

Full Length Research Paper

Patterns of skin disorder and its relationship with CD4⁺ cell count in a cohort of HIV-infected children

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Skin disorders are common in human immunodeficiency virus infected children. Clinical manifestations can thus facilitate in identifying patient's immune status. The prevalence and pattern of skin disorders in HIV-infected children was determined to understand the relationship between CD4⁺ cell count and various skin disorders. One hundred and seventy eight (178) HIV-infected children aged 6 weeks to 15 years received care at the special treatment clinic of the University of Abuja Teaching Hospital (UATH), Abuja, Nigeria. 93 (52.2%) were identified with different forms of skin disorders, 44 (47.3%) were males, and 49 (52.7%) were females. Their mean age, CD4⁺ cell count and its percentage were 4.9 ± 1.0 years, 341.8 ± 34.8 cells/ml and 11.9%, respectively. 61.3% of infected children with skin lesions were less than 3 yrs of age, while 38.7% were between the ages of 3-15 yrs. Mother to Child Transmission (69.9%) was the most frequent mode of transmission in these children. The three most common skin manifestations in the study patients were puritic papular eruption 28 (30.1%), impetigo/boil 12 (12.9%), and cutaneous candidiasis in 11 (11.8%). Skin disorders were seen more in patients with severe (58.1%) and advanced (36.5%) immune suppression when compared to those with mild (5.4%) degree of suppression ($p < 0.001$). Multiple skin lesions were also found to be commoner in patients with severe and advanced immune suppression. Prevalence of skin disorder is common in HIV-infected children with puritic papular eruption, impetigo/boil, and cutaneous candidiasis as the commonest manifestations, which significantly correlates with degree of immune suppression.

Keywords: Skin disorders, HIV/AIDS children, CD4⁺ cells.

INTRODUCTION

T-cells in the skin maintain a state of dormant immune activation. The pattern of immune dysregulation in the skin of human immunodeficiency virus (HIV)-infected individual may provide an accurate measure of disease progression, and cutaneous anergy is one of the diagnostic features of HIV/AIDS (Cockerell, 1994; Raju et al., 2005). The mononuclear cells (monocytes, macrophages, langerhan giant cells, and dendritic cells) in the skin have CD4 cell antigen receptor and a potential target site for HIV. Thus, the numerical decrease in langerhan cells of the skin in AIDS patients, the alteration of CD4: CD8 ratio with exaggeration in CD8 response, the decrease mononuclear phagocytic function with B cells hyper or hypo functions, and the enhanced

basophilic and mast cell deregulation with histamine release are all collective patho-physiological hypersensitive response to HIV infection (Raju et al., 2005; Sadick et al., 1993). In addition to the above reasons, the bacterial, mycobacterial, viral, fungal infections, as well as Kaposi sarcoma and other cutaneous lymphomas are additional causes of skin disorder in HIV patients (Berger, 1993; Burns et al., 1993).

A variety of skin disorders have been reported to be high among HIV infected children (Rongkavilit et al., 2000; Stefanaki et al., 2002; Nance et al., 1991; Wananukul et al., 1999; Wananukul et al., 2003; Lim et al., 1990; Hachem et al., 1998; Mysowski et al., 1996; Martinez-Rojano et al., 2000). Mucocutaneous diseases have also been reported to occur more frequently with advancing immune suppression (Wananukul et al., 2003; Lim et al., 1990; Ray et al., 1994; Carvalho et al., 2008).

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Reports of skin disorders in HIV infected children vary from region to region. While oral candidiasis, puritic papular eruption, drug rash and seborrheic dermatitis were found to be the leading skin disorders in one study population (Wananukul et al., 2003). Lim et al. (1990) noted molluscum contagiosum, herpes zoster, seborrheic dermatitis and ichthyosis as the main skin manifestations in children (1990). Kaposi sarcoma and cutaneous lymphomas were rarely reported in such study group (Wananukul et al., 1999; Wananukul et al., 2003; Lim et al., 1990). In African for example, there are many sub-types of HIV-I virus ranging from A to D. A and D are common in East and Central Africa, sub-type C is commoner in South Africa, whereas sub-type A recombinant is predominant in West Africa. Sub-type C that causes over 90% of infection in South Africa is more virulent than the other sub-types (Co et al., 1990). In Abuja, the seat of power of the country, the sero-prevalence of HIV infection in children was 5.7% (Oniyangi et al., 2006), with the overall sero-prevalence of 4.6% (Federal Ministry of Health, 2010). With the various sub-types of HIV 1 and their varying degree of virulence, one wonders whether the pattern and prevalence of skin manifestation will be similar across all nations. Hence, the aim of the present study is to document the prevalence and pattern of skin infection in HIV/AIDS children in Abuja, Nigeria, as well as relating it to the degree of immune suppression, since no such study has been carried out in children in this environment.

SUBJECTS AND METHOD

An 18 month cross sectional study of skin manifestations in HIV/AIDS children was carried out at the Paediatric Outpatient Special Treatment Clinic (POSTC) of the University of Abuja Teaching Hospital (UATH), Gwagwalada, from November 2007 to April 2009. UATH is a 350 bed referral hospital, providing care to residents of the Federal Capital Territory (FCT), Abuja, Nigeria, and five neighboring states with a population of approximately five million. The POSTC provides care to infants and children who are exposed or infected with HIV. Patients were recruited if they are less than 18 months with a viral particle detected by HIV deoxy-ribonucleic acid (DNA) polymerase chain reaction (PCR) or by positive HIV antibodies rapid HIV tests when greater than 18 months of age. HIV antibody test was done using double rapid antibody test (STAT PAK by chembio diagnostic system INC New York, and determine by Abbot Laboratories Japan). Participants who received care at POSTC were followed up in the clinic for antiretroviral medication or prophylactic drugs treatment for opportunistic infections.

Patients with skin manifestations at recruitment had a thorough history and physical examination including history of presenting complain, duration of such complain,

age, sex, general physical examination, as well as system-by-system examination. A complete dermatological examination of the scalp, face, neck, trunk, and extremities was performed on each patient. The diagnosis of cutaneous lesion was clinically made and confirmed by appropriate scrapping, cultures or biopsy when necessary. No virology and mycobacterial cultures were available, but specimens for fungal and bacterial cultures were obtained when necessary. Baseline full blood count and differentials were obtained using automated cell counters (Mamx, Coultrorusc TM Margency, France), while CD4 cell count and its percentage were obtained using automated Partec Cyflow easy count kit (Partec 05-8401, Western Germany). On recruitment of HIV infected children with dermatological conditions, WHO clinical staging system for HIV infection in children and adolescents (see appendix) were carried out to determine WHO clinical stage of the disease.

The sample size for the study was calculated using the formula by Araoye (2004). Prevalence rate of paediatric HIV infection in Abuja is 5.7% (Oniyangi et al., 2006), with a population size-less than 10,000, attrition rate of 10%, and a minimum sample size of 178 was derived.

Prior to this study, approval from the Ethical Board Committee of the hospital was obtained as well as a written consent taken from each parent or guardian. Each subject was assigned a confidential code and obtained research data were kept under the hospital's privacy and confidentiality protection. Data analysis was conducted using SPSS version 13.5 which provided standard deviation, frequency tables and test of significance.

RESULTS

A total of 178 HIV positive children were seen during 18 months review period. 93 (52.2%) were diagnosed as having different types of skin disorders; out of which 44 (47.3%) were males and 49 (52.7%) were females, with male to female ratio of 0.9:1. The patients had a mean age of 4.9 ± 1.0 years, CD4 cell count and percentage of 341.8 ± 34.8 cells/ml and 11.9%, respectively. 58.1% of the patient had a severe and 36.5% advance form of immune suppression, while 5.4% had a mild degree of immune suppression (Table 1).

Table 2 shows the age distribution of the HIV children with skin lesion, and probable route of HIV acquisition. 61.3% of HIV infected children with skin infection were less than 3 years, while 38.7% were between the ages of 3-15 years. Mother to Child Transmission (MTCT) was the most frequent mode of transmission and was documented in 69.9% of cases. Probable transmission through blood transfusion, and use of non-disinfected hairdressing implements such as clippers, shaving blades and scissors was also recorded in 5.4% each, while through sexual abuse/ sex related and use of non-

Table 1. Demographic characteristics of recruited patients.

	WHO Clinical Staging in Recruited Subjects			Total
	Stage 4	Stage 3	Stage 2	
	Severe Immune Suppression	Advanced Immune Suppression	Mild Immune Suppression	
No of patients (%)	54 (58.1)	34 (36.5)	5(5.4)	93
Male (%)	26 (59.1)	15 (34.1)	3(6.8)	44(47.3)
Female (%)	28 (57.1)	19(38.8)	2(4.08)	49(52.7)
Age in years	3.8±0.3	5.8 (± 0.2)	5.1±1.1	*4.9±1.0
CD4 cell count/mm ³	*184.7±23.3	*317.5±44.7	*523.2±36.4	341.8±34.8
CD4%	*5.6%	*12.9%	*17.2%	11.9%

*Values are mean ± SD.

Table 2. Probable source of paediatric HIV infection.

Age (years)	Through MTCT (%)	Through blood transfusion (%)	Through tattooing and ear piercing (%)	Sexual abuse/ sex related (%)	Through barbing (%)	Through non sterile needle (%)	Unidentified source (%)	Total
0.2 – <1	24(25.8)	0(0.0)	2(2.15)	0(0.0)	0(0.0)	0(0.0)	1(1.1)	27(29.0)
1 - < 3	25(26.9)	2(2.15)	1(1.1)	0(0.0)	1(1.1)	0(0.0)	1(1.1)	30(32.3)
3 - < 5	14(15.05)	2(2.15)	0(0.0)	0(0.0)	1(1.1)	1(1.1)	2(2.15)	20(21.5)
5 - 15	2(2.15)	1(1.1)	0(0.0)	4(4.3)	3(3.2)	3(3.2)	3(3.2)	16(17.2)
Total	65(69.9%)	5(5.4%)	3(3.2%)	4(4.3%)	5(5.4%)	4(4.3%)	7(7.5%)	93(100%)

Table 3. Distribution of skin lesions in HIV infected children by WHO clinical staging.

Skin manifestations	Severe Immune Suppression	Advanced Immune Suppression	Mild Immune Suppression	Total
Puritic papular eruption	19	9	-	28 (30.1)
Impetigo/boil	4	6	2	12 (12.9)
Cutaneous candidiasis	6	5	-	11 (11.8)
Seborrheic Dermatitis	5	3	-	8 (8.6)
Flat warts	2	4	-	6 (6.5)
Herpes stomatitis	4	1	-	5 (5.4)
Molluscum contagiosum	4	1	-	5 (5.4)
Scabies	1	2	2	5 (5.4)
Tinea capitis/corporis	2	1	1	4 (4.3)
Herpes zoster	-	2	-	2 (2.2)
Drug reaction	2	-	-	2 (2.2)
Peri-anal wart	2	-	-	2 (2.2)
Kaposi Sarcoma	1	-	-	1 (1.1)
Cancrum oris	1	-	-	1 (1.1)
Chicken pox	1	-	-	1 (1.1)
Total	54 (58.1%)	34 (36.5)	5 (5.4)	93(100.0)

sterile/reused needles were seen in 4.3% each. The source of infection was unidentified in 7.5% of cases.

Skin lesions in HIV infected children and WHO clinical staging

The distribution of skin lesions according to WHO clinical

staging is shown in Table 3. While three commonest skin disorders seen in HIV positive patients were puritic papular eruption (30.1%), impetigo/boil (12.9%), and cutaneous candidiasis (11.8%), chicken pox, Kaposi sarcoma (figure 3a), and cancrum oris (1.1%) each were the rarest skin disorders seen. The mean duration of these skin lesions at presentation was 5.3 ± 2.6 months. Puritic papular eruption (PPE), cutaneous candidiasis,

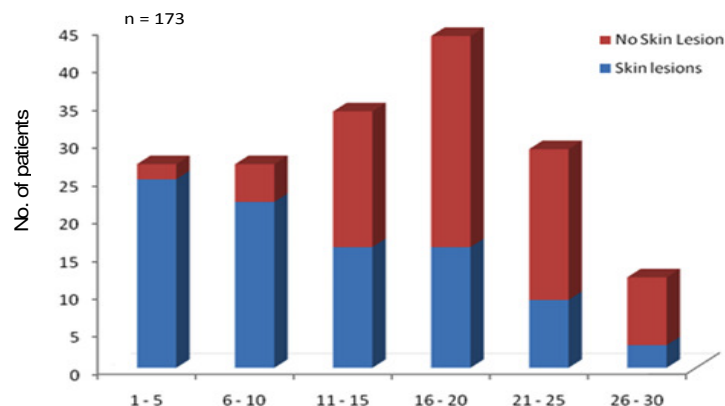


Figure 1. Skin findings and CD4 cell percentage of total lymphocyte count among HIV positive children.



Figure 2a. Infected Florid Molluscum Contagiosum.

empetigo/boil, herpes stomatitis/zoster, extensive florid molluscum contagiosum were seen more in patients with severe as well as advanced immune suppression, while tinea corporis/capitis and scabies were commoner in those with mild immune suppression. Skin disorders were statistically commoner in patients with severe ($\chi^2 = 29.7$, $p < 0.001$) and advanced ($\chi^2 = 24.8$, $p < 0.001$) immune suppression than in those with mild suppression (5.4%). The two drug reactions seen were a case of Steven Johnson syndrome following co-trimoxazol ingestion for opportunistic infection, and one case of generalized erythematous vesico-papular skin eruption after nevirapine administration. PPE, the commonest skin manifestation in HIV children in this study, showed histological features of superficial and mid-dermal perivascular and perifollicular mononuclear cell infiltrates interspersed with eosinophils with various degree of follicular damage. Patient with florid Molluscum contagiosum (Figure 2a) histologically showed flask shaped craters with red eosinophilic molluscum bodies. There are focal areas of hyperplasia

and keratinocyte containing molluscum bodies at various stages of maturation (Figure 2b). The patient that presented with Kaposi sarcoma also had fungating infiltrative lesion of both lower extremities, worse on the left leg with massive lymphoedema (Figure 3a). Histology report shows proliferating spindle shaped cells, separated by slit like spaces, some with red blood cells and hyperchromatic nuclei. Most of the vascular like spaces are not lined by endothelial cells, and there is no abnormal mitotic figure (Figure 3b). Patients with impetigo/boils cultured mainly *staphylococcus aureus*, and *pseudomonas areuginosa*. One patient, whose isolate showed *pseudomonas areuginosa*, had severe neutropenia and ecthyma gangrenosum. All patients responded to antibiotics. Because of our laboratory limitations, bacteria serotype, viral, and parasitic cultures were not done.

Skin lesions and CD4 cell count in HIV infected children

Table 4 showed the number of patients, their skin lesions with corresponding CD4 percentage and WHO clinical staging. Number of skin lesions increased as the CD4 percentage of total lymphocytes decreased, as well as when the WHO clinical stage increased. Multiple skin lesions were found to be commoner in patients with very low CD4 cell percentage. Those with two or more skin lesions had a corresponding CD4 cell percentage of 10.5 and 4.1%, respectively.

Figure 1 is a graphical representation of patients and their CD4 percentage of the total lymphocyte count. Patients with very low CD4 percentage had more skin lesions than those with higher CD4 percentage. Figures 2a and 3 are pictorial representation of cutaneous lesions seen in two HIV positive children, while Figures 2b and 3b are histology features of patients with PPE and Kaposi

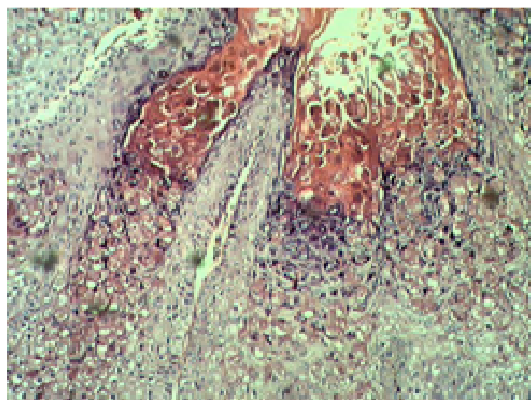


Figure 2b. Histology of florid Molluscum Contagiosum showing flask shaped craters with red eosinophilic molluscum bodies.



Figure 3a. Kaposi sarcoma involving the left foot showing exophytic, disquamated, dirty yellowish brown, hyperkeratotic nodular skin lesions.

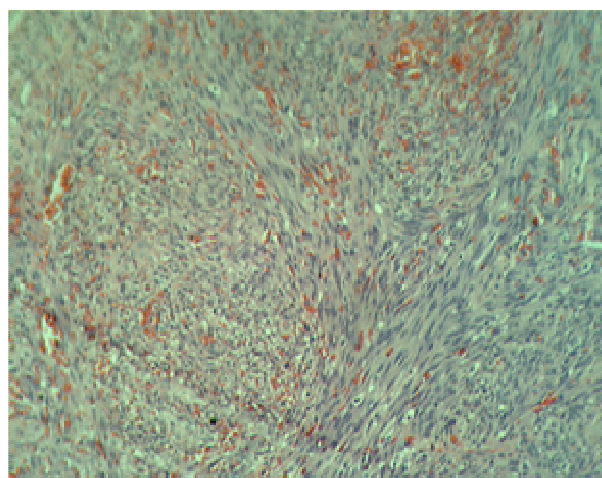


Figure 3b. Histology of Kaposi sarcoma showing fibro vascular lesion of proliferating spindle cells forming slit like spaces containing red blood cells

Table 4. Number of skin lesion, CD4 cell count and WHO clinical staging.

No. of skin lesions	Frequency	CD4%	Clinical stage
1	18 (19.4)	15.8	2,3
2	41 (44.1)	10.5	3,4
3	34 (36.5)	4.1	4

sarcoma. Figure 2 represents infected extensive Molluscum contagiosum in HIV positive girl, while Figure 3 is Kaposi sarcoma of the left leg also in a positive child.

DISCUSSION

Cutaneous manifestations in HIV infected children in this study were mostly inflammatory and infectious in nature. They are more wide spread, and respond less to conventional therapy. The study not only documents high prevalence (52.2%) of skin disorders among the infected children, but also shows skin lesion to be commoner in those with severe (58.1%) and advanced (36.5%) immune suppression. The prevalence of 52.2% observed was comparable to 51.6 and 53.0% by Wananukul et al. (2003), Co et al. (1990) and 46.0% by El Hachem et al. (1998). It was, however, lower than 69 and 80.0% reported by Muñoz-Pérez et al. (1998) and Martinez-Rojano et al. (2000).

Several dermatological disorders have been associated with HIV infection in children (Rongkavilit et al., 2000; Stefanaki et al., 2002; Nance et al., 1991; Wananukul et al., 1999; Wananukul et al., 2003; Lim et al., 1990; Hachem et al., 1998; Mysowski et al., 1996; Martinez-Rojano et al., 2000). The pattern also varies from region to region. Most researchers have reported infective conditions especially of fungal origin as the leading cause of skin disorders in most HIV infected children and adults (Stefanaki et al., 2002; Nance et al., 1991; Wananukul et al., 1999; Wananukul et al., 2003). The present study noted inflammatory conditions, PPE (30.1%) as the commonest skin lesion among their study population. It was also described as the commonest skin manifestation in HIV infected adults and children in Haiti, most African and Asian countries (Mysowski et al., 1996; Martinez-Rojano et al., 2000; Co et al., 1990; Goh et al 2007)). The etiology of this disease still remains unknown. However, the finding of similar density of the lesion on the exposed and unexposed part of the skin excludes insect bite reaction, but may suggest a generalized type of hypersensitivity reaction to arthropod (mosquito) salivary gland product similar to what is seen in papular urticaria, or it may be as a result of direct effect of HIV infection. Other workers, however, consider it a variant of eosinophilic folliculitis, which is a chronic eruption of multiple sterile, pruritic follicular and non-follicular

erythematous papules and papulopustules involving the face, trunk and extremities, and usually seen in patients with CD4 cell count of less than 100 cells/mm³, and a good marker for deteriorating immune function. This is believed to be a form of hypersensitivity of the skin to *demodex folliculorum* mite, a normal commensal of the hair follicle. PPE runs a chronic course and does not respond to either antihistamine or steroids, but most improves on starting highly active antiretroviral drugs (HAART).

Bacterial infection in form of impetigo/boil was seen in 12.9% of HIV-infected patients. Wananukul et al. (2003) reported 7% in their study population, while Safi Eldein El Nour (2004) documented 13.3% among their adult population. *S. aureus* was the predominate organism isolated from them (impetigo/boils and furuncles); *p. aruginosa* was isolated from one patient. All patients responded to conventional antibiotics. Cutaneous candidiasis was the next commonest skin lesion seen in 11.8% of patients in the present study. Candidiasis, involving the mucous membrane, has been reported as the most common muco-cutaneous manifestation in HIV patients infected children (Wananukul et al., 1999; Wananukul et al., 2003). Most of the patients responded to clotrimazole cream and oral fluconazole. Recurrent rate was not high especially after commencement of HAART.

Seborrheic dermatitis is another common (8.6%) inflammatory chronic papulosquamous disorder found in HIV-infected children in this study. In the dark skin, they appeared as a diffused hypopigmented patches, which sometimes coalesce to form polycyclic lesions or eczematous patches with follicular papules. It is mostly seen in the scalp, face, axillae, trunk and genital region or in the groin. Seborrheic dermatitis is one of the most cutaneous manifestations in adult HIV patients (Mysowski et al., 1996; Ray et al., 1994; Reymanud-Mendel et al., 1996), sometimes seen in 40-83% of cases. The etiology of the disease is unclear but the yeast, *pityrosporum ovale* has been incriminated. Under appropriate condition like immune suppression, the saprophytic yeast is converted to pathogenic mycelia phase which causes clinical disease. The cause of the hypopigmentation is also not clear, but the extract from *P. ovale* culture containing C9-11 dicarboxylic acid that competitively inhibits tyrosinase has been incriminated. Relapse is common and most patients responded to antifungal agents, steroid cream or sulphur containing ointments. This type of lesion was seen predominantly in patient with moderate immune suppression. Flat warts (6.5%), herpes stomatitis (5.4%), and 2 cases of perianal warts were the commonest viral skin lesion seen in children with severe and advanced immune suppression, most improved with anti-viral agents and after the commencement of antiretroviral drugs. Drug reactions found to be common among adult patients with advanced/severe immune-suppression from other studies (Muñoz-Pérez et al 1998;

Goh et al 2007) were not very common in children in this study; only 2 cases was recorded in severe immune-suppression patients. The rarity of skin tumours in positive children in this study was also reported by others among adult population (Goh et al., 2007; Muñoz-Pérez et al., 1998). Only one case of Kaposi sarcoma was seen in an older boy who responded well to cytotoxic drugs and HAART.

Patients (both children and adults) with low CD4 cell count were noticed to have more skin lesions (Muñoz-Pérez et al., 1998; Goh et al., 2007; Carvalho et al., 2008; Co et al., 1990; Lim et al., 1990; Wananukul et al., 2003). Similar finding was also seen in this study where 58.1% of patients with severe immunosuppression had different forms of skin manifestations, and greater than 30% had more than two skin manifestations. Skin, as a primary T-cell organ, has CD4 cell antigen receptor, and a potential target site for HIV infection. The pattern of immune dysregulation in HIV infected individual may provide an accurate measure of disease progression (Cockerell, 1994; Raju et al., 2005). Thus, the numerical decrease in CD4 cell with severe or advanced immunosuppression could probably explain the frequent and multiple skin lesions seen in this organ in this group of patients.

CONCLUSION

Skin disorder is common in HIV infected children in this environment, and appeared similar with findings elsewhere. Its prevalence, multiplicity and severity was directly related to the degree of immunosuppression, and most improved on HAART with minimal recurrent rate especially when adherence to HAART is good.

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Appendix

Revised WHO Clinical Staging of HIV/AIDS for Infants and Children.

Clinical Stage 1 (Asymptomatic)

Asymptomatic stage, persistent generalized lymphadenopathy or hepatosplenomegaly.

Clinical Stage 11 (Mild)

Disease is manifested by unexplained persistent generalized lymphadenopathy, ~~papular~~ puritic papular eruptions, extensive warts viral infections, extensive molluscum contagiosum, seborrhea dermatitis, recurrent oral ulcers, unexplained persistent parotid enlargement, lineal gingival erythema, herpes zoster, recurrent/ chronic upper respiratory infections (otitis media, otorrhoea, sinusitis), fungal nail infections.

Clinical Stage 111 (Advanced)

Features include unexplained moderate malnutrition not responding to standard therapy, unexplained persistent diarrhea (14 days or more), unexplained persistent fever ($>37.5^{\circ}\text{C}$, intermittent/ constant, $>1\text{month}$), persistent oral candidiasis ($> 1^{\text{st}}$ 6 weeks of life), oral hairy leukoplakia, lymph node tuberculosis, pulmonary tuberculosis, acute necrotizing ulcerative gingivitis/periodontal, severe recurrent bacterial pneumonia, lymphoid interstitial pneumonitis, unexplained anemia ($<8.0\text{g /dl}$), neutropenia ($<0.5 \times 10^9/\text{l}^3$), chronic thrombocytopenia ($<50 \times 10^9/\text{l}^3$).

Clinical Stage 1V (Severe)

Consist of unexplained severe wasting or severe malnutrition not responding to standard treatment, pneumocystic pneumonia, recurrent severe bacterial infections (e.g emphysema pyomyositis, bone or joint infection but excluding pneumonia), chronic herpes simplex infection (orolabial or cutaneous $>1\text{month}$ or visceral at any site), extra pulmonary tuberculosis, Kaposi sarcoma, esophageal candidiasis (or candida of the trachea, bronchi or lungs), central nervous system toxoplasmosis (after the neonatal period), HIV encephalopathy, cytomegalovirus virus infection: retinitis or infection affecting another organ with onset $>1\text{month}$), extra pulmonary cryptococcosis (including meningitis), disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidiomycosis), chronic cryptosporidiosis (with diarrhea), chronic isosporidiosis, disseminated non-tuberculous mycobacterial infection, cerebral or B cell non-Hodgkin lymphoma, progressive multifocal leucoencephalopathy, HIV associated cardiomyopathy or nephropathy, and HIV associated recto-vaginal fistula.