

Global Surveillance of HIV Diversity and Evaluation of Test Performance Using Viral Panels Derived from Recently Infected Blood Donors

HIV continues to spread epidemically in most regions of the world. Due to its quasispecies nature and high rates of error-prone replication, hypermutation and recombination, HIV-1 has evolved into 7 major clades and over 25 circulating recombinant forms (crfs). This rapid evolution of HIV presents serious challenges for vaccine development and for maintaining sensitive serological and nucleic acid tests for blood screening, epidemiological surveillance and diagnosis and clinical management of infected persons. For example some NAT screening and viral load platforms amplify different genetic targets (Roche = Gag; Abbott = Pol; Gen-Probe/Chiron = Gag and Pol) of the virus which could contribute to documented failures on donor NAT and variations in viral loads observed with different assays. Some of the viruses previously used to evaluate assay performance were not pure strains but rather chimeras (e.g. most clade G are A/G recombinants) as it is common practice to sequence one or at most two genes to identify which clade the virus belongs to. Moreover, the virus panels that are currently available for assay development and evaluations were isolated more than a decade ago. This has two important implications. First, the viruses that are currently in circulation have significantly evolved and recombined in the human population over the past decade. Second, the current panels are incompletely characterized in molecular terms which make it difficult to know if assay comparisons are valid. Therefore, a set of fully characterized viruses derived from currently circulating strains are needed for developing new assays, validating platforms, and to assist regulatory bodies in evaluating assay performance.

Early in 2008, a working group was initiated to determine the feasibility of generating a standardized set of viral panels for use in validating NAT platforms. The group supports the concept that the monitoring and characterization of divergent HIV isolates needs to be performed on an ongoing basis in order to keep up with viral evolution. It will be critically important to identify and quantify extent of spread of new recombinants on a global basis for several reasons. First blood screening and diagnostic assays are sold in the global market by a limited number of test vendors. Second trials for assessing vaccine and microbicide products are conducted in regions that are a hot bed of viral diversity. A further concern is monitoring drug resistance, especially with the expanded use of therapies in resource-limited settings and the introduction of new treatments with novel mechanisms of action.

The working group would prefer to use plasma instead of viral isolates as it is more real world and the panel descriptors can also include serological assay performance characteristics. This should be achievable for common strains that make up the majority of HIV infections but will be more difficult for rare strains, for which labs may have to rely on viral isolation in culture and utilize those isolates for constructing the panels. Based on input from participating Transfusion Medicine experts, the working group believes that blood banks around the world are uniquely positioned to contribute to this important global HIV surveillance and test evaluation program. Blood banks detect thousands of HIV infected donors annually, and can discriminate recently infected donors based on RNA and early seroconversion antibody positive (i.e. LS-EIA negative, WB positive) characteristics, thus allowing for identification of plasma components from donors with recently transmitted/acquired HIV infections. Plasma from recently infected donors detected by incidence assays can also be studied to characterize and track viral diversity and drug resistance in recently transmitted viruses around the world. This kind of surveillance is already in place in the US, Brazil, South Africa and France, and could be implemented in other countries of particular interest such as Thailand, India, China, E Europe and selected African countries. HIV infected plasma samples/units from blood donor populations from regions of the world with diverse HIVs also provide a unique resource for estimating window periods for

incidence assays (detuned EIAs, BED, avidity tests) and for obtaining large volumes of HIV seropositive plasma for development, validation and quality control of these important assays

Although the need and opportunity are compelling, there are several scientific, funding and logistical issues that need to be addressed. NIH is supporting this initiative by funding labs in the US, South Africa and South America to characterize (i.e. in biological, serological, and molecular terms) strains, and has partnered with a repository to manage, store, construct, and distribute panels to any lab interested in evaluating, comparing or validating HIV viral load platforms. It is anticipated that this effort will be tied in with current monitoring and surveillance programs coordinated by WHO and in the EU, national blood donor programs and organizations (such as GCBS), research institutions and industry to obtain recent HIV positive samples to fully evaluate. With respect to blood bank participation, pressing problems include obtaining funding for coordinating the effort and for local blood bank collaborators who will contribute HIV+ plasma units, as well as working on IRB approvals for samples to be transferred out of countries as well as shipping and transportation logistics. We have several federal agencies that are participating including NIH, FDA, USMHRP, PEPFAR and CDC, together with CHAVI, IAVI, academic researchers and public blood centers around the world. We are in the process of involving non-profits, such as the Gates Foundation, and requesting logistical support from WHO which has been supportive of our efforts.

The working group is cognizant that this will be a collaborative effort between US-based researchers and health care professionals in the affected countries. The NIH will make every effort to involve scientific participation with all researchers and encourage further interaction with in-country scientists. The group will be willing to share data with the researchers or MOH of the host country so that they can better understand what new recombinants or strains are currently circulating within the population. Finally, the program could supply the participating labs with limited numbers of panels for their own use. Our intent is to be able to supply the entire HIV field with relevant and fully characterized global HIV strains for evaluating assays, validating platforms and regulatory activities. This effort would be very useful in the near future as labs start validating different nucleic acid assay platforms for use as an endpoint for developing a vaccine and for therapeutic intervention. Clearly this is a long-term program, since viral panel development will need to be revisited on an annual basis to evaluate viral genetic diversity on a global scale and to supplement the panels with newly emerging isolates.