Human Immunodeficiency Virus Type -1 (HIV-1), a causative agent for AIDS is one of the most devastating infectious diseases to have emerged in the recent history. Since its first identification almost four decades ago, HIV-1 has been a major burden on public health and around 80 million people have been infected while around 36.3 million people have died due to the HIV-1 related cause.

A well-known therapy for HIV-1/AIDS includes a combination of several drugs targeting different steps of HIV-1 replication cycle known as antiretroviral therapies (ART). ART has been successful to control the infection, reduce the morbidity and mortality. However, ART is not curative as HIV-1 hides in infected cells by switching off its replication machinery and therefore become invisible to immune system recognition and therapy. This phenomenon is known as viral latency. Latent reservoir is a major barrier to HIV-1 cure as it can lead to viral rebound upon ART interruption.

A new strategy to eradicate the latent viral reservoir is “shock-and kill” therapy where latent virus is activated by latency reversal agents (LRAs) and therefore induce viral protein production followed by the elimination of infected cells by host immune system or infected cells die due to cytopathic effects. Despite “shock-and-kill” effects on reactivating virus from latency it fails to reduce the latent viral reservoir in clinical trails. The “Shock-and-kill” therapy mainly relieve transcriptional blocks to viral production but apparently do not act at post-transcriptional blocks.

A recently explored field known as epitranscriptomics involves covalent modification of RNA. Addition of methylation at N^6-position of adenosine (m^6A) is the most predominant modification. The m^6A modification of RNA affects RNA splicing, stability, nuclear export, and translation of RNA. Recently published studies and our preliminary results have shown that m^6A modification of HIV-1 RNA regulates virus production.

Here in this project, we plan to modulate the m^6A pathway to potentiate the viral reactivation from latency taking advantage of small chemical compounds. Aim of this project is to provide a proof-of-concept that modulation of post-transcriptional m^6A processes potentiates LRAs-mediated reactivation. Results from this proposal will open a window of opportunities to further develop target molecules relieving post-transcriptional epitranscriptomic blocks.