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Inside the Aids virus: Research finds chink in the armour that protects HIV in breakthrough that could lead to a new class of drugs

The cone-shaped “capsid” is what protects the virus’s lethal package of genetic material until the time comes to release it inside a human cell.

The breakthrough could enable researchers to find new ways of attacking the integrity of the capsid, in order to interfere with the virus’s ability to replicate itself once it enters the body.

Researchers said their findings could lead to a new class of drug that could complement the existing anti-retroviral Aids medications, some of which have led to resistant forms of HIV as well as causing serious side-effects in some patients.

Using a combination of high-magnification microscopy, detailed X-ray analysis, and ultra-fast supercomputers, the researchers were able to piece together the precise positions of millions of atoms within the 1,300 proteins that form the capsid’s unusual structure.

Although the capsid’s overall shape has been known about for many years, this is the first study to reveal the precise position of the structural proteins that form its three-dimensional cone, which could lead to a new generation of anti-HIV drugs based on destroying the capsid’s vital function.

“The HIV capsid has actually two completely opposite properties. It has to protect the genetic material but, once it gets inside the cell, it has to release the genetic material,” said Professor Klaus Schulten of the University of Illinois based at Urbana-Champaign.

“That has to happen with really good timing. Too quick is not good, too slow is not good. And this is a moment when you can throw a wrench into the system,” said Professor Schulten, one of the authors of the study published in the journal Nature.

“The timing of the opening of the capsid is essential for the degree of virulence of the virus. This is where we could perhaps best interfere with HIV infection,” he said.

The work revealed that the capsid’s shell, inset below, is composed of a matrix of identical proteins linked in a complicated lattice of 200 hexagons. These are composed of six protein sub-units, which form the flat surfaces of the capsid, and about 12 pentagons of five sub-units each, which form the curved corners at the two ends of the capsid.

“The capsid is critically important for HIV replication, so knowing its structure in detail could lead us to new drugs that can treat or prevent the infection,” said Peijun Zhang of the University of Pittsburgh, a co-author of the study. “This approach has the potential to be a powerful alternative to our current HIV therapies, which work by targeting certain enzymes, but drug resistance is an enormous challenge due to the virus’s high mutation rate,” Dr Zhang said.

Immensely powerful supercomputers revealed the precise geometric positions of the capsid’s protein building blocks, showing critical molecular interactions at the “seams” or interfaces of the capsid, which could be vulnerable to attack.

“The capsid is very sensitive to mutation, so if we can disrupt those interfaces, we could interfere with capsid function. The capsid has to remain intact to protect the HIV genome and get it into the human cell,” Dr Zhang added.

“But, once inside, it has to come apart to release its contents so that the virus can replicate. Developing drugs that cause capsid dysfunction by preventing its assembly or disassembly might stop the virus from reproducing,” she said.