We previously described the polymorphism in the interferon regulatory factor-1 (IRF-1) gene as a novel correlate of resistance to HIV-1 infection in a Kenyan female sex worker cohort. However, the underlying mechanisms likely mediating this association remained to be elucidated. The initiation of HIV-1 long terminal repeat (LTR) transcription in peripheral blood mononuclear cells (PBMCs) from subjects with different IRF-1 haplotypes, representing protective, intermediate and the least protective IRF-1 allele combinations, were investigated here. A single-cycle pseudovirus construct expressing vesicular stomatitis virus envelop G-protein (VSV-G) and having an HIV-1 pNL4.3 backbone with luciferase insert was used to infect PBMCs with different IRF-1 haplotypes. The efficiency of early HIV-1 LTR transcription was monitored using a luciferase assay. IRF-1 protein levels induced by the infection were measured by quantitative Western blot. Our results showed that PBMCs with the protective IRF-1 genotype demonstrated significantly lower HIV-1 LTR transcription during the initial stages of infection compared to PBMCs with other haplotypes, which correlated with the kinetics of IRF-1 responsiveness to HIV-1 infection in the cells. It suggests that IRF-1 genotypes alter the efficiency of early HIV-1 LTR transcription, likely via modulating expression of IRF-1. This may represent one mechanism mediating the association between IRF-1 polymorphisms and resistance to HIV-1 infection.