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Potentially High Number of Ineffective Drugs with the Standard Shorter Course Regimen for Multidrug-Resistant Tuberculosis Treatment in Haiti

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Abstract. Multidrug-resistant tuberculosis (MDR-TB) outcomes are poor partly because of the long treatment duration; the World Health Organization conditionally recommends a shorter course regimen to potentially improve treatment outcomes. Here, we describe the drug susceptibility patterns of a cohort of MDR-TB patients in Haiti and determine the number of likely effective drugs if they were treated with the recommended shorter course regimen. We retrospectively examined drug susceptibility patterns of adults initiating MDR-TB treatment between 2008 and 2015 at the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections in Port-au-Prince, Haiti. First- and second-line drug susceptibility testing (DST) was analyzed and used to determine the number of presumed effective drugs. Of the 239 patients analyzed, 226 (95%), 183 (77%), 135 (57%), and 38 (16%) isolates were resistant to high-dose isoniazid, ethambutol, pyrazinamide, and ethionamide, respectively. Eight patients (3%) had resistance to either a fluoroquinolone or a second-line injectable and none had extensively resistant TB. Of the 239 patients, 132 (55%) would have fewer than five likely effective drugs in the intensive phase of the recommended shorter course regimen and 121 (51%) would have two or fewer likely effective drugs in the continuation phase. Because of the high rates of resistance to first-line TB medications, about 50% of MDR-TB patients would be left with only two effective drugs in the continuation phase of the recommended shorter course regimen, raising concerns about the effectiveness of this regimen in Haiti and the importance of using DST to guide treatment.

INTRODUCTION

The estimated global incidence of multidrug-resistant (MDR) and rifampin-resistant (RR) tuberculosis (TB) was 490,000 cases in 2016, with only 153,111 cases of MDR/RR-TB notified to national TB programs and the World Health Organization (WHO); only 22% of the estimated incident cases started treatment. Of the 2014 global cohort of patients with MDR/RR-TB who initiated treatment, only 54% achieved treatment completion or cure.[1] High rates of unsuccessful treatment are due to the length of treatment, toxic drug effects, and high number and low efficacy of standard MDR-TB medications. WHO–recommended second-line drug regimens are based on a fluoroquinolone and injectable agent backbone plus additional agents to achieve a regimen with at least five drugs likely to be effective for the intensive phase and four drugs for the continuation phase of treatment.[2] Although WHO did release new longer course treatment regimen guidelines recently removing second-line injectables, these have not yet been implemented globally.[3]

In October 2016, WHO recommended a shorter course MDR-TB regimen lasting from 9 to 12 months composed of a fluoroquinolone (gatifloxacin or moxifloxacin), kanamycin, prothionamide, clofazimine, high-dose isoniazid, ethambutol, and pyrazinamide for a 4-month intensive phase and a fluoroquinolone (gatifloxacin or moxifloxacin), clofazimine, pyrazinamide, and ethambutol for a 5-month continuation phase.[4] This recommendation is conditional on not having been treated with second-line drugs previously and having no evidence of fluoroquinolone or second-line injectable resistance. This shorter course regimen is based on observational data from 10 countries, including studies from Bangladesh,[5] Niger,[6] and Cameroon[7] which demonstrated successful treatment rates of 87.9%, 89.2%, and 89.0%, respectively.[2] When comparing aggregate success versus failure or relapse, the shorter course had a 97.5% rate of success versus 91.2% in the long-course regimens.[4] The evaluation of a standardized treatment regimen of anti-TB drugs for patients with Multidrug-resistant Tuberculosis (STREAM) trial is an ongoing multicenter randomized clinical trial to assess non-inferiority of this shorter course regimen compared with the standard long-course regimen.[8] Preliminary results presented in October 2017 indicate that the shorter course regimen failed to achieve non-inferiority, with treatment success of 78.1% in patients receiving the shorter course and 80.6% in patients receiving the long-course regimen.[9,10] In response, the WHO conducted an expedited review of the data from the STREAM trial and concluded that the 2016 conditional recommendation on the use of the shorter course regimen remains in place.[11]

Haiti is a severe resource-limited country with an estimated MDR/RR-TB incidence of 7.1 per 100,000 persons.[12] The Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), located in Port-au-Prince, is one of the main centers for MDR-TB treatment. We examined drug resistance patterns among adult MDR-TB patients at GHESKIO to evaluate the likely number of effective drugs for the recommended shorter course regimen.

METHODS

Study site. The Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) is located in Port-au-Prince, Haiti. It is the largest provider of human immunodeficiency virus (HIV) and TB care in the Caribbean region. In 2015, GHESKIO diagnosed 2,437 TB cases and

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3,115 HIV cases.[13] The Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections has had designated inpatient treatment capacity for patients with MDR-TB since 2008, with an associated biosafety level three laboratory which serves as a national mycobacteriology reference laboratory for Haiti.

Study population. Between June 1, 2008 and December 31, 2015, 252 patients were diagnosed with MDR-TB. Thirteen patients were excluded as they were less than 18 years of age. The final cohort included 239 patients aged at least 18 years with culture-positive MDR-TB.

Multidrug-resistant-tuberculosis diagnosis and drug susceptibility testing. Patients with suspected TB underwent clinical evaluation, chest radiography, and sputum testing. Before July 2012, sputum samples from high-risk patients were referred for molecular testing for drug resistance with either Genotype MTBDRplus (Hain Life Sciences, Nehren, Germany) or GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA) depending on the availability of the assay at the time of diagnosis. Beginning in July 2012, GeneXpert MTB/RIF was performed as the first-line screening and diagnostic test for all patients screened for TB.

Clinical samples were decontaminated using the sodium hydroxide/*N*-acetyl-*L*-cysteine method and cultured using liquid (BACTEC MGIT 960 tube) and solid (Lowenstein-Jensen slant) commercially available media (Becton Dickenson, Franklin Lakes, NJ). Rapid tests (SD-Bioline Standard Diagnostics, Inc., Yongin, Korea and Capilia TB-Neo Tauns Laboratories, Inc., Izunokuni, Japan) identified MTB isolates via MPT64 antigen detection.

First- and second-line drug susceptibility testing (DST) was performed on all samples with molecular evidence for rifampin resistance. First-line DST was performed on-site with BACTEC MGIT 960 SIRE and PZA kits (Becton, Dickinseon) according to the manufacturer's recommendations at the following concentrations: isoniazid 0.1 μg/mL, rifampin 1.0 μg/mL, ethambutol 5.0 μg/mL, pyrazinamide 100 μg/mL, and streptomycin 1.0 μg/mL. Before 2013, MTB sample isolates were shipped to the New York State Laboratory for second-line DST using the standard proportion method on 7H10 medium agar at the following concentrations: isoniazid 0.2 and 1.0 μg/mL, rifampin 1.0 μg/mL, ethambutol 5.0 and 10.0 μg/mL, amikacin 2.0 and 4.0 μg/mL, kanamycin 5.0 μg/mL, capreomycin 10.0 μg/mL, streptomycin 2.0 and 10.0 μg/mL, ofloxacin 2.0 and 4.0 μg/mL, cycloserine 30.0 μg/mL, ethionamide 5.0 μg/mL, and p-aminosalicylic acid 2.0 μg/mL. Beginning in 2013, second-line DST was performed on-site at GHESKIO using the same method, drugs, and concentrations.

Less than half of the DSTs were performed at the New York State Laboratory. Clofazimine was not available in Haiti during this time period and clofazimine susceptibility was assumed for all patients. Quality control for the New York State Laboratory was maintained in accordance with the New York State Department of Health. The GHESKIO laboratory is certified by the Division of AIDS of the U.S. National Institutes of Health and successfully participates in external quality assessments through verified external quality assessment organizations: Instand eV (Düsseldorf, Germany) for mycobacterial identification, culture, and DST, and SmartSpot Quality (Johannesburg, South Africa) for Hain and Xpert assays.

Description of drug regimens and clinical care. Patients were started on a standardized regimen, which was individualized once DST results were available. Drug regimens changed over time based on drug availability in Haiti and changes in Haitian national guidelines and WHO guidelines.[4,14,15] Each regimen was composed around a backbone of a fluoroquinolone plus injectable agent for the intensive phase with the goal of achieving five effective drugs including pyrazinamide and four second-line medications.[4] Patients were hospitalized during initial months of treatment and discharged once deemed non-infectious by physician staff. The intensive phase, defined by the inclusion of a second-line injectable agent, lasted for 8–10 months depending on culture conversion, and the continuation phase, without injectable, lasted for 14–16 months to complete 24 months of treatment. Despite suffering a devastating earthquake in 2010, MDR-TB treatment outcomes have been excellent with cure rates as high as 88%.[16,17]

Ethics. This study was approved by the institutional review boards of all affiliated institutions.

Data analysis. Patient data were extracted from the GHESKIO electronic medical record, laboratory database, and hard-copy paper charts. Patient baseline characteristics and resistance patterns were stratified by HIV status.

RESULTS

Between June 16, 2008 and December 31, 2015, 239 adults were diagnosed with MDR-TB and initiated treatment; of these, 48 (20%) were HIV positive (Table 1). Among HIV-negative patients, median age was 29 (interquartile range [IQR]: 23, 39), 100 (52%) were male, and 186 (97%) had been on first-line TB treatment previously. Among HIV-positive patients, median age was 32 (IQR: 26, 40), 22 (46%) were male, and all patients had previously been on first-line TB treatment.

Individual drug resistance results are described in Table 2. All patients were resistant to low-dose isoniazid. Among HIV-negative patients, 179 (94%), 146 (76%), 110 (58%), and 28 (15%) were resistant to high-dose isoniazid, ethambutol, pyrazinamide, and ethionamide, respectively. Three (2%) HIV-negative patients were resistant to kanamycin and two (1%) were resistant to ofloxacin. Among HIV-positive patients, 47 (98%), 37 (77%), 25 (52%), and 10 (21%) were resistant to high-dose isoniazid, ethambutol, pyrazinamide, and ethionamide, respectively. Two (4%) HIV-positive patients were resistant to kanamycin and one (2%) was resistant to ofloxacin. Based on these resistance patterns, 18% (n = 44) did not achieve four effective core second-line drugs.

Table 3 lists the individual resistance patterns and the number of likely effective drugs in the intensive and continuation phase with the standard shorter course regimen, stratified by HIV status. No patient had extensively resistant (XDR)-TB. Three patients (1%) were resistant to a fluoroquinolone, two were HIV negative, and one was HIV positive. Five patients (2%) had resistance to a second-line injectable agent, three were HIV negative and two were HIV positive. Of these eight patients with either fluoroquinolone or second-line injectable resistance, two, one, and five of these patients would have five, four, and three effective drugs in the intensive phase, respectively. One, one, five, and one would have four, three, two, and one effective drugs in the continuation phase.

Among those without pre-XDR TB (resistance to either fluoroquinolone or second-line injectable) (Table 3), 129 (54%) had pyrazinamide resistance, 107 (56%) HIV negative, and 22 (46%) HIV positive (Table 3). Among HIV-negative patients with pyrazinamide resistance, one (1%), 14 (13%), 76 (71%), and 16 (15%) were susceptible to six, five, four, and three drugs in the intensive phase; and 12 (6%) and 95 (81%)

TABLE 1
Baseline characteristics of MDR-TB patients initiating treatment, 2008–2015

Baseline characteristics	HIV negative, *N* = 191	HIV positive, *N* = 48	Total, *N* = 239
Age (years)—median (IQR)	29 (23, 39)	32 (26, 40)	30 (24, 40)
Male—no. (%)	100 (52)	22 (46)	122 (51)
Education—no. (%)			
Primary or less	61 (32)	24 (50)	85 (36)
Secondary or above	107 (56)	16 (33)	123 (52)
Missing	23 (12)	8 (17)	31 (13)
Income—no. (%)			
< 2 US dollar	146 (76)	32 (67)	178 (74)
> 2 US dollar	44 (23)	16 (33)	60 (25)
Missing	1 (0.5)	0 (0)	1 (0.4)
Marital status—no. (%)			
Single	112 (59)	21 (44)	133 (56)
Married or has partner	35 (18)	14 (29)	49 (21)
Divorced or widowed	12 (6)	6 (13)	18 (8)
Missing	32 (17)	7 (15)	39 (16)
CD4 Count at treatment Initiation—median (IQR)	–	388 (195, 759)	–
Antiretroviral therapy (ART) use—no. (%)			
On ART at time of TB treatment initiation	–	25 (52)	–
Began ART after MDR-TB	–	13 (27)	–
Unknown ART start date	–	10 (20)	–
Diabetes—no. (%)	3 (2)	0 (0)	3 (1)
Prior TB treatment—no. (%)			
First-line therapy	186 (97)	48 (100)	234 (98)
Second-line therapy	1 (0.5)	0 (0)	1 (0.4)
Missing	4 (2)	0 (0)	4 (2)

IQR = interquartile range; MDR-TB = multidrug-resistant tuberculosis.

patients were susceptible to three and two drugs in the continuation phase. Among HIV-positive patients with pyrazinamide resistance, one (4%), 18 (82%), and three (14%) were susceptible to five, four, and three drugs in the intensive phase, and two (9%) and 20 (91%) patients were susceptible to three and two drugs in the continuation phase.

There were 102 patients with no fluoroquinolone, second-line injectable or pyrazinamide resistance, 79 HIV negative, and 23 HIV positive (Table 3). Among HIV-negative patients, 25 (32%), 40 (51%), and nine (11%) were susceptible to six, five, and four drugs in the intensive phase; 30 (38%) and 49 (62%) were susceptible to four and three drugs in the continuation phase. Among HIV-positive patients, eight (35%), 11 (48%), and nine (39%) patients were susceptible to six, five, and four drugs in the intensive phase; nine (39%) and 14 (61%) have susceptibility to four and three drugs in the continuation phase.

Of all patients, 193 (81%) were infected with TB resistant to some combination of first-line drugs but with no resistance to second-line medications. In the intensive phase, 132 (55%) patients would have less than five likely effective drugs and 199 (83%) patients would have less than four likely effective drugs in the continuation phase.

TABLE 2
Resistance by individual drug, stratified by HIV status

	Resistance by drug		
Drug	HIV negative, *N* = 191 (%)	HIV positive, *N* = 48 (%)	Total patients, *N* = 239 (%)
Isoniazid^{LD}	191 (100)	48 (100)	239 (100)
Isoniazid^{HD}	179 (94)	47 (98)	226 (95)
Ethambutol	146 (76)	37 (77)	183 (77)
Pyrazinamide	110 (58)	25 (52)	135 (57)
Streptomycin	97 (51)	25 (52)	122 (51)
Ethionamide	28 (15)	10 (21)	38 (16)
Cycloserine	0 (0)	0 (0)	0 (0)
P-aminosalicylic acid	3 (2)	1 (2)	4 (2)
Kanamycin*	3 (2)	2 (4)	5 (2)
Capreomycin	0 (0)	0 (0)	0 (0)
Amikacin*	1 (0.5)	0 (0)	1 (0.4)
Ofloxacin	2 (1)	1 (2)	3 (1)

Isoniazid^{LD} = low-dose isoniazid; Isoniazid^{HD} = high-dose isoniazid.
* The organism resistant to amikacin was also resistant to kanamycin. No patients had capreomycin resistance.

DISCUSSION

There is a high rate of resistance to first-line TB medications among patients with MDR-TB in Haiti, with 95% resistant to high-dose isoniazid, 77% resistant to ethambutol, and 57% resistant to pyrazinamide. It is estimated that nearly one in 10 patients would receive only three likely effective drugs in the intensive phase of the standard shorter course regimen (kanamycin, moxifloxacin, and clofazimine), and more than half of the patients would receive only two likely effective drugs (moxifloxacin and clofazimine) in the continuation phase. Furthermore, 98% of MDR-TB strains isolated from these patients are resistant to at least one of the drugs in the regimen, likely increasing drug toxicity without clinical benefit. One possible reason for the high rate of first-line drug resistance is that most patients reported previous antituberculous therapy, which frequently was received outside Port-au-Prince, where accessibility to rapid molecular testing is limited. Rates of resistance to fluoroquinolones and second-line injectable medications are very low in Haiti (3%), and thus this population may not be excluded from the WHO recommendation regarding the use of the shorter course regimen. However, based on the high rates of resistance to first-line medications, we believe the recommended shorter course regimen is not optimal for use in Haiti. Our data highlight the

TABLE 3
Resistance patterns and presumed effective drugs in the shorter course regimen

Resistance patterns	Number of effective drugs remaining in proposed shorter course regimen*		HIV negative, *N* = 191 (%)	HIV positive, *N* = 48 (%)	Total patients, *N* = 239 (%)
	Intensive phase 4–6 km-Mfx-Pto-Cfz-Z-H^{HD}-E	Continuation phase 5 Mfx-Cfz-Z-E			
Fluoroquinolone or injectable resistance			5 (3)	3 (6)	8 (3)
R + H^{HD} + E + Z + KM/amikacin	**Mfx-Pto-Cfz**	Mfx-Cfz	1 (0.5)	0 (0)	1 (0.4)
R + H^{HD} + E + Z + KM	**Mfx-Pto-Cfz**	Mfx-Cfz	1 (0.5)	2 (4)	3 (1)
R + H^{HD} + KM	Mfx-Pto-Cfz-Z-E	Mfx-Cfz-Z-E	1 (0.5)	0 (0)	1 (0.4)
R + H^{HD} + E + Z + Ofx	**Km-Pto-Cfz**	Cfz	0 (0)	1 (2)	1 (0.4)
R + H^{HD} + Z + Ofx	**Km-Pto-Cfz-E**	Cfz-E	1 (0.5)	0 (0)	1 (0.4)
R + H^{HD} + Ofx	Km-Pto-Cfz-Z-E	Cfz-Z-E	1 (0.5)	0 (0)	1 (0.4)
Resistant to Pyrazinamide			**107 (56)**	**22 (46)**	**129 (54)**
R + H^{HD} + E + Z + Eto	**Km-Mfx-Cfz**	Mfx-Cfz	15 (8)	3 (6)	18 (8)
R + H^{HD} + E + Z + Eto + PAS	**Km-Mfx-Cfz**	Mfx-Cfz	1 (0.5)	0 (0)	1 (0.4)
R + H^{HD} + Z + Eto	**Km-Mfx-Cfz-E**	Mfx-Cfz-E	1 (0.5)	1 (2)	2 (1)
R + H^{HD} + E + Z	**Km-Mfx-Pto-Cfz**	Mfx-Cfz	75 (40)	17 (35)	92 (39)
R + H^{LD} + E + Z	Km-Mfx-Pto-Cfz-H^{HD}	Mfx-Cfz	4 (2)	0 (0)	4 (2)
R + H^{HD} + Z	Km-Mfx-Pto-Cfz-E	Mfx-Cfz-E	10 (5)	1 (2)	11 (5)
R + H^{LD} + Z	Km-Mfx-Pto-Cfz-H^{HD}-E	Mfx-Cfz-E	1 (0.5)	0 (0)	1 (0.4)
Other Resistance Patterns			**79 (41)**	**23 (48)**	**102 (43)**
R + H^{HD} + E + Eto + PAS	**Km-Mfx-Cfz-Z**	Mfx-Cfz-Z	2 (1)	1 (2)	3 (1)
R + H^{HD} + E + Eto	**Km-Mfx-Cfz-Z**	Mfx-Cfz-Z	7 (4)	3 (6)	10 (4)
R + H^{HD} + Eto	Km-Mfx-Cfz-Z-E	Mfx-Cfz-Z-E	1 (0.5)	1 (2)	2 (1)
R + H^{LD} + Eto	Km-Mfx-Cfz-Z-H^{HD}-E	Mfx-Cfz-Z-E	1 (0.5)	1 (2)	2 (1)
R + H^{HD} + E	Km-Mfx-Pto-Cfz-Z	Mfx-Cfz-Z	39 (20)	10 (21)	49 (21)
R + H^{LD} + E	Km-Mfx-Pto-Cfz-Z- H^{HD}	Mfx-Cfz-Z	1 (0.5)	0 (0)	1 (0.4)
R + H^{HD}	Km-Mfx-Pto-Cfz-Z-E	Mfx-Cfz-Z-E	23 (12)	7 (15)	30 (13)
R + H^{LD}	Km-Mfx-Pto-Cfz-Z-H^{HD}-E	Mfx-Cfz-Z-E	5 (3)	0 (0)	5 (2)

Cfz = clofazimine; E = ethambutol; Eto = ethionamide; H^{HD} = high-dose INH; H^{LD} = low-dose isoniazid; KM = kanamycin; Mfx = moxifloxacin; Ofx = ofloxacin; PAS = para-aminosalicylic acid; Pto = prothionamide; R = rifampin; Z = pyrazinamide. **Bold-faced drugs** are those with regimens composed of less than five likely effective drugs in the intensive phase.
* Mfx and Pto sensitivity was presumed based on ofloxacin and ethionamide sensitivity testing, respectively. Clofazimine sensitivity presumed for all patients.

essential importance of DST for every patient with MDR-TB so as to optimize each individual's treatment regimen. A shorter course regimen is needed but would ideally be based on DST to ensure that patients are receiving the appropriate number of effective medications.

Although retrospective cohort data suggested overall treatment success rates of 90% for the shorter course regimen, the STREAM trial failed to demonstrate non-inferiority compared with standard long-course therapy.[4,9] According to interim results, 78.1% of the shorter course group achieved favorable outcomes compared with 80.6% of the long-course group. Among patients living with HIV, 17% had an unfavorable outcome with the shorter course compared with 8% with the long-course regimen.[18] The higher mortality of patients infected with HIV in STREAM and other shorter course studies is concerning.[19] It is unlikely that outcomes with standard shorter course treatment in a more pragmatic setting will be superior to those preliminarily reported from the STREAM trial.

The baseline DST profiles of STREAM participants have not yet been presented, and the impact of resistance patterns on outcomes is unknown. Baseline DST results for the shorter course treatment cohorts in Niger and Bangladesh indicate similarly high rates of ethambutol resistance (64–78%) to Haiti with much lower rates of pyrazinamide resistance (14–26%), similar rates of second-line injectable resistance (0–1.8%); but higher fluoroquinolone resistance was seen in Bangladesh (up to 10.3%).[5,6] Differences in baseline drug susceptibility profiles may have contributed to differences in STREAM outcomes and may also affect outcomes in Haiti if the shorter course regimen was used. WHO recently released updated guidelines on the treatment of MDR-TB, highlighting that observational studies examining shorter course regimens were not only associated with lower risk of interruption in treatment but also a higher risk of relapse and failure particularly. This higher risk was thought to be likely related to resistance to key drugs in the shorter course regimen.[3] This correlates with our findings on the impact of the shorter course regimen in Haiti and highlights the importance of DST in guiding selection of appropriate patients for the shorter course regimen.

One main concern regarding the use of the WHO-recommended shorter course regimen for patients with MDR-TB in Haiti is that it will add toxicity without clinical benefit. Second-line antituberculous drugs have significant individual adverse effects which can be exacerbated by an increased number of drugs in a regimen or by concomitant use with antiretrovirals. Common adverse reactions to high-dose isoniazid, ethambutol, and pyrazinamide—all drugs with high rates of resistance in Haiti—include hepatotoxicity, nausea, vomiting, malaise, arthralgia, rash, neuropathy, and visual disturbances.[20–22] Patients who are receiving concurrent treatment for HIV and MDR-TB are more likely to have adverse events, particularly if they have severe immunologic suppression.[23] Of particular concern for persons on both antiretroviral and antituberculous treatment is the risk of neuropathy, central nervous system side effects, and drug-induced liver toxicity, which are reported for anti-TB medications such as isoniazid, as well as antiretroviral therapy agents.[24,25] The final safety data from the current STREAM trial of the shorter course have not yet been published; however, adverse event data from other shorter course studies demonstrate a high prevalence of adverse events, with 63% of patients reporting at least one adverse drug event among those receiving short-course regimen in Niger, with 20% reporting hearing impairment.[6] An independent patient data meta-analysis examining adverse events among patients receiving various shorter course regimens found that 18% of patients experienced a grade three or four adverse event.[26] The use of a shorter course regimen, wherein the full

potential of drug-induced toxicity is unknown, would necessitate significant conversation between individual patient-provider teams so that patients are fully aware of the possibility of adverse drug events.

Reported rates of pyrazinamide resistance vary widely. Of patients tested in a MDR-TB cohort in nine western and central African countries, 51% of strains were found to be resistant to pyrazinamide, which is similar to the rate in Haiti. This MDR-TB cohort was treated with a shorter course regimen similar to that recommended by the WHO; those with pyrazinamide resistance had a nonstatistically significant trend toward higher failure.[27] According to a meta-analysis examining pyrazinamide resistance from MDR-TB cohorts across eight WHO regions, pooled prevalence ranged from 49% (Western Pacific) to 80% (Eastern Mediterranean), and 53% in the Americas.[28] Among RR TB culture isolates from 12 sub-Saharan African countries, the prevalence of pyrazinamide resistance was 52% overall, ranging from 21% in Togo to 80% in Burkina Faso.[29]

Pyrazinamide resistance has been associated with poor treatment outcomes among patients with MDR-TB.[4] According to a meta-analysis that included cohorts of patients infected with MDR and XDR-TB, those with pyrazinamide susceptibility had 1.6 greater odds of achieving successful outcome.[30] Significantly, a large independent patient data meta-analysis examining the effectiveness of shorter course regimens found that pyrazinamide resistance was associated with eight times higher odds of treatment failure or relapse (odds ratio 8, 95% confidence interval 2, 38).[26] Knowing pyrazinamide susceptibility before initiating a treatment regimen is therefore important to achieve successful treatment outcomes. Determining accurate pyrazinamide susceptibility testing can be difficult because of concerns that the most common method of pyrazinamide DST, BACTEC 960 MGIT, may have a lack of reproducibility and false positives due in part to the variable amount of inoculum used in the DST process.[31] Despite this, there is still good concordance with DST performed with BACTEC 960 MGIT when compared with the standard of pyrazinamide DST, BACTEC 460TB.[32,33] Given the potential clinical importance of pyrazinamide susceptibility, pyrazinamide resistance testing may provide useful clinical information, despite its limitations. Continued research into rapid molecular tests and better methods of determining pyrazinamide susceptibility are urgently needed.

Prevalence of ethambutol resistance also varies widely among MDR-TB cohorts. In Bangladesh, the National TB Drug Resistance Survey reported that 4% of new and retreatment smear-positive patients had ethambutol resistance; this cohort included both drug-susceptible, MDR-TB and polydrug-resistant TB patients.[34] This is lower than that seen in our cohort and in many areas of the world. Niger reported a much higher prevalence of ethambutol resistance of 69%.[6] In the Americas, prevalence estimates range as high as 49% (3,825/7,760) among MDR-TB clinical isolates at a national reference laboratory in Peru.[35]

High-dose isoniazid has been increasingly used in MDR-TB regimens as it may reduce time to culture conversion.[36] In our population, 95% of MTB isolates had high-dose isoniazid resistance. Reported rates of katG mutations, which are associated with high-dose isoniazid resistance, are 82%, 97%, 62%, and 84% in South Africa,[37] Ethiopia,[38] China,[39] and Bangladesh,[40] respectively. Several of these countries have used shorter course regimens. It is unclear whether high-dose isoniazid is effective in patients with high-level resistance, and more research needs to be performed in this area.

The extensive first-line drug resistance in our study population suggests that a shorter course regimen including newer or repurposed drugs such as bedaquiline, delamanid, and linezolid may be preferable to the WHO-recommended standard shorter course regimen in Haiti. There are several ongoing clinical trials examining such novel regimens.[41–43] Treatment outcomes for MDR-TB in Haiti are among the best in the world,[16,17] with the use of standard long-course therapy in conjunction with DST. The Haitian National TB Program is in the process of selecting a shorter course regimen that would lead to continued high success rates, without increasing toxicity.

These findings have some limitations. This is a retrospective study of DST patterns that indicates extensive first-line drug resistance in our population; nevertheless, the standard shorter course regimen may result in similar outcomes to long-course therapy. Given the variability in DST testing methods, geographic diversity, and treatment regimens, it is challenging to compare outcomes for MDR-TB patient cohorts in different settings. In addition, we sought to examine the number of effective drugs in the proposed shorter course regimen based on DST against individual drugs without accounting for possible synergy between drugs. Such synergy may provide a clinical benefit that would not be reflected by DST patterns.[44,45]

CONCLUSION

We found extensive first-line drug resistance in the largest reported cohort of MDR-TB patients in Haiti. If the standard shorter course regimen was implemented, half of the patients would be left with only two likely effective drugs in the continuation phase, suggesting suboptimal outcomes and unnecessary toxicity. Haiti's drug susceptibility patterns are not unique and regions with similar rates of first-line TB drug resistance may face the same dilemma, highlighting the need to consider newer MDR-TB drugs in a shorter course regimen. Our data highlight the importance of routine DST when it is feasible, to facilitate the selection of an optimal regimen for each patient.

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