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Extension of the intensive phase reduces unfavourable outcomes with the 8-month thioacetazone regimen

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SUMMARY

SETTING: Damien Foundation tuberculosis (TB) control projects in Bangladesh.

OBJECTIVE: To assess the effectiveness of a 1-month extension of the intensive phase for smear-positives at 2 months of an 8-month regimen with a continuation phase consisting of isoniazid (INH) and thioacetazone (Th).

DESIGN: A prospective study of two cohorts of newly registered smear-positive cases, with extension of the intensive phase for the control cohort, but not for the study cohort. Culture and drug susceptibility testing (DST) of smear-defined failures and relapses and of random samples of new cases.

RESULTS: Among 8230 study patients (86.7% 2-month conversion) and 7206 controls (83.4% conversion), smear-defined failure or relapse outcome was 3.0% for 2-month smear-negatives vs. 3.1% for 2-month smear-positives with extension (non-significant, NS), and 8.2% for 2-month smear-positives with no extension ($P < 0.00001$). Culture-confirmed failure and relapse reached 1.9% in 2-month smear-negatives and 1.6% (NS) in 2-month smear-positives with vs. 3.7% ($P < 0.001$) in 2-month smear-positives with no extension. The relative risk (RR) of non-extension in 2-month smear-positives was 2.4 (cultures) to 2.7 (smears). The same RR and borderline significance was found for non-extension of patients with pan-susceptible strains.

CONCLUSIONS: Extension of the intensive phase considerably reduces failures and relapses with a weaker regimen in patients smear-positive at 2 months. Its effectiveness may vary with extent of initial drug resistance vs. power of the regimen.

KEY WORDS: tuberculosis; conversion; relapse; failure

EXTENSION of the intensive phase (PhI) of tuberculosis (TB) treatment by 1 month in case of smear positivity at the end of the phase is recommended in global guidelines,[1,2] and has become the standard in National Tuberculosis Programmes (NTP). Higher rates of treatment failure have been reported in patients who are smear-positive at the end of PhI,[3] but predictive value remained low.[4] The effectiveness of prolongation has been questioned,[4,5] particularly for regimens with rifampicin (R, RMP) throughout.[6] Trébucq and Rieder have defended the practice based on indirect evidence from controlled clinical trials.[7–9] Smear positivity after 2 months of short-course chemotherapy has been reported to be as high as 15% when checking one morning specimen,[10] but cultures often remain negative.[11] Extensive disease, high positive diagnostic smears and old age have been identified as risk factors for delayed smear conversion,[12–14] while reports on association with human immunodeficiency virus (HIV) status are conflicting.[12,14–16]

We assessed the unknown benefit of extension vs. increased cost and possible adverse effects through a prospective multi-centre study in Damien Foundation Bangladesh projects implementing TB control on behalf of the NTP. This setting was considered suitable because of the close treatment monitoring, highly reliable microscopy for acid-fast bacilli (AFB) and accurate, detailed recording. At the time of the study, the Bangladesh NTP was using the 8-month regimen with 2 months of ethambutol (E), isoniazid (H), rifampicin (R, RMP) and pyrazinamide (Z) in PhI, followed by 6 months of H and thioacetazone (T, Th) in the continuation phase for new patients (Category 1, 2EHRZ/6HT).

METHODS

All new smear-positive pulmonary TB patients diagnosed in 75 centres in Damien Foundation implemented areas were eligible for the study. The study cohort, for whom PhI was not extended (contrary to NTP guidelines), were patients registered during the last quarter of 2000 and the first three quarters of 2001. Extension was exceptionally allowed on prescription by a medical officer. The control cohort for which exten-

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sion of PhI by 30 days was practised in case of a 2-month positive smear (2M+) comprised all patients registered during two quarters preceding and two quarters following the study cohort. The duration of the continuation phase was kept constant, at 6 months. Cut-off for smear positivity was four AFB/100 oil-immersion fields (OIF). Declaration of failure was based on smear positivity at 5 months or later in treatment, confirmed by at least one more positive smear of two morning sputum samples examined 2–4 weeks later. Diagnosis of new or relapse smear-positive cases required two sputum samples containing AFB, one of them cut-off positive.

Treatment was supervised as often as possible, preferably daily, during PhI but not during the continuation phase. Drugs were supplied by the NTP, and no interruptions occurred at patient level. Follow-up for relapse was passive. To limit confusion with reinfection and to equalise the follow-up period for the different cohorts, bacteriologically confirmed recurrences more than 2 years after the end of treatment were excluded from analysis.

AFB examination used the hot Ziehl-Neelsen (ZN) method, as described previously.[17] All centres were covered continuously by rechecking quality assessment, showing high quality of AFB smears (<1% false positive, with sensitivity relative to the controllers >90%).

To monitor drug resistance, besides the periodical random surveys, sputum samples from failure and relapse patients were systematically sent for culture, identification and drug susceptibility testing (DST).[18] Cultures and DST were performed at the Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium, as described previously,[19,20] but from mid-2002 onwards primary isolation was done in the project's reference laboratory.

All individual patient and drug resistance data were entered and analysed using Epi Info 6.04d (Centers for Disease Control, Atlanta, GA, USA). Pearson's χ^2 test or Fisher's exact test were used for comparison of proportions. Student's *t*-test was used for differences of the means. Exclusion criteria were gross treatment irregularity (<75%) and breach of protocol (extension with 2-month result negative or scanty 1–3 AFB/100 OIF [2M−], extension of 2M+ study patients and non-extension of 2M+ control cohort patients).

Clearance for the study was granted by the Bangladesh Medical Research Council Ethical Review Committee. As the benefits and risks of either practice were unknown, informed consent was not requested.

RESULTS

Of 9208 new smear-positive patients enrolled in the (non-extended) study cohort, 8690 reached the end of PhI and 8648 (93.9%) had PhI-end smears done, against respectively 7609 and 7535 (93.7%) of 8044 controls. Table 1 also shows details of patients who did not reach the end of PhI due to death, default or transfer. Few patients were excluded from the analysis, and were excluded mainly because of serious treatment irregularity. The final analysis comprised 8230 study and 7206 control patients. There were 13.5% smear positives at 2 months (2M+) in the study and 16.7% in the control cohort.

Table 1 Details of enrolment, status at 2 months and excluded patients

	Control cohort (extension) *n*	Study cohort (no extension) *n*
Enrolled	8044	9208
Did not end phase I		
Died	236	267
Defaulted	166	212
Transferred	33	39
Ended phase I	7609	8690
2M smear		
Not done	74	42
Done	7535	8648
2M+ (%)*	1262 (16.7)	1164 (13.5)
Excluded		
2M− extended†	26	17
2M+ protocol breach*	21	14
Irregular <75%‡	282	387
Evaluated	7206	8230
2M−†	6010	7132
2M+ (%)*	1196 (16.6)	1098 (13.3)

* Smear at 2 months positive (≥4 AFB/100 OIF).
† Smear at 2 months negative or scanty AFB below the cut-off.
‡ Irregular <75%: intensive phase taken with regularity below 75%.
AFB = acid-fast bacilli; OIF = oil immersion field.

The proportion of 2M+ was higher for the first compared to the second part of the control cohort (18.4% vs. 14.5%, $P < 0.00001$), but the proportion of enrolled patients evaluated was similar (89.1% vs. 90.2%; details not shown).

Table 2 shows failure and relapse outcome (F/R) by 2-month smear and extension cohort. Smear-defined failure or relapse differed little between the study and control cohort 2M−, but for 2M+ both were clearly

Table 2 Unfavourable bacteriological outcome of evaluated patients, by cohort and smear at 2 months

	Cohorts and smear at 2 months			
	Control (extension for 2M+ only) (n = 7206)		Study (no extension) (n = 8230)	
	2M−* *n* (%)	2M+† *n* (%)	2M−* *n* (%)	2M+† *n* (%)
Totals	6010	1196	7132	1098
Failure, smear	58 (1.0)	23 (1.9)	75 (1.1)	53 (4.8)
Relapse, smear	106 (1.8)	14 (1.2)	160 (2.2)	37 (3.4)
Failure, smear and culture	31 (0.5)	8 (0.7)	41 (0.6)	15 (1.4)
Relapse, smear and culture	70 (1.2)	11 (0.9)	110 (1.5)	26 (2.4)

* Smear at 2 months positive (≥4 AFB/100 OIF).
† Smear at 2 months negative or scanty AFB below the cut-off.
AFB = acid-fast bacilli; OIF = oil immersion fields.

Table 3 Summary analysis of failure/relapse outcome by cohort, from smear or smear and culture criteria

	Cohorts and smear at 2 months			
	Control (extension for 2M+* only)		Study (no extension)	
	2M− *n* (%)†	2M+ *n* (%)*	2M− *n* (%)†	2M+ *n* (%)*
F/R from smear	164 (2.7)	37 (3.1)	235 (3.3)	90 (8.2)
RR (95%CI) vs. 2M−†		1.1 (0.8–1.6)		2.5 (2.0–3.2)
(*P* value)		(0.44)		(<0.000001)
RR (95%CI) vs. 2M+* controls				2.7 (1.8–3.9)
(*P* value)				(<0.000001)
F/R from smear and culture	101 (1.7)	19 (1.6)	151 (2.1)	41 (3.7)
RR (95%CI) vs. 2M−†		1.0 (0.6–1.5)		1.8 (1.3–2.5)
(*P* value)		(0.79)		(<0.001)
RR (95%CI) vs. 2M+* controls				2.4 (1.4–4.0)
(*P* value)				(<0.001)

* Smear at 2 months positive (⩾ 4 AFB/100 OIF).
† Smear at 2 months negative or scanty AFB below the cut-off.
F/R = failure and relapse outcome; RR = relative risk; CI = confidence interval; AFB = acid-fast bacilli; OIF = oil immersion fields.

higher in the study cohort. Cultures were performed for respectively 300 (92%) and 185 (92%) F/R from the study and control cohorts; only *Mycobacterium tuberculosis* positive cultures are shown in Table 1. Smear-positive failures were confirmed by culture in about half of 2M− and one third of 2M+ patients. In 2M+ patients, culture-confirmed failures reached 1.4% for the study cohort against 0.7% for the control cohort. Two-thirds of smear-positive relapses were culture-positive, and occurred more often in the study cohort (2.4% in 2M+ and 1.5% in 2M− vs. 0.9% and 1.2% in controls).

Table 3 shows F/R summary results, from smears or smears and cultures, by 2-month conversion status and cohort. Among 2M− patients, F/R was slightly higher in the study cohort (smear-defined 3.3% vs. 2.7%, $P = 0.045$; culture-confirmed 2.1% vs. 1.7%, non-significant). Overall F/R among 2M− patients was 3.0% from smear or 1.9% from smear and culture. F/R did not differ between 2M+ (extended) and 2M− patients in the control cohort (3.1% vs. 2.7% smear-defined, 1.6% vs. 1.7% culture-confirmed), but it did for the study cohort (without extension) (8.2% vs. 3.3% and 3.7% vs. 2.1%, respectively). Relative risk (RR) of non-extension in 2M+ was 2.7 (95% confidence interval [CI] 1.8–3.9) for smear− and 2.4 (95%CI 1.4–4.0) for culture-confirmed F/R. Irrespective of 2-month conversion, smear-defined F/R reached 325 (3.9% of 8230) for the total study cohort, of whom 192 (2.3%) were also culture-positive. For the total control cohort, this was respectively 201 (2.8%) and 120 (1.7%), both statistically significant, with RR 1.4 (95%CI 1.2–1.7 from smear and 95%CI 1.1–1.8 from smear and culture).

There was a significant difference between the earlier and later group of the control cohort, in that the earlier group had higher F/R rates. As a result, the differences in 2M+ F/R rates between the later control group and the study group were significant for smear-defined F/R (RR 1.9, 95%CI 1.1–3.3) but not for the smaller number of culture-defined F/R (RR 1.81, 95%CI 0.8–4.0).

Table 4 analyses the outcome by initial drug resis-

Table 4 Bacteriologically unfavourable outcome of 8-month short-course treatment, by initial drug resistance, sputum smear conversion and extension of the intensive phase at 2 months

Drug resistance profile, smear status at 2 months and intensive phase extension	*N*	A Total patients *n* (% of *N*)	F/R on smears *n* (% of A)	F/R culture-positive/ culture done *n* (%)
Pan-susceptible*	1235			
Negative, no extension		1002 (81)	16 (1.6)	6/10 (60)
Positive and extended		101 (8)	1 (1)	0/0 (0)
Positive and not extended		132 (11)	4 (3)	3/3 (100)
Resistant to INH non-MDR†	104			
Negative, no extension		86 (83)	21 (25)	13/15 (87)
Positive and extended		12 (11)	3 (25)	2/2 (100)
Positive and not extended		6 (6)	1 (17)	1/1 (100)
MDR	14			
Negative, no extension		6 (43)	4 (67)	2/3 (67)
Positive and extended		6 (43)	3 (50)	2/2 (100)
Positive and not extended		2 (4)	2 (100)	2/2 (100)
Other than INH or RMP resistance	55			
Negative, no extension		48 (87)	3 (6)	3/3 (100)
Positive and extended		0 (0)	0 (0)	0 (0)
Positive and not extended		7 (13)	3 (43)	1/2 (50)

* INH, RMP, SM and EMB.
† Resistant to INH-only or INH+SM and/or EMB.
F/R = failure plus relapse, or total bacteriologically unfavourable outcome; INH = isoniazid; MDR = multidrug resistance; RMP = rifampicin; SM = streptomycin; EMB = ethambutol.

tance profile found in our random surveys of 1995 (2M+ extended) and 2001 (part of the study cohort, 2M+ non-extended). With pan-susceptible strains, F/R occurred in 1.6% of 2M− vs. 1% and 3% of extended and non-extended 2M+ respectively (RR vs. 2M− or 2M+ extended 2.8, $P = 0.07$). As expected with this regimen, F/R was higher with resistant strains, particularly with multidrug resistance. Due to the small numbers of 2M+ patients involved, differences according to extension status were less clear and always non-significant.

Using the same exclusion criteria as for the prospective study, we analysed all new smear-positive registrations treated with the 8-month Th regimen from 1995 to 2001 (Figure). With the exclusion of about 2% per year due to non-respect of this rule, PhI was consistently extended from 4 AFB/100 OIF onwards. The proportion of F/R showed a downward trend, reversing in the study cohort (year 01 in the Figure), with a peak in 2M+ patients. On average, F/R was higher in PhI non-extended 2-month scanty 1–3 AFB/100 OIF than in 2M− or PhI extended 2M+ patients (4.6% vs. 3%, data not shown).

Using the same database, we looked for an association between smear conversion and number of AFB at start of treatment (highest result) and PhI regularity (expressed as the per cent number of days prescribed vs. actual duration). Averages were calculated assigning a number of AFB per OIF to each score on the scale (20 for 3+, 5 for 2+, 0.5 for 1+, and the exact value expressed as 0.01–0.09 for scanty). Of new smear-positive cases, 33 217 2M− had on average 7.8 AFB/OIF at diagnosis (median 2+; 39% with 3+) and were 97.6% regular, while 9060 2M+ had on average 10.7 AFB/OIF (median 3+, found in 61%) with 96.8% regularity. The difference of the means was highly significant for both parameters ($P < 10^{-6}$).

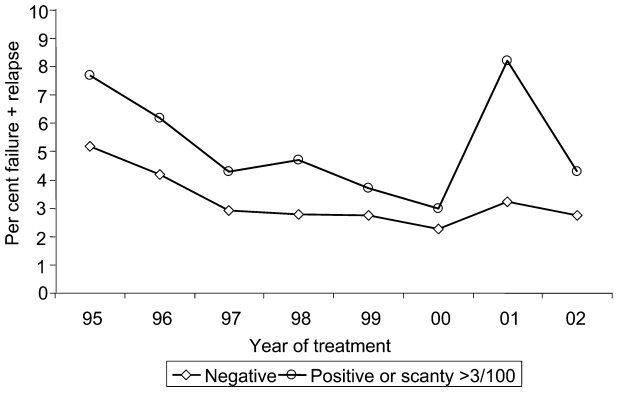

Figure Smear-based failure and relapse outcome by quantified smear result and intensive phase extension at 2 months, by year of registration. Intensive phase extension was practised for all positives or high scanty (>3/100 oil immersion fields), except during the year of the study, indicated as 01 above. It was not practised for 2-month negatives. Yearly totals increased between 1995 and 2001 from 1019 to 5549 negatives and 221 to 1391 positives/high scanty at 2 months.

Table 5 Side effects registered during the intensive phase (PhI), by duration (all new smear-positives, 1995–2001)

Side effects	With 2 months PhI (n = 35 280) n (%)	With 3 months PhI, one month extension included (n = 5062) n (%)
None	28 610 (81.1)	3 901 (77.1)
Arthralgia	2 664 (7.6)	832 (16.4)
Nausea and vomiting	1 857 (5.3)	264 (5.2)
Rashes	1 605 (4.6)	152 (3.0)
Jaundice	626 (1.8)	75 (1.5)
Peripheral neuritis	413 (1.2)	138 (2.7)
Severe allergy	318 (0.9)	25 (0.5)
Mental disturbance	88 (0.3)	14 (0.3)

The same patient may have had more than one side effect. Patients with PhI duration increased by at least 1 month due to serious treatment irregularity have been excluded.

Table 5 compares registered side effects. These were significantly more common with PhI extension, mainly due to a clearly increased incidence of arthralgia and peripheral neuritis.

DISCUSSION

Extension of PhI has been universal practice since the early days of NTP short-course chemotherapy, without ever being challenged, presumably because the numbers required for proof of its effectiveness by far exceed what is feasible in a rigorously controlled clinical trial. Our prospective study was not conducted with such rigour, but despite its limitations we believe that it provides the first trial-based evidence of the effectiveness of extension in 2M+ patients. Extension by 1 month reduced F/R frequency from 8.2% to 3.1% (smear-defined) and from 3.7% to 1.6% (culture-confirmed), or to the level of 2M−. The RR of non-extension vs. extension was respectively 2.7 and 2.4, while after extension no difference in risk remained with 2M− patients. The same RR of non-extension was found when considering patients with pan-susceptible strains only, comparing historical cohorts, but the numbers involved were too small to allow meaningful analysis for other resistance profiles. Although low scanty 2-month smears (1–3 AFB/100 OIF) were not covered by the trial, our routine data suggest that extension of PhI might be beneficial for these as well.

Extent of disease was the main reason for positive smears at 2 months, as suggested by the average number of AFB in diagnostic smears (3+ smears in 39% of 2M− vs. 61% of 2M+). PhI regularity was significantly lower in late converters, but this may be explained by the very high numbers studied, while the difference was very small (96.8 vs. 97.6%). Moreover, patients in need of extension due to extreme treatment irregularity had been excluded from the analysis.

Our study has several limitations:

- The cohorts were defined historically, as this was least disrupting for routine activities and manage-

able without additional resources in a study covering a population of 20 million, in contrast to true randomisation. To counteract the effect of trends, the control cohort was enrolled half before and half after the study cohort, and we studied the prospective cohorts within the trend determined from our complete database since 1995. This showed that time-related bias did not occur, while the study cohort F/R clearly peaked from the existing trend in 2M+ patients. The trend observed may be caused by a documented decrease of drug resistance levels,[18,20] and particularly by the expanded indications for the retreatment regimen since 1997. Seasonal variations in case presentation, with higher bacillary load at diagnosis and lower 2-month conversion during monsoon, may explain the different conversion between the two parts of the control cohort. The drop in 2-month positives for the entire study cohort suggests that these smears were examined less carefully, while it was known that their result would have no therapeutic consequences, tending towards equalisation between 2M+ and 2M− F/R in the study cohort with underestimation of the effect of extension. However, F/R remained significantly higher for the total study cohort, irrespective of 2-month smears (overall RR 1.4), and less careful microscopy in the study cohort does not invalidate our results.

- For field management, F/R declaration was based on smears, but cultures were also done for over 90% of F/R outcomes from both cohorts. The approximately 70% culture positivity obtained from 2M− failures and relapses indicates that sensitivity was suboptimal due to transport delays. However, false failure diagnoses due to non-viable bacilli are known to occur with highly sensitive smears,[10,21,22] and this may explain why failure cultures remained negative in two thirds of 2M+ patients. The true F/R frequencies may thus have been in between these based on smear and culture criteria, and as the smear/culture positivity ratios were sufficiently consistent between cohorts, we believe that the comparisons made remain valid.
- Due to the numbers involved and the context, relapse follow-up could only be passive, and this certainly resulted in underestimation, but the level of error may have been similar for both cohorts. It may also have been relatively low, as suggested by systematic questioning and sputum examination of 1251 cured patients during our gender survey.[23] Only five (0.4%) unknown relapses were found compared to the average 2.1% registered for this study.
- Our study could not differentiate between relapse and re-infection, which might have caused overdiagnosis of relapse in this high prevalence, densely populated area.[24] The error should have been similar in both cohorts, and restricting relapse analysis to registrations up to 2 years after the end of treatment is believed to have limited its extent, as well as equalising the follow-up period for successively enrolled cohorts.
- We did not try to document the HIV status of our patients. Co-infection might have a profound effect on F/R with the 8-month regimens, but HIV is so rare in Bangladesh that its effect would not have been measurable.
- The 2EHRZ/6HT regimen has been almost completely abandoned (also by the Bangladesh NTP). Because of its better sterilising activity, the effect of extending the PhI is likely to be lesser or even absent with a Category 1 regimen containing RMP throughout, and initial non-MDR drug resistance may not matter.[25] However, our data suggest a more pronounced influence of drug resistance on treatment outcome than is known from small-scale clinical trials. Similar studies involving high numbers of patients might show some drug resistance related gradient also for more powerful regimens. A study concerning the effect of PhI extension during a regimen with RMP throughout is underway in the same population.
- Such a comparative study might help us to understand the unexpectedly large F/R difference between 8-month HE continuation regimens and 2EHRZ/4HR recently reported from a clinical trial without PhI extension.[26] As the sterilising power of the HE continuation phase is more similar to HT than to HR, our study lends credibility to the authors' hypothesis that 10% F/R with 2EHRZ/6HE is partly caused by this omission. Its effect might be amplified in populations with high levels of drug resistance and/or HIV.

In spite of a RR reduction by at least 2.5, the absolute gain from PhI extension thus remains modest in low HIV, low drug resistance populations, and the cost needs to be considered. The observed increase in mild side effects might be acceptable. In our setting, PhI had to be extended for 20/50 patients to prevent one (smear/culture-defined) F/R case. Moreover, it requires that all patients undergo a quality smear test at 2 months. This can be seen as a further burden on the service, or as an independent essential element of the DOTS strategy, reinforcing the bond between patient and provider so crucial to treatment success.

CONCLUSIONS

Our study shows that extension of PhI for 2M+ patients during the 8-month Th-containing regimen reduces the risk of F/R to the level of 2M−. Its effect is expected to differ by population, depending on factors such as prevalence of drug resistance and HIV. Its effectiveness with more powerful RMP-throughout regimens remains to be shown.

References

1 World Health Organization. Treatment of tuberculosis: guidelines for national programmes. 3rd ed. WHO/CDS/TB/2003. 313. Geneva, Switzerland: WHO, 2003.
2 Enarson D A, Rieder H L, Arnadottir T, Trébucq A. Management of tuberculosis. A guide for low income countries. 5th ed. Paris, France: International Union Against Tuberculosis and Lung Disease, 2000.
3 Zhao F Z, Levy M H, Sumin W. Sputum microscopy results at two and three months predict outcome of tuberculosis treatment. Int J Tuberc Lung Dis 1997; 1: 570–572.
4 Wilkinson D, Bechan S, Connolly C, Standing E, Short G M. Should we take a history of prior treatment, and check sputum status at 2–3 months when treating patients for tuberculosis? Int J Tuberc Lung Dis 1998; 2: 52–55.
5 De Cock K M, Wilkinson D. Tuberculosis control in resource-poor countries: alternative approaches in the era of HIV. Lancet 1995; 346: 675–677.
6 Barker R D, Millard F J C. Two excellent management tools for national tuberculosis programmes. [Correspondence] Int J Tuberc Lung Dis 1999; 3: 454–455.
7 Trébucq A, Rieder H L. Two excellent management tools for national tuberculosis programmes: history of prior treatment and sputum status at two months. [Counterpoint] Int J Tuberc Lung Dis 1998; 2: 184–186.
8 Trébucq A, Rieder H L. Two excellent management tools for national tuberculosis programmes. In reply. [Correspondence] Int J Tuberc Lung Dis 1999; 3: 455.
9 Hong Kong Chest Service, British Medical Research Council. Controlled trial of 4 three-times-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Second report: the results up to 24 months. Tubercle 1982; 63: 89–98.
10 Rieder H L. Sputum smear conversion during directly observed treatment for tuberculosis. Tubercle Lung Dis 1996; 77: 124–129.
11 Ramarokoto H, Randriamiharisoa H, Rakotoarisaonina A, et al. Bacteriological follow-up of tuberculosis treatment: a comparative study of smear microscopy and culture results at the second month of treatment. Int J Tuberc Lung Dis 2002; 6: 909–912.
12 Domínguez-Castellano A, Muniain M A, Rodriguez-Baño J, et al. Factors associated with time to sputum smear conversion in active pulmonary tuberculosis. Int J Tuberc Lung Dis 2003; 7: 432–438.
13 Singla R, Osman M M, Khan N, Al-Sharif N, Al-Sayegh M O, Shaikh M A. Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment. Int J Tuberc Lung Dis 2003; 7: 58–64.
14 Telzak E E, Fazal B A, Pollard C L, Turett G S, Justman J E, Blum S. Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis. Clin Infect Dis 1997; 25: 666–670.
15 Aliyu M H, Salihu H M, Ratard R. HIV infection and sputum-culture conversion in patients diagnosed with *Mycobacterium tuberculosis*: a population-based study. Wien Klin Wochenschr 2003; 115: 340–346.
16 Brindle R J, Nunn P P, Githui W, Allen B W, Gathua S, Waiyaki P. Quantitative bacillary response to treatment in HIV-associated pulmonary tuberculosis. Am Rev Respir Dis 1993; 147: 958–961.
17 Van Deun A, Hamid Salim A, Aung K J M, et al. Performance of variations of carbolfuchsin staining of sputum smears for AFB under field conditions. Int J Tuberc Lung Dis 2005; 9: 1127–1133.
18 Van Deun A, Hamid Salim A, Rigouts L, Rahman M, Fissette K, Portaels F. Evaluation of tuberculosis control by periodic or routine susceptibility testing in previously treated cases. Int J Tuberc Lung Dis 2001; 5: 329–338.
19 Van Deun A, Aung K J M, Chowdhury S, et al. Drug susceptibility of *Mycobacterium tuberculosis* in a rural area of Bangladesh and its relevance to the national treatment regimens. Int J Tuberc Lung Dis 1999; 3: 143–148.
20 Van Deun A, Salim A H, Daru P, et al. Drug resistance monitoring: combined rates may be the best indicator of programme performance. Int J Tuberc Lung Dis 2004; 8: 23–30.
21 Al-Moamary M S, Black W, Bessuille E, Elwood R K, Vedal S. The significance of the persistent presence of acid-fast bacilli in sputum smears in pulmonary tuberculosis. Chest 1999; 116: 726–731.
22 Vidal R, Martin-Casabona N, Juan A, Falgueras T, Miravitlles M. Incidence and significance of acid-fast bacilli in sputum smears at the end of antituberculosis treatment. Chest 1996; 109: 1562–1565.
23 Hamid Salim M A, Declerq E, Van Deun A, Saki K A R. Gender differences in tuberculosis: a prevalence survey done in Bangladesh. Int J Tuberc Lung Dis 2004; 8: 952–957.
24 Lambert M L, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Van der Stuyft P. Recurrence in tuberculosis: relapse or re-infection? Lancet Infect Dis 2003; 3: 282–287.
25 Enarson D A, Jindani A, Kuaban C, et al. Appropriateness of extending the intensive phase of treatment based on smear results. [Correspondence] Int J Tuberc Lung Dis 2004; 8: 114–116.
26 Jindani A, Nunn A J, Enarson D A. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 2004; 364: 1244–1251.

RÉSUMÉ

CONTEXTE : Projets de lutte contre la tuberculose de la Fondation Damien au Bangladesh.

OBJECTIF : Evaluer l'efficacité d'une prolongation d'un mois de la phase intensive chez les patients à frottis positifs après 2 mois d'un traitement de 8 mois avec de l'isoniazide et de la thiacetazone en phase de continuation.

SCHÉMA : Etude prospective de deux cohortes de patients à frottis positifs nouvellement enregistrés, avec extension de la phase intensive pour le groupe témoin, mais sans extension pour le groupe d'étude. Culture et tests de sensibilité des échecs et rechutes identifiés par frottis, et d'un échantillon aléatoire de nouveaux cas.

RÉSULTATS : Parmi 8230 patients du groupe étudié (86,7% de négativation à 2 mois) et 7206 témoins (83,4% de négativation), les taux d'échecs ou de rechutes identifiés par frottis ont été de 3,0% pour les patients négatifs à 2 mois contre 3,1% pour les patients positifs à 2 mois avec prolongation (non significatif, NS) et 8,2% pour les patients positifs à 2 mois sans prolongation ($P < 0{,}00001$). Les taux d'échec et de rechute confirmés par culture ont atteint 1,9% chez les patients à frottis négatifs à 2 mois, pour 1,6% (NS) chez ceux à frottis positifs à 2 mois avec prolongation et 3,7% chez ceux à frottis positifs sans prolongation ($P < 0{,}001$). Le risque relatif (RR) lié à la non-prolongation de la phase intensive chez les patients positifs à 2 mois a été de 2,4 (culture) à 2,7 (frottis). Les

mêmes RR et signification marginale ont été trouvés pour la non-prolongation chez les patients dont les souches étaient totalement sensibles.
CONCLUSIONS : La prolongation de la phase intensive diminue de manière considérable les échecs et les rechutes chez les patients à frottis positifs après 2 mois d'un régime thérapeutique relativement faible. Son efficacité peut varier avec le degré de résistance initiale ainsi qu'avec la puissance du régime thérapeutique.

RESUMEN

MARCO DE REFERENCIA : Los proyectos de la Fundación Damien para el control de la tuberculosis (TB) en Bangladesh.
OBJETIVO : Evaluar la eficacia de la prolongación de 1 mes desde 2 meses de la fase intensiva del tratamiento para casos con baciloscopia positiva en una pauta de 8 meses con isoniacida y tioacetazona en la fase de continuación.
MÉTODO : Fue este un estudio prospectivo de dos cohortes de casos bacilíferos recién registrados, con prolongación de la fase intensiva para la cohorte testigo y sin prolongación para la cohorte experimental. Se practicaron cultivos y pruebas de sensibilidad a los medicamentos en los casos de fracaso y recaída definidos por la baciloscopia y en muestras aleatorias de los casos nuevos.
RESULTADOS : De los 8230 pacientes en estudio (86,7% de conversión a 2 meses) y de los 7206 testigos (83,4% de conversión), los desenlaces de fracaso o recaída definidos por la baciloscopia fueron del 3,0% en los casos de baciloscopia negativa a los 2 meses contra 3,1% en los casos de baciloscopia positiva con prolongación (diferencia no significativa, NS) y de 8,2% en los casos de baciloscopia positiva sin prolongación ($P < 0{,}00001$). Los fracasos y recaídas confirmados por cultivo alcanzaron 1,9% en los casos con baciloscopia negativa a los 2 meses y 1,6% (NS) en los casos con baciloscopia positiva a los 2 meses contra 3,7% ($P < 0{,}001$) en los casos de baciloscopia positiva a los 2 meses sin prolongación. El riesgo relativo (RR) de la falta de prolongación en los casos con baciloscopia positiva a los 2 meses fue de 2,4 (cultivos) a 2,7 (baciloscopias). Se observó igual RR y límite de significación para la ausencia de prolongación en pacientes con cepas totalmente sensibles a los medicamentos.
CONCLUSIONES : La prolongación de la fase intensiva reduce considerablemente los fracasos y recaídas de un esquema terapéutico menos potente en los casos con baciloscopia positiva a los 2 meses. La eficacia de la prolongación puede variar en función del grado inicial de resistencia a los medicamentos y de la potencia del esquema de tratamiento.