HIV vaccine candidate plus microbicide decreases SIV infection risk by more than 90%

Breakthroughs in developing an effective human immunodeficiency virus (HIV) vaccine have been rare despite decades of effort. By combining vaccination with a topical microbicide that also potentiates vaccine-induced immunity, 16 out of 20 female macaques were protected against vaginal acquisition of the highly pathogenic simian immunodeficiency virus (SIV).

This is a summary of:
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The problem

The HIV epidemic has been a monumental global challenge since its onset in the early 1980s. Transmission has declined, but the epidemic has become endemic; an estimated 1.5 million people acquired HIV in 2021. Effective antiretroviral therapies for individuals who are infected have limited reach, and patients are largely untreated in regions such as sub-Saharan Africa, where cultural barriers to therapy disproportionately affect adolescent women. The next substantial and equitable step towards eliminating HIV must come from innovation overcoming existing biological, cultural and socioeconomic barriers. Unlike other pathogens, HIV thrives on inflammation and hijacks the very same host immune responses elicited by vaccination, such as activated $CD4^+$ T cells. We developed a potentially effective HIV preventive strategy by leveraging the synergy of a topical microbicide with a novel HIV vaccine candidate to limit $CD4^+$ T cell activation and kill virus-infected cells, while maintaining tissue homeostasis.

The discovery

Infection of macaques with pathogenic SIV_{mac251} is a model that has replicated or predicted the results of HIV vaccine trials, including RV144, the only human trial demonstrating reduced risk of HIV acquisition (31.2%)[1–3]. We previously improved the recombinant ALVAC-HIV/gp120/alum RV144 platform by priming with virus-like particles, engineered by V1 envelope deletion in a DNA platform (ΔV1env/Gag DNAs), followed by recombinant ALVAC and ΔV1gp120/alum, and decreased the risk of SIV_{mac251} acquisition in female macaques by up to 69%[4,5]. Now, we have combined vaccination with the topical microbicide SAMT-247, which inhibits HIV or SIV infectivity by disrupting the nucleocapsid protein zinc fingers. Administering ΔV1DNA-ALVAC/gp120/alum vaccine and SAMT-247 together protected 16 out of 20 female macaques from SIV_{mac251} infection after repeated exposure to the virus. Mechanistically, SAMT-247 synergized with vaccination by increasing vaccine-induced protective responses and by decreasing the level of $CD4^+$ T cells expressing the viral CCR5 co-receptor, linked to increased zinc availability in immune cells.

As expected, ΔV1DNA-ALVAC/gp120/alum vaccination alone decreased virus acquisition by approximately 65%. When combined with SAMT-247 treatment, vaccine efficacy jumped to a remarkable 92.7% reduction in per-challenge risk of virus acquisition (Fig. 1). SAMT-247 alone failed to significantly decrease acquisition, from which we inferred synergy between the vaccine and microbicide beyond any SAMT-247 antiviral effect. In vitro, SAMT-247 enhanced multiple mechanisms of protection afforded by the vaccine, including innate and adaptive responses known to correlate with reduced risk of virus acquisition. The effect of SAMT-247 on immunity is related to its ability to eject zinc from transcription factors and enzymes. Zinc has a well-known role in immunity, and its increased availability here may enable zinc-mediated, anti-inflammatory responses, in addition to vaccine-induced protective responses.

The implications

We concluded that SAMT-247 synergizes with the ΔV1DNA-ALVAC/gp120/alum vaccine regimen as an immune modulator by augmenting the immunological function of effector cells, and reducing target cells for viral infection: $CD4^+$ T cells expressing the viral co-receptor CCR5, at mucosal site. Our findings support further development of the ΔV1DNA-ALVAC/gp120/alum vaccine platform, planned for testing in a phase I trial at National Institutes of Health, by again showing its previously observed effectiveness and extending its usefulness for humans in combination with SAMT-247. The identification of a major role for zinc modulation in preventing SIV acquisition and its related mechanics in this study provide a roadmap for the integration of dietary zinc supplements into the next vaccine renditions.

Although we believe our results are compelling evidence of a unique synergy that enables zinc-mediated protection, we cannot exclude that the antiviral effect of SAMT-247, even if not sufficient alone, may have contributed to enhanced protection in the vaccine + microbicide combination. The protective effect of SAMT-247 was first observed in animals mock-immunized with empty vector and alum, which are by themselves key components and contributors to the immunogenicity of this ΔV1DNA-ALVAC/gp120/alum vaccine. Apart from its mechanistic effect, the safety of SAMT-247 for use in humans has not yet been established.

Our findings signal a potentially central role for zinc mediation in a finished vaccine regimen and invite a targeted effort to integrate dietary zinc supplements together with candidate vaccine platforms. These results represent an exciting step towards creating an effective HIV vaccine.

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EXPERT OPINION

"Vaccination studies in humans have had minimal success, with only one study showing some efficacy (RV144). This current study relates to that efficacy study, and any increase in effectiveness of such a vaccine regimen is an important advance." **Steven C. de Rosa, Fred Hutchinson Cancer Research Center, Seattle, WA, USA.**

FIGURE

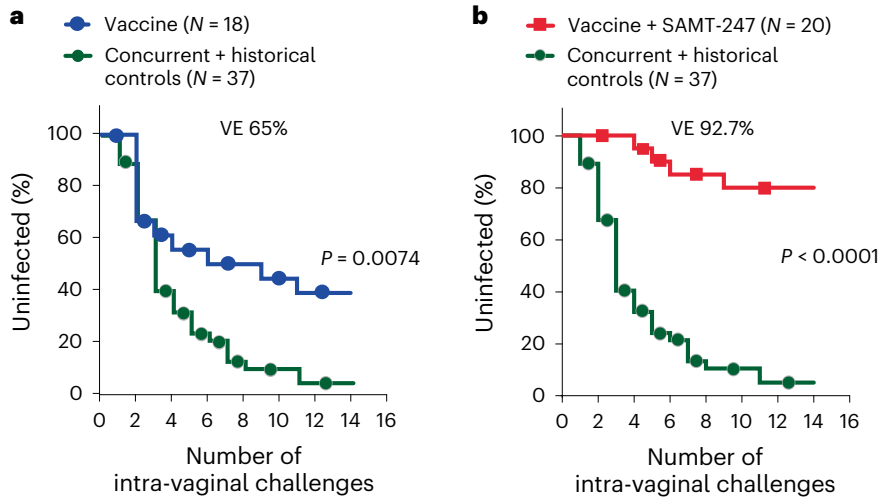

Fig. 1 | SAMT-247 treatment enhances vaccine efficacy. a,**b**, Rhesus macaques were divided into groups and administered vaccine only ($n = 18$), vaccine + SAMT-247 microbicide ($n = 20$) or microbicide only ($n = 6$). All groups were compared to 6 concurrent plus 31 historical controls from previous studies ($n = 37$). Protective efficacy against SIV_{mac251} was assessed by subjecting macaques to 14 weekly intra-vaginal viral exposures without (**a**) or with (**b**) microbicide until infection was confirmed. Significant protection against infection (vaccine efficacy, VE) was observed in animals treated with vaccine only (left, 65%) and animals treated with vaccine plus SAMT-247 microbicide (right, 92.7%).

BEHIND THE PAPER

This work began before the SARS-CoV-2 pandemic and was completed by the dedication and endurance of our team. The positive results were generated from a combination of scientific discoveries — some serendipitous. Dr M. Guroff, whose office adjoined mine, was testing the zinc-finger inhibitor SAMT-247 with her Ad5-based HIV vaccine candidate, in collaboration with Drs E. Appella and D. Appella. She found no synergy between an Ad5-based vaccine and SAMT-247. At the same time, my lab had found that the efficacy of the ΔV1DNA-ALVAC/gp120/alum HIV vaccine candidate was linked to decreased expression of the zinc finger protein ZC3H7A5, raising the hypothesis that a zinc-finger inhibitor could improve vaccine efficacy. With additional support from the NCI Center for Cancer Research leadership, we were able to acquire the necessary number of animals to test our hypothesis in this high-risk project. **G.F.**

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   This paper shows the importance of engagement of the CCL2/CCR2 axis and pro-resolution efferocytes to the efficacy of our HIV vaccine candidate.

FROM THE EDITOR

"This study tests the effects of a combination of V1-deleted/V2-enhanced SIV envelope immunogens with the zinc-finger inhibitor SAMT-247 on vaginal SIV acquisition in rhesus macaques. The huge impact of HIV in women with limited access to antiretroviral therapy, coupled with the impressive results, including a 92% reduction in the risk of virus acquisition, make this of broad interest and provide excellent evidence to underpin human clinical trials." **Susan Jones, Chief Editor, *Nature Microbiology*.**