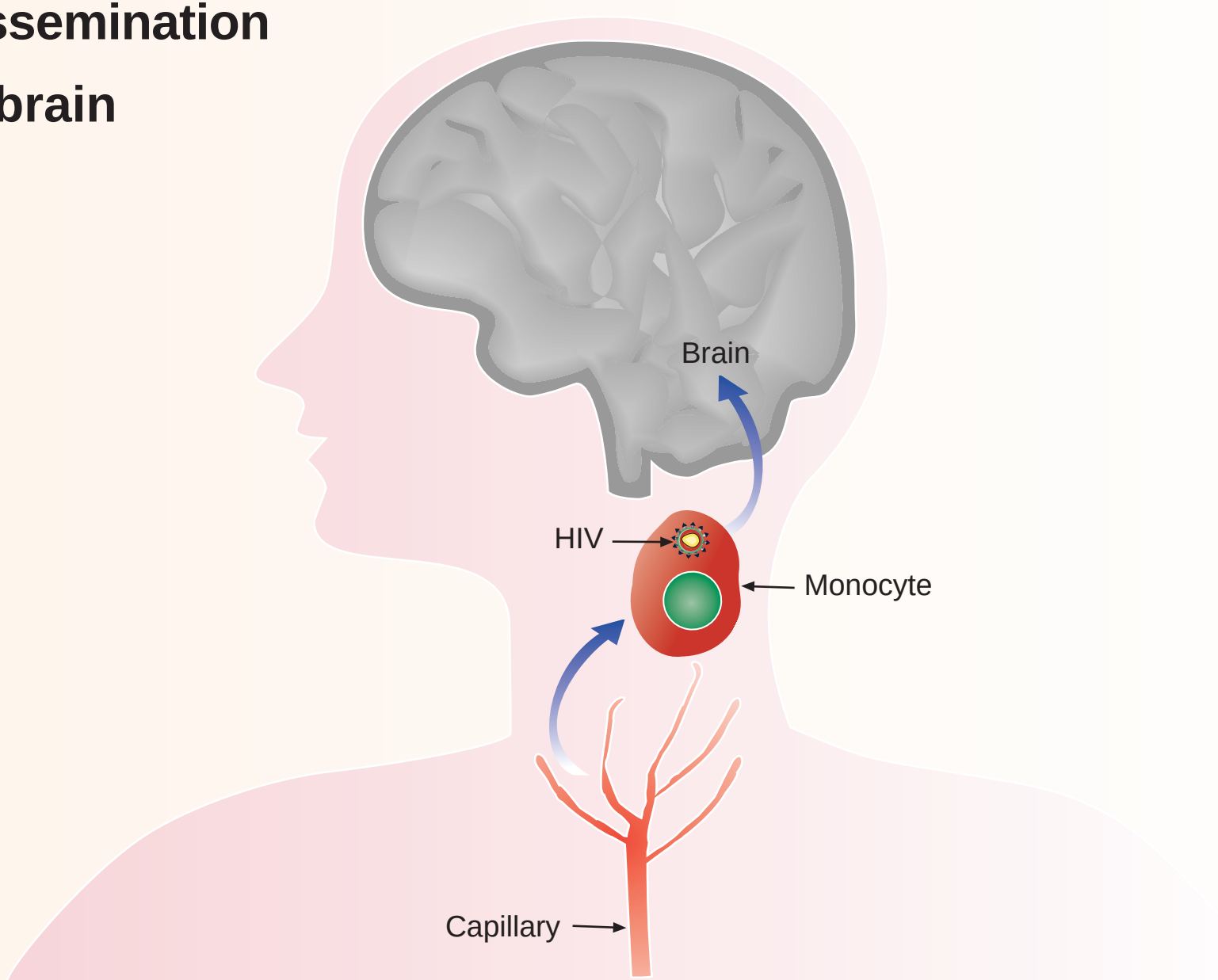
HIV dissemination to the brain



NEXT

HIV seeds the brain early during acute infection when viraemia is high. Due to a competent antiviral immune response and the brain being an “immune privileged” site where T cell activation is regulated, HIV fails to induce encephalitis and remains latent throughout chronic infection. The blood-brain barrier prevents virus particles from diffusing into the brain and it is thought that transmigration of infected monocytes from peripheral blood allows HIV to penetrate the brain. Bone-marrow derived monocytes enter the brain via post-capillary venules. They then differentiate into perivascular macrophages or microglial cells that support viral replication and can transmit the virus to uninfected cells.

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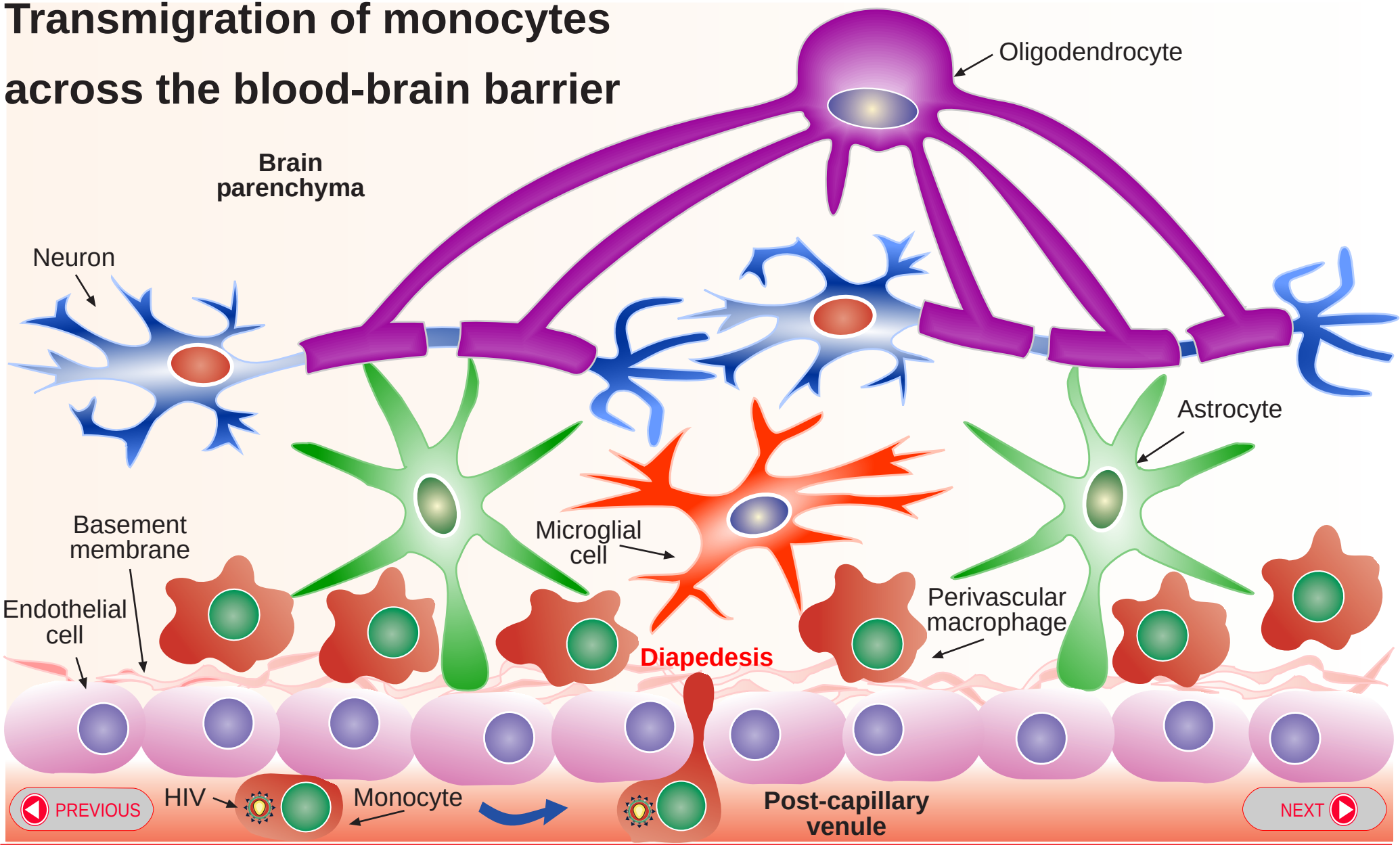
Transmigration of monocytes across the blood-brain barrier



Bone-marrow derived monocytes are recruited to the brain where they mature into resident tissue macrophages (perivascular macrophages) or specialised brain macrophages (microglial cells). HIV can infect monocytes at a low level and it is thought that during the high viraemia associated with acute infection, a small number of monocytes in peripheral blood become infected and some of these will enter the brain via the post-capillary venules (diapedesis). It is unlikely that virus particles can directly penetrate the brain because of the blood-brain barrier. Tight-junctions between capillary endothelial cells and the presence of a basement membrane prevents diffusion of large molecules into the brain.

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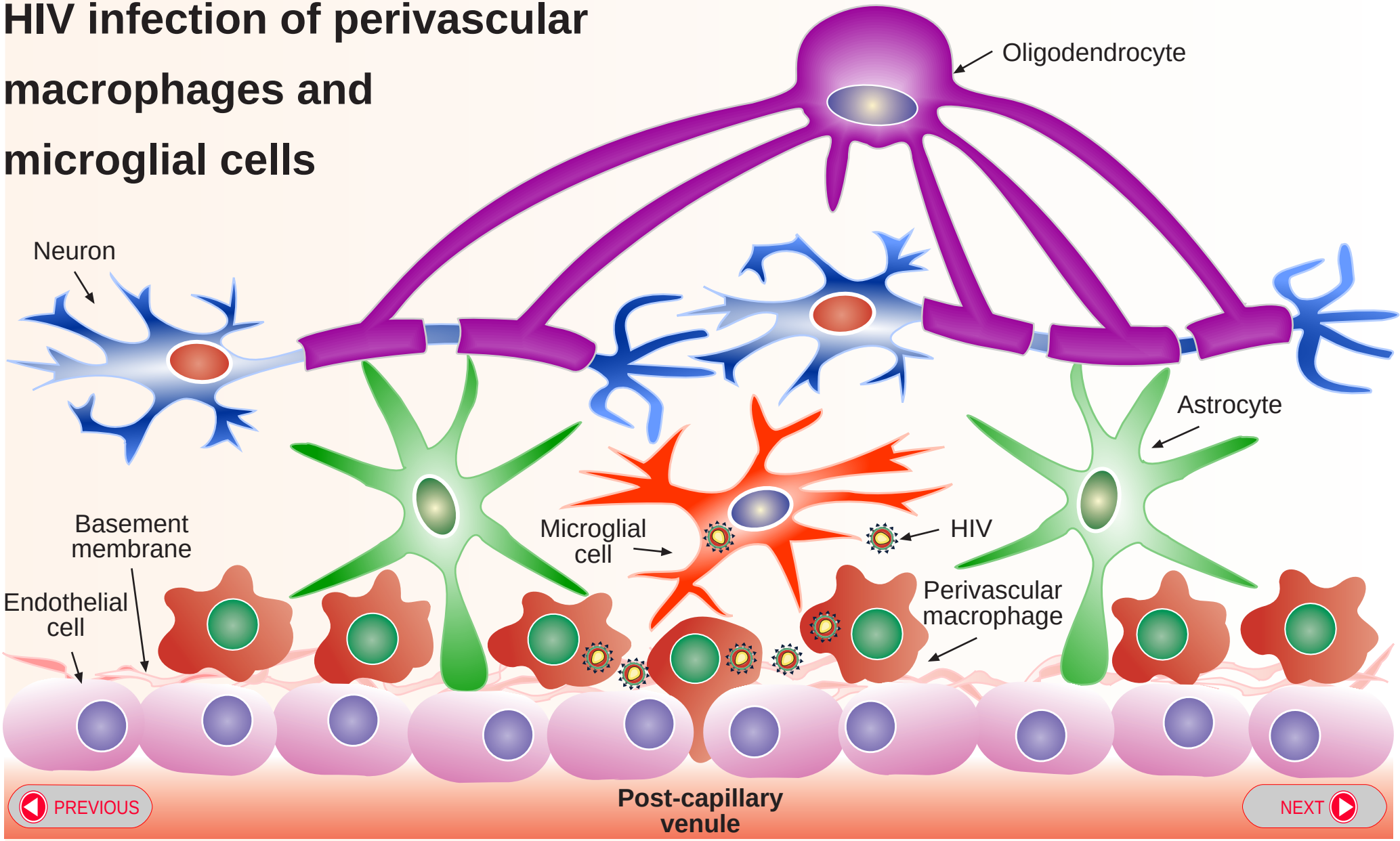
HIV infection of perivascular macrophages and microglial cells



PREVIOUS
NEXT

Once infected monocytes have entered the brain, they differentiate into resident perivascular macrophages or microglial cells which support virus replication well. Virus transmission to uninfected perivascular macrophages or microglial cells can also occur. Early penetration of the brain by HIV, however, does not result in active encephalitis and this is due to antiviral cell-mediated immune responses generated in the periphery that provide protection to the brain. In addition, the brain is an “immune privileged” site where T cell responses are regulated. HIV replicates most efficiently in activated CD4+ T cells whereas infection of macrophages and microglial cells is slow in turnover or latent.

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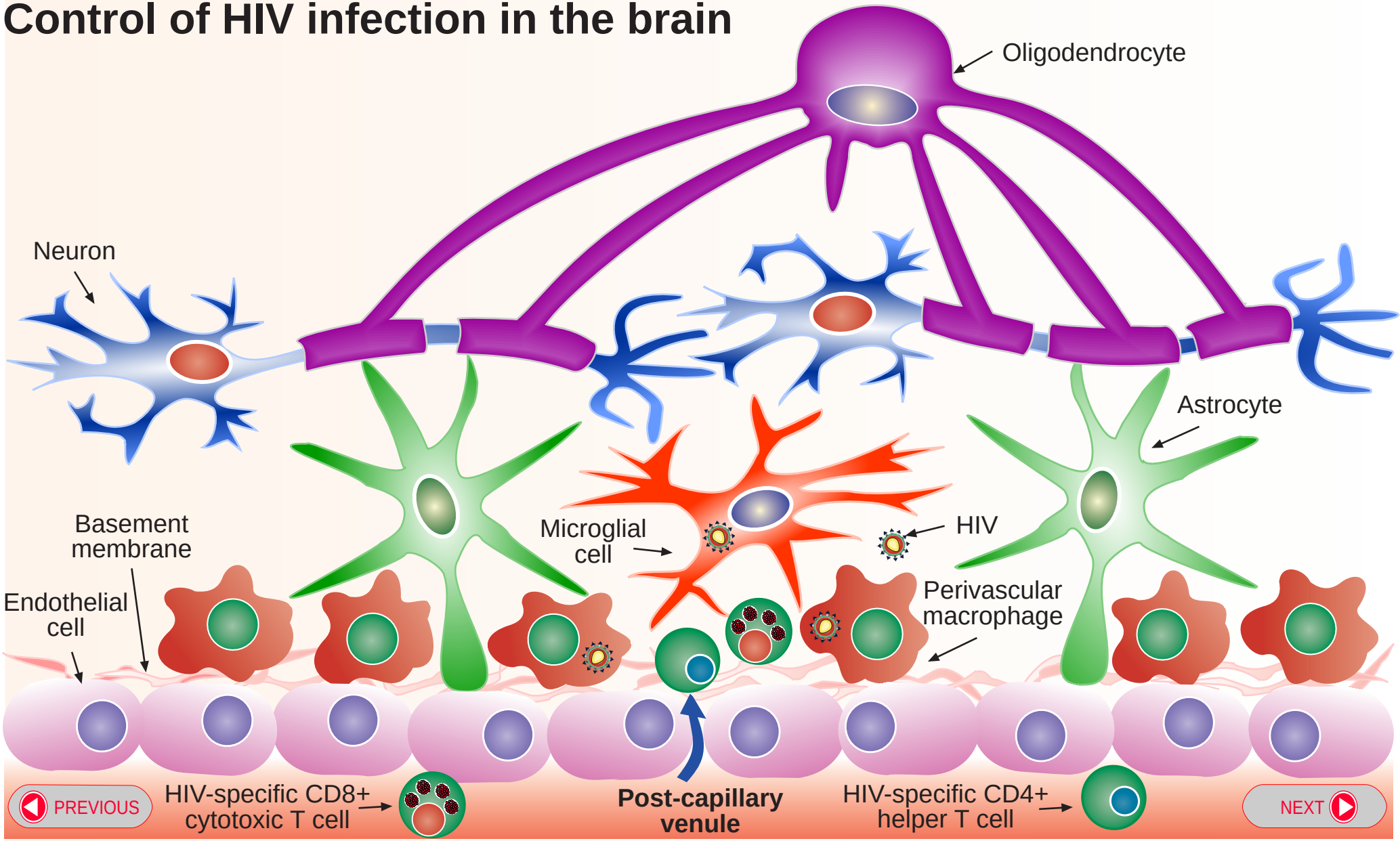
Control of HIV infection in the brain



Following penetration of the brain by HIV and infection of perivascular macrophages and microglial cells, HIV-specific CD4+ helper T lymphocytes and CD8+ cytotoxic T lymphocytes primed and activated in the periphery traffic to the brain and mediate control of HIV replication. In addition, excessive proliferation of T cells in the brain is regulated by suppressive mechanisms found in “immune privilege” sites which protects neurons and other brain cells from immune-mediated damage. Thus HIV replication in the brain does not progress and instead remains latent until the peripheral immune system weakens. HIV can then cause encephilitis which damages neurons and leads to HIV-associated dementia.

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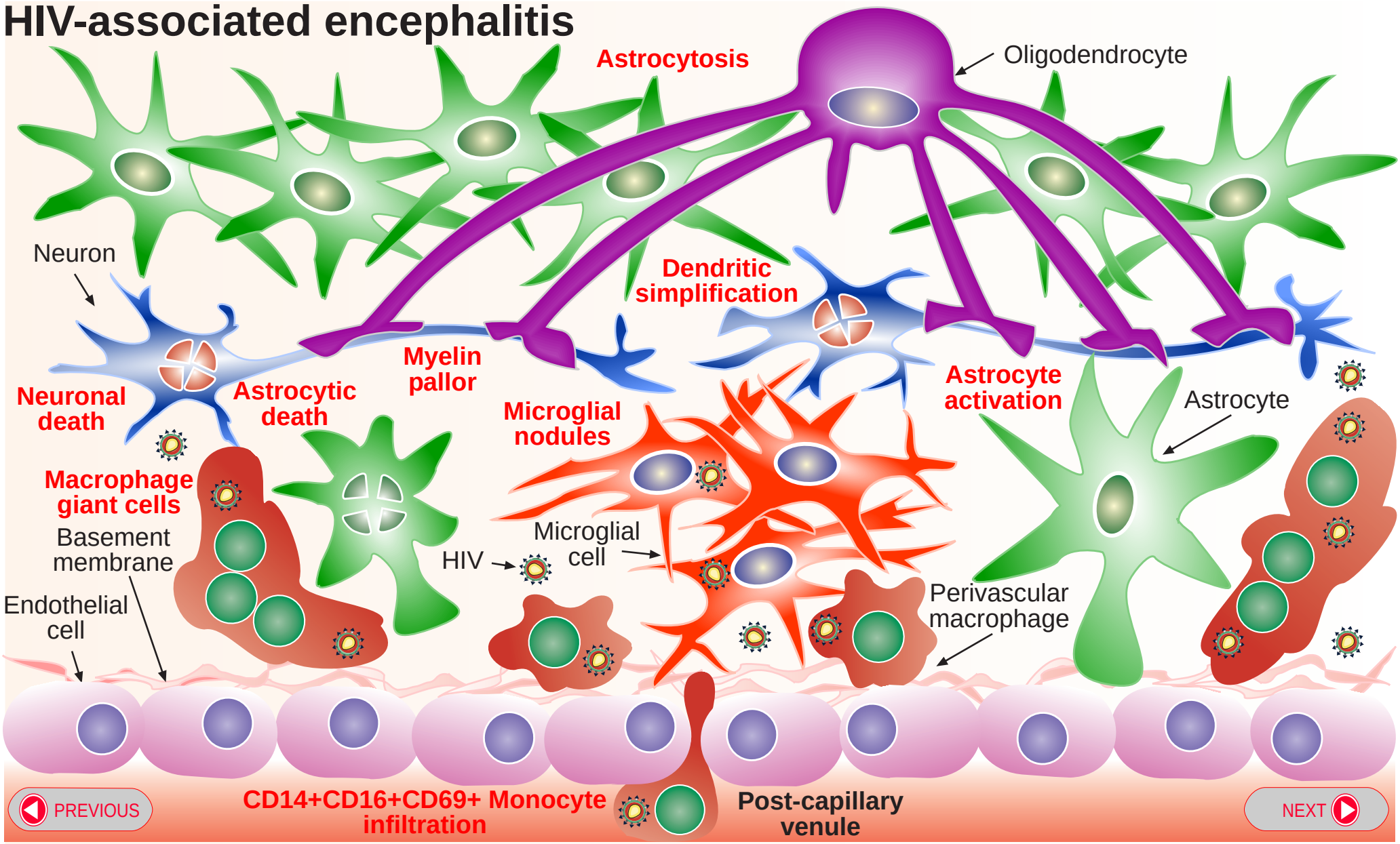
HIV-associated encephalitis



When peripheral immunity weakens, such as late in chronic infection or AIDS, control of HIV replication in the brain is also compromised. Increases in inflammatory responses overwhelm the immunosuppressive mechanisms that protect neurons from immune-mediated damage and results in neurodegeneration and AIDS dementia. Neuropathological manifestations include neuronal and astrocytic death, astrocyte and microglial cell activation, microglial nodule formation, dendritic simplification and demyelination, macrophage giant cell formation, viral replication in microglial cells and perivascular macrophages and increased infiltration of CD14+CD16+CD69+ monocytes (activated by gut-derived LPS) that re-seed the brain with HIV.

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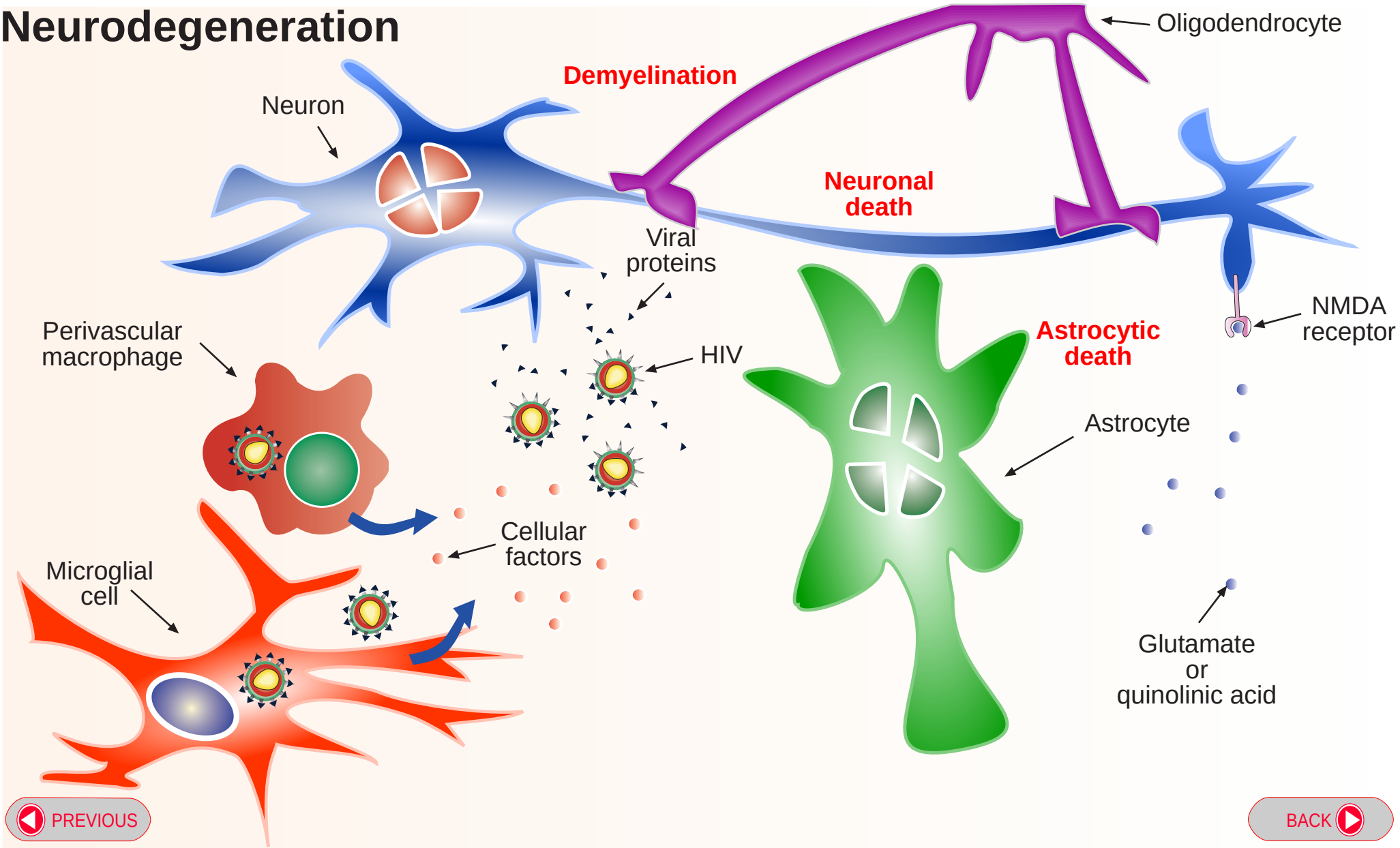
Neurodegeneration



PREVIOUS
BACK

Neurodegeneration is indirectly mediated by excessive pro-inflammatory immune responses as well as products of HIV replication. Neurotoxic factors such as quinolinic and arachidonic acids, nitric oxide, platelet activating factor, superoxide anions, matrix metalloproteases, chemokines, growth factors and pro-inflammatory cytokines are secreted by activated perivascular macrophages and microglial cells. HIV infected cells release neurotoxic viral proteins such as gp120, tat and vpr. Myelinating oligodendrocytes are damaged as well as astrocytes needed for glutamate uptake and maintenance of neurons. Excitatory molecules (glutamate and quinolinic acid) overstimulate NMDA receptors on neurons and promote apoptosis.

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