoL. It is also recommended that when planning for care of HIV seropositive patients in RVPGH, the hospital authorities ought to give priority to HIV related skin diseases since they affect a significant population of patients at the hospital

6.3.2 Future epidemiologic research

Further studies involving both new and old patients need to be conducted in order to validate these findings and explore other factors that may influence PPE prevalence. A similar study involving children, adolescents and adults should be conducted in order to establish the overall prevalence of HIV related skin diseases in East Africa.

REFERENCES

Aires, J., Rosateli J., Figueriredo J. & Roselino A. (2000) Cytokines in the pruritic papular eruption of HIV. *International Journal of Dermatology.* **39**:903-906.

Ajithkumar, K., Soshamma G. & George P. (2001) Abnormal insect bite reactions: A manifestation of immunosuppression of HIV infection? *Indian Journal of Dermatology Venereology and Leprology.* **67**(2):72-74

Altraide, D., Olumide Y, Mohammed TT (2010) Predictive value of seborrheic dermatitis for HIV infection in Lagos Nigeria. *Port Harcourt Medical Journal.* **5**(1): 30-36.

Annam, V., Yelikar B., Inamadar A. & Palit A. (2009) Histopathological study of pruritic papular eruptions in HIV-infected patients in relationship with CD4, CD8 counts. *Indian Journal of Pathology and Microbiology.* **52**:321-324.

Ashack, R., Frost M. & Norins A. (1989) Papular pruritic eruption of Demodex folliculorum in patients with acquired immunodeficiency syndrome. *Journal of the American Academy of Dermatology.* **21**:306-307.

Banuls, J., Rammon D., Elfidia A., Esperanza J. & Vicente T. (1991) Papular pruritic eruption with HIV infection. *International Journal of Dermatology.* **30**(11):801-804.

Bason, M. M., Berger T. & Nesbit L. (1993) Pruritic papular eruption of HIV disease. *International Journal of Dermatology.* **32** (11):784-789

Berman, B., Flores F. & George B. (1998) Efficacy of pentoxyfylline in the treatment of HIV infected persons. *Journal of American Academy of Dermatology.* **38**:955-959.

Blanes, M., Belinchón I., Merino E., Portilla J., Sánchez-Payá J. and Betlloch I. (2010) Current prevalence and characteristics of dermatoses associated with Human Immunodeficiency Virus infection. *Actas Dermosifiliografricas.* **101**(8):702–709.

Boonchai, W., Laohasrisakul R., Manonukul J. & Kulthanan K. (1999) Pruritic papular eruption in HIV seropositive patients: a cutaneous marker for immunosuppression. *International Journal of Dermatology.* **38**:348-350.

Budavari, M. & Grayson W. (2007) Papular follicular eruptions in human immunodeficiency virus patients in South Africa. *International Journal of Dermatology.* **46**: 706-710.

Castelnuovo, B., Byakwaga H., Menten J., Schaefer P., Kamya M. & Colebunders R. (2008) Can response of a pruritic papular eruption to antiretroviral therapy be used as a clinical parameter to monitor virological outcome? *AIDS* **22** (2): 269-273

Cedeno-Laurent, F., Gómez-Flores M., Mendez N. (2011) New insights into HIV-1-primary skin disorders. *Journal of International AIDS Society.* **14**:5-8

Chua, S. & Maurer, T. (2009). Recurrence of the pruritic papular eruption of HIV with immunologic failure of antiretroviral therapy. *Journal of American Academy of Dermatology.* **60** (3):AB121

Colebunders, R., Mann J. & Francis H. (1987) Generalised papular eruption in African patients with human immunodeficiency syndrome. *AIDS.* **1**: 117-121

Coopman, S. & Stern R. (1991) Cutaneous drug reactions in human immunodeficiency virus infection. *Archives of Dermatology.* **127**: 714–717.

Daniel, W. (1999) Biostatistics: A Foundation for Analysis in the Health Sciences. 7th edition. New York: John Wiley & Sons.

Evers, A., Lu Y., Duller P., Van de Valk P., Kraalmant F. & Van de Karkhof P. (2005) Common burden of chronic skin diseases. Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *British Journal of Dermatology.* **152**(6):1275-1281.

Feldman, S., Menter A. & Koo J. (2004) Improved health related quality of life following randomized controlled trial of Alefacept treatment in patients with chronic plaque psoriasis. *British Journal of Dermatology.* **150**(2):317-326.

Finlay, A. & Khan G. (1994) Dermatology Life Quality Index (DLQI) A simple practical measure for routine clinical use. *Clinical and Experimental Dermatology.* **19**: 210-216.

Fiza, S. & Rudikoft D. (2003) HIV associated pruritus, etiology and management. *American Journal of Clinical Dermatology.* **4**(3):177-188.

Garg, A., Levin A., Bernhard D. (2008) Dermatologic Diagnosis in Fitzpatrick's Dermatology in general medicine, 7th Edn. McGraw Hill, New York. 23-25

Ghate, M., Mehendale S., Mahajan B., Yadav R., Brahme R., Divekar A. (2000) Relationship between clinical condition and CD4 cell counts in HIV-infected persons, Pune, Maharashtra, India. *National Medical Journal of India* **13**: 183-187.

Goh, B., Chan R., Sen P., Theng C., Tan H., Wu Y., Paton N. (2007) Spectrum of skin disorders in human immunodeficiency virus-infected patients in Singapore and the relationship to CD4 lymphocyte counts. *International Journal of Dermatology* **46**, 695–699

Goldstein, B., Berman B., Sukenik E. & Frankel S. (1997) Correlations of skin disorders with CD4 lymphocyte counts in patients with HIV/AIDS. *Journal of American Academy of Dermatology.* **36** (2):262-264.

Halioua, B., & Beaumont M. (2000) Quality of life in dermatology. *International Journal of Dermatology.* **34**(11):801-806.

Heuring, M. (2004) Patients advocacy and patient perspective of skin diseases. *Journal of Investigative Dermatology* **9**(2):104-107.

Hevia, O., Jimenez-Acosta F. & Ceballos P. (1991) Pruritic papular eruption of the acquired immunodeficiency syndrome: a clinicopathologic study. *Journal of the American Academy of Dermatology.* **24**:231-235.

Holm, E., Wulf H., Stegman H. & Jemec G. (2006) Life quality assessment among patients with atopic eczema. *British Journal of Dermatology* **154**(4):719-725.

Hongbo, Y., Thomas L., Harrison A., Salek S. & Finlay A. (2005) Translating the science of quality of life into practice: What do dermatology life quality index mean? *Journal of Investigative Dermatology.* **125**: 659-664.

Howard, R. & Frieden I. (1996) Papular urticaria in children. *Paediatric dermatology.* **13**(3): 246-249.

Hu, J., McKoy K., Papier A., Klaus S., Ryan T., Grossman H., Masenga J., Sethi A., & Craft N. (2011) Dermatology and HIV in Africa. *Journal of Global Infectious Diseases.* **3**(3): 275-280

James, W., Redfiel R. & Lupton G. (1985) A papular eruption associated with human T cell lymphotropic virus type III disease. *Journal of American Academy of Dermatology.* **13**: 563-566.

Josephine, M., Issac E., George A., Ngole M. & Albert S. (2004) Patterns of skin manifestations and their relationships with CD4 counts among HIV/AIDS patients in Cameroon. *International Journal of Dermatology* **45**(3):280-284.

Jung, A., & Paauw D. (1998) Diagnosing HIV-related disease using the CD4 count as a guide. *Journal of General International Medicine.* **13**(2): 131–136.

Keibert, G., Sorrensen S., Revick D., Fagan S.., Doyle J., Cohen J. & Fiveson D. (2002) Atopic dermatitis is associated with a decrement in health-related quality of life. *International Journal of Dermatology.* **41**(3):151-158.

Kent, A., Thomas C., Ponciano D. (2001) Use of the HIV-DERMDEX quality of life instrument in HIV-infected patients with skin diseases. *International Journal of Dermatology.* **40**:472-484

Kumarasamy, N., Solomon S., Madhivanan P., Ravikumar B., Thyagarajan P. & Yesudian P. (2000) Dermatological manifestation among human immunodeficiency virus patients in south India. *International Journal of Dermatology.* **39**:192-195

Lakshmi, S., Rao G., Ramalakshmi S., Rao K., Prasad P. & Kumar Y. (2008) Pruritic papular eruptions of HIV: A clinicopathologic and therapeutic study. *Indian Journal of Dermatology Venereology and Leprology.* **74**:501-503.

Liautand, B., Pape J. & De Hovitz J. (1989) Pruritic Skin Lesions: a common initial presentation of acquired immunodeficiency syndrome. *Archives of Dermatology.* **125**:629-632.

Lowe, S., Ferrand R., Mangeya N., Salisbury J., Morris J., Miller R. & Corbett E. (2010) Skin diseases in hospitalized adolescents in Harare, Zimbabwe: a strong indicator of underlying advanced HIV infection. *Paediatric Infectious Diseases Journal.* **29**(4):346-351.

Lumbiganon, D., Lumbiganon P., Kosalaraska P. & Loapaiboon M. (2009) Clinical manifestations and survival of children with HIV infection in North-east Thailand. *Asian Biomedline.* **3**(2):143-150.

Mathes, B. & Douglass M. **(**1985**)** Seborrheic dermatitis in patients with acquired immunodeficiency syndrome**.** *Journal of the American Academy of Dermatology.***13**:947-951

Maurer, T. & Amerson H. (2010) Dermatologic manifestation of HIV in Africa. *Topical HIV Medicine.* **18**: 16-22

Mawenzi, L., Onyango R. & Ngare D. (2007) Quality of life among adults with chronic skin diseases consulting at Rift Valley Provincial Hospital. *Unpublished Research Thesis of Maseno University., Kenya*

Mgonda, A. (2004) Sero-prevalence of hepatitis B surface antigen among individuals with HIV-related cutaneous disorders in a tertiary referral dermatology clinic in Dar es Salaam. *Tanzania Medical Journal.***19** (2):1-5.

Muhammad, B., Eligius L., Mugusi F., Aris E., Pallangyo N., Sandstrom E., Mhalu F., Biberfeld G. & Pallangyo K. (2003) The prevalence and pattern of skin diseases in relation to CD4 counts among HIV infected police officers in Dar es Salaam. *Tropical Doctor.* **33**(1):44-48.

Muyinda, H, Seeley J, Pickerine H, Barton T. (1997) Social aspects of AIDS-related stigma in rural Uganda. *Health Place*. **3**:143-147.

National AIDS control council of Kenya (2009)

Navarini, A., Stoecke M., Susanne N., Erick M., Boniface S., Rehema M., Marco M., Patience K., Marcel T., Christopher H. & Peter S. (2010) Antihistamines are superior to topical steroids in managing human immunodeficiency virus associated PPE. *International Journal of Dermatology.* **49**:83-86.

Olumide, Y., Dada A., Sogbanmu I. & Aruna G. (1997) Seroprevalence study of HIV-I, HIV-II & HTLV-I among patients at the dermato-venereology clinic of the Lagos University Teaching Hospital. *International Journal of Dermatology.***36**(10):741- 744

Ongenae, K., Beelaaert L., Van Geel N. & Naeyaert J. (2006) Psychological effects of vitiligo. *Journal of European Academy of Dermatology and Venereology.* **20**(1):1-5.

Palangyo, K. (1992) Cutaneous findings associated with HIV disease including AIDS: experiences from Sub-Saharan Africa. *Tropical Doctor.***1**:35-41

Pitche, P., Tchangai W., Napo G., (1995) Prevalence of skin manifestations in AIDS patients in the Lome-Tokoin University hospital (Togo). *Sante.* **5**: 349–352.

Puttaiah, K., Sunith V., Mallikarjun N. (2010) A hospital based cross sectional study of mucocutaneous manifestations in the HIV infected. *International Journal of Collaborative Research on Internal Medicine & Public Health* (IJCRIMPH) p 21441 > March 1,

Queiroz-Zancanaro, P., McGirt L. & Mamelak A. (2006) Cutaneous manifestations of HIV in the era of highly active antiretroviral therapy: An institutional urban clinic experience *Journal of American Academy of Dermatology* **54**: 581-588

Raju, P., Rao, G., Ramani, T. & Vandana S. (2004) Skin disease: clinical indicator of immune status in human immunodeficiency virus (HIV) infection. *International Journal of Dermatology.* **48**(8): 646-649.

Resneck, J., Marta van Beek, Furamanski L., Oyugi J., LeBoit E., Katabira E., Kambugu F., Maurer T., Berger T., Pletcher M. & Machtinger L. (2004) Etiology of pruritic papular eruption with HIV infection in Uganda. *Journal of American Medical Association.* **292**(21): 2614-2621.

Rigopoulos, D. Paparizos, V., Katsambas, A. (2004) Cutaneous markers of HIV infection. *Clinical Dermatology* **22**:487–498

Roberto, C. (2000) Pruritic papular eruption of the acquired immunodeficiency syndrome: predominance of CD8 positive cells. *International Journal of Dermatology* **38**:872-880

Rosateli, J. & Roselino A. (2001) Hyper-IgE, Eosinophilia and immediate cutaneous hypersensitivity to insect antigens in the pruritic papular eruption of human immunodeficiency virus. *Archives of Dermatology.* **137**:672-673

Rosateli, J., Fernando A. & Roselino A. (2008) Pruritic popular eruption of the acquired immunodeficiency syndrome: predominance of CD8 positive cells. *International Journal of Dermatology.* **39**(11):873-874.

Rosateli, J., Machado A., Roselino A. (1997) Dermatoses among Brazilian HIV positive patients: correlation with the evolutionary phases of AIDS. *International Journal of Dermatology* **36**:729-734.

Rosenthal, D., LeBoit P. & Klumpp L., Berger T. (1991) Human immunodeficiency virus associated eosinophilic folliculitis. *Archives of Dermatology* **127**:206-209.

Salim, A. & Lawrence P. (2003) Mucocutaneous manifestations in children with HIV infection. *Current Allergy and Immunology.* **16** (2):48-52.

Samanta, M., Kundu C., Sarkar M., Bhattacharyya S. & Chatterjee S. (2009) Papular pruritic eruptions: A marker of progressive HIV disease in children: Experience from eastern India. *Indian Journal of Sexually Transmitted Diseases.* **30**(2):79-83

Sen, S., Halder S., Mandal S., Pal P., Halder A., Bhaumik P. (2009) Clinico-epidemiological profile of cutaneous manifestations among human immunodeficiency virus positive patients in the sub-Himalayan region. Indian Journal of Dermatology, Venereology and Leprology; **75** (4):403-405

Sharma, A., Chaudhary D., Modi M., Misty D. & Marfatia Y. (2007) Non-infectious cutaneous manifestation of HIV/AIDS. *Indian Journal of Sexually Transmitted Diseases.* **28** (1):19-22

Sharma, B., Sawhney M., Bhakuni D., Gera V. (2004) Orocutaneous Manifestations as markers of disease progression in HIV Infection in Indian setting. *MJAFI* **60** : 239-243.

Simpson-Dent, S., Fearfield L., & Staughton R. (1999) HIV associated eosinophilic folliculitis--differential diagnosis and management. *Sexually Transmitted Infections* **75**: 291-293.

Singh, H., Dulhani N., Tiwari P., Singh P. & Sinha T. (2009) A prospective observational cohort study to elicit adverse effects of antiretroviral agents in a remote resource-restricted tribal population of Chhattisgarh. *Indian journal of pharmacology* **41**: 224-226.

Singh, P., Tiwari P., Dey V., Dulhani N. & Singh A. (2009) Dermatological manifestation in HIV infected patients at a tertiary care hospital in a tribal (Bastar) region of Chattisgarah India. *Indian Journal of Dermatology* **54:**338-341.

Supanaranond, W., Desarkan V., Sitakalin C., Naing N. & Chirankul P. (2001) Cutaneous manifestation in HIV positive patients. *Southeast Asian Journal of Tropical Medicine.* **32** (1):171-176.

Teofoli, P., Barbieri C., Pallotta S., Ferranti P. & Puddu P. (2002) Pruritic Eosinophilic Papular Eruptions Revealing HIV infection. *European Journal of Dermatology.* **12** (6):600-602.

Thompson, D., Bain B. & East-Innis A. (2008) The prevalence of mucocutaneous disorders among HIV-positive patients attending an out-patient clinic in Kingston, Jamaica. *West Indian Medical Journal.* **57** (1): 17-21

Toutous-Trellu, L., Abraham S., Pechère M., Chavaz P., Lübbe J., Schiffer V., Hirschel B., Saurat J. & Piguet V. (2005) Topical tacrolimus for effective treatment of eosinophilic folliculitis associated with human immunodeficiency virus infection. *Archives of Dermatology.***141**:1203-1208.

Uthayakumar, S., Nandwani R., Drinkwater T., Nayagam A., Darley C. (1997) The prevalence of skin disease in HIV infection and its relationship to the degree of immunosuppression. *British Journal of Dermatology.***137**:595–598.

Wananukul, S. & Thisyakorn U. (2002) Mucocutaneous manifestation of HIV infections of HIV infection in 91 children born to HIV-seropositive women. *Paediatric Dermatology* **16**(5):359-363.

Wiwanitkit, V. (2004) Prevalence of dermatological disorders in Thai HIV-infected patients correlated with different CD4 lymphocyte count statuses: A note on 120 cases. *International Journal of Dermatology*. **43**:265-268.

World Health Organisation, (2006) WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-related disease in Adults and Children.

Yahya, H. (2007) Change in pattern of skin disease in Kaduna, north-central Nigeria. *International Journal of Dermatology.***46**: 936–943