Letter to Editor (Annals of Oncology):

Inconsistent HIV reservoir dynamics and immune responses following anti-PD-1 therapy in cancer patients with HIV infection

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Conflicts of Interest: T.J.H. receives grant support from Gilead Biosciences and consults for Merck and Co.

Funding: NIH Delaney AIDS Research Enterprise (DARE; AI096109 and UM1AI126611); NIH/NIAID R01AI122862 (T.J.H); NIH/NIAID K08AI116344 (E.P.S.) Creative and Novel Ideas in HIV Research Program (CNIHR) through a supplement to the UCSF Center For AIDS Research funding (P30 AI027763); The Foundation for AIDS Research (amfAR) Institute for HIV Cure Research. This funding was made possible by collaborative efforts of the Office of AIDS Research, the National Institute of Allergy and Infectious Diseases, and the International AIDS Society (E.P.S).

In the February 2018 issue of Annals of Oncology, Guihot and colleagues describe an HIV-infected individual who received anti-PD-1 therapy with nivolumab for lung cancer. During therapy, the individual experienced a >2 $\log_{10}$ reduction in cell-associated(ca) HIV-DNA accompanied by a transient increase in detectable plasma HIV RNA and HIV-specific HIV CD8+ T cell responses[1]. However, another case report showed no major changes to measures of HIV persistence during nivolumab treatment[2]. Immune checkpoint inhibition is being studied as an HIV-1 curative strategy offering the hypothetical potential to simultaneously reactivate latent HIV-1 and enhance antiviral responses, but experience with PD-1 blockade in HIV-1-infected individuals is limited. Here, we report the viral dynamics and immune phenotypes observed in three adult men on antiretroviral therapy (ART) with long-term viral suppression (2 to 25 years) who received anti-PD1 therapy for malignancies.

Over the course of repeated cycles of anti-PD-1 therapy (nivolumab or pembrolizumab) targeting malignancies, HIV persistence and HIV-specific immune responses were characterized as previously described[3]. Institutional Committees on Human Research approved the study and informed consent was obtained from participants. Participant 1 was treated for recurrent squamous cell carcinoma of the head and neck with standard dosing of nivolimumab for 18 months, achieving a complete response. Participant 2 received four doses of nivolumab for head and neck SCC. Participant 3 received pembrolizumab for squamous cell carcinoma of the skin. Participant 3 developed possible autoimmune dermatitis in the context of pre-existent psoriasis, but remained on therapy.

No consistent changes in CD4+ T caHIV-1 RNA and DNA or residual low-level plasma viremia were found in any of the participants(**Figure 1a**). The frequency of total or activated CD4+ and CD8+ T cells also did not show a consistent pattern among participants(**Figure 1b,c**), but PD-1 binding decreased following initiation of therapy in Participants 1 and 2, and only transiently in

Participant 3(**Figure 1d**). Bulk T cell responses to EBV/CMV virus lysate or T-cell receptor stimulation were unchanged (data not shown), and minimal HIV/Gag-specific CD4+ and CD8+ T cell responses were observed. HIV-specific antibody levels remained stable during PD-1 blockade.

Repeated cycles of anti-PD1 therapy during concomitant ART did not lead to consistent changes in markers of HIV persistence, or in HIV-1- specific T cell responses in these patients. Our results are in contrast to those reported by Guihot *et al*., although it is notable that we quantified HIV-DNA in isolated CD4+ T cells and measured only responses to Gag peptides. Guihot *et al*. noted a modest increase in HIV- reverse transcriptase(RT)/Nef peptide responses and not Gag T cell responses[1]. Of note, a separate prior report did not find changes in HIV RT-Nef responses and also saw no change in HIV DNA[2]. In light of Participant 1's complete oncologic response to therapy, successful activation of immune responses to malignancy may not predict changes in HIV-1-specific measures. Our results suggest that studies of PD-1 blockade as a curative strategy in HIV should proceed with caution; benefits may only be observed in restricted group with uncertain predictors, and immune checkpoint blockade carries risk of adverse autoimmune sequelae[4].

Figure 1. Longitudinal measures of HIV persistence and immunological phenotype/function during anti-PD-1 therapy are shown. Low-level residual plasma HIV RNA as measured by single copy assay (SCA) and CD4+ T cell-associated HIV-1 RNA and DNA are shown in (**A**). Percentages of CD4+ and CD8+ T cells remained stable during therapy (**B**), and no consistent pattern was observed for markers of T cell activation (dual expression of CD38 and HLA-DR; **C**). PD-1 expression decreased after a single dose of anti-PD1 therapy, and was sustained for Participants 1 and 2 throughout treatment (**D**). Frequencies of interferon (IFN)γ expressing CD4+ T cells (total or memory) following HIV-1 gag peptide stimulations were low overall, with no detectable responses observed in CD8+ T cells (**E**).

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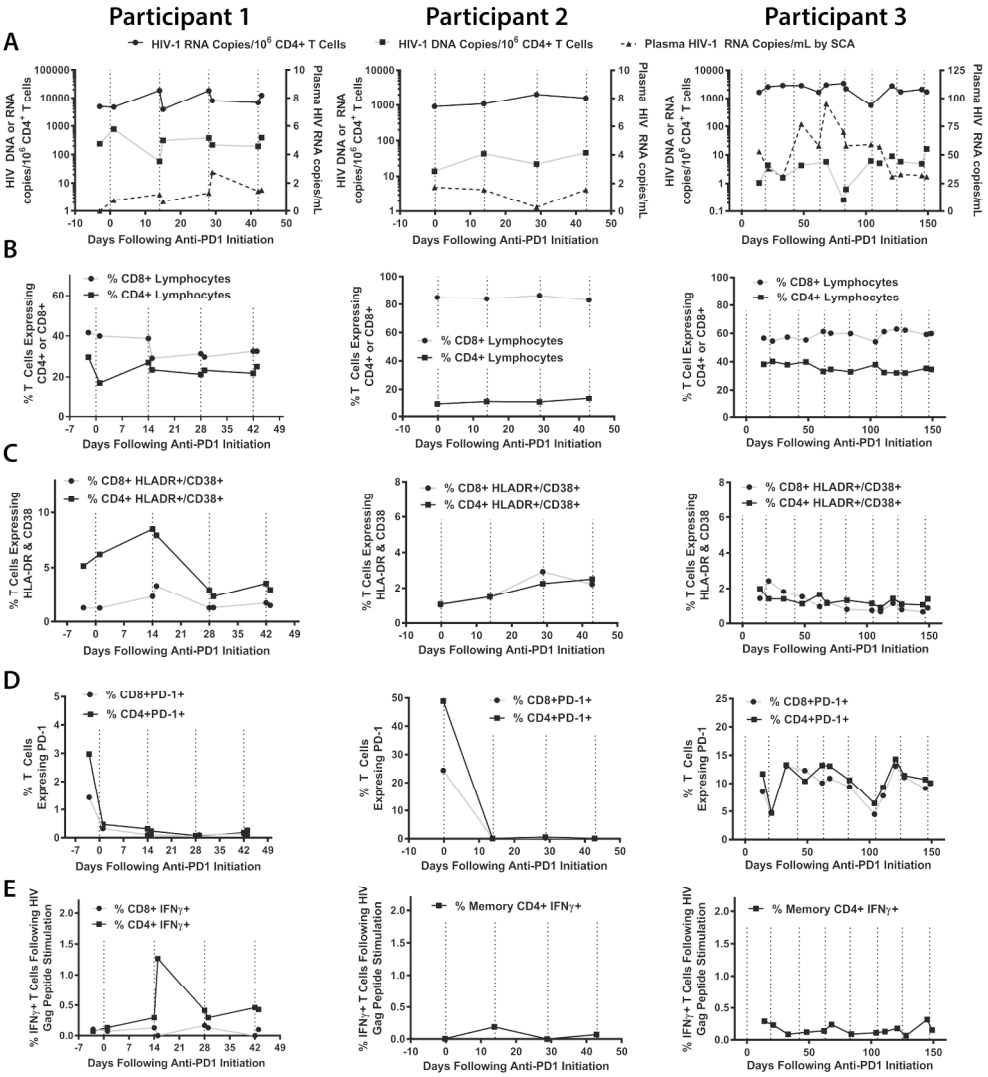

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