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A U5 repressor of reverse transcription is required for optimal HIV-1 infectivity and replication

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Here we provide strong evidence that a highly conserved stem loop structure in the U5 region of the HIV-1 RNA leader harbours a repressor of reverse transcription (RRT). We showed that two sequences in U5, at +143-145 and +151-153, are essential for RRT function. Mutation of either site strongly and unexpectedly increased endogenous reverse transcription, and cell infection assays showed that both mutations dramatically increased negative strand strong stop DNA synthesis. Early, late, 1-LTR and 2-LTR reverse transcription products were present proportionally, indicating that the downstream reverse transcription events were not affected. *In vitro* structural probing of the wild type and mutant RNA revealed an unexpected destabilization effect of the mutations on the whole U5 stem loop, which would explain the loss of regulation of reverse transcription. This functional effect was not observed *in vitro*, where, in the absence of viral proteins other than RT and cellular factors, all RNA performed similarly. These U5 mutations decreased virus replication in Jurkat and primary T-cells, which could be attributed to a marked defect in viral integration. Analysis of 1-LTR and 2-LTR circular DNA isolated from infected cells revealed that substantial deletions were present, indicating that the viral DNA was degraded by cellular nucleases. Together, our experiments suggest that regulated reverse transcription initiation is essential to allow synthesis of the viral DNA in a cellular environment that supports the assembly of a functional HIV-1 pre-integration complex, which also protects the proviral DNA from cellular degradation processes.