

Research Article

Incidence Rate of Myocardial Infarction in HIV–Infected Individuals: A Systematic Review and Meta–Analysis

Camoya Gersom^{1*}, Savannah Quila Thirza¹

¹Medical Faculty of Brawijaya University

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**Corresponding author:*

E-mail: camogersom94@gmail.com

ABSTRACT

Background: The incidence rate of myocardial infarction has been reportedly higher in human immunodeficiency virus (HIV)–infected individuals compared to in uninfected individuals. HIV infection is suggested to have increased the risk of myocardial infarction (MI). To review the incidence rate of myocardial infarction in HIV–infected individuals compared to in uninfected individuals in its relation to HIV infection as a potential risk factor of MI incident. A literature search was performed in Google Scholar, PubMed, and Cochrane databases with keywords “HIV risk myocardial infarction” and “myocardial infarction in HIV” ranging from 2013 to 2019. Inclusion criteria was full-text observational studies that reported the incidence rate of myocardial infarction in HIV–infected individuals compared to in uninfected individuals. A total of 6 studies were eligible for review. We performed the meta–analysis with Review Manager 5.3 in May 2019. We reviewed several studies that discussed the association between HIV infection and myocardial infarction. The incidence rate of MI is higher in HIV–infected individuals compared to in non–infected individuals. It is suggested that Framingham Risk Score does not directly contribute to the higher incidence of MI in patients with HIV. Several studies also reported that low CD4 cell count and HIV–1 RNA levels less than 500 copies/mL contribute directly to the risk of myocardial infarction. There is a higher incidence rate of myocardial infarction among HIV–infected individuals compared to among non–infected individuals. Several suggested factors include low CD4 cell count and HIV–1 RNA levels less than 500 copies/mL. Thus, it may be suggested that HIV infection is a potential risk factor of MI. Further studies are needed to better understand the mechanism of HIV infection as a risk factor of MI incident.

Keywords: human immunodeficiency virus, incidence rate, myocardial infarction

Introduction

The World Health Organization estimates that approximately 37 million people are currently living with HIV infection. This number is estimated to be growing in the next years and the aging HIV population is increasingly at risk to get non communicable disease–related morbidity and mortality such as by cardiovascular diseases (CVD), especially since the role of antiretroviral therapy (ART) has dramatically increased the life expectancy among Human Immunodeficiency Virus (HIV)–infected individuals [1–5]. Although traditional CVD risk factors are prevalent among HIV–infected individuals, cumulative

exposure to chronic inflammation and immune activation that persists in persons with treated HIV infection may also contribute to the development of atherosclerotic CVD (ASCVD) [6]. There is a strong evidence that suggests traditional CVD risks occur in clusters, which can simply be categorized as CVD risk factor profiles [7]. But additionally, there’s also an evidence that suggests HIV–related variables such as immunological factors, use of cART, and co–infection with other viruses which may directly contribute to the increased risk of ASCVD among HIV–infected individuals [8–10].

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Whether HIV infection is directly associated to the risk of AMI is not yet clear. With ART to help lengthen the life expectancy of HIV-infected individuals, it is important to recognize the risks that may follow, which in this study is myocardial infarction. Therefore, we conducted a systematic review and a meta-analysis of published medical literature to compare the incidence rate of myocardial infarction between among HIV-infected individuals and among uninfected individuals. This study is hoped to contribute in determining the association between HIV infection and myocardial infarction incidence among HIV-infected individuals.

Material and Methods

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [11]. The determined inclusion criteria was full-text observational studies that reported the incidence rate of myocardial infarction in HIV-infected individuals compared to in uninfected individuals. We excluded unpublished articles, abstracts, and studies not written in English or Bahasa Indonesia from this study. The eligibility criteria for this review has been developed based on the Population, Intervention, Comparator, and Outcome (PICO) framework, which can be seen in Table 1.

Table 1. Eligibility criteria based on PICO

Patient	Patients with myocardial infarction incident who have HIV infection history and without HIV infection history with a total sample of 838.113 patients.
Intervention	Retroprospective study on MI events among individuals with HIV infection ranging from 2003 to 2014.
Comparison	Retroprospective study on MI events among individuals without HIV infection ranging from 2003 to 2014.
Outcome	Odds ratio of MI events in individuals with HIV infection compared to individuals without HIV infection.

Studies were obtained by search electronic databases in Google Scholar, PubMed, and Cochrane databases ranging from 2013 to 2019. The studies we included were full-text observational studies that reported the incidence rate of myocardial infarction in HIV-infected individuals compared to in uninfected individuals. The authors used the keywords “HIV risk myocardial infarction” and “myocardial infarction in HIV”. A total of 6 studies were eligible for review. Study selection and data collection were performed independently in an unblinded standardized manner by two reviewers (CG and SQT). Discrepancies between the reviewers were resolved by discussion. Data regarding the incidence rate of myocardial infarction in HIV-infected individuals compared to in uninfected individuals were extracted and analyzed. Meta-analysis was performed using Review Manager 5.3. The outcome was myocardial infarction incidence among patients with HIV infection and

without HIV infection. This outcome was evaluated for all studies and the Odds Ratio (OR) was calculated.

We reported the phases of this review in the flow diagram as depicted in Figure 1. We initially included 13 articles after performing the literature search and removing duplicates. The full texts of these articles were retrieved and reviewed. After the final selection using the inclusion criteria, there are only 6 studies that are eligible to be included in this systematic review and meta-analysis.

We calculated the effect size using Odds Ratio (OR) and 95% confidence interval (CI) for MI events among patients with HIV infection versus without HIV infection. Homogeneity of study results is determined using Cochran Q test. The random effect model (REM) is used if statistical heterogeneity was found in the study ($I^2 > 75\%$). Otherwise, the fixed effect model (FEM) was used.

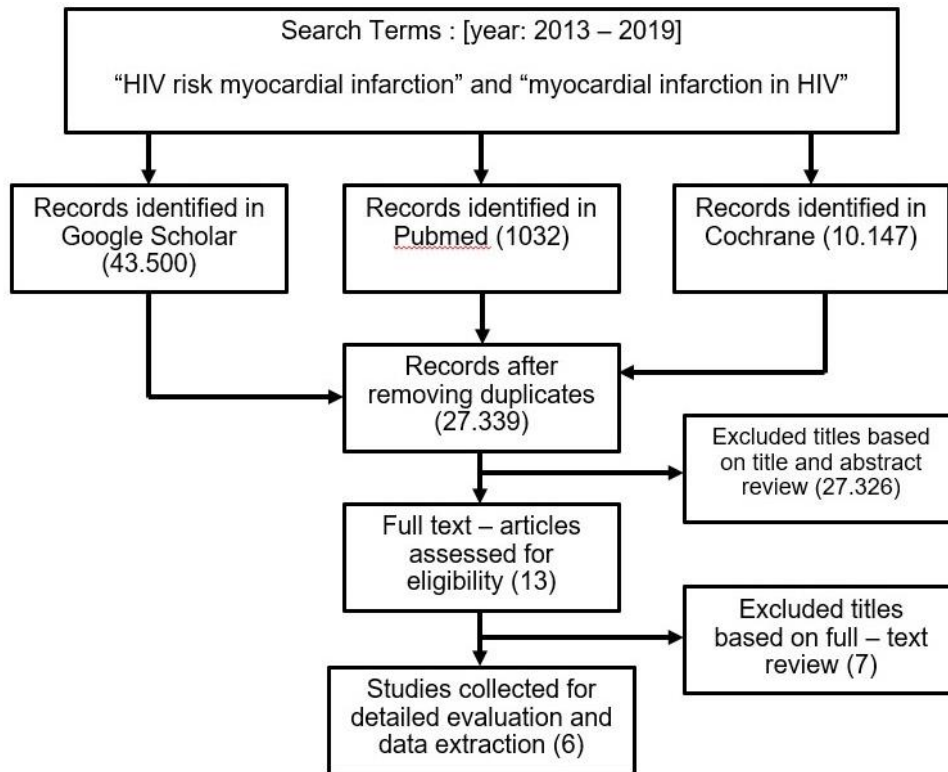


Figure 1. Flow diagram of the article search and study selection

Results and Discussion

Result

This review included a total of 838.118 patients from 6 studies ranging from 2013 to 2015, 133.804 with HIV infection and 704.309 without HIV infection. Based on the meta-analysis, we calculated that the pooled odds ratio for MI

events (with HIV infection vs. without HIV infection) is 1.42 (1.34, 1.50) with 95% CI. The results are homogenous as displayed by $\chi^2 = 1.12$, $df = 5$ ($P = 0.95$); $I^2 = 0\%$. The fixed model effect was used. Test for overall effect shows $Z = 12.59$ ($P < 0.00001$).

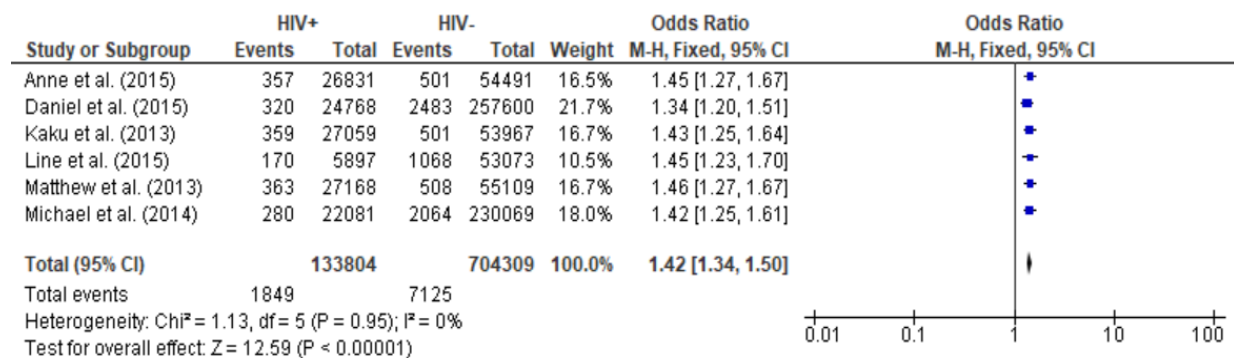


Figure 2. Forest Plot comparing MI events among patients with HIV infection and without HIV infection

A study by Matthew et al. reported 871 MI events (41,7% HIV-positive) among total sample of 82.277 patients (27.168 HIV-positive and 55.109 uninfected) in the span of 5,9 years follow-up. The odds ratio shows 1.46 (1.27, 1.67) [21]. Kaku et al. reported 359 MI events among

HIV-infected individuals, showing the odds ratio of 1.43 (1.25, 1.64) [22]. Michael et al. reported 280 MI events among HIV-infected individuals, showing the odds ratio of 1.42 (1.25, 1.61) [23]. Anne et al. reported 357 MI events among HIV – infected individuals, showing the odds ratio of

1.45 (1.27, 1.67) [24]. Daniel et al. reported 320 MI events among HIV – infected individuals, showing the odds ratio of 1.34 (1.20, 1.51) [25]. Line et al. reported 320 MI events among HIV–infected individuals, showing the odds ratio of 1.45 (1.23, 1.70) [26]. The forest plot in Figure 2 also shows that the pooled odds ratio of these studies are shown in the diamond shape which does not cross the midline, therefore the study findings are considered significant.

Discussion

This systematic review and meta-analysis included 6 studies as they met the eligibility criteria required for inclusion. The findings reported higher incidence rate of myocardial infarction among HIV–infected individuals compared to among individuals without HIV infection. The mechanism by which HIV infection increases the risk of MI is not yet known. Several studies have reported possible mechanisms which involve inflammation, CD4 cell count depletion, altered coagulation, dyslipidemia, impaired arterial elasticity, and endothelial dysfunction. There are also reports regarding ART usage being associated with metabolic changes and abnormal fat distribution which relates to MI risk [13–20].

All 6 studies reported that the incidence rate of MI events is higher in patients with HIV infection compared to the patients without HIV infection, therefore suggesting that HIV infection may be a potential risk factor that may contribute to the prevalence of myocardial infarction. As previously mentioned, the pooled odds ratio for MI events (with HIV infection vs. without HIV infection) is 1.42 (1.34, 1.50) with 95% CI. Among the 6 studies, 2 studies accounted Framingham risk score in the samples and reported that Framingham risk score does not directly contribute to the prevalence of MI in HIV–infected individuals. These studies also reported that even after the adjustment for Framingham risk factors, comorbidities, and substance use, patients with HIV infection have a significantly higher risk of MI compared with demographically similar patients without HIV infection [21–24].

Studies by Matthew et al., Michael et al., and Anne et al. reported that MI events occur the most in patients with CD4 cell count less than 200 cells/ml which suggests that the virus infection itself plays a large role in causing myocardi-

al infarction to have increased risk to occur in infected patients. This finding supports studies that documented accelerated atherosclerosis and coronary artery calcium rate of progression mostly driven by traditional vascular risk factors, along with the higher viral loads and CD4 cell count less than 200 cells/ml [21, 23, 24–28].

Meanwhile, studies by Matthew et al., Kaku et al., and Anne et al. reported that the incidence rate persisted among those achieving HIV–1 RNA levels less than 500 copies/ml over time among patients who underwent ART. ART is associated with metabolic changes and abnormal fat distribution which in turn are linked with insulin resistance, diabetes, and dyslipidemia. However, we are lacking the data to further investigate whether ART consumption directly affects the risk factor of myocardial infarction or it's tied to other factors as well [21, 22, 24].

Conclusion

In this review, it can be concluded that the incidence rate of myocardial infarction in HIV–infected individuals is higher compared to in uninfected individuals. This review also suggests that HIV infection is an independent risk factor of myocardial infarction based on the studies which suggested that Framingham risk score does not directly contribute to the prevalence of myocardial infarction among HIV–infected individuals. Several studies also reported the possible correlation between CD4 cell count depletion and HIV–1 RNA levels less than 500 copies/mL may also suggest that ART contributes to the increased risk of myocardial infarction among HIV–infected individuals. Further studies are still required to confirm the relation of ART regimen to the increased incidence rate of myocardial infarction among HIV–infected individuals compared to in uninfected individuals.

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