CD4 cell counts level and risks of Cutaneous Adverse Drug Reactions in HIV-infected patients receiving standard anti-tuberculosis drugs in Thailand

Miss Lakkana Boonyagars

A Thesis Submitted in Partial Fulfillment of the Requirements
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ผลของระดับปริมาณเม็ดเลือดขาวซีดี4ต่ออัตราการเกิดผลข้างเคียงทางผิวหนังในผู้ป่วยโรคเอดส์ที่ได้รับยาวัณโรคสูตรมาตรฐานในประเทศไทย

นางสาวลักขณา บุญญกาศ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Thesis Title	CD4 cell counts level and risks of Cutaneous Adverse Drug Reactions in HIV-infected patients receiving standard anti-tuberculosis drugs in Thailand
By	Miss Lakkana Boonyagars
Field of Study	Health Development
Thesis Advisor	Associate ProfessorPrakobkiat Hirunwiwatkul, M.D.

Accepted by the Faculty of Medicine, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

.....Dean of the Faculty of Medicine

(ProfessorSuttipong Wacharasindhu, M.D.)

THESIS COMMITTEE

.....Chairman

(ProfessorPichet Sampatanukul, M.D.)

.....Thesis Advisor

(Associate ProfessorPrakobkiat Hirunwiwatkul, M.D.)

.....Examiner

(Assistant ProfessorChulalak Komoltri, Ph.D.)

.....External Examiner

(Associate ProfessorNitipatana Chierakul, M.D.)

ลักขณา บุญญกาศ : ผลของระดับปริมาณเม็ดเลือดขาวซีดี4ต่ออัตราการเกิดผลข้างเคียงทางผิวหนังในผู้ป่วยโรคเอดส์ที่ได้รับยาวัณโรคสูตรมาตรฐานในประเทศไทย (CD4 cell counts level and risks of Cutaneous Adverse Drug Reactions in HIV-infected patients receiving standard anti-tuberculosis drugs in Thailand) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. นพ.ประกอบเกียรติ หิรัญวิวัฒน์กุล, 47 หน้า.

วัตถุประสงค์และความเป็นมา: วัณโรคเป็นสาเหตุสำคัญของการเจ็บป่วยและเสียชีวิตในผู้ติดเชื้อเอชไอวี การรักษาโดยใช้ยารักษาวัณโรคสามารถมีผลข้างเคียงทางผิวหนังจากยาได้ การศึกษานี้จัดทำโดยมีวัตถุประสงค์เพื่อศึกษาความแตกต่างของอุบัติการณ์ในการเกิดผลข้างเคียงทางผิวหนังระหว่างผู้ติดเชื้อวัณโรคร่วมกับเชื้อเอชไอวีที่มีปริมาณเม็ดเลือดขาวซีดี 4 สูงและซีดี 4 ต่ำ รวมถึงศึกษาปัจจัยเสี่ยงของการเกิดข้างเคียงทางผิวหนังในผู้ติดเชื้อวัณโรคร่วมกับเชื้อเอชไอวี

วิธีการ: เป็นการศึกษาโดยการเก็บข้อมูลย้อนหลังโดยศึกษาในติดผู้เชื้อวัณโรคร่วมกับเชื้อเอชไอวีที่เป็นผู้ใหญ่ที่ได้รับยารักษาวัณโรคสูตรมาตรฐาน เก็บข้อมูลตั้งแต่ 1 มกราคม 2551 ถึง 31 ธันวาคม 2558 ณ โรงพยาบาลวชิระ ประเทศไทย โดยการศึกษาได้ทำการเก็บข้อมูลพื้นฐาน ลักษณะอาการทางคลินิก และศึกษาปัจจัยที่สัมพันธ์กับการเกิดเกิดผลข้างเคียงทางผิวหนัง รวมถึงศึกษาปัจจัยทางด้านปริมาณเม็ดเลือดขาวซีดี 4

ผลการศึกษา: พบการเกิดผลข้างเคียงทางผิวหนังในผู้ป่วย 48 รายจากจำนวนผู้ป่วยทั้งหมด 307 รายในช่วงระยะเวลา 6 เดือนที่ได้รับยารักษาวัณโรค (อัตราการเกิดอุบัติการณ์ 0.41 ครั้งต่อคนต่อปี) ลักษณะผื่นที่พบมากที่สุดคือผื่นแดงตามตัว การที่มีปริมาณเม็ดเลือดขาวซีดี 4 ต่ำไม่พบว่าเป็นปัจจัยเสี่ยงของการเกิดผลข้างเคียงทางผิวหนัง จากการศึกษาพบว่า ภาวะการทำงานของไตลดลงในระดับปานกลาง ประวัติการแพ้ยาในอดีต และการที่ผู้ป่วยได้รับยาโคไทรม็อกซาโซลร่วมด้วยในการรักษา เป็นปัจจัยเสี่ยงของการเกิดผลข้างเคียงทางผิวหนัง ในทางกลับกัน การที่ผู้ป่วยได้รับต้านไวรัสเอชไอวีร่วมด้วยในการรักษาเป็นปัจจัยที่ลดความเสี่ยงของการเกิดผลข้างเคียงทางผิวหนัง อย่างไรก็ตาม ในการศึกษานี้ไม่พบความแตกต่างของระยะเวลาในการเกิดผลข้างเคียงทางผิวหนังระหว่างผู้ติดเชื้อวัณโรคร่วมกับเชื้อเอชไอวีที่มีปริมาณเม็ดเลือดขาวซีดี 4 สูงและซีดี 4 ต่ำ

สรุป: ในผู้ติดเชื้อวัณโรคร่วมกับเชื้อเอชไอวีสามารถพบการเกิดผลข้างเคียงทางผิวหนังได้บ่อย การวินิจฉัยภาวะนี้รวมถึงการหยุดยาที่สงสัยอย่างรวดเร็วจะสามารถป้องกันภาวะแทรกซ้อนและช่วยให้การดูแลรักษาวัณโรคมีคุณภาพที่ดีขึ้นได้

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต .....

ปีการศึกษา 2558 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

5774651830 : MAJOR HEALTH DEVELOPMENT
KEYWORDS: CD4 CELL COUNTS / CUTANEOUS ADVERSE DRUG REACTIONS / HIV / STANDARD ANTI-TUBERCULOSIS REGIMENS / TUBERCULOSIS

LAKKANA BOONYAGARS: CD4 cell counts level and risks of Cutaneous Adverse Drug Reactions in HIV-infected patients receiving standard anti-tuberculosis drugs in Thailand. ADVISOR: ASSOC. PROF.PRAKOBKIAT HIRUNWIWATKUL, M.D., 47 pp.

Objectives: Tuberculosis is the major cause of morbidity and mortality in HIV-infected patients. Anti-tuberculosis drugs can cause cutaneous adverse drug reactions (CADRs). This study was conducted to evaluate the difference in CADRs incidence between low and high CD4 cell count and to identify other CADRs risk factors in HIV/TB co-infected patients.

Methods: We collected a retrospective cohort of adult HIV/tuberculosis co-infected patients receiving a standard anti-tuberculosis regimens between 1 Jan 2008 – 31 Dec 2015 at Vajira hospital, Thailand. Baseline demographic, clinical characteristics and factors associated with CADRs included CD4 cell count status were collected.

Results: Of 307 patients enrolled, CADRs were found in 48 patients during six months period of tuberculosis treatment (Incidence rate = 0.41 events/person-year). Maculopapular rash was the most prevalent CADRs. Low CD4 cell count are not the risk of CADRs. Cox regression analysis revealed a moderate decrease in GFR, history of drug hypersensitivity and concomitant Co-trimoxazole use were all associated with CADRs. Concomitant antiretroviral use was associated with lower risk of CADRs. However, the analysis revealed no different in the time to CADRs between patients with lower and higher CD4 cell count.

Conclusions: CADRs are common in HIV/TB co-infected patients. Early recognition and prompt withdrawal of suspected agent could prevent complications and improve tuberculosis care.

Field of Study: Health Development Student's Signature .....

Academic Year: 2015 Advisor's Signature .....

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CHAPTER 1
INTRODUCTION

At present, more than 35 million people are living with HIV worldwide. Sub-Saharan Africa is the most affected region followed by the Asia-Pacific (1). Five million people were living with HIV in Asia-Pacific region in 2014. For Thailand, estimated adult living people living with HIV were 450,000 (400,000 - 490,000) people at the year 2014 (2, 3).

Tuberculosis (TB) is a major opportunistic infection and represents a leading cause of morbidity and mortality in HIV/AIDS patients worldwide, include Thailand (2, 4). WHO classified Thailand is among the top 25 countries in the world in terms of TB burden. With a population of nearly 67 million, there are 93,000 new TB cases each year and an overall estimated prevalence of TB are nearly 130,000 cases, which 16 % of whom are also HIV positive (5).

Recent studies demonstrated that HIV-infected individuals with latent TB are almost 30 times more likely to develop TB disease compared to those who are HIV uninfected, at a rate of 8-10%/year (6). WHO recommends HIV testing for patients at any age who present with signs or symptoms of TB (7).

Overall, treatment outcomes in 2013 continued to be worse for HIV-positive TB patients. The success rate was (73%) compared with HIV-negative TB patients (88%) (8). Globally, the proportion of TB patients that died during treatment was more than three times higher among HIV-positive TB patients (11% versus 3.5%). The proportion of patients categorized as lost to follow up, who may also have died of TB, was also higher for those who were HIV-positive (8).

In 2014, Thailand had Incidence of MDR-TB (multidrug resistant TB) about 2% (1.4–2.8%) of the overall new TB cases. Due to the resource-limited setting in Thailand, drug susceptibility testing of TB was not done routinely. From treatment in

registered cases in 2013, treatment success rate in Thailand was 81, 66 and 67 % for new/relapse patients, previously treated patients, and HIV/TB co-infected patients, respectively (8).

At present, WHO recommends anti-TB multidrug formulations to consist of Isoniazid (INH or H), Rifampicin (RFP or R), Pyrazinamide (PZA or Z), and Ethambutol (ETB or E) for new patients presumed or known to have drug-susceptible TB. New patients with pulmonary TB should receive regimens containing 2 months of INH, RFP, PZA, and ETB, then 4 months of INH and RFP (2HRZE/4HR), respectively. (7). Hepatitis and drug induced hypersensitivity are common adverse reactions associated with anti-TB medications (9, 10).

In HIV infected patients with TB co-infection, many issues are needed to be concerned. Disseminated TB is much more common in HIV-infected patients. Some regimens of antiretroviral drugs (ART), especially non-nucleotide reverse transcriptase inhibitors (NNRTIs) may cause cutaneous adverse drug reactions (CADRs). Besides this, some opportunistic infection prophylaxis drugs may also cause CADRs. These factors make TB treatment in HIV-infected patients are much more complicate than non HIV-infected patients.

Experienced with adverse drug reactions are frequently found in HIV/TB co-infected patients. Both ART and anti-TB drugs can cause mild to serious adverse drug reactions. Overlapping toxicities can occur in patients receiving ART, anti-TB drugs, and medications for opportunistic infection prevention such as Co-trimoxazole. Vigilant monitoring of side effects is, therefore, essential. Common ADRs associated with anti-TB drugs include: hepatitis, rashes, nausea/ vomiting, influenza-like illness and arthralgia (11, 12). When to focus on CADRs, many characteristics of reactions have been reported. The severity and nature of CADRs vary considerably and includes morbilliform rashes, maculopapular rashes, fixed drug eruptions, lichenoid drug eruptions, acute generalized exanthematous pustulosis, Steven-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TENs) (11).

The underlying mechanism driving the increased occurrence of drug hypersensitivity or drug eruptions in individuals living with HIV is not well understood, although one possible mechanism postulated is dysregulation of the immune system (13).

At present, recommendation by WHO suggests an earlier initiation of ART in HIV-infected patients to avoid opportunistic infections and non-AIDS metabolic complications. The threshold of CD4 cell count to start ART has been raised from 350 to any CD4 cell count regardless of WHO clinical stage in the year 2015 (14). In the future, more patients receiving ART concomitant with anti-TB drugs would be expected. Identifying the risk factors of CADRs in HIV/TB co-infected patients could be useful for physicians to select the high risk patients to consider for the shorter follow-up period and/or consider for more aggressive patients monitoring.

In a situation that patients receiving both anti-TB drugs and ART, one of the difficulties in studying concomitant drugs is identifying the attributable risk for each drug. Both ART and anti-TB drugs are well established risk factors of CADRs. Switching anti-TB drugs or ART to alternative regimens may cause ineffectiveness and may lead to a suboptimal treatment response. These problems could affect to long term survival of HIV-infected patients, especially in the drug-resistant setting. A further study identifying the patients at risk of CADRs are necessary and it could help physicians to give better management strategy to HIV/TB co-infected patients in the future.

CHAPTER 2
LITERATURE REVIEW

The literature review began with searching in PubMed database using the keyword [HIV and tuberculosis and cutaneous adverse drug reactions] and there were 24 articles found. There were 12 articles related to my interest. This searching method was done again in Scopus database and there were 20 articles found and the relevant articles were the same.

It is well established that HIV-infected patients experience a higher incidence of CADRs more than those without HIV. This includes CADRs from anti-TB drugs (12, 15-17). One study reported that HIV/TB co-infected patients have a 5-fold increased risk of rash or drug fever relative to TB patients without HIV (9). The range of anti-TB drugs associated CADRs was varied from 5-8% in non HIV to 20-28% in HIV-infected patients (16, 18-21). Besides HIV infection, there are other risk factors postulated to be associated with CADRs e.g. history of previous of ADR (22), genetic background (23), pre-existing renal and liver disease (24), female gender (25), older age (26) and drug dosage (27).

In HIV-infected population, One study conducted in South Africa demonstrates that HIV-infected patients with lower CD4 cell count have a higher risk of CADRs from anti-TB medications than patients with higher CD4 cell count (28). In this article, a retrospective study reported that median CD4 cell count was significantly lower among individuals with serious adverse reactions compared with those who tolerated medication (median CD4 cell count was 129.5 and 259 cells/mL, respectively) (28). Most patients experienced CADRs and hepatitis within the first two months of treatment. Limitation of this study was only 2 cases (0.8%) of patients were Asians. Generalizability to Thailand settings may not be applied. Besides this, anti-TB medications in nearly 30% of the cases enrolled in this study were not standard anti-TB regimens.

At present, Thailand, country with high prevalence of HIV and TB infection, the incidence of CADRs in HIV/TB co-infected patients receiving standard anti-TB medications are not established yet. Furthermore, the impact of the CD4 cell count level on the incidence of CADRs are not established also. From the literature review, only one study from South Africa demonstrated that HIV-infected individuals with median CD4 counts were 196 cells/mL (range 3–1, 302) had the occurence rate of skin rash almost 9% (28).

Studies on the occurrence rate of anti-TB drugs associated CADRs in HIV/TB co-infected patients compared to TB patients without HIV infection was demonstrated in **Table 1**.

Table 1. Review literature of the occurrence rate of anti-TB drugs associated CADRs in HIV/TB co-infected patients compared to TB patients without HIV infection.

From	Year	Study Site	Type of study	No. of total cases (no. of HIV infected cases)	Median CD4 (Range or IQR)	Rate of CADRs in HIV uninfected vs. HIV-infected cases
Pozniak AL, et al. (15)	1988-1989	Zimbabwe	Retrospective cohort study	906 (363)	na	9% vs. 20%
Nunn P, et al. (16)	1989-1990	Nairobi	Cross-sectional study	227 (93)	na	1% vs. 20%
Chintu C, et al. (17)	1990-1991	Zambia	Prospective observational study	237 (88)	na	2% vs. 21%

Yee et al. (9)	1990-1999	Canada	Retrospective cohort study	430 (18)	na	Total 4%
Dean, et al. (10)	1996-1999	England	Retrospective observational	188 (188)	90 (IQR, 30-180)	Total 17%
Dworkin et al. (29)	1989-2000	USA	Observational cohort study	367 (367)	120 (IQR, 20-234)	Total 27.8%
Breen R a. M, et al. (18)	1997-2003	England	Retrospective observational	312 (156)	77 (Range, 0-720)	8% vs.13%
Tan WC, et al. (19)	2004-2005	Malaysia	Retrospective observational	820 (103)	na	5% vs.13%
Marks DJB, et al. (28)	2004-2006	South Africa	Retrospective observational	400 (141)	196 (Range, 3–1302)	4% vs.9%

Na, not available IQR, interquartile range CADRs, cutaneous adverse drug reactions

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Research Question

3.1.1 Primary research question

Is there any difference in risk of cutaneous adverse drug reactions (CADRs) between low and high CD4 cell counts in HIV/TB co-infected patients receiving standard anti-TB drugs?

3.1.2 Secondary research questions

1. What are the risk factors of CADRs and risk factors of time to CADRs in HIV/TB co-infected patients?

2. What's the pattern of CADRs that commonly associated with anti-TB therapy?

3.2 Objective

3.2.1 Primary objective

To evaluate the difference of CADRs risk between low and high CD4 cell count in HIV/TB co-infected patients receiving standard anti-TB drugs.

3.2.2 Secondary objectives

1. To determines the risk factors of CADRs and risk factors of time to CADRs in HIV/TB co-infected patients.

2. To determine the patterns of CADRs that commonly associated with anti-TB therapy.

3. To determine the different of time to CADRs stratified by CD4 cell count.

3.3 Hypothesis

Research hypothesis

There was a difference in proportion of cutaneous adverse drug reactions in HIV/TB co-infected patients with CD4 cell counts less than 200 compared to at least 200 cells/mm^3.

Statistical hypothesis

Null hypothesis

There was no difference in proportion of cutaneous adverse drug reactions in HIV/TB co-infected patients with CD4 cell counts less than 200 compared to at least 200 cells/mm^3.

$$H_0: \quad \pi_1 = \pi_2$$

Alternative hypothesis

There was a difference in proportion of cutaneous adverse drug reactions in HIV/TB co-infected patients with CD4 cell counts less than 200 compared to at least 200 cells/mm^3.

$$H_a = \pi_1 \neq \pi_2$$

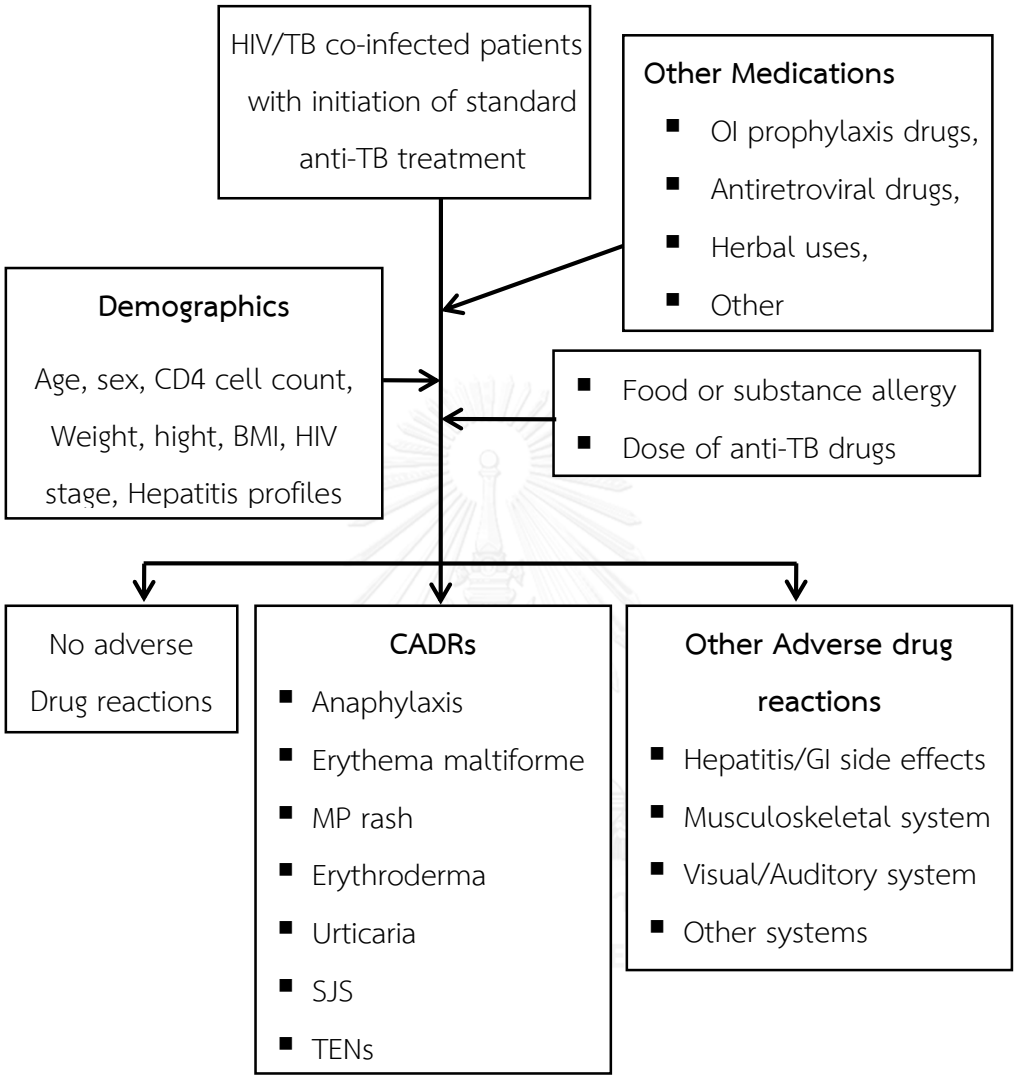
When

π_1 = Proportion of CADRs in HIV/TB co-infected patients with CD4 cell count at least 200 cells/mm^3.

π_2 = Proportion of CADRs in HIV/TB co-infected patients with CD4 cell count less than 200 cells/mm^3.

3.4 Conceptual framework

Figure 1. Conceptual framework of the study



MP, maculopapular SJS, Steven-Johnson syndrome TENs, Toxic epidermal necrolysis OI, opportunistic infections

3.5 Keywords

HIV, Tuberculosis, Cutaneous adverse drug reactions, CD4 cell counts, standard anti-tuberculosis regimens

3.6 Operation Definitions

Tuberculosis (definition according to WHO treatment of TB: guidelines 4th edition (7)): included,

Tuberculosis suspect

Any person who presents with symptoms or signs suggestive of tuberculosis. The most common symptom of pulmonary TB is a productive cough for more than 2 weeks,which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).

Case of tuberculosis

A definite case of TB (defined below) or one in which a health worker (clinician or another medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment.

Definite case of tuberculosis

A patient with Mycobacterium tuberculosis complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay. In countries that lack the laboratory capacity to routinely identify M. tuberculosis, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a “definite” case, provided that there is a functional external quality assurance (EQA) system with blind rechecking.

Standard regimens for TB (according to WHO treatment of tuberculosis: guidelines 4th edition (7))**,** consists of

- 2HRZE/4HR (2 months of INH, RFP, PZA, ETB or Streptomycin + 4 months of INH + RFP)
- Dosage recommendation
    - INH 5 (4-6) mg/kg/d, maximum 300 mg/d
    - RFP 10 (8-12) mg/kg/d, maximum 600 mg/d

- PZA 25 (20-30) mg/kg/d
- ETB 15 (12-18) mg/kg/d

Smear positive tuberculosis

A case of TB is considered to be *smear-positive* if one or more of tissue or body fluid specimens smear (e.g. sputum, pleural fluid, CSF, etc.) at the start of treatment are positive for AFB (acid fast bacilli) (provided that there is a functional EQA system with blind rechecking).

CADRs: Cutaneous Adverse Drug Reactions

Using Common Terminology Criteria for Adverse Events grading (CTCAE) (30), a standardized classification of side effects used in assessing drugs for cancer therapy, is used extensively in clinical drug trials.

Definition

Anaphylaxis: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.

Erythema multiforme: A disorder characterized by target lesions (a pink-red ring around a pale center).

Erythroderma: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area.

Rash maculo-papular (MP rash): A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus

Urticaria: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.

Stevens-Johnson syndrome (SJS): A disorder characterized by less than 10% total body skin area separation of the dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.

Toxic epidermal necrolysis (TENs): A disorder characterized by greater than 30% total body skin area separation of the dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.

Time to onset of CADRs

Defined as the time from the date first initiation of anti-TB drugs to date CADRs was recognized (first recognized by patients, or physician in the case that patients were unaware).

Treatment outcomes (according to WHO treatment of tuberculosis: guidelines 4th edition (7) and definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 (31)): included,

Cure: A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion

Treatment default: Patient A patient whose treatment was interrupted for 2 consecutive months or more.

Treatment failure: A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbor a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.

Transfer out: A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.

Died: Patient who dies for any reason during the course of treatment.

3.7 Research Design:

Retrospective cohort study

3.8 Research Methodology

3.8.1 Population: HIV with tuberculosis co-infected patients receiving standard regimens of anti-tuberculosis drugs.

3.8.2 Sample: Adult (age ≥ 18 years) HIV with tuberculosis co-infected patients from Vajira hospital receiving standard regimen anti-tuberculosis drugs between 1 Jan 2008 – 31 Dec 2015.

3.8.3 Inclusion criteria

1. Female and males with age equal or more than18 years.
2. Diagnosed as a case of tuberculosis with HIV co-infection (Case of tuberculosis: A definite case of TB or one in which a health worker has diagnosed TB and has decided to treat the patient with a full course of TB treatment).
3. Tuberculosis treatment with standard anti-tuberculosis regimens.

3.8.4 Exclusion criteria

1. Suspected of CADRs from other medication(s).
2. Duration of standard anti-TB regimens less than 2 months in a patient who didn't meet primary outcome.

3.8.5 Research Protocol

Data were collected retrospectively from electronic record of Vajira hospital, 900 beds university hospital, Bangkok, Thailand. This hospital serving more than 700,000 out-patient visits and around 30,000 in-patients admitted annually. The review was performed to evaluate whether patients compatible with inclusion/exclusion criteria. Patients with treated for TB between 2008 and 2015 were identified and enrolled consecutively, medical records were analyzed in an unselected manner.

At Vajira hospital, after diagnosis of TB, screening for HIV infection was offered to the patients at initial TB clinic attendance. In the case of the anti-HIV result was positive, patients will be counseled and scheduled to infectious clinic department for further treatment.

For TB management protocol at Vajira hospital, details of treatment and follow up schedule were responsible by Tuberculosis clinic. The scope of care included inpatients and outpatients care of TB cases. Inpatients with a diagnosis of TB will be sent to TB clinic and make follow up an appointment before they discharge.

It's a mandatory in Tuberculosis clinic that experienced healthcare personnel will review and noted in patient's record about the history of drug hypersensitivity (obtained from patient's history asking and paper medical record), and before initiation of anti-TB drugs, all patients will be advised and informed of side effects and adverse reactions after initiation of anti-TB drugs by experienced healthcare personnel and included advice on seeking medical care if they exhibited signs or symptoms of drug allergy even when follow-up date had not yet been reached. Routinely, the first follow-up will be scheduled for 2 weeks after initiation of anti-TB drugs. Patients will be asked about any side effects including rash and GI side effects, and physical examination was performed by physicians to evaluate whether patients had signs of adverse reaction from medications (e.g. jaundice, rash or other signs of drug eruptions). The result of the physical examination will be recorded in patient's medical sheets and electronic medical database. Tuberculosis was diagnosed according to WHO treatment of tuberculosis: guidelines 4th edition (described in operation definitions) (7). Anti-TB therapy was prescribed according to World Health Organization (WHO) guidelines, with initiation and continuation phases. Briefly, adult patients with no history of TB treatment received regimens consisting of two months of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol, followed by four months of Rifampicin and Isoniazid. Drugs

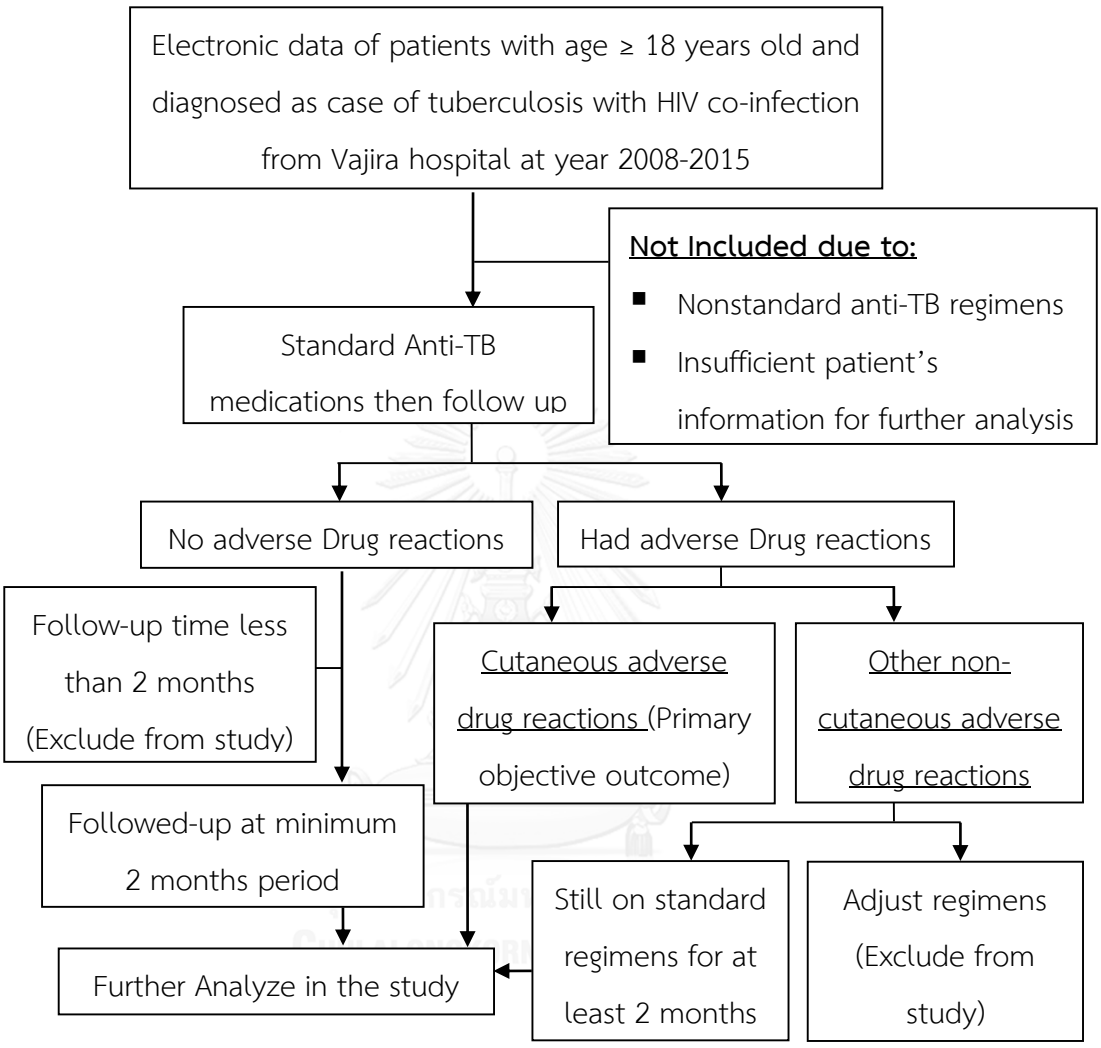
dosage were adjusted according to weight. Pyridoxine (Vitamin B6) at a daily dose of 50 mg was prescribed throughout the course of TB treatment.

Cutaneous adverse drug reactions (CADRs) were defined as in operation definitions using criteria from Common Terminology Criteria for Adverse Events grading (CTCAE) (30). Patients will be followed up 2 weeks or monthly visited depended on physician's decision at TB clinic. All of the patients were notified to seek for medical care whether they suspected of experiences of adverse drug reactions. Patients will be followed-up and seek for any signs of CADRs (meet primary outcome), the details of CADRs include severity of symptoms and management will be recorded, then patients will be followed up throughout TB treatment period. Patients without primary outcome occurred will be followed-up to the end of their treatment period (six months). Total follow-up commenced from the date of the first initiation of anti-TB drugs to the date of the last follow-up at TB clinic. All follow-up times exceeding 6 months were censored thereafter if no CADRs had occurred.

Treatment outcome was defined according to WHO treatment of tuberculosis: guidelines 4th edition (7) and definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 (31), as defined in operation definition. Other outcomes included all-cause mortality and patient transfer to another hospital.

3.8.6 Flow chart of recruit patients

Figure 2. Diagram of patient's enrollment in the study



3.8.7 Data collection

These data will be collected by research assistance using case record forms (CRF), included:

- **Demographic characteristics**
  - Assessment age, sex, weight, height, BMI, history of drug or substance hypersensitivity, concomitant medication, underlying diseases, hepatitis profiles (HBsAg, anti-HBs, anti HBc and anti-HCV), serum creatinine with GFR, Total T Lymphocytes, CD4, CD8 cell counts and

CD4/CD8 ratio; the CD4 and CD8 cell count is determined by flow cytometry technique.

- **HIV Diagnosis**
  - Date and methods of diagnosis, the status of HIV and regimens of ART treatment, opportunistic infection, and prophylaxis medication.
- **TB Diagnosis**
  - Date and method of TB diagnosis, date of start anti-TB medication, dose, and regimens of anti-TB medications, site(s) of involvement, and whether the case was new or retreatment, adherence and outcome of tuberculosis treatment
- **Occurrence of CADRs**
  - Assessment of incidence rate, time to onset, characteristics, and management of CADRs. The possible causative drug will be reviewed in patients with CADRs.

3.8.8. Data analysis

Data analysis was performed using the Statistical Package for Social Sciences software, version 22.0 (SPSS Inc., Chicago, IL, USA).

Part 1: Patient Characteristics

For categorical data, i.e. age group (18-29, 30-39, 40-49 and more than 50 years), sex, history of drug or substance hypersensitivity, GFR (normal GFR, mild, moderate and severe decrease GFR according to the classification of renal impairment using KDOQI Clinical Practice Guidelines for Chronic Kidney Disease (32)), low BMI, hepatitis profiles, underlying diseases, positive acid fast stain from tissue or body fluid specimens (yes vs. no), number of sites suspected tuberculosis involvement and outcome of treatment were presented as counts and percentages.

For continuous data, i.e. age, weight, height, BMI, CD4 cell counts, CD8 cell counts, total T lymphocyte counts and the CD4/CD8 ratio were presented as

means and standard deviations, or medians with inter-quartile ranges, depending on the normality of the variable.

Part 2: Univariate and multivariate analysis of risk factors associated with CADRs and time to CADRs.

The difference in CADRs risk between low and high CD4 cell count in HIV/TB co-infected patients receiving standard anti-TB drugs was tested using Pearson's chi-square test.

To evaluate risk factors of CADRs, binary logistic regression was employed and shown as odds ratio (OR) and 95% CI. Regarding risk factors of time to CADRs, Cox's proportional hazard regression was applied and reported as hazard ratio (HR) and 95% CI. Candidate variables for multivariate analysis were variables with univariate *P value* less than 0.2. A *P value* less than 0.05 was considered statistically significant throughout all inferential analyses.

Part 3: Univariate analysis of CD8 and CD4/CD8 ratio as factors of CADRs in patients with CD8 cell count results

Subgroup analysis to evaluate risk factors of CADRs was performed using Kaplan-Meier curve and univariate Cox proportional hazard regression. A *P value* less than 0.05 was considered statistically significant throughout all inferential analysis.

Part 4: Patterns of CADR associated with standard anti-TB regimens

The pattern of CADRs associated with standard anti-TB regimens was examined using descriptive statistics.

3.8.9 The sample size calculation

- Referred to previously studies that demonstrated the rate of CADRs was varied from 5-8% in non HIV-infected patients up to 20-28% in HIV-infected patients (16, 18-20).
- A Recent study from Marks DJB, et al. (28) demonstrated that HIV-infected patients with median CD4 cell counts were 196 cells/mL (range 3–1302) had a rate of skin rash about 9%.

Using the nQuery Advisor to calculation

Two group test of equal proportion (odds ratio = 1) (unequal n's)

Column		1	2	3	4
Test significance level, α	0.050	0.050	0.050	0.050	
1 or 2 side test?		2	2	2	2
Group 1 proportion, $\pi 1$		0.100	0.100	0.100	0.100
Group 2 proportion, $\pi 2$		0.200	0.220	0.220	0.250
Odds ratio, $\psi = \pi 2\ (1-\pi 1)/[\pi 1(1-\pi 2)]$		2.250	2.538	2.538	3.000
Power (%)		80	80	80	80
n1		170	146	124	85
n2		254	146	186	128
Ratio: n2/n1		1.500	1.000	1.500	1.500
N=n1 + n2		424	291	310	213

Group 1 Estimated proportion is the proportion of CADRs in HIV/TB co-infected patients with CD4 cell count equal or more than 200 cells/mm^3 = 0.10

Group 2 Estimated proportion is the proportion of CADRs in HIV/TB co-infected patients with CD4 cell count less than 200 cells/mm^3 = 0.22

Group 2: Group 1 ratio = 1.5:1 (From previous demographics data at Vajira hospital, estimated proportion of HIV-infected patients with CD4 cell count less than 200 cell/mm^3 is slightly higher compared to HIV-infected patients with CD4 cell counts equal or more than 200 cells/mm^3 (about 60% and 40% ,respectively).

This finding can be explained from mostly HIV-infected patients will not aware of their illness until they had opportunistic infections which reflects of low CD4 cell count conditions.

After analysis then this study will collect the data 124 cases + 186 controls (total 310) subjects.

3.8.10 Ethical consideration

- The study was conducted in accordance with the Helsinki Declaration of 2013
- Protocol approved
    - Proposal was approved by the Institutional Review Boards (IRB) of Chulalongkorn University and Vajira hospital before the beginning of the study.
- The patient's data will be collected and recorded in an electronic database using codes to maintain patient confidentiality.
- No conflict of interest of this study.

3.8.11 Limitation

1. The study investigates only CADRs in standard anti-TB regimens. Generalization for non-standard regimens may not be applied.

2. Some patients with mild CADRs or improve after self-medication or didn't require medical attention may be misinterpreted as no primary outcome.

3. To find the independent risk factors of CADRs, there may be many unknown factors and confounders that effect to the results.

3.8.12 Expected benefit and application

1. From the result of the study, we could use this information to apply to HIV/TB co-infected patients care. In patients with high risk of CADRs, intensive counseling and shorter follow-up period may be needed to reduce serious adverse reactions to the patients.

2. If we could identify the independent risk factors associated with CADRs, and the information of which drug has a higher risk of CADRs, we could use this information to modification of rechallenge technique of anti-TB medications in the HIV/TB co-infected patients with CADRs in the future.

CHAPTER 4
RESULTS

In this study, 449 HIV/TB co-infected individuals were accrued but 69 of these were not included because these patients did not receive standard anti-TB regimens. A total of 73 cases were excluded becausefollow-uptime was less than 2 months (22 cases), patients were transferred to another hospital (3 cases), there was insufficient patient information for further analysis (29 cases) or adjustments were made to regimens due to other reasons (19 cases). Finally, 307 HIV/TB co-infected individuals remained in the study with a total follow-up time of 42,968 person-days (117.72 person-years; mean follow-up time 139.96 days/person). The study flow is provided in **Figure 3**. Patients were then grouped into low CD4 cell count (< 200 cells/ mm^3) which included 216 patients, and high CD4 cell count (≥ 200 cells/ mm^3) which included 91 patients. We also conducted a subgroup analysis of the patients that had a CD8 cell count results. Characteristics of the two CD4 cell count groups and a subgroup of 68 patients with a CD8 cell count are provided in **Table 2.**

Figure 3. Flow chart of recruit patients

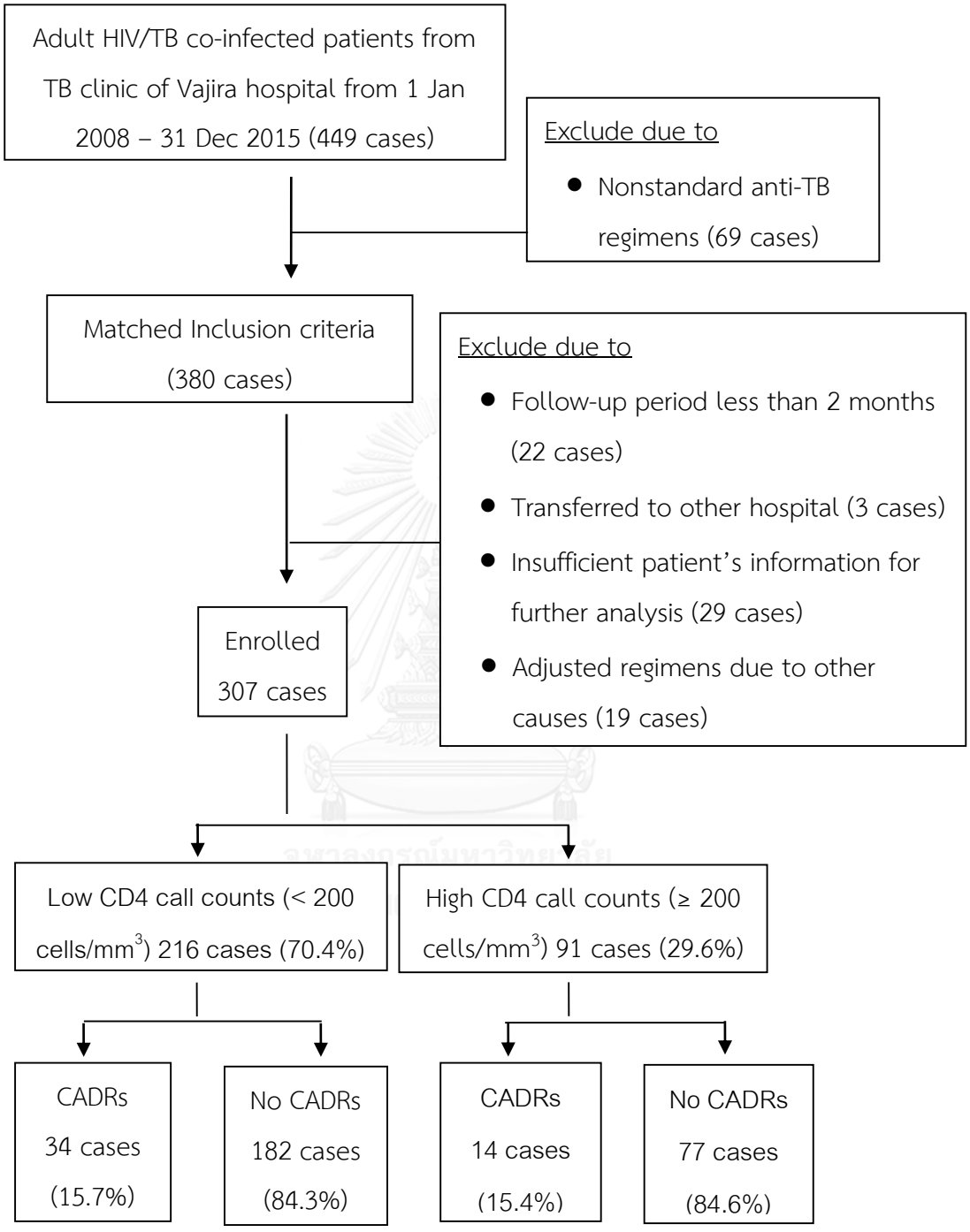


Table 2. Characteristics of 307 individuals (216 with low CD4 cell count group, 91 with high CD4 cell count group and 68 with a CD8 cell count results).

	Number (%) or Median (P25, P75)			
Variables	CD4 < 200 cells /mm^3 (n=216)	CD4 ≥ 200 cells /mm^3 (n=91)	Total (n=307)	Patients with CD8 cell count result (n=68)
Age (years): Mean ± SD	37.8 ± 10.1	38.5 ± 9.0	38.0 ± 9.8	37.4 ± 10.8
18-29	48 (22.2)	16 (17.6)	64 (20.8)	15 (22.1)
30-39	84 (38.9)	36 (39.6)	120 (39.1)	26 (38.2)
40-49	59 (27.3)	26 (28.6)	85 (27.7)	17 (25.0)
≥50	25 (11.6)	13 (14.3)	38 (12.4)	10 (14.7)
Sex, male	150 (69.4)	57 (62.6)	207 (67.4)	50 (73.5)
BMI (kg/m2): Mean ± SD	19.5 ± 4.0	20.0 ± 3.2	19.7 ± 3.8	19.8 ± 3.7
Low BMI(<18.5 kg/m2)	83 (38.4)	29 (31.9)	112 (36.5)	22 (32.4)
GFR*: Mean ± SD	91.4 ± 25.5	94.9 ± 29.0	92.4 ± 26.6	98.4 ± 33.6
Normal GFR (≥ 90)	100 (47.2)	43 (49.4)	143 (47.8)	36 (52.9)
Mild decrease GFR (60-89)	96 (45.3)	38 (43.7)	134 (44.8)	28 (41.2)
Moderate decrease GFR (30-59)	16 (7.5)	6 (6.9)	22 (7.4)	4 (5.9)
History of drug hyper-sensitivity	38 (17.6)	18 (19.8)	56 (18.2)	12 (17.6)
Concomitant medication (at time of initiation of anti-TB regimens)	111 (51.4)	35 (38.5)	146 (47.6)	38 (55.9)
Co-trimoxazole	95 (44)	9 (9.9)	104 (33.9)	30 (44.1)
Fluconazole	69 (31.9)	4 (4.4)	73 (23.8)	27 (39.7)

	Number (%) or Median (P25, P75)			
Variables	CD4 < 200 cells /mm^3 (n=216)	CD4 ≥ 200 cells /mm^3 (n=91)	Total (n=307)	Patients with CD8 cell count result (n=68)
Antiretroviral drugs	43 (19.9)	27 (29.7)	70 (22.8)	12 (17.6)
Hepatitis profiles				
HBV co-infection	27 (12.5)	3 (3.3)	30 (9.8)	11 (16.2)
HCV co-infection	39 (18.1)	14 (15.4)	53 (17.3)	16 (23.5)
Total T lymphocyte count	692 (452, 1021)	1493 (983.5, 1926.5)	866 (538, 1400)	609.5 (375.25-932.3)
CD8 cell count	441.5 (279.5, 713.5)	1133.5 (557.8, 1474)	513.5 (302, 810)	513.5 (302, 810)
CD4/CD8 ratio	0.07 (0.05, 0.13)	0.33 (0.18, 0.51)	0.10 (0.05, 0.18)	0.10 (0.05, 0.18)
CD4 cell count	55.5 (29, 97.8)	340 (250, 445)	90 (35, 232)	42.5 (23.3, 112)
Site of TB involvement >1 sites	36 (16.7)	8 (8.8)	44 (14.3)	7 (10.3)
Successful TB treatment outcome (Cured + Treatment completed)	161 (74.5)	81 (89)	242 (78.8)	49 (72.1)

*GFR was calculated by MDRD (Modification of Diet in Renal Disease) equation (ml/min/1.73 m^2), Classification of renal impairment using KDOQI Clinical Practice Guidelines for Chronic Kidney Disease classification(32).

The median CD4 cell count was 55.5 (IQR, 29, 97.8) and 340 (IQR, 250, 445) cells/mm^3 for the low and high CD4 cell count groups, respectively. Hepatitis B co-infection was higher in patients with low CD4cellcount. Co-trimoxazole and

Fluconazole use were both higher in patients with the low CD4 cell count group. History of drug hypersensitivity was noted in 38 and 18 patients for the low and high CD4 cell count groups, respectively. Of these, 8 patients had at least 2 drugs noted. The most common offending drugs were sulfa group antibiotics (24 cases), B-lactam antibiotics (12 cases), NNRTIs (13 cases), NSAIDs (7 cases), Azole antifungal (5 cases), and other drugs (10 cases).

CADRs were diagnosed in 48 out of 307 patients (15.64%) during the six months period of TB treatment (Incidence rate; IR = 0.41 events/person-year; 95%CI 0.38, 0.44). CADRs among patients with low and high CD4 cell count groups were 34 out of 216 (15.74%) and 14 out of 91 (15.38%), respectively. Univariate and multivariate analysis of CADRs using binary logistic regression analysis to estimate odds ratio (OR) and its 95% CI was provided in **Table 3.** The univariate analysis revealed that factors associated with higher risk of CADRs were: moderate decrease in GFR (30-59 ml/min/1.73 m^2) (OR 4.50, 95% CI 1.65, 12.30, *P* = 0.003), a history of drug hypersensitivity (OR 2.12, 95% CI 1.05, 4.30, *P* = 0.033), concomitant Co-trimoxazole use (OR 2.02, 95% CI 1.08, 3.77, *P* = 0.025), dose anti-TB regimens with PZA more than 30 mg/kg (OR 2.25, 95% CI 1.11, 4.58, *P* = 0.022) and ETB more than 20 mg/kg (OR 2.20, 95% CI 1.12, 4.33, *P* = 0.020). In contrast, ART use was associated with lower risk of CADRs (OR 0.35, 95% CI 0.13, 0.91, *P* = 0.026). However, there was no difference in median total T lymphocyte count and CD4 cell count between patients with and without CADRs (*P* = 0.213 and 0.732, respectively). Low CD4 cell count could not be shown to be associated with higher risk of CADRs (OR 1.03, 95% CI 0.52, 2.02, *P* = 0.937). Multivariate analysis revealed independent risk factors of CADRs were moderate decrease in GFR (OR 3.16, 95% CI 1.05, 9.52, *P* = 0.041), history of drug hypersensitivity (OR 2.51, 95%CI 1.17, 5.40, *P* = 0.019) and Co-trimoxazole use (OR 2.48, 95%CI 1.18, 5.21, *P* = 0.017). ART use was associated with lower risk of CADRs (OR 0.21, 95% CI 0.07, 0.61, *P* = 0.004). Dose anti-TB regimens with PZA more than 30 mg/kg and ETB more than 20 mg/kg could not be identified as independent risk factors of CADRs (OR 1.81, 95%CI 0.83, 3.93, *P* = 0.134 and OR 1.98, 95%CI 0.95, 4.13, *P* = 0.069, respectively) in multivariate analysis.

Table 3. Binary logistic regression of risk factors associated with CADRs in 307 HIV/TB co-infected patients.

Characteristics	Number (%) or Median (P25, P75)		Crude OR (95% CI)	Adjusted OR (95% CI)
	No CADRs (n=259)	CADRs (n=48)		
Age (years): Mean ± SD	38.1 ± 9.9	37.4 ± 9.1	-	
18-29	54 (84.4)	10 (15.6)	1	-
30-39	102 (85.0)	18 (15.0)	0.95	
40-49	71 (83.5)	14 (16.5)	1.07	
≥50	32 (84.2)	6 (15.8)	1.01	
Gender				
Female	82 (82)	18 (18)	1	-
Male	177 (85.5)	30 (14.5)	0.77	
BMI (kg/m^2)				
≥ 18.5	131 (81.9)	29 (18.1)	1	-
<18.5	94 (83.9)	18 (16.1)	0.87	
GFR[+]: Mean ± SD	93.7 ± 25.3	85.8 ± 32.0	-	
≥ 90	126 (88.1)	17 (11.9)	1	1
60-89	111 (82.8)	23 (17.2)	1.63[+]	1.37 (0.66, 2.86)
30-59	14 (63.6)	8 (36.4)	4.50**	3.16 (1.05, 9.52)*
History of drug hypersensitivity				
No	217 (86.5)	34 (13.5)	1	1
Yes	42 (75.0)	14 (25.0)	2.12*	2.51 (1.17, 5.40)*
Concomitant medications				
Antiretroviral	65 (92.9)	5 (7.1)	0.21*	0.23 (0.07, 0.61)**
Co-trimoxazole	81 (77.9)	23 (22.1)	2.02*	2.48 (1.18, 5.21)*

Hepatitis profiles				
HBV co-infection	25 (83.3)	5 (16.7)	1.06‡	-
HCV co-infection	44 (83.0)	9 (17.0)	1.08‡	-
Total T lymphocyte count	850 (535, 1350)	927 (598, 1727)	-	-
CD4 cell count (cells/mm^3)	86 (35, 230)	109 (37, 236.3)	-	-
≥ 200	77 (84.6)	14 (15.4)	1	1
< 200	182 (84.3)	34 (15.7)	1.03	0.71 (0.32, 1.55)
Sites involvement				
Single	222 (84.4)	41 (15.6)	1	-
Multi	37 (84.1)	7 (15.9)	1.02	
Dose anti-TB regimens				
INH > 8 mg/kg	13 (81.3)	3 (18.8)	1.26	-
RFP > 12 mg/kg	25 (92.6)	2 (7.4)	0.41	-
PZA > 30 mg/kg	40 (74.1)	14 (25.9)	2.25*	1.81 (0.83, 3.93)+
ETB > 20 mg/kg	48 (75.0)	16 (25.0)	2.20*	1.98 (0.95, 4.13)+

*** P < 0.001 ** P <0.01 * P < 0.05 + P <0.2,

† GFR was calculated by MDRD (Modification of Diet in Renal Disease) equation (ml/min/1.73 m^2)

‡ Reference = Patients without viral hepatitis

Univariate analysis of time to CADRs were performed using Kaplan-Meier survival curves, log-rank test and Simple Cox's regression (Table 4 and Figures 4, 5). Since survival functions were above 0.5, median time to CADRs was unavailable. Kaplan-Meier curves of time to CADRs by CD4 cell counts (<200 vs. ≥ 200 cells/mm^3) were provided in **Figure 4** showing no difference between patients with low and high CD4 cell counts (*P* = 0.920). Kaplan-Meier curves of time to CADRs by Co-trimoxazole and ART use were provided in **Figure 5A.** It revealed that there was a difference in the time to CADRs between patients with and without concomitant Co-

trimoxazole use (*P* = 0.020); and between ART use and not use (*P* = 0.028); **Figure 5B.**

Among 48 patients with CADRs, the median time to CADR was 14 (IQR 7.25-17.75) days. When compared between patients with low and high CD4 cell counts, the median time to CADRs was 14 (IQR 7.0-17.25) and 14 (IQR 11.0-21.25) days, respectively.

The univariate analysis using Cox's regression revealed that factors associated with higher risk of CADRs were as follows: moderate decrease in GFR (30-59 ml/min/1.73 m^2) (HR 3.75, 95% CI 1.62, 8.70, *P* = 0.002), a history of drug hypersensitivity (HR 2.05, 95% CI 1.10, 3.81, *P* = 0.024), concomitant Co-trimoxazole use (HR 1.93, 95% CI 1.10, 3.41, *P* = 0.022), dose anti-TB regimens with PZA more than 30 mg/kg (HR 2.02, 95% CI 1.08, 3.77, *P* = 0.027) and ETB more than 20 mg/kg (HR 2.01, 95% CI 1.10, 3.66, *P* = 0.023). In contrast, ART use was associated with lower risk of CADRs (HR 0.37, 95% CI 0.15, 0.94, *P* = 0.036). Low CD4 cell count could not be shown to be associated with higher risk of CADRs (HR 1.03, 95% CI 0.55, 1.92, *P* = 0.920).

Seven variables with univariate p-value less than 0.2 were entered in multivariate Cox's regression analysis (Table 4). Results revealed independent risk factors of CADRs were as follows: moderate decrease in GFR (HR 2.85, 95% CI 1.20, 6.79, P = 0.018), history of drug hypersensitivity (HR 2.46, 95%CI 1.29, 4.69, P = 0.006) and Co-trimoxazole use (HR 2.36, 95%CI 1.26, 4.41, P = 0.007). ART use was associated with lower risk of CADRs (HR 0.23, 95% CI 0.09, 0.61, P = 0.003). Dose anti-TB regimens with PZA more than 30 mg/kg and ETB more than 20 mg/kg could not be identified as independent risk factors of CADRs(HR 1.58, 95%CI 0.82, 3.04, P = 0.168 and HR 1.88, 95%CI 0.99, 3.54, P = 0.052, respectively) in multivariate analysis.

Table 4. Univariate and multivariate analysis of time to CADRs in 307 HIV/TB co-infected patients.

Characteristics	Crude HR (95% CI)	Adjusted HR (95% CI)
Age (years): Ref = 18-29		
30-39	0.97	-
40-49	1.08	-
≥50	1.01	-
Gender: Male	0.78	-
BMI (kg/m^2): < 18.5	0.87	-
GFR†: (Ref = ≥ 90)		
60-89	1.52^{+}	1.25 (0.65, 2.41)
30-59	3.75**	2.85 (1.20, 6.79)*
History of drug hypersensitivity: Yes	2.05*	2.46 (1.29, 4.69)**
Concomitant medications		
Antiretroviral	0.37*	0.23 (0.09, 0.61)**
Co-trimoxazole	1.93*	2.36 (1.26, 4.41)*
Hepatitis profiles		
HBV co-infection	1.03‡	-
HCV co-infection	1.07‡	-
Total T lymphocyte count	-	-
CD4 cell count (cells/mm^3): < 200	1.03	0.69 (0.36, 1.35)
Sites involvement: Multiple	1.01	-
Dose anti-TB regimens		
INH > 8 mg/kg	1.27	-
RFP > 12 mg/kg	0.42	-

PZA > 30 mg/kg	2.02*	1.58 (0.82, 3.04)$^{+}$
ETB > 20 mg/kg	2.01*	1.88 (0.99, 3.54)$^{+}$

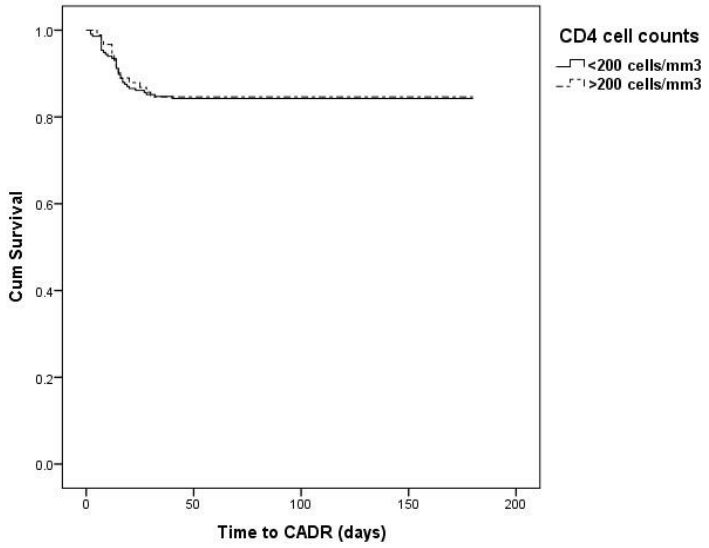
*** P < 0.001 ** P <0.01 * P < 0.05 $^{+}$ P <0.2

† GFR was calculated by MDRD (Modification of Diet in Renal Disease) equation (ml/min/1.73 m^2)

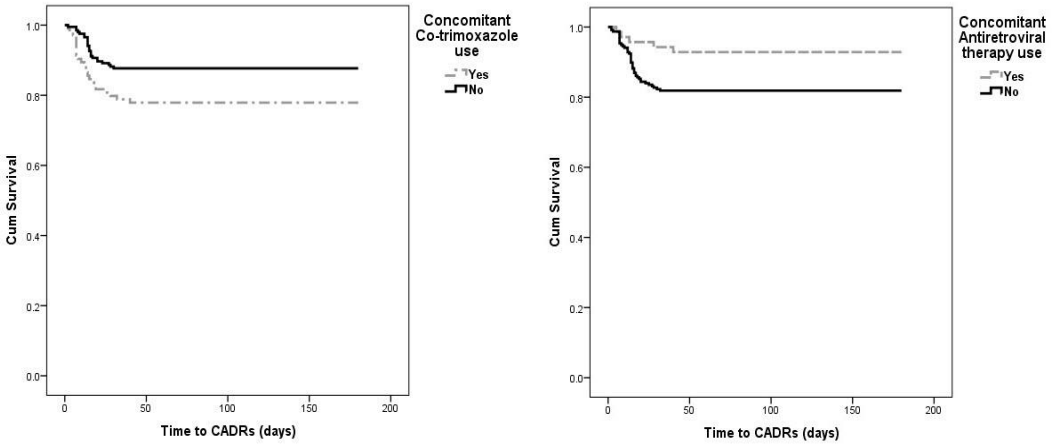
‡ Reference = Patients without viral hepatitis

In terms of treatment outcome, unsuccessful outcome (failed + died + lost to follow-up) was noted in 8 out of 48 (16.67%) and 47 out of 259 (18.15%) in patients with and without CADRs, respectively.

Figure 4. Kaplan-Meier curves of time to CADRs by CD4 cell counts (<200 vs. ≥ 200 cells/mm^3)



<u>Figure 5.</u> Kaplan-Meier curves of time to CADRs by (A) history of concomitant Co-trimoxazole use and (B) history of concomitant ART use.



A B

Baseline characteristics and univariate analysis in a subgroup (68 out of 307) patients with a CD8 cell count are provided in **Tables 2** and **4,** respectively**.** Univariate analysis via Cox's regression demonstrated that CD8 cell count and CD4/CD8 ratio more than 0.1 were not associated with higher risk of CADRs (HR 1.00, 95% CI 1.00, 1.00, *P* = 0.270 and HR 2.62, 95%CI 0.79, 8.72, *P* = 0.116, respectively).

Table 5. Univariate analysis of risk factors associated with time to CADRs in 68 HIV/TB co-infected patients with data on CD8 cell count

Characteristics	Number (%) or Median (IQR)		*P-value*	Crude HR (95% CI)
	No CADRs (n=56)	CADRs (n=12)		
CD8 cell count	479.5 (289.8, 763.5)	755.5 (425.3, 1,082)	0.270	1.00 (1.00, 1.00)
CD4/CD8 ratio	0.08 (0.05, 0.18)	0.14 (0.07, 0.30)	0.112	2.81 (0.79, 10.03)
CD4/CD8 ratio				
≤ 0.1	33 (89.2)	4 (10.8)	-	1
> 0.1	23 (74.2)	8 (25.8)	0.116	2.62 (0.79, 8.72)

Clinical characteristic of patients who had CADRs is provided in **Table 5.** Among the patients with CADRs, 44 out of 48 cases (91.7%) were managed with outpatient care and4 out of 48 cases (8.3%) required hospitalization. There are 34 out of 48 cases (70.8%)needed modification of anti-TB regimens after the occurrence of CADRs and 34 out of 48 cases (70.8%) required an extension of their TB treatment to more than 6 months. The most common pattern of CADRs observed included MP rash (39, 81.3%), followed by urticaria (3, 6.3%), both classified as mild CADRs. There were 4 patients with severe CADRs (1 case with anaphylaxis from RFP, 2 cases with SJS from RFP and 1case with TENs from an unspecified drug). In terms of the onset of CADRs after TB treatment, we observed that 94% of patients had CADRs within 4 weeks after commencing TB treatment. In our study, RFP and PZA were the most common offensive drugs (each 14 out of 48 patients), followed by ETB (5 out of 48 patients) and INH (3 out of 48 patients). There were 18 patients with unspecified causative anti-TB drugs. In these 18 patients, patients noted with concomitant Co-trimoxazole use was prescribed Co-trimoxazole throughout the study period without an interruption or suspected CADRs from Co-trimoxazole.

Table 6. Characteristics of 48 patients with CADRs from standard anti-TB regimens.

Characteristics of CADRs	Number of patients			The number of patients required to		
	Low CD4 cell count group	High CD4 cell count group	Total	Modifi-cation of anti-TB Regimens	Extended duration of TB treatment	Hospitali-zation
Non-Severe Reaction						
- Urticaria	2	1	3	2	2	-
- Erythema multiforme	-	1	1	1	1	-
- Maculopapular rash	28	11	39	27	26	-
- Erythroderma	1	-	1	-	1	-
Severe Reaction						
- Anaphylaxis	1	-	1	1	1	1
- Stevens-Johnson syndrome (SJS):	1	1	2	2	2	2
- Toxic epidermal necrolysis (TENs):	1	-	1	1	1	1
Total	34	14	48	34	34	4

CHAPTER 5
DISCUSSION

Study of CADRs in HIV/TB co-infected patients is important. In addition to much higher incidence compared to TB in the general population, HIV-infected patients also experienced higher drug interactions, multi-drugs resistant TB, disseminated infection, along with other adverse events making TB treatment of HIV-infected patients challenging. Compared to previous studies (9, 33), our study emphasizes TB treatment in HIV- infected patients in the context of the resource-limited healthcare setting. Moreover, diagnostic methods, CADR classification and treatment regimens in our study are standard and well established.

The burden of both HIV and TB are particularly high in many Asian countries. This is the first study to consider the HIV/TB co-infected population in an Asian context. A common struggle for TB treatment is the incidence of CADRs, a condition particularly prevalent in HIV-infected patients receiving anti-TB drugs. In our cohort, 15.64% (48/307: IR = 0.41 events/person-year; 95%CI 0.38, 0.44) of patients experienced CADRs from standard anti-TB regimens, during our six months follow up, a level consistent with previous epidemiological studies of HIV/TB patients in other parts of the world (9, 33). We demonstrate that HIV/TB co-infected patients with a history of drug hypersensitivity, concomitant Co-trimoxazole use, and a moderate decrease in GFR are particularly at risk of CADRs. Whereas, concomitant ART was demonstrated as protective against CADRs. Like previous studies of TB in the general population (22, 24, 34), we demonstrated a moderate decrease in GFR and history of drug hypersensitivity are independent risk factors of CADRs in the HIV/TB co-infected population. Also, these studies identified female sex and older age as risk factors of CADRs in TB patients. However, in contrast to the findings of other studies (25, 26), we found no evidence that sex or age are associated with CADRs in TB patients co-infected with HIV.

In our study, HIV/TB co-infected patients with concomitant Co-trimoxazole use exhibited increased risk of CADRs. One of the difficulties in studying concomitant drugsis identifying the attributable risk for each drug. Both Co-trimoxazole and anti-TB drugs are well established risk factors of CADRs. However, previous studies have demonstrated that CADRs due to Co-trimoxazole are likely to occur within 1-2 weeks of commencing this treatment (35-37). In our study, all patients noted with concomitant Co-trimoxazole use were prescribed this drug before initiation of anti-TB drugs for at least 1-2 weeks. For this reason, CADRs diagnosed in patients from our cohort were likely to have developed this condition due to their anti-TB drug regimen. Moreover, patients noted with concomitant Co-trimoxazole use was prescribed Co-trimoxazole throughout the study period without an interruption or suspected CADRs from Co-trimoxazole. To date, this is the first study to identify Co-trimoxazole as a risk factor of CADRs in HIV-infected patients. The reason concomitant Co-trimoxazole increases risk CADRs remains unclear. One explanation may be related to the immunologic pathogenesis of CADRs.

We identified concomitant ART use as independently associated with lower risk of CADRs. A possible explanation for this may be the threshold of T-cell activation may be lowered by the HIV virus leading to immune dysregulation and T cell stimulation (38, 39). In patients with ART, the decline of HIV viral load by ART may lead to improvement of immune function and elevate the threshold of T-cell activation. In our study, all patients prescribed ART were given NNRTIs-based regimens (due to drug interaction between RFP and PIs-based ART). Currently, little is known about the effect of ART on the risk of CADRs. One study from South Africa reported no significant association between the use of ART and adverse events (28). However, the South Africa study only included 23 (16.3%) patients who received ART, and the lack of association in their study may be explained by this low number of patients, rather than the absence of an association.

Our study found no association between the level of CD4, total T lymphocyte counts and incidence of CADRs from anti-TB drugs. Previous studies have

demonstrated the incidence of CADRs from any drugs increases deterioration of immune function (40), especially in patients with CD4 cell count below 200 cells/mm^3 (41, 42). A study by Carr et al., (1993) suggests that HIV-infected patients with high levels of CD8 cell count and high CD4:CD8 ratio (more than 0.10) have a higher risk of CADRs (43). Our subgroup analysis of patients with CD8 results could not demonstrate that higher level of CD8 cell count and CD4:CD8 ratio are associated with higher risk of CADRs. However, it should be noted that subgroup used for this analysis was relatively small, and this analysis is likely to be underpowered.

In our study, most CADRs events occurred within 4 weeks of commencing TB treatment, a finding comparable with previous studies (9, 17, 19, 44). The incidence of CADRs during our six months of TB treatment course in HIV/TB co-infected patients is considerably higher than previous studies which were conducted in patients with TB alone (IR = 0.41events/person-year in our study compared to 0.03 events/person-year in the patients with TB alone) (9). When focusing on HIV/TB co-infected population, our CADRs rate (48 out of 307 patients; 15.64 %) are similar to the previous studies from South Africa which had a rate of CADRs varies between 9-20% in HIV/TB co-infected patients (15-17, 28).

Our study did have some limitations. First, we used a retrospective cohort. Some adverse events may not have been recorded or under-reporting and there were some missing values for some variables. However, in most cases, these missing data were not in the study effects of main interests. To minimize missing values, we used multiple sources of data including both electronic and paper-based medical records, and the TB registry book. Second, the retrospective nature of the study made it impossible to monitor patient adherence to their anti-TB drugs, and patients with poor adherence are less likely to develop CADRs. However, the high success rate of TB treatment outcomes in our cohort (overall: 78.8%), suggests overall adherence was satisfactory. Another possible limitation is that it was conducted in a single hospital with little variation in ethnicity, and whether Thai HIV/TB co-infected

patients are representative of the broader Asian, or indeed, any other HIV/TB population is unknown.

This study had a number of strengths. First, our sample size was comparatively large (n=307), and represented a wide range of disease severity and clinical presentations. Second, the inclusion criteria, CADRs definitions, diagnostic and outcome criteria of TB were both comparable to other studies and strictly adhered to the international guidelines on CADRs (30). TB diagnosis and outcome definition (7, 31). Third, patient care teams which included physicians and counseling nurses were the same throughout the entire study period.

There're potential biases in our study. In concerned of biases from losses to follow-up, from exclusion criteria, we excluded patients without CADRs which had a duration of standard anti-TB regimens less than 2 months from the study, this could prevent losses to follow-up patients before the occurrence of a primary outcome (CADRs). Moreover, due to a median time to CADRs in our study was 14 days and the longest time to CADRs in our study was 40 days, all patients with loss-to follow up exceeding 2 months are less likely to developed CADRs. From data review, no patients noted with CADRs was loss to follow-up after CADRs was diagnosed. Another potential bias was CADRs diagnosis which may have variation in degree or severity of CADRs, in mild CADRs, undetected this condition by the patient or physician would lead to an underestimate of CADRs event. In our cohort, we had 14 out of 48 cases of mild CADRs which adjustment of anti-TB regimens was not required, this imply that our patient care teams can detect patients with mild CADRs. To decrease this bias, it may be required to conduct the prospective study and patient evaluation by an experienced dermatologist.

CHAPTER 6
CONCLUSION

At present, our knowledge about the CADRs is still limited. There have been few studies of CADRs in HIV/TB co-infected patients, and our study represents the first to be conducted in the Asian population. In a resource-limited healthcare setting with a high burden of HIV and TB infection, it is important to evaluate whether patients are at risk of CADRs. Close monitoring should be arranged in these patients because early recognition of symptoms with the prompt withdrawal of suspected agent could avoid CADRs and improve patients care. HIV/TB co-infected patients receiving anti-TB drugs with a history of drug hypersensitivity, using Co-trimoxazole, a moderate decrease in GFR and HIV naïve without ART are particularly at risk of CADRs. In the future, our finding could be used to develop risk score models to identify and surveil for CADRs in HIV/TB co-infected patients. Moreover, such risk scores could be further improved if biomarkers predictive of CADRs could be investigated. After all, this is only a single study, future research should be conducted to verify these findings.

REFERENCES

1. WHO | HIV/AIDS [updated 2016/02/18/09:25:31]. Available from: http://www.who.int/mediacentre/factsheets/fs360/en/.
2. WHO | Data and statistics [updated 2014/08/25/06:36:00]. Available from: http://www.who.int/hiv/data/en/.
3. Thailand [updated 2016/05/18/13:12:58]. Available from: http://www.unaids.org/en/regionscountries/countries/thailand.
4. WHO | Tuberculosis [updated 2014/08/25/07:14:01]. Available from: http://www.who.int/mediacentre/factsheets/fs104/en/.
5. SEARO | Tuberculosis (TB) [updated 2014/08/26/06:37:00]. Available from: http://www.searo.who.int/thailand/areas/tuberculosis/en/.
6. WHO | Global tuberculosis report 2014 [updated 2014/11/08/08:07:47]. Available from: http://www.who.int/tb/publications/global_report/en/.
7. Treatment of Tuberculosis: Guidelines. 4th ed. Geneva: World Health Organization; 2010 2010.
8. WHO | Global tuberculosis report 2015 [updated 2016/02/18/12:47:16]. Available from: http://www.who.int/tb/publications/global_report/en/.
9. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med. 2003;167(11):1472-7.
10. Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS. 2002;16(1):75-83.
11. Lehloenya RJ, Dheda K. Cutaneous adverse drug reactions to anti-tuberculosis drugs: state of the art and into the future. Expert Rev Anti Infect Ther. 2012;10(4):475-86.
12. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf. 2006;5(2):231-49.

13. Schluger NW, Burzynski J. Tuberculosis and HIV infection: epidemiology, immunology, and treatment. HIV Clin Trials. 2001;2(4):356-65.

14. Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. Geneva: World Health Organization; 2015 2015.

15. Pozniak AL, MacLeod GA, Mahari M, Legg W, Weinberg J. The influence of HIV status on single and multiple drug reactions to antituberculous therapy in Africa. AIDS. 1992;6(8):809-14.

16. Nunn P, Gicheha C, Hayes R, Gathua S, Brindle R, Kibuga D, et al. Cross-sectional survey of HIV infection among patients with tuberculosis in Nairobi, Kenya. Tuber Lung Dis. 1992;73(1):45-51.

17. Chintu C, Luo C, Bhat G, Raviglione M, DuPont H, Zumla A. Cutaneous hypersensitivity reactions due to thiacetazone in the treatment of tuberculosis in Zambian children infected with HIV-I. Arch Dis Child. 1993;68(5):665-8.

18. Breen RaM, Miller RF, Gorsuch T, Smith CJ, Schwenk A, Holmes W, et al. Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax. 2006;61(9):791-4.

19. Tan WC, Ong CK, Kang SCL, Razak MA. Two years review of cutaneous adverse drug reaction from first line anti-tuberculous drugs. Med J Malaysia. 2007;62(2):143-6.

20. Kuaban C, Bercion R, Koulla-Shiro S. HIV seroprevalence rate and incidence of adverse skin reactions in adults with pulmonary tuberculosis receiving thiacetazone free anti-tuberculosis treatment in Yaounde, Cameroon. East Afr Med J. 1997;74(8):474-7.

21. Nunn P, Kibuga D, Gathua S, Brindle R, Imalingat A, Wasunna K, et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. Lancet. 1991;337(8742):627-30.

22. Montastruc J-L, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. Fundam Clin Pharmacol. 2002;16(5):343-6.

23. Roujeau J-C. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005;209(2):123-9.

24. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331(19):1272-85.

25. Asero R. Detection of patients with multiple drug allergy syndrome by elective tolerance tests. Ann Allergy Asthma Immunol. 1998;80(2):185-8.

26. Demoly P, Bousquet J. Epidemiology of drug allergy. Curr Opin Allergy Clin Immunol. 2001;1(4):305-10.

27. Guglielmi L, Guglielmi P, Demoly P. Drug hypersensitivity: epidemiology and risk factors. Curr Pharm Des. 2006;12(26):3309-12.

28. Marks DJB, Dheda K, Dawson R, Ainslie G, Miller RF. Adverse events to antituberculosis therapy: influence of HIV and antiretroviral drugs. Int J STD AIDS. 2009;20(5):339-45.

29. Dworkin MS, Adams MR, Cohn DL, Davidson AJ, Buskin S, Horwitch C, et al. Factors that complicate the treatment of tuberculosis in HIV-infected patients. J Acquir Immune Defic Syndr. 2005;39(4):464-70.

30. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. US Department of Health And Human Services, NIH, National Cancer Institute, Bethesda, MD, USA (2010).

31. WHO | Definitions and reporting framework for tuberculosis [updated 2016/03/13/21:44:19]. Available from: http://www.who.int/tb/publications/definitions/en/.

32. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266.

33. Kuaban C, Bercion R, Koula-Shiro S. Current HIV seroprevalence rate and incidence of adverse skin reactions in adults with pulmonary tuberculosis receiving thiacetazone-free antituberculosis treatment in Yaounde, Cameroon. Cent Afr J Med. 1998;44(2):34-7.

34. Hurwitz N. Predisposing factors in adverse reactions to drugs. Br Med J. 1969;1(5643):536-9.

35. Choquet-Kastylevsky G, Vial T, Descotes J. Allergic adverse reactions to sulfonamides. Curr Allergy Asthma Rep. 2002;2(1):16-25.

36. Dibbern DA, Montanaro A. Allergies to sulfonamide antibiotics and sulfur-containing drugs. Ann Allergy Asthma Immunol. 2008;100(2):91-100; quiz -3, 11.

37. Wanat KA, Anadkat MJ, Klekotka PA. Seasonal variation of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with trimethoprim-sulfamethoxazole. J Am Acad Dermatol. 2009;60(4):589-94.

38. Adam J, Pichler WJ, Yerly D. Delayed drug hypersensitivity: models of T-cell stimulation. Br J Clin Pharmacol. 2011;71(5):701-7.

39. Pichler WJ, Adam J, Daubner B, Gentinetta T, Keller M, Yerly D. Drug hypersensitivity reactions: pathomechanism and clinical symptoms. Med Clin North Am. 2010;94(4):645-64, xv.

40. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. N Engl J Med. 1993;328(23):1670-4.

41. Smith KJ, Skelton HG, Yeager J, Ledsky R, Ng TH, Wagner KF. Increased drug reactions in HIV-1-positive patients: a possible explanation based on patterns of immune dysregulation seen in HIV-1 disease. The Military Medical Consortium for the Advancement of Retroviral Research (MMCARR). Clin Exp Dermatol. 1997;22(3):118-23.

42. Veenstra J, Veugelers PJ, Keet IP, van der Ven AJ, Miedema F, Lange JM, et al. Rapid disease progression in human immunodeficiency virus type 1-infected individuals with adverse reactions to trimethoprim-sulfamethoxazole prophylaxis. Clin Infect Dis. 1997;24(5):936-41.

43. Carr A, Swanson C, Penny R, Cooper DA. Clinical and laboratory markers of hypersensitivity to trimethoprim-sulfamethoxazole in patients with Pneumocystis carinii pneumonia and AIDS. J Infect Dis. 1993;167(1):180-5.

44. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. Tuber Lung Dis. 1996;77(1):37-42.

APPENDIX

Appendix A. Case Record Form

Code..... Date of data collected.....

Baseline Characteristics

Sex ☐ M ☐ F Age..... Wt.....kg Ht.....cm BMI.....kg/m^2

Previously allergic history ☐ N ☐ Y.....

Hepatitis profiles HBsAg..... AntiHBs..... Anti HBc..... Anti HCV.....

Underlying diseases (HIV non-related) ☐ N ☐ Y, details.....

Concomitant medications ☐ N ☐ Y, details ☐ Co-trimoxazole ☐

Fluconazole ☐ Steroids ☐ Antiretrovirals ☐

Others.....

HIV Diagnosis

Date of diagnosis.....

Method for diagnosis ☐ 2 methods of ELISA ☐ PCR HIV ☐ Other.....

CD4 at time of TB diagnosis..... cells/mm^3

ARV Medication ☐ Naïve ☐ Previously (date stop.....)

☐ Currently (date start.....) ARV regimens taking.....

OI prophylaxis medication

☐ Co-trimoxazole (date start.....)

☐ Fluconazole (date start.....)

Other Medication

1..... Date of start.....

2..... Date of start.....

3..... Date of start.....

Previous OI ☐ N ☐ Y (if yes ☐ PJP, ☐ CMV, ☐ Crypto, ☐ Salmonella, ☐ Other.....

TB Diagnosis

Date of Diagnosis.....Date of start anti-TB medication.....

Suspected Site ☐ 1 sites ☐ More than 1 sites, Involvement ☐ Pulmonary TB ☐ TB pleuritis ☐ TB LN ☐ TB Meningitis ☐ TB GI tract ☐ TB pericarditis ☐ TB Bone and Joints ☐ Others.....

Diagnosis method: Specimens investigations ☐ Not done ☐ Done, if done

☐ Histological tissue or body fluid specimens positive for AFB (sites.....)

☐ Histological tissue or body fluid culture positive for *M. tuberculosis* (sites.....)

☐ Nucleic acid amplification assay positive for *M. tuberculosis* (sites.....)

☐ Negative AFB stain or culture

Anti-TB Medication ☐ Naïve

☐ Previously, year..... Regimens used.....

Standard regimens ☐ Y ☐ N, regimens.....

Proper dosage adjusts for weight ☐ Y ☐ N, details.....

Adherence (if noted) ☐ 91-100% ☐ 71-90% ☐ 51-70% ☐ less than 50%

Outcome

CADR ☐ N ☐ Y Type.....

CADR was recognized by ☐ Patients and relatives ☐ Physicians

Associated symptoms ☐ Fever ☐ Transaminitis ☐ Jaundice ☐ Other.....

Date of CADR (1st recognized)..... Days after anti-TB treatment.....

Mx ☐ Outpatient care ☐ Inpatient care, admit/discharge date.....

Presume causative drug (if noted).....

Complete treatment (6 mo) ☐ Y ☐ N, detail.....

In case with CADR, outcome of CADR

☐ Dead

☐ Improve with sequelae, detail.....

☐ Complete recovery

Management after CADR

☐ Stop suspected drug

☐ Stop all anti-TBdrug

☐ Continue same regimens with ± follow up

Rechallenge with suspected drug ☐ N ☐ Y, outcome: Re-CADR ☐ N ☐ Y

Regimen modification ☐ N ☐ Y detail.....

Tuberculosis outcome

☐ Cure/Completion of treatment ☐ Treatment default ☐ Treatment failure

☐ Transfer out ☐ Dead

VITA

Name: Lakkana Boonyagars

Date of birth: May 24th, 1979

Place of birth: Bangkok, Thailand

Educational credentials:

1995 - 2001: MD, Bangkok Metropolitan Medical Collage and Vajira hospital, Mahidol University, Thailand

2004-2005: Certificate of Medical Science, Mahidol University

2005-2007: Residency training in Internal Medicine, Bangkok Metropolitan Medical Collage and Vajira hospital

2008-2010: Fellowship in Infectious Diseases, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Work experiences:

Since 2010: Division of Infectious disease, Department of Medicine, Faculty of Medicine, Vajira hospital