Girard. J Infect Dis Epidemiol 2015, 1:1
ISSN: 2474-3658

Journal of
Infectious Diseases and Epidemiology

Editorial: Open Access

HIV-1 Prevention and Cure: Where Do We Stand?

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As of 2014, UNAIDS estimated that some 35 million people were living with HIV-1 worldwide, of whom more than 25 million were in Sub-Saharan Africa. There is no doubt that the use of anti-retroviral therapy (ART) in a preventative manner has allowed to at least partially limit the extension of the disease. The best example is the major success that was achieved with the implementation of ART in HIV-1-infected pregnant mothers to prevent the infection of their baby. This year, Cuba was the first country worldwide to celebrate the complete elimination of mother-to-child transmission of HIV. Still, the use of ART is expensive, it requires full compliance from the patient and it is not without possibly severe side-effects. The search for an HIV vaccine thus remains an urgent necessity to control the HIV-1 epidemic in the world.

Is a HIV vaccine feasible? Since 1985, there have been at least five Phase III efficacy trials of candidate HIV-1 vaccines, but all except one were total failures, and the last one (the RV144 trial in Thailand) only elicited a mediocre 31% protection. These failures could be related, at least in part, to the absence of induction of efficient HIV-1 neutralizing antibodies by the candidate vaccine. Paradoxically, however, potent broadly neutralizing antibodies (bNAbs) have been isolated, especially during the last ten years, that are able to neutralize most circulating HIV-1 strains, including tier -2 or -3 variants from multiple virus clades. These bNAbs can be recovered from the blood of 20-25% HIV-infected individuals after an average 2.5 years of infection. They were also recently recovered as early as 20 months after birth in a few HIV-1-infected infants. Sequencing of the genes encoding such bNAbs has revealed the extensive hypermutation of the variable regions of the molecule that mediate binding specificities, with especially long complementary determining regions (HCDR3). Many bNAbs were also found to arise from the selective expansion of rare clones of autoreactive B cells. It is increasingly obvious that B cells must repeatedly encounter virus over months or years to progressively mature and accumulate mutations that enable the generation of bNAbs.

It is therefore not surprising that little success has been achieved so far in the induction of bNAbs by active immunization, in spite of numerous efforts to design new immunogens, such as the SOSIP trimers, and to develop new immunization strategies that could drive B-cell somatic hypermutation. The hope remains that one could elicit the evolution and maturation of bNAbs in uninfected people by sequential injections of progressively divergent immunogens, but this goal remains theoretical at this time and it will certainly not be easy to achieve.

For these reasons, it was reasoned that bNAbs could be highly useful as a tool for passive immunization, whether in a preventative or a therapeutic goal, and several clinical trials have begun to assess the efficacy of broadly neutralizing monoclonal antibodies in such scenarios. Better even, it was thought that vaccination could be replaced by the injection of an appropriate recombinant vector such as an Adenovirus-associated virus (AAV), which would carry the genes of the heavy and light chains of a bNAb and would thus provide the continuous synthesis of the bNAb in the body. This "genetic immunization" strategy, also called "vectored immunoprophylaxis", offers an interesting possibility especially for populations or countries with high HIV incidence rates, as it would allow continuous, hopefully life-long maintenance of high titers of highly potent bNAbs after a single injection of the recombinant vector. A Phase I clinical study of the process is in progress.

In addition, one should not forget vaccines that elicit T cell-based immunity, such as recombinant vectored vaccines and DNA vaccines. Many of these vaccines have shown promise in non-human primates and in some cases in human volunteers. Indeed, the RV144 trial in Thailand was based on the use of a recombinant canarypox vector associated in a prime-boost combination with purified gp120. Since then, the field has seen many small advances, especially in the development of Poxvirus (MVA, NYVAC) and Adenovirus (Ad26, Ad35) vectors that could be combined together or with DNA vaccines in prime-boost vaccination strategies. There is now a strong need for testing these new vaccine approaches in clinical efficacy trials. In parallel, a remarkable result has been obtained in a non-human primate model using a SIV vaccine prepared with a live simian Cytomegalovirus (CMV) vector encoding SIV genes *gag, pol, nef, rev, tat* and *env*: vaccination allowed one half of the vaccinated animals to totally cure their SIV infection within one year after virus challenge. Protection was apparently associated with the continuous production and stimulation of SIV-specific $CD8^+$ T lymphocytes. The search for a similar vector that could be safely used in humans is on-going.

Meanwhile, and in view of the difficulty met with the development of an efficient HIV vaccine, many efforts have been dedicated to try to cure patients of their HIV infection. It is evident; however, that even the most stringent anti-viral treatment of HIV infection does not yield a cure. Patients must be treated with drugs daily for their entire lives, and any interruption leads to a recrudescence of the infection. The recurrent virus is often not drug-resistant, suggesting that it was not replicating but existed in a latent form in some cell reservoir. One of the identified reservoirs is the follicular helper $CD4^+$ T cells (T_{FH}) in lymph node germinal centers, which accumulate within hyperplastic B cell follicles in SIV-chronically infected macaques and serve as targets for SIV replication and reservoir formation. B cell follicles constitute sanctuaries that are largely inaccessible to $CD8^+$ T cells.

Citation: Girard MP (2015) HIV-1 Prevention and Cure: Where Do We Stand?. J Infect Dis Epidemiol 1:003e

Received: September 23, 2015: **Accepted:** September 25, 2015: **Published:** September 28, 2015

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Other cells such as $CD4^+$ T_{CM} cells, especially $CD4^+$ $CCR6^+$ $CXCR3^+$ T_{CM} cells, which are predominant in the GALT, and macrophages, could also harbor latent HIV or SIV genomes.

Whether one could purge these reservoirs in order to cure the HIV positive patient is still an open question. Many drugs have been tested, including histone deacetylase inhibitors, but none has proven effective, and the reservoir has remained. Interestingly, however, the early initiation of ART, at or near the time of infection, was found to reduce virus load, decrease the size of the virus reservoir, and sustain uninfected T_{CM} cells. Early initiation of ART in HIV-1-infected infants significantly reduced levels of proviral and replicating HIV-1 and promoted continuous decay of viral reservoirs in perinatally infected children. However, no cure has been reported yet, as viral rebound may occur despite extremely low or even undetectable HIV load, as illustrated by the Mississipi baby, who appeared to be cured but showed virus rebound at 27 months.

In view of the impossibility so far to obtain an HIV cure, a more reasonable goal would be to aim for a functional cure of the HIV-1-infected patient. As an example, in the ANRS VISCONTI study, 14 HIV patients were identified who had initiated ART at the time of primary infection and eventually stopped treatment but remarkably showed full control of their viremia for years after interruption of the treatment. More recently, we heard of the case of the French girl who had been infected with HIV-1 at birth, and immediately started on ART; her family had the treatment stopped when she was 6. Twelve years later, the young lady appears to be in good health and shows no virus in her blood. These "post-treatment controllers" are still HIV-1-infected, but they have developed long-term control of their infection in the absence of further therapy, and this endpoint may represent the most sensible and achievable goal we can aim for at this time.