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## Post treatment Controllers: What do they tell us?

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## **ABSTRACT**

### **Purpose of the review**

The post-treatment controllers (PTC), also known as the VISCONTI patients, are able to control HIV infection and maintain a durable viral control after interruption of an early treatment. They are different from HIV controllers who present a viral control while they never received treatment. PTC is the proof-of-concept of remission induced by antiretroviral treatment.

### **Recent findings**

PTC supports the idea that early treatment could be especially beneficial. They show a sort of specific equilibrium between a low blood reservoir level and HIV-1 specific immune responses. PTC represent between 5 and 15% of patients with early cART interruption that could be considered a low frequency. However, more potent antiretroviral therapy, with a good penetration into lymphoid tissues, initiated earlier and maintained for at least four years might increase this frequency.

### **Summary**

Understanding of the mechanisms underlying such a durable viral control will help to gain knowledge on HIV pathogenesis. Besides research on HIV eradication, the objective to induce a durable remission seems a realistic goal in the medium term.

### **Keywords**

Remission, Post-Treatment Controllers, control of viremia, treatment in acute infection.

In 2013, we reported a large group of Post treatment Controllers (PTCs), also known as the VISCONTI patients (Viro-Immunological Sustained Control after Treatment Interruption). These individuals show a remarkable capacity to keep efficient repression of viremia long time after therapy discontinuation, supporting the idea that remission of HIV infection may be achievable, at least in some patients (1). We now follow twenty cases with a median time of remission of 9.3 years, with the longest period of control of more than 12 years so far (range: 4.5-12.5).

Interestingly, the VISCONTI study has attracted much interest but also some doubts about the possibility that PTCs might be natural HIV controllers who received an early treatment. We addressed this question and showed that PTCs were different from HIV Controllers. Differently from natural controllers, PTCs presented a symptomatic primary HIV-1 infection with high viral load and low CD4 T cell counts. Most of them do not carry protective HLA class I alleles but rather neutral or high risk alleles (such as HLA-B\*35 or B\*07) and have very weak CD8+ T cell responses. The levels of T cell activation are also higher in HIC than in PTC. (1). Altogether, these parameters suggest that the mechanism of the viral control observed in PTC, although remains elusive, is different from those reported in HIV controllers (2). Few PTC cases have been reported and documented so far and all of them are observational cases (3, 4, 5, 6, 7). However, the concept of remission is now well proven and very informative in many ways.

### **PTCs have received early treatment in primary infection**

The first thing that PTCs tell us is that very early treatment in primary HIV-1 infection (PHI) could be one of the main factors having a role in the long-term control off therapy. To date, no case with such a very long-term control have been reported among patients treated at the chronic phase of HIV infection. We previously showed that treatment initiated during primary infection might have a greater impact than treatment initiated later in reducing rapidly the size of the reservoirs and achieving optimal immune reconstitution (8). By blocking viral replication, very early treatment can limit the establishment of the viral reservoir and interrupt the big cytokine storm, particularly important during the first phase of primary infection (9, 10, 11). It has been also reported that early cART resulted in very low levels of markers of HIV persistence in children who started cART before 6 months of age

(12). Early cART may also limit viral diversity and protect the major innate and specific immune functions from the deleterious effect of chronic immune activation (13, 14). Early cART also helps to preserve and/or restore immune functions in the gut of HIV infected patients (15, 16). It has been recently reported than treatment initiated later, within 6 months of infection, can also be associated with a lower T-cell activation and a smaller reservoir size (17).

Longer treatment duration is also likely to have a further impact on viral reservoirs. We showed that in the majority of patients receiving early treatment, the slope of total HIV-DNA decrease continues over years, indicating that the impact of early treatment, at least regarding the reservoir, is continued for several years, while among patients treated at the chronic phase, the HIV DNA level no longer decreases beyond 2 years of treatment (8). The questions about the optimal treatment duration and the existence of a window of opportunity for treatment initiation are still open. Based in our observational data, at least four years of treatment appears to be required to obtain both a low level reservoirs and good markers of immune restoration, such as CD4+ T cell count and CD4 /CD8 ratio (8).

Recent studies suggest and discuss that both the timing to initiate therapy and the duration of HAART might play a role in inducing durable HIV control (18, 19). In PTC, not only the very early HAART initiation but also the lengthy treatment period (a median of three years in our group of patients) likely played an important role inducing a viral control after treatment interruption, (3). Thus, PTCs reinforce the idea that initiating treatment as soon as possible, and maintaining it for years is essential and can have individual and general benefits.

### **PTCs maintain a low T cell activation status**

PTCs have a low T cell activation status in contrast with the strong expression of HLA-DR observed in spontaneous HIV controllers. So, The PTC status tells us that during remission the equilibrium between the virus and the immune system is very particular. They maintain a very low level of viral replication in front of a stable CD4 cell count and a low capacity of CD8 T cells to suppress HIV-1 infection of autologous CD4+ T cells. Moreover, HIV-1 specific CD8+ T cells produce low level of IFN-G. This low and stable T cell activation level in PTCs could offer protection to innate and specific immunity from the deleterious effect of chronic activation. The first weeks of viral replication might have induced specific cellular responses and their protection by the early treatment could have played a major role to maintain those

specific immune responses and to protect cell functionality, even at a low level. Moreover, we observed that strong specific antibody responses are detectable in PTCs by western-blot analysis suggesting that B cell functions have been also preserved (personal data). Further studies of innate immunity and specific antibody functions are in progress to explore their eventual participation in the maintenance of the viral control (20).

### **PTC maintain a very low HIV blood reservoir level**

The PTCs did tell us that to have a low HIV reservoir level in central memory CD4 T cells (TCM) is certainly one of the main conditions to maintain this very specific status (1).

While in chronic treated patients, TCM are the major contributors to the blood reservoir (21Chomont et al), in HIV controllers both TCM and TTM (transitional memory cells) subsets contributed equally to the HIV reservoirs (22). In PTCs, those long-lived resting CD4+ T cells (TCM) contributed minimally to the HIV reservoir and might have been protected from infection by the early treatment (1). Recent studies have demonstrated that very early ART limits the seeding in long-lived TCM (23). In contrast, when treatment is initiated within 6 months, the viral CD4 T cell reservoir consisted more dominantly in the long-lasting central memory and T memory stem cells (24). Altogether, those results suggest that the very early treatment initiation might have a strong impact not only on the size of the reservoirs but also on the distribution in the T cell subsets, protecting major contributors to the immune system, such as TCM (25).

Even after many years of treatment discontinuation, the level of the blood reservoirs remains extremely low in all PTCs. Interestingly, while in some of them, the blood HIV-DNA level is stable, even after years off therapy, we showed that in five patients it continues to progressively decline over time. This might be related to the progressive decrease of the number of infected TTM. This also might explain that this status is maintained with a low level of immune activation and low level of residual replication. However, studies are needed to explore the long-term dynamics of HIV reservoirs in these remarkable patients to characterize the residual reservoir after more than 12 years off therapy.

The PTCs tell us that measuring the blood HIV reservoir with the simple HIV DNA real time PCR technique can easily estimate the overall reservoir level (26, 27) and its dynamics. It is true that this technique does not permit to characterize the functional reservoir, but

variations in total HIV DNA likely reflect proportionally variations in the functional reservoir. Due to the extremely low level of HIV-DNA in peripheral blood cells of PTC, it was very difficult to test different techniques to quantify inducible blood reservoirs, 2-LTR circles and integrated HIV-DNA (28). However, with a different viral culture technique we showed that, despite those very low levels of infection, HIV replication was inducible from the resting memory CD4 T cell subsets (1). So, PTC did tell us that they have been infected with a replicative and infectious virus. They also indicate that to explore HIV reservoirs might bring important information to patients and physicians, particularly in case of long-term early initiated HAART and to eventually take the decision to interrupt treatment. However, the question of the level of residual replication in the genital compartment remains important regarding the risk of sexual transmission and many patients prefer to maintain their treatment. There is a need to identify biological markers that eventually allow treatment discontinuation and identify cases with viral control.

Lastly, having an extremely low reservoir level is certainly a necessary but not a sufficient condition to characterize a future remission status and to guarantee viral control off therapy. More than 85 % of the patients who have been treated early and stopped their treatment needed treatment resumption, while the majority of them had a low reservoir level.

This is well demonstrated by the two “Boston” cases and the “Mississippi baby” who presented a viral rebound after few months off therapy without detectable viral replication (29, 30). Unlike PTC, all these cases showed no detectable specific HIV-1 antibody responses. The context of the two Boston cases who received a hematopoietic stem cell transplantation is very different from the child’s case which is closer to the PTCs. This infant born to an HIV-1 seropositive mother received HAART 30 h after birth; while a positive HIV-RNA confirmed that she was in utero infected. As in utero infection occurred late in utero, this infant had an acute HIV-1 infection at birth. The very early treatment initiated soon after birth reduced extremely the viral reservoir level and allowed to observe this fascinating case of remission in a child. Unfortunately, this child lost viral control after two years of treatment interruption. That could be explained by the immature immune system, which has been too shortly exposed to viral antigens to induce specific T and B memory responses. In contrast, PTCs have had a longer exposure to the virus, since they have been treated within several

weeks post infection. Studies in PTC will help to identify the mechanism responsible of the maintenance of such a low reservoir level.

### **Could we increase the frequency of PTC?**

While initiation of HAART during primary HIV-1 infection could occasionally result in transient control of viral replication after treatment interruption, the vast majority of patients experience a rebound in plasma viremia. Given the small number of PTCs cases the precise estimation of the frequency of the phenomenon is difficult to assess. Different epidemiological studies suggest that the probability of durable post-treatment control may be of 5 to 15% among patients who initiated treatment during the first months following contamination and kept the treatment for more than 12 months (1, 3, 4, 5). This frequency of remission could be considered low. However it is very larger than that of HIV controllers, which is much lower than 1%.

The question is whether it is possible to increase this frequency. If the phenomenon is genetically driven and the status pre-determined, it won't be possible to really increase the frequency. However, if early treatment is systematically initiated the number could be increased. We could also imagine that some highly potent drugs could have a major impact reducing the global level of infection in blood and tissues. It would be particularly important to test drugs with high tissue penetration particularly in lymph nodes where the first steps of viral replication during acute infection are so high. Recent results in animal models showed that some drugs such as atazanavir, are poorly penetrating within different tissues such as lymph nodes (31). The question of which are the best treatments that should be selected in primary infection is probably important to explore. Moreover, systematic pharmacological studies in humans have to be included in the development of new antiretroviral drugs.

PTCs did tell us that remission has been obtained with classical antiretroviral associations, those that were available 14 years ago. So, none of them received the new potent drugs that did no exist at that time. It is possible that combining the use of new potent drugs with early treatment initiation in acute infection might increase the number of cases.

Moreover, the question why so few cases have been reported to date is easy to answer. First, the early diagnosis of acute HIV infection is rarely offered and facilitate. Second, the very early treatment was not recommended until recently (32, 33). Third, treatment must be maintained for several years. As for example, In the Spartac trial, the duration of early

treatment was probably too short to sufficiently reduce reservoirs. Thus, the majority of patients experienced viral rebound (18, 19). Lastly, the decision to discontinue treatment has been proved deleterious in patients treated in chronic phase; thus, it is not recommended. To date, all those conditions have been rarely combined, eliminating any chance of inducing more remission cases.

## **Conclusion**

The first lesson learnt from PTCs is the proof-of-concept that long-term remission is a feasible and realistic goal, even with the current drugs used everyday. They definitely represent a model to search strategy for inducing viral remission. Understanding the mechanisms of the viral control in PTCs is an important challenge. There is need for further studies in these patients to better understand HIV pathogenesis and to determine the factors responsible for this long-lasting viral remission (34). It is likely that both viral and host factors are involved, as it has been reported in rhesus macaques which spontaneously control SIVagm replication (35).

PTCs confirm the major impact of early treatment initiation. All patients diagnosed at the time of primary infection may benefit from early treatment and some of them may become PTCs. Moreover, more potent antiretroviral therapy, with a good penetration into lymphoid tissues, initiated earlier and maintained for at least four years might increase the number of patients in remission. Access to testing in highly exposed people could also greatly increase the number of early diagnosis, facilitate early treatment initiation and reduce the risk of transmission in high exposed groups. In fact, one can imagine that the number of PTCs could be increased.

Studies of PTC could help to identify markers predicting success after treatment interruption. In the absence of such markers, this procedure remains no recommended outside therapeutical protocols. Purging HIV reservoirs to induce a complete eradication seems much more difficult than initially estimated. PTCs are a realistic example of durable remission showing that it could be a reasonable goal besides the search for an HIV cure.

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