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## Editorial

# Hepatitis C – Human Immunodeficiency Virus Coinfection and the Risk of Cerebro-Cardiovascular Diseases: Is There Enough Evidence to Draw Conclusion and Establish Guideline?

## Editorial

During the last decade, the link between Human Immunodeficiency Virus (HIV) infection and cardiovascular disease has received much attention. Recent meta-analysis by Islam et al. [1], concluded that HIV infection increases the risk of cardiovascular diseases (CVD). They found the relative risk (RR) of CVD among people living with HIV (PLHIV) was 1.61 (95% CI 1.43–1.81). Despite the introduction of antiretroviral therapy (ART) which increase survival of PLHIV, ART itself increase the risk of CVD (RR 2,00 95% CI 1,70–2,37) [1]. Management of HIV has shifted from treating the disease to managing complication and chronic condition such as atherosclerosis [2].

The link between HIV and CVD explained well by recent literature reviews by Nou et al. [2] and Bloomfield et al. [3]. There is an interplay between inflammation, HIV proteins, immune dysfunction, ART effect, malnutrition, and other factors in understanding the pathophysiological basis of CVD among PLHIV. Studies using carotid intima-media thickness (CIMT) found that PLHIV asymptomatic had increased subclinical atherosclerosis [4,5]. Furthermore, study using coronary CT angiography (CCTA) confirmed that PLHIV had increase coronary plaque even after controlling traditional CVD risk factors [6]. Interestingly, it was stated that PLHIV had unique plaque which altered morphology that susceptible to rupture. Traditional risk factors for CVD, including smoking, hypertension, diabetes, and dyslipidemia, reported more prevalent among PLHIV. Monocyte dysregulation could account for CVD among PLHIV. Soluble CD14 (sCD14) which correspond to monocyte-macrophage activation tend to be higher among PLHIV and associated with subclinical atherosclerosis. Soluble CD163 (sCD163) as another monocyte-macrophage activation also higher among PLHIV [2,3].

Besides robust evidence to support the link between HIV and CVD, recent evidence also support the hypothesis that

link hepatitis C virus (HCV) infection and CVD. As HIV and HCV share common route of transmission, knowledge about contribution of HCV in HIV-HCV coinfection toward CVD become interesting to be investigated. Coinfection with HCV associated with more increased sCD163 which account for arterial inflammation subclinical atherosclerosis [2]. HCV-HIV coinfecting patients reported to have higher inflammation biomarkers, coagulation, and microbial translocation according SMART study findings [7]. Fernández-Montero et al (2015) conducted a cohort to estimate CVD risk between HCV-HIV coinfecting, HIV mono-infected, and HCV mono-infected patients. HCV-HIV coinfecting patients had higher incidence of cardiovascular events compared to HIV mono-infected patients (4% vs 1.2%,  $p=0.004$ ). HCV-HIV coinfecting patients increased risk of cardiovascular events with adjusted hazard ratio 2.91 95% CI 1.19–7.12,  $p=0.02$ . Interestingly, this study conducted in subjects with high prevalence of smoking (39.2% as active smokers). Coinfecting patients even had higher prevalence than other groups (46%). Although they made adjustment for potential confounders, the importance of traditional risk factors need to be explored more. The length of active smoking and cigarettes per day did not reported [8].

Recent meta-analysis to evaluate the relationship between HCV and CVD was published [9]. They found that HCV infected patients had increased risks of CVD related mortality (odds ratio [OR] 1.65 95% CI 1.07–2.56,  $p=0.02$ ), carotid plaques (OR 2.27 95% CI 1.76–2.94,  $p<0.001$ ), and cerebrocardiovascular events (OR 1.30 95% CI 1.10–1.55  $p=0.002$ ). Moreover, the results were heterogeneous and the pooled estimate of HCV effect toward CVD mortality did not adjusted with potential confounders. When they conducted stratified analysis based on potential confounders, the results were interesting. The pooled OR for cerebrocardiovascular events was different between population with different prevalence of diabetes. The pooled OR only significant when analysis performed in population

with diabetes prevalence more than 20%. The pooled OR for cerebrocardiovascular events in setting with low prevalence of diabetes was OR 1.00 95% CI 0.72–1.40,  $p=1.00$ . Similarly, pooled OR for carotid atherosclerosis was not significant in setting with low prevalence (<20%) of smoking OR 1.07 95% CI 0.57–2.01,  $p=0.84$ . This reflect the need to control traditional risk factors among HCV-HIV coinfecting patients despite the fact that coinfection probably increase the risk of CVD.

The treatment protocol for HCV-HIV coinfection management to prevent CVD is still limited. In 2013, ACC-AHA guideline stated that 74% HIV with high-risk plague did not receive statin therapy. Lifestyle modification also play important role to decrease risk of CVD among PLHIV. Smoking cessation estimated to lower CVD risk by 42%. This lifestyle intervention should be emphasized as lipodystrophy in PLHIV receiving ART tend to has adverse metabolic consequences that favour CVD. Meanwhile, such interventions still lacked of evidence from randomized controlled trials as stated by Nou et al. [2]. The evidence to support treatment for PLHIV regarding CVD risk is needed. PLHIV with CVD faced increase rate of hospitalization for recurrent coronary event, restenosis and percutaneous revascularization post percutaneous coronary intervention (PCI) [3]. Moreover, HCV-HIV coinfection should take into account in future guideline. Current predictor of CVD among PLHIV also did not include newer evidence about HCV coinfection as potential predictors of CVD [10]. Study by Chew et al showed that antiviral treatment for HCV infection lower liver complications and specifically lower systemic inflammation based on CVD biomarkers [11].

Currently, promoting lifestyle changes among HCV-HIV coinfection patients seems the most effective and beneficial way despite lack of specific guidelines. Physicians could start statin therapy for those with multiple risks of cerebro-cardiovascular diseases. However, further evidence was needed, especially good quality randomized controlled trials recruiting HCV-HIV coinfection patients which evaluate cerebro-cardiovascular diseases as outcomes.

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