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Time to Culture Conversion of Bedaquiline and High-Dose Isoniazid for Drug-Resistant Tuberculosis

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Patients with multidrug-resistant tuberculosis who received regimens containing high-dose isoniazid (INH[HD]) had similar time to culture conversion and treatment outcomes as patients who received regimens with bedaquiline. INH[HD] is an inexpensive and safe medication that may contribute additive efficacy in combination regimens.

Keywords. bedaquiline; drug-resistant tuberculosis; high-dose isoniazid; time to culture conversion; treatment outcomes.

Multidrug resistant tuberculosis (MDR-TB), resistant to both isoniazid and rifampin, carries high mortality worldwide [1]. With the development of new drugs such as bedaquiline (BDQ), treatment regimens for MDR-TB have improved, with an all-oral regimen now the standard of care [1]. Although no longer including injectable agents, these regimens are still of long duration and associated with substantial toxicity.

High-dose isoniazid (INH[HD]) was previously recommended by the World Health Organization (WHO). Although INH[HD] is still included in short-course MDR-TB regimens recommended by the WHO, it was removed from standard treatment recommendations in 2019, due to insufficient efficacy data [1].

However, there are data to suggest that INH[HD] may be effective in the treatment of MDR-TB [2–5]. We previously demonstrated that among human immunodeficiency virus (HIV)-negative patients with MDR-TB in Haiti, the time to culture conversion was significantly shorter among those who received regimens including INH[HD], compared to those who received regimens without INH[HD] [6]. We updated this analysis to include HIV-negative patients with MDR-TB who received a standard-of-care regimen that included BDQ.

METHODS

This study was conducted at the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) in Port-au-Prince, Haiti, the largest provider of tuberculosis care in the Caribbean. The initial evaluation included clinical assessment, chest radiograph, and molecular testing using Xpert MTB/RIF (Cepheid, Sunnyvale, CA) and/or Genotype MTBDR*plus* (Hain LifeScience, Nehren, German). All samples with rifampin resistance detected by molecular testing were cultured using liquid media (BACTEC MGIT 960; Becton Dickinson, Franklin Lakes, NJ) and solid media (Lowenstein-Jensen slant). First and second-line drug susceptibility testing was conducted per routine protocol as described previously [6]. All patients with MDR-TB were treated in accordance with WHO and Haitian national guidelines [1, 7, 8].

Between June 2008 and September 2011, all HIV-negative patients with MDR-TB were empirically started on a regimen that included a second-line injectable (kanamycin or capreomycin), a fluoroquinolone (levofloxacin [LFX] or moxifloxacin), cycloserine (CS), ethionamide, pyrazinamide, and *p*-aminosalicylic acid (PAS). In October 2011, INH[HD] (16–18 mg/kg) replaced PAS; in November 2014, INH[HD] was removed from the regimen, but the other 5 drugs were continued [6]. In August 2018, the Haitian National TB Program recommended that BDQ should replace the second-line injectable as standard of care. Starting in April 2019, all newly diagnosed patients with MDR-TB received an all-oral regimen of BDQ, LFX, linezolid, clofazimine, and PZA. Culture was performed monthly (intensive phase), every other month (continuation phase), and finally monthly (last 3–5 months of treatment).

For this analysis, patients were divided into 3 groups: those who received regimens with INH[HD], those who received regimens with BDQ, and those who received regimens with neither INH[HD] nor BDQ. There was no overlap between groups. Culture conversion was defined as 2 consecutive negative cultures at least 30 days apart. Time to culture conversion was defined as time in days between initial positive diagnostic *Mycobacterium tuberculosis* culture in the BACTEC liquid culture system to first negative liquid culture. Time to culture conversion between groups was evaluated using Kaplan-Meier survival analysis and log-rank test for comparison. Patients

who died before achieving culture conversion (INH^{HD} n = 5; neither INH^{HD} nor BDQ n = 6) were censored at the date of their death; patients without culture conversion due to ongoing treatment or loss to follow up were excluded from the survival analysis (BDQ n = 2). Treatment outcomes were defined in accordance with WHO guidelines [9]. The proportion of patients cured in each treatment group were compared using analysis of variance.

Patient Consent Statement

Because this was a retrospective review of clinical outcomes, it was not possible to obtain patient consent. This study used data abstraction of routinely collected clinical data from patients who received care at GHESKIO, which is approved by all relevant institutional review boards.

RESULTS

Between June 2008 and December 2020, 338 HIV-negative adults aged ≥18 years were diagnosed with MDR-TB and initiated on treatment at GHESKIO. Ninety-nine patients (29%) received regimens with INH^{HD}, 60 patients (18%) received regimens with BDQ, and 179 patients (53%) received regimens with neither drug included (Table 1). Median age was 30 (interquartile range, 24–40). One hundred fifty-six (46%) patients were female. The median time to culture conversion was 49 days (95% confidence interval [CI], 44–58) in the INH^{HD} group, 53 days (95% CI, 49–57) in the BDQ group, and 61 days (95% CI, 51–65) in the group that received neither drug (Figure 1). There was no significant difference in time to culture conversion between the BDQ and INH^{HD} groups

(P = .270). Time to culture conversion was faster in both of these groups compared to the group that received neither drug (P < .001). There was no difference in median time to culture conversion before or after April 2019, when the companion drugs in the BDQ regimen changed.

Of those receiving regimens with INH^{HD}, 88 (89%) achieved cure and of those receiving BDQ regimens, 49 (82%) achieved cure. There was no statistically significant difference in the proportion of patients who achieved cure between those who received regimens with BDQ compared to those who received regimens with INH^{HD} (P = .203). As of May 11, 2022, 7 patients receiving regimens with BDQ were still on treatment. There was no statistically significant difference in the proportion of patients who achieved cure between groups whether these patients were included as "cure" (P = .575) or were excluded from the analysis (P = .203). No patients required permanent discontinuation of INH^{HD} or BDQ, suggesting a lack of significant toxicity with these drugs.

DISCUSSION

In our previous report, we demonstrated that HIV-negative adults who received INH^{HD} as part of their MDR-TB regimen had significantly faster time to culture conversion and had higher odds of achieving a successful outcome compared to those who did not receive INH^{HD} [6]. In our updated analysis, we found that there is no significant difference in time to culture conversion between HIV-negative adults who received regimens including INH^{HD} and those who received regimens including BDQ, nor is there any difference in the proportion of patients who achieved cure between these groups.

The individual patient meta-analysis upon which the current WHO guidelines rely lacked data on INH^{HD} in longer regimens, thus making it difficult for a recommendation to be made as to its continued use [1, 10]. However, there are data to suggest that it may provide additional activity, in combination with other effective medications. The INH^{HD} is included in the WHO-approved, short-course regimens, based on favorable outcomes in observational studies and randomized trials [1, 4, 11, 12].

Furthermore, the AIDS Clinical Trials Group study A5312 demonstrated that INH^{HD} (10–15 mg/kg) provides similar early bactericidal activity against *M tuberculosis* strains with *inhA* mutations as standard-dose INH (5 mg/kg) against drug-susceptible strains [3]. In an individual patient meta-analysis of pediatric cases of MDR-TB (age <15 years old), regimens including INH^{HD} (15–20 mg/kg) were associated with favorable treatment outcomes [5].

A major concern with the use of INH^{HD} is the potential lack of efficacy against *M tuberculosis* strains with *katG*-mediated resistance. A5312 expanded enrollment to patients with *katG* mutations, with participants randomized to receive INH at 15 or 20 mg/kg, and the independent effect of INH in this population is being examined (ClinicalTrials.gov identifier

Table 1. Patient Characteristics, Stratified by Drug Regimen

Characteristic	BDQ n = 60	INH^{HD} n = 99	Neither BDQ nor INH^{HD} n = 179	P Value
Age, median [IQR]	31 [25.0–46.3]	29 [23.0–38.0]	30 [25.0–40.0]	.239
Sex, male, n (%)	31 (51.7)	51 (51.5)	100 (55.9)	.732
History of diabetes, n (%)	2 (3.3)	0 (0.0)	5 (2.8)	.22
Treatment Outcome, n (%)				
Cure/treatment completion	49 (81.7)	88 (88.9)	145 (81.0)	<.001
Death	3 (5.0)	7 (7.1)	15 (8.4)	
Loss to follow up	2 (3.3)	4 (4.0)	19 (10.6)	
On treatment	6 (10.0)	0 (0.0)	0 (0.0)	
Drug resistance, n (%)				
Pyrazinamide	25 (41.7)	61 (61.6)	92 (51.4)	.014
Kanamycin	0 (0.0)	1 (1.0)	3 (1.7)	.028
Amikacin	0 (0.0)	1 (1.0)	0 (0.0)	.016
Capreomycin	2 (3.3)	0 (0.0)	0 (0.0)	.001
Ofloxacin	0 (0.0)	1 (1.0)	2 (1.1)	.06
Ethionamide	10 (16.7)	15 (15.2)	24 (13.4)	.054
PAS	1 (1.7)	3 (3.0)	2 (1.1)	<.001

Abbreviation: BDQ, bedaquiline; INH^{HD}, high-dose isoniazid; IQR, interquartile range; PAS, *p*-aminosalicylic acid.
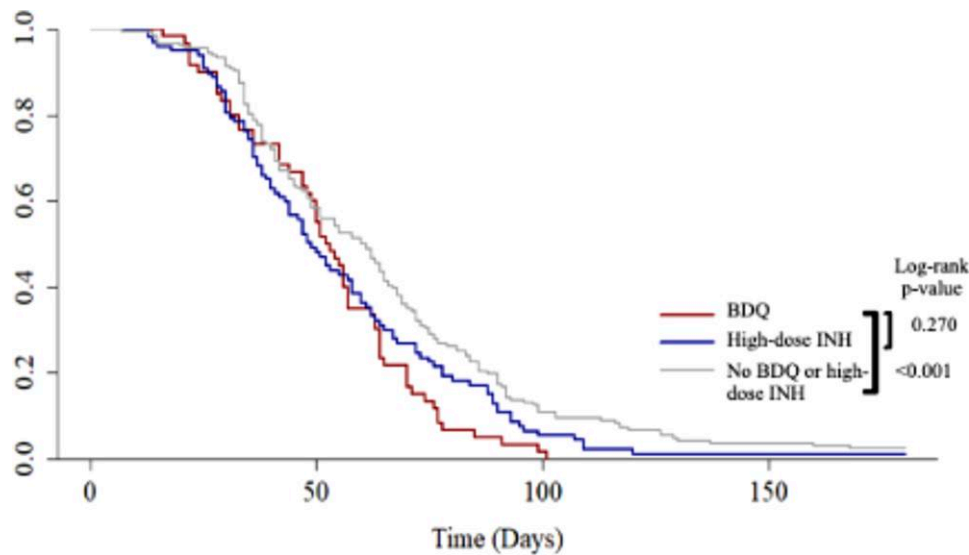
Figure 1. Time to culture conversion (in days) of regimens containing high-dose isoniazid (INH), bedaquiline (BDQ), and regimens containing neither drug.

NCT01936831). In our cohort in Haiti, the majority of patients with MDR-TB have *katG*-mediated resistance, further supporting the potential efficacy of INH[HD].

Our findings do have some limitations. Given the changes in regimens over time, there may be contributions from other medications that are not captured in this analysis but which influenced the efficacy of the INH[HD]- or BDQ-containing regimens. Changes in patient care practices over time may also have affected our results. Systematic reporting of toxicities associated with MDR-TB regimens were not captured although no patients permanently discontinued either INH[HD] or BDQ.

CONCLUSIONS

In summary, INH[HD] is a well tolerated, inexpensive, widely available drug, which may contribute individual efficacy in combination regimens adding to the efficacy of BDQ-based regimens. The efficacy and safety of INH[HD] should be evaluated in future studies of patients with MDR-TB.

References

1. World Health Organization. WHO consolidated guidelines on tuberculosis treatment. Geneva: World Health Organization, **2019**.
2. Katiyar SK, Bihari S, Prakash S, Mamtani M, Kulkarni H. A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis **2008**; 12:139–45.
3. Dooley KE, Miyahara S, von Groote-Bidlingmaier F, et al. Early bactericidal activity of different isoniazid doses for drug-resistant tuberculosis (INHindsight): a randomized, open-label clinical trial. Am J Respir Crit Care Med **2020**; 201: 1416–24.
4. Nunn AJ, Phillips PJP, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med **2019**; 380:1201–13.
5. Harausz EP, Garcia-Prats AJ, Law S, et al. Treatment and outcomes in children with multidrug-resistant tuberculosis: a systematic review and individual patient data meta-analysis. PLoS Med **2018**; 15:e1002591.
6. Walsh KF, Vilbrun SC, Souroutzidis A, et al. Improved outcomes with high-dose isoniazid in multidrug-resistant tuberculosis treatment in Haiti. Clin Infect Dis **2019**; 69:717–9.
7. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. Geneva: World Health Organization, **2016**:56.
8. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis 2011 update. Geneva: World Health Organization, 2011.
9. Rich M, Jaramillo E. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization, 2014.
10. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet **2018**; 392:821–34.
11. World Health Organization. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization, **2022**.
12. Ndjeka N, Campbell JR, Meintjes G, et al. Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study. Lancet Infect Dis **2022**; 22:1042–51.