Title: Reply to Meijide (word count limit: 500 words)

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Key words: HIV, AIDS, antiretroviral therapy, cancer,

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We thank Meijide and colleagues [1] for their interest in our paper [2]. They rightly point out that the short follow up in the Strategic Timing of Antiretroviral Treatment (START) study [3] and an inherent low cancer risk at study entry hampered our ability to identify factors independently associated with infection-unrelated malignancies. Efforts are underway to extend follow up beyond 2017 among START participants. This will allow us to determine with more accuracy the predictors for infection-unrelated cancer and better understand the effects of immediate versus deferred combination antiretroviral therapy (cART) initiation on cancer risk. In the meantime, data from large prospective cohort studies with long follow up remain an invaluable source to determine risk factors for cancer among HIV+ persons.

Mejide and colleagues report the findings from an investigation involving HIV+ persons carried out at their hospital in Spain [1]. They retrospectively classified malignancies into AIDS-defining and non-AIDS-defining cancer. An association was found between hepatitis C virus (HCV) co-infection and risk for non-AIDS-defining cancer in analyses adjusted for age, gender and HIV transmission route. On the basis of this, they hypothesize that HCV co-infection may facilitate the development of malignancies other than hepatocellular carcinoma.

A direct comparison between Mejide results and our report is difficult owing to differences in recruitment period, study design and categorization of malignancies. As mentioned in our report [2], we opted for classifying incident malignancies in START into infection-related and infection-unrelated cancer. Although not perfect, this classification takes into account emerging data from epidemiological surveillance [4] and establishes a framework to study the interactions between HIV, co-infection by pro-oncogenic viruses and cancer development.

Hepatocellular carcinoma is a non-AIDS-defining cancer that may be classified as an infection-related or infection-unrelated malignancy depending on whether the patient is co-infected or not with HCV or hepatitis B virus (HBV). In START, the only hepatocellular carcinoma event was classified as an infection-unrelated cancer because it occurred in a participant without HCV or HBV co-infection. We wonder whether the increased risk of non-AIDS-defining cancer among HCV co-infected participants in Mejide's report was driven by an association with hepatocellular carcinoma. Shepherd and colleagues have recently published a paper informative to this debate [5]. They investigated factors associated with infection-related and infection-unrelated cancer in EuroSIDA, a large HIV cohort with participants from across Europe, Israel and Argentina. In analyses adjusted for demographics, HIV-specific variables, co-morbidities and smoking, there was no association between HCV co-infection and risk for infection-unrelated cancer (adjusted hazard ratio [95% CI]: 0.90 [0.60, 1.37), p=0.62).

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