Journal of Pharmacogenomics & Pharmacoproteomics

Chantratita et al., J Pharmacogenom Pharmacoproteomics 2011, S6
DOI: 10.4172/2153-0645.S6-001

Review Article Open Access

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

Wasun Chantratita[1]*, Soranun Chantarangsu[2], Sasisopin Kiertiburanakul[3], Somnuek Sungkanuparph[3], Angkana Charoenyingwattana[4] and Surakameth Mahasirimongkol[5]

[1]*Unit of Virology and Molecular Microbiology, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, 10400 Thailand*
[2]*Department of Oral Pathology, Faculty of Dentistry, Chulalongkorn University, Bangkok, 10330 Thailand*
[3]*Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, 10400 Thailand*
[4]*Pharmacogenomics project under collaboration between Thailand Center of Excellence for Life Sciences, Mahidol University, Bangkok, 10400 Thailand*
[5]*Medical Genetic Section, National Institute of Health, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, 11000 Thailand*

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

***Corresponding author:** Wasun Chantratita, Ph.D, Unit of Virology and Molecular Microbiology, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, 10400 Thailand, Tel: +66-2201-2754; Fax: +66-2201-1470; E-mail: rawct@mahidol.ac.th

Received August 24, 2011; **Accepted** November 02, 2011; **Published** November 06, 2011

Citation: Chantratita W, Chantarangsu S, Kiertiburanakul S, Sungkanuparph S, Charoenyingwattana A, et al. (2011) Integrating HIV-1 Pharmacogenomics into the Universal Coverage Health-Care System in Thailand: From Scientific Evidence to Policy. J Pharmacogenom Pharmacoproteomics S6:001. doi:10.4172/2153-0645.S6-001

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	[92]
Stavudine	HIV-1 infection and AIDS	Lipodystrophy	HLA-B*4001	[39]
Allopurinol,	Hyperuricemia and chronic gout	SJS/TEN	HLA-B*5801	[78, 93]
Carbamazepine	Epilepsy seizures, bipolar disorder, and mood stabilizing	SJS/TEN	HLA-B*1502	[79,94,95]

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 [96].

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

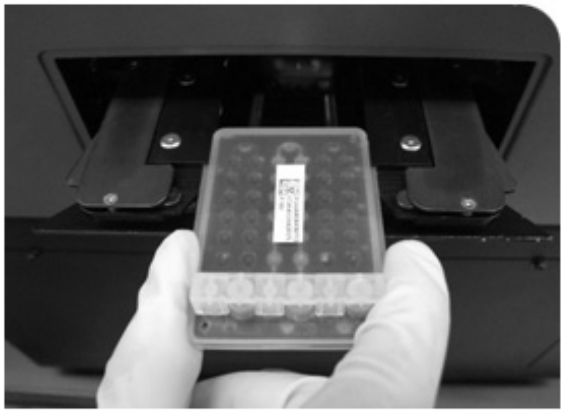

Figure 1: A low cost, fully automated, user-friendly, lab on a chip genotyping analysis system (TPSA-003) predicting the risk of rashes by identifying DNA polymorphism markers (HLA-B*3505) that indicate a high correlation with the risk of drug rash occurrence, which is a side effect of the antiretroviral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

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.

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 [75-78]. 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) [8,33,79], 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 [4,5,8,79]. Thai people have had to rely on cheaper generic versions of drugs, of which some are prone to serious adverse events [36,39,44,45,80,81]. In contrast, physicians in developed countries have been much quicker in adopting genetic testing to guide other antiretroviral drugs, in abacavir treatment for instance [80-84]. Individuals with specific forms of the HLA-B*5701 allele are hypersensitive to the HIV drug [85]. 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 [86], and widespread transmission of drug-resistant viruses, similar to that seen with multidrug-resistant tuberculosis [87].

Noncompliance to the strict antiretroviral regimen is common

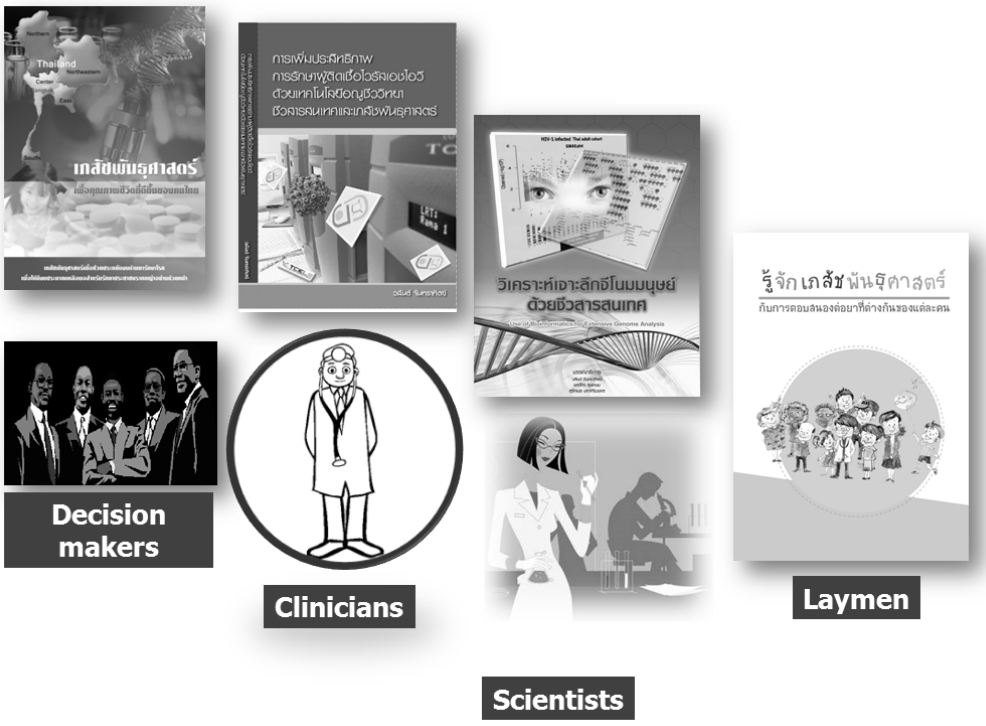

Figure 2: Readers handbooks on pharmacogenomics at various levels were published in Thai and distributed at no cost in order to gain support from the public, decision makers and funding bodies.

for two main reasons. One is related to drug side effects, while the second is associated with specific daily lifestyle [88]. However, only noncompliance based on daily lifestyle can be improved through an existing adherence counseling program [89,90], 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 [91].

References

1. Shastry BS (2006) Pharmacogenetics and the concept of individualized medicine. Pharmacogenomics J 6: 16-21.
2. Deverka PA, Vernon J, McLeod HL (2010) Economic opportunities and challenges for pharmacogenomics. Annu Rev Pharmacol Toxicol 50: 423-437.
3. Lesko LJ, Zineh I (2010) DNA, drugs and chariots: on a decade of pharmacogenomics at the US FDA. Pharmacogenomics 11: 507-512.
4. Seguin B, Essajee I, Jimenez-Sanchez G, Singer PA, Daar AS (2007) Human genomic variation studies and pharmacogenomics are critical for global health. Landes Bioscience.
5. Hardy BJ, Seguin B, Goodsaid F, Jimenez-Sanchez G, Singer PA, et al. (2008) The next steps for genomic medicine: challenges and opportunities for the developing world. Nat Rev Genet 1: 23-27.
6. Singer PA, Daar AS (2001) Harnessing genomics and biotechnology to improve global health equity. Science 294: 87-89.

7. Seguin B, Hardy BJ, Singer PA, Daar AS (2008) Human genomic variation initiatives in emerging economies and developing countries. Nat Rev Genet 1: 3-4.

8. Seguin B, Hardy BJ, Singer PA, Daar AS (2008) Universal health care, genomic medicine and Thailand: investing in today and tomorrow. Nat Rev Genet 1: 14-19.

9. Yang CW, Hung SI, Juo CG, Lin YP, Fang WH, et al. (2007) HLA-B*1502-bound peptides: implications for the pathogenesis of carbamazepine-induced Stevens-Johnson syndrome. J Allergy Clin Immunol 120: 870-877.

10. Man CB, Kwan P, Baum L, Yu E, Lau KM, et al. (2007) Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 48: 1015-1018.

11. Ferrell PB, McLeod HL (2008) Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics 9: 1543-1546.

12. Daar AS, Singer PA (2005) Pharmacogenetics and geographical ancestry: implications for drug development and global health. Nat Rev Genet 6: 241-246.

13. Lang L (2009) FDA grants tentative approval for 75th generic antiretroviral drug. Gastroenterology 136: 5.

14. Seguin B, Hardy BJ, Singer PA, Daar AS (2008) Genomics, public health and developing countries: the case of the Mexican National Institute of Genomic Medicine (INMEGEN). Nat Rev Genet 1: 5-9.

15. Hardy BJ, Seguin B, Singer PA, Mukerji M, Brahmachari SK, et al. (2008) From diversity to delivery: the case of the Indian Genome Variation initiative. Nat Rev Genet 9: 9-14.

16. Hardy BJ, Seguin B, Ramesar R, Singer PA, Daar AS (2008) South Africa: from species cradle to genomic applications. Nat Rev Genet 1: 19-23.

17. The Thai AIDS Epidemic Now. The World Bank (2007) Available at: http://siteresources.worldbank.org/INTEAPREGTOPHIVAIDS/Resources/AIDS-Treatment-effectiveness-ch2.pdf. Accessed 18 July 2011.

18. Fosy MM, Gough K, Quan CM, Harris K, Ibanez D, et al. (2000) Hospitalization due to adverse drug reactions and drug interactions before and after HAART. Can J Infect Dis 11: 193-201.

19. Heilman E. Managing HIV: A Life-Long Commitment HealthyPlace.com (2008) Available at: http://www.healthyplace.com/sex/diseases/managing-hiv-a-life-long-commitment/menu-id-66/. Accessed 18 July 2011.

20. Niche Area Three: Improved access to treatment for opportunistic infections and anti-retroviral therapy: Tearfund International learning Zone; Available at: http://tilz.tearfund.org/webdocs/Tilz/Topics/HIV-AIDS/Good%20Practice/3%20Access%20to%20Treatment.doc. Accessed 18 July 2011.

21. Beardsell A, Lai C, Hogg R, McLeod WA, Yip B (1999) Utilization and adherence of a population-based post-exposure prophylaxis program. Proceedings of the 6th Conference on Retroviruses and Opportunistic Infections, Chicago.

22. Wu A, Yu-Isenberg K, McGrath M, Jacobson D (1999) Reliability, validity, and usefulness of touch-screen administration of QOL and adherence instruments in an outpatient clinic. Proceedings of the 6th Conference on Retroviruses and Opportunistic Infections, Chicago.

23. Tuldra A, Ferrer M, Rodriguez C, Bayes R, Burger D et al. (1998) A proposed model to predict compliance with antiretroviral therapy. Proceedings of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California.

24. Piroth L, Grappin M, Waldner A (1998) Discontinuation of antiprotease inhibitor therapy due to drug toxicity: study of a cohort of 309 patients. Proceedings of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California.

25. Mateu S, Calvo G, Torres F, Sambeat M, Domingo P, et al. (2002) Impact of adverse drug reactions (ADRs) on HIV infected outpatients care. Proceedings of the 14th International Conference on AIDS, Barcelona, Spain.

26. International Labour Organization (2004) A Technical Note to the Government: Financing Universal Health Care in Thailand. Available at: http://www.ilo.org/public/english/protection/secsoc/downloads/publ/995sp1.pdf Accessed 18 July 2011.

27. National AIDS Prevention and Alleviation Committee (2008) UNGASS Country Progress Report, Thailand, Reporting period: January 2006 December 2007. Available at: http://data.unaids.org/pub/report/2008/thailand_2008_country_progress_report_en.pdf. Accessed 18 July 2011.

28. Rangsin R, Piyaraj P, Sirisanthana T, Sirisopana N, Short O, et al. (2007) The natural history of HIV-1 subtype E infection in young men in Thailand with up to 14 years of follow-up. AIDS 21: 39-46.

29. UNFPA Country Technical Services Team for East and South-East Asia. (2005) Reproductive health of women in thailand: progress and challenges towards attainment of international development goals. Available at: http://thailand.unfpa.org/documents/thai_rh.pdf. Accessed 18 July 2011.

30. Bureau of Information. Ministry of Public Health. (2009) Access to Antiretroviral Treatment under Universal Health Care Scheme. Available at: http://translate.google.co.th/translate?u=http%3A%2F%2Fwww.moph.go.th%2Fops%2Fiprg%2Finclude%2Fadmin_hotnew%2Fshow_hotnew.php%3FidHot_new%3D4046&sl=th&tl=en&hl=&ie=UTF-8. Accessed 18 July 2011.

31. Thailand Centre of Excellence for Life Sciences (2009) Background of The Thailand Centre of Excellence for Life Sciences. Available at: http://www.tcels.or.th/en/Corporateinfo.aspx. Accessed 18 July 2011.

32. Thailand Centre of Excellence for Life Sciences (2009) Pharmacogenomics Project. Available at: http://www.tcels.or.th/en/Projects.aspx?id=94. Accessed 18 July 2011.

33. Center of pharmacogenomics and bioinformatics (2010) Pharmacogenomics collaborative project. Available at: http://www.pharmagtc.net/index.php?option=com_content&task=view&id=83&Itemid=1. Accessed 18 July 2011.

34. Phongsamart W (2004) Safety and efficacy of GPO-VIR in HIV-infected Thai children. Available at: http://gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102282271.html. Accessed 18 July 2011.

35. Renaud-Thery F, Nguimfack BD, Vitoria M, Lee E, Graaff P, et al. (2007) Use of antiretroviral therapy in resource-limited countries in 2006: distribution and uptake of first- and second-line regimens. AIDS 4: 89-95.

36. Chantarangsu S, Mushiroda T, Mahasirimongkol S, Kiertiburanakul S, Sungkanuparph S, et al. (2009) HLA-B*3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients. Pharmacogenet Genomics 19: 139-146.

37. Kiertiburanakul S, Sungkanuparph S, Malathum K, Watcharananan S, Sathapatayavongs B, et al. (2009) A model and risk score for predicting nevirapine-associated rash among HIV-infected patients: in settings of low CD4 cell counts and resource limitation. Open AIDS J 3: 24-30.

38. Kiertiburanakul S, Khongnorasat S, Rattanasiri S, Sungkanuparph S (2007) Efficacy of a generic fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIR) in Thai HIV-infected patients. J Med Assoc Thai 90: 237-243.

39. Wangsomboonsiri W, Mahasirimongkol S, Chantarangsu S, Kiertiburanakul S, Charoenyingwattana A, et al. (2010) Association between HLA-B*4001 and lipodystrophy among HIV-infected patients from Thailand who received a stavudine-containing antiretroviral regimen. Clin Infect Dis 50: 597-604.

40. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, et al. (2001) Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 15: 71-75.

41. Thai Food and Drug Administration (2008) Severe skin adverse drug reactions:Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Available at: http://thaihpvc.fda.moph.go.th/thaihvc/Public/main.jsf. Accessed 18 July 2011.

42. Phanuphak N, Apornpong T, Teeratakulpisarn S, Chaithongwongwatthana S, Taweepolcharoen C, et al. (2007) Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women. HIV Med 8: 357-366.

43. The Ministry of Public Health and the National Health Security Office, Thailand (2007) Facts and Evidences on the 10 Burning Issues. Available at: http://www.moph.go.th/hot/White%20Paper%20CL-EN.pdf. Accessed 18 July 2011.

44. Chantarangsu S, Cressey TR, Mahasirimongkol S, Capparelli E, Tawon Y, et al. (2009) Influence of CYP2B6 polymorphisms on the persistence of plasma nevirapine concentrations following a single intra-partum dose for the prevention of mother to child transmission in HIV-infected Thai women. J Antimicrob Chemother 64: 1265-1273.

45. Uttayamakul S, Likanonsakul S, Manosuthi W, Wichukchinda N, Kalambaheti T, et al. (2010) Effects of CYP2B6 G516T polymorphisms on plasma efavirenz and nevirapine levels when co-administered with rifampicin in HIV/TB co-infected Thai adults. AIDS Res Ther 7: 8.

46. HIV Treatment Information Base (2008) CNS side effects: mood changes, anxiety, dizzyness, sleep disturbance. Available at: http://i-base.info/guides/side/cns-side-effects. Accessed 18 July 2011.

47. Laurent C, Kouanfack C, Koulla-Shiro S, Nkoue N, Bourgeois A, et al. (2004) Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. Lancet 364: 29-34.

48. van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, et al. (2004) Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet 363: 1253-1263.

49. Manosuthi W, Chimsuntorn S, Likanonsakul S, Sungkanuparph S (2007) Safety and efficacy of a generic fixed-dose combination of stavudine, lamivudine and nevirapine antiretroviral therapy between HIV-infected patients with baseline CD4 <50 versus CD4 > or = 50 cells/mm3. AIDS Res Ther 4: 6.

50. Cote HC, Brumme ZL, Craib KJ, Alexander CS, Wynhoven B, et al. (2002) Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. N Engl J Med 346: 811-820.

51. Velsor LW, Kovacevic M, Goldstein M, Leitner HM, Lewis W, et al. (2004) Mitochondrial oxidative stress in human hepatoma cells exposed to stavudine. Toxicol Appl Pharmacol 199: 10-19.

52. Walker UA, Bauerle J, Laguno M, Murillas J, Mauss S, et al. (2004) Depletion of mitochondrial DNA in liver under antiretroviral therapy with didanosine, stavudine, or zalcitabine. Hepatology 39: 311-317.

53. Lee H, Hanes J, Johnson KA (2003) Toxicity of nucleoside analogues used to treat AIDS and the selectivity of the mitochondrial DNA polymerase. Biochemistry 42: 14711-14729.

54. Boubaker K, Flepp M, Sudre P, Furrer H, Haensel A, et al. (2001) Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. Clin Infect Dis 33: 1931-1937.

55. Songa PM, Castelnuovo B, Mugasha EB, Ocama P, Kambugu A (2007) Symptomatic hyperlactatemia associated with nucleoside analogue reverse-transcriptase inhibitor use in HIV-infected patients: a report of 24 cases in a resource-limited setting (Uganda). Clin Infect Dis 45: 514-517.

56. Manosuthi W, Prasithsirikul W, Chumpathat N, Suntisuklappon B, Athichathanabadi C, et al. (2008) Risk factors for mortality in symptomatic hyperlactatemia among HIV-infected patients receiving antiretroviral therapy in a resource-limited setting. Int J Infect Dis 12: 582-586.

57. Hulgan T, Haas DW, Haines JL, Ritchie MD, Robbins GK, et al. (2005) Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: an adult AIDS clinical trials group study. AIDS 19: 1341-1349.

58. Sacktor N, Nakasujja N, Skolasky RL, Robertson K, Musisi S, et al. (2009) Benefits and risks of stavudine therapy for HIV-associated neurologic complications in Uganda. Neurology 72:165-170.

59. Riedel DJ, Gebo KA, Moore RD, Lucas GM (2008) A ten-year analysis of the incidence and risk factors for acute pancreatitis requiring hospitalization in an urban HIV clinical cohort. AIDS Patient Care STDS 22: 113-121.

60. Dragovic G, Milic N, Jevtovic DJ (2005) Incidence of acute pancreatitis and nucleoside reverse transcriptase inhibitors usage. Int J STD AIDS 16: 427-429.

61. Gaou I, Malliti M, Guimont MC, Letteron P, Demeilliers C, et al. (2001) Effect of stavudine on mitochondrial genome and fatty acid oxidation in lean and obese mice. J Pharmacol Exp Ther 297: 516-523.

62. Nolan D, Hammond E, James I, McKinnon E, Mallal S (2003) Contribution of nucleoside-analogue reverse transcriptase inhibitor therapy to lipoatrophy from the population to the cellular level. Antivir Ther 8: 617-626.

63. van der Valk M, Casula M, Weverlingz GJ, van Kuijk K, van Eck-Smit B, et al. (2004) Prevalence of lipoatrophy and mitochondrial DNA content of blood and subcutaneous fat in HIV-1-infected patients randomly allocated to zidovudine- or stavudine-based therapy. Antivir Ther 9: 385-393.

64. Jones K, Finlon C (2005) The Eye of the Beholder: Psychological Perspectives on Lipodystrophy. Available at: http://www.thebody.com/content/art14265.html. Accessed 18 July 2011.

65. Loongban S (2003) Discrepancy of HIV-realated treatment cost of HIV patients before and after receiving GPO-VIR in Saraburi province. Available at: http://cuir.car.chula.ac.th/handle/123456789/11582. Accessed 18 July 2011.

66. The Scientist (2010) Thailand Center of Excellent for Life Sciences. Available at: http://classic.the-scientist.com/article/display/57336/. Accessed 18 July 2011.

67. Wang WY, Barratt BJ, Clayton DG, Todd JA (2005) Genome-wide association studies: theoretical and practical concerns. Nat Rev Genet 6: 109-118.

68. McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, et al. (2008) Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet 9: 356-369.

69. Chantarangsu S, Mushiroda T, Mahasirimongkol S, Kiertiburanakul S, Sungkanuparph S, et al. (2011) Genome-wide association study identifies variations in 6p21.3 associated with nevirapine-induced rash. Clin Infect Dis 53: 341-348.

70. Pharmacogenomics: Nevirapine Intermountain Healthcare (2010) Nevirapine (Viramune) sensitivity. Available at: https://intermountainhealthcare.org/ext/Dcmnt?ncid=521050305&tfrm=default. Accessed 18 July 2011.

71. Rakhmanina NY, van den Anker JN (2009) Efavirenz in the therapy of HIV infection. Expert Opin Drug Metab Toxicol 6: 95-103.

72. Riken Genesis (2009) Latest genotype analysis system provided to Thailand Clinical research begins to verify the method to guide appropriate use of AIDS drugs based on genetic information. Available at: http://www.rikengenesis.jp/en/newsevent/press20090622.html. Accessed 18 July 2011.

73. Yuan J, Guo S, Hall D, Cammett AM, Jayadev S, et al. (2011) Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. AIDS 25: 1271-1280.

74. Umapathy S, Pawar A, Bajpai S, Pazare AR, Ghosh K (2011) HLA involvement in nevirapine-induced dermatological reaction in antiretroviral-treated HIV-1 patients. J Pharmacol Pharmacother 2: 114-115.

75. Sukasem C, Churdboonchart V, Sukeepaisarncharoen W, Piroj W, Inwisai T, et al. (2008) Genotypic resistance profiles in antiretroviral-naive HIV-1 infections before and after initiation of first-line HAART: impact of polymorphism on resistance to therapy. Int J Antimicrob Agents 31: 277-281.

76. Sukasem C, Churdboonchart V, Sirisidthi K, Riengrojpitak S, Chasombat S, et al. (2007) Genotypic resistance mutations in treatment-naive and treatment-experienced patients under widespread use of antiretroviral drugs in Thailand: implications for further epidemiologic surveillance. Jpn J Infect Dis 60: 284-289.

77. Sukasem C, Churdboonchart V, Chasombat S, Kohreanudom S, Watitpun C, et al. (2007) Prevalence of antiretroviral drug resistance in treated HIV-1 infected patients: under the initiative of access to the NNRTI-based regimen in Thailand. J Chemother 19: 528-535.

78. Sukasem C, Churdboonchart V, Chasombat S, Kohreanudom S, Watitpun C, et al. (2007) Surveillance of genotypic resistance mutations in chronic HIV-1 treated individuals after completion of the National Access to Antiretroviral Program in Thailand. Infection 35: 81-88.

79. Seguin B, Hardy BJ, Singer PA, Daar AS (2008) Genomic medicine and developing countries: creating a room of their own. Nat Rev Genet 9: 487-493.

80. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, et al. (2009) Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 19: 704-709.

81. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, et al. (2010) Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. Epilepsia 51: 926-930.

82. Lalonde RG, Thomas R, Rachlis A, Gill MJ, Roger M, et al. (2009) Successful implementation of a national HLA-B*5701 genetic testing service in Canada. Tissue Antigens 75: 12-18.

83. Orkin C, Sadiq ST, Rice L, Jackson F (2009) Prospective epidemiological study of the prevalence of human leukocyte antigen (HLA)-B*5701 in HIV-1-infected UK subjects. HIV Med 11: 187-192.

84. Watson ME, Patel LG, Ha B, Wannamaker P, Cuffe R, et al. (2009) A study of HIV provider attitudes toward HLA-B 5701 testing in the United States. AIDS Patient Care STDS 23: 957-963.

85. Lucas A, Nolan D, Mallal S (2007) HLA-B*5701 screening for susceptibility to abacavir hypersensitivity. J Antimicrob Chemother 59: 591-593.

86. Mehta S, Moore RD, Graham NM (1997) Potential factors affecting adherence with HIV therapy. AIDS 11: 1665-1670.

87. Sharma SK, Mohan A (2006) Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. Chest 130: 261-272.

88. Cleemput I, Kesteloot K, DeGeest S (2002) A review of the literature on the economics of noncompliance. Room for methodological improvement. Health Policy 59: 65-94.

89. Golin CE, Smith SR, Reif S (2004) Adherence counseling practice s of generalist and specialist physicians caring for people living with HIV/AIDS in North Carolina. J Gen Intern Med 19: 16-27.

90. Cook PF, McCabe MM, Emiliozzi S, Pointer L (2009) Telephone nurse counseling improves HIV medication adherence: an effectiveness study. J Assoc Nurses AIDS Care 20: 316-325.

91. UNAIDS (2008) The global AIDS epidemic. Available at: http://data.unaids.org/pub/FactSheet/2009/20091124_FS_global_en.pdf. Accessed 18 July 2011.

92. Nieves Calatrava D, Calle-Martin OD, Iribarren-Loyarte JA, Rivero-Roman A, Garcia-Bujalance L, et al. (2010) Cost-effectiveness analysis of HLA-B*5701 typing in the prevention of hypersensitivity to abacavir in HIV+ patients in Spain. Enferm Infecc Microbiol Clin 28: 590-595.

93. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, et al. (2008) HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. Pharmacogenomics 9: 1617-1622.

94. Mehta TY, Prajapati LM, Mittal B, Joshi CG, Sheth JJ, et al. (2009) Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. Indian J Dermatol Venereol Leprol 75: 579-582.

95. Ingelman-Sundberg M (2008) Pharmacogenomic biomarkers for prediction of severe adverse drug reactions. N Engl J Med 358: 637-639.

96. International Health Policy Program (IHPP), Ministry of Public Health, Thailand (2007) Healthcare Financing in Thailand: an update in 2007. Available at: http://siteresources.worldbank.org/INTTHAILAND/Resources/333200-1089943634036/475256-1151398858396/HHealthcare_Financing_in_Thailand_2007_IHPP.ppt. Accessed 18 July 2011.

This article was originally published in a special issue, **Pharmacogenetics:HIV** handled by Editor(s). Dr. Awewura Kwara, Brown University, USA; Dr. Adrian L Lerena, University of Extremadura, Spain