HUMAN T CELL LYMPHOTROPHIC VIRUS 1 ASSOCIATED INFECTIVE DERMATITIS IN KWAZULU NATAL SOUTH AFRICA

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Supervisor Dr A Mosam

DECLARATION

I hereby declare that this is my original work and has not previously been submitted to this or any other university.

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Carol Hlela

CONGRESS PRESENTATIONS

1. Hlela C, Mosam A, Dlova NC, Aboobaker J, Bhigjee A. *HTLV1 associated* infective *dermatitis in KwaZulu Natal*, South Africa. Galderma Fellowship Feedback. Dermatology Congress of the Dermatological Society in South Africa, April 2005, Sun City , Mpumalanga.

2. Hlela C, Mosam A, Ramdial PK , Bhigjee A, Dlova NC, Aboobaker J. *HTLV1 associated infective dermatitis in KZN*, South Africa. 11th Prague Dermatology Symposium, Czech Republic, 15-17 September 2005.

3. Hlela C, Mosam A, Ramdial PK , Bhigjee A. *HTLV1 associated infective dermatitits in KwaZulu Natal, South Africa,* Congress of the Dermatological Society of South Africa. April 2006, Durban.

AWARDS

1. GALDERMA FELLOWSHIP AWARD - R35 000

Awarded to registrars conducting research in their respective fields. A stipend to assist young researchers in starting up a research project. This is a national award administered by the Dermatological Society of South Africa. Judges are heads of Dermatology Departments countrywide.

2. YOUNG DERMATOLOGIST TRAVEL AWARD - $ 1000

Awarded to junior consultants within 5 years of registering as a specialist. This international award is administered by the International Dermatological Society. The award of $ 1000 is paid towards travel expenses for attendance and presentation in an international dermatology congress. In addition congress registration and accommodation is paid by the Society.

PUBLICATIONS

Alcantara LCJ , de Oliveira T, Gordon M, Pybus O, Mascarenhas RE, Gonçalves M, Seixas MO, Hlela C, Cassol S and Galvao-Castro B (2006). **Tracing the origin of Brazilian HTLV1 in as determined by analysis of host and viral genes**, *AIDS,* 20 (5) : 780-782.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ATLL	Adult T cell leukaemia / lymphoma
AD	Atopic dermatitis
BHS	Beta Haemolytic Streptococcus
CF	Chronic folliculitis
ESR	Erythrocyte sedimentation ratio
ELISA	Enzyme linked immunosorbent assay
FBC	Full blood count
HAID	Human T cell lymphotropic virus type 1 associated infective dermatitis
HAM	Human T cell lymphotropic virus type 1 associated myelopathy
HIV	Human Immunodeficiency Virus
HIV- VL	Human immunodeficiency virus viral load
HLA	Human leucocyte antigen
HTLV-I	Human T cell lymphotropic virus type 1
HTLV-II	Human T cell lymphotropic virus type 2
KEH	King Edward VIII Hospital
KZN	KwaZulu-Natal
LCV	Leucocytoclastic vasculitis
LD	Lichenoid dermatitis
LTR	Long tandem repeat
MF	Mycosis Fungoides
PCR	Polymerase Chain Reaction
PTCL	Peripheral T cell lymphoma
S.aureus	*Staphylococcus aureus*
Seb derm	Seborrhoeic dermatitis
SD/ PVD	Superficial and deep perivascular dermatitis
SPEP	Serum Protein Electrophoresis
TSP	Tropical spastic paraparesis
WCC	White cell count
WB	Western Blot

ABSTRACT

Background

Human T cell Lymphotropic Virus Type I (HTLV-I) associated infective dermatitis, first described by Sweet in Jamaican children, is a pattern of eczema characterized by exudation, crusting around the nostrils, ears and scalp with eventual appearance of a generalized fine papular rash. More recently LeGranade and co-workers have proposed major and minor criteria in establishing the diagnosis of HTLV-I associated infective dermatitis (HAID).

HTLV-I has been aetiologically linked to Adult T cell leukaemia/lymphoma (ATLL) and tropical spastic paraparesis (TSP). HAID is not only a marker of childhood infection with HTLV-I but may be a harbinger of more serious HTLV-I associated diseases later on in life such as ATLL or TSP. The pathogenesis of HAID is poorly understood so are the histopathological features of this entity. The effects of co-infection with human immunodeficiency virus- 1 (HIV-1) are inconclusive.

HAID is described in Sub Saharan Africa, Senegal but no data is published on this entity in Southern Africa, characterizing the clinical, laboratory features and the histopathology of this entity.

Aims and Objectives

1) To describe the clinical and histological features of HTLV-I associated infective dermatitis in KZN, South Africa
2) To determine the virological characteristics of HTLV-I in KZN, South Africa
3) To assess for HTLV-I / HIV co-infection

Methods

This was a prospective study of all patients with HAID who presented to King Edward VIII hospital (KEH), outpatient department over a period of 42 months. These were patients who fulfilled the clinical criteria of HAID. Enrolled patients were subjected to a confirmatory HTLV-I serology testing. Demographic data was obtained from all HTLV-I

seropositive patients. Their clinical examination included dermatological, neurological and pathological examination. A blood count, immunoglobulin levels, serum protein electrophoresis measuring albumin levels and globulin fractions were measured. For bacteriological assessment skin swabs were taken from the affected sites with stool samples examined for parasites, ova and cysts.

The HIV-1 status together with HIV-1 viral load were determined on those enrolled. The CD4 count, CD8 counts and CD4/CD8 ratio were also calculated. Skin biopsies were taken for histological examination. PCR for HTLV subtyping was performed on a subset of the cohort.

Results

Demography

Of the 60 patients recruited, 33 fulfilled criteria for HAID. The majority of patients fell between age categories of 6 to 10years. The male to female ratio was 1:1. There were more females in the adult group than there were within the childhood group. All of the patients in our cohort were African.

Clinical features

The lesions were erythematous, scaly, exudative, and crusted in all cases. The distribution of lesions was as follows: scalp (77.4%), retroauricular areas (71%), the axilla (65%) and paranasal areas (58%) were the sites more commonly affected. Nasal crusting was not a significant feature in this series.

Bacteriology

Culture was positive for *Staphylococcus aureus* (*S. aureus*) in 90%, with streptococcal group of organisms found in 68% of the skin swabs taken from the lesional skin.

Haematological

Our patients were mildly anaemic as has been shown in previous studies. They had a mean Hb of 11.5g/dl. In 12 of the 14 patients tested, the erythrocyte sedimentation rate (ESR) was elevated. Serum protein electrophoresis and levels of Immunoglobulin A, G and M were raised. The mean CD4 count in the entire group was elevated at 1730 cells/µl, CD8 was 1299 cells/µl.

Histopathology

The major histological findings were as follows: 38% demonstrated a superficial and deep perivascular inflammatory infiltrate, 28% had a superficial and deep perivascular inflammatory infiltrate together with a lichenoid dermatitis, 12.9% had features of superficial and deep inflammatory infiltrate with an interface dermatitis, 6.4% revealed features of seborrhoeic dermatitis.

Genotyping

Our patients were infected with the strains belonging to the *Cosmopolitan, A Subtype* (HTLV-Ia).

Complications

Complications were low in this series with the commonest being scabies in 6(18.1%), corneal opacities in 3(8.6%), 2(6 %) with HAM/TSP. No parasitic worm infestations were isolated.

HIV/HTLV-I co-infection

Of the 33 patients, 9 (30 %) were co-infected with HIV. The mean viral load in this group was 52 000 copies/ml. Their mean CD4 count was also elevated at 1505cells/µl with a CD8 of 1704 cells/µl and a CD4/CD8 ratio of 1.15.

Discussion

Thirty three of the 60 patients enrolled met the diagnosis for HAID according to the established criteria. The mean age in this series was 17 years (range: 8 months-46 years) however; almost a third (30.3%) were children under 12 years, reinforcing the entity as a childhood infective condition.

There was an equal male female distribution in the childhood group and a female predominance in the adult group.

Clinically patients presented with infected erythematous, scaly lesions mainly on the scalp, neck and post- auricular area. The clinical features were in keeping with other series worldwide. The complication rate was low in our cohort.

S. aureus was the predominant organism in both anterior nares and lesional skin. The most common histological pattern was superficial and deep perivascular inflammatory infiltrate. The subtype in our series was the *Cosmopolitan Subtype A* (HTLV-Ia) as opposed to *subtype B* in Japan. We share with Brazil a common subtype.

A subset of our patients (30%) was co-infected with HIV. The CD4 cell count in this subgroup was lower than the entire group but this was not statistically significant. The histological patterns found in this subgroup infected with HIV were similar to the rest of the group except for a more intense eosinophilic infiltrate in these skin biopsy specimens.

Conclusion

HTLV-I associated infective dermatitis is distinct entity which affects the African population of KwaZulu Natal, South Africa. It is predominantly a disease of childhood with an equal female to male ratio in children. The clinical features are an exudative, erythematous scaly rash most commonly found involving the scalp, axillae, paranasal and retroauricular areas. HTLV-I positivity is essential for the diagnosis; the *Cosmopolitan Subtype A* is commonest in South Africa. The commonest histological pattern is a superficial and deep perivascular infiltrate in 38%. A subset, 30%, was co-infected with HIV.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Human T cell lymphotropic virus type I (HTLV-I) associated infective dermatitis is a chronic and severe form of childhood dermatitis characterized by an exudative, infective dermatitis involving mainly the scalp, neck and ears. Other symptoms include a generalized papular rash, nasal discharge and crusting of the nostrils. The majority of described patients with this condition originate from Jamaica.[1]

The disease has also been reported in several HTLV-I endemic populations including Japan, Trinidad, Brazil and Columbia. Diagnosis is based on specific clinical and laboratory criteria, *Table 1*. The average onset is 2 years and 60% of patients are female. The incidence and prevalence are undefined, as is the pathogenesis. The skin manifestation becomes less severe with age. [2] Long-term clinical studies have demonstrated that the rash is often followed by the development of HAM/TSP or ATLL.[3]

Table 1. Clinical criteria of HAID[4]

MAJOR
1. Eczema of scalp, axillae and groin external ear and retro-auricular areas, eyelid margins, paranasal skin and/or neck
2. Chronic watery nasal discharge without other signs of rhinitis and/or crusting of the anterior nares
3. Chronic relapsing dermatitis with prompt response to appropriate therapy but prompt recurrence on withdrawal of use of antibiotic
4. Usual onset in early childhood
5. Human T cell lymphotropic virus type 1 antibody seropositivity

Table 1: Clinical Criteria of HAID[4] (Ctd)

MINOR
1. Positive cultures for *Staphylococcal aureus* and/or Beta-haemolytic streptococci from the skin or anterior nares
2. Generalized fine papular rash (in most severe cases)
3. Generalized lymphadenopathy with dermatopathic lymphadenitis
4. Anaemia
5. Elevated erythrocyte sedimentation rate
6. Hyperimmunoglobulinaemia (IgD and IgE)
7. Elevated CD4 count, CD8 count, and CD4/CD8 ratio

**** Of the major criteria, 4 are required for the diagnosis with mandatory inclusion of 1, 2 and 5; to fulfil criteria 1, involvement of at least 2 sites are required.***

1.1 Background

Recognition of this condition dates back to 1966 when RD Sweet brought the world's attention to a unique pattern of eczema in a group of children and adults that seemed to vary from the patterns seen in Europeans.[5] He recognized that 17 of 28 patients who had been diagnosed with eczema were Jamaican. He noted that this peculiar type of eczema started at the age of 2 years. The lesions were infected from the time of onset and were located on nostrils, ears and spread to the rest of the face, the scalp and around the neck. He documented that some of these children developed a generalized fine papular eruption and that some patients came from the same family.[5] He observed that the eruption cleared rapidly when treated with an antibiotic and steroid therapy and that the condition tended to relapse when these patients returned home after discharge on withdrawal of antibiotics. Recognising that this pattern defied the tidy classification of eczema he was accustomed to, he named it "A pattern of eczema in Jamaica".[5]

The following year Margaret Walshe documented a study of 40 Jamaican children, 25 of whom suffered from the condition which had been described as "infective dermatitis" by Sweet.[6] She amplified Sweet's original description, established criteria for diagnosis and

documented bacteriological findings. She also documented a high incidence of carriage of staphylococci or beta haemolytic streptococci or both in the noses or the skins of the patients with infective dermatitis than in those with other dermatoses. She also postulated that these children might be immunosuppressed and tentatively suggested malnutrition as the possible cause for the immunosuppression.[6]

It was 10 years after the discovery of HTLV-I[7] that the first link of this early life infection with HTLV-I was documented. Le Granade and co-workers studied 147 consecutive patients between the ages 2 and 17 years over a period of one year, 14 of whom met the clinical definition of infective dermatitis. Each of these 14 children from Jamaica underwent testing for HTLV-I and all 14 were positive for antibodies to HTLV-I.[8]

This relationship was later confirmed in a much larger number of patients where 50 infective dermatitis patients were compared with 35 atopic dermatitis patients.[4] In this case controlled study all 50 patients with infective dermatitis had results seropositive for HTLV-I. Only 5 of the 35 patients with atopic dermatitis were seropositive for HTLV-I. The results were negative for HIV-1 for all patients in the study, suggesting an aetiologic role for HTLV-I in infective dermatitis. In both groups, microbiologic studies showed frequent colonization with *S. aureus* or BHS. On comparing the blood count findings between the two groups, patients with infective dermatitis were anaemic, had higher WCC and had an elevated ESR than patients with AD. They also had a significantly higher incidence of abnormal serum proteins and dermatopathic lymphadenopathy.[4] Le Granade and co-workers in this study proposed a new designation of infective dermatitis ("HTLV-I associated infective dermatitis") and the major and minor criteria for the diagnosis, *Table1*.[4]

Since the original report in 1990, cases of infective dermatitis have been described from Trinidad, Tobago, Japan, and Columbia, Barbados and among Haitian immigrant children in Miami but the numbers so far have been small. In Trinidad and Tobago, 15 people were described with chronic relapsing infective dermatitis all of whom were seropositive for antibody to HTLV-I.[9]

In Africa, the only published study was the one conducted in Senegal where 5 cases of this condition was reported.[10]

More recently a group of investigators documented the frequency of HAID in Salvador, Brazil confirming 23 cases in patients attending a dermatology outpatient clinic of the Federal University of Bahia. In this study all 23 patients demonstrated clinical features of HAID and were positive for HTLV-I. These children were followed up for a median of 3 years and 5 developed HAM/TSP.[11]

There have been fewer than 10 original papers documenting the entity of HAID worldwide. These have mainly come from areas endemic with HTLV-I. There has been one study from Africa, none from Southern Africa. *Table 2* emphasises the paucity of the work done so far on this entity.

Table 2: Studies describing HTLV-I associated infective dermatitis

Author Name	***Country***	***Enrolled/Infected patients***
Sweet 1966	Jamaica	28/17
Walshe 1967	Jamaica	40/25
Le Granade 1990	Brazil	147/14
Suite M *et.al.* 1994	Trinidad and Tobago	15/15
Le Granade *et.al.* 1998	Jamaica	50/50
Mahe A *et.al.* 2004	Senegal	5 cases
Oliveira MdeFSP 2005	Bahia, Brazil	23 cases

1.2 Virological Characteristics

HTLV-I is an enveloped double stranded RNA, type C virus (Retroviridae family, subfamily oncovirus).[3] Mature virions are 110 -140 nm in diameter, characterized by a spherical, centrally located nucleiod enveloped by a glycoprotein membrane with short spikes.

The HTLV-I envelope is a lipid bilayer in which the smaller transmembrane viral protein (gp21) and the larger outer protein (gp46) are anchored.[12]

The core consists of a diploid RNA genome of high molecular weight (approximately 9056 bp long) with structural features common to all retroviruses, namely the genes for group specific antigen (*gag*), reverse transcriptase (*pol*) and envelope protein (*env*), and flanked by long terminal repeat (LTR) sequences on either end, (*Figure 1*).[12]

The LTR comprises three distinct domains, U3, R and U5, in a 5' to 3' direction. The length of the repeat I sequence (228bp) of the LTR region is no longer than in the other retroviruses. HTLV-I also contains unique regulatory genes encoding for transactivating proteins (*tax* and *rex*) enveloped between the 3' untranslated end of the provirus and the *env* gene. The *tax* gene stimulates transcription of all genes from the 5' LTR sequences. The *rex* gene is a positive post-transcriptional regulator for the *gag* and *env* expression and is also a negative regulator capable of inhibiting expression and replication of HTLV-I in vivo.[12]

Transmission of HTLV-I is by cell-cell contact. The receptor(s) for entry of HTLV-I into the host's cell are unknown. More recently, studies have been reporting GLUT as the likely receptor for entry of HTLV-I into the cell.[13] As a provirus within the infected cell, HTLV-I integrates itself into the host genome. Inside the cell, it synthesizes copies of

DNA by reverse transcriptase.[3] Laboratory studies have shown that T cells are then transformed and immortalized. Unlike other type C transforming viruses, HTLV-I has not been found to possess cell derived oncogenes.[3]

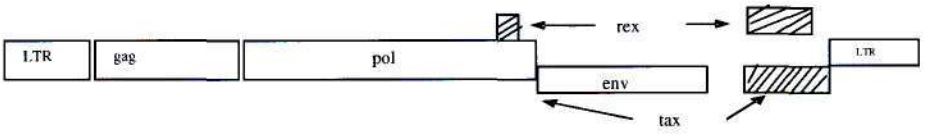


Figure 1: *A schematic map of the HTLV-1 genome*[14]

1.3 Epidemiology

Infection with HTLV-I is a global epidemic affecting 10-20 million people worldwide.[2] HTLV-I infection, is particularly endemic in southern Japan, but foci of infection are found in geographical clusters, the Caribbean, parts of Africa, the Middle East, South America, the Pacific Malanesian Islands, and Papua New Guinea. In USA and Europe HTLV-I infection is found in the carriers among immigrants from endemic areas.[3] The virus is endemic in KZN.[15]

1.3.1 Seroprevalence

There are very few population based studies conducted on the epidemiology of HTLV-I infection. In areas where the studies were conducted, it was shown that HTLV-I seroprevalence ranges from 3-6% in Trinidad, Jamaica, and other Caribbean Islands to 30% in rural Miyazaki, southern Japan.[3] USA and Europe has the lowest seroprevalence rate, found to be less than 1% among low risk populations.[3] Population studies have shown that HTLV-I seroprevalence increases with age and is twice as high in females.[3] There is paucity of epidemiological evidence for HTLV-I in Africa. A few population studies conducted in parts of Africa have indicated an overall seroprevalence of 4%. This can be broken down into 1-15% prevalence in Zaire, 0.9% in Ghanaian refugees in

Belguim and 0.2% in pregnant women in South Africa.[12] Small studies conducted in South Africa (KZN) have shown an HTLV-I seroprevalence of 0.5-3.3% in different ethnic and geographical areas.[15]

HAID incidence and prevalence remains unknown.[3] The incidence rates of HAID in countries where it has been reported have not been published. However Trinidad's rates of ATLL and HAM/TSP are similar to Jamaica, whereas Japan has similar rates of ATLL but lower rates of HAM/TSP (0.4/100 000). Incidence rates for HTLV-I associated diseases in Columbia and Brazil have not been reported. However, the prevalence of HAM/TSP is known to be high (100/100 000 population) in Tumaco, Columbia.[16] Reports of HTLV-I positive ATLL in Africans remain scanty, probably because laboratory facilities and pathologists are scarce.[17]

1.4 Geographical Subtypes

Six different genetic subtypes of HTLV-I have been proposed based on phylogenetic analyses, summarised in *Table 3*: **a –** or **Cosmopolitan** which is distributed worldwide;[18] **b –** from Central Africa;[19] **c –** a highly divergent Melanesian strain from Papua Guinea and Australia;[20] **d –** isolated from Central African Republic (CAR) pygmies, and from two patients in Cameroon and Gabon;[21,22] **e –** isolated in a single sample from an Efe pygmy in the Democratic Republic of Congo (DRC); and subtype **f –** detected in an individual from Gabon.[23] The most widespread and best studied subtype, Cosmopolitan, is further divided into five subgroups based on geographical distribution : **Transcontinental** (A), **Japanese** (B), **West African / Caribbean** (C), **North African** (D) and **Black Peruvian** (E).[18,24,25,26] Previous studies have reported that HTLV-I strains from KwaZulu Natal, South Africa belong to the A subgroup of the Cosmopolitan (HTLV-Ia subtype).[27]

Table 3: HTLV-I subtypes

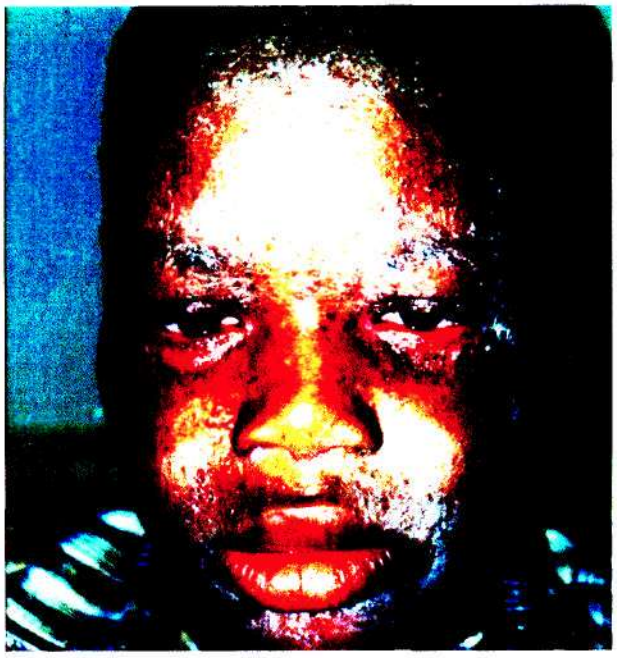
Strain	Name	Geographical Distribution
a	Cosmopolitan	Worldwide
	Transcontinental (A)	
	Japanese (B)	
	West Africa/Caribbean I	
	North Africa (D)	
	Black Peruvian (E)	
b		Central Africa
c	Melanesian (highly-divergent)	Papua New Guinea + Australia
d		Central African Republic
e		Democratic Republic of Congo
f		Gabon

1.5 Clinical Features of HAID

HAID is a chronic and recurrent eczema occurring during childhood and adolescence. It is distinctive, often beginning with a rhinitis labelled by the mother as a "cold".[28] This is followed by an oozing, weeping eruption on the scalp, ears, neck, axillae, umbilicus, groin, perineum and natal cleft often associated with a blepharo-conjunctivitis.[28] The full clinical picture is that of a severe exudative dermatitis with crusting of the scalp, neck, axillae, groin, external ear, and retro-auricular areas; watery nasal discharge, and/or crusting of the anterior nares; generalized fine papular rash, culture from the anterior nares or skin showing *Staphylococcus aureus (S.aureus)* and/or beta-haemolytic *streptococcus (BHS)*; and prompt response to appropriate antibiotic therapy and equally

rapid relapse, if such antibiotics are withdrawn. *Figures 2a and 2b* show the typical clinical appearance of a patient during a relapse.

2a)



2b)

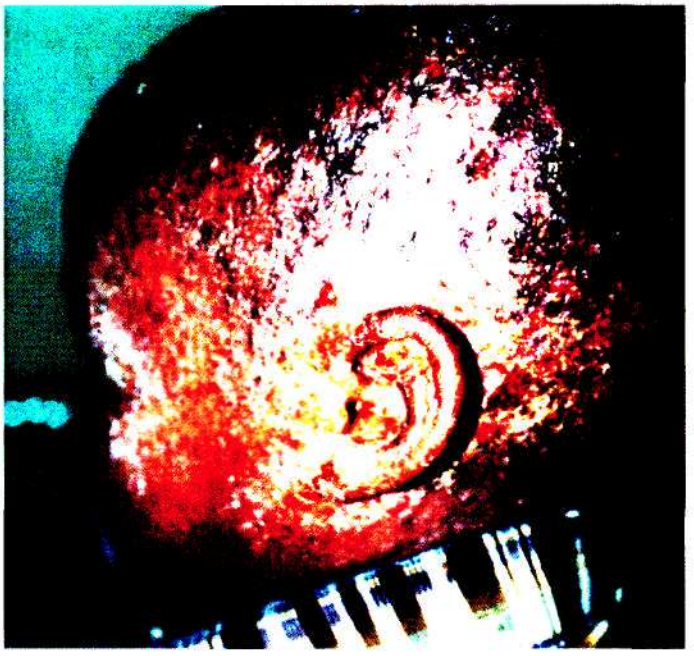


Figure 2a and 2b: *Clinical picture of a relapse in a patient with HAID*

1.6 Pathogenesis

The pathogenesis of HAID is poorly understood. It is the resistance to treatment, the frequent exacerbations and the infections with bacteria that are usually non-virulent in those affected which raises the possibility that infective dermatitis may be a disorder of immunosuppression.[7]

Data demonstrate evidence of altered immune function with hyperactivity of both humoral and cellular immune systems but the precise immunological abnormality remains to be elucidated.[29]

The question of why some children infected with HTLV-I develop HAID while others are asymptomatic remains unanswered. This observation suggests the role of other factors in the development of HAID, the possibilities being environment or lifestyle related to socioeconomic status since patients are usually from the lower socioeconomic sectors of the population, as well as the immuno-genetic background. [29]

Postulated so far is that HTLV-I alters the immune system of affected patients, rendering them incapable of overcoming infection with Staphylococcus and BHS resulting in chronic bacterial infections.[28]

The fact that immune suppression played a role in the pathogenesis was suggested as early as in the cases described by Walshe. She postulated that children with this disease were immunosuppressed and suggested malnutrition as a possible cause of the immunosuppression. However, she herself noted that only a minority were in fact obviously malnourished.[28]

HTLV-I is tropic for cells with a CD4 phenotype and infected cells can express type MHC haplotypes (HLA-DR) as well as CD25.[30]

Recent data suggest HTLV-I infection might be the cause of the immune dysfunction among HAID patients. [29] by inducing an increased expression of interleukin -2 (IL-2) receptors in HTLV-I infected cells. This may result in preferential binding of soluble IL-2 with consequent reduction in the effective concentration of IL-2.[8] In addition, a change in the functional phenotype induced by HTLV-I creates a deficiency in cell-cell interaction resulting in immune dysregulation.[8] Genes of several proinflammatory cytokines such as interleukin 1, interleukin 6 and tumour necrosis factor α, are transactivated by the viral *tax* protein. It is postulated that the secretion of such cytokines by infected cells amplifies and/or maintains the inflammatory reaction in the skin and that this may be responsible for the recalcitrant nature of HAID.[31]

Genetic studies done in a single family, a mother and her two sons, indicate that there is a possible genetic predisposition contributing to the development of HAID. The results in this study showed the index case and her two sons to be the only family members to share a common haplotype namely DRB1*DQB1* (1101- 0301). This is one of the haplotypes associated with HAM/TSP among Japanese patients which correlates with high immune response and high antibody titers to HTLV-I. It is postulated that haplotype DRB1*DQB1* (1101-0301) may determine susceptibility to HAID.[29] These observations point to the similarities of genetic background between patients with HAID and those with HAM/TSP. This therefore suggests that susceptibility to these diseases observed in patients with HAID could marked by these HLA haplotypes.[16]

Whether HTLV-I is involved in the pathogenesis of the skin lesions or is present in the skin because inflammatory cells containing virus migrated to the lesion remains a question. The skin cells in addition to lymphocytes may be infected by the virus.[32]

1.7 Pathology

The histopathological features characterizing this entity have yet to be determined. There is a paucity of literature on this subject. The investigators who searched for specific features of this entity found that pathological aspects were similar to other types of chronic eczema.[8]

More recently, 19 patients with HAID were studied histologically and immunohistologically using the following antibodies: anti-CD3, CD45RO, CD20, CD79a, CD4, CD8, CD57, TIA-1, granzyme-B and perforin A.[33] Chronic dermatitis features similar to that of seborrhoeic dermatitis was observed in 15 of these patients, whereas architecturally aspects mimicking mycoses fungoides (MF) were observed in the remaining 4 patients. The specific features that characterize HAID remain to be answered. It was with this background above that we set out to investigate histological features of HAID.

1.8 Disease Transmission

HTLV-I infection is blood borne and can be transmitted by blood-blood contact as well as by sexual contact. Transfusion is the most efficient mode of virus transmission. It has been shown that the probability of seroconversion in a recipient of contaminated blood can be as high as 40-60% with the median time to seroconversion of 51 days.[3] Sexual intercourse is recognized as an important factor for HTLV-I transmission.[34] Sexual intercourse is recognized as an important factor for HTLV-I transmission.[34] HTLV-I has been detected in the semen and cervical secretion of infected persons. Most HTLV-I infections are attributable to transmission from mother to child with the mother's milk being a major risk factor of infection.[35] The probability of mother to infant transmission is 18-30%.[3] Maternal risk factors include higher HTLV-I antibody titre, prolonged ruptured membranes during delivery and low socioeconomic status. Breastfeeding for more than 6 months has been associated with transmission which has led to the hypothesis that shortening the duration of breastfeeding may reduce the risk of HTLV-I transmission. However infection still occurs in about 3% of patients who are not breastfed.[3]

1.9 Modes of Detection

HTLV-I infection can be easily detected by screening blood for specific antibodies, using enzyme-linked immunoassay (EIA or ELISA) techniques. Gelatin particle agglutination (GPA or PA), immunoflouresence (IF), radioimmunoprecipitation assays (RIPA) are other common serological screening used in the diagnosis. Samples that react repeatedly in anti-HTLV-I screening assays need to be retested in an immunoblot assay. Highly sensitive HTLV-1/2 immunoblot assays like the Line immunoassay (LIA) and Western blot (WB) are most commonly used. [35] Advanced methods, such as the HTLV- specific polymerase chain reaction (PCR) tests in combination with T-cells culture may be of additional value since they are able to detect the viruses with increased sensitivity.

Guidelines from the US Public Health Service, WHO and other international groups such as the HERN (HTLV European Research Network)[36], recommend that newly identified

seropositive individuals have additional blood collected for repeat testing to eliminate possible technical errors, also to distinguish HTLV-I from HTLV-II. HTLV-II has 65% sequence homology to HTLV-I. HTLV-II infection is present predominantly amongst intravenous drug users (IVDU) and is usually a co-infection with HIV-I. It is difficult to distinguish the two from one another unless virus specific reagents are used. The distinction is important because HTLV-II is less pathogenic than HTLV-I.

1.10 HTLV-I associated diseases

HTLV-I was the first human retrovirus described as causing disease. It was first isolated from cell lines from patients with ATLL.[37] Since then HTLV-I has been shown to be aetiologically associated with a number of diseases, *Table 4*. Of these ATLL, TSP/HAM and HAID are most widely researched.

Table 4. HTLV-I associated diseases [2,3,38]

Non-dermatological	**Dermatological**
Pneumonitis	HTLV-I associated infective dermatitis
Uveitis	Acquired ichthyosis
HAM/TSP	Seborrhoeic dermatitis
Vasculitis	Dermatophytosis
Polymyositis	
Cryoglobulinaemia	
Facial Nerve Palsy	
Sjogrens syndrome	
Strongyloidiasis	
ATLL	

1.10.1 Adult T cell leukaemia / lymphoma (ATLL)

ATLL is a uniformly fatal T-cell malignancy. Among HTLV-I carriers, less than 5% of individuals develop ATLL. HTLV-I is an indolent virus. A long latency period between infection and subsequent development of disease has been documented.[8] ATLL occurs predominantly in the age range of 40-70 years with average age of onset being about 60 years in Japan but only 40 in Jamaica, Trinidad and Brazil. This difference is unexplained.[3] It is rapidly progressive, usually resistant to chemotherapy. Most patients die of this disease within a few months. It appears to be restricted to individuals with a lifelong infection.[39] Combination chemotherapy has been used to treat ATLL, but long term survival has been very limited especially in the acute and lymphoma types.[2]

1.10.2 HTLV-I Associated Myelopathy / Tropical Spastic Paraparesis (HAM/TSP)

A chronic disabling demyelinating neurological disorder characterized by slowly progressive spastic paraparesis and bladder disturbances.[1] The disease commonly follows adult acquired infection by either sexual contact or through blood transfusion but may follow a childhood infection. Symptom progression seems to be more rapid in blood transfusion associated HAM/TSP than in the cases of mother to child transmission.[2] The incubation period from infection to the onset of myelopathic symptoms is believed to range from months to decades.[2] This is a progressively disabling disorder with studies showing that one-half of patients with this disease become wheel chair bound within 10 years of acquiring it.[17] There is no definite therapy for this condition.[2] Secondary complications may lead to death after many years.[3]

1.10.3 HTLV-I Associated Uveitis

This intraocular inflammatory disorder has been associated with a variety of infectious causes including tuberculosis, syphilis, cytomegalovirus, toxoplomosis or non-infections causes such as Behçet's, sarcoidosis and Vogt-Koyanagi-Harada syndrome(reviewed in [3]). In about 40% of cases, a firm cause is not identified. It was a high number unexplained

cases of uveitis (idiopathic uveitis) in HTLV-I endemic areas that led to speculation that HTLV-I might be the cause. An association with HTLV-I was established when 35% of patients with idiopathic uveitis were found to be HTLV-I positive compared with 10% of uveitis cases where another cause has been identified. A patient with HTLV-I uveitis presents with a variety of clinical symptoms including blurred or foggy vision and acute, sudden onset of "floaters" (reviewed in [3]). Iritis, vitreous opacity, retinal vasculitis, retinal exudates and haemorrhages are all signs that may be found on ophthalmologic examination. PCR is used to establish clinical diagnosis through detection of proviral DNA in mononuclear cells in peripheral blood and vitreous humour. Topical and systemic corticosteroids may improve visual acuity (reviewed in [3]).

1.11 Complications

Long term HTLV-I infection may be entirely asymptomatic but clinical or subclinical consequences may affect various organ systems. Complications occur in 30-35% of patients.[28]

Asymptomatic carriers of HTLV-I have been reported to harbour various infections including strongyloidiasis, trypanosomiasis and leishmaniasis.[8] Other complications include: scabies, corneal opacities, chronic bronchiectasis, regressing atypical histiocytosis, glomerulonephritis and lymphocytic interstitial pneumonia.[28,37] Some patients with HAID where HTLV-I is endemic may go on and develop severe HTLV-I related illnesses such as TSP/HAM or ATLL.[11]

In addition to HAID, *Strongyloides stercoralis* (Ss) infection has been proposed as a cofactor of ATLL.[40]

1.12 Natural History

The steps leading from virus infection to the development of the different HTLV-I associated conditions are partly understood.[40] Some patients become carriers of the disease while others go on to develop HTLV-I related illnesses.

Although HTLV-I infection is frequently asymptomatic, the risk of disease in long term infection has been under recognized yet it could have significant health implications.[39] Early diagnosis of HTLV-I allows neurological and lymphoreticular symptoms to be taken into account in the clinical care of patients and makes it possible to provide preventative counselling to reduce the likelihood of infection transmission.[38]

It is estimated that the cumulative lifetime risk of developing a life threatening or debilitating disease as a result of HTLV-I is approximately 5% increasing to 8-10% when the patient has other illnesses.[2]

Epidemiological data suggest that HAID is not only a marker for childhood HTLV-I infection but also a possible harbinger of more serious HTLV-I associated disorders later in life as there have been reports on occurrence of ATLL in patients 12-25 years after a diagnosis of HAID.[29]

A suggested postulate is that an exaggerated host response to the presence of HTLV-I, coupled with the virus's ability to immortalise T cell-clones predisposes them to malignant transformation due to accumulation of genomic mutations.[30] Among HTLV-I carriers less than 5% of individuals develop ATLL or HAM/TSP and there is usually a long latency of decades between infection and subsequent development of disease with the exception of transfusion associated HAM/TSP which can develop several weeks to months following infection from contaminated blood components.[3]

1.13 Treatment

Treatment of HAID is currently aimed at controlling infection with *S. aureus* and BHS by using appropriate antibiotic therapy. This measure alone keeps the dermatitis fairly well controlled and may require addition of mild topical steroids for full control. Prolonged use of antibiotics is recommended in the literature until puberty at which time the severity of the bacterial infection seems to lessen.[28] Relapses always occur following the withdrawal of the drug treatment. A combination of artificial feeding, prophylactic immunoglobulin and perhaps antiretroviral therapy need to be investigated for possible use in the control of infection. Some investigators are also exploring the feasibility of an HTLV-I vaccine.[3]

1.14 HIV / HTLV-I co-infection

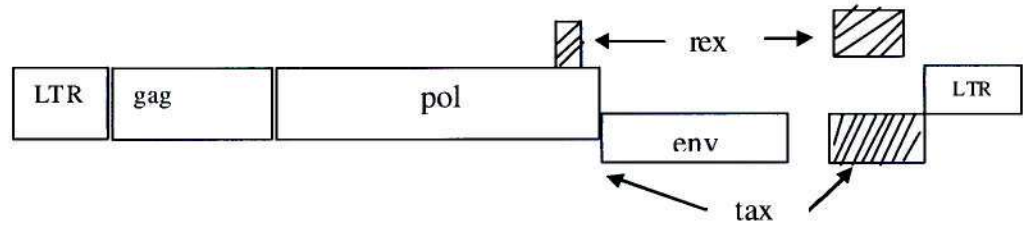
1.14.1 Historical Review

A year after the discovery of HTLV-I, a cluster of patients with a novel disease of acquired cellular immunodeficiency, later known as the acquired immunodefiency syndrome (AIDS), was first described.[17] In the following 2 years several groups isolated a retrovirus from patients with AIDS. This virus was called lymphadenopathy – associated virus (LAV), Human T cell lymphoma virus type III (HTLV-III) or Aids Related Virus (ARV). In 1986 these isolates were grouped under the name Human Immunodeficiency Virus (HIV).[17] This later discovery of HIV has given rise to the massive interest in HIV and AIDS worldwide.

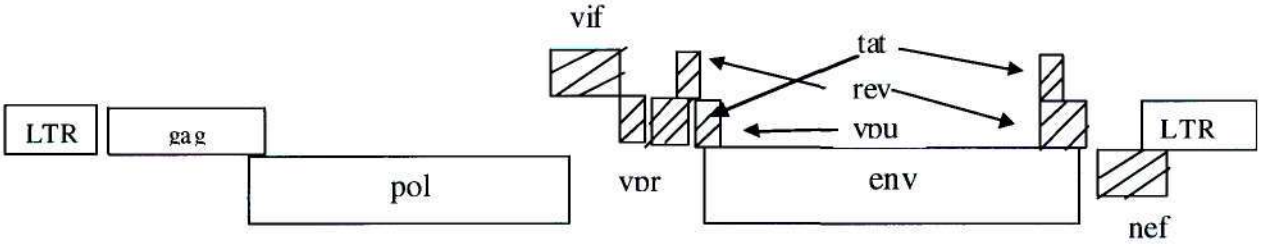
1.14.2 Structural Differences

Structural features are common to all retroviruses, (*Figure 3).* The core proteins of HIV and HTLV-I have similar molecular weights and are designated p15, p17 and p24 (p26 in HIV-II).[17] Glycoprotein's120 (gp120) and130 (gp130) are major glycoproteins of HIV-I and HIV-II is respectively. In contrast to HIV, the size of the cleaved glycoprotein precursor of HTLV's gp68 is much smaller. The HIV virus encode additional proteins called virion infectivity factor (*vif*), transactivator (*tat*), a regulator protein of expression

of virion proteins (*rev*) and a negative factor (*nef*) which inhibit the replication of the HIV. In contrast, HTLV have a *rex* and *tax* which encode a p40 and p27/p21 molecule respectively which is not present within the HIV structure. The p40 augments viral RNA expression, while p27/p21 enhances the expression of viral genes.[16] Despite the similarities, HIV is classified as belonging to the family of *Lentivirinae* as it is associated with slowly progressive inflammatory and degenerative disorders while HTLV belongs to the family *Oncovirinae* as these viruses are associated with malignancies.[17]



HTLV-I/II



HIV-I

Figure 3: *A schematic map of HTLV-I/II genome in comparison with HIV genome* [14]

Similar modes of transmission are observed with both retroviruses and are by three routes, namely, (1) intimate sexual contact, (2) perinatally (predominantly through breastfeeding and (3) parentrally (through blood transfusion or exposure to needles and syringes contaminated with blood). The risk of male infection is increased with concomitant penile ulcers and concurrent syphilis, which holds true for both retroviruses.[3]

Co-infection with HTLV-I is common in some populations infected with HIV,[41] particularly from regions with high HIV prevalence, e.g. KZN in South Africa. Whether HTLV-I /II influences the outcome in patients with HIV remains to be known.[42]

HIV positive patients co-infected with HTLV-I seem to have more severe immunosuppression than do the HTLV-I seronegatives.[8] HTLV-I can increases HIV replication in vitro and several studies suggest that HTLV-I accelerates the progression of HIV and in turn progression to AIDS.[43] Several other studies have suggested that HTLV-I does not appear to affect HIV viral load, currently considered to be the best marker of HIV disease progression.[43]

Several mechanisms have been proposed concerning HTLV-I and HIV co-infections (in vitro studies): CD4 lymphocytes infected with HTLV-I are immortalized via stimulation of IL-2 and its receptor. Translocation of the replicating factor, NFκB in the nucleus activates the T lymphocytes. The product of HTLV-I *tax* gene will also have a transactivating effect on the provirus HIV-LTR replication. Finally infection with HTLV-I may facilitate HIV by inducing CD4, expression in non-expressing cells.[44]

1.14.3 Local Experience

The first cases of HAM/TSP in the Orange Free State were reported by van der Ryst and colleagues where 18% of HTLV-I positive patients with spastic myelopathy had HAM/TSP.[45] Most work has been carried out by Bhigjee and colleagues in the Ngwelezana district in 1993; a 2.6% seroprevalence was found .[15] A follow up study at Ubombo showed a seroprevalence rate of 3.33%.[12] This emphasized the fact HTLV-I is endemic in KZN.

Previous studies have reported that HTLV-I strains from KZN, South Africa belong to the A subgroup of the *Cosmopolitan* (HTLV-Ia) subtype.[27] HTLV-I associated infective dermatitis from the southern part of Africa is not as well documented as it is in the Caribbean Islands. There has not been any study documenting this entity in patients

presenting with a typical rash neither has there been any characterizing the histopathology in South Africa.

CHAPTER 2

2.1. Aims

To document the clinicopathological and virological characteristics of HTLV-I associated infective dermatitis in KZN, South Africa.

2.2. Objectives

1. To describe the clinical and histological features of HTLV-I associated infective dermatitis in KZN, South Africa.
2. To determine the virological characteristics of HTLV-I in KZN, South Africa.
3. To assess for HTLV-I / HIV co-infection.

2.3 Methods

This was a prospective study carried out in the dermatology outpatient department of King Edward VIII Hospital, a major tertiary referral hospital in KZN, South Africa. The study was carried out over a 3 year period starting from January 2003 till December 2005. This study commenced following ethics approval from the University of KZN's Biomedical Research Ethics Committee (H181/03).

All patients who presented with clinical features in keeping HTLV-I associated infective dermatitis were informed of the study and were invited to participate. Only those who gave informed consent were recruited. Patients with features of seborrhoeic dermatitis who were HTLV-I negative, were found to be HIV infected. We did not come across patients who had clinical features of HAID who were HTLV-I and HIV negative. They had features of HIV seborrhoeic dermatitis and were therefore an unsuitable comparison group for HAID.

Those recruited were then subjected to confirmatory HTLV-I testing. Where possible, parents and siblings of the participants were also recruited.

The various components of the study were:

2.3.1 Clinical examination (see appendix)

2.3.2 Laboratory investigations

2.3.3 Histological investigation

2.3.4 PCR and sequencing

2.3.1 Clinical examination

Clinical assessments performed for all patients included a medical history, a general and a detailed dermatological assessment. The diagnosis of HTLV-I associated infective dermatitis was made according to previously established criteria. Ophthalmologic examination was performed on all patients who had visual complaints. All patients with signs of neurological abnormalities were sent to the neurology department for a detailed neurological evaluation.

2.3.2 Laboratory investigation

The following laboratory tests were performed for patients with suspected HAID: These have been summarised in *Table 5*, below.

Table 5. Laboratory tests performed on participants

Routine haematological	FBC , ESR
Immunological	SPEP, Immunoglobulins
Virology	HTLV-I , HIV , HIV viral load
Microbiology	Skin swabs, stool for culture
Haematological	CD4, CD8 counts, CD4/8 ratio
Radiology	Chest radiograph

Haematological analysis included complete blood count with differential white cell count (WCC) and measurement of erythrocyte sedimentation rate (ESR). Serum protein electrophoresis was used to measure albumin levels and globulin fractions. Measurement of serum levels of IgA, IgE, IgG, IgM. Skin swabs were taken from nasal, perinasal and lesional skin. These were referred for bacteriological studies. Skin scrapings were carried out for those patients with clinical features suggestive of scabies in search of scabies mites/ova or faecal pellets. Stool samples were examined for parasitic organisms, ova and/or cysts.

Diagnosis for HTLV-I infection was determined according to the recommended stepwise procedure for the diagnosis of HTLV-I or II, i.e.screening for antibodies to HTLV-I was done using a particle agglutination test (Serodia ATLA, Fuji Rebio, Tokyo) as has been discussed in section 1.9. Positive sera were confirmed using the most widely used immunoblot assay, WB (HTLV Blot 2,4 Genelabs Diagnostics, Singapore). This test was used also in order to distinguish HTLV-I from HTLV-II.

HIV-I positive sera were identified on all HTLV-I seropositive patients using Vironostika HIV-1 IMPVD Microelisa system (Biomerieux, Durham, NC). HIV-I viral loads using Nuclisens EasyQ HIV-I system (Biomerieux) were determined. CD4 and CD8 lymphocyte subsets counts were calculated and the CD4/CD8 ratio was determined. A chest radiograph was done on all patients in search of chest related HTLV-I complication such as lymphocytic interstitial pneumonia.

2.3.3 Histological Investigations

4mm punch biopsy skin specimens were taken from lesional skin on all those enrolled patients who gave consent for histological analysis. One dermatopathologist was responsible for the histological analysis. This pathologist was blinded as to the HIV status of the patients.

Tissue specimens for histological examination were examined by light microscopy. Biopsies were fixed in buffered formalin and processes routinely for paraffin-wax embedding. Up to 15 serial histological sections were obtained from each biopsy specimen.

2.3.4 PCR and Sequencing

DNA was extracted from the peripheral blood morphonuclear cells DNA using QiaAmp Blood kit (Quiagen). Amplification of HTLV LTR region was performed as two overlapping fragments, an LTR-gag product of 473 bp and a tax-LTR product of 458 bp. Nested hot-start PCR and AmpliTaq Gold were used with cycling conducted on a Perkin Elmer 9700 thermal cycler under standard reaction conditions. Following separation on 1% agarose gels, the PCR products were purified using a Qiaquick Gel Extraction kit (Quiagen) and subjected to cycle sequencing on an Applied Biosystems 3100 capillary sequencer. Edited sequences were aligned and analysed using a variety of different phylogenetic software programs (Maximum Likelihood, Neighbour Joining and PAUP methods). Molecular clock evaluation was tested using the Likelihood Ratio Test (LTR) of Felsenstein.

CHAPTER 3

RESULTS

Among the patients who presented at King Edward VIII outpatients department during the period of January 2003 and December 2005, 60 patients had clinical features suspected to be due to HAID. Of these thirty three (33) met the diagnostic criteria for HTLV-I associated infective dermatitis based on the following: HTLV-I seropositivity, onset of disease in early childhood, eczema with crusting of the scalp, external ear and retro-auricular area, relapsing and remitting clinical course during withdrawal and resumption of therapy respectively. Evidence consistent with minor criteria included a generalized fine papular rash, generalized lymphadenopathy, anaemia, raised erythrocyte sedimentation rate, raised CD4 count, CD8 count and CD4/8 ratio.

3.1 Demography

3.1.1 Age

The mean age of patients with HAID was 17 years (SD 12.3) range (8 months- 46 years). One third (30.3%) of the patients fell between the ages 6 and 10 years, represented in *(Figure 4),* below.

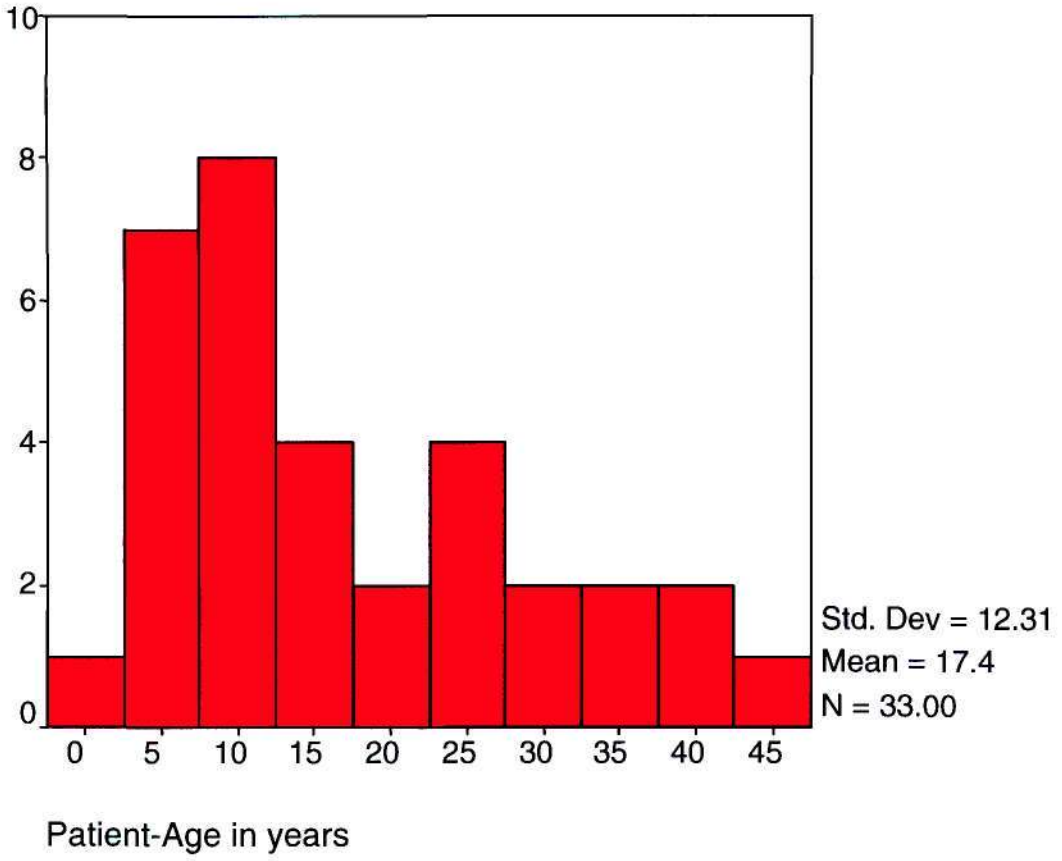


Figure 4: *A histogram of the age distribution in the cohort, age on the x axis and number of individuals on the y axis.*

3.1.2 Gender

In the sample, 24 (72.7%) were female while 9 (22.27%) male, hence a female to male ratio of 2.6:1. In the age group < 12yrs, the female to male ratio was 1:1. In the over 12 year group, 93.7% were females and only 6.7% were males, *(Figure 5)*.

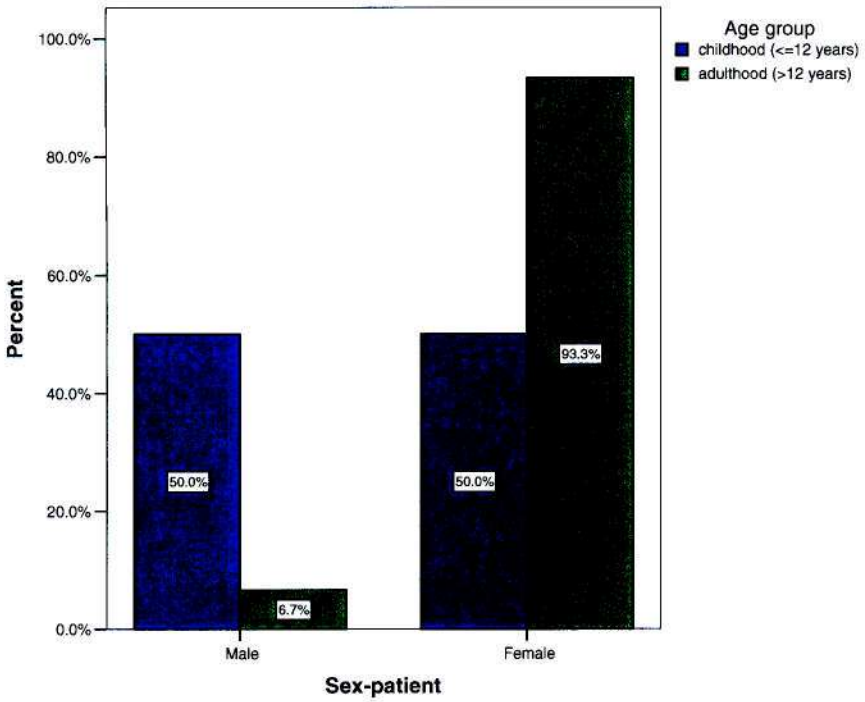


Figure 5: *Gender distribution between adults and children in patients with HAID*

3.1.3 Racial distribution

All 33 (100%) of patients were of African origin.

3.2 Study patients

Of the 60 patients screened, 33 were confirmed HTLV-I associated infective dermatitis cases. A total of 27 patients were excluded from this study either because their HTLV-I serology was negative (n=22) or because their HTLV-I results could not be retrieved (n=4), while one (n=1) patient was HTLV-I positive but did not have other features of HAID. Refusal rate was nil.

The 33 patients who fulfilled the clinical criteria had eczema in the following sites: exudative eczema on the scalp, neck and groin, a generalized papular rash and nasal

discharge and/or crusting of the anterior nares. An example of some of these features is shown in (*Figures 6a and 6b).*

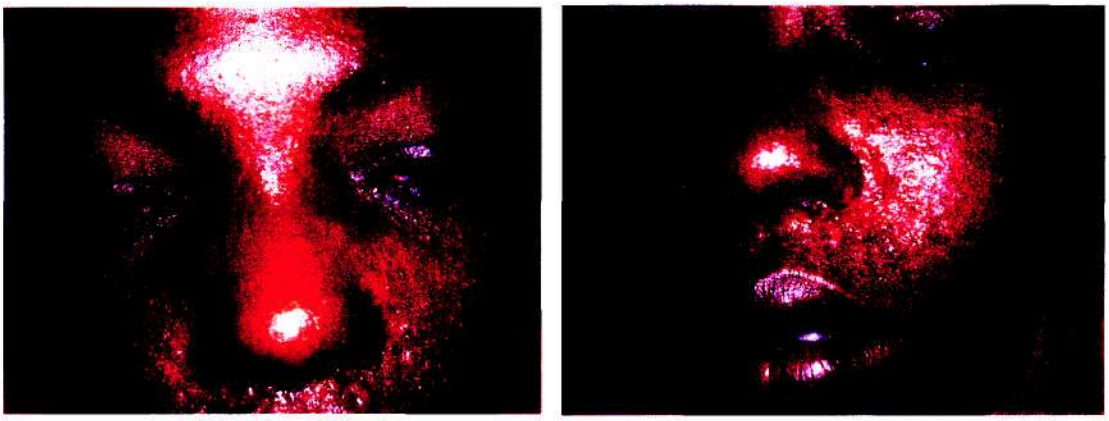


Figure 6a and 6b: *A typical exudative eczema with nasal crusting*

3.3 Dermatological examination

The scalp was the commonest site of involvement, with 77.4% of all patients affected. This site was closely followed by ear involvement, with both the external ear and retroauricular areas involved, making up about 71%. The axillae were affected in 65% of patients (*Figure 7*). Paranasal involvement 58%, groin 55%, eyelid 52% and neck 39%. These skin lesions were erythematous, scaly and exudative with adherent yellowish crusts. Retroauricular fissures were also seen. Blepharoconjuctivitis was observed in 3 (8.26%) of patients. A disseminated follicular papular eruption was found in 16 patients (23.5%), see (*Figure 8).* Lymphadenopathy was present in 18 (54.5%) patients. Chronic nasal discharge was observed in 16 (48.4%) patients, whereas crusting of the anterior nares was found in 13(39.3%). The remaining four patients (12.1%) exhibited neither chronic nasal discharge nor crusting of the anterior nares. *Figure 9* graphically illustrates the frequent sites of skin involvement in our cohort with HAID.

Figure 7: *Picture of patient demonstrating flexural involvement*

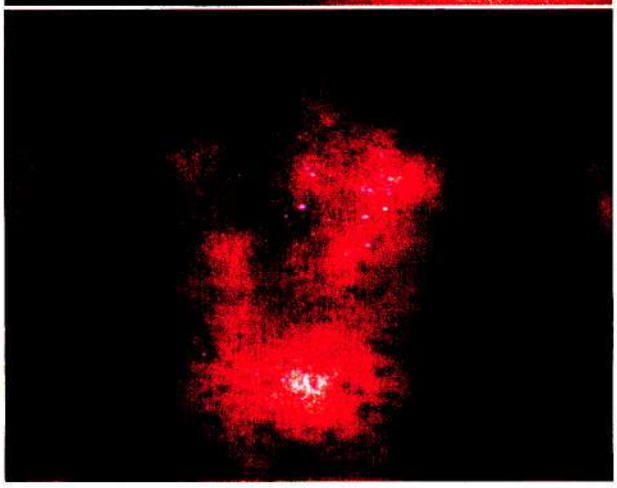


Figure 8: *A generalised papular eruption in HAID*

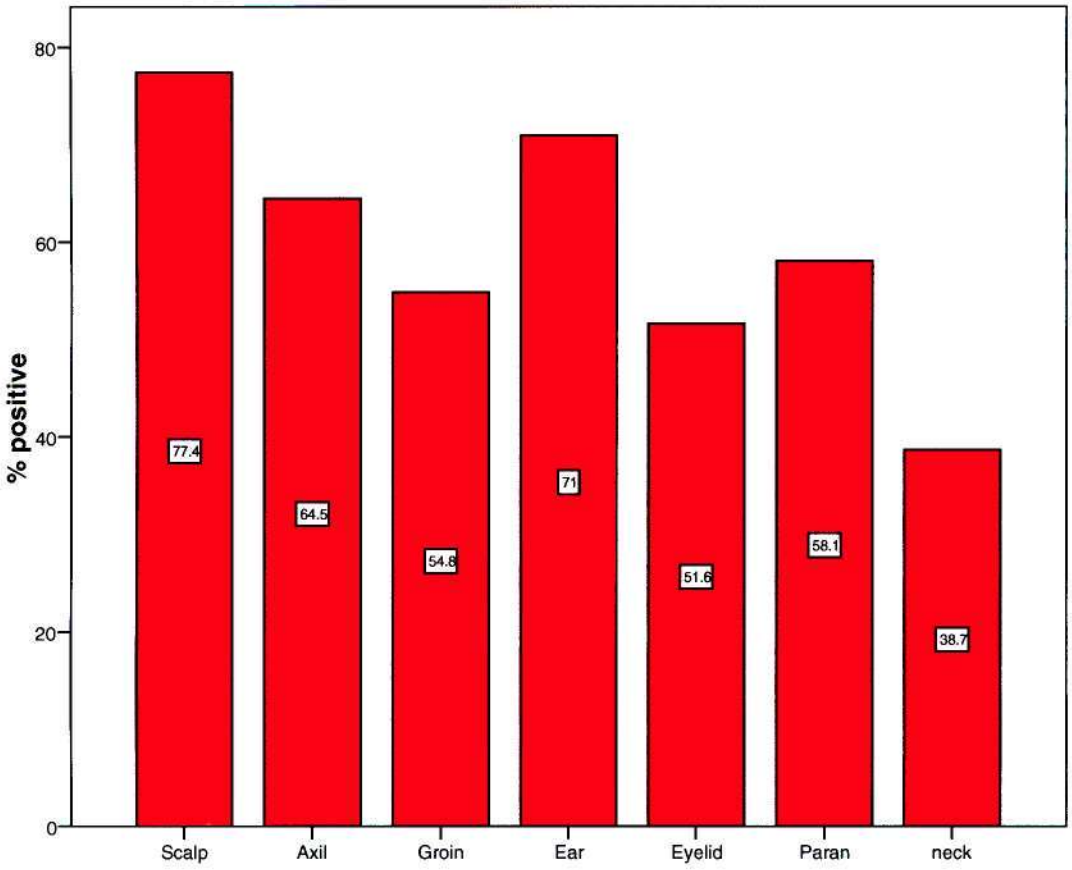


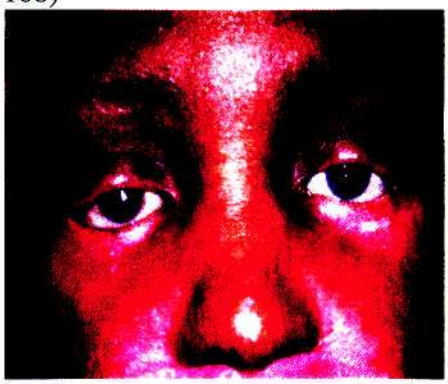
Figure 9: *Anatomical sites involved in the HAID patients*

3.4 Complications

A total of 11(33.3%) individuals in our cohort had complications associated with HAID. These were corneal opacities in 3 (8.26 %) patients (*Figures 10a and 10b).* Scabies was confirmed in 6 (18.1%) patients, while 2 (6%) patients had HAM / TSP. None of the patients had evidence of lymphocytic interstitial pneumonitis on chest radiograph.

10a)

10b)



Figures 10a and 10b: *Pictures demonstrating corneal opacities affecting some patients with HAID*

3.5 Microscopy results

3.5.1 Skin swabs

As skins swabs were taken from more than 1 site in some patients, a total of 41 specimens were collected. A single swab was taken from the perinasal skin, 18 swabs from anterior nares while 22 were taken from lesional skin. The single swab taken from perinasal skin revealed colonisation with *Streptococcus pneumoniae*. From the nasal skin swabs, results of the 18 swabs taken revealed that 14 (77.7%) of those were colonised by S. *aureus*. Streptococcal species were isolated in only 2 (11.1%) specimens taken from this site. Multiplicity of organisms was also found in 2 (11.1%) specimens. Findings from the swabs taken from lesional skin showed that *S. aureus was present* in 20 (90.9%) specimens while 15 (68.1%) of which also had Streptococcus species. Multiplicity of organisms was found in 1(4.5%) swab. These findings are summarised in *Figure 11*. The streptococcal species, isolated from the different regions were a combination of: *ß-haemolytic streptococcus* (BHS), groups A, B, C and G, together with *streptococcus pyogenes*. The most common of these was BHS group G, which was found in 5/15 (33.3%) swabs taken from the lesional skin.

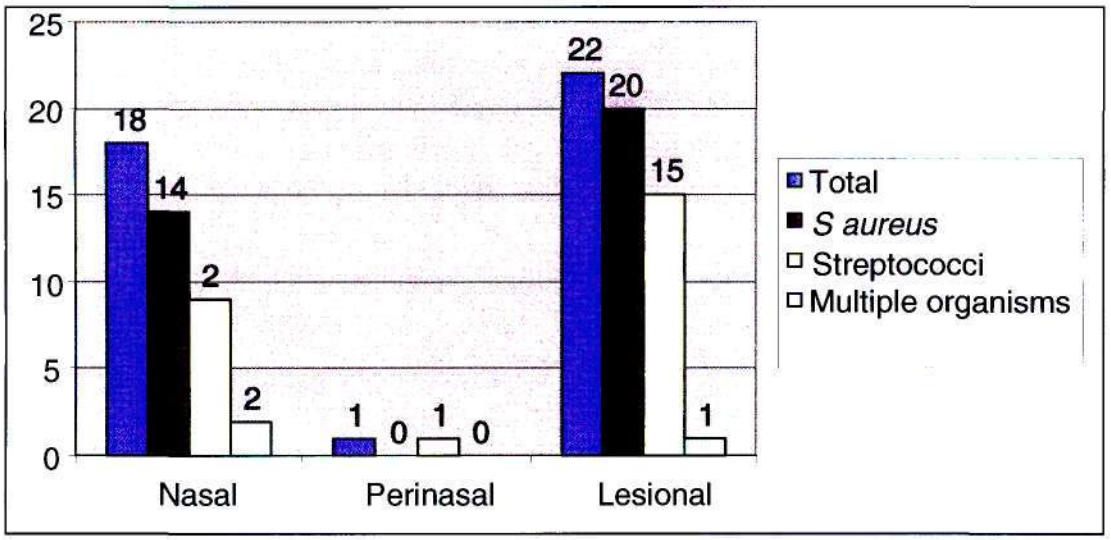


Figure 11: *A histogram showing the distribution of bacteriology results*

3.5.2 Stool sample results

Stool samples were collected in 12 of the 33 patients and neither parasites nor ova were isolated from any of these specimens.

3.6 Bloods Results

3.6.1 Haematology

A complete blood count could be retrieved in 25 of the 33 patients. Haemoglobin levels ranged from 8.0 to 14 g/dl. They had a mean Hb of 11.5g/dl. This was indicative of a mild anaemia which was defined as haemoglobin < 12 g/dl. The mean white cell count, differential counts and the platelet counts were within the normal limits, *Table 6.*

Table 6: Summary of the blood count results

	Haemoglobin	**White cell count**	**Platelet count**
Normal	11.5 -13.5 g/dl	4.0 – 11.0 x 10^9/l	150 – 450 x 10^9/l
Mean Levels (n = 33)	11.5 g/dl	10.1 x 10^9/l	405 x 10^9/l
Minimum	8 g/dl	5.3 x 10^9/l	116 x 10^9/l
Maximum	14g/dl	17.4 x 10^9/l	607 x 10^9/l

3.6.2 Erythrocyte Sedimentation Rate (ESR)

ESR results were available in 14 of the 33 patients. Of these, the mean was 53 mm/hr (range 10-130 mm/hr) and 12 (85.7%) patients had elevated (ESR > 15mm/hr) levels.

3.6.3 HIV/HTLV-I co-infection

All 33 (100%) patients with features of HAID were seropositive for HTLV-I serology. HIV results were retrieved in 30 of the 33 patients tested for this. Of these 9 (30%) were HIV positive, 21 (70 %) were HIV negative. Of the 9 HIV positive patients 8 were adults (age range 15- 41 years) and 1 was a child aged 8 months. Eighty-eight percent (88%) of the HIV positive patients were female. The mean viral load in this group was 52 000 copies/ml.

3.6.4 Immunology

IgG levels were high in 16 (48.4%) of the patients evaluated. IgA was high in 8 (24.2%) of patients while IgM was found to be elevated in 2 (6%) of patients. The mean levels are depicted in *Table 7*. Levels for the IgD and IgE could not be determined due to the non-availability of reagents in our laboratory,

Table 7: Immunologic parameters among patients with HAID

Variable (normal range)	**Mean Levels**
IgA (0.68 – 3.78 g/l)	3.94 g/l
IgG (6.94 – 16.18 g/l)	21.41 g/l
IgM (0.60 – 2.63 g/l)	1.62 g/l

Table 8: Results of serum electrophoresis in patients with HAID

Variable (normal range)	Mean levels
Albumin (32-50 g/l)	31.00 g/l
Alpha 1 globulin (1.72 – 3.30g/l)	4.0059 g/l
Alpha 2 globulin (4.2 – 8.7 g/l)	11.1412 g/l
Beta globulin (5.2 – 10.5 g/l)	11.494 g/l
Gamma globulin (7.1 – 14.5 g/l)	26.781 g/l

Table 8 include the results of the serum electrophoresis in all the enrolled patients, this is further illustrated in (*Figure 12*) below.

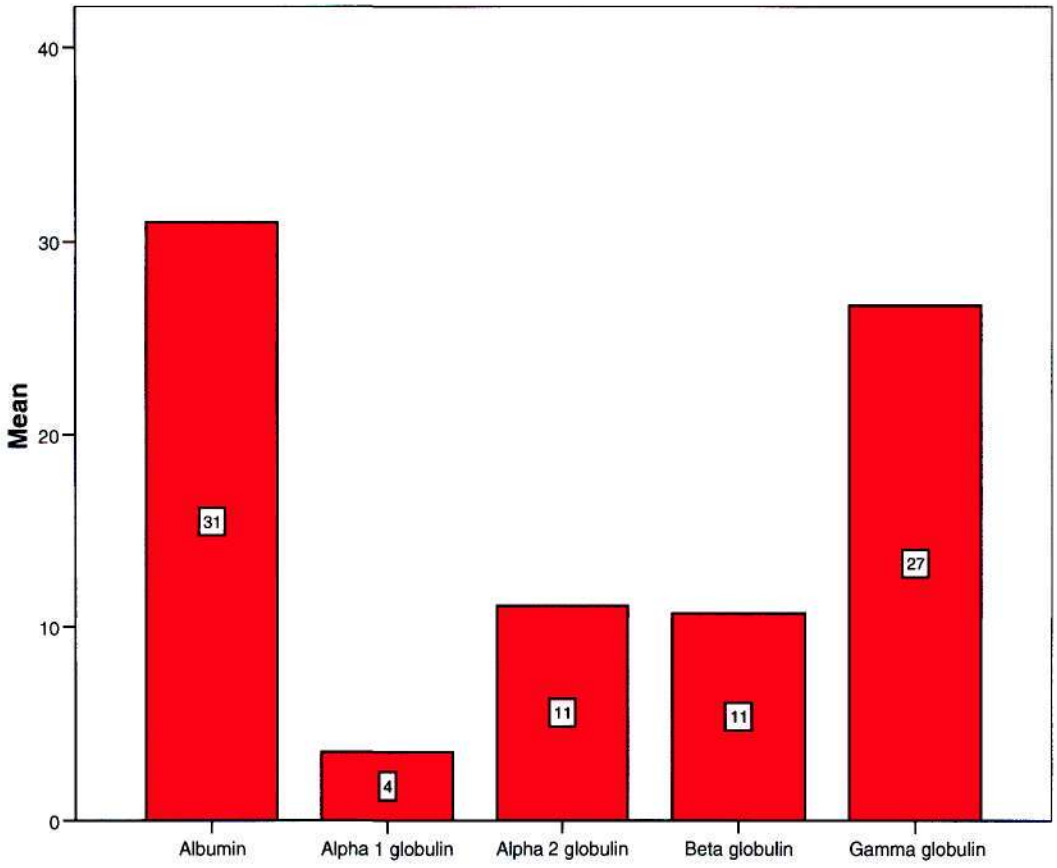


Figure 12: *Schematic diagram of Protein Electrophoresis Result*

3.6.5 CD4/ CD8 (entire group)

CD4 counts were tested in 18 of the 33 patients. Their mean CD4 count levels was 1730 cells/µl (range 114 – 3134 cells/µl) with a mean CD8 count of 1299 cells/µl (range 436 – 3433 cells /µl). The CD4:CD8 ratio of the group was therefore 1.33. CD4 and CD8 counts were checked for in 6 of the 9 patients co-infected with HIV. In this group CD4 count levels were 1505 cells/µl, a CD8 level of 1704 cells/µl and therefore a ratio of 1:15. These results are shown in *Table 9.*

Table 9: CD4 and CD8 count analysis

	CD4 cells/µl	**CD8cells/µl**	**CD4/CD8 ratio**
Normal	550-1955	250-1200	0.5-1
HTLV-1 (n=18)	1730	1299	1.33
HTLV-1+ HIV (n=6)	1505	1704	1.15

3.7 Virology

All 33 patients were HTLV-I positive (particle agglutination test, confirmed on Western Blot). Only 12 of the 33 were subtyped, the predominant strain was found to be the *Cosmopolitan, Subtype Ia.*

3.8 Histopathology results

Histopathological examination was performed on punch biopsies of 31 patients. These biopsies were of various lesions in different stages of evolution and included papules, patches, eczematous areas and macules. The average number of biopsies per patient was two. A wide spectrum of histopathological features ware present and the salient features that were assessed were as follows:

- superficial perivascular dermatitis (SD)
- deep perivascular dermatitis (PVD)
- superficial and deep perivascular dermatitis (S/D-PVD)
- lichenoid inflammatory dermatitis (LID)
- interface dermatitis (ID)
- seborrrhoeic dermatitis features (seb derm)
- leucocytoclastic vasculitis (LCV)
- chronic folliculitis (CF)

Strict definitions of the above terms were used when assessing the biopsies e.g. Superficial perivascular dermatitis when viewed at scanning magnification is one of the most common reaction patterns in inflammatory skin pathology , characterized by the presence of inflammatory cells around venules in the upper reticular dermis. The inflammation may be confined to a zone around the venules (perivascular only) and may also occupy the interstitium (perivacular and interstitial) where the inflammatory cells are scattered within the collagen bundles. If the inflammation involved the venules deep within the dermis then this was called deep perivascular dermatitis.

When epidermis was involved by the inflammatory infiltrate in a manner that obscured the dermoepidermal junction then this pattern was called interface dermatitis and if the inflammation was continuous along the interface with associated vacuolar alteration then this was called a lichenoid inflammatory dermatitis.

Seborrhoeic dermatitis was diagnosed when mounds of scale crust in the epidermis were demonstrated with occasional neutrophils. Additional features were intercellular oedema causing widening between keratinocytes beneath the epidermis (spongiotic dermatitis). A dermal superficial perivascular and interstitial dermatitis was also present in some of the specimens.

Exudation of neutrophils with fibrin around dermal venules with nuclear dust and extravasation of red cells was designated leucocytoclastic vasculitis.

When lymphocytes were identified within the hair follicules especially infundibular epithelium, this was designated chronic folliculitis.

Superficial and deep perivascular dermatitis (S/D-PVD) was a major histological feature in our cohort with HAID. It was found present a single feature in 12 (38%) of the 31 cases (*Figure 13).* S/D-PVD was also noted associated with a lichenoid inflammatory dermatitis (LID) in 28% of cases (*Figure 14*). Chronic dermatitis characterised by SVD-PVD with interface dermatitis (ID) was found in I4 (12.9%) of the specimens. ID is shown in *Figure 15.* Two (6.4%) of the skin specimens had features in keeping with seborrhoeic dermatitis (seb derm), (*Figure 16a and 16b).* Seb derm is one clinical condition that can be mistaken for HAID.

S/D-PVD was found associated with chronic folliculitis (CF) (*Figure 17*), in one (3.2%) case. There single cases (3.2%) of LID, CF and CF together with LID, respectively. One patient (3.2%) showed features of leucocytoclastic vasculitis (LCV). The patients who were co-infected with HIV showed similar features dominated by S/D-PVD but in addition their histology sections were studded with eosinophils.

Figure 13: *Superficial and deep perivascular dermatitis (S/D-PVD)*

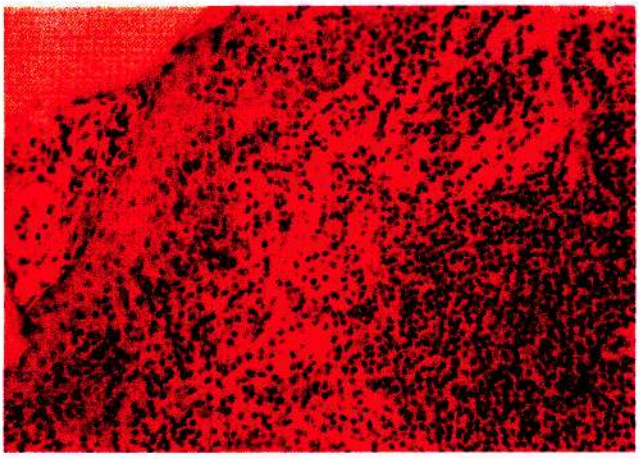


Figure 14: *SVD-PVD + Lichenoid inflammatory dermatitis (LID)*

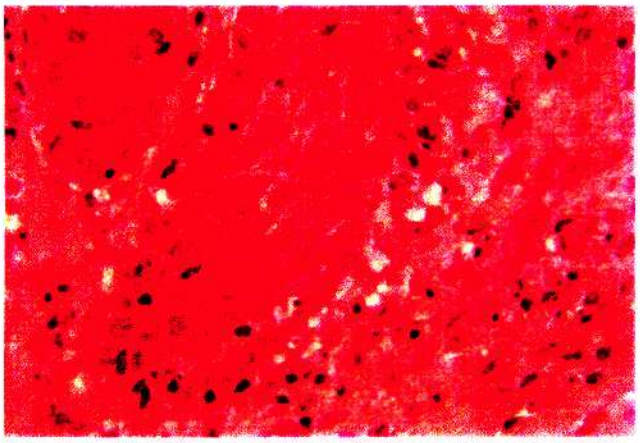


Figure 15*: Interface Dermatitis (ID)*

Figure 16a: *Seborrhoeic dermatitis: Skin demonstrating mounds of scale crust with occasional neutrophils. Beneath this there is pallor of keratinocytes. A dermal superficial perivascular and interstitial dermatitis is also seen.*

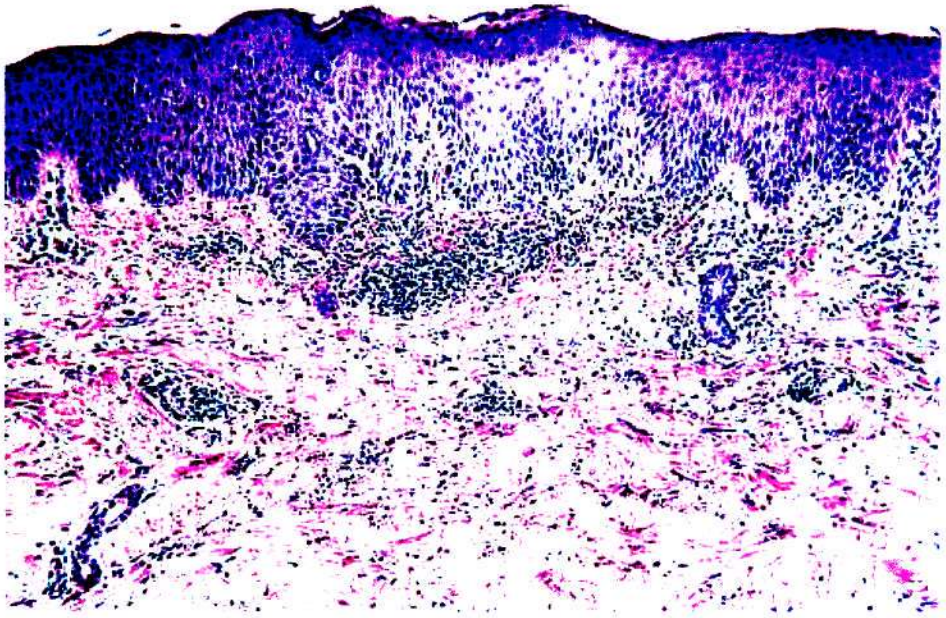


Figure 16b: *Skin demonstrating spongiotic dermatitis in seborrhoeic dermatitis*

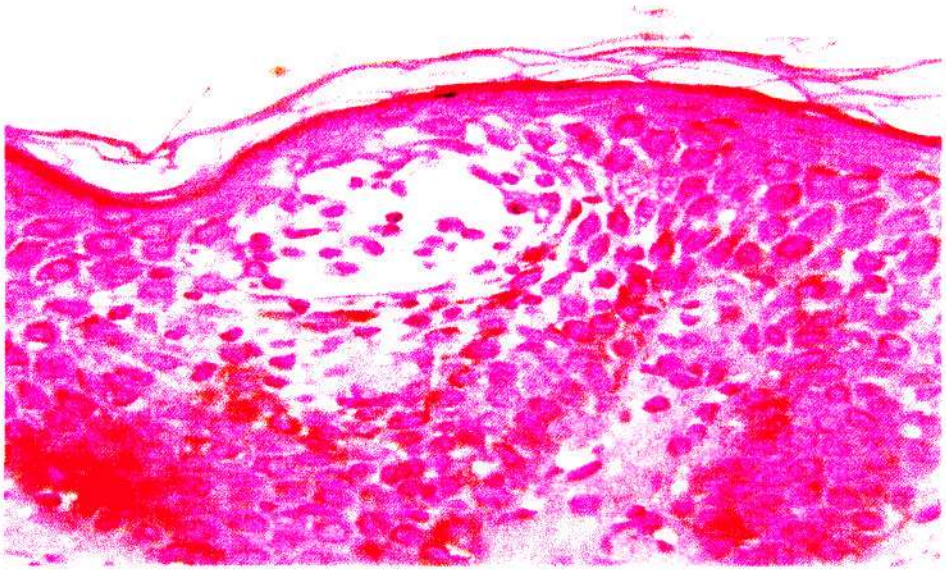


Figure 17a: *Chronic folliculitis (CF): Skin demonstrating lymphocytes within follicular especially infundibular epithelium.*

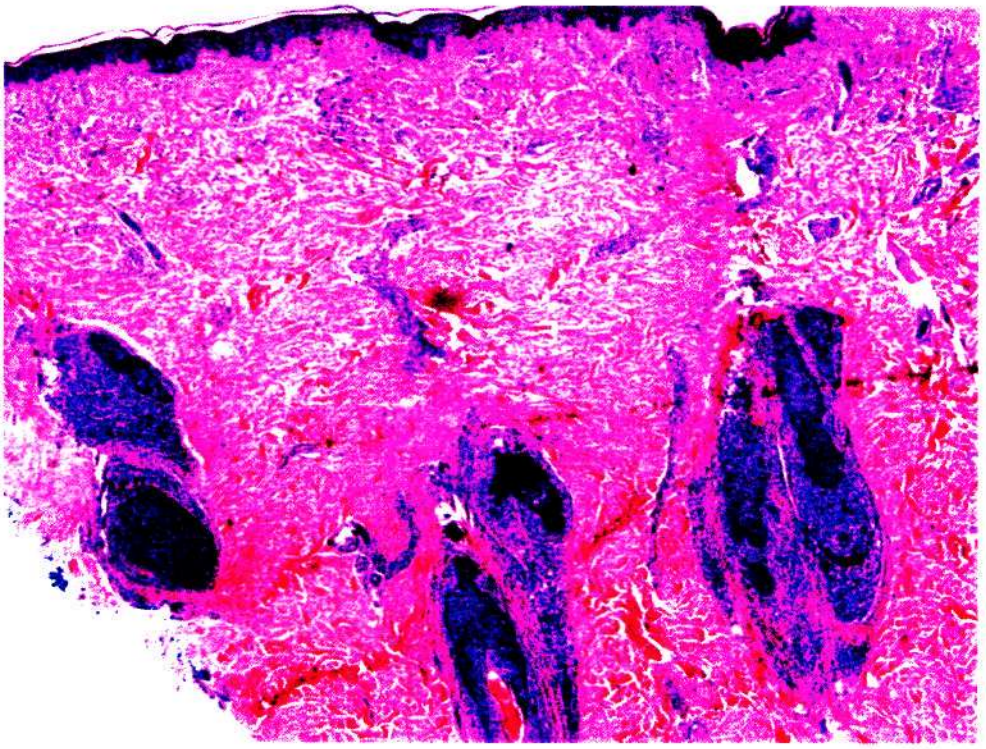
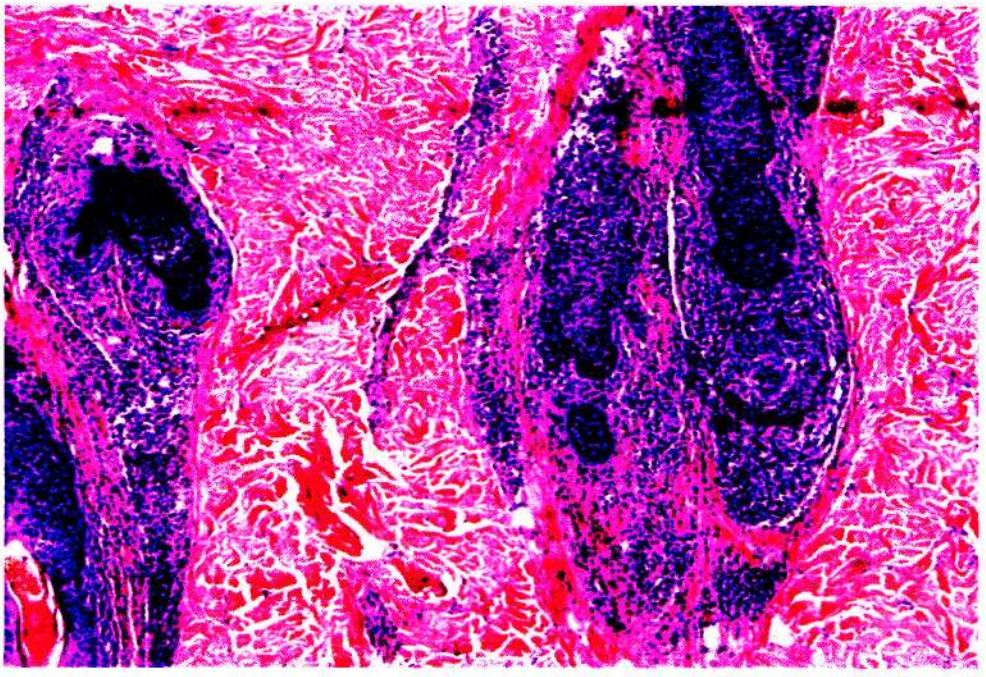
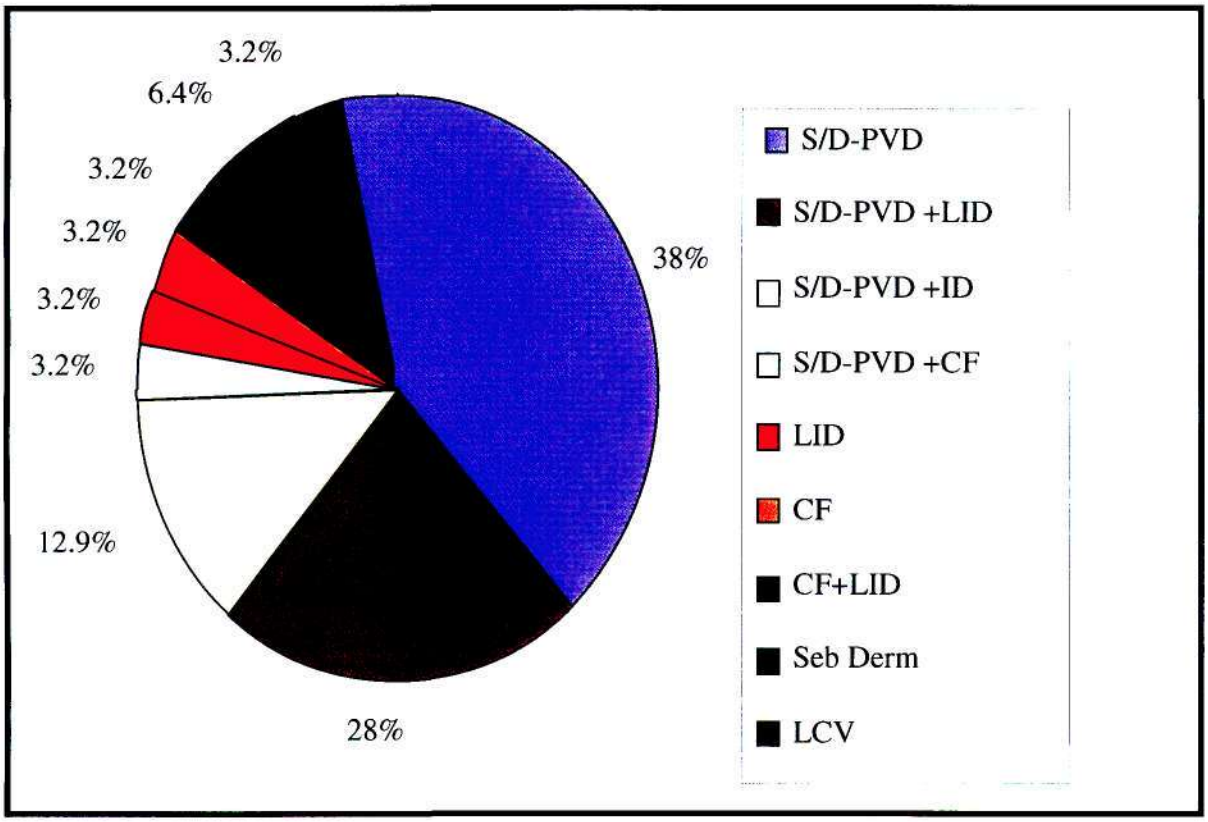


Figure 17 b*: A deep section demonstrating chronic folliculitis*



The spectrum of the histological features that were found in this group of patients is summarized in a pie diagram below (*Figure18*).

Figure 18: *Histological characteristics of HAID*



3.9 Data for the family members

First degree relatives of 9 patients were assessed. Of these, 5 were mother - child pairs, 2 fathers, and 2 siblings. They were examined for features of HAID and tested for HTLV-I. Of the mother and child pairs, 4 mothers and their 4 children had both clinical lesions of HAID and were HTLV-I positive. One mother had no features for HAID but the HTLV-I test was not performed. Both the fathers enrolled had no features for HAID and were HTLV-I negative. The siblings who were assessed showed clinical features suggestive of HAID but testing for HTLV-I was not done (*Table 10*).

Table 10: Results of the family studies

Patient No	Family member	Clinical features	HTLV-I result
1	mother	HAID	positive
2	mother	HAID	positive
3	mother	HAID	positive
4	mother	HAID	positive
5	mother	No HAID	not done
6	father	No HAID	negative
7	father	No HAID	negative
8	sibling	HAID	not done
9	sibling	HAID	Not done

CHAPTER 4

DISCUSSION

Approximately half of the patients recruited met the established criteria for diagnosis of HAID. This may be indicative of the low sensitivity of the current criteria which may not distinguish the entity of HAID from the other clinical simulators.

Demography

4.1.1 Age

The mean age in our patients was 17 years (range 8 months - 45 years). The majority of these were between the ages 6 and 10 years. Studies from Jamaica, where most work on this entity has been done, have shown that the usual onset of HAID is between the ages 2 and 3. Therefore our study findings of mainly patients between ages 6 and 10 years were not out of keeping with the expected time of presentation, since in this study, only the age of presentation could be determined but not the onset of disease. The youngest in our series was just 8 months old. Symptoms appeared earlier in this patient than has been reported in the literature. However, there are some reports of HAID in patients as young 6 months of age.[46] This 8 month old patient was also co-infected with HIV and it is not known if the presence of the additional virus may have contributed to the early manifestation of symptoms in this patient.

4.1.2 Gender

There was an equal predominance of males and females in the childhood group, M: F = 1:1 Studies of HAID have been mainly done in children and they have shown an overall predominance of females.[3] This was not the case in our series as it was only in the adult group that a female predominance was observed with a M:F ratio of 1:2.5. Studies have documented a more efficient male-to-female transmission of HTLV-I compared to female-to-male transmission. However, there has been mixed findings from prospective studies with one study showing a higher male-female transmission[47] whereas two others showed no significant difference in the transmission between the genders. The prevailing

postulate is that the differing male to female ratios in the childhood and adulthood group is reflective of the two modes of transmission of HTLV-I, vertical in the childhood group and sexual in the adults. Hormonal factors are thought to play a role in female susceptibility.[47]

4.1.3 Racial distribution

All 33 (100%) participants were African in our cohort. This sample was drawn from a tertiary hospital in KZN which mainly serves the African community in KZN, partly explaining this bias. In other studies conducted in South Africa, [15] in the Ngwelezane district in rural KZN, HTLV-I was found to be prevalent, the majority of the population is Black-African in this region, hence the link with poor socioeconomic status, but other populations have not been tested.

4.2 Dermatological Examination

4.2.1 Distribution of lesions

The morphology and distribution of lesions were similar to that described in other studies with characteristic extensive involvement of the scalp and retroauricular areas with exudative crusted, infected lesions more common. Eyelid margins, paranasal skin, neck and axillae were also involved. Crusts were also noted in the nostrils and fissures were found behind the ears. The above characteristic features were observed more in the childhood group while the older age group exhibited these features in a less severe form. This was in keeping with studies showing that the bacterial infection tend to diminish with increasing age as the patients' immunity matures.[11]

4.2.2 Nasal crusting

The cases studied fulfilled all the major criteria of LeGranade et al [4]. Almost half (48.4%) of our patients had chronic nasal discharge without crusting in the nostrils, while 40% had crusting in the nostrils. It was noted that those that had chronic nasal discharge did not have crusting whereas the patients that had crusting of the nares did not have chronic

nasal discharge. 12% in our cohort had neither features. This finding was also described by Suite and colleagues who reported no chronic nasal discharge in 15 patients with HAID.[48] Our results are in agreement with deOliviera and colleagues, who argue that nasal crusting or rhinorrhoea should not be made obligatory for the diagnosis of HAID.[11] The criteria may require revision because of the discrepancy between studies regarding the mandatory feature of "nasal crusting and/ or chronic nasal discharge". Our patients fulfilled most of the criteria for HAID except for the 4 patients that did not have the nasal crusting and/or discharge but fulfilled all other criteria. Due to the presence of the other criteria in these patients, including some of the minor criteria, we still felt that these four patients did have HAID.

4.3 Complications

Complications have been reported to occur in 30-35% of patients with this entity. In our group of patients, scabies was the most common complication affecting about 8.1% of all patients. None of these patients with scabies had the crusted type which is in contrast with what has been reported in the literature. A robust immune system in our cohort may explain the lack of development of crusted scabies, known to be associated with immunosuppression.

The literature provides no clear explanation for the development of parasitic infestations like scabies. Postulations are that patients with HAID may be immunosuppressed and therefore predisposed to opportunistic infections, such as scabies. This postulate is being further explored by the authors.

4.3.1 HAM/TSP

Of the cohort of 33, 2(5.7%) had HTLV-I associated myelopathy. The two patients with myelopathy were adults aged 27 and 47 years, respectively. Both these patients complained of lower limb weakness and difficulty in walking. This was subsequently confirmed on neurological examination. In a series of 23 patients with HAID in Brazil, 5

of the cases (21.7%) were found to have myelopathy.[11] In another study of 20 patients with HAID, 6 (30%) were found to have HAM/TSP. Both of these studies indicate a higher frequency of HAM/TSP in patients with HAID compared to what was found in our series. The average age of diagnosis of HAM/TSP is about 40 years and is thought to be preceded by adult acquired infection.[3] The exact time when our 2 patients acquired HTLV-I infection could not be determined. In general, myelopathy occurs more commonly in the absence of HAID but in the presence of HTLV-I. Our 2 patients may have acquired the infection in adulthood since both were adults. Should that be the case, then the development of myelopathy in them would have followed the natural history of the disease. However, development of this type of myelopathy in patients occurring between 12 and 25 years following the diagnosis of HAID has also been reported. Childhood infection with HTLV-I and later development of HAM/TSP cannot be ruled in these 2 patients.

4.4 Microbiology

Studies have shown that culture from the anterior nares and lesional skin yield *S. aureus* and/ or *S. haemolyticus*. In our patients *S. aureus* was the predominant organism found in both lesional skin and the anterior nares. *S. aureus* was isolated in 90% of swabs taken from lesional skin and this organism present together with streptococcal species in 68% of swabs taken from the same site. No pathogens were isolated from stool and urine. Most studies have performed this particular investigation aiming to exclude *Strongyloides stercoralis* which has been proposed as a co-factor of ATLL. A number of case reports have documented that this pathogen may be associated with a short latency period to ATLL. *Ascaris lumbricoides* has been the most common organism identified microscopically in stool of children. It is a normal pathogen in children with or without HAID but even this common pathogen was not cultured in our series.

4.5 Blood results

4.5.1 Haemoglobin concentration

In the cases we report only a mild anaemia, with the mean Hb of 11.5 g/dl (11.5 - 13.5g/dl). The type of anaemia was not characterized in our study; hence we are unable to speculate on a cause. However, with chronic skin conditions a normocytic normochromic anaemia initially occurs and as the condition progresses, there may be an iron deficiency picture due to loss of iron from the skin, dietary factors and concomitant infections. In other studies the anaemia was of the iron deficiency type.[4]

4.5.2 WCC

The mean WCC in our patients was 10.1x10^9/l. this was within the normal range. This is in contrast to other studies which have demonstrated high total white cell counts with lymphocytosis.[4] One of the reasons that our patients did not have an elevated WCC may have been related to the low level of complications in our group.

4.5.3 ESR

The ESR in our series was raised and this can be explained by the chronic underlying dermatosis. However, the level was 53mm/hr indicates that ESR which is only marginally raised. Should the ESR levels have been raised much higher > 50 mm/hr one would have search for underlying complications such as ATLL.

4.5.4 Immunoglobulins results

In keeping with previous studies, which have shown that HAID patients have a significant increase in their total immunoglobulins,[28] immunoglobulin levels were also elevated in our patients. The mean levels were 3.94g/l (IgA), 21.41g/l (IgG) and 1.62g/l (IgM). In view of the fact that IgD and IgE could not be determined in our setting, the significance of elevation of IgA, IgG and IgM levels could not be determined.

4.5.5 CD4/ CD8 Levels

Studies for circulating T lymphocytes showed higher levels of activated T lymphocytes, an absolute CD4 count of 1730 cells/μl for the entire group of patients with HAID an increased CD4/CD8 ratio of 1.33.

However, when analysed separately the HIV / HTLV-I co-infected group of patients had a mean CD4 count level of 1505 cells/μl compared to the mean CD4 count of the entire group of 1730 cells/μl. This was not statistically significant (p=0.41). Previous studies have also shown a high CD4 count in patients who are HIV/HTLV-I co-infected. This can be interpreted as a reactional lymphocytosis and provides no benefit to the affected patients.[41] CD4-count is therefore an unreliable parameter in HIV/HTLV-I co-infection. HIV viral load is the remains the only reliable parameter to be used to assess HIV stage in cases of HIV/HTLV-I co-infection. Studies have postulated that the elevation in the total lymphocyte count together with increased number of activated T cells and an increased CD4 / CD8 ratio is evidence of an altered immune function that seem to prevail in patients with HAID.[37]

4.5.6 HIV/HTLV-I co-infection

A total of 9 (30%) of the patients were co-infected with HIV. Of these, 8 were adults and 1 was a child. The mean age in the adult group was 29.6 years and the age of the child was 8 months old. However, this child did not have PCR to exclude the presence of maternal antibodies to HIV. The fact that the majority of patients in this group came from the adults whereas the childhood group was predominantly HIV negative may represent co-incidental HIV co-infection in a group already at risk for HIV. It is possible that these patients already had HTLV-I infection since childhood and later acquired the HIV due to the high background prevalence of HIV in KwaZulu Natal. In South Africa, the HIV prevalence has reached its highest level with 29.5% of pregnant women being HIV positive in 2005. There is significant regional variation with the highest prevalence of 39.1% recorded in KwaZulu-Natal, and the lowest in the Western Cape at 15.4%. [49]

4.6 Genotyping

A subgroup of the entire cohort was evaluated for genotyping. Of the 12 specimens which were sub-typed, all 12 were of the A subgroup of the Cosmopolitan (HTLV-I a) subtype. This finding was consistent with a previous study conducted in KZN, [26] where 5 patients were assessed.[27] The *Cosmopolitan, Subtype A* is said to cause the majority of human infections studied to date.[47] One hypothesis suggests that this worldwide distribution may have occurred over the past several hundred years via European voyages of discovery, the slave trade or other human migrations.[47]

4.7 Data for the family members

Clusters of HAID were observed in the present study in at least 5 of the 9 families studied. The familial clustering suggests a genetic background and /or vertical spread. None of the family clusters were further analysed to exclude HAM/ TSP or ATLL.

In a study of 23 patients with HAID with family members, which included 20 mothers and 41 siblings of the children who were participants, [11] 17 of the 20 mothers, and 6 of the 41 siblings tested were found to be seropositive for HTLV-I. Three of these family clusters were found to have HAM/TSP. In another study, one family cluster showed that both the mother and her 9 year old son had HAID and HAM/TSP, while her other 2 year old son was only seropositive for HTLV-I but did not have any HTLV-I associated disease. [29] This family also underwent genetic studies which revealed that they shared a similar haplotype DRB1*DQB1*. This is the same haplotype that has been described among Japanese patients with HAM/TSP. This haplotype is thought to have contributed to their risk for development of HAM/TSP. In these studies the enrolled patients were analysed further to ascertain if they had other HTLV-I associated illnesses whereas in our series, the families were only assessed to exclude HAID.

4.8 Histopathology

Previous studies investigating the histology of HAID patients have not found any specific features. Features found were in keeping with chronic dermatitis characterized by interface dermatitis.[8] However, in contrast to these findings described above, a wide spectrum of features was found in the current study. The major histological finding in this series was superficial and deep perivascular dermatitis SVD-PVD making up to 38% of all specimens analysed. The second was SVD-PVD together with a lichenoid inflammatory dermatitis (LID) making 28% of specimens analysed. Chronic dermatitis characterised by (SVD-PVD) together with interface dermatitis (ID) found in other studies was only found in only 12.9% of our cases. Other histological findings found in our series were individual cases of LCV, LID, CF. One section (3.2%) featured a combination of CF and LID. 3.2% of specimens showed a combination of SVD-PVD together with CF.

However, in the HIV positive group, the main histological finding was also SVD-PVD with additional findings of an eosinophilic inflammatory infiltrate in the same specimens. Our finding of only 6.4% of patients with distinct features of seborrhoeic dermatitis histologically, supports the thinking that HAID is a unique entity and that it is not the same as seborrhoeic dermatitis.

4.9 Study Limitations

The first limitation of this study is that the dermatosis under question, HAID, is an uncommon condition. This has impacted on the small sample size, a total of only 33 recruited over a period of 3 years, hence the results extrapolated may not be as representative as they would have been had the sample size been larger. This was purely a descriptive study and the results would have been more robust had there been a control arm of HTLV negative seborrhoeic dermatitis to compare with. The difficulty with recruiting this arm was due to the fact that most of the patients with seborrhoeic dermatitis who present to outpatient clinics in the public sector are infected with HIV.

Patients who are HIV negative HTLV negative, in our opinion, have such a mild disease that they either do not present or are seen in the private sector. However, the current study on HAID has given birth to another on HIV associated seborrhoeic dermatitis and will attempt to characterise the clinico-pathological characteristics of this entity.

Having all the study results would have been ideal but in view of the study being carried out in a public hospital setting, loss of data is one of the major problems we have to face. Specimens have to be sent to different laboratory facilities. Due to logistics and poor sample handling, many results are commonly lost. Every attempt was made to chase all the results but despite all this some results were irretrievable.

CHAPTER 5

CONCLUSION

The dearth of published data characterising the entity of HTLV-I associated infective dermatitis in Africa and in Southern Africa in particular, underlines the importance of the objectives of this study. Characterising HAID in our local population, KZN, South Africa and comparing it to those described elsewhere is crucial to our understanding of the condition and adds to the current body of knowledge available worldwide. It also heightens awareness of this condition, which is currently under reported and under diagnosed and yet has devastating complications.

HAID is an under recognised condition for various reasons: ignorance of the entity, a very mild dermatitis which may go undiagnosed and its resemblance and hence confusion with seborrhoeic dermatitis. With KZN being the epicentre of HIV/AIDS in the country and with South Africa having the highest number of persons estimated to be living with HIV, seborrhoeic dermatitis is one of the commonest inflammatory dermatoses that affects HIV infected individuals in our population. Clinical sites of involvement viz. scalp, retroauricular, axillae and paranasal involvement are common to both. However, HTLV-I seropositive status, the papular truncal rash and absence of groin involvement are peculiar features of HAID.

The importance of establishing the entity and increasing awareness of HAID lies in the fact that it is a marker of underlying HTLV-I infection. These patients can then be followed up more closely so that complications such as ATLL, TSP and corneal opacities can be diagnosed and treated timeously. First degree relatives can also be screened for the infection and if necessary followed up more closely.

The entity of HAID which we have described is mainly a disease of Africans in KZN, South Africa. This is in keeping with publications form other parts of Africa and reinforces the tendency for infection to be associated with low socio-economic status. It

usually manifests in childhood and continues into adulthood, characterised by remissions and relapses. Clinically the significant pattern was that of an extensive exudative eczematous eruption involving the scalp and retroauricular area. Involvement of the eyelid margins, perinasal skin, neck and axillae were also significant. Chronic nasal discharge and/or nasal crusting were present in the majority of our cohort but were not found in all the confirmed HAID patients. The latter finding is in keeping with other studies and supports the idea of its removal as a major criterion for the diagnosis of HAID.The secondary infection by microbes is a constant feature and explains the remissions and relapses, prompt response to antibiotic therapy and relapses when antibiotics are withdrawn.

Genotyping revealed that the strain of HTLV-I infection affecting our cohort of patients in KZN, South Africa is the *Cosmopolitan, Subtype A* (HTLV-Ia). This is shared with the strain that is found in HAID patients in Brazil and supports the shared origin of this virus.

The most common histological pattern was superficial and deep perivascular dermatitis with a small proportion having histological features of seborrhoeic dermatitis. Hence this feature is important in differentiating the entities of seborrhoeic dermatitis from HAID. The histological finding of superficial and deep perivascular dermatitis is non-specific and can be found in many other inflammatory and infectious conditions, however positive serology and clinical features of HAID will be necessary to make the diagnosis.

The rate of co-infection with HIV was 30%, thought to be co-incidental due to the high HIV seroprevalence in adults in KZN, South Africa. However, there were no significant differences between the two groups except a more intense eosinophilic infiltrate on histological examination, a well described feature of HIV cutaneous pathology and HIV infection.

In this study, we have described HAID as a distinct entity in African children in KZN, South Africa, characterised by exudative crusts of the scalp, retroauricular areas, axillae and perinasal skin confirmed by HTLV -I seropositivity. The subtype is *Cosmopolitan,*

Subtype A (HTLV-Ia) and the commonest pattern histologically is a superficial and deep perivascular infiltrate. Although the complication rate in our series was low, their occurrence is associated with high morbidity and mortality hence underlining the importance of HAID as a marker for infection with HTLV-I infection.

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HTLV1 ASSOCIATED INFECTIVE DERMATITIS - DATA SHEET

CLINICAL FEATURES		YES	NO
ECZEMA	Scalp		
	Groin		
	Retroauricular		
	axillae		
	Eyelids		
	paranasal		
	neck		
ONSET IN CHILDHOOD			
RECURRENT DEMATITIS			
LYMPHADENOPATHY			
GENERALISED PAPULAR RASH			
CHRONIC NASAL DISCHARGE			
CORNEAL OPACITIES			
SCABIES			
HTLV1 MYELOPATHY			
BLOODS			
	BLOOD COUNT		
	ESR		
	SPEP		
	IMMUNOGLOBULINS		
	HIV	**Subjects**	**Mothers**
	HTLV1	**Subjects**	**Sibling**
	CD4 count	**Ratio**	

id	pid	case	htlv1	name	num	albumin	sex	age	agegroup
1	1	case	Positive	SIBUSISO THWALA	98,422,781		Male	11.0	11-15 years
2	2	case	Positive	HLOPE LONDIWE	98,233,363		Female	5.0	0-5 years
3	3	case	Positive	NYANDENI PRUDENCE THOKOZ	96,005,641		Female	23.0	21-25 years
4	4	case	Positive	DLAMINI MLUNGISI	98,294,557		Male	12.0	11-15 years
5	5	case	Positive	ZUNGU MTSHINGENI	98,467,201		Male	30.0	26-30 years
6	6	case	Positive	ALICE NDLOVU	98,286,675		Female	41.0	41-45 years
7	7	case	Positive	MHLONGO PETROS	98,208,795	25	Male	8.0	6-10 years
8	8	case	Positive	NINGI NGCOBO SIBONGILE	98,398,952		Female		
9	9	case	Positive	SITHOLE YOLANDA	98,111,657	30	Female	6.0	6-10 years
10	10	case	Positive	SHOZI LONDIWE	98,400,620		Female	7.0	6-10 years
11	11	case	Positive	SUKUDE THEMBI	98,089,088	27	Female	37.0	36-40 years
13	13	case	Positive		98,316,491		Female	41.0	41-45 years
14	14	case	Positive	GUMEDE MUSAWENKOSI	98,450,932		Male	9.0	6-10 years
15	15	case	Positive	NZIMANDE HLENGIWE	98,188,961		Female	13.0	11-15 years
16	16	case	Positive	MBUTHO SIPHO	98,251,441	31	Male	7.0	6-10 years
17	17	case	Positive	MAPHUMULO ZANDILE	98,037,343		Female	26.0	26-30 years
18	18	case	Positive	MBUYAZI SITHEMBELE	98,314,818	33	Female	15.0	11-15 years
19	19	case	Positive	MTHEMBU SAMKELISIWE	98,083,367		Female	7.0	6-10 years
20	20	case	Positive	MGENGE ROSEMARY			Female	35.0	31-35 years
21	21	case	Positive	HLOPE NOKUTHULA	98,523,227	27	Female	28.0	26-30 years
22	22	case	Positive	MKHOSINI NOTHANDO	98,605,365	38	Female	8.0	6-10 years
23	23	case	Positive	MGOBHOZI SANELISIWE	98,186,095	36	Female	8.0	6-10 years
24	24	case	Positive	THULISILE MAKHAYE	98,546,650		Female	23.0	21-25 years
25	25	case	Positive	NYANDENI SIBONISO	98,562,106		Male	7.0	6-10 years
26	26	case	Positive	MTHEMBU PHILISANDE	98,559,442	35	Male	4.0	0-5 years
27	27	case	Positive	CEBILE NKOSI	95,020,638	22	Female	21.0	21-25 years
29	29	case	Positive	DUMA THOBILE	98,558,625	27	Female	15.0	11-15 years
32	32	case	Positive	MSABANE MBALI	98,055,807		Female		
33	33	case	Positive	NSINDISO SHEZI	98,157,250	34	Male	8.0	6-10 years
34	34	case	Positive	NSIBANDE SIMANGELE	98,672,790		Female	11.0	11-15 years
35	35	case	Positive	THABISILE MPUNGOSE	98,254,890		Female	15.0	11-15 years
36	36	case	Positive	NOLUTHANDO SHANGE	98,674,055		Female	0.7	0-5 years
38	38	case	Positive	LINAH MTHEMBU	98,083,399		Female	46.0	46-50 years
63	63	control		THULANI XABA	98,586,406		Male		
64	64	control		SENZEKELE MALINGA	98,554,862		Female		

65	65 control		NDIYATHA MBONGWA	98,157,232	Female	44.0	41-45 years
66	66 control		ANDILE NTSHA	98,519,734	Male		
67	67 control		XOLILE SILANGWE	98,632,072	Female	28.0	26-30 years
68	68 control		ZANELE KHUZWAYO	98,548,167	Female		
69	68 control	Negative	VIKA VICTOR MAZIBUKO	98,639,522	Male	41.0	41-45 years
70	70 control		THABISILE BLOSE	98,648,267	Female		
71	71 control		NOBUHLE NDLOVU	98,604,188	Female		
72	72 control		NTOMBENHLE NZAMA	98,649,012	Female		
73	73 control	Negative	MELTA PHINDOKUHLE MANQEL	9,866,154	Female	44.0	41-45 years
74	74 control	Negative	THABANI BHENGU	98,522,221	Male	2.0	0-5 years
75	75 control		BONGISIPHO MTHEMBU	98,047,888	Male	10.0	6-10 years
76	76 control		NOKUPHUKA DLAMINI	1,717	Female	29.0	26-30 years
77	77 control		MLUNGISI JACA	14,474	Male	40.0	36-40 years
78	78 control	Negative	SAMSON BUSA	98,675,791	Male	50.0	46-50 years
79	79 control		SABISILE ZANELE DLADLA	98,667,303	Female	23.0	21-25 years
80	80 control	Negative	MUSAWENKOSI SKHAKHANE	98,612,795	Male	36.0	36-40 years
81	81 control	Negative	NONHLANHLA SIMELANE	94,034,155	Female	28.0	26-30 years
82	82 control	Negative	RAYMOND NTSHANGASE	98,633,633	Male	36.0	36-40 years
83	83 control	Negative	REBECCA WILLIAMS	98,586,129	Female	69.0	>60 years
84	94 control		SHINGA M S	98,216,559	Female	22.0	21-25 years
85	85 control	Negative	JUDITH MARTINS	98,679,170	Female	33.0	31-35 years
86	86 control		STHANDILE MEHLO	98,688,519	Female	6.0	6-10 years
87	87 control	Negative	THEMBA HADEBE	98,323,693	Male	30.0	26-30 years
88	88 control		JABULILE SITHOLE	98,649,118			
89	89 control	Negative	DELISILE EUNICE MTHEMBU	98,685,251	Female		
90	90 control	Negative	BULELANI SIQITHI	98,668,345	Male	15.0	11-15 years
91	91 control	Negative	BONGANI WELCOME NXUMALO	98,342,156	Male	41.0	41-45 years
92	92 control		MUNTUZA KHESWA	98,422,157	Female		
93	93 control		THANDAZILE PRUDENCE MAKH	98,694,174	Female	29.0	26-30 years
94	94 control	Negative	SIHLE MTHWETHWA	98,467,936	Male	15.0	11-15 years
95	95 control		SIBONISA KHOZA	98,701,161	Female		

agesplit	scalp	axil	groin	ear	eyelid	paran	neck	nasald	crust	recderm
childhood (<=12 years)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
childhood (<=12 years)	Y	Y	N	Y	Y	Y	Y	Y	N	Y
adulthood (>12 years)	Y	Y	N	Y	N	N	Y	Y	N	N
childhood (<=12 years)	N	N	N	N	N	N	N	N	N	N
adulthood (>12 years)	N	N	N	N	N	N	N	N	N	N
adulthood (>12 years)	Y	Y	Y	Y	Y	Y	N	N	Y	Y
childhood (<=12 years)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
childhood (<=12 years)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
childhood (<=12 years)	Y	N	N	Y	Y	N	N	Y	N	Y
adulthood (>12 years)	Y	Y	N	Y	Y	Y	Y	Y	N	Y
adulthood (>12 years)	N	N	N	N	N	N	N	N	N	N
childhood (<=12 years)	Y	N	N	Y	Y	N	N	N	Y	Y
adulthood (>12 years)	Y	Y	Y	Y	N	Y	N	N	N	Y
childhood (<=12 years)	N	Y	Y	Y	Y	Y	Y	N	Y	Y
adulthood (>12 years)	Y	N	Y	N	Y	Y	N	Y	N	N
adulthood (>12 years)	Y	Y	Y	Y	Y	Y	N	N	Y	Y
childhood (<=12 years)	Y	Y	N	Y	Y	N	N	N	Y	Y
adulthood (>12 years)	Y	N	N	Y	N	Y	N	N	N	Y
adulthood (>12 years)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
childhood (<=12 years)	Y	Y	Y	Y	Y	N	N	Y	Y	Y
childhood (<=12 years)	Y	Y	Y	Y	N	N	N	N	N	Y
adulthood (>12 years)	Y	Y	Y	Y	N	Y	Y	Y	N	Y
childhood (<=12 years)	N	N	N	N	N	N	N	N	N	N
childhood (<=12 years)	Y	Y	Y	Y	N	N	N	Y	N	Y
adulthood (>12 years)	N	N	N	N	N	Y	N	Y	Y	Y
adulthood (>12 years)	Y	Y	N	N	Y	N	N	N	N	Y
	Y	Y	Y	Y	N	Y	Y	N	N	Y
childhood (<=12 years)	N	Y	Y	N	N	N	N	N	Y	N
childhood (<=12 years)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
adulthood (>12 years)	Y	N	N	N	N	Y	N	Y	N	Y
childhood (<=12 years)	Y	Y	Y							
adulthood (>12 years)	Y	Y	Y							

adulthood (>12 years)

adulthood (>12 years)

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childhood (<=12 years)
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childhood (<=12 years)
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adulthood (>12 years)

adulthood (>12 years)
adulthood (>12 years)

childo	lymph	rash	hbd	hb	anaemia	esrd	esr	esrelev
Y	Y	N		12.3	absent	high		
Y	N	N		13.0	absent	TO REPEAT		
N	N	Y		8.0	present	NOT DONE		
N	N	N		9.7	present	not done		
N	N	N				not done		
N	Y	Y		11.4	present	80	80	yes
Y	Y	Y		13.2	absent	14	14	no
N	Y	Y	not done			not done		
Y	Y	Y	MICROCYTIC HYPOCHROMIC AN	10.8	present	93	93	yes
Y	N	Y		13.0	absent		47	yes
N	Y	N	NORMOCHROMIC ANEMIA	9.6	present	130	130	yes
N	N	N	NOT DONE			NOT DONE		
Y	Y	Y	NOT DONE			NOT DONE		
Y	Y	Y		14.4	absent	29	29	yes
Y	N	Y		14.4	absent	NOT DONE		
N	Y	N	TO CHECK			TO CHECK		
Y	N	N		11.6	absent	30	30	yes
Y	N	Y		11.6	absent	22	22	yes
Y	N	Y	NOT DONE			NOT DONE		
N	Y	Y	MICROSCOPIC HYPOCHROMIC	8.8	present	124	124	yes
Y	Y	Y		12.3	absent	40	40	yes
Y	Y	Y	HYPOCHROMIC MICROCYTIC	10.2	present	40	40	yes
Y	Y	N		8.0	present	10	10	no
N	N	N	NOT DONE			NOT DONE		
Y	N	N	NORMOCHROMIC	10.2	present	NOT DONE		
Y	N	N	NORMOCHROMIC	8.6	present	134		
N	Y	N	NORMOCHROMIC HYPOCHROMI	14.0	absent	60	60	yes
Y	N	N	NOT DONE			NOT DONE		
N	Y	Y	NORMOCHROMIC	12.0	absent	36	36	yes
Y	Y	Y		13.7	absent	28		
Y	Y	N		13.0	absent	21		
			not done					

spepd	spepd2	alb	a1g	a2g	bglob	gglob	immgd	igg	iggcat
	non specific findings	20	5.00	15.00	16.0	21.0		16.10	normal
non specific findings		31	3.00	10.00	9.0	17.0		19.80	high
NOT DONE							NOT DONE		
not done									
			4.00	8.00	8.0	36.0		32.40	high
			5.00	13.00	11.0	25.0		25.30	high
not done							not done		
NON SPEFIC FINDINGS		37	4.00	14.00	12.0	29.0		26.50	high
NON SPECIFIC FINDING		30	5.00	15.00	11.0	23.0		17.80	high
NON SPECIFIC FINDING		25	3.00	11.00	9.0	49.0		51.30	high
NOT DONE									
NOT DONE							NOT DONE		
NOT DONE								20.10	high
		31	2.00	10.00	8.0	14.0	NO RESULT		
TO CHECK							TO CHECK		
			4.00	10.00		31.0		31.70	high
			9.00	11.00	24.0			23.00	high
NOT DONE							NOT DONE		
POLYCLONAL GAMMOP		27	3.00	11.00	12.0	30.0		42.30	high
		38	2.00	8.00	10.0	22.0		21.60	high
	POLYCLONAL GAMMOP	34	4.00	10.00	13.0	32.0		28.00	high
TO CHECK							TO CHECK		
NOT DONE							NOT DONE		
NON SPECIFIC FINDING			5.00	13.00	10.0	17.0		14.90	normal
TO CHECK								18.00	high
NON SPECIFIC FINDING		31	4.00	10.00	12.0	28.0		26.90	high
NOT DONE							NOT DONE		
NON SPECIFIC FINDING		34	3.00	11.00	10.0	21.0		22.20	high
not done							not done		
non specific findings		42	3.10	9.40	8.9	33.5		19.48	high
not done							not done		
not done							not done		

iga	igacat	igm	igmcat	hivd	htlv1d	cd4d	cd4d2	cd4	cd8	cd48r	vl	
	5.62 high		0.98 normal	Negative				3,003	856	3.5		
	2.41 normal		1.38 normal	Negative				3,134	1,723	1.8		
				Positive				3,003	3,433	0.8		
				Negative				1,920	1,445			
				Positive				1,426	2,759	0.5		
	5.64 high		1.50 normal	Positive				1,887	1,070	1.8	46,000	
	5.64 high		0.43 low	Negative		NOT DONE						
				Negative		not done						
	2.93 normal		1.10 normal	Negative				2,152	785	2.7		
	1.35 normal		3.31 high	Negative				1,996	504	3.9		
	3.24 normal		3.71 high	Positive		NOT DONE						
				Negative				1,008	454	2.2		
				Negative		NOT DONE						
	2.61 normal		1.63 normal	Negative		NOT DONE						
				Negative				880	2,278	0.3		
				Positive				310	1,052	0.2	2,700,000	
	3.60 normal		1.39 normal	Negative				1,722	503	3.4		
	5.00 high		1.70 normal	Negative		NOT DONE						
				Negative		NOT DONE						
	5.50 high		2.45 normal	Positive				2,287	1,425	1.6	44,000	
	1.32 normal		2.25 normal	not done		NOT DONE						
	3.44 normal		2.17 normal	Negative		TO CHECK		822	1,958	0.4	230,000	
				Positive				114	489		52,000	
				Negative				3,008	1,580	1.9		
	1.11 normal		1.05 normal	not done								
	6.86 high		0.87 normal	Negative				954	633	1.5		
	8.00 high		0.98 normal	not done		NOT DONE						
				not done		NOT DONE						
	1.85 normal		0.90 normal	Negative				1,523	436	3.4		
				Negative		not done						
	4.88 high		1.42 normal	Positive		not done						
				Positive		not done						
				Negative		not done						
				Negative								

Positive

Positive
Positive

Positive
Positive
Positive
Positive
Positive
Positive
Positive

Positive

Positive

Positive
Positive
Positive

Negative

stapha	strepb	stool	skin	skinb	cxr	corn	scabies	myel	photo	treat
Y	Y	NO PARASITE	Y		Y	N	N	N	N	ANTIBIOTIC
Y	Y	NO PARASITE	Y	RS 21062 ?x2	N	N	Y	N	Y	antibiotics
Y	N	NOT DONE	N	NOT DONE	N	N	N	N	N	ANTIBIOTIC
N	N	not done	N		N	N	N	N	N	antibiotics
N	N	not done	N		N	N	N	N	N	antibiotics
Y	Y	NO PARASITE	Y	RS 21433	Y	N	N	Y	Y	antibiotics
Y	N	NO PARASITE	Y	RS 22877,16539	Y	N	Y	N	Y	ANTIBIOTIC
N	N	not done	N		N	N	N	N	N	antibiotics
Y	Y	NO PARASITE	Y	RS 19836	Y	N	N	N	Y	ANTIBIOTIC
N	N	NO PARASITE	Y		Y	N	N	N	N	ANTIBIOTIC
N	Y	NO PARASITE			Y	N	N	N	N	ANTIBIOTIC
N	N				N	N	N	N	N	ANTIBIOTIC
N	N		N		N	N	N	N	N	ANTIBIOTIC
Y	Y	NOT DONE	N	NOT DONE	N	N	N	N	N	ANTIBIOTIC
Y	N		N		Y	Y	N	N	N	ANTIBIOTIC
Y	Y	TO CHECK	Y	RS 14085	Y	N	N	N	N	ANTIBIOTIC
Y	N	NOT DONE	Y		N	N	Y	N	N	antibiotics
N	N	NO PARASITE	N	NOT DONE	N	N	N	N	N	ANTIBIOTIC
N	N	NOT DONE	N		N	N	N	N	N	ANTIBIOTIC
Y	N	NO PARASITE	Y	RS 4213	Y	N	N	N	Y	ANTIBIOTIC
Y	N	TO CHECK	N		Y	N	N	N	N	ANTIBIOTCS
Y	Y	NOT DONE	Y	RS 20640,22544	Y	N	Y	N	Y	ANTIBIOTIC
N	N	TO CHECK	Y	RS 5129, 5130	Y	Y	Y	Y	Y	ANTIBIOTIC
N	N	NOT DONE	Y		Y	N	Y	N	N	NONE
Y	N	TO CHECK	Y	RS 1826	Y	N	N	N	Y	ANTIBIOTIC
		TO CHECK	Y		Y	N	N	N	N	ANTIBIOTIC
N	N	NOT DONE	N		N	N	N	N	Y	ANTIBIOTIC
N	Y	NOT DONE	N		N	N	N	N	N	ANTIBIOTIC
N	N	NO PARASITE	Y	RS 7224,19184	N	N	N	N	Y	ANTIBIOTIC
Y	Y	no parasites	Y	RS 182001, 18201	Y	N	N	N	Y	antibiotics
Y	N	no parasites	Y	RS 19789/90	Y	N	N	N	Y	antibiotics
			Y	RS 18822	Y	N	N	N	Y	antibiotics
			Y	RS 20851	N	N	N	N	N	antibiotics
			Y	RS 19333						
			Y	RS 16532						

Y	RS 26527	
Y	RS 26647	
Y	RS 28345/04	
Y	RS 2005/54	
Y	RS 2458	
Y	RS 6569	
Y	RS 6565	
Y	RS 8252	
Y	12756,21212/3	
Y	RS 15678	
Y	RS 18058	
Y	RS 19183	
Y	RS 19182	
Y	RS 19484/5	
Y	RS 20669, 20670	
Y		
Y	RS 20667/8	
Y	RS 20991	
Y	RS 21240/1	
Y	RS 21795	
Y	RS 2005/21796	
Y		
Y		
Y	RS 6874	
Y	RS 23788/9	
Y	RS 15750	
Y		Y
Y		
Y		
Y		

family	htlv	htlv2	contr	pcr	scalpn	axiln	groinn
N			No		Yes	Yes	Yes
MOTHER-NOKUTHULA HLOPHI	also HTLV-1 positive		No	NOT DONE	Yes	Yes	No
CHILD- SBUSISO NYANDENI	also HTLV-1 positive		No	NOT DONE	Yes	Yes	No
none			No		No	No	No
none			No		No	No	No
CHILD - REBECCA NDLOVU	positive		No		Yes	Yes	Yes
FATHER	negative		No		Yes	Yes	Yes
none			No		Yes	Yes	Yes
FATHER - ORLANZO SITHOLE	NEGATIVE		No		Yes	Yes	Yes
NONE			No		Yes	No	No
NONE			No		Yes	Yes	No
NONE			No		No	No	No
NONE			No		Yes	No	No
NONE			No		Yes	Yes	Yes
NONE			No		No	Yes	Yes
NONE			No		Yes	No	Yes
sister and brother assessed	status unknowm but similar rash		No		Yes	Yes	Yes
NONE			No		Yes	Yes	No
NONE			No		Yes	No	No
DAUGHTER-LONDIWE HLOPHI	POSITIVE		No		Yes	Yes	Yes
NONE			No		Yes	Yes	Yes
SISTER-SAMKELO MGOBHOZI	NOT DONE		No		Yes	Yes	Yes
NONE			No		Yes	Yes	Yes
MOTHER-PRUDENCE NYANDE	POSITIVE		No		No	No	No
NONE			No		Yes	Yes	Yes
NONE			No		No	No	No
NONE			No		Yes	Yes	No
NONE			No		Yes	Yes	Yes
MOTHER- THOKOZILE SHEZI			No		No	Yes	Yes
none			No		Yes	No	Yes
none			No		Yes	No	No
none			No		Yes	Yes	Yes
none			No		Yes	Yes	Yes
			Yes				
			Yes				

	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
to be excluded as a control?	Yes
	Yes

earn	eyelidn	parann	neckn	stastrep
Yes	Yes	Yes	Yes	yes
Yes	Yes	Yes	Yes	yes
Yes	No	No	Yes	
No	No	No	No	
No	No	No	No	
Yes	Yes	Yes	No	yes
Yes	Yes	Yes	Yes	
Yes	Yes	Yes	Yes	
Yes	No	Yes	Yes	yes
Yes	Yes	No	No	
Yes	Yes	Yes	Yes	
No	No	No	No	
Yes	Yes	No	No	
Yes	No	Yes	No	yes
Yes	Yes	Yes	Yes	
No	Yes	Yes	No	yes
Yes	Yes	Yes	No	
Yes	Yes	No	No	
Yes	No	Yes	No	
Yes	Yes	Yes	Yes	
Yes	Yes	No	No	
Yes	No	No	No	yes
Yes	No	Yes	Yes	
No	No	No	No	
Yes	No	No	No	
No	No	Yes	No	
No	Yes	No	No	
Yes	No	Yes	Yes	
No	No	No	No	
Yes	Yes	Yes	Yes	yes
No	No	Yes	No	