For patients with both HIV and tuberculosis the timing of drug therapies is critical

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In sub-Saharan Africa, tuberculosis is the disease that most often brings people with HIV into the clinic for treatment. Infection with both diseases is so common that in South Africa, for instance, 70% of tuberculosis patients are HIV positive. How best to treat these doubly infected patients-- who number around 700,000 globally-- is the subject of a new study, published in *The New England Journal of Medicine,* by scientists at Columbia University's Mailman School of Public Health and CAPRISA (Centre for the AIDS Programme of Research in South Africa). The authors had previously shown that integrating antiretroviral therapy (ART) concurrently with tuberculosis treatment reduces mortality among these patients and is preferable to treating the diseases sequentially. The new study investigates the best timing for introducing treatment for HIV. The researchers find that the optimal time for antiretroviral treatment depends on the patient's immune status. Patients with very low T-cell counts, a measure of how well the immune system is working, appear to do better with an earlier integration of treatment for HIV.

Full study findings are available online in the October 20 issue of *NEJM*.

The SAPIT (Starting Antiretroviral Therapy at Three Points in Tuberculosis) study is the first randomized, controlled trial to examine the timing of the dual therapy. Conducted in South Africa, the study involved 642 patients, all with confirmed tuberculosis (TB) and HIV infection. The current paper look at results for 429 patients, half of whom were randomly assigned to begin treatment for HIV within the

first four weeks of starting drug therapy for tuberculosis and half of whom were assigned to later treatment—about 3 months after beginning the TB drugs. (A third arm of the study, with 213 patients treated for HIV only after their TB treatment was complete, was discontinued when it became clear that waiting to start ART till after completing TB treatment brought poorer results.)

Overall, the rates of AIDS or death were similar for the TB patients who received early ART and those who received later ART during TB treatment. However, the find¬ings in severely immune-compromised patients dif¬fered substantially. Among patients with CD4+ T-cell counts of less than 50 per cubic millimeter (advanced HIV disease), starting anti-retroviral therapy earlier was associated with a rate of AIDS or death that was about two-thirds lower than for those with a later start.

"We found that recommendations by the World Health Organization (WHO) to start ART as soon as possible after initiating of tu¬berculosis treatment for patients with very low T-cell counts were in line with our findings," noted Salim Abdool-Karim, MD, a professor of epidemiology at the Mailman School and director of CAPRISA. "However, the results for patients with tuberculosis and HIV who have a higher T-cell count call for a different approach." In light of this evidence, he said, "WHO recommendations may need to be revisited."

All patients in the study received a standard tuberculosis treatment regimen that began with an "intensive" phase of four drugs: rifampin, isoniazid, ethambutol, and pyrazinamide, followed by a four-month "continuing" phase of treatment with just two drugs—isoniazid and rifampmicin. Patients in the early-ART group (214 individuals) began retroviral drug treatment during the intensive phase, at a median of 21 days after beginning TB therapy. The later-ART group (215 patients) began retroviral therapy during the continuing phrase, at a median of 97 days.

While starting ART earlier was of great benefit for patient with advanced HIV disease, waiting till after three months of TB treatment to start ART may be an appropriate option for those with less advanced HIV disease, as indicated by higher T-cell counts.

"In fact, we found that the later initiation of ART actually cut the risk of an adverse reaction called IRIS (immune reconstitution inflammatory syndrome) by about half and lowered significantly the need to switch antiretroviral drugs because of side effects," noted Dr. Karim. However, waiting longer to start ART till after TB treatment is completed would be a mistake, he observes, especially in light of earlier findings that such delay was associated with 56% higher mortality.

"Starting antiretroviral therapy during TB treatment saves lives," observes Wafaa El-Sadr, MD, professor of epidemiology at the Mailman School, director of ICAP, and a co-author of the paper. "The evidence is in and we now must take the findings to scale."

The researchers report no significant differences between the earlier-ART and later-ART groups in the outcomes of tuberculosis treatment.

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