

Arden Nasveschuk - Abstract

The advent of effective combination antiretroviral therapy (ART) in 1996 has drastically improved the life expectancy for people living with human immunodeficiency virus (HIV). This development has shifted HIV from an acute condition to a chronic one, leading to a different set of health challenges in treating people living with HIV. Even when durably suppressed with ART, HIV infection is associated with a variety of chronic inflammatory diseases, including HIV-associated neurocognitive deficits and an increased risk of acute coronary syndrome. Researchers have suggested that persistent low-level transcription of defective HIV RNAs may drive these inflammatory conditions through activation of innate immune sensing pathways. Recent research suggests that defective HIV RNAs can be generated through intragenic transcriptional activity. HIV transcription typically originates in the long terminal repeat (LTR)—the canonical HIV promoter—at the start of the HIV genome. Previous work identified an intragenic promoter in the envelope region of HIV-1 that likely contributes to the generation of non-canonical defective HIV transcripts. This study utilized plasmid constructs to evaluate the importance of this internal element in HIV transcription and replication, specifically analyzing its role as a potential transcriptional enhancer. The results indicate that this intragenic transcriptional element significantly increases gene expression compared to control sequences that lack transcriptional activity when cloned in front of a minimal promoter and luciferase reporter. Since nearby promoters often interfere with each other, these results suggest that the envelope-region intragenic transcriptional element acts as an enhancer. This finding has implications for understanding the biochemical mechanisms of both canonical and non-canonical HIV transcription and eventually addressing the underlying cause of chronic inflammatory responses in people living with HIV.