Every day, 4,000 people become infected with human immunodeficiency virus (HIV), and it remains a leading cause of death in many countries. In 2021, someone died from acquired immune deficiency syndrome (AIDS) every minute, equating to around 650,000 AIDS-related deaths.

Around 75% of people who carry the virus responsible for AIDS, HIV, have access to anti-retroviral treatment. This prevents the condition from progressing and has improved overall life expectancy. However, researchers are still learning about how living with HIV infection can impact health in the long term. A paradigm shift is happening in the research arena towards enhancing the quality of life for people living with HIV infection.

Neurological complications of AIDS
HIV attacks the body’s immune system, including white blood cells. The virus hijacks the cellular machinery and causes epigenetic changes which alter gene expression. HIV infection can also affect cells of the central nervous system, leading to inflammation that can impair brain function. The collection of cognitive changes associated with HIV infection is known as NeuroAIDS.

One type of a NeuroAIDS disorder is HIV-associated neurocognitive disorder (HAND), which includes symptoms such as behaviour changes, depression, and memory loss. Specialist methods have been used to characterise some of the changes in the brain resulting from HAND and showed that alterations in genes and proteins are associated with metabolic pathways, neurodegenerative disorders, and dementia.

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The exact mechanism of HAND is unclear. However, we do know that HIV does not directly infect neurons; instead, it indirectly leads to disrupted glial function (glial cells support and protect neurons), neuronal dysfunction, or death. Despite effective anti-retroviral therapy, around 50% of people with HIV may have HAND.

Epigenetic mechanisms
Dr Samikkannu Thangavel at Texas A&M University, USA, aims to understand more about HAND progression. He explains that HIV may alter the normal functions of cells by changing gene expression – in other words, whether a gene within the cell is switched on or off. When a gene is switched on, this means that the instructions in our DNA can be converted into an end product, for example a particular protein. In particular, Thangavel is interested in an aspect of gene modification called epigenetics.

Epigenetics is a reversible change in the way that genes are read, caused by your behaviours and environment. For example, some epigenetic changes increase the risk of developing cancer, as they alter the way that a certain gene functions. While gene expression may change, the underlying DNA sequence remains the same.
Epigenetic mechanisms can include the addition of a chemical group to one end of a protein, a process called N-terminal acetylation. Protein synthesis within the cell happens in ribosomes, cellular machines that link smaller building blocks together to form larger proteins. Sometimes proteins are altered, or modified, during this stage of production.

HIV can modify immune cells

Thangavel is particularly interested in N-terminal acetylation within an important cell type in the brain, the microglia. Microglia cells are often known as the immune cells of the central nervous system, and play important roles in brain infections, such as HAND. During infection with HIV, the microglia are unable to carry out their normal protective roles and this can promote inflammatory responses within the brain.

Thangavel proposes that N-terminal acetylation changes could explain how the virus and body interact.

Alterations to proteins within the microglia cells through N-terminal acetylation can have a number of consequences, such as impairment of the mitochondrial energy production and metabolic functions within the microglia, which cause misfolded or degraded proteins, or alterations to signalling pathways within the cell. There may also be issues with oxidative stress and redox imbalance, meaning an imbalance between oxidants and antioxidants. This is likely to affect energy resources and metabolic fuel within the microglia. Many of these changes have already been linked to the development of neurodegenerative disorders.

Research has shown that HIV can interrupt the way these energy powerhouse structures work, including increasing the release of harmful molecules that can contribute to the progression of HAND. In addition, this energy is needed for effective gene expression within the cell. Studies done by Thangavel’s research group at Texas A&M University have already shed light on the epigenetic changes in the human brain that cause energy dysfunction, which can contribute to HAND.

Thangavel also suggests that N-terminal acetylation may impact the signalling cascade of gene expression which has been shown to be significantly associated with depressive behaviours, problems with forming memories, and dementia. He proposes that N-terminal acetylation changes induced by viral infections could explain how the virus and body interact. He also explains that if more can be understood about how HIV affects the cell’s energy source, it may be possible to develop therapeutic approaches to prevent HAND, as well as new ways to test for the condition.

Improving quality of life

Further research is still needed to learn more about the relationship between HIV infection, modifications to proteins via N-terminal acetylation or other mechanisms, and cognitive impairment or behavioural changes. It is likely that epigenetic modifications regulate both gene expression in the energy-producing compartments of a cell, as well as gene expression more broadly. Improved diagnosis and management of cognitive disorders in people with HIV infection, which is well managed through medications, means that overall quality of life can be improved for those living with the virus.