Original Article

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A Study of Factors Associated with, and Echocardiographic Findings of HIV Related Heart Failure

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Abstract

Background: With increasing incidence of Human Immunodeficiency Virus (HIV) related heart failure, evidence suggests that diastolic rather than systolic dysfunction is predominant. The pathology of pericardium, myocardium or coronary and pulmonary vasculature is related to heart failure in HIV. Echocardiography helps in detecting cardiac dysfunction before overt clinical manifestations develop. *Objectives:* To assess cardiac structure, function and cardiac abnormalities related to heart failure in HIV-infected subjects attending medicine department of a tertiary care teaching hospital. *Methodology:* This was a prospective cross-sectional study of 102 HIV-infected patients presenting with cardiac complaints at the medical department of a tertiary care hospital in western Maharashtra from July 2016 to September 2017. *Results:* A total of 102 HIV infected patients were included with cardiac complaints, 50 (49%) were in heart failure (HF). Commonest causes of HF were left ventricular hypertrophy, pulmonary hypertension, dilated cardiomyopathy and anaemia. Male gender (OR 4.03), low education (OR 4.91), previous history of tuberculosis (OR 3.01), and low haemoglobin (OR 0.83), were independently associated with diagnosis of HF ($p<0.05$ for all). *Conclusion:* Left ventricular wall thickness and function should be monitored regularly in HIV subjects. The echocardiography is a useful and relevant tool in management of HIV infected patients especially in the era of ART.

Keywords: Echocardiography; HIV; Heart Failure.

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Introduction

India has the third largest HIV epidemic in the world which is progressing towards gaining number one position. In 2016 statistics, HIV prevalence in India was an estimated 0.26%. Overall, India's HIV epidemic is slowing down, with a 32% decline in new HIV infections and a 54% decline in AIDS-related deaths between 2007 and 2015. Despite this, 51% of HIV related deaths in Asia are in India [1,2].

Cardiovascular diseases, including heart failure are a known complication of HIV infection both in developing and in developed countries [3,4,5]. In a recent publication from the Heart of Soweto study, 9.7% of newly presenting heart failure cases were attributable to HIV infection [6].

HIV infection is frequently associated with cardiac involvement. HIV may affect all layers of the heart; endocardium, myocardium or pericardium.[7] Cardiac involvement may either be due to direct infection, as HIV nucleic acid sequences have been detected in cardiac myocytes or to opportunistic infections [7,8]. The exact pathogenesis of the cardiac manifestations remains unclear, but is most likely multifactorial [3,8,9].

Several factors play part in the progression from asymptomatic cardiac involvement to overt clinical symptoms and heart failure among HIV patients. The reasons for the paucity of knowledge about the aetiology of HIV associated heart failure are:

1. The heart was thought to be unaffected by HIV infection because the cardiomyocytes do not have CD4 receptors.

2. Presence of cardiovascular risk factors like poor nutrition, alcohol and drugs that can lead on to cardiac disease in HIV infected individuals.
3. Cardiac disease remains relatively asymptomatic in early stages of HIV infection.
4. Symptoms of breathlessness, fatigue and poor exercise intolerance are frequently ascribed to other conditions associated with HIV infection [10].

In developing countries where opportunistic infections, low socio-economic status coupled with poor nutrition are a problem, progression towards heart failure may be multifactorial. A number of factors including smoking, alcohol consumption and low socioeconomic status were associated with a diagnosis of dilated cardiomyopathy in apparently asymptomatic, HAART naive HIV infected patients.

Infection with HIV is a leading cause of acquired heart disease worldwide manifesting with symptomatic heart failure, pulmonary arterial hypertension and left ventricular hypertrophy [16]. HIV is also implicated in causation of dyslipidaemia (hypercholesterolemia, hypertriglyceridemia and reduced HDL) thereby accelerating the atherosclerosis [11,12]. However, it is unclear if these factors are also independently associated with the development of heart failure fromany form of cardiac pathology among HIV infected patients.

Recently a study of 30 HIV-infected men and uninfected controls, patients with HIV were found to have a higher prevalence of diastolic dysfunction, lower calculated ejection fraction (EF), and higher pulmonary artery pressure compared with uninfected controls [15]. Dilated cardiomyopathy has also been found to affect 10-20% of those with HIV infection and has been shown to account for approximately a third of HIV related deaths [7].

The Heart of Soweto Study was undertaken to investigate the impact of the HIV/AIDS.518 of 5328 (9.7%) of HIV-patients, almost third, presented with LV systolic dysfunction (N=148; 29%) and 196 (38%) had HIV-related cardiomyopathy (which encompassed both systolic and diastolic dysfunction in both symptomatic and asymptomatic patients) [6]. Two to fiveyears incidence of symptomatic heart failure ranges from 4% to 28%, suggesting a prevalence of symptomatic HIV-related heart failure of between 4 and 5 million cases worldwide.

The HIV prevalence among the low risk general population in Ahmednagar district is moderate at 0.55% (PPTCT, 2008). The trend has been constant over the past 6-years (HSS, ANC 2003-08). The prevalence has been relatively higher in the high-risk men at 10.13% (CLINIC walk-in males, 2008) and female sex workers at 14.80% (HSS, FSWs, 2008). The district has a moderate epidemic potential among general population, but a high prevalence among the high-risk groups with a potential to further spread the infection into the low-risk population [18].

Echocardiography is helpful in detecting cardiac dysfunction at an early stage, much before overt clinical manifestations develop [24]. The most common sign of cardiac involvement is impairment of LV fractional shortening (%FS) [19]. Determining the deleterious effects of HIV may prove echocardiography to be a useful, non-invasive tool to assess cardiac function and monitor for cardiac abnormalities. This study was undertaken to assess cardiac dysfunctions with the help of 2D ECHO findings in patients with HIV/AIDS and its clinical correlation.

Aims And Objectives

To assess cardiac structure and function as well as cardiac abnormalities in HIV-infected subjects attending medicine department of a tertiary care teaching hospital.

Methodology

The study was conducted between July 2016 and September 2017.

Inclusion Criteria

All consenting HIV infected patients aged 18 years and older admitted at medicine wards and patients attending OPD at the time of study were included in the study.

Exclusion Criteria

a. Patients under 18 years
b. Congenital heart disease,
c. Rheumatic heart disease
d. Ischemic heart disease
e. Hypertensive heart disease
f. Valvular heart disease

Clinical assessment and laboratory tests

A structured questionnaire was used to collect socio-demographic information, medical and past medical history including detailed drug use apart from ART. Information on ART types and duration was obtained from patients ICTC card number for patients on ART. Patients were examined for pallor, jaundice, cyanosis, respiratory rate, pulse rate, body temperature, blood pressure, skin changes and liver size were recorded. All patients were tested for complete blood count and CD4 count. The New York Heart Association (NYHA) functional classification was used to group patients into classes 1- 4 according to their symptoms at presentation. HIV clinical staging was done using the World Health Organization classification criteria (WHO, 2007).

Echocardiography

Echocardiographic evaluation was done in all patients by the cardiologist.

Echocardiographic Definition of Dilated Cardiomyopathy

Dilated cardiomyopathy was defined as the presence of diffuse left ventricular hypokinesia (ejection fraction, <45 percent) and dilatation (left ventricular end-diastolic volume index, >80 ml per square meter) [32].

Diagnostic criteria (or major criteria; both must be present)

1. LV ejection fraction <45% and/or fractional shortening <25%, diagnosed by Echocardiogram, isotopes or ventriculography [37].

2. Left ventricular end-diastolic diameter>117% of the predicted value corrected for age and body surface area, which corresponds to 2 standard deviations from the expected normal limit + 5% (applying Henry's formula) [22].

Echocardiographic Definition of systolic dysfunction

The denominator is the ejection fraction (EF) = stroke volume (SV) /end diastolic volume (EDV) determined by Modified Simpsons method. According to recommendations of American Society of Echocardiography (ASE):> 55% - normal, 45% to 54% - mildly abnormal, 30% to 44% - moderately abnormal and below 30% - severely abnormal.

Echocardiographic definition of diastolic dysfunction

Advanced diastolic dysfunction can lead to isolated diastolic heart failure, now referred to as heart failure with normal ejection fraction (HFNEF).

Diagnosis of HFNEF was based on following criteria:

1. Presence of clinical syndrome of heart failure
2. Presence of normal ejection fraction (EF) (>50%),
3. Presence of diastolic dysfunction,
4. E/E' (ratio of mitral Doppler E wave velocity to tissue Doppler
5. Early diastolic velocity, i.e. E' greater than 15:1 indicative of increased LV filling pressure, and
6. Usually non-dilated heart. Echocardiography can confidently assess diastolic functions by evaluating mitral inflow Doppler, tissue Doppler, pulmonary vein, LA volume index etc [8].

Echocardiographic diagnosis of pulmonary hypertension

Echocardiographic features of PAH included right atrial enlargement, right ventricular enlargement and dysfunction, small under filled left-sided heart chambers, interventricular septal flattening, tricuspid regurgitation with elevated velocity, and reduced tricuspid annular plane systolic excursion (TAPSE) [9].

Pulmonary hypertension was defined as echocardiographically estimated pulmonary arterial pressure >35mmHg with or without dilated and/or hypertrophied right ventricle and in the presence of dyspnoea.

Heart failure was defined as per NYHA grading along with confirmed structural heart abnormality one chocardiography and LV ejection fraction <50% or Doppler evidence of LV diastolic dysfunctions.

Results

A total of 102 HIV infected patients presented with cardiac complaints during the 8 months study period. The patients' mean age was 42.4 years (range = 18–72 years). The proportion of women was 68.6%. Of the 102 patients, 50 (49%) were in heart failure based on the presence of NYHA

symptoms and confirmed on Echocardiogram. Compared to patients without heart failure, those with heart failure were younger, included more men, and had shorter duration of HIV ($p < 0.05$). They also had lower body mass index, haemoglobin and CD4+ cell counts when compared to patients without heart failure, all $p<0.01$ (Table 1).

Presenting symptoms in patients with and without heart failure

Although cough, shortness of breath and chest pain (symptoms of heart disease were considerable in our patients, their clinical implications were taken with caution, as they could be attributable to pulmonary disorders. Patients with HIV infection develop multiple pulmonary opportunistic infections, leading to differential diagnosis with cardiovascular disease. As expected, significantly more patients with heart failure presented with shortness of breath, orthopnoea, paroxysmal nocturnal dyspnoea and oedema of lower limbs when compared to patients without heart failure ($p<0.05$), (Table 2). On the other hand, palpitations and chest pain as presenting symptoms were unspecific, being not significantly different between the two groups of patients (Table 2).

Causes of heart failure in the patients with heart failure

The main causes of heart failure were left ventricular hypertrophy, pulmonary arterial hypertension and dilated cardiomyopathy. Anaemia as the sole cause of heart failure was present in 8% (Pie Diagram 1 See page 29).

Table 1: Sociodemographic Characteristics and Laboratory Findings in Patients with and without Heart Failure

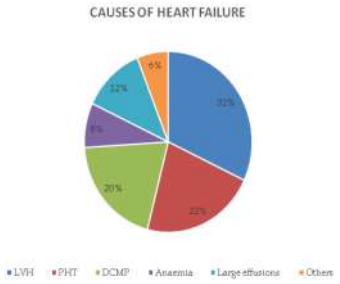
Characteristics (n (%) or Mean (± SD))	Heart failure		P value
	Present (n = 50)	Absent (n = 52)	
Mean Age in years	39.7 ± 10.4	45.1 ± 11.6	0.015
Men, n (%)	21 (42.0)	11 (21.1)	0.023
Education primary or less, n (%)	42 (84)	34 (65.4)	0.031
Smoking, n (%)	8 (16)	1 (1.9)	0.012
Alcohol intake, n (%)	16 (32)	7 (13.5)	0.025
Mean Systolic BP (mmHg)	126 ± 23	132 ± 20	0.134
Mean Diastolic BP (mmHg)	78 ± 19	83 ± 11	0.062
Mean Haemoglobin (g/dl)	9.6 ± 2.7	11.4 ± 4.0	0.008
Anaemia, n (%)	43 (86.0)	32 (61.5)	0.005
Mean Total WBC count	5.7 ± 3.7	5.6 ± 3.1	0.887
Mean CD4+ cell count	209 ± 192	385 ± 259	< .001
Mean ESR (mmhr-1)	78 ± 34	64 ± 44	0.094
Mean HIV duration (months)	20 ± 20	43 ± 48	0.003
ART Users, n (%)	31 (62.0)	39 (75.0)	0.157
Mean ART duration (months)	22 ± 22	37 ± 28	0.02

Table 2: Symptoms Suggestive of Heart Failure

Symptoms	Incidence, n (%) (Total No. 102)	Heart failure		P Value
		Present, n (%) (Total No. 50)	Absent, n (%) (Total No. 52)	
Palpitation	93 (94.86)	45 (90.0)	48 (92.3%)	0.681
Dyspnoea	71 (72.42)	44 (88.0)	27 (51.9)	<0.001
Orthopnoea	33 (33.66)	25 (50.0)	8 (15.4)	<0.001
PND	20 (20.4)	16 (32.0)	4 (7.7)	0.002
Cough	47 (47.94)	31 (62.0)	16 (30.8)	0.002
Chest Pain	29 (29.58)	17 (34.0)	12 (23.1)	0.221
Pedal Edema	42 (42.84)	31 (62.0)	11 (21.2)	<0.001

Opportunistic infections among patients with and without heart failure

Previous history of tuberculosis (pulmonary and extra-pulmonary) was the only opportunistic illness that was significantly more prevalent among patients with heart failure compared to those without heart failure (50% *versus* 17.3% respectively), p<0.001 (Table 3).



Pie Diagram 1: Causes of Heart Failure In Hiv

Abbreviations: LVH- Left Ventricular Hypertrophy, PHT- Pulmonary Hypertension, DCMP- Dilated Cardiomyopathy

Echocardiography in HIV associated heart failure

Our findings confirm that progressive left ventricular dilation accompanies disease progression in HIV infection. Left ventricular systolic dysfunction also shows a similar degradation as disease progresses. Diastolic dysfunction usually precedes systolic dysfunction which is an important feature of HIV associated heart disease that is also shown in a recent study [18].

The patients with heart failure had significantly larger ventricles, larger left atrium diameter as well as higher LV mass and LV mass index when compared to patients without heart failure (<0.001) (Table 4).

LV systolic function as assessed by endocardial %FS and EF was significantly lower in patients with heart failure (all p<0.001) (Table 4). The peak early (E) to late(A) ventricular filling trans-mitral Doppler flow velocity (E/A) ratio was higher in patients with heart failure and both,the isovolumic relaxation time and E deceleration time were shorter in patients with heart failure, reflecting restrictive physiology (Table 4).

Table 3: Incidenceopportunistic Infections

Opportunistic Infection	Incidence, n (%) (Total No. 102)	Heart failure		P Value
		Present, n (%) (Total No. 50)	Absent, n (%) (Total No. 52)	
History of Tuberculosis	34	25 (50.45)	9 (17.3)	<0.001
Oral candidiasis	33	12 (24)	11 (21.2)	0.731
Herpes Zoster	30	13 (26)	17 (32.7)	0.458
Recurrent Pneumonia	22	11 (22.0)	11 (21.2)	0.917
Meningitis	02	2 (4.0)	0 (0.0)	0.145

Table 4: Echocardiographic Findings in Hiv Patients with or without Heart Failure

Variable	Heart Failure (n=50)	No Heart Failure (n=52)	P Value
	Mean ± SD		
LV end systolic diameter (cm)	3.81 ± 1.30	2.49 ± 0.37	<0.001
LV end diastolic diameter (cm)	5.14 ± 1.10	4.15 ± 0.47	<0.001
LV mass (g)	211 ± 84	153 ± 56	<0.001
LV mass index (g/m2)	135 ± 56	91 ± 27	<0.001
LA end systolic diameter (cm)	4.05 ± 0.72	3.33 ± 0.58	<0.001
Fractional shortening (%)	28 ± 12	39 ± 5	<0.001
Ejection fraction (%)	48 ± 16	65 ± 6	<0.001
Relative wall thickness	0.42 ± 0.15	0.49 ± 0.14	0.017
RV end diastolic diameter (cm)	3.3 ± 0.7	2.7 ± 0.4	<0.001
Posterior Wall Thickness (cm)	1.03 ± 0.25	1.01 ± 0.23	0.837
Interventricular septum (cm)	1.09 ± 0.28	1.14 ± 0.32	0.484
E/A ratio	1.3 ± 0.6	0.9 ± 0.4	0.003
Isovolumic relaxation time (msec)	65 ± 24	76 ± 21	0.033
E deceleration time (msec)	161 ± 64	187 ± 57	0.063

Discussion

From echocardiographic studies in developed and developing world, it is known that cardiac involvement in HIV infected patients is common and that although small in contribution, cardiac abnormalities are a known cause of mortality among HIV infected patients [21,22]. Few studies have reported on echocardiographic findings in HIV infected patients presenting with cardiac symptoms, and there is paucity of data from studies addressing factorsassociated with heart failure in such patients.

Conflicting results have been reported on the association between left ventricular hypertrophy and HIV infection, with some suggesting that left ventricular hypertrophy is more common in HIV infected patients while others have found no association [25]. In our study, left ventricular hypertrophy was the main cause of heart failure [23,24]. Left ventricular hypertrophy has been reported as the main cause of heart failure in several studies [26,27].

The present study reiterates the current knowledget hat heart failure is present in almost half of HIVinfected patients presenting with cardiac symptoms, that left ventricular hypertrophy is the maincause of heart failure in such patients, and that anaemia and previous history of tuberculosis infection are modifiable factors that are independently associated with heart failure in HIV infected patients.

Our finding that heart failure is present in 49% of HIV infected patients with cardiac symptoms is higher than that reported in the Heart of Soweto study, in which 29% of HIV infected patients who presented *de novo* with cardiac complaints had LV systolic dysfunction [6]. The duration of HIV and use of antiretroviral medications was not independently associated with LVH in HIV infected patients with cardiac symptoms [31]. Left ventricular hypertrophy, dilated cardiomyopathy and large pericardial effusion were important causes heart failure in HIV patients [3,28].

Anaemia was found to be very common (73.5%) in the current study. The incidence was significantly higher in those with heart failure (86% *vs* 61.5%). Furthermore, lower haemoglobin was found to be independently associated with heart failure in multivariate analysis. The relationship between anaemia and heart failure is double sided as anaemia exacerbates heart failure, on the other hand heart failure can itself cause anaemia. It is probable that anaemia has exacerbated heart failure, as the prevalence of anaemia has previously been reported to be high in HIV infected and antiretroviral naïve patients. Severe anaemia was the only responsible cause of heart failure in four patients in this study.

Our finding that previous history of tuberculosis was independently associated with heart failure was somehow unexpected and information linking the two is lacking although tuberculosis is known to further impair immunity in HIV infected patients Tuberculosis is known to further impair immunity in HIV infected patients and may contribute to the occurrence of dilated cardiomyopathy, which is known to occur in patients with advanced immunodepression [3,19,27].

In our study low CD4+ count was associated with heart failure in univariate analysis.We found a significant gender difference in relation to heart failure in this study which was also reported in previous studies, with men comprising of only a third of the HIV infected subjects [29]. Firstly, men were less represented (only 31% in the test population) probably reflecting the gender difference in the prevalence of HIV in the general population (THMIS, 2008). Secondly, in this study male gender was independently associated with the diagnosis of heart failure in multivariate analysis, a finding that has previously been reported in both population and hospital based studies. This study has reported that the prevalence of heart failure is higher among men compared to women.

Alcohol consumption and cigarette smoking were associated with heart failure in univariate analysis in our study [19].

Low education level is often linked to low socio-economic status, therefore our finding that low education was independently associated with the diagnosis of heart failure among.

HIV infected patients is in keeping with reports from other studies that low socio-economic status is an independent predictor of cardiac disease in HIV infected patients [4,25].

Patients with low socio economicstatus often have less access to health care and often lack better understanding of their health, which could explain the increased likelihood of these patients to present late to hospital when the disease is more advanced.

Conclusion

In conclusion, this study demonstrates that the cardiac complaints among HIV patients are non-specific and are frequent presentation of the HIV patients without heart failure as well. These findings

emphasize the importance of echocardiography in diagnosis of HIV associated heart failure as also the importance of early diagnosing and correction of predisposing/precipitating factors.This finding is in agreement the other studies done on the subject.

References

1. http://www.unaids.org/sites/default/files/media_asset/2016-prevention-gap-report_en.pdf.
2. http://naco.gov.in/sites/default/files/Annual%20Report%202015-16_NACO.pdf.
3. Nzuobontane D, Blackett KN, Kuaban C. Cardiac involvement in HIV infected people in Yaounde, Cameroon. Postgraduate Medical Journal. 2002;78: 678-81.
4. Longo-Mnenza B, Seghers L, Vita E, et al. Assessment of ventricular diastolic function i n AIDS patients from Congo:a Doppler ECHOcardiographic study. Heart 1998;80:184-9.
5. Adeel A. Butt, Chung-Chou Chang, Lewis Kuller, Dr PH; et al. Arch Intern Med. 2011:171(8):737-43.
6. Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. Eur Heart J. 2012;33:866-74.
7. Rerkpattanapipat P, Wongpraparut N, Jacobs LE, Kotler MN. Cardiac manifestations of acquired immunodeficiency syndrome. ArchIntern Med. 2000;160:602-08.
8. Prendergast B.D. HIV and Cardiovascular Medicine. Heart 2003;89:793-800.
9. Remick J, Georgiopoulou V, Marti C, Ofotokun I, Kalogeropoulos A, Lewis W et al. Heart Failure in Patients With Human Immunodeficiency Virus Infection: Epidemiology, Pathophysiology, Treatment, and Future Research. Circulation. 2014;129(17):1781-89.
10. William Lewis, Peter F. Currie. HIV/AIDS and the Cardiovascular System. Hurst's The Heart,12th edition chapter 92:2118-31.
11. The DAD. Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007;356:1723–35.
12. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med 2005;352:48–62.
13. De Castro S, Migliau G, Silvestri A, D'Amati G, Giannantoni P, et al. Heart involvement in AIDS: a prospective study during various stages of the disease. Eur Heart J 1992;13:1452-59.
14. Barbaro G, Fisher SD, Giancaspro G, Lipshultz SE. HIV associated cardiovascular complications: a new challenge for emergency physicians. Am J Emerg Med. 2001;19:566-74.
15. Giuseppe Barbaro, Gabriella Di Lorenzo, Benvenuto Grisorio, and Giorgio Barbarini. For the Gruppo Italiano per lo Studio Cardiologico dei Pazienti Affetti da AIDS. N Engl J Med 1998; 339:1093-99.
16. D.J. Sahn, A. De Maria, J. Kissilo and A. Weyman. Re-commendations Regarding Quantitations in M—Mode ECHO Cardiography.Circulation. 1988;58(6):1072-83.
17. Hsue PY, Hunt PW, Ho JE, Farah HH, Schnell A, Hoh R, et al. Impact of HIV infection on diastolic function and left ventricular mass. Circ Heart Fail. 2010;3(1):132-9. doi: 10.1161/CIRCHEARTFAILURE.109.854943. Epub 2009 Nov 20.
18. HIV/AIDS Situation and Response in Ahmadnagar District: Epidemiological Appraisal Using Data Triangulation, 2010 May;38:219-27.
19. Lipshultz S. Dilated Cardiomyopathy in HIV-Infected Patients. New England Journal of Medicine. 1998;339(16):1153-55.
20. Smith C., Sabin C.A., Lundgren J.D., Thiebaut R., Weber R., Law M., Monforte A., Kirk O., Friis-Moller N., Phillips A., Reiss P., El Sadr W., Pradier C. & Worm S.W. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. *AIDS*. 2010;24(10):1537-48.
21. Leone S., Gregis G., Quinzan G., Velenti D., Cologni G., Soavi L., Ravasio V., Ripamonti D., Suter F. & Maggiolo F. Causes of death and risk factors among HIV-infected persons in the HAART era: analysis of a large urban cohort. Infection 2011;39:13-20.
22. Gazzaruso C., Bruno R., Garzaniti A., Giordanetti S., Fratino P., Sacchi P. & Filice, G. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. Journal of Hypertension 2003;21:1377-82.
23. Seaberg E.C., Muñoz A., Lu M., Detels, R., Margolick J.B., Riddler S.A., Williams C.M. & Phair J.P. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS 2005;*19:953-960.
24. Stewart S., Wilkinson D., Hansen C., Vaghela V., Mvungi R., McMurray J. & Sliwa K. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. *Circulation* 2008;118:2360-67.
25. Bloomfield GS, Alenezi F, Barasa FA, Lumsden R, Mayosi BM, Velazquez EJ. Human Immunodeficiency Virus and Heart Failure in Low- and Middle-Income Countries: A State-of-the-Art Review. *JACC* Heartfailure. 2015;3(8):579-90.

26. Friis-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, Thiébaut R, Morfeldt L, De Wit S, Pradier C, Calvo G, Law MG, Kirk O, Phillips AN, Lundgren JD; Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. N Eng J Med 2003;349:1993-2003.

27. Daglan E, Yamin D, Manu B, Streinu-Cercel A. Cardiac involvement in HIV-positive patients. GERMS. 2013;3(1):8-13.

28. Silva A, Reis R, Nogueira J, Gir E. Quality of life, clinical characteristics and treatment adherence of people living with HIV/AIDS. Revista Latino-Americana de Enfermagem. 2014;22(6):994-1000.

29. Mata-Marín J, Gaytán-Martínez J, Grados-Chavarría B, Fuentes-Allen J, Arroyo-Anduiza C, Alfaro-Mejía A. Correlation between HIV viral load and aminotransferases as damage markers in HIV infected naive patients: a concordance cross-sectional study. Virology Journal. 2009;6(1):181.

30. Mestroni L, Maisch B, McKenna WJ, Schwartz K, Charron P, Rocco C, Tesson F, Richter A, Wilke A, Komajda M. Collaborative research group of the European human and capital mobility project on familial dilated cardiomyopathy. Guidelines for the study of familial dilated cardiomyopathies. European Heart Journal; 1999;20:93–102.

31. F. Thienemann, K. Sliwa, J. K. Rockstroh. HIV and the heart: the impact of antiretroviral therapy: a global perspective. European Heart Journal 2013;34:3538-46.

32. Himelman RB, Chung WS, Chernoff DN, Schiller NB, Hollander H. Cardiac manifestations of human immunodeficiency virus infection: a two-dimensional echocardiographic study. J Am Coll Cardiol 1989;13:1030-36.