EAR, NOSE AND THROAT - HEAD AND NECK MANIFESTATIONS AND EFFECT OF ANTIRETROVIRAL THERAPY IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN CHILDREN.

A CASE CONTROL STUDY.

A thesis submitted in part fulfillment of the requirements for the Degree of Masters of Medicine in Ear, Nose and Throat-Head and Neck Surgery, at the University of Nairobi 2007.

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DECLARATION

This is my original work and has not been presented for a degree in any other university.

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ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AOM	Acute otitis media
ART	Antiretroviral therapy
CD	Cluster of differentiation
CSOM	Chronic suppurative otitis media
ENT-HN	Ear, Nose and Throat - Head and Neck
FNAC	Fine needle aspirate cytology
HIV	Human immunodeficiency virus
KS	Kaposi's sarcoma
MTCT	Maternal to child transmission
NHL	Non- Hodgkin's lymphoma
PCR	Polymerase chain reaction
PGL	Persistent generalized lymphadenopathy
SPSS	Statistical package for social sciences
UON	University of Nairobi
WHO	World Health Organization

ABSTRACT

Background: HIV/AIDS has had a huge negative impact on the morbidity and mortality of the Kenyan paediatric population. A high number of these children may present to the otorhinolaryngologist even before the diagnosis of HIV has been made.

Objectives: The main aim of this study was to determine the ENT-HN manifestations and effect of antiretroviral therapy (ART) in HIV-infected children seen in Kenyatta National Hospital (KNH). The study also sought to correlate ENT-HN manifestations in HIV-infected children with the immunological stage of HIV disease.

Design: Case control study.

Setting: Kenyatta National Hospital.

Methods: There were three study groups each with 115 HIV-infected children. The first group comprised of ART-naive children. The second group was made up of children on ART for not more than 6 months while the third group comprised of those children who had been on ART for more than 6 months. Diagnosis of the various manifestations was made clinically and through FNAC where necessary. Each patient had HIV clinical and immunological staging using the WHO recommendations. Correlation between the ENT-HN manifestations and use of ART was made. In the ART-naïve patients, correlation was made between these manifestations and the HIV immunological stage.

Results: At least one ENT-HN manifestation was observed in 56.5% of ART-naïve children, 42.6% of children on ART for not more than 6 months and 38.3% of those who had been on ART for more than 6 months. The commonest manifestations in ART-naïve children were oral candidiasis (13.9%), cervical lymphadenopathy (10.4%), papulo pruritic dermatitis (10.4%), acute recurrent rhinosinusitis (9.6%) and chronic bilateral parotitis (8.7%). Use of ART beyond 6 months was found to significantly reduce the prevalence of oral candidiasis, chronic bilateral parotitis, cervical lymphadenopathy and papulo pruritic dermatitis. Initiation of ART was associated with a significant increase in the prevalence of CSOM within the first 6 months of therapy. In the ART-naïve children, the study showed that oral candidiasis was significantly associated with severe immunosuppression.

Conclusions: Children with HIV infection commonly present with unusual ENT-HN diseases such as oral candidiasis, cervical lymphadenopathy, chronic bilateral parotitis and papulo pruritic dermatitis. Use of ART is significantly associated with a reduction of these manifestations. CSOM may be a component of immune reconstitution inflammatory syndrome.

INTRODUCTION

In 1981, doctors in New York, San Francisco and Los Angeles noted a number of young homosexual men who were diagnosed with a number of diseases typically associated with impaired immune system. Later on a similar clinical presentation was seen in haemophiliacs and intravenous drug users. This clinical pattern was named Acquired Immunodeficiency Syndrome (AIDS). By 1984, scientists at the Pasteur Institute in Paris, National Cancer Institute and University of California, San Francisco had separately identified a retrovirus as the cause of AIDS which they respectively named lymphadenopathy associated virus (LAV), human T-cell lymphotrophic virus (HTLV) III and AIDS associated virus (ARV). In 1986, the International Committee for the Taxonomy of Viruses named it Human Immunodeficiency Virus (HIV) (1).

HIV/AIDS has spread rapidly to affect the whole world. The sub-Saharan Africa with 10% of the World's population accounts for 60% of the global AIDS cases (2). In Kenya, the most affected are women in the age group 15-49 years hence an increasing number of children with vertically transmitted HIV infection (3). The pandemic is mainly spread by the HIV type 1 variant (HIV-1) with the HIV-2 being confined mainly in Western Africa. Unless otherwise indicated in this study, all mention of HIV refers to HIV-1.

About half of the children with HIV presents with Ear, Nose and Throat-Head and Neck (ENT-HN) manifestations (4). For some of these children the otorhinolaryngologist is the first clinician to encounter them. This study documents the prevalence of the various ENT-HN manifestations in HIV and the effect of antiretroviral therapy among the Kenyan paediatric population.

PATHOPHYSIOLOGY OF HIV

HIV is a RNA virus belonging to the family retroviridae. It is cytolytic to a subset of T-lymphocytes, which express the cluster of differentiation (CD) 4 antigen. These CD4+ T-lymphocytes are functionally T-helper cells and are central to both humoral and cell mediated immunity. They mediate antigenic stimulation of antibody production by β-lymphocytes and also influence the functions of other T-cells, macrophages and natural killer cells (5, 6).

The glycoprotein gp 120 on the viral envelope binds to the CD4 antigen on the surface of the T-lymphocyte leading to internalisation of the virus. Inside the cell, the viral enzyme reverse transcriptase synthesizes viral DNA from the viral RNA, which is then integrated into the host DNA by the viral enzyme intergrase. The host's cellular and biochemical mechanisms are then used to synthesize viral RNA and proteins, which assemble to form more viral particles. This replication leads to cell lysis with release of newly formed viral particles, which infect other T-lymphocytes (5). The decline in CD4+ T-lymphocytes in HIV infection is further contributed by the cytotoxic CD8+ T-lymphocytes, which kill both infected CD4+ T-cells expressing the gp 120 and uninfected CD4+ T-cells coated with soluble gp 120 (6). HIV causes polyclonal activation of β lymphocytes leading to a non-specific hypergammaglobulinaemia. The end result of these immunological changes is a decline of both humoral and cell mediated immunity and impaired proliferative responses of T lymphocytes to specific antigen stimulation (5).

Secondary to the impaired humoral immunity and an immature immune system, HIV infected children are overwhelmingly prone to infections by capsulated bacteria especially Streptococcus pneumonia. They also manifest with opportunistic infections caused by viruses such as Herpes simplex virus (HSV) and Cytomegalovirus (CMV); bacteria such as Mycobacterium, Campylobacter; fungi such as Candida, Aspergillus and protozoa such as Pneumocystis carinii and Toxoplasma gondii (7, 8, 9, 10).

HIV transmission and progression in children

Transmission of the HIV occurs through sexual contact, mother to child transmission (MTCT) or vertical transmission, blood transfusion or through use of or accidental injury by

contaminated needlesticks. Over 90% of the infections in children are through MTCT (4). This can occur prenatally during pregnancy, perinatally during labour or delivery and postnatally through breast miik.

All children born to HIV infected mothers are positive for the HIV antibody. However, not all are infected by the virus. In a Kenyan study, 36.7% of children born to HIV infected mothers and breastfed were ultimately infected by two years of age (11). Advanced maternal disease characterised by a high viral load and low CD4+ T-cell count increases the risk of prenatal transmission (12, 13). Obstetric factors such as prolonged rupture of membranes, episiotomy and vaginal lacerations increase the risk of perinatal transmission (14). Breast-feeding increases the risk of postnatal transmission by 14-29% (11, 15). In the resource rich nations, HIV positive mothers are advised against breastfeeding but in resource poor countries such as Kenya, mortality during the first two years of life in formula fed infants born to HIV positive mothers was found to be similar to that in breastfed infants born to HIV positive mothers (16).

In vertically infected children, the disease has a bimodal course with a rapid progression and mortality before the age of two years and a lower progression thereafter. In a local prospective cohort study, death occurred in 52% of children before the age of 2 years and the median age of death was 6.2 months. The leading cause of death was pneumonia and diarrhoeal diseases (17, 18). Maternal factors associated with rapid disease progression are advanced maternal disease, low haemoglobin level during pregnancy and maternal death. Infant factors associated with rapid progression and early mortality are high viral load, CD4+ T-cell percentage of less than 15, low birth weight and early onset of HIV related symptoms (18).

Parallel to the clinical course, immunological changes do occur. CD4+ T-cell count declines progressively with age in the general population and is significantly lower in HIV-infected children. The percentage of CD8+ T-cells increases progressively regardless of the disease stage (19). On the basis of this abnormal CD4+ T-cell decline in HIV infection, the World Health Organization (WHO) has developed guidelines on the immunological staging of paediatric HIV disease (Appendix III).

EPIDEMIOLOGY OF HIV

Globally, the number of people living with HIV by end of 2005 has been estimated to be between 33.4 and 46.0 million. Amongst these, 2.3 million are children with more than 60% of them living in sub-Saharan Africa. The number of Kenyans living with HIV by the end of 2005 was 1.5 million of whom 150,000 were children (2).

CLINICAL FEATURES

HIV infected children commonly present with frequent infections, growth and developmental abnormalities. They exhibit an increase in the frequency and severity of common bacterial infections of childhood such as pneumonia and otitis media in association with a high incidence of opportunistic infections such as Pneumocystis carinii pneumonia and oropharyngeal candidiasis. Viral infections such as Cytomegalovirus (CMV) chorioretinitis and orolabial Herpes simplex are also seen more frequently than in the general paediatric population (7, 8, 18, 20).

Non-infectious manifestations commonly seen are weight loss or failure to thrive, persistent generalised lymphadenopathy (PGL), hepatosplenomegally and delayed milestones (4,8). An increase in the incidence of childhood malignancies specifically that of non-Hodgkin's lymphoma (NHL) has been observed (21). The WHO has developed a clinical staging system of paediatric HIV infection based on the various manifestations (Appendix III).

EAR, NOSE AND THROAT-HEAD AND NECK (ENT-HN) MANIFESTATIONS

About 50% of children with HIV infection present with ENT-HN illnesses, with 55% presenting with their first symptom before the age of 3 years and 98% by the age of 9 years (4). Previously documented manifestations are as follows: -

Ear

External ear: An increased risk of developing acute otitis externa and malignant otitis externa is seen due to reduced cellular immunity, eczema, papulo-pruritic dermatitis and seborrhoeic dermatitis. As in the general population, the primary aetiological agent is Pseudomonas aeruginosa (8). These children present with otalgia, erythema of the pinna and external auditory canal and the external auditory canal may be partially occluded by oedema, seropurulent discharge and cellular debris. Malignant otitis externa may cause petrositis or erosion of the temporal bone with paralysis of the seventh and eighth cranial nerves (22). Pneumocystis carinii infection of the ear is only seen in HIV infection and in the external auditory canal, presents as a polyp. Aspergillus and Candida species are the commonest cause of otomycosis. Candida presents with itching, canal erythema and a whitish fungal material while Aspergillus will present with black fungal material or as a malignant otitis externa (9, 22).

Middle ear: Acute, chronic and serous otitis media are prevalent in HIV infected children due to the underlying immunosuppression, sinonasal disease and adenoid hypertrophy (8, 23). Acute otitis media (AOM) is commonly seen in young children while serous otitis media is seen more commonly in older children and adults. Incidence of AOM is twice in those children with CD4+ T-cell count of less than 1500/mm^3 during the first 3 years of life (24). Affected children present with otalgia, irritability, fever and on examination they may have tenderness over the mastoid, an inflamed, bulging tympanic membrane and purulent external auditory canal discharge if the tympanic membrane has already perforated. Organisms isolated in HIV infected children are similar to those in the general paediatric population though a higher incidence of Staphylococcus aureus has been found in the severely immunosuppressed patients (23, 25). Chronic suppurative otitis media (CSOM) is characterised by persistent discharge or perforation for more than 14 days. Majority of these cases in HIV infection are due to mixed organisms, most commonly being Pseudomonas aeruginosa, followed up by Proteus mirabilis (8). Opportunistic infections are also caused by Pneumocystitis carinii, which presents with otalgia, otorrhoea, hearing loss and an aural polyp and Aspergillus fumigatus presenting as an invasive infection of the middle ear with involvement of seventh and eighth cranial nerves (9, 22).

Inner ear: CSOM and other invasive infections of the middle may spread to the inner ear causing labyrinthitis or erosion of the sensory structures. This presents as tinnitus, vertigo and sensorineural hearing loss (22). Hearing loss has also been showed to be due to HIV labyrinthitis or neuronitis and secondary to central nervous diseases such as cryptococcal meningitis. This hearing loss can either be sudden or progressive (26, 27).

Nose and paranasal sinuses

The prevalence of rhinosinusitis in the HIV infected population has been reported to be as high as 70% (28). As a result of polyclonal activation of β-lymphocytes, there is an increase in immunoglobulin E levels. This presents as atopy, which predisposes to allergic rhinosinusitis and chronic sinusitis. Due to impaired immunity and mucociliary dysfunction, the spectrum of causative organisms is wider and the symptoms more prolonged and severe. With CD4+ T-cell counts above 200/mm^3, the patient commonly presents with features of acute rhinosinusitis. With CD4+ T-cell counts below 200/mm^3, the symptoms become prolonged and more sinuses get involved hence the clinical picture changes to that of chronic sinusitis. Fungal sinusitis is most commonly due to Aspergillus fumigatus and this is seen with CD4+ T-cell count of less than 50/mm^3. This may present as a unilateral nasal discharge not responding to antibiotic therapy, facial paraesthesia and proptosis (29, 30).

The diagnosis of paediatric rhinosinusitis is made on clinical basis. The Consensus Panel on Paediatric Rhinosinusitis has defined acute rhinosinusitis as presence of rhinorrhoea of any quality, nasal congestion, headache or facial pain with or without irritability or fever for less than 12 weeks in the absence of an upper respiratory tract infection. Chronic rhinosinusitis is defined as the presence of these symptoms and signs for more than 12 weeks (31).

Oral cavity

Oral candidiasis occurring outside the neonatal period is one of the commonest manifestations of paediatric HIV infection (4, 8). Four clinical variants namely pseudomembranous (classical thrush), atrophic, hyperplastic and angular cheilitis may be seen. In pseudomembranous candidiasis, the lesions can be scraped off, leaving an erythematous bleeding base. Atrophic candidiasis presents as zones of hyperaemia on the tongue or hard palate while hypertrophic candidiasis presents as raised white plaques on the tongue dorsum that cannot be scraped off. Angular cheilitis will present as tender erythematous ulcerations at the angle of the mouth.

Oral hairy leukoplakia, rarely seen in children, is associated with Epstein Barr virus (EBV) and presents as white patches on the lateral border of the tongue that are not removable by scraping (32). Opportunistic infections caused by CMV, EBV and Herpes simplex virus have been documented in a significant number of children with HIV infection. They may be asymptomatic or present as oral mucosal ulcerations. Herpes infection in these patients is likely to be more persistent and have less localized lesions (10).

Pharynx and Larynx

As the immune status declines, the candidiasis initially noted in the oral cavity spreads to involve the oropharynx, oesophagus, larynx and trachea. The child presents with odynophagia, dysphagia and hoarseness. The generalised lymphoid hyperplasia seen in HIV may involve the lymphoid tissue of Waldeyer's ring leading to adenoid hypertrophy, which may predispose to serous otitis media. As in other infections, the incidence of upper respiratory tract infections and tonsillitis is increased with HIV. Examination of the oropharynx may reveal generalised inflammation with tonsillar hypertrophy as a result of lymphoid hyperplasia (4, 7, 8).

Head and Neck

Cervical lymphadenopathy: Cervical lymphadenopathy and oral candidiasis have been documented as the most common ENT-HN manifestations of HIV infection in children (4,8). The lymphadenopathy usually occurs as a component of PGL. PGL occurs early in HIV infection and is defined as lymphadenopathy involving 2 or more extra-inguinal nodal sites for more than 3 months in the absence of an infection or neoplastic disease. These nodes are usually symmetrical, asymptomatic and less than 2cm in diameter. In the ENT-HN region, the posterior cervical triangle is most commonly affected. Histologically, the nodes show a reactive hyperplasia similar to that seen in other viral infections such as infectious mononucleosis (33).

Other infectious and neoplastic causes of lymphadenopathy should be ruled out. Lymphadenitis due to pyogenic organisms will have an acute onset and the lymph node will be tender on palpation. The child may have an obvious focus of infection and be febrile. Tuberculous adenitis is commonly seen in paediatric HIV infection and presents as a unilateral painless firm swelling in the posterior triangle (34). A chest X-ray may reveal concurrent pulmonary tuberculosis. Fine needle aspirate cytology (FNAC) shows a granulomatous reaction and at times may reveal the acid-fast bacilli on Ziehl-Neelsen staining. Nontuberculous mycobacteria cause lymphadenitis in the submandibular, upper jugular and pre-auricular regions. They do not resolve on antituberculosis therapy. Culture of the lymph node specimen may be necessary to differentiate these from Mycobacterium tuberculosis (35). A non-tender

enlarging cervical node may be due to a malignancy such as NHL or KS (36, 37). If a lymphoma is diagnosed on FNAC, an open biopsy should be done to confirm the histological type.

Salivary glands: Benign parotid disease presenting as bilateral parotid enlargement occurs in upto 30% of paediatric HIV infected patients (7, 8, 38). Histological spectrum of the disease ranges from benign lymphocytic infiltration of the gland parenchyma to benign lymphoepithelial cyst. The former is commoner in children (39). Parotid enlargement may also be due to benign and malignant lymphoproliferative processes in the intraparotid lymph nodes such as PGL and lymphomas (33, 36).

Non Hodgkin's Lymphoma (NHL): Between 0.9-1.4% of children in Europe and United States of America present with NHL as the first AIDS indicator disease (40). NHL occurs in advanced HIV disease. Among HIV infected children below 5 years in the United Kingdom, the incidence is estimated as 2,500 times greater than in the non-infected population. This high incidence is attributed to reduced immune surveillance and activation of other viruses particularly the EBV (21). Patients present with a unilateral, painless and progressively enlarging mass. In the head and neck region, it commonly arises from the cervical lymph nodes. Extra-nodal sites of origin include mandible, oral cavity, paranasal sinuses, oropharynx and nasopharynx. Majority of NHLs associated with HIV are high-grade B cell lymphomas (36, 41). FNAC may show the various lymphoma cells but tissue biopsy is mandatory in determining the histological type. Due to the high rate of dissemination, bone marrow aspirate and cerebrospinal fluid cytology are necessary to determine spread of the disease.

Kaposi's sarcoma (KS): The epidemic type is associated with HIV. This type is more aggressive, responds poorly to treatment and has a higher rate of recurrence. It occurs in the mucosal surfaces of the oral cavity, skin and lymph nodes (37). It is mainly seen in homosexual men with HIV infection and is now known to be caused by the Kaposi's sarcoma herpes virus (KHSV) (42). Studies done in Kenya have failed to show an increase in KS among paediatric HIV patients (43, 44). Clinically, cutaneous KS presents as multiple purple- red macular lesions that are non-tender and non-blanching. Mucosal KS presents with pain, ulceration and bleeding. Histology shows spindle cell proliferation with slit-like vascular channels. Biopsy can be attended by worrisome bleeding.

Facial Nerve Paralysis: This can occur as an isolated facial nerve palsy or may be accompanied by other cranial neuropathies and neurological abnormalities. Facial nerve paralysis with other cranial neuropathies may be associated with meningitis, progressive multifocal leucoencephalopathy, toxoplasmosis and CNS lymphomas (26). Treatable causes of facial nerve paralysis such as malignant otitis externa, CSOM and parotid tumours are ruled out through physical examination.

Herpes Zoster: This presents as painful skin vesicles along one or more dermatomes. It is due to reactivation of a latent Varicella zoster virus secondary to decreased cellular immunity. In the Ramsay Hunt syndrome, it affects the geniculate ganglion leading to facial nerve paralysis, skin vesicles on the pinna, retroauricular region and external auditory meatus. Involvement of the trigeminal ganglion will present with painful vesicles on the face, lips, palate and gingiva.

Skin Manifestations: These are not specific to the head and neck region but may involve any area of the body. They include bacterial skin infections, papulo-pruritic dermatitis and seborrhoeic dermatitis. In the head and neck region, seborrhoeic dermatitis has a predilection for the postauricular, nasal and malar regions (45). Oral-facial molluscum contagiosum has been found to be highly prevalent in institutionalised paediatric HIV patients (46).

ENT-HN MANIFESTATIONS OF HIV AND STAGING OF HIV DISEASE

In the Revised WHO Staging of Paediatric HIV/AIDS Disease (Appendix III), specific ENT-HN manifestations are related to specific stages as follows: -

Table i: ENT-HN manifestations and staging of HIV disease.

WHO stage 1	• Persistent generalised lymphadenopathy
WHO stage 2	• Angular cheilitis • Linear gingival erythema • Recurrent oral ulcerations • Extensive human papilloma virus or molluscum infection (> 5% of body surface/face) • Parotid enlargement • Recurrent or chronic upper respiratory tract infection: Otitis media, otorrhoea or sinusitis (>2 episodes/6 months)
WHO stage 3	• Oral candidiasis (outside the neonatal period) • Oral hairy leukoplakia • Acute necrotizing ulcerative gingivitis/periodontitis
WHO Stage 4	• Chronic orolabial or cutaneous Herpes simplex virus (lasting more than 1 month) • Extra-pulmonary tuberculosis • Kaposi's sarcoma • Oesophageal candidiasis • Candida of trachea, bronchi or lungs • B-cell NHL

EPIDEMIOLOGY OF ENT-HN MANIFESTATIONS IN HIV INFECTED CHILDREN

Singh A et al, in 2003 (4) reviewed case files of 107 HIV seropositive children in the paediatric HIV unit of St. Mary's Hospital, London. Fifty percent of the children had ENT-HN illnesses. Fifty five percent presented with their first ENT-HN symptom before the age of 3 years and 98% had ENT-HN manifestations by 9 years. Amongst the ENT-HN manifestations lymphadenopathy comprised (70%), otitis media (46%), oral candidiasis (35%) and adenotonsillar disease (31%).

Makokha EP et al, in 2003 (7) did a prospective cohort study on 52 children aged 4.5 to 13 years with vertically transmitted HIV-1 infection in Cottolengo Children's Home, Nairobi. The commonest illnesses among them were; URTI (85.3%), pneumonia (56.2%), TB (56.1%) tonsillitis (34.1%), parotitis (28%) and acute otitis media (25%). They also found that the occurrence of TB, acute otitis media and parotitis significantly correlated with decreased CD4+ T-cell count while that of URTI was independent of the CD4+ T-cell count.

Chaloryoo S et al, in 1998(8) did a retrospective study on AIDS in ENT in children at the Children's Hospital, Thailand between January 1992 and December 1995. Two hundred and fifty children diagnosed to have HIV were evaluated. Their results on prevalence were as follows; oral candidiasis (59.6%), cervical lymphadenopathy (41.6%), upper respiratory tract infection

(39.5%), otitis media (18.4%), parotitis (5.2%), sinusitis, hoarseness, candida oesophagitis (or tracheitis) and delayed speech (0.8%) each. Of the 14 cases of parotitis diagnosed, 13 of them were bilateral. As a follow-up to the same study, 50 HIV positive children were randomly sent to the ENT outpatient department for ear examination between February and June 1996. Fourteen patients (28%) were found to have acute otitis media (AOM) and 5 patients (10%) were found to have chronic suppurative otitis media (CSOM).

The Singh A et al and Chaloryoo S et al studies were both retrospective. These studies just documented the ENT-HN manifestations in children with HIV and they did not correlate those manifestations to the clinical and immunological stage of the disease. The study done by Makokha EP et al related the clinical manifestations with the immunological stage of HIV disease. However, the sample size of this study was only 52 children. None of these studies has looked at the effects of antiretroviral therapy (ART) on the ENT-HN manifestations in HIV infected children.

The main findings of these studies and others that have been done to determine the epidemiological patterns of the various ENT-HN manifestations in HIV-infected children are tabulated below: -

Table ii: Epidemiology of ENT-HN manifestations in HIV-infected children.

Condition	Reference	Sampie size	Type of study	Main finding
Otitis media	7	52	Prospective cohort	▪ 25% of HIV-1 seroconverters developed acute otitis media (AOM) during the 27- month study period ▪ AOM was significantly associated with decreased CD4 + count.
Otitis media	8	250 50	Retrospective Cross-sectional survey	▪ 18.4% of the children studied had otitis media ▪ 28% of the children studied had AOM while ▪ 10% had chronic suppurative otitis media (CSOM)
Otitis media	23	72	Retrospective	▪ 44.4% of children with HIV-1 presented with at least 1 episode of otitis media. ▪ Severity of immunosuppression was associated with high incidence and severity of otitis media.
Sinusitis	28	71	Retrospective	▪ 49 out 71 patients had radiological findings suggestive of sinusitis. Sinusitis was noted to be more prevalent in HIV infected patients. In this group, severity of disease related inversely with the CD+4 count.
Oral candidiasis	8	250	Retrospective	▪ 59.6% of the children presented with oral candidias

				and 0.8% had candidal oesophagitis/tracheitis
Viral infection of the oral cavity	10	180	Prospective cohort	▪ By means of viral PCR, EBV, HSV and CMV were identified in 177, 116 and 105 children respectively.
Tonsillitis	7	52	Prospective cohort	▪ 34.1% of the children developed tonsillitis within the 27-month study period.
Cervical lymphadenopathy	8	250	Retrospective	▪ 41.6% of the children were noted to have cervical lymphadenopathy
Parotitis	7	52	Prospective cohort	▪ 28% of the children developed parotitis during the 27-month study period.
Parotitis	38	579	Prospective cohort	▪ 23.3% of children aged 0-15 years developed chronic hypertrophic parotitis
Malignancies	21	302	Prospective cohort	▪ 7 children developed non-Hodgkin's lymphoma (NHL) and 2 Kaposi's sarcoma (KS)
Molluscum contagiosum	46	169	Case control	▪ 21% of HIV infected children from an institutional home had oral-facial molluscum contagiosum.
Dermatitis	45	58	Prospective cohort	▪ 21% of the children had bacterial skin infections while 19% had papulo- pruritic dermatitis

DIAGNOSIS OF HIV

Clinical suspicion based on the medical history and physical examination findings is of great importance in the diagnosis of paediatric HIV infection. Particularly important features include severe wasting or failure to thrive, severe pneumonias (both typical and atypical), severe sepsis, and oropharyngeal candidiasis among others. However, these clinical features overlap with those of other common childhood diseases such as malnutrition. Confirmed maternal HIV infection should raise further suspicion. Infants born to HIV-infected mothers should have laboratory diagnostic tests done as early as possible as diagnosis when already symptomatic is too late since they may succumb to the presenting AIDS-defining opportunistic infection.

Laboratory confirmation of the diagnosis is by non-quantitative detection of HIV. In children above 18 months, this is done by detection of HIV specific antibodies by enzyme - linked immunosorbent assay (ELISA) or western blot assay. In younger children, HIV DNA polymerase chain reaction (PCR) is used. Once the diagnosis of HIV has been confirmed quantification of the viral load can be done using HIV RNA assays. CD4+ T- lymphocyte count is an indicator of disease progression. Due to wide variations in absolute number of lymphocytes (and $CD4^+$ T- lymphocytes) in individuals and races, the CD4+ T-cell percentage should be considered as of more reliability (19). Other laboratory parameters requiring quantification are total blood count, urea, electrolytes and liver function tests as HIV, opportunistic infections and pharmacological agents can alter them.

TREATMENT OF HIV

This includes use of antiretroviral therapy (ART) and co-trimoxazole prophylaxis where indicated together with prompt treatment of opportunistic infections when they occur. Effective ART suppresses HIV replication and causes an increase in CD4+ T-cell count. Clinically, this is evidenced by decreased incidence of some opportunistic infections even without use of antimicrobial agents (47, 48, 49). Some patients develop self-limiting inflammatory responses to opportunistic infections within the first 6 months of initiation of ART. These responses, commonly seen in Mycobacterium tuberculosis and Herpes zoster infections are known as Immune Reconstitution Disorders (50). ART, once initiated is lifelong. The Ministry of Health has developed specific medical and psychosocial criteria that must be met before commencement of ART. Medical criteria comprise confirmed HIV infection as well as one or more of the factors tabulated below: -

Table iii: Guidelines for ART therapy in Kenya (51).

Age	Clinical stage	CD4%	CD4 Count (cells/mm^3)
<18 months	WHO 3 or 4	<25%	<1500
18 months - 5 years	WHO 3 or 4	<15%	<500
>5 years	WHO 3 or 4	<15%	<200

Psychosocial criteria involves a parent or guardian who understands treatment requirements, able to correctly administer the medications and able to attend clinics regularly.

The Ministry of Health has recommended the use of zidovudine, lamivudine and nevirapine for children below 3 years or less than 10 kilograms weight as the first line regimen. For children above this, evafirenz is used instead of nevirapine. In case of toxicity or treatment failure, the second line regimen of didanosine, abacavir and ritonavir or lopinavir is used. However, for children of all ages exposed to single dose nevirapine for prophylaxis against MTCT, zidovudine, lamivudine and kaletra or nelfinavir are used. All children being initiated on ART should be screened for tuberculosis (51). Co-trimoxazole prophylaxis should be initiated in all HIV infected children starting at six weeks of age unless contra-indicated. A double blind randomised placebo-controlled trial in Zambia showed a 28% mortality rate in children receiving co-trimoxazole compared to a 42% mortality rate in the placebo group (52).

DIAGNOSIS OF ENT-HN CONDITIONS

The infection-associated manifestations are routinely diagnosed clinically. In some cases, laboratory verification is necessary when one wants to find out the specific microbial agent or when the infection fails to respond to the standard antimicrobial agents.

Head and neck masses including lymph node enlargement are routinely diagnosed through FNAC. Conditions such as tuberculous adenitis and some lymphomas are treatable and can be diagnosed by FNAC and treated promptly hence reducing morbidity in the affected children. Other diseases such as generalized lymphoid hyperplasia and benign lymphoepithelial lesions of the parotid seen in HIV-infection are also diagnosed by FNAC and treated conservatively. The sensitivity of FNAC in the diagnosis of head and neck masses ranges from 87-97%. It has been showed to be inexpensive, time-saving and not associated with any complications (53, 54, 55).

Standard approach to diagnosis of the ENT-HN conditions is summarized in the table below:-

Table iv: Standard approach to diagnosis of ENT-HN conditions.

EARS (a) Infections (b) Hearing loss	 -Clinical assessment -Clinical assessment, audiometric tests, auditory brainstem reflexes
SINONASAL TRACT (a)Vestibulitis (b)Rhinosinusitis	 -Clinical assessment -Clinical assessment (The Consensus Panel on Paediatric Rhinosinusitis)
ORAL CAVITY (a)Infections (b)Kaposi's sarcoma	 -Clinical assessment -Punch biopsy
PHARYNX AND LARYNX Infections	 -Clinical assessment
HEAD AND NECK (a)Masses (b)Others-Facial nerve palsy, Herpes zoster, Molluscum contagiosum	 -FNAC, open biopsy -Clinical assessment

STUDY JUSTIFICATION

The HIV/AIDS pandemic has negatively impacted on Kenya's health, social and economic development. The otorhinolaryngologist may be the first clinician to encounter a child who has not been previously diagnosed to have HIV infection. Its various manifestations in the general paediatric population have been widely studied. However, few systematic studies have specifically looked at the ENT- HN manifestations in children with HIV infection and no such study had been previously undertaken in Kenya. This study was undertaken to document the various ENT- HN manifestations in HIV-infected Kenyan children and to assess the impact of ART on ENT-HN disease pattern.

OBJECTIVES

Main objective

Determine ENT- HN manifestations and the effect of antiretroviral therapy in HIV-infected children.

Specific objectives

(i) Determine the prevalence of ENT-HN manifestations in ART naïve and treated HIV-infected children.

(ii) Compare ENT-HN manifestations of ART naïve HIV-infected children with those of HIV-infected children on ART.

(iii) Correlate ENT-HN manifestations of ART-naïve HIV-infected children with the immunological stage of HIV disease.

METHODOLOGY

Design

Case control study.

Study setting

This study was carried out in Kenyatta National Hospital (KNH) at the Comprehensive Care Clinic (CCC), ENT - HN and Paediatric departments. KNH is situated in Nairobi, Kenya and it serves as the national referral hospital and also as the teaching hospital for the University of Nairobi (UON), College of Health Sciences. The CCC is an outpatient clinic whereby patients with HIV infection are followed up by doctors from both KNH and UON. It also offers free medicines including ART, laboratory and counselling services.

Study population

Children with confirmed HIV infection who met the inclusion criteria were inducted into the study. There were three study groups each comprising of 115 children. The first group was made up of ART naïve HIV-infected children. The second was made up of HIV-infected children on ART for not more than 6 months and the third group by those on ART for more than 6 months.

Inclusion and Exclusion criteria

a. Inclusion criteria:
   All children with HIV infection aged 12 years and below.
b. Exclusion criteria:
   (i) Children whose parents or guardians did not consent for the study.
   (ii) Children with conditions not related to HIV but known to cause immunosuppresion such as diabetes mellitus and those who had been on cytotoxic therapy.

Sample size

The sample size was determined using the formula below.

$$N = \frac{\left\{ Z\alpha/2 \sqrt{2P(1-P)} + Z\beta \sqrt{P1\,(1-P1) + P2\,(1-P2)} \right\}^2}{(P1 - P2)^2}$$

Where, $Z\alpha/2 = 1.96$

$P1 = 0.35$, the prevalence of oral candidiasis in ART-naïve patients in the study by Nikolau-Galitis et al (48).

$P2 = 0.19$, the prevalence of oral candidiasis in patients on HAART (48).

$$P = \frac{P1 + P2}{2}$$

$Z\beta = 1.282$ at 90% power

$N = 115$

Thus the minimum number of patients in each group of 115.

Sampling method

Consecutive sampling technique was used. All the patients who met the inclusion criteria for each study group were recruited until the desired sample size was achieved.

Study period

This study was conducted in a three-month period between February and April 2007.

Materials and equipment

1. Head lamp (portable)
2. Aural specula
3. Otoscope
4. Nasal specula
5. Spatulas
6. Gloves
7. Face masks
8. Dry cells
9. Sterile cotton wool and surgical spirit
10. Twenty- ml syringes, 21-gauge needles, slides, slide holder and absolute alcohol

Procedure

All the children inducted in the study had been confirmed to be HIV-infected. An ELISA test for HIV antibodies was used to make the diagnosis of HIV infection in children above 18 months. For HIV antibody positive children below 18 months, an HIV-DNA PCR test was done to confirm HIV infection.

The principal investigator introduced himself to the parents or guardians of the children and informed them of his intention to do this study. He further explained to them the nature of the study and any questions they had about HIV/AIDS or the study were answered. All the patients who met the inclusion criteria were inducted into the study after their parents or guardians had signed a written consent. A study number was then assigned to each patient.

The patient's age, sex, weight and height were entered into the Patient Case Report Form (Appendix II). After establishing whether the patient was on ART or not and the duration of such treatment, the patient was assigned to the appropriate study group. A medical history primarily focusing on ENT-HN symptoms and a systemic enquiry were then conducted. For those children previously admitted with pneumonia or septicaemia and for those with symptoms suggestive of acute otitis media, rhinosinusitis, oral ulcerations and herpes zoster the number of recurrences in the past 6-12 months was noted. A physical examination was then conducted on each patient. Results of latest total blood count and CD4+ T-cell count were then recorded. The patient's nutritional status was assessed in the form of Z-score, which was calculated using the Epi Info (version 3.3.2) software. All the history and physical examination findings, together with the results of the investigations done were recorded in the Patient Case Report Form. After noting all past and present diseases, Z-score and the laboratory investigations, clinical and immunological staging of HIV disease was made according to the WHO guidelines (Appendix III). Examination of the various sites was conducted as follows: -

Ears

Both ears were examined. A portable headlamp was used to examine the pinna and the mastoid regions while the external auditory canal, tympanic membrane and middle ear were examined using an otoscope. Otalgia associated with either an erythematous or bulging tympanic membrane with or without mucopurulent otorrhoea was diagnosed as AOM. Reported otorrhoea for a period exceeding 14 days and the presence of a tympanic membrane perforation was diagnostic of CSOM. Otitis media with effusion was diagnosed on the basis of a dark bluish appearing tympanic membrane.

Nose and paranasal sinuses

The external nose was inspected with the aid of a portable headlamp. Both nasal cavities were then examined in turn whereby a Thudicum nasal speculum was used to facilitate exposure. Vestibulitis was diagnosed by the presence of erythema, oedema and tenderness of the nasal vestibule. Patients were diagnosed to have rhinosinusitis if they had rhinorrhoea, nasal congestion, frontal headaches or facial pains with or without fever. Symptoms lasting less than

12 weeks were indicative of acute rhinosinusitis while those lasting for more than 12 weeks for chronic rhinosinusitis. This clinical diagnosis was consistent with the recommendations by the Consensus Panel on Paediatric Rhinosinusitis.

Oral cavity

The lips were inspected first. Examination of the oral cavity and oropharynx was then conducted using a headlamp and a spatula. Presence of either whitish plaques that were easily scraped using a spatula and tender erythematous ulcerations of the oral fissure was suggestive of oral candidiasis and angular cheilitis respectively. Oral hairy leukoplakia was diagnosed by the presence of whitish plaques on the lateral border of the tongue.

Pharynx and larynx

Inflammation of the oropharynx and tonsils with or without enlarged tonsils, associated with sore throat and odynophagia was diagnosed as tonsillopharyngitis. Oropharyngeal candidiasis was diagnosed by the presence of whitish plaques in the oropharynx.

Head and neck

Inspection was done and any abnormality observed was noted. All masses were palpated and defined in terms of site, size, mobility, tenderness and consistency. For the neck lymph nodes and masses, the level of the neck involved was determined as follows:-

Level I: submandibular and submental lymph nodes.

Level II: upper deep cervical lymph nodes (or from base of skull to level of hyoid bone).

Level III: mid deep cervical lymph nodes (or from level of hyoid bone to level of cricoid cartilage).

Level IV: lower deep cervical lymph nodes (or from level of cricoid cartilage downwards).

Level V: posterior cervical lymph nodes.

Level VI: prelaryngeal and pretracheal lymph nodes.

Fine needle aspirate (FNA) was done for the head and neck masses and lymph nodes by the principal investigator. In performing FNA, a 20ml syringe and a 21-gauge needle were used. With the examiner wearing clean gloves, the skin overlying the mass was cleaned with surgical spirit. The mass was then stabilised with the left hand as the needle was introduced. Suction was applied and maintained as several radial passes were made within the substance of the mass and released as the needle was withdrawn through the skin. The needle was disconnected and 10 ml of air aspirated into the syringe after which the needle was reconnected and the specimen expelled on to a slide. A second slide was used to smear the specimen. In the course of this study, 2 sets of smears were prepared from each specimen. Those for cytological studies were fixed immediately with alcohol. Smears intended for Ziehl- Neelsen staining for mycobacterial studies were air-dried.

Quality control

The Patient Case Report Form was pretested before commencement of data collection and appropriate modifications made. The principal investigator conducted the history and physical examination of all the patients. All laboratory investigations were done at the KNH/UON facilities.

Data analysis

All data was checked for completeness, consistency and accuracy. The data was then coded and analyzed using the Statistical Package for Social Sciences (SPSS) version 10.0 with the help of a statistician. The prevalence of the various ENT-HN manifestations in HIV-infected children was determined and correlated with the immunological status of the patient. The results were presented in text, graphs, tables and charts. Conclusions and recommendations based on the results were made.

Difficulties encountered

FNA was not done in three children with cervical lymphadenopathy. One parent declined to consent for this procedure and two patients were too apprehensive to allow the procedure to be done.

Ethical considerations

(i) Study was done after approval by the Kenyatta National Hospital Ethical and Research Committee.
(ii) Participation in the study was voiuntary, by consent of the parent or guardian.
(iii) No patient incurred an extra cost during the study.
(iv) Information obtained will be kept confidential.
(v) Results of the study will be published and made available to members of the medical fraternity.

RESULTS

This was a case control study comprising of three groups of HIV-infected children. The first group was made up of ART-naïve children. The second group was made up of children on ART for not more than 6 months while the third group by those children on ART for more than 6 months. All the children were on co-trimoxazole prophylaxis. Clinical and immunological staging of HIV disease of each patient was made in accordance to the WHO guidelines (Appendix III).

Table 1: Demographic and HIV disease characteristics.

	ART naïve		6 months or less ART		>6 moths ART	
	N=115	(%)	N=115	(%)	N=115	(%)
Age (months)						
<12	13	(11.3)	6	(5.2)	1	(0.9)
12-35	27	(23.5)	42	(36.5)	25	(22.7)
36-59	17	(14.8)	15	(13.1)	20	(17.4)
>60	58	(50.4)	52	(45.2)	69	(60.0)
Sex						
Male	64	(55.7)	55	(47.8)	55	(47.8)
Female	51	(44.3)	60	(52.2)	60	(55.2)
HIV clinical stage						
I	19	(16.5)	6	(5.2)	9	(7.8)
II	29	(25.2)	16	(13.9)	29	(25.2)
III	48	(41.8)	75	(65.2)	59	(51.3)
IV	19	(16.5)	18	(15.7)	18	(15.7)
HIV immunological stage						
Not significant	18	(15.6)	17	(14.8)	57	(49.6)
Mild	7	(6.1)	15	(13.0)	22	(19.1)
Advanced	20	(17.4)	20	(17.4)	19	(16.5)
Severe	70	(60.9)	63	(54.8)	17	(14.8)

The median age of HIV-naïve patients was 60 months. That of patients on ART for not more than 6 months was 51 months and that of patients on ART for more than 6 months was 72 months. Majority of patients in all study groups were above 60 months. Among the ART-naïve patients, 64 (55.7%) were male and in each of the other two study groups 55 (47.8%) were male. In each of the groups studied, majority of the patients were in WHO clinical stage III. In patients who were ART-naïve and those on ART for not more than 6 months, majority (60.9% and 54.8% respectively) were severely immunosuppresed. However, only 14.8% were severely immunosuppressed among those on treatment for more than 6 months **(table 1).**

Figure 1: ENT-HN manifestations in HIV-infected children.

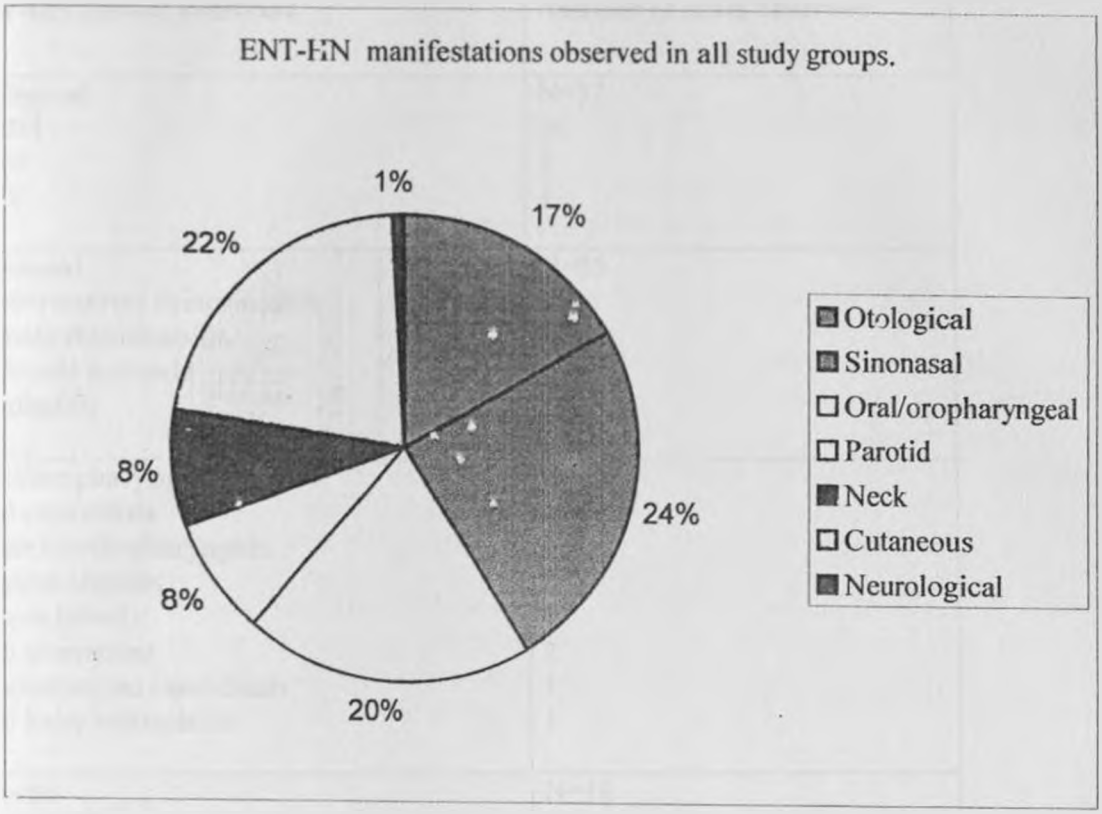

Figure 1 shows the distribution of ENT-HN manifestations observed during this study without categorization of the patients into treatment groups. A total of 222 different ENT-HN manifestations were observed in all the three categories. Some children had more than one disease condition. Of these 222 manifestations, the most common were sinonasal (24%), cutaneous (22%), oral/oropharyngeal (20%) and otological (17%). The specific disease entities are showed in **table 2** below.

Table 2: ENT-HN manifestations in HIV-infected children.

ENT-HN disease condition	Number of cases observed
Otological	N=37
CSOM	34
AOM	2
OME	1
Sinonasal	N=55
Acute recurrent rhinosinusitis	41
Chronic rhinosinusitis	11
Recurrent epistaxis	2
Vestibulitis	1
Oral/oropharyngeal	N=44
Oral candidiasis	23
Acute tonsillopharyngitis	7
Angular cheilitis	5
Herpes labialis	5
Oral ulcerations	2
Oropharyngeal candidiasis	1
Oral hairy leukoplakia	1
Parotid	N=18
Chronic bilateral parotitis	13
Acute parotitis	3
Parotid cyst	1
Parotid abscess	1
Neck	N=18
Cervical lymphadenopathy	16
Cervical abscess	2
Cutaneous	N=48
Papulo pruritic dermatitis	21
Tinea capitis	14
Molluscum contagiosum	7
Eczematous dermatitis	3
Furunculosis	2
Post herpetic scar	1
Neurological	N=2
Facial nerve palsy	2

Table 2 shows the specific ENT-HN manifestations that were observed in the entire study population.

Otological diseases: Thirty-four out of the 37 (91.9%) otological conditions seen were CSOM. Two (5.4%) cases of AOM were noted. One of these patients presented with a sudden onset otorrhoea accompanied by ipsilateral facial nerve palsy.

Sinonasal diseases: These were 55 in number with the majority (74.5%) being acute recurrent rhinosinusitis. Chronic rhinosinusitis was noted in 11 (20%) patients. Two patients with recurrent epistaxis were noted. Both had normal haematological parameters and the cause of the epistaxis was not established.

Oral/oropharyngeal diseases: A total of 44 oral/oropharyngeal manifestations were noted. Oral candidiasis was the most common disease in this category whereby 23 (52.3%) patients were seen. Seven (15.9%) patients were noted to have acute tonsillopharyngitis and 5 (11.4%) each with angular cheilitis and herpes labialis. Oral hairy leukoplakia, a rare manifestation of paediatric HIV was only seen in one patient.

Neck diseases: There were 18 cases noted in this category with cervical lymphadenopathy accounting for 16 (88.9%) cases. The other disease condition in this category was cervical abscess whereby 2 (11.1%) were seen. Of the 16 patients with cervical lymphadenopathy, all but one had bilateral cervical lymphnode enlargement. Ten of them had associated axillary and inguinal lymphnode enlargement and a diagnosis of persistent generallised lymphadenopathy was made clinically. From the 15 patients with bilateral cervical lymphadenopathy, FNAC was done in 12 patients and revealed reactive lymphnode hyperplasia. One patient had a reactive submandibular lymphadenopathy. Two cases of cervical abscesses were noted, one in the supraclavicular region and the other in the submandibular region. The former revealed an acute necrotizing-suppurative adenitis suspicious of tuberculous infection and the latter was due to lymphnode suppuration. In both cases, no AAFBs were seen on Z-N staining.

Parotid diseases: These were 18 in total. Chronic bilateral parotitis was the most common disease in this category with 13 (72.2%) patients noted. Cytology of 11 of these patients showed a mixed population of chronic inflammatory cells in a background of epithelial cells suggestive of chronic parotitis. There was one case of granulomatous parotitis (no AAFBs on Z-N staining) and one case of reactive lymphoid hyperplasia. One patient with chronic inflammatory parotitis developed a recurrence of left parotid abscess and was admitted for surgical drainage. Three (16.6%) patients were noted to have acute parotitis.

Cutaneous diseases: Cutaneous manifestations were observed in 48 patients. Papulo pruritic dermatitis was the most common and was seen in 21 (43.8%) of these patients. Fourteen (29.2%) cases of tinea capitis and 7 (14.6%) of molluscum contagiosum were seen. Three patients (6.3%) were noted to have eczematous dermatitis and 2 (4.2%) to have facial furunculosis. Only one (2.1%) case of post herpetic scar was observed.

Neurological diseases: The only neurological disease noted was facial nerve palsy. This was seen in two patients both of whom were over 5 years old and ART-naive with severe immunosuppression. One patient had multiple cerebral infarcts with an isolated facial nerve palsy while the other had acute otitis media.

Figure 2: Relationship between ENT-HN manifestations and ART treatment.

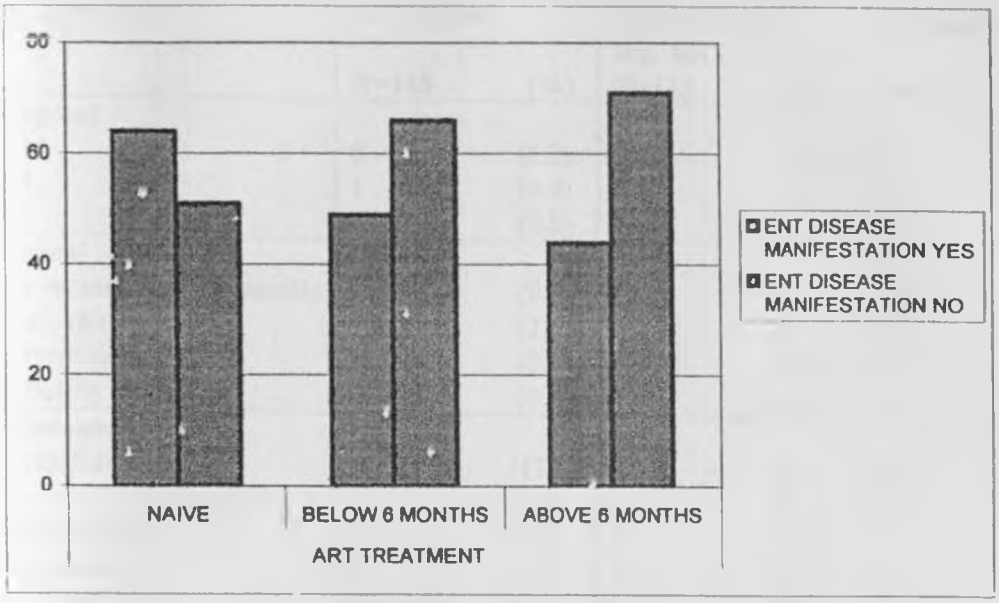

Figure 2 shows the number of patients in each treatment category that presented with at least one ENT-HN disease manifestation. Sixty-five (56.5%) ART-naive children had at least one ENT-HN disease manifestation. However, only 49 (42.6%) were noted to have an ENT-HN manifestation amongst those on ART for not more than 6 months. The lowest rate was seen in children who had been on ART for more than 6 months whereby 44 (38.3%) of them presented with at least one ENT-HN manifestation.

Table 3: Association between presence of ENT-HN disease and ART status.

	Disease Status				
Categories	*+ve (%)*	*(-ve %)*	*OR (95CI%)*	*p-value*	*x^2-trend*
No ART	41	27	1.00		
ART ≤ 6	31	35	0.59(0.3-1.0)	0.065	6.99
ART > 6	28	38	0.49(0.3-0.9)	0.012	

Table 3: The risk of patients on ART for not more than 6 months to present with an ENT-HN disease was OR 0.59(95% CI 0.3-1.0) p=0.065 when compared to ART-naïve patients. However, this risk was significantly reduced OR 0.49(0.3-0.9) p=0.012 when patients on ART for more than 6 months were compared to ART-naïve patients. There was no significant difference in the occurrence of ENT-HN disease when patients on ART for more than 6 months were compared to those on ART for not more than 6 months (p=0.59).

Table 4: Prevalence of ENT manifestations among the various treatment categories.

ENT Condition	ART naïve		6 months or less ART		>6 months ART	
	N=115	(%)	N=115	(%)	N=115	(%)
Otological						
CSOM	6	(5.2)	17	(14.8)	11	(9.6)
AOM	1	(0.8)	1	(0.8)	0	(0.0)
OME	0	(0.0)	0	(0.0)	1	(0.8)
Sinonasal						
Acute recurrent rhinosinusitis	11	(9.6)	11	(9.6)	19	(16.5)
Chronic rhinosinusitis	3	(2.6)	4	(3.5)	4	(3.5)
Recurrent epistaxis	1	(0.8)	0	(0.0)	1	(0.8)
Vestibulitis	0	(0.0)	1	(0.8)	0	(0.0)
Oral/oropharyngeal						
Oral candidiasis	16	(13.9)	7	(6.1)	0	(0.0)
Acute tonsillopharyngitis	3	(2.6)	2	(1.7)	2	(1.7)
Angular cheilitis	3	(2.6)	2	(1.7)	0	(0.0)
Herpes labialis	2	(1.7)	1	(0.8)	1	(0.8)
Oral ulcerations	2	(1.7)	0	(0.0)	0	(0.0)
Oropharyngeal candidiasis	0	(0.0)	1	(0.8)	0	(0.0)
Oral hairy leukoplakia	0	(0.0)	1	(0.8)	0	(0.0)
Parotid						
Chronic bilateral parotitis	10	(8.7)	3	(2.6)	0	(0.0)
Acute parotitis	1	(0.8)	0	(0.0)	2	(1.7)
Parotid cyst	1	(0.8)	0	(0.0)	0	(0.0)
Parotid abscess	1	(0.8)	0	(0.0)	0	(0.0)
Neck						
Cervical lymphadenopathy	12	(10.4)	4	(3.5)	0	(0.0)
Cervical abscess	1	(0.8)	1	(0.8)	0	(0.0)
Cutaneous						
Papulo pruritic dermatitis	12	(10.4)	7	(6.1)	2	(1.6)
Tinea capitis	7	(6.1)	3	(2.6)	4	(3.5)
Molluscum contagiosum	2	(1.7)	3	(2.6)	2	(1.6)
Eczematous dermatitis	0	(0.0)	1	(0.8)	2	(1.6)
Furunculosis	1	(0.8)	1	(0.8)	0	(0.0)
Post herpetic scars	1	(0.8)	0	(0.0)	0	(0.0)
Neurological						
Facial nerve palsy	2	(1.7)	0	(0.0)	0	(0.0)

The commonest manifestations in the ART-naïve patients were oral candidiasis (13.9%), cervical lymphadenopathy (10.4%), papulo pruritic dermatitis (10.4%), acute recurrent rhinosinusitis (9.6%), chronic bilateral parotitis (8.7%) and CSOM (5.2%).

In patients on ART for not more than 6 months, the most common disease was CSOM (14.8%). Others were acute recurrent rhinosinusitis (9.6%), oral candidiasis (6.1%), papulo pruritic dermatitis (6.1%), cervical lymphadenopathy (3.5%) and chronic bilateral parotitis (2.6%).

Among patients on ART for more than 6 months, the commonest diseases noted were acute recurrent rhinosinusitis (16.5%), CSOM (9.6%), chronic rhinosinusitis (3.5%) and tinea capitis (3.5%).

Table 5: Association between ENT-HN manifestations in ART status.

ENT Condition	ART naïve	ART ≤ 6 months			ART > 6 months			x^2-trend
	n = 115	n =115	OR (95%CI)	p	n =115	OR (95%CI)	p	
Otological	7(6.0)	18 (15.6)	2.9 (1.1-8.0)	0.034	12 (10.4)	1.8 (0.6-5.3)	0.338	1.132
CSOM	6 (5.2)	17 (14.8)	3.2 (1.1-9.4)	0.028	11 (9.6)	2.1 (0.7-6.6)	0.220	1.712
Sinonasal	15 (13.0)	16 (13.9)	1.1 (0.5-2.5)	1.000	24 (20.8)	1.8 (0.8-3.8)	0.160	2.620
Acute recurrent rhinosinusitis	11 (9.6)	11 (9.6)	1.0 (0.4-2.6)	0.822	19 (16.5)	1.9 (0.8-4.5)	0.17	2.650
Chronic rhinosinusitis	3 (2.6)	4 (3.5)	1.4 (0.3-7.8)	0.5	4 (3.5)	1.4 (0.3-7.8)	0.5	0.140
Oral/pharyngeal	24 (22.5)	14 (11.9)	0.5 (0.2-1.1)	0.11	3 (2.5)	0.1 (0.0-0.4)	<0.001	18.26
Oral candidiasis	16 (13.9)	7 (6.1)	0.4 (0.1-1.1)	0.07	0 (0.0)	-	<0.001	17.83
Others	8 (7.6)	7 (6.1)	0.9 (0.3-2.8)	1.0	3 (2.5)	0.4 (0.1-1.5)	0.21	2.19
Parotid	13 (11.1)	3 (2.6)	0.2 (0.1-0.8)	0.01	2 (1.7)	0.14 (0.0-0.7)	0.007	10.61
Chronic parotitis	10 (8.7)	3 (2.6)	0.3 (0.1-1.2)	0.08	0 (0.0)	-	0.003	11.96
Neck	13 (11.2)	5 (4.3)	0.4 (0.1-1.1)	0.080	0 (0.0)	-	<0.001	14.82
lymphadenopathy	12 (10.4)	4 (3.5)	0.3 (0.1-1.2)	0.103	0 (0.0)	-	<0.001	14.12
Cutaneous	23 (19.8)	15 (12.9)	0.6 (0.3-1.3)	0.214	10 (9.6)	0.4 (0.2-0.9)	0.024	6.117
Papulo pruritic dermatitis	12 (10.4)	7 (6.1)	0.4 (0.2-0.9)	0.024	2 (1.6)	0.2 (0.0-0.7)	0.013	7.584
Tinea capitis	7 (6.1)	3 (2.6)	0.4 (0.1-1.8)	0.332	4 (3.5)	0.6 (0.1-2.2)	0.537	1.002
Others	4 (3.5)	5 (4.3)	1.3 (0.3-5.8)	0.5	4 (3.5)	1.0 (0.2 4.9)	0.639	0.000

Otological diseases: Compared to ART-naïve children, there was a significant 3 fold increased risk of otological disease among children on ART for ≤ 6 months, OR 2.9(1.1-8.0) p=0.034. Children on ART for > 6 months had a non-significant 2 fold increased risk of otological disease, OR 1.8(0.6-5.3) p=0.338. The most common disease in all the study groups was CSOM. The highest prevalence (14.8%) was found in patients on ≤ 6 months ART. Compared to ART-naïve children, the risk of developing CSOM was significantly increased, OR 3.2 (95% CI 1.1-9.4) p=0.028 in children on ≤ 6 months ART and non-significantly increased, OR 2.1 (95% CI 0.7-6.6) p= 0.220 in children on ART > 6 months. However, no significant difference was noted in occurrence of CSOM between those on ART for ≤ 6 months and those on ART for > 6 months (p=0.23).

Sinonasal diseases: The risk of sinonasal disease was similar in ART-naïve and those on ART for ≤ 6 months. Compared to ART-naïve children, there was a non-significant 2 fold increased risk of sinonasal disease among children on ART for > 6 months, OR 1.8(0.8-3.8) p=0.160. Acute recurrent rhinosinusitis was the most common sinonasal affection. The highest prevalence (16.5%) was seen in patients on ART for more than 6 months. Compared to ART-naïve children, the risk of acute recurrent rhinosinusitis was OR 1.0 (95% CI 0.4-2.6) p=0.822 in children on ART for ≤ 6 months and OR 1.9 (95% CI 0.8-4.5) p=0.170 in children on ART for >6 months. No significant difference was noted in occurrence of acute recurrent rhinosinusitis between those on ART for ≤ 6 months and those on ART for >6 months (p=0.170). Chronic rhinosinusitis was the second most frequent disease in this category. The highest prevalence (3.5%) was equal in both treatment categories. The risk of chronic rhinosinusitis was non-significantly increased in the ART exposed children when compared to ART-naïve children OR 1.4 (0.3-7.8) p=0.5.

Oral/oropharyngeal diseases: Compared to ART-naïve children, there was a non-significant decreased risk of oral/oropharyngeal disease among children on ART for ≤ 6 months,

OR 0.5(0.2-1.1) p=0.11. Children on ART for > 6 months had a significant 10 fold decreased risk of oral/oropharyngeal disease, OR 0.1(0.0-0.4) p<0.001. The most common disease was oral candidiasis. The highest prevalence (13.9%) of oral candidiasis was noted in the ART-naïve children. Compared to ART-naïve children, the risk of oral candidiasis was non-significantly lower, OR 0.4 (95% CI 0.1-1.1) p=0.07 in children on ART for ≤ 6 months. There was a significant decline in occurrence of oral candidiasis when ART-naïve children were compared to those on ART for > 6 months (p<0.001). However, the odds ratio was incalculable as this condition was not seen in any child on ART for > 6 months. The occurrence of oral candidiasis declined when children on ART for > 6 months were compared to those on ART for ≤ 6 months (p=0.007).

Parotid diseases: The risk of a parotid gland disease was significantly lower in children on ART for ≤ 6 months, OR 0.2(95% CI 0.1-0.8) p=0.01 and in children on ART for > 6 months, OR 0.14(95% CI 0.0-0.7) p=0.007 when compared to the ART-naïve children. Chronic bilateral parotitis was the most common of all parotid diseases. The prevalence among the ART-naïve was 8.7% while that in patients on ART for not more than 6 months was 2.6%. No cases were noted in patients who had been on ART for more than 6 months. Compared to ART-naïve children, the risk of chronic bilateral parotitis was non-significantly lower, OR 0.3 (95% CI 0.1-1.2) p=0.08 for children on ART for ≤ 6 months. There was a significant decline in occurrence of chronic bilateral parotitis when children on ART for > 6 months were compared to the ART-naive (p=0.003) though the odds ratio was incalculable. However, the difference in occurrence of this condition in children on ART for ≤ 6 months when compared to those on ART for >6 months was not significant (p=0.123).

Neck: The risk of a neck disease was non-significantly lowered in children on ART for ≤ 6 months, OR 0.4(95% CI 0.1-1.1) p=0.08 but significantly lowered in children on ART for > 6 months, (OR incalculable) p=0.007 when compared to the ART-naïve children. Cervical lymphadenopathy was only seen in the ART-naïve (10.4%) and in children on ART for ≤ 6 months (3.5%). Compared to ART-naïve children, the risk of cervical lymphadenopathy was non-significantly reduced, OR 0.3 (95% CI 0.1-1.2) p=0.103 for children on ART for ≤ 6 months. There was a significant decline in the occurrence of cervical lymphadenopathy when those children on ART for > 6 months were compared to ART-naïve children (p=0.001) but the odds ratio was incalculable. However, the difference in occurrence of this condition in children on ART for ≤ 6 months when compared to those on treatment for more than 6 months was not significant (p=0.06).

Cutaneous diseases: The risk of a cutaneous manifestation was non-significantly decreased in children on ART for ≤ 6 months, OR 0.6(95% CI 0.3-1.3) p=0.214 but was significantly decreased in children on ART for > 6 months, OR 0.4(95% CI 0.2-0.9) p=0.024 when compared to the ART-naïve children. Papulo pruritic dermatitis and tinea capitis were the most common cutaneous diseases. The prevalence of papulo pruritic dermatitis was highest (10.4%) in the ART-naïve patients and lowest in those patients who had been on ART for more than 6 months (1.7%). Compared to ART-naïve children, the risk of papulo pruritic dermatitis significantly declined, OR 0.4 (95% CI 0.2-0.9) p=0.024 in children on ART for ≤ 6 months and OR 0.2 (95% CI 0.0-0.7) p=0.013 in children on ART for > 6 months. However, the difference in occurrence of this condition in children on ART for ≤ 6 months when compared to those on treatment for > 6 months was not significant (p=0.085). The highest prevalence (6.1%) of tinea capitis was found in ART-naïve children. Compared to ART-naïve children, the risk of tinea capitis was non-significantly lowered, OR 0.4 (95% CI 0.1-1.8) p=0.332 in children on ART for ≤ 6 months and OR 0.6 (95% CI 0.1-2.2) p=0.537 in children on ART for > 6 months. The difference in occurrence of this condition in children on ART for ≤ 6 months when compared to those on treatment for > 6 months was not significant (p=0.5).

Figure 3: Relationship between ENT-HN manifestations and HIV immunological stage among the ART-naïve patients.

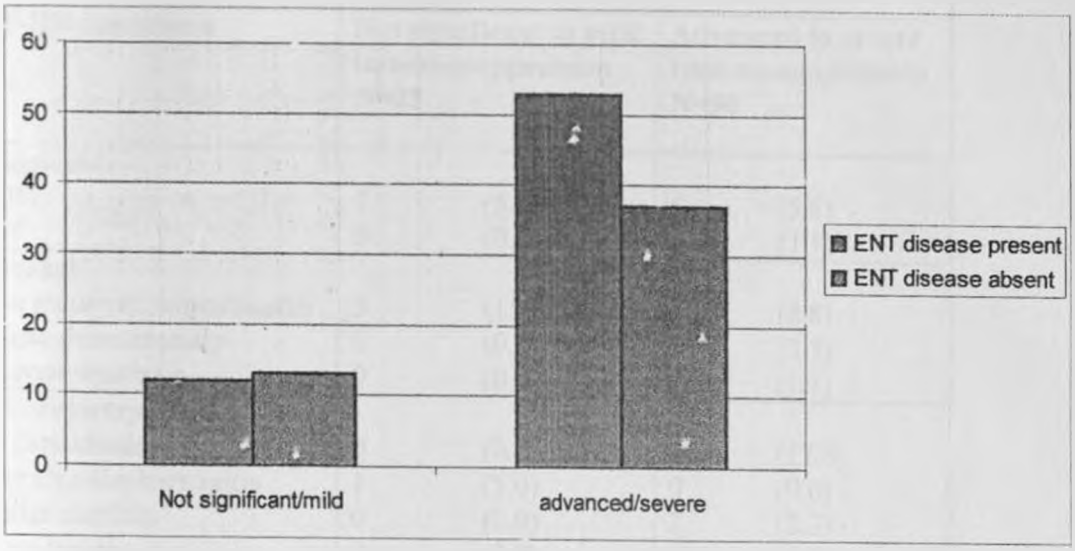

Figure 3 shows that out of the 25 patients with no significant or mild immunosuppression, 12 (48%) had at least one ENT-HN disease. This is in contrast to 53 out of 90 patients (58.8%) with advanced or severe immunosuppression who had at least one ENT-HN disease. The risk of occurrence of at least one ENT-HN manifestation was non-significantly increased, OR 1.5(95% CI 0.5-4.0) p=0.492 in patients with advanced/severe immunosuppression when compared to those with no significant/mild immunosuppression.

Table 6: Prevalence of ENT-HN conditions among ART-naïve children.

ENT-HN conditions	WHO immunological stage of HIV disease			
	Not significant to mild immunosuppression N=25		Advanced to severe immunosuppression N=90	
Otological				
CSOM	1	(5.0)*	5	(5.6)
AOM	0	(0.0)	1	(1.1)
Sinonasal				
Acute recurrent rhinosinusitis	3	(15.0)	8	(8.8)
Chronic rhinosinusitis	0	(0.0)	3	(3.3)
Recurrent epistaxis	0	(0.0)	1	(1.1)
Oral/oropharyngeal				
Oral candidiasis	0	(0.0)	16	(17.8)
Acute tonsillopharyngitis	1	(5.0)	0	(0.0)
Angular cheilitis	0	(0.0)	3	(3.3)
Herpes labialis	0	(0.0)	2	(2.2)
Oral ulcerations	1	(5.0)	1	(1.1)
Parotid				
Chronic bilateral parotitis	3	(15.0)	7	(7.8)
Acute parotitis	1	(5.0)	0	(0.0)
Parotid cyst	1	(5.0)	0	(0.0)
Parotid abscess	0	(0.0)	1	(1.1)
Neck				
Cervical lymphadenopathy	2	(10.0)	10	(11.1)
Cervical abscess	0	(0.0)	1	(1.1)
Cutaneous				
Papulo pruritic dermatitis	2	(10.0)	10	(11.1)
Tinea capitis	1	(5.0)	6	(6.7)
Molluscum contagiosum	1	(5.0)	1	(1.1)
Furunculosis	0	(0.0)	1	(1.1)
Post herpetic scars	0	(0.0)	1	(1.1)
Neurological				
Facial nerve palsy	0	(0.0)	2	(2.2)

* Figures in parentheses represent percentage.

Table 7: Association between ENT-HN manifestations and HIV clinical stage in ART-naïve children.

ENT-HN Conditions	WHO Immunological Stages of HIV disease				OR (95%CI)	p-value
	No Significant to mild immunosuppression		Advanced to severe immunosuppression			
	n = 25	%	n = 90	%		
Otological	1	5.0	6	6.7	1.7 (0.2-39.6)	0.526
CSOM	1	5.0	5	5.6	1.4 (0.2-33.5)	0.611
AOM	0	0.0	1	1.1	-	0.783
Sinonasal	3	15.0	12	13.2	1.1 (0.3-5.6)	0.581
Acute rec. rhinosinusitis	3	15.0	8	8.8	0.7 (0.2-3.7)	0.443
Chronic rhinosinusitis	0	0.0	3	3.3	-	
Recurrent epistaxis	0	0.0	1	1.1	-	
Oral/oropharyngeal	2	10.0	22	24.4	3.7 (0.8-24.8)	0.131
Oral candidiasis	0	0.0	16	17.8	-	0.014
Acute tonsillopharyngitis	1	5.0	0	0.0	-	
Angular cheilitis	0	0.0	3	3.3	-	
Herpes labialis	0	0.0	2	2.2	-	
Oral ulcerations	1	5.0	1	1.1	0.27 (0.1-10.3)	0.389
Parotid	5	25.0	8	8.8	0.4 (0.1-1.6)	0.118
Chronic bilateral parotitis	3	15.0	7	7.7	0.6 (0.1-3.3)	0.374
Acute parotitis	1	5.0	0	0.0	-	
Parotid cyst	1	5.0	0	0.0	-	
Parotid abscess	0	0.0	1	1.1	-	
Neck	2	10.0	11	12.1	1.6 (0.3-11.3)	0.429
Cervical lymphadenopathy	2	10.0	10	11.1	1.4 (0.3-10.2)	0.491
Cervical abscess	0	0.0	1	1.1	-	
Cutaneous	4	20.0	19	21.1	1.4 (0.4 -5.5)	0.777
Papulo pruritic dermatitis	2	10.0	10	11.1	1.4 (0.3-10.3)	0.491
Tinea capitis	1	5.0	6	6.7	1.7 (0.2-39.6)	0.526
Molluscum contagiosum	1	5.0	1	1.1	0.27 (0.1-10.3)	0.389
Furunculosis	0	0.0	1	1.1	-	
Post herpetic scars	0	0.0	1	1.1	-	
Neurological	0	0.0	2	2.2	-	
Facial nerve palsy	0	0.0	2	2.2	-	

Otological diseases: The risk of an otological disease was non-significantly increased, OR 1.71 (95% CI 0.2-39.6) p= 0.526 when children with advanced/severe immunosuppression were compared with those with no significant/mild immunosuppression. It's only CSOM that was seen in both immune categories. This was in 1 of the 25 (5%) children with no significant/mild immunosuppression and in 5 of the 90 (5.6%) with advanced/severe immunosuppression. The risk of CSOM was non-significantly increased, OR 1.4(95% CI 0.2-33.5) p=0.611 in children with advanced/severe immunosuppression when compared to those with no significant/advanced immunosuppressoin

Sinonasal diseases: The risk of a sinonasal disease was almost equal, OR 1.1 (95% CI 0.3-5.6) p= 0.581 when children with advanced/severe immunosuppression were compared with those with no significant/mild immunosuppression. Acute recurrent rhinosinusitis was the only disease noted in both categories. Three (15%) children were noted in the group with no

significant/mild immunosuppression and 8 (8.8%) among children with advanced/severe immunosuppression. The risk of acute recurrent rhinosinusitis was non-significantly decreased, OR 0.7 (95% CI 0.2-3.7) p=0.443 in patients with advanced/severe immunosuppression when compared to those with no significant/advanced immunosuppression.

Oral/oropharyngeal diseases: Compared to the children with no significant/mild immunosuppression, there was a 4-fold risk of an oral/oropharyngeal disease among children with advanced/severe immunosuppression ,OR 3.7 (95% CI 0.8-24.8) p= 0.131. All the 16 patients with oral candidiasis had severe immunosuppression. There was a significant increase in the occurrence of oral candidiasis among the children with advanced/severe immunosuppression when compared to those with no significant/mild immunosuppression, OR incalculable (p=0.014).

Parotid diseases: The risk of a parotid disease was non-significantly reduced, OR 0.39 (95% CI 0.1-1.6) p= 0.39 when children with advanced/severe immunosuppression were compared to those with no significant/mild immunosuppression. Three (15%) children with no significant/mild immunosuppression and 7 (7.8%) children with advanced/severe immunosuppression were noted to have chronic bilateral parotitis. The risk of chronic bilateral parotitis was not significant, OR 0.62 (95% CI 0.1-3.3) p= 0.377 when patients with advanced/severe were compared to those with no significant/mild immunosuppression.

Neck diseases: The risk of a neck disease was not significant, OR 1.6 (95% CI 0.3-11.3) p= 0.429 when patients with advanced/severe immunosuppression were compared to those with no significant/mild immunosuppression. Cervical lymphadenopathy was noted in 2 (10%) patients with no significant/mild immunosuppression and in 10 (11.1%) patients with advanced/severe immunosuppression. The risk of this disease was non-significantly increased, OR 1.4 (95% CI 0.2-10.2) p= 0.491 when patients with advanced/severe were compared to those with no significant/mild immunosuppression.

Cutaneous diseases: The risk of a cutaneous disease was almost equal, OR 1.1 (95% CI 0.4-5.5) p= 0.777 when patients with advanced/severe immunosuppression were compared to those with no significant/mild immunosuppression. Papulo pruritic dermatitis was seen in 2 (10%) patients with no significant/mild immunosuppression and 10 (11.1%) patients with advanced/severe immunosuppression. The risk of this disease was OR 1.4 (95% CI 0.3-10.3) p= 0.491 when patients with advanced/severe were compared to those with no significant/mild immunosuppression.

DISCUSSION

The main aim of this study was to determine the most common ENT-HN manifestations in HIV-infected children and assess the impact of ART on these manifestations. Overall, the occurrence of these manifestations decreased significantly with ART. This study found out that 56.5% of ART-naïve children presented with at least one ENT-HN disease condition. Among children on ART for not more than 6 months and those on ART for more than 6 months, 42.6% and 38.3 % respectively had at least one ENT-HN disease. Singh A et al (4) showed that 50% of children with HIV presented with ENT-HN illnesses.

The most common manifestations noted in ART-naïve patients were oral candidiasis (13.9%), cervical lymphadenopathy (10.4%), papulo pruritic dermatitis (10.4%), acute recurrent rhinosinusitis (9.6%), chronic bilateral parotitis (8.7%), tinea capitis (6.1%) and CSOM (5.2%). There was a significant association between presence of at least one ENT-HN manifestation and use of ART but none between the presence of such manifestations and duration of treatment. The lower prevalence of disease conditions in children on ART has been reported in previous studies and is due to the ability of effective ART to suppress viral replication leading to a gradual and sustained rise in CD4+ T-cell count (47, 48, 49). The present study did not show immunological stage of HIV disease to be a significant determinant of occurrence of an ENT-HN disease condition.

CSOM was found to be the commonest otological condition in all treatment categories in this study. Chaloryoo et al (8) found a prevalence of 10% in HIV-infected Thai children. Other conditions identified in the present study were AOM and otitis media with effusion whereby one case of each was identified. The prevalence of AOM was much lower than previously reported (7, 8, 23). The prevalence of CSOM was significantly higher in children already on ART compared to ART-naïve children. This could be an immune reconstitution inflammatory response to ART. This hypothesis can be confirmed or rejected by a prospective cohort study. Among the ART-naïve children, immunological stage did not influence prevalence of CSOM. Nina L S et al (23) showed that the severity of immunosuppression was associated with a higher incidence and severity of otitis media.

Acute recurrent rhinosinusitis was the commonest sinonasal disease in all study groups. A high prevalence of acute upper respiratory tract infections (URTI) in HIV-infected children of upto 70% has been reported previously (8, 28). The present study did not show a significant association between this disease and use of ART), duration of ART and WHO immunological stage Similarly, Makokha E P et al (7) showed that the occurrence of URTI in children with HIV was independent of CD4+ T-cell count.

All studies reviewed report oral candidiasis to be one of the commonest manifestations in paediatric HIV infection (4, 8). In this study, oral candidiasis, was the most common (13.9%) ENT-HN manifestation in ART-naïve children. Its occurrence was strongly associated with WHO HIV immunological stage ($p=0.01$). All the cases noted had severe immunosuppression and none of the children on ART for more than 6 months had oral candidiasis. These findings are similar to those in a Greek study by Nicolatou-Galitis et al (49) who found that use of ART with a consequent increase in CD4+ T-cell count reduced the occurrence of oral manifestations in HIV infection.

Cervical lymphadenopathy had a prevalence of 10.4% in ART-naïve children and an overall prevalence of 4.6%. All other studies reviewed quote higher rates than these. Chaloryoo S et al (8) reported a prevalence of 41.6% in Thai children while Madhivanan P (45) reported a prevalence of 14% in Indian HIV-infected children. Majority of cervical lymphadenopathy was found to occur in the background of persistent generalized lymphadenopathy. It's possible that the difference in the rate of this condition in this study and the other studies is due to differences in the clinical and immunological profiles of the studied populations. However, use of ART beyond 6 months was showed to significantly reduce the occurrence of cervical

lymphadenopathy. None of the children on treatment for more than 6 months had this condition. This study did not show any significant correlation between WHO immunological stage and occurrence of cervical lymphadenopathy among the ART-naïve children.

The overall prevalence of chronic bilateral parotitis was 3.8% while in the ART-naïve children was 8.7%. Chaloryoo S et al (8) found a prevalence of 5.2% and Madelena L et al (38) found a prevalence of 23.3% among children with HIV infection. The commonest cytopathological lesion in the present study was benign infiltration of the gland by chronic inflammatory cells, a finding that has been reported previously (39). Use of ART was found to significantly reduce the prevalence of chronic bilateral parotitis and this condition was not seen in any child on ART for more than 6 months. In ART-naïve children, the association with the immunological stage was found not to be significant.

Previous studies have reported a high prevalence of skin diseases in paediatric HIV infection. The pattern and prevalence of dermatological conditions noted in this study is comparable to what has been reported in other studies (45, 46, 48). However, the high prevalence (4.1%) of tinea capitis seen in this study has not been reported in the other studies. It's probable that this common occurrence is a reflection of the environmental background of the study population as there was no significant association with immunological stage or use of ART. The occurrence of papulo pruritic dermatitis was found to be significantly lower in patients on ART. Seoane E et al (48) showed that use of ART is associated with a reduction of mucocutaneous manifestations in HIV-infected children.

Oral candidiasis, chronic bilateral parotitis, cervical lymphadenopathy and papulo pruritic dermatitis are conditions that are very characteristic of HIV and may lead to involuntary disclosure of the child's HIV status. These conditions were also found to resolve significantly with ART. Resolution of oral candidiasis may be associated with better feeding, weight gain and ultimately an improvement in the immune status.

Previous studies have found that children with HIV infection commonly present with ENT-HN manifestations (4, 8). These two and most of the other studies reviewed are retrospective with small sample populations. The sample size in the present study is higher than in these other studies and data was obtained in a prospective manner. However, the CD4+ T-cell count used in this study was not done on the same day as the examination of the patient. Thus the clinical picture noted may not exactly correlate with the immunological stage of HIV disease.

CONCLUSIONS

ENT-HN manifestations are common in Kenyan HIV-infected children.The commonest ENT-HN manifestations in children with HIV infection seen in KNH are acute recurrent rhinosinusitis, CSOM, oral candidiasis, papulo pruritic dermatitis, cervical lymphadenopathy, tinea capitis, chronic bilateral parotitis and chronic rhinosinusitis.

Oral candidiasis, chronic bilateral parotitis, cervical lymphadenopathy and papulo pruritic dermatitis significantly resolve on ART.

The commonest cytopathological lesion of cervical lymphadenopathy is reactive lymphnode hyperplasia. Majority of parotid enlargement is due to chronic parotitis characterized by infiltration of the gland by chronic inflammatory cells.

CSOM may be the only ENT-HN disease that is a component of the immune reconstitution inflammatory syndrome.

RECOMMENDATIONS

Children presenting to the otolaryngologist with oral candidiasis and chronic bilateral parotitis, cervical lymphadenopathy and papulo pruritic dermatitis should have diagnostic counselling and testing for HIV.

Any child with HIV infection should be started on ART if he meets the MOH guidelines on initiation of ART. The clinician can reassure the parents that some of the HIV associated stigmata such as oral candidiasis, parotid enlargement, cervical lymphadenopathy and papulo pruritic dermatitis will resolve spontaneously upon initiation of treatment.

More specific studies preferably prospective cohort studies require to be done to determine if CSOM is a component of immune reconstitution syndrome.

APPENDIX II

PATIENT CASE REPORT FORM

IP NO: _____ STUDY NO: _____

AGE: _____ Yr: _____ Mo. SEX: _____

WEIGHT: _____ Kg HEIGHT: _____ Cm

MEDICAL HISTORY

1. HISTORY OF ART
   - Yes ☐
   - No ☐
   - If yes; Regimen: First line ☐
     Second line ☐
     Duration _____ months
2. FAMILY HISTORY OF ATOPY
   - Yes ☐
   - No ☐
3. OTOLOGICAL SYMPTOMS

		Right	Left
a)	Otorrhoea (tick response)		
	Yes	☐	☐
	No	☐	☐
If yes			
(i)	Duration		
	≤14 days	☐	☐
	>14 days	☐	☐
(ii)	Frequency last 6 months		
	≤2 episodes	☐	☐
	>2 episodes	☐	☐
b)	Otalgia (tick response)		
	Yes	☐	☐
	No	☐	☐
c)	Hearing loss (tick response)		
	Yes	☐	
	No	☐	
	If yes; persistent	☐	
	fluctuant	☐	
d)	Aural swelling (tick response)	☐	☐
e)	Others (specify)		

4. RHINOLOGIC

	Right	Left
a) Nasal discharge (tick response)		
Yes	☐	☐
No	☐	☐
If yes;		
Watery	☐	☐
Purulent	☐	☐
Blood stained	☐	☐
Duration ≤ 3 months	☐	☐
	☐	☐

> 3 months

b) Epistaxis (tick response)
   Yes ☐ ☐
   No ☐ ☐

c) Nasal blockage (tick response)
   Yes ☐ ☐
   No ☐ ☐
   If yes;
   Duration ≤ 3 months ☐ ☐
   > 3 months ☐ ☐

d) Nasal swelling (tick response)
   Yes ☐ ☐
   No ☐ ☐

e) Others (specify) .....
.....

5. LIPS AND ORAL CAVITY (tick response) YES NO
   a) Labial / oral swelling ☐ ☐
   b) Labial/ oral ulcers ☐ ☐
   c) Bleeding from oral cavity ☐ ☐
   d) Others (specify) .....
.....

6. PHARYNX AND LARYNX (tick response) YES NO
   a) Odynophagia ☐ ☐
   b) Dysphagia ☐ ☐
   c) Hoarseness ☐ ☐
   d) Others (specify) .....
.....

7. SALIVARY GLANDS (tick response) YES NO
   a) Parotid swelling ☐ ☐
   b) Submandibular swelling ☐ ☐
   c) Others (specify) .....
.....

8. HEAD (tick response) YES NO
   a) Facial weakness or asymmetry ☐ ☐
   b) Faciai swellings ☐ ☐
   c) Cutaneous lesions ☐ ☐
   d) Herpetic eruptions ☐ ☐
   If yes; frequency last 12 months
   <2 ☐ ☐
   >2 ☐ ☐
   e) Others (specify) .....

9. NECK (tick response) YES NO
   a) Swelling ☐ ☐
   b) Ulcers / wounds/ sinuses ☐ ☐
   c) Others (specify) .....
.....

10. SYSTEMIC ENQUIRY
   a) Central nervous system (specify disease)
.....
.....

b) Respiratory system (specify disease and number of episodes past 1 year)

.....

.....

(c) Cardiovascular system (specify disease)

.....

.....

(d) Gastrointestinal system (specify disease)

.....

.....

(e) Genito-urinary system (specify disease)

.....

.....

(f) Haematological diseases (specify disease)

.....

.....

EXAMINATION FINDINGS

1. OTOLOGIC

a) Pinna (tick response)

		Right		Left	
		Yes	No	Yes	No
(i)	Normal	☐	☐	☐	☐
(ii)	Perichondritis	☐	☐	☐	☐
(iii)	Dermatitis	☐	☐	☐	☐
(iv)	Mass	☐	☐	☐	☐

If mass present describe .....

(v) Others (specify) .....

.....

b) External auditory canal (tick response)

		Right		Left	
		Yes	No	Yes	No
(i)	Normal	☐	☐	☐	☐
(ii)	Discharge	☐	☐	☐	☐
	If discharge; purulent	☐	☐	☐	☐
	Mucoid	☐	☐	☐	☐
	Blood stained	☐	☐	☐	☐
	Foul smelling	☐	☐	☐	☐
(iii)	Inflammed	☐	☐	☐	☐
(iv)	Debris	☐	☐	☐	☐
(iv)	Aural mass	☐	☐	☐	☐

If mass present, describe .....

.....

(v) Others (specify) .....

c) Tympanic membrane (tick response)

(i) Colour; Normal ☐ ☐ ☐ ☐

Red
Dull
(ii) Position; Normal
Retracted
Bulging
(iii) Integrity; Normal
Perforated
(iv) Light reflex; present

d) Others (specify).....
.....

2. RHINOLOGIC (tick response)

	Right YES	Right NO	Left YES	Left NO
a) Vestibulitis				
b) Nasal discharge;				
(i) Watery				
(ii) Mucopurulent				
(iii) Bloody				
c) Hypertrophied inferior turbinates				
d) Atrophic rhinitis				
e) Nasal mass				

f) Facial tenderness
Yes
No

If mass present; describe .....
.....
g) Others (specify) .....
.....

3. LIPS, ORAL CAVITY (Tick response) YES NO

a) Lips
(i) Ulcers
(ii) Mass

If ulcers / mass present; describe .....
.....

b) Tongue
(i) Candidiasis
(ii) Ulcers
(iii) Mass
(iv) Hairy cell leukoplakia

If any present describe .....
.....

c) Palate
(i) Candidiasis
(ii) Ulcer
(iii) Mass

If any present, describe .....
.....

d) Buccal mucosa

(i) Candidiasis ☐ ☐

(ii) Ulcer ☐ ☐

(iii) Mass ☐ ☐

If any present describe .....

.....

e) Others (specify) .....

.....

4. OROPHARYNX (Tick response) YES NO

a) Candidiasis ☐ ☐

b) Pharyngotonsillitis ☐ ☐

c) Oropharyngeal mass ☐ ☐

If mass present, describe .....

.....

d) Others (specify) .....

.....

5. SALIVARY GLANDS (Tick response) YES NO

a) Parotid

(i) Hypertrophied ☐ ☐

(ii) Tender ☐ ☐

b) submandibular

(i) Hypertrophied ☐ ☐

(ii) Tender ☐ ☐

c) Others (specify) .....

.....

6. HEAD (Tick response) YES NO

a) Facial nerve paralysis ☐ ☐

b) Herpes zoster eruptions/scars ☐ ☐

c) Papulo-pruritic dermatitis ☐ ☐

d) Seborrhoeic dermatitis ☐ ☐

e) Masses ☐ ☐

If masses present describe .....

.....

f) Others (specify) .....

.....

7. NECK

		Right Yes	Right No	Left Yes	Left No
a)	Abscesses	☐	☐	☐	☐
b)	Lymphadenopathy				
(i)	Solitary	☐	☐	☐	☐
(ii)	Multiple – discrete	☐	☐	☐	☐
	matted	☐	☐	☐	☐
(iii)	Site – level I	☐	☐	☐	☐
	II	☐	☐	☐	☐
	III	☐	☐	☐	☐
	IV	☐	☐	☐	☐
	V	☐	☐	☐	☐
	VI	☐	☐	☐	☐
(iv)	Size ≤ 2 cm	☐	☐	☐	☐
	> 2 cm	☐	☐	☐	☐
		☐	☐	☐	☐

(v) Tender

c) Others neck masses
If present, describe .....
.....

8. SYTEMIC EXAMINATION
a) Central nervous system (specify)
.....
.....
b) Respiratory system (specify)
.....
.....
c) Cardiovascular system (specify)
.....
.....
d) Gastrointestinal system (specify)
.....
.....
e) Genito-urinary system (specify)
.....
.....

INVESTIGATIONS
1. FNAC .....
.....
2. Lymphocyte count: _____/mm3
3. CD4 $^{+}$ T – Cell count
(a) Absolute: _____/mm3
(b) Percentage:_____
4. Others (specify)----------

DIAGNOSIS
(i) ----------
(ii) ----------
(iii) ----------
(iv) ----------

WHO STAGE
(i) clinical.....
(ii) immunological.....

APPENDIX III

REVISED WHO CLINICAL STAGING OF PAEDIATRIC HIV/AIDS DISEASE:

WHO Stage I	• Asymptomatic • Persistent generalized lymphadenopathy (PGL) • Hepatosplenomegaly
WHO Stage II	• Papular pruritic eruptions (PPE) • Seborrhoeic dermatitis • Fungal nail infections • Angular cheilitis • Linear gingival erythema • Extensive human papilloma virus (HPV) or molluscum infection (> 5% body area/face) • Recurrent oral ulcerations (> 2 episodes/ 6 months) • Parotid enlargement • Herpes zoster (> 1 episode/12months) • Recurrent or chronic upper respiratory infection (URTI): Otitis media, otorrhoea, sinusitis (> 2 episodes / 6 months)
WHO Stage III	• Unexplained moderate malnutrition (- 2 SD or Z score) not responding to standard therapy • Unexplained persistent fever (intermittent or constant, > 1 month) • Oral candidiasis (outside the neonatal period) • Oral hairy leucoplakia • Pulmonary tuberculosis • Severe recurrent presumed bacterial pneumonia (> 2 epidodes/12 months) • Acute necrotizing ulcerative gingivitis/periodontitis • Lymphoid interstitial pneumonia • Unexplained anaemia (<8g/dl), neutropenia (<1000/mm^3) or thrombocytopenia (< 30,000/mm^3) for > 1 month • HIV related cardiomyopathy • HIV related nephropathy
WHO Stage IV	• Unexplained severe wasting as severe malnutrition (- 3 SD or Z score) not responding to standard therapy • Pneumocystis pneumonia • Recurrent severe bacterial infections (> 2 episodes/12 months excluding pneumonia) • Chronic orolabial or cutaneous HSV (lasting > 1 month) • Extrapulmonary tuberculosis • Oesophageal candidiasis • Central nervous system toxoplasmosis • Cryptococcal meningitis • Any disseminated endemic mycosis • Cryptosporidiosis or isosporiasis (with diarrhea > 1 month) • CMV infection of organ other than liver, spleen, lymph nodes (and onset age > 1 month) • Disseminated mycobacterium disease other than

	tuberculosis • Candida of trachea, bronchi or lungs • Acquired recto-vesicular fistula • Cerebral or b-cell non Hodgkin lymphoma • Progressive multifocal leucoencephalopathy (PML) • HIV encephalopathy **Presumptive stage 4 diagnosis in HIV-antibody positive children less than 18 months old where virological confirmation of infection is not available.** Two or more of the following; • Oral candidiasis/thrush • Severe pneumonia requiring oxygen • Severe wasting/failure to thrive • Severe sepsis requiring injectable antibiotics

WHO IMMUNOLOGICAL STAGING OF PAEDIATRIC HIV/AIDS DISEASE:

HIV Associated Immunodeficiency	CD4+Count (% CD4+ or absolute count)			
	<12 months	12-35 months (%)	36-59 months (%)	>5 years (Count)
Not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	210-349
Severe	<25	<20	<15	<200

APPENDIX IV

SYMPTOMS AND SIGNS OF PAEDIATRIC RHINOSINUSITIS
(Consensus Panel on Paediatric Rhinosinusitis, Brussels 1996).

NON-SEVERE ACUTE RHINOSINUSITIS	SEVERE ACUTE RHINOSINUSITIS
▪ Rhinorrhoea (any quality) ▪ Nasal congestion ▪ Cough ▪ Headache, facial pain and irritability (variable) ▪ Low grade or no fever	▪ Purulent rhinorrhoea ▪ Nasal congestion ▪ Facial pain or headache ▪ Periorbital oedema (variable) ▪ High fever (temperature above 39 degrees Celsius)

Symptoms and signs less than 12 weeks = Acute rhinosinusitis.
Symptoms and signs more than 12 weeks = Chronic rhinosinusitis.

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