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Assessment of treatment outcomes of multidrug-resistant tuberculosis patients in D R Congo: A study based on drug regimens used between 2007 to 2017

Évaluation des issues thérapeutiques des patients atteints de la tuberculose à bacilles multi résistants : *étude basée sur les régimes de médicaments utilisés en République Démocratique du Congo de 2007 à 2017*

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Résumé

Contexte. L'issue thérapeutique de la tuberculose multi résistante (TB-MR) sous les molécules de deuxième intention n'est pas très bien connue. La présente étude a évalué les régimes thérapeutiques appliqués, en termes de succès thérapeutique et de survie. ***Méthodes***. L'étude de cohorte historique a inclu les patients TB-MR confirmés et traités entre 2007 et 2017 dans 218 centres de tuberculose en RD Congo. L'issue thérapeutique et la survie à 36 mois ont été analysées. Le score Z ou le test de chi carré ont comparé des issues. La méthode de Kaplan-Meier a décrit les courbes de survie et le test de Log Rank a comparé la survie en fonction du regime therapeutique. Les facteurs associés au succès thérapeutique et les prédicteurs de mortalité ont été analysés respectivement, par l'analyse multivariée de régression logistique et de Cox. ***Résultats***. Dans le groupe étudié (n=1724), le succès thérapeutique a été de 72% (68-74%) pour l'ensemble des régimes. Le taux était plus élevé pour le régime court (74%) et plus faible pour le régime contenant la Cyclosérine et l'Ofloxacine (68%). La moyenne de décès était de 12,8% ; mais plus élevée dans le groupe sous regime contenant la Cyclosérine et l'Ofloxacine (16%). Le taux de décès était significativement plus élevé en milieu urbain (15,2% versus 14,9 %, p = 0,013) et également chez les sujets co-infectés par la MDR-TB et le VIH (28.4% vs 15.7%, p <0,001). La survie médiane dans le groupe était de 722,7 jours contre 601,1 jours chez les co-infectés MDR-TB/VIH, et de 736,7 jours) chez les patients VIH négatifs (p<0,001). ***Conclusion***. Les succès thérapeutiques sont acceptables en particulier, pour le régime court ; toutefois, le taux de décès demeure encore très élevé dans le groupe sous Cyclosérine et Ofloxacine. Les prédicteurs de mortalité sont l'infection à VIH et la vie citadine.

Mots clés : Tuberculose multi résistante, déterminants, succès thérapeutiques, survie
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Summary

Context. Little is known about therapeutic successes in MDR-TB patients under regimens containing second-line molecules. The present study aimed to assess therapeutic outcomes in patients under therapeutic regimens applied in DR Congo. ***Methods***. This historical cohort study has included confirmed MDR-TB patients who received treatment between 2007 and 2017 in 218 TB centers in DR Congo. Treatment outcome and survival at 36 months were analyzed using Z-score and chi square test. Kaplan-Meier method was performed to describe survival and Log Rank test helped in comparing curve based on the therapeutical regimen. Factors associated with therapeutic success and mortality predictors were assessed using multivariate logistic regression and Cox regression analysis, respectively. ***Results***. The therapeutic success in the study group (n=1,724) was 72% (range 68-74%) for all regimen combined. The average death rate was 12.8% although the group of patients receiving Cyclosérine and Ofloxacine was the most affected (16%). The death rate was significantly higher in patients living in urban areas (15.2% versus 14.9%, p = 0.013) and also among MDR-TB/HIV co-infected patients (28.4% vs 15.7%, p<0.001) patients. The median survival of the study group was 722.7 days compared to 601.1 days for MDR-TB/HIV co-infected patients, and 736.7 days for HIV negative patients (p<0.001). ***Conclusion***. Therapeutic successes are significant for the short regimen. However, the death rate remains high when Cycloserine and Ofloxacin are included in the regimen. The predictors of mortality are HIV infection and living in urban areas.

Keywords: Multi-drugresistant tuberculosis, correlates, therapeutic success, survival

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Introduction

The World Health Organization (WHO) estimates multidrug-resistant tuberculosis (MDR-TB) cases at 601 (IC95% 541-664) in thousands, of which the prevalence is 4.1% (IC 95% 2.8-5.3) among new patients and 19% (IC95% 9.8-27.0) among previously treated ones (with acquired MDR-TB). Since the endorsement and the intensive use of rapid diagnostic test (including Xpert-MTB/RIF) MDR-TB/RR) performances were improved from less than 10% in 2000 to more than 30% in 2016 (1).

There is a balance between diagnosed patients and patients really under treatment. The rapid molecular testing has a double effect, the increase in diagnostic accessibility with an increase in the number of patients with confirmed rifampin resistance, and at the same time induces a second-line drug shortage. In 2016, only 65% of diagnosed patients started the second-line drug treatment (1).

With the focus of MDR-TB control, several treatment regimens containing second-line anti-tuberculosis drugs are available. Despite their variability from country to country, TB treatment regimen remain consistent with the WHO and the UNION against Tuberculosis and Lung Diseases recommandations according to used drugs (2-4).

Molecules included in TB treatment are classified in accordance with their chemical families, modes of action… or even the ways of administration. That is the case of fluoroquinolones and injectable drugs that have long been yielded as determinants of therapeutic success.

Fluoroquinolones appear as one of the key molecules in this of treatment, as evidenced by some previous studies, such as those by Mitnick *et al*. (5) and Nathanson *et al*. (6), which evaluated the first DOTS-plus pilot projects by making a comparative study between regimens in different populations (5,7). Different generations of fluoroquinoles are currentely endorsed by WHO for the treatment of MDR-TB. That is the case of ofloxacin (ofx), levofloxacin (lfx), gatifloxacin (gfx) and Moxifoxacin (mfx); these drugs have revolutionized the treatment of MDR-TB, helping to reduce the length of treatment and improving the efficacy (7). The short-term treatment of 9 to 12 months is reported to have a therapeutic success of 90% in some cohorts (8-10).

The second group of drugs that stands as essential in the treatment of MDR-TB are injectables medicines including: kanamycin (KM), capreomycin (CM) and amikacin (AM)). They have been used for several decades in the second-line regimens and their use has undoubtedly reduced the morbidity and mortality caused by the disease (6). However, their known history of adverse reactions, especially ototoxicity and the occurrence of new molecules (bedaquiline and Delamanid) limit their use today as stated by Reuter *et al.* 2017 (11); and even, their use as key molecules is currentely questionned (12). The extension of the intensive treatment phase to a minimum of 6 months from the initiation of the treatment or to 6 months after the conversion of the sputum has been recommended, relaying on an analysis of the results of the different regimens conducted in 2011 (4).

Several therapeutic regimen for MDR-TB include INH despite the known resistance of M. tuberculosis to this drug. This use of INH is supported by results from a randomized study carried out in Bangladesh using 3 applied regimens (13). Rieder and Van Deun (14) have reported therapeutic success in more than 50% patients when high doses of INH were used with second-line drugs during the DOTS-Plus pilot projects (6). The therapeutic successes of as high as 70% have been reported in MDR-TB cohort studies, which identified bacteriological characteristics, early diagnosis and type of regimen as the 3 main determinants (6, 9, 14).

In DR Congo, the first standardized treatment was implemented in the city of Kinshasa, using private funding and the first cohort recorded in 2004 (15). Later, the treatment of MDR-TB patients was extended to other provinces through the TB Diagnostic and Treatment Centers (CSDT). Over the years, the National Tuberculosis Program (PNLT) had adopted regimen containing second-line anti-tuberculosis drugs following international guidelines (15-18).

In 2006, the DR Congo received the official approval for a standardized treatment and recognized the DOTS – Plus pilot project (19).

The present study aimed at assessing treatment outcomes of second-line drug regimens used in

DR Congo in terms of therapeutic success and survival from 2007 to 2017.

Methods

Design, sampling and study setting

This historitical cohort study has included all confirmed MDR-TB patients, registered in all 11 provinces of DR Congo and under a standardized regimen containing second-line drugs between January 1st, 2007 and December 31st, 2017.

Standards for the evaluation of therapeutic regimens recommend duration of at least 24 months after the last enrolment as defined in normative documents (2, 3, 17).

Inclusion criteria

All patients with confirmed pulmonary TB-MR/RR and under standardized treatment with second-line anti-tuberculosis drugs during the study period were included.

Exclusion criteria

All cases of clinically diagnosed or confirmed extrapulmonary TB as well as those under second-line treatment without confirmed MDR-TB/RR, were excluded.

Patients not registered in the NTP and those not under the recommended standardized regimens were excluded as well.

Data Sources

Anthropometric parameters, socio-demographic data, history of previous TB episodes, and HIV status informations were collected from registries at the health center or the provincial treatment center and co-ordination levels. Laboratory results were centralized in an electronic registry. The quality control of data was performed between the laboratory, the processing center and provincial coordination files.

Therapeutic regimens, drug administration and patient follow-up

The Standardized therapeutic regimens for MDR-TB patients were applied to all patients with confirmed or suspected MDR-TB. These regimens were established according to the standards set out by the WHO, relaying on the consensus of experts, as repored in international guides for the management of MDR-TB (2, 17).

Patients received their medications mainly ambulatory at the CSDT, under the direct supervision of a healthcare worker, with the support of a community or a family member. Injectable drugs were administered daily during the intensive phase. Patients benefited also with nutritional support and transportation incentives, but not regularly.

The daily dosage of drug administred was as follows: KM:15-20 mg/kg/day (max 1000 mg); CM:15-20 mg/kg/day (max 1000 mg); Ofx:15-20 mg/kg/day (max 800 mg); Lfx:16 mg/kg/day (max 1000 mg); Mfx: 400 mg/day; Prothionamide (Pto): 15 mg/kg/day(max 750 mg) Cycloserine(Cs): 15 mg/kg/day (max 750 mg); Clofazimine (Cfz): 100 mg/day; EMB: 20-25 mg/kg/day (max 1500 mg); PZA: 30-35 mg/kg/day (max 2000 mg) and Hhd: 10 mg/kg/day (max 600 mg). Only KM and CM were administered as an injection (deep intramuscular), the rest were orally administered.

The clinical follow-up was provided by the teams of nurses and physicians from the CSDT. Bacteriological monitoring was carried out through a smear sample at the CSDT and the culture at the National Reference Laboratory, on a monthly basis during the intensive phase, except on the 1st year where it was on a quarterly basis. Eithr the smear sample or the culture results were considered for the evaluation, and each positive result was considered and rated positive for the the control. For standardization purpose, the bacteriological monitoring results included harmonized parameters registered monthly during the first 6 months and on a quarterly basis for the remaining period.

End point

The first end point of the present study was therapeutic outcomes (failure, success); and therapeutic success meaning the sum of cured patients and those who completed the treatment period. The second endpoint was patient or time to death. Time zero (To) was the date of the setting of the diagnosis of MDR-TB. Patient survival referred to those who reached the end of the study, at December 31st, 2018. Patients lost to follow-up were censored.

Operational definitions

The definition of the concepts adopted in this study is consistent with the WHO recommendations, included in the national guidelines (17, 20).

Table 1 shows the definitions of different types of presumed and therapeutic outcomes.

Table 1: Definition of concepts used

Therapeutic outcome	
Cured	Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Therapeutic failure	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: − lack of conversion by the end of the intensive phase, or − bacteriological reversion in the continuation phase after conversion to negative, or −evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or − adverse drug reactions (ADRs).
Death	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Non evaluated	A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown)
Treatment success	The sum of cured and treatment completed

Source: World Health Organization: Definitions and reporting framework for tuberculosis, Revision 2014 (20)

Studied parameters included sociodemographic data such as: age, gender, and province of residence.

The time of access to treatment was obtained from the date of the diagnosis presumption of MDR-TB and that of starting of the treatment.

Statistical analysis

The data were compiled into an Excel file, then a clean-up and consistency was established. All analyses were performed using Epi Info 7.0, STATA 10.0 and SPSS 20.0 software. Averages of numerical variables and standard deviation (SD) were calculated. Proportions were presented in percentage with IC 95%. The comparison of the means was realized with the t-test, and the Z-score helped comparing the proportions. The clusters of patients included were considered based on therapeutic regimens. The ANOVA and the homogeneity tests were applied respectively the mean of age and population inequality. The associations between the patient profile and treatment outcomes were assessed throught bivariate and multivariate logistic regression analysis. Survival curves were described by the Kaplan Meier method and were compared using Log rank test. The Cox regression model identified predictors of mortality. The value of p at level of 5% was significant.

Ethical considerations

The data of patients were collected and registred confidentialy in medical records. Even in case of clinical diagnosis the patient was directly started with MDR-TB treatment according to national guidelines.

The use of the second-line molecules in a Standardized treatment was submitted to strict ethical rules.Confidentiality rules for management and the safety of treatment were guaranted for each patient and DR Congo received approval from the WHO-associated MDR-TB working group (and the GLC) in 2006 for 1100 patients (21).

This study has been approved by the National Ethics Committee of the Public Health School **N°ESP/CE/066/2018**.

Results

Figure 1 shows Flow chart of patients on second line treatment

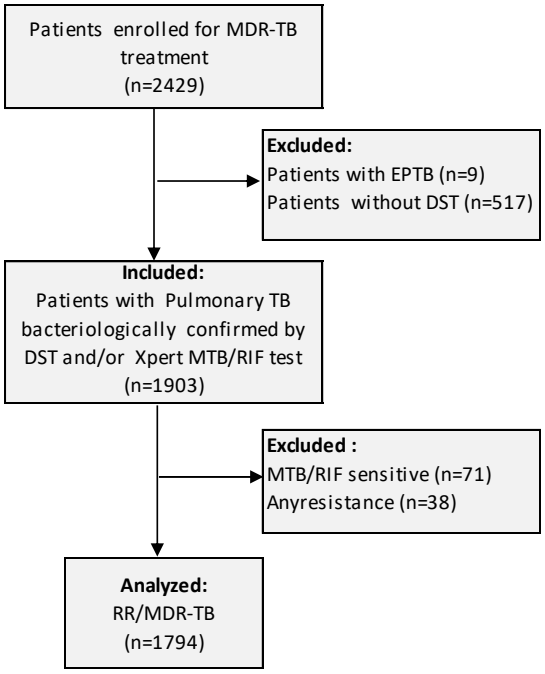

Figure 1. Flow chart of patients on second line treatment analyzed

Legend: EPT: extra-pulmonary tuberculosis. DST: drug sensitivity test. MTB-RIF: presence of rifampin sensitivity on Xpert MTB-RIF test

General characteristics of study population

The patient characteristics are displayed in Table 2.

The mean age of the whole group was 34.2 (SD=13.5) years; 32.3 (SD=12.9) years for females and 34.9 (SD=12.3) years for males. The sex ratio M/F is 1.5.

Less than a half of patients (748/1764, 41.7%) were aware of their HIV status; 23.7% among them were HIV positive.

The average duration between the first episode and the diagnosis of MDR-TB was 2.9 years (range 0-29 years), that between the latter episode and the diagnosis of MDR-TB was 0.9 years (range 0-14 years); showing no differencies according to different therapeutic regimens (p=0.2509).

More than half of patients were previously failures. New patients represented 14%; out of them 12% were patients had identified a previous contact with a MDR/TB case.

Cohorts Evaluation groups

Four standard regimens were identified during the studying period; and 1,794 (73.9 %) were eligible for this evaluation.

The characteristics of each treatment regimen are illustrated in Table 3.

The regimen 2 has been used for the longest period in the country (from 2008 to 2013). The year 2013 appeared as a transitional year, with three regimens applied. The ofloxacin has been withdrawalled during this period and concommitently the short 9-month regimen was implemented. The year 2014 experienced an increase in patients enrolled for treatment with consequently, the number of eligible cases doubled compared to the previous year.

Therapeutic outcomes of MDR-TB patients

Bacteriological Monitoring

Sputum control conversion assessment

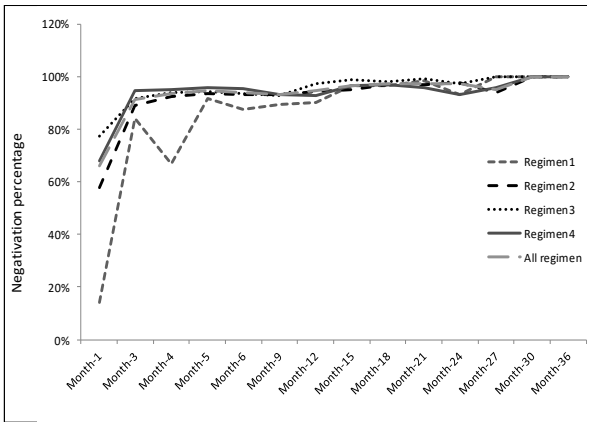

Figure 2. the plot of sputum conversion according to regimen and time followed up

This plot shows the sputum conversion based on smear and culture controls for each and for regimens as a whole. In the third month of treatment, the rate of sputum conversion was respectively of 84.3%, 89.2%, 91.8%, 94.6% for these successive regimens and 91.4% for the total (p= 0.001). A slight increase was observed at the 6th month of almost 3% on average, presenting as following: 87.5%; 93.1%; 93.7% and 95.4% respectively, and 94.1% for the total (p=0.0042).

The result at the 9th month of: 89.4%; 93.3%; 92.8%; 93.3% and 92.9% (p= 0.2739) for total, was not statistically different.At this moment, most patients under regimen 4 are at the end of their treatment. That was also the case for the patients at the 12th and 15th months representing the post-therapeutic phase for the regimen 4 and the continuity phase for the remaining regimens, there was no significant differences in sputum conversion. The rate of sputum conversion at these periods were as following: 90.3% /96.4%; 94.2%/95.2%; 97.5%/ 98.9%; and 92.7%/96. 6% respectively and for total 94.6% / 96.4% (p= 0.0481/ 0.0485), with no significant differencies.

The post-therapy follow-up has shown a good rate of sputum conversion whatever the regimen used.

Assessement of patients'survival

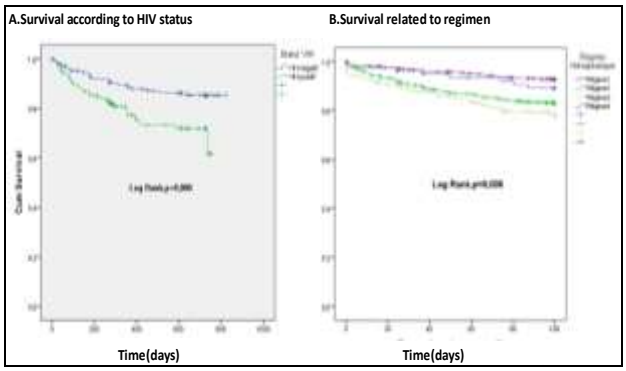

Figure 3. Curve of Kaplan-Meier (A) by HIV status and (B) according to different treatment regimens

In figure 3 (B), the treatment period has been expressed as percentage of time.

The rate of deaths was 37/168 (22.2%) for HIV-positive patients versus 62,541 (11.6%) for HIV-negative. Median survival for TB-MR/HIV co-infected patients was 601.1 days (IC 95% 557.9 – 644.4) and 736.7 days (IC95% 715.9 – 757.3) for HIV-negative patients (Log Rank p< 0.001).

The proportion of deaths was 37/168 (22.2%) for HIV-positive patients and 62,541 (11.6%) for HIV-negative patients. Median survival for TB-MR/HIV co-infected patients was 601.1 days (IC95% 557.9 – 644.4) and 736.7 days (IC95% 715.9 – 757.3) for HIV-negative patients (Log Rank p<0.001).

For a good comparison, we looked at the processing time as a percentage for each regimen. The Median survival was better for Regimen 4, the numbering represents regimens (Log Rank p <0.001).

Discussion

This study analyzed 1,794 patients with confirmed MDR-TB whatever their previous history, enrolled from January 2007 to December 2017 in DRC. All the patients were under one of the four-treatment regimen in use including the 2nd line anti-TB drugs according to the NTP guidelines. Among them, more than half were previous failures or "chronic" cases, the main target of previous treatment strategies (2, 15, 22). In the all group, the rate of HIV positivity was around 23 % ans less than a half knew their HIV status. In this study the HIV

prevalence is higher than previously reported reported in TB patients in DRC (24).

Changes in treatment regimens relayed on the duration and the composition. Regimen-1 had a 24 months duration, with an intensive phase of 3 months; ofloxacin was the fluoroquinolone used. This molecule was withdrawalled by the WHO in 2011 (4, 23), but this recommendation has been applied 2 years later in DR Congo. The major changes implemented in the regimen 2 were the addition of cycloserine and the extension of the intensive phase to at least 6 months. The regimen 3 consisted of substitution of ofloxacine by levofloxacin, the intensive phase could be extended with 2 additional months in case of non sputum conversion; and the shortening of the all treatment to 20 months. Regimen 4 or short regimen was introduced during the multicentre short treatment study in 9 African countries by the Union against Tuberculosis and Lung Diseases (8, 24).

The 72% of treatment success rate in the present study are relatively low compared to the 80% recorded elsewhere in previous reports (6,8,24).This rate however , is higher than that reported in Republic of South Africa and even than the is 56-69% describe by the WHO report in 2016 (1). The disparities with RSA could be explained by different patients' management approaches such as: the involvement of the community, which is strong in the DRC, the non-standardized management in RSA, despite a sufficiently funded health system and the prevalence of HIV infection.

According to the duration in different treatment regimens, the relevance of shorter duration and short use of injectable drugs has been illustrated in this study.

With the WHO report in 2016 mentionned above, the differencies could relay on that the WHO reports assess all the patients registered with DR-TB, without confirmation or not of MDR-TB/RR. In our study patients without the confirmation of RMP resistance were excluded from the analysis.

The regimen-1 in the current study, containing ofloxacin has shown a treatment success rate of 69%, in agreement with the stuty Van Deun *et al* who evaluated a similar regimen in Bangladesh within 21 months (13).

No statistical difference was observed in the comparison between the three long treatment regimens (the first three ones regimens). Short duration treatment regimen(regimen 4) apperared more efficient than the three others ;as observed in the Union's multicentre study carried out in 9 countries of the African region (24), and earlier in Bangladesh (8); leading to its endorsement by the WHO in 2016 (18, 25).

The Cycloserine inclusion in treatment regimens 2 and 3 is strehghtenned by its pharmacological properties; indeed this drug has no cross-resistance with other anti-tuberculosis drugs due to its mechanism targeting the incorporation of alanine in an alanyl-dipeptide alanine, an essential component of the bacterial cell wall (2,5). Cycloserine promotes the sputum conversion maintenance; despite having many adverse effects as described by Kalpesh (18) and Furin *et al.* (26).

The unfavorable outcomes rates showed no differences between all treatment regimens as shown in Table 3. The sum of patients lost to follow-up and non-evaluated remained relatively high. This is not related to the type of regimen but could be in link with other factors such as the organization of care, the lack of patient restraint measures and other behavioural indicators.

Changes in treatment regimens were concomitantly coupled with upgraduade of the therapeutic strategies. At the beginning of the management of MDR-TB cases, some chronic cases were treated with or without bacteriological evidence; shortening the time to starting the treatment. The results of the sensitivity tests allowed the continuation or not of the standardized treatment. Currently, since the implementation of molecular tests (Xpert machines) this strategy is no longer applied (10, 17, 24- 25).

According to treatment success, a strong relation has been found with HIV serologic status and the use of the short regimen by cox-regression analysis (table 4); as highlighted in few previous studies (6,24). As illustrated elsewhere (9, 23-24) the current survey has not identified a link between the the number of previous TB episodes or history of treatment failure with rifampicin containing regimen with unfavorable outcome. HIV-status stands as a main determinant of poor outcome whatever the treatment regimen in use.

Limitations

The present study has some limitations; such as those links to the analysis of historical cohorts that are often leading to information biases, due to different registration methods related to change of recommendations.

Strengths

The large number of included patients has empowered statistical analyses and the routine monitoring over a long period is mandatory for a good assessment of variation over time.

Conclusion

Therapeutic successes are significant in particular for the short regimen, but with a death rate that remains high when Cycloserine and Ofloxacin where used. The predictors of mortality are HIV infection and living in urban areas.

Conflict of interest: No conflict of interest declared.

Contributions for authors

SBF, JKN, PKK: designed, interpreted and wrote the manuscript

PKK, SBF, ESK: data analysis,

PMS, JTR: collected data,

KMZ, PMS, KOB: supervised the study

HSN, ESK, JKN, PKK for proofreading and editing of the final form of article. All authors approved the final version of the manuscript.

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Table 2: Characteristics of patients at the time of diagnosis of MDR-TB/RR distributed by sex

Characteristic	Male n=1066	Female n=728	Total N=1,794	P
A. Age range (years)				< 0.001
< 35	561 (52.6)	418 (57.4)	979 (54.6)	
≥ 35	505 (47.4)	310 (42.6)	815 (45.4)	
B. Number of prior episodes				
none	138 (12.9)	106 (14.6)	244 (13.6)	0.3776
1 episode	234 (22.0)	143 (19.6)	377 (21.0)	
2 episodes	633 (59.4)	428 (58.8)	1061 (59.1)	
3 episodes or more	61 (5.7)	51 (7.0)	112 (6.2)	
C. Outcome at the last episode				
Success ther (relapse)	150 (14.1)	85 (11.7)	235 (13.1)	0.0046
defaults	40 (3.8)	8 (1.1)	48 (2.7)	
failure	707(66.3)	504 (69.2)	1211 (67.5)	
unknown	31(2.9)	25 (3.4)	56 (3.1)	
D. Serologic HIV status				
Positive	72(6.8)	105(14.4)	177(9.9)	< 0.001
Negative	342(32.1)	229(31.5)	571(31.8)	
unknown	652(61.2)	394(54.1)	1046(58.3)	
E. Origin of patients				
Rural	319 (29.9)	173(23.8)	492(27.4)	0.0048
Urban	747(70.1)	555(76.2)	1302(72.6)	

Table 3: Characteristics and treatment outcomes of patients according to regimens applied

	Regimen 1	Regimen 2	Regimen 3	Regimen 4	All Regimens	p-value
A. Composition						
Intensive phase	3-6Km-Ofx-Pto-E-Z	6Km-Ofx-Pto-Cs-E-Z	6-8Km(Cm)-Lfx-Pto-Cs-E-Z	4Km-Mfx-Pto-Clo-H^{hd}-E-Z	-	-
Continuation phase	18-21 Ofx-Pto-E-Z	18 Ofx-Pto-Cs-E-Z	12-14 Lfx-Pto-Cs-E-Z	5 Mfx-Clo-H^{hd}-E-Z		
B. Treatment duration (days)						
Average (±SD)	626.8(±209.9)	591.7(±239.4)	505.9(±200.2)	262.1(±65.9)	470.9(±240.7)	<0.001
Median	**730**	**730**	**610**	**275**	**540**	
Maximum	**772**	**823**	**744**	**460**	**823**	
C. Delay between suspicion and treatment (days)						
Mean (±SD)	0.1(±0.4)	16.8(±64.9)	37.1(±61.5)	29.9(±34.1)	24.9(±55.3)	<0.001
patients characteristics						
Number of patients/n (%)	82(4.6)	679(37.8)	516(28.8)	517(28.8)	1794(100)	-
Mean (±SD) years	33.3(±12.2)	33.8(±12.3)	34.2(±13.5)	33.8(±12.3)	33.9(±12.6)	0.7412
Male / n (%)	41(50.0)	363(53.5)	343(66.5)	319(61.7)	1066(59.4)	<0.001
Female/ n (%)	41(50.0)	316(46.5)	173(33.5)	198(38.3)	728(40.6)	-
Sex ratio M/F	1.0	1.1	2.0	1.6	1.5	-
average BMI (±SD) at the beginning (kg/m^2)	-	18.47(±3.13)	18.19(±2.98)	18.06(±2.98)	18.14(±2.99)	0.8419

D. Therapeutic outcomes of MDR-TB patients

	Regimen-1	Regimen-2	Regimen-3	Regimen-4	all Regimens	
Ther Success	57(69.5)	464(68.6)	359(69.6)	407(78.7)	1287(71.7)	< 0.001
Abandon	12(14.6)	81(12.0)	42(8.1)	42(8.1)	177(9.9)	
Death	8(9.8)	108(16.0)	76(14.7)	37(7.2)	229(12.8)	
Failure	4(4.9)	21(3.1)	8(1.6)	25(4.8)	58(3.2)	
NE	1(1.2)	5(0.7)	31 (6.0)	6(1.2)	43(2.4)	

SD=standard deviation, NE=not evaluated

Data observed did not showed statistical differences between the sub-populations.

Table 4: Bivariate and multivariate analysis of associated factors with treatment success

Variable		Bivariate analyze				Multivariate analyze			
		aOR	**IC 95%**		**p**	**aOR**	**IC 95%**		**p**
Sex	Female		1						
	Male	1.014	0.823	1.25	**0.893**	-	-	-	-
Age (years)	< 35		1						
	≥ 35	1.024	0.832	1.26	**0.822**	-	-	-	-
Origin	Urban		1				1		
	Rural	1.458	1.122	1.893	**0.005**	0.787	0.432	1.432	**0.433**
Type of patient	Previously treated		1						
	New patient	1.132	0.83	1.544	**0.433**	-	-	-	-
Number of previous TB treatment	0 episode		1				1		
	1 episode	0.967	0.745	1.256	**0.803**	1.955	0.644	5.936	**0.237**
	2 episode or more	1.633	1.051	2.536	**0.029**	1.251	0.454	3.447	**0.666**
Time between the first episode and the current one	≥3 years		1				1		
	<3 years	0.617	0.422	0.904	**0.013**	1.395	0.9	2.16	**0.136**
Outcome at the latter episode	Success		1				1		
	Abandon	1.0339	0.7962	1.3424	**0.195**	2.646	0.516	13.575	**0.243**
	Failure	0.6125	0.3943	0.9513	**0.05**	3.346	0.666	16.803	**0.142**
Number of additional resistances to RMP et INH	RH+1(E or S)		1						
	RH+ 2(E and S)	1.092	0.802	1.486	**0.577**	-	-	-	-
VIH serologic status	Negative		1				1		
	Positive	0.437	0.304	0.627	**0,000**	0.458	0.277	0.756	**0.002**
BMI	≤18		1				1		
	> 18	1.464	1.028	2.085	**0.035**	0.735	0.46	1.175	**0.199**
Time of access to treatment	>3 days		1				1		
	≤3 days	1.448	1.164	1.802	**0.001**	0.879	0.534	1.447	**0.613**
Treatment regimen	Regimen 4		1				1		
	Regimen 1	0.944	0.737	1.209	**0.065**	-	-	-	-
	Regimen 2	0.583	0.447	0.761	**0.002**	0.336	0.17	0.664	**<0.001**
	Regimen 3	0.463	0.292	0.549	**0.000**	0.292	0.171	0.498	**0.001**

Table 5: Cox regression bivariate and multivariate analysis of factors associated with mortality

Variable		Bivariate analyze				Multivariate analyze			
		HR	IC 95%		p	HRa	IC 95%		p
Sex	Female			1					
	Male	1.120	0.849	1.477	**0.424**	-	-	-	-
Age (years)	**< 35**			1					
	≥ 35	1.256	0.953	1.565	**0.106**	-	-	-	-
Origin	Rural			1				1	
	Urban	1.360	1.006	1.838	**0.045**	1.816	1.130	2.916	**0.014**
Type of patient	New patient			1					
	Previous treated	1.132	0.830	1.544	**0.433**	-	-	-	-
Number of previous TB treatment	0 episode			1				1	
	1 episode	1.126	0.687	1.845	**0.637**	-	-	-	-
	2 episodes	1.141	0.751	1.733	**0.536**	-	-	-	-
	3 episodes	1.873	1.037	3.385	**0.038**	-	-	-	-
Time between the first and the present episode	≥3 years			1				1	
	<3 years	0.617	0.422	0.904	**0.013**	1.395	0.900	2.160	**0.136**
Outcome at the latter episode	Success			1				1	
	Abandon	1.132	0.435	2.948	**0.799**	-	-	-	-
	Failure	1.318	0.789	2.220	**0.299**	-	-	-	-
VIH serologic status	Negative			1				1	
	Positive	1.640	1.121	2.460	**0.011**	1.987	1.196	3.301	**0.008**
BMI	≤18			1					
	> 18	1.535	0.934	2.525	**0.910**	-	-	-	-
Regimen therapeutic	Regimen 4			1				1	
	Regimen 1	1.491	0.694	3.201	**0.306**	-	-	-	-
	Regimen 2	2.413	3.506	3.506	**<0.001**	2.976	1.506	5.882	**<0.001**
	Regimen 3	3.403	2.295	5.046	**<0.001**	3.424	2.008	5.847	**<0.001**

BMI: body mass index. HRa: hazard ratio adjusted