Final Report

Pharmaceutical Equivalence Drugs Assessment-I (PEDA-I): Assess the pharmaceutical equivalence of generic antiretrovirals distributed in Thailand

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บทคัดย่อภาษาไทย

วัตถุประสงค์: ประเทศไทยมีแนวนโยบายที่จะขยายขอบข่ายการรักษา ผู้ป่วยติดเชื้อไวรัสเอชไอวีในทุกระดับซีดีสี่ เพื่อลดการกระจายเชื้อ และ การดำเนินโรคไปเป็นโรคเอดส์เต็มขั้น เมื่อพิจารณาจากสภาพเศรษฐกิจ ยาในรูปแบบยาสามัญจึงถูกนำมาใช้อย่างแพร่หลายเนื่องจากมีความจำเป็นในแง่ของประสิทธิผลและความคุ้มทุน แต่ในอดีตจนถึงปัจจุบัน ได้มีรายงานอุบัติการณ์ที่เกี่ยวกับยาที่มีคุณภาพต่ำกว่ามาตรฐานเทียบกับยาต้นแบบในประเทศด้อยหรือกำลังพัฒนา ซึ่งมีผลเสียต่อผู้ป่วยและระบบสุขภาพ ดังนั้นการประกันคุณภาพยาให้ได้มาตรฐานเป็นหนึ่งสิ่งที่จำเป็นเพื่อให้เกิดความมั่นใจในด้านประสิทธิภาพและความปลอดภัยของยานั้นๆ โครงการวิจัยนี้เป็นการศึกษาวิจัยเพื่อประกันคุณภาพยาโดยสุ่มยาต้านไวรัสเอชไอวี ในรูปแบบสามัญตามแหล่งต่างๆในประเทศไทย รวมถึงประเทศเวียดนาม

วิธีการ: โครงการนี้ได้สุ่มตัวอย่างยาสามัญ Tenofovir 300 mg, Efavirenz 600 mg และ Lopinavir/ritonavir 200/50mg จากโรงพยาบาลชุมชน 10 แห่งตามภาคต่างๆในประเทศไทยที่มีการจ่ายยาต้านตามสิทธิ์สปสช. คลินิกที่การจ่ายยาต้านไวรัส 2 แห่ง และร้านขายยาเอกชนอีก 3 แห่ง (ในประเทศไทย 2 แห่งและเวียดนาม 1 แห่ง) ทีมผู้วิจัยจากคณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัยเป็นผู้วิเคราะห์คุณภาพยา โดยการตรวจสอบชนิดและปริมาณของสารออกฤทธิ์ในเม็ดยา ความสม่ำเสมอของมวลเม็ดยาและการละลาย โดยเปรียบเทียบกับค่ามาตรฐานที่อ้างอิงกับตำรับยานานาชาติขององค์การอนามัยโลก

ผลการศึกษา: โครงการสุ่มยาตัวอย่างทั้งหมด 42 ชุด จากทั้งหมด 15 แหล่ง ในเดือนมกราคม-มีนาคม พศ.2558 ซึ่งยาเหล่านี้เป็นยาสามัญที่ผลิตในประเทศไทย 23 ชุด ประเทศอินเดีย 17 ชุด ประเทศจีน 1 ชุด และประเทศเวียดนาม 1 ชุด การวิเคราะห์ยาพบว่า ยาตัวอย่างทั้งหมดมีค่าการวิเคราะห์เข้าได้กับมาตรฐานตำรับยานานาชาติ แต่อย่างไรก็ตามทางทีมวิจับพบว่า การซื้อยาต้านจากร้านขายยาทั่วไปสามารถทำได้โดยไม่ต้องมีขบวนการสั่งยาจากแพทย์

สรุป: การศึกษาวิจัยนี้พบว่า ตัวอย่างยาต้านไวรัสเอชไอวีที่สุ่มมามีคุณภาพที่ได้มาตรฐาน แต่การที่ยาต้านสามารถหาซื้อได้จากร้านขายยาอาจมีผลทำให้ผู้ติดเชื้อเอชไอวีขาดการติดตามการรักษาที่เหมาะสม ซึ่งอาจส่งผลต่อเนื่องในแง่การกินยาสม่ำเสมอระยะยาว และการดื้อยาต่อไป

Pharmaceutical Equivalence of Distributed Generic Antiretroviral (ARV) in Asian settings: the cross-sectional surveillance study -PEDA study

Abstract

Objectives: Ensuring that medicines meet quality standards is mandatory for ensuring safety and efficacy. There have been occasional reports of substandard generic medicines, especially in resource-limiting settings where policies to control quality may be less rigorous. As HIV treatment in Thailand depends mostly on affordable generic antiretrovirals (ARV), we performed quality assurance testing of several generic ARV available from different sources in Thailand and a source from Vietnam.

Methods: We sampled Tenofovir 300 mg, Efavirenz 600 mg and Lopinavir/ritonavir 200/50mg from 10 primary hospitals randomly selected from those participating in the National AIDS Program, 2 non-government organization ARV clinics, and 3 private drug stores. Quality of ARV was analyzed by blinded investigators at the Faculty of Pharmaceutical Science, Chulalongkorn University. The analysis included an identification test for drug molecules, a chemical composition assay to quantitate the active ingredients, a uniformity of mass test and a dissolution test to assess in-vitro drug release. Comparisons were made against the standards described in the WHO international pharmacopeia.

Results: A total of 42 batches of ARV from 15 sources were sampled from January – March 2015. Among those generics, 23, 17, 1 and 1 were Thai-made, Indian-made and Chinese-made and Vitenam-made respectively. All sampled products, regardless of manufacturers or sources, met the International Pharmacopeia standards for composition assay, mass uniformity and dissolution. Although local regulations restrict ARV supply to hospitals and clinics, samples of ARV could be bought from private drug stores even without formal prescription.

Conclusion: Sampled generic ARVs distributed within Thailand and 1 Vietnamese pharmacy showed consistent quality. However some products were illegally supplied without prescription, highlighting the importance of dispensing ARV for treatment or prevention in facilities where continuity along the HIV treatment and care cascade is available.

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Introduction

In 2014, there were an estimated of 450,000 people living with HIV in Thailand, with 8000 total new infections[1]. Since there is no definitive cure, HIV is a chronic disease requiring life-long treatment. In October 2014, new Thai National HIV/AIDS guidelines were launched which recommend initiating treatment "regardless of CD4 count"[2]. Early ARV initiation has public health benefits by minimizing sexual transmission of HIV[3], and also benefits the individual by preventing the development of serious AIDS and non-AIDS-related events[4]. While there is an attempt to scale up ARV for HIV infected individuals, drug accessibility remains a global challenge, especially where financial resources are constrained[5]. In Thailand, 100% of financial resources for HIV treatment are domestic[1]; the country depends mostly on generic ARV products.

Generic drugs, according to U.S. food and drug administration (FDA), are the same as their branded counterparts in dosage, strength, safety, route of administration, indication and action; in fact, they are supposed to be therapeutically equivalent. By FDA regulations, a generic drug must contain an identical amount of the active ingredient(s) as in the branded product. The active ingredient is any component in a tablet that produces the pharmacological effect for an expected medical purpose[6]. The Thai FDA has guidelines for approval of generic drugs which requires evidence of product interchangeability equivalence, namely bioequivalence studies, comparative in vitro dissolution/release studies, comparative clinical studies, and comparative pharmacodynamics studies[7]. The World Health Organization (WHO) has defined two specific terms that relate to quality aspects of medicines: substandard and counterfeit medicines. Substandard medicines are legal products that do not meet quality standards and specifications; they may occur as a result of human error, negligence, or resource restriction. In contrast, counterfeit or fake drugs are intentionally and fraudulently disguised regarding drug components, active ingredients, packaging and labeling, and are made illegally by non-licensed companies[8].

Incidents regarding poor-quality generic drugs have been regularly reported, particularly among life-saving anti-infective drugs within resource-limiting regions where there are less rigorous restrictions on procurement and sale, and less public awareness[9-11]. According to the U.S. Pharmacopeial Convention (USP) reports during 2003-2013, the proportion of substandard medicines in Asia was 2.9%; lower than that described in Africa and South America. However, Asia was reported to have the

highest proportion of counterfeit medicines with a total number of 70 samples (out of 81 counterfeit products), representing 86% of sampled counterfeit products. Prevalence of sampled substandard medicine in Asia was 2.9% and Thailand was one of the least consistent in reporting data to a medicines quality database[12]. Problems associated with poor-quality drugs include increased morbidity and mortality, unnecessary adverse effects, suboptimal treatment leading to drug resistance, and also loss of confidence in health systems and waste of financial resources[13]. Therefore, it is very important for generic ARVs to be consistently monitored. Our study sampled generic ARV available from different sources in Thailand and assessed the quality by analyzing the pharmaceutical equivalence of the products.

Method:

Sampling from sources

In order to represent ARVs distributed in Thailand, we obtained ARVs from primary hospitals participating in the National Universal Coverage program under the auspices of the National Health Security Office (NHSO), non-government organization (NGO) ARV clinics, and private drug stores. From a total of 603 primary hospitals that distributed ARVs through the NHSO (assessed data August 2011), two hospitals in each of the 5 regions of the country (North, South, East, West, and Central) were randomly selected. For NGO sources, we collected ARV from the Thai Red Cross AIDS Research Center and the HIV-Netherlands-Australia-Thailand Research Collaboration (HIVNAT) pharmacies. For private sources, we bought ARV from 2 private pharmacies in Bangkok and 1 private pharmacy in Vietnam. [Manuscript]

Selection of ARVs

We selected two preferred first line ARVs (Tenofovir (TDF) 300mg and Efavirenz (EFV) 600mg) and one preferred second line ARV (Lopinavir/ritonavir (LPV/r) 200/50mg) recommended in the Thai National HIV/AIDS guidelines for this study. Each ARV sample contained an adequate amount of tablets for Pharmaceutical analysis (at least 90 tablets), and had a shelf life extending beyond the analysis date. [Manuscript]

Drug profile:

- **Tenofovir (TDF)** belongs to Nucleoside Reverse Transcriptase Inhibitor class (NRTI). In Thailand, there is in a single tablet formulation, or combines with emtricitabine as Truvada or with emtricitabine (FTC) and efavirenz (EFV) as Atripla. There are three branded products (Viread, Truvada and Atripla) and two generics (Tenofovir, and Ricovir-EM). According to international pharmacopoeia, Tenofovir tablets contain tenofovirdisoproxilfumarate not

less than 90.0% and not more than 110.0% of the amount of tenofovirdisoproxilfumarate, stated on the label.

- **Efavirenz (EFV)** belongs to Non-nucleoside Reverse Transcriptase Inhibitor class (NNRTI). In Thailand, it is available in both capsule and tablet formulations. There are five branded products (Stocrin 50 mg, 200 mg, 600 mg and combination as Atripla) and two generics (Efavirenz 200 mg, 600mg). According to international pharmacopoeia, Efavirenz tablets contain not less than 90.0% and not more than 110.0% of the amount efavirenz, stated on the label.
- **Lopinavir/ritonavir (LPV/r)** belongs to Protease Inhibitors class (PIs). In Thailand, there is in tablet, capsuleand solution formulation. There are three branded product (Aluvia LPV/r 100mg/25mg and Kaletra LPV/r 133mg/33mg and oral solution 80 mg/20 mg) and two generic product (LPV/r 200mg/50mg and oral solution 80 mg/20 mg). According to international pharmacopoeia, Lopinavir and ritonavir tablets containlopinavir and ritonavir not less than 90.0% and not more than 110.0% of the amounts of lopinavir and ritonavir, stated on the label.

Collection of ARVs

For hospital sources, Local Pharmacists (who voluntarily collaborated with this study) were asked to randomly collect 1-3 bottles of each designated ARV from dispensing shelves. In addition, they completed a drug record form for each ARV sample, recording information including product name, dose, batch number, storage condition, manufactured date and expiry date. Pharmacists then shipped sampled ARVs along with completed drug record forms to the study team. Transportation to the analysis site was done using the Thai Express Mail Service and temperature was monitored during shipment.

For NGO ARV clinics and private sources, ARVs were bought by study coordinators. LPV/r (200/50mg) tablets were unavailable at 2 NGO clinics and 1 private pharmacy. Required documents including temperature assessment were not available for ARV purchased from the private pharmacies.

Pharmaceutical Analysis of ARVs

Evaluation of ARVs quality was conducted according to standard procedures for pharmaceutical analysis described under specific product monographs, namely, Lopinavir and Ritonavir tablets, Efavirenz tablets, and Tenofovir tablets, published in the International Pharmacopeia (4^{th} edition) by WHO. To assess the quality of medicines in this study, four different parameters including identity test, assay, uniformity of mass, and dissolution were selected for ARVs analysis. Counterfeit medicines are commonly associated with the absence of the active substance. Therefore, the Identity test was conducted to confirm the presence and identity of the active substance in the tested formulation. The content and strength of drug were determined by a quantitative assay of the amount of active substance in dosage form. Uniformity of mass was tested to confirm homogeneity of the amount of active substances among tablets manufactured in the same batch. Dissolution of ARVs, with the exception of Efavirenz tablets due to the lack of an official analytical method in pharmacopeia, was conducted to test the performance of the ARV tablet that the drug substance will release with an acceptable rate which greatly affects the bioavailability of the medicine. Drug analysis was performed by the Pharmaceutical Technology Service Center, Faculty of Pharmaceutical Science, Chulalongkorn University. Evaluation of ARV quality was based on acceptance criteria of each specification described in the drug monograph. Sources and storage conditions were blinded from the analysts[14].

Result

Table 1.A Lopinavir (200 mg)/Ritonavir (50 mg) drug sources and characteristics

Site ID	Lot No.	Manu-facturer	country	Trade name	WHO Pre-qualified	Expiry date	Iden-tification for LPV/RTV	% of label amount LPV/RTV	Uniformity, %		Dissolution, % (LPV/RTV)	
									Min	Max	Min	Max
001	W570041	GPO	THA	Lopinavir/ Ritonavir	NO	21Jan16	Positive	102.1/ 100.8	-1.20	1.64	97.6/ 98.8	98.2/ 99.7
002	W560404	GPO	THA	Lopinavir/ Ritonavir	NO	13Jul15	Positive	103.2/ 102.4	-1.28	1.48	98.1/ 100.8	99.1/ 102.2
003	W570169	GPO	THA	Lopinavir/ Ritonavir	NO	17Mar16	Positive	102.1/ 103.6	-1.11	1.25	99.1/ 100.0	101.2/ 103.1
004	W570175	GPO	THA	Lopinavir/ Ritonavir	NO	17Mar16	Positive	101.0/ 103.3	-2.22	2.08	97.7/ 99.0	101.9/ 102.5
005	W570450	GPO	THA	Lopinavir/ Ritonavir	NO	17Jul16	Positive	99.4/ 101.8	-2.16	1.07	97.5/ 99.0	101.3/ 102.8
006	W560432	GPO	THA	Lopinavir/ Ritonavir	NO	23Jul15	Positive	99.0/ 103.0	-2.10	1.87	98.5/ 100.3	102.6/ 104.6
007	W570457	GPO	THA	Lopinavir/ Ritonavir	NO	20Jul16	Positive	98.6/ 101.5	-1.74	2.05	98.7/ 95.0	99.8/ 97.0
008	W570152	GPO	THA	Lopinavir/ Ritonavir	NO	10Mar16	Positive	99.4/ 101.4	-2.09	1.76	96.2/ 99.0	98.7/ 102.8
009	W570285	GPO	THA	Lopinavir/ Ritonavir	NO	15May16	Positive	98.4/ 101.0	2.53	1.94	96.8/ 99.9	99.8/ 102.7
010	W560556	GPO	THA	Lopinavir/ Ritonavir	NO	22Oct15	Positive	97.8/ 101.5	-1.47	1.70	99.1/ 101.4	101.7/ 103.7
011	W570169	GPO	THA	Lopinavir/ Ritonavir	NO	17Mar16	Positive	98.2/ 101.2	-1.33	1.52	94.9/ 100.0	97.6/ 102.8
012	8000458	Mylan	IND	Lopinavir/ Ritonavir	YES	30Jun16	Positive	99.7/ 101.4	1.69	1.31	93.4/ 96.3	98.6/ 102.9

Abbreviations: Lopinavir,LPV; Ritonavir, RTV; the Government Pharmaceutical Organization, GPO; Thailand, THA; India, IND.

Table 1.B Tenofovir (300 mg) drug sources and characteristics

Site ID	Lot No.	Manu-factu rer	country	Trade name	WHO Pre-quali fied	Expiry date	Iden-tification	% of label amount	Uniformity, %		Dissolution, %	
									Min	Max	Min	Max
013	A570270	GPO	THA	Tenofovir GPO 300	NO	12Feb16	Positive	103.0	-0.81	1.46	102.3	103.3
014	A562265	GPO	THA	Tenofovir GPO 300	NO	27Jun15	Positive	100.0	-1.84	1.08	100.5	101.2
015	A570273	GPO	THA	Tenofovir GPO 300	NO	12Feb16	Positive	101.6	-1.44	1.26	101.1	102.8
016	A570554	GPO	THA	Tenofovir GPO 300	NO	18Mar16	Positive	99.6	-1.16	1.17	99.6	101.5
017	A570375	GPO	THA	Tenofovir GPO 300	NO	20Feb16	Positive	102.4	-1.34	0.70	98.7	101.8
018	A570324	GPO	THA	Tenofovir GPO 300	NO	17Feb16	Positive	103.4	-1.45	0.80	99.3	101.4
019	A570560	GPO	THA	Tenofovir GPO 300	NO	20Mar16	Positive	100.3	-1.42	1.19	100.9	102.4
020	A570322	GPO	THA	Tenofovir GPO 300	NO	13Feb16	Positive	98.6	-1.08	1.21	100.2	102.5
021	A570557	GPO	THA	Tenofovir GPO 300	NO	19Mar16	Positive	98.4	-0.79	1.19	101.0	104.3
022	A570742	GPO	THA	Tenofovir GPO 300	NO	22Apr16	Positive	97.0	-0.82	1.18	101.0	102.2
023	8027079	Mylan	IND	RICOVIR	YES	31Jul17	Positive	102.5	-4.54	4.47	98.2	100.9
024	020414	STADA	VN	Tenofovir STADA	NO	02Feb16	Positive	100.6	-2.49	2.05	96.9	100.9
025	2507153	RANBAXY	IND	TEVIR	NO	31Mar15	Positive	98.0	-1.42	1.21	100.3	101.6
026	8027079	Mylan	IND	RICOVIR	YES	31Jul17	Positive	98.4	-2.61	3.55	96.7	101.0
027	E131707	Hetero	IND	TENOF	YES	31Jul15	Positive	97.5	-2.10	2.14	90.3	109.0

Abbreviations: Tenofovir, TDF; the Government Pharmaceutical Organization, GPO; Thailand, THA; India, IND; Vietnam, VN.

Table 1.C Efavirenz (600 mg) drug sources and characteristics

Site ID	Lot No.	Manu-facturer	country	Trade name	WHO Pre-qualified	Expiry date	Iden-tification	% of label amount	Uniformity, %		Dissolution, %	
									Min	Max	Min	Max
028	EM27186	Mylan	IND	Efavirenz	YES	31May17	Positive	96.3	-2.22	1.25	-	-
029	EM35108	Emcure	IND	Efavirenz	YES	30Apr15	Positive	96.8	-1.83	2.21	-	-
030	3027189	Mylan	IND	Efavirenz	YES	31May17	Positive	96.9	-1.86	1.62	-	-
031	3027187	Mylan	IND	Efavirenz	YES	31May17	Positive	97.6	-2.85	1.67	-	-
032	3027185	Mylan	IND	Efavirenz	YES	31May17	Positive	97.3	-2.21	1.84	-	-
033	3027486	Mylan	IND	Efavirenz	YES	31May17	Positive	97.8	-1.06	0.80	-	-
034	3031217	Mylan	IND	Efavirenz	YES	30Sep17	Positive	97.6	-1.11	1.14	-	-
035	A570303	GPO	THA	Efavirenz	NO	10Sep15	Positive	95.4	-1.56	1.28	-	-
036	3031198	Mylan	IND	Efavirenz	YES	31Aug17	Positive	97.8	-1.51	1.83	-	-
037	3031240	Mylan	IND	Efavirenz	YES	30Sep17	Positive	97.7	-1.76	1.91	-	-
038	3026355	Mylan	IND	EFAMAT	YES	30Ap17	Positive	96.8	-2.25	2.08	-	-
039	EFZ113033A	Hetero	IND	ESTIVA-600	YES	30Nov16	Positive	98.9	-0.98	0.86	-	-
040	A570845	GPO	THA	Efavirenz	NO	22Oct15	Positive	95.6	-2.08	2.25	-	-
041	Y1723	Zhejian Huahai Pharmaceutical	CHI	STOCRIN	YES	03Mar16	Positive	95.6	-1.01	0.75	-	-
042	E140542	Hetero	IND	ESTIVA-600	YES	28Feb17	Positive	94.9	-2.59	1.02	-	-

Abbreviations: Efavirenz, EFV; the Government Pharmaceutical Organization, GPO; Thailand, THA; China, CHI; India, IND.

Table 2 Descriptive statistics of drug content, uniformity and dissolution test

ARV	N	% of label amount (L.A.)				Uniformity, %			Dissolution, %		
		WHO Spec.	Min	Max	Mean (SD)	WHO Spec.	Min	Max	WHO Spec.	Min	Max
LPV /RTV	12	90.0–110.0%	97.8/ 100.8	103.2/ 103.6	99.9 (1.76)/ 101.9 (0.93)	±5%	-2.53	2.08	≥ 80% L.A.	93.4/9 5.0	102.6/1 04.6
TDF	15	90.0 110.0%	97.0	103.4	100.1 (2.10)	±5%	-4.54	4.47	≥ 80% L.A.	90.3	109.0
EFV	15	90.0-110.0%	94.9	98.9	96.9 (1.11)	±5%	-2.85	2.25	-	-	-

Abbreviations: Lopinavir,LPV; Ritonavir, RTV; Tenofovir, TDF; Efavirenz, EFV; Label amount, L.A.; Standard deviation, SD

Forty-two batches of ARV (TDF, EFV, LPV/r) from 15 sources (10 primary hospitals, 2 NGO clinics and 3 private drug stores) were collected between January - March 2015. Temperature during shipment of ARV samples from sites to the analysis facility did not substantially exceed 30 °C, except for 5 shipments from primary hospitals where the temperature was over 30^{0} C for ≤2 hours. All ARV samples came in the original package and no broken pills were observed. Of 15 TDF samples collected, 10 samples (from all hospitals) were made locally in Thailand (not WHO prequalified); the rest were generics made in India (3 WHO prequalified, and Vietnam (1 not WHO prequalified)). Fifteen samples of EFV were collected. Two samples (1 each from a primary hospital and 1 from an NGO clinic) were Thai-made generics (not WHO prequalified), 1 sample was a generic made in China (WHO prequalified) and the rest were Indian-made generics (WHO prequalified). LPV/r obtained from the 10 hospital sources was a Thai-made generic formulation (not WHO prequalified). We also sampled 1 Thai-made (not WHO prequalified) and 1 Indian-made (WHO prequalified) LPV/r generic tablets from 2 private sources (Assess the WHO prequalification database at http://apps.who.int/prequal/)[15]. [Table 1.A.B.C]

For ARV obtained from hospital sources, *ARV Storage conditions* were assessed from self-administered questionnaires completed by a hospital pharmacist. Nine out of 10 hospitals had air conditioned storage facilities with temperature less than 30 °C. Seven out of 10 hospitals had humidity monitoring. Humidity was less than 60 % relative humidity (RH) at most of the hospitals where monitoring was undertaken. There was 1 site with humidity of 67 %RH. One hospital site had neither humidity nor temperature monitoring, because drugs were stored at the ARV clinic, not in pharmacy facility. NGO ARV clinics also had temperature and humidity controlled to be less than 30 °C and 60 %RH respectively. We could not assess storage conditions at private pharmacies. Of note, while a doctor's prescription is required for ARV dispensed at hospitals and the NGO ARV clinics, no formal prescription was needed in the private pharmacies where our ARV samples were procured.

Identification test and Chemical composition assay

The drug identities are demonstrated by the same retention time as corresponding International pharmacopeia reference standards using the relevant drug content assay. Each sample met the International pharmacopeia standard for drug content [Figure 3]. Mean drug content values, as described in [Table 2], were close to 100% of the labelled amount; 99.9%/101.9% for LPV/r, 100% for TDF, and 96.9% for EFV. The standard deviations of all drug content assay values were relatively close; 1.76/0.93 for LPV/r, 2.10 for TDF, and 1.11 for EFV.

Uniformity of mass

Uniformity of mass was used to assess uniformity of production batch for all the samples. The results ranged from -2.53% to 2.08% for LPV/r, -4.54% to 4.47% for TDF and -2.85% to 2.25% for EFV. All results were within the accepted values which range from -5% to 5%. The % deviation under uniformity of mass is calculated from the difference between the weight of individual unit and the average weight of the sample. The acceptance range is based on the criteria in the International pharmacopeia.

Test for dissolution

For dissolution tests, the cumulative amount of drug (percentage of labelled amount) that dissolves over a period of time in a dissolution medium is measured. As shown in Table 2, LPV/r and TDF samples comply with the international pharmacopeia dissolution test limit of ≥ 80% of the labeled amount.

There was no significant association between sources of ARV, WHO prequalification status, manufactured sites and storage conditions and the results of this pharmaceutical equivalence analysis.

Discussion:

The primary goal of this research study was to perform independent surveillance on the quality of commonly used generic ARV available for patients in Thailand. Although this could not represent whole ARV distributing in the region, the findings showed satisfactory quality of all ARV samples from different sources and types based on drug content, uniformity of mass and dissolution even though some batches (including those manufactured in Thailand) are not WHO prequalified. TDF test results varied most widely when compared to EFV and LPV/r, however all parameters were within the International Pharmacopeia standards. These wider ranges might reflect more variability in manufacturing sites of TDF, while LPV/r samples were retrieved from a smaller number of manufacturers. Although our findings are supported by previous studies[16-18], two samples of ARV from Thailand were found to be substandard in a USP convention database report in 2008 (http://www.usp.org/worldwide/medQualityDatabase)[19] . Therefore, continuous monitoring is required to ensure that products used in National Treatment Programs meet the quality standards necessary to ensure an effective and safe response to HIV. In addition, counterfeit medicines, particularly anti-malarials have frequently been found when reviewing the quality of medicines in Southeast Asian countries[9, 10] , and WHO estimates the use of counterfeit drugs causes approximately 1 million deaths per year[20].

Although ARVs are life-saving medications, they can cause adverse events if taken incorrectly and reduce a patient's options for future treatment if they continue to be dosed in the presence of genotypic resistance. HIV care is life-long and requires multidisciplinary support, and monitoring of viral load and other safety parameters. Our finding that generic ARV could be purchased from two private pharmacies without a formal prescription, despite their supply being restricted only to hospitals and registered clinics, highlights the important public health issue of getting patients into the proper healthcare system cascade. Self-treatment with ARV, either for treatment or prevention, without proper follow up from healthcare professionals skilled in managing HIV might lead to adverse events, adherence problems, and consequently drug resistance[21-23]. While we promote ARV accessibility by generic

importation/licensing, regulation is necessary to ensure that ARV are dispensed with a proper monitoring and follow-up system in place.

There are some limitations of our study. First, the small number of ARV samples assayed limits the power to detect any abnormalities. However, we maximized our resources by randomly selecting a majority of primary hospitals where they supposedly have the least quality control systems. Second, almost all LPV/r sampled were Thai-made generics; this reflects the situation in the past that Thailand had issues compulsory licenses for antiretroviral drugs including Abbott's Kaletra®, to cope with the enormous expenditure necessary to provide life-long treatment with ARV for approximately 1% of the population. Nevertheless, although Thai ARV are not WHO pre-qualified, a study has shown comparable pharmacokinetics between Thai generic and Indian generics[24] , and the Thai FDA has rigorous standards for bioequivalence. Finally, although we were unable to include all pharmaceutical analysis methods, namely impurities and breaking forces, we covered the three most important components relating to bioavailability and efficacy: active ingredient, uniformity and dissolution. Some strengths of our study are also noteworthy. The sampling and collection of ARV were processed in systematic and fashion. In addition, our ARV sources and storage conditions were blinded from analysts so they did not pose any bias during analysis. Lastly, while occasional surveillance of drug quality in Thailand already takes place[25] , the surveillance might not focus on ARV. Our study is independent and focuses on commonly used ARV in the Thai National Treatment Program.

Suggestion and study further :

In conclusion, many sectors in Thailand have worked together to scale up ARV treatment; this study ensures the quality of the sampled drug being utilized, emphasizes further continuous monitoring, and at the same time, points out that ARV dispensing should occur in facility-based settings where regular follow-up and care are delivered.

Study Outcome :

Besides ensuring the quality of sampled generic ARV, the study helps in setting up system for independent quality monitoring of drugs. It could be scaled up in term of drug classes and sites, covering Asean Economic Community which will formally start at the end of 2015.

The study team has written the manuscript named "Pharmaceutical Equivalence of Distributed Generic Antiretroviral (ARV) in Asian settings: the cross-sectional surveillance study -PEDA study". It was submitted to journal and in the process of review.

Publication :

See Apendix

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Appendix

- Supplement tables
- Publication
- Study team biosketch

Supplementary table

Supplementary Table 1.A Descriptive statistics of Lopinavir (200 mg)/Ritonavir (50 mg) drug content, uniformity of mass and dissolution tests, by WHO pre-qualification status, Sampling site, and country of manufacture

Variables	n (N=12)	% of label amount (L.A.) (WHO Specification: 90.0-110.0%)			Uniformity of mass, % (WHO Spec. ±5%)		Dissolution, % (WHO Spec. ≥ 80% L.A.)	
		Min	Max	Mean (SD)	Min	Max	Min	Max
WHO pre-qualification status								
Yes	1	-	-	99.7 (0)/101.4 (0)	-1.69	1.31	93.4/96.3	98.6/102.9
No	11	97.8/100.8	103.2/103.6	99.9 (1.85)/102.0 (0.97)	-2.53	2.08	94.9/95.0	102.6/104.6
Sampling sites								
Hospital	10	97.8/100.8	103.2/103.6	100.1 (1.86)/102.0 (0.99)	-2.53	2.08	96.2/95.0	102.6/104.6
NGO Clinic	-	-	-	-	-	-	-	-
Private	2	98.2/101.2	99.7/101.4	99.0 (1.06)/101.3 (0.14)	-1.69	1.52	93.4/96.3	98.6/102.9
Manufacturer Countries								
Thailand	11	97.8/100.8	103.2/103.6	99.9 (1.85)/102.0 (0.97)	-2.53	2.08	94.9/95.0	102.6/104.6
India	1	-	-	99.7 (0)/101.4 (0)	-1.69	1.31	93.4/96.3	98.6/102.9

Abbreviations: Non-Governmental Organizations, NGO

Supplementary Table 1.B Descriptive statistics of Tenofovir drug (300 mg) content, uniformity of mass and dissolution tests, by WHO pre-qualification status, Sampling site, and country of manufacture

Variables	n (N=15)	% of label amount (L.A.) (WHO Spec, 90.0-110.0%)			Uniformity of mass, % (WHO Spec, ±5%)		Dissolution, % (WHO Spec, ≥ 80% L.A.)	
		Min	Max	Mean (SD)	Min	Max	Min	Max
WHO pre-qualification Status								
Yes	3	97.5	102.5	99.5 (2.67)	-4.54	4.47	90.3	109.0
No	12	97.0	103.4	100.2 (2.05)	-2.49	2.05	96.9	104.3
Sampling sites								
Hospital	10	97.0	103.4	100.4 (2.13)	-1.84	1.46	98.7	104.3
NGO Clinic	2	97.5	98.0	97.8 (0.35)	-2.10	2.14	90.3	109.0
Private	3	98.4	102.5	100.5 (20.5)	-4.54	4.47	96.7	101.0
Manufacturer Countries								
Thailand	10	97.0	103.4	100.4 (2.12)	-1.84	1.46	98.7	104.3
India	5	97.5	102.5	99.4 (2.10)	-4.54	4.47	90.3	109.0

Abbreviations: Non-Governmental Organizations, NGO

Supplementary Table 1.C Descriptive statistics of Efavirenz drug (600 mg) content, uniformity of mass and dissolution tests, by WHO pre-qualification status, Sampling site, and country of manufacture

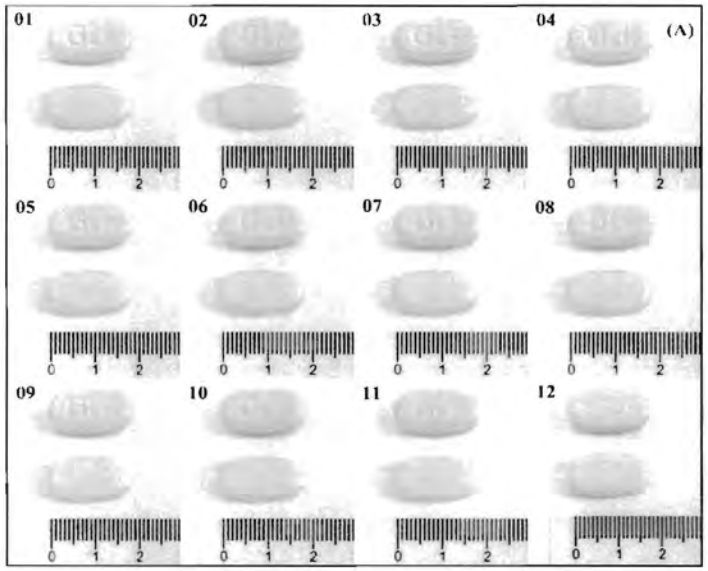
Variables	N (N=15)	% of label amount (L.A.) (WHO Spec, 90.0-110.0%)			Uniformity of mass, % (WHO Spec, ±5%)		Dissolution, % (WHO Spec, ≥ 80% L.A.)	
		Min	Max	Mean (SD)	Min	Max	Min	Max
WHO pre-qualification status								
Yes	13	94.9	98.9	97.1 (1.04)	-2.85	2.21	-	-
No	2	95.4	95.6	95.5 (0.14)	-2.08	2.25	-	-
Sampling sites								
Hospital	10	95.4	97.8	97.1 (0.78)	-2.85	2.21	-	-
NGO Clinic	2	94.9	95.6	95.3 (0.49)	-2.59	2.25	-	-
Private	3	95.6	98.9	97.1 (1.67)	-2.25	2.08	-	-
Manufacturer Countries								
Thailand	2	95.4	95.6	95.5 (0.14)	-2.08	2.25	-	-
India	12	94.9	98.9	97.2 (0.99)	-2.85	2.21	-	-
China	1	-	-	95.6 (0)	-1.01	0.75	-	-

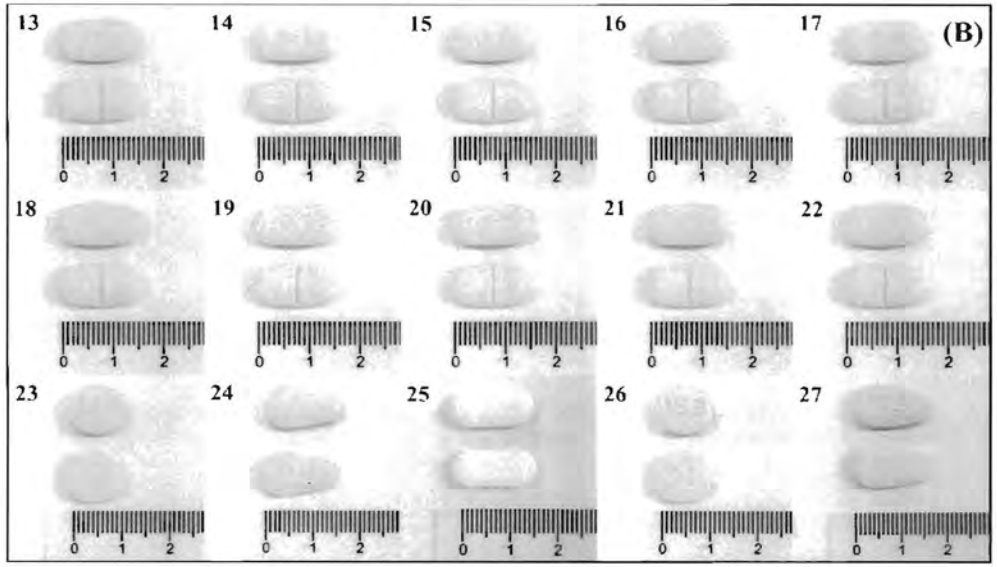
Abbreviations: Non-Governmental Organizations, NGO

FIGURES

Figure 1 Geographic location of sampling sites in Thailand and Vietnam[1]

[1] Source: http://www.mapcruzin.com/free-thailand-maps.htm





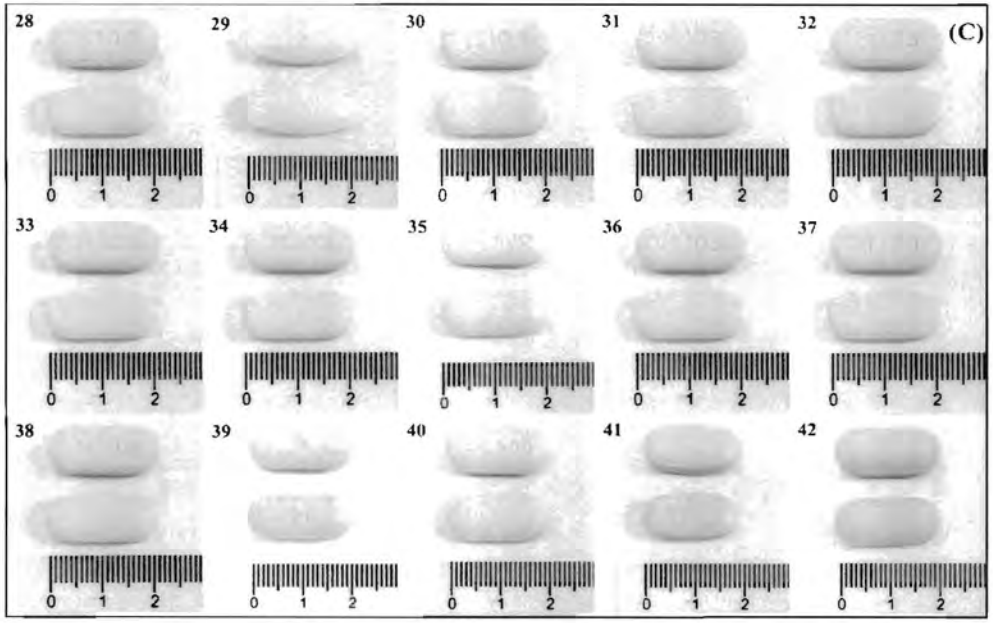
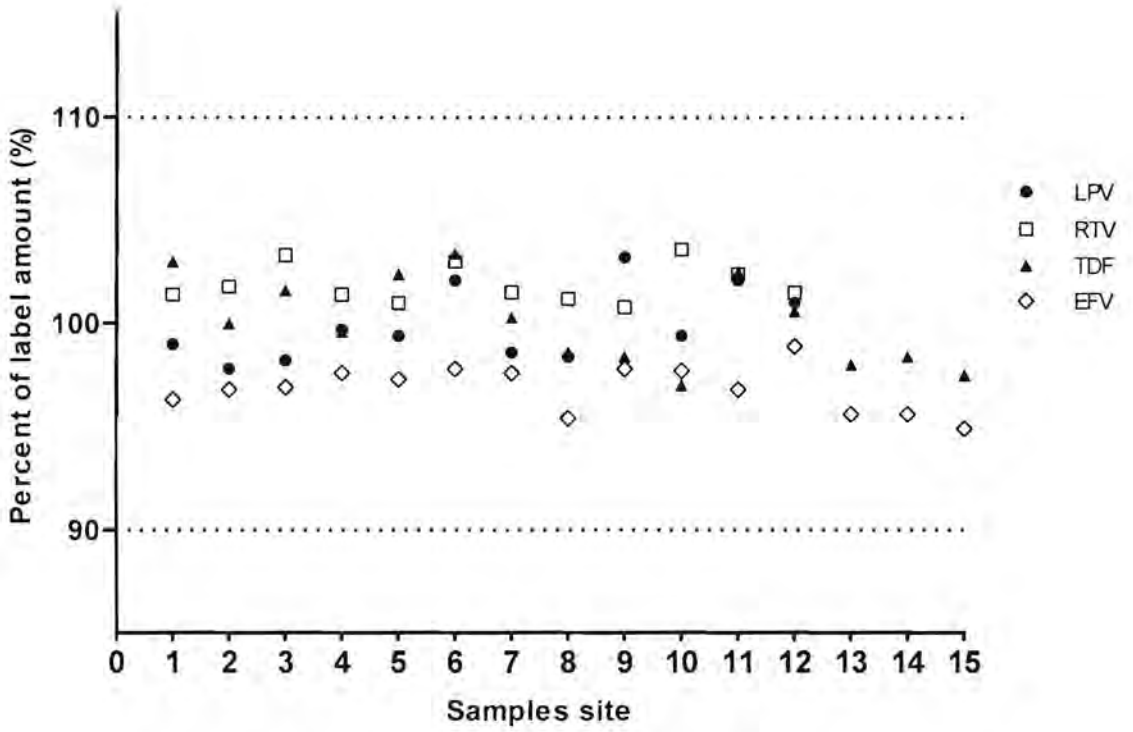


Figure 2 Sampled drugs, ordered by site id

(A) LPV/RTV
(B) TDF
(C) EFV



NOTE: WHO specification of drug quality, 90-110%

Figure 3: percent of label amount of each sampled ARV, by sampling site

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RESEARCH ARTICLE

Pharmaceutical Equivalence of Distributed Generic Antiretroviral (ARV) in Asian Settings: The Cross-Sectional Surveillance Study – PEDA Study

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Abstract

Objectives

Ensuring that medicines meet quality standards is mandatory for ensuring safety and efficacy. There have been occasional reports of substandard generic medicines, especially in resource-limiting settings where policies to control quality may be less rigorous. As HIV treatment in Thailand depends mostly on affordable generic antiretrovirals (ARV), we performed quality assurance testing of several generic ARV available from different sources in Thailand and a source from Vietnam.

Methods

We sampled Tenofovir 300mg, Efavirenz 600mg and Lopinavir/ritonavir 200/50mg from 10 primary hospitals randomly selected from those participating in the National AIDS Program, 2 non-government organization ARV clinics, and 3 private drug stores. Quality of ARV was analyzed by blinded investigators at the Faculty of Pharmaceutical Science, Chulalongkorn University. The analysis included an identification test for drug molecules, a chemical composition assay to quantitate the active ingredients, a uniformity of mass test and a dissolution test to assess in-vitro drug release. Comparisons were made against the standards described in the WHO international pharmacopeia.

Results

A total of 42 batches of ARV from 15 sources were sampled from January–March 2015. Among those generics, 23, 17, 1, and 1 were Thai-made, Indian-made, Vietnamese-made and Chinese-made, respectively. All sampled products, regardless of manufacturers or

responsibility for the decision to submit the manuscript for publication.

Competing Interests: KR has received the Senior Research Scholar Award from the Thailand Research Fund, and the Research Professor Fund from Chulalongkorn University, Bangkok, Thailand. KR also received honoraria or consultation fees from Merck, Roche, Jensen-Cilag, Tibotec, Mylan and GPO (Governmental pharmaceutical organization, Thailand) as well as participated in a company sponsored speaker's bureau from Abbott, Gilead, Bristol-Myers Squibb, Merck, Roche, Jensen-Cilag, GlaxoSmithKline, and GPO (Governmental pharmaceutical organization). The rest of the authors declare no conflict of interest. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

sources, met the International Pharmacopeia standards for composition assay, mass uniformity and dissolution. Although local regulations restrict ARV supply to hospitals and clinics, samples of ARV could be bought from private drug stores even without formal prescription.

Conclusion

Sampled generic ARVs distributed within Thailand and 1 Vietnamese pharmacy showed consistent quality. However some products were illegally supplied without prescription, highlighting the importance of dispensing ARV for treatment or prevention in facilities where continuity along the HIV treatment and care cascade is available.

Introduction

In 2014, there were an estimated of 450,000 people living with HIV in Thailand, with 8000 total new infections[1]. Since there is no definitive cure, HIV is a chronic disease requiring lifelong treatment. In October 2014, new Thai National HIV/AIDS guidelines were launched which recommend initiating treatment "regardless of CD4 count"[2]. Early ARV initiation has public health benefits by minimizing sexual transmission of HIV[3], and also benefits the individual by preventing the development of serious AIDS and non-AIDS-related events[4]. While there is an attempt to scale up ARV for HIV infected individuals, drug accessibility remains a global challenge, especially where financial resources are constrained[5]. In Thailand, 100% of financial resources for HIV treatment are domestic[1]; the country depends mostly on generic ARV products.

Generic drugs, according to U.S. food and drug administration (FDA), are the same as their branded counterparts in dosage, strength, safety, route of administration, indication and action; in fact, they are supposed to be therapeutically equivalent. By FDA regulations, a generic drug must contain an identical amount of the active ingredient(s) as in the branded product[6]. The active ingredient is any component in a tablet that produces the pharmacological effect for an expected medical purpose[7]. However, an active ingredient is just one component of the quality requirements, and is not in itself sufficient to ensure therapeutic equivalence. The Thai FDA has guidelines for approval of generic drugs which requires evidence of product interchangeability equivalence, namely bioequivalence studies, comparative in vitro dissolution/release studies, comparative clinical studies, and comparative pharmacodynamics studies[8]. The World Health Organization (WHO) has a recommended survey protocol that defines specific items that relate to quality aspects of medicines, and substandard and counterfeit medicines. Substandard medicines are legal products that do not meet quality standards and specifications; they may occur as a result of human error, negligence, or resource restriction. In contrast, counterfeit or fake drugs are intentionally and fraudulently disguised regarding drug components, active ingredients, packaging and labeling, and are made illegally by non-licensed companies[9].

Incidents regarding poor-quality generic drugs have been regularly reported, particularly among life-saving anti-infective drugs within resource-limiting regions where there are less rigorous restrictions on procurement and sale, and less public awareness[10–12]. According to the U.S. Pharmacopeial Convention (USP) reports during 2003–2013, the proportion of substandard medicines in Asia was 2.9%; lower than that described in Africa and South America. However, Asia was reported to have the highest proportion of counterfeit medicines with a

total number of 70 samples (out of 81 counterfeit products), representing 86% of sampled counterfeit products. Prevalence of sampled substandard medicine in Asia was 2.9% and Thailand was one of the least consistent in reporting data to a medicines quality database[13]. Problems associated with poor-quality drugs include increased morbidity and mortality, unnecessary adverse effects, suboptimal treatment leading to drug resistance, and also loss of confidence in health systems and waste of financial resources[14]. Therefore, it is very important for generic ARVs to be consistently monitored. Our study sampled generic ARV available from different sources in Thailand and assessed the quality by analyzing the pharmaceutical equivalence of the products.

Materials and Methods

The methodology has been reported in accordance with existing literature on medicines' quality surveys[9,15].

Sampling from sources

In order to represent ARVs distributed in Thailand, we obtained ARVs from primary hospitals participating in the National Universal Coverage program under the auspices of the National Health Security Office (NHSO), non-government organization (NGO) ARV clinics, and private drug stores. Six hundred and three primary hospitals that distributed ARVs through the NHSO (assessed data August 2011) were grouped by geographical location (North, South, East, West, and Central), and 2 hospitals from each region were randomly selected. For NGO sources, we collected ARV from the Thai Red Cross AIDS Research Center and the HIV-Netherlands-Australia-Thailand Research Collaboration (HIVNAT) pharmacies. For private sources, we bought ARV from 2 private pharmacies in Bangkok and 1 private pharmacy in Vietnam. [Fig 1] Convenience sampling was used to select these ARV in locations where the HIV prevalence is high.

Selection of ARVs

We selected two preferred first line ARVs (Tenofovir (TDF) 300mg and Efavirenz (EFV) 600mg) and one preferred second line ARV (Lopinavir/ritonavir (LPV/r) 200/50mg) recommended in the Thai National HIV/AIDS guidelines for this study[2]. Each ARV sample contained an adequate amount of tablets for Pharmaceutical analysis (at least 90 tablets), and had a shelf life extending beyond the analysis date. [Fig 2]

Collection of ARVs

For hospital sources, Local Pharmacists (who voluntarily collaborated with this study) were asked to randomly collect 1–3 bottles of each designated ARV from dispensing shelves. In addition, they completed a drug record form for each ARV sample, recording information including product name, dose, batch number, storage condition, manufactured date and expiry date. Pharmacists then shipped sampled ARVs along with completed drug record forms to the study team. Transportation to the analysis site was done using the Thai Express Mail Service and temperature was monitored during shipment.

For NGO ARV clinics and private sources, ARVs were bought by study coordinators. They acted as mystery shoppers and did not declare the objective of study to the seller. LPV/r (200/50mg) tablets were unavailable at 2 NGO clinics and 1 private pharmacy. Required documents including temperature assessment were not available for ARV purchased from the private pharmacies.

Fig 1. Geographic location of sampling sites in Thailand and Vietnam.

doi:10.1371/journal.pone.0157039.g001

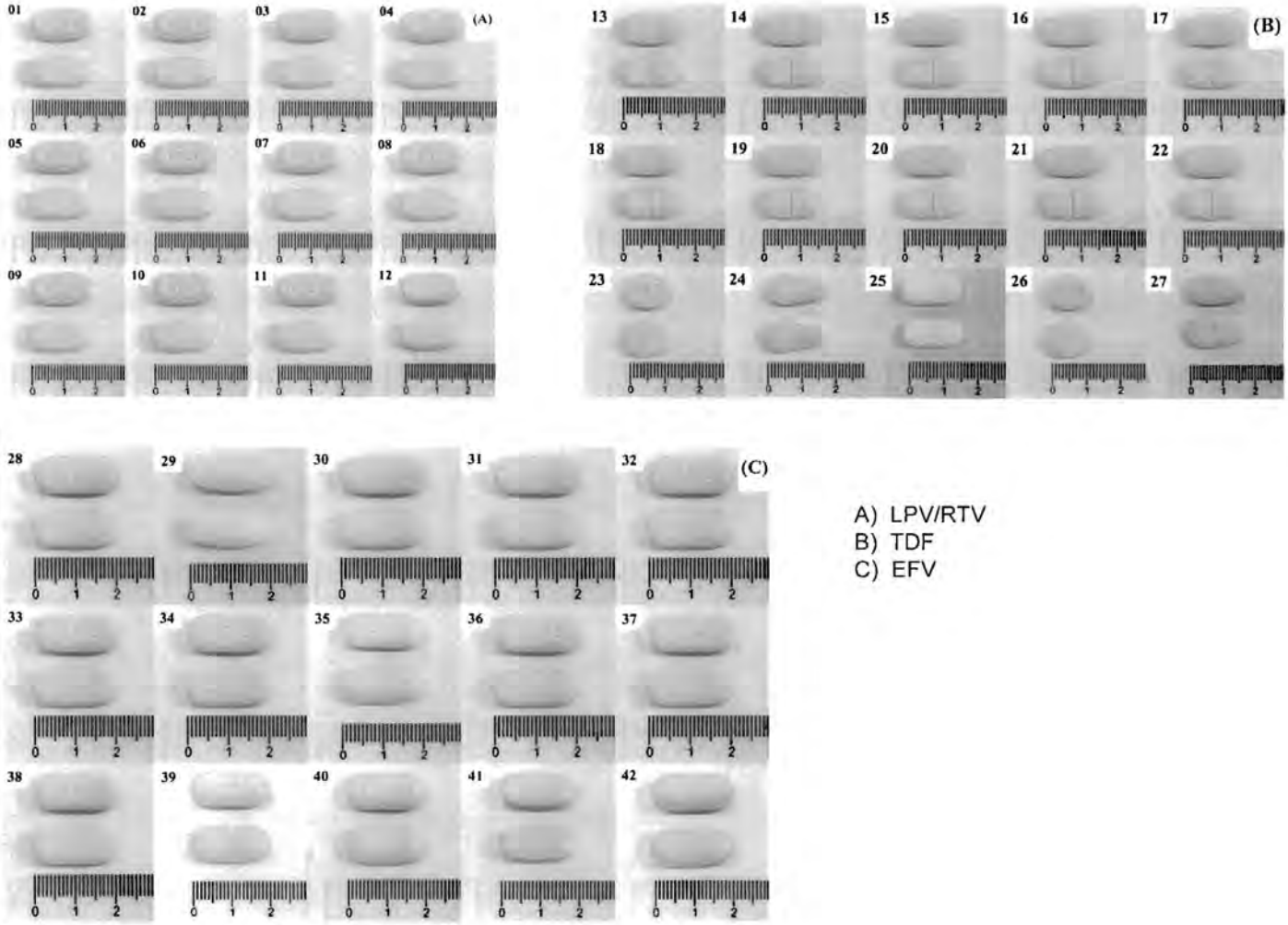

Fig 2. Sampled drugs, ordered by site ID.

doi:10.1371/journal.pone.0157039.g002

Pharmaceutical Analysis of ARVs

Evaluation of ARVs quality was conducted according to standard procedures for pharmaceutical analysis described under specific product monographs, namely, Lopinavir and Ritonavir tablets, Efavirenz tablets, and Tenofovir tablets, published in the International Pharmacopeia (4^{th} edition) by WHO. To assess the quality of medicines in this study, four different parameters including identity test, quantitative assay, uniformity of mass, and dissolution were selected for ARVs analysis. Counterfeit and substandard medicines are partly associated with the absence or insufficient quantities of the active substance. Therefore, the Identity test was conducted to confirm the presence and identity of the active substance in the tested formulation. The content and strength of drug were determined by a quantitative assay of the amount of active substance in dosage form. Uniformity of mass was tested to confirm homogeneity of the amount of active substances among tablets manufactured in the same batch. Dissolution of ARVs, with the exception of Efavirenz tablets due to the lack of an official analytical method in pharmacopeia, was conducted to test the performance of the ARV tablet that the drug substance will release with an acceptable rate which greatly affects the bioavailability of the

medicine. Drug analysis was performed by the Pharmaceutical Technology Service Center, Faculty of Pharmaceutical Science, Chulalongkorn University. Pharmaceutical Technology Service Center is an accredited laboratory complying with the ISO/IEC 17025:2005 and the requirements of the Bureau of Laboratory Quality Standards in the field of drug testing. Evaluation of ARV quality was based on acceptance criteria of each specification described in the drug monograph, and descriptive summary statistics were calculated using Stata 14 (Statacorp, College Station, TX, USA). Sources and storage conditions were blinded from the analysts[16].

This research study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University since October 2013. Informed consent process is not required by the ethics committee/IRB because the study was conducted and analyzed for the medicine tablets that were collected. This study was not conducted in patients.

This research study was not conducted in collaboration with Thailand Drug Regulation Authority (Thai FDA) because one objective of this study was to create an independent medicine quality surveillance system. However, a summary of the study results will be disseminated to relevant agencies and organizations with an interesting drug safety and quality.

Results

Forty-two batches of ARV (TDF, EFV, LPV/r) from 15 sources (10 primary hospitals, 2 NGO clinics and 3 private drug stores) were collected between January–March 2015. Temperature during shipment of ARV samples from sites to the analysis facility did not substantially exceed 30 °C, except for 5 shipments from primary hospitals where the temperature was over 30^0 C for $\leq$2 hours. All ARV samples came in the original package and no broken pills were observed. Of 15 TDF samples collected, 10 samples (from all hospitals) were made locally in Thailand (not WHO prequalified); the rest were generics made in India (3 WHO prequalified, 1 not) and Vietnam (1 not WHO prequalified). Fifteen samples of EFV were collected. Two samples (1 each from a primary hospital and 1 from an NGO clinic) were Thai-made generics (not WHO prequalified), 1 sample was a generic made in China (WHO prequalified) and the rest were Indian-made generics (WHO prequalified). LPV/r obtained from the 10 hospital sources was a Thai-made generic formulation (not WHO prequalified). We also sampled 1 Thai-made (not WHO prequalified) and 1 Indian-made (WHO prequalified) LPV/r generic tablets from 2 private sources (Assess the WHO prequalification database at http://apps.who.int/prequal/)[17,18] [Tables 1, 2 and 3].

For ARV obtained from hospital sources, *ARV Storage conditions* were assessed from self-administered questionnaires completed by a hospital pharmacist. Nine out of 10 hospitals had air conditioned storage facilities with temperature less than 30°C. Seven out of 10 hospitals had humidity monitoring. Humidity was less than 60% relative humidity (RH) at most of the hospitals where monitoring was undertaken. There was 1 site with humidity of 67%RH. One hospital site had neither humidity nor temperature monitoring, because drugs were stored at the ARV clinic, not in pharmacy facility. NGO ARV clinics also had temperature and humidity controlled to be less than 30°C and 60%RH respectively. We could not assess storage conditions at private pharmacies. Of note, while a doctor's prescription is required for ARV dispensed at hospitals and the NGO ARV clinics, no formal prescription was needed in the private pharmacies where our ARV samples were procured.

Identification test and Chemical composition assay

The drug identities are demonstrated by the same retention time as corresponding International pharmacopeia reference standards using the relevant drug content assay. Each sample met the International pharmacopeia standard for drug content [Fig 3]. Mean drug content values, as described in [Table 4], were close to 100% of the labelled amount; 99.9%/101.9% for

Table 1. Lopinavir (200 mg)/Ritonavir (50 mg) drug sources and characteristics.

Site	Lot No.	Manufacturer	Country	Trade name	WHO Prequal.	Expiry date	Identification	% of label amount	Uniformity of mass, %		Dissolution, % (LPV/RTV)	
									Min	Max	Min	Max
001	W570041	GPO	THA	Lopinavir/ Ritonavir	NO	21 Jan 16	Positive	102.1/100.8	-1.20	1.64	97.6/ 98.8	98.2/ 99.7
002	W560404	GPO	THA	Lopinavir/ Ritonavir	NO	13 Jul 15	Positive	103.2/102.4	-1.28	1.48	98.1/ 100.8	99.1/ 102.2
003	W570169	GPO	THA	Lopinavir/ Ritonavir	NO	17 Mar 16	Positive	102.1/103.6	-1.11	1.25	99.1/ 100.0	101.2/ 103.1
004	W570175	GPO	THA	Lopinavir/ Ritonavir	NO	17 Mar 16	Positive	101.0/103.3	-2.22	2.08	97.7/ 99.0	101.9/ 102.5
005	W570450	GPO	THA	Lopinavir/ Ritonavir	NO	17 Jul 16	Positive	99.4/101.8	-2.16	1.07	97.5/ 99.0	101.3/ 102.8
006	W560432	GPO	THA	Lopinavir/ Ritonavir	NO	23 Jul 15	Positive	99.0/103.0	-2.10	1.87	98.5/ 100.3	102.6/ 104.6
007	W570457	GPO	THA	Lopinavir/ Ritonavir	NO	20 Jul 16	Positive	98.6/101.5	-1.74	2.05	98.7/ 95.0	99.8/ 97.0
008	W570152	GPO	THA	Lopinavir/ Ritonavir	NO	10 Mar 16	Positive	99.4/101.4	-2.09	1.76	96.2/ 99.0	98.7/ 102.8
009	W570285	GPO	THA	Lopinavir/ Ritonavir	NO	15 May 16	Positive	98.4/101.0	-2.53	1.94	96.8/ 99.9	99.8/ 102.7
010	W560556	GPO	THA	Lopinavir/ Ritonavir	NO	22 Oct 15	Positive	97.8/101.5	-1.47	1.70	99.1/ 101.4	101.7/ 103.7
011	W570169	GPO	THA	Lopinavir/ Ritonavir	NO	17 Mar 16	Positive	98.2/101.2	-1.33	1.52	94.9/ 100.0	97.6/ 102.8
012	8000458	Mylan	IND	Lopinavir/ Ritonavir	YES	30 Jun 16	Positive	99.7/101.4	-1.69	1.31	93.4/ 96.3	98.6/ 102.9

Abbreviations: Lopinavir,LPV; Ritonavir, RTV; the Government Pharmaceutical Organization, GPO; Thailand, THA; India, IND.

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LPV/r, 100% for TDF, and 96.9% for EFV. The standard deviations of all drug content assay values were relatively close; 1.76/0.93 for LPV/r, 2.10 for TDF, and 1.11 for EFV.

Uniformity of mass

Uniformity of mass was used to assess uniformity of production batch for all the samples. The results ranged from -2.53% to 2.08% for LPV/r, -4.54% to 4.47% for TDF and -2.85% to 2.25% for EFV. All results were within the accepted values which range from -5% to 5%. The % deviation under uniformity of mass is calculated from the difference between the weight of individual unit and the average weight of the sample. The acceptance range is based on the criteria in the International pharmacopeia.

Test for dissolution

For dissolution tests, the cumulative amount of drug (percentage of labelled amount) that dissolves over a period of time in a dissolution medium is measured. As shown in Table 4, LPV/r and TDF samples comply with the international pharmacopeia dissolution test limit of $\geq$ 80% of the labeled amount.

There was no significant association between sources of ARV, WHO prequalification status, manufactured sites and storage conditions and the results of this pharmaceutical equivalence analysis.

Table 2. Tenofovir (300 mg) drug sources and characteristics.

Site	Lot No.	Manufacturer	Country	Trade name	WHO Prequal.	Expiry date	Identification	% of label amount	Uniformity of mass, %		Dissolution, %	
									Min	Max	Min	Max
013	A570270	GPO	THA	Tenofovir GPO 300	NO	12 Feb 16	Positive	103.0	-0.81	1.46	102.3	103.3
014	A562265	GPO	THA	Tenofovir GPO 300	NO	27 Jun 15	Positive	100.0	-1.84	1.08	100.5	101.2
015	A570273	GPO	THA	Tenofovir GPO 300	NO	12 Feb 16	Positive	101.6	-1.44	1.26	101.1	102.8
016	A570554	GPO	THA	Tenofovir GPO 300	NO	18 Mar 16	Positive	99.6	-1.16	1.17	99.6	101.5
017	A570375	GPO	THA	Tenofovir GPO 300	NO	20 Feb 16	Positive	102.4	-1.34	0.70	98.7	101.8
018	A570324	GPO	THA	Tenofovir GPO 300	NO	17 Feb 16	Positive	103.4	-1.45	0.80	99.3	101.4
019	A570560	GPO	THA	Tenofovir GPO 300	NO	20 Mar 16	Positive	100.3	-1.42	1.19	100.9	102.4
020	A570322	GPO	THA	Tenofovir GPO 300	NO	13 Feb 16	Positive	98.6	-1.08	1.21	100.2	102.5
021	A570557	GPO	THA	Tenofovir GPO 300	NO	19 Mar 16	Positive	98,4	-0.79	1.19	101.0	104.3
022	A570742	GPO	THA	Tenofovir GPO 300	NO	22 Apr 16	Positive	97.0	-0.82	1.18	101.0	102.2
023	8027079	Mylan	IND	RICOVIR	YES	31 Jul 17	Positive	102.5	-4.54	4.47	98.2	100.9
024	020414	STADA	VN	Tenofovir STADA	NO	02 Feb 16	Positive	100.6	-2.49	2.05	96.9	100.9
025	2507153	RANBAXY	IND	TEVIR	NO	31 Mar 15	Positive	98.0	-1.42	1.21	100.3	101.6
026	8027079	Mylan	IND	RICOVIR	YES	31 Jul 17	Positive	98.4	-2.61	3.55	96.7	101.0
027	E131707	Hetero	IND	TENOF	YES	31 Jul 15	Positive	97.5	-2.10	2.14	90.3	109.0

Abbreviations: Tenofovir, TDF; the Government Pharmaceutical Organization, GPO; Thailand, THA; India, IND; Vietnam, VN.

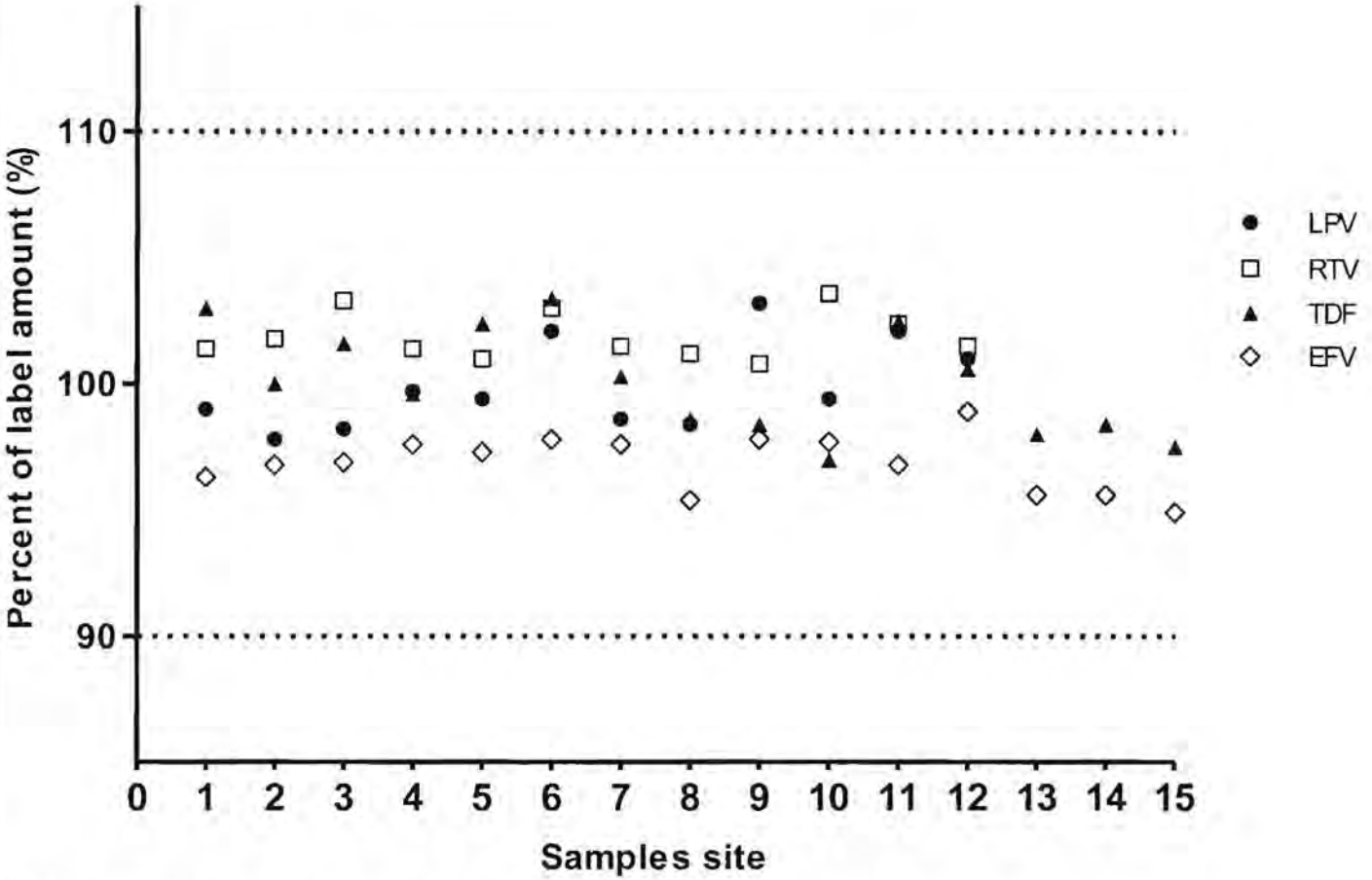
doi:10.1371/journal.pone.0157039.t002

Table 3. Efavirenz (600 mg) drug sources and characteristics.

Site	Lot No.	Manufacturer	Country	Trade name	WHO Prequal.	Expiry date	Identification	% of label amount	Uniformity of mass, %		Dissolution, %	
									Min	Max	Min	Max
028	EM27186	Mylan	IND	Efavirenz	YES	31 May 17	Positive	96.3	-2.22	1.25	-	-
029	EM35108	Emcure	IND	Efavirenz	YES	30 Apr 15	Positive	96.8	-1.83	2.21	-	-
030	3027189	Mylan	IND	Efavirenz	YES	31 May 17	Positive	96.9	-1.86	1.62	-	-
031	3027187	Mylan	IND	Efavirenz	YES	31 May 17	Positive	97.6	-2.85	1.67	-	-
032	3027185	Mylan	IND	Efavirenz	YES	31 May 17	Positive	97.3	-2.21	1.84	-	-
033	3027486	Mylan	IND	Efavirenz	YES	31 May 17	Positive	97.8	-1.06	0.80	-	-
034	3031217	Mylan	IND	Efavirenz	YES	30 Sep 17	Positive	97.6	-1.11	1.14	-	-
035	A570303	GPO	THA	Efavirenz	NO	10 Sep 15	Positive	95.4	-1.56	1.28	-	-
036	3031198	Mylan	IND	Efavirenz	YES	31 Aug 17	Positive	97.8	-1.51	1.83	-	-
037	3031240	Mylan	IND	Efavirenz	YES	30 Sep 17	Positive	97.7	-1.76	1.91	-	-
038	3026355	Mylan	IND	EFAMAT	YES	30 Apr 17	Positive	96.8	-2.25	2.08	-	-
039	EFZ113033A	Hetero	IND	ESTIVA-600	YES	30 Nov 16	Positive	98.9	-0.98	0.86	-	-
040	A570845	GPO	THA	Efavirenz	NO	22 Oct 15	Positive	95.6	-2.08	2.25	-	-
041	Y1723	Zhejian Huahai Pharm.	CHI	STOCRIN	YES	03 Mar 16	Positive	95.6	-1.01	0.75	-	-
042	E140542	Hetero	IND	ESTIVA-600	YES	28 Feb 17	Positive	94.9	-2.59	1.02	-	-

Abbreviations: Efavirenz, EFV; the Government Pharmaceutical Organization, GPO; Thailand, THA; China, CHI; India, IND.

doi:10.1371/journal.pone.0157039.t003



NOTE: WHO specification of drug quality, 90-110%

Fig 3. Percent of label amount of each sampled ARV, by sampling site.

doi:10.1371/journal.pone.0157039.g003

Discussion

The primary goal of this research study was to perform independent surveillance on the quality of commonly used generic ARV available for patients in Thailand. Although this could not represent whole ARV distributing in the region, the findings showed satisfactory quality of all

Table 4. Descriptive statistics of drug content, uniformity of mass and dissolution tests.

ARV	N	% of label amount (L.A.)				Uniformity of mass, %			Dissolution, %		
		WHO Specification	Min	Max	Mean (SD)	WHO Spec.	Min	Max	WHO Spec.	Min	Max
LPV/ RTV	12	90.0–110.0%	97.8/ 100.8	103.2/ 103.6	99.9 (1.76)/101.9 (0.93)	±5%	-2.53	2.08	≥ 80% L. A.	93.4/ 95.0	102.6/ 104.6
TDF	15	90.0–110.0%	97.0	103.4	100.1 (2.10)	±5%	-4.54	4.47	≥ 80% L. A.	90.3	109.0
EFV	15	90.0–110.0%	94.9	98.9	96.9 (1.11)	±5%	-2.85	2.25	-	-	-

Abbreviations: Lopinavir,LPV; Ritonavir, RTV; Tenofovir, TDF; Efavirenz, EFV; Label amount, L.A.; Standard deviation, SD

doi:10.1371/journal.pone.0157039.t004

ARV samples from different sources and types based on drug content, uniformity of mass and dissolution even though some batches (including those manufactured in Thailand) are not WHO prequalified. TDF test results varied most widely when compared to EFV and LPV/r, however all parameters were within the International Pharmacopeia standards. These wider ranges might reflect more variability in manufacturing sites of TDF, while LPV/r samples were retrieved from a smaller number of manufacturers. Although our findings are supported by previous studies[19–21], two samples of ARV from Thailand were found to be substandard in a USP convention database report in 2008 (http://www.usp.org/worldwide/medQualityDatabase) [22]. Therefore, continuous monitoring is required to ensure that products used in National Treatment Programs meet the quality standards necessary to ensure an effective and safe response to HIV. In addition, counterfeit medicines, particularly anti-malarials have frequently been found when reviewing the quality of medicines in Southeast Asian countries [11,12], and WHO estimates the use of counterfeit drugs causes approximately 1 million deaths per year[23].

Although ARVs are life-saving medications, they can cause adverse events if taken incorrectly and reduce a patient's options for future treatment if they continue to be dosed in the presence of genotypic resistance. HIV care is life-long and requires multidisciplinary support, and monitoring of viral load and other safety parameters. Our finding that generic ARV could be purchased from two private pharmacies without a formal prescription, despite their supply being restricted only to hospitals and registered clinics, highlights the important public health issue of getting patients into the proper healthcare system cascade. Self-treatment with ARV, either for treatment or prevention, without proper follow up from healthcare professionals skilled in managing HIV might lead to adverse events, adherence problems, and consequently drug resistance[24–26]. While we promote ARV accessibility by generic importation/licensing, regulation is necessary to ensure that ARV are dispensed with a proper monitoring and follow-up system in place.

There are some limitations of our study. First, the small number of ARV samples assayed limits the power to detect any abnormalities. However, we maximized our resources by sampling ARV from primary hospitals which in theory, have the least rigorous quality control systems in place. The fact that hospital ARV samples were selected by local pharmacists, could potentially result in a "positive" selection bias Second, since there is no mechanism to check the availability of ARV in facilities outside the NHSO system, convenience sampling was used for ARV from private pharmacies and NGO's in locations where we suspected ARV would be available. This approach could miss stores in other areas who might have substandard products. Third, almost all LPV/r tablet sampled were Thai-made generics; this reflects the situation in the past when Thailand issued compulsory licenses for antiretroviral drugs including Abbott's Kaletra®, to cope with the enormous expenditure incurred by procurement of brand name ARV. Nevertheless, although Thai ARV are not WHO pre-qualified, a study has shown comparable pharmacokinetics between Thai generic and Indian generics [27], and the Thai FDA has rigorous standards for bioequivalence[8]. Finally, we were unable to include all pharmaceutical analysis methods, namely impurities and related substances, thus not allowing to us to exclude the presence of possible contaminants and resulting potential for toxicity. However, we covered the three most important components relating to bioavailability and efficacy: active ingredient, uniformity and dissolution. Some strengths of our study are also noteworthy. The collection of ARV were processed in systematic fashion. In addition, our ARV sources and storage conditions were blinded from analysts so they did not pose any bias during analysis. Lastly, while occasional surveillance of drug quality in Thailand already takes place [28], the surveillance might not focus on ARV. Our study is independent and focuses on commonly used ARV in the Thai National Treatment Program.

In conclusion, many sectors in Thailand have worked together to scale up ARV treatment; this study ensures the quality of the sampled drug being utilized, emphasizes further continuous monitoring, and at the same time, points out that ARV dispensing should occur in facility-based settings where regular follow-up and care are delivered.

Supporting Information

S1 Data. Minimum data set.
(XLS)

S1 Table. Descriptive statistics of Lopinavir (200 mg)/Ritonavir (50 mg) drug content, uniformity of mass and dissolution tests, by WHO pre-qualification status, Sampling site, and country of manufacture.
(DOCX)

S2 Table. Descriptive statistics of Tenofovir drug (300 mg) content, uniformity of mass and dissolution tests, by WHO pre-qualification status, Sampling site, and country of manufacture.
(DOCX)

S3 Table. Descriptive statistics of Efavirenz drug (600 mg) content, uniformity of mass and dissolution tests, by WHO pre-qualification status, Sampling site, and country of manufacture.
(DOCX)

Acknowledgments

PEDA study team

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Author Contributions

Conceived and designed the experiments: VS VV NT SK AA PP KR. Performed the experiments: VV. Analyzed the data: VS PR SK. Wrote the paper: VS VV NT SK AA PP KR. Coordinated the study: KP.

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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

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eRA COMMONS USER NAME (agency login):

POSITION TITLE: CTU Co-Investigator/CRS Leader/Study PI/Investigator of Record

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Faculty of Medicine, Chiangmai University, Chiang Mai	MD	03/1979	Medicine
Department of Medicine, Faculty of Medicine Chulalongkorn University, Bangkok	MS	05/1989	Allergy and Clinical Immunology

A. Personal Statement

I am primarily responsible for all of the research activities including fulfilling all of the study-specific objectives and requirements; taking primary responsibility for GCP compliance; carrying out appropriate communication with local government and regulatory agencies and ensuring that the completion of local IRB and OHRP requirements are done in a timely manner or within the designated timeframe for the study protocol; chairing the monthly meetings and taking the final responsibility for all of the specific tasks delegated to the research staff; carrying out protocol training for its site personnel; supervising all local staffs; attending all related meetings and taking conference calls; performing as the Study Physician if needed; and prescribing study drugs.

B. Positions and Honors

Positions and Employment

1995 - Faculty member, Division of Allergy and Clinical Immunology Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok

1996 - Deputy Director, HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok

2000 - Director, HIV-NAT Research Laboratory/Chula Clinical Research Lab (ChulaCRL), Bangkok

2007 - Professor of Medicine, Chulalongkorn University, Bangkok

2014 - CTU Co-Investigator/CRS Leader/Study PI/Investigator of Record, HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok

Other Experience and Professional Memberships

1989 - 1990 Guest Researcher, Johns Hopkins Hospital, Baltimore, Maryland, USA (Sponsored by USAID, Supervisor: Thomas C. Quinn, MD)

1991 - 1993 Visiting Researcher, Clinical and Molecular Retrovirology Section, Laboratory of Immunoregulation, NIAID, NIH, Bethesda, MD, USA (Supervisor: H. Clifford Lane)

1997 - Principal investigator , more than 40 phase I, II or III clinical trials both in HIV and HIV-related (co-infection) studies

1997 - Co-investigator , more than 40 phase I, II or III clinical trials both in HIV-related (co-infection) studies

2003 - Member, The Thai AIDS Society (TAS)

2004 - Member, The Allergy, Asthma and Immunology Association, Thailand (AAIAT)

2004 - Advisory member , National laboratory network for HIV/AIDS vaccine trial, treatment and care of the Bureau of AIDS, TB and STDs, CDC, Ministry of Public Health, Thailand

2004 -	Co-chair of Track A (Basic Science) Scientific Committee, the XV International AIDS Conference held in Bangkok, Thailand
2005 - 2011	Sub-committee member, AIDS Research Fund on Biomedical research
2006 -	Member, Thai National AIDS committee
2006 -	Member of the Vaccine Research and Development Sub-Committee, National Vaccine Committee, Ministry of Public Health
2010 -	Member, International AIDS Society (IAS)
2010 -	Chair , Social Security Office for the HIV/AIDS treatment and care subcommittee
2012 -	Chair of the Research sub-committee and the member, The Royal College of Physician, Thailand (RCPT)
2012 - 2013	Co-Chair of the Basic Sciences Track (Track A), 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2013), 30 June - 3 July 2013 in Kuala Lumpur, Malaysia
2012 - 2013	Chair of the scientific Track B (getting to zero death) committee , 11th International Congress on AIDS in Asia and the Pacific in Bangkok in 2013.

Honors

2006	Outstanding Internist Award on Medical Academy, Royal College of Physicians, Thailand
2007	Outstanding Researcher Award, and the Highest Citation Award, Chulalongkorn University, Bangkok, Thailand
2011	Senior Research Scholar Award, The Thailand Research Fund
2011	Outstanding Researcher Award, The National Research Council, Thailand
2015	Senior Research Scholar Award, The Thailand Research Fund
2015	Outstanding Research Award, The Thailand Research Fund

C. Contribution to Science

1. My participation as a site co-investigator in the IeDEA regional network since the beginning in 2006 has led to multiple publications that have informed our understanding of the impact of HIV and treatment outcomes in the Asia-Pacific. In addition to demonstrating the slow uptake of antiretroviral therapy and very low initial CD4 levels in our referral centers, our analyses have evaluated the impact of co-infections, regimen choice, country income level, and sex on treatment outcomes. We organized the first regional study of transmitted and acquired drug resistance and are participating in the IeDEA TB study exploring the molecular epidemiology of drug-resistant Mycobacterium tuberculosis in the context of HIV, using whole genome sequences, across different IeDEA regions.

    a. Praditpornsilpa K, Avihingsanon A, Chaiwatanarat T, Chaiyahong P, Wongsabut J, Ubolyam S, Chulakadabba A, Avihingsanon Y, Ruxrungtham K, Tunsanga K, Eiam-Ong S, Phanuphak P. Comparisons between validated estimated glomerular filtration rate equations and isotopic glomerular filtration rate in HIV patients. AIDS. 2012 Sep 10;26(14):1781-8. PubMed PMID: 22713478; PubMed Central PMCID: PMC3782632.

    b. Boettiger DC, Nguyen VK, Durier N, Bui HV, Heng Sim BL, Azwa I, Law M, Ruxrungtham K. Efficacy of second-line antiretroviral therapy among people living with HIV/AIDS in Asia: results from the TREAT Asia HIV observational database. J Acquir Immune Defic Syndr. 2015 Feb 1;68(2):186-95. PubMed PMID: 25590271; PubMed Central PMCID: PMC4296907.

    c. Sirivichayakul S, Kantor R, DeLong AK, Wongkunya R, Mekprasan S, Ruxrungtham K, Sohn AH, Phanuphak P. Transmitted HIV drug resistance at the Thai Red Cross anonymous clinic in Bangkok: results from three consecutive years of annual surveillance. J Antimicrob Chemother. 2015 Apr;70(4):1146-9. PubMed PMID: 25525199; PubMed Central PMCID: PMC4375389.

2. A key priority for my clinical and scientific work has been to improve our local understanding of the HIV epidemic in Thailand. I have published multiple papers on HIV outcomes among adults and children in my country. From work which I am the PI of the NIH funded PREDICT study, we have increased the understanding of when to start antiretroviral therapy in children older than 1 year of age.

a. Avihingsanon A, Manosuthi W, Kantipong P, Chuchotaworn C, Moolphate S, Sakornjun W, Gorowara M, Yamada N, Yanai H, Mitarai S, Ishikawa N, Cooper DA, Phanuphak P, Burger D, Ruxrungtham K. Pharmacokinetics and 48-week efficacy of nevirapine: 400 mg versus 600 mg per day in HIV-tuberculosis coinfection receiving rifampicin. Antivir Ther. 2008;13(4):529-36. PubMed PMID: 18672531.

b. Avihingsanon A, Lewin SR, Kerr S, Chang JJ, Piyawat K, Napissanant N, Matthews GV, Dore GJ, Bowden S, Lange J, Ruxrungtham K. Efficacy of tenofovir disoproxil fumarate/emtricitabine compared with emtricitabine alone in antiretroviral-naive HIV-HBV coinfection in Thailand. Antivir Ther. 2010;15(6):917-22. PubMed PMID: 20834105.

c. Bunupuradah T, Chetchotisakd P, Ananworanich J, Munsakul W, Jirajariyavej S, Kantipong P, Prasithsirikul W, Sungkanuparph S, Bowonwatanuwong C, Klinbuayaem V, Kerr SJ, Sophonphan J, Bhakeecheep S, Hirschel B, Ruxrungtham K. A randomized comparison of second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir in patients failing NNRTI regimens: the HIV STAR study. Antivir Ther. 2012;17(7):1351-61. PubMed PMID: 23075703.

d. Puthanakit T, Saphonn V, Ananworanich J, Kosalaraksa P, Hansudewechakul R, Vibol U, Kerr SJ, Kanjanavanit S, Ngampiyaskul C, Wongsawat J, Luesomboon W, Ngo-Giang-Huong N, Chettra K, Cheunyam T, Suwarnlerk T, Ubolyam S, Shearer WT, Paul R, Mofenson LM, Fox L, Law MG, Cooper DA, Phanuphak P, Vun MC, Ruxrungtham K. Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial. Lancet Infect Dis. 2012 Dec;12(12):933-41. PubMed PMID: 23059199; PubMed Central PMCID: PMC3541427.

I and my center have conducted a number of pharmacokinetic and efficacy researches to address dose optimization for Thai patients such as lopinavir, atazanavir, and efavirenz. The results supported that an approximately 30% lower the dose of these antiretrovirals are efficacious and better tolerated. Our recent randomized controlled non-inferiority study has demonstrated that atazanavir 200 mg was non-inferior to 300 mg when boosted with ritonavir 100 mg once daily in well virologic suppressed patients. These strong evidences will lead to a near future recommendation in the Thai guidelines; and will result to a better tolerable regimen and to a significant cost saving.

a. Avihingsanon A, van der Lugt J, Kerr SJ, Gorowara M, Chanmano S, Ohata P, Lange J, Cooper DA, Phanuphak P, Burger DM, Ruxrungtham K. A low dose of ritonavir-boosted atazanavir provides adequate pharmacokinetic parameters in HIV-1-infected Thai adults. Clin Pharmacol Ther. 2009 Apr;85(4):402-8. PubMed PMID: 19118378.

b. Puthanakit T, van der Lugt J, Bunupuradah T, Ananworanich J, Gorowara M, Phasomsap C, Jupimai T, Boonrak P, Pancharoen C, Burger D, Ruxrungtham K. Pharmacokinetics and 48 week efficacy of low-dose lopinavir/ritonavir in HIV-infected children. J Antimicrob Chemother. 2009 Nov;64(5):1080-6. PubMed PMID: 19729375.

c. Gorowara M, Burger D, Hill A, Ruxrungtham K. Pharmacokinetics of low-dose protease inhibitors and efavirenz in low- and middle-income countries. Curr Opin HIV AIDS. 2010 Jan;5(1):90-6. PubMed PMID: 20046153.

d. Klinklom A, Puthanakit T, Gorowara M, Phasomsap C, Kerr S, Sriheara C, Ananworanich J, Burger D, Ruxrungtham K, Pancharoen C. Low dose lopinavir/ritonavir tablet achieves adequate pharmacokinetic parameters in HIV-infected Thai adolescents. Antivir Ther. 2012;17(2):283-9. PubMed PMID: 22293065.

I am involved in international randomized studies. The outcome of these studies had shown the drugs' efficacy and safety, which could led to a new treatment option for patients.

a. Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, Norris D, Lefebvre E, de Béthune MP, Tomaka F, De Pauw M, Vangeneugden T, Spinosa-Guzman S. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet. 2007 Jul 7;370(9581):49-58. PubMed PMID: 17617272.

b. Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, Pedersen C, Ruxrungtham K, Lewin SR, Emery S, Neaton JD, Brenchley JM, Deeks SG, Sereti I, Douek DC. Plasma levels of soluble CD14 independently predict mortality in HIV infection. J Infect Dis. 2011 Mar 15;203(6):780-90. PubMed PMID: 21252259; PubMed Central PMCID: PMC3071127.

c. Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, Johnson MA, Ruxrungtham K, Wu H, Zorrilla C, Crauwels H, Rimsky LT, Vanveggel S, Boven K. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet. 2011 Jul 16;378(9787):229-37. PubMed PMID: 21763935.

d. Cahn P, Ruxrungtham K, Gazzard B, Diaz RS, Gori A, Kotler DP, Vriesema A, Georgiou NA, Garssen J, Clerici M, Lange JM. The immunomodulatory nutritional intervention NR100157 reduced CD4+ T-cell decline and immune activation: a 1-year multicenter randomized controlled double-blind trial in HIV-infected persons not receiving antiretroviral therapy (The BITE Study). Clin Infect Dis. 2013 Jul;57(1):139-46. PubMed PMID: 23511299.

Complete List of Published Work in My Bibliography:
http://1.usa.gov/1IrLL0k

D. Research Support

Ongoing Research Support

A5316, NIH
Daar E (PI)
04/29/15-01/01/21
Evaluating pharmacokinetics interactions with vaginal ring contraceptive and ART
This study will look at a method of hormonal birth control, called the NuvaRing, and specific anti-HIV medications, called antiretrovirals (ARVs).
Role: PI

A5288 (MULTI-OCTAVE) , NIH
Daar E (PI)
03/04/15-01/01/20
Management Using the Latest Technologies in Resource-limited Settings to Optimize Combination Therapy After Viral Failure
To use novel agents and contemporary management tools, including standard genotyping to select an appropriate third-line regimen, interventions to improve adherence and plasma viral load (VL) monitoring, in order to achieve a â ¥ 65% rate of virologic control at 48 weeks of follow-up
Role: PI

A5332 , NIH
Grinspoon S (PI)
01/08/15-01/01/22
REPRIEVE
This is a randomized trial to prevent vascular events in HIV, tests whether a daily dose of a statin will reduce the risk of cardiovascular disease among HIV-infected individuals (for whom statins are not already recommended according to 2013 US Cholesterol Treatment Guidelines)
Role: PI

A5279 , NIH
Campbell T (PI)
10/28/14-01/01/19

Phase III Clinical Trial of Ultra-Short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection
To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to a standard 9-month (36 week) daily INH regimen for TB prevention in HIV-infected individuals
Role: PI

IRC003 and IRC004, NIH
Beigel J (PI)
08/01/11-11/01/20
IRC003 and IRC004
to evaluate the efficacy of the combination antivirals (oseltamivir/amantadine/ribavirin) as compared to oseltamivir alone in the treatment of at-risk subjects with confirmed influenza infection (Primary Efficacy Population).
Role: PI

A5349, NIH
Nahid P and Dorman S (PI)
08/05/15-08/05/18
Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial
This study will evaluate the efficacy of a rifapentine-containing regimen to determine whether the single substitution of rifapentine for rifampin makes it possible to reduce to seventeen weeks the duration of treatment for drug-susceptible pulmonary tuberculosis.
Role: PI

Completed Research Support

09-I-0108 , NIH
Neaton (PI)
03/01/09-12/31/15
START (Strategic Timing of Anti-Retroviral Treatment)
The purpose of this randomized study is to determine whether immediate initiation of antiretroviral treatment (ART) is superior to deferral of ART until the CD4+ declines below 350 cells/mm3 in terms of morbidity and mortality in HIV-1 infected persons who are antiretroviral naive with a CD4+ count above 500 cells/mm3.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Sapsirisavat, Vorapot

eRA COMMONS USER NAME (agency login):

POSITION TITLE: Co-investigator/study physician

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Mahidol University, Faculty of Medicine Siriraj Hospital, Bangkok	MD	2012	Medicine
Peking University, Department of Pediatric and Department of Traditional Chinese Medicine, Beijing	Other training	2009	General Pediatric and Chinese Traditional Medicine
University of Massachusetts Medical School Department of Pediatric, Endocrinology/Diabetes division, Boston, MA	Other training	2012	Pediatric Endocrinology and Diabetes
HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok	Other training	02/2014	Infectious Diseases Control
University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA	Other training	2014	HIV research among MSM in the developing world

A. Personal Statement

I am primarily responsible for all of the research activities including carrying out targeted physical examinations among study volunteers; performing all study related clinical assessments, clinical counseling of medical test results, and implementing appropriate referrals; prescribing study drugs; assessing all drug-related toxicity and adverse events, immediately responding with emergency treatment if needed; alerting the PI regarding any Expedited Adverse Event (EAE); completing all medical records and CRFs related to clinical activities, such as clinical evaluations, physical examinations, and so forth; assisting, if necessary, in recruiting volunteers, community education, conducting consent; taking responsibility for all medical issues; attending all related meetings and taking conference calls; and taking responsibility for GCP compliance.

B. Positions and Honors

Positions and Employment

2007 - 2007 Public Relations Officer, ACTION 2007- Asian Collaborative Training On Infectious, Outbreak Disaster and Refugee Management-Phuket, Bangkok

2007 - 2008 National officer, Standing Committee on Human Right and Peace, IFMSA, Bangkok

2008 - 2009 Regional Coordinator, IFMSA- International Federation of Medical Students'

	Associations, Bangkok
2008 - 2009	standing Committee on Human Right and Peace, IFMSA- International Federation of Medical Students' Associations, Bangkok
2012 - 2013	Intern doctor, Damnernsaduak hospital, Ratchaburi
2013 -	Clinical Trial Physician, HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok
2013 - 2013	Rapporteur, MSM and TG on drug use session, APCOM-Asia Pacific Coalition on Male Sexual Health Pre-ICAAP11 Conference, Bangkok
2014 -	Co-investigator/study physician, HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok
2014 - 2014	Moderator, 17th Bangkok International Symposium, Bangkok

Other Experience and Professional Memberships

Honors

C. Contribution to Science

1. There is evidence of high interindividual variability of the pharmacokinetics of Tenofovir (TFV). The effect of several clinical conditions on the pharmacokinetics of TFV has been observed and may partly explain its variability. We assessed factors influencing the pharmacokinetics of TFV in Thai patients. We fond that TFV exposures were independently associated with PI regimens, mild renal impairment, lower body weight, and increasing RTV AUC0-24. Clinicians should be aware of the effect of these factors on TFV exposure when this drug is prescribed.

    a. Kerr SJ, Punyawudho B, Thammajaruk N, Colbers A, Chaiyahong P, Phonphithak S, Sapsirisavat V, Ruxrungtham K, Burger DM, Avihingsanon A. Factors associated with daily tenofovir exposure in Thai subjects taking combination antiretroviral therapy. AIDS Res Hum Retroviruses. 2015 Apr;31(4):368-74. PubMed PMID: 25384393.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/1p7UuO0Pwbd5y/bibliography/47564687/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

A5316, NIH 2015/04/29-2021/01/01
Daar E (PI)
Evaluating pharmacokinetics interactions with vaginal ring contraceptive and ART
This study will look at a method of hormonal birth control, called the NuvaRing, and specific anti-HIV medications, called antiretrovirals (ARVs).
Role: Co-Investigator

A5288 (MULTI-OCTAVE) , NIH 2015/03/04-2020/01/01
Daar E (PI)
Management Using the Latest Technologies in Resource-limited Settings to Optimize Combination Therapy After Viral Failure
To use novel agents and contemporary management tools, including standard genotyping to select an appropriate third-line regimen, interventions to improve adherence and plasma viral load (VL) monitoring, in order to achieve a ≥ 65% rate of virologic control at 48 weeks of follow-up
Role: Co-Investigator

A5332, NIH 2015/01/08-2022/01/01
Grinspoon S (PI)
REPRIEVE
This is a randomized trial to prevent vascular events in HIV, tests whether a daily dose of a statin will reduce the risk of cardiovascular disease among HIV-infected individuals (for whom statins are not already recommended according to 2013 US Cholesterol Treatment Guidelines)
Role: Co-Investigator

A5279 , NIH 2014/10/28-2019/01/01
Campbell T (PI)
Phase III Clinical Trial of Ultra-Short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection
To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to a standard 9-month (36 week) daily INH regimen for TB prevention in HIV-infected individuals
Role: Co-Investigator

PEDA-I, Thai Fiscal Year budget 2014/10/15-2016/10/30
Sapsirisavat, Vorapot (PI)
Pharmaceutical Equivalence Drugs Assessment-I
The goal of this study is to assess the pharmaceutical equivalence of generic antiretrovirals distributed in Thailand both form official and unofficial sources
Role: Co-Investigator

FAITH, amfAR GMT initiative 2014/09/01-2015/09/01
Sapsirisavat, Vorapot (PI)
Factors that Attribute to unknown HIV seropositivity and Influence to HIV Testing pattern among High MSM in Bangkok
The goal of this study is to identify psychosocial factors that associated with unknown HIV positive and delayed HIV diagnosis among high risk MSM in Bangkok
Role: PI

IRC004, NIH/INSIGHT 2011/08/01-2020/09/01
Beigel J (PI)
IRC004
to evaluate the virologic efficacy of the antiviral Oseltamivir compared to placebo in the treatment of subjects with confirmed influenza (Primary Efficacy Population)
Role: Co-Investigator

IRC003, NIH/INSIGHT 2011/08/01-2020/09/01
Beigel J (PI)
IRC003
to evaluate the efficacy of the combination antiviral (Oseltamivir/Amantadine/Ribavirin) as compared to oseltamivir alone in the treatment of at-risk subjects with confirmed influenza infection (Primary Efficacy Population
Role: Co-Investigator

Hepatitis C Co-Infection Study, amFAR TREAT Asia 2013/12/01-2018/12/30

Durier N (PI)
HCV screening study and treatment demonstration project for HIV-positive patients
Role: Co-Investigator

FLU002, NIH/INSIGHT 2009/09/01-2020/10/01
Losso MH (PI)
An International Observational Study to Characterize Adults with Influenza
to describe participants in geographically diverse locations with Influenza virus infection (including influenza A subtypes such as H3N2 and 2009 H1N1, or influenza B) and their clinical course over a 14-day period following enrollment
Role: Co-Investigator

FLU003 , NIH/INSIGHT 2009/09/01-2020/10/01
Davey Jr., RT (PI)
An International Observational Study to Characterize Adults Who Are Hospitalized with Complications of Influenza
: to describe the characteristics and outcomes over a 60-day follow-up period of participants with influenza virus infection (including influenza A subtypes such as H3N2 and 2009 H1N1, or influenza B) who are hospitalized with severe illness and/or complications, in geographically diverse locations.
Role: Co-Investigator

START, NIH/INSIGHT 2009/03/01-2015/12/31
Neaton, JD (PI)
Strategic Timing of Anti-retroviral Treatment
to evaluate the timing of starting HIV treatment
Role: Co-Investigator

HIV-NAT 006, Thai National Health Security office 2002/10/28-2020/11/01
Phanuphak P (PI)
Long-term HIV cohort
A long-term follow-up of HIV-infected patients
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Avihingsanon, Anchalee

eRA COMMONS USER NAME (agency login):

POSITION TITLE: Co-investigator/study physician

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Khon Kaen University, Khon Kaen	MD	1992	Medicine
Amsterdam University, Amsterdam	PHD	2013	HIV and Coinfection

A. Personal Statement

I am primarily responsible for all of the research activities including fulfilling all of the study-specific objectives and requirements; carrying out targeted physical examinations among study volunteers; performing all study related clinical assessments, clinical counseling of medical test results, and implementing appropriate referrals; prescribing study drugs; assessing all drug-related toxicity and adverse events, immediately responding with emergency treatment if needed; alerting the PI regarding any Expedited Adverse Event (EAE); completing all medical records and CRFs related to clinical activities, such as clinical evaluations, physical examinations, and so forth; assisting, if necessary, in recruiting volunteers, community education, conducting consent; carrying out appropriate communication with local government and regulatory agencies and ensures the completion of local IRB and OHRP requirements; chairing the monthly meetings and taking the final responsibility for all of the specific tasks delegated to the research staff; carrying out protocol training for its site personnel; supervising all local staffs; attending all related meetings and taking conference calls; collecting vaginal specimens, taking responsibility for all medical issues; and taking responsibility for GCP compliance.

B. Positions and Honors

Positions and Employment

1992 - 1994 General practitioner, Khon Kaen Hospital, Khon Kaen
1996 - 1998 Internal Medicine, Samutsakorn Hospital, Samutsakorn
1999 - 2000 Volunteer, Harvard School of Public Health, Boston, MA
2000 - 2002 Research Fellow, Division of Infectious Diseases, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA
2000 - 2002 Project Coordinator for Metabolic and Bone Associated HAART, Beth Israel Hospital, Boston, MA
2003 - Clinical trial coordinator, HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok
2003 - HIV consultant, Thongburi Hospital, Bangkok
2003 - Member, Community Advisory Board for HIV/AIDS research at the Thai Red Cross AIDS Research Centre, Bangkok
2003 - HIV expert working group and consultant, Thailand National Health Security Office, Bangkok
2003 - HIV consultant, Taksin Hospital, Bangkok

2003 -	HIV consultant and educator, Wednesday Friend's Club, Bangkok
2011 -	Committee member, Thai AIDS Society, Bangkok
2014 -	Committee member, Hepatitis Transformation (ACTG)
2014 -	Co-investigator/study physician, HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok

Other Experience and Professional Memberships

1997 -	member, The Royal College of Physicians of Thailand
1999 -	Member, The Infectious Diseases Society of Thailand
2005 -	Member, The Thai AIDS Society
2007 -	Member, the International AIDS Society (IAS)

Honors

1997	Chief resident of internal medicine, King Chulalongkorn Memorial Hospital
1998	Best Doctor honor, Samutsakorn Provincial Hospital
2006	International scholarship, Conference on Retroviruses and Opportunistic Infections
2006	International scholarship, Australian Society for HIV Medicine
2007	International Scholarship, International AIDS Society
2007	International scholarship, Conference on Retroviruses and Opportunistic Infections
2008	International scholarship, Conference on Retroviruses and Opportunistic Infections
2008	Resource Limited Scholarship, Ninth International Congress on Drug Therapy in HIV Infection
2009	International scholarship, International AIDS Society
2009	International scholarship, European AIDS Conference
2009	International scholarship, Conference on Retroviruses and Opportunistic Infections
2010	International scholarship, Conferences on Retroviruses and Opportunistic Infections
2010	Resource Limited Scholarship, Tenth International Congress on Drug Therapy in HIV Infection
2011	NUFFIC PhD grant award, The Netherlands Embassy
2011	Scholarship award, 1st Global Workshop in HCV
2011	Fellowship Leader Award, AUSAIDS
2012	International scholarship, Conference on Retroviruses and Opportunistic Infections
2012	Resource Limited Scholarship, 10th International Congress on Drug Therapy in HIV Infection
2014	International scholarship, Conference on Retroviruses and Opportunistic Infections
2014	Scholarship, International AIDS Conference
2015	International scholarship , Conference on Retroviruses and Opportunistic Infections
2015	Australia- APEC Women in Research Fellowship award, Asia Pacific Economic Cooperation

C. Contribution to Science

1. We noticed that many of our patients on standard dose of antiretroviral drugs had a lot of side effects. Therefore we checked the drug levels and found out that all of the patients had very high drug levels. Henceforth, the Thai guideline has revised its recommendation as per our findings.Not only did this decrease side effects but also was cost-effective for the country.

    a. Avihingsanon A, van der Lugt J, Kerr SJ, Gorowara M, Chanmano S, Ohata P, Lange J, Cooper DA, Phanuphak P, Burger DM, Ruxrungtham K. A low dose of ritonavir-boosted atazanavir provides adequate pharmacokinetic parameters in HIV-1-infected Thai adults. Clin Pharmacol Ther. 2009 Apr;85(4):402-8. PubMed PMID: 19118378.

b. van der Lugt J, Gorowara M, Avihingsanon A, Burger D, Ananworanich J, Sringam K, Kerr S, Wit F, Lange J, Ruxrungtham K. Reducing the boosting dose of ritonavir does not affect saquinavir plasma concentrations in HIV-1-infected individuals. AIDS. 2009 Jun 1;23(9):1176-9. PubMed PMID: 19451794.

c. Ananworanich J, Gorowara M, Avihingsanon A, Kerr SJ, van Heesch N, Khongpetch C, Uanithirat A, Hill A, Ruxrungtham K, Burger DM. Pharmacokinetics of and short-term virologic response to low-dose 400-milligram once-daily raltegravir maintenance therapy. Antimicrob Agents Chemother. 2012 Apr;56(4):1892-8. PubMed PMID: 22252825; PubMed Central PMCID: PMC3318383.

d. Avihingsanon A, van der Lugt J, Singphore U, Gorowara M, Boyd M, Ananworanich J, Phanuphak P, Burger D, Ruxrungtham K. Pharmacokinetics and 48 week efficacy of adjusted dose indinavir/ritonavir in rifampicin-treated HIV/tuberculosis-coinfected patients: a pilot study. AIDS Res Hum Retroviruses. 2012 Oct;28(10):1170-6. PubMed PMID: 22250979.

2. We now have solid proof that ART should be started early. This finding has changed the BHIVA guidelines.

a. Carr A, Grund B, Neuhaus J, Schwartz A, Bernardino JI, White D, Badel-Faesen S, Avihingsanon A, Ensrud K, Hoy J. Prevalence of and risk factors for low bone mineral density in untreated HIV infection: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:137-46. PubMed PMID: 25711332; PubMed Central PMCID: PMC4341957.

b. Lundgren J, Babiker A, Gordin F, Emery S, Fätkenheuer G, Molina JM, Wood R, Neaton JD. Why START? Reflections that led to the conduct of this large long-term strategic HIV trial. HIV Med. 2015 Apr;16 Suppl 1:1-9. PubMed PMID: 25711317; PubMed Central PMCID: PMC4347998.

3. Many of the findings from our TB studies have impacted the HIV treatment guidelines worldwide.

a. Avihingsanon A, Manosuthi W, Kantipong P, Chuchotaworn C, Moolphate S, Sakornjun W, Gorowara M, Yamada N, Yanai H, Mitarai S, Ishikawa N, Cooper DA, Phanuphak P, Burger D, Ruxrungtham K. Pharmacokinetics and 48-week efficacy of nevirapine: 400 mg versus 600 mg per day in HIV-tuberculosis coinfection receiving rifampicin. Antivir Ther. 2008;13(4):529-36. PubMed PMID: 18672531.

b. Tieu HV, Ananworanich J, Avihingsanon A, Apateerapong W, Sirivichayakul S, Siangphoe U, Klongugkara S, Boonchokchai B, Hammer SM, Manosuthi W. Immunologic markers as predictors of tuberculosis-associated immune reconstitution inflammatory syndrome in HIV and tuberculosis coinfected persons in Thailand. AIDS Res Hum Retroviruses. 2009 Nov;25(11):1083-9. PubMed PMID: 19886838; PubMed Central PMCID: PMC2828258.

c. Avihingsanon A, van der Lugt J, Singphore U, Gorowara M, Boyd M, Ananworanich J, Phanuphak P, Burger D, Ruxrungtham K. Pharmacokinetics and 48 week efficacy of adjusted dose indinavir/ritonavir in rifampicin-treated HIV/tuberculosis-coinfected patients: a pilot study. AIDS Res Hum Retroviruses. 2012 Oct;28(10):1170-6. PubMed PMID: 22250979.

d. Ballif M, Nhandu V, Wood R, Dusingize JC, Carter EJ, Cortes CP, McGowan CC, Diero L, Graber C, Renner L, Hawerlander D, Kiertiburanakul S, Du QT, Sterling TR, Egger M, Fenner L. Detection and management of drug-resistant tuberculosis in HIV-infected patients in lower-income countries. Int J Tuberc Lung Dis. 2014 Nov;18(11):1327-36. PubMed PMID: 25299866; PubMed Central PMCID: PMC4323497.

4. Many of our findings from the hepatitis studies have globally influenced the HIV treatment guidelines. I was also able to influence the Thai guidelines so now HBV treatment and testing

are available through the national program for all HIV-infected patients. Likewise, HCV treatment and testing are available through the national program for all HIV-infected patients.

a. Matthews GV, Seaberg EC, Avihingsanon A, Bowden S, Dore GJ, Lewin SR, Sasadeusz J, Revill PA, Littlejohn M, Hoy JF, Finlayson R, Ruxrungtham K, Saulynas M, Locarnini S, Thio CL. Patterns and causes of suboptimal response to tenofovir-based therapy in individuals coinfected with HIV and hepatitis B virus. Clin Infect Dis. 2013 May;56(9):e87-94. PubMed PMID: 23315316; PubMed Central PMCID: PMC3693490.

b. Avihingsanon A, Jitmitraparp S, Tangkijvanich P, Ramautarsing RA, Apornpong T, Jirajariyavej S, Putcharoen O, Treeprasertsuk S, Akkarathamrongsin S, Poovorawan Y, Matthews GV, Lange JM, Ruxrungtham K. Advanced liver fibrosis by transient elastography, fibrosis 4, and alanine aminotransferase/platelet ratio index among Asian hepatitis C with and without human immunodeficiency virus infection: role of vitamin D levels. J Gastroenterol Hepatol. 2014 Sep;29(9):1706-14. PubMed PMID: 24730732.

c. Thong VD, Akkarathamrongsin S, Avihingsanon A, Theamboonlers A, Poovorawan Y, Tangkijvanich P. The correlation between hepatitis C core antigen and hepatitis C virus RNA levels with respect to human immunodeficiency virus status, hepatitis C virus genotype and interferon-lambda-4 polymorphism. Intervirology. 2015;58(2):73-9. PubMed PMID: 25677196.

d. Obach D, Yazdanpanah Y, Esmat G, Avihingsanon A, Dewedar S, Durier N, Attia A, Anwar WA, Cousien A, Tangkijvanich P, Eholié SP, Doss W, Mostafa A, Fontanet A, Mohamed MK, Deuffic-Burban S. How to optimize hepatitis C virus treatment impact on life years saved in resource-constrained countries. Hepatology. 2015 Jul;62(1):31-9. PubMed PMID: 25581111.

Complete List of Published Work in My Bibliography:
http://1.usa.gov/1kDvg74

D. Research Support

Ongoing Research Support

A5316, NIH Daar E (PI) 04/29/15-01/01/21
Evaluating pharmacokinetics interactions with vaginal ring contraceptive and ART
This study will look at a method of hormonal birth control, called the NuvaRing, and specific anti-HIV medications, called antiretrovirals (ARVs).
Role: Co-Investigator

A5288, NIH Daar E (PI) 03/04/15-01/01/20
Management Using the Latest Technologies in Resource-limited Settings to Optimize Combination Therapy After Viral Failure
To use novel agents and contemporary management tools, including standard genotyping to select an appropriate third-line regimen, interventions to improve adherence and plasma viral load (VL) monitoring, in order to achieve a ≥ 65% rate of virologic control at 48 weeks of follow-up
Role: Co-Investigator

A5332 , NIH Grinspoon S (PI) 01/08/15-01/01/22
REPRIEVE, a randomized trial to prevent vascular events in HIV, tests whether a daily dose of a statin will reduce the risk of cardiovascular disease among HIV-infected individuals (for whom statins are not already recommended according to 2013 US Cholesterol Treatment Guidelines)
This is a randomized trial to prevent vascular events in HIV, tests whether a daily dose of a statin will reduce the risk of cardiovascular disease among HIV-infected individuals (for whom statins are not already recommended according to 2013 US Cholesterol Treatment Guidelines)

Role: Co-Investigator

A5279, NIH Campbell T (PI) 10/28/14-01/01/19
Phase III Clinical Trial of Ultra short Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection
To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to a standard 9-month (36 week) daily INH regimen for TB prevention in HIV-infected individuals
Role: Co-Investigator

IRC003 and IRC004, NIH Beigel J and Treanor J (PI) 05/01/12-06/01/20
IRC003 and IRC004
Comparing the Efficacy, Safety, and Tolerability of Combination Antivirals (Amantadine, Ribavirin, Oseltamivir) Versus Oseltamivir for the Treatment of Influenza in Adults at Risk for Complications
Role: Co-Investigator

START, NIAID, NIH Ruxrungtham K (PI) 01/01/10-12/01/16
Strategic Timing of AntiRetroviral Treatment
Role: Co-Investigator

A5349, NIH Nahid P and Dorman S (PI) 08/05/15-08/05/18
Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial
This study will evaluate the efficacy of a rifapentine-containing regimen to determine whether the single substitution of rifapentine for rifampin makes it possible to reduce to seventeen weeks the duration of treatment for drug-susceptible pulmonary tuberculosis.
Role: Co-Investigator

Completed Research Support

HIV-NAT 116, HIV-NAT Avihingsanon A (PI) 01/01/14-12/01/15
Efficacy and PK of adjusted dose of Lopinavir/ritonavir and rifabutin in active HIV/TB
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Avihingsanon, Anchalee

eRA COMMONS USER NAME (agency login):

POSITION TITLE: Co-investigator/study physician

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Khon Kaen University, Khon Kaen	MD	1992	Medicine
Amsterdam University, Amsterdam	PHD	2013	HIV and Coinfection

A. Personal Statement

I am primarily responsible for all of the research activities including fulfilling all of the study-specific objectives and requirements; carrying out targeted physical examinations among study volunteers; performing all study related clinical assessments, clinical counseling of medical test results, and implementing appropriate referrals; prescribing study drugs; assessing all drug-related toxicity and adverse events, immediately responding with emergency treatment if needed; alerting the PI regarding any Expedited Adverse Event (EAE); completing all medical records and CRFs related to clinical activities, such as clinical evaluations, physical examinations, and so forth; assisting, if necessary, in recruiting volunteers, community education, conducting consent; carrying out appropriate communication with local government and regulatory agencies and ensures the completion of local IRB and OHRP requirements; chairing the monthly meetings and taking the final responsibility for all of the specific tasks delegated to the research staff; carrying out protocol training for its site personnel; supervising all local staffs; attending all related meetings and taking conference calls; collecting vaginal specimens, taking responsibility for all medical issues; and taking responsibility for GCP compliance.

B. Positions and Honors

Positions and Employment

1992 - 1994	General practitioner, Khon Kaen Hospital, Khon Kaen
1996 - 1998	Internal Medicine, Samutsakorn Hospital, Samutsakorn
1999 - 2000	Volunteer, Harvard School of Public Health, Boston, MA
2000 - 2002	Research Fellow, Division of Infectious Diseases, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA
2000 - 2002	Project Coordinator for Metabolic and Bone Associated HAART, Beth Israel Hospital, Boston, MA
2003 -	Clinical trial coordinator, HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok
2003 -	HIV consultant, Thongburi Hospital, Bangkok
2003 -	Member, Community Advisory Board for HIV/AIDS research at the Thai Red Cross AIDS Research Centre, Bangkok
2003 -	HIV expert working group and consultant, Thailand National Health Security Office, Bangkok
2003 -	HIV consultant, Taksin Hospital, Bangkok

2003 -	HIV consultant and educator, Wednesday Friend's Club, Bangkok
2011 -	Committee member, Thai AIDS Society, Bangkok
2014 -	Committee member, Hepatitis Transformation (ACTG)
2014 -	Co-investigator/study physician, HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok

Other Experience and Professional Memberships

1997 -	member, The Royal College of Physicians of Thailand
1999 -	Member, The Infectious Diseases Society of Thailand
2005 -	Member, The Thai AIDS Society
2007 -	Member, the International AIDS Society (IAS)

Honors

1997	Chief resident of internal medicine, King Chulalongkorn Memorial Hospital
1998	Best Doctor honor, Samutsakorn Provincial Hospital
2006	International scholarship, Conference on Retroviruses and Opportunistic Infections
2006	International scholarship, Australian Society for HIV Medicine
2007	International Scholarship, International AIDS Society
2007	International scholarship, Conference on Retroviruses and Opportunistic Infections
2008	International scholarship, Conference on Retroviruses and Opportunistic Infections
2008	Resource Limited Scholarship, Ninth International Congress on Drug Therapy in HIV Infection
2009	International scholarship, International AIDS Society
2009	International scholarship, European AIDS Conference
2009	International scholarship, Conference on Retroviruses and Opportunistic Infections
2010	International scholarship, Conferences on Retroviruses and Opportunistic Infections
2010	Resource Limited Scholarship, Tenth International Congress on Drug Therapy in HIV Infection
2011	NUFFIC PhD grant award, The Netherlands Embassy
2011	Scholarship award, 1st Global Workshop in HCV
2011	Fellowship Leader Award, AUSAIDS
2012	International scholarship, Conference on Retroviruses and Opportunistic Infections
2012	Resource Limited Scholarship, 10th International Congress on Drug Therapy in HIV Infection
2014	International scholarship, Conference on Retroviruses and Opportunistic Infections
2014	Scholarship, International AIDS Conference
2015	International scholarship , Conference on Retroviruses and Opportunistic Infections
2015	Australia- APEC Women in Research Fellowship award, Asia Pacific Economic Cooperation

C. Contribution to Science

1. We noticed that many of our patients on standard dose of antiretroviral drugs had a lot of side effects. Therefore we checked the drug levels and found out that all of the patients had very high drug levels. Henceforth, the Thai guideline has revised its recommendation as per our findings.Not only did this decrease side effects but also was cost-effective for the country.

    a. Avihingsanon A, van der Lugt J, Kerr SJ, Gorowara M, Chanmano S, Ohata P, Lange J, Cooper DA, Phanuphak P, Burger DM, Ruxrungtham K. A low dose of ritonavir-boosted atazanavir provides adequate pharmacokinetic parameters in HIV-1-infected Thai adults. Clin Pharmacol Ther. 2009 Apr;85(4):402-8. PubMed PMID: 19118378.

b. van der Lugt J, Gorowara M, Avihingsanon A, Burger D, Ananworanich J, Sringam K, Kerr S, Wit F, Lange J, Ruxrungtham K. Reducing the boosting dose of ritonavir does not affect saquinavir plasma concentrations in HIV-1-infected individuals. AIDS. 2009 Jun 1;23(9):1176-9. PubMed PMID: 19451794.

c. Ananworanich J, Gorowara M, Avihingsanon A, Kerr SJ, van Heesch N, Khongpetch C, Uanithirat A, Hill A, Ruxrungtham K, Burger DM. Pharmacokinetics of and short-term virologic response to low-dose 400-milligram once-daily raltegravir maintenance therapy. Antimicrob Agents Chemother. 2012 Apr;56(4):1892-8. PubMed PMID: 22252825; PubMed Central PMCID: PMC3318383.

d. Avihingsanon A, van der Lugt J, Singphore U, Gorowara M, Boyd M, Ananworanich J, Phanuphak P, Burger D, Ruxrungtham K. Pharmacokinetics and 48 week efficacy of adjusted dose indinavir/ritonavir in rifampicin-treated HIV/tuberculosis-coinfected patients: a pilot study. AIDS Res Hum Retroviruses. 2012 Oct;28(10):1170-6. PubMed PMID: 22250979.

2. We now have solid proof that ART should be started early. This finding has changed the BHIVA guidelines.

a. Carr A, Grund B, Neuhaus J, Schwartz A, Bernardino JI, White D, Badel-Faesen S, Avihingsanon A, Ensrud K, Hoy J. Prevalence of and risk factors for low bone mineral density in untreated HIV infection: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med. 2015 Apr;16 Suppl 1:137-46. PubMed PMID: 25711332; PubMed Central PMCID: PMC4341957.

b. Lundgren J, Babiker A, Gordin F, Emery S, Fätkenheuer G, Molina JM, Wood R, Neaton JD. Why START? Reflections that led to the conduct of this large long-term strategic HIV trial. HIV Med. 2015 Apr;16 Suppl 1:1-9. PubMed PMID: 25711317; PubMed Central PMCID: PMC4347998.

3. Many of the findings from our TB studies have impacted the HIV treatment guidelines worldwide.

a. Avihingsanon A, Manosuthi W, Kantipong P, Chuchotaworn C, Moolphate S, Sakornjun W, Gorowara M, Yamada N, Yanai H, Mitarai S, Ishikawa N, Cooper DA, Phanuphak P, Burger D, Ruxrungtham K. Pharmacokinetics and 48-week efficacy of nevirapine: 400 mg versus 600 mg per day in HIV-tuberculosis coinfection receiving rifampicin. Antivir Ther. 2008;13(4):529-36. PubMed PMID: 18672531.

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are available through the national program for all HIV-infected patients. Likewise, HCV treatment and testing are available through the national program for all HIV-infected patients.

a. Matthews GV, Seaberg EC, Avihingsanon A, Bowden S, Dore GJ, Lewin SR, Sasadeusz J, Revill PA, Littlejohn M, Hoy JF, Finlayson R, Ruxrungtham K, Saulynas M, Locarnini S, Thio CL. Patterns and causes of suboptimal response to tenofovir-based therapy in individuals coinfected with HIV and hepatitis B virus. Clin Infect Dis. 2013 May;56(9):e87-94. PubMed PMID: 23315316; PubMed Central PMCID: PMC3693490.

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http://1.usa.gov/1kDvg74

D. Research Support

Ongoing Research Support

A5316, NIH Daar E (PI) 04/29/15-01/01/21
Evaluating pharmacokinetics interactions with vaginal ring contraceptive and ART
This study will look at a method of hormonal birth control, called the NuvaRing, and specific anti-HIV medications, called antiretrovirals (ARVs).
Role: Co-Investigator

A5288, NIH Daar E (PI) 03/04/15-01/01/20
Management Using the Latest Technologies in Resource-limited Settings to Optimize Combination Therapy After Viral Failure
To use novel agents and contemporary management tools, including standard genotyping to select an appropriate third-line regimen, interventions to improve adherence and plasma viral load (VL) monitoring, in order to achieve a ≥ 65% rate of virologic control at 48 weeks of follow-up
Role: Co-Investigator

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REPRIEVE, a randomized trial to prevent vascular events in HIV, tests whether a daily dose of a statin will reduce the risk of cardiovascular disease among HIV-infected individuals (for whom statins are not already recommended according to 2013 US Cholesterol Treatment Guidelines)
This is a randomized trial to prevent vascular events in HIV, tests whether a daily dose of a statin will reduce the risk of cardiovascular disease among HIV-infected individuals (for whom statins are not already recommended according to 2013 US Cholesterol Treatment Guidelines)

Role: Co-Investigator

A5279, NIH Campbell T (PI) 10/28/14-01/01/19
Phase III Clinical Trial of Ultra short Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection
To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to a standard 9-month (36 week) daily INH regimen for TB prevention in HIV-infected individuals
Role: Co-Investigator

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IRC003 and IRC004
Comparing the Efficacy, Safety, and Tolerability of Combination Antivirals (Amantadine, Ribavirin, Oseltamivir) Versus Oseltamivir for the Treatment of Influenza in Adults at Risk for Complications
Role: Co-Investigator

START, NIAID, NIH Ruxrungtham K (PI) 01/01/10-12/01/16
Strategic Timing of AntiRetroviral Treatment
Role: Co-Investigator

A5349, NIH Nahid P and Dorman S (PI) 08/05/15-08/05/18
Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial
This study will evaluate the efficacy of a rifapentine-containing regimen to determine whether the single substitution of rifapentine for rifampin makes it possible to reduce to seventeen weeks the duration of treatment for drug-susceptible pulmonary tuberculosis.
Role: Co-Investigator

Completed Research Support

HIV-NAT 116, HIV-NAT Avihingsanon A (PI) 01/01/14-12/01/15
Efficacy and PK of adjusted dose of Lopinavir/ritonavir and rifabutin in active HIV/TB
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Kerr, Stephen	Head of Biostatistics, HIV-NAT, Thai Red Cross AIDS Research Centre
eRA COMMONS USER NAME (credential, e.g., agency login) STEVEKR	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Sydney	BPharm	02/85	Pharmacy
University of New South Wales	Ph.D.	02/97	Neuropharmacology
Brigham and Women's Hospital	Postdoctoral	01/99	NeuroAIDS
University of Sydney	MIPH	04/04	Biostatistics

A. Personal Statement

I am Head of Biostatistics and Data Management at the TRC-ARC, and hold a joint appointment in the Biostatistics and Databases Program at the Kirby Institute, Faculty of Medicine at the University of New South Wales. My background in clinical pharmacy, pharmacology, international public health and biostatistics assist in my understanding of the methodologic and clinical issues which are important in pharmacokinetic, prevention and therapeutic studies. I am biostatistician for several NIH funded clinical studies detailed below in this document. I have taught Survival Analysis, Meta-analysis, Critical Appraisal and Rational Drug Use at Chulalongkorn University in Bangkok, and have supervised and mentored PhD students and Junior Investigators in Australia and Thailand. I have also conducted training in Biostatistics for under the Fogarty Training Grants Program and for TREAT ASIA. Under my direction, the Biostatistics Unit at the TRC-ARC has been built up from a team of 2 to a team of 7 biostatisticians, who provide guidance to clinicians on the biostatistical aspects of conducting and analyzing clinical trial and cohort studies in accordance with International regulations and guidelines.

B. Positions and Honors

Positions and Employment

1985-1989 Clinical Pharmacist, Sydney Children's Hospital, Randwick, NSW, Australia
1990 Senior Tutor, Department of Pharmacy, University of Sydney, NSW, Australia
1991-1992 Clinical Pharmacist (Oncology/Immunology), St. Vincent's Hospital, Sydney, NSW, Australia
1992-1994 Consultant Pharmacist, NSW Medicines Information Centre, Sydney, Australia
1993-1998 Research Assistant, Centre for Immunology, St. Vincent's Hospital, Sydney, NSW, Australia
1999 Postdoctoral Fellow, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA
2000-2004 Decision Support Program Manager, National Prescribing Service, Sydney, NSW, Australia
2000-2004 Adjunct Lecturer, Department of Pharmacy, University of Queensland, Brisbane, QLD
2004- Senior Lecturer, The Kirby Institute, University of New South Wales, Sydney, Australia
2004-2006 Biostatistician, HIV-Netherlands-Australia-Thailand Research Collaboration (HIV-NAT), Thailand
2006- Head of Biostatistics, HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Other Experience and Professional Memberships

2001-2004 Member, General Practice Computing Group, Royal Australian College of General Practitioners
2002-2004 Member, Australian Department of Health, Mediconnect Technical Working Group
2002-2004 Member, Australian Department of Health, Mediconnect Evaluation Working Group
2003 The Australian COX-2 Specific Inhibitor (CSI) Prescribing Group

2003-2004	Member, Australian Council for Safety and Quality in Health Care PDS Working Group
2003-2004	Department of Health and Ageing electronic Decision Support Officers Network
2003-2004	National Prescribing Service Evaluation Working Group
2004	Third Australian National Medicines Symposium Scientific Program Committee
2004-2006	Mentor, Thailand Research Council
2004-2008	Asian Association of Schools of Pharmacy (AASP)
2004-2010	International Society of Pharmacoepidemiology (ISPE)
2007-	International Epidemiologic Databases to Evaluate AIDS (IeDEA) Cancer Working Group
2009-	Biostatistics Reviewer for The Lancet, The Lancet Infectious Diseases
2009-	Member, Australasian Society of HIV Medicine (ASHM)
2011-	Member, International AIDS Society
2011-	Member, American Statistical Association

Honors

1993	Research Scholarship, University of New South Wales, Sydney, Australia
1996	Young Investigator Award, Centre for Immunology, University of New South Wales
1996	Award for Excellence in Research, St Vincent's Hospital/University of New South Wales
1998	Award for Excellence in Research, St Vincent's Hospital/University of New South Wales
1999	CJ Martin Fellowship, National Health and Medical Research Council (NHMRC), Australia

C. Selected Peer-reviewed Publications (Selected from 62 peer-reviewed publications)

1. **Kerr SJ**, Armati PJ, Pemberton LA, Smythe G, Tattam B, Brew BJ. Kynurenine pathway inhibition reduces neurotoxicity of HIV-1-infected macrophages. Neurology. 1997 Dec;49(6):1671-81. PubMed PMID: 9409365.
2. **Kerr SJ**, Mant A, Horn FE, McGeechan K, Sayer GP. Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners. Med J Aust. 2003 Oct 20;179(8):403-7. PubMed PMID: 14558862.
3. Duncombe C, **Kerr SJ**, Ruxrungtham K, Dore GJ, Law MG, Emery S, Lange JM, Phanuphak P, Cooper DA. HIV disease progression in a patient cohort treated via a clinical research network in a resource limited setting. AIDS. 2005 Jan 28;19(2):169-78. PubMed PMID: 15668542.
4. **Kerr SJ**, Duncombe C, Avihingsanon A, Ananworanich J, Boyd M, Sopa B, Medtech B, Chuenyam T, Cooper DA, Lange JM, Phanuphak P, Ruxrungtham K. Dyslipidemia in an Asian population after treatment for two years with protease inhibitor-containing regimens. J Int Assoc Physicians AIDS Care (Chic). 2007 Mar;6(1):36-46. PubMed PMID: 17329503.
5. Avihingsanon A, van der Lugt J, **Kerr SJ**, Gorowara M, Chanmano S, Ohata P, Lange J, Cooper DA, Phanuphak P, Burger DM, Ruxrungtham K. A low dose of ritonavir-boosted atazanavir provides adequate pharmacokinetic parameters in HIV-1-infected Thai adults. Clin Pharmacol Ther. 2009 Apr;85(4):402-8. doi:10.1038/clpt.2008.244. Epub 2008 Dec 31. PubMed PMID: 19118378.
6. Winston A, Duncombe C, Li PC, Gill JM, **Kerr SJ**, Puls R, Petoumenos K,Taylor-Robinson SD, Emery S, Cooper DA; Altair Study Group. Does choice of combination antiretroviral therapy (cART) alter changes in cerebral function testing after 48 weeks in treatment-naive, HIV-1-infected individuals commencing cART? A randomized, controlled study. Clin Infect Dis. 2010 Mar 15;50(6):920-9. doi: 10.1086/650743. Erratum in: Clin Infect Dis. 2010 Sep 1;51(5):638. PubMed PMID: 20146627.
7. Avihingsanon A, Lewin SR, **Kerr S**, Chang JJ, Piyawat K, Napissanant N, Matthews GV, Dore GJ, Bowden S, Lange J, Ruxrungtham K. Efficacy of tenofovir disoproxil fumarate/emtricitabine compared with emtricitabine alone in antiretroviral-naive HIV-HBV coinfection in Thailand. Antivir Ther. 2010;15(6):917-22. doi: 10.3851/IMP1645. PubMed PMID: 20834105.
8. Hoare A, **Kerr SJ**, Ruxrungtham K, Ananworanich J, Law MG, Cooper DA, Phanuphak P, Wilson DP. Hidden drug resistant HIV to emerge in the era of universal treatment access in Southeast Asia. PLoS One. 2010 Jun 8;5(6):e10981. PubMed PMID: 20544022; PubMed Central PMCID: PMC2882328

9. Ananworanich J, Apornpong T, Kosalaraksa P, Jaimulwong T, Hansudewechakul R, Pancharoen C, Bunupuradah T, Chandara M, Puthanakit T, Ngampiyasakul C, Wongsawat J, Kanjanavanit S, Luesomboon W, Klangsinsirikul P, Ngo-Giang-Huong N, **Kerr SJ**, Ubolyam S, Mengthaisong T, Gelman RS, Pattanapanyasat K, Saphonn V, Ruxrungtham K, Shearer WT; PREDICT Study Group. Characteristics of lymphocyte subsets in HIV-infected, long-term nonprogressor, and healthy Asian children through 12 years of age. J Allergy Clin Immunol. 2010 Dec;126(6):1294-301.e10. doi: 10.1016/j.jaci.2010.09.038. PubMed PMID: 21134574; PubMed Central PMCID: PMC3004741.
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12. Edwards-Jackson N, **Kerr S**, Tieu H, Ananworanich J, Hammer S, Ruxrungtham K, Phanuphak P, Avihingsanon A; HIV-NAT 006 Study Team. Cardiovascular risk assessment in persons with HIV infection in the developing world: comparing three risk equations in a cohort of HIV-infected Thais. HIV Med. 2011 Sep;12(8):510-5. doi: 10.1111/j.1468-1293.2011.00916.x. Epub 2011 Mar 6. PubMed PMID: 21375686.
13. **Kerr SJ**, Avihingsanon A, Putcharoen O, Chetchotisakd P, Layton M, Ubolyam S, Ruxrungtham K, Cooper DA, Phanuphak P, Duncombe C. Assessing adherence in Thai patients taking combination antiretroviral therapy. Int J STD AIDS. 2012 Mar;23(3):160-5. doi: 10.1258/ijsa.2009.009152. PubMed PMID: 22581867.
14. Winston A, Puls R, **Kerr SJ**, Duncombe C, Li PC, Gill JM, Taylor-Robinson SD, Emery S, Cooper DA; Altair Study Group. Dynamics of cognitive change in HIV-infected individuals commencing three different initial antiretroviral regimens: a randomized, controlled study. HIV Med. 2012 Apr;13(4):245-51. doi: 10.1111/j.1468-1293.2011.00962.x. Epub 2011 Dec 12. PubMed PMID: 22151608.
15. Puthanakit T, Saphonn V, Ananworanich J, Kosalaraksa P, Hansudewechakul R, Vibol U, **Kerr SJ**, Kanjanavanit S, Ngampiyaskul C, Wongsawat J, Luesomboon W, Ngo-Giang-Huong N, Chettra K, Cheunyam T, Suwarnlerk T, Ubolyam S, Shearer WT, Paul R, Mofenson LM, Fox L, Law MG, Cooper DA, Phanuphak P, Vun MC, Ruxrungtham K; on behalf of the PREDICT Study Group. Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial. Lancet Infect Dis. 2012 Dec;12(12):933-941. doi: 10.1016/S1473-3099(12)70242-6. Epub 2012 Oct 9. PubMed PMID: 23059199.

D. Research Support

Ongoing Research Support

R01MH089722 Ananworanich (PI) 05/18/2010-31/2014
Neurodevelopment and brain imaging among HIV-infected Children
The effect of immediate versus deferred antiretroviral initiation on neurodevelopment in children with HIV in Cambodia and Thailand (n=300, 11 sites)
Role: Biostatistician

ViiV Healthcare and UNICEF Kerr (PI) 06/2012 – 07/2013
A Randomised trial comparing two interventions to improve adherence to combination antiretroviral therapy (cART) in adolescents and young adults with HIV in Thailand.

This trial compares cognitive restructuring and SMS prompts and a combination of the two strategies to improve adherence in adolescents living with HIV.
Role: PI

1R01HD073972-01 Phanuphak (PI) 08/2012- 07/2017
Human Papillomavirus Infection n Perinatally HIV-infected Adolescents in Asia
This study will evaluate the early natural history of HPV infection and risk factors for HPV acquisition and persistence among HIV-infected and –uninfected adolescents in Asia by monitoring for cervical, vaginal, anal (female and male), oral (female and male), penile, and scrotal HPV infection, and cervical intraepithelial neoplasia.
Role: Biostatistician

108459-52-ISTA, amfAR, TREAT Asia Phanuphak (PI) 07/2012- 06/2013
Identifying Biomarkers of Anal Intraepithelial Neoplasia in Thai MSM
This study aims to assess the usefulness of biomarkers, including p16 proteins, MCM proteins, high-risk HPV types, and E6 and E7 mRNA/oncoproteins, as adjunct tools to anal Pap smear in identifying HGAIN and to study the impact of HIV infection on the characteristics of anal cytology (by anal Pap smear) and biomarkers.
Role: Biostatistician

108383-52-IPTA, amfAR, TREAT Asia Ananworanich (PI) 07/2012- 05/2013
Optimizing HIV Treatment for Children in Asia
This is a longitudinal observational cohort study to monitor for treatment failure to second-line ART in Asian children. This study has been implemented in 8 sites, 4 countries.
Role: Senior Biostatistician

Completed Research Support

CIPRA 1 U19 AI 53741-01A1 Ananworanich (PI) 12/2004 – 05/2012
The National Institutes of Health
Pediatric Randomized of Early vs Deferred Initiation in Cambodia and Thailand (PREDICT)
An open label, randomized study to compare antiretroviral therapy initiation when CD4+ is between 15-24% to ART initiation when CD4+ falls below 15% in children with HIV infection and moderate immune suppression.
Role: Biostatistician

R01MH089722 Ananworanich (PI) 05/18/2010-03/31/2011
National Institute of Child & Health Development (NICHD) and National Institute of Mental Health (NIMH)
Neurodevelopment and brain imaging among HIV-infected Children
The effect of immediate versus deferred antiretroviral initiation on neurodevelopment in children with HIV in Cambodia and Thailand (n=300, 11 sites)
Role: Biostatistician

Department of Veterans Affairs, Australia Mant (PI) 2007- 2010
Time to all cause mortality analysis for NSAID and COXIB users
This study will assess mortality in patients using NSAID and COXIB.
Role: Biostatistician

5U01AI069907/107694-46- /107798-47-IGTA Phanuphak (PI) 07/2009-06/2010
Biomarkers to detect anal intraepithelial neoplasia among Thai men who have sex with men
This study will investigate which biomarkers can reliably and accurately detect anal intraepithelial neoplasia in Thai men who have sex with men.
Role: Biostatistician

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Thammajaruk, Narukjaporn

eRA COMMONS USER NAME (agency login):

POSITION TITLE: Clinical Laboratory Pharmacologist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Faculty of Pharmaceutical Science, Chulalongkorn University, Bangkok	BS	03/2008	Microbiology
Faculty of Pharmaceutical Science, Chulalongkorn University, Bangkok	MS	04/2010	Microbiology
HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok	Other training	2010	HIV Medicine
HIV-NAT Laboratory, Thai Red Cross - AIDS Research Centre, Bangkok	Other training	2010	HPLC Operation
World Courier, Bangkok	Other training	2011	Shipping of infectious substances & biological substances, category B
Kinetex, Bangkok	Other training	2011	Kinetex Core-Shell Technology Columns Ultra-high Performance on ANY LC System
HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok	Other training	2011	basic knowledge in HIV pediatrics
Faculty of Medicine, Chulalongkorn University, Bangkok	Other training	2011	Laboratory Equipment Quality Management for Minimize Risk
Faculty of Medicine, Chulalongkorn University, Bangkok	Other training	2011	ISO/IEC 17025:2005 for Technical requirements
Merck Millipore, Bangkok	Other training	2012	Lab water; an Innovation Solution
Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok	Other training	2012	Population Pharmacokinetic Modeling Workshop
HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok	Other training	2012	Management Scientific instruments with PIC/S Regulations
International AIDS Society (IAS), Kuala Lumpur	Other training	2013	7th Conference on HIV Pathogenesis, Treatment and Prevention
Chulabhorn Research Institute, Bangkok	Other training	2013	Sithiporn Scientific & Technology Conference
Air Course, Bangkok	Other training	2014	Dangerous Goods Awareness with Concentration on preparing, handling & transporting Infectious Substances

A. Personal Statement

I am currently the clinical laboratory pharmacologist for TRCARC HIV Treatment Clinical Research Site under the Thailand HIV/AIDS and Infectious Disease Clinical Trials Unit (THAI CTU). I am primarily responsible for complying with GCP/GCLP and all SOPs applicable to ACTG responsibilities; performing the duties of a study coordinator for PK/PD project; working with clinical operations, developing the operational strategies for clinical pharmacology studies; providing consultations for implementing pharmacologic studies, operations, and monitoring adherence to the protocol; managing program timelines for clinical pharmacology studies; analyzing data, interpreting results, and other clinical pharmacology-related clinical documentation, including: clinical protocols; study reports and other various internal and external documents and communications, as needed; collecting, preparing and processing study specimens for the Clinical Laboratory; assessing the levels of the ART drugs in the study samples; performing, recording, and reporting laboratory results, confirming normal results; reviewing the Quality Control (QC) results daily by using acceptability criteria and L-J chart , Westguard Rules before reporting the patient's results; performing Proficiency Testing (PT); verifying and approving laboratory results; keeping and maintaining records of tests performed, laboratory records ;conducting and documenting appropriate quality control and assurance procedures for monitoring an evaluating the quality of the testing process of each method; maintaining communication between laboratory and clinical staff; coordinating with HIV-NAT study nurses , physicians and others for the shipment of biological specimens according to the IATA guidelines; conducting, managing and performing laboratory equipment/instrument maintenance system; maintaining high standards of laboratory house keeping, ensuring laboratory supplies and stocks are managed; using appropriate Personal Protective Equipment (PPE); demonstrating compliance with infection control policies and procedures; and performing work in a manner that reduces risk of transmission of infection to patients, self, and co-workers. I have around 4 years experience as a clinical laboratory pharmacologist for the HIV-NAT lab and can develop and validate assays for various drugs.

B. Positions and Honors

Positions and Employment

2010 - Clinical Laboratory Pharmacologist , HIV-NAT, Thai Red Cross - AIDS Research Centre, Bangkok

Other Experience and Professional Memberships

2008 - Member, Pharmacy Council of Thailand

2013 - Member, International AIDS Society (IAS)

Honors

2014 HIV Research Trust Scholarship, Wellcome Trust

C. Contribution to Science

1. The findings from these studies will help the sexual health/reproductive pharmacokinetics field

   a. Landolt NK, Phanuphak N, Ubolyam S, Pinyakorn S, Kriengsinyot R, Ahluwalia J, Thongpaeng P, Gorowara M, Thammajaruk N, Chaithongwongwatthana S, Lange JM, Ananworanich J. Efavirenz, in contrast to nevirapine, is associated with unfavorable progesterone and antiretroviral levels when coadministered with combined oral contraceptives. J Acquir Immune Defic Syndr. 2013 Apr 15;62(5):534-9. PubMed PMID: 23187949.

   b. Landolt NK, Phanuphak N, Ubolyam S, Pinyakorn S, Kerr S, Ahluwalia J, Thongpaeng P, Thammajaruk N, Cremers S, Thomas T, Chaithongwongwatthana S, Lange JM, Ananworanich J. Significant decrease of ethinylestradiol with nevirapine, and of

etonogestrel with efavirenz in HIV-positive women. J Acquir Immune Defic Syndr. 2014 Jun 1;66(2):e50-2. PubMed PMID: 24608892.

2. The findings from these studies will help the pharmacokinetics field

   a. Bunupuradah T, Techasaensiri C, Keadpudsa S, Thammajaruk N, Srimuan A, Sahakijpicharn T, Prasitsuebsai W, Ananworanich J, Puthanakit T. Pharmacokinetics of atazanavir/ritonavir among HIV-infected Thai children concomitantly taking tenofovir disoproxil fumarate. Pediatr Infect Dis J. 2014 Dec;33(12):e316-9. PubMed PMID: 24983717.

   b. Kerr SJ, Punyawudho B, Thammajaruk N, Colbers A, Chaiyahong P, Phonphithak S, Sapsirisavat V, Ruxrungtham K, Burger DM, Avihingsanon A. Factors associated with daily tenofovir exposure in Thai subjects taking combination antiretroviral therapy. AIDS Res Hum Retroviruses. 2015 Apr;31(4):368-74. PubMed PMID: 25384393.

3. The finding from this study will contribute to the pharmacogenomics field for TDF

   a. Rungtivasuwan K, Avihingsanon A, Thammajaruk N, Mitruk S, Burger DM, Ruxrungtham K, Punyawudho B, Pengsuparp T. Influence of ABCC2 and ABCC4 polymorphisms on tenofovir plasma concentrations in Thai HIV-infected patients. Antimicrob Agents Chemother. 2015 Jun;59(6):3240-5. PubMed PMID: 25801567; PubMed Central PMCID: PMC4432150.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/1rA9IAGUETmQD/bibliography/47600351/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

2010/03/01-2020/01/01
Tenofovir Renal Toxicity and Glomerular Filtration Rate (GFR) Validation, Office of the National Research Council of Thailand
Phanupak P (PI)
Incidence and Predictor of TDF Associated Nephrotoxicity and Pharmacokinetic of TDF in HIV-1 Infected Thai Patients: A Sub-study of HIV-NAT 006 Long Term Cohort
To assess and validate equation eGFR in HIV-infected subjects and -uninfected Thai patients
Role: OP

A5279 , NIH 2014/10/28-2019/01/01
Campbell T (PI)
Phase III Clinical Trial of Ultra-Short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection
To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to a standard 9-month (36 week) daily INH regimen for TB prevention in HIV-infected individuals
Role: OP

A5332 , NIH 2015/01/08-2022/01/01
Grinspoon S (PI)
REPRIEVE
This is a randomized trial to prevent vascular events in HIV, tests whether a daily dose of a statin will reduce the risk of cardiovascular disease among HIV-infected individuals (for whom statins are not already recommended according to 2013 US Cholesterol Treatment Guidelines)

Role: OP

A5288 (MULTI-OCTAVE) , NIH 2015/03/04-2020/01/01
Daar E (PI)
Management Using the Latest Technologies in Resource-limited Settings to Optimize Combination Therapy After Viral Failure
To use novel agents and contemporary management tools, including standard genotyping to select an appropriate third-line regimen, interventions to improve adherence and plasma viral load (VL) monitoring, in order to achieve a ≥ 65% rate of virologic control at 48 weeks of follow-up
Role: OP

A5316, NIH 2015/04/29-2021/01/01
Daar E (PI)
Evaluating pharmacokinetics interactions with vaginal ring contraceptive and ART
This study will look at a method of hormonal birth control, called the NuvaRing, and specific anti-HIV medications, called antiretrovirals (ARVs).
Role: OP

Completed Research Support

2010/12/01-2013/07/01
HIV-NAT 147, Ratchadaphiseksomphot Fund, Faculty of Medicine, Chulalongkorn University
Ananworanich J (PI)
Hormonal contraception in HIV positive women
This is a prospective cohort study with 200 Thai HIV-positive women on HAART and willing to use hormonal contraception provided as a standard low-dose COC pill for two months.
Role: OP

HIV-NAT 146, amfAR, Treat Asia; NHSO; and GPO 2011/07/01-2012/01/01
Bunupuradah T (PI)
The study of ATV/r-based HAART in Thai HIV-infected children
This trial will study the pharmacokinetics of ATV/r in HIV-infected Thai children
Role: OP

CURRICULUM VITAE

Suwapit Prasertthanawut

PERSONAL

Date of Birth:	7 April 1988
Address:	HIV-NAT, The HIV Netherlands Australia Thailand Research Collaboration and Thai Red Cross AIDS Research Centre, 104 Ratchdamri Road, Pathumwan, Bangkok 10330, Thailand
Phone:	0-2652-3040-9 Ext.136 (Office), 086-388-0213 (Mobile)
Email:	suwapit.p@hivnat.org

EDUCATION

Bachelor of Pharmacy 2007-2011

Faculty of Pharmacy

Srinakharinwirot University

POSITION

Present: Clinical research associate

August 2012 – August 2013:

- Junior clinical research associate (Monitor) at The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT)

April 2012 - August 2012:

- **CRA Assistant** at The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT)

TRAINING EXPERIENCE

August 2012	11th HIV/ AIDS workshop 2012 by THAI AIDS SOCIETY
June 2012	International "Standard Course in Clinical Trials" by faculty of Medicine, Chulalongkorn University
May 2012	Good Clinical Practice & Human Subject Protection by HIV-NAT
October 2011	CRA Intership at Bayer company