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**Early Antiretroviral Therapy Reduces AIDS Progression/Death in Individuals with Acute Opportunistic Infections: A Multicenter Randomized Strategy Trial**

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**Background**

Optimal timing of ART initiation for individuals presenting with AIDS-related OIs has not been defined.

**Methods and Findings**

A5164 was a randomized strategy trial of “early ART”--given within 14 days of starting acute OI treatment versus “deferred ART”--given after acute OI treatment is completed. Randomization was stratified by presenting OI and entry CD4 count. The primary week 48 endpoint was 3-level ordered categorical variable: 1. Death/AIDS progression; 2. No progression with incomplete viral suppression (i.e. HIV viral load (VL) > or = 50 copies/mL); 3. No progression with optimal viral suppression (i.e. HIV VL <50 copies/mL). Secondary endpoints included: AIDS progression/death; plasma HIV RNA and CD4 responses and safety parameters including IRIS. 282 subjects were evaluable; 141 per arm. Entry OIs

included *Pneumocystis jirovecii* pneumonia 63 percent, cryptococcal meningitis 12 percent, and bacterial infections 12 percent. The early and deferred arms started ART a median of 12 and 45 days after start of OI treatment, respectively. THE DIFFERENCE IN THE PRIMARY ENDPOINT DID NOT REACH STATISTICAL SIGNIFICANCE: AIDS progression/death was seen in 20 (14%) vs 34 (24%); whereas no progression but with incomplete viral suppression was seen in 54 (38%) vs 44 (31%); and no progression with optimal viral suppression in 67 (48%) vs 63 (45%) in the early vs deferred arm, respectively (p = 0.22). However, the early ART arm had fewer AIDS progression/deaths (OR = 0.51; 95% CI = 0.27-0.94) and a longer time to AIDS progression/death (stratified HR = 0.53; 95% CI = 0.30-0.92). The early ART had shorter time to achieving a CD4 count above 50 cells/mL (p<0.001) and no increase in adverse events.

**Conclusions**

Early ART resulted in less AIDS progression/death with no increase in adverse events or loss of virologic response compared to deferred ART. These results support the early initiation of ART in patients presenting with acute AIDS-related OIs, absent major contraindications.

**Comments**

The current standard guidelines do not clarify when HIV-positive patients with a newly diagnosed opportunistic infection (OI) should be received antiretroviral therapy. In this ACTG A5164 study,

Zolopa and colleagues enrolled 282 patients within 14 days after they had started treatment for a proven or presumptive OI. Participants were then randomized to receive antiretroviral therapy (ART) either within 48 hours after enrollment (the early group) or between 4 and 32 weeks after enrollment (the delayed group). The ART regimen was lopinavir/ritonavir, emtricitabine, tenofovir, and stavudine, but use of any antiretroviral agent approved by the United States Food and Drug Administration for the initial treatment of HIV infection was also allowed. All patients in the early group and 91 percent of those in the delayed group actually initiated ART at a median of 12 and 45 days, respectively, after initiation of treatment for the OI.

Study patients were mainly men (85%); 70 percent had baseline CD4 counts of  $<50$  cells/mm<sup>3</sup>, and more than 90 percent were ART-naive. The most common OIs were *Pneumocystis jirovecii* pneumonia (PCP) (63% of subjects), cryptococcal meningitis (12%), serious bacterial infections (12%), toxoplasmosis (5%) and *Mycobacterium avium* complex (2%). Thirty-three percent of patients had multiple OIs.

At 48 weeks after enrollment, the incidence of AIDS progression or death was significantly lower in the early group than in the delayed group (14% vs 24%), and the early group's time to AIDS progression or death was significantly longer. The mean viral load and CD4 cell counts at 48 weeks did not differ significantly between the two groups. There were 20 confirmed cases of the immune reconstitution inflammatory syndrome (IRIS) (8 in the early group and 12 in the delayed group). The IRIS developed in a median of 33 days after ART initiation. The IRIS incidence did not differ significantly between participants who received steroids and those who did not.

The limitation of this study is that PCP was such a predominant OI, with other OIs especially tuberculosis (a major OI in Thailand) not represented in this study. However, this finding suggests that early initiation of ART in the setting of PCP as an active OI should be considered and is actually beneficial much to most patients. Specific management in the setting with high prevalence of mycobacterial infections or fungal infections as the active OIs still need validated.