

## Chapter IX

# Laboratory Services

### OVERVIEW

Laboratory diagnosis of HIV infection, staging of disease progression, and monitoring of therapies, including management of antiretroviral toxicities and the response to therapy are essential components of HIV care and treatment. The significant current expense of these tests mandates a careful assessment of the required tests and their use. Price negotiations with suppliers are ongoing.

The laboratory services established as part of this programme incorporate the best available evidence and international guidelines in order to establish a judicious laboratory plan. Moreover, the high volumes that will be required to support the HIV and AIDS care and treatment programme make significant reductions in the price of CD4 and viral load tests likely.

The guiding principles of the laboratory services component of the ARV treatment programme are:

- To support best practices of patient care.
- To monitor for the development of drug resistance.
- To establish evidence-based, cost-effective and sustainable laboratory services.
- To expand currently available capacity within the NHLS to offer best support to the clinical services.

The National Health Laboratory Service (NHLS) will take responsibility for the laboratory services as required to support the HIV and AIDS care and treatment programme. Although the NHLS has a strong infrastructure base, additional infrastructure and capital equipment expenditure will be required to support the programme's laboratory needs, as will targeted improvements in sample collection, specimen transport, laboratory training, and information systems. Initial working capital will be required to support initial implementation operations. The NHLS could contract out work to the private laboratories

as a contingency measure.

The NHLS operational plan is outlined at the end of this chapter, following a brief summary of the laboratory services to be provided under the care and treatment plan and a brief discussion of additional laboratory issues relevant to the HIV and AIDS care and treatment programme.

## **BACKGROUND AND RATIONALE**

### **Laboratory Services to Support HIV Care and Treatment**

A set of diagnostic assays is central to HIV care and treatment, in accordance with national and international guidelines:

- HIV diagnostic tests (rapid tests, ELISAs, and infant diagnostics)
- CD4 counts
- Viral loads (currently by quantifying HIV RNA. Other technologies may become available.)
- Toxicity assays (such as FBC and ALT)
- Resistance monitoring
- Diagnostics for opportunistic infections

### **Clinical Monitoring Protocol**

The NHLS laboratory services will follow the requirements dictated by the ARV treatment clinical protocols (see Chapter I, *Prevention, Care and Treatment*). The protocol for clinical monitoring of HIV disease has been evolving since the mid-1990s, when antiretroviral drugs to treat HIV infection and new laboratory assays - particularly viral loads - were first introduced. While there is consensus on some issues, there is as yet no well-established protocol for laboratory and clinical monitoring. Recent guidelines were set forth by the World Health Organization and by the United States Public Health Service, but revisions of these recommendations are expected in the near future. In order to remain vigilant of new developments in monitoring, the Department of Health will develop periodic updated guidelines for the ARV treatment programme. (See Chapter I, *Prevention, Care and Treatment*, and Chapter XII, *Monitoring and Evaluation*.)

### **CD4 Count and Viral Load**

The CD4 count assay is the cornerstone of HIV disease monitoring. CD4 counts provide an assessment of the immune system in HIV-infected patients and are used to track both the decline in immune function in untreated patients, and the rise in immune function following the initiation of ARV treatment. A CD4 count below 200 cells/mm<sup>3</sup> will be the major laboratory determinant of entry into ARV treatment until further evidence indicates otherwise, and CD4 counts will also determine the need for specific interventions to prevent opportunistic infections.

To perform these tests the NHLS will require significant investment in laboratory infrastructure, capital equipment and ongoing operational expenditures. Based on current projections, a cumulative total of between 14 and 20 million CD4 counts will be performed after the first five years of the ARV programme. To meet these targets, infrastructure and equipment to support CD4 count testing will need to be developed in all NHLS regions. Of the NHLS sites selected for CD4 testing, capacity is currently available in Cape Town, Durban, Johannesburg and Bloemfontein. To meet targets, CD4 laboratories will be established in Nelspruit, Polokwane, Umtata, Ngwelezana, and Port Elizabeth. New sites in Newcastle, Port Shepstone and Tshepong could be established by the fifth year of the programme to handle the projected increased needs.

Specimen transport capacity to ensure timely delivery of samples to the designated CD4 laboratories will be upgraded where necessary. Overall CD4 testing capacity will need to be expanded approximately six to eight-fold after five years. Training will have to be expanded to equip the new technical staff required (see the outline of the NHLS operational plan below).

Viral load assays measure the amount of HIV present in the plasma of an infected individual. They serve three functions: as a marker of progression from HIV infection to AIDS; as a measure of the response to ARV treatment; and as a sentinel indicator for development of treatment failure, possibly due to drug resistance. The assays are technically complex to perform, and require sample separation within eight hours of collection and subsequent sample refrigeration. Based on current projections, a cumulative total of approximately three million viral load assays will be performed after

the first five years of the programme.

Of the NHLS sites selected for viral load testing, capacity is currently available in Cape Town, Durban, and Johannesburg. To meet targets, viral load laboratories will be established in Bloemfontein, Umtata, Ngwelezana and Polokwane, as well as one additional site to be determined based on need. To maximize cost effectiveness and thus reduce costs to the DoH, viral load and CD4 testing will remain centralized as far as possible, particularly in the first five years of the project, or until the technology changes sufficiently to permit cost effective service to be offered closer to the point of service.

The NICD would form an additional facility to handle any specimen demand in excess of current capacity. A detailed table of facilities upgraded to perform these two assays by year is included in the summary of the NHLS operational plan.

South Africa's CD4 and viral load volumes will likely expand the global market for these assays by 50-100 percent. In order to minimize the budgetary impact, significant price reductions can be achieved through strategic partnerships with international manufacturers of the CD4 and viral load testing equipment and reagents. These partnerships should involve not merely volume discounting, but innovative ways to reduce the costs of production and distribution and guarantee supply, and the development of local manufacture of consumables or reagent kits will be explored. Such partners may be used to fast track new technology for African and global use. Commercial partners should be selected on their ability to provide the highest quality equipment and test kits using protocols designed for resource-constrained settings, at affordable pricing.

### **Toxicity Monitoring/Pharmacovigilance**

The existing infrastructure of the NHLS is sufficient to handle the routine assays used for toxicity monitoring, particularly given the anticipated upgrades to several previously disadvantaged district and central laboratories, and to specimen transport capacity that will take place within the ambit of this project. As the programme expands additional infrastructure development of district laboratories and service sites for routine haematology and chemistry is anticipated, particularly in provinces where current peripheral laboratory capacity is limited.

The clinical monitoring protocol calls for laboratory assays to monitor the toxicities of the antiretroviral medications. These include monitoring for the development of liver toxicity after the initiation of the first ARV regimen, and testing for anaemia and cholesterol abnormalities for patients receiving the second regimen. These assays are technically simpler (and therefore less expensive) than CD4 and viral load testing, and are currently performed routinely by the NHLS. In addition, it is anticipated that other tests to monitor potential toxicities not identifiable through routine screening will be clinically indicated for a subset of patients (such as pancreatitis, lactic acidosis, and glucose intolerance). The ability to perform these assays on an as needed basis has been budgeted into the laboratory component of the programme, based on projections of the frequency of ARV side effects. (See Chapter XIII, *Pharmacovigilance*.)

## **APPROACH**

The availability of high quality laboratory services is an essential component of the HIV and AIDS care and treatment programme. There are a number of key principles that apply. Testing will need to be performed using the best international standards. Investment in high quality laboratory infrastructure will have to be made to monitor patient safety, response to therapy and eligibility for ARV therapy. This investment will also improve access to laboratory services nationally. Although national standards will proscribe certain tests, these tests will need to be available as clinically indicated. In addition, price negotiations should be conducted to achieve lower prices for higher volumes of tests being performed.

### **National Health Laboratory Services (NHLS) Operational Plan**

The NHLS will provide the laboratory services for the ARV programme within the resources available to it. This is in accordance with legislation currently in effect in South Africa. Should the NHLS infrastructure prove inadequate for the workload, work could be contracted out to the private pathology sector by the NHLS. In reviewing its capacity to meet the needs of the programme, the NHLS has identified seven priority areas for development:

- Enhancing laboratory infrastructure to support CD4 count and viral load testing.

- Improving specimen transport infrastructure in currently under-serviced areas.
- Improving information technology and laboratory information systems to facilitate transfer of patient details and results between clinical service sites and the laboratories. This will also permit improved data mining capability.
- Upgrading district hospital infrastructure where necessary for basic laboratory assays and specimen processing.
- Expanding laboratory staff training to support increased need for viral load and CD4 testing, quality assurance and information technology.
- Implementing dried blood spot technologies for support of VCT external quality assessment (EQA).
- Identifying and supporting research priorities in affordable HIV related diagnostics, monitoring and surveillance.

Support for the NHLS in each of these priority areas is included in the operational plan and outlined briefly here.

### **Laboratory Infrastructure to Support CD4 Count and Viral Load Testing**

Implementation of the ARV treatment programme nationally will require expansion of central laboratory facilities extending into all regional divisions of the NHLS. The facility expansion plan will be reassessed regularly by NHLS in coordination with the Department of Health, particularly in the first phase of the programme when uptake may be variable across the provinces. By increasing capacity at existing facilities and diverting specimen transport, the NHLS can flexibly meet unexpected increases in demand. By the third phase of the programme, sufficient capacity should exist in each province to meet local/regional CD4, viral load, and toxicity testing needs.

### ***Specimen Transport Infrastructure***

CD4 counts and particularly viral load assays have unique specimen handling constraints, further complicating laboratory operations. A comprehensive plan to identify geographic areas and existing laboratories needing specimen transport upgrades has been conducted by the NHLS. Areas in need of additional transportation resources (including four-wheel drive vehicles) will be prioritised, in order to ensure that laboratory services are equitably distributed and do not hinder programme implementation. Specimen transport should be monitored and addressed on an ongoing basis by the NHLS. In addition, technologies to reduce the impact of specimen transport issues, such as dried blood spots for viral load

assays and point-of-care diagnostics, will be developed, evaluated, and implemented as they become available.

### **Information Technology (IT) and Laboratory Information Systems (LIS)**

The existing laboratory information system in place at NHLS laboratories will be expanded to meet the needs of the ARV treatment programme. This will facilitate improved turn-around-times. Data mining will also be possible within the existing Laboratory Information System (LIS). Computer hardware and licensed software will need to be brought into several existing peripheral laboratories, to improve the interface with the rest of the NHLS. Implementation of the IT expansion also encompasses system installation and LIS training for laboratory personnel. The existing LIS infrastructure will also be utilised by the NHLS to monitor laboratory ordering practices and laboratory costs, as well as regional uptake of laboratory services. (For further details, see Chapter XI, *Patient Information Systems*, and Chapter XII, *Monitoring and Evaluation*). This data will be communicated to the DoH. Demographic details and laboratory results may also readily be accessed in NHLS data repositories for additional analyses.

### **District Hospital Infrastructure**

In addition to the creation of additional central laboratories for CD4 count and viral load testing, several district hospitals may be upgraded to enable CD4 count and viral load testing based on demand. While essential laboratory assays (such as HIV ELISAs, FBCs, or liver enzymes) are already well established and generally sufficient for the needs of this project, upgrades will be implemented where necessary. Such upgrades will need to be undertaken in order to ensure that laboratory services are available in geographical settings appropriate to demand across the country.

### **Laboratory Staff Development**

The laboratory expansion also necessitates a significant expansion in the numbers of trained laboratory personnel, particularly with respect to CD4 and viral load testing. Technical laboratory training for laboratory technologists and technicians is currently coordinated through the NHLS, the professional registration bodies, and technical training institutes. Training capacity will be enhanced by the establishment of a national training centre at the NICD (National Institute for Communicable Diseases) campus in

Johannesburg. Educational and training efforts will be coordinated with the appropriate certification boards and will be determined by the laboratory-specific human resource needs in each region. Training manuals and short courses on laboratory techniques associated with the ARV treatment programme have been developed and are currently available through the NHLS. In addition, the companies supplying equipment and reagents for the viral load testing should offer equipment and assay-specific training. (For further details, see Chapter V, *Human Resources and Training*).

### **Dried Blood Spot Technologies for VCT External Quality Assessment**

As support for the VCT needs associated with the ARV treatment programme, an external quality assessment (EQA) programme for rapid HIV test kits will be developed. This EQA programme will take advantage of advances in dried blood spot (DBS) technology. Specimens collected as dried blood spots for EQA at service sites and VCT centres can be collected, stored, and shipped to the NICD laboratories for EQA cheaply and reliably. Establishment of an expanded EQA Programme will include improvements in basic infrastructure, additional training for laboratory staff, training for VCT site staff on DBS sample collection, and capital equipment and reagent purchases, including DBS punch elution equipment and DBS packets for VCT sites.

### **Research**

A research programme focused on operational questions central to the ARV programme and on the development of affordable technologies for HIV laboratory services will need to be established within NHLS. Research will include developing methods for improving laboratory services. The research agenda should include resistance monitoring, strategies for optimal ARV laboratory monitoring, and clinical utility of assays at each time point during treatment, the appropriate laboratory evaluation at the initiation of therapy, and the development of new, inexpensive methods for CD4 count and viral load determination. Further details of the research programme can be found in Chapter XIV, *Research Priorities*.

## **SPECIAL CONSIDERATIONS**

### **Laboratory aspects of Voluntary Counselling and Testing (VCT)**

The VCT programme will be an important point of entry into the ARV treatment programme. The existing VCT programme now encompasses 1,625 sites and nearly 5,000 trained VCT counsellors. With the introduction of antiretroviral therapy, it is anticipated that demand for VCT services will increase significantly. Coordination between the ARV treatment programme and the VCT programme will be established to ensure that there is appropriate procurement of HIV testing kits and ready supply at VCT sites. In addition, the NHLS will expand their external quality assessment (EQA) programme for the HIV rapid test kits now in widespread use throughout the VCT initiative. Moreover, contingency plans to address either excess demand or low uptake of ARV treatment programme services need to be coordinated between the VCT and ARV treatment programmes. This may require increased HIV ELISA testing capacity within the NHLS.

### **Resistance monitoring**

As the affordable range of antiretroviral drugs available for use against resistant virus is limited, ensuring that development of drug resistant HIV in patients receiving ARVs is minimized is a high priority of this programme. Resistance monitoring has been established as part of the monitoring and evaluation of this programme, as well as a high priority for research (see Chapter XII, *Monitoring and Evaluation*, and Chapter XIV, *Research Priorities*). The National Institute for Communicable Diseases can support the research needs for resistance testing, which is technically complex. The Department of Health will be responsible to review and report regularly on developments in the field of resistance monitoring, including opportunities for price reductions and the establishment of guidelines for the use of resistance assays.

### **Opportunistic infection diagnostics**

Several laboratory tests are commonly ordered in the context of HIV care to diagnose HIV-related opportunistic infections. Current capacity exists within the NHLS to support these assays, including cryptococcal antigen tests, tests for cytomegalovirus, hepatitis and herpes viruses, and others. The Department of Health, in coordination with the NHLS, will undertake periodic review of OI diagnostics.

### **Infant diagnostics**

Standard HIV antibody test kits (i.e. rapid tests and antibody ELISAs) cannot reliably diagnose HIV infection in infants until approximately 18 months of age. Assays that may be used to determine whether an infant born to an HIV-infected mother is infected prior to 18 months of age include P24 antigen serology and HIV DNA PCR. While available in many laboratories within the NHLS, these assays are not always in routine use. Strategies for infant diagnostics are currently coordinated by the PMTCT programme. It is recommended that a Paediatric Monitoring Task Force be established, and charged with coordinating protocols for infant diagnostics and monitoring with the PMTCT programme and the NHLS.

### **ADMINISTRATIVE STRUCTURE**

The National Health Laboratory Service (NHLS) will implement the laboratory component of the ARV programme.

Because of the cost of laboratory testing and the scope of laboratory services in the ARV programme, the laboratory component represents a significant fraction of the overall budget, despite the development of a monitoring protocol that attempts to minimize unnecessary testing without compromising clinical care. Strategic partnerships with suppliers that include centralized purchasing, predictable volumes and innovative cost reduction initiatives are expected to lead to cost reductions in the necessary equipment and reagents. Procurement plans will be coordinated with NHLS and the Department of Health as the project progresses. These may change with time depending on changes in pricing structures and availability of new technologies.

### **PROGRAMME ASSESSMENT**

The SMT will monitor the laboratory costs of the ARV treatment programme on a regular basis, and will meet regularly with NHLS executives to review data on laboratory utilization, turn-around times, patient friendliness, costs, and new diagnostic assays. The Department of Health will assess the protocols used for initiating ARV therapy and for monitoring patients receiving ARVs on an ongoing basis, including reviewing laboratory

monitoring protocols, based on new developments in HIV laboratory technologies and evolving international guidelines.