

## Cardiovascular disease risk in HIV-Positive Populations in Indonesia: A Literature Review

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### Abstract

HIV is a significant health problem in the world. HIV infection has the effect of reducing immunity status and increasing the risk of cardiovascular disease. Antiretroviral (ART) use as a therapy for HIV also increases the risk of heart disease. This literature review aims to identify cardiovascular disease risk and factor-related in HIV-positive populations in Indonesia. The literature review of articles published January 2009 to September 2018 using search keywords namely 'Anti-retroviral therapy,' 'Cardiovascular disease,' 'Coronary artery disease,' and 'HIV' in databases namely Pubmed, Cochrane Library, EbscoHost, and Google Scholar. Five relevant articles were extracted in this study to gather information related to cardiovascular disease risk and factor-related in HIV-positive populations in Indonesia. The results showed that HIV-positive people in Indonesia have the chance for structural heart damaged, abnormal heart functions, inflammatory heart response, and coronary artery damage. Factor-Related cardiovascular disease risk in HIV-positive populations in Indonesia was the use of ART and smoking behavior. HIV patients have a high risk of developing cardiovascular disorders. This is a challenge for health workers, the government and researchers, to develop appropriate strategies and methods in reducing the risk of cardiovascular complications especially in Indonesia.

**Keyword:** AIDS, Anti-retroviral therapy, cardiovascular disease, HIV, HIV in Indonesia

### 1. Background

Cardiovascular disease, especially coronary heart disease, is a concern for HIV patients (1–7). Since the introduction of antiretroviral therapy (ART) as HIV therapy, it can cause a decrease in morbidity and mortality in HIV patients, but on the other hand, some studies report that the use of ART is suspected of increasing the risk of cardiovascular disease (8). Also, chronic infections and inflammatory mechanisms have a significant role in the arrangement of cardiovascular disorders in HIV patients (2,3).

A study conducted the prediction of the risk of cardiovascular disease in HIV patients. The results of a study conducted in 341 HIV patients in Brazil stated that 46% of HIV patients were at risk of developing heart disease (9). Another study conducted in Brazil aimed at predicting the risk of heart disease in HIV patients using the Framingham cardiovascular risk score found that 30% of HIV patients were at risk of CAD, and 55% were at risk of developing hypertension (10). Another similar study was

carried out in India where the results of the study explained that as many as 36% of HIV patients were at risk of developing coronary artery disease (CAD) within five years after being exposed to HIV (11). In addition to the inflammatory response and use of ART, smoking behavior is also a factor that contributes to the risk of heart disease in HIV patients. Research shows that around 40-70% of HIV patients are smokers, where smoking is a traditional factor for the risk of heart disease (12).

HIV incidence is increasing in the low middle-income country (LMICs)(13,14). For Indonesia, a LMIC, the prevalence of newly infected HIV in 2017 ranged from 41,000 - 432,000 and there were around 806 – 1,000 deaths due to AIDS in one year of 2016 (24). Furthermore, the need for antiretroviral therapy in Indonesia is expected to increase from approximately 30,000 patients in 2008 to almost 87,000 patients in 2014 (24). With such an incidence, studies on the prevalence of cardiovascular disease in HIV patients in Indonesia are still limited. This literature review aims to identify cardiovascular disease risk and factor-related in HIV-positive populations in Indonesia.

## **2. Objective**

This literature review aims to identify cardiovascular disease risk and factor-related in HIV-positive populations in Indonesia

## **3. Method**

The research method is a literature review. To collect data, the authors used several databases to search for literature sources to be reviewed, namely, Pubmed, Cochrane Library, EbscoHost, and Google Scholar. The inclusion criteria including 1) an article discussing cardiovascular disease in HIV patients; and (2) English and Indonesian-language articles. Published articles are restricted from January 2009 to September 2018. The author also uses several search keywords, " Anti-retroviral therapy ", 'Cardiovascular disease,' 'Coronary artery disease,' 'HIV.' The article chosen was a quantitative study relating to cardiovascular disease in HIV patients. The research method used is a systematic review, meta-analysis, RCT, cohort, case-control, case study, cross-sectional study.

## **4. Result**

Five journal articles were found that discussed the cardiovascular disorders risk among HIV patients in Indonesia specifically. The research method used in the findings of the journal is three articles of cross-sectional studies, 1 article of a comprehensive survey, and 1 article of a cohort study. The journal article reports on cardiovascular disease risk in HIV-positive populations in Indonesia showed on table 1.

### **4.1 Cardiovascular disease risk in HIV-Positive**

#### **4.1.1 Structural damage and abnormal heart function**

People with HIV-positive have a risk for structural damage and abnormal heart function. The study was carried out by Hidayat et al., 2018 in Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia through a cross-sectional approach aimed at anticipating cardiovascular disease in people with AIDS. The sample used in the study amounted to 52 people with AIDS. Respondents were divided into 2 clusters namely respondents with  $CD4 \leq 200 / mm^3$  and respondents with  $CD4 \text{ counts} \geq 200 / mm^3$ . Furthermore, respondents were assessed for function and structure of the heart by echocardiographic examination. The results revealed that the average age of respondents was 33 years, with men as the dominant gender (71.2%). In the group with

a CD4 count of  $\leq 200$  / mm<sup>3</sup>, the Left ventricle mass index (LVMI) was higher than the group of respondents who had a CD4  $\geq 200$  / mm<sup>3</sup> (113.08 vs. 39.99; p-value = 0.018). Then the group with CD4 cell count  $\leq 200$  / mm<sup>3</sup> was at risk of developing diastolic dysfunction (OR 9.35, 95% CI, p = 0.018) and pericardial effusion (OR 3.83, 95% CI, p = 0.048) (3).

The results of other study conducted by Price (2017) revealed that the average age of respondents was 31 years, with men 46 people, while 37% of respondents were smokers, and 51% of respondents were diagnosed with tuberculosis before ART. They explain the association between ART and markers of cardiovascular disorders in which the left ventricular mass index (LVMI), carotid intimal media thickness (cIMT), and ejection fraction have the same value as healthy people. Furthermore, after 12 weeks (V12) there is an increase in the left ventricular mass index (LVMI), carotid intimal media thickness (cIMT), and decreased fraction ejection (6).

The results of a study conducted by Lubis et al. (2012) in patients who had been infected with HIV during the 6-month observation period, found that worsening E-point septal separation (EPSS) was positively associated with changes in CD4 levels. Also, the number of patients with impaired diastolic function increases. Echocardiographic evaluation in patients with HIV infection should be done periodically to be able to detect changes in left ventricular systolic and diastolic function as early as possible, so that appropriate action can be taken, especially in Indonesia where Highly Active Anti Retroviral Therapy (HAART) therapy only reaches less than 20% of sufferers need it (25).

#### **4.1.2 Inflammatory response and coronary artery damage**

Pathologically, HIV causes an abnormal inflammatory response by infecting dendritic myocardium cells and endothelial cells, causing chronic inflammation by stimulating the production of TNF alpha, interleukin 1 and 6 and other inflammatory cytokine proteins that cause myocardial injury causing fibrosis of the myocardium. In the other hand, some literature explains the relationship of HIV infection to the formation of arteriosclerotics, where infection in the coronary arteries stimulates the proliferation of vascular endothelial cells which triggers the occurrence of arteriosclerotics (20).

Another mechanism explains that the inflammatory reaction triggers the coagulation response and platelet reactivity so that it will form thrombus so that the risk of developing coronary heart disease (8). Subsequent research was conducted to assess the relationship between the value of Troponin I and CD4 levels in HIV patients in Wahidin Sudirohusodo Hospital, Makassar, Indonesia. The study was conducted from March 2017 to April 2017 with a sample of 43 patients. The results showed that respondents with high troponin had lower CD4 levels than respondents with normal troponin (144.9 118.3 vs. 293.9 111.3, p <0.001). Furthermore, in the study researchers also found a significant relationship between CD4 and troponin I value, and on echocardiographic results, researchers found 72.2% of respondents experienced diastolic dysfunction (16).

## 4.2 Factor-related cardiovascular disease risk in HIV-positive populations in Indonesia

### 4.2.1 Antiretroviral therapy (ART)

ART is thought to be a risk factor for heart disease in HIV patients<sup>2</sup>. In Indonesia, the relationship between ART and the risk of heart disease has been carried out with a cohort design study conducted by Price, 2017. The study was held at the Cipto Mangukusumo Hospital in Jakarta, Indonesia. The sample used in the study was 82 HIV patients who took antiretroviral therapy in 2013-2014 with CD4 <200 T-cells /  $\mu$ l. Next, before starting ART therapy (V0), the researchers examined pulmonary tuberculosis (X-ray and sputum acid Bacilli smear). After that, plasma HIV RNA was analyzed using AmpliPrep / COBAS® TaqMan® HIV-1 Tests (version 2.0) and CD4 T-cell. The examination is continued at the 3rd, 6th and 12th months (V3, V6, V12). To assess changes in function and cardiac structure researchers used echocardiographic and vascular Doppler (6). Also, ART therapy causes damage to mitochondrial myocytes (19). In addition to the inflammatory response, ART plays a role in coronary artery endothelial cell damage. Endothelial dysfunction secondary to antiretroviral therapy has been associated with reduced production of nitric oxide (NO), as well as an increase in reactive oxygen species (ROS) which will cause damage to coronary artery endothelial cells (20)

### 4.2.2 Smoking

Smoking plays a role in the risk of the incidence of coronary heart disease in HIV-positive population (21). A cohort study aimed at predicting the risk of coronary heart disease in smoking HIV patients in Asia, including in Indonesia concluded that HIV patients who smoke in Indonesia are three times at risk of coronary heart disease than non-smoking HIV patients, and patients who do not smoke can reduce five years risk of coronary heart disease (22). The results of the study were similar to a cohort study of 33,308 HIV patients who concluded that there was a reduced risk of myocardial infarction and heart disease after a year the patient stopped smoking, and after three years reduced the risk of half heart disease from the first year (12). The relationship of smoking to the incidence of heart disease is the effect of tobacco which inhibits the effectiveness of T cells so that it increases the risk of infection, decreasing the efficacy of T cells causes an inflammatory response so that it will trigger the formation of arteriosclerotics (12).

**Table 1. Overview of the papers on cardiovascular disorders among HIV patients in Indonesia.**

Title	Reference	Main Focus	Methods	Conclusion
A cluster of Differentiation 4 Count and Left Ventricular Diastolic Function in Patients with Hiv - Aids	[3]	To anticipate the risk of cardiovascular morbidity in people with AIDS	The researchers conducted a study with 52 people with AIDS, in which Categorized into those with a cluster of differentiation 4 (CD4) count of less than 200/mm <sup>3</sup> and those with a CD4 count of	A CD4 count of less than 200/mm <sup>3</sup> is associated with a higher risk of developing diastolic cardiac dysfunction and structural abnormalities.

			more than 200/mm <sup>3</sup> . Echocardiographic examinations were done to evaluate cardiac structural and functional values.	
Factors affecting cardiovascular health in Indonesian HIV patients beginning ART	[6]	To assess how demographic factors and persistent burdens of HIV and cytomegalovirus (CMV) influence cardiovascular health in young adults beginning ART in an inner-city clinic in Jakarta, Indonesia.	cohort design study enrolled 82 ART-naïve HIV patients in 2013–2014 with <200 CD4 T-cells/μl.	The severity of HIV disease and the response to ART have only subtle effects on cardiovascular health in this young Asian population.
Relationship Between CD4 Count with Troponin I (ctni) level in HIV/AIDS Patients	[15]	To evaluate the relationship between CD4 count and troponin I level in HIV / AIDS patients.	Descriptive, analytical research with the cross-sectional method. The study was conducted in Inpatient, Outpatient installation and Pathology Laboratory Clinic of Dr. dr. Wahidin Sudirohusodo Hospital Makassar starting from March 2017 until a sufficient number of samples.	There is a relationship between CD4 count and troponin I level in HIV / AIDS patients.
Smoking and Projected Cardiovascular Risk in an HIV-Positive Asian Regional Cohort	[22]	To assess the prevalence of and characteristics associated with current smoking in an Asian HIV-positive cohort (include Indonesia), calculate the predictive risks of cardiovascular disease (CVD), coronary heart disease (CHD), and myocardial infarction (MI), and identify the impact that simulated interventions may have	The study population consisted of participants enrolled in the TREAT Asia HIV Observational Database (TAHOD). Briefly, TAHOD is a cohort observational study. Location of TAHOD was Thailand, Vietnam, Indonesia, India, Hongkong SAR, Philippines, Taiwan, Malaysia, Japan, South Korea, Singapore, and China	HIV patients who smoke in Indonesia are three times at risk of coronary heart disease than non-smoking HIV patients, and patients who do not smoke can reduce five years risk of coronary heart disease. Multiple interventions could reduce CVD, CHD, and MI risk in Asian HIV-positive patients, with smoking cessation, potentially being the most influential.
Left Ventricle Function Alterations in	[25]	To evaluated noninvasively ventricular	This study is a cross-sectional, observational prospective study.	Echocardiographic evaluation in patients with HIV infection should

HIV-infected Patients	function in HIV infected patients with no clinical evidence of cardiovascular disease, with the determination of left ventricular systolic and diastolic function, as well as measurement of CD 4.	Inclusion criteria: Patients who have been infected are infected with HIV, patients who have the results of CD 4 levels at least in the last six months, age > 15 years, and are willing to submit informed consent. Exclusion Criteria: Patients who are clinically unfit for echocardiography examination.	be done periodically to be able to detect changes in left ventricular systolic and diastolic function as early as possible so that that appropriate measures can be taken, especially in Indonesia where HAART therapy only reaches less than 20% of patients who need it.
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## 5. Discussion

Left ventricular hypertrophy (LVH) is a predictor of all deaths in the general population<sup>16</sup>. Also, LVH is a predictor of the incidence of cardiovascular disease, where this risk is increased in people infected with HIV (17). The results of a study conducted by Hidayat et al., 2018 in patients with HIV AIDS Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia showed that patients with CD4  $\leq$  200 / mm<sup>3</sup> had a higher risk of diastolic dysfunction and damage to heart structure including left ventricular abnormalities mass index (LVMI). This study is similar to the study conducted by Schwartz et al., 2012 in Botswana, Africa. In the research, Schwartz et al. explained that HIV AIDS patients in Botswana experienced cardiovascular diseases such as the abnormal structural heart (cardiomyopathy) and heart infection (pericarditis) (7).

In addition to the mechanism of infection that causes cardiac structural abnormalities, ART is also associated with cardiac structural abnormalities in HIV patients. The results of a Price study, 2017 at the Cipto Mangunkusumo Hospital in Jakarta, Indonesia, concluded that HIV patients taking antiretroviral therapy were at risk of experiencing heart structure damage after a year of use. Similar to the study conducted by Pombo et al. (2013) which found that after a year of ART use, HIV patients experienced left ventricular hypertrophy (LVH)(16). Research conducted in Germany also concluded the same results where HIV patients who take antiretroviral therapy are at high risk for changes in the left ventricular wall (18).

The relationship between coronary heart disease and HIV infection is caused by complex viral infection responses, traditional risk factors and the effects of ART therapy (20). Several studies have explained the relationship between the two, where HIV infection increases the risk of myocardial infarction (2). Another study reveals that HIV infection causes coronary artery endothelial dysfunction, thus risking myocardial infarction (12). In Indonesia, research conducted by Muzakkir Amir and H Cipta in 2017 at Wahidin Hospital Sudirohusodo Makassar, Indonesia, concluded that there was a change in cardiac troponin which is a marker of myocardial muscle damage in HIV patients.

One of the main problems regarding prevention of heart disease in people infected with HIV is to create the right method of identifying HIV patients who are at risk of developing heart disease so that these patients will benefit from the primary prevention provided (23). Smoking cessation is one of the right strategies in reducing the risk of heart disease in HIV patients, where smoking is a traditional factor that can be changed to reduce the risk of cardiovascular disorders. Smoking plays a role in the



risk of the incidence of coronary heart disease in an HIV-positive population in Indonesia (21). For a reason, an effective method is needed to help patients stop smoking, so further research is required to determine effective ways of smoking cessation in HIV-infected patients (23).

## 6. Conclusion and recommendation

HIV is a significant health problem in the world. HIV patients have a high risk of developing cardiovascular disease. HIV-positive populations in Indonesia have the chance for structural heart damaged, abnormal heart functions, inflammatory heart response, and coronary artery damage. Factor-Related cardiovascular disease risk in HIV-positive populations in Indonesia was the use of ART and smoking behavior. This is a challenge for health workers, the government and researchers, to develop appropriate strategies and methods in reducing the cardiovascular disease risk in HIV-positive populations in Indonesia.

## 7. Study limitations

This study conducted in literature review rather than meta-analysis. Thereby we could not poll the data.

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