Author's response to reviews

Title: The Impact of HAART Initiation Timing on HIV-TB co-infected patients, a retrospective cohort study

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Author's response to reviews: see over
Dear Editor:

We would like you to consider the enclosed manuscript, “The Impact of HAART Initiation Timing among HIV-TB co-infected patients, a retrospective cohort study”, for publication in your prestigious journal. Our study provided some additive information about the impact of highly active antiretroviral therapy (HAART) initiation timing on one-year survival and the risk of immune reconstitution inflammatory syndrome (IRIS) among HIV/TB co-infected patients.

Optimal timing to initiate HAART in HIV/TB co-infected patients is challenging for clinicians. Several observational studies found deferral of HAART to late in the course of TB treatment is associated with higher mortality. Nevertheless, early initiation of HAART during TB treatment is strongly associated with the occurrence of IRIS. Taiwan, like other Asian countries, had moderate TB burden (2011 prevalence was 54.5 per 100,000 population) and low HIV prevalence (0.16% in 2011). We conduct this retrospective cohort study by linking the HIV and TB registry data in Taiwan CDC from 1997 to 2006, through medical records reviewed to collect clinical data of HIV/TB co-infected patients. Our aim was to understand the TB outcome of HIV-infected adults under routine programmatic conditions in Taiwan and hope to contribute to the understanding of when to initiate HAART in co-infected patients.

A total of 229 HIV/TB co-infected cases included for analysis and 60 patients (26.2%) died within one year. Ever start HAART during TB treatment was significantly associated with survival and the aHR was 0.11 (95% CI 0.06-0.21). Cases with HCV co-infection had significant lower chance to initiate HAART during TB treatment than cases without or unknown HCV co-infection (p<0.01). As to the timing of HAART initiation, when use HAART initiating after 60 days as reference, there were no statistical differences in survival among cases initiating HAART within 15 days, at16-30 days or at 31-60 days of TB treatment. We found initiate HAART between 31-60 days after TB treatment had good survivals and the survival probabilities showed no difference compared with cases starting HAART between 15-30 days, even in cases with CD4+ lymphocyte counts of ≤50 cells/mm$^3$. The incidence of IRIS was significantly higher in cases starting HAART within 30 days compared with cases starting HAART after 30 days (36.8% vs. 10.5%, p<0.05). Cases with IRIS had significant higher rate of re-hospitalization and prolonged hospitalization duration, (49% vs. 4%, p<0.001 and 28 days vs. 18.5 days, p<0.01).
The determination of when to initiate HAART must balance the risks and benefits to the patient. According to our finding, prompt HIV testing for TB patients and proper case management program in order to linking HIV-infected persons to regular medical care were important to initiate HAART during TB treatment. Early initiation of HAART during TB treatment had non-significant better one-year survival than initiate later, though accompanied with increased risk and severity of IRIS. Deferring HAART to 31-60 days after TB treatment was not associated with increasing risk of death.

This manuscript has not been published elsewhere and does not duplicate any previous published work. All authors have contributed significantly to the work, and have seen and approved the manuscript. Please kindly address all the correspondence to us.

We suggest three potential unbiased reviewers who are experts in this field and are familiar with the topic:

1. **Weerawat Manosuthi**, MD, Department of Medicine, Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Tiwanon Road, Nonthaburi 11000, Thailand (e-mail: drweerawat@hotmail.com).

2. **Ching-Tai Huang** MD, PhD, Chief, Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, No.5, Fusing St., Gueishan Township, Taoyuan, Taiwan. (e-mail: chingtaihuang@gmail.com).

3. **Susan Shin-Jung Lee**, MD, Chief, Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Veterans General Hospital, 386, Ta-Chung First Road, Kaohsiung 813, Taiwan. (e-mail: ssjlee28@yahoo.com.tw).

We correct the conclusion paragraph of the abstract and the main manuscript according to your recommendation. The conclusion was revised as following: “Present study found start HAART during TB treatment was associated with better one-year survival. Initiation of HAART within 60 days of TB treatment only had non-significant better survival than later initiation. Initiation of HAART within 30 days significantly increased risk and severity of IRIS. Deferring HAART to 31-60 days of TB treatment may lower the risk of IRIS and was not associated with increasing mortality.”

We also point out the corresponding author in the title page.

Thank you in advance for your kind attention to our paper.
Sincerely yours,

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