

In women with HIV, TB preventive therapy poses greater risk in pregnancy than postpartum

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Study results published today help clarify how to safely prevent tuberculosis (TB) in women living with HIV who are pregnant or have recently given birth, are taking antiretroviral therapy, and live where TB is highly prevalent. Credit: NIAID

Study results published today help clarify how to safely prevent tuberculosis (TB) in women living with HIV who are pregnant or have recently given birth, are taking antiretroviral therapy, and live where TB is highly prevalent.

A clinical trial funded by the National Institutes of Health has found that for these [women](#), treatment with the antibiotic isoniazid to prevent TB was similarly safe if begun during [pregnancy](#) or 12 weeks after delivery. However, there was significantly greater risk of poor health outcomes and death for the fetuses and newborns of these women if isoniazid preventive therapy began during pregnancy than if it began 12 weeks after delivery. This finding is concerning and merits research into alternative approaches to TB preventive therapy in pregnant women, according to the study investigators. Their findings are reported in the Oct. 3 issue of *The New England Journal of Medicine*.

"Pregnant women are often excluded from clinical research, which leads to an information gap that can pose a danger to maternal and [infant health](#)," said Anthony S. Fauci, M.D. "The findings reported today give women, health-care providers and policy makers high-quality data for weighing the risks and benefits of TB preventive therapy for pregnant women living with HIV who are taking [antiretroviral therapy](#)." Dr. Fauci is Director of the National Institute of Allergy and Infectious Diseases, a component of NIH that co-funded the trial.

TB is the top infectious-disease killer worldwide and the leading cause of death for people living with HIV. Among women, TB mainly affects those of reproductive age. When active TB disease develops during pregnancy or in the weeks after birth, it is associated with poor health outcomes for both the mother and baby.

The study published today found that one or more of a set of poor health outcomes for fetuses and newborns occurred in 24% of pregnancies of women who began taking isoniazid during pregnancy and in 17% of pregnancies of women who began after delivery, a statistically significant difference. This set of poor health outcomes included stillbirth, spontaneous abortion, low birth weight, preterm delivery and congenital abnormalities. When these outcomes were evaluated individually, however, there was no statistically significant difference between the two groups. Nevertheless, the greater incidence of the set of poor pregnancy outcomes in women who began taking isoniazid during pregnancy without any reduction in the risk of TB or improvement in maternal or infant survival is troubling, the investigators conclude.

Medical experts have agreed that generally there is a net benefit to treating active TB during pregnancy and providing isoniazid to prevent active TB in people living with HIV. [World Health Organization guidelines](#) currently recommend initiating isoniazid preventive therapy in pregnant women with HIV based on data from nonpregnant adults. However, because pregnant women have previously been excluded from [clinical trials](#) of isoniazid preventive therapy, information about the safety, efficacy and appropriate timing of this approach to preventing TB in pregnant women living with HIV and taking antiretroviral therapy (ART) is lacking.

The trial reporting today, TB APPRISE (TB Ante vs. Postpartum PREvention with INH in HIV Seropositive mothers and their Exposed infants), sought to help fill this knowledge gap. The study began in August 2014 at 13 sites in Botswana, Haiti, India, South Africa, Tanzania, Thailand, Uganda and Zimbabwe. The investigators selected these countries in part because they have a high burden of TB—at least 60 of every 100,000 people have the disease.

Also known as IMPAACT P1078, the trial was conducted by the NIH-

funded IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) Network and was led by Amita Gupta, M.D., M.H.S. Dr. Gupta is a professor of medicine and international health at the Johns Hopkins School of Medicine and deputy director of the Johns Hopkins University Center for Clinical Global Health Education. The IMPAACT Network is co-funded by NIAID, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health, all part of NIH.

The TB APPRISE study team enrolled 956 pregnant women ages 18 years or older who were living with HIV and were at 14 to 34 weeks gestation. All but one of the women was taking ART at enrollment. None of the women had suspected active TB, recent known TB exposure, or TB treatment for more than 30 days in the previous year.

Study participants were assigned at random to begin taking daily oral isoniazid either during pregnancy or 12 weeks after delivery. The women who began treatment during pregnancy received tablets of 300 milligrams (mg) isoniazid to take daily from enrollment until their 28th week in the study, and then received identical placebo tablets to take daily until their 40th week after delivery. The women whose treatment was deferred received placebo tablets to take daily from enrollment until 12 weeks after delivery, and then received identical tablets of 300 mg isoniazid to take daily for 28 weeks. Neither the women nor the TB APPRISE investigators knew who was in the immediate treatment group or the deferred treatment group until the end of the trial.

The participants had follow-up visits with study staff every four weeks during pregnancy and delivery. There were 926 deliveries. Then the women and their infants were followed every four weeks after delivery for 48 weeks.

Adherence to the isoniazid treatment regimen was assessed based on self-

report and pill counts. By those measures, roughly 88% of study participants completed at least 90% of the treatment regimen. There was no difference in adherence between the two treatment groups.

Some 15% of the women in both treatment groups either experienced serious side-effects or stopped taking isoniazid because the side effects were too difficult to tolerate. There was no statistically [significant difference](#) in the rate of these events between the two groups.

Two women in the immediate group and four in the deferred group died, all during the postpartum period, but only two of these women—one in each group—had taken [isoniazid](#). Three women in each group developed TB. These differences were not statistically significant.

"The TB APPRISE study team is extremely grateful to the women who participated in this clinical trial," said Dr. Gupta. "They have helped underscore the point that data from studies in non-pregnant women cannot always be extrapolated to pregnant women, so clinical trials must include [pregnant women](#) to accurately inform global health policy."

More information: A Gupta et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. *The New England Journal of Medicine* [DOI: 10.1056/NEJMoa1813060](https://doi.org/10.1056/NEJMoa1813060) (2019).

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