

## **SECTION FIVE**

### **INFORMATION, MONITORING AND RESEARCH**

<b>CHAPTER XI</b>	<b>Patient Information Systems</b>	<b>185 - 192</b>
<b>CHAPTER XII</b>	<b>Monitoring and Evaluation</b>	<b>193 - 201</b>
<b>CHAPTER XIII</b>	<b>Pharmacovigilance</b>	<b>202 - 208</b>
<b>CHAPTER XIV</b>	<b>Research Priorities</b>	<b>209 - 225</b>

## Chapter XI

# Patient Information Systems

### OVERVIEW

The patient information system is designed to ensure that a standardised, effective and efficient system for data collection, collation, monitoring, and feedback is in place to facilitate programme implementation, ensure good quality care, and achieve good patient/programme outcomes. The specific functions are:

- To register patients utilizing a standard patient record
- To collect relevant clinical care information at baseline and subsequent follow-up visits to monitor progress of patients
- To monitor adherence to treatment
- To monitor adverse drug events
- To collect other clinical, laboratory, and non-clinical data that will be useful for programme monitoring at local, provincial and national levels

The patient information system will need to be developed as an integral part of existing health information systems in South Africa. The system will need to be integrated into existing data collection systems, and will be standardized across all facilities in the programme. Basic data should be collected at the facility level, analysed for local use, and passed on to the provincial and national levels for programme monitoring and evaluation.

### BACKGROUND AND RATIONALE

The national health information system is made up largely of three sub-systems: hospital information systems, a district health information system, and a disease notification system. All but the latter should be adapted for the ARV treatment programme.

#### Hospital-Based Systems

Patient information systems in hospitals vary across facilities, ranging from large, sophisticated systems such as Medicom and Meditech, through homegrown systems such as the Patient Administration and Billing system (PAAB), to manual paper-based systems.

The systems share a certain degree of similarity, but are not always compatible. Although there has been an attempt to standardize these systems, this has not been fully achieved.

The following is a listing of the information systems that are currently in place in the provincial hospitals:

- PAAB is implemented in a number of hospitals in Gauteng, Mpumalanga and North West.
- Medicom is implemented at 9 hospitals and 5 clinics in Gauteng and at Inkosi Albert Luthuli hospital in KwaZulu-Natal.
- Delta 9 is implemented in Limpopo and clinics in Eastern Cape.
- Systech is used in 3 academic hospitals in the Western Cape.
- Oasis is used in 6 hospitals in the Northern Cape.
- Meditech is used in 3 hospitals in the Free State.

### **District Health Information System**

The District Health Information System (DHIS) has been developed primarily to provide core information for primary health care administration. It collects basic facility information, including rosters of hospitals, health centres, and clinics, as well as a number of specific modules. A Hospital Module contains information on utilisation, bed occupancy and length of stay. A PMTCT Module and a Patient Module have been developed over the past year.

### **APPROACH**

The ARV treatment programme will modify the PAAB module as the standard for data collection. Provinces may adapt this module onto their existing systems, provided this adaptation collects the standardized information. Where the use of electronic systems is still limited, or where the electronic PAAB module cannot be integrated into existing hospital information systems, a paper-based version of the modified PAAB system will be used. These paper-based data will be converted into an electronic file, to be used for monitoring and evaluation at provincial and national levels. As the programme is implemented, paper-based systems will ultimately need to be replaced entirely by electronic records. A standard patient information form and basic dataset will need to be adapted in all provinces to ensure standardisation.

## **Data Modules**

The major component of the modified PAAB form will be known as the "Patient ARV Treatment Report Form," and will contain the following unique modules. These modules are designed to contain the minimal essential information necessary to ensure good patient outcomes and efficient programme administration.

### ***Patient registration***

All patients entering the programme should be registered using the national identification number (ID), surname and date of birth. The ID number will be used as a patient identifier across all systems at every level of health care and in any province to avoid duplication and repetition of procedures. The system should be able to identify nationality or residence status as well as medical insurances/schemes.

Demographic data contained in the Patient Registration Form include:

- Names and surname
- Address/telephone
- Date of birth: dd/mm/yy
- Identification number
- Gender
- Marital status
- Next of kin
- Population group
- Employment
- Education
- Name of local and district municipality
- Province
- Citizenship/Residence status
- Facility

### ***Medical history/examination***

At the first visit following registration, a form will be administered to capture a patient's medical history, including previous illnesses, hospitalisation, date of HIV diagnosis, date

and location of VCT, current medications, symptoms, and ARVs taken previously, including nevirapine. For women, current or planned pregnancy, access to PMTCT services and access to contraceptives will be assessed.

A baseline examination of patients will also include vital signs, weight and details of any abnormalities of the eyes, oropharynx, lymph nodes, lungs, heart, abdomen, extremities, etc. This information will be captured in the baseline medical history/examination form.

At each follow-up clinic visit, an abbreviated version of the medical history/examination form will be completed. It will include:

- Vital signs
- Interim medical history, including: illnesses, hospitalisations and visits with specialists
- Current ARVs prescribed, if any
- Assessment of ARV adherence, if taking ARVs
- Assessment of ARV side effects, including: rash, weight changes, abdominal pain, and nerve pain in the hands and feet
- Allergies and current non-ARV medications

If the patient is admitted to a hospital or treated in outpatient specialist clinics, a medical history/examination form should be completed there as well. Upon completion of treatment or hospital discharge a summary record should be generated automatically by the PAAB system to enable verification by medical records staff and enable completion of any missing information.

### ***Laboratory and other diagnostic information***

The results of laboratory tests and other diagnostic evaluations performed either at the implementation site or at designated laboratories should be captured as part of the patient record. At a minimum, the patient information system should capture the results of the CD4 cell count, viral load, and other basic tests, including those used to identify potential adverse reactions to ARVs. The frequency of these tests will be determined by the treatment protocols for ARV management. The NHLS will also retain patient laboratory information as part of its laboratory information system (LIS).

***Pharmacy and pharmacovigilance***

Data captured as part of the patient medical record will support drug dispensing for inpatients and outpatients. This part of the patient record will interface with a separate pharmacy database, which will provide for entry of prescriptions and medication orders at outpatient clinics or wards. On entry of prescription, the pharmacy database will display other drugs that have been prescribed to a particular patient. The system will need to have a controlled procedure for the authorization of all issued drugs and will maintain a separate register or controlled drugs and narcotics.

For inpatients, the National Health Care Management Information System (NHC/MIS) should maintain patient medication profiles and prepare medication administration schedules with days, times, and dosages. It should also check for allergies or sensitivities, possible drug interactions, contraindications, over dosages, and special instructions, taking into account the route, dosage, forms and times of administration. Information on adverse drug events should be captured.

Specific data elements collected in the pharmacy database will need to be coordinated with the Pharmacovigilance unit (see Chapter XIII, *Pharmacovigilance*), and will include:

- Medications
- Date treatment was commenced
- Date treatment was terminated
- Reasons for treatment termination: (e.g. patient defaulted, patient decision, patient lost to follow-up, adverse drug reactions, patient died)
- Adverse drug reactions
- Treatment adherence information

The system should, on completion of the summary or abstract of treatment details, have the tools to render the record non-modifiable. From then on, the NHC/MIS should maintain that as part of medical history, accessible to authorized users.

**Service utilization**

The modified PAAB system will have to permit scheduling of appointments and follow-up visits. The appointments may be given either for a specified time or for a time-bracket and

should enable a conscious overbooking and the handling of emergencies. The system should be able to detect appointment conflicts, enable rescheduling of appointments and hospital clinics, cancellation of appointments, and track non-compliance with scheduled visits.

The system will need to fully support the processing of admissions, discharges and transfers of inpatients, including emergency admissions. Discharges should be entered either at the nurse's station or the medical records office. The system should generate a discharge summary, especially for patients that were referred from other levels. Visits to specialists, laboratories and general clinics will need to be recorded, with recognition of first visit and subsequent visits. The system should permit recording of actual/scheduled information along with defaulters to ensure production of accurate monthly utilization reports.

### **IT Development**

As the programme moves beyond the initial phase, and the number of sites increases, there will be a significant expansion of reporting points requiring investment in health information infrastructure to upgrade electronic information systems, computer hardware and software, and to enable effective interface with laboratory and pharmacy information systems.

### **ADMINISTRATIVE STRUCTURE**

Within each facility, a clerk should complete patient registration, and the clinician or nurse attending the patient should complete clinical records. At each additional point of contact in the facility (laboratory, pharmacy, etc.) a patient-linked record will need to be completed and integrated into the patient's file. If paper forms are used, a data clerk should complete electronic entry. Each facility will have a clear information flow protocol, and checks to ensure that all records pertaining to the programme are collated at the close of each day. One individual at each facility should be assigned as the data/M&E officer to conduct checks and ensure completeness of data entry.

Data entry manuals and guides for data entry and completion should be developed at the national Strategic Management Team (SMT) and made available to facilities.

At the district level, a single M&E officer should ensure that data from each facility are collated and completed. Abstracts of these data should be made available to facilities, to the provincial office, and to the national office. The information to be passed back to facilities, the districts, and the provinces will be established by the Department of Health as part of the Monitoring and Evaluation activity (See Chapter XII, *Monitoring and Evaluation*). A succinct newsletter or ‘monitor’ will be developed and circulated to all participating facilities and provincial offices as a feedback mechanism to track progress in the programme. The M&E office will be responsible for all aspects of the data collection and management process.

Finally, simple modifications of the DHIS Hospital, PMTCT and Patient Modules will need to be made to collect information on utilization rates, ARV distribution, and other information relevant to the ARV treatment programme administration not obtainable directly from the modified PAAB patient record system.

## **PROGRAMME ASSESSMENT**

The success of the patient information system initiative depends on strong coordination at the central level (via the Cluster of Health Information, Evaluation and Research and the NHISSA committee), collaboration with the provincial health information teams, and the availability of adequate resources including personnel, training time and equipment at the district and service point level

Progress of the patient information programme will be assessed using the following measures:

- Number (and percentage) of sites using the national system
- Number (and percentage) of sites reporting complete minimum data set
- Speed and accuracy of reporting
- Progress toward migration to national system
- Progress toward complete integration of existing systems.

The Cluster of Health Information, Evaluation and Research will conduct an evaluation at the national level.

## Chapter XII

# **Monitoring and Evaluation**

### **OVERVIEW**

The goals of the HIV and AIDS care and treatment plan are to reduce HIV-related mortality, reduce the morbidity of HIV-infected people, and improve the quality of life of the HIV-infected. The success of this operational plan requires the establishment of a monitoring and evaluation (M&E) system at the outset, to monitor implementation and ensure these goals are met. Ongoing monitoring will be critical to inform activities and allow adjustments to implementation. The M&E system will collect data relevant to all resources invested in the programme, services provided by the programme, outcomes related to the programme, and the overall impact of the programme on public health and quality of life.

The national M&E unit will coordinate M&E units in each of the provinces that link with M&E efforts at the district level. Programme staff at each level will manage M&E processes and data, and will be placed nationally, in each of the nine provinces, and in the districts. Data collected by clinicians at service points will be aggregated at the district level, and incorporated into central databases housed at the provincial M&E units. Existing staff will be used to the widest extent possible. As enrolments grow over the course of the programme, additional support will be brought into the system. The overall objective of the M&E system is to provide information to maximize the programme's likelihood of success, and the achievement of the basic goals emphasised throughout this plan.

### **BACKGROUND AND RATIONALE**

The standard public health M&E framework describes a straightforward relationship among factors that lead to the achievement of a programme's goals. Indicators associated with these factors can be measured, and then used to document how successfully goals are accomplished. These factors can be segregated into four levels: Inputs include basic personnel, consumables, equipment, and other infrastructure dedicated to support activities

or services. Outputs comprise those activities and services, and might include patient care, staff trainings, education campaigns, and support services. Changes in behaviour, skills, or health status as a result of the programme's activities and service constitute Outcomes. Over time and from the perspective of a population rather than an individual, the composite effect of outcomes results in major shifts in health patterns. These shifts are identified as Impacts, and in this case might include decreased mortality and morbidity, improved quality of life, or reduced transmission of HIV. Each of these factors can be subjected to monitoring and evaluation that can rapidly inform the future inputs, outputs, outcomes and impacts and lead to enhanced care delivery and programme effectiveness. Existing surveys and other research studies will be utilised as evaluation tools.

The ultimate success of an M&E programme depends on the ability to access and evaluate the above data. In this regard, M&E is dependent on the quality of data collection. The proposed national plan provides a unique opportunity to gather data efficiently, and on an unprecedented scale, and to use the M&E effort to inform the future direction of this programme, and of similar programmes emerging elsewhere.

## **APPROACH**

Reaching the goals of the HIV and AIDS care and treatment programme requires the successful coordination of a diverse array of activities, and their timely, ongoing evaluation. The data relevant to monitor the critical health care indicators will derive from information gathered routinely in the course of care, and, when necessary, by appropriately designed studies. These uncomplicated data can also be used to monitor the large-scale accomplishments, to manage national programme activities, and to guide adjustments to national programme components.

### **Input and Output Indicators**

The national M&E unit will define a core list of indicators, consistent with this operational plan and with the delivery of HIV care. Recommended output indicators for each plan component, representing the national and provincial implementation of services and activities, are listed in Table 12.1.

**Table 12.1: Output Indicators for Monitoring and Evaluation**

Care and treatment	Percent of functional programmes; health outcomes
Nutrition	Percent of programmes providing nutrition support
Traditional medicine	Number of service points with referral linkages
Strengthening and accreditation of service points	Number of accredited service points
Drug procurement	Level / percent of drug procurement systems in place
Drug distribution	Level / percent of drug distribution systems in place
Laboratory services	Number of accredited labs performing CD4 and viral load testing
Human resources and training	Number of certified health professionals; percent of posts filled
Communications	Percent of communication programmes completed
Community mobilisation	Percent of community mobilisation programmes completed
Patient information systems	Percent of facilities with functional systems
Pharmacovigilance	Number of pharmacovigilance monitoring systems in place
Research priorities	Number of research projects initiated
Programme management	Number of provincial management structures in operation

Input data will not be collected routinely at the national and provincial levels, given the tremendous quantity of information involved. Input data are available at the district level and will be abstracted to address specific evaluation questions.

The results of the programme’s activities and services constitute outcomes, and the composite effect of these activities on health patterns constitutes impacts. For example, outcomes might include the change in the number of trained health care professionals who demonstrate improved skills, the change in the number of labs producing higher quality results, or the change in the number of HIV-positive persons in care and treatment. While the potential number of outcomes and impacts that might be evaluated is large, the national M&E effort will focus only on those associated with the delivery of care and its consequences, as listed in Table 12.2.

## Monitoring of outcomes and impact

**Table 12.2: Outcome and Impact Indicators for Monitoring and Evaluation**

Indicators
<ul style="list-style-type: none"> <li>• Number of people tested</li> <li>• Percent of people testing HIV-positive</li> <li>• Number of HIV-positive people in care and staged</li> <li>• Number of eligible patients receiving ARVs</li> <li>• Number of persons on ARVs with undetectable VL</li> <li>• Time between meeting staging criteria and receipt of ARVs</li> <li>• Mean change in CD4 among persons on ARVs</li> <li>• Rate of opportunistic infections among HIV</li> <li>• Average weight gain of patients on ARVs</li> <li>• Percent of patients on first, second regimen</li> <li>• Number of adverse events*</li> <li>• Prevalence of resistant strains (sentinel study)</li> <li>• Number and duration of inpatient visits</li> <li>• Number of casualty visits</li> <li>• Quality of life and score on Karnofsky Index</li> <li>• Number of AIDS-related deaths</li> </ul>

*Note: Numbers collected on these indicators can be used with appropriate denominator data to calculate percentages. \*Data will be collected by the Pharmacovigilance Unit and shared with the M&E office.*

At a national level, the composite picture reflecting these health improvements will document the level of achievement of the operational plan's goals. For example, prevalence of OIs, average weight gain, mean change in CD4 counts, quality of life scores, and mortality rates will be used to document realisation of the goals of reduced morbidity, increased quality of life, and decreased mortality. National profiles indicating improved survival and a better life for South Africans will represent the principal impacts of this programme.

### Training

It will be essential to ensure that there are adequately trained personnel to manage the M&E function. National and provincial M&E unit members will collaboratively define their specific training and technical assistance needs during the onset of programme implementation. Expert training in establishing M&E systems is readily available. A team from the national M&E unit responsible for maintaining straightforward curricula

will oversee the development of provincial M&E teams. The provincial teams will be responsible for basic skills development for providers and data managers within each district and service point. The national office will conduct annual training for provincial teams; as the programme unfolds, these sessions will focus on updates and issues pertinent to programme success.

The national M&E unit will conduct training for the provincial teams early during implementation. At this time, the framework of the entire project will be reviewed, and issues specific to the M&E effort addressed. Relevant curricula will be introduced for use by the provincial teams when working with district and service point staff, which will be modified based on feedback from initial trainings to reflect local needs. Provincial teams will use these revised materials to begin training sessions at the district and service point level. These sessions for both care providers and other staff will address the principles of monitoring and evaluation and describe the assistance available from provincial and national M&E units.

### **Data Management**

The management of data at national and provincial levels will require establishment of appropriate IT and database capabilities. An extensive use of information technology is projected, and full implementation over time will require considerable resources. The proposed electronic Patient Information System will require time to implement successfully, and this delay may result in initial data collection on paper at the district and health facility levels.

### **Data Collection Processes**

Implementation plan goals and core indicators identified at the national level will guide the M&E activities in the provinces and the districts. Additional indicators might be monitored at the provincial or district level, to address local questions, but only data for national indicators will be submitted to the national M&E unit. Health care indicator data will be abstracted from the Patient Information System, while programme implementation indicators will be obtained from aggregated administrative data summaries.

The majority of primary data will be gathered from service point patient and administrative records. Patient data will be linked on the basis of unique, confidential identifiers, whereas programme information will be summarized into monthly totals. This information will be submitted to the provincial office and consolidated with data from other districts. Provincial M&E units will gather data on implementation activities, including training and other programmes based at the provincial level. These data will be submitted to the national office, where all provincial information will be combined. Other primary data will also be gathered at the national level, tied to the activities conducted within the national venue.

The actual data collection process will evolve in conjunction with the development of the Patient Information System (see Chapter XI, *Patient Information Systems*). Consequently, the initial data collection system will be a combination of paper forms and electronic media, the latter linked to existing patient data systems.

The M&E data system also will become the basis for more concentrated work, providing a foundation for sentinel or other surveillance studies and for formal research. These latter studies will build upon the M&E system and augment inferences obtained from this evolving health care system. Decisions regarding access to these data and to service points will follow the formal procedures outlined by the national SMT and the Health Information, Evaluation and Research Cluster, which coordinates the research agenda (see Chapter XIV, *Research Priorities*). Research findings that impact the M&E systems will be made available and utilised to fine-tune the M&E framework; this will create a productive bi-directional relationship between M&E and research.

## **SPECIAL CONSIDERATIONS**

In conjunction with this M&E programme, one priority sentinel study will need to be introduced at the outset of the implementation plan to function as an early warning system for the emergence of drug resistance. This early warning system will, in turn, provide a measure of the success of the ARV treatment programme. The significant negative consequences associated with drug resistance are profound and require very close monitoring as the care and treatment programme rolls unfolds across the country.

This sentinel study, which represents a link between the research, pharmacovigilance, and M&E programmes, will be situated in a number of sentinel sites, chosen for their potential to rapidly yield resistance information. Two different cohorts are to be monitored in this study. The first group will include individuals who are currently receiving ARV treatment. These persons will be monitored for the emergence of resistance, as indicated by treatment failure. A second group will include persons who are verified as recent infections, through the use of detuned assays to identify new infections. These persons will need to undergo specialized resistance testing to ascertain the presence of, and by inference, the recent transmission of resistant strains.

### **ADMINISTRATIVE STRUCTURE**

The general configuration of the M&E system follows the tiered structure of the national health care system. Overall coordination and support for M&E will rest with the M&E Unit and with the national Department of Health.

Within the M&E system, roles and responsibilities are defined according to the level of the health care system and the programme activities. Overall responsibility rests with the national M&E unit. While the various roles taken by the national office are replicated at each lower level, the scope of responsibilities will differ. The national M&E unit will define the core indicators to be used for national programming. Aggregate M&E data will be collected and managed by this office, and regular reports will be disseminated to, and reviewed with, the provinces and other appropriate agencies of government. This feedback will prove vital to programming, offering guidance for the modification of provincial activities. The national M&E office will create and sustain a training and technical assistance capacity, offering support to provincial and district offices. Partnerships with external entities will be emphasized both to increase capacity for care delivery and research, and to utilise additional expertise for training and technical assistance activities. When appropriate, national dissemination activities will target national and international outlets and journals.

Comparable roles and responsibilities will be situated at the nine provincial M&E units. The scope of these activities will be smaller, although the primary roles will remain the same. Each province will work with district and other local constituencies to define any additional indicators to supplement those developed by the national SMT. Provincial aggregate data will be collected and maintained at this level, and reports will provide feedback to the districts and to the national office. Ongoing dialogue and feedback between the national and district M&E units will ensure the successful implementation of programme and M&E activities. The province will provide training and technical assistance to the districts when requested, although some requests will be better served by national training and technical assistance programmes.

At the district level, M&E responsibilities include support for service point activities and for submission of information to the provincial office. Districts will work closely with service points to support programming and M&E, and to define specific aspects for the local effort. Some districts may choose to add indicators to those defined by the province and by the national office. Districts will manage data for their administrative areas, conducting the first phase of electronic data entry and initial stages of aggregation for the provincial office. Training and technical assistance requests to the district will be screened according to the capacity of the district, and many of these requests are expected to receive support from the provincial and national offices.

In addition to the M&E structure integrating the national programme, provinces, and health districts, the national M&E office will coordinate linkages with PLWHA groups; the private sector; NGOs; bilateral, multilateral and private funders; South African universities and research institutions; and international universities. These additional linkages will serve as a platform to share information, to standardize and coordinate effort, and to provide a framework for more focused research. This part of the M&E system is designed to facilitate partnerships to expand the delivery of care.

Human resource needs for the M&E system target two primary areas: programme management and data management/analysis. Programme management personnel requirements occur throughout the system. Data management requirements are tied to the evaluation of the large data sets. Specific personnel requirements of the M&E programme

include an M&E specialist in the national office. This person will be supported by a data manager, an epidemiologist/statistician, and a behavioural/social scientist. The provincial units will be led by an M&E specialist and supported by an epidemiologist/statistician and a data manager/data entry person. At the district level, a single person will oversee the M&E system. This individual should manage the local M&E effort, manage the data collection process, and act as liaison with the province. Preceding the implementation of the new Patient Information System, the M&E coordination office, with NHISSA representatives, will ensure that appropriate data hardware and software are in place. The district M&E officer will circulate among the service sites to enter information into an electronic format. This procedure will permit the retention of forms at the service sites, and limits the data entry process and need for specialised skills until an electronic system is fully implemented.

Data forms will include only unique patient identifiers, ensuring confidentiality above the district level. One additional staff position is required at the district level, although some exceptions might be made where districts include only a small number of service points. Under these circumstances, an existing district staff worker can initially assume these duties. It is anticipated that this process will evolve as growing enrolments lead to a greater need for dedicated positions.

Personnel requirements at the level of individual service points will be limited. An existing staff person can assume responsibility for the assembly of information for submission to the district office. In the future, this responsibility may demand considerable time and, consequently, the creation of a new position.

## Chapter XIII

# Pharmacovigilance

### OVERVIEW

The plan highlights the need for a comprehensive pharmacovigilance programme as an integral part of the antiretroviral programme. Historically, the reporting of adverse drug reactions for all medicines has been poor, and remains limited in the case of antiretroviral agents. Pharmaceutical companies conduct and report required regulatory monitoring, but individual practitioner reports are less common. Health professionals are more likely to identify and report adverse drug reactions if they have sufficient knowledge and the ability to identify, manage and prevent such reactions. The need for ongoing training and aggressive advocacy is essential.

The goal of the pharmacovigilance programme is to ensure the safe and effective use of ARVs and other medicines commonly used in HIV and AIDS patients. Ultimately, pharmacovigilance should improve patient well-being and public health. The approach will involve regulatory activities performed by the Medicines Control Council, and active surveillance and training through the clinical pharmacology departments of medical schools attached to health facilities, including those in underserved areas. The pharmacovigilance units will be identified based on their technical capacity, ability to provide broad-based support to underserved areas, and ability to facilitate collaboration among the relevant departments of involved institutions.

The specific aims of the antiretroviral pharmacovigilance programme are:

- To determine the burden of drug-related morbidity and mortality in patients with HIV and AIDS, particularly associated with ARV use, and develop measures to minimize their impact.
- To provide training and information to health personnel and patients on the safe use of antiretrovirals and other medicines commonly used in HIV-infected and AIDS patients.
- To develop systems to assess the risks and benefits of treatment commonly used in patients with HIV, STI and TB, including over the counter (OTC) medication / phyto-therapeutic agents.

- To identify, assess and communicate any new safety concerns associated with the use of antiretrovirals and other HIV medicines.
- To support regulatory and public health decision-making through an efficient, national post-marketing surveillance system, monitoring the quality, benefits and risk or harm associated with ARVs and other medicines currently used in the health sector.
- To minimize the impact of misleading or unproven associations between adverse events and ARV therapy.
- To detect, assess, and respond to safety concerns related to complementary and traditional medicines used in HIV-infected patients.
- To establish an early warning system for resistance to antimicrobials commonly used in HIV, including, but not limited to, antiretrovirals (see Chapter XII, *Monitoring and Evaluation*)
- To respond to unfounded and unsubstantiated claims of efficacy of untested products and treatment modalities

## **BACKGROUND AND RATIONALE**

### **Current Status of Pharmacovigilance Activities in South Africa**

A regulatory infrastructure for pharmacovigilance activities in South Africa has been established since 1987. The Medicines and Related Substances Control Act (101 of 1965) mandates that applicants for registration should submit adverse drug reaction forms associated with the use of their products without delay. There is also limited experience reporting some serious adverse events as part of clinical trials. Further clarifications and more comprehensive requirements were included in recent legislation, providing clear instructions for voluntary reporting of any adverse drug reactions associated with the use of medicines registered in South Africa. An Adverse Drug Reaction (ADR) reporting form is attached as Annex XIII.1. A national adverse drug reaction reporting database (ADRI) has also been developed, compatible with the World Health Organization's pharmacovigilance database. All ADRs reported in South Africa are fed into an international pharmacovigilance database housed in Uppsala, Sweden.

### **Pharmacovigilance of the HIV and AIDS Care and Treatment Programme**

The potential impact of ARV-related adverse effects on our population needs to be carefully monitored and considered. The risk of previously undiscovered or poorly documented adverse effects, long-term toxicities, teratogenicity and new drug-drug or

drug-food interactions also need to be carefully investigated in the South African population.

***Safety profile of ARVs***

Antiretrovirals are internationally recognized for their positive impact on life expectancy in HIV-infected people. In recent years, however, concerns among communities and health professionals about the safety of combination ARV therapies have been raised. ARVs are also known to cause serious, and sometimes fatal adverse effects. Toxicities such as lactic acidosis and other metabolic derangements, haematological toxicity, serious skin reactions, liver toxicity (hepatotoxicity), and neurotoxicity result from the ARVs selected as part of first and second regimens. Table 13.1 lists the expected rates of known acute toxicities. Moreover, some ARVs have important drug interactions that can render the ARVs or other medicines ineffective or enhance their potential for side effects.

**Table 13.1: Expected Rates of Toxicities for ARVs used in Programme Regimens**

ARV drug	System Affected/Toxicity					
	Haem	Hepatic	Pancreatic	Skin	Metabolic	Neurologic
Stavudine	+	++++	++++	-	Lactic acidosis	++++
Lamivudine	++	++	+++	++	Lactic acidosis	+++
Efavirenz	+	++	-	++++	-	Wide range
Nevirapine	++	+++	-	++++	-	+
Didanosine	+	+++	+++	-	Lactic acidosis	++++
Lopinavir/ Ritonavir	+	++	+	++	Lipid/glucose abnormalities	++
Zidovudine	++++	++	-	-	Lactic acidosis	-

*Scale: +++++ >10%    +++ 5-9%    ++ 1-4%    + <1%    - Not reported or rare*

The National Adverse Drug Event Monitoring Centre in Cape Town has received a total of 83 adverse drug reaction reports associated with the use of one or more antiretroviral medicines. Table 13.2 provides a breakdown of the number of reports received for individual ARVs (noting that more than one drug may be suspected in a single case).

**Table 13.2: Number of ADR reports associated with ARV agents**

Antiretroviral Agent	Number of Reports
Abacavir / Ziagen	8
AZT / Retrovir / Combivir	17
3TC / Lamivudine / Combivir	51
Efavirenz / Stocrin	25
d4T / Stavudine / Zerit	24
DdI / Didanosine / Videx	19
Lopinavir-Ritonavir / Kaletra	3
ddC / Hivid	3

*Documented in the National ADRI database (as at 30 August 2003)*

This relatively low number of reports on ARVs suggests the possibility of significant underreporting, but could also reflect the relatively small number of patients currently on ARVs. Training clinicians to better recognize and evaluate drug-related conditions is crucial to establishing a systematic reporting of ADRs.

To address these issues, the pharmacovigilance plan will evaluate long-term toxicities, potential for teratogenicity, drug-drug and drug-food interactions, and the impact of complementary and traditional medicines and additional drugs. The programme should improve and expand on the existing pharmacovigilance system to detect and evaluate previously unknown or poorly understood safety concerns associated with ARV use.

This plan, while focusing on the requirements for an ARV surveillance programme, will also consider the general pharmacovigilance needs of the country, particularly those likely to enhance the safety of medicines in patients with HIV and AIDS. While pharmacovigilance activities in South Africa have typically had a regulatory focus, the ARV pharmacovigilance programme should augment the general clinical care of patients on ARVs.

### ***Antimicrobial Agents***

HIV-infected persons are at increased risk of infection caused by antibiotic-resistant microorganisms. Containment of resistance to antimicrobial agents requires the establishment of appropriate early-warning systems overseen by a dedicated team of experts. Key elements in a containment strategy include the prudent use of antimicrobial agents, educational intervention, integrated surveillance and monitoring systems in all areas as well as good infection control practice. In addition, risk assessment and management strategies within a regulatory framework play an important role in containing antimicrobial resistance.

## **APPROACH**

The national pharmacovigilance programme will pursue a phased plan of action over the coming three years, reflecting short, medium, and long-term goals.

### **Priorities**

- Training and information support for health care teams and strengthening of the existing spontaneous reporting system. Advocacy on pharmacovigilance and ADR reporting can be initiated as part of enhancing spontaneous adverse event reporting. Strengthening the MCC and its regulatory infrastructure should be initiated in the first few months.
- Strengthening regulatory infrastructure and further provision of online support, including the development of a database that will be functional in 2005.
- Initiation of focused surveillance and novel pharmacovigilance methods for addressing key research questions, including maternal and perinatal surveillance and phytovigilance

### **Activities**

- Enhance national spontaneous reporting system with active feedback to decision-makers, prescribers, reporters, patients and the public.
- Develop and improve regulatory procedures to support the defined objectives.
- Further development of a sustainable, functional, user-friendly database to support activity 1.
- Provision of unbiased, evidence-based information on the safety profile of ARVs, the safe and effective use of ARVs and the management of potential complications.
- Introduce targeted sentinel surveillance systems to evaluate signals of safety issues of potential public health importance (e.g. high risk groups such as pregnant women,

infants, HIV/TB co-morbidity). This will include resistance monitoring and documentation of trends to facilitate an early warning system.

- Develop novel pharmacovigilance methods to complement and support spontaneous reporting and sentinel surveillance systems.
- Develop key indicator(s) for estimating the prevalence of drug-related morbidity and mortality.
- Develop a phytovigilance programme for safety monitoring of complementary and African traditional medicines.

## **SPECIAL CONSIDERATIONS**

### **Pharmacovigilance of Traditional and Complementary Medications**

In the South African context, phytovigilance includes the safety of complementary African traditional medicines. Any phytovigilance plan should involve traditional and alternative health practitioners and should recognize the pivotal roles of the Traditional Health Practitioner Council and the Allied Health Professions Council.

There are several challenges associated with developing a phytovigilance system in South Africa, particularly given the early stages of regulation of complementary and traditional medicines. A National Reference Centre has been established, as a partnership among the DoH, MRC and the CSIR. Among other functions, this centre will serve the purpose of testing traditional and herbal products that make medicinal claims. Special attention must be given to building expertise and developing novel monitoring systems to assess risks and benefits of traditional and complementary medicine.

## **ADMINISTRATIVE STRUCTURE**

Pharmacovigilance activities will continue to be maintained by the Medicines Control Council. The MCC will work with the national pharmacovigilance unit in Cape Town, as well as with two new focused pharmacovigilance units established at academic departments, including clinical pharmacology departments at MEDUNSA and in the Free State. Findings pertinent to the success of the HIV and AIDS care and treatment programme will be communicated directly to the Department of Health.

## **PROGRAMME ASSESSMENT**

The following factors are critical to the success of the pharmacovigilance plan:

- Adequate funding and resources
- Support from the provinces
- Capacity development
- Collaboration and communication with key organizations and individuals in the public and private sector
- Ongoing assessment of the programme will be under the purview of the MCC.

## Chapter XIV

### **Research Priorities**

#### **OVERVIEW**

Research is a critical element of the plan for Comprehensive Treatment and Care for HIV and AIDS. The objective of the research agenda is to conduct studies whose answers will define the most effective provision of HIV and AIDS care and treatment, and guide programme implementation. Further new solutions for HIV and AIDS are needed as there is still no cure for AIDS, and it still proves impossible to eradicate totally the HIV virus from an infected individual, despite the progress in the past five years in the development of new antiretroviral drugs.

With regard to effective delivery of the antiretroviral drugs some of the critical questions to be asked would include: What is the most effective delivery of ARVs to persons who have progressed to a stage at which these drugs become necessary; What are the best approaches to prevent new infections with HIV; What are the best interventions, nutritional or otherwise, to extend the period in which HIV-infected people can be maintained without antiretroviral drugs - arresting progression to AIDS? The challenge is to protect the immune system from the depredations inflicted upon it by HIV infected CD4+ cells during the 5–14 years between initial seroconversion and AIDS. In Africa this decline seems to be more rapid than in developed countries.

When eventually the patient's immune system has been extensively destroyed and their CD4+ count drifts below 200 per ml, the research challenge becomes one of optimising delivery of currently available interventions such as antiretrovirals, nutritional interventions, antimicrobial prophylaxis and treatment of opportunistic infections, as well as the place of traditional and complementary medicines. Such research would include development of enhanced diagnostic and monitoring technology; new and improved drug regimens; better use of health systems to deliver these drugs; and behavioural research to improve compliance with medication regimens. This is the main thrust of the research

agenda: to conduct studies whose answers will define the most effective provision of HIV and AIDS care and treatment, and guide programme implementation.

The operational plan also seeks to engender research into one of the most important research question in AIDS: how to protect the immune system from continuing destruction caused by HIV-infected cells and other possible factors such as micronutrient deficiency, malnutrition, concomitant infection with other viruses and bacteria, and psychological stress.

Finally research in this programme on ‘immune reconstitution’ should be supported, including the effectiveness of putative immune modulators from traditional and complementary medicines – interventions that might permit AIDS patients to live out a normal and healthy lifespan despite continuing infection with HIV.

## **BACKGROUND AND RATIONALE**

The scope of the treatment effort being undertaken creates an opportunity to understand the impact of ARVs in a largely treatment-naïve population. The information currently available on the use of ARVs derives from studies not representative of the South African situation, where local factors, including poverty, endemic clades of HIV, local host genetics, and the impact of co-infections with other pathogens such as tuberculosis remain to be evaluated. At the most basic level, formal research will be essential to understand the effectiveness, safety, and appropriateness of ARV use, and to refine the HIV and AIDS care and treatment programme moving forward. ARV use in South Africa is limited, indicating the need to monitor closely treatment effects when these drugs are made available in the public sector. The considerable research infrastructure available at multiple sites in South Africa, together with the strong research leadership from South African investigators, provide a sound platform upon which to rapidly develop a research programme that runs concomitantly with the implementation of antiretroviral therapy.

Rational development of a successful research agenda requires the ability to accurately track care delivery, during programme implementation. The health system’s performance in delivering care is the essential component of any health programme, including this one.

The implementation of the ARV plan will inform the research used to guide this programme.

The establishment of a high-quality, accurate database that includes all persons initiating ARV treatment is central to this research effort (see Chapter XI, *Patient Information Systems*). Targeted sample collection and storage will be essential for addressing some basic research questions. Funding will be needed to support both human resources and infrastructure, including storage facilities. Mechanisms will be established for investigators to submit research proposals for consideration to a representative review panel with a transparent review process that will prioritise competing research projects and access to data. Linkages to established research programmes (such as the MRC, South African AIDS Vaccine Initiative, academic research programmes, Comprehensive International Programme on Research on AIDS, and International AIDS Clinical Trials Group) will provide synergy and prevent duplication of effort. The research programme will be flexible, such that it can respond to newly arising issues and provide guidance for future efforts.

The substance of the research agenda is based on extensive use of quantitative and qualitative methods. While quantitative research is essential to assess the success of specific aspects of the programme, added strength derives from associated qualitative studies. Qualitative and behavioural research provides greater insight into clinical decisions. Qualitative research also gives voice to individuals, families, communities, and illuminating circumstances. Qualitative information from HIV-infected individuals is particularly critical to the success of the programme, as the introduction of HIV and AIDS care and treatment constitutes an entirely new future for the HIV-infected population. Care and treatment will also alter the relationships among the infected and their families, communities, and care providers.

## **APPROACH**

### **Clinical Research**

Most data that guide the use of ARVs have been generated in the setting of developed countries, and have focused on different strains of virus than those responsible for the

South African epidemic. Although there is no question that ARVs can be life extending, the optimal use of these drugs has not been determined in the South African setting. Operational research to define best practices in similar settings has been limited. The performance of VCT sites to diagnose HIV infection and laboratory facilities to monitor resistance and the response to treatment are critical to the success of the programme. Development and use of new diagnostic tests for CD4, viral load, and resistance monitoring, and new parameters on the timing, frequency and location of laboratory monitoring, need to be evaluated.

A significant concern of the ARV programme is the development of resistance and the transmission of resistant strains of the virus. There is a clear, immediate need to research and develop an early warning system that indicates the onset of resistance, both at the service point level and at a national level.

The impact of antiretroviral medications on adolescent growth and development in naïve populations is a unique area of inquiry. Little has been published on the interplay of these medications on post-pubescent physiology, including issues around contraception.

### **Epidemiological Research**

Epidemiological research will constitute an important aspect of the research agenda. This area of research will augment information that is currently collected in routine reporting systems and research projects which constitute HIV and AIDS surveillance systems. These include studies such as the Department of Health annual prevalence surveys, Behavioural Surveillance, Youth Risk Surveillance surveys and HIV incidence studies. Epidemiological studies include studies that add information on the progression of the HIV and AIDS epidemic. Data collected in this ARV programme will provide important epidemiological data on morbidity and mortality related to AIDS. Epidemiological studies will be able to provide more detailed information on HIV and AIDS associated morbidity, mortality and disability in the context of the overall burden of disease in South Africa.

### **Health Systems Research**

Health systems research will include a broad range of issues including questions related to activities aimed at improving the health system's capacity to handle the increased service

requirements established by the implementation plan. Research projects may define how best to facilitate the integration of ARV programmes with general health services and with other HIV-related programmes, to avoid the creation of vertical, specialised operating silos among programmes. Specific projects will for instance evaluate whether the initial implementation, as well as integration with existing programmes at the service points, will de-stigmatise and de-mystify HIV care. Special attention will be given to identifying impact of ARV roll out on treatment behaviours, and concerns and strategies related to available HIV therapy in the workplace. Studies will also assess how the HIV and AIDS care and treatment plan affects other health programmes.

### **HIV Prevention Research**

Prevention of HIV infection is the foundation for management of HIV and AIDS. Prevention can be augmented through a successful treatment plan. The classical method of preventing viral infection is vaccination. However as yet no HIV vaccine exists, and current progress suggests that it will be at least 5–10 years before an effective vaccine is available. The well known maxim that ‘the only vaccine for HIV is prevention’ still rings true; and behavioural science research to investigate how to enable people to protect themselves from HIV infection (through modification of sexual behaviour, use of condoms, microbicides, diaphragms etc.) is a key priority in HIV and AIDS research.

### **Behavioural Research in Prevention, Treatment and Care**

HIV and AIDS is as much a psychosocial phenomenon as it is a biomedical phenomenon. Thus, the behavioural science research agenda is critical to providing insights leading to the discovery of improved treatment regimens for HIV-infected individuals. For the behavioural science research agenda a high priority is (a) designing, implementing and evaluating HIV sexual risk-reduction programmes to prevent the acquisition of HIV; (b) elucidating factors associated with adherence to antiretroviral medication and designing adherence programmes; (c) making antiretroviral medication more easily accessible; (d) reducing stigma associated with being at risk and living with HIV and AIDS. Priority behavioural research objectives for each of the following sections have been identified and are listed in the annexes (Annex XiV.1).

AIDS in South Africa is a disease that is transmitted primarily by social interactions between sexual partners. These risky sexual behaviours can be changed. Effective primary prevention programmes to prevent the further spread of HIV can assist people in making and sustaining behavioural changes that reduce the probability of transmission of HIV. A critical component of the behavioural science research agenda is to discover how to change behaviours and conditions that lead to HIV transmission including preventing their initiation and maintaining protective behaviours once they are adopted. Currently, behavioural interventions are the only effective way of slowing the spread of HIV. Cumulatively, meta-analyses evaluating the efficacy of HIV prevention studies, provide strong empirical evidence that interventions designed for individuals are efficacious in reducing high risk sexual behaviours.

Subsequent to identifying risk factors, HIV prevention research efforts must address issues related to the initiation and maintenance of HIV and AIDS risk-reduction efforts. This process requires moving beyond HIV and AIDS prevention programme efforts that only focus on providing information, education and communication (IEC). Moving beyond the IEC agenda requires the development of evidence-based HIV prevention programmes. Moreover, interventions designed to enhance adherence to antiretroviral therapy must be a research priority.

Rapid advancement of meaningful and effective HIV related social and behavioural science research requires further development of methodological tools, including those for evaluating HIV prevention interventions. As methodology represents the essential building blocks of intervention research it needs to be given special attention. Research methods are required to increase recruitment, retention and compliance to protocols for adherence and HIV prevention research. Adherence and HIV prevention intervention efficacy should be evaluated by using rigorous research methods, including randomised controlled behavioural trials. Evaluations of behavioural intervention studies should use self-reports of behavioural outcomes, as well as, HIV sero-incidence data and other biological markers as outcome measures. In addition to assessing intervention efficacy, researchers should assess the cost-effectiveness of prevention programmes. Finally, more research is needed to address the pressing ethical issues in the conduct of adherence and HIV prevention research.

### **Social Research**

The impact of HIV and AIDS is experienced not only by individuals, but also by families, communities, and societies. The effects of the epidemic at all of these levels must be understood and monitored so that strategies can be developed to prevent household, social, and economic disintegration. The predominant mode of HIV transmission in South Africa is heterosexual transmission. Thus, designing interventions involving both partners of the couple to enhance their communication skills and facilitate partner norms supportive of safer sex is critical. There has been increasing recognition of the importance of the family in preventing and adapting to HIV prevention efforts. Families may include consanguine relationships, extended families, and kin sharing similar values and norms. Fostering family norms supportive of safer sex and adherence, providing HIV and AIDS education within the context of the family, and enhancing communication skills between parent and their children to dialogue about HIV prevention can be effective strategies. Effective interventions at the community level involve the community (neighbourhoods, social network members, organizations, institutions) as a partner and can enhance community norms supportive of safer sex and adherence. Societal level interventions involve modifying economic, legal, policy, and regulatory practices such that they may facilitate safer sex and therapeutic efforts.

Women experience HIV and AIDS differently than men do in a number of important respects, some of which are physiological and some of which are social. Women progress to AIDS at lower viral load levels and higher CD4 counts than do men. Women are more vulnerable to HIV as a result of cultural attitudes, social and economic position. This may be partly explained because context of heterosexual relationships and social arrangements are often characterized by gender inequality in which women have less power than men further exacerbates their risk of HIV. It is important to understand the socially constructed aspects of male and female relationships including economic dependence, political decision making, access to health services, and education that may influence access to antiretrovirals and practice of safer sex efforts. HIV infected pregnant women have received a great deal of attention, however, this has mostly focused on their role in preventing transmission to their offspring. Greater attention must be given to the women themselves.

There has been a growing recognition that many individuals at risk of HIV and who become infected with HIV are also afflicted by a number of co-morbid conditions including other infectious diseases (hepatitis, sexually transmitted diseases, tuberculosis), substance abuse, mental illness, malaria (and other disease prevalent in South Africa) and poverty. Research needs to test the efficacy and effectiveness of interventions that simultaneously address multiple diagnoses and risk and improve HIV treatment adherence. In addition to assessing the efficacy of the interventions, research is needed to understand and improve the organization, management, access, delivery, cost-effectiveness, and cost-utility of health care, family planning, social services, drug treatment services, alcoholism treatment that reduce HIV risk behaviours and transmission.

Support research for the development, evaluation, diffusion and adoption of strategies to increase early identification, to improve treatment adherence, and to prevent or minimize the negative physical, psychological, cognitive and social consequences of HIV including stigmatisation of persons with or at risk for HIV infection. Support research strategies for promoting effective health care utilization among all persons with HIV infection and for promoting modifications in the health care delivery system to develop more effective, culturally sensitive methods to better serve treatment needs of infected populations.

### **Specific Research Projects**

Within the framework of these three areas, there are a number of research questions that are of highest priority (note that this list assumes that a national treatment cohort with a uniform database will be established; thus, this is not listed as a specific objective). These include:

#### ***HIV/TB Co-infection***

The burden of co-infection with TB presents a specific challenge in terms of treatment of HIV infection. Guidelines for initiation of therapy and for initial treatment regimens have been derived from settings lacking a high burden of TB infection. However, in South Africa, it is estimated that over 55% of persons with HIV infection may also have clinical tuberculosis<sup>1</sup>. The optimal timing of treatment of TB and HIV in co-infected persons and the optimal regimens for effective treatment remain to be determined. Thus operational

research to answer the following critical questions must be part of the initial ARV implementation plan:

- *What is the best treatment strategy for HIV-infected TB patients?*
- *What are the ARV regimen options that are most effective in the setting of concomitant clinical TB?*
- *Does malaria have an effect on ARV therapies?*

### ***Opportunistic Infection***

Research on opportunistic infections, and the mechanisms of infection and treatment should be an important component of the research agenda. A number of important research questions will arise, including:

- *What is the incidence/prevalence of various opportunistic infections in South Africa*
- *Do clinical course/severity and response to treatment differ from study populations in other geographic areas*
- *What is the role of co-infection with sexually transmitted infections (such as HSV2) on -infections with HIV*

### ***Drug Resistance***

One of the major threats to future treatment options for HIV infection is the development of antiretroviral drug resistance. Use of sequential monotherapy and dual therapies, and inadequate adherence to triple combination therapies has resulted in widespread emergence of multi-drug resistance in developed countries. Surveillance studies have indicated transmission of drug resistant viruses that compromise options for treatment of newly diagnosed infections. Success of the ARV treatment programme in South Africa will depend on the potency of the regimens used and proper adherence to these regimens. Moreover, the impact of widespread nevirapine use in PMTCT programmes on development of resistant mutations needs to be determined. Thus operational research to answer the following critical questions must be part of the initial ARV rollout plan:

- *What is the impact of nevirapine PMTCT programmes on subsequent treatment of women and their children?*
- *What is the evolution of drug resistance in the treated population as the programme is rolled out?*
- *What is the prevalence of drug resistance in the untreated population (i.e., how much drug resistant virus is being transmitted)?*

***What Are the Optimal Efficacy and Toxicity Monitoring Approaches in the South African Context?***

Most studies of ARVs have been performed in settings in which resources for monitoring efficacy and toxicity have not been limited. This has led to frequent monitoring, but the optimal frequency of monitoring has not been determined in a prospective controlled fashion, nor has the cost effectiveness of different monitoring schedules been determined. In addition, as the cost of ARVs drops, it is expected that a major economic burden will be the cost of diagnostic tests. Many new approaches to more economical monitoring, both through new monitoring techniques and through adjustment of monitoring schedule, are being developed. However, the impact of these new approaches on the quality of care delivered has not been determined. Thus a major important focus of initial research efforts should be to determine the optimal means of monitoring treatment. Operational research issues related to this effort include:

- *What is the optimal use and frequency of CD4 testing?*
- *What is the optimal use and frequency of viral load testing?*

***What Are the Behavioural/Social Issues That Affect Success of Treatment Efforts?***

The ultimate success of ARV treatment programmes is highly dependent on strict adherence to treatment regimens. Although there are clear data indicating that high levels of adherence to ARVs can be achieved in resource limited settings, the relative efficacy of different approaches to maximize adherence has not been determined. Moreover, the impact of new programmes for HIV and AIDS treatment on other aspects of the health

care delivery system has not been defined. Operational research issues related to behavioural/social issues include:

- *What are the optimum strategies to maximize and monitor drug adherence?*
- *What is the effect of the availability of ARVs on uptake of VCT?*
- *What is the effect of the ARV programme on sexual behaviour?*
- *What is the effect of the ARV programme on stigmatisation?*

***What Are the Optimal ARV Regimens and Treatment Strategies?***

Studies that have determined optimal regimens for treatment of HIV infection have largely been conducted in resource rich settings, where access to frequent laboratory monitoring is readily available. In these settings there nevertheless remain a number of inadequately addressed questions. The optimal use of ARV regimens in settings where resources are more limited, and where nutritional challenges and co-infections are more prevalent, remain to be determined. These factors pose a new set of research questions, which include:

- *What effect do different CD4 counts have on treatment outcomes as it relates to initiation of therapy?*
- *What to start: Should the initial regimen be non-nucleoside reverse transcriptase inhibitor (NNRTI) based or protease inhibitor (PI) based?*
- *When to change: Should clinical, CD4 or VL indications be used to determine when to change therapy?*
- *What to do in pregnancy? What are the optimal first and second line regimens in pregnancy?*
- *What to do in paediatric infection? What are the optimal first and second line regimens in paediatric infection?*

***What is the Role of Nutrition in Health Maintenance in HIV Infected Persons?***

HIV infection drives a hypermetabolic state with resultant weight loss and reduction in muscle mass and subcutaneous fat. With advanced HIV disease, micronutrient deficiencies may supervene, exacerbating the immune deficiency state, and increasing susceptibility to opportunistic infections. There is therefore a need to determine the following:

- *What are the optimal approaches to the delivery of essential nutritional elements to PLWHAs?*
- *To what extent do nutrition programmes prolong the period of time prior to the need for ARV treatment?*
- *Does nutritional supplementation affect the frequency of occurrence of opportunistic infections?*
- *Does nutritional supplementation augment adaptive and innate immune responses?*

***What is the role of traditional and complementary medicines in treatment of AIDS?***

Claims have been made, in South Africa and other African countries, that various African traditional medicines are able to restore immune function, with many impressive case reports that attest to improved clinical state, rising CD4+ count, and reduced viral load in people living with AIDS who take these medications. Other ‘immunopotentiators’ that have been investigated in the USA include interleukines, structured treatment interruption, Chinese herbs, lentinin (shitaki mushrooms), and other cytokines in general. Traditional healer therapies might have some immuno-restorative qualities.

Research would focus on:

- safety and toxicity of such traditional medicines
- clinical efficacy in controlled clinical trials – some of which are already underway
- drug-drug interactions with ARVs

***Does Advanced HIV Infection and AIDS Impair Absorption of Drugs?***

This has not been extensively studied but there are indications that anti-TB medications may be malabsorbed in patients with advanced HIV disease and AIDS. The public health implications of low drug serum levels include the possibility of MDR-TB associated with HIV infection. Similarly, ARVs may also be malabsorbed, predisposing to sub-therapeutic doses, and drug resistance. The research questions posed by this observation include:

- *Determination of the bio-availability of antiretroviral drugs and anti-TB medications among HIV-infected TB patients compared with non-HIV infected TB cases.*
- *Is malabsorption related to the degree of immune deficiency in HIV-infected persons?*
- *What is the effect of intestinal parasites on drug absorption.*

***Determinants of and interventions against progression of HIV to AIDS***

HIV infection typically leads to severe immune deficiency associated with the loss of CD4 T-lymphocyte populations. Although progression rates in South Africa are not known, studies in other settings indicate that HIV infected individuals will progress to clinical AIDS and death within 7-10 years. In 20% of persons this occurs within 5 years and sustained asymptomatic states without a significant decline in CD4 T cell occur in about 2% of investigated populations. There are no such data in areas of the world hardest hit by this epidemic. The factors that influence these very different disease rates are unclear, but may relate to host genetic factors, different genetic features of the infecting virus strain, and the host immune response. These observations indicate that specific aspects of the human immune system may hold important determinants for disease progression. The key research questions for predominantly treatment-naïve populations include:

- *Determination of the benefits of population-level screen for genetic determinants of progression to assist in applying appropriate interventions at the appropriate times.*
- *Determination of the utility of immune-stimulants and modulators to assist in preservation of a stable host immune system and hence slow the progression to AIDS and delay the time until ARVs are needed.*

- *Determination of the effects of ARV treatment on immune reconstitution*
- *What are the mechanisms by which the small proportion of HIV infected cells are able to induce apoptosis of other uninfected CD4+ cells – a key research question that emerged from the discussions of the International Presidential AIDS Panel in South Africa in the year 2000 - the so called ‘bystander effect’*

### ***Improving HIV care and treatment through adjunctive immune modulation***

The use of HAART has been advocated as the most important intervention for HIV and AIDS. However there remain practical and virological limitations of the current regimens. Strategies that simultaneously investigate the potential for a combined virological approach and immune modulation aimed at improving control of viremia need to be explored. The pertinent questions include:

- *Determination of the effect of immune modulation as an adjunct to HAART on survival, improved and sustained protective immune systems as evidenced by slower progression to AIDS and the decline of the incidence of opportunistic infections.*
- *Will adjunctive immune modulation impact on immune recovery or are there critical states of immune destruction which are irreversible?*
- *What proportion of the infected population will be most responsive to immune modulators and are there surrogate predictors?*
- *Can immune modulation potentially replace HAART or reduce dependence on HAART?*

### ***Cancer***

Kaposi sarcoma and Non-Hodgkin’s Lymphoma are the main cancers in AIDS with cervical cancer in women with human papilloma virus being the third. This is especially common in South Africa where cervical cancer is the leading cancer in women.

- *Basic incidence/prevalence data, and information on progression is needed*
- *Studies on diagnosis and treatment are needed.*

## **SPECIAL CONSIDERATIONS**

In addition to the highest priority research issues that will be addressed immediately, additional research issues of high merit will be considered for future study. It is expected that funds for these projects will be obtained from sources outside of the current programme. These issues include:

1. What is the role of traditional and complementary medications in the context of HIV care and ARV treatment?
2. What are the gender-specific differences in natural history of HIV disease and response to treatment? (For the former, a natural history cohort of HIV infected, untreated should be established.)
3. What are the metabolic complications of ARV treatment in the South African population?
4. Does micronutrient supplementation improve clinical disease outcomes for PLWHA?
5. What is the cost-effectiveness of ARV treatment in South Africa?
6. What are the optimal models of care for urban and rural health care facilities?
7. To what extent can one identify markers of good outcome of treatment in the early stages of intervention; likewise can one define markers of bad outcome that can allow for early intervention to improve outcome?
8. What is the overall effect of the HIV and AIDS care and treatment programme on access to health care?
9. What is the impact of the HIV and AIDS care and treatment programme on attitudes of health care providers, and on retention of health care workers?
10. Various research questions are identified in other chapters of the Operational Plan, such as the pharmacovigilance, traditional medicines and nutrition chapters.

## **ADMINISTRATIVE STRUCTURE**

The research programme will be coordinated through the Health Information, Evaluation and Research Cluster at the national Department of Health.

### **Research Oversight**

Although it is critical to the success of the programme that oversight of the research agenda remains the preserve of the Department of Health, appropriate mechanisms will be found to ensure an efficient mechanism for managing research. It is equally critical that the operational plan be subjected to ongoing critical evaluation by independent investigators. This will ensure a careful and dispassionate assessment of the HIV and AIDS care and treatment programme.

### ***Review of Applications***

A rigorous and transparent peer review process will be used to ensure that all proposals are relevant to the interests of patients and of government; are of the highest scientific quality; are conducted by scientists competent to the task; and have been authorized by the appropriate institutional review boards. Peer review could be facilitated through existing peer review mechanisms such as those of the Medical Research Council (MRC).

### ***Allocation of Support***

Recommendations for funding will be made by the Research Advisory Committee and approved by the Department of Health. Funds to support research questions deemed to be highest priority will be provided through government and other supporters.

### ***Dissemination of Research Findings***

Appropriate mechanisms will be established to disseminate the results of this research, facilitated by regular reports from funded investigators. Emphasis will be placed on using research findings to improve and strengthen the programme.

### **Sources of Funding**

It is expected that networks similar to the clinical trial consortia will be established for the research programmes described above, and that twinning with external organizations will have immense capacity to leverage direct funding and strengthen research capacity. New funding strategies will also be developed.

### **Partnerships**

The Health Information, Evaluation and Research Cluster at the national Department of Health will create and maintain links with local, regional and international organizations, institutions and collaborating partners. These linkages will facilitate exchange of ideas, especially among health systems with experience in operational research on ARV implementation.

In the field of diagnostics, especially in high TB- and HIV-burden countries, the Bill and Melinda Gates Foundation initiative, the Foundation for Innovative New Diagnostics (FINN), is expected to expand its current efforts into the development of new diagnostics to improve TB diagnosis among HIV-infected persons. It has to be emphasised that there is a need for new affordable diagnostics for HIV and other opportunistic infections that can potentially be adapted for use at programme level in resource-limited settings.

### **PROGRAMME ASSESSMENT**

Formal review of the research agenda as well as of the management structure will be performed on a yearly basis by an independent panel comprised of scientists with expertise in HIV and AIDS. This panel will report to the Minister of Health.

The HIV and AIDS care and treatment plan also represents a unique opportunity to collect data that will inform not only South Africa's programme, but nascent programmes to expand HIV and AIDS care and treatment throughout sub-Saharan Africa and other affected regions of the world.