CHAPTER III

RESEARCH METHODOLOGY

This chapter presents the methodology of this research including material and methods. Our method involve: 1) Searching; 2) Study selection; 3) Data extraction and quality assessment, and; 4) Data analysis. The detail of each topic is described below. In summary, our processes in systematic review and meta-analysis are depicted in Figure 9.

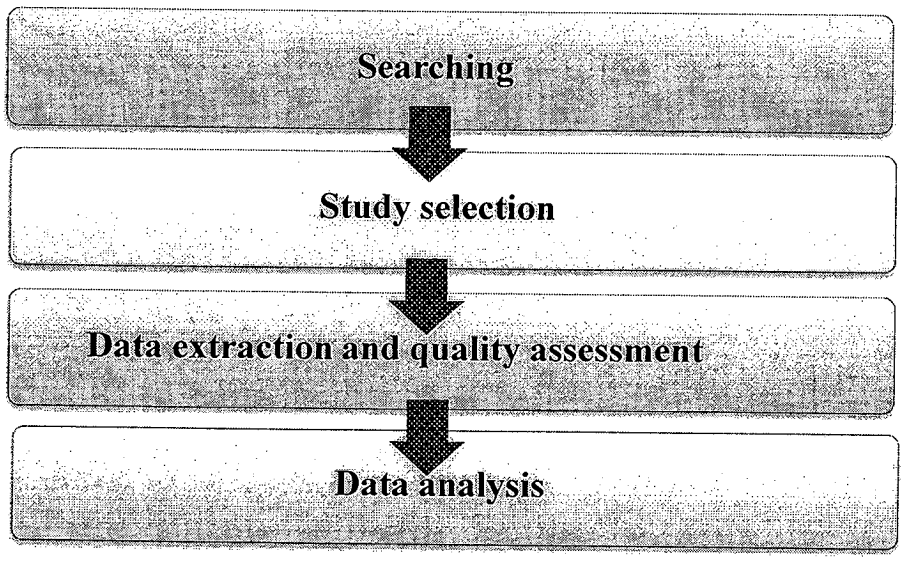

Figure 9 A step approaches in our systematic review and meta-analysis

Identification of studies

A comprehensive and systematic search was performed from the inception of the following databases: PubMed/Medline (U.S. National Library of Medicine), EMBASE (Elsevier B.V.), CINAHL (Cumulative Index to Nursing and Allied Health Literature), IPA (International Pharmaceutical Abstracts), HuGENet (Human Genome Epidemiology Network), Cochrane library and ClinicalTrials.gov using the keywords, synonyms and other terms related to HLA genotypes and anti-HIV drug (abacavir, nevirapine, stavudine).

There was no restriction on language or study design. Only human studies were included. Additional studies were retrieved from reference lists of the selected articles. For search terms used in our study, a list is shown in Table 3.

Table 3 Search terms used for identify relevant studies

Drugs	Search terms
Abacavir	("Human Leukocyte Antigen" OR HLA OR "Human Leukocyte Antigens" OR polymorphism OR genetics OR genotype OR allele OR gene) AND Abacavir AND (Hypersensitivity OR "hypersensitivity reactions" OR "hypersensitivity reaction" OR "drug hypersensitivity" OR allergy or "drug allergy")
Nevirapine	("Human Leukocyte Antigen" OR HLA OR "Human Leukocyte Antigens" OR polymorphism OR genetics OR genotype OR allele OR gene) AND Nevirapine
Stavudine	("Human Leukocyte Antigen" OR HLA OR "Human Leukocyte Antigens" OR polymorphism OR genetics OR genotype OR allele OR gene) AND Stavudine

Appraisal and selection of studies

The inclusion criteria are:

1. A study investigating an association between HLA genotypes and anti-HIV drugs induced ADRs.

2. All patients in both case and control groups received anti-HIV drugs before an HLA genotype screening.

The exclusion criteria are:

A study does not provide sufficient information for a subsequent statistical analysis.

Data extraction and quality assessment

Important information [i.e. a study design, an eligibility criteria, a diagnostic criteria for selected cases and controls, a method used to diagnose ADRs (e.g., immunological assay or clinical presentation), patient demographics, dose and duration of exposure to the anti-HIV drugs, CD4+ status and the HLA genotyping technique] were extracted and systematically tabulated into a designed table. (see Appendix A-B).

The Newcastle-Ottawa scale [24] (see Appendix C) was used to assess the quality of the case control and cohort studies. Three quality domains including selection, comparability, and outcome or exposure were taken into consideration, depending on the study design [57]. To assess the quality of randomized control studies (RCT), the risk of bias (ROB) (see Appendix D) was employed. Assessing the ROB involves 6 components including sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias [58]. For cross-sectional study, Downs and Black checklist (see Appendix E), a tool developed for evaluating the quality of randomized and non-randomized studies, was employed to assess the quality of the included studies. This checklist consists of 5 quality domains/27 items [reporting (n=10), external validity (n=3), internal validity bias (n=7), internal validity confounding (n=6), and power (n=1)] [59].

Data analyses

Systematic review

The previous studies demonstrating the association between HLA genotypes and anti-HIV drugs induced ADR(s) was characterized and summarized based on the most updated data.

Meta-analysis

Meta-analysis was performed when there are data of the same HLA genotypes, types of ADR(s), and the anti-HIV drug from two or more separate studies.

The overall odds ratios (ORs) with corresponding 95% confidence intervals (95%CIs) were calculated to determine the association between the presence of HLA genotypes and the anti-HIV drugs induced ADRs. All analyses were performed using the DerSimonian and Laird method under a random-effects model [60] (see Appendix

F). For studies with different study design, analyses were conducted separately. Statistical heterogeneity was assessed via the Q-statistics and I-squared tests. A p-value of ≤ 0.10 indicates heterogeneity between studies [61]. I-squared values of 25%, 50%, 75% denote a low, moderate, and high of heterogeneity across studies, respectively [62]. A funnel plot, Begg's test, and Egger's test was used to evaluate publication bias [63, 64]. If the publication bias is identified, the trim-and-fill method was employed to correct for this bias [65]. Subgroup analyses (e.g., study design, ethnicity, and diagnostic method) were conducted to explore potential sources of heterogeneity. All statistical analyses were performed using the STATA software version 11.0 (StataCorp., College Station, TX, USA).