

## **HIV/AIDS: FIRST DATA OF THE PHASE II CLINICAL TRIAL OF THERAPEUTIC VACCINATION WITH TAT IN HAART-TREATED INDIVIDUALS**

Barbara Ensoli, Director of the National AIDS Center, and Enrico Garaci, President of the Istituto Superiore di Sanità (ISS), are publishing today in *PloS ONE* ([www.plosone.org](http://www.plosone.org)) the data of the interim analysis on the Phase II Clinical Trial with the Tat vaccine.

The results of the 48-weeks interim analysis conducted in 87 patients on HAART therapy show that the immunization with Tat “is capable of arriving where therapy alone cannot”.

The strategy based on the use of Tat as a vaccine ( “ Tat vaccine”) had already shown a remarkable potential during the pre-clinical testing (1, 2). After the phase I results (3-8), which confirmed the safety of the vaccine used for the first time in humans, the data from the interim analysis of the ongoing phase II trial allow to consider therapeutic immunization with Tat vaccine as a promising tool to potentiate HAART. Tat immunization of HAART-treated patients appears to restore the equilibrium (homeostasis) of the immune system, which is severely compromised by HIV, and to enhance the drugs’ effects.

### **The rationale**

The antiretroviral therapy suppresses HIV replication, but it is often unable to restore the “immune system homeostasis”, as it was before the HIV infection. Thus, despite successful HAART, HIV-positive individuals have an increased risk to develop non-AIDS-related illnesses such as cardiovascular, neurological, liver, kidney, tumoral diseases, which generally appear in elderly people (premature aging). In fact, although upon HAART the HIV viral load is reduced to undetectable levels and the CD4<sup>+</sup> T cell counts are restored to almost normal values, the subjects often remain still compromised by a kind of continuous “alert” of the immune system, called “immune activation”. This is probably a consequence of HIV persistence in those cells/sites where the virus resides and resists to therapy (the so called sanctuaries).

In fact, even under effective HAART, CD4<sup>+</sup> T cells, the main viral target, as well as other cell types hit by the virus, continue to express HIV regulatory proteins, including Tat, even when viral replication is undetectable in blood.

### **What is the role of Tat?**

Tat is a regulatory protein necessary for HIV replication. Tat contributes to increase immune activation that is necessary for the virus to infect new target cells both at the beginning of infection or under effective HAART when the virus tries to reactivate infection, explaining the persistent viral reactivation. The chronic expression of Tat, which is also released in the extracellular fluids, exerts a “continuous pressure” on viral replication and causes an hyperactivation of the immune system. This, in turn, leads to the persistence of the disease and the appearance of new non-AIDS-related pathologies that are now seen in successfully HAART-treated individuals.

Immunization with the Tat vaccine appears as a very promising new therapeutic approach since it acts, in a selective and focused fashion, against a viral product (Tat) that promotes virus replication and the continuous activation of the immune system.

## **Main results**

The publication shows results of the 48-weeks interim analysis on 87 virologically-suppressed HAART-treated individuals, enrolled in the ongoing phase II multicentric clinical trial of therapeutic immunization with Tat. The Tat vaccine was administered monthly 3 or 5 times by the intradermal route at the dose of 7.5 or 30 µg. An intergroup comparison was performed with 88 virologically-suppressed HAART-treated individuals, enrolled in a parallel prospective observational study conducted at the same clinical sites and evaluated by the same centralized core laboratory.

The data of the phase II clinical trial indicate that immunization with Tat is safe, induces durable humoral and cellular immune responses, and can act in synergy with HAART to restore the homeostasis of the immune system. Of note, more immune-compromised individuals experience greater therapeutic effects from Tat immunization.

For a long time immunologists have aimed at contrasting the immune activation and restoring proper immunological functions which too often are not achieved by HAART since, although it suppresses virus replication, HAART does not entirely control HIV infection. Therefore, it is probable that the immunization with Tat will considerably reduce the risk to develop new and severe pathologies associated with the residual and persistent immune activation that the antiretroviral drugs are unable to eliminate.

In fact, as compared to the Reference Group, Tat-immunized patients show, in addition to an increase of CD4<sup>+</sup> T cells, significant increments of B cells, both key players of the immune system that are severely reduced during the infection. Furthermore, the patients immunized with Tat vaccine show a significant recovery of the immune system function (regulatory and memory T cells increase) and a marked reduction of the chronic immune activation status (CD8<sup>+</sup> CD38<sup>+</sup> lymphocytes, serum beta2-microglobulin and neopterin) considered as a primary cause of non-AIDS-related pathologies and complications as the premature aging.

## **Which are the implications?**

These data indicate that HAART can work better when the HIV-1 Tat protein is blocked, and further suggest that the more immune-compromised HAART-treated individuals may benefit the most from the immunization with the Tat vaccine. Therefore, thanks to these results, the regulatory bodies supervising the trial conduction recently approved an amendment to the clinical protocol, to expand patient recruitment to more immune compromised subjects, and to increase the number of participants from 128 to 160. Thus, it is now possible and of utmost importance to enrol new patients for the study completion, in order to accelerate the initiation of further trials based on the Tat vaccine.

## **Who are the actors of this discovery?**

The ISS National AIDS Center directed by Barbara Ensoli; San Gallicano Hospital, the core lab for all the immunological and virological testing; the 10 (now 11) Italian Clinical Centres conducting the trial (all co-authors of the paper); the vaccine production staff (Diatheva) and the staff of the vaccine formulation and kit preparation (Injectalia); the enrolment patients; all the control and supporting organizations such as the

Contract Research Organization (OPERA), the Data Safety Monitoring Board (DSMB), the Community Advisory Boards (CAB), the International Advisory Board (IAB), and the AIDS toll-free Help line.

The Istituto Superiore di Sanità, directed by Prof. Garaci, is the sponsor of the trial that was conducted with special funds of the Italian Ministry of Health.

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## **On the publication Journal**

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## **Supplementary information**

<http://www.hiv1tat-vaccines.info/>

<http://www.iss.it/aids/>

<http://clinicaltrials.gov/ct2/show/NCT00751595?term=nct00751595&rank=1>

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