GLOBAL STANDARDS OF LABORATORY PRACTICE FOR HIV TESTING

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Introduction and Background

This discussion will focus on standards in laboratory practice globally, rather than global standards because attaining the latter may be impossible. There are many different standards of testing and different ways of interpreting results. Therefore, it becomes very difficult to compare results across networks. HIV testing is conducted for diagnosis, blood screening, epidemiology, for global vaccine studies, clinical trials in countries other than the U.S., etc and in many different laboratories with differing standards. Thus, the adoption of standards globally is highly relevant to the success of testing outcomes.

1. Standards for HIV testing

Definition of Standards

Standards ensure that no harm results from poor quality tests or testing, and that outputs and outcomes are generally of the highest quality. The definition of standards that I will use is "standards are consensus guidelines on how to achieve and maintain agreed and acceptable levels of performance." A "consensus" is important because this sets the minimum acceptable performance level. Secondly, "agreed and acceptable" are also important because unless the group that is actually applying the standards participates in developing them, they will not be adopted universally or maintained. Once these are set, then the laboratories that perform best within the standards establish the benchmark performance level.

To attain best practice we could propose inventing a set of global standards. These could be quantitative standards. For example, we could stipulate that only the use of tests with 99.5% sensitivity and specificity would be acceptable. This would seem impractical and not allow for those who at the time of adoption of the standards were unable to meet the quantitative limits. Therefore quantitative standards could not be applied at a point in time or met globally and they may be achieved without other standards such as safety standards or quality performances being met. Alternatively, qualitative standards could be applied to account for the variations seen in laboratories, samples etc. I propose here that qualitative standards including "consistency", "reproducibility", "traceability", and "efficiency" (or cost effectiveness) for HIV testing could be adopted globally. Consensus and agreements could then be established between laboratories or within areas or regions on how these qualitative standards could be met. A standard performance level could be created for a given network or region allowing for continuous improvement. Networks could ensure an environment of constant improvement and comparison and perhaps may be measured quantitatively in the future.

If we accept that the setting and maintaining of standards is a collaborative and collegiate effort we must invoke other groups in addition to laboratory personnel (Fig 1). We have found in setting up regional or network quality assurance programs that if we involve groups other than laboratory personnel that we have greater success. Regulators and sponsors of the test

kits are important to draw into the development of standards as well as the governmental infrastructure.

Difficulties in conducting HIV testing in under-resourced areas

The objective of the present paper is to describe standards for HIV testing that could be used globally. We should remember that HIV testing has established the benchmark in performance for all testing in medicine in well-resourced countries. The tests are highly quality assured both at the manufacturing and testing level in well-resourced countries. Difficulties in conducting HIV testing in under-resourced areas are enormous. The levels of standards accepted in well-resourced countries or networks are not attainable without resources (money, training, delivery systems, support, government regulations and so on). Apportioning resources for these commodities are not high priority in under-resourced countries - they cannot be! Therefore in proposing standards that are to be useful globally these differences and as near to cost neutral approaches as possible must be taken into account.

2. Achieving Standards Globally - the Infrastructure

While individual laboratories anywhere in the world may deliver an excellent performance, if we want the standard of "excellence in performance" to disseminate fully, then we must have suitable infrastructure in all areas (Fig 2). Regulations or even laws may be required to maintain and perpetuate the standards. Interactions with manufacturers and suppliers are necessary. Such infrastructure, or even parts of it, is not often found in under-resourced countries. Many of the bodies that develop and promote standards do not operate in under-resourced areas. There are no resources to achieve or enforce the standards they require. There is no infrastructure for supporting the quality assurance that these programs demand.

It is reasonable to propose that a major mechanism to assure that standards are established and maintained is the use of quality assurance programs. The use of quality assurance programs is the mechanism to disseminate, promote, perpetuate and document standards. The mechanisms for assuring quality are qualitative and can be adopted generally. Quantitative outputs for assessing performance are a requirement of quality assurance programs. Eventually, standards may be achieved throughout a region through the judicious use of quality assurance programs.

What or who is setting the standards presently?

There are a number of bodies whose function is to develop and assure standards, such as the International Organization for Standardization (ISO) or EN series of guidelines. Then there are government bodies that enforce standards, such as Good Manufacturing Practice or CLIA ‘88. There are peer reviewers, such as American and Australian Colleges of Pathologists, and commercial bodies now who are applying standards and offering standards in accreditations. International groups conducting studies or trials, etc. can exert international pressures to foster the development of standards globally (Fig 2). While all are of importance, none has the ability to achieve standards globally. On the other hand, if the proposed qualitative standards were the tenet of each group this would promote standards to be attained globally.

3. Differences between the standards in under-resourced and well-resourced areas

The Elements of Quality Assurance

The elements of a Quality Assurance Program are shown in Figure 3. Each element of a quality assurance program requires resources. Samples that are appropriate with capacity for their storage are necessary.

Collection of such samples is difficult, even in countries like Thailand where there is a huge number of HIV infected people. It was difficult to set up evaluation panels, because of various morays and lack of government support for this function. They required regulations. Facilities for data collection and processing are required. You understand how difficult some of these elements are to arrange in the United States or Australia. What about their arrangement in the countries in which we plan clinical and epidemiological studies?

Governmental Support

To institute quality assurance programs, especially in under-resourced countries, it has been almost impossible to gain government support. Laboratories and issues of testing are often incidental and of no interest to government. But this interest is crucial to adopting standards globally for HIV testing. In well-resourced countries governments are becoming more and more involved in regulation through adoption of standards.

Setting Standards in Under-resourced Countries

There is a range of difficulties in setting standards in under-resourced countries. Laboratory facilities may be extremely poor and grossly under-funded. Often there are a variety of laboratories with differing performance levels. The laboratories may have differing needs and different problems. The basic requirements of water and electricity may not be available. Equipment, supplies and maintenance may be poor. Supplies and shipment of goods and samples may be impossible to secure with regularity. The availability of trained and suitable personnel in sufficient numbers may not be optimal. Safety procedures may be non-existent or poorly developed. Somehow these difficulties must be taken care of and in a manner that is achieved by consensus. Where there is a lack of government supported infrastructure the difficulties are accentuated and mechanisms to overcome these are burdensome and often seem impossible.

In under-resourced areas, we have to be very careful how we place our well-intentioned means and how we can place them into the infrastructure and context that exist.

Evidence for the Difficulties

Using a high quality photograph of a subjectively read particle agglutination assay, we investigated variations between readers and laboratories. The differences we saw are probably true of all subjectively read assays which are used widely. Often we see problems in reading assays when they are first introduced. Extrapolating from these results we can predict that differences may arise from inexperience and lack of proficiency with reading other subjective tests, such as Western blot (Fig 4). The experiment that we performed with the particle agglutination assay could equally well apply to Western blot, another subjectively read test. If there are differences between readers, differences between laboratories, and differences between blots, and then differences in interpretation criteria are added, it is not difficult to imagine that errors in HIV diagnosis are occurring

In our overseas Quality Assessment Program (QAP) there are around thirteen laboratories that use Western blots. Only five of those use appro-

priate criteria for the immuno-blots they use. (Fig 5). The rest use criteria that originated through the WHO, CDC, APHL (formerly ASTPHLD), and the NRL. Developed countries with their laboratory practices exert an enormous amount of influence on laboratories in under-resourced countries. Furthermore evaluation and protocol development procedures may not be followed when variations occur.

The NRL Australia sends out regional QAPs two to three times a year. Examination of results that differ from reference results (discrepant results) show that when the assays are first introduced the discrepancy rates are high and then they fall off gradually, as the assay or technique becomes better known to the laboratories (e.g. in 1991 the results were 13.33% discrepant with rapid assays compared with no discrepant results reported in 1997). The underdeveloped countries may adopt new tests, but not necessarily the standards, proficiency or training levels that well-resourced areas may use when the assays are introduced. So the discrepant results for the regional laboratories overall are around 2.7%, 1.4% in the positive samples; and 4.8% in the negative samples. The results could be explained by changes in assay quality with time but the same trend is seen for all assays whenever they were introduced. Discrepancies also occur in interpretation (Fig 4) and so exaggerate the discrepancy between assay performances.

4. Methods to achieve quality standards globally

When this evidence is put together, we can see that laboratories in under-resourced countries often are missing influences including quality assurance, training, government support etc. Therefore, the only useful pressure to adopt standards may be international pressure. It is very important that local infrastructure is used and in raising standards globally, that we exert pressures on the local infrastructure. I propose that methods for achieving quality standards globally must emphasise the importance of international pressures. The types of pressures include the demand for conforming to or adopting standards, or at least being aware of these. Six years ago in workshops, delegates had little idea of what a "standard operating procedure" was, but now they are well informed about quality systems. Our QAP demonstrates that laboratories are keen to adopt and promote improvements (or standards).

There is a great opportunity while there are so many international studies in progress, to exert these pressures for adopting standards globally. Clinical trials and research improve this opportunity and should use local personnel and laboratories in under-resourced countries wherever possible.

The development of international standards requires putting together quality assessment programs and other quality assurance mechanisms for wide ranges of laboratories. Training assumes certain standards. So when training is delivered, we should assume and impart the appropriate descriptions of standards and other methods by which they can be attained.

There are a variety of international quality assurance programs, and laboratories in under-resourced countries should be part of those. We need to promote regional networks and conduct workshops and training to transfer technology that is appropriate. We need to provide sustainable solutions to problems. We need to provide infrastructure where possible. Biosafety training should assume priority. Regional quality assurance programs, collaboration with manufacturers, and testing strategies that are appropriate to meet regional needs need to be set up and supported. We should not transfer the testing strategies used in well-resourced countries, fine as they may be. There are more appropriate ones for under-resourced countries. We have extraordinary expectations of HIV testing in well-

resourced countries. We must transfer those expectations to developing countries.

Many countries now demand that an HIV test is done before someone can immigrate. It should also be demanded that the appropriate standards are observed and demonstrated.

We should promote demonstration models. In 1989, the Thai group that we have been working with started participating in the quality assessment program from NRL, and as you know, it was around this time that they recognized what an incredible problem they had with HIV infection. In 1994 they decided they were going to set up a national reference laboratory and there was a consultancy to develop a quality assurance program and evaluations for their kits. At the same time, they introduced a law to say that the kits had to be evaluated. In 1995 there was another consultant to advise on quality assurance panels, and on quality assurance generally, the use of the results, etc. They developed their own HIV testing policy with guidelines. In 1998 they have changed their notification policy or their law, so that their evaluation of their kits is now going to be conducted in larger panels. They have developed a Thai accreditation body for the laboratories, and Thai staff are for the first time acting as consultants within the region. Within 1999 that national laboratory will pursue accreditation on an international level. Licensing is now required for all screening tests in Thailand. Over the last few years 44 HIV kits have been evaluated. Before all this happened there was exploitation of Thai laboratories. The Thai system is working toward standards that include consistency, reproducibility, traceability and efficiency.

In summary, I have tried to: 1) describe the standards (consistency, reproducibility, traceability and efficiency) that I think are appropriate for HIV testing (and other serology) in laboratories in both well-resourced and under-resourced countries, 2) demonstrate some difficulty in conducting that testing in under-resourced areas, 3) describe differences between the standards in under-resourced and well-resourced areas, and 4) propose methods to achieve quality standards globally. My "take home message" is that most of us in well-resourced countries are in a position to apply appropriate international pressures. We have quality assessment programs. We have appropriate standards. We have panels, such as the Clyde panel, that Dr. Patricia Reichelderfer described. We can develop consensus guidelines on how to achieve and maintain agreed and acceptable standards and therefore establish standards globally.

Acknowledgments

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Figure 1

Figure 2

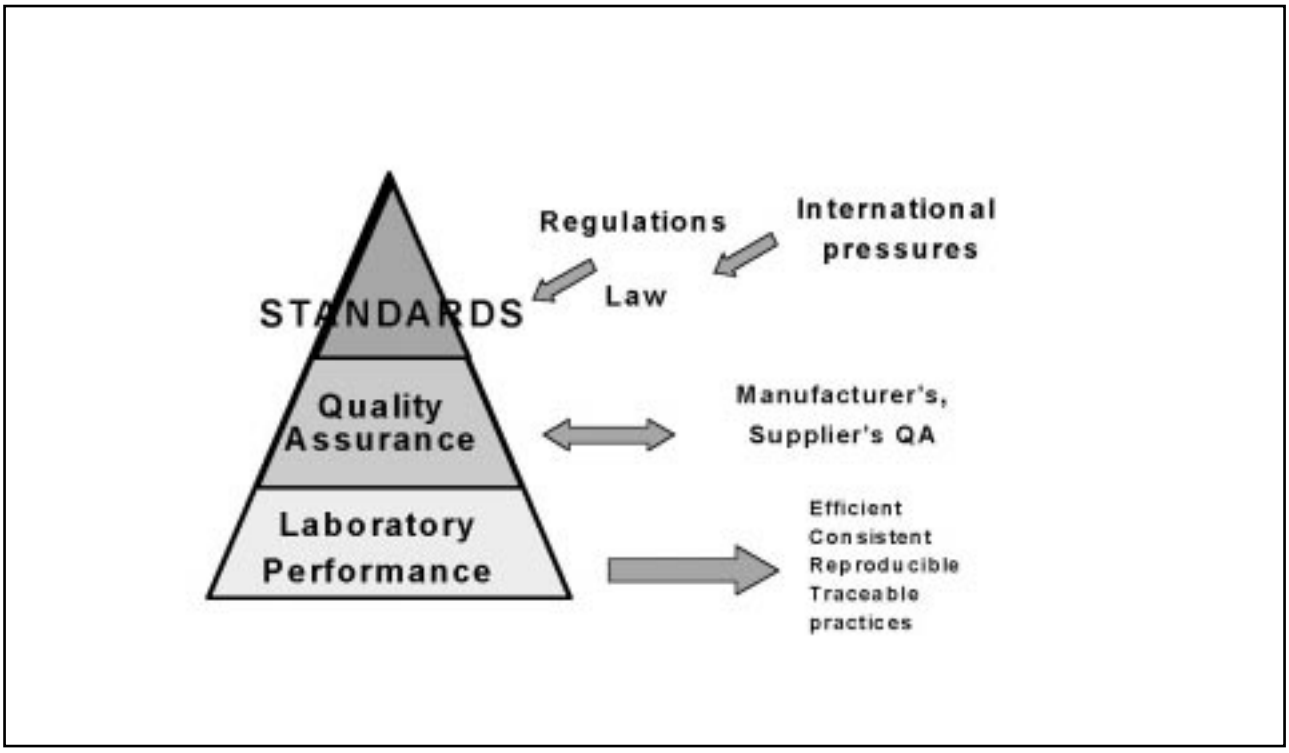


Figure 3

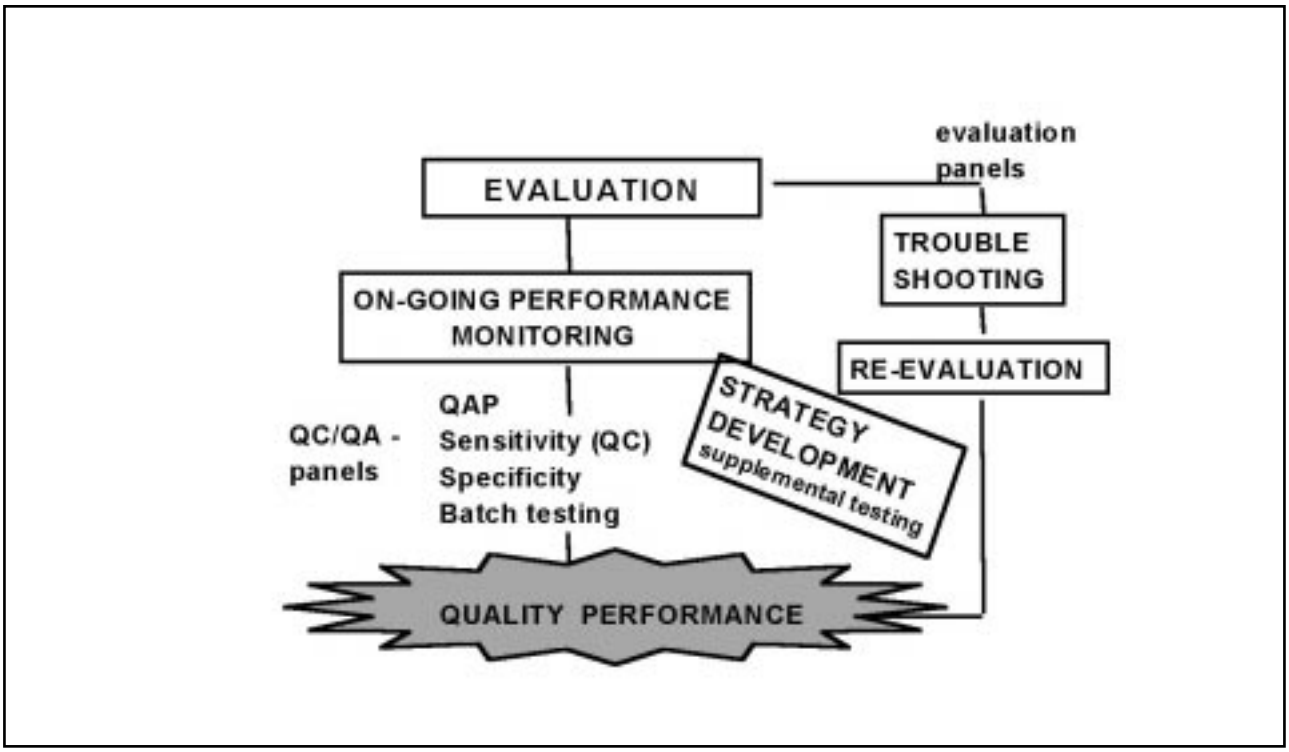
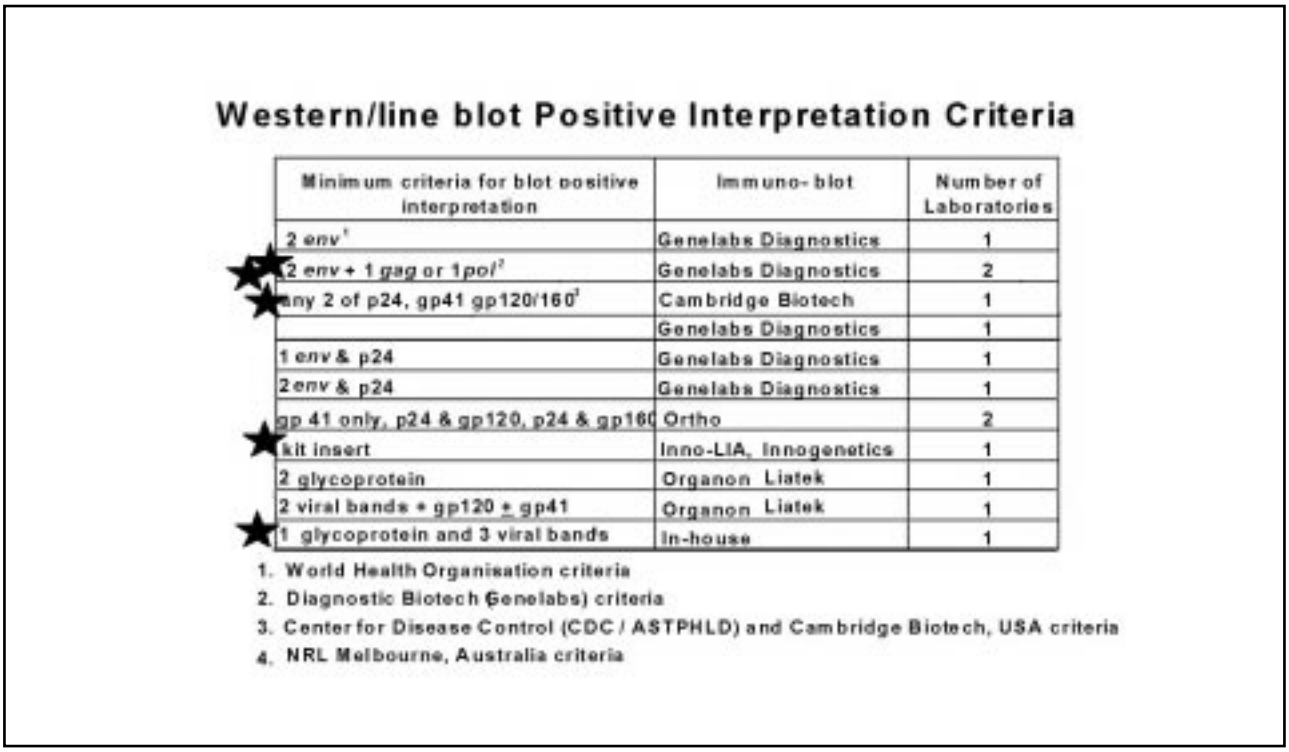


Figure 4

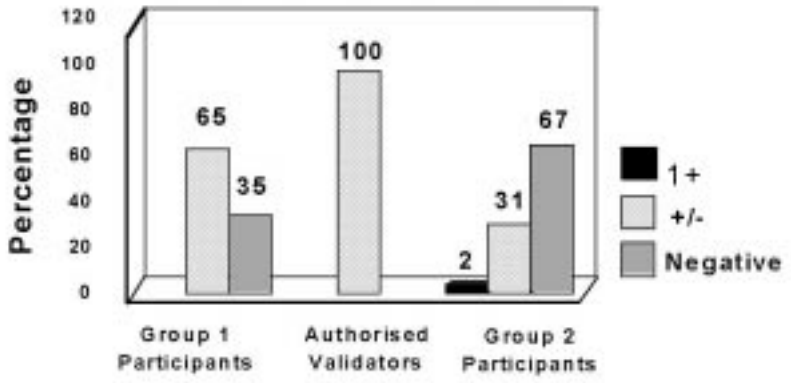


Western/line blot Positive Interpretation Criteria

Minimum criteria for blot positive interpretation	Immuno-blot	Number of Laboratories
2 *env*[1]	Genelabs Diagnostics	1
2 *env* + 1 *gag* or 1*pol*[2]	Genelabs Diagnostics	2
any 2 of p24, gp41 gp120/160[3]	Cambridge Biotech	1
	Genelabs Diagnostics	1
1 *env* & p24	Genelabs Diagnostics	1
2 *env* & p24	Genelabs Diagnostics	1
gp 41 only, p24 & gp120, p24 & gp160	Ortho	2
kit insert	Inno-LIA, Innogenetics	1
2 glycoprotein	Organon Liatek	1
2 viral bands + gp120 ± gp41	Organon Liatek	1
1 glycoprotein and 3 viral bands	In-house	1

1. World Health Organisation criteria
2. Diagnostic Biotech (Genelabs) criteria
3. Center for Disease Control (CDC / ASTPHLD) and Cambridge Biotech, USA criteria
4. NRL Melbourne, Australia criteria

Figure 5


Percentage
120
100
80
60
40
20
0
65
35
100
2
31
67
1+
+/-
Negative
Group 1 Participants
Authorised Validators
Group 2 Participants