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 MTBDRplus (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\textsuperscript{HD} n = 5; neither INH\textsuperscript{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.

Table 1. Patient Characteristics, Stratified by Drug Regimen

| Characteristic               | BDQ n = 60 | INH\textsuperscript{HD} n = 99 | Neither BDQ nor INH\textsuperscript{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 (%)    | 49 (81.7)   | 88 (88.9)                     | 145 (81.0)                                   | <.001  |
| Cure/treatment completion    |            |                               |                                               |        |
| 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\textsuperscript{HD}, high-dose isoniazid; IQR, interquartile range; PAS, p-aminoosalicylic acid.

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\textsuperscript{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\textsuperscript{HD} group, 61 days (95% CI, 51–65) in the BDQ group, and 53 days (95% CI, 49–57) in the group that received neither drug. There was no significant difference in time to culture conversion between those who received regimens with BDQ compared to those who received regimens with INH\textsuperscript{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 those who were included as “cure” (P = .575) or were excluded from the analysis (P = .203). No patients required permanent discontinuation of INH\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{HD} (15–20 mg/kg) were associated with favorable treatment outcomes [5].

A major concern with the use of INH\textsuperscript{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...
In our cohort in Haiti, the majority of patients with MDR-TB have katG-mediated resistance, further supporting the potential efficacy of $\text{INH}^{\text{HD}}$.

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 $\text{INH}^{\text{HD}}$- 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 $\text{INH}^{\text{HD}}$ or BDQ.

**CONCLUSIONS**

In summary, $\text{INH}^{\text{HD}}$ 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 $\text{INH}^{\text{HD}}$ should be evaluated in future studies of patients with MDR-TB.

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