



**Memo: Step ancillary studies update and specimen availability for infection cases
January 2009**

Over the past year, the Step Scientific Review Committee (SRC) has reviewed 22 proposals and recommended seven as high priority studies to gather more information to explain the Step study outcome. Eight proposals were considered of potential interest but could be conducted using specimens from related HVTN trials rather than Step or required additional information to support the rationale for use of valuable Step specimens. The remaining seven were viewed as low priority, based on scientific rationale or because similar studies were already in progress within the HVTN or Merck laboratories. A summary of the SRC comments and recommendations were provided to each applicant. The HVTN has initiated joint institutional Material Transfer Agreements and other regulatory compliance documentation with investigators who have or will receive specimens; these documents have been finalized in most cases. A summary of the fifteen accepted proposals (seven of high priority and eight “of interest”) is provided in the Table below.

One major study approved by the SRC is viral sequencing and analysis of the earliest blood HIV isolates in Step cases (study participants who acquired HIV infection after study week 8). In preparation for plasma distribution to the viral sequencing laboratories, it was discovered that plasma from Step cases that should have been stored from visit time points after HIV-1 diagnosis (from visits immediately after confirmation of HIV infection up to 6-18 months post-infection) were mistakenly discarded at Merck’s contract diagnostic laboratory. This error was due to a misunderstanding regarding the retention of leftover plasma aliquots once the primary testing for HIV viral load had been completed. The protocol had specified that samples be tested for HIV RNA at multiple timepoints post-infection and that those samples with an HIV RNA viral load >5000 copies should be retained for further testing. As this error only affected samples collected after confirmed infection, plasma samples from earlier time points, including the initial sample when HIV infection was first diagnosed in a given subject, were retained properly. In addition, all laboratory tests (including HIV RNA quantification and CD4 cell count estimation) specified at the protocol at each time point were performed. Once this unfortunate circumstance was identified, steps were taken in March 2008 to make sure that the appropriate plasma aliquots were retained. Post-infection plasma, if collected, should be available when indicated for study visits occurring after March 2008, and to date the HVTN Laboratory has received partial shipments of the post-March 2008 specimens. Of note, serum from post-infection time points was not collected and stored, as this was not listed as a required specimen in the study protocol. In short, viral load measurements during the diagnostic and post-infection period are not impacted by this error, but plasma samples from post seroconversion time points scheduled to occur between the inception of the trial and March 2008 are not available for most HIV-1 infected participants.



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PBMC were successfully isolated and stored at both pre- and post-infection time points designated in the study protocol. To date, the SRC as well as the HVTN Laboratory Sciences Advisory Committee have recommended that these stored PBMC be evaluated for T cell responses, especially for defining epitope specificities relative to the infecting viral strain of these individuals. These studies will be performed by the HVTN laboratories in collaboration with the Mullins and McCutchan laboratories.

The Step trial partners (Merck, NIAID/DAIDS, and HVTN) regret that for a significant period of time in the Step trial, post-infection plasma samples are not available for additional analyses. We hope that sufficient information will be gained from longitudinally collected post-infection plasma from cases identified after March 2008. Furthermore, this problem does not impact the specimens (plasma, serum, PBMC) from cases in the Phambili trial. The Phambili specimen processing and repository activities were contracted and managed by the HVTN with different laboratories using a different protocol.

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Table 1: Proposals approved by the Step Scientific Review Committee involving specimens from Step or related trials evaluating Merck candidate HIV vaccines.

Applicants	Title of Proposal	Institution
Francine McCutchan Jim Mullins	Sequencing and Analysis of Viral Breakthroughs in Step Trial	Henry Jackson / University of Washington
Dan Geraghty	Host Genetics HLA class II and KIR typing	FHCRC / NCI
Dan Barouch	Ad Seroprevalence in the Step Study	Brigham and Womens Hospital
Tuofu Zhu	Determination of the adenoviral vector persistence in PBMC and purified populations of potential Ag-presenting cells after Ad5 vaccination in Ad5 vector vaccinees	FHCRC/UW
John Moore	HIV-1 specific IgG isotype serology in infected volunteers from the STEP study	Cornell University
Otto Yang	Potential CTL failure mechanisms in STEP	UCLA
Donald Forthal	Does Ad5 Gag-Pol-Nef Vaccination Elicit Antibodies that Enhance HIV Infection	University of California, Irvine
David Goldstein <u>Collaborators:</u> Norman Letvin, Bart Haynes, Mary Carrington Dan Geraghty	Proposal for a host genetics genome-wide association study on the STEP samples	Duke University Submitted on behalf of CHAVI
Michael Heckerman Bruce Walker <u>Collaborators:</u> Jonathan Carlson (Microsoft), Christian Brander (PARC)	Are CD8 responses to decoy epitopes partially responsible for increased susceptibility to infection among vaccinees in the STEP study	Microsoft Corporation / Harvard Medical School (PARC)
Michael Katze	Transcriptional profiling of archived PBMCs to characterize vaccine and placebo recipients as a function of baseline Ad5 titers	University of Washington
Gary Nabel	Analysis of the specificity of neutralizing antibodies to Ad5 and correlation with vaccine-induced immunity and infection in the STEP study	NIH – VRC
Janardan Pandey	Genetic Regulation of Humoral Immunity to HIV and Ad5 Epitopes	Medical University of South Carolina
Ha Youn Lee	Quantitative assessment of Ad5-HIV gag/pol/nef vaccine efficacy based on activated CD4 T cell level, calibrated transmitted HIV specific CD8 T cell level, and viral load at set point	University of Rochester Medical Center
Jill Gilmour <u>Collaborators:</u> Peter Hayes, Bruce Walker, Julie McElrath	Evaluation of HIV-1 vaccine potency and potential efficacy by measurement of CD8 T cell mediated inhibition of HIV-1 in vitro	International AIDS Vaccine Initiative
Minh Dinh, Thomas Hope	Effects of HIV-Ad5 Vaccine on HIV interactions in the Male Foreskin	Northwestern University