

To: Laboratories supporting the ACTG, IMPAACT, HPTN, HVTN, and MTN
From: The Cross-Network Laboratory Focus Group
CC: The DAIDS Clinical Laboratory Oversight Team
Re: Viral load platforms for HIV clinical trials
Date: February 6, 2009

The Cross Network Laboratory Focus Group (LFG) is responsible for oversight of laboratory activities for the following NIH-sponsored HIV clinical trials networks: ACTG, HPTN, HVTN, IMPAACT, and MTN. In the past few months, the LFG has worked with the DAIDS-sponsored Viral Quality Assurance (VQA) laboratory to evaluate the two FDA-cleared HIV viral load platforms based on real-time PCR, the Abbott RealTime Viral Load Test on the m2000 system (Abbott RT/m2000 assay), and the Roche COBAS Ampliprep/COBAS Taqman HIV-1 version 1.0 assay (Roche COBAS AP/TM v1.0 assay), for use in our clinical trials.

First, we would like to emphasize that Roche Diagnostics has made a formal commitment to continue to manufacture the Roche COBAS AMPLICOR HIV-1 MONITOR v1.5 assay, the Roche AMPLICOR HIV-1 MONITOR Microwell v1.5 assay, and AMPLICOR HIV-1 DNA assay for our existing Network protocols, so that we may complete these protocols without interruption, and to continue to provide support for COBAS AMPLICOR systems. The LFG has provided Roche Diagnostics the estimated numbers of such kits that are needed to support existing protocols over the next several years. There is currently no plan to change the requirements for viral load testing for trials that are already in progress, or are about to start. Those trials would continue to use the currently specified viral load platforms.

For future protocols (ACTG A5257, IMPAACT P1081 and those opening in mid-2009 and beyond), the LFG recently prepared a consensus recommendation that was reviewed and approved by the leadership of the five networks. For ACTG, IMPAACT, HPTN, and MTN trials, sites will be asked to use of the Abbott RT/m2000 assay for all primary endpoint determinations for protocols initiated in mid-2009 and beyond. This recommendation applies to testing performed at US and non-US clinical trial site laboratories, as well as the centralized Network Laboratories in the US. In some cases, this will require international sites to ship primary endpoint samples to other laboratories, if they do not have the Abbott RT/m2000 assay in place. Note that either of the two assays (the Abbott RT/m2000 assay or the Roche COBAS AP/TM v1.0 assay) may be used for non-endpoint viral load determinations at the discretion of the protocol teams, with the approval of the appropriate Network Laboratory. For HVTN protocols, sites should contact their Primary Network Laboratory (PNL) to determine which viral load platform(s) should be used.

Roche Diagnostics is planning to release a new version of the Roche COBAS AP/TM (v2.0) in the near future. This was one factor in the LFG's decision to recommend the Abbott RT/m2000 assay for primary endpoint determinations. We did not feel that it would be appropriate to start new protocols with the COBAS AP/TM v1.0, and then switch to the v2.0 assay in one to two-years time. Moreover, without additional comparison data, we could not support using both the Roche COBAS AP/TM v1.0 and Abbott RT/m2000 assays for endpoint determinations. The LFG will consider use of the Roche COBAS AP/TM v2.0 assay for primary endpoint testing after this assay has

received FDA-clearance, has been validated by the VQA Program and compared to the Abbott RT/m2000 assay in a head-to-head comparison using existing, well-characterized samples from existing virologic endpoint studies. Such a comparison will be needed to determine whether the two assays can be used interchangeably for endpoint determination in our protocols. Both of the real-time viral load platforms performed better than the current Roche AMPLICOR HIV-1 MONITOR assays in terms of assay precision. For this reason, we felt that it was important for the networks to transition to one of the two new PCR platforms for our upcoming 2009 protocols, rather than waiting for FDA-clearance and VQA validation of the COBAS AP/TM version 2.0 assay. There were a number of other issues that the LFG considered in our recommendation of the Abbott RT/m2000 assay including: access to residual (dead-space) sample for other studies, option to test lower volume samples, option to perform manual specimen preparation, and overall suitability of each platform for non-blood compartment samples and dried blood spots, as well as other issues.

In summary, sites should continue to use the protocol-specified viral load assays for current trials. For trials opening in mid-2009 and beyond, sites should be prepared to test primary endpoint samples with the Abbott RT/m2000, either on-site, at an approved back-up laboratory, or at a central testing laboratory (e.g., Johns Hopkins University for ACTG protocols), depending on the protocol. The Roche COBAS AP/TM v1.0 may be used for non-endpoint testing in some circumstances. Any HIV viral load platform must be validated before it is used for protocol testing. Please contact your PNL to discuss any issues relevant to this new recommendation, and its implementation for future network protocols at your site.