Incidence of Active Tuberculosis in HIV-Infected Adults and Mortality in Thailand

P-R4

Abstract 831

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INTRODUCTION

Background

- In 2013, an estimated 1.1 million HIV-infected people developed active TB and 360,000 HIV-TB co-infected people died from TB, accounting for 25% of all TB deaths
- Thailand is one of the 22 high tuberculosis (TB) burden countries listed by the WHO

Objectives

In a large HIV cohort in Thailand:

- Estimate the incidence of active TB in HIV-infected adults
- Investigate the association between characteristics at antiretroviral therapy (ART) initiation and TB diagnosis
- Compare survival rates between HIV-infected adults with and without active TB

METHODS

Study Design and Population

- Study design: multicenter, prospective Program for HIV Prevention and Treatment (PHPT) cohort study (NCT00433030)
- Study population: ART-naïve adults enrolled in the PHPT cohort between 1999 and 2012

Baseline Data and Follow-up

- Before ART initiation + at least every 6 months thereafter:
  - screening for active TB based on interview, clinical examination, chest X-ray, tuberculin skin test, sputum acid-fast bacillus smear (TB infection status determined by the physician's diagnosis)
  - HIV RNA load, CD4 count, complete blood count

- Characteristics at ART initiation considered as potential predictors of TB diagnosis: sex, age, BMI, date of enrollment, highest education level, HIV RNA load, CD4 count and complete blood count parameters

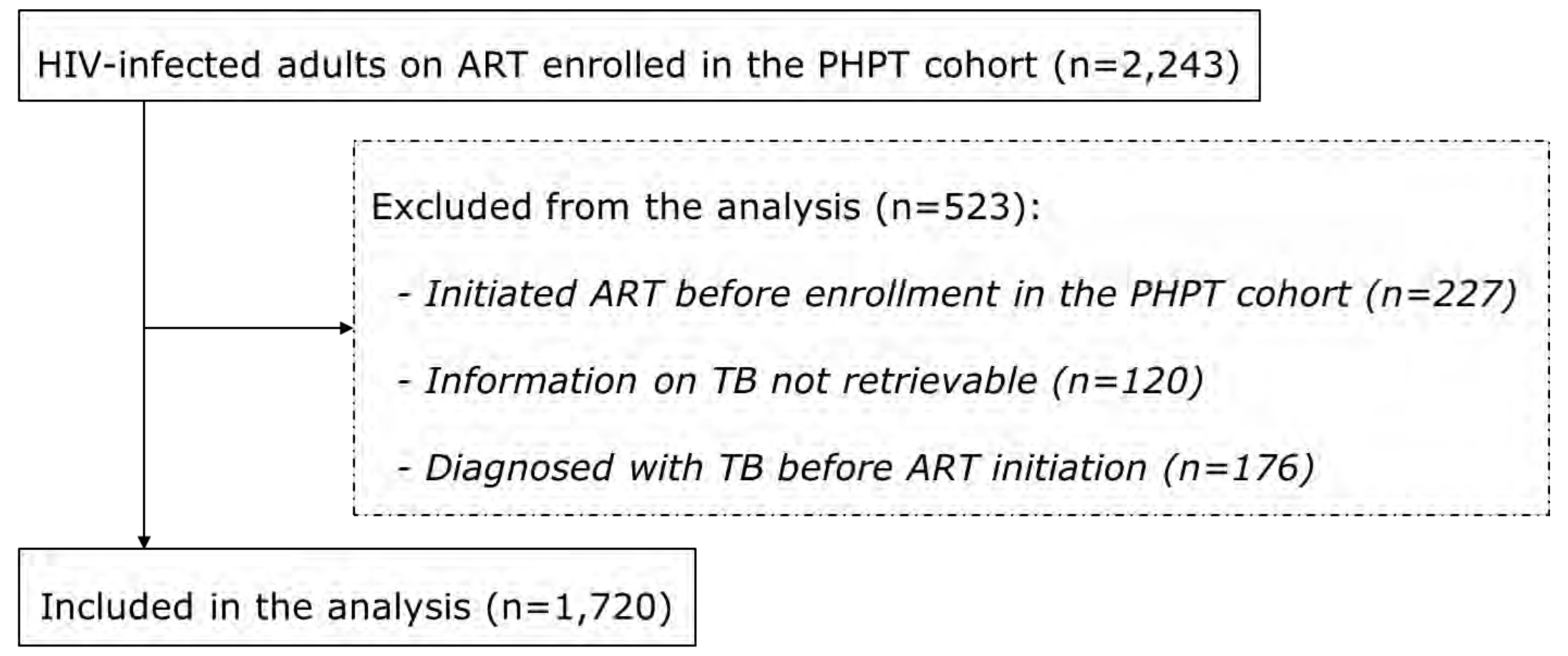
Statistical Analysis

- Right censoring: – at the date of last clinic visit if lost to follow-up (≥1 missed scheduled visit + no contact with site staff for ≥6 months) or voluntarily withdrew from study
  – or on December 31, 2013, whichever occurred first
- Incidence rate: number of new cases of active TB / total number of person-years of follow-up (PYFU)
- Poisson regression models to identify predictors of active TB infection:
  - All continuous variables categorized in 2 or 3 groups according to the magnitude of model coefficients in the univariate analysis
  - All variables with $p<0.20$ in the univariate analysis included in the multivariate analysis
  - Backward stepwise regression to keep only the strongest predictors ($p<0.05$)
  - For multivariate analysis, missing values imputed using multivariate imputation by chained equations (continuous variables: predictive mean matching; categorical variables: binary/multinomial logistic regression)
- Kaplan-Meier method and log-rank test to estimate and compare survival rates

RESULTS

Study Population

Figure 1. Study population flowchart



HIV-infected adults on ART enrolled in the PHPT cohort (n=2,243)

Excluded from the analysis (n=523):
- *Initiated ART before enrollment in the PHPT cohort (n=227)*
- *Information on TB not retrievable (n=120)*
- *Diagnosed with TB before ART initiation (n=176)*

Included in the analysis (n=1,720)

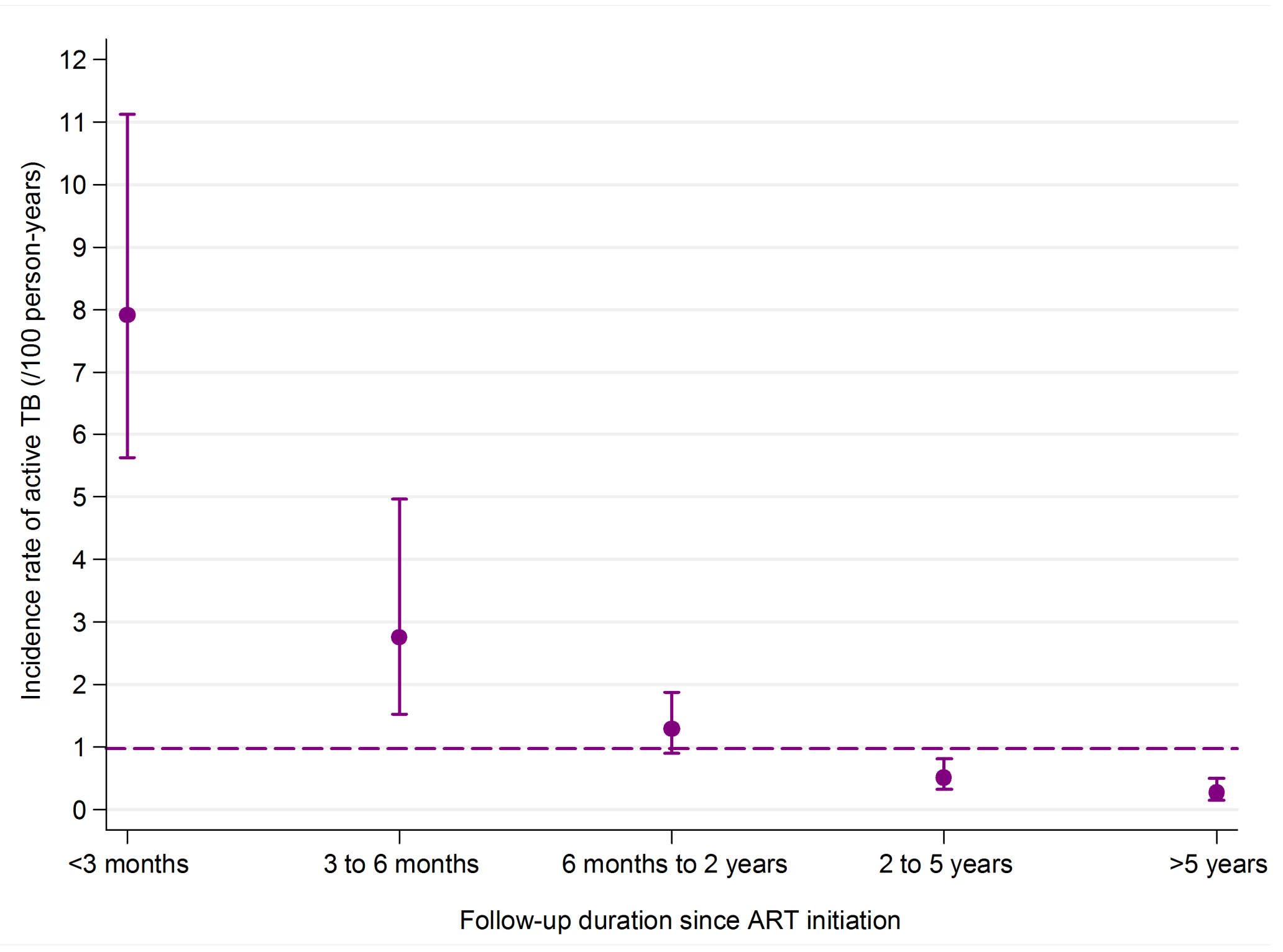
Characteristics

- ART initiation (baseline):
  - 1,406 (82%) females
  - median age: 31.6 years (interquartile range 27.1-36.9)
  - median BMI: 20.8 kg/m^2 (18.7-23.2)
  - median HIV RNA load: 4.8 log$_{10}$ copies/mL (4.1-5.2)
  - median CD4 count: 144 cells/mm^3 (67-218)
- Follow-up:
  - median follow-up: 7.0 years (2.9-8.4)
  - 771 (45%) adults not on follow-up at the end of study:
    - 328 lost to follow-up
    - 324 voluntarily withdrew from study
    - 119 died

Incidence of Active TB

- 100 adults diagnosed with active TB after ART initiation over 3,884 PYFU
- Median time until TB diagnosis: 8.0 months (IQR 1.4-28.8)
- Overall incidence rate of active TB: 0.97/100 PYFU (95% CI 0.80-1.18)
  - in males: 1.62/100 PYFU (1.14-2.31)
  - in females: 0.82/100 PYFU (0.65-1.04)
- Incidence rates decreased with ART duration from 7.9/100 PYFU within the first 6 months to 0.27/100 PYFU after 5 years

Figure 2. Incidence rates of active TB during follow-up



(Circles: estimated incidence rates. Segments: 95% CI for the incidence rates. Dotted line: overall incidence rate.)

Predictors of Active TB

In the multivariate analysis, the following factors at ART initiation were independent predictors of active TB infection (all $p<0.05$):

- Demographics: male gender, younger age, thinness
- Laboratory: higher HIV RNA load, lower hemoglobin, lower lymphocytes
- Earlier enrollment in the cohort

Table 1. Factors at ART initiation associated with a higher risk of active TB infection during follow-up

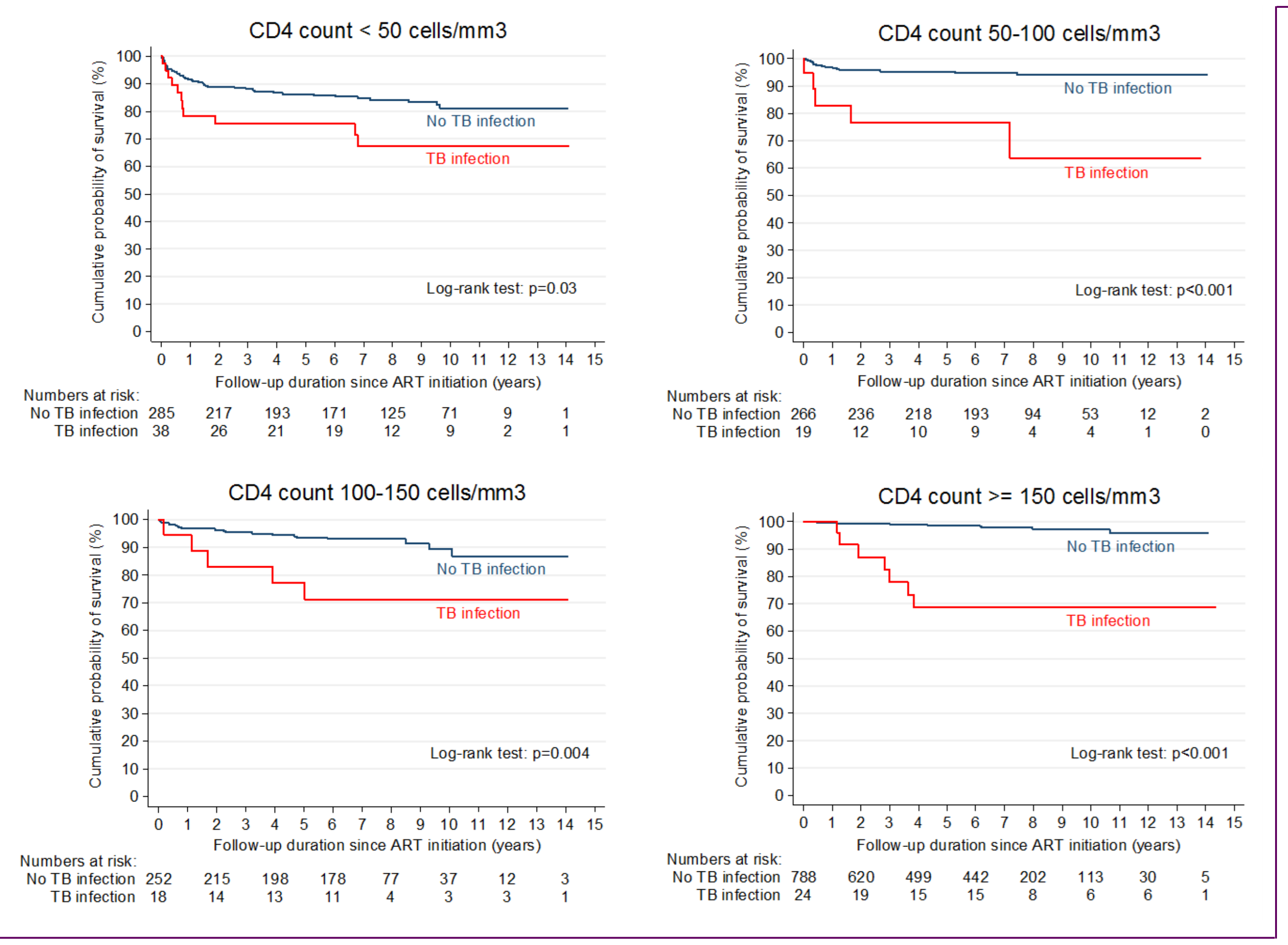
Risk factors	Multivariate analysis	
	IRR (95% CI)	*p*-value
Male gender	2.8 (1.8-4.5)	**<0.001**
Age < 25 years	2.3 (1.4-4.0)	**0.001**
BMI < 18.5 kg/m^2	2.9 (1.9-4.3)	**<0.001**
Enrollment period < 2002	2.4 (1.4-4.0)	**0.001**
HIV RNA load		**0.003**
< 4.5 log$_{10}$ copies/mL	Ref. -	-
4.5 – 5.0 log$_{10}$ copies/mL	1.8 (0.9-3.4)	*0.07*
≥ 5.0 log$_{10}$ copies/mL	2.6 (1.5-4.5)	***0.001***
Hemoglobin		**0.001**
< 10 g/dL	2.8 (1.6-4.8)	***<0.001***
10 – 12 g/dL	1.5 (0.9-2.5)	*0.11*
≥ 12 g/dL	Ref. -	-
Lymphocytes		**0.04**
< 2,000 cells/mm^3	1.9 (1.2-3.1)	***0.01***
2,000 – 4,000 cells/mm^3	1.4 (0.8-2.3)	*0.21*
≥ 4,000 cells/mm^3	Ref. -	-

(IRR: incidence rate ratio)

Mortality

- Of the 100 adults with TB diagnosis, 29 died
- Causes of death: 23 TB-related, 5 non-TB-related and 1 unknown

Figure 3. Kaplan-Meier estimates of overall survival, stratified by CD4 count at ART initiation



Numbers at risk:

CD4 count < 50 cells/mm3

	0	2	4	6	8	10	12	14
No TB infection	285	217	193	171	125	71	9	1
TB infection	38	26	21	19	12	9	2	1

CD4 count 50-100 cells/mm3

	0	2	4	6	8	10	12	14
No TB infection	266	236	218	193	94	53	12	2
TB infection	19	12	10	9	4	4	1	0

CD4 count 100-150 cells/mm3

	0	2	4	6	8	10	12	14
No TB infection	252	215	198	178	77	37	12	3
TB infection	18	14	13	11	4	3	3	1

CD4 count >= 150 cells/mm3

	0	2	4	6	8	10	12	14
No TB infection	788	620	499	442	202	113	30	5
TB infection	24	19	15	15	8	6	6	1

- Median survival time after TB diagnosis: 2.9 months (IQR 1.1-8.9)
- Cumulative probability of overall survival at 1, 5 and 10 years after ART initiation:
  - 97%, 95% and 92% in adults with no active TB
  - 87%, 73% and 67% in adults with active TB
  (log-rank test: $p<0.001$)

CONCLUSIONS

- Active TB is a major cause of death in this HIV cohort in Thailand as in many settings
- Most reported predictors are available in many ART programs and should be carefully considered to accelerate TB diagnosis and treatment in patients initiating ART

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