Journal of Infectious Diseases and Treatment
ISSN: 2472-1093

Open access Commentary

The Role of Proviral Reservoirs in HIV Persistence and the Challenge to Cure

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DESCRIPTION

HIV infection remains a significant global health challenge, primarily due to its ability to establish latent reservoirs of the virus that are resistant to the immune system and antiretroviral therapies. Despite the effectiveness of modern antiretroviral therapy (ART) in reducing viral loads to undetectable levels in the blood, the persistence of proviral reservoirs is one of the primary obstacles to curing HIV. Proviral reservoirs are long-lived, non-replicating forms of the virus that hide within various cells and tissues in the body, evading both the immune response and ART. These reservoirs contribute to the difficulty in eradicating HIV, as the virus can reactivate from these latent reservoirs if treatment is interrupted or if immune responses are weakened. Understanding the nature of proviral reservoirs, their composition, and the mechanisms by which HIV maintains these hidden sanctuaries is critical to developing strategies aimed at achieving a functional cure for HIV. The proviral reservoirs consist of infected cells that harbor the integrated HIV genome within their DNA. These infected cells can reside in a variety of anatomical sites throughout the body, including the lymphoid tissues (such as the lymph nodes and spleen), the central nervous system, the gastrointestinal tract, and even the bone marrow. In particular, CD4+ T cells, a type of immune cell that HIV preferentially infects, are known to be key reservoirs for the virus. These cells can harbor the integrated HIV genome for extended periods, often in a latent or non-replicative state. The virus remains dormant within these cells, evading immune detection and immune-mediated destruction. This latent infection can persist for years, contributing to the chronic nature of HIV. Importantly, while ART is highly effective at suppressing viral replication, it does not eradicate the virus from these reservoirs. ART primarily works by inhibiting the replication of HIV in actively infected cells, but it does not target the latent forms of the virus stored in the reservoirs. As a result, HIV reservoirs continue to be a significant barrier to achieving a cure. When ART is stopped, even after years of successful treatment, the virus can rapidly rebound from these reservoirs, leading to the reappearance of detectable viral loads and the return of disease progression. This relapse underscores the persistent challenge of completely eliminating HIV from the body. The mechanisms by which HIV establishes and maintains reservoirs are complex and not fully understood. One of the key factors is the ability of the virus to integrate its genetic material into the host cell's DNA, a process facilitated by the viral enzyme integrase. Once integrated, the viral DNA exists as a provirus, and it can either remain dormant or be activated at a later time. In the case of latent infection, the provirus does not produce new viral particles, but it can persist within the host cell, often for the lifetime of the cell. This latency is maintained through a combination of factors, including transcriptional silencing of the proviral genome and epigenetic modifications that suppress viral gene expression. There are several potential strategies being explored to eliminate or control HIV reservoirs. One approach is known as "shock and kill," which aims to reactivate the latent virus in reservoirs to make it detectable and vulnerable to immune responses or antiretroviral drugs. By using certain molecules, researchers hope to "shock" the latent virus out of dormancy, exposing it to the immune system or ART, which could then help clear the infected cells. However, this approach faces several challenges, including the risk that some reactivated virus may remain hidden or that the immune response may not be sufficient to clear the infected cells once the virus is reactivated. Despite the advances in understanding the role of proviral reservoirs, a complete cure for HIV remains elusive.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The author declares there is no conflict of interest in publishing this article.

Received:	30-October-2024	**Manuscript No:**	IPJIDT-25-22109
Editor assigned:	01-November-2024	**PreQC No:**	IPJIDT-25-22109 (PQ)
Reviewed:	15-November-2024	**QC No:**	IPJIDT-25-22109
Revised:	20-November-2024	**Manuscript No:**	IPJIDT-25-22109 (R)
Published:	27-November-2024	**DOI:**	10.36648/2472-1093-10.11.102

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Citation Raven T (2024) The Role of Proviral Reservoirs in HIV Persistence and the Challenge to Cure. J Infect Dis Treat. 10:102.