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**Treatment Action Group (TAG) Statement on Halted Merck HIV Vaccine Trial**

New York, NY, September 24, 2007 - The Treatment Action Group (TAG) today issued the following statement about the discontinuation of the STEP study, an HIV vaccine efficacy trial conducted by Merck Research Laboratories and the HIV Vaccine Trials Network (HVTN):

TAG is deeply disappointed by the failure of Merck's adenovirus-based HIV vaccine candidate to offer protection against acquisition of HIV infection or reduce short-term viral load levels in vaccine recipients that became infected.

HIV vaccine researchers have long sought a vaccine candidate that can reliably induce a type of immune defense called a killer CD8 T cell response, because CD8 T cells have been consistently associated with control of viral replication in animal models. Merck's vaccine represented a breakthrough because it was able to induce HIV-specific CD8 T cell responses (and the supportive HIV-specific CD4 T cells that are needed to sustain them) in the majority of people who received it. Hence there were sound reasons to hope that the vaccine might reduce viral load and slow disease progression to a significant degree.

The interim STEP study results show that this hope has not been borne out, raising critical and difficult questions for the HIV vaccine field as a whole. It will be crucial to analyze the outcomes in the STEP study in detail and assess how they might impact other HIV vaccine candidates in development.

Despite these disappointing results, TAG recognizes and salutes the work of the researchers at Merck and the HVTN who developed the vaccine and executed the trial, along with the thousands of trial participants who made the work possible by their altruistic contribution to the advancement of HIV prevention science.

In this regard, continued follow-up of STEP study volunteers is essential. Participants have already made a vital contribution to HIV vaccine research, but extended follow up of both vaccine and placebo recipients is crucial for obtaining data that can improve the chances of success in future trials.

While the failure of Merck's HIV vaccine represents extremely discouraging news for T cell-based HIV vaccines, it would be premature at this juncture to conclude that all such approaches are doomed to failure. Due to the difficulty of inducing effective neutralizing antibodies against HIV, most HIV vaccines currently in the pipeline aim to induce T cell responses.

The next planned HIV vaccine efficacy trial involves two constructs developed by the Vaccine Research Center (VRC) at the National Institutes of Health. Like Merck's vaccine, it includes an adenovirus component, but there are several differences in the approach that could potentially be important, including a "priming" immunization using a different DNA-based vaccine, plus several additional proteins (the envelope proteins derived from three different subtypes or clades of HIV).

These differences highlight some of the near-term options for HIV vaccine researchers in the light of Merck's results: exploring whether the quality – in other words, the functionality - of the T cell response induced by a vaccine is an important factor (i.e. DNA priming may lead to a qualitatively different T cell response) and also whether the parts of HIV included in the vaccine influence the outcome. Merck's vaccine included the HIV proteins Gag, Pol and Nef because these proteins are most frequently targeted by T cells *in infected people*. Strategies targeting additional structural and regulatory proteins from HIV also need to be evaluated.

A broad range of additional issues will need to be explored in detail in the coming months, including (but not limited to):

- Long term comparisons of the outcomes in vaccine and placebo recipients that became infected, including viral load levels, CD4 T cell counts and levels of immune activation.
- Correlations (if any) between the functional properties of the HIV-specific CD4 and CD8 T cell responses induced by the vaccine and the outcomes in the trial.
- The immune system genetics of trial participants, particularly HLA types which are an important genetic determinant of the ability to mount a T cell response against a given pathogen.
- The genetics of the infecting viral strains.
- The timing of the infections; there is some published evidence to suggest that the transient activation of CD4 T cells by the vaccine immediately after immunization could have a detrimental effect by providing more target cells for HIV (the study began with two immunizations just a month apart).
- Outcomes in women, who made up more than a third of the total volunteers in the trial.
- Outcomes in the 1,500 study participants not included in the interim analysis that has been reported; these individuals had higher titers of antibodies against the carrier construct used in the Merck vaccine, a type of adenovirus which (in a non-weakened natural form) causes severe colds.
- The implications of the results for future of use of the SIV/macaque challenge model in HIV vaccine development.

TAG also urges all involved parties to ensure that the data from these studies are thoroughly analyzed and made available to scientists whose specialist knowledge about T cell biology and immunology may be able to shed light on the outcomes. We note that the two prior AIDS vaccine efficacy trials (conducted by a company called VaxGen)

represented a potential trove of data on the factors associated with acquisition of – and, possibly, protection against – HIV infection but that very little information from these studies has been presented and published. This cannot be allowed to happen again. One of the implications of Merck’s results is that vaccine challenge studies conducted in macaques are not predictive of what happens in people, making the information from vaccine and other prevention studies even more important to the future research effort.

TAG recommends redoubling efforts to develop effective neutralizing antibodies against HIV and efforts to understand and mimic the success that has been obtained in animal models using live attenuated vaccines. TAG also stresses the need to encourage novel thinking about approaches to HIV vaccination, and are seriously concerned that large “big science” mechanisms such as the Global Vaccine Enterprise and the Center for HIV/AIDS Vaccine Immunology may be ill-equipped to support truly innovative investigator-initiated research efforts. Additional incentives to innovation in HIV vaccine research need urgent consideration.

TAG will continue to review and comment on the results of the STEP study as more details become available.

For ongoing coverage and commentary of this and other issues in HIV science, visit TAG’s Michael Palm Basic Science, Vaccines and Prevention Project blog: <http://tagbasicscienceproject.typepad.com>

About Treatment Action Group (TAG):

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive life saving treatment, care, and information.

We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policymakers to end AIDS.