

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.