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*Editorial*

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# Connecting PLWHA in Rural Virginia to Health and Mental Health Care-Perspectives from the Life Worlds of Frontline Health Workers and PLWHA

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## ISSUE

Many areas in the rural south have historically been impoverished and medically underserved.[1-4] Virginia encompasses two geographically underserved regions: Appalachia and the Southeast. According to the Virginia HIV Epidemiology Profile (2011), at the end of 2009, approximately 18% of residents resided in rural locations. Virginia's Rural Health Plan (2008) utilizes the Isserman rural definition which combines all counties and county equivalents that are classified as rural or mixed rural as "rural" (see "defining rural" http://www.va-srhp.org/docs/plan/11-appendix-d.pdf). Among this population, nearly 53% had progressed to AIDS. Seventy-five percent of rural Persons Living with HIV/AIDS (PLWHA) were male, and 60% were African American. The majority of rural PLWHA without evidence of care were male (79%) and African American (47%). Forty-nine percent of rural PLWHA with unmet need reported a risk of MSM followed by high-risk heterosexual contact (19%). Cené and colleagues (2011) and the research teams of Akers et al.[5] and Sutton et al.[6] found that rural African American PLWHA are concentrated in areas lacking crucial resources necessary for self-sufficiency which may lead to engagement in high-risk behaviors as an escape mechanism. Other researchers concluded that there is a great need to assess the conditions of rural PLWHA regarding their susceptibility to new infections of HIV and to uncover the barriers to affective delivery of HIV testing, care, and treatment. Further, they contend that such efforts can serve a dual role by identifying unmet needs for a wide range of services (i.e. mental health, substance abuse, STI screening) for PLWHA in the rural south.[7,8]

A number of studies[9-13] reveal that African Americans who reside in rural southern areas face a number of health care challenges, including geographic isolation, poverty, limited employment opportunities, inadequate education, stigma directed toward those who engage in risky behaviors or have been diagnosed with HIV or AIDS, and close-knit social networks which make it difficult both to seek and to disclose confidential HIV testing and attain prevention services. Many of these barriers are unique to PLWHA in rural areas and can prohibit them from seeking HIV testing, counselling, and care, as well as related services such as drug and alcohol treatment and mental health counseling.[14-16,3]

In rural Virginia, African American MSM accounted for nearly half of all HIV infections and AIDS cases. Many MSM, especially African Americans, do not self-identify as gay, have sexual intercourse with both men and women without disclosing their sexual behavior partners, and are inconsistent in their use of condoms.[17,18] African American women in rural settings face a number of obstacles as well including higher exposure to drug and alcohol usage, unemployment, limited health care, gender inequality making it difficult to negotiate [for them] condom use with their male partners, socioeconomic disadvantages preventing access to medical care, and poor knowledge about HIV/AIDS.[19-21]

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To address the growing inequities in HIV/AIDS prevention and treatment among rural populations, the Centers for Diseases Control (CDC) recommends the following steps to reduce HIV infections: (1) intensifying HIV prevention efforts in communities with high prevalence, (2) increasing education efforts for all Americans, and (3) increasing the numbers of PLWHA in care and treatment.[22] Further, the Division of AIDS Research (DAR) identifies the development of strategies to increase HIV-testing and improving linkages to care and timely treatment as an area of high priority. A PLWHA is considered to have an unmet need for care (or be out of care) when there is no evidence that he/she received any of the following four components of HIV primary medical care: (1) viral load testing; (2) CD4 count; (3) provision of anti-retroviral therapy; or (4) provision of HIV or AIDS related medical visit. Recent reports reveal inadequacies in the delivery of mental and physical health care services to PLWHA in rural southern areas.[2,5,14,23,24]

## SIGNIFICANCE

Despite substantial attention in the past decade to the co-morbidities of mental health and substance abuse problems among PLWHA these problems remain a significant barrier to maintaining the delivery of mental and physical health care.[7,8] These inequities are even greater when applied to a rural setting, particularly in areas that are medically underserved.[2,9,14,23,24] Further, researchers have found that PLWHA are more at risk of developing a mental health disorder than the general population.[25] Collins (2006) found that mental health providers were reluctant to talk to psychiatric patients about sexuality or HIV/AIDS prevention.[26] This is unfortunate as integrating psychosocial and psychiatric interventions into HIV care settings substantially improves the quality of life of PLWHA.[25,27] Other researchers recommend the use of HIV-care settings to provide an important opportunity to assess substance and mental health needs among PLWHA and provide or make referrals for appropriate services.[7,8] Coordination across agencies is required to ensure that psychosocial, psychiatric and health needs are met.[2,6] To date, there is scarce research regarding the coordination of service provision to PLWHA across multiple agencies. More specifically, there is a relative lack of attention to the perspective of *frontline workers (*Defined as agency employees whose job description is HIV/AIDS counseling and subsequent referral to support agencies. In community-based organizations the position is a Community HIV Outreach Worker (CHOW); in public health clinics the position is a Disease Intervention Specialist (DIS); and in mental and behavioral health clinics the position is a HIV Prevention Specialist (HPS) and PLWHA themselves (both in and out of care). This gap widens when discussing frontline workers and PLWHA in rural settings.[15,16]

More research is needed to examine the systemic and contextual issues that prohibit linkages to mental and physical health care and timely treatment in medically underserved rural areas. The perspectives and experiences of frontline workers in multiple agencies and rural PLWHA in and out of care would be an ideal focus for such a study. The overall goal is to gain an understanding of barriers to service delivery in one location that can be broadened to multiple locations in a larger study. The larger study would provide systematic enhancers that will assist in improving linkages to care and timely treatment for rural African American PLWHA in and out of care in Southeastern Virginia.

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*Editorial*

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# CD4:CD8 Ratio and Non AIDS Defining Events in Virally Suppressed HIV Infected Patients: Need to Look Beyond CD4+ T cell Counts

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## ISSUE

### CD4 Count and CD4:CD8 Ratio

Antiretroviral therapy has led to improvement in life-expectancy through viral suppression and improved immune status. This brings in the concern about the non-AIDS defining illnesses which are mostly age associated such as cardiovascular disease, stroke, renal disease, liver disease, neurocognitive disorders, and non-AIDS malignancies.[1-6] These are reported to be present at comparatively younger ages in HIV-infected patients.[7] It also raises questions on the usefulness of CD4 T cell counts in patients with full HIV RNA suppression.[2,8] CD4 count remains the most important predictor of clinical progression in people with HIV infection, but it does not predict immune activation in chronic HIV infection and non-AIDS illnesses.[9] Several immunological alterations characteristic of HIV infection, such as immune activation and inflammation, are similar to the immunological alterations associated with normal aging. This finding has led to an intersection of the fields of aging and HIV disease, especially with regard to immune alterations. Inversion of the CD4:CD8 ratio (<1) has been identified as a hallmark of immunosenescence and an independent predictor of all-cause mortality in the general population.[10,11] This information has prompted the evaluation of the CD4:CD8 ratio as a surrogate marker for the risk of morbidity and mortality in HIV-positive people in the current era of Antiretroviral therapy (ART).

### Immune Activation and CD4:CD8 Ratio

Immune activation in HIV infected, marked by levels of circulating markers of innate immune activation is widely accepted as the major driving factor of immunosenescence. Immunosenescence, an observed age-associated decline in immune competence that ultimately yields to disease progression and adverse outcomes, including age-associated disease. Independent association has been found between CD4 and CD8 activation and senescence and between CD4:CD8 ratio and circulating markers of innate immune activation.[12-14] Since persistent immune activation in treated HIV infection drives non-AIDS-associated diseases, CD4:CD8 could be a marker for long lasting immune activation despite ART.[12]

To measure CD4 and CD8+ T cell activation, biomarkers such as Ki67, HLA-DR, cytokines IL-6 and TNF-α and analysis of expression of CD14, CD163, CD28 and CD38 on T cell subsets are employed.[6] Evidence points to the fact that expression of inflammatory markers correlate strongly with risk of mortality and cardiovascular events. For example, biomarkers showing the greatest relative risks in outcome for all cause mortality were D-dimer and Interleukin (IL)-6.[15] Studies so far have found merely association between these activated T cell phenotypes and markers of age related dysfunctions. But the cause effect relationship predicting the events is still not evaluated, limiting its clinical application. Whereas, CD4:CD8 ratio is

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an easily available cost effective investigation that could instruct the clinical care of HIV infected on ART.

#### Non AIDS Defining Event (NADE)

A large European study of over 12000 HIV patients reported NADE incidence of 1.77 per 100 person-years of follow-up and almost a 7-fold increased risk of death after a non-AIDS event.[16] Other than the infection itself, NADEs are one of the most important factors affecting the prognosis of HIV patients. It is still not clear whether HIV infected are at higher risk of NADEs. The raised risk could be due to life style of the individuals such as IV drug use or HIV infection itself. It is assumed to be fuelled by residual HIV replication in HIV reservoirs or asymptomatic multiplication of co-infecting pathogens or Cytomegalovirus (CMV) specifc immune stimulation and damage to gut mucosal immunity.[1,2,6]

#### CD4:CD8 Ratio Normalization and NADE

Recently published two longitudinal studies with large sample size from Spain and Italy, have established that CD4:CD8 ratio was significantly lower in those with NADEs including NADE deaths independent of CD4 count through rigorous statistical analysis.[1-2] The CD4:CD8 ratio reflects the health of the immune system and a normal ratio is between 1 and 4. In people with HIV, the CD4:CD8 ratio has been linked to T cell activation, the CD4 cell death due to HIV and the bystander CD4 cells death by HIV mediated apoptosis.[1,17,18] CD4 count decreases by about 30% and CD8 count may increase by about 40%, thus inverting the ratio that is generally less than 1, within six months of seroconversion. The ratio may revert toward normal after initiating antiretroviral therapy. It has been observed that CD4:CD8 ratio remains low in substantial proportion of patients with CD4 T cell immune recovery and viral suppression following ART. Fewer than 15% in an Italian cohort, attained a normal CD4:CD8 ratio after reaching an undetectable viral load with Antiretroviral therapy (ART).[1] The estimated probability of normalization was 4.4% at 1 year, 11.5% at 2 years, and 29.4% at 5 years of ART initiation among those whose CD4:CD8 ratio normalized after ART initiation. Median time to a normal ratio was reported to be 10.1 years.[1,19,20]

Factors described to be associated with normalization include high CD4:CD8 ratio at ART initiation, high pre ART CD4 and negative cytomegalovirus cytology. Those less likely to achieve normalization were older, route of HIV transmission was through homosexual contact or intravenous drug use, longer interval between ART initiation and first viral suppression and more likely to have been treated with zidoviduine and lamivudine, didanosine and stavudine as compared to emtricitabine and tenofovir.[1,12,19,20] Tenofovir and emtricitabine which have lesser toxicity on bone marrow could contribute to early normalization of the ratio.[1] Moreover positive correlation of higher CD4 count at ART initiation with CD4:CD8 recovery supports early initiation of ART. Early ART initiation may contribute to more rapid and robust CD4:CD8 ratio normalization, and the ratio may be a useful clinical endpoint to be used in evaluating novel therapies for ongoing immune dysfunction during treated infection and for HIV eradication.[12] It has been suggested that MSM might have higher prevalence of bacterial and viral infections such as CMV which could increase the activation of the immune system resulting in persistent expansion of CD8 cell population leading to low CD4:CD8 ratio.

Studies have explored CD4:CD8 ratio cutoff with greatest clinical significance to predict clinical progression in terms of occurrence of NADE or death due to NADE. The Madrid study, found that the most accurate cutoff of the CD4:CD8 ratio for the detection of non-AIDS events in a sensitivity/specificity plot was 0.4, with a sensitivity of 0.83 and a specificity of 0.45.[2,12] Whereas, the Italian study used CD4:CD8 ratio as continuous and as categorical variables with the cutoff of less than 0.30, 0.30-0.45 and more than 0.45. It showed that a ratio below 0.30 raised the incidence rate a non-AIDS defining event by double when compared with a ratio above 0.45 and between 0.3 to 0.45.[19] These findings suggest that complete reversion of HIV induced immunological dysfunction is rare. Chronic inflammatory status occurs in HIV infection and can persist despite supressive ART. Despite recovery of CD4, persisting imbalance between CD4 and CD8 cell population leading to low CD4:CD8 ratio identify patients with worse prognosis.[1]

#### Role of Immune-Modulators

As it has been established that persistent immune activation in treated HIV infection is the driver of NADEs, role of immunomodulators aimed at reduction of inflammation is being studied. Adjuvant therapy such as recombinant human IL-7, rifaximin for controlling translocation for deaccelerating senescence, SB-728-T, a gene therapy, TAT2 (cycloastragenol) are being investigated.[21-24] Broad non-specific immunomodulators such as statins, chloroquine, hydroxychloroquine, aspirin, methotrexate, and several other anti-inflammatory drugs are also being developed as possible adjuncts to standard antiretroviral drugs.[6] Currently, such approaches are limited to *in vitro* studies and early phases of clinical trials, though these provide a glimpse of future possibilities.

#### Implications

Though CD4 T cell counts are used to assess clinical progression to AIDS in HIV infected individuals, these do not predict immune activation and risk of non-AID events.[9] Low CD4:CD8 ratio is a risk for clinical progression in virally suppressed indivduals on ART therapy. It is an easy to obtain marker for clinicians to predict the risk of serious non-AIDS defining events and death independently of CD4 restoration.

As authors suggest, these findings have potential implications for, one, targeting immune dysfunction in chronically treated HIV-infected individuals, in particular those with

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persistent expansion of CD8+ T cells despite adequate CD4+ T cell recovery. Two, CD4:CD8 ratio may be useful in monitoring response to therapies aimed at reducing residual immune activation, and HIV persistence. Finally, ART-suppressed HIV-infected individuals who do not have an increase in the CD4:CD8 ratio might benefit from screening programs or aggressive management of concomitant risk factors for aging-associated disease.[2,12]

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*Research*

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# Cardiac Manifestations in HIV Infected Children. Are they under Diagnosed?

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## ABSTRACT

**Background:** The aim of this study was to evaluate cardiac manifestations in HIV-infected children in India.
**Methods & Results:** This was a cross sectional study in HIV positive children up to 18 years of age, at a pediatric HIV clinic of a tertiary care teaching hospital in Maharashtra, India. All children were thoroughly evaluated by detailed history, clinical examination and underwent chest radiograph, Electrocardiograph (ECG) and Echocardiography (Echo). Of the 119 children who completed the study, the male to female ratio was 1.16:1 and the mean age was 8.9 years (range 2-17 years). Cardiovascular abnormalities were detected in 74 (62%) children on echo and / or ECG. Echocardiography alone was abnormal in 44 (36.9%) children and ECG alone was abnormal in 56 (47%) children. However, only 11(9%) children were found to be symptomatic with cardiovascular symptoms. The prevalence of Congenital Heart Disease (CHD) was 4%. The most common ECG abnormality observed in the study was sinus tachycardia in 35 (29%) followed by ST-T changes in 20 (16.8%).The most common echocardiographic abnormality encountered was LV systolic dysfunction seen in 31 (26%) cases, followed by Low LV ejection fraction in 24 (20%) cases. Children with abnormal echo and ECG were in higher WHO clinical and immunological stages (III & IV), however the association between the two was not found to be statistically significant.
**Conclusions:** This study establishes that subclinical cardiac manifestations are prevalent in HIV infected children. More research should be done on the clinical significance of these findings and the need for long-term follow up.

**KEYWORDS:** HIV; Cardiac manifestations; Electrocardiogram; Left ventricular function.

## INTRODUCTION

Human Immunodeficiency Virus (HIV) is a virus that causes multisystem disease, affecting almost all body systems. The severity of each manifestation varies with organ system and can be related to multiple etiologies.[1] Children infected with HIV may develop a wide range of cardiovascular abnormalities, some of which are known to be associated with poor survival.[2] With the introduction of Anti-retroviral therapy (ART), HIV infection is now recognized as a chronic manageable disease, rather than a terminal illness. As pulmonary diseases and infections in HIV-infected individuals are more effectively prevented and treated, the proportional

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morbidity and mortality of cardiovascular diseases among children with HIV/ AIDS are increasing.[3] Subclinical cardiac abnormalities in HIV-infected children are common, persistent, and often progressive.[3] The spectrum of cardiovascular manifestations includes tachycardia, LV dysfunction, pericardial effusion, myocarditis, dilated cardiomyopathy, endocarditis, coronary artery disease, pulmonary hypertension, vasculitis, aneurysm formation, and cardiac tumors.[3] Multifactorial etiologies like autoimmunity, autonomic dysfunction, abnormal ventricular growth, HIV infection per se or other associated viral infection and/ or side effects from ART may be causative and/or further exacerbate the cardiac morbidities. This study intends to evaluate cardiac manifestations among HIV infected children in India and their correlation with HIV disease status.

## Methods

### Study Design and Patients

This cross sectional study was conducted among HIV infected children up to 18 years of age for a period of 2 years from September 2009 to August 2011 at a pediatric HIV clinic of a tertiary care teaching hospital in Maharashtra, India. Ethical clearance was obtained from an institutional ethical committee. The diagnosis of HIV, clinical categorization and immunological categorization were based on WHO guidelines.

After obtaining informed consent of the parent/caregiver, children were enrolled in the study. A detailed history was obtained from the parents or care giver and a thorough clinical examination was done to detect any systemic manifestation as per predetermined criteria. All testing was done as per protocol based on NACO guidelines. The subjects were evaluated for cardiovascular abnormalities by chest X ray, Electrocardiography (ECG) and Echocardiography (Echo).

### Outcomes:

1. Cardiac manifestations were studied with respect to abnormality detected, clinically, chest-X-ray, ECG or Echocardiography.

2. Cardiac manifestations were correlated with WHO clinical and immunological categories of the subjects.

### Echocardiography:

An experienced pediatric cardiologist using the Hewlett Packard Sonos 2000 model echo machine performed echocardiography, following the criteria of the American Society of Echocardiography.[4] Long parasternal views with M-mode were used for measuring the heart chamber dimensions in diastole and systole. The variables studied on echo included the following: Left ventricular end-diastolic dimension (LVDD); Left ventricular end-systolic dimension (LVSD), inter ventricular septal thickness/posterior wall segment thickness (IVS/PWS), Left Ventricular Fractional Shortening (LVFS), Left Ventricular Ejection Fraction (LVEF), pericardial effusion and any structural lesion. Specific criteria for diagnosing these entities are below:

- Left Ventricular Fractional Shortening (LVFS) was automatically computed by the Hewlett Packard Sonos 2000 model echo machine, which was also sufficient to assess left ventricular function.[5] The normal range of fractional shortening is 28-44%.[6]

- Estimation of the pulmonary artery systolic pressure was derived from measuring a tricuspid regurgitate jet using Bernoulli's equation.[7,8] A fixed value of right atrial pressure, 5 or 10 mm of Hg, was added to the trans-tricuspid pressure gradient to yield Systolic Right Ventricular Pressure (SRVP). Doppler and color flow studies were done to study valve and orifice pressure gradient and directionality of blood flow.

### Mode of Diagnosis on Echo

The values of parameters assessed on echo were as follows:

- LV systolic dysfunction was defined as LVFS<28%.

- Low LVEF was defined as a reading below 55%.

- Regurgitation was considered mild if the back flow seen on color doppler did not reach the middle, moderate if the flow reached the middle and severe if it exceeded the middle of the receiving chamber.

- Pericardial Effusion (PE) was diagnosed when effusion measured more than 4 mm.

### Statistical Analyses

Data analysis was done by using SPSS (Statistical Package for Social Sciences) using statistical software version 17.0. We calculated correlation coefficient, Chi-square test and Fisher's exact test to find the significance in various parameters. The statistical test was used at 95% confidence interval.

## Results

A total of 130 consecutively enrolled HIV infected children were evaluated in the study. Eleven children were lost to follow up and were excluded. Out of the total 119 children in the study, the largest number of abnormalities was seen in the age group of 5-10 years (41.2%) followed by 10-18 years (39.5%) and <5 years (18.3%). The mean age in the study population was 8.9 years (range 2 - 17 years). The majority of the children were males (53.7%) with male: female ratio of 1.16: 1. The age of HIV diagnosis varied from 6 months to 14 years. The mode of HIV transmission was vertical in 116 (97%) children. Three children

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had acquired HIV through transfusion, of which two had thalassemia major. Protein energy malnutrition was observed in 94 (79%) children.

According to WHO clinical staging, the distribution of cases were as follows: - Clinical stage- I, 48 (40%) cases, stage-II, 41(35%), stage-III, 25(21%) and stage- IV, 5(4%) cases and Immunological stage as stage-I in 39 (33%) cases, stage-II 13(11%), stage III-42(35%) and stage IV in 25(21%) cases. The distribution according to WHO Clinical and Immunological staging of study population is shown in figure 1.

### Cardiovascular manifestations

Cardiovascular abnormalities were detected in 74 (62%) children on echo and/or ECG (Figure 2). Abnormalities were detected on echocardiography in 44 (36.9%) and by ECG in 56 (47%) children. Both echo and ECG were abnormal in 26 (21.8%) children. Chest radiographs detected cardiomegaly in 13 (11%) cases.

### Cardiovascular symptom/signs

Breathlessness was reported in 11 (9%) children in our study, of which 10 had abnormal echo and 7 abnormal ECG findings. Chest pain was reported by 4 children and all of them had abnormal echo in the form of low LV fractional shortening as well as LV dysfunction and ECG showed monofocal ectopics and sinus tachycardia. None of the children or their caretakers reported other cardiac symptoms like cyanosis, edema, palpitations or syncope. Clinical examination revealed tachycardia as the most common finding among the subjects in 43 (36%). No child had an audible murmur or abnormal S2. Hepatomegaly was observed in 52 (43%) children but none had raised JVP or

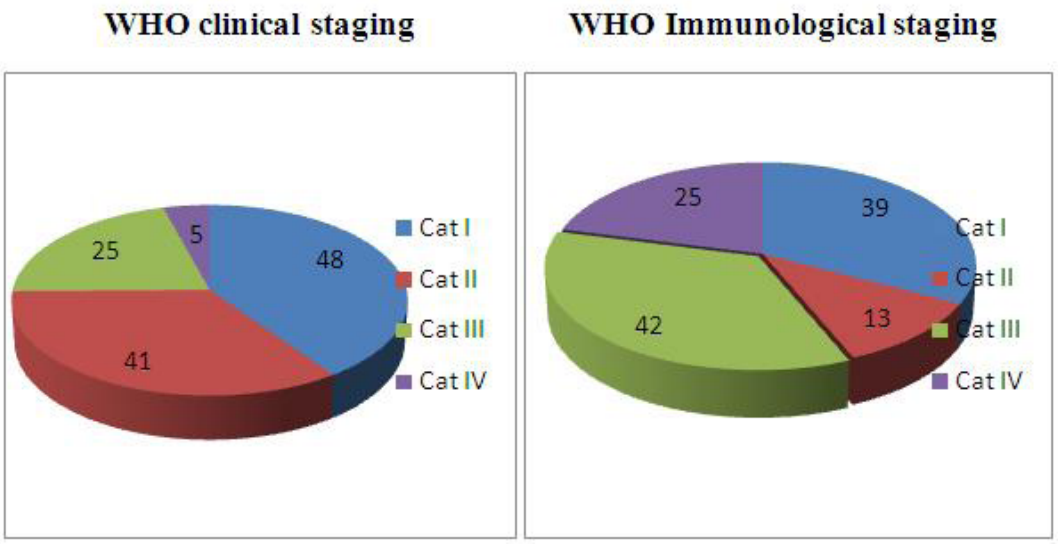


**Figure 1:** WHO Clinical and Immunological staging of study population at enrolment.

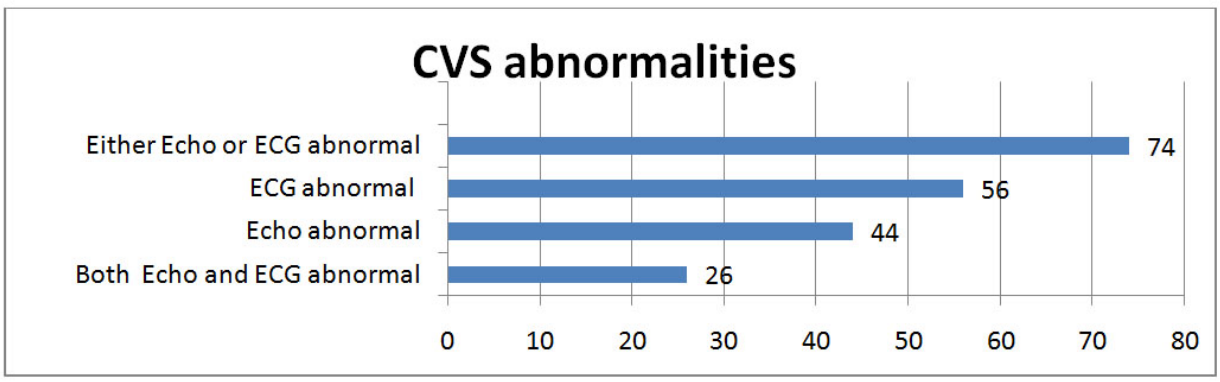


**Figure 2:** Cardiovascular abnormalities detected in the study.

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pedal edema.

### Chest X ray

In our study 46 (36%) children had an abnormal Chest X Ray. Non Homogenous Opacity (NHO) was the commonest finding seen in 17 (14%) cases, cardiomegaly in 13 (11%), hilar-adenopathy in 9 (7%) cases, bronchiectatic changes in 3 and diffuse reticulonodular infiltration and pleural effusion in 2 each.

### ECG

ECG abnormalities were detected in 56 (47%) children and the most common ECG abnormality was sinus tachycardia in 35 (29%) followed by ST-T changes in 20 (16.8%). The association was evaluated between ECG findings and clinical staging as well as immunological staging and was not found to be statistically significant. The association between presence of cardiac symptoms and ECG findings was found to be statistically significant as shown in table 1.

| S. No. | Cardiac Symptoms | ECG abnormal n= 56 (%) | ECG normal n= 63 (%) | Statistical analysis |
|---|---|---|---|---|
| 1 | Present | 39(70) | 10(15) | Chi-sq -35.388 p< 0.001 significant |
| 2 | Absent | 17(30) | 53(85) | |

**Table 1:** Abnormal Electrocardiography (ECG) with cardiac symptomatology.

### Echocardiography

Echocardiography was found to be abnormal in 44 (36.9%) children and the most common abnormality detected was LV systolic dysfunction as measured by LV Fractional Shortening (LVFS) in 31 (26%) followed by Left Ventricular Ejection Fraction (LVEF) noted in 24 (20%) children. Congenital heart disease was detected in 5 (4%) children: three had bicuspid aortic valve, one secundum Atrial Septal Defect (ASD) and one Mitral Valve Prolapse (MVP). Two children with bicuspid aortic valve complained of breathlessness and both had abnormal echo parameters (diminished LVFS and low LVEF). Two children in the study had minimal Pericardial Effusion (PE) on echo and both were in clinical stage III. Pericardiocentesis was not done owing to small volume of effusion. One child was initiated on tuberculosis therapy. None of the children had vegetations on echocardiography or any evidence of pulmonary arterial hypertension. The mean echocardiographic parameters and abnormalities noted are depicted in tables 2 and 3.

Abnormal Echo was considered as presence of any of the following abnormalities: low LVEF, diminished LVFS, structural heart disease, pericardial effusion or valvular regurgitation. Although there were more children with abnormal Echo in higher WHO clinical or immunological categories, there was no statistically significant association between the two. There was similarly no statistically significant association between the clinical or immunological staging with LV fractional shortening or LVEF. The association between presence of cardiac symptoms and abnormal Echo was found to be statistically significant as depicted in table 4.

| S. No. | Parameter | Mean ±SD |
|---|---|---|
| 1 | Mean Left ventricular end-systolic dimension (LVSD) | 21.9 ± 3.46 |
| 2 | Mean Left ventricular end-diastolic dimension (LVDD) | 33.0 ± 4.58 |
| 3 | Mean Left Ventricular Fractional Shortening (LVFS) % | 33.4 ± 6.41 |
| 4 | Mean Left Ventricular Ejection Fraction (LVEF )% | 60.7 ± 6.54 |
| 5 | Mean Inter Ventricular Septal thickness (IVS) | 7.9 ± 5.0 |
| 6 | Mean Posterior Wall Segment thickness(PWS) | 7.7 ± 1.31 |

**Table 2:** Mean parameters on Echocardiography.

| S. No | Echocardiographic abnormality | Number of patients | N=119 (%) |
|---|---|---|---|
| 1 | LV fractional shortening (systolic dysfunction) | 31 | 26.0 |
| 2 | Low LV Ejection Fraction | 24 | 20.1 |
| 3. | Congenital heart disease | 5 | 4.2 |
| 4. | Tricuspid regurgitation | 3 | 2.5 |
| 5. | Pericardial effusion | 2 | 1. 7 |
| 6. | Mitral regurgitation | 2 | 1.7 |

**Table 3:** Echocardiographic abnormalities in study population.

| S. No. | Cardiac symptom and signs | Echo abnormal n=44 (%) | Echo normal n=75 (%) | Statistical analysis |
|---|---|---|---|---|
| 1 | Present | 27(61) | 22(29) | Chi square= 1.52, p<0.001, significant |
| 2 | Absent | 17(39) | 53(71) | |

**Table 4:** Abnormal Echocardiography with cardiac symptom and signs.

Mean Haemoglobin (Hb) of children with low LVEF was 10.2 gm% as compared to mean Hb of 11.0 gm% in children with normal LVEF. The correlation coefficient was 0.279 (p=0.002), so there was a significant but very poor correlation between haemoglobin and LVEF.

## DISCUSSION

In our study of 119 HIV infected children, subclinical cardiac abnormalities were observed in 74 (62%) children detected either on echo and/or ECG. The most common cardiac symptom reported was breathlessness in 11 (9%) children and

the most common sign on clinical examination was tachycardia observed in 43 (36%) children. In the P2C2 (Pediatric Pulmonary and Cardiovascular complications of vertically transmitted Human Immunodeficiency Virus Infection)[9] study, a prospective multicentre study of 197 HIV-infected children, tachycardia was also the most common clinical finding.[2] The authors found echocardiographic changes in all symptomatic children.

In our study the most common echo abnormality was LV systolic dysfunction observed in 31 (26%) children. This is consistent with other similar studies that have reported a prevalence ranging between 18%-78%.[9-19] Specifically, LV dysfunction of 37% was reported from a Thai study in 2004.[8] The African study reported echocardiographic abnormalities in 51% abnormalities of the study population. In the P2C2 trial fractional shortening was a significant clinical predictor of mortality (RR=1.91, $p$<0.001). The same P2C2 trial later reported abnormalities in 31% of 196 children who underwent echocardiography[9] in subsequent publication. In a Brazilian study 52% of children had echo abnormalities of which only 20% had clinical findings.[10] In our study cardiac abnormalities were more frequently encountered in children with higher immunological category III & IV; however this association was not statistically significant. There was a statistically significant association between the presence of abnormalities in ECG or echo and cardiac symptoms.

The prevalence of Congenital Heart Disease (CHD) was 4% of all the children studied, comparable with previous studies, who reported prevalence of 2-3%[11,12] and this prevalence was higher than that found in the general population of 0.8%.[13] The most common congenital cardiovascular abnormality detected in our study was bicuspid aortic valve; none of the children had a ventricular septal defect, which is the most common form of congenital heart disease in healthy populations and similar studies.[11,12,14]

Pericardial Effusion (PE) was seen in 2 out of the 119 children (1.6 %), contrary to 14% to 60% incidence of PE seen in other studies of HIV-infected children.[11,12] Starcet al found no PE in 201 children with HIV, the majority of whom had symptomatic HIV disease.[15] Mild Tricuspid Regurgitation (TR) was found in three cases in our study however there was no evidence of Pulmonary Arterial Hypertension (PAH) in any of these children. None of the children had any vegetations, rheumatic heart disease, and PAH. ECG abnormalities were seen in 56 children (47%), which is comparable to the previously reported similar studies observed abnormal ECG in 26.5% -55% cases.[16,17] The prevalence in our study was much lower than that of Lipshultz, et al. who reported abnormal ECG in 93% children, possibly because 24-hour ambulatory ECG was utilized in that study in addition to the standard 12 lead ECG.[14] The most common ECG abnormality detected in our study was sinus tachycardia commensurate with similar studies.[14,16] The autonomic imbalance and neuropathy, which are present in early HIV infection and progress with worsening HIV disease, are possible explanations for the sinus tachycardia.[20] In our study 46 (36%) children had abnormal chest X ray, comparable to other similar studies.[8] We did not find any significant cardiac mortality in our study period, which may be explained by the advances in the management of HIV-infected children, such as prophylaxis against secondary infections, effective HAART, nutritional interventions, and closer cardiac monitoring.

## CONCLUSION

This study establishes that subclinical cardiac manifestations are prevalent in HIV infected children. More research should be done on the clinical significance of these findings and the need for long-term follow up.

## LIMITATIONS

The study is confined to an ART center in Maharashtra on a small study population, and larger studies may be conducted to further strengthen the results.

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SB, RG conceived the study and involved in data collection. PK, MS and DS helped in evaluation of cases, echocardiography. MS, PK and DS supervised the study and revised the manuscript.

## ETHICAL CLEARANCE

Obtained from the Institutional Ethical Committee.

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# Immunologic and Virologic Responses to Nevirapine Based Antiretroviral Therapy (ART) Among HIV-tuberculosis Co-infected Ugandan Children on Rifampicin Based Anti-tubercular Treatment

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**ABSTRACT**

**Background:** Children co-infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) require concurrent treatment with anti-tuberculosis drugs and Antiretroviral therapy (ART). Drug interaction between nevirapine and rifampicin leads to decreased nevirapine levels. The impact of this drug-drug interaction on virologic and immunologic outcomes in the treatment of HIV - TB co-infected children has not been fully studied. A retrospective analysis was conducted to compare the response to nevirapine-based ART regimen among HIV- infected Ugandan children on a rifampicin containing anti-TB regimen for TB disease *versus* those only on ART.

**Methods:** We analyzed data from HIV infected children aged 6 months to 12 years attending a Paediatric HIV clinic in Kampala, Uganda who between October 2004-June 2006 were enrolled into an ART program based on the 2002 World Health Organization (WHO) ART guidelines for Resource Limited Settings. In this retrospective analysis, children were divided into two groups; those on nevirapine based ART and rifampicin containing anti-TB treatment (TB group) and those on ART alone (no TB group). CD4 cell percent and viral load data obtained at baseline and thereafter 12 weekly until 48 weeks was compared using Wilcoxon rank sum test. Kaplan Meir plots were used to compare virologic success between the two groups over the 48 week follow up period.

**Results:** The analysis included a total of 127 children of whom 20% (26/127) were in the TB group. Median $\log_{10}$ HIV RNA (Interquatile range-IQR) at baseline was 5.69 (5.19-6.19) in the TB group *versus* 5.59 (4.86-6.32) in the no TB group; $p$=0.576. Median viral load was undetectable for all children by 12 weeks post ART initiation and this was sustained through 48 weeks irrespective of receiving rifampicin. Baseline median CD4% was not significantly different between the two groups. The median CD4% (IQR) during follow- up for the TB group *versus* the no TB group was: 17.0 (8.0-26) *versus* 20.9 (8.0- 33.8), $p$=0.147 by 12 weeks; 26.0 (12.7-39.3) *versus* 22.9 (7.5-38.3), $p$=0.472 by 24 weeks; 26.6 (13.6-39.6) *versus* 26.4 (12.3-40.5), $p$=0.927 by 36 weeks and 29.0 (20.0-38) *versus* 28.9 (16.8-41), $p$=0.931 by 48 weeks respectively.

**Conclusion:** HIV/TB co-infected children receiving rifampicin demonstrated satisfactory immunologic and virologic responses to nevirapine based ART, similar to children not on anti- TB treatment. These findings provide evidence that nevirapine based ART may remain effective

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among HIV positive children co-infected with TB who receive rifampicin-based anti-TB treatment.

**KEYWORDS:** Nevirapine and rifampicin co-administration; HIV-TB co-infected children; Immunologic and virologic outcomes.

## INTRODUCTION

The global estimate of HIV infected children at the end of 2013 stood at 3.2 million with 91% in sub-Saharan Africa.[1] TB is among the most common opportunistic infections affecting HIV infected children. In 2013, the World Health Organization (WHO) estimated that there were 550,000 TB cases and 80,000 TB deaths among children.[2] WHO recommends initiating ART as soon as possible for any HIV infected child diagnosed with TB disease.[3] In areas of high HIV/TB incidence such as sub-Saharan Africa, co-administration of ART and anti-TB treatment is very common.

Despite the general trend of increasing availability of ART in Sub-Saharan Africa over the past decade, paediatric ART in resource-limited settings still faces multiple challenges, particularly the availability of appropriate, affordable and simplified pediatric ARV formulations. Nevirapine (NVP) is widely used in sub-Saharan Africa because of its availability in fixed dose formulations which provides easy drug administration, reduced pill burden, convenient storage and low cost. In resource-limited settings, NVP is the most widely used Non-nucleoside reverse transcriptase inhibitor (NNRTI) in first line ART regimens for children unless contraindicated. WHO currently recommends a Lopinavir/ritonavir (LPV/r) based regimen for first line ART among all children under 3 years of age, however NVP is still recommended for this age group if a LPV/r regimen is not feasible.[3] HIV/TB co-infected children under 3 years of age cannot use an Efavirenz (EFV) containing ART regimen, therefore NVP and LPV/r are commonly used with rifampicin (back bone for the short course anti-TB treatment regimen) resulting in drug-drug interactions.

Although other rifamycins like rifabutin are associated with less drug-drug interactions if used with these ARV regimens, they are more costly and not readily available in resource-limited settings. Rifampicin is thus the most frequently used and preferred primary drug in the treatment of TB in these settings. Studies in Uganda, Zambia and Thailand have shown decreased NVP levels in HIV-TB co infected children on a NVP based ART regimen and a rifampicin containing anti-TB regimen with about half of the children with sub therapeutic trough levels.[4-6] Adult studies have demonstrated that the drug interaction between NVP and rifampicin results in decreased levels of NVP that may be suboptimal for complete viral suppression.[7,8]

We conducted a retrospective analysis to compare the immunologic and virologic response to NVP based ART regimen among HIV-TB Co- infected Ugandan children on rifampicin based anti-TB treatment compared to those on ART alone.

## METHODS

### Study Setting and Population

Between October 2004 and June 2006, HIV-infected children aged 6 months to 12 years attending the Mulago Hospital Paediatric HIV clinic and the Makerere University – Johns Hopkins University Research Collaboration (MUJHU) Research clinic in Kampala Uganda, were screened for initiation of ART based on the WHO antiretroviral therapy guidelines for Resource Limited Settings, 2002.[9] Those children who were eligible for ART were initiated on treatment.

Screening evaluations for the ART program were performed over 3 weekly visits. Prior to ART initiation, all the children and their care givers were screened to assess clinical eligibility as well as psychosocial readiness to initiate ART and to provide counseling on adherence and HIV care. Clinical assessments included screening for Opportunistic Infections (OIs) and since TB is a common OI in this setting, all children underwent TB screening prior to initiation of ART. Screening laboratory assessments included CD4 cell count/percent, baseline liver and kidney function tests.

The criteria for ART initiation in the ART program was based on WHO antiretroviral therapy guidelines for Resource Limited Settings, 2002 and included; symptomatic HIV infected children (WHO stage III or IV); WHO clinical stage III (2003) and or CD4 cell percentage, 20% or, 15% in those younger than 1 year and older than 1 year, respectively; creatinine <1.2 mg/dL in children under 2 years, <1.7 mg/dL in children 2 years and older; Alanine transferase (ALT)/Aspartate transferase (AST) <5 x upper limit of normal and parent/care taker psychosocial readiness.[9]

Some of the children enrolled into the ART program were enrolled into an observational ART cohort study whose objective was to compare the response to NVP based ART regimens among Ugandan HIV infected children exposed and non-exposed to single dose nevirapine (sdNVP) at birth as described elsewhere.[10] In addition to the criteria for ART initiation in the ART program indicated above, eligibility criteria for enrollment into the study included; confirmed HIV infection by HIV rapid tests (Determine and Unigold in series) or 2 positive HIV-1 DNA Polymerase Chain Reaction (PCR) tests (Roche Amplicor, Roche Diagnostics, Indianapolis, IN) for those children under 18 months of age, hemoglobin >7.0 g/dL, platelet count >49,000 /mm$^3$, absolute neutrophil count >250 /mm$^3$, Alanine transferase (ALT)/Aspartate transferase (AST) ≥5 x upper limit of normal, parent/care taker willing to provide informed consent for child's study participation, residing within 20 km radius of the study clinic and parent/care taker willing to be visited at home by study staff . Exclusion criteria for the study included

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known hypersensitivity to Nevirepine (NVP), malignancy, or on current cytotoxic chemotherapy.[10,11] Before enrollment into the study, children underwent the standard screening procedures for the ART program as earlier described. Specifically for the study, these included adherence counseling, clinical and psychosocial assessments, details on history of single dose nevirapine (sdNVP) exposure and a home visit. Parents/caretakers provided informed consent for enrollment of their children into the study. Children were assigned to cohort 1 if they had history of exposure to sdNVP at birth and to cohort 2 if they had no prior exposure to sdNVP.[10]

### Antiretoviral Treatment Regimens

Following determination of eligibility for ART initiation, children were started on adult fixed dose Triomune tablet (30/40 mg d4T/150 mg 3TC/200 mg NVP) manufactured by CIPLA India or stavudine (d4T), lamivudine (3TC) and NVP syrups for those who weighed less than 10 kg. Dosage was based on the children's weight bands as shown in Table 1. These dosing weight bands were developed prior to the 2006 WHO dosing weight bands.[12]

| Dosing of Triomune by weight | | NVP dosing mg/kg |
|---|---|---|
| Weight of patient (kg) | Drug dose | mg/kg/dose |
| <10 kg | syrups | 4mg/kg/dose for 14 days 7mg/kg/dose maintenance |
| 10-12.9 kg | ¼ tab Triomune 40 bd | 3.9-5.0 |
| 13-15.5 kg | ½ tab Triomune 30 bd | 6.3-7.7 |
| 16-25.5 kg | ½ tab Triomune 40 bd | 3.9-6.25 |
| 26-59.5 kg | 1 tab Triomune 30 bd | 3.5-7.7 |
| >60 kg | 1 tab Triomune 40 bd | 3.3 |

**Table 1:** Weight band dosing used for the study children on Fixed Dose Combination Triomune.

In summary, 127 eligible children aged 6 months to 12 years were initiated on ART according to the 2002 WHO ART guidelines.

After initiation of ART, the children in the program and study were reviewed at routine study visits, weekly for the first month, every 2 weeks for the second month and then every 4 weeks until 48 weeks. In the second year of follow up, routine visits were conducted every 3 months until week 96. Clinical monitoring was done at every routine study visit and laboratory monitoring was done at baseline, 12, 24, 36, 48, 72 and 96 weeks after initiating ART. Laboratory monitoring included; Complete Blood Count (CBC) and CD4 cell count (absolute and percent). Quantitative HIV-1 Ribonucleic acid (RNA) Polymerase Chain Reaction (PCR) was not routine standard of care at that time under the ART program and was performed for only children in the observational cohort study at 3 monthly intervals in year one of follow up and then every 6 months in year 2 of follow up. Children in the study also had plasma samples stored for future HIV resistance testing.[13] Chemistries (ALT and AST) were done at baseline, 2 weeks after ART initiation and then subsequently if clinically indicated for all children.

### Study Design

We conducted a retrospective analysis of the data collected from Ugandan HIV infected children on NVP based ART regimen who were grouped according to whether they were on a rifampicin containing regimen for TB treatment or not on treatment for TB disease. In this analysis we compared two groups, 101 HIV infected children without TB disease initiated on a NVP based ART regimen (no TB group) and 26 HIV infected children co-infected with TB, receiving rifampicin containing anti-TB treatment and NVP based ART (TB group) (Figure 1). Children who were already on a rifampicin anti-TB treatment regimen for TB disease at the time of ART initiation were also included in the latter group.

For this analysis data over 48 weeks of follow up was included. Immunologic and virologic outcome data over the second year of follow up was incomplete and was excluded from the analysis.

### TB Diagnosis and Treatment

As part of the routine screening evaluations for ART initiation and clinical monitoring while on ART, all children were screened for TB disease at enrollment and during study follow up when clinically indicated. Clinical symptoms/signs, history of PTB contact, tuberculin (PPD) skin testing and Chest X-ray (CXR) were used for TB screening. A PPD of ≥5 mm skin induration was considered positive. The diagnosis of tuberculosis infection was based on the WHO criteria and categorized as probable TB or confirmed TB.[14]

All children with tuberculosis disease were treated with a 6 month short course anti-TB regimen of rifampicin/isoniazid/pyrazinamide in the 2 months intensive phase followed by 4 months of rifampicin/isoniazid. Clinical monitoring was done monthly at scheduled anti-TB drug refill visits. At each follow up study visit a history and examination was done including assessment of TB signs and symptoms, adherence to medication, and measurement of weight and height. A CXR was done at completion of the TB treatment.

### Immunologic and Virologic Monitoring

Immunologic and virologic outcomes of children in the two groups were assessed by absolute CD4 cell count/percent and plasma HIV-1 RNA PCR, respectively. Tests were performed at baseline, every 12 weeks until 48 weeks of follow-up and then 6 monthly until 96 weeks of follow up. Viral load testing was not routine standard of care at that time and was performed for children in the observational cohort study. In the present analysis, we included immunologic and virologic outcome data up to 48 weeks of follow up because a large percentage of children in

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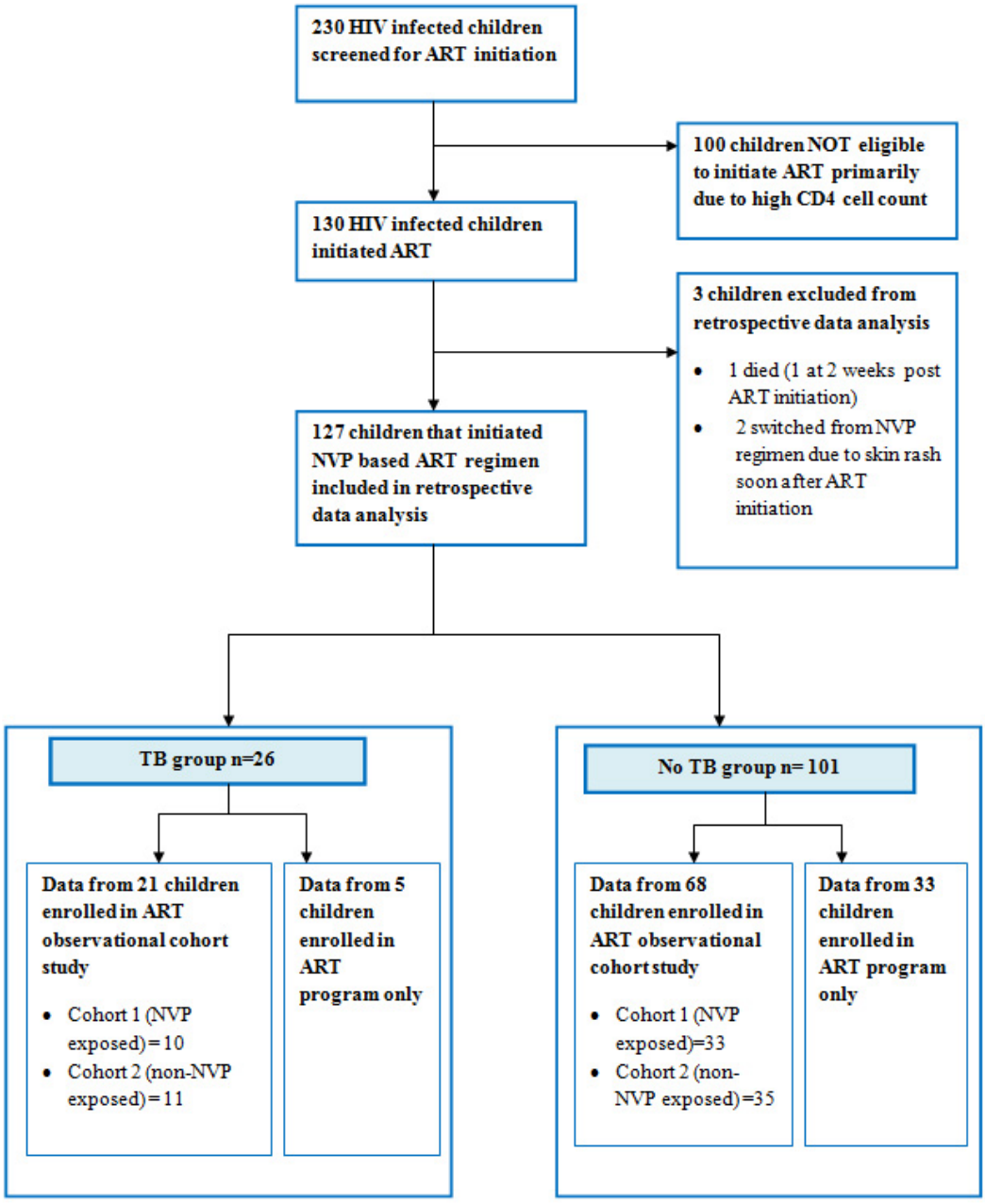


**Figure 1:** Study Profile

both groups did not have CD4 cell count and viral load data at week 72 and week 96.

In the TB group, 15/26 (58%) and 16/26 (62%) of the children did not have viral load and CD4 cell count data at week 72 and 96 respectively. In the no TB group, 24/100 (26%) and 35/100 (35%) of the children did not have both CD4 cell count and viral load data at week 72 and week 96 respectively.

### Adverse Drug Reaction Monitoring

An assessment of clinical signs and symptoms was conducted at each study visit to monitor adverse drug reactions. ALT and AST were assessed at baseline, 2 weeks after ART initiation and thereafter when clinically indicated, to monitor NVP toxicity.

### Laboratory Methods

The CD4 cell counts/ percent, HIV-1 RNA and Liver Function Tests (LFTs) were done at the College of American Pathologists (CAP) certified MUJHU core Research Laboratory in Kampala, Uganda. CD4 cell testing was performed using a fluorescence-activated cell sorting instrument (Becton-Dickinson, San Jose CA, USA). Quantitative HIV-1 RNA PCR was performed using the Roche HIV-1 Amplicor MONITOR assay

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v1.5 kit (Roche Diagnostics, Indianapolis IN, USA) on plasma separated from whole blood and frozen at -70 °C within 24 hours of collection.

### Data Collection and Statistical analysis

Data of ART eligible children enrolled in the ART program and ART observational cohort at MUJHU were obtained from the study database and through chart review of participant source files.

Baseline characteristics (sex, age, WHO clinical staging, weight for age and height for age Z scores with respect to the WHO-based reference population of children of similar age and gender) of the children in the TB group and those in the no TB group were compared using Chi square ($\chi^2$) and Wilcoxon rank sum test. Statistical comparisons of CD4 cell percent and HIV-1 RNA PCR at baseline, every 12 weeks until 48 weeks are based on the student's t-test and Wilcoxon rank sum test. Graphs of mean and 95% Confidence Interval (CI) bars are used to illustrate virologic and immunologic trends during 48 weeks of follow up. Differences in virologic outcome of the two groups over the follow up period by Kaplan Meir plots were assessed for statistical significance using the log rank test. The *p*-values are evaluated for statistical significance at the 0.05 two sided alpha significance level. All data analysis was performed with STATA Version 10 (StataCorp.2007. Statistical Software: Release 10, College Station, TX, StataCorp LP).

### Ethical Approvals

Institutional Review Board (IRB) approval was obtained from Makerere University, Faculty of Medicine Research and Ethics Committee and the Uganda National Counsel of Science and Technology (UNCST) for the primary observational cohort study. Written informed consent was obtained from parents/legal guardians of the children enrolled in the ART observational cohort study before study specific procedures were performed; however written assent was not obtained from the children because it was not an IRB requirement at that time.

## RESULTS

### Baseline Characteristics

A total of 127 HIV infected Ugandan children on a NVP containing ART regimen were included in the retrospective analysis. Twenty-six (20.5%) of these 127 children were also treated with a rifampicin containing regimen for TB disease (TB group) and 101 (79.5%) received ART alone (no TB group). Three of the 26 (11%) children in the TB group were diagnosed with TB disease and started anti-TB treatment from other care centers prior to initiating ART at the MUJHU clinic. The rest, 23/26 (89%) were diagnosed during follow up in the ART program and were classified as probable TB. There were no cases of culture confirmed tuberculosis. The baseline characteristics of the children in both groups are shown in Table 2. Children in the TB group were significantly younger than those in the no TB group with median age of 2.7 years (IQR 1.2-4.4) *versus* 5.2 years (IQR 2.4-7.0) ($p$=0.034). There was no significant difference in the WHO clinical stage of the two groups with about 1/3 of the children in each group in WHO clinical stage 3 & 4 ($p$=0.085). There were no significant differences in sex, median weight for age and height for age Z scores between the two groups at baseline.

### Immunologic Outcomes

Children in both the TB group and no TB group were severely immunosuppressed at enrollment with a median baseline CD4 cell percent (IQR) of 9.2 (0.5-17.5) *versus* 12.9 (2.1-23.7) respectively. There was a robust increase in median CD4

| Variable | TB group (n=26) | No TB group (n=101) | *p* value |
|---|---|---|---|
| Sex Male (%) | 15 (58%) | 48 (48%) | 0.355 |
| Primary Caregiver mother (%) | 18 (69%) | 68 (67%) | 0.648 |
| Caregiver level of education (%) | 04 (15.4%) | 11 (10.9%) | 0.507 |
| No education | | | |
| Primary, Higher & Tertiary level | 22 (84.6%) | 90 (89.1%) | |
| Median age in years (IQR) | 2.7 (1.2-4.4) | 5.2 (2.4-7.0) | 0.034 |
| WHO clinical stage 3 & 4 | 10 (38%) | 29 (29%) | 0.085 |
| Median weight for age Z score (IQR) | -2.41 ((-3.17)-(-0.87)) | -1.76(-2.66-0.914) | 0.129 |
| Median height for age Z score (IQR) | -0.42 (-1.31-0.36) | -0.34 (0.98-0.57) | 0.369 |

**Table 2:** Baseline characteristics of HIV infected Ugandan children on a nevirapine based ART regimen grouped by treatment with or without rifampicin.

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cell percent by 12 weeks and a sustained 3 fold increase with a median increase of 19.8% in the TB group *versus* 16% in the no TB group by 48 weeks of follow-up. The median CD4% (IQR) during follow-up for the TB group *versus* the no TB group was: 17.0 (8.0-26) *versus* 20.9 (8.0-33.8), $p$=0.147 by 12 weeks; 26.0 (12.7-39.3) *versus* 22.9 (7.5-38.3), $p$= 0.472 by 24 weeks; 26.6 (13.6-39.6) *versus* 26.4 (12.3-40.5), $p$= 0.927 by 36 weeks and 29.0 (20.0-38) *versus* 28.9 (16.8-41), $p$=0.931 by 48 weeks respectively.

There was no significant difference in immunologic response to treatment between the children on NVP ART alone and those on NVP ART and rifampicin (see Figure 2).

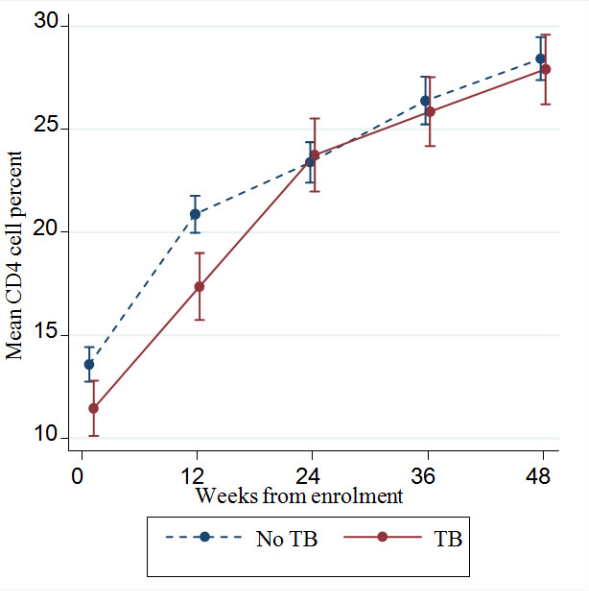


**Figure 2:** Immunologic response of HIV infected Ugandan children on a nevirapine based ART regimen with or without concurrent rifampicin anti-TB treatment.

### Virologic Outcomes

There was no significant difference in the median $\log_{10}$ RNA copies (IQR) between the TB group and the no TB group at baseline with values of 5.69 (5.19-6.19) *versus* 5.59 (4.86-6.32); $p$=0.576. By 12 weeks and through 48 weeks, children in both groups had median $\log_{10}$ RNA copies of 2.60 (undetectable viral load). Median $\log_{10}$ RNA copies (IQR) during follow up for the TB group *versus* the no TB group was as follows: 2.60 (2.60-3.06) *versus* 2.60 (2.48-2.72); $p$=0.86 by 12 weeks; 2.60 (2.60-2.99) *versus* 2.60 (2.60-2.60); $p$=0.358 by 24 weeks; 2.60 (2.60-2.89) *versus* 2.60 (2.60-2.60); $p$=0.706 by 36 weeks and 2.60 (2.60-2.99) *versus* 2.60 (2.60-2.60); $p$=0.327 by 48 weeks respectively. All children attained a 3 fold drop (0.5 $\log_{10}$) in mean viral load by 12 weeks which was sustained through 48 weeks irrespective of receiving rifampicin (Figure 3). Kaplan-Meier plot for achieving virologic success (viral load <400 copies/ml) demonstrates success in about 60% of the children in both groups by 12 weeks on ART (Figure 4). By 24 weeks, at least 80% of all children attained virologic success, with no significant difference between the two groups $p$=0.637.

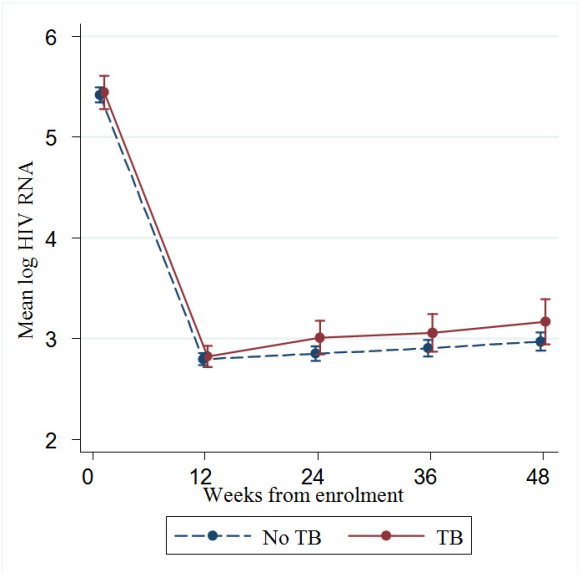


**Figure 3:** Virologic response of HIV infected Ugandan children on a nevirapine based ART regimen with or without concurrent rifampicin anti-TB treatment.

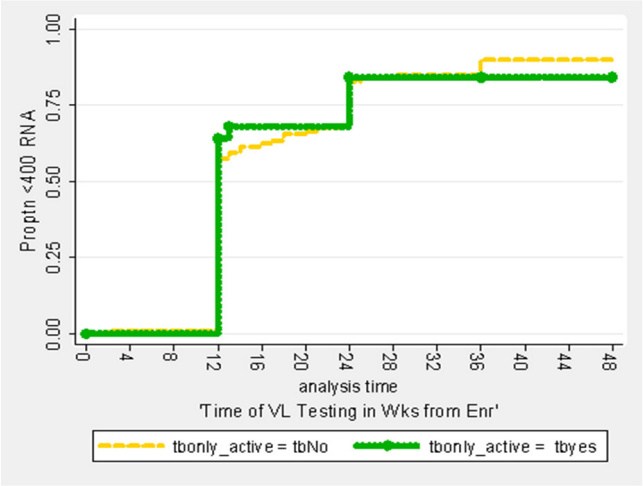


**Figure 4:** Kaplan Meier analysis for virologic success (<400copies/ml) over time in HIV infected Ugandan children on nevirapine based ART regimen alone or with a rifampicin anti-TB regimen for TB disease treatment, baseline to 48 weeks after ART initiation.

### Adverse drug reactions

Overall there were few (seven) adverse events classified as suspected adverse drug reactions. Skin rash occurred in 3 of the 127 children, with 2 in the TB group and 1 in no TB group. Raised ALT/AST was observed in 3/127 (2.4%) of the children with one in the TB group and two in the no TB group. All the events were of mild to moderate severity and none warranted stopping either the anti-TB treatment or ART. All suspected adverse drug reactions resolved spontaneously during follow-up. There was one death due to HIV nephropathy in the no TB group at 44 weeks of follow-up.

## DISCUSSION

Nevirapine is still widely used as part of the first line ART regimen in sub-Saharan Africa and HIV-TB co-infection

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presents a treatment dilemma especially in children where ARV drug options are limited. Currently, WHO recommends initiation of ART for all HIV infected children ≤5 years of age, regardless of WHO clinical stage or CD4 count. For HIV-TB co-infected children, both ART and anti-TB treatment should be initiated as soon as the diagnosis of either is made.[3] If TB diagnosis is made prior to initiation of ART, TB treatment should be initiated first and then ART started as soon as possible thereafter (preferably within 2-8 weeks of initiation of TB treatment).[3] Despite the current WHO recommendations on using a LPV/r based regimen as first line ART for all HIV infected infants under 3 years of age, the need for NVP based ART regimens in this age group has not been eliminated because many countries in Africa have limited access to Protease Inhibitor (PI) - based regimens due to cost implications and the need to maintain a cold chain. Although a triple nucleoside ART regimen provides a suitable option in the treatment of HIV-TB co-infection in children under 3 years of age, currently "there is limited data on the efficacy of this regimen in the context of TB".[3] It is thus very important to study the potential effect of concomitant use of rifampicin with a NVP based ART regimen in children.

Our study demonstrated that concomitant use of a rifampicin anti-TB regimen for treatment of TB in HIV infected children on a NVP based ART regimen does not significantly alter their early immunologic and virologic response over 48 weeks of treatment. All children on NVP based ART including those who were severely immunosuppressed at baseline with CD4% <15, were able to attain a significant immune response by 48 weeks of follow up, irrespective of receiving rifampicin. These children were also able to achieve virologic suppression which was sustained through 48 weeks. Our findings are similar to those reported by Manosuthi et al where there was no difference in long term virologic and immunologic outcomes on NVP based ART (at a dose of 400 mg/day) among HIV/TB co-infected adults receiving rifampicin compared to adults without TB co-infection.[15] In this prospective observational study, 70 HIV-TB co-infected adults on rifampicin and 70 HIV infected adults on NVP based ART, were followed for 4 years of ART and their immunologic and virologic outcomes evaluated 12 weekly until 96 weeks and then every 24 weeks thereafter. The percentage of patients who achieved HIV-1 RNA <50 copies/ml was 52.9% in the TB group and 50% in the control group ($p$=0.866).[15] A retrospective study done in Botswana (n=310) also found no difference in the immunologic and virologic outcomes of HIV positive adults on NVP based ART as compared to EFV based ART irrespective of rifampicin co-administration for TB treatment over the first 12 months on ART.[16]

A recent open label randomized trial conducted in Mozambique involving over 500 HIV-TB co-infected adults randomized to receive either a NVP based ART regimen or EFV based ART regimen demonstrated no significant difference in virologic outcomes between the two groups at 48 weeks.[17] In the paediatric population, published data in this area is limited and mainly focused on pharmacokinetics of NVP. There are limited published studies directly evaluating the effect of rifampicin on immunologic and virologic outcomes in HIV-TB co-infected children on NVP based ART regimens and it is important to study this because unlike adults, children tend to have higher viral loads and are thus less likely to be adequately suppressed with lower plasma NVP drug levels.[18]

Rifampicin is a known strong inducer of cytochrome P450 and as such results in reduced plasma concentrations of NNRTIs and PIs if used concurrently with these drugs.[19] Both adult and paediatric studies done in Africa, Thailand and India have shown varying levels of the effect on NVP plasma levels as a result of the drug-drug interaction during concomitant use of a rifampicin containing anti-TB regimen and a NVP based ART regimen.[4-6,8,20-23] An intensive pharmacokinetic study of standard-dose NVP with and without rifampicin in South African adults found sub-therapeutic NVP levels in 6 of 16 patients during rifampicin dosing.[8] A pharmacokinetic sub analysis conducted on 20 of the children in this study as reported by Barlow Mosha et al. also found that NVP trough concentration was significantly reduced in children who received rifampicin and NVP concurrently.[5] This is consistent with findings from another pharmacokinetic study in 37 Zambian HIV infected children aged <3 years which reported reductions in NVP plasma levels among 41% of children on a NVP based ART regimen and concomitant tuberculosis therapy with rifampicin compared to those on NVP alone ($p$=<0.001).[6] These findings raise concerns about increased risk of resistance in these circumstances of suboptimal NVP plasma concentrations and this has been documented in a sub population of children included in this analysis.[13] Resistance testing was performed on samples from 74 children who were enrolled in our primary observational ART cohort study and pre-ART samples from 2 children (2.7%) were found to have resistance to NNRTIs and Nucleoside Reverse Transcriptase Inhibitors (NRTIs).[13] In addition, 5 (9.8%) pre-ART samples from 51 of children with HIV sub-type A and D among the 74 children were found to have selected NVP resistance mutations (K103N, Y181C, and G190A), with majority (68%) of these children having had prior exposure to single dose NVP (sdNVP) for Prevention of Mother To Child HIV Transmission (PMTCT). Resistance testing was performed on 12 samples from the 74 children who had pre-ART samples analysed for resistance and were not virologically suppressed at 48 weeks. All the 12 samples had resistance to NNRTIs including NVP (n=12), EFV (n=2) and delavirdine (n=10).[13] Five of the 12 children who had NVP resistance mutations had history of sdNVP exposure at birth and 1 of these children initiated ART at 12 months of age while the rest initiated ART between 14 and 16 months of age. However, in this drug resistance analysis, the effect of concomitant administration of rifampicin among HIV-TB co-infected children was not specifically evaluated.

The effect of suboptimal NVP concentrations on immunologic and virologic response has not been fully explored in

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children. Studies evaluating immunologic, virologic responses and ARV drug resistance in HIV-TB co-infected children in relation to concomitant rifampicin and NVP ART regimen administration are crucial. Adult studies have demonstrated that the decreased bioavailability of NVP due to rifampicin co-administration could be overcome by increasing the dose of NVP.[24] Findings from a study done in India indicate that concomitant administration of a NVP ART regimen and rifampicin in HIV-TB co-infected children does not alter NVP blood levels if the NVP dose is increased by 50-90 mg/m$^2$/day.[25] This however was a cross- sectional study involving only 7 HIV- TB co-infected children and was not powered enough to draw generalizable conclusions. WHO currently recommends an increased dose of NVP of 200 mg/m$^2$ when co-administered with rifampicin among children under 3 years of age.[3] Further research is therefore needed to document pharmacokinetic responses as well as efficacy of higher dose NVP when co-administered with rifampicin among children.

The virologic and immunologic treatment success in both groups of children in this retrospective analysis could probably be attributed to possible high adherence rates to ART in this study setting with intensive participant follow up, frequent adherence counseling/support, the use of a Fixed Dose Combination (FDC), and close clinical monitoring. Although a study done in Zambia and Malawi demonstrated that children who received half or quarter tablet of Triomune FDC were more likely to be under dosed with NVP as compared to those who received a full tablet findings from this observational cohort of Ugandan children showed sustained clinical, immunologic and virologic response in children who received the divided adult Triomune tablet.[11] Other studies in Sub Saharan Africa have demonstrated similar immunologic and virologic outcomes among children on Triomune FDC followed for 6-12 months as well as other newer NVP based pediatric FDCs.[26,27]

The strengths of this study include the longitudinal laboratory and clinical monitoring as well as high rates of follow up in the parent study. The TB and No TB groups were immunologically and virologically comparable at baseline.

One limitation of this study is the variation in duration of TB treatment in relation to time of ART initiation. The follow up period of 48 weeks and a relatively small sample size of HIV/TB co-infected children may not be used to generalize long term immunologic and virologic outcomes of HIV-TB co-infected children. Longer duration study with larger sample size could confirm the findings of this study.

## CONCLUSION

The results of this study are encouraging and suggest that NVP based ART may remain effective among children co-infected with TB who received rifampicin-based treatment for TB disease. The TB-group demonstrated satisfactory immunologic and virologic responses to nevirapine - based ART similar to those children without TB disease. These findings should be confirmed through larger prospective studies and would be helpful in countries with high HIV/TB burden and limited antiretroviral options. Since NVP is a convenient and relatively affordable antiretroviral drug because of its availability in generic fixed-dose combinations, large robust studies to evaluate the efficacy of the currently recommended higher dose of NVP with concurrent use of rifampicin in paediatric HIV-TB co-infection, particularly among children under 3 years of age, will further inform the current WHO recommendations.[3]

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**CONFLICTS OF INTEREST:** None.

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Research

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# Thunderclap Headache in HIV Positive Patients: Aetiology, Clinical Findings and Long Term Follow-up of a Series of 5 Cases

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## ABSTRACT

**Background:** Thunderclap headache is a severe headache of sudden onset that peaks within a few seconds. The aim of this study was to describe the clinical characteristics, etiologies and long-term prognosis of thunderclap headaches in HIV positive patients.
**Patients and Methods:** This was a 5-year retrospective study of thunderclap headaches in HIV positive patients with a long-term follow-up at the Neurology Unit of the Internal Medicine Department of the Douala General Hospital. All patients had a cerebral magnetic resonance imaging and cerebrospinal fluid analysis. Patients were followed-up at the out-patient department after hospitalization.
**Results:** 65 patients were recorded with thunderclap headaches over the study period, and 5 were infected with HIV type 1 (7, 69%). The mean age was 50, 8±15, 4 years. There were three females and the mean CD4 count was 328, 6±195, 8 cells/mm$^3$. The aetiologies of thunderclap headache were one case each of subarachnoid haemorrhage, ischemic stroke, primary thunderclap headache, cryptoccocal meningitis and migraine without aura respectively. The mean duration of the out-patient follow-up was 17 months±10, 2 (1-25) months; 95% CI (5, 7-24). There was no relapse of thunderclap headache and the mortality rate was 20%.
**Conclusion:** Thunderclap headache in HIV positive patients occurs spontaneously and is independent of the level of CD4 count. The aetiologies are heterogeneous, and show no predominance of subarachnoid haemorrhage thus highlighting the important role of neuroimaging in the diagnosis of its cause.

**KEYWORDS:** Thunderclap headache; HIV; Aetiologies; Outcome.

## INTRODUCTION

Headache is a common cause of consultation in medicine.[1,2] Its prevalence in the general population is estimated at 90%.[3] Headache is major public health problem due to its influence on the Quality of Life (QoL) of patients and its related cost of healthcare.[4,5] In 2010, it was among the ten top causes of disabilities worldwide.[6] Headache has a variety of causes. According to the International Headache Society classification in 2004 there are, primary

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headaches of which migraine and tension-type headaches are the most common; secondary headaches attributed to an organic cause; cranial neuralgias, primary and central facial neuralgias; and the other primary headaches.[7] Thunderclap headache is a rare form of headache.[7] It is an acute and severe headache of instantaneous onset, with its maximal intensity in a few seconds or minutes.[8,9] Thunderclap headache could be a primary headache with benign outcome, or secondary headache due to a variety of aetiologies leading to serious morbidity and mortality.[8] The most common aetiology of thunderclap headache is subarachnoid haemorrhage.[7,10] There are other varieties of causes depending on authors and include; intracerebral haemorrhage, brain tumours, cerebral venous thrombosis, meningitis, acute glaucoma and sinusitis.[11-13] The incidence of thunderclap headache worldwide is not known because of this multitude of aetiologies.[8,10] In Cameroon, the prevalence of HIV infection in adults is 5, 3%.[14] The aim of this study was to describe the clinical characteristics, aetiologies and outcome of thunderclap headaches in HIV positive patients.

## PATIENTS AND METHODS

This was a retrospective study of medical records of patients admitted for thunderclap headache and HIV infection over a period of 5 years from 1st January to 31st December 2014 at the Neurology Unit of the Internal Medicine Department of Douala General Hospital. Cases were identified from patients' medical records, registers of admissions and out-patient departments. For each patient the following data was collected: age, sex and marital status; characteristics of headaches: circumstances at onset (coughing, coitus, physical effort, defecation, intellectual effort, sudden emotion, bathing, head movements, spontaneous); trigger factors (postpartum, drugs and alcohol); localization of the pain (temporal, bitemporal, occipital, frontal, diffuse); associated signs and symptoms (nausea, vomiting, agitation, photophobia, seizures, focal neurological deficits, altered state of consciousness, fever, neck stiffness). Toxicological past history was also investigated (alcohol consumption, tobacco smoking, drug use and medications). As investigations, all our patients had had a cerebral Magnetic Resonance Imaging with MRI – Angiography and a lumbar tap. All cerebrospinal fluids were analysed for cytology, bacteriology, Indian ink stain, detection of soluble antigens and culture. After discharge from the hospital, patients were followed-up at the out-patient department. The total duration of follow-up was estimated in month. We searched for relapse of thunderclap headache, the occurrence of other forms of primary headaches (migraine, tension-type headache, and unspecified headaches) and death.

### Statistical Analysis

Data was analysed using the SPSS (Statistical Package for the Social Sciences) version 20.0 software. Qualitative data were expressed as percentages and quantitative variables as mean and standard deviations.

### Ethical considerations

The study was approved by the Institutional Ethical Committee of the University of Douala.

## RESULTS

Over the study period 65 cases of thunderclap headache were recorded of which five were infected with HIV type 1 (7.69 %). The mean age of patients was 50, 8±15, 4 years (38-69), CI 95% (39-62, 6). The median age was 43 years. Four of the five patients were known HIV positive patients while the thunderclap headache revealed the HIV infection in one patient. The mean CD4 cell count was 328, 6±195, 8 cells/mm$^3$ (104-609); CI 95% (85, 2-252, 6). Four patients were on antiretroviral treatment comprising: 2 patients on the Zidovudine – Lamivudine – Nevirapine and 2 patients on the Zidovudine – Lamivudine – Effavirenz combinations respectively. One patient was not yet eligible for antiretroviral treatment. The clinical profile of patients' is shown in Table 1. The aetiologies were different for the five patients: subarachnoid haemorrhage (class II of the World Federation of Neurology), ischaemic stroke, cryptococcal meningitis, migraine without aura and a case of primary thunderclap headache. Four of the five patients were admitted in the hospital, the mean duration of admission was 15±7, 7 (5-22) days; CI 95% (1-9, 81). No case of death was registered during admission, the duration of follow-up in the out-patient department was 17 months±10, 2 (1-25) months; CI 95% (5, 7-24). There was no relapse of thunderclap headache during the period of follow-up. One patient with the diagnosis of primary thunderclap headache had a sudden death giving a mortality rate of 20%. The death occurred at the 22nd month of follow-up. During the follow-up period, three patients including the patient with subarachnoid haemorrhage had no symptoms, while the patient with cryptococcal meningitis developed tension – type headache.

| | Number (N) | Percentage (%) |
|---|---|---|
| **Context of occurrence** | | |
| Spontaneous | 4 | 80 |
| Bathing | 1 | 20 |
| **Localization of thunderclap headache** | | |
| Occipital | 2 | 40 |
| Frontal | 2 | 40 |
| Diffuse | 2 | 40 |
| Parietal | 1 | 20 |
| Temporal | 1 | 20 |
| **Signs and Symptoms** | | |
| Vomiting | 3 | 60 |
| Photophobia | 3 | 60 |
| Nausea | 2 | 40 |
| Neck stiffness | 2 | 40 |
| Fever | 2 | 40 |
| Focal neurological deficit | 2 | 40 |
| Altered state of consciousness | 1 | 20 |

**Table 1:** Clinical characteristics of thunderclap headache in HIV positive patients.

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## DISCUSSION

This study shows the clinical profile, aetiological aspects and evolution of thunderclap headache in HIV infected patients. It is of interest as it is one of the first studies on thunderclap headache focussing only on HIV positive patients. Classically, headache occurs in about 83% of HIV positive patients with the aetiologies being mainly infections of the central nervous system as cerebral toxoplasmosis as cryptococcal meningitis.[15] Thunderclap headache is specific with its acute and severe sudden onset with peak intensity in a few seconds. Its main aetiology is subarachnoid haemorrhage.[8,16] The occurrence of thunderclap headaches in HIV positive patients led us to enquire about its aetiological characteristics and outcome. The first lesson is that there should exist some clinical specificities as 80% of cases were on spontaneous occurrence compared to 63% reported by Landtblom and colleagues[10] in a series of HIV negative patients. The mean age of occurrence was 50.8 years as opposed to 40 years reported in HIV negative patients by other authors.[10,17]

The second lesson is that the occurrence of thunderclap headache in HIV positive patients is independent of the level of CD4 count, as the mean CD4 count of the 5 patients was 328, 6±195, 8 cells/mm$^3$ with a range from 104 to 609 cells/mm$^3$. The question arises whether antiretroviral treatment could influence the occurrence of thunderclap headaches, however, we cannot answer that with this study design.

The third lesson is that the aetiologies of thunderclap headache on HIV are variable and subarachnoid haemorrhage does not seem to predominate. We recorded 20% of cases due to subarachnoid haemorrhage in our series of HIV positive as against 40% reported by other authors in HIV negative patients.[8,10] This heterogeneity of causes reemphasizes the need of cerebral neuroimaging in HIV positive patients with thunderclap headache. For example, the ischaemic stroke was diagnosed on cerebral MRI which showed infarction at the superficial territory of the middle cerebral artery meanwhile a prior head CT scan was normal. The cerebrospinal fluid analysis ruled out the diagnosis of minimal subarachnoid haemorrhage and infectious causes as bacteria or fungi. The case of primary thunderclap headache was diagnosed based on a normal CSF and brain MRI. The long-term outcome was favourable for all the cases. We could not explain the cause of sudden death in the patient primary thunderclap headache. This patient had no cerebrovascular risk factors as hypertension, diabetes, smoking and dyslipidaemia. He had benefited from neuroimaging procedures with a brain MRI and angio-MRI which were normal. Our findings however have certain limitations given our small sample number of cases.

## CONCLUSION

Thunderclap headache in HIV positive patients occurs spontaneously and is independent of the CD4 count. The aetiologies are variable without any predominance of subarachnoid haemorrhage, thus highlighting the importance of neuroimaging. The outcome of thunderclap headache on HIV is favourable.

## CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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