Rifapentine and isoniazid in the continuation phase of a 6-month regimen. Final report at 5 years: prognostic value of various measures

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SUMMARY

SETTING: Clinical trial in 762 patients with newly diagnosed pulmonary tuberculosis in Hong Kong. After an initial 2 months of a four-drug intensive phase consisting of streptomycin, isoniazid, rifampicin and pyrazinamide (SHRZ), a random allocation was made to a continuation phase of once-weekly rifapentine + isoniazid (HRp_1), HRp_1 given in 2 of every 3 weeks ($HRp_1.2/3$), or to three times weekly isoniazid + rifampicin (HR_3).

OBJECTIVE: Final report evaluating relapse rates after 4.5 years follow-up and the prognostic influence of sputum culture at 2 months.

METHODS: Kaplan-Meier analysis of relapse rates and Cox proportional hazards analysis of prognostic factors.

RESULTS: The two rifapentine regimens, HRp_1 and $HRp_1.2/3$ had similar final rates of adverse events (relapses or 1 failure) of 10.8% and 11.7%, respectively, compared to 4.2% for the HR_3 regimen ($p = 0.02$ and 0.009, respectively). In the initial univariate proportional hazards analysis, adverse events were significantly related to the regimen, age, sex, pretreatment radiographic extent of disease and cavitation, and also to sputum culture at 2 months. In the final multivariate analysis, after step-wise removal of non-significant factors, adverse events were related only to the regimen, sex of patients and pretreatment radiographic extent of disease. Elderly male patients were more at risk of an adverse event as were those with more severe disease. Adverse events occurred at life table rates of 9.0% in patients with drug-sensitive strains and in 8.9% of those with initially isoniazid-resistant organisms at 4.5 years of follow-up.

CONCLUSIONS: The two rifapentine regimens were unsatisfactory because of their high incidence of adverse events. Older males have a poor immune status. Isoniazid

appeared not to contribute to preventing relapse. Further studies with increased rifapentine dosage are necessary.

KEY WORDS: tuberculosis; rifapentine; isoniazid; age; sex; relapse rates

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Initial[1] and interim[2] reports of the first clinical trial of once-weekly rifapentine and isoniazid in the continuation phase of the treatment of pulmonary tuberculosis in Hong Kong have shown a substantially higher relapse rate after chemotherapy in the two rifapentine arms than in the control rifampicin arm. Furthermore, evidence from patients with initial isoniazid-resistant strains and the results of isoniazid acetylation genotyping has indicated that isoniazid had no bactericidal role during the continuation phase. The present report has been prepared after the completion of the 5-year study period (4.5 years of follow-up after treatment). An analysis of the prognostic value of pretreatment assessments has been made. Also included are the prognostic value of 2-month and 3-month sputum culture results since there is current interest in the use of surrogate markers for relapse as adjuncts to the development of new anti-tuberculosis drugs.[3]

METHODS

Rifapentine is a rifamycin which shows complete cross-resistance with rifampicin but has a long half-life in the mouse and in humans.[4] Rifapentine of Chinese manufacture was used in the clinical trial because no drug of Western manufacture was then available.[5] Of the 672 patients admitted, 592 satisfied initial criteria and were treated with an initial 2 months of streptomycin + rifampicin + isoniazid + pyrazinamide given 3-times weekly,

the standard frequency of drug administration in the Hong Kong government service. They were then randomly allocated to one of three regimens given for 4 months: (1) the control regimen of isoniazid + rifampicin 3-times weekly (HR_3); (2) isoniazid + rifapentine once weekly (HRp_1); (3) HRp_1 with the weekly dose omitted every third week to simulate poor compliance ($HRp_{1.}2/3$). Before each dose of rifapentine, patients ate a fast-food sandwich shown to promote its absorption efficiently.[6] Standard drug doses were given including a 600 mg dose of rifapentine. Because of its poor bioavailability, the dose of 600 mg rifapentine used throughout treatment for the first 62% of patients was increased to 750 mg in the last 38%.[7] These doses gave serum concentrations similar to 450 mg and then to 600 mg of well absorbed drug manufactured by Merrell Dow Lepetit. The latter preparation appears to have produced concentrations in the blood of volunteers at least as high as the preparation produced currently by Hoechst Marion Rousell.[8] Sputum was examined by smear and culture monthly during the 6 months of treatment and for 18 months after treatment ceased; thereafter sputum was examined 3-monthly and eventually 6-monthly until a 4.5-year follow-up had been completed. The 47 adverse events were either a radiographic failure in 1 HRp_1 patient at 6 months or a relapse (usually bacteriological and radiographic) during follow-up in 46 patients.

Statistical procedures

Pretreatment assessments for cavitation were scored as present (1) or not (0). Radiographic extent of disease was scored relating the combined area of lesions to the area of the right upper lobe (RUL): the scores were 1, where the lesional area was less than RUL, 3, where it was greater than RUL and 2 where is was intermediate between 1 and 3. The number of colonies on Lowenstein Jensen slopes were scored as 1 for 1-3

colonies, 2 for 4-10 colonies, 3 for 10-19 colonies, 4 for 20 to 100 colonies, 5 for innumerable discrete colonies and 6 for confluent growth. Pairs of sputum culture were obtained from each patient pretreatment and at 2 and 3 months. The result on the first sputum collected was used in analysis except that if it was contaminated or otherwise unavailable, the result from the second specimen was substitued. The results in the study were entered into and analysed in EPI INFO version 6.04b.[9] The Kaplan-Meier and Cox proportional hazard analyses was done in Stata release 6 (Stata Corp., College Station, Texas). Notification rates and numbers of notifications by age and sex were taken from the Annual Report 1995 of the Chest Service of the Department of Health, Hong Kong.

RESULTS

After exclusion of 35 patients for drug toxicity, 18 who defaulted during treatment and 5 not followed for miscellaneous reasons, there remained 534 patients available for follow-up after the end of treatment. During the follow-up period of 4.5 years (54 months), there was a slow loss of patients due mainly to default, including travel to the Chinese mainland, and also 6 patients who died from non-tuberculous causes. Those available were 90.1% of the original total at 12 months, 84.6% at 24 months and 75.3% at 54 months (Table 1). No additional adverse events had occurred since the 47 described in the interim report [2], consisting of 1 failure at 6 months and 46 relapses during the follow-up. The life table proportions of adverse events were 3.6%, 7.9% and 10.5% at 12 months after the end of treatment in the HR_3, HRp_1 and HRp_1.2/3 regimens, respectively. These proportions widened to 4.2%, 10.2% and 11.1%, respectively, at 24 months. The Kaplan-Meier curves for the probability of no adverse event are shown in Fig 1. Log rank

tests on the curves found significant differences between the rates in the HR_3 and either the HRp_1 ($p = 0.02$) or the $HRp_1.2/3$ ($p = 0.009$) regimens but not between the HRp_1 and the $HRp_1.2/3$ regimens ($p = 0.7$).

Prognosis analysis

The initial results of the univariate proportional hazards analysis indicate significant effects of the regimens, the age of patients, their sex, the pretreatment radiographic extent of disease and presence of cavitation, and the culture results at 2 months (Table 2). After step-wise discard of those factors that were not significant, the only factors that remained as independently significant in the final multivariate analysis were the regimens, the sex of patients and their pretreatment radiographic extent of disease. No interaction was found between the findings in the three regimens, implying that the factors had similar effects in all of them. This conclusion is supported by a further analysis of the results in the two rifapentine-containing regimens alone, which yielded similar results to those in the main analysis (Table 2).

Separate analyses were then done on factors that achieved significance in the initial model. The number of adverse events according to pretreatment radiographic extent, age and sex are set out in Table 3. Taking the sex association first, adverse events were found in 41 (11.9%) of 346 male patients but in only 6 (3.2%) of 188 female patients. The number of cases in the study and the adverse events in males are compared with the notification rates per 100,000 population (scaled up by a factor of 50 to aid visibility in the graph) and the number of notifications in Hong Kong in 1995 (at the end of the intake) by age in Fig 2. The notification rates and the notifications in the two sexes have closely similar shapes with similar rates and numbers up 30 years. Thereafter, both rates

and numbers diverge with less disease in females than in males. The number of cases in the study also has the same pattern, though the divergence between males and females appears slightly greater. The numbers of adverse events show rather different patterns. In males, the curve for adverse events rises after the age of 40 years when the number of cases is slowly falling, indicating that relapses are more frequent in the older age groups (see also Table 3). There are insufficient adverse events in females to make a similar comparison, though 4 of the 6 adverse event happened in patients below 45 years. A possible causative factor is that the pretreatment radiographic extent of disease increased with increasing age in males by a mean increase of 0.0081 in the extent score for every year of age ($F_{1,342} = 12.8$; $P<0.001$). No asssociation between extent of disease and age was found in females ($F_{1,184} = 0.8$; NS). The effect of pretreatment radiographic extent of disease is set out in Table 4. Adverse events occurred in 3.4% of 298 patients with a grade of 1, increasing to 24.6% of 57 patients with a grade of 3. The association was found in all three regimens.

Table 5 shows that adverse events occurred in 8 (17%) of 46 patients with a positive culture at 2-months and in 35 (7.3%) of 476 patients with a negative culture. The association is evident in all 3 regimens. No additional weight was added to the association by considering the number of colonies found in the cultures. Even though the hazard ratio was higher for positive cultures at 3 months than at 2 months (Table 2), there were insufficient positive cultures at 3 months for any association with adverse events to be assessable.

Considering next the relationship between adverse events and the sensitivity to isoniazid of pretreatment cultures, there was an unfortunate error, which did not affect the

conclusions, in the relevant table previously published in the interim report.[2] Although the number of adverse events remains the same, the correct figures are set out in Table 6. There is no suggestion that adverse events occurred more frequently in the 23 patients with initial resistance to isoniazid, including 11 with additional resistance to streptomycin (Log rank test for equality of survival: $\chi^2 = 0.00$, $p = 0.995$). Life table rates of adverse events in all 3 regimens were 7.31%, 8.56% and 9.00% in those with sensitive organisms at follow-up for 12, 24 and 54 months, respectively, while a closely similar rate of 8.90% was found at each of these months in those with initially resistant organisms.

DISCUSSION

The life-table rates of adverse events were higher after a 4.5-year follow-up in the HRp_1 series (10.8%) and the HRp_1.2/3 (11.7%) than in the HR_3 series (4.2%). There is a great similarity in life table rates found at the 2-year follow-up in the three available clinical trials. Thus in the present Hong Kong study, the rates in the HRp_1 and the control HR_3 regimens were 10.2% and 4.2%, respectively, whereas the corresponding rates in the Hoechst Marion Rousell licensing study 008 were 12.4% in the HRp_1 and 6.6% in the HR_2 (dosage twice a week) regimens, and in CDC study 22, they were 9.2% in the HRp_1 and 4.5% in the HR_2 regimen. These results indicate that the dose of 600 mg rifapentine used in all three studies was inadequate and that studies of higher doses of rifapentine are necessary.

In the prognosis analyses, a striking finding was the strong association, in the initial univariate analysis, between adverse events and the sex and age of patients and between adverse events and sex alone in the final multivariate analysis (Table 2). A similar strong

association with sex was found in study 008 where, as in Hong Kong, male patients were much more likely than female patients to have a relapse. We will define as "immunological"all factors leading to disease that arise within the patient, and as "environmental" all factors outside the patient such as the chance of meeting someone with infectious tuberculosis. Clearly the chance of a relapse can only be due to immunological factors. Fig 2 and Table 2 show that immunological factors leading to relapse are greater in males than in females and also in males over the age of 40 years than in those younger. This propensity is accompanied by the occurrence of more severe disease at diagnosis in older males; the association accounts for the disappearance of age during step-wise analysis. As the immunological propensity is likely to extend to the general population and the sex/age discrepancy is greater in the occurrence of adverse events than in notification rates, there is some evidence that immunological factors are more important than environmental factors in causing the greater tendency for older males to develop tuberculosis shown in the notification rates in Fig 2.

A number of factors are interlinked in leading to adverse events. These are radiographic extent of disease, the presence of cavitation and culture positivity at 2 months and 3 months. The most important of these was extent of disease, and the others were therefore eliminated during the step-wise multivariate analyses. This does not however, mean that their associations with adverse events do not exist. There is a current search for surrogate markers for relapse to enable rapid assessment of new anti-tuberculosis drugs. The high hazard ratio of 2.49 for 2-month bacteriology supports the potential importance of this assessment as a surrogate marker. A previous investigation of prognostic factors in studies of short-course chemotherapy in Hong Kong found that of pretreatment factors,

age, but not sex, and colony counts of sputum were most predictive of relapse, older patients with high colony counts being more likely to relapse. Smear and culture results at 2 months were also highly predictive of relapse.

Initial bacillary isoniazid resistance had no apparent influence on the occurrence of adverse events. This finding together with the evidence, previously published, that the distribution of isoniazid genotypes is closely similar in those with and without an adverse event provides evidence that isoniazid does not contribute to the bactericidal action of the continuation phase of the regimen. In previous studies on once-weekly chemotherapy, clear-cut associations were found with regimens of isoniazid plus streptomycin or rifampicin which started early in treatment. No such association was however found with relapse occurring after treatment in a study of intermittent ethambutol/isoniazid, indicating the greater importance of the bactericidal activity of isoniazid early rather than late in treatment. A weak association has been found in CDC study 22 between 5-hr isoniazid plasma concentrations and adverse events in a sample of 152 patients ($p=0.02$), but no association was evident with the AUC. The disagreement with our findings suggests either that isoniazid has a very small influence on adverse events that was not detected in our study or that the sample of 142 patients in study 22 was slightly biased by selection of only the 5-hr plasma results, or by chance. It would seem unlikely that the discrepancy could be due to differences in the patient populations in the two studies in their response to chemotherapy.

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References

1. Tam CM, Chan SL, Lam CW et al. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis: Initial report. Am J Respir Crit Care Med 1998; 157: 1726-1733.
2. Tam CM, Chan SL, Kam KM, Sim E, Staples D, Sole KM, Al-Ghusein Al, Mitchison DA. Rifapentine and isoniazid in the continuation phase of a 6-month regimen. Interim report: no activity of isoniazid in the continuation phase. Int J Tuberc Lung Dis 2000; 4: 262-267.
3. Global Alliance for TB Drug Development for TB drug development. Tuberculosis 2001; 81 (Suppl 1): 1–52.Scientific Blueprint
4. Mitchison DA, Ellard GA, Grosset J. New antibacterial drugs for the treatment of mycobacterial disease in man. British Medical Bulletin 1988; 44: 757-774.
5. Mitchison DA. Development of rifapentine: the way ahead. Int J Tuberc Lung Dis 1998; 2: 612-615.
6. Chan SL, Yew WW, Porter JHD et al. Comparison of Chinese and Western rifapentines and improvement in bioavailability by prior taking of various meals. Int J Antimicrob Agents 1994; 3: 267-274.
7. Tam CM, Chan SL, Lam CW, Dickinson JM, Mitchison DA. Bioavailability of Chinese rifapentine during a clinical trial in Hong Kong. Int J Tuberc Lung Dis 1997; 1:411-416.
8. Keung A, Reith K, Eller MG, McKenzie KA, Cheng L, Weir S J. Enzyme induction observed in healthy volunteers after repeated administration of rifapentine and its lack

of effect on steady-state rifapentine pharmacokinetics: Part I. Int J Tuberc Lung Dis 1999; 3: 426-436.

9. Dean AG, Dean JA, Contombier D, Brendel KA, Smith DC, Burton AH, et al. Epi Info, Version 6: a word processing, database, and statistics program for epidemiology on microcomputers. Centers for Disease Control and Prevention, Atlanta, Georgia, USA, 1994.
10. Vernon A for the TB Trials Consortium. TBTC Study 22 (Rifapentine Trial): Preliminary results in HIV-negative patients. Am J Respir Crit Care Med 2000; 161(3): A252.
11. Das S, Chan S L, Allen B W, Mitchison D A, Lowrie D B. Application of DNA fingerprinting with IS986 to sequential mycobacterial isolates obtained from pulmonary tuberculosis patients in Hong Kong before, during and after short-course chemotherapy. Tubercle Lung Dis1993; 74: 47–51.
12. Wallis RS, Patil S, Cheon S-H, et al. Drug tolerance in Mycobacterium tuberculosis. Antimicrob Agents Chemother 1999; 43: 2600–2606.
13. Aber VR, Nunn AJ. Factors affecting relapse following short-course chemotherapy. Bull Int Union Tuberc Lung Dis 1978; 53: 260-264.
14. Tuberculosis Chemotherapy Centre, Madras. A controlled comparison of two fully supervised once-weekly regimens in the treatment of newly diagnosed pulmonary tuberculosis. Tubercle 1973; 54: 23-45.
15. Singapore Tuberculosis Service/British Medical Research Council. Controlled trial of intermittent regimens of rifampin plus isoniazid for pulmonary tuberculosis in Singapore. The results up to 30 months. Am Rev Respir Dis 1977; 116: 807-820.

16. Tuberculosis Research Centre, Madras. Ethambutol plus isoniazid for the treatment of pulmonary tuberculosis – a controlled trial of four regimens. Tubercle 1981; 61: 13-29.

17. Weiner M, Khan A, Benator D, Peloquin C, Burman W. and the TB Trials Consortium, CDC, Atlanta GA. Low isoniazid (INH) levels are associated with TB treatment failure/relapse with once-weekly rifapentine (RPT) and INH.

Fig 1 Kaplan-Meier graph of adverse treatment events in the three regimens

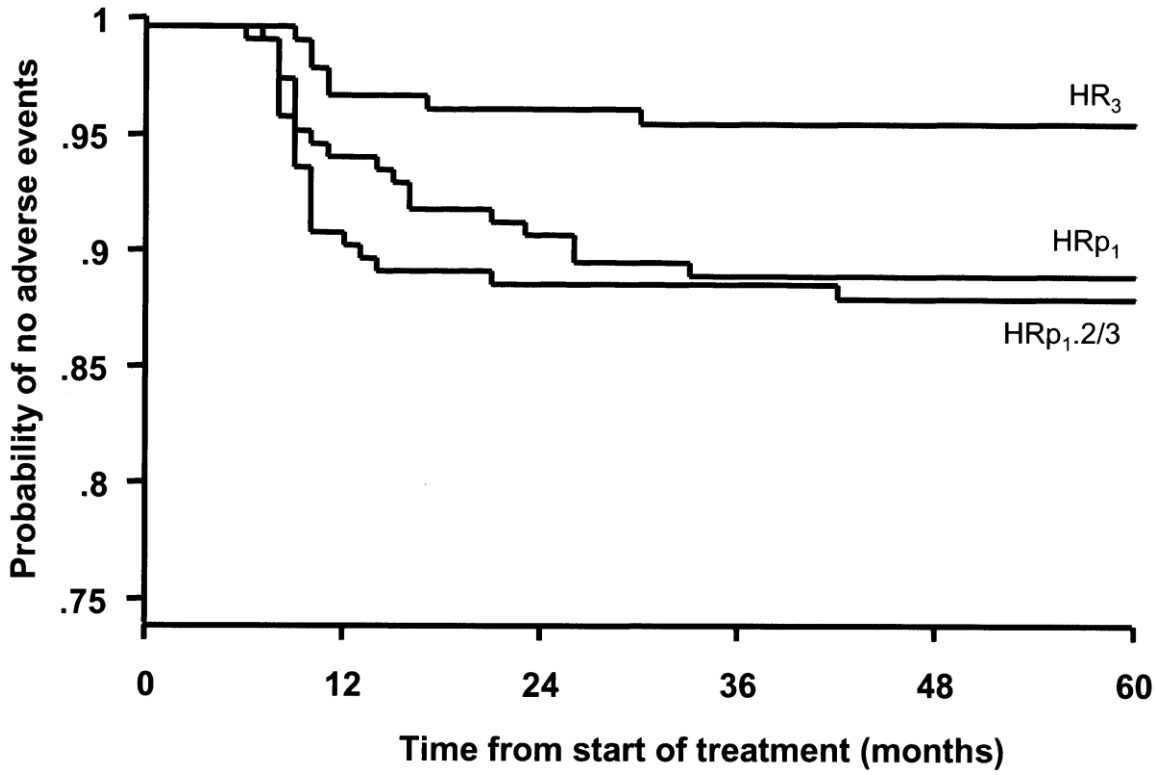

Table 1 Patients available and life-table rates of adverse events during follow-up

Follow-up period (months)	HR_3			HRp_1			$HRp_1.2/3$			Total available	
		Adverse			Adverse			Adverse		Adverse	
	Avail.	No.	%	Avail.	No.	%	Avail.	No.	%	No.	%
0	172	0	*0*	179	1	*0.5*	183	0	*0*	534	*100*
6	166	5	*3.0*	169	10	*5.6*	163	17	*9.4*	498	*93.3*
12	160	6	*3.6*	163	14	*7.9*	158	19	*10.5*	481	*90.1*
24	152	7	*4.2*	151	18	*10.2*	149	20	*11.1*	452	*84.6*
36	141	7	*4.2*	145	19	*10.8*	143	21	*11.7*	429	*80.3*
54	133	7	*4.2*	140	19	*10.8*	129	21	*11.7*	402	*75.3*

Table 2 Results of proportional hazards analysis

Variable	Hazard ratio	95% CL	p
Initial results			
(univariate analysis)			
Regimen			
HR_3	1.0		
HRp_2	2.65	1.11 - 6.30	
$HRp_1.2/3$	2.96	1.26 - 6.97	0.04
Age	1.03	1.01 - 1.05	0.001
Sex			
Female	1.0		
Male	3.96	1.68 - 9.34	0.002
Body weight	0.99	0.95 - 1.03	0.7
Pretreatment			
Radio. extent	2.82	1.94 - 4.09	<0.001
Cavitation	1.77	1.00 - 3.14	0.05
Bacteriology	1.08	0.87 - 1.34	0.5
INH resistance	1.00	0.24 - 4.14	1.0
2 mth pos. culture	2.49	1.16 - 5.33	0.02
3 mth pos. culture	3.54	0.86 – 14.59	0.08
Final results			
(multivariate analysis)			
Regimen			
HR_3	1.0		
$HRp_1.2/3$	2.98	1.25 – 7.12	
$HRp_1.2/3$	2.82	1.20 – 6.65	0.03
Sex			
Female	1.0		
Male	3.83	1.62 – 9.02	0.002
	(3.92	1.54 – 10.01	0.004)*
Pretreatment			
Radio. extent	2.90	1.98 – 4.25	<0.001
	(3.03	2.00 – 4.59	<0.001)*

* Analysis of combined results in rifapentine regimens (Rp_1 & $Rp_1.2/3$) only.

Table 3 Adverse events by radiographic extent of disease (radio.extent), age and sex

	Male			Female		
Age	No.	Mean radio. extent	Adverse events	No.	Mean radio. extent	Adverse events
10 - 19	17	(1.50)*	3	20	1.65	0
20 - 29	83	1.31	3	69	1.46	1
30 - 39	73	1.55	4	60	1.37	3
40 - 49	60	1.71	15	23	1.36	1
50 - 59	46	1.65	5	9	(1.44)	0
60 - 69	55	1.73	9	7	(2.00)	1
70 - 79	11	(1.82)	2	0	-	0
80 - 89	1	(1.00)	0	0	-	0
Total	346		41	188		6

* Percentages in parenthesis based on less than 20 patients

Table 4 Adverse events by radiographic extent of disease and regimen

	HR_3		HRp_1		$HRp_1.2/3$		All		
Radiographic extent	Total patients	Adverse events	Total patients	Adverse events	Total patients	Adverse events	Total patients	Adverse events No.	Adverse events %
0	0	0	1	0	1	0	2	0	*(0)**
1	98	2	97	3	103	5	298	10	*3.4*
2	54	3	65	11	54	9	173	23	*13.3*
3	18	2	15	5	24	7	57	14	*24.6*
Total	170	7	178	19	182	21	530	47	*8.9*

* Percentage in parenthesis based on less than 20 patients

Table 5 Adverse events according to 2-month culture result

Regimen	Adverse event	Total patients	Culture			No. of colonies in cultures			
			Neg.	Pos.		1-3	4-19	20-100	>100
				No.	%				
HR_3	Yes	6	4	2	*33*	0	0	2	0
	No	161	149	12	*7.5*	4	2	5	1
HRp_1	Yes	19	16	3	*16*	0	0	3	0
	No	158	146	12	*7.6*	4	0	7	1
$HRp_1.2/3$	Yes	21	18	3	*14*	2	0	1	0
	No	157	146	11	*4.5*	3	1	6	1
All	Yes	46	38	8	*17*	2	0	6	0
	No	476	441	35	*7.3*	11	3	18	3

Table 6 Adverse events in patients initially sensitive or resistant to isoniazid (INH)

Pretreatment	HR_3		HRp_1 + HRp_1.2/3	
susceptibility	n	%	n	%
INH-sensitive				
Adverse event	7	(4.2)	3.8	(11.0)
Total	165		346	
INH-resistant				
Adverse event	0	(0.0)	2	(12.5)
Total	7		16	

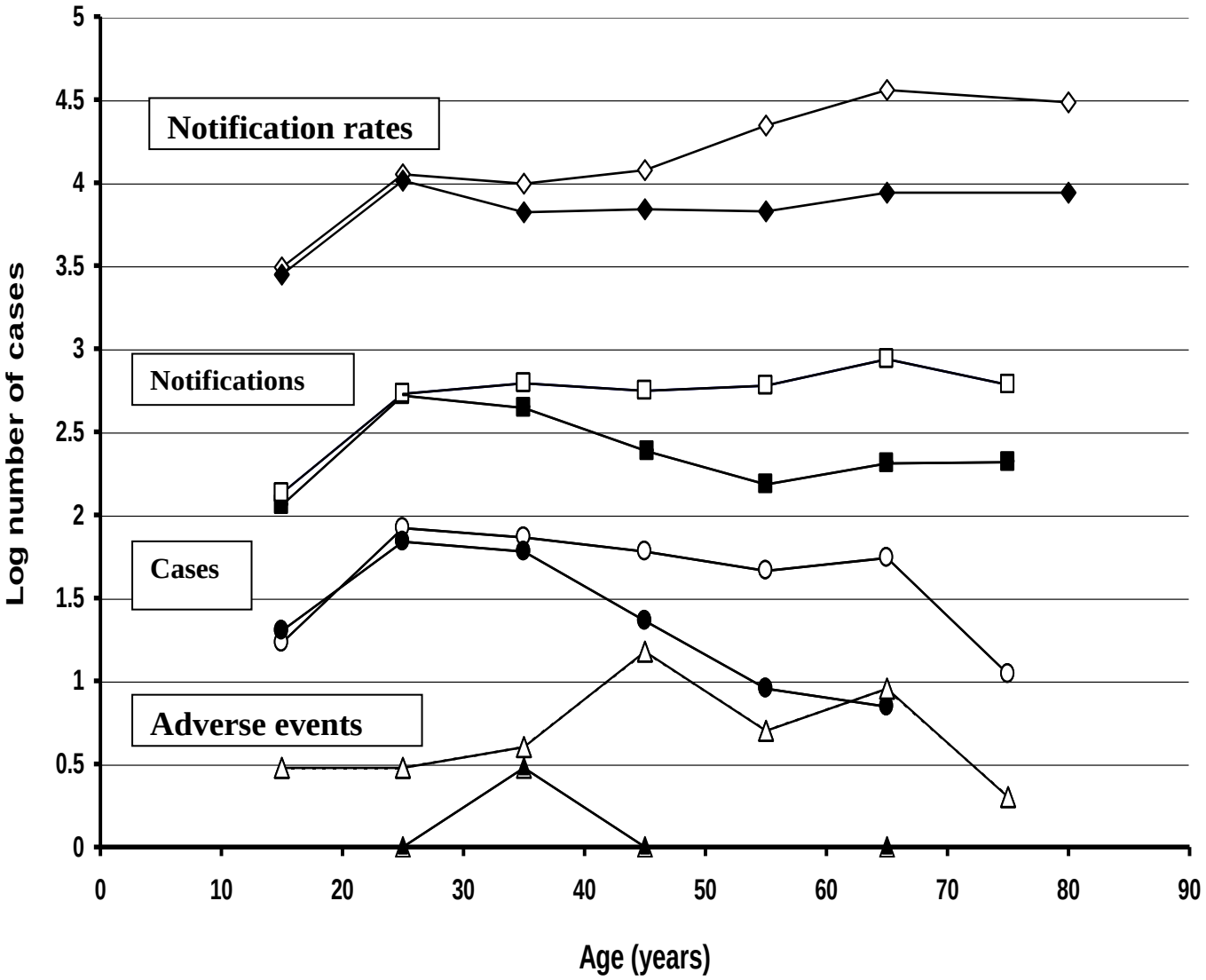
Notification rates
Notifications
Cases
Adverse events
Log number of cases
Age (years)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
0
10
20
30
40
50
60
70
80
90

Fig 2 Notification rates of pulmonary tuberculosis per 5,000,000 of population in Hong Kong (top curves), notification numbers in Hong Kong (2^{nd} from top), cases in the study (3^{rd} from top) and numbers of adverse events (bottom curves) by age and sex. Males: open symbols. Females: closed symbols.