

Post-treatment HIV controllers or spontaneous controllers in disguise?

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AIDS 2017, **31**:587–589

Keywords: cure, elite controllers, HIV post-treatment controllers, remission, spontaneous controllers

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 [1]. Yet, intriguingly, a small subset of HIV-infected patients is able to maintain natural control of HIV replication after stopping ART [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 [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 [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 [4]. The most comprehensive evaluation of PTCs has

been through the French VISCONTI cohort of 14 individuals treated during early infection [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 [12,13]. In addition, PTCs rarely have the protective HLA alleles, immune activation, or strong HIV-specific CD8⁺ cell responses that are enriched in HIV spontaneous controllers [8]. Finally, PTCs have also been identified in those who initiated ART in the setting of chronic HIV infection [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.* [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

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Received: 2 December 2016; accepted: 12 December 2016.

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

Reference	Cohort	Timing of ART	Total, N	ART duration (median) (years) ^a	VF threshold ^b	PTC prevalence (%)
Hocqueloux <i>et al.</i> [5]	ANRS	Acute	32	5.0	>50 copies/ml	15.6
Lodi <i>et al.</i> [6]	CASCADE	Acute	259	1.0	>50 copies/ml	5.5
Goujard <i>et al.</i> [7]	ANRS PRIMO	Acute	164	1.7	>50 copies/ml	8.5
Saez-Cirion <i>et al.</i> [8]	VISCONTI	Acute	70	3.0	>50 copies/ml	15.3
Maenza <i>et al.</i> [9]	SeaPIP	Acute	22	2.4	>500 copies/ml	4.5
Gianella <i>et al.</i> [10]	SD PIC	Acute	16	1.8	>50 or >400 copies/ml	0
Assoumou <i>et al.</i> [11]	ANRS SALTO	Chronic	95	5.3	>400 copies/ml	4.2

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

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

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

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 sex, 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, HIV-specific CD8⁺ T-cell responses, and markers of cellular immune exhaustion and activation.

There are several differences between this study and previously published PTC studies that should be taken into account when putting this study into the context of the existing literature. The definition of post-treatment control used in this study (16 weeks of virologic suppression less than 400 copies/ml within the first year off ART) is a far shorter period of time than previously published studies, although the actual duration of HIV remission was more than 52 weeks for the vast majority of PTCs who were treated with more than 12 weeks of ART. The duration of ART for the SPARTAC participants was also more abbreviated than those in prior reports (Table 1), even in the SPARTAC arm treated with prolonged ART, in which the median duration of treatment was 48 weeks.

Despite these caveats, the study by Martin *et al.* [15] adds to the growing body of evidence that a substantial

proportion of the PTC population is distinct from HIV spontaneous controllers and comprises HIV-infected patients who would have been unable to achieve HIV remission without the early initiation of ART. This report presents further justification for the early initiation of ART and provides impetus for additional studies focused on understanding HIV PTCs. Elucidating the mechanisms behind their virologic suppression may inform the design of novel therapeutics and boost efforts to induce sustained HIV remission amongst all HIV-infected patients.

Acknowledgements

The work was supported in part by the National Institutes of Health grant AI125109 (to J.Z.L.).

Conflicts of interest

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

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