

What is the significance of posttreatment control of HIV infection *vis-à-vis* functional cure?

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An important challenge of HIV research today is ‘functional cure’ or HIV remission, that is interventions to keep viral load at low or undetectable level after interrupting combined antiretroviral treatment (cART). It has been suggested that so-called ‘elite controllers’ may provide important clues in this quest [1]. By definition elite controllers are able to maintain their viral loads below the clinical level of detection (<50 copies of viral RNA/ml) ‘spontaneously’ that is without ever being treated [2,3]. During the last few years reports have emerged on patients who were first treated with cART and who kept control over the virus after treatment interruption. These patients have been called ‘secondary controllers’ [4] or ‘posttreatment controllers’ (PTC) [5]. This PTC status may provide additional information to develop a functional cure.

Several large studies in chronically HIV-1 infected (CHI) patients showed that treatment interruption (TI) after long-term cART resulted in prompt rebound and could be harmful, especially in patients with low CD4⁺ T-cell nadir [6,7]. Observational studies [8–11] and clinical trials [12,13] suggest that cART initiated during primary HIV-1 infection (PHI) followed by treatment interruption, results in delayed rebound of viremia and delayed disease progression [14]. Interestingly, in some cases rebound remained absent during many months or years of follow-up. Steingrover identified four out of 24 patients treated during PHI (PHI was defined as having a negative or

indeterminate western blot for HIV-1 antibodies in combination with a positive test for either p24 antigen or a detectable HIV-1 RNA concentration, or a negative result on an HIV screening test within 6 months before seroconversion), who kept viral load less than 50 copies/ml for at least 48 weeks after treatment interruption [15]. Similarly, Hocqueloux described five out of 32 treated PHI (PHI was defined as a negative/incomplete HIV-1 western blot and a p24 Ag positive test, and/or a current positive HIV antibody test with a negative one within the previous 3 months) patients with viral load less than 50 copies for a median of 75 months after treatment interruption [16]. Within the French ANRS PRIMO cohort, 164 patients interrupted cART, initiated during PHI (PHI was diagnosed in the basis of a negative or incomplete western blot with detectable HIV-1 RNA or an interval of < 3 months between a negative and a positive ELISA.): viral load remained less than 50 copies/ml in 14 patients for a median of 4.5 years [17] and additional PTC were described in the European seroconverter CASCADE cohort (patients initiated cART within 3 months after seroconversion) [18]. In most of these studies, pretreatment viral load had been documented, but, as cART was started very soon after infection, it is not excluded that at least some of these apparent PTC could in fact have been elite controllers, who would have controlled viremia even if they had been left untreated. Moreover, these clinical studies did not provide insight in underlying immune or viral mechanisms.

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The French VISCONTI study analyzed 14 PTC, who had been treated with cART in the acute (primary infection was defined as symptoms associated with an incomplete HIV-1 Western blot and a positive p24 antigen test or detectable plasma HIV RNA, and/or seroconversion documented by a positive HIV antibody test that was preceded by a negative test less than 3 months before) phase and did not show viral rebound or showed intermittent blips only for 48–113 months after TI. The HLA profile of these PTC was different from that of elite controllers. In the acute phase (before treatment), the PTC also had a higher viral load and a lower CD4⁺ T-cell count than elite controllers. Conversely, in the posttreatment aviremic state, PTC had lower immune activation and much lower CD8⁺ T-cell suppressor activity as compared to elite controllers. The cellular proviral DNA of PTC after TI was very low, it was mainly associated with transitional memory CD4⁺ T cells and, remarkably, tended to further decrease over time in the absence of treatment in some PTC. Nevertheless, in all cases, HIV could be cultured, but fitness of these viruses was not evaluated. [5].

Recently, four patients were described, who had been treated in the chronic viremic phase of the infection for several years, interrupted treatment for a variety of reasons and maintained controlled viremia. Whereas their T-cell responses were largely unremarkable and no HLA association was found, all four PTC had a low viral reservoir as assessed by proviral DNA and no intracellular viral mRNA species could be measured. Moreover, virus cultivation from CD4⁺ T cells repeatedly failed in one patient and showed delayed kinetics and low fitness in two others. After 5 years of follow-up, two PTC with low CD4⁺ T-cell counts were restarted on cART in the absence of viral rebound, whereas the two others, with high CD4⁺ T cells, maintained viral control (with intermittent blips) without treatment [4].

In conclusion, a small proportion of HIV-1 infected patients can maintain viral suppression after stopping cART. They seem to challenge the common wisdom that antiretroviral treatment needs to be taken lifelong to prevent rebound and disease progression [19]. Most of these PTC were originally treated in the acute phase, but there is emerging evidence that, in rare instances, patients, who started treatment in the chronic progressive stage, can also control viremia after TI. PTC patients are distinct from elite controllers for example host genetics are different and CD8⁺ T-cell responses do not seem to be involved in viral control in PTC, while they do play a role in elite controllers. Importantly, although the few PTC described until now are a heterogeneous group, they all have a very low proviral reservoir, which is even lower than in long-term nonprogressors [20].

Obviously, all these studies have included few patients, with rather limited pre and on-treatment data. Therefore,

ANRS (French National Agency for Research on AIDS and Viral Hepatitis) has recently launched a first initiative to study PTC in a larger international cohort (visconti@anrs.fr). This cohort aims to identify mechanisms underlying control of infection in PTC and factors that may help to predict PTC outcome after treatment interruption in patients receiving antiretroviral treatment. Patients who initiated antiretroviral treatment with viral loads above 2000 copies/ml, kept viremia suppressed under treatment for at least one year and have documented viral loads below 400 copies/ml for more than one year after treatment interruption will be eligible to participate in this cohort.

It has repeatedly been argued that analytical treatment interruption (ATI) in selected patients (with high CD4⁺ T-cell counts) may be acceptable to evaluate interventions aimed at functional cure [21,22]. To gain more definitive insight into possible mechanisms and predictors of PTC, prospective studies are needed, but candidates should be selected carefully. The data, summarized above, suggest that some patients with elevated CD4⁺ T-cell numbers and an exceptionally low proviral load after a prolonged period on cART, who consider treatment interruption, might control the virus after treatment interruption. In depth studies of pre, on and posttreatment clinical, immunological but especially (pro)viral characteristics, including viral fitness evaluation, in those who control the virus after treatment interruption versus noncontrollers might provide clues to understand the nature of PTC. A possible mechanism of PTC is that drug (and immune) pressure has resulted in crippling mutations in the virus. Obviously very strict monitoring, with prompt reinitiation of cART, according to preset viral rebound criteria, would be a prerequisite for such a study.

Clearly, this type of larger observational cohorts and well designed ATI studies might reveal modifiable factors that could inspire novel treatment strategies aiming at functional cure.

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Conflicts of interest

There are no conflicts of interest.

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