INT J TUBERC LUNG DIS 15(4):433–439

doi:10.5588/ijtld.09.0439

Evidence for promoting fixed-dose combination drugs in tuberculosis treatment and control: a review

I. Monedero,*† J. A. Caminero*‡

*MDR-TB Unit, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France; †Departament de Pediatria, Ginecologia i Medicina Preventiva, Universitat Autònoma de Barcelona, Barcelona, ‡Servicio de Neumología, Hospital General de Gran Canaria 'Dr Negrin', Las Palmas de Gran Canaria, Spain

SUMMARY

Uptake of fixed-dosed combinations (FDCs) of anti-tuberculosis drugs remains low worldwide, despite decades of recommendations. FDCs are thought to be important tools for tuberculosis (TB) control and drug resistance (DR) prevention. However, evidence relating to this is limited. This article provides a critical review of the most relevant studies on anti-tuberculosis FDCs. The majority of published studies have sought to demonstrate that FDCs and single drugs have similar efficacy. This hypothesis has been proved with relation to similar sputum conversion, cure and relapse rates in a range of studies over the last 20 years using FDCs of two, three and four anti-tuberculosis drugs. However, one of the most relevant features of FDCs, the prevention of DR, has been addressed in only one study. Nevertheless, based on their similar efficacy, user-friendliness, lower costs, and operational and logistical advantages, generalised use of FDCs should continue to be recommended.

KEY WORDS: tuberculosis; TB; fixed-dose combinations; FDC; multidrug resistance; MDR

THE FIRST and most important intervention in tuberculosis (TB) control in the community is the attainment of high cure rates. To cure as many patients as possible, two equally important measures are necessary: 1) short-course standardised treatment regimens, which are highly effective, particularly if rifampicin (RMP) is used throughout;[1] and 2) ensuring that all patients complete treatment correctly. The greatest challenge for all National Tuberculosis Programmes (NTPs) is ensuring treatment adherence. Poor adherence not only reduces cure rates, it also creates a selection of naturally resistant mutant bacilli.[2] Several methods have been adopted to ensure and facilitate the correct intake of medications during the 6–8 months of anti-tuberculosis treatment. Of these, the DOTS strategy is one of the most effective.[3] Another widely recommended intervention is the use of fixed-dose combinations (FDCs) of two anti-tuberculosis drugs (2FDCs, usually RMP + isoniazid [INH]), three drugs (3FDCs, RMP + INH + pyrazinamide [PZA]) and four drugs (4FDCs, RMP + INH + PZA + ethambutol [EMB]).

During the 1980s and 1990s, the quality of FDCs was a matter of concern, as substandard FDCs and relatively poor bioavailability of RMP were documented in the global market.[4,5] However, current FDCs are fully bioequivalent to single-drug reference products,[6–9] with stable efficacy even after 6 months in tropical conditions.[10–12]

The rationale for recommending FDCs[9,13,14] is that if all drugs are provided in the same tablet, drug selection by the patient and consequent monotherapy can be avoided. Furthermore, FDCs facilitate dosage calculation and prevent prescription errors due to the simplified, standardised chemotherapy regimens. The pill burden is also drastically reduced, increasing acceptance by patients while facilitating health education and adherence. FDCs offer several logistical advantages for NTPs, such as the facilitation of drug planning, ordering, storage and management. These improve drug handling and delivery and reduce the likelihood of drug shortages. If widely applied in the field, FDCs result in improved TB outcomes and prevent anti-tuberculosis drug resistance (DR).

As the logic that FDCs prevent selection of resistance in the field was considered unequivocal, very few doubts have been expressed about this aspect; studies undertaken in the 1980s and 1990s did not seek to demonstrate the prevention of resistance, but only their similar efficacy.

This article provides a critical review of available evidence on the efficacy and other aspects of anti-tuberculosis FDCs in comparison with separate drugs.

METHODS

A review of the literature was conducted between May and July 2009 using PubMed. The terms 'tuberculosis',

Correspondence to: Ignacio Monedero, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, 68 bd Saint-Michel, 75006 Paris, France. Tel: (+34) 928 450 563. Fax: (+34) 928 450 085. e-mail: imonedero@theunion.org

Table 1 Description and clinical outcomes of the studies reviewed

Study, reference, year, country	Design	Study duration	Intervention		Comparison		Clinical outcomes	Intervention, FDCs vs. comparison regimen, separate drugs	*P* value
			n	Treatment	*n*	Treatment			
Geiter et al.,[15] 1987, USA	RCT SAT	6 months	169	2 months 3FDC/4 months 2FDC	532	Separate drugs	Sputum conversion at 2 months	86.6% vs. 77.7%, absolute difference 8.9% (95%CI 1.1–16.7)	<0.05
Bellabas et al.,[16] 1989, Algiers	RCT DOT	2 months	125	3FDC	125	Separate drugs	Culture conversion at 2 months (193 susceptible cases)	95% vs. 91%	>0.05
Agounitestane et al.,[17] 1990, Algiers (*continuation of previous study*[16])	RCT DOT	12 months	125	2 months 3FDC/4 months 2FDC	125	2 months separate drugs/ 4 months 2FDC	Failures and relapses after 6 months among INH-susceptible patients	0% vs. 0% 0% vs. 0%	ND ND
Chaulet et al.,[18] 1995, Algiers	RCT DOT	24 months	124	2 months 3FDC	126	2 months separate drugs	Failure at 6 months and relapse at 24 months (combined)	2% vs.1%	>0.05
Hong Kong Chest Service/BMRC,[19] 1989, China	RCT DOT	2–4 months	314	2 months 3FDC + SM three times weekly	313	2 months separate drugs three times weekly	No clinical outcomes included		
Hong Kong Chest Service/BMRC,[20] 1991, China	RCT DOT	30 months follow up	420	Different treatment protocols, including 3FDC three times weekly	966	Different treatment protocols with separate drugs three times weekly	Culture conversion at 2 months Relapse after 30 months (in initially susceptible cases)	93% vs. 91% 5.1% vs. 4.6%	>0.05 >0.05
Singapore Tuberculosis Service/BMRC,[21] 1991, Singapore	RCT DOT	18 months	155	Different treatment protocols, including daily 3FDC for first 2 months	155	Same protocols with separate drugs daily for first 2 months	Culture conversion at 2 months Relapse at 18 months	96% vs. 95% 6% (n = 8) vs. 1% (n = 2)	>0.05 0.04
Teo,[22] 1999, Singapore; (*continuation of previous study*[21])	RCT DOT	60 months	155	Different treatment protocols, including daily 3FDC for first 2 months	155	Different treatment protocols with separate drugs daily for first 2 months	Relapse at 60 months (per sputum and culture)	7.9% (n = 12) vs. 2.2% (n = 3)	0.03
Zhu et al.,[23] 1998, China	RCT	6 months	227	2 months 3FDC/4 months 2FDC	81	Separate drugs	Sputum conversion 1) at 2 months 2) at 6 months CXR improvement Default rates	 91.2% vs. 86.4% 98.7% vs. 97.5% 95.2% vs. 93.8% 4.3% vs. 7.8%	 NA NA NA NA
Su & Perng,[24] 2002, Taiwan, China	RCT SAT	2 years	57	2 months 3FDC + EMB/ 4 months 2FDC	48	Separate drugs	Sputum conversion 1) at 2 months 2) at 6 months	 95.0% vs. 100% 100% vs. 100%	 >0.05 ND
Gravendeel et al.,[25] 2003, Indonesia	RCT DOT	6 months	198	Initial phase daily 4FDC/ continuation phase three times weekly 2FDC	162	Separate drugs daily	Sputum conversion at 2 months Treatment success	94% vs. 89% 95% vs. 95%	0.23 ND

Suryanto et al.,[26] 2008, Indonesia (*continuation of previous study*[25])	RCT	4.3 years	236	Initial phase 4FDC/ continuation phase three times weekly 2FDC	198	Separate drugs	Bacteriological relapse	10.1% vs. 2.7%	0.074
Moulding et al.,[27] 2004, USA	Multicentre field study/ SAT	5 years intervention 2 years follow-up	4000 (estimation)	Self-administered intermittent 2FDCs Group A: patients only on FDCs Group B: patients mostly using FDCs + all patients in Group A Group C: all patients on FDCs	1337	SAT separate drugs	Acquired drug resistance	Creation of MDR-TB: Group A: 0.1% vs. 1% Group B: 0.2% vs. 1% Group C: 0.47% vs. 1%	NK
The Union,[28,30] 2008, multicentre	Multicentre RCT DOT	6–12 months		Initial phase 4FDC/ continuation 2FDC (n = 583)		Separate drugs (n = 581)	Cure, relapse after 12 months, complaints	Preliminary results, FDC non inferior to separate drugs in cure and relapse rates after 1 year	
Bartacek et al.,[29] 2009, multicentre	Multicentre RCT	12 months	582	Initial phase 4FDC (Rimstar®)/ continuation 2FDC (Rimatazid®) Daily	577	Separate drugs Daily	Cure Relapse at 12 months	ITT: 80.4% vs. 82.7% PP: 98.1% vs. 98.6% (non inferior) ITT: 1.75% vs. 0.97% PP: 1.74% vs. 0.87% (non inferior)	

FDC = fixed-drug combination; RCT = randomised controlled trial; SAT = self-administered treatment; 3FDC = RMP+INH+PZA; 2FDC = RMP + INH; CI = confidence interval; DOT = directly observed treatment; INH = isoniazid; ND = no difference; BMRC = British Medical Research Council; EMB = ethambutol; NA = not available; SM = streptomycin; 4FDC = RMP+INH+PZA+EMB; CXR = chest X-ray; MDR-TB = multidrug-resistant tuberculosis; NK = not known; ITT = intention-to-treat population; PP = per-protocol population; RMP = rifampicin; PZA = pyrazinamide.

'fixed-dose combination', 'drug resistance', 'multidrug resistance', 'risk factor' and 'private sector' were used in a range of combinations. Two researchers selected articles by title and abstract according to their relevance to the research question. Randomised or quasi-randomised controlled trials (RCTs) and field trials that met the following review inclusion criteria were included: adult TB patients, comparisons of FDCs and single drugs and study outcome measure, including at least one of the following: smear conversion, culture, cure, relapse, adherence, side effects, acquisition of drug resistance and cost. No measures of methodological quality, language or date were applied in the selection of studies.

RESULTS

Of 15 articles published between 1987 and 2009 identified,[15–29] 12 were original research studies and the remainder were re-evaluations of previous studies at different points in time.[17,22,26] The key results and methodology of these articles are summarised in Tables 1 and 2. Almost all studies were unblinded and involved smear-positive and new, probably susceptible cases. Three studies were conducted under programme conditions, without complete directly observed treatment (DOT) or self supervision.[15,24,27] Information on treatment modality was not available for two articles,[23,29] while the remaining studies were performed under DOT and controlled study conditions.[16,18–21,25,28] Of these, one was an unpublished RCT,[28] with only preliminary results available.[30] No studies measuring the possible impact of FDCs in the private sector were found.

Studies comparing the efficacy of FDCs vs. single drugs

All the 11 original trials comparing efficacy, all of which compared sputum conversion, culture and cure rates, obtained similar results regardless of the drug formulation (no statistically significant difference at $P > 0.05$ or non-inferiority to single drugs).[15–18,20,21,23–25,27–30] Of these, only three studies compared 4FDCs, recommended in the current standard treatment regimen.[25,28,29]

Studies comparing relapses with FDCs vs. single drugs

Relapses are probably the most controversial issue in FDC use. Of the seven original studies that address this issue, six (85%) obtained a statistically ($P > 0.05$) similar number of relapses or non-inferiority after 6 months,[16,17] 12 months,[29,30] 24 months,[18] 30 months[20] and 4.3 years.[25,26] Only one trial using 3FDCs[21] found statistically significant differences ($P = 0.04$) in relapse rates 18 months after treatment initiation (6% relapses with FDCs vs. 1% with separate drugs). However, absolute numbers were small (310 total patients: 8 relapses with FDCs vs. 2 with separate drugs) and

Table 2 Other outcomes and methodological issues in the studies reviewed

Study, reference, year, country	Other outcomes	Intervention, FDCs vs. comparison regimen, separate drugs	*P* value	Methodological and results issues
Geiter et al.,[15] 1987, USA	Adherence measures (urine testing, pill counting, self reporting)	At 2 months: 96.5% vs. 98.1% At 6 months: 88.5% vs. 87.3%	>0.05 >0.05	Treatment and comparison groups enrolled at different times Exclusion and loss to follow-up >30% ITT analysis not reported
Bellabas et al.,[16] 1989, Algiers	Side effects Patient satisfaction interview	20% vs. 36% 97% vs. 95%	<0.02 >0.05	ITT analysis not reported Exclusion and loss to follow-up >20%
Agounitestane et al.,[17] 1990, Algiers (*continuation of previous study*[16])	Not measured			ITT analysis not reported Loss to follow-up >40% in clinical outcome
Chaulet et al.,[18] 1995, Algiers	Side effects at 2 months	19% vs. 36%	<0.02	ITT analysis not reported Exclusion and loss to follow-up >20%
Hong Kong Chest Service/BMRC,[19] 1989, China	Clinical side effects Difficulty swallowing Brought own drink to swallow pills	38% vs. 39% 1% vs. 5% 32% vs. 45%	>0.05 <0.05 <0.01	ITT analysis not reported
Hong Kong Chest Service/BMRC,[20] 1991, China	Not measured			Treatment and comparison groups enrolled at different times Exclusion and loss to follow-up >30% ITT analysis not reported
Singapore Tuberculosis Service/BMRC,[21] 1991, Singapore	Side effects at 2 months	8% vs. 7%	>0.05	ITT analysis not reported
Teo,[22] 1999, Singapore; (*continuation of previous study*[21])	Not measured			Re-infection not evaluated despite long-term (>2 years) relapse assessment HIV not measured in original study and follow-up population Lower number of relapses: 12 vs. 3 $P = 0.03$, 95%CIs overlap on the main result (7.9%, 95%CI 4.1–14.7 vs. 2.2%, 95%CI 0.7–6.4)
Zhu et al.,[23] 1998, China	Not measured			Limited information in methodology
Su & Perng,[24] 2002, Taiwan, China	Adherent: not lost to follow-up or no change in treatment	70.2% vs. 66.7%	>0.05	Considerable loss to follow-up (50% by 2 years) ITT analysis not reported
Gravendeel et al.,[25] 2003, Indonesia	Complaints during initial phase Gastrointestinal Muscle-joint	 41% vs. 56% 32% vs. 46%	 <0.01 <0.01	
Suryanto et al.,[26] 2008, Indonesia (*continuation of previous study*[25])	Not measured			Differential length of follow-up (0.1–5.8 years) Relapse assessment not the original design, including 74 additional patients without clear inclusion criteria Possible observation bias: proxy interviews, verbal autopsy Bacteriological measures in only 39% of the population study Re-infection not evaluated
Moulding et al.,[27] 2004, USA	Not measured			Programme conditions. Failure to find cases and migration of cases during treatment not evaluated. Numbers based on estimations. Retrospective study. Difficulties differentiating acquired from primary drug resistance (7/25 patients with acquired drug resistance were treated previously)
The Union,[28,30] 2008, multicentre	Information not available			Non-inferiority test Preliminary results
Bartacek et al.,[29] 2009, multicentre	Patient satisfaction (difficulty swallowing, number of tablets and taste) Drug-related adverse events	Statistically significant differences in PP and ITT favouring FDC 73.3% vs. 63.5%	0.03	Non-inferiority test. Missing data imputed to relapses and no information about DOT practices. Differential number of deaths not completely addressed

FDC = fixed-drug combination; ITT = intention-to-treat population; BMRC = British Medical Research Council; HIV = human immunodeficiency virus; CI = confidence interval; PP = per-protocol population; Union = International Union Against Tuberculosis and Lung Disease; DOT = directly observed treatment.

just one addition relapse could have affected the statistical significance. A re-evaluation of the cohort after 60 months[22] found greater differences ($P = 0.03$), with 12 cases on FDCs vs. 3 on separate drugs. However, the 95% confidence intervals (CIs) overlapped within the estimated proportions (7.9%, 95%CI 4.1–14.7 vs. 2.2%, 95%CI 0.7–6.4). Despite a long-term assessment of relapse (>2 years), re-infection and human immunodeficiency virus (HIV) status were not evaluated. As in the original study, slight differences could have affected the statistical significance.

The role of re-infection confirmed by DNA fingerprinting was mentioned in only one study.[30] According to the studies reviewed, FDCs and separate drugs have similar efficacy in terms of sputum conversion, cure and probably relapse rates.

DISCUSSION

Efficacy and other secondary outcomes were evaluated in the studies reviewed. Acceptability, side effects and adherence were measured in nine studies;[15,16,18,19,21,24,25,28,29] all obtained similar or better results in patients treated with FDCs. Only one study reported on the possible role of FDCs in the prevention of drug resistance, one of the principal motives for recommending FDCs worldwide.[27] This study reported lower levels of acquired DR (0.47% vs. 1%) in patients taking self-administered 2FDCs or mostly 2FDCs. Despite its limitations in methodology (Table 2), the main advantage of this study is that it reproduces the real circumstances of a well-performed NTP, without using DOT. Although all studies reported similar efficacy regardless of drug formulation, studies that included DOT[16,18–21,25,28] obtained outstanding cure rates (between 93% and 100%). Efficacy results differ widely between controlled studies and those conducted under real conditions. For example, an RCT comparing trial results with national rates found highly disparate treatment success rates (95% vs. 74%, $P < 0.01$).[25] As it was unlikely that patients enrolled in DOT-based studies would be subjected to drug shortages, prescription errors, monotherapy or allowed to select drugs, such studies measured efficacy rather than the effectiveness of FDCs as compared to single drugs.

Ten of the 22 high-burden countries reported shortages of first-line drugs to the World Health Organization (WHO) in 2007, and the logistical benefits of FDCs, which remain an unresolved issue, could play a crucial role at the policy level.[31] However, it is likely that the key issue is not the type of formulation administered, but the kind of formulation used in settings with substandard DOT.

The only study to report slightly poorer results on FDCs (relapses), mentions that when DOT is deficient, the other advantages of FDC-based regimens would probably compensate for the small difference in efficacy.[22] The WHO estimates that 37% of incident TB cases are not being treated in DOTS-based programmes.[31] It is well known, however, that DOT is incorrectly applied in many countries that apply the DOTS strategy. Moreover, DOT is rarely performed in the private sector, which covers more than 15% of the global TB burden[32] and is associated with substandard TB care.[32–35] Most low- and middle-income countries have a large and growing private sector.[34] Under suboptimal DOTS conditions, FDCs are likely to play a relevant role in cure rates and prevention of DR. However, no evidence was found in this regard. Furthermore, evidence of the prevention of DR in treatment with FDCs was limited to one study,[27] and no RCTs have been conducted to support this hypothesis. Nevertheless, effectiveness could be key in the application of this intervention given the similar efficacy of the two approaches.

Global uptake of FDCs

Although many countries have adopted FDCs over the past decades, uptake remains extremely low, despite international recommendations.[36] According to the Global Drug Facility (GDF),[36] FDCs were being used by only half of the 136 countries reporting TB to the WHO in 2007. Moreover, globally only 15% of new cases were being treated with FDCs.[36] Treatment with FDCs was infrequent not only in developing countries but also in the United States, where in 2006 the ratio of money spent on RMP was 1 to 10 for single formulations.[37] Infrequent use of FDCs in the private sector is also thought to be an important and neglected cause of DR.[27,37]

There is a multitude of potential reasons for this low uptake. Issues such as the perceived inferiority of treatment and the need for separate drugs in case of toxicity during FDC use may have discouraged NTPs. At least 2% of adults experience adverse reactions, requiring cessation of treatment and the subsequent reintroduction of treatment using separate drugs.[38] NTPs therefore always retain a certain supply of single drugs for this limited but constant number of cases.

As a disease of the poor, for many decades TB has been considered an unprofitable market, and 'old' tools such as FDCs are still unavailable in many settings. Conversely, such a prevalent disease has a potentially large treatment market, especially for FDCs.[39] A full FDC-based treatment regimen for susceptible TB patients bought through the GDF currently costs about US$22.40.[40] According to 2000 data, the cost of FDCs was approximately 50% less than for single drugs.[41] As this appears to still hold true, use of FDCs could increase access to quality TB treatment for even the poorest programmes.

Limitations

The findings of this review are subject to limitations, as most of the studies faced methodological

constraints (see Table 2), while one of the best studies[30] reported only preliminary results. Most of the studies were published 10–20 years ago and some of the compounds tested are no longer on the market in the same dosages. As the logistical advantages of FDCs remain unevaluated, it is probable that RCTs comparing FDCs and single drugs under self-administered treatment, family supervised DOT or the private sector would provide stronger evidence of their impact in terms of effectiveness and averted DR.

CONCLUSIONS

According to the studies reviewed, and taking into account their important limitations, anti-tuberculosis FDCs appear to have similar clinical efficacy to separate drugs in terms of sputum conversion, cure and probably relapse rates. The role of FDCs in averting drug resistance by preventing monotherapy and patient selection remains unclear, and evidence was reduced to a single, limited study. Other issues, such as acceptability, adherence, logistical or operational advantages and costs, make FDCs a better option than single drugs. Nevertheless, global uptake of anti-tuberculosis FDCs remains extremely low. If FDCs and separate drugs deliver the same outcomes and secondary issues favour FDCs, global access to FDCs should be advocated. Promotion should be particularly strong in those settings where DOT is not fully guaranteed, such as the private sector and weaker health care systems.

Acknowledgement

The authors thank C Merle from the London School of Hygiene & Tropical Medicine for her support and guidance during the initial planning of this review.

References

1 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.
2 Mitchison D A. How drug resistance emerges as a result of poor compliance during short course chemotherapy of tuberculosis. Int J Tuberc Lung Dis 1998; 2: 10–15.
3 Caminero Luna J A. A tuberculosis guide for specialist physicians. Paris, France: International Union Against Tuberculosis and Lung Disease, 2004.
4 Pillai G, Fourie P B, Padayatchi N, et al. Recent bioequivalence studies on fixed-dose combination anti-tuberculosis drug formulations available on the global market. Int J Tuberc Lung Dis 1999; 3 (Suppl 3): S309–S316; discussion S17–S21.
5 Laserson K F, Kenyon A S, Kenyon T A, Layloff T, Binkin N J. Substandard tuberculosis drugs on the global market and their simple detection. Int J Tuberc Lung Dis 2001; 5: 448–454.
6 Agrawal S, Singh I, Kaur K J, Bhade S R, Kaul C L, Panchagnula R. Comparative bioavailability of rifampicin, isoniazid and pyrazinamide from a four drug fixed dose combination with separate formulations at the same dose levels. Int J Pharm 2004; 276: 41–49.
7 Panchagnula R, Agrawal S, Kaur K J, Singh I, Kaul C L. Evaluation of rifampicin bioequivalence in fixed-dose combinations using the WHO/IUATLD recommended protocol. Int J Tuberc Lung Dis 2000; 4: 1169–1172.
8 Agrawal S, Kaur K J, Singh I, Bhade S R, Kaul C L, Panchagnula R. Assessment of bioequivalence of rifampicin, isoniazid and pyrazinamide in a four drug fixed dose combination with separate formulations at the same dose levels. Int J Pharm 2002; 233: 169–177.
9 Blomberg B, Fourie B. Fixed-dose combination drugs for tuberculosis: application in standardised treatment regimens. Drugs 2003; 63: 535–553.
10 Bhutani H, Mariappan T T, Singh S. The physical and chemical stability of anti-tuberculosis fixed-dose combination products under accelerated climatic conditions. Int J Tuberc Lung Dis 2004; 8: 1073–1080.
11 Ashokraj Y, Kohli G, Kaul C L, Panchagnula R. Quality control of anti-tuberculosis FDC formulations in the global market: Part II. Accelerated stability studies. Int J Tuberc Lung Dis 2005; 9: 1266–1272.
12 Gabriels G A, McIlleron H, Smith P J, Folb PI, Fourie P B. Modification to improve efficiency of sampling schedules for BA/BE testing of FDC anti-tuberculosis drugs. Int J Tuberc Lung Dis 2007; 11: 181–188.
13 Chaulet P. Implementation of fixed-dose combinations in tuberculosis control: outline of responsibilities. Int J Tuberc Lung Dis 1999; 3 (Suppl 3): S353–S357; discussion S381–S387.
14 Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. Bull World Health Organ 2001; 79: 61–68.
15 Geiter L J, O'Brien R J, Combs D L, Snider D E Jr. United States Public Health Service Tuberculosis Therapy Trial 21: preliminary results of an evaluation of a combination tablet of isoniazid, rifampin and pyrazinamide. Tubercle 1987; 68 (Suppl): S41–S46.
16 Bellabas M, Khaled S, Aït-Khaled N, Boulahbal F, Chaulet P. [Therapeutic trial of a combination of isoniazid, rifampicin and pyrazinamide in the first 2 months of treatment of pulmonary tuberculosis]. Rev Mal Respir 1989; 6: 59–64. [French]
17 Agounitestane D, Chiheb M, Khaled S, Aït-Khaled N, Boulahbal F, Chaulet P. [A therapeutic trial of a combination of 3 essential drugs in a short course of chemotherapy in tuberculosis. Results 6 months after the end of treatment]. Rev Mal Respir 1990; 7: 209–213. [French]
18 Chaulet P, Boulahbal F. [Clinical trial of a combination of three drugs in fixed proportions in the treatment of tuberculosis. Groupe de Travail sur la Chimiotherapie de la Tuberculose]. Tubercle Lung Dis 1995; 76: 407–412. [French]
19 Acceptability, compliance, and adverse reactions when isoniazid, rifampin, and pyrazinamide are given as a combined formulation or separately during three-times-weekly antituberculosis chemotherapy. Hong Kong Chest Service/British Medical Research Council. Am Rev Respir Dis 1989; 140: 1618–1622.
20 Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. Hong Kong Chest Service/British Medical Research Council. Am Rev Respir Dis 1991; 143 (4 Pt 1): 700–706.
21 Assessment of a daily combined preparation of isoniazid, rifampin, and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. Am Rev Respir Dis 1991; 143 (4 Pt 1): 707–712.
22 Teo S K. Assessment of a combined preparation of isoniazid, rifampicin and pyrazinamide (Rifater) in the initial phase of chemotherapy in three 6-month regimens for smear-positive pulmonary tuberculosis: a five-year follow-up report. Int J Tuberc Lung Dis 1999; 3: 126–132.
23 Zhu L, Yan B, Ma W. [Controlled clinical study on efficacy

of fixed-dose compounds rifater/rifinah in antituberculous chemotherapy]. Zhonghua Jie He He Hu Xi Za Zhi 1998; 21: 645–647. [Chinese]
24 Su W J, Perng R P. Fixed-dose combination chemotherapy (Rifater/Rifinah) for active pulmonary tuberculosis in Taiwan: a two-year follow-up. Int J Tuberc Lung Dis 2002; 6: 1029–1032.
25 Gravendeel J M, Asapa A S, Becx-Bleumink M, Vrakking H A. Preliminary results of an operational field study to compare side-effects, complaints and treatment results of a single-drug short-course regimen with a four-drug fixed-dose combination (4FDC) regimen in South Sulawesi, Republic of Indonesia. Tuberculosis (Edinb) 2003; 83: 183–186.
26 Suryanto A A, van den Broek J, Hatta M, de Soldenhoff R, van der Werf M J. Is there an increased risk of TB relapse in patients treated with fixed-dose combination drugs in Indonesia? Int J Tuberc Lung Dis 2008; 12: 174–179.
27 Moulding T S, Le H Q, Rikleen D, Davidson P. Preventing drug-resistant tuberculosis with a fixed dose combination of isoniazid and rifampin. Int J Tuberc Lung Dis 2004; 8: 743–748.
28 International Union Against Tuberculosis and Lung Disease. Multicentre trial for the evaluation of a fixed dose combined tablet for the treatment of pulmonary tuberculosis. Paris, France: The Union, 2007. http://clinicaltrials.gov/show/NCT00216333 Accessed January 2011.
29 Bartacek A, Schutt D, Panosch B, Borek M. Comparison of a four-drug fixed-dose combination regimen with a single tablet regimen in smear-positive pulmonary tuberculosis. Int J Tuberc Lung Dis 2009; 13: 760–766.
30 Lienhardt C, Cook S, Yorke-Edwards V, et al. Investigation of the safety and efficacy of a 4-FDC for the treatment of tuberculosis (Study C): methods and preliminary results of the 12 month follow-up of patients. 39th Union World Conference on Lung Health, Paris, France: 2008. Int J Tuberc Lung Dis 2008; 12 (Suppl 2): S46. [Symposium Abstract]
31 World Health Organization. Global tuberculosis control: epidemiology, strategy, financing. WHO report 2009. WHO/HTM/TB/2009.411. Geneva, Switzerland: WHO, 2009. http://www.who.int/tb/publications/global_report/2009/en/index.html Accessed February 2010.
32 World Health Organization. Anti-tuberculosis drug resistance in the world. Report no 3. WHO/HTM/TB/2004.343. Geneva, Switzerland: WHO, 2004.
33 Uplekar M, Lönnroth K. MDR and XDR—the price of delaying engagement with all care providers for control of TB and TB/HIV. Trop Med Int Health 2007; 12: 473–474.
34 Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. Lancet 2001; 358: 912–916.
35 Uplekar M. Involving private health care providers in delivery of TB care: global strategy. Tuberculosis (Edinb) 2003; 83: 156–164.
36 Matiru R. Marking up the medicines. Geneva, Switzerland: Global Drug Facility, 2008: pp 1–2. http://www.stoptb.org/assets/documents/gdf/whatis/Marking%20up%20the%20Medicine.pdf Accessed January 2011.
37 Moulding T. Failure to mention fixed-dose drug combinations in the ATS/CDC/IDSA tuberculosis control statement. Am J Respir Crit Care Med 2006; 173: 684; author reply: 684–685.
38 Hinderaker S G, Ysykeeva J, Veen J, Enarson D A. Serious adverse reactions in a tuberculosis programme setting in Kyrgyzstan. Int J Tuberc Lung Dis 2009; 13: 1560–1562.
39 Norval P Y, Blomberg B, Kitler M E, Dye C, Spinaci S. Estimate of the global market for rifampicin-containing fixed-dose combination tablets. Int J Tuberc Lung Dis 1999; 3 (Suppl 3): S292–S300; discussion S317–S321.
40 Stop TB Partnership. TB facts and figures. Geneva, Switzerland: WHO, 2009. http: //www.stoptb.org/gdf/whatis/facts_and_figures. asp Accessed July 2010.
41 Laing R O, McGoldrick K M. Tuberculosis drug issues: prices, fixed-dose combination products and second-line drugs. Int J Tuberc Lung Dis 2000; 4 (Suppl 2): S194–S207.

RÉSUMÉ

En dépit de décennies de recommandations, l'utilisation de combinaisons de médicaments antituberculeux à dose fixe (FDC) reste faible au niveau mondial. Les FDC sont considérées comme des outils importants pour la lutte antituberculeuse et la prévention de la résistance aux médicaments. Toutefois, les éléments probants sont limités à ce sujet. Cet article constitue une revue critique des études les plus pertinentes concernant les FDC antituberculeuses. La grande majorité des études publiées ont cherché à démontrer que les FDC et les médicaments isolés ont une efficacité similaire. Cette hypothèse a été démontrée par une négativation similaire des expectorations et des taux similaires de guérison et de rechute dans une série d'expériences au cours des 20 dernières années utilisant des FDC avec deux, trois ou quatre médicaments antituberculeux. Toutefois, une des caractéristiques les plus importantes des FDC est d'éviter la résistance ; celle-ci n'a été envisagée que dans une seule étude. Néanmoins, en se basant sur une efficacité similaire, la facilité d'emploi, les coûts plus faibles, les avantages opérationnels et logistiques, il y a lieu de continuer à recommander la généralisation des FDC.

RESUMEN

A pesar de décadas de recomendaciones, el uso de medicación anti-tuberculosa en combinaciones de dosis fijas (FDC) sigue siendo bajo a nivel mundial. Se cree que los FDC son herramientas importantes en el control de la tuberculosis y en la prevención de resistencias. Sin embargo, las evidencias al respecto son limitadas. Este artículo proporciona una revisión crítica de los estudios más relevantes sobre los FDC de medicamentos antituberculosos. La gran mayoría de los estudios publicados ha buscado demostrar que los FDC y los medicamentos sueltos tienen la misma eficacia. Esta hipótesis se ha comprobado en relación a la conversión del esputo, tasas de curación y recaídas en distintas experiencias durante los últimos 20 años usando FDC de dos, tres y cuatro medicamentos anti-tuberculosos. No obstante, una de las características más relevantes de los FDC, la capacidad para evitar resistencias medicamentosas, solo ha sido tratada en un estudio. A pesar de ello, basado en similar eficacia, uso sencillo, menor coste y ventajas logísticas y operacionales, el uso generalizado de los FDC debería continuar recomendándose.