HIV Persistence during Therapy
Seventh International Workshop

December 8-11, 2015
Florida Miami USA
MARRIOTT BISCAYNE BAY

Newsletter, February 2015

Diving into the HIV reservoir – could it be the key to a cure for HIV?

Interview, Dr Nicolas Chomont

Since 1997, safe, effective therapies have been available to treat HIV and today, many patients can look forward to a long life. It is appropriate, therefore, that now, more than ever, researchers focus on the race for a cure.

One leading investigator has turned his attention to the distinguishing features between patients treated early with antiretroviral therapy and those treated at a later stage.

"It is absolutely clear that people who received ART within the first few weeks after infection harbour a smaller reservoir than those who started during the chronic phase," said Nicolas Chomont, Assistant Professor in the Department of Microbiology, Infectiology and Immunology at the University of Montréal and a researcher at the University's hospital research center.

"We are currently working with Dr Jintanat Ananworanich at the US Military HIV Research Program to better understand not only quantitatively but also qualitatively the effects of early ART on HIV persistence," he said. Dr Chomont reports that the earlier ART is initiated, the smaller the reservoir will be after one or two years of therapy. "This raises hope that initiation of ART very early after infection could prevent the establishment of a clinically significant pool of latently infected cells, although this will require much more work to be demonstrated," he said.

Dr Chomont's research program aims to localise, quantify and characterise the cells in which HIV persists in individuals receiving antiretroviral therapy, with the ultimate goal of eliminating these cells and contributing to the development of a cure for HIV infection.

Understanding and breaking open the HIV reservoir remains at the heart of much research on HIV and many believe it to be the key to finding a cure.

"At the anatomic level, it is now clear that several tissues serve as a reservoir for HIV: gut, lymph nodes and probably the brain," said Dr Chomont. In addition, other tissues may also harbour persistent HIV and Dr Chomont believes they have been largely neglected in studies, eg the liver and testis.

"Most of the data available on tissue reservoirs were generated using assays that do not necessarily measure replication competent HIV," he explained. "In addition to the difficulty in accessing such tissues from virally suppressed individuals, it is technically challenging to outgrow HIV from these tissues. Many investigators agree that tissues are the place we should look at... We need to develop better assays to characterise and measure these tissue reservoirs."

Dr Chomont said that at the cellular level, HIV mainly persisted in CD4+ T cells, although other cell types may also harbour HIV, particularly tissue macrophages. "The quantitative contribution of these alternate reservoirs may be small compared to CD4+ T cells, but their qualitative contribution is largely unknown," he said.

There are also many lessons to be learned from the case of the two Boston patients in whom HIV re-emerged following experimental antiretroviral therapy interruption after receiving bone marrow stem cell transplants for cancer treatment.

"The example of the Boston patients indicates that viral rebound can occur after months of control and suggests that it may not take many infected cells to reignite infection," Dr Chomont pointed out. "The qualitative contribution of the different cellular reservoirs is difficult to evaluate in vivo, but more and more groups are investigating these questions."

Clearly, the immune system plays an essential role in HIV persistence. "The major cellular reservoirs for HIV are memory CD4+ T cells, a pool of cells that ensure the maintenance of a long-lived cellular immunity," Dr Chomont said. "Therefore, the immunological mechanisms that contribute to the maintenance of these cells are also responsible for HIV persistence." He went on to explain that some of these cells, like central memory, had an intrinsic ability to survive for decades, as a result of a pro-survival signalling program, while others, such as effector memory cells, persisted through continuous slow division, a mechanism called homeostatic proliferation. "In addition to the persistence of a pool of latently infected T cells, HIV may also replicate at low levels, particularly in tissues," he said. "In that case, residual inflammation, which is an unresolved dysregulation of the immune system, will also contribute to HIV persistence."

While trials in HDAC inhibitors have not successfully shown functional HIV remission, Dr Chomont believes they do provide useful indicators for future research. "The HDACi used so far did not eradicate HIV, but perturbed the reservoir in some ways, which in my opinion, is already a success," he said. "Of course, these molecules are not potent enough to eradicate HIV in all reservoirs and ensure their clearance, not to mention the fact that they have no effect on residual levels of viral replication. Nevertheless, the HDACi currently tested such as panobinostat and romidepsin have shown promising results."

Dr Chomont further distilled the results of the recent 'shock and kill' studies, in which dormant proviruses are 'turned back on,' making them 'visible' and vulnerable to the immune system's cytolytic 'killer' T cells, and then eliminating every last infected cell from the body while antiretroviral drugs prevent any new cells from becoming infected.

"The 'killing' part is just beginning and recent data from the group of Bob Siciliano suggest that it may be more difficult than we thought," he said. "The 'shock and kill' approach certainly needs more development, but alternative strategies should be explored in parallel."

Dr Chomont cited the Sangamo study proposing a re-set of the immune system through infusion of protected cells. "I think it is a fascinating approach that has shown promising results," he said. "I think we should think more often outside of the box."

Over and above his studies into when patients receive ART, in his own laboratory Dr Chomont and his colleagues are exploring the immunological mechanisms responsible for the prevalence persistently infected cells. "In addition to PD-1, we have recently identified other cellular markers that can be used to enrich in latently infected cells and that could be manipulated to clear persistently infected cells."

In addition, the group is also investigating latency mechanisms in different cellular subsets of central and effector memory cells that contribute to the HIV reservoir. "Our data suggest that these distinct reservoirs ensure viral persistence through distinct mechanisms and that eradication strategies may have differential effects on these cells," he said.

Further, Dr Chomont is developing novel assays to characterize and measure the frequency of latently infected cells, which will be essential to assess the efficacy of eradication strategies.

We look forward to hearing more from Dr Chomont at the HIV Persistence Workshop in Miami this coming December, where leading global investigators gather for an important update on the most pressing issues facing AIDS research today.