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, i.e. 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"(EC) may provide important clues in this quest [1]. By definition EC are able to maintain their viral loads (VL) below the clinical level of detection (< 50 copies of viral RNA/ml) "spontaneously" i.e. 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 (TI). These patients have been called "secondary controllers" [4] or "post treatment controllers" (PTC) [5]. This PTC status may provide additional information to develop a functional cure.

Several large studies in chronically HIV-1 infected (CHI) subjects showed that TI after long-term cART resulted in prompt rebound and could be harmful, especially in subjects 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 TI, 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 4 out of 24 patients treated during PHI[1)], who kept VL < 50 copies/ml *for at least 48 weeks* after TI [15]. Similarly, Hocqueloux described 5 out of 32 treated PHI[2)] patients with VL < 50 copies for *a median of 75 months* after TI [16]. Within the French ANRS PRIMO cohort, 164 patients interrupted cART, initiated during PHI[3)]: VL remained <50 copies/mL in 14 subjects for a

median of 4.5 years [17] and additional PTC were described in the European seroconverter CASCADE cohort[4)] [18]. In most of these studies, pretreatment VL had been documented, but, since cART was started very soon after infection, it is not excluded that at least some of these apparent PTC could in fact have been ECs, 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.

The French VISCONTI study analyzed 14 PTC, who had been treated with cART in the acute[5)] 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 EC. In the acute phase (before treatment), the PTC also had a higher VL and a lower CD4 T count than EC. Conversely, in the post-treatment aviremic state, PTC had lower immune activation and much lower CD8 T cell suppressor activity as compared to EC. 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 1 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 subjects 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 EC e.g. 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 EC. 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 non-progressors [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 TI in patients receiving antiretroviral treatment. Patients who initiated antiretroviral treatment with viral loads above 2,000 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 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 TI. In depth studies of pre-, on and post-treatment clinical, immunological but especially (pro)viral characteristics, including viral fitness evaluation, in those who control the virus after TI versus non-controllers 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 re-initiation 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.

Note on PHI definition:

[1)] 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.

[2)] 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.

[3)] 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.

[4)] Patients initiated cART within 3 months after seroconversion.

[5)] 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.

References

1. Autran B, Descours B, Avettand-Fenoel V, Rouzioux C. **Elite controllers as a model of functional cure.** *Curr Opin HIV AIDS* 2011; **6:**181-187.

2. Walker BD. **Elite control of HIV Infection: implications for vaccines and treatment.** *Top HIV Med* 2007; **15:**134-136.

3. Saez-Cirion A, Pancino G. **HIV controllers: a genetically determined or inducible phenotype?** *Immunological reviews* 2013; **254:**281-294.

4. Van Gulck E, Bracke L, Heyndrickx L, Coppens S, Atkinson D, Merlin C, *et al.* **Immune and Viral Correlates of "Secondary Viral Control" after Treatment Interruption in Chronically HIV-1 Infected Patients.** *PLoS One* 2012; **7:**e37792.

5. Saez-Cirion A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, *et al.* **Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study.** *PLoS Pathog* 2013; **9:**e1003211.

6. El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, Arduino RC, *et al.* **CD4+ count-guided interruption of antiretroviral treatment.** *N Engl J Med* 2006; **355:**2283-2296.

7. Danel C, Moh R, Minga A, Anzian A, Ba-Gomis O, Kanga C, *et al.* **CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial.** *Lancet* 2006; **367:**1981-1989.

8. Rosenberg ES, Altfeld M, Poon SH, Phillips MN, Wilkes BM, Eldridge RL, *et al*. **Immune control of HIV-1 after early treatment of acute infection.** *Nature* 2000; **407:**523-526.

9. Kaufmann DE, Lichterfeld M, Altfeld M, Addo MM, Johnston MN, Lee PK, *et al.* **Limited durability of viral control following treated acute HIV infection.** *PLoS Med* 2004; **1:**e36.

10. Volberding P, Demeter L, Bosch RJ, Aga E, Pettinelli C, Hirsch M, *et al.* **Antiretroviral therapy in acute and recent HIV infection: a prospective multicenter stratified trial of intentionally interrupted treatment.** *AIDS* 2009; **23:**1987-1995.

11. Wyl V, Gianella S, Fischer M, Niederoest B, Kuster H, Battegay M, *et al.* **Early antiretroviral therapy during primary HIV-1 infection results in a transient reduction of the viral setpoint upon treatment interruption.** *PLoS One* 2011; **6:**e27463.

12. Grijsen ML, Steingrover R, Wit FW, Jurriaans S, Verbon A, Brinkman K, *et al.* **No Treatment versus 24 or 60 Weeks of Antiretroviral Treatment during Primary HIV Infection: The Randomized Primo-SHM Trial.** *PLoS Med* 2012; **9:**e1001196.

13. Fidler S, Porter K, Ewings F, Frater J, Ramjee G, Cooper D, *et al.* **Short-course antiretroviral therapy in primary HIV infection.** *N Engl J Med* 2013; **368:**207-217.

14. Hamlyn E, Ewings FM, Porter K, Cooper DA, Tambussi G, Schechter M, *et al.* **Plasma HIV viral rebound following protocol-indicated cessation of ART commenced in primary and chronic HIV infection.** *PLoS One* 2012; **7:**e43754.

15. Steingrover R, Pogany K, Fernandez Garcia E, Jurriaans S, Brinkman K, Schuitemaker H, *et al*. **HIV-1 viral rebound dynamics after a single treatment interruption depends on time of initiation of highly active antiretroviral therapy.** *AIDS* 2008; **22:**1583-1588.

16. Hocqueloux L, Prazuck T, Avettand-Fenoel V, Lafeuillade A, Cardon B, Viard JP, *et al.* **Long-term immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection.** *AIDS* 2010; **24:**1598-1601.

17. Goujard C, Girault I, Rouzioux C, Lecuroux C, Deveau C, Chaix ML, *et al.* **HIV-1 control after transient antiretroviral treatment initiated in primary infection: role of patient characteristics and effect of therapy.** *Antivir Ther* 2012; **17:**1001-1009.

18. Lodi S, Meyer L, Kelleher AD, Rosinska M, Ghosn J, Sannes M, *et al.* **Immunovirologic control 24 months after interruption of antiretroviral therapy initiated close to HIV seroconversion.** *Arch Intern Med* 2012; **172:**1252-1255.

19. Siliciano JD, Kajdas J, Finzi D, Quinn TC, Chadwick K, Margolick JB, *et al.* **Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells.** *Nat Med* 2003; **9:**727-728.

20. Lewin SR, Rouzioux C. **HIV cure and eradication: how will we get from the laboratory to effective clinical trials?** *AIDS* 2011; **25:**885-897.

21. Routy JP, Boulassel MR, Nicolette CA, Jacobson JM. **Assessing risk of a short-term antiretroviral therapy discontinuation as a read-out of viral control in immune-based therapy.** *J Med Virol* 2012; **84:**885-889.

22. Machado C, Rios-Villegas MJ, Galvez-Acebal J, Dominguez-Castellano A, Fernandez-Cuenca F, Palomo V, *et al.* **Long-term outcome of patients after a single interruption of antiretroviral therapy: a cohort study.** *BMC Res Notes* 2012; **5:**578.