Letter to the Editor

Suspected Immune-Related Adverse Events with an Anti-PD-1 Inhibitor in Healthy People with HIV

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**Conflict of Interest Statement:**

CLG receives research support from Gilead Sciences and ViiV Healthcare. CAB has received research support from Gilead and served as a consultant for GlaxoSmithKline and ViiV Healthcare. ETO receives research support from Janssen, ViiV Healthcare, and Gilead Sciences through his university and serves as a consultant for Merck, ViiV Healthcare, and Theratechnologies. BJM has received research support from Gilead Sciences. DRK has received research support and/or consulting honoraria from Gilead, GlaxoSmithKline, Merck, and ViiV. E.M. is an employee of Regeneron Pharmaceuticals. WDH serves as a consultant for Enochian Biosciences, Gilead, Merck, and ViiV/GSK. RJB, AM, KFM, CLW, SMH, CJ, RT, JJE, report no conflicts.

**Prior presentation:** Data from this study were presented virtually as an oral presentation at the Pre-CROI Community HIV Cure Symposium and at the Annual ACTG Scientific Retreat in March 2020.

The trial is registered with ClinicalTrials.gov at [https://clinicaltrials.gov](https://clinicaltrials.gov) with the ClinicalTrials.gov Identifier NCT03787095.
**Key Words:** Anti-PD-1 inhibitor, immune checkpoint inhibitors, immune-related adverse event, thyroiditis, hepatitis, HIV cure, HIV latency

**Letter to the Editor**

Reversing T cell exhaustion using antibodies to immune checkpoint inhibitors (ICIs) has revolutionized cancer therapy. As T cell exhaustion, mediated by PD-1/PD-L1, may be a barrier to HIV cure\(^1,2\) and CD4\(^+\) T cells expressing PD-1 are enriched for latent HIV,\(^2,5\) treatment with anti-PD-1 antibodies may provide a strategy for targeting the latent HIV reservoir. Given that elimination of latently infected cells harboring replication-competent provirus will be necessary to cure HIV infection, we initiated a phase I/IIa, double-blind, placebo-controlled, dose-escalating safety and immunotherapeutic study of two infusions of an anti-PD-1 antibody (cemiplimab) in virally suppressed persons with HIV (PWH). Although participants were not anticipated to receive direct benefit from this study and ICIs are associated with potentially irreversible immune-related adverse events (irAEs), feedback from PWH and the scientific and HIV communities encouraged the team to pursue this HIV cure intervention. Moreover, preliminary data\(^6,7\) provided a reasonable expectation that cemiplimab would improve HIV-specific immune responses, reverse HIV latency, and thus advance the field. This risk versus benefit assessment\(^8\) led to the incorporation of strict measures to limit risk to participants (e.g., history of autoimmune disease was exclusionary). Four of five participants enrolled were randomized to receive 0.3 mg/kg of cemiplimab at weeks 0 and 6; one participant received placebo. Possible irAEs occurred in two participants:

**Case 1.** 50-year-old male enrolled with baseline CD4\(^+\) T cell count of 1.957*10^9/L and normal thyroid-stimulating hormone (TSH) and free thyroxine (free T4) levels. Four weeks after the first infusion of cemiplimab (0.3 mg/kg), a TSH of 0.02 μg/mL and free T4 of 2.73 ng/dL were consistent with hyperthyroidism (Table 1). Mild fatigue was the only symptom reported. Repeat labs at week 5 and consultation with an
endocrinologist confirmed thyroiditis (Table 1), assessed as probably related to cemiplimab. Both TSH and free T4 normalized by week 24 without medical intervention. Fatigue resolved and no new symptoms were reported.

Case 2. 57-year-old male with baseline CD4⁺ T cell count of $0.911 \times 10^9$/L had normal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels at screening. Just prior to the first infusion of cemiplimab (0.3 mg/kg), asymptomatic grade 1 elevations in AST and ALT were observed (Table 1). Routine safety assessment 2 weeks following the first infusion revealed asymptomatic grade 3 AST and ALT elevations (Table 1). On further questioning, the participant reported acetaminophen (500 mg x 1) and alcohol use (six beers and two whiskey drinks) the evening before the week 2 visit. Hepatology consultation revealed no autoimmune etiology or hepatic synthetic dysfunction but elicited chronic alcohol use. The pattern of the hepatic enzyme elevations and their slow resolution were deemed inconsistent with acute alcohol toxicity, and therefore judged to be possibly related to cemiplimab. Elevated AST and ALT resolved 35 days post-infusion without intervention. Liver biopsy was not pursued, given the participant’s asymptomatic course and gradual improvement without intervention. This significantly limited definitive assessment of causality due to drug-induced liver injury versus immune-related hepatitis versus the contribution of acute or chronic alcohol use.

Per protocol-specified management of suspected irAEs, the second infusion at week 6 was held for both participants. A detailed, unblinded review of safety data from both cases by the independent Safety Monitoring Committee (SMC) was triggered and all study infusions held. Due to the probability of one irAE and possibility of a second irAE, the SMC recommended halting accrual of additional study participants and holding further cemiplimab infusions. Of note, two participants who received two cemiplimab infusions prior to the occurrence of these events remained asymptomatic without laboratory abnormalities. All four cemiplimab-treated participants completed the study with no further irAEs or other safety events through 48 weeks post first cemiplimab infusion.
irAEs like these two cases are well described with other ICIs and frequently managed in cancer patients receiving this immunotherapy\textsuperscript{9,10} although the resolution of the participant’s thyroid abnormality in this study has not been commonly described. irAEs can occur after a single infusion, though typically associated with higher doses, and as early as 14 days post-infusion. Given the lack of anticipated direct benefit to study participants and the frequency of possible/probable irAEs (two of four participants) at the lowest dose of study drug, the study was closed to accrual. Of note, ICIs have shown an acceptable risk:benefit profile in PWH treated for cancer in prior studies\textsuperscript{11}. Whether well-suppressed HIV infection in otherwise healthy individuals without cancer contributed to risk of irAEs in this study remains unknown.

The reduction or elimination of latent HIV reservoirs in PWH receiving suppressive antiretroviral therapy will likely require a combination of multiple therapeutic modalities including interventions that enhance HIV-1-specific immune responses to clear or contain these cells when activated to express replication-competent virus. Strategies to reverse HIV-specific immune exhaustion and also target latently infected cells must be tested. These may require more targeted PD-1 blockade than that obtained with systemic administration of antibodies, coupled with a better understanding of risks for immune-mediated adverse events, in order to pursue studies of ICIs in healthy, virologically suppressed PWH. Our experience underscores the value of the multiple, carefully considered steps to minimize risk to study participants built into this study. These included engagement with representatives of the PWH community before, during, and after the study, highly restrictive entry criteria, active participation of physician investigators in the informed consent process, written assessment of understanding to document the adequacy of the informed consent process, frequent safety visits and phone contact with participants following each infusion, a 6-week observation period between infusions for safety assessment, and a detailed, pre-determined toxicity management plan incorporating rapid review by our SMC in response to suspected irAEs. This
study underscores the potential challenges of translating successful immunotherapeutic interventions from the high morbidity/mortality cancer field to healthy virologically suppressed PWH.

Acknowledgements
We are indebted to the PWH who volunteered for this study and the research teams that ensured their safety. We acknowledge our gratitude to the members of the Safety Monitoring Committee for their rapid and thoughtful guidance. We greatly appreciate the support and expertise from the entire A5370 team.

References


Table: Laboratory Values for Participants with Possible Immune-related AEs after Receipt of One Dose of Cemiplimab 0.3 mg/kg (bold type = outside reference range)

### Case 1

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Screen</th>
<th>Pre-entry</th>
<th>Entry</th>
<th>Wk 4</th>
<th>Wk 5</th>
<th>Wk 6</th>
<th>Wk 12</th>
<th>Wk 16</th>
<th>Wk 24</th>
<th>Wk 36</th>
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<td>(-70)</td>
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<td>(36)</td>
<td>(42)</td>
<td>(92)</td>
<td>(120)</td>
<td>(176)</td>
<td>(253 )</td>
<td>(267)</td>
<td>(337)</td>
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<td>TSH (0.27-4.2 mIU/L)</td>
<td>1.91</td>
<td>3.91</td>
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<td>3.97</td>
<td>2.87</td>
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<td>1.55</td>
<td>3.5</td>
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<td>Thyroxine (4.5-10.9 mcg/dL)</td>
<td>7.1</td>
<td><strong>13.4</strong></td>
<td>16.7</td>
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<td>Free T4 (0.93-1.7 ng/dL)</td>
<td></td>
<td>2.73</td>
<td>4.1</td>
<td>3.06</td>
<td>0.81</td>
<td><strong>0.86</strong></td>
<td>1.01</td>
<td>1.20</td>
<td>1.12</td>
<td>1.02</td>
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<td>Thyroglobulin antibody (0.0-4.0)</td>
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<td><strong>80.4</strong></td>
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<td>TSH receptor antibody (≤122)</td>
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### Case 2

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<th>Entry</th>
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<th>Wk 2.2</th>
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<th>Wk 5</th>
<th>Wk 6</th>
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<th>Wk 28</th>
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<td>Liver Laboratory Test (reference range)</td>
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<tr>
<td>AST (0-40 IU/L)</td>
<td>30</td>
<td>23</td>
<td>53</td>
<td><strong>261 (G3)</strong></td>
<td>192 (G2)</td>
<td><strong>149 (G2)</strong></td>
<td>61</td>
<td>50</td>
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<tr>
<td>ALT (0-44 IU/L)</td>
<td>23</td>
<td>21</td>
<td>58</td>
<td><strong>287 (G3)</strong></td>
<td><strong>272 (G2)</strong></td>
<td><strong>238 (G2)</strong></td>
<td>93 (G1)</td>
<td>48</td>
<td>31</td>
<td>19</td>
<td>20</td>
<td><strong>66</strong></td>
<td>41</td>
<td><strong>65</strong></td>
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<tr>
<td>Total bilirubin (0.0-1.2 mg/dL)</td>
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<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>1</td>
<td>0.8</td>
<td>0.5</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>0.4</td>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
<td>0.7</td>
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<td>Prothrombin time (10.2-12.8 s)</td>
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G = Grade