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Volunteer Information Sheet for Rao *et al.* The RNA surveillance proteins UPF1, UPF2 and SMG6 affect HIV-1 reactivation at a post-transcriptional level. *Retrovirology. June 2018*

Volunteer donation of blood, generously provided by anonymous volunteers, allowed us to examine ways to better treat and possibly cure HIV. These study results were published in the journal of *Retrovirology* in June of 2018.

A major hurdle in developing a cure for HIV is that some amount of the virus hides in very small, yet threatening latent "reservoirs" in the blood and various other sites in the body (gut, lymph nodes, central nervous system, etc.). Virus in these reservoir cell types is not responsive or accessible to otherwise effective antiretroviral therapy (ART), nor to the control functions of the preserved immune system. ART extends life and reduces disease significantly, but when ART is stopped, the remaining HIV viruses in these "sleeping" or "quiet" reservoirs can again copy themselves after lying in wait and soon rebound throughout the entire body. ART and the immune system cannot "see" or control the hidden HIV until this rebound. The way that latency is established to create these reservoirs or is later perturbed to release awaiting HIV covers many biological steps starting from how virus acts to infect a cell, take over its genetic machinery, and then multiply by hijacking the copy process ("transcription") before emerging. Our study looks especially at the later steps, when HIV tries to finish transcription and emerge from latent reservoir. This focus on the later steps is a relatively new and, we think, underappreciated, area of study. One feature of our immune system is that it contains an "RNA quality-control mechanism" which uses proteins to identify and get rid of deformed RNA in order to prevent toxicity from accumulating within healthy human immune system cells. But viruses like HIV have developed strategies to bypass these RNA quality-control mechanisms of the cells they infect and also to invigorate or stabilize the virus' own instructions to copy, travel and survive at the expense of the human cell. Not all of these viral strategies are completely successful, however, and they represent a weak point in the ability of latent HIV to reactivate itself from viral reservoirs.

1) **What was the goal of our study?**
   This study investigates the role of the various RNA surveillance proteins in HIV latency by manipulating their presence or absence in cell cultures in the laboratory and looking for how HIV could emerge or stay hidden in reservoir cells.

2) **How is this study related to a cure for HIV? or to treatment for HIV comorbidities?**
   By understanding more about the role of surveillance proteins in HIV latency, researches can learn how to manipulate and control the activities of these proteins, and possibly in time, create new latency-reversing drugs that restore surveillance control to normal cell activity and to perturb the reservoir in a way where the immune system or ART could be made to see and kill the infection. This approach is often known as the "shock and kill" approach to a cure for HIV.

3) **Why are participant samples important to this research?**
   Peripheral blood mononuclear cells (PBMCs) used in this study were isolated from blood collected from people without HIV; we took those cells and created a separate laboratory space to infect them with HIV and recreate all the steps of latency and perturbation outside of the body.

4) **What was learned? What next?**
   The findings from this study inform efforts to bolster the reactivation of the HIV to decrease the size of the viral reservoir using a shock and kill approach. Additionally, this research informs efforts to develop effective latency-reversing agents (LRAs), a novel set of antiretrovirals. We would need to see how this process works inside of a living animal and then in people with HIV to be ultimately confident in our approach.