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**Manuscript**

Mapping mutational effects along the evolutionary landscape of HIV envelope

**Digest**

HIV, the virus that causes AIDS, consists of genetic material and proteins encased in a membrane. On the surface of these viruses is a protein called Env, which enables HIV to infect the cells. Env can also be recognised by antibodies generated by the immune system. These antibodies can block the virus from infecting cells, or target the virus for destruction. But unfortunately, Env evolves very quickly, which means that HIV can evade our immune defences. However, there are limits to how much Env can change, since it still needs to perform its essential role in helping viruses enter cells.

In the century since HIV infected humans, the virus has evolved considerably. There are now many diverse HIV strains that infect humans, and they bear Env proteins that differ substantially in their sequences. However, it is not clear if these changes in sequence have resulted in differences in which mutations different Env proteins can tolerate.

Haddox et al. compared how the Env proteins from two strains of HIV tolerate all the individual mutations that can be made to their sequences. They did this by creating all of the individual mutations, and then testing the resulting collection of mutated viruses for their ability to infect cells in the laboratory.

Most mutations had similar effects in both Env proteins. This allowed Haddox et al. to identify which portions of the protein most easily accommodate changes, and which portions must remain unchanged for viruses to remain infectious—at least in the laboratory.Some of these mutations are under different types of pressures when the virus is in the body and faces the immune system, and Haddox et al used computational approaches to identify those mutations.

However, some mutations were tolerated differently by the two Env proteins. Therefore, different viral strains differ in the capability of their Env proteins to evolve. Interestingly, the parts of the protein that differed in mutational tolerance were not always the same parts that differed in sequence, showing that a sequence change in one part of the Env protein can affect the evolutionary capacity of distant portions of the protein.

It remains to be determined whether changes in tolerance to mutations translate into differences in how the virus can escape immunity. This is an important question given that the rapid evolution of Env is a major obstacle to creating a vaccine for HIV.