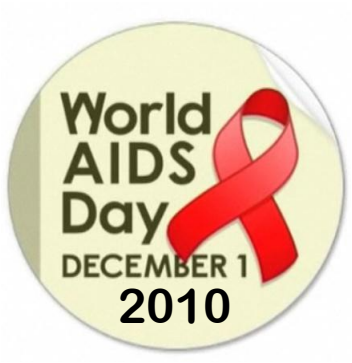
Pharmacogenomics in a resource-limited setting, Thailand.

Wasun Chantratita, Ph.D.
Ramathibodi hospital

http://virusrama.blogspot.com

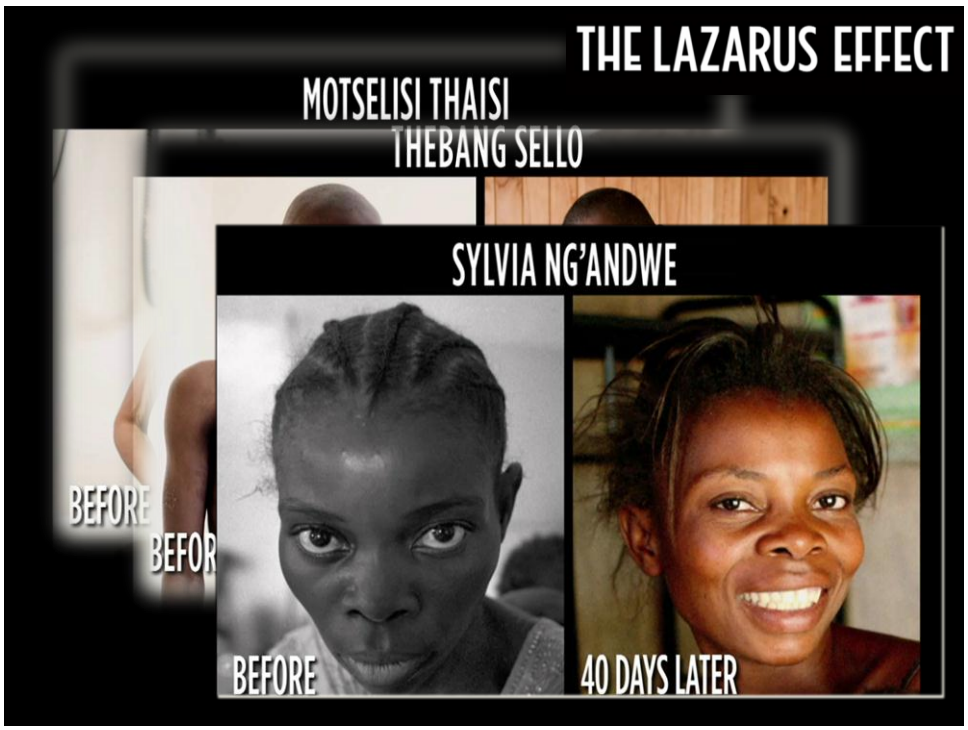


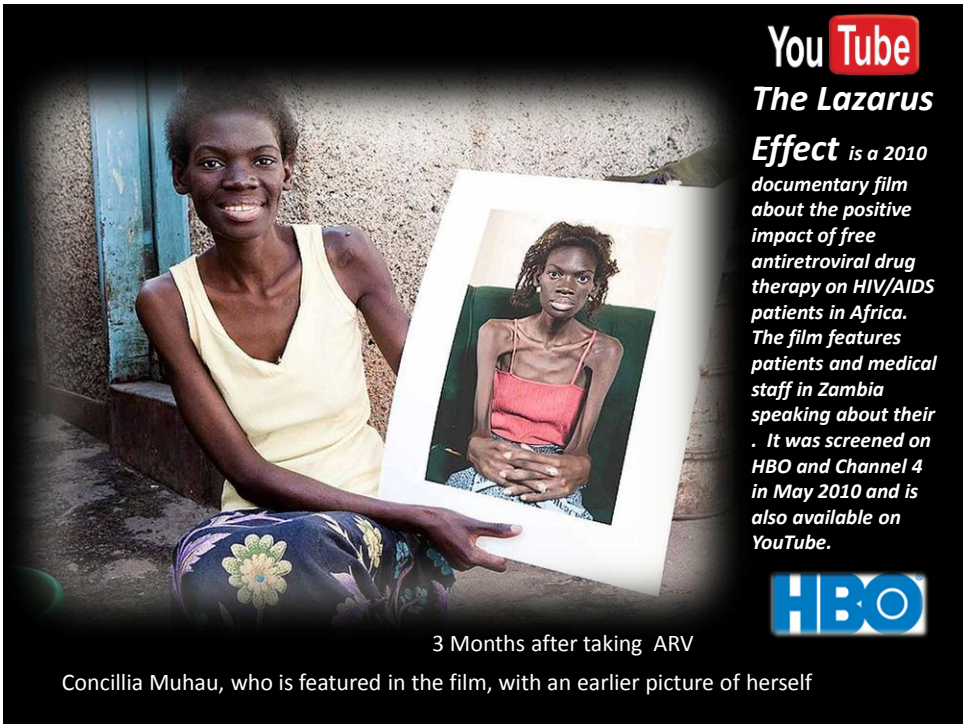
World AIDS Day theme:

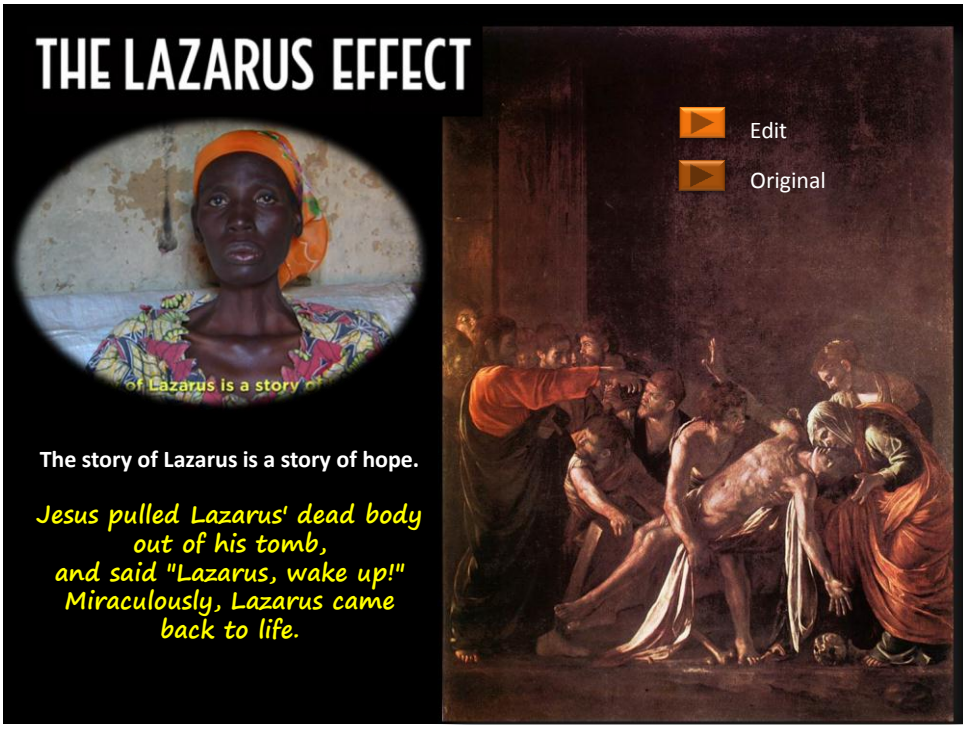
Universal Access (to AIDS treatment) and Human Rights

Access for all to HIV prevention, treatment, care and support is a critical part of human rights.


IN RECENT YEARS,
ANTIRETROVIRAL (ARV) MEDICATION
HAS BEEN HELPING PEOPLE STAY ALIVE
IN AS FEW AS 40 DAYS, PEOPLE ON
ARVs CAN UNDERGO
A REMARKABLE TRANSFORMATION


THE LAZARUS EFFECT
MOTSELISI THAISI
THEBANG SELLO
SYLVIA NG'ANDWE
BEFORE
BEFOR
BEFORE
40 DAYS LATER


YouTube
The Lazarus Effect is a 2010 documentary film about the positive impact of free antiretroviral drug therapy on HIV/AIDS patients in Africa. The film features patients and medical staff in Zambia speaking about their . It was screened on HBO and Channel 4 in May 2010 and is also available on YouTube.
HBO
3 Months after taking ARV
Concillia Muhau, who is featured in the film, with an earlier picture of herself

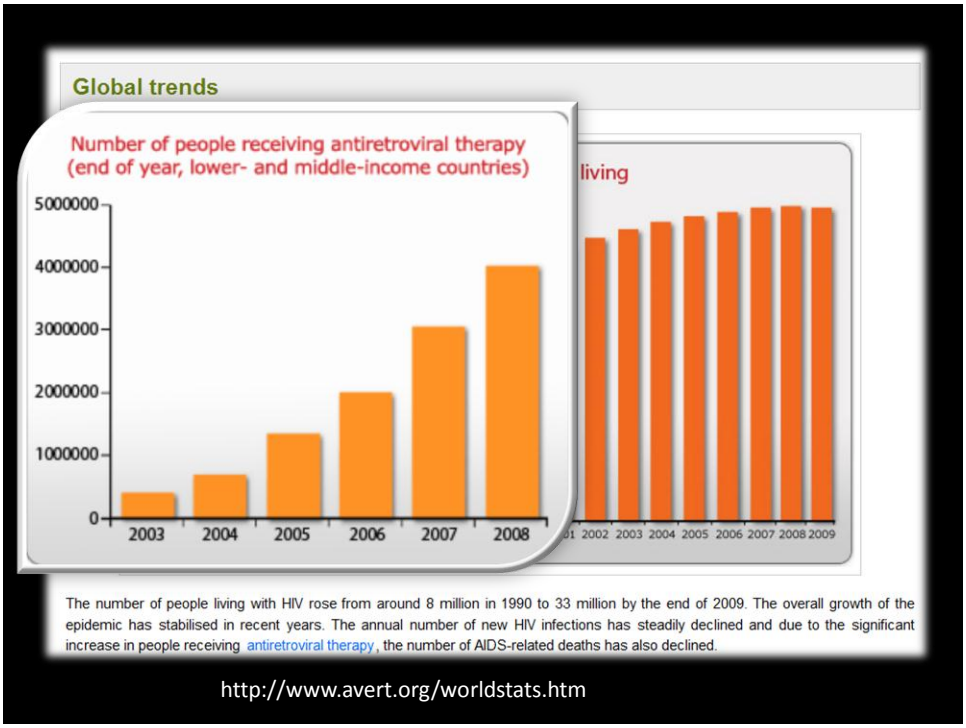

THE LAZARUS EFFECT
Edit
Original
The story of Lazarus is a story of hope.
Jesus pulled Lazarus' dead body out of his tomb, and said "Lazarus, wake up!" Miraculously, Lazarus came back to life.

2010

OVER 3 MILLION PEOPLE ARE RECEIVING FREE ARVs ACROSS AFRICA

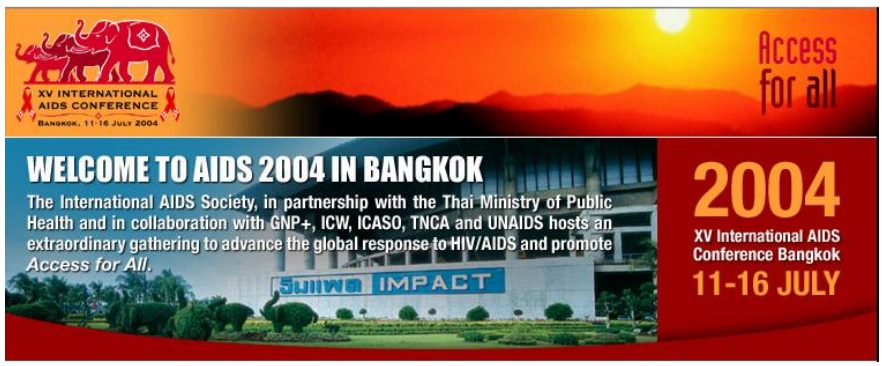
3,800 PEOPLE STILL DIE IN AFRICA EVERY DAY FROM AIDS

IT COSTS ABOUT 40 CENTS A DAY TO PROVIDE A PERSON WITH LIFE-SAVING ANTIRETROVIRAL MEDICATION



http://www.avert.org/worldstats.htm

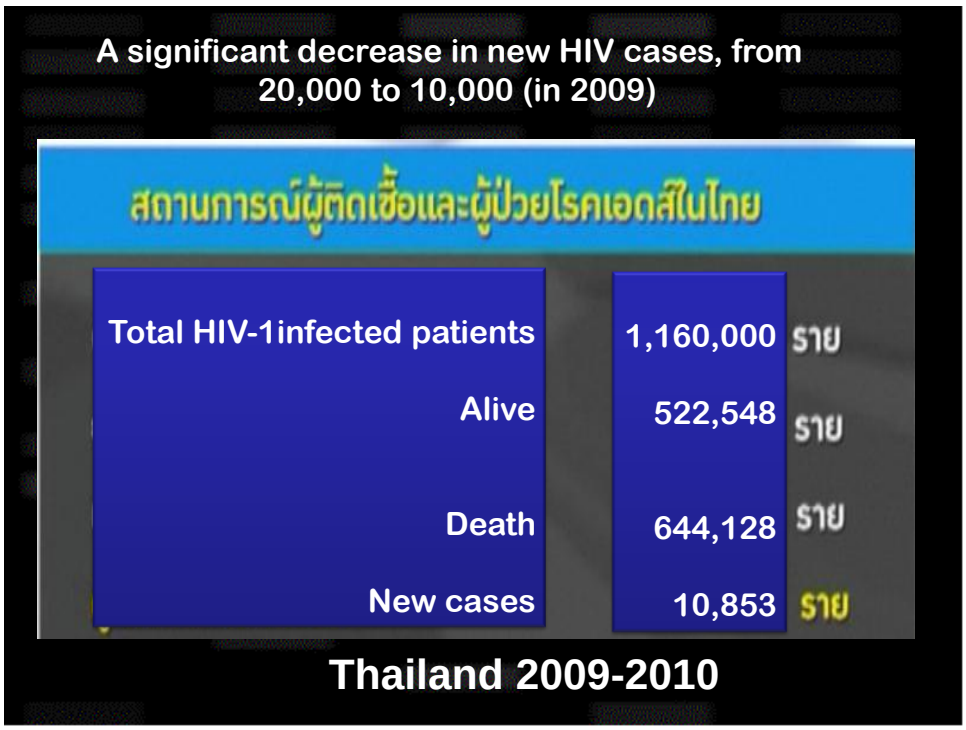
How about Thailand?



Thai Prime Minister Thaksin Shinawatra on Sunday in opening remarks at the XV International AIDS Conference pledged that his administration would provide antiretroviral drug treatment to all HIV-positive people who need it in Thailand, according to *Agence France-Presse* (*Agence France-Presse*, 7/11).

A remarkable event happened on World AIDS Day in 2004, when the Thai government adopted antiretroviral treatment in its Universal Health-Care System

In Thailand we have used ARV for more than 8 years, the good news is…



In Thailand,
the bad news is…

HIV Drug Resistance Rates => Increase!

เอดส์ดื้อยาพุ่ง หลังใช้ยารักษาหลายสูตร โดยเฉพาะผู้ป่วยเอดส์ที่ใช้สิทธิสิทธิบัตรทอง สูงถึง 140,000 คน จาก 2 แสนคน...

สปสช.
สำนักงานหลักประกันสุขภาพแห่งชาติ

เมื่อวันที่ 1 ธ.ค. นพ.สรกิจ ภาคีชีพ ผู้จัดการกองทุนเพื่อบริการผู้ติดเชื้อเอชไอวี ผู้ป่วยเอดส์ สำนักงานหลักประกันสุขภาพแห่งชาติ (สปสช.) กล่าวว่า ปัจจุบันผู้ติดเชื้อเอชไอวีที่ใช้สิทธิหลักประกันสุขภาพแห่งชาติ ที่ขึ้นทะเบียนและมีชีวิตอยู่มีจำนวน 140,000 คน โดยในจำนวนนี้ไม่สามารถใช้ยาสูตรพื้นฐานประมาณ 10,000 คน เนื่องจากมีภาวะดื้อยาสูตรแรก ทั้งยาซิโดวูดีน (Zidovudine) ลามิวูดีน (lamivudine) สตาวูดีน (stavudine) เอฟาไวเรนซ์ (Efavirenz) หรือ เนวิราพีน (Nevirapine) จึงต้องหันมาใช้ยาสูตรสำรองหรือยาสูตร 2 ซึ่งส่วนใหญ่จะใช้ยายาโลพินาเวียร์/ริโทนาเวียร์ (Lopinavir/Ritronavir) เป็นยาที่ประกาศสิทธิเหนือสิทธิบัตรยา หรือซีแอล นอกจากมีภาวะแทรกซ้อน อาทิ ไขมันสูง อาเจียน แพทย์จะเปลี่ยนเป็นยาอะทาซานาเวียร์ (Atazanavir) ซึ่งเป็นยาสูตร 2 เช่นกัน โดยยาดังกล่าวต้องมีข้อบ่งชี้ และต้องอนุญาตโดยแพทย์ เนื่องจากเป็นยาที่มีราคาแพง ตกค่าใช้จ่ายเดือนละ 5,000 บาท

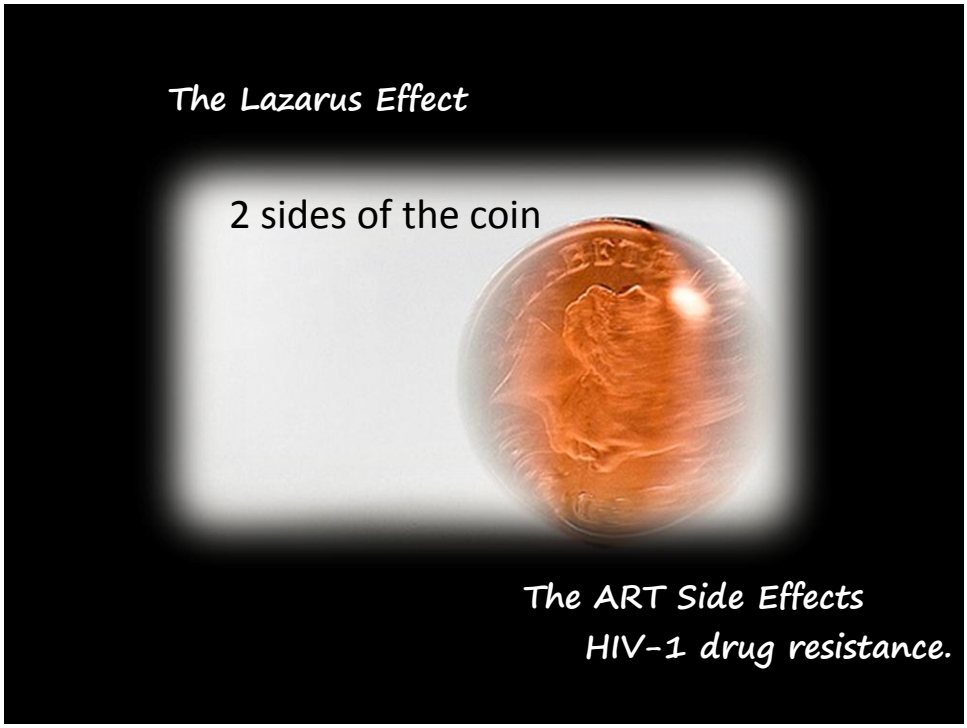
ปัจจุบันมีผู้ป่วยในระบบทานยาอะทาซานาเวียร์ประมาณ 500 คน แต่ที่น่ากังวลคือ ยังผู้

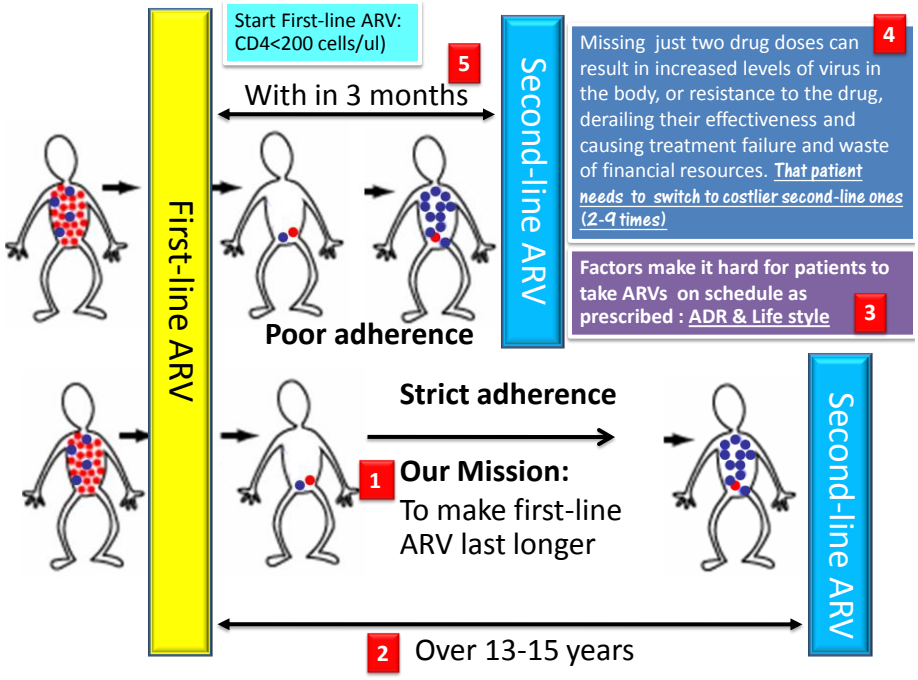
HIV-1 infected patients who are receiving antiretroviral drugs(ARV) => 140,000.

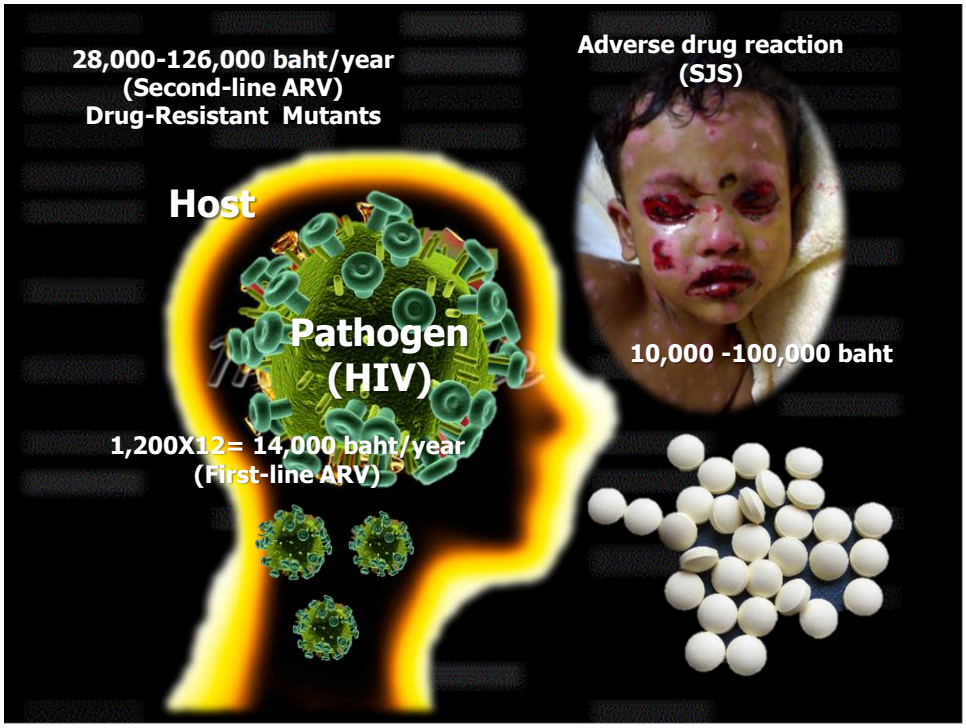
About 10,000 can no longer use the first line regimen (GPOvir) because of drug resistance (7%). Only, 500 are now being treated with the costlier second-line drugs(5,000 baht/month) under the supervision of HIV experts, and 300 (from 500) need the third line regimen due to the ADR of the second line regimen.

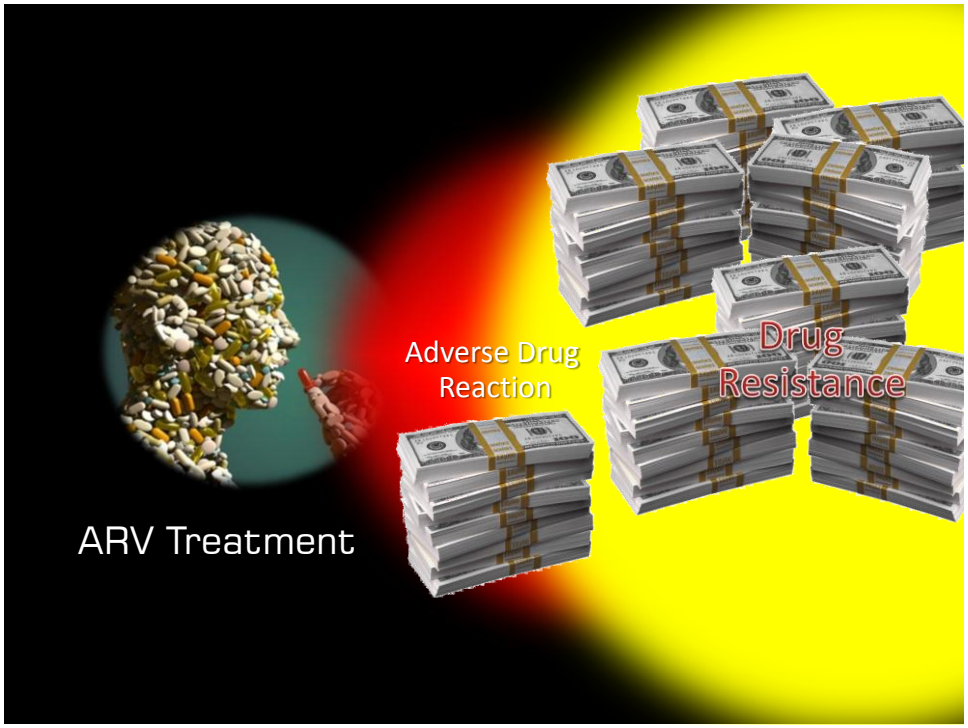
For those third line regimen (8,000 baht/month), it has not yet been included in the Universal healthcare coverage from the time being due to the high cost.

รักษาฟรีประมาณ 140,000 คน แต่มีประมาณ 500 คน ที่ต้องใช้ยากลุ่มนี้ ทำให้การนำเข้าสู่บัญชียาหลักไม่ใช่เรื่องง่าย อาจต้องรอให้ราคายาลดลงเหลือประมาณ 5,000 บาทต่อเดือน จากปัจจุบันตกเดือนละ 7,000-8,000 บาท" นพ.สรกิจ กล่าว.




First-line ARV
Start First-line ARV: CD4<200 cells/ul)
5
With in 3 months
Second-line ARV
4
Missing just two drug doses can result in increased levels of virus in the body, or resistance to the drug, derailing their effectiveness and causing treatment failure and waste of financial resources. That patient needs to switch to costlier second-line ones (2-9 times)
Factors make it hard for patients to take ARVs on schedule as prescribed : ADR & Life style
3
Poor adherence
Strict adherence
1
Our Mission:
To make first-line ARV last longer
Second-line ARV
2
Over 13-15 years

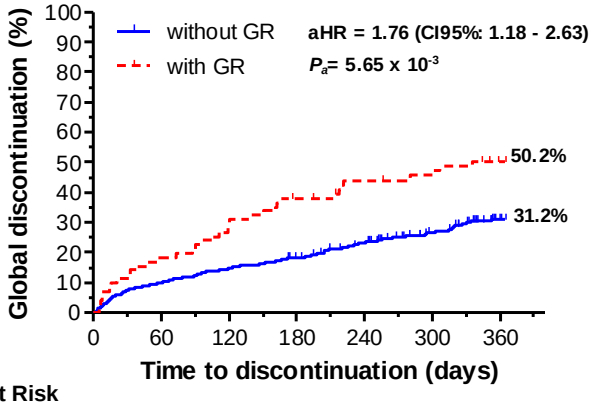

28,000-126,000 baht/year
(Second-line ARV)
Drug-Resistant Mutants
Adverse drug reaction
(SJS)
Host
Pathogen
(HIV)
10,000 -100,000 baht
1,200X12= 14,000 baht/year
(First-line ARV)


Adverse Drug Reaction
Drug Resistance
ARV Treatment


Genetic risk markers
Or
Genetic predictive markers

DRUGS WITH GENETIC MARKERS	INTERMEDIATE PHENOTYPE	CLINICAL EFFECT
*Efavirenz	High plasma levels	CNS toxicity
Atazanavir	Increased bilirubin	Gilbert syndrome
Lopinavir	Increased lipid levels	Cardiovascular diseases
Tenofovir	Phosphaturia, glucosuria, etc…	Renal toxicity
**Abacavir		Hypersensitivity
**Nevirapine		Hypersensitivity

577 individuals starting first line ART 2004-2007



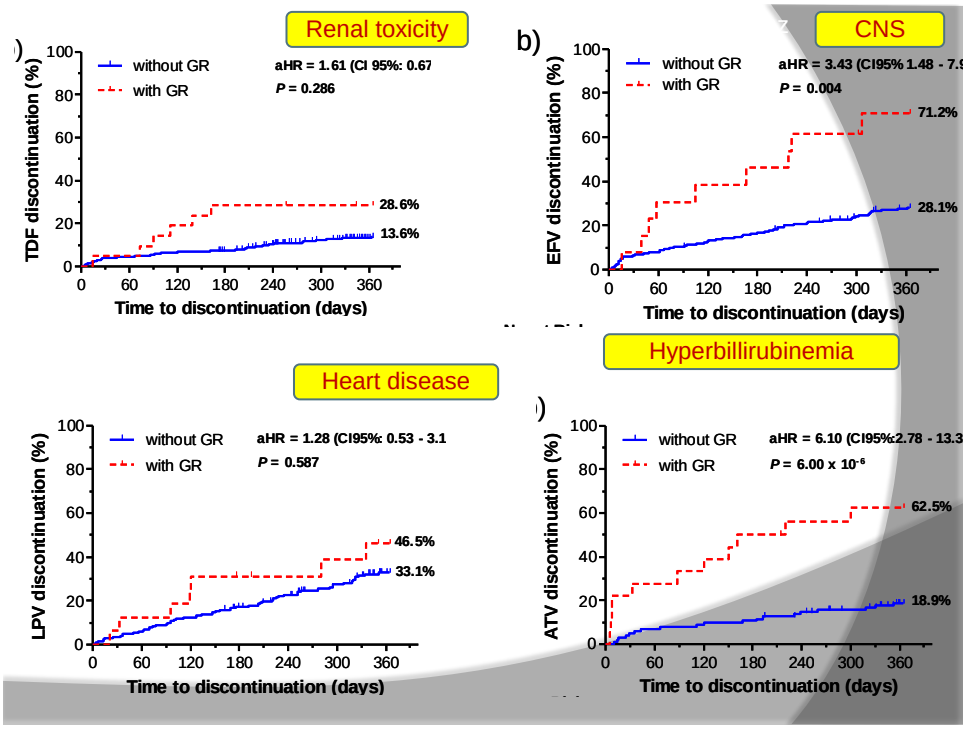
No. at Risk

without GR	506	458	432	411	380	347	305
with GR	71	59	51	44	38	35	29

SWISS HIV COHORT STUDY

Hypothesis

Individuals carrying genetic risk markers (GR) will discontinue the initial treatment more frequently/earlier than individuals without GR



The main cost considered in the pharmaco-economic analysis
(*Based on the evidence from Ramathibodi hospital, 2005)

		$/pt/day	$/pt/year	$/pt
①	NVP containing regimen (First-line regimen)* · GPOvir (NVP200/d4T30/3TC150)	2	890	-
②	Substitute for GPOvir (Second-regimen)* · EFV600/d4T30/3TC150	3	890	-
③	Drug resistant test	-	-	250
④	Treatment of SJS/TEN*			
	4.1 Supportive drug treatment			1,498
	4.2 Lab test (e.g. chemical pathology, haematology, serology, radiology and cultures)			137
	4.3 Outpatient clinic visit			967
	Total			2,603
⑤	Treatment of mild rash*			
	4.1 Supportive drug treatment			2
	4.2 Lab test (e.g. chemical pathology, haematology, serology, radiology and cultures)			1
	4.3 Outpatient clinic visit			487
	Total			490
⑥	Genetic test for prediction of NVP-induced skin rash	-		50

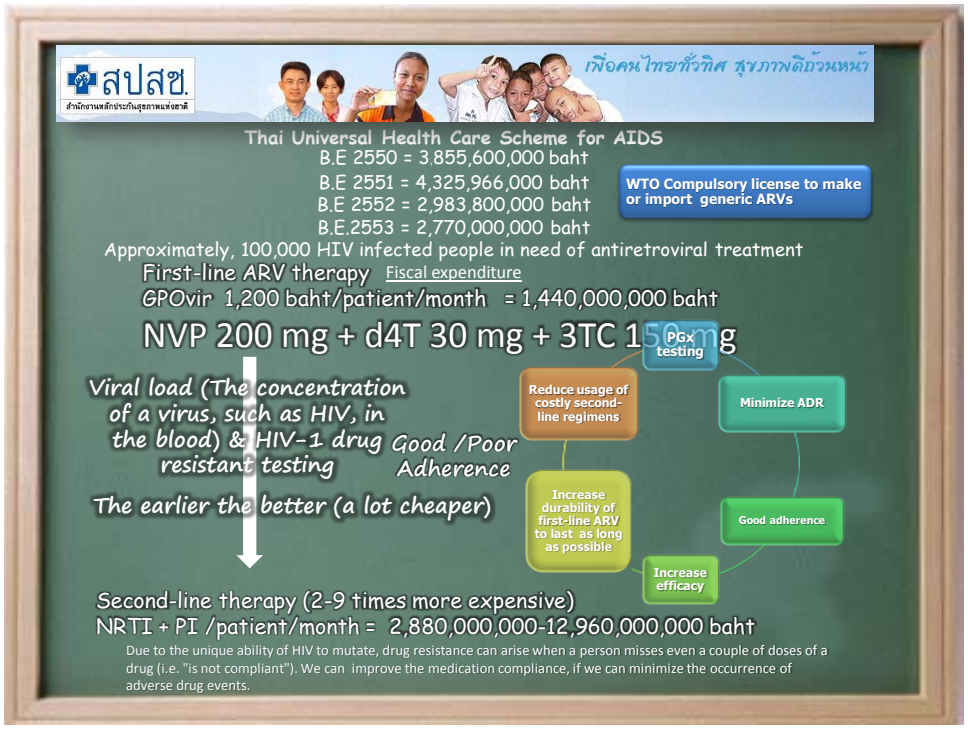
Individual crisis

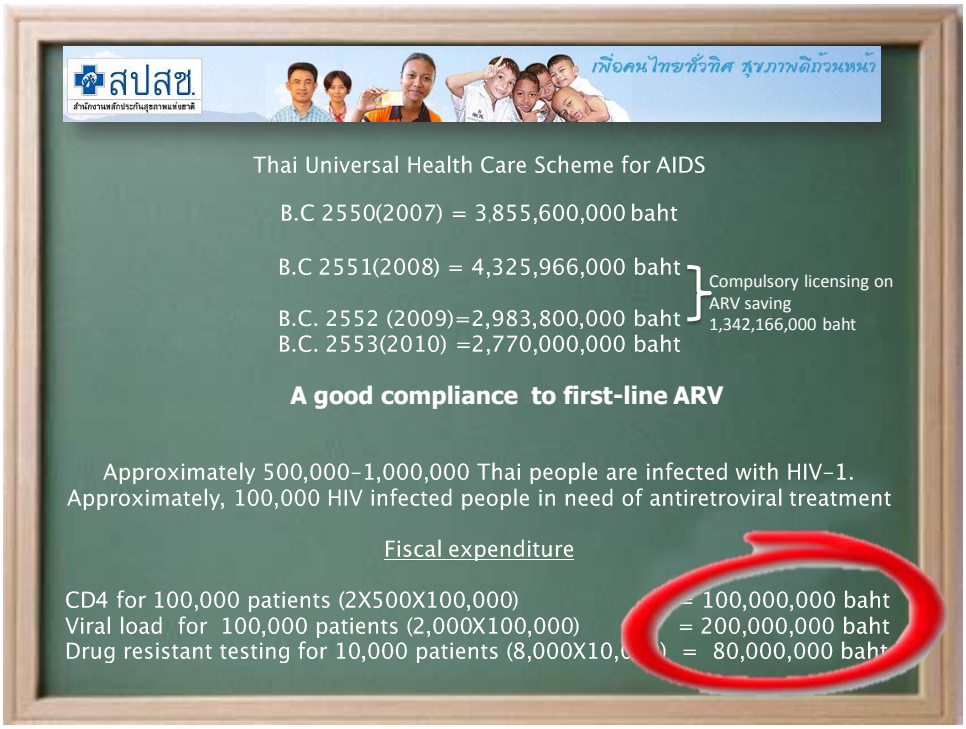
ประมาณ 1 แสนบาท

ประมาณ 2 หมื่นบาท

ประมาณ 2 พันบาท

Total expenditure on medical and diagnostic laboratory services in HIV-1 treatment





ยา 10 อันดับ ที่เกิดการแพ้ในประเทศไทย

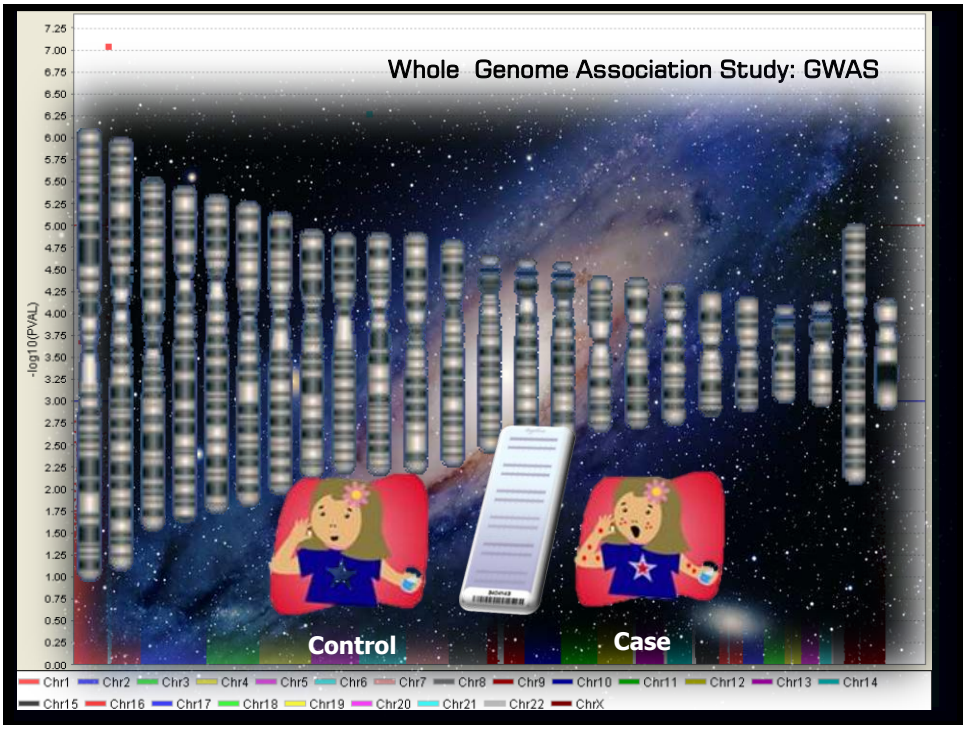
ชื่อยา	จำนวนคนแพ้ยา
1. SULFAMETHOXAZONE+ TRIMETHOPRIM	1,234
2. CARBAMAZEPINE	703
3. ALLOPURINOL	664
4. PHENYTOIN	451
5. AMOXYCILLIN	342
6. STAVUDINE + LAMIVUDINE+NEVIRAPINE	313
7. PHNOBARBITAL	189
8. IBUPROFEN	156
9. NEVIRAPINE	122
10. TETRACYCLINE	113

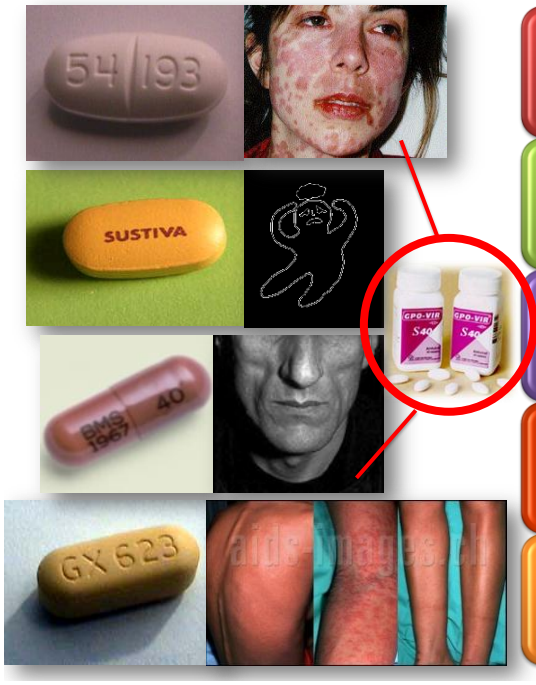
HLA-B

ข้อมูลจาก สำนักงานคณะกรรมการอาหารและยา, 2551

TCELS ผนึกรามาฯแถลงผลสำเร็จนักวิทย์ไทยค้นพบยีนแพ้ยาต้านเอดส์ครั้งแรกของโลก

TCELS ผนึกรามาธิบดี แถลงความสำเร็จการใช้เทคโนโลยี สกัดดีเอ็นเอ ตรวจวินิจฉัยยีนแพ้ยาและยีนก่อผลข้างเคียงจากการใช้ ยาต้านไวรัสเอดส์ " สตาวูดีน " ในผู้ป่วยแต่ละราย เป็นนวัตกรรมชิ้นโบว์แดงครั้งแรกในโลก เผยใช้ต้นทุนตรวจไม่ถึง 1,000 บาท แต่ผลสุดคุ้ม สามารถตรวจหายีนแพ้ยาได้หลายร้อยตัวในคราวเดียว ลดเสี่ยงอันตรายแพ้ยาซ้ำรอบ5 ปี พบคนไทยมียีนแพ้ยา 4 ตัว คือยาต้านอาการชัก ยาลดกรดยูริกและยาต้านไวรัส 2 ตัว พร้อมแบ่งปันประสบการณ์แพทย์ผู้สนใจทั่วประเทศ





Tenofovir: Acute renal failure

Nevirapine: Rash (15-20%), SJS (2.6%) : **HLA-B*3505** + SNPs

Efavirenz: CNS, strange dreams, day dreaming, more worired, more upset than usual. Up to 20% may switch over the first year.

D4T: Lipodystrophy 26% : **HLA-B*4001**+ SNPs

Abacavir: Hypersensitivity (reaction 5%), screening test (called **HLA-B*5701**), reduces this risk.

A non-p
HLA-B*3
finding.

Pharmacogenomics: Nevirapine — 2010

Nevirapine Sensitivity

Pharmacologic agent: Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1).

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS
Hepatoxicity: Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients. Female gender and higher $CD4^+$ cell counts at initiation of therapy place patients at increased risk; women with $CD4^+$ cell counts > 250 cells/mm^3, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk.

Skin Reactions: Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction.

Pharmacogenomic information: Patients who carry the HLA-B*3505 allele and are of Thai descent appear to be at high risk for developing a hypersensitivity skin reaction to nevirapine[1]. This finding needs to be confirmed in additional studies and other populations. The FDA has not changed the label at this time.

Action:
- **Screening for the HLA-B*3505 allele could be considered in patients of Thai descent who are being started on Nevirapine. If this is present consideration of an alternative may be appropriate.**

Reference & Resources
- Soranun, C. 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. 19:139-46.

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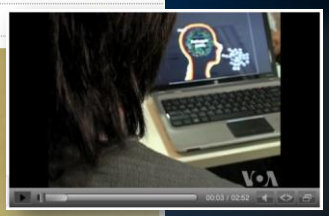
Thai Government Plans to Screen for HIV Drug Resistance

29 November 2010

Photo: VOA

A nurse preps an HIV-infected patient in Bangkok, Thailand, for a round of anti-retroviral drugs, Nov 2010



Many HIV-infected patients have adverse reactions to anti-retroviral drugs, and others fail to take the drugs properly, which means resistance to the drugs may increase.

In Thailand, the government plans to provide free DNA testing to screen for adverse reactions, to help reduce the threat of resistance.

Many HIV-infected patients have adverse reactions to anti-retroviral drugs, and others fail to take the drugs properly, which means resistance to the drugs may increase. In Thailand, the government plans to provide free DNA testing to screen for adverse reactions, to help reduce the threat of resistance.

One man in Bangkok had adverse reaction to an antiretroviral drug used to delay the onset of AIDS. He panicked, he said, when a rash turned his body red.

What worries experts is that such reactions force patients to stop treatment, creating the risk that they will develop resistance to the most effective and affordable HIV drugs.

In Thailand, Mahidol University's Wasun Chantratita studies DNA samples of HIV patients with adverse reactions to the antiretroviral drugs or ARVs. ARVs put pressure on the virus when taken as scheduled. But easing that pressure by pausing treatment means resistant cells may be able to replicate faster. Wasun said missing just two or three treatments can cause resistance.

"The resistance, when it happens, it means the medication can no longer control the virus," said Wasun.

Thailand has a very low resistance rate of about 2 percent, compared with 10 percent in some other countries. Laura Birmingham is the World Health Organization representative here. "But it's very important because you have 216,000 people on medicine and we would like to keep them on the first line of regimen as long as possible, not only for their own sake - it's a simpler regimen to take - but also because of the cost implication."

Thailand, like some other countries, manufactures generic versions of ARVs. That enables the government to provide free ARV treatment, using the so-called first-line drugs, at a cost of about $450 a year per patient.

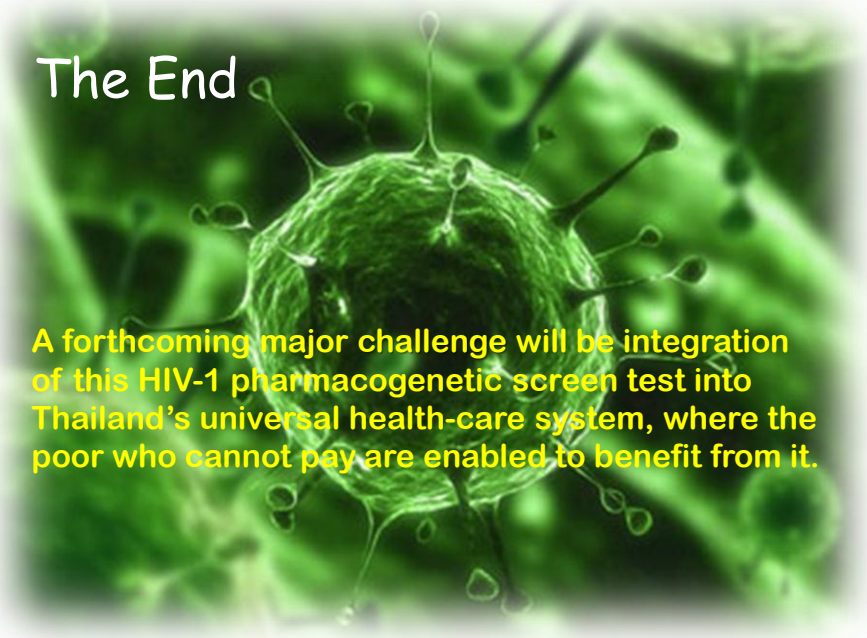
"If they resist to the first-line regimen, then we have to use the second-line which cost two to nine times higher than [we pay] right now," said Wasun.

Thai health professionals recently sought help from international experts on stemming adverse reactions and resistance to keep affordable generics useful for a longer time.

Professor Chen Yuan-Tsong of Taiwan's Academia Sinica helped discover DNA markers that can tell if a person will develop an adverse reaction. "We are all different. And one person is more sensitive to one particular drug than others. This is because of genetic makeup. Once you figure out what is this genetic makeup, then you can do the screening."

Screening patients' DNA enables doctors to avoid prescribing drugs that will cause a reaction.

Technicians at Mahidol University are testing a small device that can detect sensitivity to an ARV. They hope to bring this screening technology to hospitals and clinics in the countryside.


The End
A forthcoming major challenge will be integration of this HIV-1 pharmacogenetic screen test into Thailand's universal health-care system, where the poor who cannot pay are enabled to benefit from it.