This document provides guidance on surveillance of the toxicity of antiretroviral (ARV) drugs. It is intended for national HIV/AIDS programme managers and implementing partners, such as non-governmental agencies and academic institutions, that are responsible for implementing systems to monitor the safety of ARV drugs. It focuses on approaches that address the particular needs of the HIV/AIDS treatment programmes to monitor the toxicity of ARVs. The proposed approaches include the development and maintenance of (i) targeted spontaneous reporting; (ii) active surveillance for specific toxicities within sentinel cohorts; and (iii) cohort event monitoring.

The document describes briefly the methods employed, their strengths and limitations, tools available for implementing them and practical issues that would need to be considered for particular settings or countries.

Main messages

1. The July 2013 World Health Organization (WHO) consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection now recommend to start treatment in adults as soon as the CD4 cell count drops to <500 /mm³ or less, and to start antiretroviral therapy – irrespective of CD4 count – in all children with HIV under 5 years of age, all pregnant and breastfeeding women with HIV, in all people with HIV with active tuberculosis and severe hepatitis B, and all HIV-positive partners where one partner in the relationship is uninfected. A daily single fixed-dose combination of tenofovir/lamivudine (or emtricitabine)/efavirenz is the preferred recommended first line regimen.

2. The new recommendations will result in more people on treatment, with earlier and prolonged exposure to ART in HIV infection, often with the intent to prevent HIV transmission.¹

3. On the basis of current evidence, WHO has determined that the risk of starting antiretroviral therapy earlier is far less than its benefits, but has also identified the need for more data to better understand the frequency and clinical relevance of ARV-associated toxicities. To assess the toxicity associated with ARVs in both the short- and long-term, the guidelines recommend implementation of toxicity surveillance within ART programmes.

4. ARV toxicity surveillance is an integral component of monitoring and evaluation within ART programmes. Technical requirements, including data collection, reporting, data outputs and feedback should be incorporated into HIV monitoring and evaluation activities of the programme.

5. Three surveillance approaches are suggested to assess ARV toxicity, namely: (i) targeted spontaneous reporting; (ii) active surveillance for specific toxicities within sentinel cohorts; and (iii) cohort event monitoring.

6. National priorities and objectives should dictate the type of monitoring approaches used in ARV toxicity surveillance; local needs, health-system characteristics, and available human, financial and technical resources should guide the selection of priority toxicity questions and the monitoring approach(es) used to address them.

7. Targeted spontaneous reporting and active surveillance within cohorts are complementary approaches and, where resources permit, adoption of both approaches should be considered.

8. Communication with and feedback to relevant stakeholders, including patients receiving ART, health-care providers, drug regulators and policy-makers, donors and international agencies, is an essential component of the performance and sustainability of the surveillance system.

9. Collaboration with partner organizations, national and international monitoring systems, cohort consortiums and clinical trial agencies, should be considered because it allows sharing of technical expertise and pooled analyses of toxicity data.

10. WHO provides advocacy tools, technical guidance and assistance to countries and partner organizations for the development and implementation of ARV toxicity surveillance and its inclusion into the Monitoring and Evaluation effort of antiretroviral treatment programmes. WHO also collaborates with scientific and research agencies to implement strengthened surveillance and research on ARV toxicity matching the needs that have been identified to inform future HIV global prevention and treatment policies.

Why is surveillance of the toxicity of ARV drugs within ART programmes important?

The new recommendations of the 2013 World Health Organization (WHO) consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1) encourage:

“all countries to initiate treatment in adults earlier (CD4<500 cells/mm³ or less), to provide antiretroviral therapy – irrespective of their CD4 count – to all children with HIV under 5 years of age, all pregnant and breastfeeding women with HIV, and to all HIV-positive partners where one partner in the relationship is uninfected. The Organization continues to recommend that all people with HIV with active tuberculosis or with hepatitis B disease receive antiretroviral therapy. A daily single fixed-dose combination of tenofovir/lamivudine (or emtricitabine)/efavirenz is the preferred recommended first line regimen. It is easier to take and safer than alternative combinations previously recommended and can be used in adults, pregnant women, adolescents and older children” (1).

These new recommendations aim at, and will result in, an increased and prolonged exposure to ART within HIV-infected populations. On the basis of current evidence, WHO has determined that the risk of harm from the recommended antiretroviral regimens is small and largely outweighed by their benefits. The reviews conducted for the guidelines highlighted that available evidence is restricted to studies with limited sample size and short duration, mainly in industrialized or high-income countries. The guidelines also highlight remaining evidence gaps and sensitive questions about toxicity that require attention (see Box 1).

The guidelines recommend implementation of toxicity surveillance within ART programmes, to provide data and assess the frequency and clinical relevance of specific types of toxicity associated with both the short- and long-term use of ART; increase confidence in the use of the drugs; identify populations with risk factors; and plan preventive strategies. It is notably essential to implement toxicity surveillance in low-resource settings, where toxicities may present a different pattern in association with environmental or behavioral factors and the prevalence of other conditions, and where ARV drugs are used in association with other medicines.
Goals and objectives of monitoring the toxicity of ARV drugs

The goal of monitoring is to support the safe use of ART, thus improving the quality of care and treatment outcomes, and to inform national guidelines and global policies on the use of ART in adults, adolescents and children.2

Specific objectives are to:

1. determine and minimize the incidence of drug toxicities associated with the use of (and introduction of new) ARV drugs;
2. monitor the impact of toxicities on treatment outcomes, including treatment discontinuation, medical significance, disability or incapacity, inpatient hospitalization or prolonged existing hospitalization, life-threatening illness and death, and congenital anomalies;3
3. determine the impact of risk factors, including other comorbidities, and the association with other medicines or traditional medicines on the incidence, nature or severity of ARV toxicity;
4. identify rare toxicities or toxicities associated with long-term use that have not previously been identified.

2 In 2010, WHO recommended that countries shift away from using stavudine because of issues with toxicity, and instead opt for zidovudine- and tenofovir-based regimen. The toxicity concerns have led to a progressive decline of stavudine globally over the past 5 years. Continued efforts are needed to replace stavudine by a tenofovir-based regimen in line with the 2013 WHO ARV guidelines (1, 2).

3 The surveillance of toxicity of ARVs in pregnancy and breastfeeding is addressed in a separate technical brief (2).
traditional spontaneous reporting, TSR can also be a means of detecting signals of adverse reactions that have not previously been reported. An example of a TSR approach is illustrated in Box 2.

Reporting should be incorporated into the routine monitoring and evaluation reporting requirements of ART programmes and be clearly differentiated from the existing national spontaneous reporting system. However, the programme should share its results with the latter system.

The TSR approach cannot be used to determine the incidence of serious adverse drug reactions because the denominator to calculate it – the size of the patient population exposed to the ARV drugs used – is unknown, and because the quality of reports may vary, and underreporting is likely to occur. However, if a targeted toxicity is reported at a frequency equal to or higher than a rough estimate of its expected incidence would suggest, this would warrant formal assessment of its incidence and, if serious, immediate remedial decision and action.

**Active surveillance for specific toxicities within sentinel cohorts**

Active surveillance for specific toxicities nests within existing cohorts set up in a country for research or monitoring and evaluation purposes. Cohorts selected for active surveillance of toxicities need to have a reliable system for capturing clinical and toxicity data. This approach determines the incidence of important drug toxicities as there is reliable denominator data on number of patients exposed to the drug of interest and the duration of exposure.

Working with existing cohorts, with a focus on exposure to one drug and the incidence of one or few toxicities of interest, enables optimization of the cohort size (which needs to be large when the defined toxicity is rare, but can be small if the toxicity is known to be relatively high). A focus on a relatively small number of toxicities can also improve the accuracy of their assessment. Toxicities can be detected from routine laboratory assessment, active case finding, or tracking regimen changes. Regardless of the approach adopted within the cohort, it is important that individual reports are assessed for causality in a scientifically sound, standardized manner.

Maintaining sentinel cohorts is resource intensive. Limiting the number of patients studied, for example through the selection of sentinel sites, limits the costs and increases the efficiency of the system. However, in sites that have a functioning electronic patient-monitoring system, it is increasingly possible to limit the cost, as these electronic monitoring systems can be reliably assessed and including the reporting of defined toxicities and serious adverse reactions would add very little to their running costs. One example of this approach is illustrated in Box 3.

**Cohort event monitoring**

The cohort event monitoring (CEM) approach is a prospective observational cohort study of adverse events associated with one or more medicines. In CEM, all adverse events occurring in a patient taking ARV drugs are collected, irrespective of the causality or relationship with the ARV drugs. CEM would optimally involve the recruitment of approximately 15 000 to 20 000 patients receiving an ARV regimen. Advantages of CEM (over spontaneous reporting) include the ability to produce rates of events, early detection of signals, fewer missing data and less reporting bias.

---

**BOX 2 TARGETED SPONTANEOUS REPORTING IN WESTERN CAPE PROVINCE IN SOUTH AFRICA**

A targeted spontaneous reporting system was implemented in early 2005. It is coordinated by the provincial government in collaboration with the Medicines Information Centre at the University of Cape Town. The system was designed to collect data on toxicities suspected for ARV drugs and other medicines in patients concurrently being treated with ARV drugs.

Case definitions of each of the solicited toxicities (e.g. lactic acidosis, hepatotoxicity, nephrotoxicity, major birth defects, etc.) are provided on the case-reporting form, as well simple guidance on reporting procedures (i.e. the what, when, how and where of reporting). The system is being constantly evaluated according to the changing needs of the programme: for example, when tenofovir was introduced into the treatment programme, the reporting form was updated to include nephrotoxicity. Feedback is provided to reporters in the form of an annual newsletter. Data derived from the system are routinely reported to the national programme managers and to the medicines regulatory authority.

---

4 An adverse event is defined as “Any untoward medical occurrence that may present during the treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment” (9).
BOX 3 ACTIVE SURVEILLANCE OF SPECIFIC TOXICITIES IN SENTINEL COHORTS IN WESTERN CAPE PROVINCE IN SOUTH AFRICA

Data from two existing sentinel HIV cohorts in Gugulethu and Khayelitsha, Cape Town, were used to explore the time to, and reason for, single ARV drug substitutions in patients on first-line ART. Single drug substitutions were used as an indicator of significant drug intolerance. This cohort analysis included 2679 individuals, all of whom were on non-nucleoside reverse transcriptase inhibitor-based therapy, and 75% initiated on stavudine. This study found that substitutions due to toxicity occurred early for nevirapine, efavirenz and zidovudine, with 8%, 2% and 8% of patients respectively having been substituted by 3 years. Rates of substitution for stavudine (owing to symptomatic hyperlactataemia, lipoatrophy and peripheral neuropathy) continued to accumulate over time, reaching 21% by 3 years. Women weighing more than 75 kg and on ART for more than 6 months were found to be at increased risk of hyperlactataemia. This, and other cohort studies, provided data that led to recommendations to avoid stavudine in obese women, and subsequently to tenofovir being recommended in place of stavudine, in WHO treatment guidelines.

However, as CEM requires a comprehensive cohort follow-up structure to be set up, it needs extensive financial and human resources. Where existing cohorts of HIV-infected people on treatment are being monitored, efforts to include event monitoring into their existing monitoring and research activities may be reasonably cost efficient. However, developing new cohorts exclusively for toxicity surveillance is not recommended. An example of a CEM approach is presented in Box 4.

Important considerations when developing a surveillance system

Surveillance priorities should be chosen for the local context, in consultation with national or regional clinical and epidemiologic experts and WHO guidance. It is very important to choose surveillance approaches that are appropriate for those objectives. TSR and active surveillance for specific toxicities within cohorts are complementary approaches and, where resources permit, adoption of both approaches should be considered. CEM could be pursued when cohort studies with very large scope are planned or ongoing.

Working within existing programme monitoring systems allows for efficient use of resources and integration of toxicity surveillance into routine monitoring and evaluation activities. Technical requirements include data collection, reporting data outputs and feedback.

Individual patient monitoring for toxicity should be integral to the delivery of high-quality patient care. Facility-based records can provide valuable information, if regular and accurate records are kept of key aspects of the care and treatment offered to patients. Patient-monitoring systems also record information on clinical and laboratory toxicity monitoring for individual case management. Aggregated reports generated through these systems could contribute towards documenting the impact of ARV-related toxicities on treatment outcomes. It would require that electronic medical record systems for patients on ARV regimens are accessible, to enable data extraction and aggregation.

In many countries, signals and information on the toxicity of the ARV regimens may arise not only from the toxicity surveillance system, but also from national and international sources of regulatory pharmacovigilance systems. Often, data arising from spontaneous reports, other regulatory data, and investigator-initiated research may contribute towards better understanding of the data derived from programmatic toxicity surveillance systems. Moreover, programmatic surveillance data can be used to improve the quality, efficacy and safety of medicines used nationally, by contributing to regulatory decision-making.
Therefore, programme managers, drug regulators, academic researchers and pharmaceutical manufacturers need to develop platforms that facilitate the exchange of information on the efficacy and safety of medicines used in the programmes.

Improving patient care and informing national and global HIV treatment and prevention policies

The value of a national toxicity surveillance system lies in its ability to inform policy and improve clinical care (see Figure 1). This can be achieved by ensuring that there is continual feedback and communication with relevant stakeholders, including patients and their communities, health-care staff, district/state/provincial/national authorities, the medicines regulatory agency, pharmaceutical manufacturers, the media and the national and international scientific community. Feedback should serve to guide and assist health-care staff in better managing patients and should therefore be directed both to health-care staff who submit reports and, collectively, to all health-care staff involved in the care of patients on ART. Educational and training initiatives should refer to data (including cases) and findings of the surveillance system and should prepare health-care staff for dealing with issues relating to toxicity concerns.

All public communications with stakeholders need to be skillfully prepared and relevant expertise employed to ensure that messages are clear, informative, contextual and delivered in the appropriate format/forum. A comprehensive communication plan, including a crisis-communication plan, needs to be developed as part of the surveillance system. If, for instance, the surveillance system identifies new significant risks associated with recommended treatment regimens that may warrant a revision of national guidelines, procedures should be already in place beforehand on how such issues should be handled.

### CHALLENGES AND HOW TO ADDRESS THEM

<table>
<thead>
<tr>
<th>CHALLENGES</th>
<th>SOLUTIONS</th>
</tr>
</thead>
</table>
| Underreporting, poor quality of reports and reporter “fatigue” within TSR | • Solicit reports for a specific window in time  
• Field-test forms and procedures  
• Provide training on why reporting priority toxicities is important  
• Give feedback to reporters to value the programme and their own practice  
• Provide simple clinically appropriate case definitions  
• Provide reporting guidelines and simple reporting procedures |
| Poor quality of the denominator within sentinel cohorts                    | • Allocate resources to ensure accurate data for calculation of incidence  
• Use triangulation of approaches – i.e. use of patient cohort data, pharmacy records and clinic registers  
• Acknowledge uncertainties |
| Difference among facilities in laboratory and clinical monitoring capacity  | • Assess laboratory monitoring and diagnostic capacity at candidate sentinel sites  
• Match the surveillance approach to laboratory and clinical monitoring capacity |
| Reliable and standardized causality assessment and decisions for policy     | • Adopt an internationally standardized and systematic approach to causality assessment (9)  
• Establish a panel of experts to review individual and collective data  
• Collaborate with national and international experts |
| Sustainability                                                              | • Provide feedback to patients, facility staff, administrators and policy-makers  
• Identify and address site staff concerns  
• Minimize additional responsibilities of routine health-care staff  
• Limit the reporting requirements (e.g. with electronic management systems) |
What is WHO doing?

The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1) recommend strengthening toxicity surveillance activities to increase evidence and inform future guidelines on toxicity in key areas.

In this context, WHO provides advocacy tools, technical guidance and assistance to countries and partner organizations for the development and implementation of ARV toxicity surveillance and its inclusion into the Monitoring and Evaluation effort of antiretroviral treatment programmes.\(^5\)

WHO also collaborates with scientific and research agencies to implement strengthened surveillance and research on ARV toxicity matching the needs that have been identified to inform future HIV global prevention and treatment policies.

WHO is convening a Steering Group on ARV Toxicity Surveillance, constituted by international experts and representatives of research agencies. The Group will advise WHO on the production of normative guidance and technical updates and enhance collaboration on toxicity surveillance to inform the clinical guidelines process.

WHO encourages countries to include ARV toxicity surveillance activities under the monitoring and evaluation component in the new Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) financing model, to mobilize funding to support ART toxicity surveillance within ARV treatment and PMTCT programmes (12).

The content of this technical brief was informed by pilot projects on toxicity surveillance that WHO has supported in several countries since 2011. More information on these projects can be found at: http://www.who.int/hiv/topics/arv_toxicity/en/index.html.

---

\(^5\) Technical consolidated guidance for monitoring and evaluation in HIV programmes will be available in 2014.
REFERENCES


USEFUL LINKS AND DOCUMENTS
