THE PREVALENCE AND CHARACTERISTICS OF CARDIOVASCULAR DISORDERS IN CHILDREN INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) AT MUHIMBILI NATIONAL HOSPITAL.

By
Sulende D. M. Kubhoja, M.D (DAR)

A dissertation submitted in partial fulfillment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the University of Dar es Salaam.

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the university of Dar es Salaam a dissertation entitled*: The prevalence and characteristics of cardiovascular disorders in children infected with human immunodeficiency virus type 1 (HIV -1) at Muhimbili National Hospital,* in partial fulfillment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health).

Dr. FESTUS M. KALOKOLA, MD., MMED., DIPL. HAEM/ONCOL.
(SUPERVISOR)

Dr. JOHNSON M. LWAKATARE, MB ChB., MRCP.
(CO-SUPERVISOR)

Date: 11/9/02

DECLARATION AND COPYRIGHT

I, Sulende Daudi Munubhi Kubhoja, 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.

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DEDICATION

To my daughters, Suzanne, Grace and my son Bwire.

To my beloved wife Jamillah.

To my teachers.

ABSTRACT

Introduction and review of Literature.

The prevalence and characteristics of HIV cardiac disorders vary from one area to another, and these have seldom been elucidated in African children. The cardiac disorders include disturbances of rhythm, pericardial effusions, cardiomyopathies, endocarditis, arteriopathies and other cardiac diseases.

Study objective

To determine the prevalence and characteristics of cardiovascular disorders in children infected with Human Immunodeficiency Virus type 1 (HIV-1).

Study design

A cross-sectional comparative hospital based study.

Setting

The study was conducted in the General Paediatric wards and General Paediatric outpatient clinics of Muhimbili National Hospital (MNH) in Dar es Salaam, from April 2001 to January 2002.

Subjects

A total of 280 children aged between 18 months to 7 years who were admitted in the wards or seen at outpatient clinic, were recruited for the study.

Methodology

All children aged between 18 months to 7 years attending Paediatric outpatient clinics or admitted to MNH medical Paediatric wards whose parents/guardians consented for the study and for HIV testing were enrolled for study.

A thorough history and physical examination was done on recruitment.

All children who tested positive for HIV infection formed the study group.

Children who tested negative for HIV infection formed the comparable group. Both groups were further subjected to cardiovascular assessment including chest X-Ray, Electrocardiogram and Echocardiogram.

Main outcome measures

The main outcome measures were the magnitude and characteristics of cardiovascular disorders among the two studied groups.

Results

The overall prevalence of cardiovascular disorders was 83/280. (29.6%)

The prevalence of cardiovascular disorders in HIV infected children was higher at 36/78 (46.2%) compared to 47/202 (23.3%) in HIV uninfected children.

The difference was statistically significant in the two studied groups, p=0.00017.

The common cardiac disorders strongly associated with HIV-infected children were; pericardial effusion 26.9%, Left ventricular dysfunction 24.7%, cardiomyopathy 24.4% and tachycardia 20.5%.

Conclusions and Recommendations.

1. Cardiovascular disorders are common among HIV-1 infected children at MNH.
2. Echocardiogram was the most important tool in diagnosing cardiac disorders.
3. Cardiac disorders in HIV-1 positive children were similar to those reported in other centres.
4. It is recommended that a thorough cardiovascular evaluation including Echocardiogram should be done in HIV infected children so as to diagnose cardiac disorders easily and offer better management.

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LIST OF ABBREVIATIONS AND ACRONYMS:

1. ACEI - Angiotensin converting enzyme inhibitors
2. AIDS - Acquired Immunodeficiency Syndrome
3. AMREF - African Medical and Research Foundation
4. BP - Blood Pressure
5. CCF - Congestive Cardiac Failure
6. CHD - Congenital Heart Disease
7. CHF - Congestive Heart Failure
8. CMV - Cytomegalovirus
9. CT ratio - Cardiothoracic ratio
10. DCM - Dilated Cardiomyopathy
11. 2D-ECHO - Two Dimensional Echocardiogram
12. EBV - Epstein-Barr Virus
13. ECG - Electrocardiogram
14. ELISA - Enzyme Linked Immunosorbent Assay
15. EF - Ejection Fraction
16. FDA - Food And Drug Administration
17. FS - Fractional Shortening
18. HAART - Highly Active Antiretroviral Therapy
19. HIV - Human Immunodeficiency Virus
20. LIP - Lymphoid Interstitial Pneumonitis
21. LV - Left Ventricle

22. LVIDd - Left Ventricular Internal Dimension at end diastole
23. LVIDs - Left Ventricular Internal Dimension at end systole
24. LVFS - Left Ventricular Fractional Shortening
25. MCT - Mother (maternal) To Child Transmission
26. MMC - Muhimbili Medical Centre
27. MNH - Muhimbili National Hospital
28. MOH - Ministry Of Health
29. M-mode - Motion mode echocardiography
30. MUCHS - Muhimbili University College Of Health Sciences
31. NACP - National AIDS Control Program
32. P^2C^2 - The Pediatric Pulmonary and Cardiac Complication of Vertically Transmitted HIV infection study group.
33. PCP - Pneumocystis Carinii Pneumonia
34. PLH - Pulmonary Lymphoid Hyperplasia
35. RHD - Rheumatic Heart Disease
36. UNAIDS - Joint United Nations Programme on HIV/AIDS
37. WHO - World Health Organization

1.0 REVIEW OF LITERATURE

1.1.1 History of HIV.

HIV was first identified in 1983; however studies of previously stored blood samples indicate that the virus entered the United States population sometime in the late 1970's. [1,2]

The HIV virus probably entered in Tanzania in the early 1980's. The first three cases of AIDS were reported in 1983 in Kagera region. Since then, cases have continued to increase, and by 1986 all regions of the country had reported AIDS cases. [3,4]

1.1.2 Epidemiology of HIV.

Twenty years after the first clinical evidence of AIDS was reported, AIDS has become the most devastating disease humankind has ever faced.

In 1991 it was predicted that in Sub-Saharan Africa, by the end of the decade, nine million people would be infected and five million would die, a threefold underestimation. [1,5,6]

HIV/AIDS is now the leading cause of death in Sub-Saharan Africa.

Worldwide, it is the fourth biggest killer. [1]

The most recent UNAIDS/WHO estimates show that, in 2001 alone, 5.4 million people were newly infected with HIV, of these; 800,000 were children below 15 years.[1]

Since the epidemic begun, more than 60 million people have been infected with the virus. The number of people living with HIV/AIDS globally at the end of 2001 were 40 million, of these; 2.7 million were children below 15 years.

In Sub - Saharan Africa, people estimated to be living with HIV/AIDS as of end 2001 were 24.5 million, 2.4 million being children below 15 years of age, the region where only 10% of world's population live. [1]

1.1.3 HIV/AIDS situation in Tanzania

An estimated number of people living with HIV /AIDS by the end of 1999 in Tanzania were 1.3 million. [6] About 60,000 AIDS cases are estimated to have occurred in the year 2000 alone and a cumulative total of 660,000 AIDS cases since the beginning of the epidemic in the country. [1,6]

Over 86% of AIDS cases are between the ages 20-49 years, and estimated AIDS deaths in Tanzania among adults and children in 1999 alone were 140,000. [6]

A total of 8,675 AIDS cases were reported to the NACP from 20 regions in 1998.

An estimated number of children (0-14 years) living with HIV/AIDS by the end of 1999 was 140,000. In the year 2000 AIDS cases aged 0-9 years were 600 (5%) of the reported cases. A significant number of AIDS cases are seen in children aged 0-4 years and very few AIDS cases in the age group 4-14 years. [1,6,7]

From 1987 to 2000 a total of 4,357 AIDS cases (4.13% of the total) were children between 0-4 years of age with a case rate of 78.8, while children between 5-9 years were 943 (0.89%) with case rate of 18.3. NACP estimates that only one out of five AIDS cases are reported; this is due to under utilization of Health Services, under-diagnosis, under reporting and delays in reporting. [6] In Dar Es Salaam reported AIDS cases in the year 2000 alone were 1,410 with case rate of 63.1. [6]

At MNH, HIV/AIDS cases ranked the 7th among all the diseases in Paediatric wards for the years 1997-1999. The prevalence of paediatric HIV infection among paediatric admissions increased from 0.7% to 5.6% in 1991/92 to 1997/98 respectively. [8].

In the paediatric Annual report of the year 1999/2000, out of 9453 total admissions, 413 (4.36%) cases were seropositive for HIV infection. [8]

A study done in Dar es Salaam at MNH in 1996 by Kawo et al, reported an overall prevalence of 19.2% for HIV-1 infection among all hospitalized children in general paediatric wards. The study also showed that, 24% of HIV infected children were below 4 months of age. [7]

1.1.4 Aetiology of HIV

Human Immunodeficiency viruses (HIV), which causes AIDS, are RNA cytopathic human retroviruses, named in 1986 by the International committee on viral nomenclature. These viruses are particularly trophic for T-helper (CD4) lymphocytes and macrophages, and humans are the only reservours. [9].

The most common type of HIV in East, Central and Southern Africa is HIV-1 while HIV-2 is found along with HIV-1 in parts of West Africa.

HIV-2 is rare outside West Africa. It is more common in towns and along routes of communication, less common in rural areas. HIV-1 and HIV-2 are both antigenically and genetically related and both demonstrate similar tropism to the T lymphocyte [10].

It has been reported that HIV-1 subtypes a, c and d in Tanzania are prevalent in Kagera, Dar es Salaam and Mbeya regions. In addition, recombinant strains have been identified in Mbeya. [11]

1.1.5 Mode of Transmission of HIV in Paediatrics

HIV has been found in blood, semen, saliva, tears, nervous system tissues, breast milk, and female genital tract secretions; however, only blood, semen, female genital tract secretions and breast milk have been proven to transmit the infection. [9,10,11] Epidemiological studies worldwide have documented three main modes of HIV transmission, namely: - sexual transmission, parenteral transmission, and perinatal transmission (vertical transmission). [10, 11,12] Vertical transmission of HIV infection from mother to child is estimated to account for over 80% of Paediatric HIV infection. It occurs in several ways:-

- The virus may cross the placenta, in some cases this may happen very early in gestation. HIV transmission from an infected mother to her baby is estimated to occur in about 15% to 45% of cases, in the absence of intervention. Vertical transmission may occur before, during or shortly after birth. [9, 10, 11, 12]
- Research from many different countries has shown that HIV is mostly transmitted through blood late in pregnancy, during labour and at delivery. Transmission during delivery may be due to mixing of maternal and fetal blood during contractions, contamination through mucous membranes, or via swallowing of infected maternal blood or cervical – vaginal secretions when the fetus passes through the birth canal.
- HIV can also be transmitted through breast milk. [12]

1.1.6 Risk factors for vertical Transmission

Recent studies confirm previous circumstantial evidence that maternal characteristics may influence vertical transmission. [12] This include a mother's clinical and immunological status during pregnancy and the duration of her infection and the viral load. The factors influencing viral load are: -

- Primary infection,
- Factors stimulating the immune system such as other chronic infections and intravenous drug use.
- Mode of delivery, whereby it has been suggested that an elective caesarian section delivery may reduce the rate of transmission because of reduced exposure to contaminated blood or cervical secretions. [12]

1.2 Pathogenesis of HIV-infection in Paediatrics

HIV infection is a multi-system disease causing a wide spectrum of manifestations. [13] Researchers world wide, have addressed the problem of clinical manifestations of HIV disease in children by carrying out clinical observations, biochemical, radiological imaging, autopsies and histochemical studies. [13,14,15,16]

Abuzaitoun et al. [17], revealed that, the clinical manifestations of HIV disease in children is a reflection of the multiple organ systems involved.

The severity of each manifestation varies by organ system and can be related in many cases to multifactorial causes.

These are; HIV replication in the affected tissues, concomitant opportunistic infection of the organ, effect of concurrent immunodeficiency or autoimmune mechanisms on the organ, and adverse end-organ drug effect (primary HIV therapy or prophylaxis regimes). Previous studies indicate that there is a need for further studies to ellucidate the pathogenesis of the systemic effect of HIV on different organ systems.[16,17]

After an acute non-specific illness, most vertically infected children show HIV-related manifestations in early infancy. [14]

At birth Neonates born to HIV-infected mothers and who will eventually prove to be infected may have no clinical signs of disease and may be indistinguishable from those who will be found to be uninfected.

A variety of pathologic lesions of infectious, degenerative, proliferative and vascular changes in tissues and organs of the different systems have been documented in HIV infected children. [14,15,16]

A classification of these multisystems has been formulated

and can be divided into four pathogenetic categories: -

- Primary lesions due to HIV infection itself of tissues or organs for example Lymphoreticular system and brain.
- Second category are associated lesions related to direct or indirect sequelae of HIV infection (opportunistic infections, PLH/ LIP complex.)
- The third category, are lesions of undetermined pathogenesis, for example, cardiomyopathy, arteriopathy, thrombocytopenia, nephropathy.

- Last, some lesions may be related to more than one pathogenetic mechanism (multifactorial) such as neoplastic disorders for example Kaposi's sarcoma and leiomyosarcomatosis of the gastro-intestinal tract . [16,17]

It has been documented that patients with HIV/AIDS get cardiac complications related to HIV infection. These include pericardial diseases such as pericardial effusions, disturbances of rhythm, malignant infiltration (neoplasms), marantic endocarditis and heart muscle diseases (myocarditis, cardiomyopathies). Pulmonary hypertension, drug related cardiotoxicity and thromboembolic diseases are also reported in HIV infected children. [16,17]

1.2.1 Associated lesions with possible effect on cardiac manifestations:

1.2.1.1 Opportunistic and repeated bacteria infections.

These infections are the most frequent life-threatening sequelae of HIV infection. They are the major causes of death, the most common being pneumocystis carinii, mycobacterium avium complex (MAC) and pseudomonas aeuroginosa infections. [18] Others include Toxoplasma gondii, cryptosporidia, fungi (candida and aspergillus species) and viruses (cytomegalo virus [CMV], herpes simplex). Certain opportunistic infections are much more common in adults than in children with HIV. Some have been implicated to cause cardiac abnormalities, such as pericarditis, at times with large pericardial effusions and often with cardiac tamponade.

In most cases the etiology of pericarditis has not been established, although in some cases known pathogens such as Mycobacterium tuberculosis, Staphylococcus, Cryptococcus, and herpes simplex were found. [13,14-18]

Herdy et al, [19] found pericarditis, endocarditis and Kaposi's sarcoma in 15/50 pathological findings in a retrospective study of HIV infected patients aged 3 months to 40 years. Hakim et al [20] at Zimbabwe did echocardiographic survey in HIV patients aged 15 to 60 years and reported a prevalence of pericardial diseases to be 19%, there were 2(1.3%) cases of constrictive pericarditis. Other studies have reported pericardial diseases including cardiovascular tumors and pulmonary hypertension in children infected with HIV. Pericardial diseases particularly pericardial effusion had a prevalence rate of 16 to 26% in HIV positive children. There was also a high prevalence and association of opportunistic infections in these children. [21,22]

The prevention, diagnosis and treatment of opportunistic bacterial infections remains the most significant day-to-day challenge to clinicians who care for HIV infected children. Repeated bacterial infections are common in children, presumably because the humoral immune response of the vertically infected child become defective before wide exposure to bacterial antigens has occurred and while the Immune system is still relatively immature. [13,18]

Cellular immunity plays a central role in preventing opportunistic infections. Studies have found that HIV-infected children with a CD4+ Count less than 200cells/mm^3 were six times more at risk than those with a CD4+ Count greater than 200cells/mm^3 to develop opportunistic infections. [18,21]

1.2.1.2 Pulmonary and Systemic Lymphoid Lesions:

Probably associated with Epstein-Barr virus causing right ventricular dysfunctions. Respiratory symptoms and signs are common in children with HIV/AIDS. Pulmonary Lymphoid lesions and pneumocystis carinii pneumonia are seen in many of these patients. The lesions are characterized by a spectrum extending from pulmonary lymphoid hyperplasia (PLH) to lymphoid interstitial pneumonitis (LIP). [21,22]

In many cases, there is an overlap between PLH and LIP, hence the designation PLH/LIP complex that is associated with a characteristic linear-nodular pattern on chest X-rays. [22]

Severe pulmonary diseases are frequent in patients with advanced HIV disease, and right ventricular failure (cor -pulmonale) is not unusual. [22]

Left and right ventricular dysfunction, recurrent bronchopulmonary disease, and primary pulmonary hypertension have also been reported by Lipshultz et al in P^2C^2 HIV Study group. [23]

1.2.1.3 Cardiac lesions related to inanition resulting from chronic debilitating disease process of AIDS:

Although deficiency of specific nutritional factor(s) has not been documented, nutritional status remains subnormal and failure to thrive continues despite adequate diet and nutritional support in these patients. [22]

There are reports describing selenium deficiency in patients with HIV disease. Assays of the heart muscle from patients with advanced HIV disease, has revealed a cardiomyopathy similar to Keshan disease. [22,24]

A potentially fatal form of cardiomyopathy caused by deficiency of the essential mineral selenium (Keshan disease). It was first observed in Keshan province in China and since has been found elsewhere in areas where selenium level in the soil is low. It has been also associated with coxsackie virus in individuals with selenium deficient or vitamin E deficient. [24]

1.2.2 Lesions of undetermined pathogenesis:

1.2.2.1 HIV Cardiomyopathy in paediatrics

Research in the area of HIV cardiomyopathy and other cardiac complications due to HIV has followed several avenues.

Early works by Joshi et al, [16] reported that some pediatric patients with HIV presented with cardiovascular compromise evidenced by shortness of breath, fatigability, costal and subcostal retraction, sinus tachycardia with gallop rhythm, tender hepatomegally, basal scattered rales and weak peripheral arterial pulses.

At autopsy, the hearts of these children were enlarged and overweight.

Biventricular dilatations were observed with no gross abnormalities of the valves or coronary arteries. The heart chambers or appendages contained no mural thrombi. Hypertrophies of the ventricular walls were not seen, probably due to dilatation. Intramural fibrosis was not observed on gross examination.

Microscopic examination of the myocardium revealed hypertrophy indicated by nuclear enlargement, increased diameter of myocardial fibers, and foci of vacuolation. This findings probably were related to hydropic or fatty change in the myocardium.

The myocardial interstitial were oedematous with or without foci of myxoid. Occasional small foci of myocardial fibrosis and endocardial thickening, particularly of the left ventricle was seen. [17,22,25]

Other autopsy findings related to congestive heart failure included serous effusions and visceral congestion. Florid congestive heart failure was the cause of death in one case.

Other rare focal cardiac changes included: -

- Sparse mononuclear and lymphocytic inflammatory infiltrates with or without myocyte necrosis.
- Intranuclear CMV inclusions in the endocardium and capillary endothelium without inflammatory reaction;
- Slight focal intimal fibrosis or medial calcification of small branches of the coronary arteries without significant luminal narrowing and
- Small chronic inflammatory infiltrates of the pericardium.

  In one case, Electron microscopic examination of the myocardium showed degenerative changes characterized by lipid droplets, swelling of mitochondria, sarcoplasmic reticulum, and cellular oedema. [22]

Few researchers have tried to look into the pathogenesis of dilated cardiomyopathy in paediatric HIV infection. Up to date the exact nature is not known. [16,22,25]

Infections, Immunologic factors, anemia, deficiency of nutritional factors, longer survivals due to early diagnosis and aggressive antimicrobials, HAART and supportive therapy have been implicated as one of the causes of dilated cardiomyopathy.

In a study to detect viral genomes by polymerase chain reaction in the myocardium of paediatric patients with advanced HIV disease, Bowles et al. [25] concluded that the presence of viral nucleic acid in the myocardium is common in HIV infected children. This was related to the development of myocarditis, dilated cardiomyopathy (DCM), congestive heart failure (CHF), and contributed to rapid progression of HIV disease. [25] The cellular and humoral immunodeficiency in children with AIDS have been associated with more severe damage by infections with cardiotropic viruses or by the more frequent occurrence of myocardial damage with viral infections (EBV or CMV) causing dilated cardiomyopathy (DCM) .Myocardial involvement with these viral infections occurs rarely in immunologically intact hosts. [17,25-33]

Lipshultz et al [29] has reported a prevalence of 30% for dilated cardiomyopathy in HIV infected children with encephalopathy versus 2% of those without encephalopathy. In another study, reported a 2-year cumulative incidence of 4.7% for CCF with dilated cardiomyopathy. [30] In a Zimbabwean study in adults, 14/151 (9%) of HIV infected patients had dilated cardiomyopathy by echocardiography. [20] Starc et al [31] reported an approximately 20% of HIV-infected children do develop depressed LV function or LV dilation (DCM). In addition, approximately 10% of HIV infected children studied (range 0.1-14 years) median age 22months had CHF or were treated with cardiac medications.

In study reports, DCM appeared to be more common in HIV-infected children than in seroreverted children and increased in frequency as HIV infected children progress to AIDS.

Cardiomyopathy appeared to reduce survival in HIV infected children. A relative risk of death of 2.76 in children with cardiomyopathy compared with children without cardiomyopathies have been documented. In these studies children were more likely to be short-term survivors (< 5 years) if cardiomyopathy was present. [26, 29, 30]

In one center, 25% of HIV-infected children who died had cardiomyopathy or died suddenly, 83% of these children had premorbid cardiomyopathy or arrhythmias. [30]

In general most of the published studies in dilated cardiomyopathy has been done in adults, little and its prevalence is known in paediatric age group.

1.2.2.2 Left ventricular dysfunctions in HIV infection

Left ventricular dysfunction is a frequent manifestation of HIV infection in children. Although it is commonly found in HIV infected children, the clinical significance is not fully understood. [27] Lipshultz et al in separate studies found a higher mortality in children who had decreased LVFS and increased LV dimension, thickness, mass or wall stress independent of CD4 count. [23,29] The P^2C^2 HIV study also found that in HIV infected children, 25% of them had a FS more than two standard deviations below normal and 42% of these patients also had depressed contractility. [29]

The prevalence of decreased left ventricular function in HIV infected children was 5.7% (Fs < 25%) with a two year cumulative incidence of 15.3% in another study. [31]

Twenty percent of HIV infected children developed LV dilatation or depressed left ventricular function in a similar study.

The incidence of CHF was 10% and LV hypertrophy was also commonly seen. Also found was an increase in heart rate or blood pressure. [31]

These results suggested that measures of LV function are clinically significant and that they may predict an increased risk of death in HIV infected children. [29]

1.2.3 HIV-Myocarditis in children

This has been found to be a common cause of left ventricular systolic dysfunctions. The most common viruses found in affected tissues are adenovirus and CMV in HIV infected children. [22,25,32]

Myocarditis have also been associated with dilated cardiomyopathy, or congestive heart failure in HIV infected children. Kovacs et al, [32] found that children who acquire CMV infection by 18 months of age had a higher rate of cardiomyopathy than those with HIV infection without CMV infection, [32]

1.2.4 Cardiac conduction System and HIV.

Bharati et al [34] reported on cardiac conduction system in six children with AIDS. These were fragmentation of the bundle of His with lobulation and fibrosis, vacuolation and fibrosis of the bundle branches, inflammatory infiltration of the myocardium and vessels of the different parts of the conduction system at autopsy were observed. In one child, left hemiblock on electrocardiogram that corresponded to pathologic abnormalities seen in left bundle branch was observed. The pathogenesis of the lesions of the conduction system is still unclear. [34, 35]

Herdy et al, [19] reported in a retrospective study that involved patients aged 3 months to 40 years in some of the E.C.G findings. These were sinus tachycardia, ST and T wave changes, low voltage, ST segment elevations and extrasystoles.

The results did not specify age and ECG abnormalities, and the cardiac lesions were very important even in patients without clinical signs. In another study ECG showed flattened T waves in five of eight with left ventricular hypertrophy, right ventricular hypertrophy, or both in seven of eight. Lipshultz et al and others in separate studies reported on electrocardiographic abnormalities to be prominent in children with HIV infection.

The abnormalities reported include tachycardia in 49 to 70% in children with HIV infection. Among the rhythm disturbances found are sinus arrhythmia, atrial ectopy, and ventricular arrhythmias. [23,29,30]

1.2.5 HIV Arteriopathy:

These lesions are seen in small and medium sized arteries of different organs, characterized by intimal fibrosis, fragmentation of elastic tissue fibrosis and calcification of media with variable luminal narrowing. [22,35]

A case report of extensive vascular calcification in an 8-years-old girl with perinatally acquired AIDS have been documented by Marquis et al. [36]

Complicating factors included cardiomyopathy, chronic lung disease, disseminated mycobacterium avium complex (MAC), and wasting syndrome. Plain abdominal films and CT of the abdomen revealed dense calcification of major vessels. Autopsy revealed calcification in the media of most major vessels typical of HIV arteriopathy. [36]

Arteriopathy, inflammatory lesions and atherosclerotic lesions have also been reported by Lipshultz et al. [29,31] Aortic root dilatation have been described in children with HIV infection aged two to nine years. Aortic root dilatation was found to be associated with increased viral load and lower CD4 count suggesting a direct pathogenic effect of the HIV virus. [31]

1.3.0 Risk factors for cardiac disease in HIV

Studies have revealed that, encephalopathy, wasting, decreased CD4 count and a prior history of a serious cardiac event are all predictors of cardiac complications associated with HIV infection in children. [26] Rapid progressors (those children who have an AIDS-defining condition other than LIP/PLH or severe immunosuppression in the first year of life) have been found to have increased respiratory rate, increased heart rate, and decreased fractional shortening on serial echocardiographic measurements. [27]

It is also documented that cardiac abnormalities that are present in rapid progressors lead to poor outcomes including an increased mortality rate. [27]

In one study, fifty-one percent (51%) of the children with HIV-related deaths had chronic cardiac disease diagnosed prior to death. [21] In another study serious cardiac events were found in 28% of patients after AIDS diagnosis, and cardiac dysfunction was found in 35% of patients who died during the study. [26] The same study reported serious cardiac events, which included transient and chronic congestive heart failure, hypotension, severe dysrhythmia, cardiac tamponade, cerebrovascular accidents associated with hemodynamic instability, or cardiac arrest. [26]

1.3.1 Congenital cardiovascular disorders with HIV infection

Congenital cardiovascular malformations have also been described in children with HIV infection. When comparing rates of congenital cardiovascular malformations in HIV-infected and uninfected children from the P2C2 HIV study no statistical significant differences was found in the prevalence rate between the two groups of children. [28]

In the P2C2 HIV study it was pointed out that the presence of cardiac abnormalities in fetuses of HIV positive women was confounded by various maternal factors. These fetuses may also be exposed to smoking, illicit drug use, Nutritional deficiencies, or co-infections that may affect the fetus regardless of HIV status. [28]

1.3.2 Drugs and cardiac disorders in paediatric HIV:

Bezold et al, [37] demonstrated that angiotensin converting enzyme inhibitors (ACEI) appeared to improve survival in HIV infected children with dilated cardiomyopathy (DCM). Controversies regarding the possible myocardial depressant effect of highly active antiretroviral therapy (HAART) for example Zidovudine has been reported. [37] This was later studied by Domanski et al. [38] Who came to a conclusion that; treating HIV infected children with AZT may be associated with the development of cardiomyopathy. [38]

Culnane et al [39] could see no adverse effects in HIV infected children in utero and neonatal exposure to Zidovudine followed up for as long as 5 to 6 years. [39]

1.3.3 HIV and CCF.

Thomas et al [40] reported that an approximate 10% of HIV infected children develop CCF or are treated with cardiac medications.

In addition, approximately 20% of HIV infected children develop LV dilatation with depressed LV function leading to CCF. Lipshultz et al [29] reported similar findings.

In general, higher prevalence rates of heart disease, ranging from 14% to 45% have been reported by echocardiographic method. [40]

1.4 Diagnostic procedures of cardiac diseases:

1.4.1 Clinical approach.

The history and thorough cardiovascular physical examination are used to screen for symptoms and signs of cardiac disease. Cardiovascular abnormalities can be detected clinically by examining arterial pulses (pulse rate, rhythm, character, volume, delay) blood pressure, venous pulses and precordium.

With this examination, conditions such as pericarditis, pericardial effusions and congestive cardiac failure can be detected. [41]

1.4.2 Roentgenographic Examination:

Chest X-Ray films provide information about cardiac sizes, chamber dilatations and shape. Features like dense calcifications of major vessels, which directly relate to the status of the cardiovascular system are also detected. Other conditions such as Tuberculosis, PCP, LIP/PLH, pleural effusion, changes in pulmonary vasculature and mediasternal widening can be detected.

The cardiac size is assessed by taking the maximum width of the cardiac shadow in a mid inspiration posteroanterior film. A vertical line is drawn down the middle of the sternal shadow and perpendicular lines from the sternal line to the extreme right and left borders of the heart; the sum of the lengths of these lines is the maximal cardiac width. The maximal chest width is obtained by drawing a horizontal line between the right and left inner borders of the rib cage at the level of the top of the right diaphragm. When the ratio is greater than 60% the heart is said to be enlarged. The normal range does not exceed 60% in paediatrics.

1.4.3 The electrocardiogram (ECG):

The electrocardiogram demonstrates anatomic and hemodynamic features principally by changes in the P, R,S,T wave, P-Q interval, QRS complex morphology. This can be demonstrated by a standard 12 lead or 15 lead surface ECG, exercise ECG, and 24 hours ambulatory ECG monitoring (Holter monitoring). The diagnosis of atrial enlargement, right or left ventricular hypertrophy, atrial-ventricular blocks, bundle branch blocks, dysrythmias and ischaemic changes can be made.

1.4.4 ECHOCARDIOGRAPHY (Ultra sonography)

Echocardiography has become an extremely important technique in the diagnosis of cardiac diseases in infants and children. There are no known risks to diagnostic ultrasound. This method can be used repeatedly in individual patients. Furthermore, it can be used to evaluate cardiac performance in a variety of circumstances, such as drug induced cardiac toxicity. [41]

1.4.4.1 Motion mode (M-mode).

This method is used to define the presence or absence of individual anatomic structures and their relationship to one another and to evaluate valvular and cardiac function in general. (41)

1.4.4.2 Cross section / two-dimensional Echocardiography.

This has greatly enhanced the ability to visualize spatial relationships of the cardiac structures by means of a number of different views.

Motion mode and two-dimensional Echocardiography complement each other with pulse continuous wave and color Doppler method with or contrast echocardiography. (41)

Using these methods, congestive heart failure, pericardial fluid accumulation, atrial or ventricular septal defects, cardiac valve problems, vegetations due to infective endocarditis, intracardiac tumors or hematoma, etc can easily be detected. When patients are examined by echocardiography, underlying cardiac abnormalities are confirmed or detected more often than using clinical symptoms and physical examination.

Echocardiography in patients with advanced HIV disease who otherwise do not have clinical cardiac signs may demonstrate abnormalities.

Echocardiography can detect impending tamponade and can identify cardiac abnormalities in 25% to 75% of adult patients with HIV infection. (20)

1.4.5. Microscopic Examinations and cultures:

Microscopic examination and cultures of the pericardial fluid can yield an etiologic agent, such as bacterial, fungal infection or lymphoma, which is amenable to therapy.

1.4.6 Histopathological diagnosis:

From the very beginning of the AIDS epidemic, cardiac involvement was first recognized at autopsy and later by non-invasive techniques, such as echocardiography. Paraf et al [33] reported that clinical cardiac manifestations are rare in the course of AIDS, but cardiac lesions could be found at autopsy in 60% of cases. Endomyocardial biopsy can be done to identify any treatable cause.

Kaposi's sarcoma (KS) and non-Hodgkin's Lymphoma involving the heart and pericardium can also be diagnosed through biopsy. [41]

1.5. Pediatric HIV/AIDS and cardiac disorders in Tanzania.

The available published research data in this subject have been done mainly in USA and Europe but little in Africa.

In Tanzania, two published studies in adult patients have been done at MNH, Lwakatare et al [42] wrote on Tuberculous pericarditis in patients with or without HIV infection while Cegielski et al [43] wrote on pericardial disease and HIV.

2.0 RATIONALE AND OBJECTIVES OF THE STUDY

2.1 Rationale

Cardiac abnormalities have been reported in HIV infected children.

The prevalence of paediatric HIV/AIDS in a hospital setting is quite high 19%.

A high mortality of 21.4% seen in HIV-1 infected children, which is 2.5 times higher than in HIV-uninfected children at our center is alarming. Clinical observations indicate that cardiac manifestations are high, but are as yet has not been studied.

However the prevalence of cardiac diseases in HIV infected children in Tanzania is not well known.

Morbidity and mortality in paediatric HIV/AIDS is attributable to opportunistic infections and diseases such as anemia, thrombocytopenia, LIP/PLH, or cardiac diseases. The control and proper management of these conditions is likely to have a positive effect on the quality of life of HIV infected children. A better understanding of cardiac abnormalities and the associated factors in HIV infected children is imperative because of the therapeutic benefits.

The study aimed at determining the prevalence and characteristics of cardiac abnormalities among HIV infected children seen at MNH, so as to determine to what extent pediatric HIV /AIDS contributes to cardiac morbidity.

2.2 Hypothesis:

There is a higher prevalence of cardiac abnormalities in HIV-infected children than in non-HIV infected children in our community.

2.3 OBJECTIVES:

2.3.1 Broad objective:

To determine the prevalence and characteristics of cardiac abnormalities among children with and those without Human Immunodeficiency virus infection at Muhimbili National Hospital, Dar- es- Salaam.

2.3.2 Specific objectives were:

1. To determine the prevalence of cardiac abnormalities among children with and without HIV infection.
2. To describe the demographic pattern of children with cardiac abnormalities with or without HIV infection.
3. To describe the presenting clinical features in children with cardiac abnormalities with and without HIV infection.
4. To describe the radiological, electrocardiographic (ECG) and echocardiographic, abnormalities in HIV and non-HIV infected children.

3.0 METHODOLOGY

3.1 Study design:

A cross-sectional comparative hospital based study.

3.2 Study setting:

The study was done in all Paediatric wards and Paediatric outpatient clinics of Muhimbili National Hospital (MNH) in Dar-es-salaam, Tanzania.

Muhimbili National Hospital is the largest tertiary referral and university teaching hospital in the country. It has six general Pediatric wards which admit children aged 1 month to 7 years with an average of 700 patients per month, including readmission's. [8] Majority of children come either as self referral or referred from Dar-Es-salaam urban and periurban hospitals, health centers and dispensaries. Some of children are referred from upcountry Hospitals.

The department also runs outpatient clinics at within the hospital. This setting was selected for study convenience. The hospital is able to do HIV screening tests (ELISA) and western blots, chest x-rays, ECG, and echocardiography.

3.3 Study Population:

The study Population were all children aged 18 months to 7 years either admitted or attending outpatient clinics of the department at MNH.

Children who tested positive for HIV and whose immune status for HIV was already known to be positive at the time of the study formed the study group. Children who tested negative for HIV formed the comparison group.

3.4 Recruitment of Study subjects:

All children regardless of their clinical status were recruited, as they came in the ward/clinic for the study so long they were 18months to 7 years and parents consented.

All parents/guardians who had children aged between 18 months to 7 years admitted or seen at out patient clinics were explained about the research. They were also requested to give their written or informed consent for their children to participate in the study and for HIV testing. Pre and post-test counseling was done to all parents/guardians who consented in collaboration with the counselor. HIV testing was done according to the TNACP Guidelines. [44]

All children aged 18 months to 7 years whose parents/guardians consented were tested for HIV infection. All children who tested positive for HIV infection and those already known and confirmed to be HIV infected being followed up during the study period formed the study group. Children who tested negative for HIV infection formed the comparison group. HIV positive and negative children were recruited/enrolled into the study by the author. Those enrolled were subjected to further physical and cardiovascular assessment including Chest X-ray, ECG and Echocardiogram. Recruitment and assessment was done daily except on Saturdays, Sundays and public holidays due to inaccessibility of the laboratory; until a required sample size of 280 children were attained. If a child was re-admitted during the study period while already in the study group, both the first and subsequent admission data were considered together.

3.5 The exclusion criteria were:

- Children below 18 months of age and above 7 years.
- Unwillingness of the parents/guardians to participate in the study.

3.6 Sample Size estimation.

The sample size was determined using EPI-INFO version 6-computer program software. The prevalence of cardiac manifestations in HIV infected children aged one day to 15 years from previous studies range from 14% to 45%. [16,17,22,25,29,30,31,40]

Assuming a 95% confidence interval and Power of 80%. Average percentage of HIV infected children with cardiac disorders being 14%(the "worst acceptable" value), and average percentage of HIV uninfected children with cardiac disorders of 4.0%; (From pilot study and previous studies done at MMC). [8,45] Using EPI-INFO (version 6) – computer program software, with the following specifications the total sample size was 256 children.

- Group 1/group 2: 1.0
- Percentage group 1 14.0%
- Percentage group 2 4.0%
- Power 80%
- Confidence level 95%
- Sample required in group 1 128
- Sample required in group 2 128
- Total number 256
- The estimated minimal sample size was a total number of 256 children.

Alternatively, the following statistical formula applies;

Formula $n = \frac{(Z_\alpha + Z_\beta)2 \times [P1(1-P1) + P2(1-P2)]}{(P1-P2)2}$

Where; P1 = Proportion of HIV infected children with cardiac disorders (= 14.0%)

P2 = Proportion of HIV uninfected children with cardiac disorders (=4.0%)

Z_α = Percentage point on the SND corresponding to 5% level significance (= 1.96)

Z_β = percentage point on the SND corresponding to 80% power (=1.28)

n = required sample size in each group.

$$n = \frac{(1.96 + 1.28)2 \times [(0.14)(1-0.14) + 0.04(1 - 0.04)]}{(0.14 - 0.04)2}$$

$$= 130$$

$$130 \times 2 = 260.$$

The sample size was increased by 10% in order to allow for non-response, dropouts, incomplete investigations, tabulation and other factors that decrease the yield of usable responses. Therefore, the estimated minimal sample size was 280 children.

3.7 Duration of study:

According to the 1996/97 to 1999/2000 statistics from the Department of Pediatrics and Child Health annual reports, 42% of the total admissions are children aged 18months and above. From the same statistics, HIV/AIDS cases ranked the sixth of the total admissions in general pediatric wards with an average of 35HIV/AIDS cases per month while at the general outpatient clinics having an average of 12 new cases per month. [8] The prevalence of HIV-1 infection in the 1995/96 MMC pediatric study among all admitted children was 19.2%. [7] In 1988 among malnourished children admitted to MMC showed an HIV-1 prevalence of 25%, [46] while in 1989 in children with chronic diarrhoea showed an HIV-1 prevalence of 39%.[47] On average in all studies, about 40% of HIV/AIDS patients were children aged 18 months and above. With a minimum of two to three children per day, it meant about six months (240 days) were needed for recruitment of the estimated minimal sample size of 280 children.

3.8 Data collection:

A structured questionnaire (Appendix I) was used to obtain social demographic data; history; and record clinical findings and laboratory investigation results.

3.8.1 Parents/guardians interviews:

Upon enrolment into the study, child's parents /guardians were interviewed using a structured questionnaire developed for this purpose. For all patients in the target population, a detailed history was taken. Demographic data for each patient included name; address (residence); age; sex. (Appendix I)

3.8.2 Physical examination:

A thorough physical general and cardiovascular examination was done for each patient by the investigator. The findings were recorded in the space provided in the questionnaire (Appendix I).

Clinical data included main presenting symptoms: fever, cough, diarrhea, failure to thrive. Clinical features on examination included; anaemia, pulse rate, blood pressure, respiratory rate, temperature, precodial abnormalities, heart sounds, murmurs.

3.8.3 Anthropometric measurements:

Weight: Weight was taken using solar cell SECA weighing machine to the nearest 10g. [48] Nutritional status assessment was based on the Welcome classification using anthropometric reference values for use in the African region. [49]

The children were then classified as having normal nutritional status, underweight, marasmus, marasmic kwashiorkor or kwashiorkor as recommended by the welcome Trust International working Party. [50]

By this classification, children had normal nutritional status if weight for age was above 80% of the standard and overweight if weight for age was above 120% of the standard. They had marasmus if weight for age was less than 60% of the standard with no oedema. They had marasmic kwashiorkor if they had edema and weight for age of less than 60% of the standard, and those whose weight for age was between 60% and 80% of the standard and had oedema were classified as having kwashiorkor. [50]

3.9 Cardiac assessments:

A thorough cardiovascular assessment was done according to the principles of evaluating the cardiovascular system in paediatrics [41]

3.9.1 Physical examination

The author examined children. Important features noted included, pulse rate, blood pressure (B/P); taken in supine position using pediatric cuff standard for age and mercury sphygmomanometer. The cuff covered two thirds of the length of the upper arm and the manometer was at the same level as the patient's heart.

Respiratory rate, temperature, palmer pallor, and a complete cardiovascular system examination including assessment of heart sounds, murmurs, and gallop rhythm were done. Vital signs in children (cut off points), for pulse rate, respiratory rate, blood pressure, were based on pediatric vital signs reference values in children. [41]

3.9.2 Chest X-Ray.

An antero-posterior Chest radiograph view was taken and reported by the same radiologist who was blinded about the HIV status of the child. The report specified the presence or absence of cardiomegaly and other abnormalities. Mother or caretaker assisted the radiographer in positioning children below 4 years of age in supine position on the table while wearing protective lead apron. Children were protected with gonadal shields. The distance between the X-Ray tube to the patient's chest was 100 cm to avoid distortion of the image. Children above four years, a postero-anterior view was taken with maximum inspiratory effort in standing position unless the child was very sick or irritable. Ten to twelve inch cassettes for pediatric purposes were used. A voltage of between 48Kv to 55Kv depending on body size in 0.13sec. was applied to produce between 4mAs to 6.3mAs.

3.9.3 Electrocardiogram (ECG).

A 12 lead surface electrocardiogram was taken (A standard 12 lead ECG). Pre-medication with diazepam 0.5mg/kg was given rectally. Patients were maintained in a warm and relaxed condition in order to avoid shivering/shaking or muscle tremor hence interfering with display and good ECG record.

A conventional ECG consisting of 12 leads in order to scan the electrical activity of the heart from 12 arbitrary viewpoints was used. Six in the frontal plane (the standard and unipolar leads) and six in the transverse or horizontal plane (the chest leads) of voltage against time.

Using a CARDIOVIT AT-4 ECG recorder with 3-channel Schiller ECG (EKG) unit, the same technician was used after taking care of all precautions according to the manufacturer's guide. A thorough cleaning of the area for electrodes with 70% alcohol was done, then a layer of gel (electrode cream) was applied between the electrode and the skin, and a recorded ECG paper was obtained and used for interpretation.

In this study, standard diagnostic ECG definitions and interpretations was done based on infants, children and adolescents ECG measurements. [53]

3.9.4 Echocardiogram

Motion Mode (M-Mode), Two -dimensional (2D)

Echocardiographic and Doppler studies of cardiac functions were performed in a standardized way, at the Pediatric Cardiology Echo-Laboratory. Pre-medication with diazepam 0.5mg/kg was given rectally. Echocardiography was done using a TOSHIBA phased array unit with a 3.5 mega hertz transducer with Doppler and colour capability. Subxyphoid, apical and parasternal views were used to define intracardiac anatomy and obtain cardiac measurements and indices of cardiac function in a standardized manner under my supervisor, an experienced cardiologist in echocardiogram examinations. The findings were recorded in videocassettes, and then entered in a structured data collection sheet. (Appendix I). The investigator under supervision interpreted the results.

The echocardiographic reports/interpretations and analyses of cardiac findings in this study are based on measurements obtained from echocardiography in pediatric heart disease. [54]

3.10 Laboratory diagnosis of HIV infection and Haemoglobin estimation.

Two milliliters of venous blood was taken from the anterior cubital fossa using non-reusable syringes and needles, after a thorough cleaning of the venepuncture site with a swab soaked in 70% alcohol. Blood was put in an empty sterile bottle labelled with serial number (code number) of patients for ELISA screening test for HIV infection. Another 1.2mls was collected in Ethylene Diamino Tetra Acetic Acid (EDTA) glass container for haemoglobin estimation. Haemoglobin (Hb) was measured by spectrophotometery after lysing red blood cells. For practical purposes and for research purposes, the Hb of > 11g/dl was considered normal, ≥ 8g/dl up to 11g/dl mild anaemia, 4 to 8g/dl as moderate anaemia and < 4g/dl as severe anaemia. [51]

3.10.1 HIV status assay.

HIV status was assayed using Enzyme Linked Immunosorbent Assay (ELISA) to all children, except those already known to be HIV positive (confirmed by available laboratory results) at the time of enrolment. HIV status assay was done by testing plasma with Dade Behring Enzygnost anti-HIV-1/2 plus ELISA (Dade Behring, Marburg, Germany) and reactive samples were further tested by wellcozyme anti-HIV-1 ELISA (Murex Biotech Diagnostics Ltd., Dartford DA15LR, UK). Samples reactive on both assays were considered positive for HIV-1 antibodies, and those with discordant reactivities were further tested by a western blot assay. (HIV Blot 2.2, Diagnostic Biotechnology Ltd., Singapore).

3.11 Ethical Issues/Clearance:

In this study patients were treated according to the usual ward protocols.

Parents/guardians were explained about the research and gave their written or informed consent to participate in the study and for HIV testing.

Pre and post-test counseling was done to all parents/guardians in collaboration with the counselor. HIV testing was done according to the Tanzanian National AIDS Control Programme (TNACP) Guidelines. [44]

Ethical clearance and permission to conduct this study was sought from the MUCHS High Degree, Ethical Committee of the Research and publications committee.

3.12 Management of children and Benefits to participants:

Children were managed according to the management protocols of the respective paediatric ward, (along routine lines of patient care at the center). The diagnosed cardiac disorder(s) were communicated to the paediatrician/physician taking care of the child, and used the results to manage the child accordingly.

All children at the end of the study, were continued to be managed by the respective pediatricians in the concerned unit/ward(s) for management and close long term follow-up. Those with cardiac abnormalities are still followed by the investigator.

3.13 Data analysis:

The SPSS/Epiinfo 6 program was used to analyze the data. Data entry was done by the investigator with the help of a computer programmer who is familiar with research.

Interim data analysis was done during data collection.

Appropriate tests of significance were done where indicated. Frequency distribution was used to determine prevalence. Differences in proportions were tested by the X^2 test method. P-Value of < 0.05 was considered to indicate statistically significant differences. Sensitivity which is the ability of a test to identify correctly all diseased individuals, was calculated by dividing the number of patients with cardiac abnormality who had a positive screening test, by the total number of children with cardiac abnormalities. Specificity, which is the ability of the test to correctly identify all patients without abnormality was calculated by dividing the number of patients with a negative test and having no cardiac abnormality, by the total number of patients with no cardiac abnormality.

Positive predictive value, which is the likelihood that a patient with a positive test will actually have the infection, was calculated by dividing the number of patients with abnormality having positive test by the total number of children with a positive test. In the analysis, odds ratios and positive predictive values was calculated to assess the influence of potential risk factors of HIV serostatus on cardiac lesions.

3.14 Quality control

Quality control system was used to ensure the accuracy and completeness of the data collected. From the time of patient enrollment to data collection, all precautions were taken to minimize errors. Echocardiographic measurements and ECG findings were reviewed and verified by the same cardiologist. Data was entered in the data master sheet on a daily basis after results. Interpretation of each finding/result was under the direction of the same cardiologist, supervisor and statistician.

3.15 Limitations of the study:

Children below 18 months were excluded from the study.

Like in many developing countries where diagnostic facilities are minimal and expensive, it was not possible to diagnose HIV infection with certainty in children below 18 months of age born to HIV -infected mothers. P24 antigen assay and PCR was not available at MNH during the study period. The detection of HIV-1 IgG antibodies in children in this age group does not necessarily indicate HIV infection due to the presence of maternal HIV IgG antibodies in the infants blood.

4.0 **RESULTS**

4.1 **Patients characteristics**

During the study period (April 2001 to January 2002) a total of 2,486 children were admitted to general paediatric wards or seen at paediatric outpatient department of Muhimbili National Hospital, Dar es Salaam. Of these 1,104 (44%) were children aged 18 months to 7 years.

Two hundred and eighty (25.4%) children aged between 18 months to 7 years were recruited for the study. Seventeen parents refused to consent for fear of HIV results. Twelve patients were known HIV-1 positive and were included in the study.

Due to frequent inaccessibility of the laboratory and lack of X-ray films, it took time to reach the sample size. Fifteen patients were not included in the analysis because of incomplete investigations and it was difficult to trace them until the end of the study.

There were 202 (72.1%) HIV negative children and 78 (27.9%) HIV positive children. The distribution of children according to sex, age and residence by HIV serostatus is shown in table 1.

There were 160 (57.1%) males, 43 (26.9%) were HIV-1 Positive and 117 (73.1%) were HIV negative. One hundred and twenty (42.9%) were females, 35 (29.2%) were HIV-1 positive and 85 (70.8%) were HIV negative, giving a male: female ratio of 1:1.3. There was no statistical significant difference in distribution of study groups by sex ($P = 0.672$), Table 1.

The children recruited for the study were between the age of 18 and 84 months. Most of them 154 (55%) were between 18 – 42 months. There was no statistical significant difference in distribution of study groups by age (P = 0.601), Table 1.

Table 1: **Distribution of children according to Sex, Age, Residence and HIV serostatus:**

Patient characteristics		HIV positive n (%)	HIV negative n (%)	TOTAL n (%)	P-value
Sex	Male	43 (26.9)	117 (73.1)	160 (57.1)	
	Female	35 (29.2)	85 (70.8)	120 (42.9)	0.18
Age (months)					
	18 – 30	35 (30.4)	80 (69.6)	115 (41.0)	
	31 – 42	10 (25.6)	29 (74.4)	39 (14.0)	
	43 – 54	11 (26.2)	31 (73.8)	42 (15.0)	
	55 – 66	9 (33.3)	18 (66.7)	27 (9.6)	
	67 – 78	9 (31)	20 (69.0)	29 (10.4)	
	79 – 84	4 (14.3)	24 (85.7)	28 (10.0)	0.60
Mean Age ± SD		41.167±20.559	44.594 ± 22.202		0.24
Residence:					
	Ilala	21 (30.4)	48 (69.6)	69 (24.6)	
	Kinondoni	28 (30.1)	65 (69.9)	93 (33.3)	
	Temeke	23 (33.3)	46 (66.2)	69 (24.6)	
	Other	6 (12.2)	43 (87.8)	49 (17.5)	
	TOTAL	78 (27.9)	202 (72.1)	280 (100.0)	0.059

Residence

Of the 280 children, 69 (24.6%) were from Ilala district, 93 (33.3%) from Kinondoni district, 69 (24.6) from Temeke district and 49 (17.5%) from other areas.

Majority of children (33.3%) came from Kinondoni district. Other areas (outside Dar es Salaam) had the lowest proportion (17.5%).

The demographic profiles (sex, age and residence) of the HIV-infected and HIV-uninfected children were similar.

Level of Anaemia

Table 2 shows the distribution of studied children according to level of anemia, nutritional status and HIV serostatus.

Fifteen children (19.2%) HIV-1 infected had normal haemoglobin, compared to 100(49.5%) children HIV uninfected with normal haemoglobin level.

There was a strong association between HIV serostatus and levels of haemoglobin (anaemia) among the studied groups. Children who were HIV-1 positive were more likely to be anaemic compared to those who are HIV negative. The difference was statistically significant. ($P = 0.0000198$), Table 2.

Table 2: **Distribution of children according to Nutritional Status, Level of anaemia and HIV serostatus.**

Patient characteristics	HIV positive n (%)	HIV negative n (%)	TOTAL n (%)	P-value
Level of Anaemia (Hb)				
Normal Hb	15 (19.2)	100(49.5)	115 (41.1)	
Mild	34 (43.6)	49 (24.3)	83 (29.6)	
Moderate	25 (32.1)	38 (18.8)	63 (22.5)	
Severe	4 (5.1)	15 (7.4)	19 (6.8)	< 0.001
Mean Hb ±SD	6.8±2.1 SD	8.2± 1.9SD		<0.001
Nutritional status				
Normal	14 (17.9)	135 (66.8)	149 (53.2)	
Underweight	46 (59.1)	50 (24.8)	96 (34.3)	
Kwashiorkor	3 (3.8)	4 (2.0)	7 (2.5)	
Marasmus	11 (14.1)	11 (5.4)	22 (7.9)	
Marasmus kwashiorkor	4 (5.1)	2 (1.0)	6 (2.1)	<0.001
TOTAL	78 (27.9%)	202 (72.1%)	280 (100.0)	

Nutritional status

Fourteen children (17.9%) were HIV-1 infected with normal nutritional status, compared with 135 (66.8%) children with normal nutritional status in HIV uninfected group. In all groups of abnormal nutritional status, HIV-1 infected children had higher percentages. There was a strong association between HIV infection and abnormal nutritional status. The difference was statistically significant. ($P < 0.001$), Table 2.

Symptoms

Table 3 shows the distribution of children according to symptoms reported among the two groups. In the analysis of symptoms reported, All the HIV infected children had higher percentages of reported symptoms (fever, cough, diarrhea and Recurrent infections) compared to HIV uninfected group.

There was a strong association between HIV infection and the reported symptoms

The difference was statistically significant. ($P < 0.001$) Table 3.

Table 3: **Distribution of Symptoms reported for HIV-1 positive and negative children.**

	HIV Positive N=78	HIV negative N=202	TOTAL N=280			P-value
Symptoms	n (%)	n (%)	n (%)	OR	95% CI	
Fever	71 (91)	157 (77.7)	228 (81.4)	2.91	1.18-7.51	0.01
Cough	68 (87.2)	134 (66.3)	202 (72.1)	3.45	1.59-7.69	<0.01
Diarrhoea	33 (42.3)	21 (10.4)	54 (19.3)	6.32	3.17-12.66	<0.01
Recurrent infections	61 (78.2)	41 (20.3)	102 (36.4)	14.09	7.09-28.32	<0.01

History of HAART drugs

None of the recruited children in the HIV-1 infected group was on or had a history of HAART either during prenatal, natal or postnatal period.

Physical findings suggestive of cardiac abnormality

Table 4 summarizes the distribution of children according to physical findings suggestive of cardiac abnormalities among the two studied groups.

The physical findings referable to the cardiovascular system were tachypnea, dyspnea, tachycardia, abnormal BP, abnormal precodium, displacement of apex beat, distant heart sounds, presence of murmur, hepatomegally, pulmonary congestion, and abnormal first and second heart sounds. In the univariate analysis, the most important physical findings (signs) associated with HIV-1 infection were tachypnea, dyspnea, tachycardia and pulmonary congestion ($P < 0.001$); followed by hepatomegaly and distant heart sounds ($P < 0.05$). The differences were statistically significant.

The abnormal precodium, the presence of the murmur and abnormal 1^{st} and 2^{nd} heart sounds, were more prevalent in HIV-uninfected group than HIV-infected group, but the difference was statistically not significant ($P > 0.2$).

Table 4: **Distribution of physical findings suggestive of cardiac abnormality for HIV-1 positive and HIV negative children.**

	HIV positive N=78	HIV negative N=202	TOTAL N=280			P-value
Physical findings Suggestive of cardiac Abnormality	n (%)	n (%)	n (%)	OR	95%CI	
Tachypnea	28 (35.9)	25 (12.4)	53 (18.9)	3.96	2.02-7.81	<0.01
Dyspnea	21 (26.9)	16 (7.9)	37 (13.2)	4.28	1.97-9.37	<0.01
Tachycardia	16 (20.5)	9 (4.5)	25 (8.9)	5.53	2.15-14.49	<0.01
Abnormal BP	8 (10.3)	12 (5.9)	20 (7.1)	0.55	0.20-1.57	0.21
Abnormal precodium	3 (3.8)	13 (6.4)	16 (5.7)	0.58	0.13-2.30	0.4026
Displacement of Apex beat	7 (8.9)	15 (7.4)	22 (7.9)	1.23	0.43-3.41	0.6659
Presence of murmur	7 (8.9)	28 (13.9)	35 (12.5)	0.61	0.23-1.57	0.2677
Hepatomegaly	31 (39.7)	55 (27.2)	86 (30.7)	1.76	0.98-3.18	0.042
Pulmonary congestion	18 (23.1)	14 (6.9)	32 (11.4)	4.03	1.77-9.24	<0.001
Distant Heart Sounds	6 (7.7)	3 (1.5)	9 (3.2)	5.53	1.17-29.1	0.0158●
Abnormal 1st and 2nd Heart Sounds (S_1S_2)	8 (10.3)	31 (15.3)	39 (13.9)	1.39	0.59-3.35	0.270

●Fisher exact 2-tailed test

There were 20 (7.1%) children with abnormal BP, 8(10.3%) were HIV-1 infected. These 8, four had hypotension and another 4 were hypertensive. From HIV-uninfected group there were 12(5.9%) children with abnormal BP, all were hypertensive. Twenty-two (7.9%) children had displacement of apex beat, 7 (8,9%) were HIV positive and 15 (7.4%) were HIV-negative. The observed differences for abnormal BP and displacement of apex beat between HIV-1 positive and HIVnegative children were not statistically significant. ($P > 0.2$). Table 4.

Radiological findings:

Cardiomegaly

Twenty-four (8.6%) radiographs had increased cardiothoracic ratio (cardiomegaly), 8 (10.3%) from HIV-1 infected group and 16 (7.9%) from HIV uninfected group. The mean cardiothoracic ratio (CT- ratio) was 55.692 ± 6.681cm SD, for HIV infected group and 54.470 ± 5.536 SD for those who were HIV negative. The difference in the percentages of children with cardiomegaly in HIV-1 positive and HIV negative ($P = 0.531$) as well as the difference in the mean CT- ratio between the two groups ($P = 0.1198$) radiologicaly was statistically not significant. Table 5.

Table 5: **Distribution of Chest-X-ray (radiological) findings in children according to HIV-serostatus.**

	HIV positive N = 78	HIV-negative N = 202	TOTAL N = 280			P-value
Radiological report (findings)	n (%)	n (%)	n (%)	OR	95%CI	
Increased CT ratio (Cardiomegaly) (n)	8 (10.3)	16 (7.9)	24 (8.6)			0.531
Mean CT ratio ± SD (cm)	55.692 ± 6.681	54.470 ± 5.536				0.1198
Pneumonia	52 (66.7)	74 (36.6)	126 (45.0)	3.46	1.92-6.27	<0.001
Pleural effusion	2 (2.6)	2 (1.0)	4 (1.4)	2.63	0.26-27.07	0.320●
Mediastinal widening	24 (30.8)	18 (8.9)	42 (15.0)	4.54	2.17-9.57	<0.001
Increased vascular Markings	12 (15.4)	16 (7.9)	28 (10.0)			0.062
Normal CX-Ray	3 (3.8)	114 (56.4)	117 (41.8)			<0.001

●Fisher exact test: 2-tailed P-value.

Table 5 shows that of the 280 children studied, 126 (45.0%) had a radiological report of pneumonia. Fifty-two (66.7%) were HIV infected and 74 (36.6%) were HIV uninfected. There was a strong association between HIV infection and radiological evidence of pneumonia. The difference was statistically significant ($P < 0.001$). Table 5.

Four (1.4%) out of 280 children studied had pleural effusion. Two (2.6%) children were HIV-1 infected and 2 (1.0%) were HIV uninfected. There was no association between pleural effusion and HIV serostatus.

The difference was statistically not significant. (P = 0.32). Table 5.

Forty-two (15.0%) children had mediastinal widening. Twenty four (30.8%) were HIV infected and 18 (8.9%) were HIV uninfected. Radiologicaly there was a strong association between HIV infection and mediastinal widening.

The difference was statistically significant (P < 0.01). Table 5.

Twenty-eight (10.0%) children had increased pulmonary vascular markings. Twelve (15.4%) were HIV positive and 16 (7.9%) were HIV negative. There was no association between HIV infection and an increase in pulmonary vascular markings radiologicaly. The difference was statistically not significant (P = 0.062). Table 5.

Electrocardiographic findings.

A total of 26 (9.3%) children had sinus tachycardia, 16 (20.5%) were HIV infected and 10 (5.0%) were HIV uninfected, there was a strong association between HIV infection and ECG sinus tachycardia. The difference was statistically significant. Odds ratio[OR] 4.95; 95% CI, 1.98 to 12.57. (P < 0.001). Table 6.

There were six (2.1%) children with sinus bradycardia, and all of them were HIV negative.

Fifty (17.9%) children had abnormal T-wave changes on ECG, 15(19.2%) were HIV infected and 35 (17.3%) were HIV uninfected.

There were no associations between HIV serostatus and ECG T-wave changes.

The difference was statistically not significant. (P = 0.7092). Table 6.

Table 6: **Distribution of Electrocardiographic (ECG) findings in children according to HIV serostatus:**

	HIV positive N=78	HIV negative N =202	TOTAL N=280	P-value
E.C.G findings	n (%)	n (%)	n (%)	
Sinus Tachycardia	16 (20.5)	10 (5.0) OR = 4.95	26 (9.3) 95% CI = 1.98-12.57	0.00005764
Sinus bradycardia	0 (0.0)	6 (3.0)	6 (2.1)	0.1908 *
Sinus rhythm	77(98.7)	199(98.5)	276(98.6)	0.897
Ectopics	1(1.3)	3(1.5)	4(1.4)	1.00•
Abnormal QRS complexes	14(17.9)	32(15.8)	46(16.4)	0.6697
Abnormal T-wave changes	15 (19.2)	35 (17.3)	50(17.9)	0.70919
ST-segment changes	11(14.1)	27(13.4)	38(13.6)	0.8719
LVH	4(5.1)	24(11.9)	28(0.1)	0.0913
RVH	4(5.1)	17(8.4)	21(7.5)	0.3491
Electrical Alternans	7 (9.0)	13 (6.4)	20 (7.1)	0.459628

Electrical alternans:

Twenty (7.1%) children had ECG electrical alternans, 7 (9.0%) were HIV infected and 13 (6.4%) were HIV uninfected children. There was no association between HIV serostatus and ECG electrical alternans. (P = 0.46). Table 6.

Two hundred and seventy six (98.6%) children had sinus rhythm, 77 (98.7%) were HIV positive and 199 (98.5%) were HIV negative, there were no difference or association between HIV serostatus and ECG sinus rhythm. (P = 0.1901) Table 6.

Four (1.4%) children had ventricular ectopics on ECG, 3 (1.5%) were HIV negative and 1(1.3%)) was HIV positive. There was no association between HIV serostatus and ectopics on ECG (P = 1.00) Table 6.

Forty six (16.4%) children had abnormal QRS complexes which included partial left or right bundle branch blocks, 3.2 (15.8%) were HIV negative and 14(17.9%) were HIV-1 positive. There was no association between HIV serostatus and abnormal QRS complexes. The difference was statistically not significant. (P = 0.6697). Table 6.

Thirty-eight (13.6%) children had ST-segment changes on ECG. Twenty-seven (13.4%) were HIV negative and 11(14.1%) were HIV positive. There was no association between HIV serostatus and ST-segment changes on ECG. The difference was statistically not significant. (P = 0.8719). Table 6.

Twenty-eight (10%) children showed LVH on ECG. Four (5.1%) were HIV positive and 24 (11.9%) were HIV negative. There was no association between HIV serostatus and LVH on ECG. The difference was statistically not significant (P = 0.0913).

Twenty one (7.5%) children showed RVH on ECG. Four (5.1%) were HIV positive and 17 (8.4%) were HIV negative.

There was no association between HIV serostatus and RVH on ECG. The difference was statistically not significant. (P = 0.3491)

Echocardiographic findings (diagnosis):

All studied children were subjected for echocardiogram and all were interpretable. Table 7 summarizes the echocardiographic abnormalities that were identified in 83/280 (29.6%) children. There were 36 (46.2%) HIV infected children with abnormal echocardiographic report compared with $^{47}/_{202}$ (23.3%) HIV uninfected children. There was a high prevalence (46.2%) of cardiac abnormalities in HIV infected children than in HIV uninfected children (23.3%). The difference was statistically significant ($P < 0.001$). Table 7.

There was 4(1.4%) children with pericarditis, 2(2.6%) were HIV-1 infected and 2(1.0%) were HIV uninfected children. The 2 HIV infected children had dilated cardiomyopathy and were receiving ant-Tuberculosis drugs. The other 2 HIV uninfected children were also found to have endomyocardial fibrosis (EMF).

There were no association between HIV serostatus and pericarditis. ($P = 0.319$). Table 7.

Table 7: **Distribution of Echocardiographic diagnoses (report) and HIV serostatus**

Echocardiographic Diagnosis	HIV positive N =78 (27.9)	HIV negative N=202 (72.1)	TOTAL N=280 (100.0)			P-value
	n %	n %	n %	OR	95% CI	
Pericardial diseases (Pericardial effusion)	21 (26.9)	8 (4.0)	29 (10.4)	8.9	4.61-39.88	0.00002
Dilated Cardiomyopathy	19 (24.4)	5 (2.5)	24 (8.6)	12.5	4.19-41.14	0.0000
Endocarditis (vegetations)	1 (1.3)	2 (1.0)	3 (1.1)			1.000•
R.H.D	1 (1.3)	9 (4.5)	10 (3.6)			0.2925•
CHD	1 (1.3)	25 (12.4)	26 (9.3)			0.00413
EMF	0 (0.0)	3 (1.5)	3 (1.1)			0.5625•
CCF (CHF)	3 (3.8)	4 (2.0)	7 (2.5)			0.402•

●Fisher exact test: 2-tailed P-value.

Rheumatic heart disease (RHD).

Ten (3.6%) children had RHD, 9 (4.5%) were HIV negative and one (1.3%) with HIV infection. There was no statistical significant difference between RHD and HIV serostatus. (P = 0.293). Table 7.

Congenital heart diseases (CHD)

The overall prevalence of CHD was $^{26}/_{280}$ (9,3%). Only one (1.3%) of these 26 children with CHD was HIV infected. For CHD, the association found was in the opposite direction; CHD diagnosis was more common in HIV-uninfected children than in HIV-1-infected children. The difference was statistically significant. (P = 0.00413). Table 7.

Endomyocardial fibrosis (EMF)

There were 3 (1.1%) children, all above 5 years with EMF and pericardial effusion all were HIV negative.

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Congestive Heart Failure (CCF)

Seven (2.5%) children who had an abnormal echocardiographic diagnoses of CCF, 4 (2.0%) HIV negative were also found to be severely anaemic. Three (3.8%) of these were HIV infected children, and all had cardiomyopathy. There was no statistical significant difference detected in CCF prevalence between the two groups. ($P = 0.402$). Table 7.

Pericardial effusion

Twenty-nine (10.4%) children had pericardial effusion. Twenty-seven had mild to moderate pericardial effusion and 2 had severe effusion leading to tamponade and requiring pericardiocentesis. Of the total children with pericardial effusions, Twenty one (26.9%) were HIV infected compared with 8 (4.0%) among HIV uninfected children. There was a high prevalence and association of pericardial effusions with HIV infected children compared with HIV uninfected children. The differences were highly statistically significant, odds ratio [OR] 8.9;95% CI, 4.19 to 41.14, with a positive predictive value of 72.4%. ($P < 0.001$). Table 7.

Cardiomyopathy

Twenty four (8.6%) children had dilated cardiomyopathy, 19 (24.4%) were HIV-1 infected and 5 (2.5%) were HIV uninfected. Of the 19 HIV infected children, 8 children had associated pericardial effusions. There was a strong association between HIV infection and development of cardiomyopathy in children. . The differences were highly statistically significant. Odds ratio [OR] 12.5; 95%CI, 4.19 to 41.14 with a positive predictive value of 79.17%. ($P < 0.001$). Table 7.

Endocarditis

Three (1.1%) children were found to have Endocarditis, 2 (1.0%) children were HIV negative and had also congenital heart diseases. One (1.3%) HIV infected child had endocarditis. There was no statistical significant difference between HIV positive and HIV negative children with endocarditis. ($P = 1.00$). Table 7.

Table 8. Summarizes the echocardiographic report of LV functions. Left ventricular fractional shortening (LVFS) less than 28% was taken to indicate cardiac dysfunction. Six children were excluded in LVFS-measurements, one from HIV infected group and Five from HIV-uninfected group, due to LV-wall abnormalities, abnormal Ventricular Septa motion and CHD.

Nineteen (24.7%) HIV-infected children had LV dysfunction against 10 (5.1%) in HIV-uninfected children. In the remaining LVFS groups of 28% - 38% and above 38%,

HIV-uninfected children had higher percentages of good LVFS.

There was a strong association between HIV infection and LV cardiac dysfunction.

The differences were highly statistically significant. ($P < 0.001$). Table 8.

Table 8: **Distribution of children according to Left Ventricular function. Motion-mode echocardiographic Left Ventricular Fractional Shortening (LVFS)• findings and HIV serostatus.**

M-mode Echocardiographic LVFS (percentage)	HIV positive N=77 (28.1)	HIV negative N=197 (71.9)	TOTAL N=274 (100.0	P-value
< 28%	19 (24.7)	10 (5.1)	29 (10.6)	
28% – 38%	47 (61.0)	131 (66.5)	178 (64.9)	
> 38%	11 (14.3)	56 (28.4)	67 (24.5)	0.00004

•LVFS (%): Left Ventricular Fractional shortening (percentage).

Table 9: **Distribution of children according to frequency of physical, radiological, electrocardiographic and Echocardiographic abnormalities (disorders) reported in children with or without HIV-1 infection: Comparison.**

Diagnostic Test	HIV positive N=78 n (%)	HIV negative N =202 n (%)	TOTAL N=280 n (%)	P-value
Physical	18 (23)	35 (17.3)	53 (18.9)	0.270846
Radiological Increased CT Ratio (Cardiomegaly)	8 (10.3)	16 (7.9)	24 (8.6)	0.531
Abnormal ECG	19 (24.4)	36 (17.8)	55 (19.6)	0.2170
Abnormal Echocardiogram	36 (46.2)	47 (23.3)	83 (29.6)	0.000170

Taking Echocardiogram as a gold standard in this study, Chest X-ray had a sensitivity of 28.9% and specificity of 70%.

Clinical diagnosis of cardiac abnormalities had a sensitivity of 63.8% and specificity of 84.7% while electrocardiogram had sensitivity of 66% and a specificity of 85.8%.

DISCUSSION

In this study the overall HIV-1 prevalence of 27.9% among the studied children at Muhimbili National Hospital is significantly higher compared to that of 19.2% reported by Kawo et al [7] in children aged one month to seven years in1996. The same study reported the age specific prevalence rate of 17.8% in children aged 18 months to seven years.

In 1988 Mgone et al conducted a study among malnourished children admitted to the same center showed an HIV-1 prevalence of 25%, [46] the seroprevalence rate was equally high in malnourished children above the age of 18 months (25.5%) as in those below this age. In another cross-sectional study in 1989, Cegliesk et al reported in children with chronic diarrhea aged 15 months up to 5 years an HIV-1 prevalence of 39%. [47]

Another study among pregnant mothers delivering at the same centre, reported HIV-1 prevalence rates were 12.5% in 1991, 11.5% in 1992, 11.3% in 1993 and 12.8% in 1994. [52]

Putting together this data it implies that there is still a high infection rate of HIV-1 among children admitted in the paediatric wards and this might be a reflection of the general high prevalence of HIV-1 in the community.

This is the first study of cardiac disorders in HIV-1 infected children in Tanzania.

The associations of HIV infection with cardiac disorders have been described previously in a number of studies and different cardiac disorders have been noted.

Despite the fact that HIV/AIDS is now the leading cause of death in sub Saharan Africa, [1] there is limited reports on HIV and cardiac disorders in paediatrics.

It has been noted that children with HIV/AIDS do get cardiac abnormalities ranging from vascular, pericardial, myocardial and endocardial disorders.

These have been reported based on clinical, electrocardiographic, radiological, echocardiographic, histochemistry and autopsy findings. [14,16-40]

Cardiac disorders have been causally linked to primary HIV infection of the myocardium, by bacterial, other viruses, fungal, parasitic, sequelae of drug therapy, renal impairment, pulmonary diseases, malignancies and idiopathic causes. [16,17,18]

This study show that the prevalence of cardiovascular disorders in HIV-1 infected children to be approximately 46.2% compared to 23.3% in HIV-1 uninfected children. The difference is statistically significant. The prevalence of cardiac disorders among HIV-1 positive children in this study is higher than that reported in previous studies which ranged from 14% to 45% using echocardiogram. [29-31,40]

These findings show that cardiac disorders associated with HIV-1 infection in children in our society are common at a ratio of 2 to1; i.e. for every two HIV-1 infected children there is one who has a cardiac abnormality.

The commonest findings in this study were pericardial effusions (26.9%), dilated cardiomyopathy (24.4%) and tachycardia (20.5%).

The presence of pericardial effusion and dilated cardiomyopathy in children is highly suggestive of underlying HIV-1 infection by a positive predictive value of 72% and 79% respectively.

These findings, and the high rate of unexpected left ventricular dysfunction (24.7%) in HIV-1 infected children (ref. Table 8), suggests that cardiac contractile abnormalities also involve a significant number of children with HIV-1 infection.

Of the children with HIV-1 infection, 26.9% had cardiomyopathy, one patient with dilated cardiomyopathy was in CCF. Other children with dilated cardiomyopathy did not have clinical evidence of CCF.

These results indicate that cardiomyopathy is common in children with HIV-1 infection but often is clinically unsuspected.

Although there was no echocardiographic follow up to all children studied, a sub group of these children who were seen in routine follow ups appeared to progress to symptomatic heart failure. It is well established that a principal complication of virtually all forms of heart disease is heart failure. The absence of CCF found in studied HIV-1 infected children with dilated cardiomyopathy is difficult to explain. In one study 25% of HIV-infected children who died had cardiomyopathy while CCF appeared to occur chronically in 10% of HIV-infected children and transiently in another 10%. [23]

The possible explanations for high prevalence rate of cardiovascular disorders in HIV-1 infected children could be multifactorial. Most of studied patients in HIV-1 infected group were anaemic (80.8%), with mean Hb of 6.8±2.1SD and/or malnourished (82.1%)

compared to HIV-1 negative children who had normal haemoglobin level (mean 8.2±1.9SD) and normal nutritional status (49.5% and 66.8% respectively).

In an anaemic child, physical findings associated with anaemia include tachycardia and a hyperdynamic precodium.

A systolic murmur is often heard, these cardiac findings disappear when the anaemia is corrected. In these patients especially those who had severe anaemia, tachycardia persisted despite correction of anaemia, hence anaemia alone cannot explain a high prevalence of cardiac abnormalities.

It is known that nutrition plays a central role in paediatric immune defenses, children with poor nutritional status with or without co-morbidity of HIV infection are at a great risk of repeated infections. [14, 18] This can also explain why majority of HIV-1 infected children had history of repeated infections.

In the co-morbidity of HIV infection, anaemia, malnutrition, opportunistic infections and malignancies associated with HIV infection, all this factors may affect the heart [16,17,18,]

The nutritional as well as anaemia aspects were not addressed in previous studies, this need to be studied further. It is possible therefore a co-morbidity of HIV infection, anaemia and malnutrition to contribute to high prevalence of cardiac disorders which was seen in HIV-1 infected children in this study.

None of the children in this study was on HAART for HIV infection. This differs significantly to reports of more than 90% of HIV infected patients in USA where most of these studies have been done who are on HAART. [27] The protective effects of HAART in reducing the viral load and subsequently reduces the frequency of repeated

bacterial and opportunistic infections that have been documented before was not the case in the studied children. It is therefore not surprising that the prevalence and characteristics of cardiac disorders in the studied children differs from that of the developed countries.

It is speculated that when cardiac abnormalities develop in a child with HIV infection, the signs and symptoms are often non specific and often misinterpreted to be the result of other causes such as pulmonary pathology or systemic infection which mimic cardiac diseases.

In this study an association between HIV-1 infection and symptoms/signs that are included in the definition of AIDS in children were found. [2] Other studies have documented these same clinical features to be common also in other childhood disease in the tropics. [7, 12, 13, 18]

Signs and symptoms of respiratory tract infections (cough, dyspnea, tachypnea, tachycardia,) were found to be strongly associated with HIV-1 infection.

Clinical features which were more informative in diagnosing or at least pointing to an underlying cardiac disorder in HIV-1 infected children were dyspnea (26.9%) and tachycardia (20.5%) [with a P-value < 0.01.]

The prevalence of such symptoms were specifically more predominant in children with HIV-1 infection and cardiac disorders such as cardiomyopathy and pericardial effusions. Such similar findings were documented in previous studies. [23,26,27]

The presenting features in most of cardiac disorders in children are non-specific unless overt CHF develops. The diagnosis of CHF may also be difficult in children with HIV

infection because of co-morbidities that are common in these children, which may also cause tachycardia, tachypnea, dyspnea and hepatomegally. Therefore a clinical diagnosis of congestive cardiac failure or other cardiac abnormalities may be difficult and may require a high index of suspicion.

Thorough examinations including laboratory tests such as ECG, chest-X-ray and echocardiogram are needed to make proper diagnosis of cardiac disorders in these children.

In this study, 20.5% of HIV-1 infected children had tachycardia compared to 4.5% in HIV uninfected children ($p<0.01$). Other studies have also reported tachycardia as a feature of myocarditis, which can be secondary to HIV infection, other infections or fever. [26, 27,29,30]

Tachycardia has been reported to be a result of excessive sympathetic stimulation from autonomic imbalance or stimulation of β receptors by the gp120 protein viruses. [31,35] Tachycardia has been shown to predict heart failure in LV dysfunction. [23]

If a hyperadrenergic state can be demonstrated in these children, then an interventional trial of β adrenergic blockade may be warranted to determine if it reduces tachycardia and LV dysfunctions. This could be an important tool in the management of affected children.

The real cause of tachycardia in HIV infected children is not well established, but many cases seem to be related to an underlying myocardial dysfunction. [29,30] This may also be due to a direct or indirect effect of HIV, but could be confounded by other potential pathogenic factors such as anemia, nutritional deficiencies and opportunistic infections.

In this study tachycardia had a positive predictive value of 64% in HIV infected children. All HIV infected children with tachycardia should be considered as having an underlying cardiac disorder.

As such patients who present with tachycardia and/or pericardial effusion or dilated cardiomyopathy, HIV infection need to be considered as part of the assessment.

Twenty-seven children (34.6%) who were HIV-1 infected had abnormal ECG findings including sinus tachycardia, non-specific T-wave changes, ST-segment changes, electrical alternans, QRS complex changes, RVH, and LVH. Apart from sinus tachycardia, there was no association between HIV serostatus and other ECG findings. These non-specific ECG findings have been reported in other studies. [29,30]

The prevalence of ECG abnormalities ranging from 49-70% in HIV infected children have been reported. [27,29,30] The prevalence rate of 34.6% in this study is low, the reasons for such higher prevalence rate of ECG changes in other studies higher than this study findings remain unclear.

In this study, radiology had a sensitivity of 28.9% and a specificity of 70% in detecting cardiac abnormalities, thus chest X-ray could reveal a normal cardio-thoracic ratio while there was a clinical cardiac abnormality in children. In general, it was less sensitive in detecting cardiac dysfunctions. It showed cardiomegally in 8.6% of all studied children. It also helped diagnosing related non-cardiac conditions such as pneumonia, pleural effusion, pulmonary oedema, mediastinal widening and vascular redistribution.

It is important in the diagnosis of co-morbidity especially pneumonia which precipitates heart failure. Such findings have been previously documented. [21,29,31]

Echocardiogram was more informative in this study compared to clinical, ECG and radiological findings. Given its simplicity, specificity, sensitivity and reproducibility, it is undoubtedly highly valuable in patient management.

The ECG showed similar non-specific changes in both HIV and non-HIV infected children with no statistical significance. In comparing clinical, radiological, ECG and echocardiogram, ref. Table 9. Taking echocardiogram as a gold standard in diagnosing cardiac abnormalities, chest X-ray had a lowest sensitivity (28.9%) and specificity (70%). ECG had a sensitivity of 66% and a specificity of 85.8%. Radiography had abnormal cardiac findings in 24 (8.6%) patients, ECG in 55(19.6%) and clinical in 53(18.9%) of all patients.

By echocardiogram we were able to see pericardial diseases including pericardial effusions and pericarditis. Also LV dysfunctions and dilated cardiomyopathies were seen even at early stages of reduced fractional shortening, which is not the case with other tests hence stressing the importance of echocardiogram. This shows that clinical examination underestimates most cardiac abnormalities.

This study demonstrates 21 (26.9%) of HIV-1 infected children had pericardial effusions. Most with small pericardial effusions and two children had severe pericardial effusion (tamponade) requiring pericardiocentesis. Pericardial fluid analysis was done but no specific organism was identified. They were managed accordingly and improved. This is in agreement with previous reports, which reported small pericardial effusions with a prevalence of 16% to 26% in HIV-1 infected children. [30,31].

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In this study, echocardiogram showed 19(24.4%) children with HIV-1 infection had dilated cardiomyopathy against 5 (2.5%) of HIV uninfected children with cardiomyopathy. These findings are similar to that described by Lipshultz et al. [29] in P^2C^2 study group and Al-Attar et al [26] where dilated cardiomyopathy have been identified in 10 to 25% of HIV-infected children. It has been reported to increase in frequency as HIV-infected children progress to AIDS or develop HIV-encephalopathy. [26,27]

The high prevalence of dilated cardiomyopathy in HIV-1 infected children in this study could also be confounded by high prevalence rate of malnutrition, recurrent infections, and anaemia.

Other factors also possibly plays a role in the causation of dilated cardiomyopathy in our set up like selenium deficiency and Keshan disease reported in China. [24] In this study, dilated cardiomyopathy had a positive predictive value of 72.4% in HIV-1 infected children hence the role of HIV-1 itself also remain a possibility.

One HIV-1 infected child had endocarditis out of 3 children with endocarditis in the study. The findings suggest that, this is not a common problem in the community.

Nineteen (24.7%) HIV-1 infected children had LV-dysfunction in this study similar to previous studies. [23,40] It has been established that echocardiographic measurements of LV structure and performance provide non-invasive, independent marker of disease and death in HIV-infected children that may be clinically useful. [23,29]

One patient aged 6year had RHD in the HIV-1 infected group out of 10 total patients with RHD. In this study the overall prevalence of RHD was 3.6%. When taking patients with cardiac abnormalities 12% had RHD, these compares with Kazimoto et al findings of 16.85% of RHD in cardiac children aged 1month to 15 years at the same center. [45] It appears that HIV has no influence on RHD.

The prevalence of CHD in HIV negative group was 12.4% compared to 1.3% in HIV-1 positive group. The reason for such findings could be, Muhimbili is a tertiary hospital where all children with CHD are referred from upcountry hospitals for further management. It is also possible that when co-morbidity of HIV and CHD coexist in a child, the chances for him/her to die in early infancy are high.

The overall prevalence of congenital cardiovascular malformations (9.3%) in the study was higher than the prevalence reported in population based epidemiological studies in USA (0.4% to 1.4%). [28] This also supports previous hospital based findings of high proportional of CHD in children with cardiac abnormalities (77.6%) by Kazimoto et al [45]

Studies in children indicate that majority of HIV vertically transmitted cases occur either late in pregnancy or during the perinatal period. It is likely that, HIV infection in a substantial percentage of vertically transmitted cases occur after the completion of cardiac development (organogenesis) at 6 to 8 weeks of fetal life. This could partly explain why there is no/or little association between HIV infection and CHD as revealed in this study and also reported by other researchers [28,40]

In case there is early HIV infection during organogenesis, the chances of fetal loss are high.

6. Conclusion

- Cardiovascular disorders are common among HIV-infected children attending MNH.
- Ordinary physical examination, use of chest X-Rays and Electrocardiographic investigations alone cannot specifically diagnose cardiac disorders.
- Echocardiogram was the most important tools in diagnosing cardiac disorders.
- Tachycardia in HIV infected children suggests underlying cardiac abnormality.
- The presence of tachycardia, pericardial effusion and dilated cardiomyopathy in children with signs and symptoms of paediatric AIDS is suggestive of underlying HIV infection.

RECOMMENDATIONS

- The study recommends that a thorough cardiovascular evaluation including use of echocardiogram (especially in children who develop symptoms of heart or lung disease), should be done in HIV infected children so as to diagnose cardiac disorders easily and offer better management in order to reduce morbidity, mortality and hence prolong their life.
- A Large study including children below 18 months of age is recommended to investigate the role of HIV in DCM and pericardial diseases.

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