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## **ANALYSIS OF THE TRANSCRIPTIONAL ACTIVITY OF HIV-1 LONG TERMINAL REPEATS FROM CENTRAL NERVOUS SYSTEM-DERIVED ISOLATES OF PATIENTS WITH HIV-1 ASSOCIATED DEMENTIA**

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**OBJECTIVES:** HIV-1 infection of the central nervous system (CNS) and resulting HIV-associated dementia (HAD) is an important complication in patients infected with HIV-1. Recent analysis of HIV-1 long terminal repeats (LTRs) derived from a number of autopsy brain tissues by our laboratory demonstrated unique promoter sequences in comparison to the peripheral tissues from the same patient. These data suggest unique regulatory mechanisms may exist in the CNS and impact upon the transcriptional activity of the HIV-1 LTR. Understanding the transcriptional regulation of HIV-1 in the CNS will provide valuable insights into the pathogenesis of HAD. In this study we examined the relative transcriptional activity of matched CNS and periphery derived HIV-1 LTRs.

**METHODS:** HIV-1 LTR sequences were PCR amplified from a cohort of seven HAD autopsy subjects consisting of matched CNS- (frontal lobe, cerebral spinal fluid, or spinal cord) and periphery- (lymph node, spleen, or peripheral blood mononuclear cells) derived isolates. The CNS and periphery derived LTRs were cloned into the pGL3-Basic luciferase reporter vector and transfected into the SVG astrocyte cell line and Jurkat T cell line. Transcriptional activity was assayed by luciferase activity in lysates prepared from the transfected cells. Sequence and transcription factor binding site analysis of the LTRs was also performed.

**RESULTS:** Nucleotide sequence and phylogenetic analyses of brain-derived and non-brain derived HIV-1 isolates showed that LTR sequences were compartmentalised to reflect the tissue of origin. Transcription factor motif analyses of these LTRs revealed differences in transcription factor binding motifs between CNS and non-CNS derived LTR sequences. Transcriptional activities of these LTR sequences suggested cell type specific variations in promoter activities. These data may suggest

adaptation of the HIV-1 LTR to brain associated transcription factors.

**CONCLUSIONS:** These data suggests unique transcriptional mechanisms exist within the CNS impacting on the transcriptional activity of the HIV-1 LTR promoter.

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HIV Diversity, Tropism and Compartmentalization

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