Anti-TB Drugs: New Drugs and the “Old” Reliables

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Principles of treatment in children

- Cure the patient of TB
- Prevent death from TB disease or its late effects
- Prevent relapse of TB
- Prevent the development and transmission of drug-resistant TB
- Reduce transmission of TB to others
- Achieve all this with minimal toxicity

TABLE 5.1 **WHO recommended grouping of anti-TB drugs**

GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 1. First-line oral agents	Isoniazid	H
	Rifampicin	R
	Ethambutol	E
	Pyrazinamide	Z
	Rifabutin[a]	Rfb
	Rifapentine[a]	Rpt
Group 2. Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin[b]	S
	Kanamycin	Km
	Amikacin	Am
	Capreomycin	Cm
Group 3. Fluoroquinolones (FQs)[d]	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Gatifloxacin[c]	Gfx
Group 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
	Prothionamide	Pto
	Cycloserine	Cs
	Terizidone[e]	Trd
	Para-aminosalicylic acid	PAS
	Para-aminosalicylate sodium	PAS-Na

GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)	Bedaquiline	Bdq
	Delamanid	Dlm
	Linezolid	Lzd
	Clofazimine	Cfz
	Amoxicillin/ clavulanate	Amx/Clv
	Imipenem/cilastatin[f]	Ipm/Cln
	Meropenem[f]	Mpm
	High-dose isoniazid	High dose H
	Thioacetazone[g]	T
	Clarithromycin[g]	Clr

[a] Rifabutin and rifapentine have similar microbiological activity as rifampicin. Rifabutin is not on the *WHO list of essential medicines*, however it has been added here as it is used routinely in patients on protease inhibitors in many settings. Rifapentine is part of a latent TB infection and active TB treatment in some countries but to date is not part of any WHO endorsed treatment regimens.

[b] There are high rates of streptomycin resistance in strains of MDR-TB; therefore, streptomycin is not considered a second-line anti-TB injectable agent.

[c] Gatifloxacin can have severe side-effects including serious diabetes (dysglycaemia). The drug has been removed from the market of a number of countries as safer alternatives whenever possible are available for the diseases for which the drug is labeled. Safer alternatives are discussed below in the section of Group 5 drugs.

[d] Ofloxacin is considered a weaker agent with less activity against TB than other fluoroquinolones and has been removed as a choice in Group 3 drugs (see section below on Group 3 – Fluoroquinolones for more information).

[e] Terizidone has limited programme data and effectiveness data as compared to cycloserine.

[f] Clavulanate (Clv) is recommended as an adjunctive agent to imipenem/cilastatin and meropenem.

[g] Limited data on the role of thioacetazone and clarithromycin in MDR-TB treatment has resulted in many experts not including these drugs as options for Group 5.

[a] This regrouping is intended to guide the design of longer regimens; the composition of the recommended shorter MDR-TB regimen is standardized (see Section A).

[b] Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations; see text).

[c] Refer to the text for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of XDR-TB (26).

[d] Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.

[e] HIV-status must be confirmed to be negative before thioacetazone is started.

Table 6. Medicines recommended for the treatment of RR-TB and MDR-TB[a]

Group A. Fluoroquinolones[b]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[f]	(S)
Group C. Other core second-line agents[b]		Ethionamide / prothionamide	Eto / Pto
		Cycloserine / terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[a]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem–cilastatin[d]	Ipm
		Meropenem[d]	Mpm
		Amoxicillin-clavulanate[d]	Amx-Clv
		(Thioacetazone)[e]	(T)

The pharmacologic basis of therapeutics

- FIRST LINE MEDICINES FOR TB (**Group 1**) in children
  - Isoniazid
  - Rifampicin
  - Pyrazinamide
  - Ethambutol

Isoniazid (H)

- MOA: Synthetic agent, pro-drug, activated within *M. tuberculosis* by the enzyme katG; INH-derived reactive intermediates form adducts with NAD+ and NADP+ block mycolic acid synthesis; katG gene encodes for mycobacterial catalase peroxidase and organisms lacking this gene do not synthesize catalase or peroxidase and show INH resistance
- Resistance occurs at a rate of about 1 in 10^7 organisms
- MIC = 0.01-0.25 ug/mL; bactericidal with MBC ~ MIC
- With prolonged exposure, H produced a prolonged PAE (~ 5 days)
- Lacks clinically significant cross-resistance with other TB drugs, except ethionamide

Isoniazid (H)

- PK(1):
  - Good absorption form GIT and IM; Food, including high-fat food, reduces oral absorption (Best on a empty stomach); H reacts with reducing sugars, limiting the choices for sweeteners for oral solutions to non-reducing sugars (sorbitol)
  - T_{max}~ 0.5 – 2 hr after oral doses; C_{max} ~ 3-5 ug/mL after 300 mg doses and 9-15 ug/mL after 900 mg doses; C_{max} MAY be lower in fast acetylators (due to greater first pass metabolism)
  - Widely distributed into most body tissues and fluids; V_d ~ 0.7L/kg; low protein binding (~10%) and penetrates into CSF even in absence of inflammation (20-100% of plasma conc); crosses placenta and excreted in breast milk; enters macrophages and displays intracellular activity vs *M. tuberculosis*

Isoniazid (H)

- PK(2):
  - Extensively metabolized (esp. liver) to inactive compounds by acetylation and dehydrazination
  - NAT2 forms acetyl-INH, which is further metabolized to mono- and diacetylhydrazine
  - Slow acetylation is due a deficiency of NAT2 (autosomal recessive); Rapid acetylation can be heterozygous or homozygous
  - 50% of white & black are slow acetylators; 80-90% of asians & alaskan indigenous are rapid acetylators
  - $t_{1/2}$ of INH ~ 1-1.8 hrs in rapid acetylators and 3-4 hrs in slow acetylators; over 80% is excreted in urine in 24 hrs as unchanged drug or metabolites

Isoniazid (H)

- Outcomes in rapid vs slow acetylators:
  - Historically, acetylator status has not been correlated with treatment efficacy when H is given at least 2x/week (challenged recently)
    - Pasipanodya JG, Srivastava S, and Gumbo T. Meta-analysis of clinical studies supports the pharmacokinetic variability hypothesis for acquired drug resistance and failure of antituberculosis therapy. Clin Infect Dis 2012;55(2):169-77
  - Rapid acetylators receiving once weekly INH therapy had poorer outcomes
    - Iwainsky H. Mode of action, biotransformation and pharmacokinetics of antituberculosis drugs in animals and man. In: Bartman K (ed). Antituberculosis drugs. Berlin: Springer Verlag, 1988, 399-553.
    - Ellard GA and Gammon PT. Acetylator phenotyping of tuberculosis patients using matric isoniazid or sulphadimidine and its prognostic significance for treatment with several intermitted isoniazid-containing regimens. Br J Clin Pharmcol 1977; 4(1): 5-14

Isoniazid (H)

- Adverse effects & Drug interactions:
  - Subclinical hepatitis or hepatitis is independent of INH plasma levels
  - In combination with other anti-TB meds can produce additive effect (Z, R)
  - Rheumatologic complications (arthralgias)
  - Drug-induced lupus syndrome
  - Neuropathies due to formation of hydrazones preventing the conversion of pyridoxine to pyridoxal phosphate (slow acetylators & those receiving >8 mg/kg/day at greater risk)
  - Overdose: CNS effects (psychosis, delirium, euphoria, somnolence), coma, seizures and possible death
  - Antidote: pyridoxine in doses equal to ingested isoniazid
  - Paracetamol toxicity; Histaminase inhibition in patients ingesting tuna and other fish; may affect anticonvulsants (phenytoin, carbamazepine, phenobarbital)

Rifampicin (R)

- KEY anti tuberculosis drug, allowing for ‘short-course’ regiments of 6-9 months, due to excellent sterilizing activity.
- Bactericidal vs *M. tuberculosis* and several other mycobacterial spp. (*bovis* and *kansasii*)
- *In vitro* bactericidal activity is concentration dependent
- Excellent sterilizing activity *in vivo* vs. semi-dormant M. tb, due to its rapid onset of action

Rifampicin (R)

- MOA: inhibits DNA-dependent RNA polymerase, blocking transcription
- Resistance results from single AA substitutions in the βsubunit of RNA polymerase, altering the binding of RIF (degree of resistance depending on the location and nature of AA substitution)
- Mutations leading to this resistance occur at a rate of 1 in 10^8
- Higher doses as monotherapy does not prevent emergence of resistance
- Subinhibitory concentrations enhance selection of resistant organisms

Rifampicin (R)

- PK (1)
  - At 600 mg, C_{max} = 8-24 µg/mL, 2 hrs post dose
  - Food decreases C_{max} by 36% and AUC by a lesser degree; concentration-dependent – give on empty stomach
  - Absorption of H and Z in FDC is not affected by combined formulations but R's absorption is reduced by Z
  - Widely distributed in the body, V_d ~ 0.7 L/kg
  - Variable CNS penetration and better with inflamed meninges
  - Protein binding ~ 85%
  - Extensively metabolized by intestinal & hepatic esterases (deacetylated); t1/2 ~ 3-4 hrs (single dose) and ~ 2 hrs (steady state)
  - Main metabolite (desacetyl-RIF) are largely excreted in bile and eliminated in feces; 10% excreted in urine as unchanged drug

Rifampicin (R)

- PK (2)
  - Unlike other TB drugs, the dose is not increased to accommodate 2 or 3x weekly dosing regimens
  - Predominantly cleared by the liver, no dosage adjustment in renal impairment
  - Used safely in pregnant women
  - Crosses human placenta, and on rare occasions, fetal malformations have occurred

Rifampicin (R)

- AEs and DIs
  - Risk of hepatotoxicity with other anti-TB meds
    - Risk factors (advanced age, alcohol, DM, other hepatotoxic agents)
  - Other AEs:
    - ‘flu-like’ syndrome in the first 3 months of treatment (dose related & in intermittent dosing); thrombocytopenia, hemolytic anemia, ARF

  Profound inducer of CYP3A4, other hepatic & intestinal P450 and other transporters – **RULE OF THUMB: MOST HEPATICALLY METABOLIZED DRUGS WILL HAVE SHORTER HALF LIVES IN THE PRESENCE OF RIF**

Pyrazinamide (Z)

- Contributes important sterilizing activity to the treatment regimens during the first two months of therapy
- Used for longer duration in MDR-TB and synergistic with newer drugs for MDR-TB

Pyrazinamide (Z)

- MOA: pro-drug activated by the pyrazinamidase enzyme in mycobacteria
- Useful activity only vs *M. tb* and *M. africanum*
- Pyrazinoic acid appears to be the active moiety, although it is only the pyrazinoic acid created within tubercle bacilli that appears to be active because the organisms do not appear to take up significant amounts of the acid from their surroundings
- Mutations in the *pncA* gene that encodes the pyrazinamidase enzyme are associated with PZA resistance

Pyrazinamide (Z)

- PK:
  - Most reliably absorbed TB drug
  - T_{max} ~ 1-2hrs, concentrations generally increase linearly with dose
  - Most C_{max} = 20-60 ug/mL, and as high as 90 ug/mL with larger twice weekly doses
  - Vd ~ 0.6 L/kg, and protein binding data unavailable
  - CSF penetration is good (50-100% plasma concentrations)
  - Metabolized to pyrazinoic acid and 5-OH-pyrazinoic acid, which do not appear to contribute to the activity
  - t1/2 ~ 9 hrs
  - While well absorbed in adults, may not be the same in children with HIV

Pyrazinamide (Z)

- AEs and DIs:
  - GI upset and arthralgias
  - Routinely increases plasma uric acid concentrations but not true gout (normal UA during PZA generally indicate non compliance)
  - Hepatotoxicity is the most important PZA associated toxicity
  - Not associated with significant drug interactions. And when co-formulated with RIF and INH, the absorption of RIF is decreased by ~ 13%

Ethambutol (E)

- Only the dextro-isomer of the chiral compound is used clinically, and it is active against only mycobacteria
- MIC for TB is 0.5-2.0 ug/mL, and effects are not apparent for about 24 hours
- EMB is bacteriostatic in clinical conditions
- MOA: Inhibits arabinotransferases involved in the synthetic pathway of the mycobacterial cell wall
- Mutations in the *embB* region, specifically codon 306, appear to be the most common source of EMB resistance

WHO/HTM/TB/2006.365
WHO/FCH/CAH/2006.3

Ethambutol efficacy and toxicity:

literature review and recommendations for daily and intermittent dosage in children

This review was produced by the Stop TB Department and the Department of Child and Adolescent Health and Development of the World Health Organization.

World Health Organization

Ethambutol in children

3.3 Efficacy and toxicity of ethambutol in children

EMB has been used to treat tuberculosis almost in children as long as it has been used in adults. Its use has generally, but not always, been confined to children over 3 years of age, because of concern about the risk of ocular toxicity and the difficulty of assessing ocular function in young children. There are few, if any, totally satisfactory studies comparing the efficacy of EMB in children with that of other drugs. Many early papers record the absence of overt toxicity and express satisfaction about the availability of a drug to replace PAS, which was associated with considerable gastrointestinal discomfort and consequent patient resistance to its use.

In many studies of childhood tuberculosis, broad, subjective criteria, such as weight gain and general well-being, have been used to assess the success of a regimen – unlike adult studies, where sputum culture negativity can be used as an indisputable criterion of treatment success. Chest radiograph clearing has often been compared between regimens but, again, *statistical* comparisons are rare. Many cases of disease in childhood are also paucibacillary and a significant proportion of these would recover without any active treatment, especially in children aged 5–10 years. It is thus difficult to assess precisely the success of using EMB in children: reliance must be place on the evidence provided by adult studies to indicate the likely efficacy of EMB in children.

3.4 Pharmacokinetics of ethambutol in adults and children

"The true maximum dose is the highest dose that a patient can tolerate, hopefully while achieving the desired therapeutic response."

Charles A. Peloquin (1998)

- Serum concentrations of EMB maximal at ~2 hrs after dosing with peak concentrations following daily doses of 50 mg/kg & 23 mg/kg at 10 and 5 µg/mL, respectively (serum concentrations were proportional to dose)
- Approximately 80% of the drug is excreted unchanged in urine
- T_{max} is delayed (between 2-4hrs); C_{max} lower after a meal than in fasting conditions (4.5 µg/mL vs 3.8 µg/L after 25 mg/kg EMB)
- Tissue distribution is good with tissue concentrations higher than serum or plasma levels, except CNS
- Serum concentrations lower in children vs adults following similar doses; even much lower concentration in younger vs older children

3.4 Pharmacokinetics of ethambutol in adults and children

"The true maximum dose is the highest dose that a patient can tolerate, hopefully while achieving the desired therapeutic response."

Charles A. Peloquin (1998)

- Age-related variations
  - Ratio of extracellular to intracellular and TBW falls throughout childhood (most rapid in the first 3 months of life)
  - Liver is the most important organ for biotransformation & ratio of liver volume to unit body weight declines throughout childhood & is 2x as great at 1 year old vs 14 years old
  - Glomerular excretion increase fairly rapidly following birth and reach adult values between 2.5 – 5 months
  - Somewhat delayed absorption due to binding in the GIT

Table 4. Mean peak serum concentrations of ethambutol in relation to dose in adults

Authors[a]	No. of patients	Dose (mg/kg)	Peak serum conc. (µg/ml)
Place & Thomas (1963)	10	50	10
	10	25	5
	2	17	2
Bobrowitz & Gokulanathan (1965)	64	25	4.1
	46	15	2.6
Peets et al. (1965)	3	25	5
Gómez-Pimienta et al. (1966)	7	20	3.4
Donomae & Yamamoto (1966)	40	25	4.4
		12.5	1.2
Place et al. (1966)	10	4	0.67
	10	8	1.4
	10	12.5	2.0
	10	25	4.0
	10	50	8.5
Horsfall (1969)	25	25	4.1
Eule & Werner (1970)	10	25	4
		50	8
		75	11
Lee et al. (1977)	6	15	4.01
Israili, Rogers & El-Attar (1987)			
1st day	17	12.5	3.7
days 4–7	17	12.5	5
Kumar (1992)	10	25	8.2
			6.4
Schall et al. (1995)	20	7.5[b]	1.45
Peloquin et al. (1999)			
fasting	14	25[b]	4.5
non-fasting	14	25[b]	3.8
Zhu et al. (2004)	38	19	2.11
	18	20	2.06
	16	18[b]	3.21

[a] Summaries of the papers quoted appear in Annex IV.
[b] Healthy volunteers.

Table 5. Mean peak serum concentrations of ethambutol in relation to dose in children

Authors [a]	No. of patients	EMB dose (mg/kg)	Age (years)	Peak serum conc. (µg/ml)
Hussels & Otto (1971)	6	15	2–5	1.2
	6	15	6–9	1.1
	7	15	10–14	0.9
	4	25	2–5	2.0
	7	25	6–9	1.5
	8	25	10–14	2.8
Hussels, Kroening & Magdorf (1973)	5	35	2–5	1.5
	9	35	6–9	2.3
	14	35	10–14	3.0
	5	35 [b]	2–5	2.5
	9	35 [b]	6–9	2.5
	14	35 [b]	10–14	6.3
Benkert et al. (1974)	4	15	3–6	0.9
	4	15	7–10	2.0
	5	15	11–14	1.8
	5	25	3–6	3.0
	5	25	7–10	2.6
	3	25	11–14	3.5
Zhu et al. 2004	14	Mean 16	Mean 5.4	0.78

[a] Summaries of the papers quoted appear in Annex III.
[b] Given with rifampicin, 10 mg/kg body weight.

Ethambutol in children

- In summary: Toxicity has not been encountered in children because of insufficient exposure to the drug – the serum EMB concentrations reached in children at the doses used are considerably lower than those reached in adults

> Convincing cases of EMB-induced ocular toxicity have not been reported in children (see Trébucq, 1997; Graham et al., 1998), although in two children EMB has been stopped as result of poorly documented eye problems (Mankodi et al., 1970; Medical Research Council Tuberculosis and Chest Diseases Unit, 1989). Several studies that carefully evaluated significant numbers of children receiving EMB at doses from 15 to 30 mg/kg body weight using sophisticated laboratory and clinical techniques have produced negative results (Chavarria et al., 1970; Scheffler, 1971; Nagy et al., 1980; Junnanond, Chotibut & Lawtiantong, 1983; Seth et al., 1991). In addition, Schmid (1981) mentions – almost in passing – the fact that he has treated 2634 children with EMB without any evidence of toxic ocular damage. Little credence can be given to cases of ocular toxicity reported in association with tuberculous meningitis, as the disease itself will frequently be responsible for the pathology described (Prachakvej & Subhamgkahen, 1979; Ramachandran et al., 1986). Finally, as indicated elsewhere

EMB pharmacokinetics in children is slow and incomplete

Optic toxicity is rarer in children compared to adults

Recommended dosages

- The following dosages of anti-TB medicines should be used daily for the treatment of TB in children:
  - Isoniazid (H) 10 mg/kg (R: 7-15 mg/kg); max: 300 mg/day
  - Rifampicin (R) 15 mg/kg (R: 10-20 mg/kg); max: 600 mg/day
  - Pyrazinamide (Z) 35 mg/kg (R: 30-40 mg/kg)
  - Ethambutol (E) 20 mg/kg (R: 15-25 mg/kg)

- Rapid advice: treatment of tuberculosis in children. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Fixed dose combination vs. liquid preparations

TABLE 1 Potential Clinical Advantages and Disadvantages of Different Formulations and Routes of Administration in Children[1,2,5,43–47]

Administration and Dosage Forms	Potential Advantages	Potential Disadvantages
Oral[1,2,5,43]	Main route for (long-term) treatments in children	First-pass effect
Liquid preparations	Acceptability from term birth	Instability of multidose preparations
• Suspensions	Maximum dose flexibility	Age-appropriate dosing volume for full-dose ingestion (<5 mL in younger and <10 mL in older age groups)
• Solutions, syrup, drops	Stability, portability, good dosage uniformity	
• Powders and granules for reconstitution	Options for different doses and modified release	Dose-measuring device critical
Solid dosage forms	Better acceptability (with liquid/semi-solid food)	Shaking for dose accuracy (suspensions)
• Tablets	Dose flexibility	Incorrect dosing for oral drops (criticality of dose)
• Capsules	Ease of administration	Risks of administration without prior dispersion/dissolution
• Powders, granules, sprinkles, multiparticulates, mini-tablets	Can be used in neonates and seriously ill infants	Ability to swallow intact dosage forms
• Orodispersible/chewable preparations		Risks of choking and chewing
Administration through nasogastric tubes		Limited dose flexibility
		Dose-measuring device needed
		Compatibility with food/drinks
		Limited control over dose intake
		Taste-masking requirements
		Less stable than standard tablets
		Risk of direct swallowing
		Intellectual properties costs
		Ease of administration and dosing accuracy (volume, density, viscosity, particle size)
		Potential compatibility with feeding tube material
		Doses and rinse volume relevant to target age group
		Relevant size of feeding tubes

TABLE 3 Examples of Recently Marketed/Prequalified Novel Oral Drug Formulations for Children[97,104,108–116]

Dosage Form	International Nonproprietary Name	Regulatory Agency Authorization/WHO PQ Year
Multi-particulates[97,108–110]		
Sprinkles, granules and pellets	Para-aminosalicylate granules	WHO PQ 2009
	TFV granules	FDA 2012, EMA 2012
	Rabeprazole sprinkles	FDA 2013
Flexible dispersible formulations[97,104,111–114]		
Dispersible and orodispersible tablets	Artemether/lumefantrine dispersible tablets	Swissmedic 2008 / WHO PQ 2009
	3TC/NVP/d4T	WHO PQ 2008
	Isoniazid/pyrazinamide/rifampicin	WHO PQ 2009
	Isoniazid/rifampicin	WHO PQ 2009
	3TC/NVP/AZT (Mylan Laboratories)	WHO PQ 2009
	ABC	WHO PQ 2010
	3TC/d4T	WHO PQ 2011
	3TC/AZT	WHO PQ 2011
	EFV	WHO PQ 2012
	3TC	WHO PQ 2012
	Artemether/lumefantrine	WHO PQ 2012
	Isoniazid/pyrazinamide/rifampicin	WHO PQ 2012
	Isoniazid/rifampicin	WHO PQ 2012
	Benznidazole	WHO PQ 2012
	Lamotrigine orodispersible tablets	FDA 2012
	AZT	WHO PQ 2013
Orodispersible films (wafer)	Ondasetron	FDA 2010
Chewable dispersible tablets	Lamotrigine	FDA 2012
Orally disintegrating mini-tablets	Hydrochlorothiazide	Model drug under investigation
Other novel oral formulations[115,116]		
Chewable tablets	Atorvastatin	EMA 2011
	Raltegravir	FDA 2012

3TC, lamivudine; ABC, abacavir; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; FDA, US Food and Drug Administration; ODT, orodispersible tablet; PQ, prequalification; NVP, nevirapine; TFV, tenofovir.

Drug instability in formulations

- Seifart et al. conducted a study on the suspensions of R, H and Z, in which the suspensions of the drugs alone and their combinations were stored at 4^{o}C, 24^{o}C, and 40^{o}C for 28 days.
- Suspensions had a pH range between 4.05 – 6.10
- Different extents of decomposition were observed between suspensions of single drugs and mixtures of two and three drugs

- Seifart HI, Parkin DP, Donald PR: Stability of isoniazid, rifampin, and pyrazinamide in suspensions used for the treatment of tuberculosis in children. Pediatr Infect Dis J, 1991 Nov; 10(11):827-31

Stability of R, H and Z in suspension formulations

Drugs present	pH	Conc (mg/mL)	4°C	24°C	40°C
R	4.05	5.88	91	96	91
H	5.65	5.88	69	56	54
Z	6.10	11.76	89	80	56
R+H	5.45	5.88/5.88	14/54	-	-
R+Z	4.22	5.88/11.76	99	-	-
R+H+Z	5.23	5.88/5.88/ 11.76	3/54/95	-	2/29/95

“Newer” drugs

Group A. Fluoroquinolones. Both levofloxacin and moxifloxacin are commonly used to treat MDR-TB. Levofloxacin is more widely available than moxifloxacin, which is more expensive although a reduction in its price is expected in the coming years.

Gatifloxacin is an affordable drug that was commonly used by TB treatment programmes until the concerns about its dysglycaemic effects led to a global shortage in its supplies. If manufacture of quality-assured formulations of the drug restarts, it could provide more options for regimen design and could lower the costs of regimens by substituting more expensive fluoroquinolones.

Moxifloxacin is relatively easy to administer to older children. However, the tablet must be split to accommodate dosing in younger children and it is highly unpalatable once split or crushed. Levofloxacin is available as a suspension.

“Newer” drugs

Group B. Second-line injectable agents. These agents present problems to administer intramuscularly or intravenously on a daily basis for several months, often necessitating hospitalization. Giving injections to children and underweight adults is particularly unpleasant and unwelcome.

“Newer” drugs

Group C. Other core second-line agents. Ethionamide and prothionamide are inexpensive, readily available worldwide and easily administered.

Cycloserine has been one of the standard inexpensive drugs for the treatment of MDR-TB for several years and therefore experience in its use is widespread. Terizidone is less widely used but is available on the Global Drug Facility (GDF) Products List.

Clofazimine is relatively inexpensive but it can be difficult to procure. The implementation of the recommendation on the shorter MDR-TB regimen, of which this medicine is an irreplaceable core component, needs to ensure that sufficient quantities of this medicine are available to meet the demand and that no stock-outs occur.

When linezolid is used, there needs to be close monitoring for adverse effects, particularly anaemia, thrombocytopenia, lactic acidosis, peripheral neuropathy and optic neuropathy, as these can be severe and life threatening. Historically linezolid has been very expensive, however, it has recently come off patent and the availability of generic products has hugely reduced its market price and it may become even more affordable in future.

“Newer” drugs

Group D. Add-on agents. Pyrazinamide is inexpensive, readily available and easy to administer. Isoniazid is inexpensive. It is important to consider the epidemiology of high-level versus low-level isoniazid resistance in a population before standard treatment regimens including high-dose isoniazid are recommended. Ethambutol is inexpensive and readily available. All of these three medicines are core components of first-line regimens for drug-susceptible TB.

PAS may be difficult to obtain although it is available through the GDF. Otherwise it is relatively inexpensive and easy to administer.

Amoxicillin-clavulanate is inexpensive and easily obtainable. However, the carbapenems are expensive and are difficult to administer as they must be given two or three times per day via an intravenous line.

Thioacetazone is inexpensive but it has limited availability and is not currently available through the GDF.

“Newer” drugs

Group D2 is made up of two new drugs released in recent years – bedaquiline and delamanid. WHO issued an interim policy on the use of these medicines in 2013 and 2014 *(4,5)*. In October 2016, WHO published its revised policy on delamanid following the advice of a separate GDG which reviewed its use in children and adolescents *(6)* (see also above). At this point, bedaquiline remains only recommended for use in adults. When the results from ongoing studies and the Phase III trials become available the evidence for the effectiveness of these two new drugs will be re-evaluated with respect to the other medicines making up the MDR-TB regimen.

Bedaquiline (Sirturo™)

- Diarylquinoline antimycobacterial drug
- Recommended dosage is 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally 3 x per week (with at least 48 hours between doses) for 22 weeks (total duration of 24 weeks)
- Most common side effects: QT Prolongation, hepatotoxicity and multiple drug interactions

Delamanid (Deltyba™)

- First in a new class of TB drugs called dihydro-nitroimidazoles (inhibits the synthesis of mycobacterial cell wall components, methoxy mycolilc acid and ketomycolic acid)
- Take on empty stomach. Cmax~ 4-5 h. T1/2 ~ 38 hrs. Css ~ 10-14 days
- Dose: 100 mg twice a day, for a period of six months (higher dose, higher cardiac adverse events QTc prolongation)


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Thank you for your kind attention