Immune Responses Following Anti-PD-1 Monoclonal Antibody Infusion in Persons with HIV

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BACKGROUND

- Persistent antigen stimulation during chronic viral infection leads to T cell exhaustion which is accompanied by the expression of inhibitory receptors (IRs) such as PD-1.
- In HIV, despite suppression of plasma viremia on ART, expression of these IRs is still observed. PD-1+ CD4+ T cells have been shown to be enriched for HIV-1 DNA.
- *In vitro* and *in vivo* blockade of the PD-1/PD-L1 axis in animal models resulted in reduced viremia, prolonged survival, and increased antigen-specific T cell responses. Results of the ACTG study A5326, suggest that PD-L1 blockade may improve HIV-specific immune responses of persons with HIV (PWH) who are virally suppressed on ART.
- Here, we describe immune responses observed following infusion of the anti-PD-1 monoclonal antibody cemiplimab in four (4) ART-suppressed study participants.

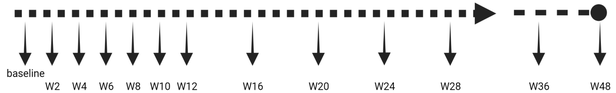
METHODS



Cryopreserved PBMC from timepoints listed below were used to assess the following immune parameters using flow cytometry:

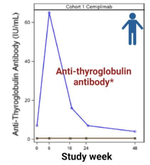
- Gag/Env/Pol-specific polyfunctional immune responses (CD107a, IFNγ, TNFα, and IL-2)
- T cell immune activation and cell cycling
- Checkpoint inhibitor/inhibitory receptor (IR) expression (PD-1, PD-L1, TIM3, CTLA4, TIGIT, and LAG3).





STUDY SUMMARY

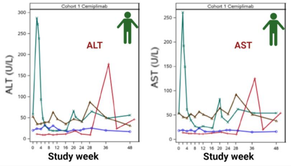
ACTG A5370 is a dose-escalating, placebo-controlled study of safety and immunotherapeutic activity of cemiplimab. We were only able to enroll the first cohort since the study was closed early due to possible immune related AEs. (Gay et al. JAIDS 2021)

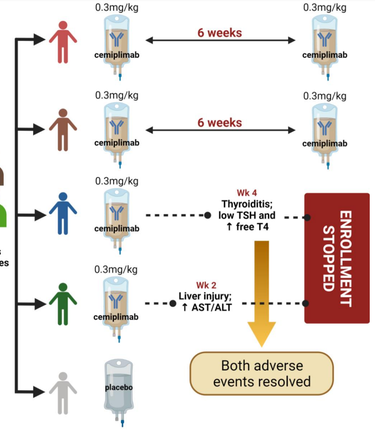


*anti-thyroglobulin antibodies were also present pre-infusion



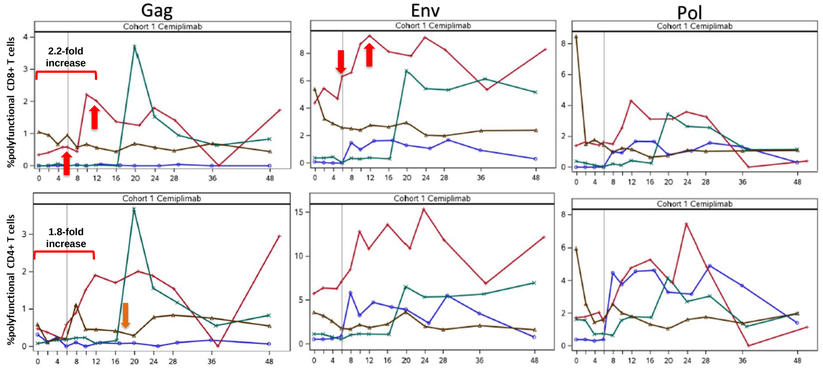
5 Enrolled: Participant colors correspond in figures





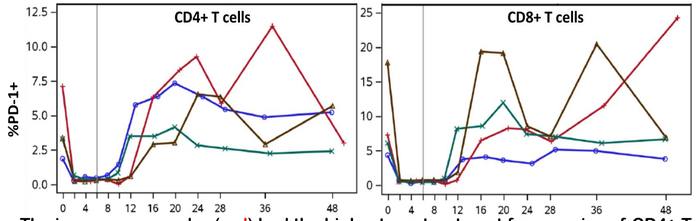
One of four participants who received cemiplimab had a possible immunologic response as shown by increased frequencies of HIV-specific polyfunctional T cells compared to baseline levels.

POLYFUNCTIONAL RESPONSES & LOW-LEVEL VIREMIA

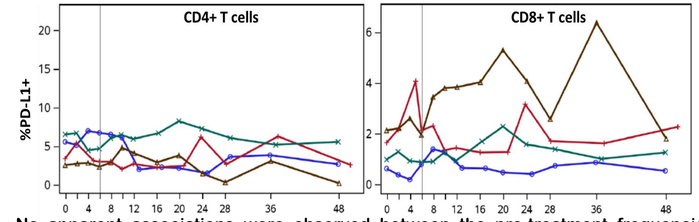


- Among the four (4) participants who received ≥1 dose of cemiplimab, the post-infusion (mean of weeks 2 to 12) %Gag-specific polyfunctional CD8+ and CD4+ T cells increased from baseline 2.2-fold and 1.8-fold, respectively (polyfunctional response defined as expressing 2 or more effector cytokines following HIV peptide pool stimulation). These increases were largely driven by one responder (red line in the figures above).
- We also observed increases in %polyfunctional T cells following stimulation with Env and Pol peptide pools. The vertical gray line denotes 2nd cemiplimab dose.
- The responder had low-level viremia at entry (23 cps/mL; measured using standard HIV-1 RNA assay), 76 cps/mL at week 6, and 57 cps/mL at week 12 (red arrows). However, plasma HIV-1 RNA was undetectable one week following the first cemiplimab infusion and there was no change one week following the 2nd dose (week 7; 71 cps/mL).
- The participant in green reported a respiratory infection at week 18 (orange arrow).

PD-1, PD-L1, AND OTHER INHIBITORY RECEPTOR EXPRESSION



- The immune responder (red) had the highest pre-treatment frequencies of CD4+ T cells expressing PD-1.
- PD-1 receptor occupancy was ≥70% 4 to 8 weeks after the last dose of cemiplimab.
- Consistent with the receptor occupancy data, we did not detect PD-1+ CD4+ and CD8+ T cells with flow cytometry following cemiplimab infusion.



- No apparent associations were observed between the pre-treatment frequencies of CD4+ and CD8+ T cells expressing PD-L1 and HIV-specific polyfunctional responses.
- Similarly, we did not observe associations between pre-treatment frequencies of T cells expressing multiple inhibitory receptors and HIV-specific immune responses.

CONCLUSIONS

- In one of four (4) participants who received at least one (1) dose of cemiplimab, we observed a possible immunologic response.
- This participant had the highest frequency of CD4+ T cells expressing PD-1 at baseline and had >70% receptor occupancy up to 8 weeks post-infusion.
- This participant had low levels of plasma viremia at entry and at several timepoints following the first and second cemiplimab infusions. It is less likely that these episodes of low-level viremia post-infusion were cemiplimab-induced.
- The benefits of this immune-based strategy for HIV should be weighed against the potential for immune-related adverse events.

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