

ICAP Journal Club

ICAP's Journal Club is designed to inform ICAP staff and colleagues of the latest scientific literature by providing a succinct summary and critical analysis of important studies, and by discussing the implications of the research on clinical work.

Article

Conradie F, Bagdasaryan TR, Borisov S, et al. **Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis.** *N Engl J Med.* 2022;387(9):810-823.

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Study Summary

The partially blind, randomized ZeNix trial evaluated the efficacy and safety of alternative doses of linezolid in the six-month oral bedaquiline–pretomanid–linezolid regimen for highly drug-resistant tuberculosis (TB).

Study Setting

- Trial sites in South Africa (4), the country of Georgia (1), Moldova (1), and Russia (5).

Methods

- Participants with pulmonary extensively drug-resistant (XDR) TB, pre-XDR TB, or rifampin-resistant TB were enrolled.
 - XDR TB was defined as resistance to rifampin, a fluoroquinolone, and an aminoglycoside.
 - Pre-XDR TB was defined as resistance to rifampin plus resistance to either a fluoroquinolone or an aminoglycoside.
 - Rifampin-resistant TB was defined as *Mycobacterium tuberculosis* resistant to rifampin (with or without resistance to isoniazid) and did not respond to treatment, or for which a second-line regimen had been discontinued because of side effects ≥ 6 months before enrollment.
- Participants were excluded if they had HIV infection and a CD4 cell count $<100/\text{mm}^3$; a risk of arrhythmia; an alanine aminotransferase level and an aspartate aminotransferase level higher than 3 times the upper limit of the normal range; peripheral neuropathy of grade 3 or higher; or had previously received any of the three trial drugs or delamanid for ≥ 2 weeks before enrollment.
- All participants received treatment for 26 weeks, with the option to extend treatment to 39 weeks if ongoing active disease was suspected between weeks 16 and 26.
- Participants were randomly assigned (1:1:1:1) to one of four linezolid regimens, with either 1200 mg or 600 mg daily for either 26 weeks or 9 weeks. Randomization was stratified according to HIV status and classification of drug resistance.

- In addition to linezolid, all participants received 26 weeks of bedaquiline (200 mg daily for 8 weeks, followed by 100 mg daily for 18 weeks) and pretomanid (200 mg daily for 26 weeks).
- The dose of linezolid could be reduced in a stepwise manner (1200 mg, 600 mg, 300 mg, or 0 mg) in response to adverse events.
- Matched placebos were used to blind the participants, site staff, and trial team to dose and duration of linezolid.
- Adherence was monitored by direct observation if the participant was in the hospital or by checking medication cards and bottles for unused tablets at site visits.
- Visits occurred weekly for the first 8 weeks, every 2 weeks until week 20, and then every 3 weeks until the end of treatment. Participants were followed for at least 78 weeks after the completion of treatment.
- At the screening visit, sputum samples were obtained for smear microscopy, molecular testing for rifampin resistance, and culture in liquid medium in a Mycobacterial Growth Indicator Tube (MGIT) system. Samples for culture in the MGIT system were then obtained weekly for 4 weeks and at weeks 6, 8, 10, 12, 16, 20, 23, and 26, and at each follow-up visit after the completion of treatment.
- *M. tuberculosis* isolates from baseline cultures and the first positive culture on or after week 16 in participants who did not have a response to treatment were sent for the MGIT minimum inhibitory concentration (MIC) of bedaquiline, pretomanid, and linezolid; MGIT drug-susceptibility testing for first-line drugs (rifampin, isoniazid, pyrazinamide, ethambutol, and streptomycin), kanamycin, and moxifloxacin; and for whole-genome sequencing. *M. tuberculosis* isolates from participants with recurrence of TB were analyzed with the use of whole-genome sequencing to distinguish between relapse and reinfection.
- Adverse events were recorded at every trial visit, and laboratory safety tests were performed weekly for the first 8 weeks and at scheduled visits during treatment. Electrocardiographic monitoring, examinations to assess vision, and assessments for peripheral neuropathy were also performed at scheduled intervals.
- The primary end point was the incidence of an unfavorable outcome, defined as treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment.
 - Bacteriologic treatment failure was defined as not attaining or maintaining negative culture status during treatment.
 - Clinical treatment failure was defined as a change from the protocol-specified TB treatment due to lack of clinical efficacy, retreatment for TB, or TB-related death by 26 weeks after completion of treatment.
- Culture conversion was defined as at least two consecutive culture-negative samples obtained at least 7 days apart. Relapse was defined as negative culture conversion status not being maintained during follow-up, and a positive culture of a *M. tuberculosis* strain was confirmed as being genetically identical to that at baseline.

- Participants were considered to have a favorable outcome if they continued to have negative culture status during treatment to the end of follow-up and if they had not already been classified as having had an unfavorable outcome.
- Secondary end points included bacteriologic or clinical treatment failure and relapse at 78 weeks after the end of treatment, and time to sputum culture conversion.
- Adverse events that occurred or worsened during the treatment period were defined as events that occurred between the start of treatment and 14 days after the end of treatment. All the participants who received at least one dose of a trial drug were included in the safety analysis population.
- A modified intention-to-treat population was used for the primary analyses, defined as all participants who underwent randomization, except those excluded because of protocol violations prior to randomization; those determined not to have drug-resistant TB (as confirmed by a sputum sample obtained within 3 months before screening); those who were lost to follow-up after successful treatment; or those who died from a cause unrelated to TB.

Study Population and Follow-up

- In total, 248 participants were screened and 181 participants underwent randomization between November 2017 and December 2019. There were 45 participants assigned to each group, except the group that received linezolid 1200 mg for 9 weeks, which had 46 participants.
- Overall, 41.4% of participants had XDR TB, 47.0% had pre-XDR TB, and 11.6% had rifampin-resistant TB. All the participants with rifampin-resistant TB had resistance to isoniazid, so they were classified as having multidrug-resistant TB.
- Of those randomized, 67% were male, 64% were White, and 80% were HIV-negative.
- Of the 143 participants with at least one positive culture between screening and week 4 that was analyzed, 11 had baseline isolates that were resistant to at least one trial drug.

Primary Outcome

- In the modified intention-to-treat analyses, participants were classified as having a favorable outcome at 26 weeks in:
 - 93% of participants that received linezolid 1200 mg for 26 weeks
 - 89% of participants that received linezolid 1200 mg for 9 weeks
 - 91% of participants that received linezolid 600 mg for 26 weeks
 - 84% of participants that received linezolid 600 mg for 9 weeks
- Treatment failure or bacteriologic relapse accounted for five of 19 unfavorable outcomes at 26 weeks of follow-up.

Secondary Outcomes

- In the modified intention-to-treat analyses, participants were classified as having a favorable outcome at 78 weeks of follow-up in:
 - 93% of participants that received linezolid 1200 mg for 26 weeks
 - 89% of participants that received linezolid 1200 mg for 9 weeks

- 89% of participants that received linezolid 600 mg for 26 weeks
 - 80% of participants that received linezolid 600 mg for 9 weeks
- Three participants had unfavorable outcomes at 78 weeks of follow-up, of whom two had received linezolid 600 mg for 9 weeks and had bacteriologic relapse and one had baseline bedaquiline and linezolid resistance. In addition, one participant who had received linezolid 600 mg for 26 weeks was treated again for TB after 39 weeks of follow-up with no positive cultures.
- The median times to culture conversion were:
 - 4 weeks (interquartile range [IQR], 2 to 8) in the groups that received linezolid 1200 mg for 26 weeks or 9 weeks
 - 6 weeks (IQR, 3 to 8) in the group that received linezolid 600 mg for 26 weeks
 - 6 weeks (IQR, 3 to 10) in the group that received linezolid 600 mg for 9 weeks

Safety Outcomes

- At least one adverse event occurred or worsened during treatment in 86.2% of participants, and serious adverse events were reported by 6.1%.
- The linezolid dose was modified (interrupted, reduced, or discontinued) in:
 - 51% of participants that received linezolid 1200 mg for 26 weeks
 - 30% of participants that received linezolid 1200 mg for 9 weeks
 - 13% of participants that received linezolid 600 mg for 26 weeks or 9 weeks
- Peripheral neuropathy of grade 3 or lower was reported in:
 - 38% of participants that received linezolid 1200 mg for 26 weeks
 - 24% of participants that received linezolid 1200 mg for 9 weeks
 - 24% of participants that received linezolid 600 mg for 26 weeks
 - 13% of participants that received linezolid 600 mg for 9 weeks
- Four participants, all of whom had received linezolid 1200 mg for 26 weeks, had optic neuropathy that resolved.
- Laboratory-confirmed myelosuppression was reported in:
 - 22% of the group that received linezolid 1200 mg for 26 weeks
 - 15% of the group that received linezolid 1200 mg for 9 weeks
 - 2% of the group that received linezolid 600 mg for 26 weeks
 - 7% of the group that received linezolid 600 mg for 9 weeks
- Across the treatment groups, 26% of participants had one or more liver-related adverse events, with similar numbers in each group.

Critical Analysis

The partially blind, randomized ZeNix trial found that an oral bedaquiline–pretomanid–linezolid regimen with 600 mg of daily linezolid for 26 weeks had the most favorable risk–benefit profile among the four regimens studied for treatment of highly drug-resistant TB. This regimen had a more favorable side-effect profile than the regimens containing 1200 mg of linezolid and a lower incidence of treatment failure compared to the group that received 600 mg of linezolid for 9 weeks.

The following points should be considered when interpreting the study findings:

- There was no standard-care control group used in this trial, which makes it difficult to assess the observed efficacy of the trial regimens. However, the observed efficacy is consistent with that in the Nix-TB study.¹
- A higher incidence of peripheral neuropathy was reported among South African participants than among those in Georgia, Moldova, or Russia, but no explanatory factors could be identified, including HIV status, suggesting this finding warrants further research.
- The planned subgroup analyses found that age, sex, and HIV status did not influence outcomes. However, 80% of participants were HIV negative and those with a CD4 cell count <100/mm³ were excluded, which limits the generalizability of these findings in populations of people living with HIV, especially among those with advanced HIV disease.
- Of the 11 participants identified with baseline resistance to at least one trial drug, only three had an unfavorable microbiologic outcome and all three received 1200 mg linezolid for 9 weeks. This suggests those receiving treatment for a shorter duration may be more vulnerable to treatment failure and highlights the need for drug-susceptibility testing.
- Even with the preferred regimen, nearly a quarter of participants had peripheral neuropathy. This may make the regimen difficult to administer for both patients and programs.

Implications

The partially blind, randomized ZeNix trial of alternative linezolid regimens in bedaquiline–pretomanid–linezolid treatment of highly drug-resistant TB found that a regimen with 600 mg of linezolid for 26 weeks had the most favorable risk–benefit profile among the four regimens studied. A bedaquiline–pretomanid–linezolid regimen has the advantage of being an all-oral regimen with high efficacy, but the high incidence of adverse events with 1200 mg of linezolid makes it challenging to administer. A lower linezolid dose of 600 mg, with fewer toxic effects and similar efficacy, has the potential to improve treatment completion rates and TB outcomes.

References

- 1) Conradie F, Diacon AH, Ngubane N, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. *N Engl J Med.* 2020; 382: 893-902.

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