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Infection and Cardiac Function: An update

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Abstract
Myocarditis is an infection of the heart valves occurs when germs get into the blood stream and settle inside the heart, often on a valve. The infection is usually caused by bacteria or viruses. HIV patients are prone to increased cardiovascular diseases and early ART treatment and aggressive cardiovascular risk assessment and management will be very helpful. Infectious and parasitic diseases can cause cardiac problems both by intrinsic mechanisms of the disease and drug intervention. Myocarditis is an uncommon complication of severe dengue fever. Awareness about Cardiac disease manifestations and the complications are essential for treatment in all infectious diseases. This review articles highlights the research findings during the last two decades on cardiac related disorders in infections by a variety of microorganisms notably Dengue and HIV.

Keywords: Myocarditis, HIV, HCV, Anti-Retroviral Therapy, Malaria.

1. Introduction
There are many causes of myocarditis, including viral infections, autoimmune diseases, environmental toxins and adverse reactions to medications, but the most common are those associated with upper respiratory tract infections. The most common cause of myocarditis is infection of the heart muscle by a virus. The virus invades the heart muscle to cause local inflammation. The prognosis is variable but chronic heart failure is the major long term complication. After the initial infection subsides, the body's immune system continues to inflict inflammatory damage to the heart muscle. Myocarditis is diagnosed by detecting signs of irritation of heart muscle and the first laboratory test that elevated is Creatine Kinase (CK).
There is currently no evidence supporting global ischemia as an underlying cause of myocardial dysfunction in sepsis; however, in septic patients with coexistent and possibly undiagnosed coronary artery disease (CAD), regional myocardial ischemia or infarction secondary to CAD may certainly occur. A circulating myocardial depressant factor in septic shock has long been proposed, and potential candidates for a myocardial depressant factor include cytokines, prostanoids and nitric oxide, among others [1]. In a population of Human Immunodeficiency Virus (HIV)-infected patients with no other active infections, cardiac abnormalities is uncommon and the echocardiographic fractional shortening and E/A ratio were not related to the survival time of such patients. Thus, there is no evidence that HIV is a direct cardiac pathogen [2]. It is conceivable that the presence of HIV nucleic acid sequences may represent a preclinical marker of impending AIDS-associated heart muscle disease. This sequela would not be recognized in many patients, who died rapidly of Pneumocystis carinii pneumonia, Kaposi's sarcoma and other well-documented manifestations of AIDS [3].
High frequency power as well as systolic and diastolic blood pressure did not differ between myocarditis and controls. HIV patients in Anti-Retroviral Therapy (ART) have increased resting heart rate and decreased short-term heart rate variability indicating parasympathetic dysfunction [4]. Factors independently associated with higher odds of comorbid HIV diagnosis were Medicaid insurance, urban hospital type, dementia, liver disease, renal disease and cancer. Over the last decade in the United States, there has been a substantial and significant rise in patients hospitalized for stroke with coexisting HIV infection. This has important public health and socioeconomic consequences [5].
Although cardiotoxic effects of highly active antiretroviral therapy (HAART) are a growing concern, there is a lack of prospective studies of subclinical involvement of the heart in HIV-infected patients. Subclinical cardiac abnormalities are frequently observed in HIV(+) patients on HAART. The usefulness of systematic noninvasive screening in such population should be considered [6]. Infection with HIV is independently associated with an increased risk for clinical heart failure, cardiomyopathies and premature atherosclerosis, including stroke and

myocardial infarction in both the pre-HAART and HAART eras. HAART is also associated with clinical cardiovascular concerns. Additional potentially damaging cardiovascular effects of HAART are present, and continuing cardiovascular risk evaluations, screening and follow-up of treated patients is necessary [7].

Treatment of HIV-infected children with Anti Zidovudine Therapy (AZT) may be associated with the development of a cardiomyopathy; didanosine does not appear to increase the risk of cardiomyopathy. The continued use of AZT in a child in whom a cardiomyopathy develops should be carefully assessed, and all children receiving AZT should be followed by serial cardiac examination and echocardiograms [8]. HIV-infected patients had a higher prevalence of diastolic dysfunction and higher left ventricular mass index compared with controls. These differences were not readily explained by differences in traditional risk factors and were independently associated with HIV infection. These results suggest that contemporary asymptomatic patients with HIV manifest mild functional and morphological cardiac abnormalities, which are independently associated with HIV infection [9].

Increased exposure to protease inhibitors is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidemia, but no evidence of such an association for nonnucleoside reverse-transcriptase inhibitors were found ; however, the number of person-years of observation for exposure to this class of drug was less than that for exposure to protease inhibitors [10].

Marked changes in arterial function and structure are observed in HIV patients leading to increased cardiovascular morbidity and mortality. Early ART and aggressive treatment of cardiovascular risk factors might be helpful [11]. Hepatitis B Virus (HBV) reactivation after the heart transplantation was common but usually well controlled with lamivudine treatment. Although post transplantation liver function deteriorated for a period, there was no HBV infection-related morbidity or mortality. Preoperative hepatitis B immunoglobulin prophylaxis can successfully prevent HBV naïve recipients from infection in some cases, but HBsAg-positive donors should only be considered in high risk situations [12]. Reactivation of HBV, characterized by increased levels of serum HBV DNA, abnormal liver function and hepatic failure is a frequent complication of immunosuppressive therapy and chemotherapy in patients with HBV infection. However, reactivation of occult HBV infection with immunosuppressive therapy or chemotherapy is rare. HBV-associated antigen should be regularly tested in patients with unknown etiological glomerulonephritis in areas with high HBV viral popular and even in those with no clinical evidence for diagnosis of HBV [13].

The prevalence of HBV and hepatitis C virus (HCV) in a large population of HTx recipients is not very different from that reported in the general population. Active viral replication of HBV and an aggressive natural history of both infections are seen in HTx recipients, however. The low prevalence of HBV and HCV-related infection in recent series probably reflects current viral screening and vaccination policies [14]. Hepatitis secondary to infection with the HCV is one of the most common causes of viral hepatitis worldwide. HCV infection may be associated with left ventricular systolic and diastolic dysfunction and cardiac arrhythmias. Multitransfused children are more liable to left ventricular diastolic dysfunction suggested by impaired relaxation probably due to iron overload and anaemia. HCV infection is an additional factor which might share in impairing left ventricular systolic function. Left ventricular performance is better preserved when chelation treatment is adjusted to maintain serum ferritin at <1000 ng/ml [15].

HCV disease burden is substantially increasing in Egyptian community and it is estimated that prevalence of HCV in Egyptian community reach 22% of total population. Recently there is a global alert of HCV cardiovascular complications [16]. HCV infection causes diastolic dysfunction without any other predisposing factors, probably due to chronic inflammatory reaction with mild fibrosis in the heart. Previous studies did not follow strict inclusion and exclusion criteria that confirm the independent role of HCV to cause diastolic dysfunction. Tissue Doppler was more sensitive to diagnose diastolic dysfunction than conventional Doppler [17]. Vigorous infection of heart tissues in vivo and striated skeletal cells in vitro are demonstrated. Derangements of Ca^{2+} storage in the infected cells may directly contribute to the presentation of myocarditis in pediatric patients. Formal clinical studies should help to assess this strategy as an alternative to conventional fluid resuscitation for severe DSS. Cardiovascular manifestations of the emerging dengue pandemic [18]. Defining the role of cardiac dysfunction in the haemodynamic compromise of severe dengue has potentially important management implications. The cardiovascular manifestations of dengue, including myocardial and vascular involvement, and conclude with a discussion of the available therapeutic options and potential future research directions [19].

Currently, HIV-infected people are treated to the same blood pressure (BP) goals (<140/90 or <130/80 mm Hg) as their uninfected counterparts. Whether HIV-infected people with elevated BP have excess AMI risk compared to uninfected people is not known. This study examines whether the association between elevated BP and AMI risk differs by HIV status. HIV, prehypertensive BP, and hypertensive BP were associated with an increased risk of AMI in a cohort of HIV-infected and -uninfected veterans. Future studies should prospectively investigate whether HIV interacts with BP to further increase AMI risk [20]. HIV subjects with recent or nadir CD4 ≥500 cells per microliter had similar MI rates compared with HIV subjects. Lower nadir CD4, in particular, seems to be independently associated with MIs. These results strengthen recommendations for earlier ART initiation [21]. By multivariable analysis, HIV infection diabetes mellitus percutaneous coronary intervention remained independent predictors of heart failure all if which HIV status influences long-term risk, although the short-term risk in HIV patients is comparable to that in uninfected patients [22].

There was no association between HCV seropositivity (rate ratio 0.86 [95% CI 0.62-1.19]), inactive HBV infection (rate ratio 1.07 [95% CI 0.79-1.43]) or active HBV infection (rate ratio 0.78 [95% CI 0.52-1.15]) and the development of myocardial infarction. No association was found between HBV or HCV coinfection and the development of myocardial infarction among HIV-infected individuals [23]. Cohort studies have demonstrated greater risk of myocardial infarction (MI) associated with specific antiretroviral use, while meta-analyses of randomized controlled trials (RCTs) have not. These differences may be due to inherent biases in the observational study design or to the limited duration of randomized trials. We conducted a new-user, active-comparator cohort study emulating an RCT comparing the initiation of several antiretrovirals as part of combination antiretroviral therapy (cART) and MI. An increased rate of MI among patients

initiating abacavir compared with tenofovir, although the association was decreased after confounding adjustment. Without a very large prospective comparative clinical trial, a much larger observational study of patients initiating cART would be needed to better define this apparent association [24]. Sensitivity analyses including the exploration of a composite outcome of acute MI and coronary interventions yielded. HCV infection was not associated with an increased risk of incident MI [25].

Involvement of the cardiovascular system in patients with infectious and parasitic diseases can result from both intrinsic mechanisms of the disease and drug intervention [26]. With the millions of malaria cases each year and the fact that such complication has never been reported in the literature. The rare occurrence of cardiac events with any of the preceding study procedures may even support a coincidental finding. Apart from acute coronary syndrome, myocarditis can be considered as a final diagnosis, but the true nature and patho-physiological explanation of the event remain unclear [27]. Impaired cardiac function contributing to clinical manifestations in P. falciparum malaria. Findings may be relevant for fluid management and should be further explored in endemic regions [28].

Postmortem evaluation of the inner cardiac muscles of the P. falciparum-infected mice after quinine therapy showed significant decline in parasite density with the no deaths of mice recorded, suggesting that significantly corroborated the findings of myocardial dysfunction as the primary cause of death in recent case reports of humans infected with P. falciparum [29]. Pulmonary tuberculosis and parasitic diseases were shown to be risk factors for each other. Co-infection may significantly inhibit the host's immune system, increase antibacterial therapy intolerance and be detrimental to the prognosis of the disease; in addition, infection with parasitic diseases can alter the protective immune response to Bacillus Calmette-Guerin vaccination against Mycobacterium tuberculosis [30]. Cachexia is an important feature of many chronic disorders. It occurs in infectious diseases such as malaria and tuberculosis, and in many other chronic illnesses including heart failure, liver cirrhosis, chronic obstructive pulmonary disease, cystic fibrosis, chronic renal failure and malignancy [31].

Elevated serum concentration levels of cystatin C; ECG abnormalities were seen in 23 patients. Assessed by troponin T, myocardial damage in falciparum malaria is rare [32]. This case recalls the potential importance of myocardial injury in the prognosis of malaria and prompts a reevaluation of current perspectives on the pathogenesis of severe falciparum infection. In the light of this, we have reviewed the cases of cardiac complications in malaria published to date [33]. Severe malaria causes multiorgan dysfunction, which is the predominant reason for mortality in these children. Cardiac enzymes have been elevated and cardiac involvement has been suspected in some of these children, however, clear cut echocardiographic evidence for it was not possible. There were isolated reports of myocardial dysfunction in malaria in adults but none in children. We present two such children with cardiac involvement and myocardial dysfunction [34].

Little is known about severe imported malaria in nonendemic industrialized countries. 94% acquired Plasmodium falciparum in sub-Saharan Africa, and 96% had taken inadequate antimalarial chemoprophylaxis. Mortality was 11% in the severe malaria group, whereas no patients died in the less severe malaria group. In the bivariable analysis, the main factors associated with death in the severe malaria group were the Simplified Acute Physiology Score, shock, acidosis, coma, pulmonary edema, and coagulation disorders. Bacterial coinfection is not infrequent and may contribute to death. Severe imported malaria remains a major threat to travelers. The most relevant World Health Organization major defining criteria were coma, shock, pulmonary edema, and acidosis [35]. Elevated plasma cytokines in severe malaria are associated with systemic pathologic abnormalities, not cerebral involvement. Both the overall magnitude of the cytokine responses and the eventual imbalance between the pro- and antiinflammatory responses are important determinants of mortality [36].

Of the drugs considered, only indinavir, lopinavir-ritonavir, didanosine, and abacavir were associated with a significantly increased risk of MI. As with any observational study, our findings must be interpreted with caution (given the potential for confounding) and in the context of the benefits that these drugs provide [37]. Dengue fever is one of the most common vector-borne viral infections in tropical countries. Myocarditis is an uncommon complication of severe dengue fever. Sometimes, dengue myocarditis masquerades as acute myocardial infarction. Later investigation confirmed she was suffering from myocarditis due to dengue fever, which mimicked acute myocardial infarction. A Medline search revealed only few other reported cases of dengue myocarditis that mimicked of acute myocardial infarction [38]. The exact incidence and pathophysiological mechanism of dengue myocarditis remain obscure, but most of these cases are self-limiting. Fatal dengue myocarditis is a very rare complication of dengue fever. The non-specific symptoms and signs of dengue myocarditis make early diagnosis difficult [39]. A fatal outcome was reported in some cases of dengue with cardiac complications. To avoid otherwise preventable morbidity and mortality, physicians should have a high index of suspicion for cardiac complications in patients with dengue illness and should manage this accordingly [40].

A typical manifestations, such as liver, central nervous system, and cardiac involvement, have been increasingly reported. An atypical and rare presentation of dengue disease marked by a dramatic and fatal cardiogenic shock due to acute myocarditis. Histopathological analysis of heart tissue showed several multifocal areas of muscle necrosis and intense interstitial oedema associated with clusters of virus particles inside the cardiomyocytes and in the interstitial space, providing evidence of a possible direct action of dengue virus on myocardium [41]. Although rare, a fatal outcome was reported in some cases of dengue with cardiac complications. To avoid otherwise preventable morbidity and mortality, physicians should have a high index of suspicion for cardiac complications in patients with dengue illness and should manage this accordingly [42]. Differences in symptoms/signs and laboratory abnormalities between DF and DHF/DSS were significant in the non-RF group but not apparent in the RF group. The diagnosis and management of dengue infection among patients with RF must be cautious, because complicated clinical courses with a higher mortality rate were well observed [43]. On multivariate analysis, subendocardial longitudinal strain independently predicted the duration of hospital stay in patients with DhF. Assessment of speckle tracking echocardiography-derived LV mechanics helps in understanding myocardial mechanics in patients with DhF and thrombocytopenia. Identification of reduced LV longitudinal strain helps in understanding the mechanism of reduced LV

myocardial performance seen in patients with DhF [44].

Cardiac complications in malaria have been infrequently associated with Plasmodium falciparum infections. However, myocarditis associated with Plasmodium vivax malaria has not been reported in the literature. We observed an unusual case of vivax malaria that was complicated by myocarditis [45]. Apart from pancytopenia, there were no other features of severe malaria. With the emergence of literature about the complications encountered in P. vivax, especially from this region, a high index of suspicion for unusual cardiovascular manifestations is necessary in cases with acute malaria [46]. Plasmodium infection (mainly p. falciparum) is usually complicated by cerebral malaria, haemolysis, acute kidney injury and respiratory distress. Myocardial involvement is a rare complication of plasmodium infection. We have reported a case of plasmodium infection (p. vivax) complicated by myocarditis [47]. A number of possible aetiological factors may explain or have contributed to this case of myocarditis including, i) P. falciparum infection, ii) rhinovirus infection, iii) unidentified pathogens, iv) hyper-immunization (the volunteer received six travel vaccines between the last immunization and the CHMI), v) atovaquone/proguanil treatment, or vi) a combination of these factors. Definitive aetiology and pathophysiological mechanism for the myocarditis have not been established [48]. Myocarditis complicating Plasmodium vivax malaria is an extremely rare complication. Cardiovascular complications are well recognized with Plasmodium falciparum malaria. Nevertheless, a high index of suspicion should be maintained for the same in Plasmodium vivax infection especially if symptoms of heart failure develop in a young patient [49].

Cardiac complications in malaria have been infrequently associated with Plasmodium falciparum infections. However, myocarditis associated with Plasmodium vivax malaria has not been reported in the literature. We observed an unusual case of vivax malaria that was complicated by myocarditis [50]. With the emergence of literature about the complications encountered in P. vivax, especially from this region, a high index of suspicion for unusual cardiovascular manifestations is necessary in cases with acute malaria [51]. Without appropriate adjustment for antiretroviral therapy, CD4 count, and HIV-1 RNA and substantially different mortality rates among those with and without HIV and HCV infection, the association between HIV, HCV, and CHD may be obscured. HIV+ HCV+ Veterans have an increased risk of CHD compared with HIV+ HCV- and HIV-HCV- Veterans [52].

An overview of potential mechanistic factors associated with CHD in HIV infection and of strategies for managing CHD risk in HIV-infected patients is also included. Specific cardiovascular and metabolic risk factors, CHD risk prediction, and the immunologic basis for CHD in HIV-infected patients will be discussed in separate reviews [53]. risk factors for HIV-associated CHD are thought to differ from those of the general population, with risk mediated by HIV-specific factors including chronic inflammation and immune activation. Therapeutic interventions tailored to traditional CHD risk factors and proven to benefit the general population may therefore not be appropriate in the setting of HIV infection [54]. Atherogenesis in HIV is affected by complex interactions between traditional and immune risk factors. cART has varied, regimen-specific effects on metabolic risk factors. Overall, cART seems to lessen proatherogenic immune activation, but does not eliminate it even in patients in whom viraemia is suppressed. Current strategies to decrease the risk of CHD in individuals infected with HIV include early initiation of cART regimens with the fewest metabolic adverse effects, and careful management of traditional CHD risk factors throughout treatment. Future strategies to prevent CHD in patients with HIV infection might involve the use of HIV-tailored CHD risk-prediction paradigms and the administration of therapies alongside cART that will further decrease proatherogenic HIV-specific immune activation [55].

After adjusting for age, race, and sex we found that coronary artery disease (CAD), diabetes mellitus (DM) as primary cause of renal failure and cirrhosis were less frequently diagnosed in the HCVHIV-coinfected subjects, whereas hepatitis B, wasting, drug and alcohol abuse, and dependence were more frequently diagnosed. Increasing age, CAD, stroke, DM, cirrhosis, wasting, cancer and drug abuse and dependence were associated with higher odds of death in the HCV monoinfected subjects, whereas cirrhosis, wasting, and smoking were the only such factors in the HCV-HIV-coinfected subjects [56]. Increasing evidence demonstrates that HCV infection is associated with atherosclerosis. However, there are contrasting findings in several studies that the atherosclerotic burden is not associated with HCV infections. Therefore, we performed a meta-analysis to clarify if HCV infection is associated with atherosclerosis compared to non-infected people. Meta-analysis indicates that HCV infection is associated with carotid atherosclerosis independent of classical risk factors. Therefore, we would recommend for HCV infected patients to be counseled on their risk for carotid atherosclerosis [57].

The influence of hepatitis C virus (HCV) infection on atherosclerosis risk in HIV-infected patients has not been adequately evaluated in real-life situations. Prevalence of subclinical carotid plaque was significantly higher in HCV-HIV co-infected patients (p=0.04), despite of the fact LDL-cholesterol and blood pressure (BP) were lower in the co-infected patients (p=0.003). HCV chronic infection (OR=10; IC: 1.5-72; p=0.02) was an independent risk factor. This cross sectional study suggests that HCV infection might be an independent cardiovascular risk factor in HCV-HIV co-infected patients. HCV infection might be considered as not only a liver infection but also as a metabolic disease in HIV patients, justifying regular cardiovascular surveillance [58].

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Overall, HBsAg seropositivity was associated with a decreased risk of ischemic stroke and MI and an increased risk of hemorrhagic stroke, with multivariable-adjusted hazard ratios (95% CIs) of 0.79 (0.68, 0.90), 0.74 (0.62, 0.87), and 1.33 (1.15, 1.52), respectively. Risks for stroke and MI were similar between HBsAg-seronegative and HBsAg-seropositive men in the absence of liver dysfunction, whereas men with both HBsAg seropositivity and liver dysfunction had a higher risk of hemorrhagic stroke and lower risks of ischemic stroke and MI compared with HBsAg-seronegative men. The association between HBsAg seropositivity and stroke and MI appears to be secondary to the liver dysfunction associated with hepatitis B viral infection. HBsAg seropositivity itself did not appear to play an important role in atherothrombosis through inducing a proinflammatory effect [60].

World-wide, hepatitis C virus (HCV) accounts for approximately 130 million chronic infections, with an overall 3% prevalence. Four to 5 million persons are co-infected with HIV. It is well established that HIV has a negative impact on the natural history of HCV, including a higher rate of viral persistence, increased viral load, and more rapid progression to fibrosis, end-stage liver disease, and death [61]. HCV-infected persons are younger and have lower lipid levels and a lower prevalence of hypertension. Despite a favorable risk profile, HCV infection is associated with a higher risk of CAD after adjustment for traditional risk factors [62]. Hepatitis C virus infection was not associated with greater carotid artery intima media thickness after adjustment for demographic and traditional cardiovascular risk factors. Further follow-up is needed to clarify whether HIV/hepatitis C virus coinfection may be associated with a greater risk of carotid plaque [63]. Understanding these complex mechanisms is of fundamental importance for the development of novel therapeutic approaches to prevent and to treat vascular complications in patients with chronic HCV infection. Currently, it seems that HCV clearance by interferon and ribavirin treatment significantly reduces non-liver-related mortality; moreover, interferon-based treatment appears to decrease the risk of ischemic stroke [64]. A moderate increase of CVD among individuals with HIV-HCV coinfection relative to those with HIV infection alone, lending support to consideration of initiation of HCV antiviral treatment [65].

Conclusion

This review article has highlighted the various research findings during the last two decades on infection induced Cardiac dysfunction in infectious diseases affected patients like HIV, Dengue, HCV, Malaria etc. Cardiac abnormalities are frequently found in HIV infected patients and treatment by ART and aggressive treatment and management of cardiovascular risk factors might be very helpful. Cardiac complications in malaria have been infrequently associated with Plasmodium falciparum infections. This review article content will give awareness among researchers to further explore research in this field of infectious diseases that causes Cardiac dysfunction and to suggest the best possible laboratory diagnosis for appropriate treatment to achieve good prognostic outcome in such patients.

Conflict of Interest: None

Reference

1. Merx MW, Weber C. Cardiovascular Involvement in General Medical Conditions. Sepsis and the Heart. Circulation 2007; 116:793-802.
2. Thuesen L, Møller A, Kristensen BO, Black F. Cardiac function in patients with human immunodeficiency virus infection and with no other active infections. Dan Med Bull 1994; 41(1):107-9.
3. Grody WW, Cheng L, Lewis W. Infection of the heart by the human immunodeficiency virus. Am J Cardiol 1990; 66(2):203.
4. Lebech AM, Kristoffersen US, Mehlsen J, Wiinberg N, Petersen CL, Hesse B *et al*. Autonomic dysfunction in HIV patients on antiretroviral therapy: studies of heart rate variability. Clin Physiol Funct Imaging 2007; 27(6):363.
5. Ovbiagele B, Nath A. Increasing incidence of ischemic stroke in patients with HIV infection. Neurology 2011; 76(5):444-50.
6. Schuster I, Thöni GJ, Edérhy S, Walther G, Nottin S, Vinet A *et al.* Subclinical cardiac abnormalities in human immunodeficiency virus-infected men receiving antiretroviral therapy. Am J Cardiol 2008; 101(8):1213.
7. Lipshultz SE, Mas CM, Henkel JM, Franco VI, Fisher SD, Miller TL. HAART to heart: highly active antiretroviral therapy and the risk of cardiovascular disease in HIV-infected or exposed children and adults. Expert Rev Anti Infect Ther 2012; 10(6):661-74
8. Domanski MJ, Sloas MM, Follmann DA, Scalise PP 3rd, Tucker EE, Egan D *et al.* Effect of zidovudine and didanosine treatment on heart function in children infected with human immunodeficiency virus. J Pediatr 1995; 127(1):137-46.
9. 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.
10. Study Group DAD, Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A. *et al.* Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007; 356(17):1723.
11. Lekakis J, Ikonomidis I. Cardiovascular complications of AIDS. Curr Opin Crit Care 2010; 16(5):408-12.
12. Chen YC, Chuang MK, Chou NK, Chi NH, Wu IH, Chen YS *et al.* Twenty-four year single-center experience of hepatitis B virus infection in heart transplantation. Transplant Proc 2012; 44(4):910-2.
13. Wenjun Du, Zhaomin Zheng, Shaolei Han, Shumin Ma, Shijun Chen. HBV reactivation in an occult HBV infection patient treated with prednisone for nephrotic syndrome: case report and literature review. BMC Infect Dis 2013; 13-394.
14. Fagiuoli S, Minniti F, Pevere S, Farinati F, Burra P, Livi U *et al.* HCV infections in heart transplant recipients. The Journal of Heart and Lung Transplantation 2001; 20(7):718-724.
15. Demir M, Demir C. Effect of hepatitis C virus infection on the left ventricular systolic and diastolic functions. South Med J 2011; 104(8):543-6.
16. Ahmed Saleh, Akira Matsumori, Hany Negm, Hany Fouad, Ahmed Onsy, Mohammed Shalaby *et al.* Assessment of cardiac involvement of hepatitis C virus; tissue Doppler imaging and NTproBNP study. J Saudi Heart Assoc 2011; 23(4):217-223.
17. Doris Martha Salgado, José Miguel Eltit, Keith Mansfield, César Panqueba, Dolly Castro, Martha Rocio Vega *et al.* Heart and Skeletal Muscle Are Targets of Dengue Virus Infection. Pediatr Infect Dis J 2010; 29(3):238-242.
18. Julie Nguyen-Pouplin, Thomas Pouplin, Toi Pham Van, Trung Dinh The, Dung Nguyen Thi, Jeremy Farrar *et al*. Fractional Clearance Studies in Acute Dengue Infection. PLoS Negl Trop Dis 2011; 5(8):e1282.
19. Sophie Yacoub, Heiman Wertheim, Cameron P. Simmons, Gavin Screaton. & Bridget Wills Nature Reviews Cardiology 2014; 11:335-345.
20. Armah KA, Chang CC, Baker JV, Ramachandran VS, Budoff MJ, Crane HM *et al.* Veterans Aging Cohort Study (VACS) Project Team. Prehypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans. Clin Infect Dis 2014; 58(1):121-9.
21. Silverberg MJ, Leyden WA, Xu L, Horberg MA, Chao CR, Towner WJ *et al.* Immunodeficiency and risk of myocardial infarction among HIV-positive individuals with access to care. J Acquir Immune Defic Syndr 2014;

65(2):160-6
22. Lorgis L, Cottenet J, Molins G, Benzenine E, Zeller M, Aube H *et al.* Outcomes after acute myocardial infarction in HIV-infected patients: analysis of data from a French nationwide hospital medical information database. Circulation 2013; 127(17):1767-74.
23. Sabin C, Reiss P, de Wit S, Worm SW, Law M, Dabis F *et al.* HBV or HCV coinfections and risk of myocardial infarction in HIV-infected individuals: the D:A:D Cohort Study. Antivir Ther 2010; 15(8):1077-86.
24. Brouwer ES, Napravnik S, Eron JJ Jr, Stalzer B, Floris-Moore M, Simpson RJ Jr *et al.* Effects of combination antiretroviral therapies on the risk of myocardial infarction among HIV patients. Epidemiology 2014; 25(3):406-17.
25. Kimberly A. Forde, Kevin Haynes, Andrea B. Troxel, Stacey Trooskin, Mark T. Osterman, Stephen E. Kimmel *et al.* Risk of Myocardial Infarction Associated with Chronic Hepatitis C Virus Infection: A Population-Based Cohort Study. J Viral Hepat 2012; 19(4):271-277.
26. Aristóteles Comte de Alencar, Filho, Marcus Vinícius Guimarães de Lacerda, Katashi Okoshi, Marina Politi Okoshi. Malaria and Vascular Endothelium. Arq Bras Cardiol 2014; 103(2):165-169.
27. An-Emmie Nieman, Quirijn de Mast, Meta Roestenberg, Jorien Wiersma, Gheorghe Pop, Anton Stalenhoef *et al.* Cardiac complication after experimental human malaria infection: a case report. Malar J 2009; 8:277.
28. Johanna Herr, Parisa Mehrfar, Stefan Schmiedel, Dominic Wichmann, Norbert W Brattig, Gerd D Burchard *et al.* Reduced cardiac output in imported Plasmodium falciparum malaria. Malar J 2011; 10:160.
29. Odaro Stanley Imade. Dysfunction: A Primary Cause of Death Due To Severe Malaria in APlasmodium falciparum-Infected Humanized Mouse Model. Iran J Parasitol 2013; 8(4):499-509.
30. Xin-Xu Li, Xiao-Nong Zhou. Co-infection of tuberculosis and parasitic diseases in humans: a systematic review. Parasites & Vectors 2013; 6:79
31. Onwuamaegbu ME, Henein M, Coats AJ. Cachexia in malaria and heart failure: therapeutic considerations in clinical practice. Postgrad Med J 2004; 80:642-649.
32. Günther A, Grobusch MP, Slevogt H, Abel W, Burchard GD. Myocardial damage in falciparum malaria detectable by cardiac troponin T is rare. Trop Med Int Health 2003; 8(1):30-2.
33. Paola Costenaro, Paolo Benedetti, Chiara Facchin, Carlo Mengoli, Giampietro Pellizzer Fatal. Myocarditis in Course of Plasmodium falciparumInfection: Case Report and Review of Cardiac Complications in Malaria. Case Rep Med 2011; 2011:202083.
34. Kumar PP, Kumar CD, Shaik FAR, Ghanta SB, "Myocardial dysfunction in severe falciparum malaria," Journal of Tropical Pediatrics 2009; 56(1):67-68.
35. Bruneel F, Hocqueloux L, Alberti C, Wolff M, Chevret S, Bédos JP *et al.* The clinical spectrum of severe imported falciparum malaria in the intensive care unit: report of 188 cases in adults. Am J Respir Crit Care Med 2003; 167(5):684-9.
36. Day NP, Hien TT, Schollaardt T, Loc PP, Chuong LV, Chau TT *et al.* The prognostic and pathophysiologic role of pro- and antiinflammatory cytokines in severe malaria. J Infect Dis 1999; 180(4):1288-97.
37. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F *et al.* Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis 2010; 201(3):318-30.
38. Patra S, Bhardwaj G, Manohar JS, Srinivasa KH, Kharge J, Manjunath CN. Acute myocardial infarction being the presentation of dengue myocarditis. J Cardiovasc Dis 2013; 4(2):159-61.
39. Lee CH, Teo C, Low AF. Fulminant dengue myocarditis masquerading as acute myocardial infarction. Int J Cardiol 2009; 136(3):69-71.
40. Ing-Kit Lee, Wen-Huei Lee, Jien-Wei Liu, Kuender D. Yang Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients
41. Miranda CH, Borges Mde C, Schmidt A, Pazin-Filho A, Rossi MA, Ramos SG *et.al.* Fonseca BAA case presentation of a fatal dengue myocarditis showing evidence for dengue virus-induced lesion. Eur Heart J Acute Cardiovasc Care 2013; 2(2):127-30.
42. Lee IK, Lee WH, Liu JW, Yang KD. Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients. Int J Infect Dis 2010; 14(10):919-22.
43. Mei-Chuan Kuo, Po-Liang Lu, Jer-Ming Chang, Ming-Yen Lin, Jih-Jin Tsai,Yen-Hsu Chen *et al.* Impact of Renal Failure on the Outcome of Dengue Viral Infection Clin J Am Soc Nephrol 2008; 3(5):1350-1356.
44. Shantanu P. Sengupta, Abhijeet Nugurwar, Rahul Jaju, Bijoy K. Khandheria· Left ventricular myocardial performance in patients with dengue hemorrhagic fever and thrombocytopenia as assessed by two-dimensional speckle tracking echocardiography. Indian Heart J 2013; 65(3):276-282.
45. Kim SA, Kim ES, Rhee MY, Choi SI, Huh HJ, Chae SL. A case of myocarditis associated with Plasmodium vivax malaria. J Travel Med 2009; 16(2):138-40.
46. Ahmad S, Dhar M, Bishnoi S, Shirazi N, Bhat NK. Acute myocarditis in vivax malaria: an extremely rare complication. Trop Doct 2013; 43(1):35-6.
47. Gantait K, Gantait I. Vivax malaria complicated by myocarditis. J Assoc Physicians India 2013; 61(12):944-5.
48. van Meer MP, Bastiaens GJ, Boulaksil M, de Mast Q, Gunasekera A, Hoffman SL *et al.* Idiopathic acute myocarditis during treatment for controlled human malaria infection: a case report. Malar J 2014; 13:38.
49. Nasir N, Lalani S, Samani ZA, Almas. A Myocarditis complicating Plasmodium vivax malaria. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP 2014; 24(2):96-8.
50. Soon Ae Kim, Eu Suk Kim, Moo Yong Rhee, Sang Il Choi, Hee Jin Huh, Seok Lae Chae. A case of myocarditis associated with Plasmodium vivax malaria. Journal of Travel Medicine 2009; 16(2):138-40.
51. Sohaib Ahmad, Minakshi Dhar, Shilpa Bishnoi, Nadia Shirazi, Nowneet K Bhat Acute myocarditis in vivax malaria: an extremely rare complication.Tropical Doctor (Impact Factor: 0.53), 2013, 02.
52. Freiberg MS, Chang CC, Skanderson M, McGinnis K, Kuller LH, Kraemer KL *et al.* Veterans Aging Cohort Study The risk of incident coronary heart disease among

veterans with and without HIV and hepatitis C. Circ Cardiovasc Qual Outcomes 2011; 4(4):425-32.
53. Virginia Triant A. HIV Infection and Coronary Heart Disease: An Intersection of Epidemics. J Infect Dis. Jun 1 2012; 205:355-361.
54. Virginia. Triant A. Epidemiology of Coronary Heart Disease in HIV Patients Virginia A. Triant.
55. Markella Zanni V., Judith Schouten, Steven K. Grinspoon, Peter Reiss. Risk of coronary heart disease in patients with HIV infection Nature Reviews Cardiology 2014; 11:728-741.
56. Butt AA, Khan UA, Skanderson M. Comorbidities and their impact on mortality in HCV and HCV-HIV-coinfected persons on dialysis. J Clin Gastroenterol 2008; 42(9):1054-59.
57. He Huang, Rongyan Kang, Zhendong. Zhao is Hepatitis C Associated with Atherosclerotic Burden? A Systematic Review and Meta-Analysis PLoS One 2014; 9(9):106-376.
58. Sosner P, Wangermez M, Chagneau-Derrode C, Le Moal G, Silvain C. Atherosclerosis risk in HIV-infected patients: the influence of hepatitis C virus co-infection. Atherosclerosis 2012; 222(1):274-7.
59. Philippe Sosner, Marc Wangermez, Carine Chagneau-Derrode, Gwenaël Le Moal, Christine Silvain Atherosclerosis risk in HIV-infected patients: the influence of hepatitis C virus co-infection. Atherosclerosis 2012; 222(1):274-7.
60. Sung J, Song YM, Choi YH, Ebrahim S, Davey Smith G. Hepatitis B virus seropositivity and the risk of stroke and myocardial infarction. Stroke 2007; 38(5):1436-41.
61. Operskalski EA, Kovacs A. HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. Curr HIV/AIDS Rep 2011; 8(1):12-22.
62. Adeel A. Butt, Wang Xiaoqiang, Matthew Budoff, David Leaf, Lewis H. Kuller *et al.* Hepatitis C Virus Infection and the Risk of Coronary Disease. Clin Infect Dis 2009; 49(2):225-232.
63. Tien PC, Schneider MF, Cole SR, Cohen MH, Glesby MJ, Lazar J *et al.* Association of hepatitis C virus and HIV infection with subclinical atherosclerosis in the women's interagency HIV study.
64. Luigi E Adinolfi, Rosa Zampino, Luciano Restivo, Amedeo Lonardo, Barbara Guerrera, Aldo Marrone *et al.* Chronic hepatitis C virus infection and atherosclerosis: Clinical impact and mechanisms World J Gastroenterol 2014; 20(13):3410-3417.
65. Gillis J, Smieja M, Cescon A, Rourke SB, Burchell AN, Cooper C *et al.* Risk of cardiovascular disease associated with HCV and HBV coinfection among antiretroviral-treated HIV-infected individuals. Antivir Ther 2014; 19(3):309-17.