CHAPTER I

INTRODUCTION

Statement of purpose

The use of antiretroviral therapy significantly decreases the mortality and morbidity rates in HIV-infected patients over the past two decades [1, 2, 3]. However, response to these drugs is a complex phenomenon and often limited by drug resistance, drug adherence and adverse drug reactions (ADR). Several ADRs caused by anti-HIV agents such as hypersensitivity reactions (HSRs) (3-50%), lipoatrophy and lipodystrophy (59%), hepatotoxicity (2-18%), and neuropathy (20-57%) vary among different populations, suggesting an involvement of genetic predisposition [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. The relationships between the risk of these adverse effects and some genotypes, particularly the polymorphic human leukocyte antigen (HLA) genotypes, have been established [14, 15, 16]. For example, there is a strong relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in some Asian populations (i.e., Han Chinese, Thai and Malaysian) [17, 18, 19, 20]. Similarly, individuals who inherit HLA-B*5801 allele also displays a high incidence of SJS/TEN after taking allopurinol [21]. These findings lead to the use of HLA genotyping as a diagnostic and/or predictive test to prevent the serious ADRs [22].

The ADRs induced by certain anti-HIV drugs such as abacavir, nevirapine, and stavudine may also be associated with some HLA genotypes as shown in recent studies [23, 24, 25, 26, 27, 28, 29, 30, 31]. The relationships between stavudine-induced facial lipoatrophy and HLA-A*4001 in Thai populations [23], nevirapine-induced cutaneous reactions (e.g., rash, SJS and TEN) and HLA-B*3505 and HLA-C*4101 [24,25], and abacavir-induced HSRs (e.g., renal or hepatic failure, fever, rash, nausea, vomiting) and HLA-B*5701 [26, 27, 28] have been reported. However, these associations remain inconsistent. For example, although the association between HLA-B*5701 and HSRs caused by abacavir is generally accepted, however, reported odds ratio across populations demonstrated high variability [29, 31, 32, 33]. Moreover,

small and variant populations as well as different diagnostic methods for HSRs were used among these studies [29,31, 32, 33]. To combine and analyze these findings, meta-analytic technique is frequently used. This systematic approach can increase power, improve precision and elucidate potential similarities and differences that would explain the findings from relevant studies.

Objectives of the study

1. Systematically review all relevant studies and quantitatively assess the magnitude of the association between certain HLA genotypes and ADRs induced by abacavir, nevirapine and stavudine.

2. To determine the association of HLA-B*5701 genotype and abacavir induced HSR

3. To determine the association of HLA-Cw*04 genotype and nevirapine-induced skin reaction

4. To determine the association of HLA-Cw*08 genotype and nevirapine-induced HSR

5. To determine the association of HLA-B*4001 genotype and stavudine-induced lipodystrophy

Hypothesis of the study

1. There is an association(s) between certain HLA genotypes and the anti-HIV drugs induced ADRs.

2. The differences in association between HLA genotypes and the anti-HIV drugs induced ADRs among relevant studies are resulted from different studied populations and/or diagnostic methods.

Scope of research

To determine the association between HLA genotypes and the anti-HIV drugs induced ADRs:

1. Anti-HIV drugs include abacavir, nevirapine and stavudine.
2. Type of ADRs and HLA genotypes are not restricted.

3. Published, peer-reviewed, original research articles from 6 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), and Cochrane library] will be included in this study. Additional studies will be retrieved from reference lists of the selected articles.

Expected outcomes

1. The association between HLA genotypes and abacavir, nevirapine and stavudine induced ADRs will be systematically determined and analyzed based on the most updated data from the databases.

2. The results of this study can be applicable in public health policy and/or physicians for support the implementation of genetic testing before initiation of abacavir, nevirapine and stavudine therapy in a high risk population.