EDITORIAL COMMENT

Post-treatment HIV controllers or spontaneous controllers in disguise?

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It has been well described that interruption of antiretroviral therapy (ART) leads to rapid viral rebound in the vast majority of HIV-infected individuals, even after prolonged courses of suppressive ART \cite{1}. Yet, intriguingly, a small subset of HIV-infected patients is able to maintain natural control of HIV replication after stopping ART \cite{2,3} and this provides hope that such a goal is attainable in the general population of HIV-infected individuals. Such post-treatment controllers (PTCs) are among the most perplexing, most clinically informative, and most understudied of HIV-infected patients \cite{4}. Due to their exquisitely low frequency and the rarity of patients undergoing closely monitored treatment interruptions, even the exact prevalence of this phenomenon has been challenging to quantify. Most studies have reported a PTC prevalence of between 4\% and 15\% after 2 years of treatment discontinuation \cite{5–11} in the context of significant heterogeneity in the reported study populations, duration of ART, and the exact definitions of post-treatment control (Table 1).

A major concern about pursuing the study of PTCs surrounds the question of whether PTCs may, in fact, represent HIV elite or spontaneous controllers who received ART during early infection, before they were able to demonstrate spontaneous virologic control. Yet, there are reasons to believe that these patients are distinct from HIV spontaneous controllers and may serve as the most realistic model for a functional cure of HIV infection \cite{4}. The most comprehensive evaluation of PTCs has been through the French VISCONTI cohort of 14 individuals treated during early infection \cite{8}. Unlike HIV spontaneous controllers, PTCs often present with symptomatic acute retroviral syndrome and pre-ART viral loads far above that seen in HIV ECs \cite{12,13}. In addition, PTCs rarely have the protective HLA alleles, immune activation, or strong HIV-specific CD8\textsuperscript{+} cell responses that are enriched in HIV spontaneous controllers \cite{8}. Finally, PTCs have also been identified in those who initiated ART in the setting of chronic HIV infection \cite{11,14}. However, the PTC studies to date have not been able to directly compare the rates of post-treatment and spontaneous control within the same cohort, which represent the most definitive way to answer this question.

In this issue, Martin et al. \cite{15} evaluated differences in PTC and spontaneous controller frequency and characteristics in a secondary analysis of the SPARTAC trial, which randomized participants infected during primary HIV infection to either 0, 12, or 48 weeks of ART before treatment discontinuation. They determined the frequency of ART-free HIV control and evaluated the differential prevalence and characteristics in those who achieved remission with or without ART. In total, 292 participants were included in the analysis, and they were stratified according to whether they received no ART, 12 weeks of ART or less, or more than 12 weeks of ART. Amongst all participants, 12.0\% met the criteria for post-treatment control. The authors made a number of...
important and novel observations: HIV remission was significantly more likely in those who received more than 12 weeks of ART compared with those who received no ART (18.6% vs. 7.9%, respectively); participants who manifested virologic control after more than 12 weeks of ART exposure had significantly higher pre-ART viral loads than those who were able to control their viremia in the absence of ART (median 2.3 vs. 3.8 log10 HIV RNA copies/ml, respectively); and the SPARTAC trial enrolled a large number of participants from international sites and no significant demographic differences were found between treated and untreated controllers in the absence of ART, HIV subtype, or country of origin. These results strongly suggest that, although some of the previously described PTCs may have eventually exhibited the spontaneous controller phenotype, early initiation of ART may indeed induce HIV remission in some patients who would not have been able to do so in the absence of ART, confirming that HIV PTCs can be distinct from spontaneous controllers. The authors also report no significant differences between ART-treated and untreated controllers in the distribution of HLA alleles, significant differences between ART -treated and spontaneous controllers. The authors also report no significance behind their virologic suppression may inform the design of novel therapeutics and boost efforts to induce sustained HIV remission amongst all HIV-infected patients.

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Conflicts of interest

J.Z.L. has received research support and served as a consultant for Gilead Sciences and Merck.

References


Table 1. Post-treatment controller prevalence at 24 months after treatment interruption reported from previously published studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort</th>
<th>Timing of ART</th>
<th>Total, N</th>
<th>ART duration (median) (years)</th>
<th>VF threshold</th>
<th>PTC prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Hocqueloux et al. [5]</td>
<td>ANRS</td>
<td>Acute</td>
<td>32</td>
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<td>&gt;50 copies/ml</td>
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<td>Lodhi et al. [6]</td>
<td>CASCADE</td>
<td>Acute</td>
<td>259</td>
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<td>5.3</td>
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<td>Goujard et al. [7]</td>
<td>ANRS PRIMO</td>
<td>Acute</td>
<td>164</td>
<td>1.7</td>
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<td>Saez-Cirion et al. [8]</td>
<td>VISCONTI</td>
<td>Acute</td>
<td>70</td>
<td>3.0</td>
<td>&gt;50 copies/ml</td>
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<td>Maenza et al. [9]</td>
<td>SeaPIP</td>
<td>Acute</td>
<td>22</td>
<td>2.4</td>
<td>&gt;300 copies/ml</td>
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<td>SD PIA</td>
<td>Acute</td>
<td>16</td>
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<td>&gt;50 or &gt;400 copies/ml</td>
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<td>Assoumou et al. [11]</td>
<td>ANRS SALTO</td>
<td>Chronic</td>
<td>95</td>
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</tbody>
</table>

ART, antiretroviral therapy; PTC, post-treatment controller; VF, virologic failure.

*ART duration for PTCs only or for overall population if PTC-specific results were not separately reported.

| Some VF definitions required confirmatory viral load and/or allowed for transient viral loads above the threshold. |


