



Integrating HIV-1 Pharmacogenomics into the Universal Coverage Health-Care System in Thailand: From Scientific Evidence to Policy

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Abstract

In addition to the direct effect adverse drug reactions (ADRs) have on increased morbidity and mortality, their indirect impact on antiretroviral adherence and subsequent drug resistance is a major problem for HIV health services in a resource-limited setting. ADR is a major factor contributing to the interruption of antiretroviral intake in patients with good adherence to highly active antiretroviral therapy (ART). Antiretroviral non-adherence results in viral drug resistance, which derails antiretroviral effectiveness and causes higher costs for complicated treatment regimens; a burden that is more significant in resource-limited countries. Moreover, the costlier second-line treatment regimens (2-9 times higher in price than first-line regimens) are unaffordable for individual or government agencies in developing countries. This situation forms the basis for development of a pharmacogenomics initiative in Thailand, with special focus on HIV. The first target is to improve the prescription algorithm by personalizing the initial drug regimen; increasing the regimens efficacy; and simultaneously avoiding ADR. The ultimate aim of this initiative is to minimize the cost of ART for the public health system by incorporating research findings. Integrating HIV-1 pharmacogenetic screening tests into Thailand's universal health-care system is a major challenge for the future and, if successfully implemented, they will eventually benefit both individuals and society.

Introduction

Adverse drug reactions (ADRs) cause more than 2.2 million hospital cases of serious illness, including 100,000 deaths per year in the U.S.A., thus making ADRs one of the leading causes of hospitalization and death in that country [1]. Currently, pharmacogenomics research enables study of variations in genes that dictate drug response, and exploration on the ways these variations are used to predict patient reaction to drugs, whether good, bad or none at all [2]. In some instances, these predictive markers can be developed into a pharmacogenetic screening test [3].

In the developing world, however, critics believe that the cost of these tests will be prohibitive for national implementation in the universal health-care coverage scheme. Better environmental conditions are more practical in improving population health [4]. Despite the promise that personalized medicine should be delivered to the patients, it is rarely discussed in developing countries if the technology is not economically feasible [5-7]. Research and development of pharmacogenomics can benefit from developing countries like Thailand, with the high prevalence of endemic diseases, lower cost of clinical research and pool of talented young biomedical researchers [5,8]. In Taiwan, the universal health program has already provided reimbursement of HLA-B*1502 for personalized carbamazepine [9-11]. It seems reasonable to assume that understanding and utilizing genomic variation (single nucleotide polymorphisms (SNPs), gene duplication and deletion, mutations in regulatory genes and large-scale copy number variation) in developing world populations would help to improve the efficiency of medication use in a resource-limited setting, and potentially develop therapeutics that meet with local health needs [12].

Regarding antiretroviral therapy (ART) in a resource-limited setting, most patented drugs are not an affordable option for the masses, as governments do not have sufficient financial resources to fund them, and by and large their citizens do not have the ability to pay

[13]. Therefore, many resource-limited countries, including Thailand, have planned to integrate genomic medicine into their health-care system in the hope that pharmacogenomics research will cut costs through selective use of safe and efficacious drugs [8,14-16]. Moreover, undersized markets in developing countries leave little incentive for multinational corporations to ensure that therapeutics achieve a good response rate with few adverse effects within a low-income population [6]. Therefore, high quality generic drugs at a lower price are the preferred option in a universal health-care system [17].

A high rate of adverse reaction has been observed in some drugs in Thailand, including nevirapine, allopurinol, carbamazepine, stavudine, abacavir, and efavirenz. These drugs are usually not the first choice for their indications in developed countries, due to their unfavorable ADR profiles (Table 1). On the contrary, these off-patent drugs have been widely used in resource-limited countries, including Thailand, due to their affordable price. However, patients in both these areas are exposed to the risk of developing ADRs (Table 1). In addition to ADR related morbidity and mortality, chronic HIV infection is of

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great concern, as resulting ADRs will eventually drive selection against the drug resistant virus [18]; thus limiting the patient access to ART. Missing only two doses of antiretroviral drugs can result in increased levels of viral resistance [19,20], thus derailing their effectiveness and causing treatment failure, as well as wasting financial resources, which are quite limited in developing countries. ADRs account for 11% to 35% of non-adherence to therapy [21-24]. In the U.S.A., ADRs affected 38% of HIV-1 treated outpatients and were a major cause of modified ART. In an approximately 3-year period, most patients (almost 70%) required modification/interruption of antiretroviral drug treatment, due to ADRs [25]. To minimize ADRs in antiretroviral treatment, Thai HIV-1 pharmacogenomics research has been conducted in order to develop an affordable pharmacogenetic screening test.

Universal health-care policy in Thailand

One of Thailand's distinguishing features in the public health delivery system is its universal health-care coverage policy, which provides universal access to necessary diagnostics, medication and treatment for all Thai citizens including those on a low income. Ninety-five percent of the Thai population has some sort of health care insurance, and 72% of them can access treatment through the Universal Health Coverage (UC) scheme [26]. The Thai UC aims at securing access to essential medicines, but it faces similar obstacles to other universal health-care schemes, in that financial resources are usually limited, and scheme managers face the dilemma of eyeing expenditure on services yielding the highest likelihood of achieving health benefit, for example, ART. HIV-1/AIDS is the leading cause of disability adjusted life year (DALYs) in Thailand (Table 2). Based on data acquired by the Thai Ministry of Public Health (Thai MOPH), 1 million people have been

infected with HIV-1 since 1994, and 641,633 have died. There are 499,324 people living with HIV-1, and 139,690 of those are on ART [27]. Without receiving antiretroviral drugs, people infected with HIV-1 live for an average of 7.8 years [28]. A remarkable event happened on World AIDS Day in 2004, when the Thai government adopted ART in its Universal Health-Care System [29]. The scheme cost the Thai government 3.8 billion Baht (approximately \$117 million) in 2007, and that expense has increased gradually each year since [30]. The authors set an ambitious aim to incorporate pharmacogenomics findings into the prescription systems in order to reduce the overall cost for the service providers in resource-limited countries, such as Thailand.

Research and development of pharmacogenomics in Thailand

Establishment of the Thailand Center of Excellence for Life Sciences (TCELS), which initiated the Thai Pharmacogenomics Project in June 2004 by Royal Decree from His Majesty the King of Thailand, started with an initial investment of 120 million Baht (approximately \$3.9 million) from the Thai government [31]. Researchers from the TCELS Pharmacogenomics Project are focusing on ADRs that are common in Thai patients. The TCELS has emphasized the value of conducting research for local benefit [32].

The TCELS Pharmacogenomics Project has collected 4,000 samples from patient populations and healthy Thais in six pharmacogenomics projects: an HIV pharmacogenomics project; adverse skin reactions to allopurinol and carbamazepine; pharmacogenomics in acute childhood lymphoblastic leukemia; pharmacogenomics of oncology-chemotherapy (fluorouracil, 5-FU); study of aspirin responsiveness; and pharmacogenomics of thalassemia-haemoglobin E [33].

| Generic name | Indication | ADRs | Pharmacogenomic test | Reference |
|---------------|---|-------------------------------------|----------------------|------------|
| Nevirapine | HIV-1 infection and AIDS | SJS/TEN | HLA-B*3505 | [36] |
| Efavirenz | HIV-1 infection and AIDS | Central nervous system side-effects | CYP2B6 | [44,45,71] |
| Abacavir | HIV-1 infection and AIDS | Hypersensitivity | HLA-B*5701 | [90] |
| Stavudine | HIV-1 infection and AIDS | Lipodystrophy | HLA-B*4001 | [39] |
| Allopurinol | Hyperuricemia and chronic gout | SJS/TEN | HLA-B*5801 | [78,91] |
| Carbamazepine | Epilepsy seizures, bipolar disorder, and mood stabilizing | SJS/TEN | HLA-B*1502 | [79,92,93] |

ADRs, adverse drug reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; HLA, human leukocyte antigen; CYP, cytochrome P450.

Table 1: Selected adverse drug reactions and their pharmacogenomic markers.

| Rank | Disease category | Male DALYs | % | Diseases category | Female DALYs | % |
|------|--------------------------------|------------|----|------------------------------------|--------------|---|
| 1 | HIV/AIDS | 960,087 | 17 | HIV/AIDS | 372,947 | 9 |
| 2 | Traffic accidents | 510,907 | 9 | Stoke | 280,673 | 7 |
| 3 | Stoke | 267,567 | 5 | Diabetes | 267,158 | 7 |
| 4 | Liver cancer | 248,083 | 4 | Depression | 145,336 | 4 |
| 5 | Diabetes | 168,372 | 3 | Liver cancer | 118,384 | 3 |
| 6 | Ischaemic heart disease | 164,094 | 3 | Osteoarthritis | 117,994 | 3 |
| 7 | COPD (emphysema) | 156,861 | 3 | Traffic accidents | 114,963 | 3 |
| 8 | Homicide and violence | 156,371 | 3 | Anaemia | 112,990 | 3 |
| 9 | Suicides | 147,988 | 3 | Ischaemic heart disease | 109,592 | 3 |
| 10 | Drug dependence/harmful use | 137,703 | 2 | Cataracts | 96,091 | 2 |
| 11 | Alcohol dependence/harmful use | 130,654 | 2 | COPD (emphysema) | 93,387 | 2 |
| 12 | Cirrhosis | 117,527 | 2 | Deafness | 87,612 | 2 |
| 13 | Lung cancer | 106,120 | 2 | Lower respiratory tract infections | 84,819 | 2 |
| 14 | Drowning | 98,464 | 2 | Low birth weight | 83,879 | 2 |
| 15 | Depression | 95,530 | 2 | Dementia | 70,191 | 2 |
| 16 | Osteoarthritis | 93,749 | 2 | Anxiety disorders | 66,835 | 2 |
| 17 | Tuberculosis | 93,695 | 2 | Schizophrenia | 60,800 | 2 |
| 18 | Deafness | 93,497 | 2 | Tuberculosis | 60,643 | 2 |
| 19 | Low birth weight | 91,934 | 2 | Brian trauma & asphyxia | 57,488 | 1 |
| 20 | Anaemia | 87,610 | 2 | Nephritis & nephrosis | 55,258 | 1 |

DALYs, disability adjusted life years.

Table 2: Top twenty causes of disability adjusted life years in Thailand [94].

This project initially set out to explore a novel field; pharmacogenomics, but as it turned out, the result from the researchers directly applied impact on the prescription patterns of physicians who participated in the study. Public health impact in Thailand is being assessed by screening HIV patients for the adverse effects of ART. In Thailand, the Government Pharmaceutical Organization (GPO) has manufactured a generic fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIR S) since 2002 for treating HIV infection [34]. These antiretroviral drugs have been also recommended by the WHO as a first-line regimen, which remains on the list of alternative second line regimens [35]. GPO-VIR S is an inexpensive and effective antiretroviral drug regimen for initiating treatment of naïve patients, but careful assessment for nevirapine-induced skin rash and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) [36-38], and stavudine-associated lipodystrophy are mandatory [39]. An alternative replacement for nevirapine; efavirenz, has its own strange CNS side-effects, and should be considered as a prescription drug as well [40]. Although there is not enough data regarding the proportion of nevirapine versus efavirenz-based regimens, which are prescribed in Thailand, a multi-country survey from The AIDS Medicines and Diagnostics Service of the World Health Organization (WHO), representing 53% of relevant patients in developing countries (including Thailand) as of June 2006, revealed the distribution of nevirapine : efavirenz-based regimens as being 77% : 17% among adults and 44% : 5% among children [35]. The Thai Food and Drug Administration (Thai FDA) listed the top ten drugs that cause SJS/TENS ADRs in Thailand, with GPO-VIR S and nevirapine sixth and ninth, respectively [41].

A generic antiretroviral medicine, GPO-VIR S and its ADRs

According to a document issued by the Thai Ministry of Public Health and the National Health Security Office, approximately 20% of patients using nevirapine-based triple antiretroviral drugs, GPO-VIR S, developed adverse reactions [42,43], namely rash (15-20%), SJS (2.6%), and high nevirapine plasma concentration (60%) [44,45]. Nevirapine can be replaced by efavirenz, as mentioned above, but it also has central nervous system side-effects in up to 20% of patients, who may need to switch to other drugs in the first year [46]. Although the stavudine-containing regimen has been proven in terms of efficacy and safety for HIV treatment in resource-limited settings [47-49], stavudine also has several adverse effects that are associated with mitochondrial toxicity [50-53], such as lactic acidosis [54-56], neuropathy [57,58], pancreatitis [59,60], and lipodystrophy [61-63]. Lipodystrophy -- including body-shape changes -- has emerged as a new and increasing challenge in the HIV epidemic. Body-shape changes can have a substantial impact on quality of life, and the significance of changes to the face is social stigma. Together, they can cause anxiety about appearance and raise new concerns about stigma and self-confidence. They could also lead to poor medication adherence, which possibly leads to drug resistance and even illness and death [64].

In addition, the pathogenesis and mechanisms of the ADRs mentioned above are not altogether well understood. Also, the expense of ADR treatment from GPO-VIR S could be considered a high proportion of hospitalization costs (48.4%) [65].

Thailand's HIV-1 pharmacogenomics project

The TCELS, under the supervision of the Royal Thai Government, launched the HIV-1 pharmacogenomics project in 2005 in collaboration with Ramathibodi Hospital, Mahidol University,

Thailand, the Thai Ministry of Public Health, and Riken Center of Genomic Medicine, Japan [66] by using a new technology called the Genome-Wide Association Study (GWAS) [67]. The study comprised two groups of HIV-1 infected participants: one consisting of patients with ADRs (cases) and the other of those without (controls). After genotyping each patient, a set of one million markers, such as SNPs and Copy Number Variations (CNVs), was scanned by computer. Then, bioinformatics was applied to survey the patients' genomes for markers of genetic variation [68]. A strong association between HLA-B*3505 and nevirapine-induced skin rash was found, and variations in the CCHCR1 gene associated with nevirapine-induced skin rash also identified [69], which may provide a novel insight into the pathogenesis of drug-induced rash in the HIV-infected population [36]. A non-profit health network in U.S. has recently suggested testing HLA-B*3505 before nevirapine prescription in Thai descent based on this finding [70]. An association between HLA-B*4001 and lipodystrophy was discovered among Thai HIV-infected patients, who had received a stavudine-containing antiretroviral regimen [39]. Recently, this technique also revealed that CYP2B6 polymorphisms account for variability of nevirapine and efavirenz concentrations in plasma [44,45]. There are reports that high blood levels of efavirenz and nevirapine are related to central nervous system side effects [44,45,71].

A model system for adoption of the pharmacogenetic screening test

As part of international collaborative research, the pharmacogenetic screening test has been under investigation for its impact in Thailand by the TCELS in collaboration with Ramathibodi Hospital, Mahidol University, Thailand, the Thai Ministry of Public Health, and Riken Center of Genomic Medicine, Japan, who jointly conducted a genotype analysis research to predict serious side-effects (drug rashes, SJS/TEN) of the antiretroviral drug, nevirapine. To investigate a genotype named HLA-B*3505, an easy to use lab on a chip genotyping system (TPSA-003) [72] simply applied purified DNA into the chip (Figure 1). Then, genomic target amplification, specific probe hybridization, and fluorescence labeled probe detection was automatically operated and monitored. An easy to use report form was later printed out from the device for clinicians to use as part of their decision making



Figure 1: A low cost, fully automated, user-friendly, lab on a chip genotyping analysis system (TPSA-003) predicting the risk of rashes by identifying DNA polymorphism markers (HLA-B*3505) that indicate a high correlation with the risk of drug rash occurrence, which is a side effect of the antiretroviral therapy, nevirapine.

on whether to include nevirapine in the first line regimen. Our recent study concluded that a predictive model, which included genetic (HLA-B*3505, and variations in the CCHCR1 gene) and clinical risk factors for nevirapine-associated rash, might be useful in lowering the incidence of rash associated with nevirapine [69]. Two groups in recent studies confirmed our finding for HLA-B*3505 in Thais [73] and Indians [74]. Our prospective trial in the Thai population will provide the costs and benefits and possibly further support for utilization and reimbursement of these genetic tests in a clinical and public health setting. A novel system is being developed to incorporate all genomic predictive markers associated with antiretroviral ADRs, namely stavudine: lipodystrophy (HLA-B*4001), abacavir: hypersensitivity (HLA-B*5701), efavirenz and efavirenz; and central nervous system side effects (CYP2B6) have been planned for inclusion in the same LabChip, under the code name “All-In-One PGX-HIV”, with an estimated cost of 1,500 Baht (approximately \$50).

By applying this affordable, fully automated system in medical practice, improved quality of medical treatment for AIDS patients would be possible by increasing medical compliance and reducing HIV drug resistance through minimizing ADRs. This would not only pertain in Thailand, but also in other developing countries, such as Africa, where people currently use similar antiretroviral drug regimens to those used in Thailand, which are recommended by the WHO [35]. Moreover, the device and assay system would help tremendously in reducing unnecessary medical costs for ADRs and HIV-1 drug resistant treatments.

This pharmacogenetic screening system would also be a major step forward, and the first of its kind in the realization of personalized antiretroviral medicines, in which appropriate, inexpensive treatment is given to each individual patient in developing countries, according to genetic information.

Evaluation of health economics

A health economic evaluation of nevirapine-induced skin ADR was based on 1,300 GPO-VIR S treated patients and conducted at Ramathibodi Hospital, Bangkok, Thailand in 2005. It indicated a cost for those who developed mild rash or SJS/TEN of 15,682 Baht (approximately \$490) and 83,285 Baht (approximately \$2,603), respectively, while the cost of pharmacogenetic screening (HLA-B*3505 genotyping) prior to GPO-VIR therapy would only be 1,500 Baht (approximately \$50). The daily cost of GPO-VIR S was equivalent to the combination of stavudine, lamivudine and efavirenz (80 Baht/\$2.44), while the cost of the antiretroviral drug resistant test was 8,000 Baht (approximately \$250) (Table 3). The average cost of health-care expenditure on HIV/AIDS would decrease with the screening test

(HLA-B*3505 genotyping), as opposed to no screening test, due to the reduction of patients who suffer from mild to severe rash, and HIV drug resistance.

Public engagement activities

For novel technology such as pharmacogenomics, public understanding and acceptance of these tests would ensure that they will be used to their full potential benefit. Researchers from the TCELS Pharmacogenomics Project have released books and reports written in Thai that including “Pharmacogenomics for decision makers”, “Pharmacogenomics for clinicians”, “Pharmacogenomics for scientists”, “Pharmacogenomics for layman”, and “Pharmacogenomics in a resource limited country, Thailand: building a better quality of life for Thai people” (Figure 2). They have been generated as part of an effort to gain support from the public, decision makers and funding bodies. Documentary news has been recently broadcasted worldwide on researching HIV-1 pharmacogenomics and its practical use for improving quality of life in resource limited settings, and reducing HIV drug resistance and medical costs for Thai HIV-1/AIDS patients [33].

Discussion

Various public health organizations in Thailand tried to meet the needs of health-care relating to the HIV epidemic by including antiretroviral medication under the universal health-care coverage scheme. Since then, drug resistance rates have been increased [73-76]. Consequently, without good strategies to reduce the cost of medical expenditure, Thailand would soon face an additional financial burden on their universal health-care coverage system. Therefore, the country has invested in its science and technology sector (for example, the TCELS) [8,33,77], which has proved worthwhile and might eventually place Thailand as a leader in research, pharmacogenomics development and implementation of the previously mentioned tests [36,72].

Pharmacogenomics research has been established since 2004, with the aim of improving the health of people and reducing medical expenditure in developing countries such as Thailand [4,5,8,77]. Thai people have had to rely on cheaper generic versions of drugs, of which some are prone to serious adverse events [36,39,44,45,78,79]. In contrast, physicians in developed countries have been much quicker in adopting genetic testing to guide other antiretroviral drugs, in abacavir treatment for instance [80-82]. Individuals with specific forms of the HLA-B*5701 allele are hypersensitive to the HIV drug [83]. The acceptance of genetic testing for antiretroviral drugs, such as abacavir, may be due to the fact that physicians treating HIV patients regularly have to deal with rapidly disruptive technologies, which make cutting edge diagnostics and treatment options more acceptable.

To increase the implementation of useful genetic tests, their advocacy must be acquired to provide public education on the implication of pharmacogenomics and communication with experts in the field. Health professionals and the general public need to be informed about the benefits of pharmacogenetics. The pharmacogenetic screening test would not only help in reducing cases of adverse drug reaction, but might also decrease HIV-1 drug-resistant cases. Regarding ADRs, the drastic consequences of poor adherence to treatment includes not only diminished outcome for the patient, but also the public health threat of multidrug-resistant HIV [84], and widespread transmission of drug-resistant viruses, similar to that seen with multidrug-resistant tuberculosis [85].

Noncompliance to the strict antiretroviral regimen is common

| Variable | Baseline value |
|---|----------------|
| Genetic testing cost | |
| Cost per test (\$) | 50 |
| Cost of antiretroviral therapy (\$/day) | |
| First line: stavudine + lamivudine + nevirapine (GPO-VIR S) | 2.44 |
| Second line: stavudine + lamivudine + efavirenz | 2.44 |
| Toxicity costs (\$) | |
| Nevirapine induced cutaneous ADRs | |
| Mild rash | 490 |
| SJS/TEN | 2603 |
| Drug resistant testing cost | |
| Cost per test (\$) | 250 |

Table 3: Baseline costs considered in the pharmaco-economic analysis based on evidence from Ramathibodi Hospital.

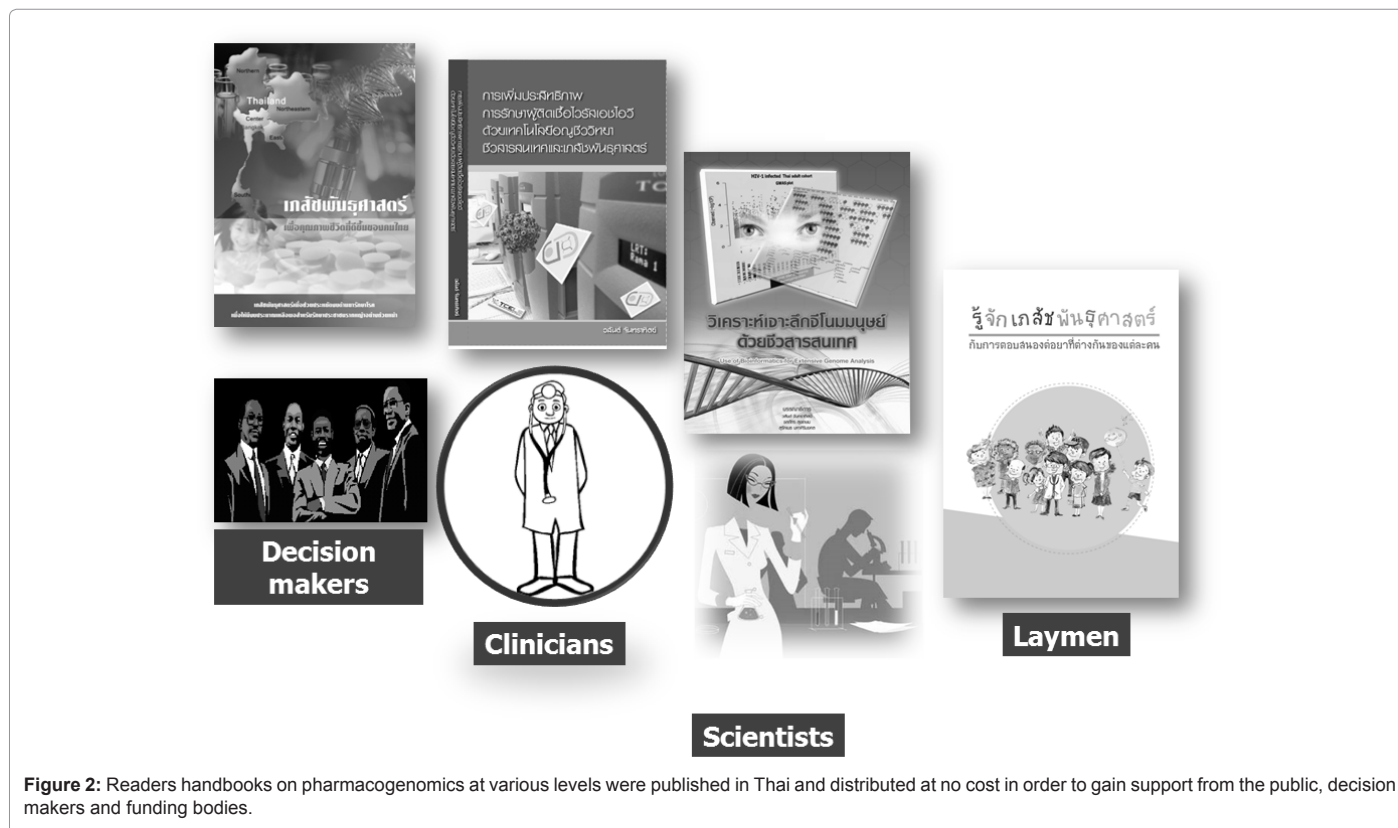


Figure 2: Readers handbooks on pharmacogenomics at various levels were published in Thai and distributed at no cost in order to gain support from the public, decision makers and funding bodies.

for two main reasons. One is related to drug side effects, while the second is associated with specific daily lifestyle [86]. However, only noncompliance based on daily lifestyle can be improved through an existing adherence counseling program [87,88], but not for ADRs. It is therefore high priority for resource limited counties, such as Thailand, to invest more in improving medication compliance among HIV-1 infected individuals through pharmacogenomics research. A consensus criteria for adopting these pharmacogenomics tests into the national insurance scheme should be developed within countries, to provide access to clinically useful tests for the low-income population and not create social stratification by providing two standards of health service based on the individual's ability to pay. This pharmacogenetic screening test would enable minimization of HIV-1 drug resistance and increase durability of first-line antiretroviral drugs, which would in turn reduce the national medical costs of using expensive second-line antiretroviral drugs.

From an individual perspective, pharmacogenetic testing is surely beneficial under the economic model (Table 3). If patients can pay for monthly antiretroviral drugs, they should take the test, especially as it is inexpensive (1,500 Baht/\$50 per test) when compared to a series of 2,000 Baht (approximately \$62) viral load tests or 8,000 Baht (approximately \$250) antiretroviral drug resistance tests, or the cost of an alternative regimen if a rash occurs. Based on this economical model, avoidance of a rash suggests more cost reduction and this model supports the test even if the pricing of efavirenz is dropping towards the current nevirapine price.

The affordable pharmacogenetic assay system, costing less than 1,500 Baht (approximately \$50) per patient, has been made possible through a collaborative research budget from Thailand and the

Japanese government. The assay system initially focused on screening ADRs related to the WHO recommendations on antiretroviral drugs, starting with a nevirapine-genomic predictive marker(s). Integration of pharmacogenetic testing into the National Health Care system may be too early, as no tests have clearly demonstrated improvement in the clinical management of patients when compared to standard care. This innovation leads to support for the importance of lab discovery and translation to a clinical trial. Results of the clinical trial will lead to advice for the policy maker. Nevertheless, it remains important that we advocate the need for continued research, as in the future, pharmacogenetic testing will become part of HIV clinical management. We are currently in the initial stage and moving towards gaining data regarding routine screening. Hopefully, this invention will eventually benefit more than 30 million HIV-1 infected patients in resource-limited countries worldwide [89].

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