

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

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1 **What is the significance of post-treatment control of HIV infection vis a vis functional cure?**

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

20 Several large studies in chronically HIV-1 infected (CHI) subjects showed that TI after long-term cART resulted in
21 prompt rebound and could be harmful, especially in subjects with low CD4 T cell nadir [6, 7]. Observational studies
22 [8-11] and clinical trials [12, 13], suggest that cART initiated during primary HIV-1 infection (PHI) followed by TI,
23 results in delayed rebound of viremia and delayed disease progression [14]. Interestingly, in some cases rebound
24 remained absent during many months or years of follow-up. Steingrover identified 4 out of 24 patients treated
25 during PHI¹⁾, who kept VL < 50 copies/ml for at least 48 weeks after TI [15]. Similarly, Hocqueloux described 5 out of
26 32 treated PHI²⁾ patients with VL < 50 copies for a median of 75 months after TI [16]. Within the French ANRS
27 PRIMO cohort, 164 patients interrupted cART, initiated during PHI³⁾: VL remained <50 copies/mL in 14 subjects for a

28 median of 4.5 years [17] and additional PTC were described in the European seroconverter CASCADE cohort⁴⁾ [18].
29 In most of these studies, pretreatment VL had been documented, but, since cART was started very soon after
30 infection, it is not excluded that at least some of these apparent PTC could in fact have been ECs, who would have
31 controlled viremia even if they had been left untreated. Moreover, these clinical studies did not provide insight in
32 underlying immune or viral mechanisms.

33 The French VISCONTI study analyzed 14 PTC, who had been treated with cART in the acute⁵⁾ phase and did not
34 show viral rebound or showed intermittent blips only for 48-113 months after TI. The HLA profile of these PTC was
35 different from that of EC. In the acute phase (before treatment), the PTC also had a higher VL and a lower CD4 T
36 count than EC. Conversely, in the post-treatment aviremic state, PTC had lower immune activation and much lower
37 CD8 T cell suppressor activity as compared to EC. The cellular proviral DNA of PTC after TI was very low, it was
38 mainly associated with transitional memory CD4 T cells and, remarkably, tended to further decrease over time in
39 the absence of treatment in some PTC. Nevertheless, in all cases, HIV could be cultured, but fitness of these viruses
40 was not evaluated. [5].

41 Recently, four patients were described, who had been treated in the chronic viremic phase of the infection for
42 several years, interrupted treatment for a variety of reasons and maintained controlled viremia. Whereas their T
43 cell responses were largely unremarkable and no HLA association was found, all four PTC had a low viral reservoir
44 as assessed by proviral DNA and no intracellular viral mRNA species could be measured. Moreover, virus cultivation
45 from CD4 T cells repeatedly failed in 1 patient and showed delayed kinetics and low fitness in two others. After 5
46 years of follow up, two PTC with low CD4 T cell counts were restarted on cART in the absence of viral rebound,
47 whereas the two others, with high CD4 T cells, maintained viral control (with intermittent blips) without treatment
48 [4].

49 In conclusion, a small proportion of HIV-1 infected subjects can maintain viral suppression after stopping cART.
50 They seem to challenge the common wisdom that antiretroviral treatment needs to be taken lifelong to prevent
51 rebound and disease progression [19]. Most of these PTC were originally treated in the acute phase, but there is
52 emerging evidence that, in rare instances, patients, who started treatment in the chronic progressive stage, can

53 also control viremia after TI. PTC patients are distinct from EC e.g. host genetics are different and CD8 T cell
54 responses do not seem to be involved in viral control in PTC, while they do play a role in EC. Importantly, although
55 the few PTC described until now are a heterogeneous group, they all have a very low proviral reservoir, which is
56 even lower than in long-term non-progressors [20].

57 Obviously, all these studies have included few patients, with rather limited pre- and on-treatment data. Therefore,
58 ANRS (French National Agency for Research on AIDS and Viral Hepatitis) has recently launched a first initiative to
59 study PTC in a larger international cohort (visconti@anrs.fr). This cohort aims to identify mechanisms underlying
60 control of infection in PTC and factors that may help to predict PTC outcome after TI in patients receiving
61 antiretroviral treatment. Patients who initiated antiretroviral treatment with viral loads above 2,000 copies/ml,
62 kept viremia suppressed under treatment for at least one year and have documented viral loads below 400
63 copies/ml for more than one year after treatment interruption will be eligible to participate in this cohort.

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

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

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78 Note on PHI definition:

79 ¹⁾ PHI was defined as having a negative or indeterminate western blot for HIV-1 antibodies in combination with
80 a positive test for either p24 antigen or a detectable HIV-1 RNA concentration, or a negative result on an HIV
81 screening test within 6 months before seroconversion.

82
83 ²⁾ PHI was defined as a negative/incomplete HIV-1 western blot and a p24 Ag positive test, and/or a current positive
84 HIV antibody test with a negative one within the previous 3 months.

85
86 ³⁾ PHI was diagnosed in the basis of a negative or incomplete western blot with detectable HIV-1 RNA or an interval
87 of < 3 months between a negative and a positive ELISA.

88 ⁴⁾ Patients initiated cART within 3 months after seroconversion.

89 ⁵⁾ Primary infection was defined as symptoms associated with an incomplete HIV-1 Western blot and
90 a positive p24 antigen test or detectable plasma HIV RNA, and/or seroconversion documented by a positive HIV
91 antibody test that was preceded by a negative test less than 3 months before.

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