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Short-course treatment outcomes and adverse events in adults and children-adolescents with MDR-TB in Niger

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SUMMARY

SETTING: Niger National Tuberculosis Programme.

OBJECTIVE: To describe the outcomes and adverse events (AEs) in a cohort of adults, children and adolescents with multidrug-resistant tuberculosis (MDR-TB) who were treated with the 'short-course regimen'.

DESIGN: The regimen comprised an intensive phase of 4–6 months with kanamycin, medium–high dose of isoniazid and prothionamide, and high doses of gatifloxacin, clofazimine, ethambutol and pyrazinamide throughout. Sixty-five patients were treated with a regimen of 12–14 months and 55 patients with a regimen of 9–11 months.

RESULTS: Of the 120 patients evaluated, 110 (92%) were adults (median age 31 years) and 10 (8%) were children or adolescents (median age 17 years). The treatment success rate was respectively 88% and 83% with the 9-month regimen, and 90% and 75% with the 12-month regimen in adults and children/adolescents. Initial resistance to ethambutol and prothionamide did not affect treatment success rates but resistance to fluoroquinolones did, although this was not statistically significant. Vomiting was the most frequently encountered AE, followed by ototoxicity and hepatotoxicity. AEs experienced were mild or moderate in severity in most patients, and did not lead to treatment interruption.

CONCLUSION: These results confirm the programmatic effectiveness and tolerability of the shorter regimen in second-line drug-naïve patients.

KEY WORDS: MDR-TB; children/adolescent; short-course; Niger

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) is defined as a strain of *Mycobacterium tuberculosis* resistant to at least rifampicin (RMP) and isoniazid (INH). MDR-TB care and prevention are difficult to achieve, and therefore represent a major public health concern for TB control. In 2016, there were an estimated 600 000 new cases of MDR-TB and RMP-resistant TB (RR-TB) worldwide, 490 000 of which were MDR-TB and 240 000 cases died.[1]

In 2016, the estimated number of RR-/MDR-TB cases in Niger was 281, with RR-TB estimated to be 2.6% of all new TB cases and 18% of retreatment cases.[1] In Niger, MDR-TB management was started in 2008 by the Damien Foundation (DF), a Belgian non-governmental organisation, along with the National Tuberculosis Programme (NTP) of Niger. Before that, chronic cases of TB were treated with inadequate therapeutic regimens by adding one or two second-line anti-tuberculosis drugs to, what was considered to be, a failing first-line regimen. At the time, the World Health Organization (WHO) recommended a regimen lasting a total of $\geqslant$20 months, with an intensive phase of $\geqslant$8 months.[2] However, treatment success remained as low as 52%,[3] because the treatment course was arduous for patients and health care workers due to severe adverse events (AEs).[4,5]

Emerging evidence supports the use of a standardised 'short' 9–12-month MDR-TB regimen (known as the 'Bangladesh regimen'), which differs from the traditional second-line regimen in terms of duration, cost and effectiveness.[6,7] In May 2016, the WHO endorsed this 'short-course' regimen in MDR-TB patients not treated previously with second-line drugs and in those without resistance to fluoroquinolones (FQs) (or for those in whom resistance to FQs was considered highly unlikely).[8] However, the WHO encourages the collection of evidence on shorter and more effective regimens to treat MDR-TB, particularly in this age of automated diagnostic test

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availability, to avoid creating more resistance with the use of inappropriate treatment combinations.[9]

Several studies, including one conducted in Niger, have shown that the short-course regimen is effective and well-tolerated among adults, despite some minor AEs.[10–12] However, no studies have focused on the safety and outcomes of the short-course MDR-TB regimen in children and adolescents.

Here, we describe the characteristics, outcomes and AEs of the short-course regimen in a cohort of adults and children/adolescents with MDR-TB between July 2008 and September 2013 in Niger. In addition, we report cases of AEs and their management among children and adolescents in the same cohort.

METHODS

Study design

This was a retrospective cohort study with a case series on MDR-TB patients treated with the short-course MDR-TB regimen.

General setting

Niger, a landlocked country in West Africa, has an estimated population of 21 million, and covers an area of ~1 267 000 km^2. Two thirds of the country is covered by the Sahara desert. The NTP, with the support of DF, has been providing MDR-TB treatment and care in the country since 2008. The NTP, which is based in Niamey, the capital city, oversees TB activities from national, regional and district offices. TB diagnostic and treatment services are integrated into the general health care system.

Between 2008 and 2010, the country had only one MDR-TB unit in Niamey. Between 2011 and 2012, two other centres, both supported by DF, were opened in the Zinder and Maradi Regions. DF, which supports TB programmes in resource-limited countries (www.actiondamien.be), has decades of experience in managing MDR-TB, and is credited with pioneering the Bangladesh regimen for MDR-TB treatment in Bangladesh at the district level in 1997.[10]

Case and treatment outcome definitions

MDR-/RR-TB cases were diagnosed using culture and drug susceptibility testing (DST) up until 2012, after which Xpert® MTB/RIF testing (Cepheid, Sunnyvale, CA, USA) was implemented and patients were started on MDR-TB treatment if RR-TB was detected. Case definitions were based on WHO guidelines: 'new cases' were defined as patients without a previous episode of TB (susceptible or resistant). Retreatment patients comprised three categories: 1) relapses (those declared 'cured' after first-line treatment but returning with a new episode of active TB; 2) lost to follow-up (patients who interrupted treatment for >2 months); and 3) failures (patients who remained smear-positive after 5 months of first-line treatment). Outcome definitions were in line with WHO definitions (Supplementary Data 3). The ototoxicity assessment before and during MDR-TB treatment is described in Supplementary Data 4. We included 1 year of follow-up after treatment completion).

Short-course MDR-TB regimen

In Niger, DF and the NTP started providing MDR-TB care in 2008 using the short-course regimen to target patients not treated previously with second-line anti-tuberculosis drugs. The regimen comprised an initial phase of 4–6 months of kanamycin (KM), medium-high-dose isoniazid (H, INH), prothionamide (PTH) and high doses of gatifloxacin (GFX), clofazimine (CFZ), ethambutol (E, EMB) and pyrazinamide (Z, PZA) throughout.

Between 2008 and 2010, treatment duration was 12–14 months, with a fixed continuation phase of 8 months (4–6KmGfxPthCfzZH^{H}E/8GfxCfzZE).[†] Sputum smear microscopy and solid culture were performed every month during the intensive phase, whereas these were performed every 2 months during the continuation phase.[11] After 3 years of encouraging outcomes, treatment duration was shortened from 2011 to 9 months (as in the original Bangladesh regimen), with a fixed continuation phase of 5 months (4–6KmGfxPthCfzZH^{H}E/5GfxCfzZE), and sputum smear microscopy and solid culture each month.[13] Clinical improvement was assessed using monthly weight measurements and physical examination. Chest X-rays were not used for follow-up purposes.

MDR-TB treatment was supervised daily by a health worker during the intensive phase and weekly during the continuation phase.[11,13] AEs were monitored and reported using a standard method of pharmacovigilance (cohort event monitoring). In the absence of paediatric-specific AE severity monitoring tools, the *Agence National de Recherche sur le SIDA* (ANRS; Paris, France) scale for grading AE severity in adults was applied to the entire cohort (Supplementary Data 2).[14] AEs were treated symptomatically with the drugs available. The most common AEs (gastrointestinal AEs) were treated with oral drugs (metoclopramide); parenteral presentations were used if no response was obtained after 2 days. In the case of mild hearing loss, KM intake was reduced to three times per week.

Study population

All confirmed MDR-TB patients (not treated previously with second-line anti-tuberculosis drugs) treat-

[†] Numbers before the letters indicate the duration in months of the phase of treatment; H^H = high-dose isoniazid.

Table 1 Demographic and clinical characteristics of multidrug-resistant tuberculosis patients at initiation of the 'short-course' regimen in Niger

Patient characteristics at treatment initiation	Children/adolescent group ($n = 10$) *n* (%)	Adult group ($n = 110$) *n* (%)
Demographic		
Male	7 (70)	92 (84)
Female	3 (30)	18 (16)
Age, years, median [IQR] (range)	17 [16–19] (6–19)	31 [31–38] (20–66)
Clinical		
HIV status		
Tested	9 (90)	104 (95)
HIV-positive	1 (10)*	5 (5)*
BMI, kg/m^2, median [IQR]	12.7 [11.7–15.3]	17 [15–19]

* Proportion of patients tested for HIV.
IQR = interquartile range; HIV = human immunodeficiency virus; BMI = body mass index

ed with the short-course regimen and registered between July 2008 and September 2013 in Niger were included in the study cohort.

Data variables and sources

Data variables in the children/adolescent group were patient type, age, sex, human immunodeficiency virus (HIV) status, body mass index (BMI) at treatment initiation, whether initially resistant to ETH, EMB and ofloxacin, treatment outcome, AEs experienced and severity of AEs. Data related to the study were sourced from the Excel™ database (MicroSoft, Redmond, WA, USA) used to monitor MDR-TB treatment activities in Niger and from individual patient medical records. Treatment outcomes were defined according to WHO guidelines (Supplementary Data 3).[15] Age group was defined according to 2016 WHO guidelines for antiretroviral prevention and treatment.[16] Patients aged 1–19 years were classified as 'children' or 'adolescents'; individuals aged $\geqslant$20 years comprised the adult group.

Data collection and analysis

Study data were extracted from a standardised electronic database (Excel) used to monitor MDR-TB treatment activities in Niger. Data were routinely entered into this database from patient files and checked for quality by NTP staff. Patient demographics, clinical characteristics, treatment outcomes and AEs encountered were described using counts and proportions. The χ^2 test or Fisher's exact test was used to test differences between groups, as appropriate; level of significance was set at $P < 0.05$. Data were analysed using EpiData Analysis v 2.2.2.187 (EpiData Association, Odense, Denmark). To report the case series, individual patient medical records were reviewed.

Ethics approval

Permission to carry out the study was obtained from the Niger NTP. Ethics clearance was obtained from the National Ethics Committee of Niger (Niamey, Niger) and Ethics Review Board of the International Union Against Tuberculosis and Lung Disease (Paris) and Médecins Sans Frontières (Paris, France). Before treatment initiation, participants provided informed consent in their local language.

RESULTS

Of the 120 confirmed MDR-TB patients treated with the short-course regimen included in the study, 119 were first-line retreatment cases and one was a new MDR-TB contact case. Among the retreatment cases, there were 88 failures after retreatment, 27 relapses after retreatment, 1 failure after first-line treatment and 1 return after being lost to follow-up. In addition to INH and RMP resistance, 87 (72.5%) had initial resistance to EMB, 18 (15%) to ethionamide (ETH) and 6 (5%) to ofloxacin. All strains were susceptible to KM; initial resistance to PZA was not analysed.

Ten patients (8%) were either children or adolescents and 110 (92%) were adults. The median age was respectively 17 years (interquartile range [IQR] 16–19) and 31 years (IQR 31–38); the median BMI was respectively 12.7 kg/m^2 (IQR 11.7–15.3) and 17 kg/m^2 (IQR 15–19) in adults and children/adolescents. The majority ($n = 99$, 83%) of the patients were male. Table 1 describes patient characteristics at MDR-TB treatment initiation.

The minimum duration of treatment for 65 (54%) patients was 12 months, and for 55 (46%) patients, this was 9 months. Treatment success rates were respectively 88% and 83% in the adult and child/adolescent groups treated for 9 months. For those treated for 12 months, success rates were respectively 90% and 75% in the adult and child/adolescent groups. The Figure shows the timing of bacteriological conversion in adults and children with MDR-TB under the shorter treatment regimen. Supplementary Data 5 gives the number of patients treated for 9 and 12 months, the number who experienced AEs and treatment outcomes by age group.

Initial resistance to ETH and EMB did not

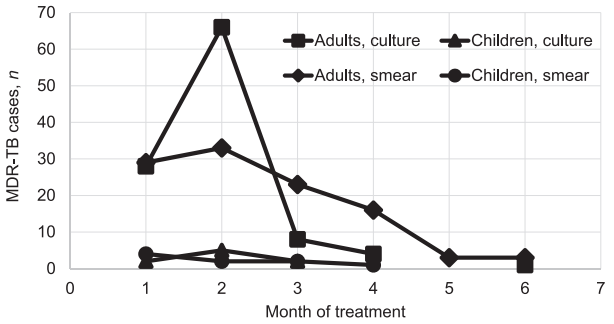

Figure Time taken for bacteriological conversion (smear and culture) of MDR-TB patients under the shorter treatment regimen, 2008–2013, Niger. MDR-TB = multidrug-resistant tuberculosis

influence treatment success; however, initial resistance to FQs was associated with a non-significant difference in treatment success (Table 2). Vomiting was the most common AE experienced by both groups, followed by ototoxicity. Hepatotoxicity was the least encountered AE. There was no statistically significant difference ($P = 0.30$) in AE frequencies across age groups (Table 3).

Other AEs, such as gastritis (4%), depression (3%), arthralgia (5%), skin rash (2%), peripheral neuropathy (3%), hyperglycaemia (7%), optic neuritis (3%), which led to the withdrawal of EMB from the regimen), and nephrotoxicity (2%) were also recorded only in adults. Five children/adolescents (50%) experienced at least one AE; however, treatment was not discontinued or interrupted (Table 4). Vomiting was encountered in 60% ($n = 3$), followed by hepatotoxicity in 40% ($n = 2$) and ototoxicity 20% ($n = 1$). One patient experienced both vomiting and hepatotoxicity. All the AEs encountered were either mild (D1, defined as mild or transient discomfort without limitation of normal daily activities; no medical intervention or corrective treatment required) or moderate in severity (D2, defined as moderate limitation of normal daily activities, with minimal medical intervention or corrective treatment required) on the ANRS scale,[14] and occurred during the intensive phase of treatment.

During follow-up of the 106 cured patients, respectively 94 and 88 patients remained culture-negative after 6 months and 1 year; only two patients relapsed within 6 months after being declared cured (Table 5).

DISCUSSION

This was the first study in the region to describe the outcomes of MDR-TB patients treated with the short-course regimen for 9 and 12 months. In the first 3 years of the study, MDR-TB patients were treated for 12 months. Treatment duration was subsequently shortened to 9 months in the latter 3 years of the study. This was also the first study to describe the AEs experienced, and treatment management and outcomes in child/adolescent MDR-TB patients. The use of the shorter-course MDR-TB treatment course (the Bangladesh regimen) was feasible and effective in Niger and could be replicated in other settings.

Successful outcomes were probably due to two core drugs: GFX (an effective bactericidal and sterilising fourth-generation FQ) and CFZ (which contributes to early culture conversion).[17,18] Two failures were recorded among those treated with the 9-month regimen, but DST later showed that the two patients were infected with a *Mycobacterium* strain resistant to quinolone. Treatment success was not influenced by resistance to EMB or ETH. Treatment success rate was lower in FQ-resistant cases than in those who were FQ-susceptible; however, this difference was not statistically significant due to the small number of patients. Two patients treated with the 9-month regimen relapsed after being declared cured; DST later showed that they were infected with strains with initial resistance to FQs.

These results are very similar to those observed in Bangladesh, Cameroon and previous studies in Niger,[6,10–12] and better than the MDR-TB treatment success rate reported by the WHO (52%) with conventional MDR-TB regimens.[1] However, in the

Table 2 Initial drug resistance and treatment success rates

Initial resistance to drugs	*n*	Treatment success *n* (%)	*P* value
Ethambutol			0.46
Susceptible	87	78 (89.6)	
Resistant	33	28 (84.8)	
Ethionamide			0.93
Susceptible	18	16 (88.9)	
Resistant	102	90 (88.2)	
Fluoroquinolone			0.14
Susceptible	114	102 (89.4)	
Resistant	6	4 (66.6)	

Table 3 Frequency and type of AEs experienced by children/adolescents and adults

AEs	Children/adolescent group ($n = 10$) *n* (%)	Adult group ($n = 110$) *n* (%)	*P* value
Patients with AEs			0.30*
Yes	5 (50)	75 (68)	
No	5 (50)	35 (32)	
Type of AE experienced			
Vomiting			0.74*
Yes	3 (30)	44 (40)	
No	7 (70)	66 (60)	
Ototoxicity			0.99*
Yes	1 (10)	20 (18)	
No	9 (90)	90 (82)	
Hepatotoxicity			0.41*
Yes	1 (10)	5 (5)	
No	9 (90)	105 (95)	

* Fisher's exact test.
AE = adverse event.

Table 4 Demographic and clinical characteristics, treatment outcomes and AEs of 10 children/adolescents with multidrug-resistant tuberculosis who received the short-course regimen, Niger

Patient	Age years	Sex	HIV	BMI kg/m^2	AE	ANRS AE severity*	Month of occurrence	Outcome
1	19	F	Negative	12.4	Ototoxicity	D2	3	Cured
2	16	M	Negative	15.4	No	—	—	Cured
3	18	M	Negative	13.0	No	—	—	Died
4	16	M	Negative	8.8	Vomiting	D2	1	Cured
5	17	M	Negative	14.5	Vomiting	D2	1	Cured
6	17	M	Positive	11.5	Vomiting	D2	1	Cured
7	17	M	Negative	15.0	No	—	—	Cured
8	19	M	Negative	15.6	No	—	—	Cured
9	17	F	Negative	12.3	No	—	—	Cured
10	19	M	Negative	15.6	Hepatotoxicity	D1	5	Failure

* D1 = mild or transient discomfort without limitation of normal daily activities; no medical intervention or corrective treatment required. D2 = moderate limitation of normal daily activities, with minimal medical intervention or corrective treatment required.
AE = adverse event; HIV = human immunodeficiency virus; BMI = body mass index; ANRS = *Agence National de Recherche sur le SIDA* (French National Agency for Research on AIDS and Hepatitis); F = female; M = male.

Bangladesh study, high-level FQ resistance was found to be predictive of poor treatment outcomes.[6] Adults, children and adolescents tolerated this regimen well. Vomiting during the initial months of treatment was the most frequently encountered AE experienced by children/adolescents (40%) and adults (30%); this was managed using anti-emetics or by dividing PTH (the drug probably responsible) into two doses a day.[19] Hearing loss affecting 21 patients was one of the main AEs, and was probably caused by KM use.[19] Hearing loss was managed by reducing the frequency of the probable offending drug to three times per week; hearing aids were provided to patients with moderate hearing loss at the end of treatment. EMB use was discontinued in two adults who developed optic neuritis, but treatment was completed.

The child/adolescent group experienced AEs similar to that suffered by adults with regard to type and frequency. Vomiting was the most frequently experienced AE and was also managed using anti-emetics such as metopimazine injections, metoclopramide tablets and ondansetron. In case of recurrence, the probable offending drug (PTH) was given in divided doses or deferred to the evening under the supervision of a mandated family member.

Our study was limited by its observational nature and small cohort size, particularly in the child/adolescent group. Despite these limitations, AE management, particularly at the ambulatory level, is expected to benefit most MDR-TB patients in resource-constrained settings. These results can therefore be used to guide case management strategies and staff training, particularly when task shifting. Moreover, although there is an absence of data from randomised clinical trials and questions remain over the generalisability of the Bangladesh regimen results, the prompt availability of a new point-of-care test capable of detecting FQ resistance could lead to an even higher cure rate.[20]

Table 5 Status of 106 cured patients at 1-year follow-up

Status	6-month follow-up *n* (%)	12-month follow-up *n* (%)
Culture-negative	94 (88.7)	88 (83.0)
Relapse	2 (1.9)	2 (1.9)
Moved to other jurisdiction	7 (6.6)	12 (11.3)
Death	3 (2.8)	4 (3.8)
Total	106 (100)	106 (100)

CONCLUSIONS

Our results add to the available evidence showing that the short-course MDR-TB treatment regimen is effective in programmatic settings in Niger and is well-tolerated regardless of age in settings with known or low risk of FQ resistance. NTP countries with conditions similar to those in Niger should encourage implementation of this regimen.

Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : Programme National Tuberculose du Niger.

OBJECTIF : Décrire les résultats et la survenue d'effets secondaires (AE) dans une cohorte d'adultes, enfants et adolescents avec la tuberculose multirésistante (TB-MDR), traités par le protocole « court ».

SCHÉMA : Le protocole comprenait une phase intensive de 4–6 mois par kanamycine, isoniazide à dose moyennement élevée et prothionamide, et des doses élevées de gatifloxacine, clofazimine, éthambutol et pyrazinamide tout au long du traitement. Soixante-cinq patients ont été traités par un protocole de 12–14 mois et 55 patients par un protocole de 9–11 mois.

RÉSULTATS : Des 120 patients analysés, 110 (92%) ont été des adultes (âge médian : 31 ans) et 10 (8%) ont été des enfants ou des adolescents, avec un âge médian de 17 ans. Le taux de succès du traitement a été de 88% et de 83% avec le protocole de 9 mois tandis qu'il a été de 90% et de 75% avec le protocole de 12 mois pour le groupe des adultes et des enfants/adolescents, respectivement. Une résistance initiale à l'éthambutol et au prothionamide n'a pas affecté le succès du traitement contrairement à la résistance à la fluoroquinolone qui l'a affecté mais sans signification statistique. Des vomissements ont été l'effet secondaire le plus souvent rencontré suivis par l'ototoxicité et l'hépatotoxicité. Les effets secondaires ont été de gravité bénigne ou modérée pour la majorité des patients mais n'ont pas abouti à une interruption du traitement.

CONCLUSION : Ces résultats confirment l'efficacité programmatique et la bonne tolérance du traitement raccourci pour des patients n'ayant jamais reçu de médicaments de deuxième ligne.

RESUMEN

MARCO DE REFERENCIA: El Programa Nacional de Tuberculosis de Níger.

OBJETIVO: Describir los desenlaces y las reacciones adversas en una cohorte de adultos, niños y adolescentes con diagnóstico de tuberculosis multirresistente (TB-MDR) que recibieron un esquema de 'tratamiento breve'.

MÉTODOS: El esquema comportaba una fase intensiva de 4–6 meses con kanamicina, isoniazida en dosis medio-altas y protionamida y altas dosis de gatifloxacina, clofazimina, etambutol y pirazinamida del principio al final del tratamiento. Sesenta y cinco pacientes recibieron un esquema de 12–14 meses y 55 pacientes un esquema de 9–11 meses.

RESULTADOS: De los 120 pacientes analizaron, 110 pacientes eran adultos (92%; mediana de la edad, 31 años) y 10 eran niños o adolescentes (8%; mediana de la edad 17 años). La tasa de éxito terapéutico con el esquema de 9 meses fue 88% y 83% en los grupos de adultos y niños o adolescentes respectivamente y de 90% y 75% con el esquema de 12 meses. La resistencia inicial a etambutol y protionamida no alteró la eficacia del tratamiento, a diferencia de la resistencia a fluoroquinolona, pero este efecto no alcanzó significación estadística. La reacción adversa observada con mayor frecuencia fue el vómito, seguido por la ototoxicidad y la hepatotoxicidad. La magnitud de las reacciones adversas fue leve a moderada en la mayoría de casos, pero no dio lugar a interrupción del tratamiento.

CONCLUSIÓN: Los presentes resultados confirman la eficacia programática y la tolerabilidad de un esquema breve de tratamiento en los pacientes que nunca han recibido fármacos de segunda línea.