**1. What background information would someone who is completely unfamiliar with your field need to know to understand the findings in your paper? (Suggested word limit: 150 words)**

HIV’s envelope protein (Env) evolves very fast. For instance, in the about 100 years since the HIV-1 virus entered humans, Env proteins in different viral strains have evolved to become as different as the typical human and mouse protein. However, what is not known is how Env’s ongoing evolution changes the *evolutionary space* available to different viral strains. For instance, can the Env proteins from different viral strains tolerate different sets of mutations? This is an important question, because Env’s ability to tolerate mutations is what enables HIV to escape from antibodies and maintain a chronic infection. It’s also what makes creating an HIV vaccine so hard.

**2. What exact research question did you set out to answer and why? (Suggested word limit: 75 words)**

We selected two Env proteins from transmitted-founder HIV strains. (These are viral strains that initiated new infections in humans, and so are most relevant to understanding HIV’s evolution.) We then systematically measured the tolerance of each of these Env proteins to *all* possible amino-acid mutations. This experiment allows us to directly compare the evolutionary space accessible to two different viral strains.

**3. What are the most important findings of your paper? (Suggested word limit: 100 words)**

Most mutations had similar effects in both Env proteins, indicating that many of the constraints on this protein are conserved during evolution. We were able to use this fact to identify parts of Env that evolve faster or slower in nature than expected from the functional constraints on Env that we measured in the lab. These sites probably evolve at different rates in nature because in addition to being under selection for the functional role that they play in HIV infection, they are also under selection to help the virus escape immunity.

But we also found some mutations (about 30 out of 659) where Env’s ability to tolerate mutations had shifted significantly between the two viral strains. These are sites that have different evolutionary potential in the two viruses that we examined. Interestingly, the sites of the protein that changed their evolutionary potential weren’t always the same sites that had changed in sequence. Therefore, evolution in one part of Env can lead to changes in the evolutionary potential of other parts of the protein.

**4. Who might eventually benefit from the findings of your study, and what would need to be done before we could achieve these benefits? (Suggested word limit: 75 words)**

An important goal in studying HIV is to understand the “fitness landscape” that determines what evolutionary space the virus can access. Our work is the most thorough experimental examination of this space so far, and should improve our ability to understand how Env can evolve. An interesting future question is how changes in the accessible evolutionary space affect the virus’s ability to escape from immunity.