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**How to hit HIV where it hurts**

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No medical procedure has saved more lives than vaccination. But, today, some pathogens have evolved which have defied successful vaccination using the empirical paradigms pioneered by Pasteur and Jenner. One characteristic of many pathogens for which successful vaccines do not exist is that they present themselves in various guises. HIV is an extreme example because of its high mutability. This highly mutable virus can evade natural or vaccine induced immune responses, often by mutating at multiple sites linked by compensatory interactions. I will describe first how by bringing to bear ideas from statistical physics (e.g., maximum entropy models, Hopfield models, Feynman variational theory) together with in vitro experiments and clinical data, the fitness landscape of HIV is beginning to be defined with explicit account for collective mutational pathways. I will describe how this knowledge can be harnessed for vaccine design. Finally, I will describe how ideas at the intersection of evolutionary biology, immunology, and statistical physics can help guide the design of strategies that may be able to induce broadly neutralizing antibodies.