DNA vaccination induces sustained virus-specific CD8+ T cell immunity in AIDS monkey model

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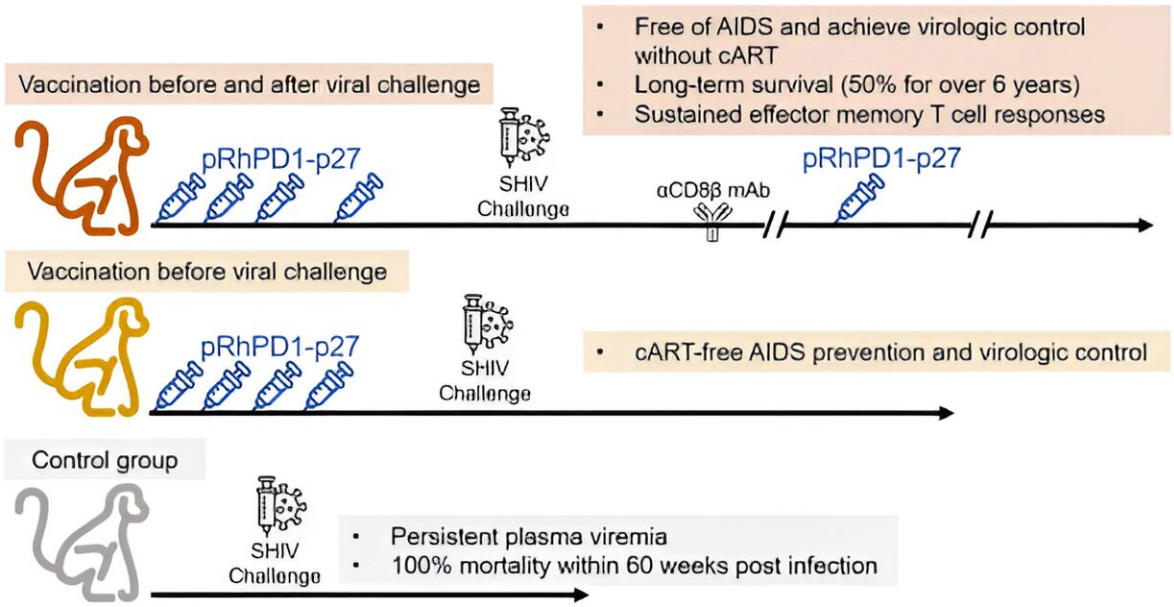

HKUMed research team discovers that the PD-1-enhanced DNA vaccine strategy is effective in achieving six-year cART-free AIDS prevention and virologic control. Credit: *Microbiology Spectrum* (2023). DOI: 10.1128/spectrum.03350-23

Researchers have found that PD-1-enhanced DNA vaccination can induce sustained virus-specific $CD8^+$ T cell immunity in an AIDS

monkey model. The vaccinated monkeys remained free of AIDS for six years and achieved virologic control without the need for combination antiretroviral therapy (cART), a treatment used to suppress viral replication in individuals living with human immunodeficiency virus (HIV).

The study also found that polyfunctional and broadly reactive effector-memory virus-specific T cells were maintained in the protected experimental macaques for more than six years. The findings provide supporting evidence that the PD-1-enhanced DNA vaccine strategy holds promise as a third-generation DNA vaccine for AIDS prevention and immunotherapy.

The study was published in *Microbiology Spectrum* and was conducted by researchers from the AIDS Institute, Department of Microbiology, School of Clinical Medicine, and the State Key Laboratory of Emerging Infectious Diseases, LKS Faculty of Medicine of the University of Hong Kong (HKUMed), in collaboration with HKU-Shenzhen Hospital, Foshan University and The Third People's Hospital of Shenzhen.

Using cART for both pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) contributes efficiently to reducing AIDS-related deaths and HIV-1 transmission cases. Despite the effectiveness of cART, HIV-1 can persist in latent reservoirs. This has made it challenging to achieve complete or sustained cART-free virologic control of HIV-1 infection for the past 40 years since the discovery of AIDS and its causative agent HIV-1 in the early 1980s.

In addition, the extensive HIV-1 genetic diversity facilitates the formation of mutational escape variants that resist cART drugs, resulting in the clinical failure of viral control. The huge number of viral variants also hampers AIDS vaccine development. Identifying novel vaccination strategies, including the induction of robust cross-reactive T cell

responses, will enhance the arsenal against HIV/ AIDS epidemic.

The researchers developed a vaccine technology known as the programmed death-1 (PD-1)-enhanced DNA vaccine strategy, which involves using a DNA vector to encode specific antigens fused with the soluble domain of PD-1 protein.

Previous murine studies by the team found that this strategy allows more efficient antigen delivery targeting to professional antigen-presenting cells, called dendritic cells. It results in the superiority of immunogenicity and the protective efficacy against both viral infection and tumorigenesis over conventional vaccines. Notably, PD-1-enhanced DNA vaccines elicit strong $CD8^+$ T cell responses.

In 2021, the researchers reported the findings of a rhesus monkey study that evaluated the potential of a PD-1-enhanced DNA vaccine against the simian—human immunodeficiency virus (SHIV). The rhesus monkeys were vaccinated with a DNA vaccine, pRhPD1-p27, designed based on the PD-1-enhanced DNA vaccine strategy.

The vaccine resulted in sustained virological control against pathogenic SHIVSF162P3CN challenge, which was mediated by a strong polyfunctional vaccine-induced effector-memory $CD8^+$ T cell response.

In a group of four pRhPD1-p27-vaccinated macaques, an aviremic state (absence of detectable virus in the blood) was maintained for two years, indicating that potential cART-free virologic control could be achievable with the PD-1-enhanced DNA vaccine. The recent follow-up study demonstrated extended cART-free virologic control for more than six years.

Efficient strategies for HIV-1 cART-free virologic control are crucial for ending the AIDS epidemic. "Our innovative PD-1-enhanced DNA

vaccine was effective not only in inducing polyfunctional effector-memory $CD8^+$ T cells for AIDS prevention in rhesus monkeys, but also in sustaining cART-free virologic control for over six years," remarked Professor Chen Zhiwei, Director of the AIDS Institute and Chair Professor of the Department of Microbiology, School of Clinical Medicine, HKUMed, who led the study.

"The encouraging outcomes validate the continuation of ongoing clinical trials investigating the potential of the PD-1-enhanced DNA vaccine for achieving HIV-1 cART-free virologic control. Hopefully, the vaccine can be employed independently or in conjunction with other biomedical interventions for individuals living with the virus in the future."

If this efficacy can be replicated in humans, a therapeutic vaccine for cART-free HIV-1 control will be on the horizon. Currently, a Phase I clinical trial, in which the HKUMed team is collaborating with The Third People's Hospital of Shenzhen to test whether the non-human primate data can be replicated in humans, is underway. The report of the trial results is expected to be available in the second quarter this year.

More information: Xiaoen He et al, A follow-up study: 6-year cART-free virologic control of rhesus macaques after PD-1-based DNA vaccination against pathogenic SHIV SF162P3CN challenge, *Microbiology Spectrum* (2023). DOI: 10.1128/spectrum.03350-23

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