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A proposed new paradigm for an anti-AIDS tolerogenic vaccine

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Abstract

Until now, despite 30 years of intensive work, the RV144 human immunodeficiency virus (HIV) vaccine trial initiated in 2003 remains so far the most protective vaccine prototype of all those tested (32% reduction in the infection rate three years after the vaccination) and the HIV epidemic is still spreading worldwide. In addition, antiretroviral therapy (ART) for people living with HIV is given for life as no other pharmacological intervention has allowed to maintain an undetectable viral load after ART withdrawal. Pr Andrieu and colleagues discovered tolerogenic CD8+T-cells that suppress simian immunodeficiency virus (SIV) specific activation, ensuing SIV reverse transcription suppression and viral replication-defective in Chinese macaques vaccinated by intragastric route with inactivated SIV particles + *Lactobacillus rhamnosus*. Moreover, in HIV-infected elite controllers with specific genetic features (*HLA-1-Bw4-80i* and *KIR3DL1* genes), Pr Andrieu found out that similar tolerogenic CD8+T-cells suppress in the same manner HIV-specific activation, HIV reverse transcription, and HIV replication. These data justify the development of a tolerogenic vaccine composed of inactivated HIV particles + *Lactobacillus rhamnosus* that could be used as a preventive or therapeutic vaccine.

Keywords

HIV, vaccine, CD8+T-cells

Introduction

Human immunodeficiency virus type 1 (HIV-1) infection is a chronic retroviral disease principally transmitted via sexual and anal contacts (as well as via the oral mucosa in the newborn) [1]. Simian immunodeficiency viruses (SIVs) are transmitted by the same mucosal routes in rhesus macaque models.

In the absence of antiviral treatment, the retrovirus induces clinically occult destruction of the immune system ending in more than 99% infected people in fatal opportunistic infections and tumors after a median of 8–9 years [2]. During these years, untreated infected individuals may transmit the infection to others. The result is that the epidemic is still spreading worldwide. In 2018, 37 million people were living with the infection; 1.8 million were newly infected and almost one million died from the consequences of the infection [3].

In this review, we will first recall the characteristics of the first stages of mucosal infection with HIV in humans or with the SIV in the rhesus macaque, its best animal model. Knowledge of these characteristics is indeed necessary to understand the mechanism of replication of the retrovirus and its inhibition by a vaccine. We will then gather the results of vaccination trials in humans and macaque. Finally, this review will be devoted to the new type of vaccine that Andrieu et al. [4–6] have discovered, its effectiveness, and the identification of its protection mechanisms. Overall, their results suggest a new approach to developing a preventive and curative HIV vaccine. All methods and results described here are available in original publications [4–6].

First steps of HIV-1 infection

It is now widely agreed that only the "transmitter/founder" virions (HIV in humans and SIV in macaques) that bear some specific "signatures" on their envelope (Env) glycoprotein can cross the epithelial barrier of genital and rectal mucosa [7, 8]. Once the transmitter/founder virus has penetrated the mucosa, it makes contact with the first encountered targets which are dendritic cells (DCs), and then CD4+T-cell [9, 10]. Among the DCs, plasmocytoïdes DCs (pDCs) detect HIV-1 through Toll-like receptor 7 (TLR 7), which mainly leads to a large amount of interferon-α (INF-α) release responsible for T-cell activation, rendering them susceptible to HIV-1 infection. Conventional DCs (cDCs) are specialized antigen-presenting cells (APCs) that capture and internalize HIV, which can be processed and presented on the cell surface for T-cell priming. This process serves as an important link between the innate immune system and the adaptive immune response, or can on the contrary be transferred to CD4+T-cells, promoting this way the HIV-1 infection and spread [11]. Then, the virus attaches to the CD4 receptor and CC chemokine receptor 5 (CCR5) co-receptor; this attachment is followed by the direct transfer of Gag and Pol antigens from the incoming virion to the CD4+T-cell membrane [12]. This transfer transforms an unspecified CD4+T-cell into a Gag+/Pol+ CD4+T-cell. At the same time, the viral RNA enters inside the Gag+/Pol+ CD4+T-cell. Further development of the infection is now depending on the activation status of the HIV RNA-infected, Gag+/Pol+ CD4+T-cell. If the cell is quiescent/non-activated, HIV RNA reverse transcription is inefficient or abortive [13–15] and the infectious process is stopped. On the other hand, if Gag+/Pol+ CD4+T-cell is in an activated state, HIV RNA is readily reverse transcribed into HIV DNA [16–18]. This step is now irreversibly followed by a cascade of cellular events ending in the production and release of large amounts of HIV particles that replicate easily in surrounded activated CD4T+T-cells. Very quickly, infectious activated CD4+T-cells as well as free viral particles spread through the organism. This is related to the fact that the early activation of a small population of infected CD4+T-cells at the portal of entry is required for the local expansion and establishment of systemic infection [19, 20]. Within a week, virus-specific cytotoxic T lymphocytes (CTL) are produced followed by antiviral antibodies. However, some proteins of the viral Env have already mutated and can thereby escape both CTL killing and antibody neutralization. HIV infection can thus perpetuate chronically. The same steps are observed with SIV in the macaque model.

Failure of classical vaccines (those that induce specific neutralizing antibodies and/or CTL) is well explained

In response to the devastating HIV pandemic, the discovery of a safe and effective vaccine remains the only solution to curb the number of new infections [21]. So far, the prevailing paradigm to develop a vaccine against HIV (or SIV in the macaque model) has remained the stimulation of long-lived memory B- and T-cells capable of protecting the host from infection via the production of high-affinity virus-specific CTLs and/or antibodies [22, 23]. However, efforts aimed at stimulating such immune responses have been so far largely unsuccessful, for proof the results of three trials, step/HVTN 502 (2004) Phambili/HTVN 503 (2005), and HTVN 505 (2009), which tested a defective replicative adenovirus (No. 5) manipulated to express *HIV-1* genes [24]. In each of the three clinical trials, the group of volunteers who, by random draw, received the vaccine, has shown a higher percentage of infected individuals than the one observed in the group of volunteers who received a placebo. This finding suggests that the vaccine because it

has elicited the activation of CD4 T lymphocytes present in the mucosa, promotes the possibility of HIV infection [25, 26]. This hypothesis of activation of HIV T CD4 targets has been confirmed in macaques vaccinated against SIV [27, 28]. Moreover, in 2020, the US National Institutes of Allergy and Infectious Diseases ended a trial of HVTN702, continuing the RV144 vaccine strategy, because it was ineffective. One shot of this two-shot vaccine contained a canarypox virus engineered to carry a piece of the HIV Env protein; the second shot contained the HIV surface glycoprotein. The canarypox was manufactured by Sanofi Pasteur and the glycoprotein was manufactured by GlaxoSmithKline [29]. And on August 31, 2021, Johnson & Johnson announced that a mid-sized clinical trial of their HIV vaccine did not provide sufficient protection against HIV infection. The trial HVTN705 was conducted in South Africa among 2,600 women at high risk of infection. At the end of the roughly four-year study, there were no significant differences in HIV acquisition between those who received the vaccine and those who got a placebo (https://www.aidsmap.com/news/feb-2022/why-did-hiv-vaccine-fail-imbokodo-trial). The disappointment provoked by this failure is the last of many disappointments linked to vaccine candidates' lineage that stretches back to the 1990s. So, despite 30 years of intensive work, the RV144 HIV vaccine trial (initiated in 2003) remains so far the only vaccine prototype that has produced some protection against virus acquisition. The infection rate was reduced by 32% by the vaccine [30].

The currently very disappointing results of vaccination trials in humans raise conceptual issues that cannot be explored for ethical reasons. This is why, shortly after the discovery of the first strain of SIV in an original Indian rhesus macaque in captivity in the USA, it was possible to explore the different phases of infection and test preventive vaccines against infectious strains of SIV such as SIVmac239 and SIVmac251. Although the best model is probably the macaque Rhesus of Chinese origin [31], the Indian rhesus macaque remained the model of choice in the USA for testing preventive vaccines because it has been used since the beginning of the epidemic in almost all preclinical studies.

The prototype of a preventive vaccine that has so far yielded results, however partial in the Indian macaque, consists of an adenovirus (No. 26) with defective replication, whose genome was manipulated to express the *Env*, *Gag*, and *Pol* genes of the SIV; this gene construction was mixed with Env protein gp140. To this experimental vaccine was added a commercial adjuvant of chemical origin, ASO1B. The set was injected into the Indian macaque by intramuscular route. After 6 intrarectal administrations of SIVmac251, 50% of macaques vaccinated showed to be protected while all controls were infected [32]. In addition, the effectiveness of this protection has been shown to correlate with the functional quality of the antibody response directed against the SIV Env protein. The HIV equivalent of this vaccine preparation has already been administered intramuscularly to healthy volunteers to study the characteristics of antibodies production [33], but trials of efficiency have yet to be made.

Another encouraging way is developed by Hansen et al. [34], aimed to induce effector T-cell with cytomegalovirus (CMV) vector [34]. They demonstrate that ΔRh110 68–1 rhesus CMV (RhCMV)/SIV-expressing homologous or heterologous SIV antigens are highly efficacious against intravaginal (IVag) SIVmac239 challenge, providing control and progressive clearance of SIV infection in 59% of vaccinated rhesus monkeys (RMs). Moreover, among 12 ΔRh110 RhCMV/SIV-vaccinated RMs that controlled and progressively cleared an initial SIV challenge, 9 were able to stringently control a second SIV challenge about 3 years after the last vaccination, demonstrating the durability of this vaccine.

All in all, the challenge of creating an HIV vaccine is cast in particularly harsh relief when compared to the speed with which scientists developed a coronavirus disease (COVID) vaccine. It demands new ideas and experimental work.

Discovery of a tolerogenic vaccine against SIV in the Chinese macaque model

Over the last fifteen years, Andrieu et al. [4, 5] has developed with the Chinese macaque model an intriguing new concept of intragastric/oral vaccination that suppressed SIV-specific activation and the ensuing SIV reverse transcription and replication.

1. In the late 1990s, this team has shown that a therapeutic vaccine (administered subcutaneously) containing DCs loaded with inactivated SIV and later with inactivated HIV had a favorable impact on SIV replication in macaques and later on HIV replication in humans [35–37]. Since SIV and HIV were transmitted mainly by mucosal contact, Lu et al. [36, 37] were interested in the construction of a mucosal vaccine. And instead of activating DCs by loading them *ex vivo* with inactivated viruses, they thought it more interesting to develop a vaccine that would directly stimulate the mucosal DCs *in vivo*.

2. The further assumption was that bacillus Calmette-Guerin (BCG), administered at the same time as the inactivated SIV vaccine, stimulating *in vivo* CDs/cells of Langerhans mucous membranes, would activate the CD4 T helper 1 (Th1) T-cell pathway which in turn would promote the response of cytotoxic lymphocytes against lymphocytes infected with SIV [38].

3. They chose the Chinese rhesus macaque to test their experimental vaccines because it is genetically closer to humans and is the best model for HIV infection [31]. And finally, they initially chose the vagina as a vaccination site because it is the main mucosal route of heterosexual infection, but rapidly, they decided to test their vaccine by the oral/intragastric route because, if successful, this route could be a precursor to a human vaccine.

4. Further, since *Lactobacillus Plantarum* (LP), a commensal intestinal bacterium, has been shown to induce a form of tolerance for its constituents, this adjuvant instead of BCG has been chosen in 2009. Further on, *Lactobacillus Rhamnosus* (LR), because it was already administered to humans unlike LP, was used to replace LP [39–41].

The vaccine consisted of killed/inactivated SIV (iSIV)mac239 particles adjuvanted by BCG or by LP or LR. When Chinese macaques were immunized by intragastric route with iSIV accompanied by one of these bacterial adjuvants and further challenged intra-rectally with a highly infectious SIV strain, almost all (23/24) Chinese macaques were sterilely protected for at least five years, while very surprisingly, anti-SIV immunoglobulin M (IgM) and IgG antibodies responses were suppressed [4, 5]. In contrast, without adjuvant, the vaccine alone did not induce any post-challenge protection although it generated high titers of anti-SIV antibodies and SIV-specific cellular immune responses. Therefore, a very unexpected and contradictory picture emerged, that of a compound vaccine of iSIV adjuvanted with BCG or LP/LR and administered by a mucosal route which induced at the same time protection against infectious SIV and suppression of humoral and cellular responses specific to the virus. This new type of vaccine, therefore, induced the inhibition of SIV-specific CD4+T-cells. This inhibition—also called tolerance for SIV, thus prevented the reverse transcription of the virus (which is dependent on the activation of the CD4 T lymphocyte) and prevented the cascade of subsequent events leading to replication and production of the virus.

Inhibition of SIV-specific CD4+T-cells by CD8-T-regulatory cells, named tolerogenic CD8+T-cells

Besides these astonishing new findings (which have been fully confirmed by an independent group led by Gianfranco Pancino from Pasteur Institute), Andrieu et al. [5] discovered that the protection induced by the tolerogenic adjuvanted vaccine in Chinese macaques was provoked by a previously unrecognized class of non-cytolytic major histocompatibility complex class Ib (MHC-Ib)/E-restricted SIV specific CD8+T-cells that could prevent the activation of SIV RNA-infected SIV Gag/Pol-CD4+T-cells which thereby inhibited the (activation-dependant) reverse-transcription of the virus and finally prevented its integration, replication, and release. They named these cells (that were not CD4+CD25+FoxP3+) “CD8+T-regulatory cells” or more explicitly “tolerogenic CD8+T-cells” [5].

1. In a series of experiments, they showed that CD8+T-cells from vaccinated macaques prevented not only the activation but also the replication of SIV in infected CD4 T-cells.

2. Moreover, the correlation between the *ex vivo* antiviral activity of CD8-Tol T-cells before administration of infectious virus and protection against SIV after administration of infectious virus

suggests that the determination of CD8-Tol T-cell-mediated antiviral activity before virus administration is predictive of vaccine efficacy.

3. In fine, to confirm the *in vivo* role of CD8-Tol T-cells in the protection of Chinese macaques, four macaques, still protected after three intrarectal inoculations (3-, 5-, and 13-month post-vaccination) received a fourth intrarectal inoculation of SIV. However, just before this inoculation, the macaques' CD8+T-cells were momentarily suppressed by the intravenous administration of an anti-CD8 antibody. As they were no longer protected at the time of SIV inoculation by the presence of their CD8-Tol T-cells, the four animals at the time of SIV inoculation by the presence of their CD8-Tol T-cells, all four animals were infected. A few weeks later, when the effect of the anti-CD8 antibodies wore off, the reappearance of their CD8-Tol cells again prevented activation of the infected CD4 cells leading to inhibition of viral reverse transcription and the cessation of viral replication within a few weeks. However, these animals retained SIV DNA in their CD4 lymphocytes. It is interesting to observe that this profile (SIV DNA+, SIV RNA–) is the same as that found in infected "elite controller (EC)" males.

It should be noted that, in contrast to Chinese macaques (that are now considered as the best vaccine model against HIV), Indian macaques (that remain the subspecies commonly used in the USA as HIV vaccine model) were not capable to mount an immune response to the intragastric administration of iSIV even given alone and were thus not an adequate model to test our oral tolerogenic vaccine [42].

To resume, Andrieu et al. [5] demonstrated that, in the SIV-macaque model, the infection can be prevented by inducing immunological tolerance against the infecting agent. The administration of iSIVmac239 and LP/LR stimulated the macaques to develop an SIV-specific tolerance. This tolerance was characterized by the suppression of SIV-specific antibody and CTL responses, and activation of a subset of CD8+T-cells that are SIV-specific, noncytolytic, and MHC-Ib/E-restricted, which suggests that CD4+T-cells specific for other antigens are not suppressed. These cells can suppress CD4+ T-cells activated by SIV and thereby prevent the establishment of productive SIV infection both *in vivo* and *in vitro*.

Discovery of tolerogenic CD8+T-cells inhibiting HIV-specific CD4+T-cells activation and thereby virus reverse transcription in human ECs

ECs are a small group (< 1%) of HIV-1 infected patients with long-term suppression of HIV replication [in the absence of any antiretroviral therapy (ART)]. Lu et al. [6] have further demonstrated in 10 human ECs that 9 of them had tolerogenic CD8+T-cells (similar to those observed in vaccinated Chinese macaques) that inhibited the activation of HIV-infected cells and thereby suppressed the (activation-dependent) reverse transcription of the virus, which, in turn, suppressed virus integration, replication, and release.

In contrast to what has been observed in Chinese macaques where there was no specific genetic profile to generate SIV specific tolerogenic CD8+T-cells and SIV protection, they found that these 9 ECs had a specific genomic profile including hetero or homozygote human leukocyte antigen class-1 (*HLA-1*) *Bw4-80i* gene (on chromosome 6) and *KIR3DL1* gene (on chromosome 19). Moreover, they showed that at the cell membrane level, it was the cooperation between the HLA Bw4-80i protein motif carried by infected CD4+T-cells and the KIR3DL1 protein motif carried by tolerogenic CD8+T-cells which was necessary for the long-term suppression of CD4+T-cell activation and HIV-1 reverse transcription and ensuing replication [6].

In conclusion, in 9 out of 10 patients of this cohort of ECs, the principal mechanism of suppression of HIV-1-replication was shown to correlate on specific genetic features regulating the interaction of effector tolerogenic CD8+T-cells expressing KIR3DL1 with target infected CD4+T-cells expressing HLA-BW4-80i. Interestingly, the cytotoxic role of CD8+T-cells was nil and suppressive soluble factors appeared at best very marginal. These findings provide the first evidence for a pivotal role of Bw4-80Ile-restricted KIR3DL1-expressing CD8+T-cells in the natural control of HIV-1 replication in ECs highlighting for the first time a mechanistic basis for the protective effect of combined Bw4-80Ile and KIR3DL1 genotypes, which was reported in several studies of molecular epidemiology [43–46].

Conclusions

Until now, no pharmacological intervention has allowed maintaining an undetectable viral load after ART withdrawal [47]. Andrieu et al. [5] discovered tolerogenic CD8+T-cells that suppress SIV-specific activation, ensuing SIV reverse transcription suppression and viral replication inhibition in Chinese macaques vaccinated by intragastric route with inactivated SIV particles and LR. Secondly, he also found out that in HIV-infected ECs with specific genetic features (*HLA-1 Bw4-80i* and *KIR3DL1* genes), similar tolerogenic CD8+T-cells suppress in the same manner HIV-specific activation, HIV reverse transcription, and HIV replication. These two discoveries justify the development of a tolerogenic vaccine that could be used for prevention and therapy.

In Europe, the frequency of the *KIR3DL1* gene is 95% while that of the *HLA-Bw4-80i* gene is 27% (altogether 25%) [48]. In this setting, the best solution will be to vaccinate all European patients who bear the *KIR3DL1* gene.

On the other hand, in Africa, the frequency of the *KIR3DL1* gene is 99% and that of HLA Bw4-80i is 70% (altogether almost 70%). This means that the tolerogenic vaccine could be highly effective in prevention but also allows 70% of infected patients to stop ART. In such a context and on behalf of regional authorities, World Health Organization (WHO) epidemiologists and statisticians would decide which risk groups should be vaccinated first (without checking their genetic background except for research studies).

Abbreviations

ART: antiretroviral therapy

BCG: bacillus Calmette-Guerin

CTL: cytotoxic T lymphocytes

DCs: dendritic cells

ECs: elite controllers

Env: envelope

HIV-1: human immunodeficiency virus type 1

HLA-1: human leukocyte antigen class-1

iSIV: inactivated simian immunodeficiency viruses

LP: *Lactobacillus Plantarum*

LR: *Lactobacillus Rhamnosus*

SIVs: simian immunodeficiency viruses

Declarations

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Author contributions

The author contributed solely to the work.

Conflicts of interest

The author declares that she has no conflicts of interest.

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