

Online Supplementary information:

Fixed Dose Combination Anti-tuberculosis Therapy: A Systematic Review and Meta-Analysis

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Literature Searches

Literature searches were conducted in the following databases:

- Medline (Ovid platform)
- Medline In-Process or other Non-Indexed Citations (Ovid platform)
- Embase (Ovid platform)
- Cochrane Library (published by Wiley) which includes Cochrane Reviews, DARE, and Central Register of Controlled Clinical Trials. The Cochrane Infectious Diseases Group Specialized Register was double-checked separately.
- LILACS (BIREME - PAHO – WHO Latin-American and Caribbean Center on Health Sciences Information)

Search terms included both subject headings, where available, and textwords (ie words in titles, subjects, abstracts, substance terms, etc.)

	Medline (Ovid) – MeSH terms in upper case; other terms are keywords (.mp)	Embase (Ovid) – Embase terms in upper case; other terms are keywords (.mp)
1	EXP TUBERCULOSIS/DT <i>or</i> EXP ANTITUBERCULAR AGENTS <i>or</i> MYCOBACTERIUM TUBERCULOSIS/DE <i>or</i> tuberculosis <i>and</i> drug <i>adj</i> (therapy <i>or</i> effect*) <i>or</i> antitubercul* <i>or</i> tuberculostatic <i>or</i> (anti <i>adj</i> tubercul*)	EXP TUBERCULOSIS/DT <i>or</i> EXP TUBERCULOSTATIC AGENT <i>or</i> MYCOBACTERIUM TUBERCULOSIS/DT <i>or</i> tuberculosis <i>and</i> drug <i>adj</i> (therapy <i>or</i> effect*) <i>or</i> antitubercul* <i>or</i> tuberculostatic <i>or</i> (anti <i>adj</i> tubercul*)
2	isoniazid <i>and</i> (rifampin <i>or</i> rifampicin)	isoniazid <i>and</i> (rifampin <i>or</i> rifampicin)
3	DRUG COMBINATIONS <i>or</i> fdc <i>or</i> 4fdc <i>or</i> 3fdc <i>or</i> (fixed <i>or</i> multiple <i>or</i> combin*) <i>adj3</i> (drug* <i>or</i> dose* <i>or</i> dosage* <i>or</i> formula* <i>or</i> preparat* <i>or</i> regimen*)	DRUG COMBINATION <i>or</i> fdc <i>or</i> 4fdc <i>or</i> 3fdc <i>or</i> (fixed <i>or</i> multiple <i>or</i> combin*) <i>adj3</i> (drug* <i>or</i> dose* <i>or</i> dosage* <i>or</i> formula* <i>or</i> preparat* <i>or</i> regimen*)
4	1980-current <i>and</i> human	1980-current <i>and</i> human
	1 <i>and</i> 2 <i>and</i> 3 <i>and</i> 4: 1716 hits (July 27, 2011)	1 and 2 and 3 and 4: 1271 hits (July 28, 2011)

	Medline In-Process – all textwords	Cochrane Library - MeSH terms in upper case; other terms "textword"
1	tuberculosis	EXP TUBERCULOSIS/DT EXP ANTITUBERCULAR AGENTS MYCOBACTERIUM TUBERCULOSIS/DE <i>or</i> tuberculosis <i>and</i> drug <i>NEXT</i> (therapy or effect*) <i>or</i> antitubercul* <i>or</i> tuberculostatic <i>or</i> anti <i>NEXT</i> tubercul*
2	drug adj (therapy <i>or</i> effect*) <i>or</i> antitubercul* <i>or</i> tuberculostatic <i>or</i> (anti adj tubercul*)	
3	isoniazid <i>and</i> (rifampin <i>or</i> rifampicin)	isoniazid <i>and</i> (rifampin <i>or</i> rifampicin)
4	fdc <i>or</i> 4fdc <i>or</i> 3fdc <i>or</i> (fixed <i>or</i> multiple <i>or</i> combin*) <i>adj3</i> (drug* <i>or</i> dose* <i>or</i> dosage* <i>or</i> formula* <i>or</i> preparat* <i>or</i> regimen*)	DRUG COMBINATIONS <i>or</i> fdc <i>or</i> 4fdc <i>or</i> 3fdc <i>or</i> (fixed <i>or</i> multiple <i>or</i> combin*) <i>NEAR/3</i> (drug* <i>or</i> dose* <i>or</i> dosage* <i>or</i> formula* <i>or</i> preparat* <i>or</i> regimen*)
5	(limits n/a)	1980-2011
	1 <i>and</i> 2 <i>and</i> 3 <i>and</i> 4: 11 hits (July 28, 2011)	1 <i>and</i> 3 <i>and</i> 4 <i>and</i> 5: 258 hits (July 27, 2011) Cochrane Reviews = 10 DARE = 5 CCRCT = 232 Economic Evaluations = 10

LILACS (http://lilacs.bvsalud.org/en/) – all terms searched as “word”	
1	tubercul\$ <i>or</i> antitubercul\$
2	isoniazid <i>and</i> (rifampin or rifampicin)
3	combin\$ <i>or</i> fdc
	1 <i>and</i> 2 <i>and</i> 3: 38 hits (July 27, 2011)

All results were exported to EndNote™ Bibliographic Management software. Approximately 2450 references were retained after duplicates were removed.

Table S1. Summary of the included cohort and non-comparative studies.

Author	Public. year	Study place	Age (Mean)	Male (%)	Treat. regimen	FDC formula	DOT	Allocation sequence ^a	Follow-up completion ^b	Non-selective outcomes ^c	Free of bias ^d
Non-comparative RCTs (no direct comparison between FDC and SDF)											
Brändli et al ^{1,2}	1993	Switzerland	48	71	HR±Z ^e	Rifater/Rimactazid	NS	Unclear	Yes	Unclear	Yes
Punnotok et al ³	1995	Thailand	35	68	HRZ	Rifater/Rifinah	No	Yes	Yes	Yes	Yes
Cohort studies											
Churchyard et al ⁴	2000	South Africa	41	NS	HRZ	NS	Yes	Yes	Unclear	Yes	Unclear
Sokolova et al ⁵	2002	Russia	NS	NS	HRZE	Myrin P	NS	Unclear	Unclear	Unclear	Unclear

Abbreviations: FDC, fixed dose combination; DOT, direct observed therapy; H, isoniazid; R, rifampicin; Z, pyrazinamide; NS, not specified.

Notes: ^a Consequence of subject recruitment; ^b Complete follow up for at least 75% of subjects, and assessment of the reasons for incomplete follow up; ^c free of selective outcome (i.e. reporting all expected or pre-specified outcomes); ^d equivalent subject characteristics and management between comparison groups, and the sample population has no specific risks that could influence their treatment outcomes; ^e either 9 months HR regimen or 6 months HRZ regimen.

Table S2. Individual study results of the comparative cohort and non-comparative studies.

Outcomes	No. of studies	FDC group		Separate drug formula group		RR (95%CI) ^a
		No. of subjects	% (95% CI)	No. of subjects	% (95% CI)	
Treatment failure or disease relapse						
<i>Sokolova et al (cohort) –DS</i>	1	258	5 (2.7, 8.5)	110	10.9 (5.9, 18.3)	0.46 (0.2, 0.98)
<i>Sokolova et al (cohort) –DR</i>	1	19	21 (6, 46)	87	35 (25, 45)	0.61 (0.24, 1.53)
<i>Brändli et al (non-comparative) ^b</i>	1	213	0.5 (0.01, 2.6)	No comparative group		
<i>Punnotok et al (non-comparative)</i>	1	97	2 (0.3, 7.3)	No comparative group		
<i>Churchyard et al (non-comparative) ^b</i>	1	1888	1.5 (1, 2)	No comparative group		
Acquired drug resistance						
<i>Brändli et al (non-comparative) ^b</i>	1	213	0 (0, 1.7)	No comparative group		
<i>Churchyard et al (non-comparative) ^b</i>	1	1888	0.26 (0.1, 0.6)	No comparative group		
TB culture conversion after 2 months of treatment						
<i>Punnotok et al (non-comparative)</i>	1	97	99 (94, 100)	No comparative group		
Adverse drug reaction						
<i>Punnotok et al (non-comparative)</i>	1	98	32 (23, 42)	No comparative group		
Patients' adherence to treatment						
<i>Churchyard et al (non-comparative) ^c</i>	1	1601	99.5 (99, 100)	No comparative group		

Abbreviations: FDC, fixed dose combination; CI, confidence interval; RR, risk ratio; DS, drug sensitive; DR, drug resistant; TB, tuberculosis. **Notes:** ^a RR measurements are limited to the comparative cohort; ^b drug resistant TB cases were excluded; ^c assessment of adherence was based on the duration of treatment interruption (less than 2 months).

Supplementary references:

1. Brändli O, Dreher D, Morger D. [Results of short-term tuberculosis therapy with isoniazid, rifampicin and pyrazinamide]. *Schweiz Med Wochenschr.* 1993 Jun 26;123(25):1300-6.
2. Brändli O, Haegi V, Villiger B, Bohn W, Baumann HR, Zäch R. [Short-term therapy of lung tuberculosis using a fixed combination of isoniazid, rifampicin and pyrazinamide. Results after 2 years]. *Schweiz Med Wochenschr.* 1989 Mar 11;119(10):299-305.
3. Punnotok J, Pumprueg U, Chakorn T. A comparison of two short course tuberculosis chemotherapy regimens, both using Rifater during an intensive phase, with a 3 year follow-up. *J Med Assoc Thai.* 1995 Jun;78(6):298-304.
4. Churchyard GJ, Corbett EL, Kleinschmidt I, Mulder D, De Cock KM. Drug-resistant tuberculosis in South African gold miners: incidence and associated factors. *Int J Tuberc Lung Dis.* 2000 May;4(5):433-40.
5. Sokolova GB, Semenova OV, Bogadel'nikova IV, Kunichan AD, Zeligier LR, Elistratova NA. [Myrin P in the combined treatment of tuberculosis]. *AntibiotKhimioter.* 2002;47(6):22-7.