Is Starting ART earlier in patients with ATT beneficial?

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The Studies:

- *Blanc XF, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med 2011; 365:1471-81.(refd as CAMELIA TRIAL)*
- *Salim S. Abdool Karim, Kogieleum Naidoo , Anneke Grobler, Nesri Padayatchi, Cheryl Baxter, Andrew L. Gray. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011; 365:1422-1501. (refd as Karim et al)*
- *Diane V. Havlir, Michelle A. Kendall, Prudence Ive, Johnstone Kumwenda, Susan Swindells, Sarojini S. Qasba. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med 2011; 365:1482-91. (refd as Haviar et al)*

TB is the most common opportunistic infection and most common cause of death in people suffering from HIV in developing countries and mortality has been reported to be around 30% when ART is withheld.

Why these studies were needed?

Doctors are unwilling to start ART and ATT at the same time as they are concerned about the increased toxic effect of the combination, increasing the likelihood of immune reconstitution inflammatory syndrome (IRIS) and lack of adherence due to increased pill load.

Study design: All three studies were prospective, randomized, multicentre controlled trials.

What the study found?

CAMELIA Trial: 661 patients were enrolled for the study and randomized. 332 patients were in the earlier treatment group who started ART 2 weeks after starting ATT and 329 were in the later treatment group starting ART 8 weeks after ATT. Median CD4+ count was 25. Risk of death in the earlier-ART group was 18% as compared to the later-ART group with 27% risk (P= 0.006). There was no significant difference in tuberculosis outcome at the end of treatment between the two groups. There were 110 incidences of IRIS in the earlier group compared to 45 in the later group (P<0.001). 6 deaths resulted due to IRIS in the earlier group as compared to 0 in the later group.

Karim et al study enrolled a total of 429 patients, and assigned 214 to the earlier-ART treatment group and 215 to the later-ART treatment group. Median CD4+ count was 150. Overall there were 18 death/AIDS cases in the earlier group as compared to 19 in the later group showing no significant difference. When the analysis was broken down with respect to CD4+ count, there was a significant advantage of earlier treatment in patients with CD4+ count of less than 50. Three out of 37 patients in the earlier treatment group had an adverse outcome while the numbers for the later treatment group were 7 out of 35 (P=0.06). There were no differences in tuberculosis outcomes at the end of treatment between the two groups. 43 patients suffered from IRIS in the earlier treatment group as compared to 18 in the later treatment group (P<0.001).

In the Haviar et al study, 806 patients were divided into two groups. 405 were in the earlier-ART group and 401 in the later-ART group Median CD4+count was 77. There were 52 adverse events in the earlier group as compared to 64 in the later group showing no difference. When the analysis was broken down with respect to CD4+ count, risk of death or adverse events was reduced to 41.7% in the earlier treatment group as compared to the later treatment group in patients with CD4+ count of less than 50 (P=0.02). IRIS was more common in the earlier group (11%) as compared to the later treatment group (5%).

What is the bottom line?

The CAMELIA trial demonstrates that starting ART in patients with advanced immunodeficiency (CD4+ count ≤ 200) on ATT at 2 weeks greatly reduces mortality when compared to starting treatment at 8 weeks.
Karim et al and Havlir et al didn't find any benefit in overall survival. However the benefit in severely immunocompromised patients (CD4+ ≤ 50) was clearly seen in these studies. In fact it was associated with a lower rate of new AIDS defining disease and deaths.