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Multidrug-resistant tuberculosis: pearls and wisdoms

Adverse effects during the treatment of MDR-TB in Viet Nam

a cohort event monitoring

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Conflict of interest disclosure

The Global Fund
To Fight AIDS, Tuberculosis and Malaria

☐ I have no Conflict of Interest to report.

☑ I have the following Conflict of Interest(s) to report:

Please tick the type of affiliation / financial interest and specify the name of the organisation:

- ☑ Receipt of grants/research supports: **Global Fund** support fund for this study
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DI ADR

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HANOI UNIVERSITY OF PHARMACY

Backgrounds

Viet Nam ■ Population 2014 **92 million**

Estimates of MDR-TB burden[a] 2014

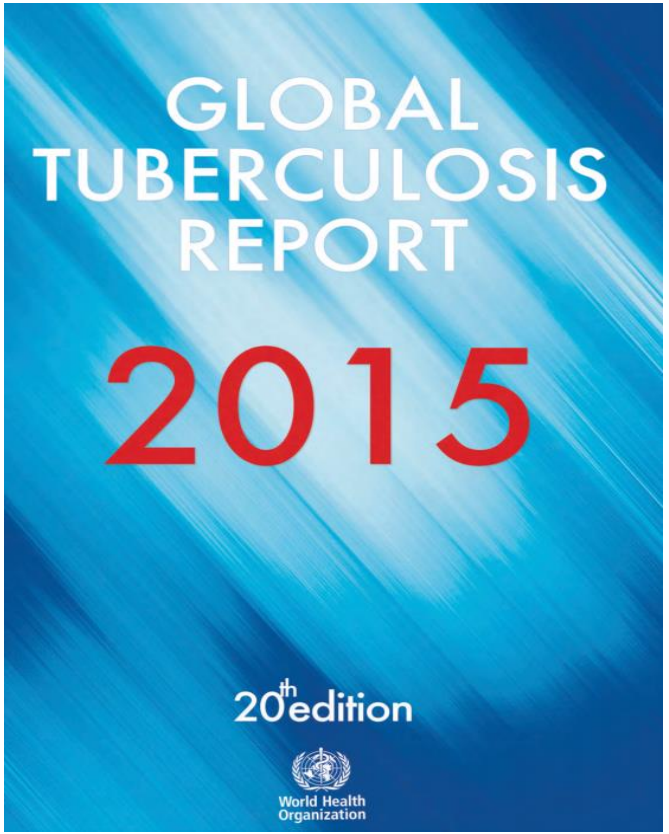
	NEW	RETREATMENT
% of TB cases with MDR-TB	4 (2.5–5.4)	23 (17–30)
MDR-TB cases among notified pulmonary TB cases	3 000 (1 900–4 100)	2 100 (1 500–2 600)

Reported cases of RR-/MDR-TB 2014

	NEW	RETREATMENT	TOTAL[b]
Cases tested for RR-/MDR-TB	2 756 (6%)	8 511 (96%)	13 829
Laboratory-confirmed RR-/MDR-TB cases			2 198
Patients started on MDR-TB treatment[c]			1 532

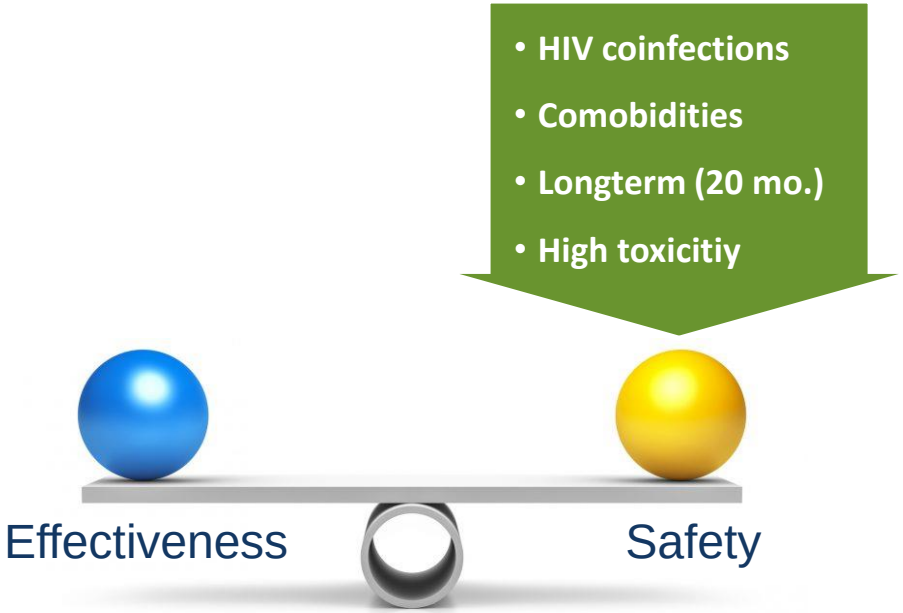
Treatment success rate and cohort size

	(%)	COHORT
New and relapse cases registered in 2013	(89)	102 196
Previously treated cases, excluding relapse, registered in 2013		
HIV-positive TB cases, all types, registered in 2013	(71)	4 453
RR-/MDR-TB cases started on second-line treatment in 2012	(71)	713



Backgrounds

- NTP started treatment for thousands MDR-TB patients since 2009
- Scale up MDR-TB treatment to many facilities national wide
- Efficacy of standardized regimens were identified (71% success)
- Safety was still questioned; Spontaneous AE reports (volunteer) to DI&ADR center was very limitted



Standardized regimens

Z E **Km/Cm** Lfx Pto Cs (PAS)

A cohort events monitoring was warrant

Aims of study

- Describe the adverse effects (AE) of 20 mos. MDR-TB treatments: types, frequency, severity, seriousness, clinical decision for AE.

- Identify predictors for the emergence of AE

Methods

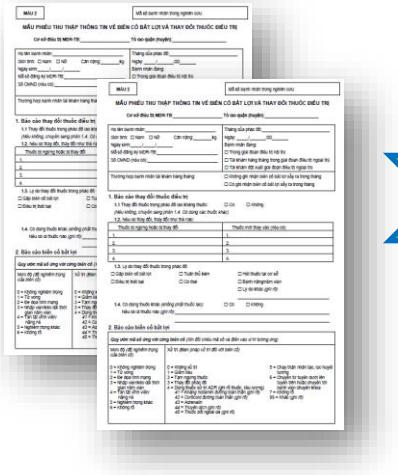
9 treatment sentinel sites in 9/63 provinces of VN

Patients: Newly MDR-TB diagnosed, adult (age >16), exclude patients in other trials (eg. STREAM).

Data collection:

- Treatment initiation: Registry paper-based form
- Follow up: AE paper-based form (AE description,, serverity and seriousness, clinical solutions, regimens ect.); clinical judgement and/or laboratory results.
- Monthly sent to DI&ADR center

Methods



Access database

SPSS 22.0

- AEs classification: WHO-ART, physicians' judgment based on NTP internal guidance.
- Data input and cleaning: Access, SPSS syntax; missing data: MICE (multiple imputation by chained equations).
- Survival analysis for event occurences: Cox regression.

Results Patient characteristics (n=659)

Information	No. patients (%)
Gender (Male)	517 (78.5)
Age (yrs.) $	41 (31 - 58)
Weight (kg) $	47 (42 -54)
New TB diagnosis	50 (7.6)
HIV co-infection	57 (8.7)
Drug addiction	22 (3.3)
Alcoholic	16 (2.4)
Comobidities	
Diabetes mellitus	104 (15.8)
Hepatic disorders	33 (5.0)
Hearing loss	11 (1.7)
Arthragia	7 (1.1)

$: median (interquartile range)

Results Treatment and follow up (n=659)

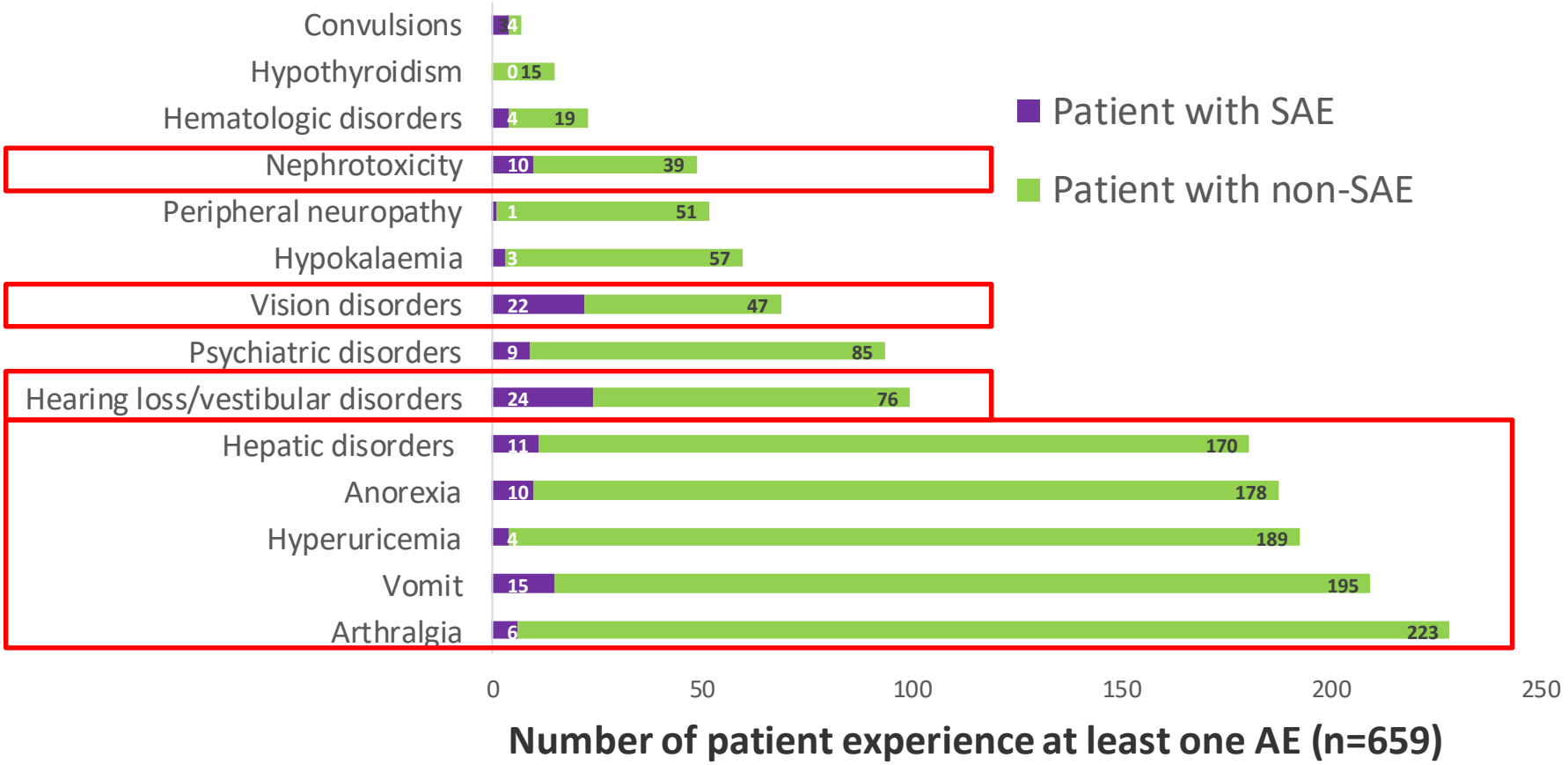
Information	No. patients (%)
Initital Treatment Regimen	
Standardized regimen 1 *(kanamycin based)*	631 (95.8)
Standardized regimen 2 *(capreomycin based)*	22 (3.3)
Individualized regimen	6 (0.9)
Treatment duration (months) $	19.2 (17.5 – 20.2)
Follow up outcome	
Cure/completion	512 (77.7)
Transfer to other healthcare facilities	17 (2.6)
Default	61 (9.3)
Failure	20 (3.0)
All cause death	49 (7.4)

$: median (interquartile range)

Standardized regimen 1: Z, E, Km, Lfx, Pto Cs (PAS); Standardized regimen 2:Z, E, Cm, Lfx, Pto Cs (PAS)

Individualized regimen: Z E Am Mfx Pto Cs PAS (2); Z E *Km* Lfx Pto (1); E *Km* Lfx Cs (1); Z Lfx Pto Cs (1); N/A (1)

Results Type and seriousness of adverse events



Results Consequence of adverse events (n=659)

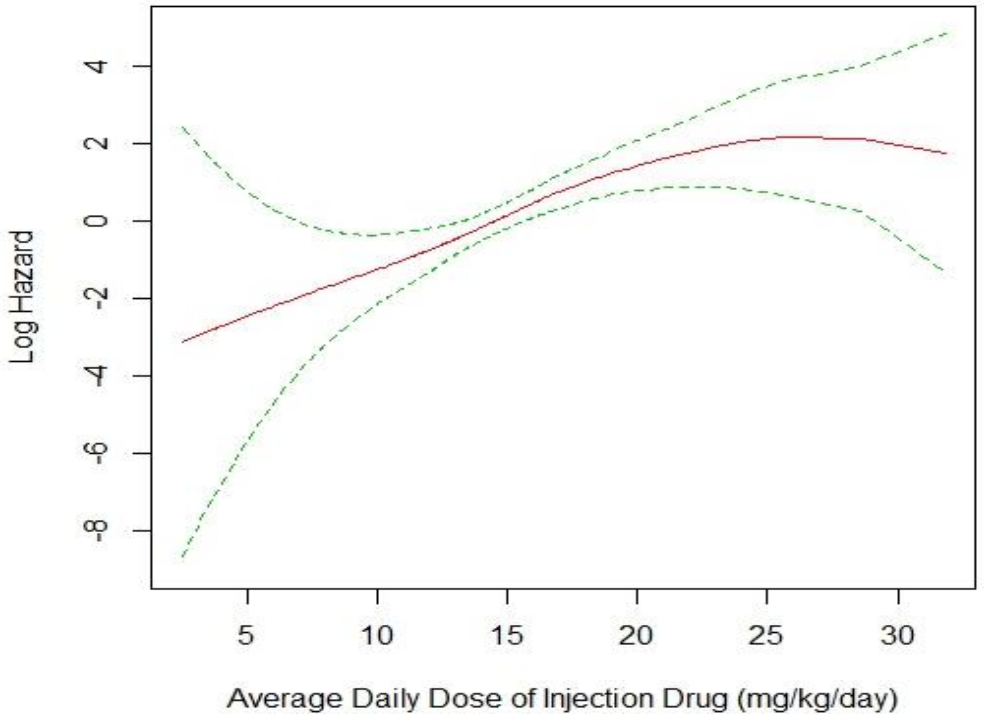
Consequence of the adverse events	No. patients (%)
With at least one AE	489 (74.2)
Required any medication/medical intervention	338 (51.3)
With at least one clinical significant AE	154 (23.4)
Drug switching	16 (2.4)
Dose reduction	29 (4.4)
Temporary/permanent drug discontinuation	53 (8.0)
With at least one SAE	120 (18.2)
Hospitalization or prolongation	95 (14.4)
Life-threatening	27 (4.1)
Persistent disability	10 (1.5)
Death$	2 (0.3)

SAE: serious adverse event; Clinical significant AE = SAE and AE required TB-regimen modification; $: relationship with AE could not be ruled out.

Results Predictor for Hyperuicemia/Nephrotoxicity/Hepatotoxicity

Adeverse event	Covariates (n/N)	aHR (90% CI)	p-value
Hyperuricemia	Alcoholic		
	No (180/643)	1	
	Yes (13/16)	5.66 (3.16-10.14)	0.000
	Drug addiction		
	No (181/637)	1	
	Yes (12/22)	2.11 (1.16-3.83)	0.014
Nephrotoxicity	Alcoholic		
	No (43/643)	1	
	Yes (6/16)	12.43 (4.75-32.54)	<0.001
	Diabetes mellitus		
	No (36/555)	1	
	Yes (13/104)	2.18 (1.09 – 4.38)	0.028
	Previous renal failure		
	No (47/654)	1	
	Yes (2/5)	10.99 (2.59 – 46.59)	0.001
	Injectable drugs daily dose (mg/kg)	1.21 (1.14 – 1.30)	<0.001
Hepatotoxicity	Alcoholic		
	No (28/643)	1	
	Yes (3/16)	6.84 (1.89 – 24.73)	0.003
	Baseline ALT (IU)	1.01 (1.00 – 1.02)	0.001

Results Risk of nephrotoxicity vs. dose of injectable drug.



Hazard ratio (solid line)

95% confidence intervals (dashed line)

Cox model adjusted for age, sex, body mass index, alcoholic, diabetes, availble renal disease.

Figure. Relationship between risk of nephrotoxicity and the average daily dose of injectable drugs (centralized at 15mg/kg)

Conclusion

- Adverse events were common (ie. arthralgia, hyperuricemia, hepatoxoticity, anorexia) among MDR-TB treatment patients (74.2%)

- several of those (18.2%) are serious (ie. hearing loss/vestibula distubant, vision disorder) or required to change treatment regimens (14.8%).

- Alcoholic, drug addiction may related to hyperuricemia; diabetes, alcoholic, and average daily dose of injectable drugs increase the risk of nephrotoxicity.

THANK YOU!

National Tuberculosis Program

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Dinh Ngoc Si
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Phan Thuong Dat
Hoang Thanh Thuy
Nguyen Binh Hoa
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