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

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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; 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. 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. 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. However, current FDCs are fully bioequivalent to single-drug reference products, with stable efficacy even after 6 months in tropical conditions.

The rationale for recommending FDCs 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’,...
Table 1  Description and clinical outcomes of the studies reviewed

<table>
<thead>
<tr>
<th>Study, reference, year, country</th>
<th>Design</th>
<th>Study duration</th>
<th>Intervention</th>
<th>n</th>
<th>Treatment</th>
<th>Comparison</th>
<th>n</th>
<th>Treatment</th>
<th>Clinical outcomes</th>
<th>Intervention, FDCs vs. comparison regimen, separate drugs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geiter et al.,15 1987, USA</td>
<td>RCT</td>
<td>6 months</td>
<td>2 months 3FDC/4 months 2FDC</td>
<td>169</td>
<td></td>
<td>Separate drugs</td>
<td>532</td>
<td></td>
<td>Sputum conversion at 2 months</td>
<td>86.6% vs. 77.7%, absolute difference 8.9% (95%CI 1.1–16.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Bellabas et al.,16 1989, Algiers</td>
<td>RCT</td>
<td>2 months</td>
<td>3FDC</td>
<td>125</td>
<td></td>
<td>Separate drugs</td>
<td>125</td>
<td></td>
<td>Culture conversion at 2 months</td>
<td>95% vs. 91%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Agouni testane et al.,17 1990, Algiers (continuation of previous study16)</td>
<td>RCT</td>
<td>12 months</td>
<td>2 months 3FDC/4 months 2FDC</td>
<td>125</td>
<td></td>
<td>2 months separate drugs/4 months 2FDC</td>
<td>125</td>
<td></td>
<td>Failures and relapses after 6 months among INH-susceptible patients</td>
<td>0% vs. 0%</td>
<td>ND</td>
</tr>
<tr>
<td>Chaulet et al.,18 1995, Algiers</td>
<td>RCT</td>
<td>24 months</td>
<td>2 months 3FDC</td>
<td>124</td>
<td></td>
<td>2 months separate drugs</td>
<td>126</td>
<td></td>
<td>Failure at 6 months and relapse at 24 months (combined)</td>
<td>2% vs. 1%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hong Kong Chest Service/BMRC,19 1989, China</td>
<td>RCT</td>
<td>2-4 months</td>
<td>2 months 3FDC + SM three times weekly</td>
<td>314</td>
<td></td>
<td>2 months separate drugs three times weekly</td>
<td>313</td>
<td></td>
<td>No clinical outcomes included</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Hong Kong Chest Service/BMRC,20 1991, China</td>
<td>RCT</td>
<td>30 months follow up</td>
<td>Different treatment protocols, including 3FDC three times weekly</td>
<td>420</td>
<td></td>
<td>Different treatment protocols with separate drugs three times weekly</td>
<td>966</td>
<td></td>
<td>Culture conversion at 2 months</td>
<td>93% vs. 91%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Singapore Tuberculosis Service/BMRC,21 1991, Singapore</td>
<td>RCT</td>
<td>18 months</td>
<td>Different treatment protocols, including daily 3FDC for first 2 months</td>
<td>155</td>
<td></td>
<td>Same protocols with separate drugs daily for first 2 months</td>
<td>155</td>
<td></td>
<td>Culture conversion at 2 months</td>
<td>96% vs. 95%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Teo,22 1999, Singapore; (continuation of previous study21)</td>
<td>RCT</td>
<td>60 months</td>
<td>Different treatment protocols, including daily 3FDC for first 2 months</td>
<td>155</td>
<td></td>
<td>Different treatment protocols with separate drugs daily for first 2 months</td>
<td>155</td>
<td></td>
<td>Relapse at 60 months (per sputum and culture)</td>
<td>7.9% (n = 12) vs. 2.2% (n = 3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Zhu et al.,23 1998, China</td>
<td>RCT</td>
<td>6 months</td>
<td>2 months 3FDC/4 months 2FDC</td>
<td>227</td>
<td></td>
<td>Separate drugs</td>
<td>81</td>
<td></td>
<td>Sputum conversion</td>
<td>91.2% vs. 86.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Su &amp; Perng,24 2002, Taiwan, China</td>
<td>RCT</td>
<td>2 years</td>
<td>2 months 3FDC + EMB/4 months 2FDC</td>
<td>57</td>
<td></td>
<td>Separate drugs</td>
<td>48</td>
<td></td>
<td>Sputum conversion</td>
<td>95.0% vs. 100%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gravendeel et al.,25 2003, Indonesia</td>
<td>RCT</td>
<td>6 months</td>
<td>Initial phase daily 4FDC/continuation phase three times weekly 2FDC</td>
<td>198</td>
<td></td>
<td>Separate drugs daily</td>
<td>162</td>
<td></td>
<td>Sputum conversion at 2 months</td>
<td>94% vs. 89%</td>
<td>0.23</td>
</tr>
</tbody>
</table>
RESULTS

Of 15 articles published between 1987 and 2009, 12 were original research studies identified. Two trials were reevaluations of previous studies and the remainder were meta-analyses of previous studies conducted under DOT and controlling study conditions. The key results and competing hypotheses of these articles are summarised in Table 1. Three studies were controlled under programme conditions, without complete directly observed treatment (DOT), while the remaining studies were controlled under DOT. The main focus of these studies was to evaluate the possible impact of FDCs in the private sector, including at least one of the following: smear conversion, culture, cure, relapse-free survival, side effects, adherence, acquisition cost, treatment failure rate, and single-drug resistance. No measures of methodological quality or date were applied in the selection of studies.
Table 2  Other outcomes and methodological issues in the studies reviewed

<table>
<thead>
<tr>
<th>Study, reference, year, country</th>
<th>Other outcomes</th>
<th>Intervention, FDCs vs. comparison regimen, separate drugs</th>
<th>P value</th>
<th>Methodological and results issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geiter et al.,15 1987, USA</td>
<td>Adherence measures (urine testing, pill counting, self reporting)</td>
<td>At 2 months: 96.5% vs. 98.1% At 6 months: 88.5% vs. 87.3%</td>
<td>&gt;0.05</td>
<td>Treatment and comparison groups enrolled at different times</td>
</tr>
<tr>
<td>Bellabas et al.,16 1989, Algiers</td>
<td>Side effects</td>
<td>Patient satisfaction interview</td>
<td>20% vs. 36% 97% vs. 95%</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Agouni et al.,17 1990, Algiers (continuation of previous study16)</td>
<td>Not measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chaulet et al.,18 1995, Algiers</td>
<td>Side effects at 2 months</td>
<td></td>
<td>19% vs. 36%</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Hong Kong Chest Service/BMRC,19 1989, China</td>
<td>Clinical side effects</td>
<td>Difficulty swallowing Brought own drink to swallow pills</td>
<td>38% vs. 39% 1% vs. 5% 32% vs. 45%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hong Kong Chest Service/BMRC,20 1991, China</td>
<td>Not measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singapore Tuberculosis Service/BMRC,21 1991, Singapore</td>
<td>Side effects at 2 months</td>
<td></td>
<td>8% vs. 7%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Teo,22 1999, Singapore; (continuation of previous study21)</td>
<td>Not measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhu et al.,23 1998, China</td>
<td>Not measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su &amp; Perng,24 2002, Taiwan, China</td>
<td>Adherent: not lost to follow-up or no change in treatment</td>
<td></td>
<td>70.2% vs. 66.7%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gravendeel et al.,25 2003, Indonesia</td>
<td>Complaints during initial phase</td>
<td>Gastrointestinal Muscle-joint</td>
<td>41% vs. 56% 32% vs. 46%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Suryanto et al.,26 2008, Indonesia (continuation of previous study25)</td>
<td>Not measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moulding et al.,27 2004, USA</td>
<td>Not measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Union,28,30 2008, multicentre</td>
<td>Information not available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bartacek et al.,29 2009, multicentre</td>
<td>Patient satisfaction (difficulty swallowing, number of tablets and taste) Drug-related adverse events</td>
<td>Statistically significant differences in PP and ITT favouring FDC 73.3% vs. 63.5%</td>
<td>0.03</td>
<td>Non-inferiority test. Missing data imputed to relapses and no information about DOT practices. Differential number of deaths not completely addressed</td>
</tr>
</tbody>
</table>

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 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. 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, 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. 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 all obtained similar or better results in patients treated with FDCs. Only one study reported outcomes of patients taking self-administered 2FDCs or mostly 2FDCs. Despite its limitations in methodology, 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 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%, $P < 0.01$). As it was unlikely that patients enrolled in DOT-based studies would 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. According to the Global Drug Facility (GDF), 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. 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. Intermittent use of FDCs in the private sector is also thought to be an important and neglected cause of DR.

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. 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. A full FDC-based treatment regimen for susceptible TB patients bought through the GDF currently costs about US$22.40. According to 2000 data, the cost of FDCs was approximately 50% less than for single drugs. 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
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

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References

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]


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.