

INPLASY PROTOCOL

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None declared.

Prevalence and Risk Factors of Cardiovascular Disease among People Living with HIV in the Asia-Pacific Region: a systematic review

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Review question / Objective: This systematic review was conducted to address the situation and associated factors both traditional and HIV-specific for CVD among adult people living with HIV who were aged ≥ 18 years in the Asia Pacific region, and focused only on the counties with the greatest impact of CVD attributable to HIV infection including Bhutan, Cambodia, Indonesia, Malaysia, Myanmar, Papua New Guinea, Solomon Islands, and Thailand in the HAART era since 2005.

Information sources: This systematic review was performed in an attempt to retrieve epidemiological studies of CVD among PLHIV in the greatest impact of CVD attributable to HIV countries in the Asia Pacific region from the following sources: • MEDLINE via PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) • Embase (<https://www.embase.com>) • the Cochrane Database of Systematic Reviews (<https://www.cochranelibrary.com>).

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INTRODUCTION

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Islands, and Thailand in the HAART era since 2005.

Rationale: The beneficial outcome of the highly active antiretroviral therapy (HAART) on people living with human immunodeficiency virus (PLHIV) is to increase quality of life and life expectancy (1). The numbers of PLHIV, aged over 50 years, have increased worldwide and are linked to an increased burden of noncommunicable diseases (NCDs). The double disease burden, HIV and NCDs in particular cardiovascular diseases (CVD), may cause a hectic burden on the economy of families and countries (2). This situation requires a global public health attention. From 1990 to 2015, the global burden of CVD attributable to HIV increased greater than 3 times from 0.74 million to 2.57 million disability-adjusted life-years (DALYs) (3). A modelling study estimated that by the end of 2030 about 70% of PLHIV will be those aged more than 50 years, and 78% will have CVD (4). The higher risk of CVD among PLHIVs other than HIV-negative individuals approximately 1.5 to 3 fold was observed although the traditional risk factors for CVD among both groups did not differ (5-9). Several recent studies suggested that underlying mechanisms of HIV-specific risk factors likely contributed to accelerated CVD in PLHIV, i.e., side effects of antiretroviral therapy (ART) and systemic chronic inflammation due to immune activation against HIV (5-10). The Asia-Pacific region is the second region with greater burden of HIV after sub-Saharan Africa, (5.8 and 25.7 million, respectively) (11). The Asia-Pacific region has currently confronted with the emerging challenge of CVD among PLHIV. A recent global burden of disease study revealed that the CVD population attributable to HIV was comparable with traditional risk factors (3). Similarly, related studies suggested an increased incidence of CVD in PLHIV. However, most studies were conducted in high income countries where epidemiologic evidence was unsuited for the Asia-Pacific region due to different socio-economic contexts (3, 7, 12-13). To substantiate the situation of CVD and its risk factors among PLHIV remains

indispensable for evidence-based public health in this low to middle income region (3, 7, 9). In this review, we address the knowable epidemiological evidence of CVD among PLHIV in the Asia-Pacific counties to provide existing scientific evidence to alert public health professionals in the region confronting the syndemic of HIV and CVD.

Condition being studied: 1) Cardiovascular disease (CVD) means atherosclerotic cardiovascular diseases that develop from atherosclerosis. Atherosclerosis is an arterial disorder occurred in form of asymmetric thickening of the intima, the inner layer of arterial wall, also called atherosclerotic plaque or lesions. As atherosclerosis progresses, the luminal size of vascular was decrease by plaques progression or sudden rupture that becomes clinically occurrence depend on the lumen compromise percentage including “Ischemic heart disease” and “Angina pectoris” (chest pain due to coronary artery disease) cause by adenosine released from ischemic cardiac muscle and more obstruct of coronary artery lead to myocardial infraction, “Transient ischemic attacks” cause by insufficient blood flow to the brain and resulted in term of neurological disorder such as functional weakness and severe obstructive of cerebral circulation that lead to cerebrovascular disease such as ischemic stroke, “Peripheral claudication” that resulted in painful of peripheral muscles and loss function, and “Blood pressure increasing” by neuroendocrine feedback of kidney after the renal perfusion decrease that lead to kidney renin release and increased blood pressure. Although, the majority of CVD cases will not become clinical cases until 75% of the artery lumen is obstructed. 2) Traditional risk factors mean well-known factors of CVD such as major traditional risk factors for CVD in PLHIV including diabetes, hypertension, dyslipidemia, and smoking. Other traditional factors for CVD such as other personal characteristic related social environmental factors including financial stress, occupational, education, marital status, cultural, etc. 3) HIV-specific and

immune related factors mean specific factors of CVD that found only PLHIV or factors that related with immune activation and dysfunction related with HIV-infection compared in those who was HIV-negative such as antiretroviral therapy (ART) that are HIV medicines to treat HIV infection including protease inhibitors (PIs), nucleoside reverse-transcriptase inhibitors (NRTIs), non-Nucleoside reverse-transcriptase inhibitors (NNRTIs), integrase inhibitors (INSTIs) & entry inhibitors (EIs), concentrations of inflammatory cytokines and immune activation markers such as CD4 T cell count, CD8 T cell count, co-infection especially chronic hepatitis c virus (HCV) and hepatitis b virus (HBV). 4) Countries with the greatest impact of CVD attributable to HIV means countries in the Asia Pacific region with the PAF or HIV attributable to CVD. DALY's of those countries equal to or over the third quartile including Bhutan, Cambodia, Indonesia, Malaysia, Myanmar, Papua New Guinea, Solomon Islands, and Thailand.

METHODS

Search strategy: This systematic review of clinical and subclinical CVD in PLHIV in countries with the greatest impact of CVD attributable to HIV in the Asia-Pacific region, i.e., Thailand, Papua New Guinea, Bhutan, Cambodia, Myanmar, the Solomon Islands, Malaysia and Indonesia was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

We identified articles published in English through searching PubMed/MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews databases from any date to 31 December 2019 that included Medical Subject Headings (MeSH) "Human immunodeficiency virus", "People living with HIV", "Cardiovascular", "Cerebrovascular", "Thailand", "Cambodia", "Myanmar", "Bhutan", "Papua New Guinea", "the Solomon Islands", "Malaysia", or "Indonesia".

Search strategy comprised with three domains, including "Human immunodeficiency virus", "Cardiovascular

disease", and "the greatest impact of CVD attributable to HIV countries in the Asia Pacific region"

Variations of key concept to be searched for the "Human immunodeficiency virus" domain including (HIV OR Human immunodeficiency virus OR Human immune deficiency virus OR AIDS OR Acquired immunodeficiency syndrome OR Acquired immune deficiency syndrome OR HIV positive OR HIV positive patients OR Human immunodeficiency virus infection OR HIV-1 OR HIV-2 OR Human immunodeficiency virus OR HIV infections OR HIV-infected OR PLWH OR PLWHA OR PLHIV OR People living with HIV OR People living with AIDS OR HIV seropositivity)

Variations of key concept to be searched for the "Cardiovascular disease" domain including (Acute coronary syndrome OR Arterial OR Arterial stiffness OR Ankle brachial index OR Atherosclerosis OR Atherosclerotic OR Acute angina OR Acute coronary OR Angina OR Angina pectoris OR Ischemia OR Ischaemia OR Ischemic OR Ischaemic OR Infarction OR Infarct OR Brain ischemia OR Brain infarction OR Basal ganglia cerebrovascular disease OR Cardiovascular disease OR Cardiovascular OR Cardiovascular event OR Cardiovascular system OR Cardiovascular disorder OR Cardiovascular mortality OR Cardiovascular death OR Cardiovascular outcome OR Cardiomyopathy OR Carotid OR Carotid intima-media thickness OR Carotid stiffness OR Carotid artery disease OR Artery OR Carotid artery thrombosis OR Cardiac OR Cardiac disease OR Cardiac arrhythmias OR Cardiac death OR Coronary OR Coronary artery calcium OR Coronary heart disease OR Coronary disease OR Coronary artery disease OR Coronary thrombosis OR Coronary syndrome OR Cerebrovascular OR Cerebrovascular disease OR Cerebrovascular accident OR Cerebrovascular disorder OR Cerebral artery infarction OR Cerebral arterial disease OR Endothelium OR Endothelial OR Endothelial dysfunction OR Myocardial OR Myocardial ischemia OR Myocardial infarction OR Myocarditis OR Myocardiopathy OR Myocardial infarct OR Flow mediated dilation OR Pulse wave

velocity OR Pulse wave analysis OR Ischemic heart disease OR Heart OR Heart disease OR Heart attack OR Heart failure OR Heart infarct OR Hypoxia-ischemia OR Hypoxic-ischemic OR Internal carotid artery dissection OR Intracranial embolism and thrombosis OR Stroke OR Subclinical atherosclerosis OR Vascular OR Vascular disease OR Vertebral artery dissection OR Unstable angina OR Unstable coronary OR Peripheral artery disease OR Peripheral arterial disease OR Peripheral vascular disease OR Vascular plaque OR "ACS" OR "AMI" OR "CVD" OR "MI" OR "CHD" OR "CIMT" OR "FMD" OR "PWV" OR "CAC" OR "ABI")

Variations of key concept to be searched for the "the greatest impact of CVD attributable to HIV countries in the Asia Pacific region" domain including (Thailand OR Cambodia OR Myanmar OR Burma OR Bhutan OR Papua New Guinea OR Solomon Islands OR Malaysia OR Indonesia OR Thai OR Cambodian OR Burmese OR Bhutanese OR Papua New Guinean OR Solomon islander OR Malaysian OR Indonesian).

Participant or population: Adult people living with HIV who were aged ≥ 18 years in the Asia Pacific region, and focused only on the counties with the greatest impact of CVD attributable to HIV infection including Bhutan, Cambodia, Indonesia, Malaysia, Myanmar, Papua New Guinea, Solomon Islands, and Thailand in the HAART era since 2005.

Intervention: This is an systematic review among observational study, the exposure of interest are risk factors of CVD including HIV-specific and traditional risk factors.

Comparator: There was no comparator in this study.

Study designs to be included: Any observational study designs, including cross-sectional study, cohort study, and case-control study.

Eligibility criteria: We included all identified articles through database searching under the search strategy and excluded studies

that 1) duplicated, 2) not published in English, 3) published before HAART era (year 2005), 4) conducted on other setting, 5) was a conference abstract article, 6) was a Case report/Case series study, 7) was a randomized controlled trial study, 8) was a review study, 9) conducted among PLHIV but was not measured any cardiovascular variable, 10) study on cardiovascular variable but was not conducted among PLHIV, 11) non-relevant studies including study that was not conducted among PLHIV and was not measured any cardiovascular variable, 12) non-human studies, 13) non-living PLHIV, 14) conducted among non-adult population (ages <18 years), and 15) cardiovascular disease was not the main outcome.

Information sources: This systematic review was performed in an attempt to retrieve epidemiological studies of CVD among PLHIV in the greatest impact of CVD attributable to HIV countries in the Asia Pacific region from the following sources: • MEDLINE via PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) • Embase (<https://www.embase.com>) • the Cochrane Database of Systematic Reviews (<https://www.cochranelibrary.com>).

Main outcome(s): Cardiovascular disease (CVD) means atherosclerotic cardiovascular diseases that develop from atherosclerosis that reported on the selected studies.

CVD in this study including "Acute coronary syndrome OR Arterial OR Arterial stiffness OR Ankle brachial index OR Atherosclerosis OR Atherosclerotic OR Acute angina OR Acute coronary OR Angina OR Angina pectoris OR Ischemia OR Ischaemia OR Ischemic OR Ischaemic OR Infarction OR Infarct OR Brain ischemia OR Brain infarction OR Basal ganglia cerebrovascular disease OR Cardiovascular disease OR Cardiovascular OR Cardiovascular event OR Cardiovascular system OR Cardiovascular disorder OR Cardiovascular mortality OR Cardiovascular death OR Cardiovascular outcome OR Cardiomyopathy OR Carotid OR Carotid intima-media thickness OR Carotid stiffness OR Carotid artery disease

OR Artery OR Carotid artery thrombosis OR Cardiac OR Cardiac disease OR Cardiac arrhythmias OR Cardiac death OR Coronary OR Coronary artery calcium OR Coronary heart disease OR Coronary disease OR Coronary artery disease OR Coronary thrombosis OR Coronary syndrome OR Cerebrovascular OR Cerebrovascular disease OR Cerebrovascular accident OR Cerebrovascular disorder OR Cerebral artery infarction OR Cerebral arterial disease OR Endothelium OR Endothelial OR Endothelial dysfunction OR Myocardial OR Myocardial ischemia OR Myocardial infarction OR Myocarditis OR Myocardiopathy OR Myocardial infarct OR Flow mediated dilation OR Pulse wave velocity OR Pulse wave analysis OR Ischemic heart disease OR Heart OR Heart disease OR Heart attack OR Heart failure OR Heart infarct OR Hypoxia-ischemia OR Hypoxic-ischemic OR Internal carotid artery dissection OR Intracranial embolism and thrombosis OR Stroke OR Subclinical atherosclerosis OR Vascular OR Vascular disease OR Vertebral artery dissection OR Unstable angina OR Unstable coronary OR Peripheral artery disease OR Peripheral arterial disease OR Peripheral vascular disease OR Vascular plaque OR "ACS" OR "AMI" OR "CVD" OR "MI" OR "CHD" OR "CIMT" OR "FMD" OR "PWV" OR "CAC" OR "ABI" "

Data management: EndNote X8 (Clarivate Analytics, PA, USA) was used to collect, deduplicate, manage and review the searched articles. The data extraction and critical appraisal were conducted by the first author (WR). The second author (MT) independently checked all the results and discussed. In case of disagreement, the third author (NA) arbitrated.

Quality assessment / Risk of bias analysis: The relevant articles were critically appraised for quality based on the study design, using the Newcastle-Ottawa scale (N-O scale) to assess the quality of cohort studies, case-control studies, and cross-sectional studies included in a systematic review. The tool comprises three domains to assess the quality of the study including

participant selection, comparability and exposure/outcome assessment in the selected studies. Criteria for converting the Newcastle-Ottawa scales to AHRQ standards including 1) Good quality means the study have 3 or 4 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain, 2) Fair quality means the study have 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain, and 3) Poor quality means the study have 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Strategy of data synthesis: Data were extracted on publication date, study area (country), study design, study period, sample size, CVD outcomes and measurements, incidence or prevalence of CVD outcomes among PLHIV and risk factors for CVD. The results of the selected studies were summarized and described depend on the group of the results, including the situation of CVD among PLHIV in the Asia-Pacific Region, Traditional risk factors for CVD among PLHIV, and HIV-specific risk factors for CVD.

Subgroup analysis: Subgroup analysis was not conducted in this study.

Sensitivity analysis: Sensitivity analysis was not conducted in this study.

Language restriction: English.

Country(ies) involved: Thailand.

Keywords: Cardiovascular diseases, cerebrovascular diseases, HIV, HAART, Asia.

Contributions of each author:

Author 1 - Witchakorn Ruamtawee - WR initiated the study issue, conducted the study, analyzed data and drafted the manuscript. All authors read and approved the final submitted version of the manuscript.

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