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ORIGINAL RESEARCH

Costs Associated with Adverse Drug Reactions Among HIV/TB Patients in Thailand

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Purpose: To assess the direct and indirect costs associated with adverse drug reactions (ADRs) in patients receiving treatment regimens for human immunodeficiency virus (HIV) infection and tuberculosis (TB) in selected Thai hospitals.

Patients and Methods: This was a retrospective study conducted between October 2014 and September 2019 at three public hospitals in Thailand. Data were obtained from a medical database and spontaneous ADR reporting system of each study site. The out-of-pocket health payments and indirect costs were determined via interviewing. All costs were updated to 2021.

Results: A total of 432 eligible patients who experienced ADRs due to HIV and TB treatment, and 93 patients were interviewed to determine direct non-medical and indirect costs. The average direct medical cost for ADR was USD 5.65 for mild cases, USD 156.54 for moderate cases, and USD 1,242.45 for severe cases. For direct non-medical costs, the average cost per episode was USD 27.29 in mild ADR, USD 70.86 in moderate ADR and USD 270.66 in severe ADR. The indirect cost incurred in each mild, moderate and severe ADR was USD 41.86, USD 89.34, and USD 552.60, respectively. The Stevens-Johnson syndrome (SJS) had the highest management costs.

Conclusion: ADRs associated with anti-tuberculosis drugs and antiretroviral drugs seem to have a substantial economic impact from a societal perspective. These findings would be useful for increasing awareness and encouraging early avoidance of ADRs.

Keywords: cost, adverse drug reaction, HIV, TB, Thai

Introduction

Human immunodeficiency virus (HIV) infection and tuberculosis (TB) have remained a serious public health burden worldwide, with roughly 38 million people living with HIV and 10 million contracting TB by 2020.[1,2] These two diseases are intersected that one in 10 active TB patients also has HIV.[3] According to the World Health Organization (WHO), Thailand has been one of the highest rates of TB and HIV/TB in Asia.[2,4] There were over 470,000 HIV-positive individuals, and about 84% of them received antiretroviral therapy.[5] As many as 105,000 cases were reported as newly diagnosed or relapsed TB, with approximately 85% successfully completing treatment.[6] To control infection, prevent transmission, and slow disease progression, three or four antiretroviral and/or anti-tuberculosis drugs are required for effective treatment of HIV and TB patients.[7–10]

It has been well recognized that the use of multiple drugs over an extended period of time can lead to adverse drug reactions (ADRs), which are defined as

> a toxic and unintended response to a drug that occurs at doses normally used in man either for disease prophylaxis, diagnosis, or therapy or for the modification of physiologic function.[11]

ADRs have been shown to be associated with an increased risk of morbidity, mortality, and economic burden,[12,13] and their severity ranges from mild to severe or life-threatening.[14–19] From this, ADRs have been considered a contributing factor to non-adherence, ultimately leading to treatment failure or poor prognosis.[20–24]

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In view of ongoing events, it is crucial to evaluate economic costs of ADRs for effective resource allocation, possibly leading to a more cost-effective use of antiretroviral and/or anti-tuberculosis drugs. A number of previous studies have examined the direct costs of ADRs associated with antiretroviral and/or anti-tuberculosis drugs in developing and developed countries.[25–29] The indirect costs caused by ADRs were identified in a few studies.[30,31] For instance, in Sweden, Gyllensten et al estimated the average indirect costs for patients who reported ADRs to be between USD 143 and USD 200 (33% of total costs), and these costs would be increased to 6 times in long-term care.[30] Another study showed that the average indirect costs for patients with ADRs were USD 3,405 or 55% of the societal costs.[31] None of direct non-medical and indirect costs of ADRs among Thai HIV/TB patients have been determined. Accordingly, the objective of this study was to assess the costs of ADRs associated with antiretroviral and/or anti-tuberculosis drugs based on a societal perspective. These findings were essential for healthcare professionals and policymakers seeking to improve patient safety, implement economic evaluation of new interventions related to ADR prevention, and reduce healthcare and family costs.

Patients and Methods

Study Setting and Population

Between October 2014 and September 2019, a retrospective observational study was conducted at three government hospitals: Nopparatrajathanee Hospital in Bangkok province, Buddhachinaraj Hospital in Phitsanulok province, and Queen Savang Vadhana Memorial Hospital in Chonburi province. During this time span, electronic medical records were reviewed for individuals with HIV, TB, or HIV/TB who had a history of ADRs to antiretroviral and/or anti-tuberculosis drugs. To assess eligibility, the following criteria were used: 1) Thai HIV, TB, or HIV/TB patients aged 18 years or older with either a history of ADRs due to antiretroviral and/or anti-tuberculosis drugs or receiving antiretroviral drugs and/or anti-tuberculosis drugs, 2) those who could communicate in Thai independently, and 3) those who experienced ADRs or drug toxicity to antiretroviral and/or anti-tuberculosis drugs as determined by a physician or pharmacist. Meanwhile, patients with systemic lupus erythematosus (SLE), malignancy, and pregnant women were excluded from this study. The study protocol was approved by the ethical committee of Institute for the Development of Human Research Protections, Ministry of Public Health in Thailand (COA No. IHRP2019054) and Faculty of Dentistry/Faculty of Pharmacy, Mahidol University, Institutional Review Board, Thailand (COA MU-DT/PY-IRB 2020/016.1603) and complied with the Declaration of Helsinki.

Data Collection

Patients in the database were solicited for enrollment by professional pharmacists based on their eligibility requirements. From October 2014 to September 2019, patients' characteristics (eg age, gender, education, health scheme, occupation, and underlying disease), clinical, and financial data were all retrieved from hospital medical databases and spontaneous ADR reporting systems. Clinical data on ADRs experienced by patients comprised suspected drug, symptoms, date of adverse event onset, treatment, and causality assessment. The Naranjo's algorithm was used to assess causality of ADR with suspected drug, categorized as definite, probable, possible, and doubtful.[32] Afterwards, the severity of ADR was assessed using the Hartwig's severity assessment scale.[33] These were assessed and recorded by physicians and pharmacists at three study sites.

Moreover, cost statistics were divided based on a societal perspective into direct medical, direct non-medical and indirect costs. Direct medical costs covered both costs related to public health facilities and out-of-pocket payments by patients. Costs of treatment at public institutions were gathered from medical databases including medications, medical supplies, laboratory tests, medical services, and hospitalizations. Out-of-pocket health payments, direct non-medical costs (eg transportation, meal, accommodation, and caregiver time loss), and indirect costs (defined as patient time lost due to morbidity or mortality) were collected via patient interviews. After receiving written informed consent, patients were recruited for direct interviews.

Sample Size

Throughout the study period, direct medical costs for all recruited samples were collected from the hospital database. Due to limited budget and time, the estimated sample size for interviews was calculated using the single population proportion formula[34] following as: $n = (Z^2 * p * (1-p))/d^2$ where Z = the probabilities at 95% confidence level as 1.96,

p = the proportion of ADRs associated with antiretroviral drugs and anti-tuberculosis drugs at 40%[35,36] and d = margin of error at 10%. Consequently, the required sample size for interviews was 93.

Cost Valuation

For each ADR, we calculated ADR episode-based cost of illness analysis from the first date of intending medical services associated with ADR diagnosis until the completion of treatment. The ending date of ADR episode was then the last date of the follow-up care. Unit cost of drugs and medical supplies was referred from the Drug and Medical Supply Information Center, Ministry of Public Health.[37] Unit cost of laboratory investigations, rooms, and medical services was mentioned from the standard cost lists for health technology assessment.[38] Out-of-pocket payment was obtained via patient interviews. Time costs of caregiver were calculated by multiplying the number of days spent caring for patients by their daily gross national income.[39] Patents' durations were determined by the number of days lost while receiving healthcare and in-home care. All costs were adjusted to 2021 using the consumer price index[40] and expressed in Thai baht (THB), which were then converted to US dollar (USD) using the Bank of Thailand's July 2021 exchange rates (USD 1 = THB 32.61).[41]

Data Analysis

Data were analyzed using Microsoft Excel and STATA version 15 software. Continuous variables were expressed as mean (standard deviation, SD) and median (interquartile, IQR). Categorical variables were reported as frequencies and percentages. Baseline demographics, clinical characteristics, and mean cost associated with ADRs in patients who had ADRs were all reported. Statistical differences in continuous variables across drug groups were executed using Mann–Whitney *U*-test (for 2 groups) or Kruskal–Wallis *H*-test (for >2 groups), while statistical differences in categorical variables were determined using chi-square test or Fisher's exact test. All statistical significances were set at a p-value of less than 0.05.

Results

A total of 432 patients who had ADRs were included in this study. Patients' characteristics are presented in Table 1. The mean age of the patients was 48.16 years, 60.42% were male. The majority of them were TB infections (51%). Out of 432 patients, 278 (64.35%) experienced with ADRs due to anti-tuberculosis drugs, while 154 (35.65%) had ADRs due to antiretroviral drugs. For patients hospitalized owing to ADRs, mean length of hospitalization was 5.6 days. Minimum and maximum length of stay was 2 to 26 days. According to Hartwig's scale for assessing the severity of ADRs, 62.04% of the reported ADRs were mild, 33.33% were moderate, and 4.63% were severe. In most cases (67.36%), causality assessment was deemed probable. ADRs due to anti-tuberculosis drugs were most prevalent with pyrazinamide (44.24%), rifampicin (21.94%), and isoniazid (12.59%) (Figure 1A), while ADRs induced by antiretroviral drugs were most prevalent with efavirenz (42.86%), nevirapine (22.73%), and zidovudine (8.44%) (Figure 1B).

Direct Medical Costs

Average direct medical costs associated with management of ADRs varied significantly by severity (p = 0.0001). Average direct medical cost caused by ADRs was USD 5.65 (THB 184.23) for mild, USD 156.54 (THB 5,104.09) for moderate, and USD 1,242.45 (THB 40,511.33) for severe (Table 2). In mild cases, cost of device and laboratory testing accounted for 79% of the total (Figure 2A), while the room cost accounted for 28% and 30% of the total in moderate and severe cases (Figure 2B and C). The average direct medical costs per episode were not significantly different for anti-tuberculosis and antiretroviral drug-induced ADRs.

As detailed in Table 2, the average cost of ADRs per episode was lowest for others (chill and mouth ulceration) (mean: USD 2.55 (THB 83.22)) and greatest for Stevens-Johnson syndrome (SJS) (mean: USD 1,349.28 (THB 43,994.70)). The treatment cost was not significantly different between patients with ADRs due to anti-tuberculosis and antiretroviral drugs, except for SJS (p = 0.041) and hepatitis (p = 0.010). From reported ADRs, the most expensive treatment was for rifampicin-induced SJS (USD 4,805.93; THB 156,702.70), followed by pyrazinamide-induced hypersensitivity syndrome (USD 2,444.11; THB 79,692.89), efavirenz-induced DRESS (USD 1,585.86; THB

Table 1 Baseline and Clinical Characteristics of Patients Occurring ADRs

Characteristics	Number of Patients; n (%)		p-value
	ADRs from Anti-Tuberculosis Drugs	ADRs from Antiretroviral Drugs	
Number of patients with ADRs	278 (64.35%)	154 (35.65%)	
Age (years)			
Mean (SD)	51.32 (17.77)	42.47 (11.03)	< 0.0001
Median (IQR)	49 (39–64)	42 (33–49)	< 0.0001
Age group (years)			
18–40	83 (29.86%)	72 (46.75%)	< 0.001
41–60	110 (39.57%)	74 (48.05%)	
> 60	85 (30.57%)	8 (5.20%)	
Gender			
Male	172 (61.87%)	89 (57.79%)	0.406
Female	106 (38.13%)	65 (42.21%)	
Severity of ADRs			
Mild	174 (62.59%)	94 (61.04%)	0.243
Moderate	88 (31.65%)	56 (36.36%)	
Severe	16 (5.76%)	4 (2.60%)	
ADRs Treatment			
No treatment	116 (41.73%)	72 (46.75%)	0.323
OPD	127 (45.68%)	59 (38.31%)	
IPD	35 (12.59%)	23 (14.94%)	
Length of stay (days)			
Mean (SD)	7.11 (6.11)	3.17 (3.02)	0.006
Median (IQR)	6 (3, 9)	3 (1, 5)	0.003
Naranjo's algorithm			
Definitely	39 (14.03%)	2 (1.30%)	< 0.001
Probable	172 (61.87%)	119 (77.27%)	
Possible	67 (24.10%)	33 (21.43%)	

51,708.71), levofloxacin-induced SJS (USD 1,498.52; THB 48,860.80), and pyrazinamide-induced SJS (USD 1,404.67; THB 45,800.67) (Table 3).

Direct Non-Medical and Indirect Costs

Results of direct non-medical cost and indirect cost analysis are summarized in Tables 4 and 5. For 93 patients interviewed with ADRs, the average direct non-medical costs differed significantly by severity. For direct non-medical costs, the average cost per episode was USD 27.29 (THB 889.88) in mild ADR, USD 70.86 (THB 2,310.46)

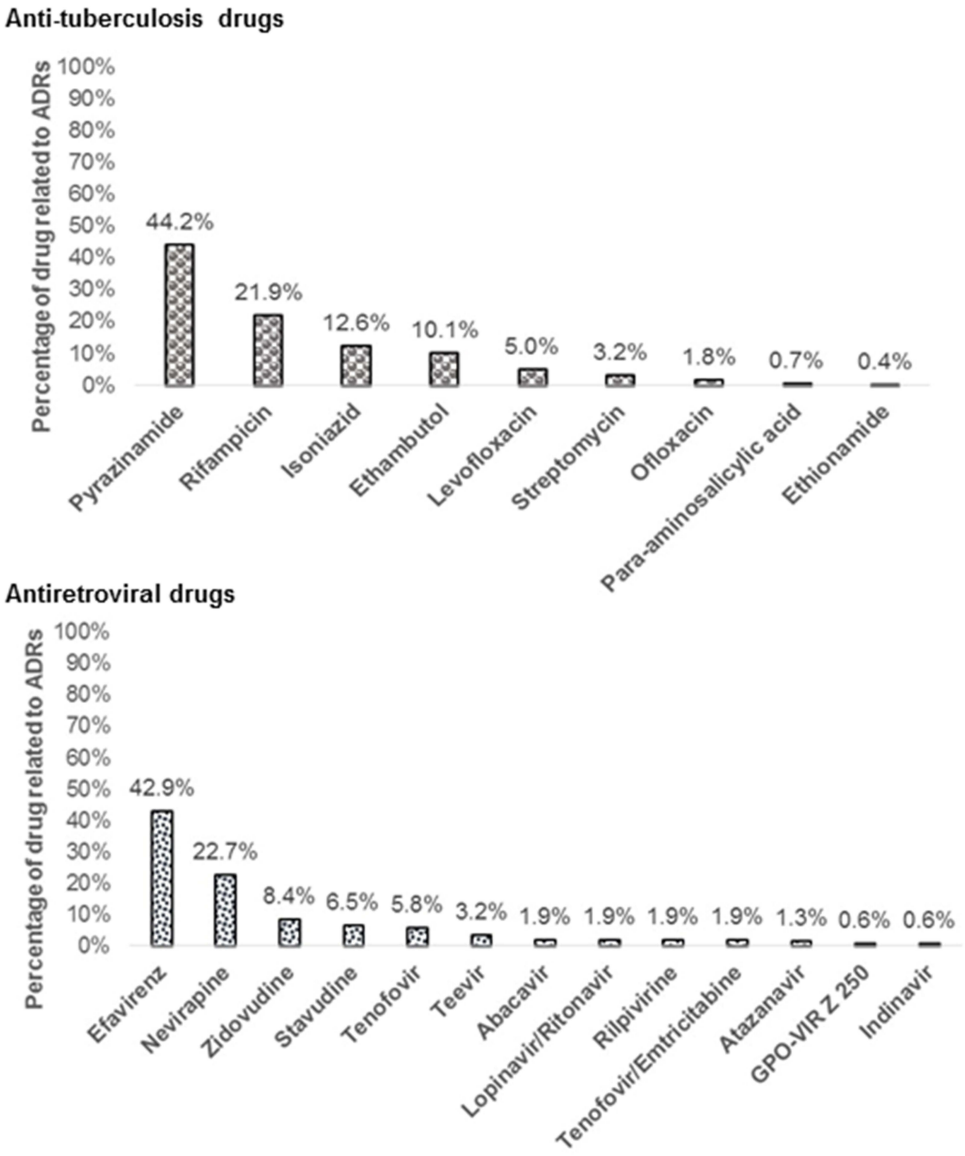

Figure 1 Percentage of reported drugs related to ADRs categorized by drug groups.

in moderate ADR, and USD 270.66 (THB 8,825.12) in severe ADR. On average, 7.4 days were wasted due to ADRs (the minimum and maximum of 1 to 106 days). The indirect cost incurred in each mild, moderate, and severe ADR was USD 41.86 (THB 1,364.83), USD 89.34 (THB 2,913.03), and USD 552.60 (THB 18,018.05), respectively. The direct non-medical and indirect costs were highest for SJS (USD 815.80; THB 26,600) and lowest for lipoatrophy (USD 21.91; THB 714.54), as shown in Table 4.

The highest cost was incurred by nevirapine-induced SJS (USD 1,220.13; THB 39,783.57), followed by amikin-induced nephrotoxicity (USD 741.98; THB 24,193.17), pyrazinamide-induced joint pain (USD 656.72; THB 21,413.17), efavirenz-induced hypersensitivity syndrome (USD 639.64; THB 20,856.09), and nevirapine-induced DRESS (USD 613.66; THB 20,009.03), as summarized in Table 5.

Discussion

This is the first cost analysis in Thailand to incorporate both direct medical, direct non-medical and indirect costs associated with managing ADRs due to anti-tuberculosis and antiretroviral drugs. During the study period, there were

Table 2 Average Direct Medical Costs of ADRs Categorized by Drug Groups (Thai Baht)

ADRs	n	Anti-Tuberculosis Drugs		n	Antiretroviral Drugs		n	Total	
		Mean (SD)	Median (IQR)		Mean (SD)	Median (IQR)		Mean (SD)	Median (IQR)
Severity									
Mild	174	208.40 (584.74)	0 (0,83.99)	94	139.48 (607.79)	0 (0,0)	268	184.23 (592.70)	0 (0, 83.50)
Moderate	88	4,571.58 (11,034.89)	751.02 (233.78, 2,310.75)	56	5,940.89 (14,226.22)	893.26 (252.91, 7,504.95)	144	5,104.09 (12,343.92)	784.94 (240.98, 4,441.93)
Severe	16	44,828.94 (43,664.83)	28,158.05 (20,017.34, 49,505.35)	4	23,240.87 (14,270.42)	23,786.33 (11,232.42, 35,249.32)	20	40,511.33 (40,197.89)	28,158.05 (18,473.44, 45,156.13)
Symptoms									
Erythema multiforme	–	–	–	3	4,506.15 (3,791.45)	5,264.99 (392.66, 7,860.79)	3	4,506.15 (3,791.45)	5,264.99 (392.66, 7,860.79)
Dermatitis exfoliate	–	–	–	2	2,233.53 (2,880.14)	2,233.53 (196.96, 4,270.09)	2	2,233.53 (2,880.14)	2,233.53 (196.96, 4,270.09)
DRESS	2	41,069.91 (35,021.12)	41,069.91 (16,306.24, 65,833.58)	5	39,974.78 (34,619.58)	37,573.25 (7,174.5, 74,777.60)	7	40,287.67 (31,681.37)	37,573.25 (7,174.50, 74,777.60)
SJS/TEN	8	49,046.80 (45,852.43)	41,511.71 (20,724.38, 49,505.35)	4	23,786.33 (12,924.59)	23,786.33 (14,647.26, 32,925.39)	12	43,994.70 (42,038.49)	35,718.62 (19,130.86, 45,800.67)
Rash, pruritis	116	1,716.60 (8,195.55)	83.75 (0, 301.74)	79	1,156.71 (3,392.88)	0 (0, 287.26)	195	1,489.77 (6,672.31)	50.39 (0, 295.81)
Blood disorders	3	923.49 (1,599.54)	0 (0, 2,770.48)	12	1,555.65 (2,615.86)	271.88 (0, 1,828.71)	15	1,429.22 (2,410.49)	167.98 (0, 1,998.98)
Nephrotoxicity	1	1,125.48	1,125.48	7	4,791.32 (6,511.28)	784.94 (198.61, 11,538.63)	8	4,333.09 (6,166.03)	955.21 (239.99, 8,076.20)
Hepatitis	81	1,286.98 (4,371.22)	82.76 (0, 562.74)	15	70.43 (201.98)	0 (0, 0)	96	1,096.89 (4,036.55)	0 (0, 531.35)
Jaundice	9	810.54 (975.20)	443.71 (0, 1,196.37)	3	0 (0)	0 (0, 0)	12	607.91 (908.86)	0 (0, 1,186.51)
Cholestasis	1	12,133.73	12,133.73	1	7,847.81	7,847.81	2	9,990.77 (3,030.60)	9,990.77 (7,847.81, 12,133.73)
Hyperuricemia	8	1,510.95 (1,549.90)	1,303.41 (91.03, 2,558.18)	–	–	–	8	1,510.95 (1,549.90)	1,303.41 (91.03, 2,558.18)
Thyroid disorders	2	1,933.90 (689.76)	1,933.90 (1,446.16, 2,421.63)	2	–	–	4	966.95 (1,185.43)	723.08 (0, 1,933.90)
Muscle & skeletal disorders	3	605.18 (877.96)	203.41 (0, 1,612.14)	1	–	–	4	453.89 (778.10)	101.71 (0, 907.78)

Metabolism disorders	1	522.74	522.74	8	240.99 (213.98)	87.17 (87.17,482.82)	9	272.29 (221.10)	87.17 (87.17, 522.74)
Cardiovascular disorders	1	–	–	1	809.99	809.99	2	404.10 (572.75)	404.10 (0, 809.99)
Angioedema	4	4,078.57 (6,985.27)	919.39 (0, 8,157.13)	2	213.10 (301.36)	213.10 (0, 426.19)	6	2,790.08 (5,768.80)	213.10 (0, 1,838.77)
Anaphylaxis	9	11,559.24 (13,775.27)	636.30 (0, 22,238.06)	–	–	–	9	11,559.24 (13,775.27)	636.30 (0, 22,238.06)
Eye disorders	15	917.27 (1,896.89)	131.47 (0, 1,597.19)	–	–	–	15	917.27 (1,896.89)	131.47 (0, 1,597.19)
Hypersensitivity syndrome	3	65,528.13 (66,563.27)	37,198.59 (17,816.02, 141,569.80)	2	8,261.20 (627.37)	8,261.20 (7,817.58, 8,704.82)	5	42,621.36 (56,562.21)	17,816.02 (8704.82, 37,198.59)
Central nervous disorders	3	335.72 (358.85)	293.25 (0, 713.92)	4	255.52 (511.05)	0 (0, 511.05)	7	289.89 (418.74)	0 (0, 713.92)
Gastrointestinal disorders	5	874.61 (841.23)	729.65 (228.46, 1,361.12)	3	44.14 (76.45)	0 (0, 132.41)	8	563.18 (768.62)	180.44 (0, 1,045.39)
Others	3	83.22 (0.94)	83.50 (82.17, 83.99)	–	–	–	3	83.22 (0.94)	83.50 (82.17, 83.99)

Notes: blood disorders eg anemia, bicytopenia, pancytopenia, thrombocytopenia; nephrotoxicity eg Fanconi syndrome, nephropathy, acute renal failure; thyroid disorders eg hypothyroid, gynecomastia; muscle and skeletal disorders eg joint pain, fatigue, tendinitis, myalgia; metabolism disorders eg lactic acidosis, lipodystrophy; cardiovascular disorders eg syncope, vasculitis; eye disorders eg eyelid edema, conjunctivitis, blurred eyes, optic neuritis; central nervous disorders eg nightmare, dizziness, neuropathy; gastrointestinal disorders eg nausea, vomiting, diarrhea; others eg mouth ulceration, chill.

Abbreviations: DRESS, Drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

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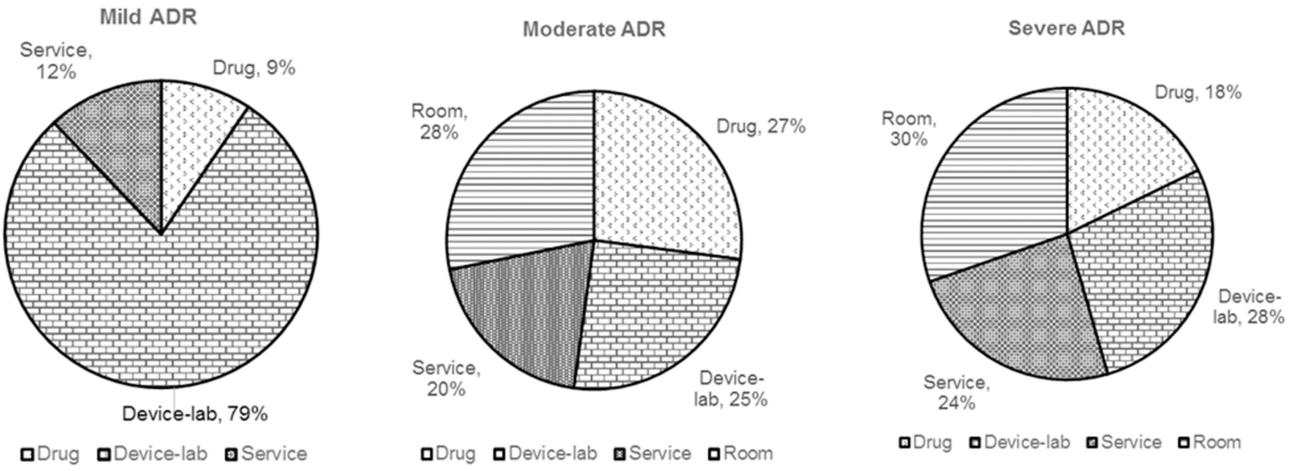

Figure 2 Proportion of component of treatment cost-associated with ADRs categorized by severity.

432 patients with ADRs, accounting for 3% of all patients enrolled in the study setting. Compared to previous studies, ADRs were probably underreported.[42,43] Male patients were more likely to encounter ADRs than female patients, because males were more susceptible to behavioral and social factors.[27,44,45] This resulted in an increase in transmission of disease.

Based on treatment costs of over half of patients with ADRs, mean direct medical cost caused by ADRs was USD 32 (THB 1,057) per outpatient and USD 738 (THB 24,079) per inpatient. About 17% of patients reporting ADRs were treated concurrently outside of public hospitals. The majority of high costs occurred in inpatient setting. The duration of stay was comparable to previous studies[27,46,47,] ranging from 2 to 26 days. The average length of stay in hospitals for ADR cases was 5.6 days, compared to the national average of 4.4 days.[48] Supporting the aforementioned findings, it has been reported that cost of ADRs was influenced by a patient's duration of stay.[47,49,50] In both developing and developed countries, numerous previous studies have reported on direct medical costs associated with ADRs[25–28,51,52] In Thailand, Chaiyanukij et al quantified treatment costs associated with ADRs among TB patients at Tuberculosis Area Center 10 in Chiang Mai province. The costs were calculated by combining labor and material costs, and the mean ADR cost per patient was USD 7 (THB 286.44) or USD 2 (THB 83.46) per episode.[25] Besides this, Srimongkol (2009) conducted a cost analysis of ADRs in 136 people living with HIV at Nakornping Hospital in Chiang Mai Province (95 patients receiving GPO-VIR S and 41 patients receiving GPO-VIR Z). Direct medical costs associated with ADRs included

Table 3 Reporting Top 10 Direct Medical Cost of ADRs Related to Anti-Tuberculosis Drugs and Antiretroviral Drugs

ADRs	n	Mean Cost (Thai Baht)				
		Drug	Device and Laboratory	Service	Room	Total Medical Cost per ADR
Rifampicin induced SJS	1	26,763.15	60,398.71	56,198.44	13,342.37	156,702.70
Pyrazinamide induced hypersensitivity syndrome	2	12,651.9	31,747.77	13,278.3	22,014.91	79,692.89
Efavirenz induced DRESS	3	21,129.54	23,239.25	2,002.96	5,336.95	51,708.71
Levofloxacin induced SJS	2	3,435.78	10,305.33	13,771.91	21,347.79	48,860.80
Pyrazinamide induced SJS	1	23,455.76	6,392.69	3,944.08	12,008.13	45,800.67
Ethambutol induced DRESS	2	5,722.99	15,008.97	4,994.23	15,343.73	41,069.91
Rilpivirine induced SJS	1	6,131.34	3,905.58	5,543.4	17,345.08	32,925.39
Isoniazid induced SJS	4	4,533.48	6,000.43	3,151.20	9,339.66	23,037.36
Nevirapine induced DRESS	2	4,652.7	3,812.26	9,239.09	4,669.83	22,373.88
Pyrazinamide induced anaphylaxis	2	5.309.96	986.02	3,880.42	6,004.07	16,180.45

Abbreviations: DRESS, Drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome.

Table 4 Average Direct Non-Medical and Indirect Costs of ADRs Categorized by Severity and Symptoms

ADRs	n	Direct Non-Medical Cost (Thai Baht)		Indirect Cost (Thai Baht)	
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Severity					
Mild	35	889.88 (954.43)	714.27 (180, 1,428.54)	1,364.83 (3,224.75)	628.54 (628.54, 628.54)
Moderate	52	2,310.46 (3,780.36)	807.14 (150, 2,505.61)	2,913.03 (4,313.57)	628.54 (628.54, 3,771.22)
Severe	6	8,825.12 (2,517.62)	9,117.56 (6,809.76, 11,156.58)	18,018.05 (23,489.67)	9,428.05 (8,799.51, 13,199.27)
ADR					
Rash	40	1,443.84 (2,066.74)	404.27 (145, 2,114.27)	2,137.03 (3,465.51)	628.54 (628.54, 1,885.61)
Erythema multiforme	1	100	100	628.54	628.54
Bone marrow suppression	1	270	270	628.54	628.54
Dermatitis exfoliate	1	1,828.54	1,828.54	628.54	628.54
DRESS	2	8,983.17 (3,073.67)	8,983.17 (6,809.76, 11,156.58)	10,999.39 (3,111.10)	10,999.39 (8,799.51, 13,199.27)
SJS	5	5,732.59 (4,382.19)	5,549.76 (1,935.61, 8,949.51)	20,867.41 (25,760.03)	10,056.58 (8,799.51, 19,484.63)
Nephrotoxicity	9	3,453.29 (6,050.27)	1,428.54 (500, 2,650)	1,117.40 (1,466.58)	628.54 (628.54, 628.54)
Hepatitis	15	2,348.49 (4,014.40)	978.54 (450, 1,800)	2,597.95 (3,282.06)	628.54 (628.54, 5,656.83)
Hyperuricemia	2	931.41 (165.65)	931.41 (814.27, 1,048.54)	628.54	628.54 (628.54, 628.54)
Gynecomastia	2	584.27 (628.29)	584.27 (140, 1,028.54)	628.54	628.54 (628.54, 628.54)
Joint pain	1	1,928.54	1,928.54	19,484.63	19,484.63
Lipoatrophy	1	86	86	628.54	628.54
Headache	1	400	400	628.54	628.54
Diarrhea, vomiting	2	100 (70.71)	100 (50, 150)	628.54	628.54
Cardiomegaly	1	1,028.54	1,028.54	628.54	628.54
Angioedema	2	382.14 (328.29)	382.14 (150, 614.27)	1,257.08 (888.88)	1,257.08 (628.54, 1,885.61)
Hypersensitivity	1	10,799.51	10,799.51	10,056.58	10,056.58
Jaundice	2	3,817.81 (5,116.35)	3,817.81 (200, 7,435.61)	628.54	628.54 (628.54, 628.54)
Others (eg fever, mouth ulceration, chest pain)	4	1,369.62 (922.39)	1,389.27 (589.27, 2,149.97)	1,099.94 (942.81)	628.54 (628.54, 1,571.35)

Abbreviations: DRESS, Drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome.

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Table 5 Reporting Top 10 Direct Non-Medical and Indirect Costs of Adverse Drug Reactions Related to Anti-Tuberculosis Drugs and Antiretroviral Drugs

ADRs	n	Mean Cost (Thai Baht)		Total Direct Non-Medical and Indirect Costs (Thai Baht)
		Direct Non-Medical Cost	Indirect Cost	
Nevirapine induced SJS	3	8,566.26	31,217.31	39,783.57
Amikin induced nephrotoxicity	1	19,164.88	5,028.29	24,193.17
Pyrazinamide induced joint pain	1	1,928.54	19,484.63	21,413.17
Efavirenz induced hypersensitivity syndrome	1	10,799.51	10,056.58	20,856.09
Nevirapine induced DRESS	1	6,809.76	13,199.27	20,009.03
IRZE induced DRESS	1	11,156.58	8,799.51	19,956.09
Rifampicin induced hepatitis	3	8,016.34	5,866.34	13,882.69
Rilpivirine induced skin rash	1	4,831.22	3,771.22	8,602.44
Efavirenz induced SJS	2	1,482.08	5,342.56	6,824.64
Isoniazid induced skin rash	3	2,599.96	2,933.17	5,533.13

Abbreviations: DRESS, Drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome.

medications, medical supplies, laboratory tests, room, food, and health care services. Mean direct medical cost of an ADR episode was USD 44 (THB 1,490) in both groups, USD 60 (THB 2,053) in the GPO-VIR S group, and USD 12 (THB 410) in the GPO-VIR Z group.[26] In India, Radhakrishnan et al demonstrated that direct costs of ADRs to HAART in 110 HIV-infected hospitalized patients were USD 186, including costs of medication, medical supply, laboratory investigation, and services.[27] In Spain, Homar et al determined costs of ADRs for 75 patients treated with fix dosage combinations and 150 patients treated with combinations of separately administered antiretroviral drugs from a single Spanish hospital. Management cost of ADRs was USD 321.[51] In the United States, Simpson et al examined the healthcare costs of ADRs in 2,548 HIV patients treated with NNRTIs. Mean cost of ADRs each episode ranged from USD 586 to USD 4,434.[52] Dekoven et al employed claims database to assess healthcare costs associated with antiretroviral drug-induced ADRs in 2,346 HIV-infected patients. Median cost per episode was USD 677, and the maximum cost was USD 12,825.[28] In South Africa, Schnippel et al showed that the average costs per ADR episode was USD 136 in moderate ADRs and USD 521 in serious ADRs during treatment course for multiple drug- and rifampicin – resistant tuberculosis.[29] However, direct comparisons between our findings and those of other studies should be made with caution due to the differences in context, such as study design, the scope of healthcare utilization, insurance systems, and county economics.

Due to lack of prior data on the costs of ADRs related to HIV/TB treatment, this study addressed this issue. In the present study, private healthcare cost, direct non-medical cost and indirect cost per patient with ADRs were USD 169 (THB 5,501), which were significantly higher than the cost per patient without ADRs. As a result, ADRs imposed a significant economic burden not only on the healthcare system but also on patients and caregivers.

The primary strength of this study was our data recruited from urban and rural regions of Thailand, which included both outpatient and inpatient care. A second strength was the fact that it incorporated detailed information on direct and indirect costs and used a consistent method of cost valuation within different settings. Despite these, this study has several limitations. First, the retrospective study was conducted using an electronic database that may include mis-classified and incomplete medical information. Second, since this study was conducted at only three tertiary hospitals in Thailand, generalizability to the national level should be performed with caution. In other settings, healthcare resource used for diagnosis, testing, or treatment might be different. Given the study's small sample size and reliance on self-reporting, the incidence findings may be underestimated. Furthermore, these study settings were involved in pharmaco-genomics for rational drug use in Thailand project, which included screening for *HLA-B*5701* and *NAT2* before commencing abacavir and isoniazid, respectively. Consequently, the incidence and economic burden of ADRs related to them were likely misrepresented. In terms of direct non-medical and indirect costs, in particular, this research is

possible owing to recollection bias. Therefore, further research is necessary to address this issue, including a prospective study and larger sample sizes.

Conclusion

Our study uncovered that ADRs related to anti-tuberculosis and antiretroviral drugs have an effect on healthcare utilization and economic burden in societal perspective. More 50% of patients with ADRs were handled in outpatient settings. Although the proportion of severe ADRs was low, the treatment costs and nonmedical costs were substantial. Our findings may serve as important criteria for future cost-effectiveness analyses of pharmacogenomics testing, thus promoting effective interventions and increasing the knowledge of healthcare professionals, policymakers, and patients towards adverse reaction avoidance.

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Author Contributions

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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