The treatment results of patients with multidrug resistant tuberculosis and factors affecting treatment outcome

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ÖZET

Çok ilaca dirençli tüberküloz hastalarının tedavi sonuçları ve tedavi sonucunu etkileyen faktörler

Çok ilaca dirençli tüberküloz (ÇİD-TB) tedavisi kompleks bir tedavidir ve sonuçlar her zaman tatmin edici değildir. Çalışmamızda hastalarımızın tedavi sonuçlarını, nüks oranlarını ve tedavi sonuçlarını etkileyen faktörleri incelemeyi amaçladık. Ocak 1995-Aralık 2000 tarihleri arasında, Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesindeki kliniğimizde, ÇİD-TB tanısı ile tedavi gören 142 hastayı ileriye dönük olarak inceledik. Tüm hastalarımız erkek ve insan immünyetmezlik virüsü negatif hastalardı. Yaş ortalaması 39 ± 11 (16-65) idi. Tedavide, biri parenteral olmak üzere, ortalama 5.5 ± 0.8 (4-8) adet ikinci sıra tüberküloz ilaçları kullanıldı. Yüz kırk iki hastanın 102 (%71.8)'sinde kür sağlandı. Tedavi başarısızlığı 10 (%7.0) hastada görüldü. Hastaların 16 (%11.3)'sı tedaviyi terketti ve 14 (%9.9) hasta tedavi sırasında kaybedildi. Cerrahi rezeksiyon 35 hastaya uygulandı ve bunların %88.5'inde kür sağlandı. Kür olan 102 hastanın 89 (%87.2)'u takip edildi ve ortalama takip süresi 19.2 ± 10.3 (12-72) aydı. Hiçbirinde nüks saptanmadı. Başarısız tedavi sonucu olan hasta grubunda; önceki tedavi rejimlerinde protionamid ve ofloksasin kullanım sıklığı, ikinci sıra tüberküloz ilaçlarının kullanım sıklığı ve sayısı, yaygın radyolojik tutulumu olan olguların sıklığı ve ilaç yan etkisi nedeniyle ilaçların kesilme oranı daha yüksekti. Sınırlı radyolojik tutulum, protionamidin daha önceki tedavi rejimlerinde kullanılmamış olması ve adjuvan cerrahi, tedavi başarısını etkileyen bağımsız faktörler olarak tespit edildi. ÇİD-TB, karmaşık, müdahalesi zor ancak tedavi edilebilir bir hastalıktır. Tedavi sonucuna etki eden faktörlerin iyi bilinmesi ve uygun koşulların sağlanması, gelecekte başarı oranlarının daha da artmasını sağlayacaktır.

Anahtar Kelimeler: *Çok ilaca direnç, pulmoner tüberküloz, tedavi.*

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SUMMARY

The treatment results of patients with multidrug resistant tuberculosis and factors affecting treatment outcome

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The treatment of multi-drug resistant tuberculosis (MDR-TB) is complicated and results are not always satisfactory. We aimed to investigate treatment results of our patients, relapse rates, factors affecting treatment outcome. We evaluated prospectively, 142 patients, who had been hospitalised with diagnosis of MDR-TB in our clinic between January 1995-December 2000 at Sureyyapasa Chest Diseases and Chest Surgery Training and Research Hospital in Istanbul, Turkey. All patients were male and human immunodeficiency virus negative. The mean age was 39 ± 11 (16-65) years. A mean number of 5.5 ± 0.8 (4-8) second line drugs, including one parenteral drug, were administered. Of 142 patients, 102 (71.8%) were classified as cured, 16 (11.3%) patients were defaulters, failure was seen in 10 (7.0%) patients and 14 (9.9%) patients died during treatment. Surgical resection was applied in 35 patients and cure was achieved in 88.5% of them. Of 102 patients who were cured, 89 (87.2%) were available for follow up and mean duration of follow up was 19.2 ± 10.3 (12-72) months. Relapse was not detected in any of them. Patients with unsuccessful outcomes had a higher incidence and higher mean number of second-line drugs usage in previous regimens, higher incidence of antecedent prothionamide and ofloxacin usage, higher incidence of extensive radiologic involvement and withdrawal of responsible drugs due to adverse effects. Limited radiologic invovement, non-usage of antecedent prothionamide and adjuvant surgery were found as significant independent factors effecting successful treatment outcome. MDR-TB is a complex but a treatable disease. To know much more about the factors effecting treatment results and to arrange the proper conditions, are expected to make increases in the success rates of MDR-TB treatment.

Key Words: *Multidrug resistance, pulmonary tuberculosis, treatment.*

Antituberculous drug resistance is one of the important factors affecting treatment success. Multi-drug resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid (H) and rifampin (R), had been thought to be difficult to treat, even impossible in developing countries (1). However, attempts to treat MDR-TB cases was initiated by Iseman in US during 1990's and successful treatment results achieved at different countries in the following years (2-4). Neverthless long duration of treatment, drug toxicity, high cost and low socioeconomic conditions made both doctors and patients exhausted during MDR-TB treatment.

The treatment of MDR-TB patients in Turkey had been iniated in Sureyyapasa Chest Diseases and Chest Surgery Center first in Istanbul and treatment results of the patients treated in our hospital, had been announced first in 2001 (5). The aim of the present study was to evaluate the treatment results of MDR-TB patients who were followed by our clinic and to analyze the factors thought to be related with treatment success.

MATERIALS and METHODS

We enrolled all patients, who had been hospitalised with diagnosis of MDR-TB in men's ward of our clinic between January 1st, 1995-December

31st, 2000 at Sureyyapasa Chest Diseases and Chest Surgery Training and Research Hospital in Istanbul, Turkey. Radiology, bacteriology, biochemistry and pathology laboratories, lung function tests, computed tomography, bronchoscopy and surgery departments are also available in our center. All patients were to recieve state social and health services and all expanses during treatment were covered by health department of Work and Social Security Ministry. Our center offers long term hospitalization and after discharge patients have a chance of rest excusing them from their work for some time. The patients were hospitalised as long as aminoglycoside injection continued lasting at least three months after culture conversion; duration of hospitalization was also related to period of sputum smear and culture conversion and adverse effects of treatment so that patient could tolerate the drugs.

We evaluated the patients prospectively according to the clinical, radiological, bacteriological findings, treatment results, relapse rates and factors affecting treatment results.

Patients

New cases of tuberculosis, receiving drugs under direct observation at hospital, were treated with first line (S) drugs according to National Tuberculosis Control Programme; namely with isoniasid, rifampin, pyrazinamide, ethambutol or streptomycin during the initial phase, and with H and rifampin during the continuation phase. Because of delay in obtaining the results of susceptibility tests (a period of 2 to 3 months), we continued treatment protocol in patients with new infections unless there was a positive smear in the fifth month after initiation of treatment. Such a smear was considered to indicate treatment failure due to MDR-TB and further treatment was individualized for these patients after resistance at least against isoniazid and rifampin was presented with drug susceptibility tests.

New cases of tuberculosis, receiving drugs without direct observation, were treated as above. If positive smear was detected at fifth month of treatment, they were also accepted as failure; neverthless as their compliance was unknown, they were retreated with eight months regimen (2HRZES + 1HRZE + 5HRE). Smear positivity at eight months of retreatment was considered as failure, and these cases were treated as MDR-TB patients with the promoting drug susceptibility test results (6).

For patients with history of previous infections (relapse or defaulter), they were considered as MDR-TB after eight months regimens containing isoniazid and rifampin were failed (6). To make the decision for initiating MDR-TB treatment, previous medical records were rewieved and resistance at least against isoniazid and rifampin was presented with drug susceptibility tests.

All patients were given an informed concent form about drugs in use, adverse affects, duration of treatment and asked to sign it before onset of treatment. Ethic approval was obtained from the Scientific and Training Programme Committee of our own hospital.

Treatment and Follow up

Second-line drugs, occasionally, an aminoglycoside (amikasin, capreomycin), a quinolone derivative (ofloxacin, ciprofloxacin), prothionamide and cycloserine were used in treatment of MDR-TB patients and some of the first line drugs, such as pyrazinamide and ethambutol, thought to be susceptible, were included in the new regimen. If quinolone derivatives and prothionamide had already been used in previous regimen, drugs such as clofazimine, para-aminosalycylic acid (PAS), thioacetazone, amoxicillin-clavulanic acid and capreomycin were included in the regimen (3,7).

During the treatment, all patients were followed with sputum smear for acid-fast bacilli and Löwenstein-Jensen culture and chest X-ray for every month. The duration of treatment for MDR-TB cases was 18 months after achieving culture conversion, however it was 24 months if there was no major drug in the regimen. At the end of the treatment, all patients were evaluted with culture to decide treatment result. Aminoglycosides were administered five days a week untill three months after culture conversion. All patients were hospitalised during aminoglycoside administration and recieved drugs under direct observati-

on. They were observed closely for drug adverse effects and when complaints were identified and persisted even though with the ancillary drugs, responsible drugs were withdrawn from the regimen. Audiometric tests were performed for all patients at the begining of the treatment and whenever complaints about hearing were detected. After discharge from hospital, one of the family members was assigned with controlling the continuation of the treatment. Follow up evaluations were done at 3rd, 6th, 12th, 18th, 24th months after the completion of treatment and included smear microscopy, culture tests and chest X-ray.

Bacteriological and Radiological Evaluation

A combination of sputum smear microscopy using Ziehl-Neelsen technique and Löwenstein-Jensen culture medium was used for diagnosis and follow up. All sputum samples were processed in laboratory of our center, homogenised with 2% N-acetyl-L-cystein, 3% NaOH, 1.47% trisodium citrate and centrifuged at 3500 rpm/rcf for 15 min. Identification of isolates was based on para-nitrobenzoic acid (500 mg/L) test. Drug susceptibility testing was performed to all the initial tuberculous patients and performed using proportion method on Löwenstein-Jensen medium, as described by Canetti et al. (8). An isolate was considered resistant if there was > 1% growth of *Mycobacterium tuberculosis* complex in the presence of 1 µg/mL for isoniazid, 40 µg/mL for rifampin, 2 µg/mL for ethambutol and >10% growth in the presence of 8 µg/mL for streptomycin. Primary resistance is defined as the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, deny having had any prior anti-tuberculous treatment (for as long as one month); whereas acquired resistance is defined as the presence of resistant isolates who admit having been treated for tuberculosis for one month or more (9).

The radiologic involvement of disease was categorised as extensive or limited according to chest X-rays. Extensive involvement was defined as sum of cavity diameters totalling 15 cm or dense infiltrates involving more than 75% of lung fields or both (10).

Treatment Results

Cure was defined as negative smear and culture throughout treatment for at least 18 months (or 24 months, in the absence of first line drugs) and if only one positive culture was reported during that time and there was no concomitant evidence of deterioration, a patient may still be considered cured, provided that this positive culture was followed by a minimum of three consecutive negative cultures. Treatment failure was defined as persistence of positive smear and culture despite treatment for 18-24 months. Defaulter was defined as failure to complete treatment for any reason. Death was accepted to be of any reason including tuberculous. Relapse was recurrence of positive smear or culture after achievement of cure.

Surgery

Surgical resection was considered as an adjuvant therapy after at least two months of therapy for the patients who met the criteria recommended by Iseman et al.: drug resistance with high probability of failure or relapse, sufficiently localized disease with adequate cardiopulmonary reserve and the availability of drugs with adequate efficacy to cause rapid healing of the bronchial stump (11). Computed thorax tomography, spirometry, quantitative lung perfusion scan, arterial blood gases and fiberoptic bronchoscopy were performed for preoperative evaluation.

Factors Affecting Treatment Outcome

Treatment outcome was classified as successful outcome (cure) and poor outcome (treatment failure, defaulter and death) and the classification was performed according to the recommendations of the World Health Organization (WHO) (12). Age of the patients, duration of tuberculous disease, radiologic involvement of disease (extensive or limited), second-line drug usage in previous treatment, presence of primary or acquired resistance, withdrawal of the responsible drugs due to adverse effects, duration of smear and culture conversion, adjuvant resectional surgery were analysed as factors thought to be related with treatment outcome.

Statistics

The data were analyzed by using SPSS for Windows 15.0 statistics programme. Differences with regard to numerical values were analyzed with the use of Student's t-test for variable with normal distributions and the Mann-Whitney U test for those without normal distributions. Nominal variables were assessed by the chi-square test. Logistic regression was used to determine independent predictive factors for successful treatment outcome. $p< 0.05$ was considered to indicate statistically significance.

RESULTS

Patients

One hundred fourty two male patients who were hospitalized in men's ward were included in our study and the mean age of patients was 39 ± 11 (16-65) years old. 49.3% (n= 70) were living out of Istanbul. 40.8% (n= 58) of patients had at least one concomitant disease. Chronic obstructive pulmonary disease (COPD) and diabetes mellitus were the most common diseases with the rate of 21.8% (n= 31) and 12% (n= 17), respectively. Extensive radiologic involvement was seen in 83 (58.5%) cases. The history of tuberculous in their families was present in 12% (n= 17) of the cases.

The mean duration of disease before hospitalization with diagnosis of MDR-TB was 7.9 ± 7.3 (range 1 to 35) years. The mean number of drugs used in previous regimens was 5.7 ± 1.7 (range 3 to 12) and second line drugs had been used in 43% (n= 61) of the patients in their previous regimens. Ofloxacin and prothionamide existed with first-line drugs in 31% and 36% of the previous regimens, respectively. The mean number of first-line drugs which resistance was shown was 4 ± 1 (2-5). Twenty three (16.2%) cases had primary resistance whereas 119 (83.8%) had acquired resistance.

Treatment and Drug Adverse Effects

The mean duration of hospitalization was 261.7 ± 127.6 (68-978) days. One patient had stayed in hospital for 978 days because of post-op complications. During hospitalization a mean number of 5.5 ± 0.8 (range 4 to 8) second line drugs, including one parenteral drug, was administered. The drugs and their dosages were shown in Table 1. The most commonly administered drugs were ofloxacin, cyloserine, prothionamide. Adverse effects of drugs were identified in 55.6% (n= 79) of the patients and were seen most commonly with cyloserine, amikasin and PAS (Table 2). Adverse effects resulted in withdrawal of responsible drugs in 35.2% (n= 50) of the patients. One patient died because of drug-induced hepatitis even after complete discontinuation of all drugs.

Treatment Results and Follow up

Smear and culture conversion had been achieved in 132 (93%) patients after a mean of 2.3 ± 1.5 (1-9) months of treatment. Of 142 patients, 102 (71.8%) were classified as cured, 16 (11.3%) patients were defaulters, failure was seen in 10 (7.0%) patients and 14 (9.9%) patients died during treatment. Causes of death related to tuberculous were: acute respiratory failure (ARF) due to extensive tuberculous in one patient, post-operative ARF in two patients and toxic hepatitis probably due to MDR-tuberculous drugs in one patient. The others died with the causes of concomitant COPD (n= 7), diabetic ketoacidosis (n= 1), chronic renal failure (n= 1) and renal amyloidosis (n= 1). Of 102 patients who were cured, 13 patients were not available for follow up after treatment completion. For the remaining 89 (87.2%) patients, the mean duration of follow up was 19.2 ± 9.9 (range 11 to 60) months. Relapse was not detected in any of them.

Surgery

Surgical resection was performed in 35 appropriate patients (24% of all) after 3 to 15 months of treatment (mean, 7.6 months). Before surgery, bacteriologic conversion was achieved in all patients. Bronchopleural fistula and empyema were detected in one patient as post-operative complication. Two patients died because of post-operative acute respiratory failure. Surgical mortality and morbidity rates were 5.7% (n= 2) and 2.8% (n= 1), respectively. Of 35 patients who underwent surgery, 31 had cures and cure rate reached to 88.5% in this group (Table 3).

Table 1. Drugs and their doses used in the treatment of MDR-TB.

Name of the drug	Number of patients (n)	%	Dose used
Ofloxacin	125	88	600-800 mg/day
Cycloserine	122	86	750-1000 mg/day
Protionamide	121	85	750-1000 mg/day
Aminosalicylic acid	118	83	12 g/day
Amikacin	110	78	15 mg/kg (mx 1 g/day)
Pyrazinamide	47	33	20-30 mg/kg/day
Ethambutol	24	17	15-25 mg/kg/day
Clarithromycin	21	15	1000 mg/day
Rifabutin	20	14	300 mg/day
Kanamycin	16	11	15 mg/kg (mx 1 g/day)
Amoxilline-clavulanic acid	15	11	2-4 g/day
Clofazimine	14	10	300 mg/day
Thiacetasone	7	5	300 mg/day
Capreomycin	6	4	15 mg/kg (mx 1 g/day)
Streptomycin	5	4	15 mg/kg (mx 1 g/day)

Table 2. Adverse effects of second line antituberculosis drugs used during treatment of MDR-TB patients.

Name of drug	Number of patients taking drugs	Number of patients with adverse effects (%)	Adverse effect
Cycloserine	122	33 (27)	Psychosis, depression
PAS	118	20 (17)	Nausea, vomiting, skin reaction
Amikacin	110	24 (22)	Hearing loss, tinnitus, vertigo
Kanamycin	16	3 (19)	Hearing loss
Protionamide	121	7 (6)	Nausea, vomiting hepatotoxicity
Ofloxacin	125	3 (3)	Nephrotoxicity
Pyrazinamide	47	1 (2)	Arthralgia

PAS: Para-aminosalycylic acid.

Table 3. The treatment results in group with surgical resection and without surgical resection.

	n	Cure	Treatment failure	Defaulter	Death
Cases with surgical resection	35	31 (88.5%)	1 (2.9%)	1 (2.9%)	2 (5.7%)
Cases without surgical resection	107	71 (66.4%)	9 (8.4%)	15 (14.0%)	12 (11.2%)
Total	**142**	**102 (71.8%)**	**10 (7.0%)**	**16 (11.3%)**	**14 (9.9%)**

Table 4. Characteristics of patients, treatment regimens and disease in relation to treatment outcome.

Variable	Unsuccessful outcome n (%)	Successful outcome n (%)	p
Previous use of minor drugs	24 (60.0)	37 (36.3)	0.01
Previous use of prothionamide	21 (52.5)	31 (30.4)	0.01
Previous use of ofloxacin	19 (47.5)	25 (24.5)	0.008
Mean number of previously used minor drugs	1.3 ± 1.4	0.8 ± 1.4	0.03
Drug withdrawal due to side effects	20 (50.0)	30 (29.4)	0.02
Extensive radiologic involvement	30 (75.0)	53 (52.0)	0.01
Application of surgery	4 (10.0)	31 (30.4)	0.01
Mean age of patients	40.8 ± 9.5	38.5 ± 12	0.2
Mean age of disease	9.6 ± 6.8	7.3 ± 7.4	0.08
Mean duration of conversion (months)	2.6 ± 1.6	2.2 ± 1.5	0.1
Drug resistance			
Primary	4 (10.0)	19 (18.6)	0.2
Acquired	36 (90.0)	83 (81.4)	0.2

Table 5. Factors effecting successful treatment outcome according to logistic regression analysis.

Variables*	ß	p	OR	95% CI
Non-usage of antecedent prothionamide	0.974	0.02	2.65	1.16-6.02
Limited radiologic involvement	1.03	0.01	2.82	1.20-6.64
Treatment without adjuvant surgery	-1.188	0.04	0.30	0.09-0.96
Constant	1.89	0.03		

* Variables included in the logistic regression model; age of the patients, radiologic involvement of disease (extensive or limited), prothionamide usage in previous treatment, presence of primary or acquired resistance, adjuvant resectional surgery.
Successful treatment outcome: 1.89 + 0.974 * non-usage of antecedent prothionamide + 1.038 * limited radiologic involvement-1.188 * treatment without adjuvant surgery.

Factors Affecting Treatment Outcome

There were no statistically significant differences between the group of patients with successful outcomes and the group with poor outcomes, with regard to age of patients, age of tuberculous disease, presence of primary or acquired resistance, duration of smear and culture conversion. However, patients with unsuccessful outcomes had a higher incidence and higher mean number of second-line drugs usage in previous regimens, higher incidence of antecedent prothionamide and ofloxacin usage, higher incidence of extensive radiologic involvement and withdrawal of responsible drugs due to adverse effects (Table 4). Adjuvant resectional surgery had been performed in 10% of the group with unsuccessful outcome and 30% of the group with successful outcome and the difference was statistically significant (p= 0.01). Logistic regression showed that limited radiologic invovement of disease, non-usage of antecedent prothionamide and adjuvant surgery had significant independent effects on successful treatment outcome (Table 5).

DISCUSSION

Prevalance of MDR-TB, constituting a serious morbidity and mortality cause, has increased in recent reports (13,14). Drug resistance has also become a great problem in Turkey because of treatment non-adherence, inappropriate and insufficient treatment approaches, treatment wit-

hout direct observation and patients' low socioeconomic status. Failure to control the use of antituberculosis drugs will inevitably make MDR-TB even more common. Untill it was prevented by ministry of health, between the years 1970-1980, commercial marketing of the combination drug included penicillin and streptomycin was widely used for infections other than tuberculous and rifampin was sold without any restrictions. In recent years, second-line antituberculosis drugs have also become available without restrictions. However, the absence of second-line drugs in previous regimens was associated with a successful outcome of MDR-TB treatment. Similarly with our study, Tahaoglu et al. had reported that inclusion of ofloxacin in previous regimens was significantly associated with a poor outcome of MDR-TB treatment (5). The present study also reported that non-usage of antecedent prothionamide had a significant independent effect on successful treatment outcome.

The treatment of MDR-TB is complicated, risky and results are not always satisfactory (13). On the other hand, a number of studies have pointed out that MDR-TB is a treatable disease (6,10). With the highlight of the present study, we also suggest that MDR-TB can be treated succesfully when appropiate conditions are fullfilled. All but two patients died out of tuberculous inducement in our study, though this result understate our treatment success, cure rate was found as 71.8%. In an early study of Goble et al. belonging to years 1973-1983, an overall response rate of 56% was reported. In more recent studies, cure rate was detected as 68% in Korea, 75% in Netherlands, 77% in Turkey, 93% in Peru (5,6,15-17). Otherwise the response rates have been higher in countries where directly observed therapy (DOT) was performed in, with the cure rates of 79% in USA, 69% in Korea, 48% in Peru (18-20).

Adherence to MDR-TB treatment is particularly difficult because of prolonged treatment regimens with higher number of drugs that have serious adverse effect profiles, but adherence to therapy is an essential element for treatment success (15,16). DOT is therefore vital to support patients with the adverse reactions, to ensure adherence to treatment, and to avoid the acquisition of resistance to additional agents (16,17,21,22). Adverse effects may increase the risk of default or irregular adherence to treatment, and poor management of them may result in death or permanent morbidity (23). In our study, withdrawal of the responsible drugs due to adverse effects was found to be related with the treatment outcome. Although the DOTS-plus strategy recommended by World Health Organization (WHO) is currently not implemented in our country, during hospitalization period (meanly 261.7 ± 127.6 days), drugs were administered to our patients under direct observation by nurses of our clinic. After discharge from hospital, one of the family members was assigned with controlling the continuation of the treatment. Though administration of drugs for three times a day is a difficulty for direct observation, methods of direct observation should be forced extensively for this population, with high risk of treatment non-adherence.

Surgical resection which has been shown to be effective and safe under appropriate surgical conditions was recommended for MDR-TB patients, with non-healing cavities or destroyed lung parenchyma according to Iseman's protocol (11,24,25). In 15 years-period between 1984-1998, surgical resection was performed in 66% of patients who were treated in Iseman's clinic. Various studies concerning MDR-TB reported that surgical resection has affected treatment outcome (5,24,26). It was reported that when adjuvant surgery was applied with a medical treatment of 18-24 months, culture yields negative results in nearly 99% of patients (11,27,28). In our study, surgical resection was performed in 35 patients and higher cure rate (88.5%) was achieved in this group corresponding with the group which surgical resection was not performed. It was found as an independent predictive factor for successful outcome, however we suggest that the effect of surgery to treatment outcome requires validation by extended and comparative studies.

Among our 102 cured patients, 88.1% were available for follow up, relapse was not detected in any of them. Various studies reported 0-4% of relapse rate, within two-four years after comple-

tion of therapy, in non-human immunodeficiency virus (HIV) patients (9,19,29-32). Munsiff et al. reported low relapse rates over a long follow-up period of up to eight years with the recommended treatment regimens, but they also indicated the difference between HIV-infected and non-infected patients. The overall relapse rate was 2.06 per 100 persons-years of follow up for HIV-infected patients while it was 0.52 for non-HIV-infected subjects (33). Relapse has traditionally been considered as endogenous rectivations of the same strain that caused the first episode but with the availibility of molecular biology techniques, a previous study has indicated that exogenous re-infection may be the leading cause of reccurence (34). This may be also interpretted as a proof of successful outcome of MDR-TB treatment.

As a conclusion, we suggest that MDR-TB is a treatable disease, although the treatment is a complex health intervention. Patients with unsuccessful treatment outcomes had a higher incidence of second line drug usage in previous regimens. In addition to the levels of drug resistant tuberculous incidence, treatment success of MDR-TB is also more likely related to the lack of a standardized therapeutic TB regimens and this result underlines the importance of TB control programmes and their quality. An effective TB control programme, constant securing a sufficient number of effective second-line anti-tuberculosis drugs and their administration under DOT, a qualified team-work with the support of thoracic surgery in case of necessity, increase the rate of treatment success and can provide satisfactory results.

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