1 Appendix D: Evidence Tables – Treatment of drug-resistant TB (RQs U, V & W)

A.1 RQs U, V & W: treatment regimens for drug-resistant TB

A.1.1 Babu Swai et al, 1988

Bibliographic reference	Babu Swai O, Aluoch JA, Githui WA et al (1988) Controlled clinical trial of a regimen of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. Tubercle 69:5-14
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: • Used, rifampicin, ethambutol, pyrazinamide (and streptomycin) Randomisation by consecutive allocation, appears unblinded (blinding is unclear) No allocation concealment Unclear if groups were comparable at baseline Subjective nature of exclusion criteria No sample size calculation/analysis Bacteriological assessment during first 6mths of treatment not stratified by treatment group Definition for doubtful response unclear Not ITT, exclusions made after admission to study Clear definitions were not provided for adverse reactions
Number of patients	n = 306 (admitted to study October 1978 – March 1982), n=80 excluded, n=226 in analysis • 4RE = 113 • 7RE = 113
Patient characteristics	*Inclusion*

	5 provincial hospitals ≥15yrs Sputum positive on smear, strains resistant to isoniazid, or isoniazid and streptomycin *Exclusion* >3km from a health unit Very poor general condition or required additional measures for survival Co-existing extra-pulmonary lesions other than lymphadenopathy, and those with non-TB disease likely to prejudice the response to or assessment of treatment (of those admitted to the study 56 excluded pretreatment) During outpatient phase patients received drugs under direct supervision of an appointed member of staff in the health unit nearest to their home
Intervention	*Initial 8-wk intensive phase (in-patient)* Streptomycin: 1.0g daily (0.75g for >40yrs, or <33kg pretreatment) Pyrazinamide: 1.5g (<50kg pretreatment), 2.0g (heavier patients) Rifampicin: 450mg (<50kg pretreatment), 600mg (heavier patients) Ethambutol: 25mg/kg for first 8wks, 15mg/kg after *Followed by (out-patient)* Rifampicin and ethambutol daily for 4mths (4RE) series
Comparison	*Initial 8-wk intensive phase (in-patient)* Streptomycin: 1.0g daily (0.75g for >40yrs, or <33kg pretreatment) Pyrazinamide: 1.5g (<50kg pretreatment), 2.0g (heavier patients)

	Rifampicin: 450mg (<50kg pretreatment), 600mg (heavier patients) Ethambutol: 25mg/kg for first 8wks, 15mg/kg after *Followed by(out-patient)* Rifampicin and ethambutol daily for 7mths (7RE) series
Length of follow up	Assessed mthly up to 12mths, 3-mthly up to 30mths (24mths after the end of chemotherapy)
Location	Kenya
Outcomes measures and effect size	Unfavourable status; sputum culture positive at the end of chemotherapy **Status at end of treatment** N=226 Resistant to isoniazid, n=179/226 Resistant to streptomycin, n=47/226 • 4RE group, initially resistant to isoniazid; n=91, n=90 favourable response, n=1 doubtful response (mixture of positive and negative culture growth during the study), n=0 unfavourable response (sputum culture positive at the end of chemotherapy) • 4RE group, initially resistant to isoniazid and streptomycin; n=22, n=20 favourable response, n=1 doubtful response (mixture of positive and negative culture growth during the study), n=1 unfavourable response (sputum culture positive at the end of chemotherapy) • 7RE group, initially resistant to isoniazid; n=88, n=80 favourable response, n=7 doubtful response (mixture of positive and negative culture growth during the study), n=1 unfavourable response (sputum culture positive at the end of chemotherapy) • 7RE group, initially resistant to isoniazid and streptomycin; n=25, n=25 favourable response • 4RE group overall, n=113, n=110 favourable response, n=2 doubtful response (mixture of positive and negative culture growth during the study), n=1 unfavourable response (sputum culture positive at the end of chemotherapy)

	• 7RE group overall, n=113, n=105 favourable response, n=7 doubtful response (mixture of positive and negative culture growth during the study), n=1 unfavourable response (sputum culture positive at the end of chemotherapy) 4RE compared with 7RE for favourable response, OR[1] (95% CI) = 2.44 (0.62, 9.70)
	Relapse N=178 (78.8%) in the relapse analysis (n=86 4RE, n=92 7RE). Bacteriological relapse defined as ≥2 cultures of ≥0 colonies growth at different mths in any 3-mth period or ≥3 positive cultures of any growth at different mths in any 4-mth period Number of patients to experience relapse • 4RE = 6/86 • 7RE = 2/92 • OR[1] (95% CI) = 3.21 (0.63 to 16.33) Resistant to isoniazid; n=5/144, 3% relapsed Resistant to isoniazid and streptomycin; n=3/34, 9% relapsed (excluded from the relapse analysis; n=6 resistant to rifampicin, ethambutol or both, n=2/6 relapsed)
	Adverse reactions N=2 considered to have had adverse reactions, n=1 4RE arthralgia, responded to treatment without change in regimen, n=1 7RE hypersensitivity to streptomycin, regimen changed
	Development of resistance n=1/2 of the patients with an unfavourable response at the end of treatment, had an initial resistance to isoniazid and streptomycin with resistance to rifampicin found at month 3 and ethambutol at month 7 There was no evidence of further resistance found in the n=9 with doubtful response
Source of funding	No details given

Comments	
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer	

A.1.2 Balasubramanian et al, 1990

Bibliographic reference	Balasubramanian R, Sivasubramanian S, Vijayan VK et al (1990) Five year results of a 3-month and two 5-month regimens for the treatment of sputum-positive pulmonary tuberculosis in South India. Tubercle 71:253-258
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest • Used, rifampicin, isoniazid, pyrazinamide (and streptomycin) Randomisation, no details of randomisation given (no details of any blinding, so unclear) No allocation concealment Unclear if groups were comparable at baseline, baseline characteristics not reported Supervision of treatment not detailed
Number of patients	n = 469 (405 drug sensitive, 64 DR) DR (17 resistant to streptomycin, 25 to isoniazid, 21 to streptomycin and isoniazid, 1 to rifampicin) • R3 = 20 • R5 = 28 • Z5 = 16
Patient characteristics	*Inclusion* Newly diagnosed pulmonary TB Sputum positive, ≥cultures positive, ≤2wks of pervious anti-tuberculosis chemotherapy Residents of Madras city, >12yrs

	Supervision of treatment not reported, but those who missed ≥1 dose or had ≥2 drugs withheld had the duration of daily or x2/wk chemotherapy extended at the end of each phase of treatment
Intervention	*R3: Daily, 3mths* Rifampicin 12mg/kg in 3 graded doses Streptomycin 0.75g Isoniazid 400mg (incorporating pyridoxine 10mg) Pyrazinamide 35mg/kg in five graded doses
Comparison	*R5: 5mths* R3 followed by twice-wkly (for 2mths) Streptomycin 0.75g Isoniazid 15mg/kg in three graded doses (incorporating pyridoxine 10mg) Pyrazinamide 70mg/kg in five graded doses
Comparison	*Z5* As for R5, without rifampicin
Length of follow up	Assessed from admission, mthly up to 24mths, after 3-mthly up to 60mths
Location	South India
Outcomes measures and effect size	Favourable response; all 6 cultures in the last 2mths of treatment were negative Doubtful response; 1 or 2 cultures were positive either in the penultimate or last month only Unfavourable response; ≥1 of the 3 cultures were positive at each of the last 2mths of treatment **Bacteriological response** 10/64 (15.6%) had unfavourable bacteriological response 46 initially resistant to isoniazid or streptomycin; 3/35, 9% (R3 and R5 series combined) compared with 6/11, 55% (Z5) had an unfavourable response ($p<0.01$).

	Relapse; ≥2 cultures positive in any 3 consecutive mthly assessment after chemotherapy up to 24mths, or in any 4 consecutive mthly assessment beyond 24mths **Relapse** 52/64 with favourable or doubtful response (18 R3; 25 R5; 9 Z5) had 5yr follow-up, 7 (4 R3; 2 R5; 1 Z5) had bacteriological relapse requiring treatment; of these 7, 2 initially resistant to streptomycin, 3 to isoniazid, 1 to rifampicin, 1 to streptomycin and isoniazid
Source of funding	No details given
Comments	

A.1.3 East African/British Medical Research Council, 1977

Bibliographic reference	East African/British Medical Research Council (1977) Results at 5 years of a controlled comparison of a 6-month and a standard 18-month regimen of chemotherapy for pulmonary tuberculosis. American Review of Respiratory Disease 116:3-8 (East African/British Medical Research Council (1972) Controlled clinical trial of short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. The Lancet 1:1079)
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: • Used, isoniazid, rifampicin, ethambutol, pyrazinamide (also thiacetazone, streptomycin) Randomisation by numbered sealed envelopes, appears unblinded (blinding is unclear) No allocation concealment Unclear if groups were comparable at baseline, some baseline data (authors commented on unequal distribution of the age of some participants between groups) Subjective nature of exclusion criteria Not ITT, exclusions made after allocation to treatment group

	Adverse reactions not clearly described, not given for DR subgroup
Number of patients	n = 448; 226 (SHR), 222 (STH/TH) (admitted to study April 1970 – September 1971, 27 centres in East Africa and Zambia), n=119 excluded, n=7 died n= 322; 176 (SHR), 146 (STH/TH) used in analysis n=31 DR (20 SHR; 11 STH/TH)
Patient characteristics	*Inclusion* African, ≥15yrs Previously untreated extensive pulmonary TB, sputum positive *Inclusion* Extra pulmonary TB requiring additional treatment Non-tuberculosis disease contraindicating the use of the antituberculosis drugs under study Very poor general health
Intervention	SHR (daily, 6mths) • Streptomycin 1g intramuscularly • Isoniazid 300mg • Rifampicin 450mg (<50kg), 600mg (heavier) (in hospital for the 6mths of chemotherapy, received all doses under supervision of hospital staff)
Comparison	STH/TH (daily, 18mths) • Thiacetazone 150mg, isoniazid 300mg – daily, 18mths • Streptomycin 1g intramuscularly – daily first 8wks (in hospital for the 2mths while having streptomycin injections, after given mthly supplies of tablets to take at home)
Length of follow up	Assessed mthly up to 30mths, then once every 3mths to 60mths, 5-yr report

Location	East Africa and Zambia
Outcomes measures and effect size	Failure during chemotherapy; persisting sputum positivity leading to a change of chemotherapy, or ≥2 positive cultures in the last 3mths of treatment, or bacteriological relapse after ≥3 consecutive mths of culture negativity **Status at end of treatment and relapse** N=31 (n=20 SHR; n=11 STH/TH) N=24 pretreatment resistance to isoniazid • n=0/14 (SHR), failure during treatment • n=1/10 (STH/TH) failure during treatment N=3 pretreatment resistance to streptomycin, all in the SHR group • n=0/3 (SHR), failure during treatment, n=0/2 relapsed N=4 pretreatment resistance to isoniazid and streptomycin • n=1/3 (SHR), failure during treatment, n=0/1 relapsed • n=1/1 (STH/TH) failure during treatment Relapse; up to 30mths, ≥2 positive cultures growing at least 10 colonies at different mths in any 3 consecutive mths; after 30mths, 2 positive cultures (1 which yielded ≥20 colonies growth) obtained either at a single 3-mthly attendance or at 2 consecutive attendances **Relapse** N=18 pretreatment resistance to isoniazid • n=3/10 relapsed (SHR, all relapsed at 7-18mths) • n=2/8 relapsed (STH/TH, n=1 relapsed at 19-36mths, n=1 at 37-60mths) N=2 pretreatment resistance to streptomycin, all in the SHR group • n=0/2 relapsed N=1 pretreatment resistance to isoniazid and streptomycin • n=0/1 relapsed (SHR)

	Adverse reactions Not reported by drug-resistance status
Source of funding	Gruppo Lepitit of Milan supplied a substantial proportion of the rifampicin used in the study for free
Comments	

A.1.4 Hong Kong Chest Service/British Medical Research Council, 1978 and Hong Kong Chest Service/British Medical Research Council, 1979

Bibliographic reference	Hong Kong Chest Service/British Medical Research Council (1979) Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis: the results up to 24mths. Tubercule 60:201-210 (earlier paper, same study; Hong Kong Chest Service/British Medical Research Council (1978) Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis. American Review of Respiratory Disease 118:219-227)
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: • Used rifampicin, isoniazid, etambutol, pyrazinamide (also streptomycin) Randomisation unclear, appears unblinded (blinding is unclear) No allocation concealment For patients with drug susceptible strains pretreatment distributions (not detailed) were considered similar for the 4 regimens for sex, age, weight and radiologic extent of disease – not reported for DR patients Analysis following exclusions applied (not ITT) No exclusion criteria Adverse reactions in the first 6mths of treatment – no subgroup analysis for DR group
Number of patients	n = 1056 patients admitted to study (October 1974 – May 1976), n=214 excluded

	n = 842 (162 DR to isoniazid, streptomycin or both(35)) Of the 842, n=73 excluded from the analysis up to 24mths, n=769 in analysis, of these n=130 DR n=130 DR in analysis; resistant to isoniazid, streptomycin or isoniazid and streptomycin • n=29, SHR • n=28, SHRZ/$S_2H_2Z_2$ • n=45, SHRE/ $S_2H_2E_2$ • n=28, $S_3H_3Z_3R_3$/ $S_2H_2Z_2$ No patient had resistance to rifampicin pretreatment, following repeated testing it was considered to be probable that no patient had ethambutol resistant cultures pretreatment In all regimens the drugs were given at the same time in a single dose, all chemotherapy given under the direct supervision of hospital or outpatient clinic staff
Patient characteristics	*Inclusion* Chinese ≥15yrs Smear positive pulmonary TB, no previous antituberculosis chemotherapy Those who had received ≤2wksof previous chemotherapy in the past yr or ≤4mths of chemotherapy >1yr previously were also eligible 85/842 (17 DR) had had previous chemotherapy up to the allowed limit – the response of these patients was not found to be affected by their previous chemotherapy Baseline: 71% (range 65% to 74%) male, <45yrs 66% (range 64% to 70%), average weight 47.3kg (SD±6.8)
Interventions and comparisons	SHR regimen (daily, 6mths) • Streptomycin 0.75g/day • Isoniazid 300mg

	• Rifampicin 450mg (600mg for ≥50kg) $SHRZ/S_2H_2Z_2$ regimen (daily for 2mths)followed by streptomycin plus isoniazid plus pyrazinamide x2/wk • Streptomycin 0.75g/day; 1g/x2 or x3/wk • Isoniazid 300mg/day; 15mg/kg x2 or x3/wk • Rifampicin 450mg (600mg for ≥50kg) • Pyrazinamide 1.5g/day; 3g x3/wk; 3g x2/wk (2, 2.5 and 3.5g for ≥50kg) $SHRE/S_2H_2E_2$ regimen as for $SHRZ/S_2H_2Z_2$ regimen with ethambutol instead of pyrazinamide in daily and x2/wkly phases • Streptomycin 0.75g/day; 1g/x2 or x3/wk • Isoniazid 300mg/day; 15mg/kg x2 or x3/wk • Rifampicin 450mg (600mg for ≥50kg) • Ethambutol 25mg/kg daily; 45mg/kg x2/wk $S_3H_3R_3Z_3/S_2H_2Z_2$ regimen (x3/wk, 4mths) followed by streptomycin plus isoniazid plus pyrazinamide x2/wk • Streptomycin 1g/x2 or x3/wk • Isoniazid 15mg/kg x2 or x3/wk • Rifampicin 450mg (600mg for ≥50kg) • Pyrazinamide 3g x3/wk; 3g x2/wk (2.5 and 3.5g for ≥50kg) Last 3 regimens, patients treated for a total period of either 6 or 8mths, allocation made at 5mths
Length of follow up	Assessed mthly up to 24mths
Location	Hong Kong
Outcomes measures and effect size	Bacteriological status based on an average of 5.7 sputum cultures/patient during the last 3mths of chemotherapy Unfavourable response; ≥2 positive results in these cultures **Status at end of treatment**

	6mth duration; unfavourable response SHR; n=6/40, 15% • Resistance to isoniazid, unfavourable 0/8 • Resistance to streptomycin, unfavourable 0/15 • Resistance to both, unfavourable 6/17, 35% SHRZ/$S_2H_2Z_2$; n=4/20, 20% • Resistance to isoniazid, unfavourable 1/3, 33% • Resistance to streptomycin, unfavourable 0/9 • Resistance to both, unfavourable 3/8, 38% SHRE/$S_2H_2Z_2$SHR, n=0/22 • Resistance to isoniazid, unfavourable 0/9 • Resistance to streptomycin, unfavourable 0/6 • Resistance to both, unfavourable 0/7 $S_3H_3Z_3R_3$/ $S_2H_2Z_2$, n=1/21, 5% • Resistance to isoniazid, unfavourable 0/8 • Resistance to streptomycin, unfavourable 0/7 • Resistance to both, unfavourable 1/6, 17% 8mth duration SHRZ/$S_2H_2Z_2$, n=4/18, 22% • Resistance to isoniazid, unfavourable 0/4 • Resistance to streptomycin, unfavourable 0/9 • Resistance to both, unfavourable 4/5 SHRE/$S_2H_2E_2$, n=0/22 • Resistance to isoniazid, unfavourable 0/11

	• Resistance to streptomycin, unfavourable 0/11 • Resistance to both, unfavourable 0/3 $S_3H_3Z_3R_3$/ $S_2H_2Z_2$, n=1/16, 6% • Resistance to isoniazid, unfavourable 0/4 • Resistance to streptomycin, unfavourable 0/6 • Resistance to both, unfavourable 1/6
	Relapse by 24mths 6mth duration SHR, n=4/29, 14% • Resistance to isoniazid, relapse 1/7, 14% • Resistance to streptomycin, relapse 2/13, 15% • Resistance to both, relapse 1/9, 11% SHRZ/$S_2H_2Z_2$, n=3/14, 21% • Resistance to isoniazid, relapse 0/2 • Resistance to streptomycin, relapse 3/9, 33% • Resistance to both, relapse 0/3 SHRE/$S_2H_2E_2$, n=9/21, 43% • Resistance to isoniazid, relapse 4/8, 50% • Resistance to streptomycin, relapse 3/6, 50% • Resistance to both, relapse 2/7, 29% $S_3H_3Z_3R_3$/ $S_2H_2Z_2$, n=2/15, 13% • Resistance to isoniazid, relapse 0/6 • Resistance to streptomycin, relapse 0/4 • Resistance to both, relapse 2/5, 40%

	8mth duration SHRZ/$S_2H_2Z_2$, n=0/14 • Resistance to isoniazid, relapse 0/4 • Resistance to streptomycin, relapse 0/9 • Resistance to both, relapse 0/1 SHRE/$S_2H_2E_2$, n=7/24, 29% • Resistance to isoniazid, relapse 2/10, 20% • Resistance to streptomycin, relapse 4/11, 36% • Resistance to both, relapse 1/3, 33% $S_3H_3Z_3R_3$/ $S_2H_2Z_2$, n=1/13, 8% • Resistance to isoniazid, relapse 0/4 • Resistance to streptomycin, relapse 0/6 • Resistance to both, relapse 1/3, 33% n=101 on the 3 regimens with both 6-mth and 8-mth treatment periods • n=14/50, 28% of those treated for 6mths compared with n=8/51, 16% of those treated for 8mths (p=0.08) • relapse rates for ethambutol regimen (SHRE/$S_2H_2E_2$) (n=9/21, 43% after 6mths, n=7/24, 29% after 8mths), significantly higher than with the regimen where pyrazinamide was given SHRZ/$S_2H_2Z_2$ regimen, (p<0.01) **Emergence of resistance** Not reported by drug-resistance status
	Adverse reactions Not reported by drug-resistance status
Source of funding	Ciba-Geigy of Basel and Gruppo Lepetit of Milan provided rifampicin at no cost

Comments	

A.1.5 Tuberculosis Research Centre, Madras and National Tuberculosis Institute, Bangalore 1986

Bibliographic reference	Tuberculosis Research Centre, Madras and National Tuberculosis Institute, Bangalore (1986) A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. American Review of Respiratory Disease 134:27-33
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: • Used rifampicin, isoniazid, pyrazinamide (also streptomycin) No details of randomisation, appears unblinded (blinding is unclear) No allocation concealment Groups were considered comparable at baseline, limited baseline characteristics reported Not ITT, exclusions made after allocation to treatment group Adverse reactions, not given for DR subgroup
Number of patients	n = 919, n=114 excluded, n=64 had missed or interrupted of ≥25% of chemotherapy In analysis: n=694 drug sensitive, • n=228 R3; n=230 R5; n=236 Z5 n=111 DR, initially resistant to ≥1 drug, • n=34 R3; n=40 R5; n=37 Z5 All patients outpatients, received chemotherapy under close supervision

Patient characteristics	*Inclusion* Residents of Madras or Bangalore City, came from poor sections of these communities Had come to outpatient clinics because of symptoms ≥12yrs Newly diagnosed pulmonary TB, not had previous chemotherapy for >2wks, x2 sputum cultures positive N=694; 70% male, 32% <25yrs, 19% ≥45yrs, mean weight 40kg
Interventions and comparisons	R3: (daily, 3mths) • rifampicin 12mg/kg in 3 graded doses • streptomycin 0.75g • isoniazid 400mg (incorporating pyridoxine 10mg) • pyrazinamide 35 mg/kg in 5 graded doses R5: as R3, followed by x2/wk regimen for 2mths (5mths) • streptomycin 0.75g • isoniazid 15mg/kg in 3 graded doses (incorporating pyridoxine 10mg) • pyrazinamide 70 mg/kg in 5 graded doses Z5: as for R5 without rifampicin (5mths) All drugs given as a single dose
Length of follow up	Assessed mthly, 24mths
Location	South India
Outcomes measures and effect size	**Death related to TB** n=3 (n=2 R3; n=1 Z5) died of TB or its related complications

	Unfavourable response; if ≥1 of 3 cultures were positive at each of the last 2mths of treatment, irrespective of the number of colonies **Status at end of treatment and relapse** Resistant to streptomycin (n=27; n=7, R3; n=9, R5; n=11, Z5) • n=1/27, 4% unfavourable response at the end of chemotherapy (n=1 Z5) Resistant to isoniazid (n=46; n=17, R3; n=17, R5; n=12, Z5) • n=7/46, 15% unfavourable response at the end of chemotherapy (n=1, R3; n=1, R5; n=5, Z5) • n=2/34 in R3 and R5 compared with n=5/12 Z5, p<0.01 Resistant to streptomycin and isoniazid (n=37; n=9, R3; n=14, R5; n=14, Z5) • n=10/37, 27% unfavourable response at the end of chemotherapy (n=1, R3; n=1, R5; n=8, Z5) • n=2/23 in R3 and R5 compared with n=8/14 Z5, p<0.01 bacteriological relapse; ≥2 cultures positive in any 3 consecutive mthly assessments **Relapse** n=89 assessed Resistant to streptomycin (n=27; n=7, R3; n=9, R5; n=11, Z5) • n=3/27, 11% relapses requiring treatment (n=1, R3; n=1, R5; n=1, Z5) Resistant to isoniazid (n=46; n=17, R3; n=17, R5; n=12, Z5) • n=7/46, 15% relapses requiring treatment (n=5, R3; n=1, R5; n=1, Z5) Resistant to streptomycin and isoniazid (n=37; n=9, R3; n=14, R5; n=14, Z5) • n=3/37, 8% relapses requiring treatment (n=1, R3; n=1, R5; n=1, Z5)
	Adverse reactions Not reported by drug-resistance status

Source of funding	Not reported
Comments	

A.1.6 Tanzania/British Medical Research Council Collaborative Investigation 1996

Bibliographic reference	Tanzania/British Medical Research Council Collaborative Investigation (1987) A controlled trial of a 4-weekly supplement of rifampicin, pyrazinamide and streptomycin in the continuation phase of a 7-month daily chemotherapy regimen for pulmonary tuberculosis. South African Medical Journal 86:960-965
Study type	RCT
Study quality	Intervention does not exactly match the intervention of interest: • isoniazid, rifampicin, pyrazinamide (also ethambutol) Randomisation by consecutively sealed envelopes, appears unblinded (blinding is unclear) Unclear allocation concealment Unclear if groups were comparable at baseline, baseline characteristics reported only for drug sensitive patients Subjective nature of exclusion criteria Not ITT, exclusions made after allocation to treatment group Adverse reactions, not given for DR subgroup
Number of patients	n = 381 (admitted to study May 1982 – May 1985), n=75 excluded, n=266 in analysis n= 40 DR (n=33 resistant to isoniazid, n=3 resistant to streptomycin, n=4 resistant to both), n=19 H, n=21 H(SRZ) All in-patients for 6mths, on discharge given enough isoniazid for 4-wks self-administration at home, unsupervised
Patient characteristics	*Inclusion* Black, African

	15-65yrs, previously untreated pulmonary TB Sputum positive on smear and culture (pretreatment characteristics given for those with drug-sensitive TB, not given for those DR) *Exclusion* Extrapulmonary TB Moribund
Interventions and comparisons	All 6-wk intensive phase: • streptomycin 1g (0.75g <33kg or >45yrs) • isoniazid 300mg • rifampicin 450mg (<50kg, 600mg heavier patients) • pyrazinamide 1.5g (<50kg, 2.0g heavier patients) H (daily, 24wks) • isoniazid 300mg H(SRZ) (24wks) • isoniazid 300mg, daily • rifampicin 450mg (<50kg, 600mg heavier patients), 2days/4wks • pyrazinamide 1.5g (<50kg, 2.0g heavier patients), 2days/4wks • streptomycin 1g (0.75g <33kg or >45yrs), on the first day
Length of follow up	Assessed mthly up to 18mths, 3mthly up to 30mths
Location	Tanzania

Outcomes measures and effect size	**Deaths** n=2/40, both resistant to isoniazid died during treatment, both in the 3rd month from diarrhoea and vomiting **Status at 30-months and relapse** Favourable response: • resistant to isoniazid, n=22/33, 67%; (n=10/15 H, 67%; n=12/18 H(SRZ), 67%) • resistant to streptomycin, n=2/3,67% • resistant to isoniazid and streptomycin, n=1/4, 25% Doubtful response: • resistant to isoniazid, n=3/33, 9%; (n=2/15 H, 13% H; n=1/18 H(SRZ), 6%) • resistant to streptomycin, n=1/3,33% • resistant to isoniazid and streptomycin, n=0/4 Failure at the end of chemotherapy: • resistant to isoniazid, n=8/33, 24%; (n=3/15 H, 20% H; n=5/18 H(SRZ), 28%) • resistant to streptomycin, n=0/3 • resistant to isoniazid and streptomycin, n=3/4,75%;(n=2/3 H, 67% H; n=1/1 H(SRZ)) **Relapse, 30-months:** • resistant to isoniazid, n=6/22 assessed, 27%; (n=4/12 H, 33% H, n=2/10 H(SRZ), 20%) • resistant to streptomycin, n=0/2 assessed • resistant to isoniazid and streptomycin, n=0 assessed
	Adverse reactions Not reported by drug-resistance status
Source of funding	Not reported

Comments	

A.1.7 Tuberculosis Research Centre/Indian Council of Medical Research, Chennai 1997

Bibliographic reference	Tuberculosis Research Centre/Indian Council of Medical Research (1997) A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 1:509-517
Study type	RCT
Study quality	Intervention uses drugs used in UK regimens: • ethambutol, isoniazid, rifampicin, pyrazinamide No details of randomisation, appears unblinded (blinding is unclear) No allocation concealment Unsupervised drug treatment Not ITT, exclusions made after allocation to treatment group Unclear if groups were comparable at baseline General nature of inclusion/exclusion criteria Adverse reactions, not given for DR subgroup
Number of patients	n = 1203 admitted to study, n=112 excluded n=266 DR (n=227 resistant to isoniazid or isoniazid and streptomycin, n=38 resistant to isoniazid and rifampicin, n=1 resistant to rifampicin) $2EHRZ_7/6EH_7$, completely unsupervised $2EHRZ_2/4EHR_2$ and $2HRZ_2/4HR_2$; divided into two groups, one group attended clinic x2/wk for administration under supervision; second group attended clinic x1/wk for administration under supervision and self-administered the other x1/wk dose

Patient characteristics	*Inclusion* ≥12yrs Free from visual defects other than refractory error, ≥2 positive sputum smears Irrespective of the duration of previous chemotherapy *Exclusion* Visual defects other than refractory error
Interventions and comparisons	$2EHRZ_7/6EH_7$ (daily, 8mths) • ethambutol 600mg • isoniazid 300mg • rifampicin 450mg • pyrazinamide 1.5g $2EHRZ_2/4EHR_2$ (x2/wk, 8mths) • ethambutol 1200mg • isoniazid 600mg • rifampicin 450mg • pyrazinamide 2g $2HRZ_2/4HR_2$ (x2/wk, 6mths) • isoniazid 600mg • rifampicin 450mg • pyrazinamide 2g

Length of follow up	24mths, assessed mthly
Location	South India

Outcomes measures and effect size	Favourable response; all 6 cultures negative in the last 2mths of chemotherapy
	Unfavourable response; ≥2 cultures positive in the last 2mths of treatment including ≥ in the last mth; those who had treatment changed for persistent bacteriological positivity or radiographic and/or clinical deterioration, those who died of TB during treatment phase
	Doubtful response; did not fulfil the criteria for favourable or unfavourable
	
	Bacteriological response
	Unfavourable response;
	• resistant to isoniazid;
	o n=16/94, 17% ($2EHRZ_7/6EH_7$);
	o n=12/59, 20% ($2EHRZ_2/4EHR_2$);
	o n=46/74, 62% ($2HRZ_2/4HR_2$);
	• resistant to isoniazid and rifampicin; n=35/38, 92% all unfavourable response
	• resistant to rifampicin; n=1 patient who had an unfavourable response
	Doubtful response;
	• resistant to isoniazid; n=1/74, 1% ($2HRZ_2/4HR_2$)
	Relapse
	n=144 in analysis (n=152 available for analysis, n=8 excluded)
	n=21/144 had relapse requiring treatment
	• n=6/21, 29% ($2EHRZ_7/6EH_7$); n=11/21, 54% ($2EHRZ_2/4EHR_2$); n=4/21, 19% ($2HRZ_2/4HR_2$);
	proportion in $2EHRZ_7/6EH_7$, compared with $2EHRZ_7/6EH_7$, difference 17% (CI: 3, 31), p=0.03
	
	Emergence of drug resistance

	N=74 resistant to isoniazid with unfavourable response, N=23 had emergence of resistance to rifampicin
	Adverse reactions Not reported by drug-resistance status
Source of funding	Not reported
Comments	