

**OTORHINOLARYNGOLOGICAL MANIFESTATIONS AMONG HIV
INFECTED PATIENTS ATTENDING HIV CLINIC AT MUHIMBILI
NATIONAL HOSPITAL**

By

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**A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of
Master of Medicine (ORL) of the Muhimbili University of Health and Allied Sciences**

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for the examination of a dissertation entitled Otorhinolaryngological Manifestations Among HIV Infected Patients Attending HIV Clinic at Muhimbili National Hospital, Dar es Salaam, in partial fulfillment of the requirements for the degree of Master of Medicine (ORL) of the Muhimbili University of Health and Allied Sciences

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DECLARATION

I, **Dr. Henry Swai**, declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature:

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ABSTRACT***Background***

AIDS is a fatal illness which breaks down the body's immunity leaving the patient vulnerable to threatening opportunistic infections, neurological disorders or unusual malignancies. Otorhinolaryngological manifestations in association with HIV infection are common in clinical practice, they are non specific therefore immunodeficiency may not be suspected.

Broad objective

To define the prevalence of all otorhinolaryngological manifestations of HIV/AIDS among HIV infected patients attending at the HIV clinic of MNH.

Study design

Cross sectional descriptive hospital based study.

Setting

HIV clinic at MNH.

Participants

A sample of 384 HIV infected patients attending HIV clinic at MNH.

All were on HAART.

Results

A total of 384 patients were involved in the study.

All of them were on HAART.

There were 129(33.6%) males and 255(66.4%) females, a ratio of about 1:2. ORL manifestations were reported in 131(34.1%) of the participants. The commonly reported manifestations included CSOM 29(22.1%), benign lymphoepithelial cyst of the parotid gland 22(16.8%) tonsillitis 20(15.3%), rhinosinusitis 14(10.7%), Kaposi sarcoma 10(7.6%) and oral cavity/oropharyngeal candidiasis 8(6.1%).

Conclusion

ORL manifestations were reported in about a third of the studied participants. The leading complaints were CSOM, benign lymphoepithelial cyst of the parotid gland, tonsillitis, rhinosinusitis, Kaposi sarcoma and oral/ oropharyngeal candidiasis. An otorhinolaryngologist should be aware of the otorhinolaryngological manifestations of HIV infection so that early

diagnosis and timely intervention by antiretroviral therapy can be instituted to improve survival rates.

ABBREVIATIONS

MNH – Muhimbili National Hospital.

MUHAS – Muhimbili University of Health and Allied Sciences.

ORL – Otorhinolaryngology.

ENT – Ears, Nose and Throat.

HIV – Human Immunodeficiency Virus.

AIDS – Acquired Immunodeficiency Syndrome.

CMV – Cytomegalovirus.

EBV – Epstein Bar Virus.

HHPV8 – Human Herpes Papilloma Virus type 8.

HAART – Highly active antiretroviral therapy.

PCR – Polymerase Chain Reaction.

DNA – Deoxyribonucleic acid.

RNA – Ribonucleic acid.

p24 – protein 24.

p7 – protein 7.

p9 – protein 9.

gp 120 – glycoprotein 120.

gp 41 – glycoprotein 41.

CCR5 – cell surface chemokine receptors found mostly on macrophages.

CXCR4 – cell surface chemokine receptors found mostly on T cells.

CSOM – chronic suppurative otitis media.

CD4 – CD4 T lymphocytes.

SNHL – sensoryneural hearing loss

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INTRODUCTION

The human Immunodeficiency Virus (HIV), a retrovirus that causes Acquired Immunodeficiency Syndrome (AIDS) was isolated in 1983 as the cause of the syndrome recognized in 1981. AIDS is a fatal illness which breaks down the body's immune system and leaves the patient vulnerable to life threatening opportunistic infections, neurological disorders and specific malignancies.^{1,2}

Transmission of HIV occurs through body fluids and tissues following a breach in the mucosa or skin or through intravenous infusion.

Modes of HIV transmission include:²

- (i) Sexual intercourse
- (ii) Sharing of needles by intravenous drug users
- (iii) Vertical transmission from mother to child
- (iv) Transfusion of contaminated blood
- (v) Occupational exposure in health care workers

The dimensions of the AIDS epidemic are staggering. Since the beginning of the epidemic 25 million people have died of HIV related causes. In 2007 alone 33 million people were living with HIV, 2.7 million people became infected and 2 million people died of HIV related causes worldwide.³

In Tanzania, 1.4 million people were infected with HIV as of 2007.⁴

In those countries heavily affected, HIV has reduced life expectancy by more than 20 years, slowed economic growth and deepened household poverty. In Sub Saharan Africa the epidemic has orphaned nearly 12 million children aged under 18 years.³

Initial manifestations of AIDS in the head and neck region occur frequently, incomplete recognition of these disorders may delay appropriate diagnosis and initiation of therapy.^{5,6}

BACKGROUND

Like most retroviruses the HIV 1 virion is spherical and contains an electron dense, cone shaped core surrounded by a lipid envelope derived from the host cell membrane.

The virus core contains:¹

- (1) major capsid protein p24
- (2) nucleocapsid protein p7/p9
- (3) two copies of genomic RNA
- (4) three viral enzymes (protease, reverse transcriptase, integrase)

The viral core is surrounded by a matrix of protein called p17, lying beneath the virion envelope. The viral envelope itself is studded by two viral glycoproteins, gp120 and gp41, critical for HIV infection of cells.¹ The HIV 1 proviral genome contains the gag, pol, and env genes which code for various viral proteins. The products of the gag and pol genes are translated initially into large precursor proteins that must be cleaved by the viral protease to yield the mature proteins.

The entry of HIV into cells requires the CD4 molecule which acts as a high affinity receptor for the virus. This explains the tropism of the virus for CD4+T cells.¹ However binding to CD4 is not sufficient for infection; the HIV envelope gp120 must also bind to other cell surface molecules (co receptors) to facilitate cell entry. Two cell surface chemokine receptors, CCR5 and CCR4 serve this role. HIV envelope gp120 which is non covalently attached to transmembrane gp41 binds initially to CD4 molecules.

This binding leads to a conformational change that exposes a new recognition site on gp120 for the CXCR4, mostly on T cells or CCR5, mostly on macrophages co receptors. The gp41 then undergoes a conformational change that allows it to insert into the target membrane and this process facilitates the fusion of the virus with the cell. After fusion the virus core containing the HIV genome enters the cytoplasm of the cell.

Once internalised the viral RNA genome undergoes reverse transcriptase leading to formation of complementary DNA (cDNA).¹ In quiescent T cells HIV proviral cDNA may remain in the cytoplasm in a linear episomal form. However in dividing T cells, the cDNA enters the nucleus and becomes integrated into the host DNA genome. After integration the provirus may

remain nontranscribed for months or years and the infection becomes latent; alternatively the proviral may be transcribed to form complete viral particles that bud from the cell membrane. Such productive infections associated with extensive viral budding lead to cell death.¹

HIV disease begins with acute infection, which is only partly controlled by the host immune response and advances to chronic progressive infection of the peripheral lymphoid tissues. As the infection spreads, the immune system mounts both humoral and cell mediated immune responses directed at viral antigens. These immune responses partially control the infection and viral production and such control is reflected by a drop in viremia to low but detectable levels by about 12 weeks after the primary exposure.

In the next chronic phase of the disease, lymph nodes and the spleen are sites of continuous HIV replication and cell destruction. During this period of the disease, the immune system remains competent at handling most of the infections with opportunistic microbes, and few or no clinical manifestations of the HIV infection are present, this phase of HIV disease is called the clinical latency period.¹

CD4 molecules are expressed on approximately 60% of mature T cells where they serve as coreceptors for T cell activation. During antigen recognition CD4 molecules on T cells bind to invariant portions of class II major histocompatibility (MHC) molecules facilitating antigen destruction.¹

CD4 T cells are also called helper T cells because they secrete cytokines, including interleukin 2, that help B cells to produce antibodies and also help macrophages to destroy phagocytosed microbes.¹

The Human Immunodeficiency Virus destroys CD4 helper cells subset severely compromising their central role in immunity.¹

The definition of AIDS include all HIV infected individuals with CD4 cell counts of less than 200cells/mm³ as well as those with certain HIV related conditions and symptoms.⁷

LITERATURE REVIEW

The ORL manifestations in association with HIV infection are atypical, common in clinical practice and are non specific therefore immunodeficiency may not be suspected.

Diseases of the ENT region in HIV infected patients involve all otorhinolaryngological sites, in USA where doctors are well informed 40% of cases of HIV infection are detected from cervicofacial manifestations.⁸

It was initially reported that 41% of patients with AIDS had head and neck manifestations, however as awareness increased, with early detection of infection processes, better follow-up and advanced diagnostic techniques it has been proven that about 80% of patients with AIDS develop head and neck manifestations.^{5,6,9,10}

A study done by Sulyman and others in Nigeria reported that 82% of HIV/AIDS patients on HAART presented with ORL manifestations.⁹

In another study done by Campanini and others in Italy it was found that the use of HAART has reduced ENT manifestations from 79% to 27%.¹⁰

Other ORL manifestations are characteristic and present more commonly in adults than in children, such as Kaposi sarcoma, B cells lymphoma, and other tumours.

The parotid gland hypertrophy is infrequent in adults but very common in children.^{11,12}

Oral candidiasis (60%), oesophageal candidiasis (16%), persistent generalised lymphadenopathy (27%) and Kaposi sarcoma (26%) have been found to be the most common ORL manifestations of AIDS.¹³

In another study done in Cameroon¹⁴ it was found that pharyngeal and oral candidiasis represented the most observed manifestations of HIV infection (30.6%) followed by peripheral facial paralysis (11.13%) and rhinosinusitis (10.58%). Parotid gland hypertrophy represented 8.23%, followed by persistent cervical lymphadenopathy (7.05%).

Kaposi sarcoma and cervical lymph node tuberculosis represented 3.53% each.¹⁴

Oropharyngeal lesions have been reported in 60.2% of patients followed by otological diseases (24.5%).⁶

In the study done by Sulyman and others among HIV/AIDS patients on HAART, oral candidiasis was reported to be 44.9% followed by cervical lymphadenopathy 33.7%.⁹

A study done by Campanini and others among AIDS patients on HAART reported significantly reduced cases of oropharyngeal candidiasis among the patients to 10% and observed that there was no patient with benign lymphoepithelial cyst of the parotid gland.¹⁰ HIV infected children seem to be more susceptible to common ORL diseases of childhood. About 90% of HIV infected children have been found to have ORL symptom(s),^{15,16} another study has reported a lower frequency (50%).¹⁷ The majority of these children had their first ORL manifestation diagnosed before HIV infection was established.¹³

The most common ORL manifestations among children included cervical lymphadenopathy (70%), otitis media (46%), oral candidiasis (35%) and adenotonsillar disease (31%).¹⁷ Another study has found that oral candidiasis (59.6%), cervical lymphadenopathy (41.6%), repeated upper respiratory tract infections (39.5%), otitis media (18.4%), parotitis (5.2%) and sinusitis (0.8%) are the common ORL manifestations of HIV infection among children.¹⁸

Raimar and others found the prevalence of chronic otitis media among HIV/AIDS children on HAART was 14.2%.⁵⁰

Cervical lymphadenopathy

Idiopathic follicular hyperplasia is the most common cause of cervical lymphadenopathy in these patients and is clinically evident in 12% to 45% of HIV infected patients.^{5,19}

Infectious and neoplastic aetiologies may also cause cervical lymphadenopathy in HIV infected patients.²

Infectious causes include:

Mycobacterial lymphadenitis, Pneumocystis lymphadenitis, viral lymphadenitis, bacterial lymphadenitis or an abscess secondary to oropharyngeal infection.

Neoplastic causes are:

Lymphoma, metastatic Kaposi sarcoma or metastatic carcinoma.

Persistent generalised lymphadenopathy is a common idiopathic cause of cervical lymphadenopathy in HIV infected patients and a common early symptom of HIV infection.² It is defined as lymphadenopathy without an identifiable infectious or neoplastic aetiology which involves two or more extralingual sites for at least 3 months in a patient at risk for or confirmed to be HIV infected.^{20,21,22}

Fine needle aspiration cytology should be the initial method of tissue sampling in most cases of suspicious cervical lymphadenopathy in HIV infected patients.

An open diagnostic biopsy should be done following negative or inconclusive fine needle cytology with a suspicion of malignancy or infection, open biopsy of suspected metastatic carcinoma should be avoided.²

Salivary glands manifestations

The majority of parotid enlargement in HIV infected patients is a result of a benign cystic lymphoproliferative process known as benign lymphoepithelial cyst.² It presents with a persistent non tender parotid enlargement with varying proportions of solid and cystic components and although only unilateral clinical disease may be evident, radiological evaluation nearly always reveals bilateral changes.¹¹

T cell analysis revealed the tendency of this lesion to occur in the early stages of immunodeficiency when T cell counts are high.

Cystic enlargement of the parotid glands occurs in HIV infected patients in a higher incidence.

In 47% of patients studied, parotid swelling was the chief complaint leading to the diagnosis of HIV infection.²³

Among children with HIV infection, 30% have been found to have bilateral parotid enlargement as a result of lymphocytic infiltration of the gland parenchyma.²⁴

Fine needle aspiration cytology was found to be useful both diagnostically and therapeutically.²³

Candidiasis

Candidiasis has been found to be the most common oral/oropharyngeal manifestation of HIV infection.^{5,13,17,18,25,26,27,28,29,30,31}

Candidiasis may present in the oral cavity as:²

- (i) atrophic candidiasis
- (ii) hyperplastic candidiasis
- (iii) pseudomembranous candidiasis

Atrophic candidiasis presents as zones of hyperaemia and tenderness on the dorsum of the tongue or the hard palate. Hyperplastic candidiasis presents as raised white plaques on the buccal mucosa that cannot be scrapped off.

Pseudomembranous candidiasis appears as a creamy, white curd like plaques on the buccal mucosa, tongue and other oral mucosal surfaces, plaques can be wiped away leaving a red or bleeding underlying surface.

Herpes simplex

Herpes labialis commonly presents as crops of blisters on the palate, gingival and other oral mucosal surfaces.² The lesions tend to be larger, more numerous and persist for a longer period than in non HIV subjects. They can also extend to adjacent skin, coalesce to form giant herpetic lesions.

Hairy leukoplakia

Presents as a white vertically corrugated lesion along the lateral border of the tongue. It occurs almost exclusively in HIV infected patients and is associated with rapid progression to full blown AIDS.

EBV is the probable cause. It has been found in 19.7% of patients with oral manifestations of AIDS.²⁶

Aphthous ulcers

Aphthous ulcers are of different types, all of which affect unattached oral mucosa.

Herpetiform ulcers are smaller than 0.2 mm in diameter and are self limited. Minor aphthous ulcers are well circumscribed, painful ulcers less than 6 mm in diameter with an erythematous halo.

In HIV infected patients the ulcers usually coalesce to form larger lesions lasting about 2 weeks.²

Malignancies

Patients with HIV/AIDS have a higher risk of acquiring certain tumours, particularly Kaposi sarcoma, non Hodgkin's lymphoma, hepatocellular carcinoma and cervical cancer.¹

This increased risk of acquiring malignancies is due to a weakened immune system with reduced ability to destroy cancer cells and fight viral infections (HPV, HHV8, and EBV) that may lead to cancer.¹

The immune system in AIDS is weakened by¹:

- (a) profound defects in T cell immunity
- (b) dysregulated B cell and monocyte functions

Kaposi sarcoma

Kaposi sarcoma (KS) is a neoplasm that often manifests with multiple vascular nodules in the skin and other organs. It is a spindle cell tumour thought to be derived from the endothelial cell lineage.³² Although true metastases appear to occur, a multifocal origin is most common. It may present as a patch, plaque, nodular, exophytic, infiltrative or lymphadenopathic Kaposi sarcoma.³³

The pattern of Kaposi sarcoma is variable, with a course ranging from indolent (only skin manifestations) to fulminant (extensive visceral involvement). It also may arise primarily in the oral mucosa, lymph nodes, and/or viscera without skin involvement.

Kaposi sarcoma (KS) is described in 4 clinical forms:³³

(i) Classical Kaposi sarcoma

Seen in elderly men and women of Mediterranean and Eastern European origin. It has a male predominance with a male to female ratio of 10-15:1. The age of onset is between 50 and 70 years.

It carries an indolent course; rarely it has lymph node, mucous membrane or visceral involvement. Its occurrence may be due to immune suppression from old age, host genetics, history of other neoplasms and possible concurrent infections such as malaria.

(ii) African endemic Kaposi sarcoma

This variant occurs primarily in males but also in women and children who are HIV seronegative in Africa and may carry an indolent or aggressive course. It was relatively common before the AIDS epidemic.

(iii) Epidemic Kaposi sarcoma

This is the variant seen in patients with HIV/AIDS. It is the most common presentation of Kaposi sarcoma and clinically the most aggressive. It is also the most common malignancy seen in HIV infected patients where access to HAART is limited.

(iv) Iatrogenic Kaposi sarcoma

This type of Kaposi sarcoma is noted in organ transplant recipients being treated with immunosuppressive medications. It is aggressive with visceral involvement being common. Withdrawal of immunosuppression may cause regression of the disease.

In ORL, Kaposi sarcoma lesions may be cutaneous (facial), oral or pharyngeal,²⁵ mainly occurring on the hard palate.³⁴

Kaposi sarcoma of the larynx has also been reported and may present with hoarseness of voice, airway obstruction, cough and dyspnoea.

The lesions are usually multifocal at presentation, with the head and neck as the primary site of involvement (62.5%).³³ Kaposi sarcoma lesions have been reported in 35% of patients with AIDS who had head and neck manifestations.²⁵ Other studies have reported Kaposi sarcoma to be a less common manifestation.^{29,30} Kaposi sarcoma was reported in only 6.6% of HIV/AIDS patients on HAART.¹⁰

The occurrence of Kaposi sarcoma lesions in HIV infected patients advances their classification to having the acquired immunodeficiency syndrome (AIDS).⁷

The lesions are unpredictable and either progress, remain static or occasionally regress spontaneously.³³ The majority of patients with AIDS who had Kaposi sarcoma involving head and neck structures were asymptomatic (80% of cases).³⁴

The mortality rate of AIDS patients with Kaposi sarcoma of the head and neck has been found to be extraordinarily high (62%) with an average longevity of 11 months following initial diagnosis.³⁴

Hearing loss

Among HIV infected patients conductive hearing loss is the main cause of hearing loss, it may be caused by otitis media with effusion due to Eustachian tube stenosis³⁵ or chronic suppurative otitis media.

Various degrees of sensory neural hearing loss may be found in as many as 49% of patients with HIV infection,³⁵ it may be unilateral or bilateral and usually worsens with increasing frequencies.

Possible aetiologies are a primary infection by HIV of the central nervous system or peripheral auditory nerve, cryptococcal meningitis, use of HAART or idiopathic.³⁵

Otitis media

The common otologic problems reported in HIV infected patients are:

- (i) recurrent acute otitis media
- (ii) suppurative otitis media

These conditions frequently affect paediatric patients with HIV infection.^{16,18}

This could be due to dysfunctioning of the Eustachian tube from adenoids hypertrophy, nasopharyngeal neoplasms or allergies and their related mucosal changes.¹⁶

Chronic suppurative otitis media has been found to be the commonest otologic manifestation of HIV infection (13%).⁵

Otitis externa

In HIV infected patients the risk of otitis externa and malignant otitis externa is increased and they have a dramatic course.³⁷

The causative agent is usually *Pseudomonas aeruginosa* although *Mycobacterium tuberculosis* has also been reported.³⁸

In otitis externa patients present with hearing loss, otalgia and purulent debris in the external auditory canal.

Malignant otitis externa (necrotising externa otitis) should be suspected among these patients when otalgia, swelling, otorrhoea and tissue necrosis persist despite therapy or when there is onset of facial nerve paralysis or other cranial nerve dysfunction.²

Early diagnosis and management of malignant otitis externa is essential since this is a life threatening disease especially in a patient with low CD4 count and neutropenia.

Other otologic manifestations

Vestibular hyporeflexia, mixed hyposmia and hypogeusia has been reported among HIV infected patients due to involvement of multiple cranial nerves.^{30,31}

Sinonasal infection

Symptoms of sinonasal disease are among the most common complaints of HIV infected individuals.

Almost 70% of these patients will report an episode of acute sinusitis and 58% of these will develop either recurrent acute or chronic sinusitis.^{40,42}

Other studies have reported a lower frequency.^{29,42}

It has also been reported to be the commonest nasal complaint (17% of patients) among patients with HIV manifestations of otolaryngology.⁵

The maxillary and ethmoid sinuses are most frequently involved.⁴²

Three pathogenic mechanisms have been proposed as contributing to the high incidence of sinusitis in HIV infected patients:⁴²

- (i) impaired systemic and local immunity leaves the host susceptible to infections
- (ii) decreased mucocilliary clearance with stasis of secretions in the sinuses and increased susceptibility to infections

(iii) increased atopy (attributed to polyclonal B cell activation with increased immunoglobulin production, including immunoglobulin E) manifesting as new or increased allergic symptoms.⁴⁴

There is a broader spectrum of bacteria implicated in sinusitis associated with HIV infection than in the general population.

The most commonly cultured organisms are *Streptococcus pneumoniae*, *Streptococcus viridians*, coagulase negative staphylococci, *Staphylococcus aureus* and *Haemophilus influenzae*.⁴²

Pseudomonas aeruginosa and fungi including *Aspergillus* and mucormycosis are important because they cause a clinically more severe sinonasal disease in HIV infected patients.²

Aspergillus fumigatus is the most common fungal pathogen in HIV sinusitis though *Candida albicans*⁴⁵ and others have also been reported.

Fungal sinusitis can extend via thrombophlebitic or hematologic spread and enter into the orbit or cranium without evidence of mucosal invasion.³⁶

Nasal allergy

In HIV infected patients there is B cell activation leading to increased production of circulating immune complexes and immunoglobulins A, G and E.

Excessive immunoglobulin E production is associated with increased immunoglobulin E mediated allergic symptoms including allergic rhinitis.^{44, 46}

Laryngeal tuberculosis

Laryngeal tuberculosis has been reported among HIV infected patients. The condition poses a significant hazard to otolaryngologists. A delay in the diagnosis of laryngeal tuberculosis has occurred in 100% of patients with HIV infection.⁴⁷

STATEMENT OF THE PROBLEM

HIV infection is an epidemic that has affected the Sub Saharan Africa more than any other part of the world. In 2007, 1.4 million people were living with HIV infection in Tanzania.⁴

Despite the large number of HIV infected individuals, information regarding otorhinolaryngological manifestations of HIV infection in Tanzania is very limited. Studies done in other countries have reported that otorhinolaryngological manifestations of HIV infection are very common.^{5,6,9}

As the CD4+ T lymphocytes levels decline, both the humoral and cell mediated immunities are impaired resulting in increased vulnerability to infections, neoplasms, increased atopy and autoimmune diseases.¹

JUSTIFICATIONS OF THE STUDY

This study will provide an update prevalence of ORL manifestations among HIV/AIDS patients attending HIV clinic at MNH.

Furthermore the study will enable health workers to be aware of signs of HIV infection including these manifestations early enough and provide timely intervention along with HAART to improve survival rates of HIV infected patients.

OBJECTIVES

Broad objective

To define the prevalence of all otorhinolaryngological manifestations of HIV/AIDS among HIV infected patients attending at the HIV clinic of MNH.

Specific objectives

1. To determine the prevalence of otorhinolaryngological manifestations among HIV/AIDS patients by age
2. To determine the prevalence of otorhinolaryngological manifestations among HIV/AIDS patients by sex
3. To determine the prevalence of otorhinolaryngological manifestations in relation to CD4+ T lymphocytes count levels.

METHODOLOGY

Study design

This was a cross sectional hospital based descriptive study.

Setting

The study was conducted at HIV clinic at MNH.

MNH (Muhimbili National Hospital) is a national referral hospital and a teaching hospital collaborating with Muhimbili University of Health and Allied Sciences (MUHAS).

Study population

This consisted of all HIV positive patients attending HIV clinic at MNH.

Inclusion criteria

The following patients were included in the study:

1. All HIV positive patients proved by laboratory HIV tests (PCR, ELISA, Rapid test, Determinant) who are attending HIV clinic at MNH.
2. Patients who consented for the study.

Exclusion criteria

The only patients excluded from the study were those who did not consent.

Sample size calculation

The sample size was calculated using formula:

$$N = Z^2P(100-P)/E^2$$

Whereby:

Z is a critical value 1.96, N is an estimated sample size

E is a margin of error (4%)

P is the prevalence of ORL manifestations of HIV infection
(in Nigeria it is 80%)

$$\text{Hence } N = (1.96)^2 \times 80(100-80)/(4)^2 = 384$$

Sampling procedure

All patients meeting the inclusion criteria were enrolled into the study.

Data collection

Data was collected by the investigator only using a designed questionnaire.

Collected data included age, sex of the patient and any otorhinolaryngological complaints reported by the patient.

A thorough otorhinolaryngological examination was conducted by the investigator on all patients and the findings were recorded accordingly.

Non invasive (X rays – nasopharynx lateral view, paranasal sinuses Water's view/Caldwell view) and invasive procedures including blood for CD4 cell count and biopsy taking were also done when appropriate.

X rays were reported by a radiologist at Muhimbili Radiology Department.

The biopsy specimens were processed at the Central Pathology Laboratory at MNH.

Data analysis

The analysis was conducted as mentioned bellow:

1. Double entry of data was done using Epi-info 6.
2. Cleaning of data was done.
3. Epi – info 6 file exported to SPSS program for analysis.
4. Descriptive statistics were performed.
 - t – test was used to determine association of quantitative variables.
 - Chi square test was used to determine the association of qualitative variables.
 - $p < 0.05$ was taken as significant.

ETHICAL CONSIDERATIONS

1. The study received ethical clearance from the Directorate of Research and Publication Committee of MUHAS and the Ethics Department of MNH.
2. Patients were included after informed verbal and written consent.
3. Patients found to have ORL manifestations were referred to the ENT department and managed accordingly.
4. Patients declining to participate in the study were not penalised in any way at all.
5. Considering the stigma associated with AIDS, patients' identity and records were treated with outmost confidence.
6. The results of the study shall be presented to the Department of Otorhinolaryngology and published in relevant reputable publications and media for the benefit of the patient, the public and medical fraternity. If necessary the patients shall be directly informed of any beneficial results immediately relevant for their management.

RESULTS

TABLE 1: AGE BY SEX

AGE GROUP (YEARS)	SEX		TOTAL
	MALE	FEMALE	
0 - 9	40(10.4%)	31(8.1%)	71(18.5%)
10 - 19	24(6.3%)	28(7.3%)	52(13.5%)
20 - 29	0	24(6.3%)	24(6.3%)
30 - 39	20(5.2%)	66(17.2%)	86(22.4%)
40 - 49	27(7.0%)	81(21.1%)	108(28.1%)
50 - 59	9(2.3%)	20(5.2%)	29(7.6%)
> 60	9(2.3%)	5(1.3%)	14(3.6%)
TOTAL	129(33.6%)	255(66.4%)	384(100%)

Chi-square test (p value < 0.05) indicated that the proportion of females (66.4%) involved in the study was statistically significant compared to that of males (33.6%).

The ratio of Male: Female was about 1:2.

The proportion of those involved in the study who were mostly aged 30 to 49 years old (50.5%) was statistically significant compared to the other age groups.

Table 2: PREVALENCE OF ORL MANIFESTATIONS BY AGE

AGE GROUP (YEARS)	ORL MANIFESTATIONS		TOTAL
	YES	NO	
0 - 9	27(38.0%)	44(62.0%)	71(18.5%)
10 - 19	16(30.8%)	36(69.2%)	52(13.5%)
20 - 29	12(50.0%)	12(50.0%)	24(6.3%)
30 - 39	32(37.2%)	54(62.8%)	86(22.4%)
40 - 49	31(28.7%)	77(71.3%)	108(28.1%)
50 - 59	7(24.1%)	22(75.9%)	29(7.6%)
> 60	6(42.9%)	8(57.1%)	14(3.6%)
TOTAL	131(34.1%)	253(65.9%)	384(100%)

Chi-square test (p value > 0.05) indicated that there is no significant association between the prevalence of ORL manifestations and the age of the patient.

Of those involved in the study 131(34.1%) were found to have ORL manifestations.

Most of those aged 20 – 29 years 12(50.0%) presented with ORL manifestations.

TABLE 3: PREVALENCE OF ORL MANIFESTATIONS BY SEX

ORL MANIFESTATIONS	SEX		TOTAL
	MALE	FEMALE	
YES	46(35.7%)	85(33.3%)	131(34.1%)
NO	83(64.3%)	170(66.7%)	253(65.9%)
TOTAL	129(33.6%)	255(66.4%)	384(100%)

The prevalence of ORL manifestations among males (35.7%) was slightly higher than that among females (33.3%).

Chi-square test (p value > 0.05) indicated no significant association between the prevalence of ORL manifestations and the sex of the patient.

TABLE 4: PREVALENCE OF ORL MANIFESTATIONS BY CD4 LEVELS

ORL MANIFESTATION	CD4 LEVELS(cells/mm ³)			TOTAL
	< 200	200 - 1000	>1000	
YES	42(56.0%)	74(29.4%)	15(26.3%)	131(34.1%)
NO	33(44.0%)	178(70.6%)	42(73.7%)	253(65.9%)
TOTAL	75(19.5%)	252(65.6%)	57(14.8%)	384(100%)

Chi-square test (p value < 0.05) indicated significant association between the level of CD4 T lymphocytes and the prevalence of ORL manifestations.

The occurrence of ORL manifestations was higher (56.0%) among AIDS patients (those with CD4 T lymphocytes count of less than 200cells/mm³) compared to those with CD4 T lymphocytes count of 200-1000cells/mm³(29.4%) and above 1000cells/mm³(26.3%).

TABLE 5: SPECIFIC ORL MANIFESTATIONS BY AGE

ORL manifestations	Age (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	>60	
Adenoids hypertrophy	1 3.7%	1 6.3%	0	0	0	0	0	2 1.5%
Tonsillitis	4 14.8%	4 25.0%	2 16.7%	4 12.5%	3 9.7%	2 28.6%	1 16.7%	20 15.3%
Rhinosinusitis	0	0	3 25.0%	5 15.6%	5 16.1%	1 14.3%	0	14 10.7%
CSOM	15 55.6%	4 25.0%	2 16.7%	1 3.1%	6 19.4%	1 14.3%	0	29 22.1%
Necrotising externa otitis	1 3.7%	1 6.3%	0	0	1 3.2%	0	0	3 2.3%
Candidiasis	2 7.4%	4 25.0%	0	2 6.3%	0	0	0	8 6.1%
Lymphoepithelial cyst (parotid)	3 11.1%	1 6.3%	0	5 15.6%	10 32.2%	1 14.3%	2 33.3%	22 16.8%
Kaposi sarcoma	1 3.7%	0	4 33.3%	5 15.6%	0	0	0	10 7.6%
Oropharyngeal malignancy	0	0	1 8.3%	1 3.1%	3 9.7%	1 14.3%	1 16.7%	7 5.3%
Parotid gland lymphoma	0	0	0	2 6.3%	0	0	1	3 2.3%
Nasopharyngeal malignancy	0	0	0	3 9.4%	0	0	0	3 2.3%
Submandibular gland abscess	0	0	0	0	1 3.2%	0	0	1 0.8%
Sinonasal malignancy	0	0	1 8.3%	3 9.4%	0	0	1 16.7%	5 3.8%
Bilateral SNHL	0	0	0	1 3.1%	2 6.5%	1 14.3%	0	4 3.1%
Total	27 20.6%	16 12.2%	12 9.2%	32 24.4%	31 23.7%	7 5.3%	6 4.6%	131 100%

ORL manifestations were common among those aged 30 – 49 years old (48.1%).

CSOM 29(22.1%), benign lymphoepithelial cyst of the parotid gland 22(16.8%), rhinosinusitis 14(10.7%) and Kaposi sarcoma 10(7.6%) were the frequently reported ORL manifestations.

Among those aged less than ten years 15(55.6%) presented with CSOM, those aged 20-29 years 4 (33.3%) presented with Kaposi sarcoma and 10(32.2%) of those aged 40-49 years presented with benign lymphoepithelial cyst of the parotid gland.

Except for one patient who was aged less than ten years who presented with Kaposi sarcoma, all other malignancies were reported among adults.

Four patients (3.1%) presented with bilateral SNHL and 3(2.3%) with necrotising otitis externa.

TABLE 6: SPECIFIC ORL MANIFESTATIONS BY SEX

ORL manifestations	Sex		Total
	Male	Female	
Adenoids hypertrophy	0	2(2.4%)	2(1.5%)
Tonsillitis	4(8.7%)	16(18.8%)	20(15.3%)
Rhinosinusitis	3(6.5%)	11(12.9%)	14(10.7%)
CSOM	16(34.8%)	13(15.3%)	29(22.1%)
Necrotising externa otitis	1(2.2%)	2(2.4%)	3(2.3%)
Candidiasis	3(6.5%)	5(5.9%)	8(6.1%)
Lymphoepithelial cyst (parotid)	9(19.6%)	13(15.3%)	22(16.8)
Kaposi sarcoma	3(6.5%)	7(8.2%)	10(7.6%)
Oropharyngeal malignancy	3(6.5%)	4(4.7%)	7(5.3%)
Parotid gland lymphoma	1(2.2%)	2(2.4%)	3(2.3%)
Nasopharyngeal malignancy	2(4.3%)	1(1.2%)	3(2.3%)
Submandibular gland abscess	0(0%)	1(1.2%)	1(0.8%)
Sinonasal malignancy	1(2.2%)	4(4.7%)	5(3.8%)
Bilateral SNHL	0	4(4.7%)	4(3.1%)
Total	46(35.1%)	85(64.9%)	131(100%)

ORL manifestations were common among females (64.9%) than among males(35.1%)

Among females the common manifestations were tonsillitis (18.8%), CSOM (15.3%), parotid cyst (15.3%) and rhinosinusitis (12.9%)

Among males the common manifestations were CSOM (34.8%), parotid cyst (19.6%) and tonsillitis (8.7%).

TABLE 7: SPECIFIC ORL MANIFESTATIONS BY CD4 LEVELS

ORL manifestations	CD4 levels (cells/mm ³)			Total
	<200	200-1000	>1000	
Adenoids hypertrophy	0	1(1.4%)	1(6.7%)	2(1.5%)
Tonsillitis	2(4.8%)	16(21.6%)	2(13.3%)	20(15.3%)
Rhinosinusitis	3(7.1%)	10(13.5%)	1(6.7%)	14(10.7%)
CSOM	6(14.3%)	16(21.6%)	7(46.7%)	29(22.1%)
Necrotising externa otitis	1(2.4%)	2(2.7%)	0	3(2.3%)
Candidiasis	7(16.7%)	0	1(6.7%)	8(6.1%)
Lymphoepithelial cyst (parotid)	6(14.3%)	13(17.6%)	3(20.0%)	22(16.8%)
Kaposi sarcoma	6(14.3%)	4(5.4%)	0	10(7.6%)
Oropharyngeal malignancy	4(9.5%)	3(4.1%)	0	7(5.3%)
Parotid gland lymphoma	1(2.4%)	2(2.7%)	0	3(2.3%)
Nasopharyngeal malignancy	1(2.4%)	2(2.7%)	0	3(2.3%)
Submandibular gland abscess	1(2.4%)	0	0	1(0.8%)
Sinonasal malignancy	3(7.1%)	2(2.7%)	0	5(3.8%)
Bilateral SNHL	1(2.4%)	3(4.1%)	0	4(3.1%)
Total	42(32.1%)	74(56.5%)	15(11.5%)	131(100%)

Most of the patients who presented with ORL manifestations 74(56.5%) had a CD4 T lymphocytes count of 200-1000 cells/mm³.

Among those with AIDS (CD4 count of less than 200cells/mm³) 16.7%, 14.3%, 14.3%, 14.3% presented with oral cavity and oropharyngeal candidiasis, CSOM, benign lymphoepithelial cyst of the parotid gland and Kaposi sarcoma respectively.

Tonsillitis (21.6%), CSOM (21.6%), benign lymphoepithelial cyst of the parotid gland (17.6%) and rhinosinusitis (13.5%) were common among patients with CD 4 count 200-1000 cells/mm³.

None of those with CD4 T lymphocyte cell count of above 1000cells/mm³ presented with Kaposi sarcoma or other malignancies.

DISCUSSION

The study was conducted among a sample of 384 HIV positive patients attending the HIV clinic at MNH.

All of these patients (100%) were on HAART.

Of these 129(33.6%) were males and 255(66.4%) were females, a ratio of 1:2.

Most of the participants 194(50.5%) were aged 30-49 years old.

This could be due to the fact that most of the HIV infection is occurring in this age group. In the 2003-2004 Tanzania HIV/AIDS Indicator Survey it was found that the prevalence of HIV infection reaches a peak at age 30-34 for women and 40-44 for men.⁴⁸

Only 14(3.6%) were 60 years old and above.

The prevalence of ORL manifestations was 34.1% in this study.

It is lower than that found in a study done by Somefun and others in Nigeria which found that 80% of patients with HIV infection present with ORL manifestations.⁶ Another study done in Nigeria by Sulyman and others among patients on HAART, ORL manifestations were reported in 82.2% of the patients.⁹ But in Italy a study done by Campanini and others reported that the use of HAART has reduced the prevalence of ENT manifestations from 79% to 27%¹⁰ (compared to a prevalence of 34.1% found in this study)

Among children younger than ten years, ORL manifestations were found in 38% of them.

Earlier studies have found that 90% of children present with ORL manifestations.^{15,16} Singh A and others reported a lower frequency of ORL manifestations among HIV infected children (50%).¹⁷

The difference could be due to the use of HAART among the studied patients.

ORL manifestations were found more in males than females, 35.7% and 33.3% respectively, it is similar to findings in a study done by Sulyman and others.⁹

In this study it was found that the occurrence of ORL manifestations was decreasing with increasing CD4 count levels. The occurrence of ORL manifestations was higher among patients with CD4 count of less than 200 cells/mm³(56.0%) compared to those with CD4

count of 200-1000cells/mm³ and above 1000cells/mm³ which were 29.4% and 26.3% respectively.

HIV infected patients with a CD4 count of less than 200cells/mm³ are classified as AIDS patients according to CDC and WHO classification⁷ therefore they are more prone to opportunistic infections and malignancies explaining the higher frequency of ORL manifestations among them.¹

CSOM (22.1%), benign lymphoepithelial cyst of the parotid gland (16.8%), tonsillitis (15.3%), rhinosinusitis (10.7%), Kaposi sarcoma (7.9%) and oral cavity/oropharyngeal candidiasis (6.1%) were the most common ORL manifestations in this study.

The low number of reported cases of oral cavity/oropharyngeal candidiasis (6.1%) and the absence of cases of idiopathic persistent cervical lymphadenopathy were noted in this study. This could be due to the use of HAART.

It is in variance to a study done by Sulyman and others which reported that oral candidiasis (44.9%) and cervical swelling (33.7%) were found among HIV/AIDS patients on HAART. A study by Campanini and others found that the use of HAART has significantly reduced the occurrence of oropharyngeal candidiasis among HIV infected patients to 10% and observed that there was no patient with benign lymphoepithelial cyst of the parotid gland.¹⁰

A study done by Ndjolo A and others in Cameroon showed that pharyngeal and oral candidiasis represented the most observed manifestations (30.6%), followed by peripheral facial paralysis (11.13%).¹⁴ The occurrence of rhinosinusitis (10.58%) was almost the same as was found in this study.¹⁴ Furthermore, parotid gland hypertrophy, persistent cervical lymphadenopathy and Kaposi sarcoma represented 8.23%, 7.05% and 3.53% respectively.¹⁴

A study done by Prasad HK and others found that rhinosinusitis was the commonest nasal complaint occurring in 17% of patients with otolaryngological manifestations of AIDS.⁵

A study carried out in Italy revealed an occurrence of 6.6% of Kaposi sarcoma in the head and neck among HIV infected patients on HAART¹⁰ (compared to 7.9% found in this study).

In another study done by Herdman RC and others it reported oral candidiasis (60%), oesophageal candidiasis (16%), persistent generalised lymphadenopathy (27%) and Kaposi sarcoma (26%) were the most common ORL manifestations of AIDS.¹³

In this study among children younger than 10 years CSOM (55.6%), tonsillitis (14.8%), benign lymphoepithelial cyst of the parotid gland (11.1%) and oral cavity/oropharyngeal candidiasis (7.4%) had a higher occurrence.

The findings are at variance to a study done by Singh and others which reported cervical lymphadenopathy (70%), otitis media (46%), oral candidiasis (35%) and adenotonsillar disease (31%) were the commonest ORL manifestations among children.¹⁷

A study done by Prasad HK and others found chronic suppurative otitis media to be the commonest otologic manifestation of HIV infection(13%).⁵

In a study done in Brazil among children on HAART, chronic otitis media was reported in 14.2% of the children.⁵⁰

Only one child presented with Kaposi sarcoma in this study. Otherwise other cases of Kaposi sarcoma (6.9%), parotid gland lymphoma (2.3%) and other malignancies including nasopharyngeal, sinonasal and oropharyngeal (comprising 11.4% of all ORL manifestations) were reported among adults.

Among patients with AIDS (CD4 less than 200cells/mm³) oral cavity/oropharyngeal candidiasis (16.7%), Kaposi sarcoma (14.3%), benign lymphoepithelial cyst of the parotid gland (14.3%) and CSOM (14.3%) were the commonly reported ORL manifestations.

These AIDS patients due to the severely compromised immunity also have a higher occurrence of ORL malignancies (21.4%) compared to only 12.2% among those with CD4 count of 200 cells/mm³ to 1000cells/mm³.

This could be due to the fact that with a weakened immune system the body has a reduced ability to destroy cancer cells and fight viral infections that may lead to cancer (HHV8, HPV and EBV).¹

None of the participants with CD4 count above 1000 cells/mm³ presented with Kaposi sarcoma or any other ORL malignancies.

CONCLUSIONS

ORL manifestations occurred in about a third of the studied HIV infected patients who were attending the HIV clinic at MNH.

All of the studied patients were on HAART.

Leading complaints were CSOM, benign lymphoepithelial cyst of the parotid gland, tonsillitis, rhinosinusitis, Kaposi sarcoma and oral cavity/oropharyngeal candidiasis.

With more people coming forward for voluntary counselling and testing for HIV infection, it is important for the otorhinolaryngologist to be aware of the otorhinolaryngological manifestations so that early diagnosis of HIV infection and timely intervention alongside appropriate antiretroviral therapy can be instituted to improve survival rates.

RECOMMENDATIONS

This is the first study to be done in Tanzania, more studies should be done to explore more this topic and especially on the impact of HAART on ORL manifestations.

Patients with HIV/AIDS should be managed by a multidisciplinary team of an Otorhinolaryngologist, a Physician or HIV/AIDS clinician and an Oncologist among others.

LIMITATION OF THE STUDY

This was a tertiary hospital based study, it could be that the participants of the study were only the very sick who were referred here from other hospitals.

IMAGES

(i) *A child with necrotising externa otitis*



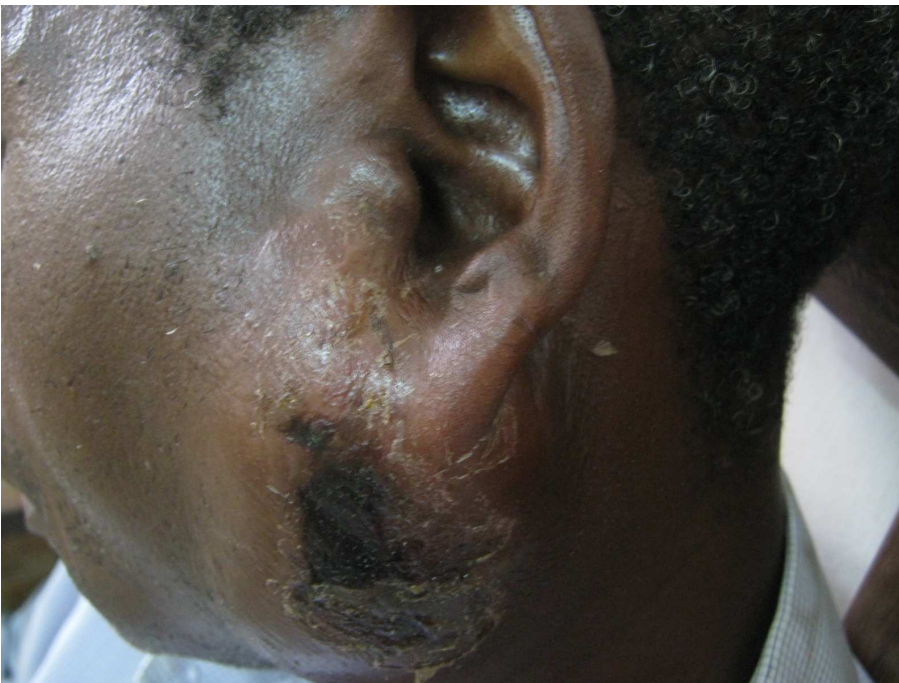
(ii) *An adult with obstructive tonsillitis.*



(iii) A patient with Kaposi sarcoma lesions in the oral and nasal cavities.



(iv) A patient with an infected parotid cyst following aspiration at a peripheral hospital.



(v) A patient with a parotid gland lymphoma. A healed open (incisional) biopsy scar is seen.



(vi) A young woman with squamous cell carcinoma of the oropharynx.



(vii) A patient with sinonasal carcinoma eroding the hard palate.



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ANNEXES

(i) INFORMED CONSENT FORM, ENGLISH VERSION

Dear patient/parent/guardian, we would like to enrol you/your child in the research that will be conducted at the HIV clinic at MNH.

Study objective

To determine the prevalence of otorhinolaryngological manifestations among HIV infected patients attending the HIV clinic at MNH.

Methodology

All patients attending the clinic will be assessed for any otorhinolaryngological manifestation(s) of HIV infection.

X rays, blood and biopsy/cytology collection will be conducted when necessary.

Benefits of the study

The study will provide an update prevalence of ORL manifestations among HIV infected patients attending the HIV clinic at MNH

The study will also enable health workers to be aware of signs of HIV infection including these manifestations early enough and provide timely intervention along with HAART to improve survival rates.

Any patient with otorhinolaryngological disease will be managed properly

Negative effects

Some of the procedures will be invasive (blood collection and biopsy/cytology taking) hence mild pain and bleeding is expected but local anaesthesia and/or analgesics will be provided when appropriate. Otherwise no major negative effects are anticipated.

Confidentiality

Participation of patients will be anonymous; particulars of patients will not be open to the public in any way.

For any problem or question please contact the following:

Research supervisor:

Prof. N.H.Moshi,
Department of ORL,
MUHAS,
P.O.BOX 65001,
Dar es Salaam.

Principle investigator:

Dr. Henry Swai,
Department of ORL,
MNH,
P.O.BOX 65000,
Dar es Salaam.

Conclusion

I have received and understood the information provided above, my questions have been answered and I am ready/not ready to participate in the study.

Signature of patient/parent/guardian

Signature of Principal Investigator

INFORMED CONSENT FORM, SWAHILI VERSION

Ndugu mgonjwa/mzazi/mlezi, tunapenda kukushirikisha/kumshirikisha mwanao kwenye utafiti wetu utakaofanyika kwenye clinic ya wenye maambukizi ya virusi vya UKIMWI.

Madhumuni ya Utafiti

Kuangalia ukubwa wa matatizo ya koo, pua na masikio miongoni mwa wagonjwa walioambukizwa virusi vya UKIMWI wanaohudhuria kliniki ya wenye maambulizi ya virusi vya UKIMWI, MNH

Namna utafiti utakavyofanyika

Wagonjwa wote wanaohudhuria kliniki ya wenye maambukizi ya virusi vya UKIMWI watachunguzwa kama wana matatizo yoyote ya koo, pua na masikio kutokana na maambukizi hayo.

Faida za Utafiti

Utafiti utatupa kiwango kipya cha matatizo ya koo, pua na masikio miongoni mwa wagonjwa wenye maambukizi ya virusi vya UKIMWI

Utafiti pia utawawezesha wahudumu wa afya kutambua dalili za maambukizi ya virusi vya UKIMWI mapema pamoja na magonjwa ya koo, pua na masikio yanayoambatana na maambukizi haya na kutoa matibabu stahili mapema ikiwa ni pamoja na dawa za kurefusha maisha ili kupunguza vifo.

Mgonjwa yeyote atakayekutwa na matatizo ya koo, pua na masikio atapatiwa matibabu stahili.

Madhara ya Utafiti

Baadhi ya vipimo vitahitaji kuchomwa sindano kwenye mshipa wa damu ili kutolewa damu au kukatwa nyama kidogo kutoka kwenye uvimbe ili ikapimwe. Vipimo hivi vitaambatana na maumivu na/au kutokwa na damu kidogo.

Dawa ya kuzuia/kutuliza maumivu itatolewa pale itakapohitajika

Vinginevyo hakuna madhara yoyote makubwa yanayotarajiwa.

Usiri

Jina na habari nyingine zote za mgonjwa zitakuwa ni siri kati ya mgonjwa na mtafiti, hakuna mtu mwingine yeyote atakayeruhusiwa kuziona.

Tafadhali usisite kuwasiliana na wafuatao kama utakuwa na maswali au matatizo yoyote kuhusiana na utafiti huu:

Msimamizi wa Utafiti

Prof. N.H. Moshi,
Idara ya Koo, Pua na Masikio,
MUHAS,
P.O.BOX 65001,
Dar es Salaam.

Mtafiti

Dr. Henry Swai,
Idara ya Koo, Pua na Masikio,
MNH,
P.O.BOX 65000,
Dar es Salaam

Hitimisho

Nimepewa na nimeelewa maelezo yote hapo juu, maswali yangu yote yamejibiwa, nimekubali/sijakubali kushiriki kwenye utafiti huu.

Sahihi ya mgonjwa/mzazi/mlezi

Sahihi ya mtafiti

(ii) QUESTIONARE

1. File No.
2. Code No.
3. Date of enrolment.....
4. Sex 1. Male
2. Female
5. Age.....
6. Place of stay: Temeke.....
Ilala.....
Kinondoni.....
Others.....
7. Marital status: 1. Single
2. Married
3. Divorced
4. Widowed
5. Cohabiting
8. Latest CD4+T lymphocytes cell count

9. Any ORL disease?

YES **NO**

(a) Oropharyngeal candidiasis

(b) Kaposi sarcoma

(c) Hairy leukoplakia

(d) Tonsillitis

(e) Adenoids hypertrophy

(f) Parotitis

(g) Cervical lymphadenopathy

(h) Otitis media

(i) Otitis externa

(j) Nasal allergy

(k) Rhinosinusitis

(l) Others (specify).....

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10. Physical findings on examination.....

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11. Histology/cytology results.....

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12. Radiological findings.....

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