The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis

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There is considerable exigency to take all necessary steps to cure tuberculosis cases and prevent further emergence of drug-resistant tuberculosis. The most important of these steps is to ensure that the treatment, particularly of sputum smear-positive cases, is adequate and that patients adhere to their treatment by supervised, direct observation of drug-taking according to the standardized regimens.

Use of fixed-dose combinations (FDCs) of tablets against tuberculosis is now being recommended by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) as an additional step to ensuring proper treatment. FDCs simplify the prescription of drugs and the management of drug supply, and may also limit the risk of drug-resistant tuberculosis arising as a result of inappropriate drug selection and monotherapy.

Only FDCs of proven quality and proven rifampicin bioavailability should be purchased and used. In most situations, blood levels of the drugs are inadequate because of poor drug quality rather than poor absorption. This is true irrespective of the human immunodeficiency virus (HIV) infection status of the tuberculosis patients (other than those with overt acquired immunodeficiency syndrome, with CD4 counts <200 cells/mm^3). Currently, WHO, IUATLD and their partners are developing strategies for ensuring that only quality FDCs are used in tuberculosis programmes. A simplified and effective protocol for assessment of rifampicin bioavailability has been developed, and laboratories are being recruited to form a supranational network for quality assurance of FDCs. Standardization of FDC drug formulations has been proposed, which limits rifampicin-containing preparations to nine (including a four-drug FDC and three paediatric FDCs).

Keywords: tuberculosis, pulmonary, drug therapy; tuberculosis, multidrug-resistant, drug therapy; drug therapy, combination; drug resistance; antitubercular agents, administration and dosage; antitubercular agents, standards; rifampin, pharmacokinetics.

Mots clés: tuberculose pulmonaire, chimiothérapie; tuberculose résistante à la polychimiothérapie, chimiothérapie; polychimiothérapie; résistance aux médicaments; antituberculeux, administration et posologie; antituberculeux, normes; rifampicine, pharmacocinétique.

Palabras clave: tuberculosis pulmonar, quimioterapia; tuberculosis resistente a multidrogas, quimioterapia; quimioterapia combinada; resistencia a las drogas; agentes antituberculosos, administración y dosificación; agentes antituberculosos, normas; rifampin, farmacocinética.

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Introduction

Tuberculosis has been a scourge of mankind for thousands of years (*1*) and remains one of the largest health problems in the world today, with an estimated 8 million new cases and at least 2 million deaths every year (*2*). This burden is increased by human immunodeficiency virus (HIV) infection, which impairs the immune system and allows large numbers of people already infected with tuberculosis to progress to active disease. In many African countries, where more than 60% of those infected with HIV reside, this has led to an exponential increase in tuberculosis cases over recent years (*3–9*). The emergence of multidrug-resistant cases of tuberculosis also poses a major challenge to control of the disease worldwide (*10*) and tuberculosis experts and health policy-makers have urged a global response (*11*).

Effective treatment of tuberculosis patients with short-course multidrug chemotherapy is the cornerstone of the modern approach to the control of the disease. To emphasize this principle, WHO and the International Union Against Tuberculosis

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and Lung Disease (IUATLD), together with their partners, recommend the use of fixed-dose combination (FDC) formulations of the essential anti-tuberculosis drugs as one further step to ensure adequate treatment of patients (*12, 13*).

This article presents the justification for the change in treatment policy from single-drug formulations to FDCs and discusses the major challenges and possible solutions in this process.

Treatment options for tuberculosis

FDCs versus single drug formulations

Multidrug therapy is necessary to cure tuberculosis patients and to prevent the selection of drug-resistant mutants, which may arise during the course of treatment. The major advantages of using FDCs to treat tuberculosis are simplified treatment and drug management, and the reduced probability of monotherapy (*12–16*). By preventing monotherapy, it is expected that FDCs can limit the risk of emergence of drug-resistant tuberculosis, although this contention remains to be validated.

Simplifying treatment

One of the constraints in the conventional treatment of tuberculosis is that patients have to take a large number of tablets, usually 9–16 per day for 2 months (initial phase of treatment), followed by 3–9 tablets daily for 4–6 months (continuation phase). Using FDCs, the number of tablets to be taken can be reduced to as few as three or four per day for the whole course of the treatment (Table 1). Having fewer pills to swallow makes treatment easier, and minimizes the probability of splitting the doses or of taking only some of the drugs in the regimen. In a study conducted in Hong Kong (*17*), only 1% of 312 patients who received FDCs complained about the quantity of drugs to be ingested or about difficulty with swallowing, compared with 5% of 308 patients receiving the single drug preparations. Complaints relating to adverse effects were similar in the two groups. Use of FDCs may therefore improve the patient's compliance with treatment and limit prescription mistakes by simplifying the calculation of dosages. Where national guidelines are not readily available, and the treatment of tuberculosis is largely left in the hands of the private sector, the use of inadequate regimens may be more commonplace (*18*). In such a situation, FDCs might be a better option than use of single-drug formulations.

Table 1. **Example of the number of tablets to be taken daily in the initial phase of anti-tuberculosis treatment by a 50-kg patient either as single drugs or as a fixed-dose combination of four drugs**

Single drug tablets	No. of tablets	Fixed-dose combination	No. of tablets
Rifampicin (R) 150 mg	3	RHZE (150 mg + 75 mg + 400 mg + 275 mg)	3
Isoniazid (H) 300 mg (100 mg)[a]	1 (3)[a]		
Pyrazinamide (Z) 400 mg	3		
Ethambutol (E) 400 mg (100 mg)	2 (7)		
Total	**9 (16)**	**Total**	**3**

[a] Figures in parentheses refer to alternative dose formulations and related number of tablets.

For each of the drugs needed in the treatment of tuberculosis, there is a well-defined recommended dose per kg body weight (Table 2). In FDCs, these dose-to-body-weight relationships are carefully balanced between all the drugs in the combination, in order to ensure adequate dose delivery of all drugs at all times. With single drugs, problems of non-availability occur for three main reasons: no buffer stock, delays in receipt of orders, and no replacements in hand on reaching the expiry date. Moreover, the four single drugs involved (rifampicin, isoniazid, pyrazinamide and ethambutol) must frequently be ordered from different manufacturers. Thus any delay in the delivery of any one drug has consequences for the distribution of the complete treatment package to the peripheral health services. This issue has also to be considered when the four drugs are put together in blister-packs. With FDCs, however, there are fewer drug formulations, thus making it easier to calculate the drug needs. Because of fewer drug formulation orders, shipments and distribution involved, the efficiency of the tuberculosis drug supply system is improved.

FDCs and prevention of drug resistance

Besides tuberculosis, several other common infectious diseases can be treated successfully with rifampicin. Thus, thefts and black-market sales of this drug are not uncommon in countries where antibiotics for other common conditions (e.g. respiratory infections and sexually transmitted infections) are not readily available. Use of rifampicin on a wide scale for conditions other than tuberculosis may therefore lead to it being given as monotherapy to patients who unsuspectedly may also suffer from tuberculosis. Treating a tuberculosis patient with a monotherapy of rifampicin rapidly leads to resistance to the drug even if it is given for short periods only. In combination drugs, the presence of isoniazid reduces the probability for the survival of rifampicin-resistant mutants.

Multidrug-resistant tuberculosis (MDR-TB) refers to resistance to at least the two key first-line anti-tuberculosis drugs, rifampicin and isoniazid, and represents a condition that is very difficult and expensive to treat (*19*). Weyer et al. in South Africa found that one week's MDR-TB treatment, including cycloserine, cost the same as the full 6-month regimen for a new patient on the first-line regimen (*20*).

In view of the enormous costs and difficulties in treating drug-resistant tuberculosis, the highest priority must be given to preventing the emergence of drug resistance in the first place. The most important step in preventing drug resistance is to

ensure adequate treatment of all tuberculosis patients, particularly the sputum smear-positive cases. Acquired resistance most commonly follows erratic drug taking, i.e. interrupting treatment frequently and for long enough to allow re-growth of bacteria which might favour resistant mutants, and/or treating with a single drug which leads to the same effect. Multiple interruptions of treatment have been shown to be the predominant cause of drug resistance (*21, 22*). When using single-drug formulations, patients are more prone to continue their treatment with one drug while interrupting the others, thereby creating a risk of monotherapy and selection of drug-resistant mutants. Furthermore, situations such as expiry date having been surpassed or drugs being out-of-stock in treatment facilities, which might lead to some drugs being continued while waiting for new stocks of the others, represent another potential source of monotherapy. Such problems are prevented more easily if FDCs are used.

Some indirect evidence exists for the effect of FDCs on drug resistance patterns in high prevalence countries. Relatively low prevalences of MDR-TB have been recorded in Brazil and South Africa where good quality FDCs have been used for decades (*10, 23*). In Brazil, 0.9% of culture-positive tuberculosis cases in 1995–96 showed initial multidrug resistance (newly infected with MDR), and 5.4% showed acquired multidrug resistance because of previously incomplete treatment. In South Africa, the respective proportions were 1.1% and 4.0%.

The recommended strengths of FDCs

A 1998 WHO survey of the global market for FDCs showed that there is a significant number of such combinations available in the market, but with very little consistency in dose formulation. In fact, most of these preparations do not conform to the WHO dose specifications (*24*). Two- and three-drug FDCs already appear in the WHO Model List of Essential Drugs (*25*). In August 1998, the Technical Research and Advisory Committee (TRAC) to WHO's former Global Tuberculosis Programme recommended that a four-drug FDC for adults, as well as three paediatric FDCs be added to the WHO Model List of Essential Drugs (*26*). Table 3 provides an overview of the recommended strengths of FDCs in daily doses and intermittent (3 times a week) doses. These recommendations are based on the WHO dosage schedule given in Table 1.

For any drug there is a therapeutic range within which it is effective and not toxic. Table 4 and Table 5 show the dosage schedules for adults and children, respectively, demonstrating that for the anti-tuberculosis drugs included in FDC tablets, the simplified schedule according to body weight ensures that the doses remain within the therapeutic margins. In many tuberculosis control programme settings where FDCs are being used, a body weight cut-off of 50 kg is usually set as the weight at which an increase in the number of tablets is indicated. Below 50 kg, a

Table 2. **Recommended doses (per kg body weight) of essential anti-tuberculosis drugs**

Anti-tuberculosis drug	Mode of action	Recommended dose (mg/kg)	
		Daily	3 × per week
Isoniazid (H)	Bactericidal	5 (4–6)[a]	10 (8–12)
Rifampicin (R)	Bactericidal	10 (8–12)	10 (8–12)
Pyrazinamide (P)	Bactericidal	25 (20–30)	35 (30–40)
Ethambutol (E)	Bacteriostatic	15 (15–20)	30 (25–35)
Streptomycin (S)	Bactericidal	15 (12–18)	15 (12–18)
Thioacetazone (T)	Bacteriostatic	2.5	Not applicable

[a] Figures in parentheses are the dose ranges in mg/kg (*48*).

Table 3. **The recommended strengths of fixed-dose combination formulations of essential anti-tuberculosis drugs** (from ref. *49*)

Drug	Forms	Strengths[a]
Daily use		
Rifampicin + isoniazid + pyrazinamide + ethambutol	Tablet	R 150 mg + H 75 mg + Z 400 mg + E 275 mg
Rifampicin + isoniazid + pyrazinamide	Tablet	R 150 mg + H 75 mg + Z 400 mg R 60 mg + H 30 mg + Z 150 mg (paediatric)[b]
Rifampicin + isoniazid	Tablet	R 300 mg + H 150 mg R 150 mg + H 75 mg R 60 mg + H 30 mg (paediatric)[b]
Isoniazid + ethambutol	Tablet	H 150 mg + E 400 mg
Thioacetazone + isoniazid	Tablet	T 50 mg + H 100 mg T 150 mg + H 300 mg
Intermittent use (3 times weekly)		
Rifampicin + isoniazid + pyrazinamide	Tablet	R 150 mg + H 150 mg + Z 500 mg
Rifampicin + isoniazid	Tablet	R 150 mg + H 150 mg R 60 mg + H 60 mg (paediatric)[b]

[a] E = ethambutol, H = isoniazid, R = rifampicin, S = streptomycin, T = thioacetazone, Z = pyrazinamide.

[b] Dispersible form preferred.

Table 4. **Dosage schedule for FDCs of WHO-recommended strengths for adults[a]**

Patient's body weight (kg)	Initial phase: 2 months		Continuation phase: 4 months		6 months
	RHZE daily	RHZ daily	RH daily	RH × 3 weekly	EH daily
30–37	2	2	2	2	1.5
38–54	3	3	3	3	2
55–70	4	4	4	4	3
⩾71	5	5	5	5	3

[a] R = rifampicin, H = isoniazid, Z = pyrazinamide, E = ethambutol.

Table 5. **Dosage schedule for FDCs of WHO-recommended strengths for children**[a]

Patient's body weight (kg)	Initial phase: 2 months	Continuation phase: 4 months	
	RHZ daily	RH daily	RH × 3 weekly
⩽ 7	1	1	1
8–9	1.5	1.5	1.5
10–14	2	2	2
15–19	3	3	3
20–24	4	4	4
25–29	5	5	5

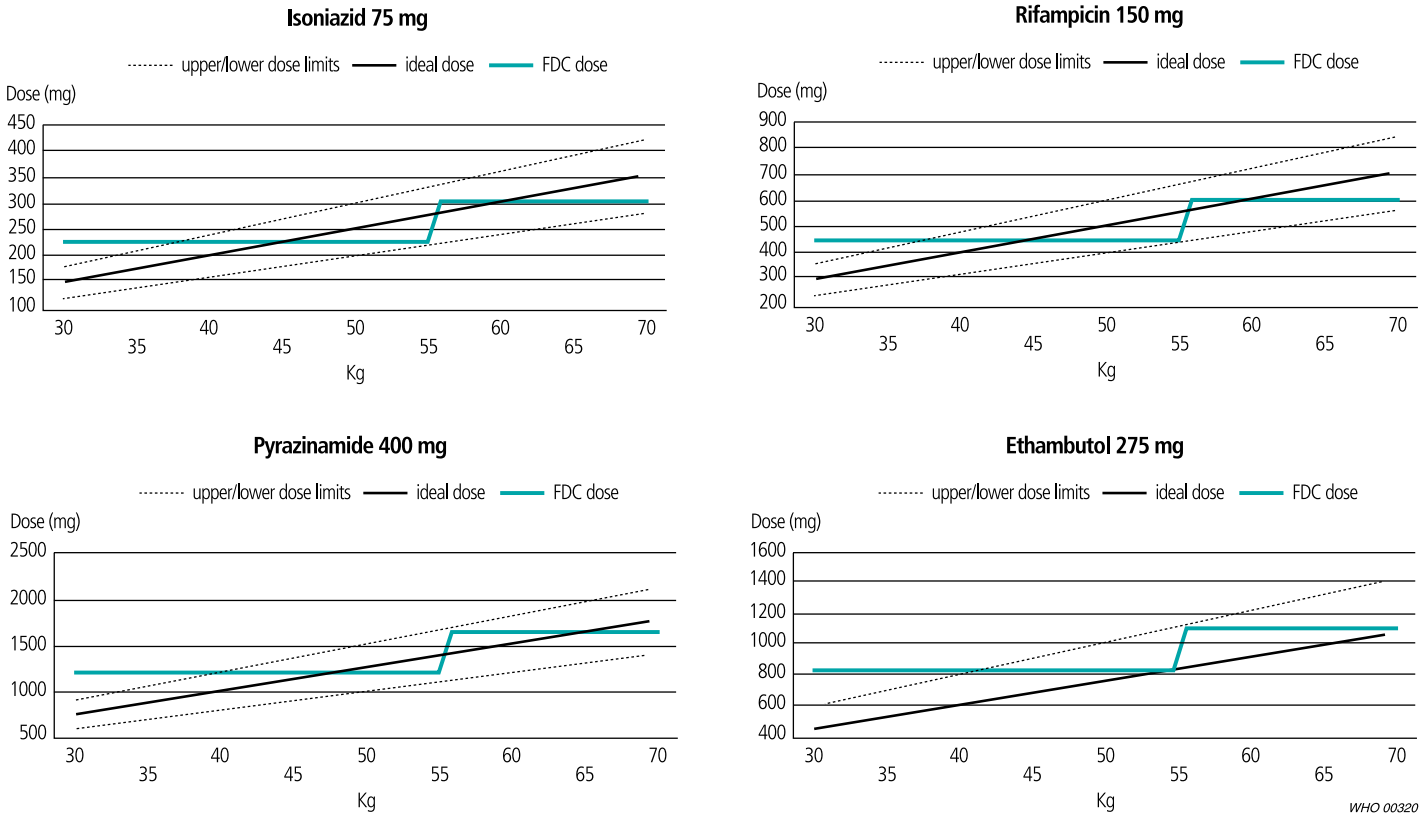
[a] R = rifampicin, H = isoniazid, Z = pyrazinamide.

patient would receive, for example, four tablets, and from 50 kg upwards, five tablets. This is done to ensure sufficient amounts of the drug to satisfy the mg/kg dose requirement in heavier patients; in other settings, different criteria are used, with an upper cut-off of 55 kg. In such a case, FDCs formulated specifically for a 50-kg body weight will be inapplicable. Current WHO-recommended FDCs, however, have been formulated in such a way that it satisfies both situations. Fig. 1 and Fig. 2 show that irrespective of whether the cut-off weight for changing from three tablets to four in the proposed four-drug FDC is at 50 kg or 55 kg, therapeutic efficacy is maintained because the mg/kg doses would be kept between the maximum and minimum recommended limits at all times; thus, for the vast majority of adults the number of tablets for both the initial phase and the continuation phase would be the same. For individuals weighing below 50 kg or 55 kg (depending on the decision of local national tuberculosis programmes) the dose would be three tablets, while for those over 55 kg it would be four tablets. For children weighing ⩾ 10 kg, the dose would be one dispersible tablet per 5 kg body weight. For lower body weights, the tablet dose would be halved and administered per 2.5 kg increments as appropriate.

FDCs and adverse effects

Adverse reactions to drugs are not more common if FDCs are used (*17, 27*). Nevertheless, whenever side-effects to one of the components in a FDC are suspected there will be a need for single-drug formulations. Adverse drug reactions, severe enough to warrant withdrawal of drugs, generally occur in only 3–6% of patients on tuberculosis treatment (*28–32*). These reactions may be more common in areas where the prevalence of HIV is high. Therefore, limited stocks of single-drug tablets should be

Fig. 1. **Plots illustrating the dose formulation of the anti-tuberculosis four-drug FDC containing isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg. Dose distributions employ a 55 kg body weight cut-off: 3 tablets up to 55 kg body weight, 4 tablets for body weight > 55 kg.** The weight range adequately covered by all drugs in the preparation, i.e. doses in mg per kg body weight not exceeding the minimum or maximum limits, is 40–72 kg



available in higher level referral centres where patients with severe adverse reactions to drugs could be managed under supervision.

The price of FDCs

A disadvantage of the three- and four-drug FDCs is that they are currently more expensive than the sum of the costs of the individual single-drug tablets. However, prices are expected to drop as competition and volumes of production increase. Indeed, some suppliers now sell the two-drug FDC with rifampicin and isoniazid at a lower price than the individual single-drug tablets of rifampicin and isoniazid (*33*). In addition, use of FDCs decreases the cost of managing drug supply, and may therefore further reduce the overall costs of delivering treatment to patients and preventing shortages of individual drugs.

FDCs and the DOT strategy

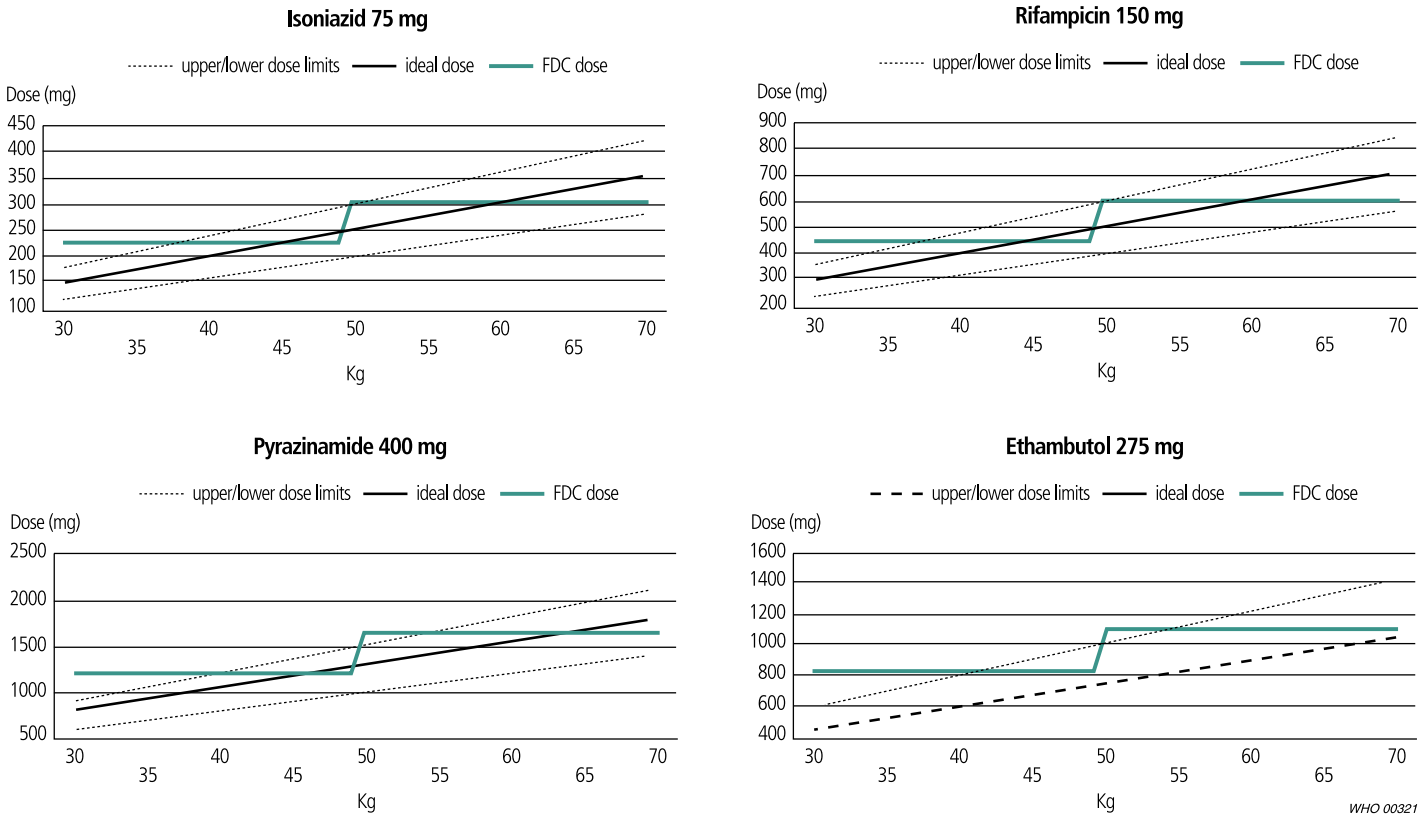
Although it simplifies both prescribing and drug taking, the use of FDCs does not eliminate the need for direct observation of treatment (DOT). Whether FDCs or single-drug tablets are used, the other components of the WHO/IUATLD recommended strategy for tuberculosis control remain vital for successful tuberculosis control. Particularly, the information system used in modern tuberculosis control programmes should be maintained so that the effects of a change in treatment policy to use FDCs can be properly monitored. Thus, FDCs are promoted as an integrated part of good service delivery, helping to ensure that the treatment given is of good quality.

FDCs of good quality facilitate accurate dose delivery, and ensure cure when given as directly observed treatment (*14*). However, inadequate doses, especially of rifampicin, may also lead to treatment failure and drug resistance. Thus, if FDCs are given unsupervised, patients can interrupt treatment repeatedly, and this may lead to emergence of drug resistance (*21*). The risk is best avoided by giving FDCs as directly observed treatment, at least during the initial phase of treatment.

Quality of FDCs

Using tuberculosis drugs of good quality is fundamental, since treatment with poor quality drugs will create drug resistance and fail to cure patients. While drug quality is important for all anti-tuberculosis drugs, there are particular concerns regarding the bioavailability of rifampicin in FDCs. Some studies have shown that while it is perfectly possible to obtain satisfactory bioavailability of rifampicin in FDCs, other studies have demonstrated inadequate bioavailability of rifampicin in some cases (*34–41*). Adequate results in dissolution tests are no guarantee that

Fig.2. **Plots illustrating the dose formulation of the anti-tuberculosis four-drug FDC containing isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg. Dose distributions employ a 50 kg body weight cut-off: 3 tablets up to 50 kg body weight, 4 tablets for body weight > 50 kg.** The weight range adequately covered by all drugs in the preparation, i.e. doses in mg per kg body weight not exceeding the minimum or maximum limits, is 40–72 kg



rifampicin will have acceptable bioavailability when FDCs are given to healthy adults (*34*). It appears that the bioavailability of rifampicin in FDCs is easily compromised if strict manufacturing procedures are not followed or poor quality raw materials are used.

If the bioavailability of rifampicin is inadequate, as might be the case in substandard FDCs, treatment failures and emergence of drug-resistant tuberculosis could follow. Thus, it is an absolute requirement to purchase and use only FDCs that have been proved to have full rifampicin bioavailability. Procurement and regulatory bodies in individual countries should be strongly encouraged to insist on obtaining data proving the bioavailability of rifampicin, in addition to other quality assurance data when purchasing and distributing FDCs.

Giving FDCs with poor rifampicin bioavailability means giving inadequate therapy, without even being aware of it. Because of a narrow therapeutic margin (*21*), the rifampicin dose is crucial. Consequently, using FDCs of poor rifampicin bioavailability could lead directly to a poor treatment outcome and may create, not prevent, drug resistance. Good quality and proven rifampicin bioavailability are absolute requirements for successful tuberculosis control in programmes utilizing FDC-based regimens. WHO, IUATLD and partners are currently establishing strategies for quality assurance of FDCs. A simplified protocol for testing of rifampicin bioavailability has been developed (*42, 43*), and laboratories are being recruited to form an international network for quality assurance and rifampicin bioavailability testing for FDCs. A global mechanism for pre-qualification of FDCs has been proposed to ensure that only quality FDCs will be purchased and used (*44*).

A further point of concern lies with the potential for poor absorption of drugs in tuberculosis patients co-infected with HIV. If this possibility turns out to be correct, it may have disastrous consequences for tuberculosis control efforts in countries with high HIV prevalence. Current indications are that poor absorption predominantly occurs in patients with symptoms of AIDS and with CD4 counts <200 cells/mm^3. In all other cases, there is no difference between HIV-positive and HIV-negative patients in the pharmacokinetics of any of the first-line tuberculosis drugs, whether administered as single drugs or as FDCs (*45, 46*).

Registration of FDCs

Pharmaceutical products of good and poor quality circulate in international trade (*47*). The registration process and the institutions responsible for registration of drugs are fundamental elements to ensure that only drugs of good quality are purchased and used in any country. Registration of pharmaceutical products should ensure not only that the product itself is of good quality, but also that the manufacturer adheres to recognized good manufacturing practices (GMP) and that proper quality control is in place. Only in this way is it possible to ensure reliable supplies and long-term availability of quality FDCs.

WHO and its partners are working to develop and strengthen mechanisms for registration of FDCs. Among other issues, the feasibility of establishing a global mechanism for pre-qualification of FDC manufacturers is being evaluated. A fast-track process for registration of four-drug FDCs and reduction of registration fees and import taxes has been proposed to help making registration of FDCs swifter (*48*). There must be strong emphasis on the quality of FDCs in the registration process, with proven rifampicin bioavailability being an absolute requirement for registration and procurement.

Careful preparation will be necessary when FDCs are introduced into a national tuberculosis programme. Operational research will need to be undertaken to assess the effect of using these drugs on patients' adherence and attitudes to the new large tablets, and a system to monitor for adverse effects. As always, cohort analysis should be used to assess the effect of the introduction of these tablets to assess outcomes. In larger countries, it may be useful to phase in the introduction of these new tablets to allow some provinces to serve as controls for other provinces where the intervention is being applied. ■

Résumé

Les raisons de recommander les associations fixes en comprimés pour le traitement de la tuberculose

Il est indispensable de prendre toutes les mesures qui s'imposent pour parvenir à la guérison des cas de tuberculose et empêcher toute nouvelle émergence de la tuberculose multirésistante. La plus importante de ces mesures consiste à assurer que le traitement, notamment celui des cas à frottis positif, est adapté et que les patients s'y conforment grâce à l'observation directe de la prise des médicaments selon la posologie standard.

L'utilisation d'associations fixes d'antituberculeux en comprimés est maintenant recommandée par l'OMS et l'Union Internationale contre la Tuberculose et les Maladies Respiratoires (UICTMR) en tant que mesure supplémentaire visant à assurer un traitement correct. Ces comprimés simplifient à la fois la prescription des médicaments et la gestion des approvisionnements et peuvent aussi limiter le risque d'apparition d'une tuberculose multirésistante à la suite d'un choix thérapeutique inapproprié et comme conséquence de la monothérapie.

Seuls les comprimés d'associations fixes de qualité avérée et dont la biodisponibilité de la rifampicine a été démontrée devront être achetés et utilisés. Dans la plupart des cas, les taux sanguins de médicaments sont insuffisants en raison d'un défaut de qualité du

médicament plutôt que d'une mauvaise résorption, et cela quel que soit le statut des malades vis-à-vis de l'infection par le virus de l'immunodéficience humaine (VIH) (à l'exception de ceux qui présentent un syndrome d'immunodéficience acquise avéré, avec une numération des CD4 inférieure à 200/mm^3). Actuellement, l'OMS, l'UICTMR et leurs partenaires mettent au point des stratégies permettant d'assurer que seuls des comprimés d'associations fixes de qualité sont utilisés dans les programmes de lutte contre la tuberculose. Un protocole simplifié et efficace d'évaluation de la biodisponibilité de la rifampicine a été établi, et un réseau supranational de laboratoires est en cours de constitution pour l'assurance de la qualité de ces comprimés. Il a été proposé de normaliser la formulation des associations fixes afin de limiter à neuf le nombre de préparations contenant de la rifampicine (dont un comprimé contenant une association de quatre médicaments et trois comprimés à usage pédiatrique).

Resumen

Razones para recomendar las combinaciones de dosis fija como tratamiento de la tuberculosis

Urge tomar todas las medidas necesarias para curar los casos de tuberculosis y evitar que siga propagándose la variante farmacorresistente de esa enfermedad. La más importante de esas medidas consiste en asegurar que el tratamiento sea el adecuado, en particular en los casos con esputo positivo, comprobando el seguimiento de la medicación mediante la observación directa y supervisada de la toma de los fármacos por el paciente de acuerdo con lo previsto en los regímenes normalizados.

La OMS y la Unión Internacional contra la Tuberculosis y las Enfermedades Pulmonares (IUATLD) recomiendan hoy el uso de combinaciones de dosis fija (CDF) contra la tuberculosis como medida adicional para garantizar un tratamiento idóneo. Las CDF simplifican la prescripción de los medicamentos y la gestión del suministro de fármacos, y además pueden limitar el riesgo de tuberculosis farmacorresistente que resulta de una selección inadecuada de medicamentos y de la monoterapia. No obstante, con las CDF sigue siendo necesaria la observación directa de los pacientes para confirmar que se tomen los medicamentos.

Sólo deben comprarse y emplearse CDF de calidad demostrada que garanticen una adecuada biodisponibilidad de la rifampicina. En la mayoría de las situaciones, los niveles sanguíneos de los medicamentos son insuficientes, de resultas no tanto de una mala absorción como de su mala calidad. Ello es así con independencia de la serología VIH de los enfermos de tuberculosis (exceptuando los casos de SIDA declarado, con recuentos de CD4 < 200 células/mm^3). Actualmente, la OMS, la IUATLD y otros asociados están desarrollando estrategias para garantizar que en los programas contra la tuberculosis sólo se empleen CDF de alta calidad. Se ha desarrollado un protocolo simplificado y eficaz para evaluar la biodisponibilidad de la rifampicina, y se está reclutando a diversos laboratorios para constituir una red supranacional de garantía de la calidad de las CDF. Se ha propuesto una normalización de los preparados de CDF, que limita a nueve los que contienen rifampicina (entre ellos una CDF de cuatro medicamentos y tres CDF de uso pediátrico).

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