

Technical Guidance Note for Global Fund HIV Proposals



UNAIDS | World Health Organization | August 2011

Pharmacovigilance for antiretroviral drugs

Rationale for including pharmacovigilance in the proposal

Pharmacovigilance is the science and activities relating to detecting, assessing, understanding and preventing adverse effects or any other possible drug-related problems. Pharmacovigilance is a key component of comprehensive patient care and the safe use of medicines. Failure to monitor, understand and manage these events can result in poor adherence and treatment failure and can reduce confidence in antiretroviral therapy among both people living with HIV and care providers.

Pharmacovigilance is well established in most high-income countries, but its practice in low- and middle-income countries is variable. Pharmacovigilance for antiretroviral therapy in resource-limited settings is critical because largely generic antiretroviral therapy drug combinations not commonly used in well-resourced settings have been rapidly scaled up. Pharmacovigilance is required not only for long-term antiretroviral therapy but also for the antiretroviral drugs used for preventing the mother-to-child transmission of HIV. There are also distinct types of comorbidity (tuberculosis and malaria) and drug–drug interactions.

The Global Fund recommends that applicants implement mechanisms to monitor adverse drug reactions according to existing international guidelines. The World Health Organization, responding to a request from the Global Fund, has produced a strategy for countries that are seeking to advance pharmacovigilance systems, through the Global Fund and similar health initiatives.

The main pharmacovigilance methods proposed include spontaneous reporting, cohort event monitoring and targeted spontaneous reporting.

In spontaneous reporting systems – the most widely used system – health professionals and pharmaceutical manufacturers voluntarily submit suspected adverse drug reactions to the national regulatory authority. This requires fewer human and financial resources than cohort event monitoring or targeted spontaneous reporting. However, a serious limitation is underreporting, and in addition, the frequency of an adverse drug reaction attributable to a product or its safety in relation to a comparator cannot be determined.

Cohort event monitoring is a prospective observational cohort study of adverse events associated with one or more medicines. In cohort event monitoring, all adverse events occurring to a person taking antiretroviral drugs are collected regardless of the causality or relationship with the antiretroviral drugs. The advantages of cohort event monitoring (over spontaneous reporting) include the ability to produce rates, rapid results, early detection of signals, fewer missing data and less reporting bias. However, cohort event monitoring requires more resources than spontaneous reporting.

Targeted spontaneous reporting is a method that builds on the principles of both spontaneous reporting and cohort event monitoring. It advances pharmacovigilance within a treatment cohort as a best practice that improves the quality of care. Targeted spontaneous reporting enables focus on a specific drug of interest (such as tenofovir or zidovudine), a specific population of interest (such as women receiving extended antiretroviral prophylaxis or treatment for preventing the mother-to-child transmission of HIV or people switching from stavudine to tenofovir) or a specific adverse drug reaction (such as anaemia). Similar to spontaneous reporting, the method relies on voluntary reporting of suspected adverse reactions by health professionals. Further, similar to cohort event monitoring, everyone within a treatment cohort is monitored, but only data covering the area of interest are collected, unlike cohort event monitoring, which actively follows up people to collect data on all events. Targeted spontaneous reporting provides a monitoring method that is affordable, feasible and sustainable in the context of lifelong antiretroviral therapy in settings with limited financial and human resources.

Elements to be considered in the situation analysis

A situation analysis should assess whether the minimum requirements for a functional national pharmacovigilance system¹ are in place and working:

- ◆ a national pharmacovigilance centre with designated staff (at least one full time), stable basic funding, clear mandates, well-defined structures and roles and collaborating with the WHO Programme for International Drug Monitoring;
- ◆ the existence of a national spontaneous reporting system with a national individual case safety report form, that is, an adverse drug-related event reporting form;
- ◆ whether the country is a member of the International Drug Monitoring Centre (and sends reports);
- ◆ a national database or system for collating and managing adverse drug-related event reports;
- ◆ what pharmacovigilance methods are in place: spontaneous reporting, cohort event monitoring and targeted spontaneous reporting;
- ◆ a national adverse drug-related event or pharmacovigilance advisory committee that can provide technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management, including crisis communication; and
- ◆ a clear communication strategy for routine communication and crisis communication.

This would identify weaknesses in the national pharmacovigilance system that should be addressed.

Strengthening pharmacovigilance for antiretroviral therapy further requires that the situation analysis consider the state of the HIV epidemic and the state of antiretroviral therapy in the country.

Epidemiology

- ◆ Prevalence of HIV, number of people on antiretroviral therapy, number of antiretroviral therapy sites

Programme review

- ◆ Existing capacity in country for pharmacovigilance for antiretroviral therapy and gaps
- ◆ Whether there is already active pharmacovigilance within antiretroviral therapy programmes and whether and how it is linked to the national pharmacovigilance system
- ◆ If any, the number and type of adverse events related to antiretroviral therapy reported to the national pharmacovigilance centre, since this might identify targets for targeted spontaneous reporting
- ◆ The need for implementing new pharmacovigilance for antiretroviral therapy programmes or for strengthening and sustaining existing ones

Capacity for delivering services

- ◆ Antiretroviral therapy service implementers: national antiretroviral therapy programme, nongovernmental organizations and private sector
- ◆ Laboratory capacity (availability and quality) to monitor drug toxicity

Norms and standards

- ◆ Reporting forms and reporting guidelines
- ◆ Management of adverse events: guidelines for service providers

¹ *Minimum requirements for pharmacovigilance in countries*. Geneva, World Health Organization (http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_presentation.ppt).

Logistics

- ◆ Computer-based system: existing resources and gaps (software and hardware)
- ◆ Access to laboratory services (sample shipment and information flow)

Human resources

- ◆ Pharmaceutical and clinical experts in pharmacovigilance
- ◆ Service providers, including laboratory technicians
- ◆ Regulatory authorities
- ◆ Programme managers
- ◆ Training needs in the country and abroad
- ◆ Integrating pharmacovigilance into national curricula

Focus populations

The focus populations include:

- ◆ people receiving antiretroviral therapy (first- and second-line regimens and/or belonging to a specific subgroup: children, women, pregnant women, people with comorbidity, TB and hepatitis; and
- ◆ people exposed to antiretroviral drugs for other indications, such as for preventing mother-to-child transmission and for post-exposure prophylaxis.

Proposed activities

Based on the results of the situation assessment, the activities to strengthen pharmacovigilance might include establishing a national system, revising a national plan or minimally improving ongoing efforts. In all cases, it is important to establish links between antiretroviral therapy programmes and the national pharmacovigilance system, strengthening the latter as needed.

Three possible scenarios will likely be encountered, as follows.

1) The country has no pre-established pharmacovigilance system

- ◆ Contact the WHO Programme for International Drug Monitoring at WHO headquarters and its collaborating centre in Uppsala (the Uppsala Monitoring Centre).
- ◆ Plan to introduce pharmacovigilance in the national pharmaceutical system.
 - ▶ Establish a national expert working group.
 - ▶ Establish links with the WHO Programme for International Drug Monitoring and the Uppsala Monitoring Centre.
 - ▶ Prepare national policy, including resource planning, training for pharmacovigilance, developing data analysis of reporting forms and guidelines on training.
 - ▶ Prepare a pilot phase based on few sentinel sites, to use the opportunity of funding for HIV to boost the national pharmacovigilance effort: for example, building on the ongoing efforts of organizations managing antiretroviral therapy programmes, trying to create a national network on pharmacovigilance for antiretroviral therapy supporting the national pharmacovigilance effort, using or introducing reporting forms to be used in the forthcoming national guidelines on adverse drug-related event reporting and pilot testing data analysis.
- ◆ Identify and consult with implementing partners and stakeholders
- ◆ Decide on reporting methods and support

- ◆ Include pharmacovigilance in national antiretroviral therapy guidelines
- ◆ Training

2) There is a pharmacovigilance system in the country but it does not cover antiretroviral therapy

- ◆ Same as above; review and evaluate existing data
- ◆ Work to implement a spontaneous reporting system for antiretroviral therapy as a minimum
- ◆ Consider targeted spontaneous reporting
- ◆ Consider introducing, in a phased manner, methods that complement targeted spontaneous reporting, such as cohort event monitoring

3) There is a pharmacovigilance system in the country and it does cover antiretroviral therapy

- ◆ Evaluate the programme
- ◆ Implement changes and introduce improvements based on gaps and lessons learned
- ◆ Consider using the national capacity to help other countries that do not have established programmes

Depending on the gap analysis, the following activities might need specific support:

- ◆ staff recruitment;
- ◆ training, initial and refreshment training of the information technology programme managers and service providers;
- ◆ setting up the communication network and mechanisms;
- ◆ providing necessary tools: forms, registers, communication tools;
- ◆ starting implementing at the delivery level;
- ◆ updating and managing information through communication such as newsletters, letters, mails and web posting;
- ◆ ensuring a feedback system for providers, for the regulatory authorities and for the pharmaceutical industry;
- ◆ monitoring and evaluating reports;
- ◆ adapting and updating the pharmacovigilance programme; and
- ◆ integrating the results of pharmacovigilance into treatment programme management.

Some key indicators

- ◆ Number of quality reports of adverse effects linked to antiretroviral therapy (to the national database and to a global database) (with a baseline value: percentage and total number of reports annually or by centre)
- ◆ Number of antiretroviral therapy centres accurately reporting antiretroviral therapy adverse drug-related events and existing antiretroviral therapy centres
- ◆ Number of new antiretroviral therapy centres beginning to report antiretroviral therapy adverse drug-related events
- ◆ Number of programme managers and health workers trained in pharmacovigilance
- ◆ Number of national or regional registries established for specific population subgroups
- ◆ Number of targeted studies performed in specific populations

Costing

- ◆ Personnel needs: reporters, data entry clerks and data analysis staff
- ◆ Training cost
- ◆ Information technology needs, including hardware and software

- ◆ Cost of advocacy and sensitization work
- ◆ Mapping of existing antiretroviral therapy centres to be selected as sentinel sites, equipped, monitored and evaluated
- ◆ Costs around information sharing (web sites, bulletins, publications and circulars)

Links with other services

- ◆ Preventing the mother-to-child transmission of HIV
- ◆ National antiretroviral therapy programme
- ◆ Drug supply programme

How gender, human rights and equity issues should be addressed

Women have or should have equal access to care and treatment. Regarding adverse events linked to the use of antiretroviral drugs, children and women represent population groups exposed to specific, yet insufficiently reported and known, drug toxicity. In particular, treatment programmes in high-income countries provide most data on the adverse events of antiretroviral therapy, and a very limited number of children are treated there. Specific studies, cohorts and surveys should be implemented to ensure that the appropriate management of adverse reactions of antiretroviral drugs strengthens patient safety in these specific groups.

Key implementing partners to be considered

- ◆ WHO Department of HIV/AIDS and Department of Essential Medicines and Pharmaceutical Policies
- ◆ WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre
- ◆ Cohort survey implementers
- ◆ Academics and researchers

Type and sources of technical assistance

Contacts at WHO headquarters:

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Documents

WHO. *A practical handbook on the pharmacovigilance of antiretroviral medicines*. 2009
<http://apps.who.int/medicinedocs/en/m/abstract/Js16882e/>

WHO. *Pharmacovigilance for antiretrovirals in resource-poor countries*. 2007
www.who.int/entity/medicines/publications/PhV_for_antiretrovirals.pdf

WHO. *The safety of medicines in public health programmes: pharmacovigilance an essential tool*. 2006
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Uppsala Monitoring Centre. *Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre*. 2000
www.who.int/medicinedocs/en/d/Jh2934e

Uppsala Monitoring Centre. Surveillance de la sécurité d'emploi des médicaments: guide pour la création et le fonctionnement d'un centre de pharmacovigilance. 2000
<http://apps.who.int/medicinedocs/documents/h2934f/h2934f.pdf>

WHO. Pharmacovigilance for antiretrovirals home page
<http://www.who.int/hiv/topics/pharmacovigilance/en/index.html>

The documents are available free of charge from Quality Assurance and Safety of Medicines at WHO headquarters (qsm@who.int).