INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Risk Factors and National Burden of Selected Noncommunicable Diseases in People Living with HIV: Systematic Review, Meta-Analysis and, Disability-Adjusted Life Years protocol

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Review question / Objective: **1. Are the prevalence/incidence of four major groups of NCDs including MetS, DM, CVD, and CKD different among adults with and without HIV infection? 2. Are there relationships between HIV status, ART (ART use, short and long-term effects of ART), traditional risk factors (BMI), and the development of four major NCDs? 3. Does the trend of NCDs burden attributable to HIV in Thailand increase according to the time?**
Information sources: **1. Electronic databases: the following databases will be searched: PubMed/Medline, Scopus, Embase, Cochrane Library Thai journals online (ThaiJO), Thai digital collection (TDC), Thai journal index (TJI), and Thai-journal citation index (TCI). 2. Authors or experts in the field will be contacted through emails for any relevant data, results and information.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 September 2022 and was last updated on 04 September 2022 (registration number INPLASY202290018).

INTRODUCTION

Review question / Objective: **1. Are the prevalence/incidence of four major groups of NCDs including MetS, DM, CVD, and CKD different among adults with and without HIV infection? 2. Are there relationships between HIV status, ART (ART use, short and long-term effects of ART), traditional risk factors (BMI), and the development of four major NCDs? 3. Does the trend of NCDs burden attributable to**

HIV in Thailand increase according to the time?

Rationale: Over the last decade, there has been a growing body of evidence linking HIV to Metabolic syndrome (MetS) and its major outcomes like diabetes mellitus (DM), cardiovascular diseases (CVD), and chronic kidney disease (CKD). The forecasting models between 2030 and 2035 in high-income countries reported that over 80% of people living with HIV/AIDS (PLWHA) will be diagnosed with at least one noncommunicable disease (NCD); the most common NCDs are DM and CVD. Likewise, the modeling study in lower-middle income country found that the proportion of PLWHA diagnosed with at least one NCD between 2015 and 2035 is expected to rise by about 30%; the most prevalent NCDs are HT and CKD.

The development of MetS and its major outcomes is caused by the complex interplay of various variables such as HIV status, HIV-related factors, antiretroviral therapy (ART), and traditional risk factors. However, the effect of some factors including HIV status, use of ART, short and long-term effects of ART as well as traditional risk factors like body mass index (BMI) is still inconclusive due to conflicting evidence from previous studies. Therefore, it is needed to assemble the results to come up with a single valid estimate of the population effect size or pool the summary effect from different selected studies in order to estimate a common effect size of these factors.

Three hypotheses for an excess of NCDs among PLWHA have been reported. First, HIV causes persistent immune activation, chronic inflammation, and excessive production of inflammatory cytokines which are linked to an increased risk of metabolic complications, organ damage, and all-cause mortality. Second, side effects of ART, especially metabolic complications may contribute to organ damage. Third, PLWHA typically have traditional risk factors for NCDs similar to the general populations such as age, gender, tobacco use, harmful use of alcohol, as well as BMI which can reflect dietary and exercise habits. These three hypothetic factors are all the drivers that cause MetS in PLWHA. MetS is a strong predictor of type 2 DM and CVD. Among the components of MetS, glucose intolerance and HT are typically associated with decline in kidney function leading to increased risk of developing CKD. Higher risk of NCDs among PLWHA may proportionally attribute to NCD burdens in high epidemic of HIV countries.

Thailand is a middle-income country with a high burden of HIV and NCDs. While NCDs were estimated to be responsible for 74% of all deaths in the Thai population, HIV prevalence in Thailand accounted for 9% of the total PLWHA in the Asia and the Pacific region. Thailand's HIV/AIDS expenditures totaled over 8000 million baths, equivalent to 1.87% of total health expenditures and 0.07% of the country's GDP. Several observational studies demonstrated high burdens of NCDs among Thai PLWHA. The overall prevalence of MetS was approximately 22%. The incidence of DM ranged from 5 to 11 per 1000 person-years. The incidence rates of organ damage like CVD and CKD were approximately 4 and 10 per 1000 person-years, respectively. In a country with a high epidemic of HIV and NCDs as Thailand, understanding attributable risks of HIV and its burdens on NCDs can provide significant information for policy maker. Disability-adjusted life years (DALYs), a summary measure of total health loss can be used to estimate both years of life lost and lived with disability. Risk-attributable DALYs is the share of DALYs that can be estimated to occur due to a specific risk factor. Therefore, the estimation of the NCDs burden in terms of DALYs attributable to HIV is required for better explaining NCDs burden associated with HIV in Thai PLWHA.

Condition being studied: The condition being studied are noncommunicable diseases in people living with HIV/AIDS; which consists of 4 major outcomes including metabolic syndrome (MetS), diabetes (DM), cardiovascular disease (CVD), and chronic kidney disease (CKD). 1. MetS: MetS is specified as the cluster of interrelated risk factors including glucose intolerance, hypertension (HT),

dyslipidaemia (DLP) and obesity. The diagnostic criteria for identifying MetS for this study include NCEP/ATP III criteria (the National Cholesterol Education Program's Adult Treatment Panel III), IDF criteria (International Diabetes Federation), EGIR criteria (European Group for Study of Insulin Resistance), WHO criteria 2. DM: the diagnostic criteria for identifying DM for this study include Expert Committee on the Diagnosis and Classification of Diabetes mellitus, ADA (the American Diabetes Association), WHO criteria, NCEP criteria, and IDF criteria 3. CVD: CVD includes coronary artery diseases such as angina and myocardial infarction (commonly known as a heart attack). Other CVDs include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous thrombosis or identifying CVD cases by ICD9 or ICD10. 4. CKD: CKD at least stage III is defined as two consecutives (>6 months apart) eGFR of 60 ml/min per 1.73 m2 or less. GFR can be estimated from calibrated serum creatinine and estimating equations, such as MDRD the Modification of Diet in Renal Disease), CKD-EPI (the chronic kidney disease-Epidemiology Collaboration), or the Cockcroft-Gault formula.

METHODS

Search strategy: Source of information and search strategies - This review will be guided and written by the Preferred Reporting Item for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2020 statement. The same searching terms will be applied in all databases. This will be developed according to PICO format: Patients, Intervention, Comparator and Outcomes. The search will be updated every 3 months during the review.

1. Electronic search: the following databases will be searched: PubMed/ Medline, Scopus, Embase, EBSCO, Thai journals online (ThaiJO), Thai digital collection (TDC), Thai journal index (TJI), and Thai-journal citation index (TCI).
2. Reference lists search: the reference lists of relevant material will be searched to identify additional studies of interest.
3. Authors or experts in the field will be contacted through emails for any relevant data, results and information.
4. Search management: the records of retrieved articles will be managed using EndNote Reference Manager X8. The included and excluded studies at each screening stage will be collected in different files.

Study screening and selection

The screening criteria checklists will involve three levels including tittle, abstract and full article screening. The checklist will be developed using Google forms and tested for applicability and reliability to select relevant studies. The selected articles will be screened by two authors to identify those reporting prevalence/ incidence, OR/RR of HIV status, HIV-related factors, ART use and traditional risk factors of four major NCDs among adults with and without HIV infection. In case of disagreement, the issues will be discussed with the third reviewer. For studies reporting prevalence/incidences of NCDs, their risk factors and those met the study inclusion criteria, the full-text will be reviewed to collect pertinent data. Studies with statistically robust methods, such as standardized and unbiased data collection with adequate sample size, will be included to ensure reproducibility and precision. The reasons for exclusion at all stages will be documented. For Screening agreement and disagreement, screening will establish the inter-rater reliability using Cohen's kappa coefficient, and disagreement will be resolved through consultation of the study coordinator if necessary.

Participant or population: Studies participants: this study focuses on adults with and without HIV infection age 15 years and older regardless of their ethnic background. The cut-off value of age was defined according to WHO case definitions of HIV for reporting and surveillance.

Intervention: HIV-infected patients treated with antiretroviral therapy.

Comparator: 1. HIV-infected patients and HIV-uninfected individuals 2. HIV-infected patients treated with antiretroviral therapy and untreated HIV patients/naive patients.

Study designs to be included: Study design: this review and meta-analysis will include observational studies such as cross-sectional, case-control and cohort studies. This review will include studies regardless of which regions they were conducted in.

Eligibility criteria: Eligibility criteria (inclusion and exclusion)Inclusion criteria. The review will include studies on the prevalence/incidence of four major NCDs including MetS, DM, CVD and CKD as well as those reporting OR/RR of HIV status, HIV-related factors, antiretroviral therapy (ART) use and traditional risk factors of four major NCDs among adults with and without HIV infection. The following factors will apply:1. Study design: this review and meta-analysis will include observational studies such as cross-sectional, case-control and cohort studies. This review will include studies regardless of which regions they were conducted in.2. Studies participants: this study focuses on adults with and without HIV infection age 15 years and older regardless of their ethnic background. The cut-off value of age was defined according to WHO case definitions of HIV for reporting and surveillance.3. Study outcome definition: the diagnosis criteria for MetS, DM, CVD and CKD 4. Time-period: the time frame for searching published studies is from January 1, 2000 to June 30, 2022. The studies carried out between 1996 and 2022 (or the Highly Active Antiretroviral Therapy/HAART era) will be included, considering changes in the definition of NCDs over this period.5. Study setting: community or population-based settings, health facilities setting within rural or urban areas of all countries will be included.6. Study languages: all studies reported in English and Thai will be considered.7. HIV status: studies considering the outcomes for PLWHA who are on ART and/or are treatment-naïve, as well as those relating to HIV-uninfected people will be included. Exclusion criteriaThe following factors will apply:1. Studies with no full text available2. Studies lacking prevalence/incidence, OR/RR of HIV status, HIV-related factors, ART use and traditional risk factors of four major NCDs and data to compute after consultation with the author.3. Duplicate publication from the same studies will be excluded. Studies provided data on the same cohort at extend follow-up time points, in such cases, the published study with the longest follow-up period will be selected.

Information sources: 1. Electronic databases: the following databases will be searched: PubMed/Medline, Scopus, Embase, Cochrane Library Thai journals online (ThaiJO), Thai digital collection (TDC), Thai journal index (TJI), and Thai-journal citation index (TCI). 2. Authors or experts in the field will be contacted through emails for any relevant data, results and information.

Main outcome(s): 1. Metabolic syndrome (MetS): MetS is specified as the cluster of interrelated risk factors including glucose intolerance, hypertension (HT), dyslipidaemia (DLP) and obesity. The diagnostic criteria for identifying MetS for this study include NCEP/ATP III criteria (the National Cholesterol Education Program's Adult Treatment Panel III), IDF criteria (International Diabetes Federation), EGIR criteria (European Group for Study of Insulin Resistance), WHO criteria
2. Diabetes (DM): the diagnostic criteria for identifying DM for this study include Expert Committee on the Diagnosis and Classification of Diabetes mellitus, ADA (the American Diabetes Association), WHO criteria, NCEP criteria, and IDF criteria
3. Cardiovascular disease (CVD): CVD includes coronary artery diseases such as angina and myocardial infarction (commonly known as a heart attack). Other CVDs include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, venous

thrombosis or identifying CVD cases by ICD9 or ICD10.
4. Chronic Kidney disease (CKD): CKD at least stage III is defined as two consecutives (>6 months apart) eGFR of 60 ml/min per 1.73 m2 or less. GFR can be estimated from calibrated serum creatinine and estimating equations, such as MDRD the Modification of Diet in Renal Disease), CKD-EPI (the chronic kidney disease-Epidemiology Collaboration), or the Cockcroft-Gault formula.

Additional outcome(s): 1. The relationships (pooled OR/RR) between HIV status, antiretroviral therapy/ART (ART use, short and long-term effect of ART), traditional risk factors (body mass index/BMI), and the development of four major NCDs (metabolic syndrome, diabetes, cardiovascular and chronic kidney disease). The pooled RR of HIV from the process of meta-analysis in this study will be use for estimating noncommunicable diseases in Thai people living with HIV (as described in additional outcomes 2 and 3)
2. Estimation of noncommunicable disease/NCDs burden attributable to HIV in Thailand
The pooled RR of HIV for DM, CVD and CKD (from meta-analysis), HIV prevalence (from Asia epidemic model 1996-2017), and national Disability-adjusted life years/ DALYs estimates for DM, CVD and CKD (form the Institute of Health Metrics and Evaluation 1996-2017) will be used to estimate the NCDs burden attributable to HIV in Thailand during 1996-2017.
- First, the population attributable fraction (PAF) attributable to HIV for each disease will be estimate as: PAF= (HIV prevalence×(pooled RR-1))/(1+(HIV prevalence×pooled RR))
- Second, the DALYs attributable to HIV for each disease will be estimated during 1996-2017 as: DALYs attributable to HIV=each NCD DALYs×PAF
3. Forecasting the DALYs attributable to HIV in Thailand beyond 2017
Auto-Regressive Integrated Moving Average (ARIMA) model will be applied to forecast the DALYs attributable to HIV for DM, CVD and CKD from 2018 to 2030.

Data management: The records of retrieved articles will be managed using EndNote Reference Manager X8. The included and excluded studies at each screening stage will be collected in different files. The screening criteria checklists will involve three levels including tittle, abstract and full article screening. The checklist will be developed using Google forms and tested for applicability and reliability to select relevant studies. The selected articles will be screened by two authors to identify those reporting prevalence/incidence, OR/ RR of HIV status, HIV-related factors, ART use and traditional risk factors of four major NCDs among adults with and without HIV infection. In case of disagreement, the issues will be discussed with the third reviewer. For studies reporting prevalence/ incidences of NCDs, their risk factors and those met the study inclusion criteria, the full-text will be reviewed to collect pertinent data. Studies with statistically robust methods, such as standardized and unbiased data collection with adequate sample size, will be included to ensure reproducibility and precision. The reasons for exclusion at all stages will be documented. For Screening agreement and disagreement, screening will establish the inter-rater reliability using Cohen's kappa coefficient, and disagreement will be resolved through consultation of the study coordinator if necessary. The data extraction and entry will be performed independently by two reviewers to establish an inter-rater reliability and avoid data entry error. In case of disagreement, the issue will be discussed with the third reviewer. The following data items will be extracted:
1. Publication details: authors, name, year of publication, journal, year(s) of study
2. Study characteristics and setting: study site, country setting, study design, sample size, length of study follow-up.
3. Study target population: HIV-positive and/or HIV-negative participants.
4. Study participant's characteristics: mean age, proportion of gender, HIV status, proportion of those on ART and ART-naïve.
5. Study outcomes: MetS, DM, CVD and CKD

6. Determinants of four major outcomes: HIV status, HIV-related factors, ART use and traditional risk factors.
7. Gaps, limitation, strengths and summary of the studies.

Quality assessment / Risk of bias analysis: The quality assessment will be conducted by two reviewers using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) framework which is often used to measure the quality of cohort, case-control and cross-sectional studies. The STROBE consists of 22 items related to title and abstract, introduction (background/rationale, objectives), methods (study design, setting, participants, variables, data source/ measurement, bias, study size, quantitative variables, statistical methods), results (participants, descriptive data, outcome data, main results, other analysis), discussion (key results, limitations, interpretation, generalizability), other information (funding). Each STROBE item will be categorized as 'yes' (meet criteria), 'no' (not meet criteria) or 'not applicable'. The Completeness of reporting (COR) score for each article will be calculated as COR score (%) = yes / (yes + no) ×100. The quality of the reviewed studies will be scored on a scale from 0% (lowest possible quality) to 100% (highest possible quality). The quality and risk of bias assessment will be presented as part of the table of characteristics of the included studies. The inter-rater agreement will be calculated using the proportion of agreement and kappa statistics.

Strategy of data synthesis: The data will be systematically described, analyzed and summarized to answer the three research questions. 1. Meta-analysis - The pooled estimates of prevalence/incidence and risk ratio of four major NCDs will be calculated in which there are at least two individual studies. Before undertaking meta-analysis, the effect sizes of all selected studies will be converted to one single effect measure with the same unit of measurement. A series of meta-analysis will be performed based on similar comparator groups among studies. The pooled effect sizes of four major NCDs will be estimated among: 1) PLWHA compared with HIV-uninfected people; 2) PLWHA who were treated with ART compared with treatment-naïve PLWHA; 3) difference of specific ART regimens and treatment duration; 4) BMI cut-off levels including underweight, normal, overweight and obese. The risk estimates will be extracted from the selected studies from either logistic regression or Cox proportional hazard model with reported confidence interval. This analysis will use estimates where the risk was already adjusted for confounding factors such as age, gender, race, lifestyle factors, the other HIV-related factors and comorbidities. The rationale to pool RRs from logistic and Cox regressions will be based on the investigation of D'Agostino et al. The prevalence/incidence and risk will be pooled according to appropriate methods. The heterogeneity tests will be used to determine whether to use a fixed-effect model or a random-effect model when pooling data. Cochrane Q test and I2 test are the methods to assess inconsistency in meta-analysis. If there is no observed heterogeneity (p-value of Cochrane Q test greater than 0.1 and I2 smaller than 25%), a fixed-effect model with inverse variance method will be used. In contrast, if p-value of Cochrane Q test is less than 0.1 and I2 greater than 25%, a random-effects model with the method of DerSimonian and Laird will be applied. Secondary analyses will be conducted using meta-regression and subgroup analysis. Meta-regression will be performed to explore covariates that may account for heterogeneity between studies estimates of the effect of identified risk factors on NCDs. Potential explanatory covariates considered are age, study design, study period, duration of follow-up, study size, patient population, geographical location and type of treatment. All statistical tests will be performed using two-tailed p-value ($p<0.05$) except for meta-regression where p-value<0.10 will be considered to detect potential heterogeneity among covariates.
2. Publication bias - Publication bias will be assessed using Funnel plot and Egger's method. The occurrence of publication bias

will be assumed if the funnel plot shows asymmetrical spread of the dots or the p-value of Egger test is less than 0.05.

Subgroup analysis: Secondary analyses will be conducted using meta-regression and subgroup analysis. Meta-regression will be performed to explore covariates that may account for heterogeneity between studies estimates of the effect of identified risk factors on four major outcomes. Potential explanatory covariates considered are age, study design, study period, duration of follow-up, study size, patient population, geographical location and type of treatment. All statistical tests will be performed using two-tailed p-value ($p<0.05$) except for meta-regression where p-value<0.10 will be considered to detect potential heterogeneity among covariates.

Sensitivity analysis: A sensitivity analysis will be performed to assess the robustness of the individual study designs and data set of the observed outcomes. The primary analysis will be repeated with statistical methods, different methods of handing missing data, definition of outcomes and risk of bias (COR score) in order to measure any changes in the estimation.

Language restriction: English and Thai language.

Country(ies) involved: Thailand.

Keywords: HIV, metabolic syndrome, diabetes, cardiovascular disease, chronic kidney disease, antiretroviral therapy, body mass index, DALYs attributable to HIV.

Dissemination plans: The final report and completed manuscript will be published in a peer-review journal. The manuscript will be separated into 2 issues including 1) systematic review and meta-analysis, 2) Estimation and forecasting of noncommunicable diseases/NCDs burden attributable to HIV in Thailand.

Contributions of each author:

Author 1 - Deondara Trachunthong - Author 1 drafted the manuscript, study protocol, and data extraction form, and is responsible for study screening/selection, data extraction and data analysis.
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Author 3 - Worrayot Darasawang - The selected articles will be screened by author1 and 2. In case of disagreement, the issues will be discussed with the Author 3.
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