12. SURVEILLANCE OF THE TOXICITY OF ANTIRETROVIRAL DRUGS DURING PREGNANCY AND BREASTFEEDING

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 11 – Monitoring and evaluation

Main messages

- Surveillance of the toxicity of ARV drugs during pregnancy and the breastfeeding period aims to assess the risk of adverse reactions in pregnant women and adverse reactions to the fetus exposed in utero and to the infant exposed to ARV drugs during breastfeeding.

- Three surveillance approaches are suggested to assess these risks: (i) a prospective pregnancy-exposure registry; (ii) a birth-defect surveillance programme; and (iii) a prospective monitoring of cohorts of mother–infant pairs, during the breastfeeding period in sentinel sites.

- The national decision on whether surveillance of the toxicity of ARV drugs during pregnancy and the breastfeeding period should be undertaken, and on which approach to use, should be informed by local needs; health system characteristics; treatment-seeking behaviour of women; the available financial, human and technical resources; and the ability to link the required recording systems.

- To ensure that the data provide prompt, robust evidence for policy-makers, nationally and internationally, the data collected should be of consistently high quality. To ensure that data can be pooled to inform national and international policies, it is desirable that they be collected in a standardized manner.

- The commitment and support of national policy-makers, programme managers and health care staff at sentinel sites are critical to the success of any of these approaches.

- The sustainability of the surveillance system depends critically on communication and feedback of the data and findings to relevant stakeholders, including women and their communities; health care providers; drug regulators and other policy-makers; donors; and international agencies.

- WHO provides advocacy tools, technical guidelines and technical assistance to countries and technical organizations planning to implement ARV toxicity surveillance during pregnancy and the breastfeeding period. WHO also collaborates with scientific and research agencies to implement strengthened surveillance and research in the area of toxicity of ARV drugs in pregnancy and during breastfeeding, to inform future guidelines on the use of ARV drugs.

Purpose of this section

Chapter 7 of the WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1), “Clinical guidance across the continuum of care: antiretroviral therapy”, describes evidence from the systematic reviews conducted on the safety of ARV drugs in pregnancy and breastfeeding. The guidelines (1) also recommend that toxicity surveillance and additional research be conducted on the safety and acceptability of lifelong ART for pregnant and breastfeeding women, and their infants, especially in resource-limited settings, where malnutrition and comorbidity are more common that in resource-rich countries, and monitoring capacity is limited.

Based on current evidence, WHO determines that the benefits of using ARV drugs during pregnancy are considerable, in terms of both avoiding infant HIV infection and benefits to the mother, and greatly outweigh the potential low risks, including the risk of congenital malformation. However, to decrease uncertainty and provide more confidence around the level of risk, if any, and strengthen the motivation of both health care providers and people living with HIV to use ART during pregnancy and the breastfeeding period, WHO recommends that toxicity surveillance activities and additional research be conducted.

This section expands on the information provided in the guidelines with an overview of proposed approaches for assessing the safety of ARV drugs used during pregnancy and the breastfeeding period. It is intended for national HIV/AIDS programme managers and implementing partners, such as nongovernmental organizations and academic institutions, that are responsible for implementing systems to monitor the safety of ARV drugs. The proposed approaches include the development and maintenance of (i) a prospective pregnancy-exposure
registry; (ii) a birth-defect surveillance programme; and (iii) a prospective monitoring of cohorts of mother–infant pairs, during the breastfeeding period at sentinel sites.

This section describes briefly the methods employed, their strengths and limitations, tools available for implementing them and practical issues that would need to be considered for a particular setting or country.

**Why is surveillance of the toxicity of ARV drugs in pregnancy and during breastfeeding important?**

The recommendations for use of ARV drugs in pregnancy and during breastfeeding in the 2013 consolidated ART guidelines will result in earlier and more prolonged exposure to ARV drugs for women, as well as increased exposure to ARV drugs for infants during the breastfeeding period (2). The likelihood of first-trimester exposure of the fetus to the new recommended regimen will increase, as women newly diagnosed with HIV initiated on treatment during one pregnancy are likely to remain on treatment during subsequent pregnancies. In addition, the 2013 guidelines recommend starting ART earlier (CD4 count of 500 cells/mm$^3$ or less) and regardless of CD4 cell count for all people with HIV with active tuberculosis, with severe hepatitis B and for serodiscordant couples. This will also increase the number of infants born following exposure to ARV drugs during the first trimester of pregnancy. The first trimester is a critical period of exposure because organogenesis occurs during this time and exposure to teratogenic medicines can cause major congenital anomalies (3). Although, based on current data, WHO currently determines that ARV drugs do not, or minimally, increase the risk of congenital anomalies, more data would provide confidence about the level of risk, if any (1). Finally, pregnant women are known to be at increased risk of side effects of drugs, in particular those that affect the liver, kidney and blood pressure and mental side effects (Box 12.1).

**Goals and objectives of monitoring the toxicity of ARV drugs in pregnancy and during breastfeeding**

The goal of toxicity surveillance in HIV programmes is to ensure that the ART regimens are safe, including when used for preventing mother-to-child transmission by pregnant and breastfeeding women and for their babies.

To obtain reliable national data that contribute to national treatment guidelines and global policies, surveillance of the toxicity of ART during pregnancy and the breastfeeding period needs to include the following three areas of focus:

- maternal health outcomes: serious toxicities associated with ART in pregnant women;
- birth outcomes: on the fetus in utero, manifesting as stillbirths, preterm births and low birth weight or manifesting as birth defects; and
- infant and child outcomes: health outcomes among infants and young children exposed to ARV drugs via breast-milk, including effects on growth and development.

**Surveillance approaches**

Based on the priority toxicity issues to be addressed by the surveillance system, health care–seeking patterns of pregnant women and mothers, and available resources, surveillance systems could comprise of any or all of the following approaches:

- a prospective pregnancy-exposure registry for toxicity among pregnant women and neonates;
- a birth-defect surveillance system for assessing birth outcomes; and
- a prospective monitoring of cohorts of mother–infant pairs.

---

21. Congenital anomalies, also known as birth defects, are structural or functional abnormalities, including metabolic disorders, that are present from birth. Congenital anomalies are a diverse group of disorders of prenatal origin that can be caused by single gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens and micronutrient deficiencies. The terms “congenital anomalies” and “birth defects” are used interchangeably in this section.

22. The surveillance of the toxicity of antiretroviral medicines within antiretroviral therapy programmes is addressed in the next section (Surveillance of the toxicity of antiretroviral medicines within antiretroviral therapy programmes).
pairs for toxicity from birth throughout the breastfeeding period, including significant growth and developmental delays.

In all of the above approaches, recruiting and assessing a concurrent group of controls comprising pregnant women not exposed to ARV drugs (women not infected with HIV) is essential to understand the relative contribution of ARV drugs to the toxicity of interest and establish whether there is any additional risk. Since many of the adverse outcomes of interest are rare, it is important to pool the data collected from several sites across several countries to obtain sufficient data to determine whether or not treatments contribute to the risk of these rare adverse outcomes. Standardized data-collection approaches that comply the norms and standards of surveillance (4), including using standard terms such as those used in the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (5) for defects of interest, should therefore be used to enable the pooling of core data across sites and countries.

Box 12.1. Pregnancy-related toxicity concerns

The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1) identified that more data are desirable on:

- the risk of serious, life-threatening and fatal skin and hepatic reactions among pregnant women exposed to nevirapine during pregnancy;
- the risk of serious reactions such as seizures and nervous system and mental effects among pregnant women exposed to efavirenz-based ART regimens during pregnancy;
- the comparative risk of preterm delivery, stillbirths and small for gestational age births associated with various ARV regimens used during pregnancy;
- very low risk of neural tube defects in infants exposed in utero to efavirenz-based regimens;
- risk of renal and bone toxicity in infants exposed in utero or during breastfeeding to tenofovir-based regimens; and
- risk factors for serious and life-threatening anaemia in pregnant women exposed to zidovudine during pregnancy and the impact on birth outcomes.

Basic technical requirements for the three surveillance approaches

Prospective pregnancy-exposure registry

- At selected antenatal clinics, pregnant women are enrolled from their first antenatal visit and followed up to term, including delivery.
- At the first visit, information is obtained from the woman on her medical, obstetric and drug-exposure history.
- The fewest number of women are enrolled if there are an equal number of exposed women (cases) to unexposed women (comparators). This approach is recommended. 23
- At each later antenatal visit, information on infections, treatments and folate supplementation 24 is updated, and any new clinical conditions or diagnoses are recorded.
- Antenatal staff members are trained to obtain and record comprehensive and precise drug and medical histories.
- Women are encouraged to attend all follow-up antenatal visits and to deliver at the health care facility.
- Any adverse reactions occurring during pregnancy are actively solicited and systematically recorded and reported.
- At delivery, all liveborn or stillborn babies have a standard, surface examination, which establishes any

23. Sample-size estimations based on background incidence, case–comparator ratio and anticipated risk, including continuity correction, are documented in the protocol for a drugs exposure pregnancy registry for implementation in resource-limited settings (6). See also the European Medicines Agency Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (7).

24. Folic acid supplementation is recommended before pregnancy and in the first three months, to prevent neural tube defects and other congenital malformations in the fetus among all women (8).
external and visible birth defects and identifies neonates needing immediate medical or surgical attention (9).

- These data are recorded on standardized data-collection sheets.
- All suspected major congenital anomalies are photographed.
- Experts in birth defects later provide diagnoses of any birth defects after reviewing the documentation and photographs.
- The data are analysed to determine whether any additional risk of adverse outcomes in infants can be attributed to the exposure to ARV drugs during pregnancy (Box 12.2).

**Box 12.2. Prospective pregnancy registry in South Africa**

South Africa is implementing a national pregnancy registry to assess the safety of the ARV regimens and other medicines commonly used in pregnancy. Concerns about medicines such as co-trimoxazole and anti-tuberculosis drugs, and other conditions that may predispose women to risks of adverse birth outcomes, have dictated the need for a prospective approach with a scope beyond ARV drugs.

At sentinel sites, all new antenatal women are recruited into the registry. The maternity case records used at the sites facilitate systematic collection of relevant information at each antenatal visit on drug exposure, occurrence of adverse reactions, comorbidity, ultrasound and other diagnostic tests and birth outcomes. A bright sticker on maternity records identifies the woman as a pregnancy registry woman and allows referral facilities and other sites to rapidly recognize women who are part of the registry so that they can inform the pregnancy registry site coordinator regarding the pregnant woman or her neonate and data entered into the registry database.

Health care staff members at the sentinel sites are trained to (i) elicit and document medical, obstetric and drug histories and other clinical information in the maternity case records; (ii) conduct and document a systematic surface examination of each neonate, using training materials developed by WHO; and (iii) take photographs and record birth defects and refer infants appropriately. A national birth-defect panel will review all reported major congenital anomalies and determine whether the cases should be included in the analyses related to teratogenicity.

The National Health Research Ethics Council has waived the need for informed consent by women enrolled in the registry, except for permission to photograph babies born with a birth defect.

**Birth-defect surveillance**

- A few facilities are selected that provide good obstetric care and with many deliveries.
- All women presenting for labour at these selected facilities are included.
- At delivery, all liveborn or stillborn babies have a standard, surface examination, which establishes any external and visible birth defects and identifies neonates in need of immediate medical or surgical attention.
- All suspected congenital anomalies are photographed.
- Before discharge, information is obtained from the woman and/or from her medical records about her medical and obstetric history and the use of medications (including ARV drugs) during the course of her pregnancy.
- These data are recorded in a standard data-collection sheet.
- Experts later provide diagnoses of any congenital anomalies after reviewing the clinical documentation and photographs.
- The data are analysed to determine whether any additional risk of adverse outcomes in infants can be attributed to the exposure to ARV drugs during pregnancy (Box 12.3).

---

25. The WHO Tropical Diseases Research and Reproductive Health and Research Programme has produced a video guide to a stepwise surface examination of neonates, to train health care workers to assess a neonate for birth defects (9). It supports a new protocol for a pregnancy registry (6).
Box 12.3. Birth-defect surveillance in Malawi

Malawi is implementing a birth-defect surveillance system in two hospitals with high numbers of deliveries (>10,000 deliveries per year). The system aims to establish a baseline prevalence of neural tube defects and other major birth defects among neonates and to compare this to the observed prevalence in ARV-exposed pregnancies. All births, both live and stillborn, delivered at the participating institutions will be systematically assessed for birth defects within a few hours of birth. The sample size will be calculated based on assumptions regarding the prevalence of HIV, the prevalence of neural tube defects and the percentage of women exposed to ARV drugs and the goal of ruling out a twofold increased risk of neural tube defects with efavirenz exposure. A structured data-collection form, including photographs, will be used at the sites to record the assessment of every facility-based birth. There will also be a uniform approach to ascertaining ARV exposure in the first trimester. There will be uniform classification and coding of birth defects using ICD-10 (5), and birth-defect experts will validate diagnoses.

Prospective monitoring of cohorts of mother–infant pairs during the breastfeeding period

- Cohorts of mother–infant pairs (infants exposed and unexposed to ARV drugs during pregnancy and breastfeeding) are enrolled at birth and followed up over the course of the breastfeeding period (typically 18–24 months).
- Depending on the ARV regimen used for breastfeeding women and infants, case definitions should be developed to assist health care staff in identifying targeted types of toxicity that should be monitored.
- Enrolled infants are assessed in a standardized, systematic manner, for bone growth, renal function (where feasible), nervous system development and HIV infection, at all facility visits (such as immunization visits, paediatric services, emergency room visits or hospitalization) during the breastfeeding period, at specific times.
- All findings, including reports of HIV infection, growth parameters, fractures, seizures and hospitalizations, are recorded.
- The data are analysed to determine whether any additional risk of adverse outcomes in infants can be attributed to the exposure to ARV drugs during breastfeeding.
- Settings with a fairly stable population, with reasonable access to care and where home-based follow-up is possible are the most suitable for this approach (Box 12.4).

Box 12.4. Malawi breastfeeding cohort

In Malawi, a surveillance programme will monitor infant growth and neurocognitive development within a cohort of breastfeeding mother–infant pairs receiving regimens including tenofovir or efavirenz. Active surveillance will be conducted for parameters that indicate growth and development problems among infants exposed to ARV drugs via breast-milk. This component has been introduced in two ongoing cohort studies conducted in Malawi that will each recruit and follow up about 1500–2000 pregnant women living with HIV until 18–24 months postpartum. All women in these cohorts will receive ART (tenofovir, lamivudine and efavirenz) according to the Malawi national protocol. The studies will implement interventions to improve the retention of mothers throughout the postpartum period.

Important considerations when developing a surveillance system

Countries with a moderate to high prevalence of HIV infection among pregnant women, and high coverage of ART during pregnancy, for preventing mother-to-child transmission; countries using efavirenz- or nevirapine-based regimens as first-line treatment among pregnant women and women of childbearing age; and those adopting option B or option B+ as a policy for preventing mother-to-child transmission should consider implementing one or more of these surveillance systems.
Decision-makers need to give priority to the key toxicity issues of concern. If there are toxicity issues concerning the pregnant woman (such as risk of hypersensitivity reactions with nevirapine), a pregnancy-exposure registry should be considered. If the priority concerns are regarding birth outcomes, a birth-defect surveillance or pregnancy-exposure registry would be suitable. If there are concerns about breastfeeding exposure, prospective cohorts of mother–infant pairs are appropriate. Logistical issues, such as availability of surveillance staff, budget, timelines for funding and sample-size requirements, need to be considered, to assess the feasibility of the different approaches. The process for decision-making related to which of these approaches to adopt at the national level depends on various factors.

The pregnancy-exposure registry has the potential to collect information on serious adverse reactions occurring among women during their pregnancies. The ability to detect and collect information on such reactions depends on the diagnostic capacity available at the antenatal clinic, awareness of safety issues among health care staff, record linkage and continuity of care between clinical services (such as emergency rooms and medical wards) and antenatal services. Programmes need to consider these issues, as well as the priority toxicity concerns in pregnant women, when determining the type of data that are collected during the pregnancy as part of the pregnancy-exposure registry.

The birth-defect surveillance approach in a setting with high HIV prevalence, high coverage with ART during pregnancy and many deliveries will allow reporting on a large number of births more quickly. If there is good record-keeping and record linkage between antenatal, labour and delivery and postnatal care, and if drug exposure during pregnancies is systematically recorded, birth-defect assessment at the hospital and organizing the data flow may the only incremental efforts required to set up birth-defect surveillance.

Both pregnancy-exposure registry and birth-defect surveillance require rigorously examining the neonate, accurate information about drug exposure and comorbidity during pregnancy and many assessments to assess the risk to the fetus of exposure to ARV drugs.

The breastfeeding mother–infant cohorts also require proper assessment of the infant, drug exposure, breastfeeding patterns and clinical history-taking throughout the breastfeeding period. Standardized but simple assessments for growth and nervous system development need to be implemented at specific times during the growth of the breastfeeding infant. Ongoing validation and quality-assurance activities need to be implemented, to ensure that the data continue to be of good, reliable quality (Fig. 12.1).

Fig. 12.1. Parameters for planning for a toxicity surveillance system of antiretroviral drugs during pregnancy and breastfeeding

From decision-making process into practice

Parameters for decision-making

- HIV prevalence and coverage of ARV medicine for preventing mother-to-child transmission
- National safety priorities for the use of ARV medicines for preventing mother-to-child transmission
- Concerns about other potentially teratogenic or harmful drug exposure
- Concerns about direct toxicity to pregnant woman
- Treatment-seeking behaviour during pregnancy and breastfeeding (such as home-based delivery; rates of losses to follow-up)
- Human and financial resources
- Sample size requirements
- Presence of electronic patient record systems
- Data-management capacity
- Record linkage system between HIV treatment services, antenatal care, services for preventing mother-to-child transmission and health services

Tools available from WHO

- Pregnancy registry protocol
- Training modules
- Procedures for systematic examination of neonates
- Model case-record forms
- WHO/CDC/ICBDSR joint manual for birth-defect surveillance
- Core data fields to facilitate data pooling

Adapted for national use

Into practice
Before initiating any approach, it will be important to consult with the national health research ethics committees on whether there is any need for written informed consent from pregnant women included in the pregnancy-exposure registry or birth-defect surveillance or whether written informed consent can be waived on the grounds that surveillance forms part of routine care and is in the interest of safety. In general, written or oral permission to take photographs of babies with a birth defect is likely to be required.

Responding to methodological and programmatic challenges in establishing ARV toxicity surveillance

Table 12.1. Surveillance challenges and how to address them

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solutions</th>
</tr>
</thead>
</table>
| High rates of home births and high rates of loss to follow-up | Intensify interventions to encourage facility-based births  
Address known barriers to accessing care – such as transport and ambulance services.  
Use automated SMS reminders to women during the pregnancy to attend scheduled visits and to prepare for delivery at a health care facility.  
Train antenatal clinic health care staff and community health nurses to visit or telephone women who miss scheduled visits. |
| Late presentations for antenatal care during pregnancy (pregnancy-exposure registry only) | Select sites with a high proportion of early uptake of antenatal services.  
Consider a birth-defect surveillance approach only, as the quality of information on first-trimester exposures is unlikely to differ between pregnancy-exposure registry and birth-defect surveillance. |
| Incomplete or poorly completed antenatal and labour or delivery records do not routinely collect the data required for the surveillance system | Design data-capture forms or systems that are easy to use and train staff in their use.  
Frequently or automatically verify data for completeness at sites.  
Validate data using other data sources.  
If feasible, identify other than routine health care staff for data capture. |
| Poor record linkage between antenatal and labour and delivery services | Flag maternity case records (antenatal cards) to alert staff to link records.  
Introduce an integrated patient-record system used by all sites and services. |
| Poor-quality data capture from source documents                | Train and supervise staff capturing data.  
Provide feedback to staff involved on issues relating to data recording. |
| Sustainability                                                | Provide frequent feedback to health care facility staff, women, administrators and policy-makers.  
Identify and address site staff concerns about the system on an ongoing basis.  
Integrate the system in the routine delivery of care.  
Limit the reporting requirements (such as with electronic practice management systems). |

Engaging stakeholders in establishing surveillance systems

A comprehensive communication strategy that identifies target groups, communication objectives and a practical communication approach (means of communication, type and frequency of outputs) needs to be developed that guides programme staff on how to engage with key stakeholders. Target groups include the pregnant women; their communities and health care providers; academic and professional associations; the national regulatory authority; nongovernmental organizations and other partners; and
the mass media. Issues around data sharing, publication agreements and dissemination of findings should be discussed and agreed on at the onset of such programmes.

Collaborative links with the regulatory pharmacovigilance systems, related programmes, such as maternal and child health programmes, and clinical services need to be established or strengthened. Programmes need to allocate adequate resources and attention to these collaborative activities, to ensure a consolidated approach to addressing issues of patient safety without duplication of efforts.

What is WHO doing?

The Sixty-third World Health Assembly in 2010 endorsed a report by the Secretariat on birth defects. This report describes the basic components of a national programme for the prevention and care of birth defects before and after birth and the priority actions recommended to the international community to assist in establishing and strengthening these national programmes (10).

In this context, WHO is working with the National Center on Birth Defects and Developmental Disabilities of the United States Centers for Disease Control and Prevention, the International Clearinghouse for Birth Defects Surveillance and Research, EUROCAT and health ministries in participating countries with high HIV prevalence to provide technical expertise at the country level for surveillance of birth defects. WHO has produced a guiding protocol (6) and training video (9) on the conduct of a systematic surface examination of newborn infants, for countries planning to implement a pregnancy registry. A joint manual has been produced that provides methods for implementing a congenital anomalies surveillance system (4).

WHO is an active member of an ARV Birth Defect Task Team with the United States President’s Emergency Plan for AIDS Relief, the United States Centers for Disease Control and Prevention and the United States National Institutes of Health. The task team provides national programmes for preventing mother-to-child transmission with coordinated technical assistance in planning and implementing birth defect surveillance programmes (11).

WHO provides advocacy tools, technical guidelines and technical assistance to countries and technical organizations implementing ARV toxicity surveillance during pregnancy and breastfeeding. WHO encourages countries to include ARV toxicity surveillance activities under the monitoring and evaluation component of the new Global Fund to Fight AIDS, Tuberculosis and Malaria funding model, to mobilize funding to support ART toxicity surveillance within ARV treatment and programmes for preventing mother-to-child transmission (12).

WHO is convening a Steering Group on ARV Toxicity Surveillance, comprising international experts and representatives of research agencies. The Group will advise WHO on producing normative guidance and technical updates and enhanced collaboration on toxicity surveillance to inform the future clinical guidelines process.
13. SURVEILLANCE OF THE TOXICITY OF ANTIRETROVIRAL DRUGS WITHIN ANTIRETROVIRAL THERAPY PROGRAMMES

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 11 – Monitoring and evaluation

Main messages

- 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.

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

- 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 approaches used to address them.

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

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

- 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.

Purpose of this section

Chapter 7 of the WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1), “Clinical guidance across the continuum of care: antiretroviral therapy” describes evidence from the systematic reviews conducted on the toxicity of ARV drugs. Based on current evidence, WHO has determined that the risk of harm from the recommended antiretroviral regimens is small and 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.

The guidelines briefly discuss the surveillance of the toxicity of ARV drugs within ART programmes and programmes for preventing mother-to-child transmission of HIV, especially in Box 7.2 on surveillance of ARV drug toxicity. This section provides guidance on surveillance of the toxicity of ARV drugs. It is intended for national HIV programme managers and implementing partners, such as nongovernmental 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 treatment programmes to monitor the toxicity of ARV drugs. The proposed approaches include developing and maintaining (i) targeted spontaneous reporting; (ii) active surveillance for specific types of toxicity within sentinel cohorts; and (iii) cohort event monitoring.

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

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

The new recommendations of the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1) aim at, and will result in, an increased and prolonged exposure to ART among people living with HIV.

The guidelines recommend implementing 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 toxicity may present a different pattern in association with environmental or behavioural 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 (Box 13.1).26

The specific objectives are:

- to determine and minimize the incidence of drug toxicity associated with the use of new and older ARV medicines;27
- monitor the effect of toxicity on treatment outcomes, including treatment discontinuation, medical significance, disability or incapacity, hospitalization or prolonged existing hospitalization, life-threatening illness and death and congenital anomalies;
- determine the impact of risk factors, including other types of comorbidity, and the association with other medicines or traditional medicines on the incidence, nature or severity of ARV toxicity; and
- identify rare types of toxicity or toxicity associated with long-term use that have not previously been identified.

**Box 13.1. Toxicity concerns**

The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (1) identified that more data are desirable on:

- the renal and bone toxicity associated with the long-term use of tenofovir;
- the bone, growth and renal toxicity of tenofovir among children and adolescents;
- the toxicity associated with efavirenz, in particular on the central nervous system;
- the safety of the use of efavirenz- and tenofovir-containing regimens during pregnancy and in breastfeeding mothers;
- the severe skin rash and hypersensitivity reactions associated with nevirapine;
- the long-term toxicity associated with the use of second- and third-line drugs; and
- the best methods for monitoring renal function in individuals using tenofovir-containing regimens.

**Surveillance approaches**

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 approaches used to address them. The following are complementary approaches to surveillance.

**Targeted spontaneous reporting**

Targeted spontaneous reporting (3) elicits reports of specified and serious adverse drug reactions from health care workers. Targeted spontaneous reporting approach cannot be used to determine the incidence of serious adverse drug reactions because the denominator used to calculate it — the number of people exposed to the ARV drugs used — is unknown, and because the quality of reports may vary and underreporting is likely to occur. However,

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

27. Section 11 in this supplement addresses the surveillance of toxicity of ARVs in pregnancy and breastfeeding.
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.

“Serious” reactions include those that result in death, are life-threatening, result in hospitalization or prolongation of hospitalization or result in permanent harm or disability. Adverse reactions that result in treatment discontinuation and a change in ART regimen are also monitored as serious. Standardized case definitions for specific solicited adverse reactions are used and should be included in training for health care workers, in guidance on reporting and on reporting forms.

This approach can be used across all sites nationally where ART is delivered or in a specific geographical region or site, depending on the specific objectives of the system and resources available. A well-functioning targeted spontaneous reporting system will allow programme managers to determine the major drug toxicity concerns of health care workers and respond to those concerns, by providing direct feedback and support, requesting further studies, retraining or revising treatment guidelines and training materials. The approach promotes safety awareness among clinical staff and provides a forum for clinicians to raise their concerns about treatment regimens.

This approach differs from the traditional spontaneous reporting approach used by medicines regulatory authorities, since reports of specific types of toxicity associated with a specific group of drugs or in a specific group of people are encouraged, for example, monitoring of renal function and growth parameters among children taking tenofovir. However, similar to traditional spontaneous reporting, targeted spontaneous reporting can also be a means of detecting signals of adverse reactions that have not previously been reported. Box 13.2 illustrates an example of a targeted spontaneous reporting approach.

Box 13.2. Targeted spontaneous reporting in Western Cape Province in South Africa

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

Case definitions of each of the solicited types of toxicity (such as lactic acidosis, hepatotoxicity, nephrotoxicity, major birth defects, etc.) are provided on the case-reporting form as well as simple guidance on reporting procedures (the what, when, how and where of reporting). The system is 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.

Targeted spontaneous 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. Targeted spontaneous reporting programmes should share its results with the latter system.

Active surveillance for specific types of toxicity within sentinel cohorts

Cohorts selected for active surveillance of toxicity need to have a reliable system for capturing clinical and toxicity data. Active surveillance for specific types of toxicity nests within existing cohorts set up in a country for research or monitoring and evaluation purposes. This approach determines the incidence of important drug toxicity, since there is reliable denominator data on the number of people exposed to the drug of interest and the duration of exposure.
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 among people receiving first-line ART. Single drug substitutions were used to indicate significant drug intolerance. This cohort analysis included 2679 individuals, all of whom were receiving therapy based on non-nucleoside reverse-transcriptase inhibitors. This study found that substitutions from toxicity occurred early for nevirapine, efavirenz and zidovudine, with 8%, 2% and 8% of people respectively having substitutions by three years. The rates of substitution for stavudine (owing to symptomatic hyperlactataemia, lipoatrophy and peripheral neuropathy) continued to accumulate over time, reaching 21% by three years. Women weighing more than 75 kg and receiving ART for more than six months were found to be at increased risk of hyperlactataemia (4). This, and other cohort studies, provided data that led to recommendations to avoid stavudine in obese women, and subsequently to tenofovir being recommended in WHO treatment guidelines in place of stavudine.

**Cohort event monitoring**

The cohort event monitoring approach 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 ARV drugs are collected, irrespective of the causality or relationship with the ARV drugs. Cohort event monitoring would optimally involve recruiting about 15 000 to 20 000 people receiving an ARV regimen.

The advantages of cohort event monitoring (over spontaneous reporting) include the ability to produce rates of events, early detection of signals, fewer missing data and less reporting bias (5).

However, cohort event monitoring requires a comprehensive cohort follow-up structure to be set up and therefore extensive financial and human resources. Where existing cohorts of people living with HIV receiving 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. Box 13.4 presents an example of a cohort event monitoring approach.

**Box 13.4. ART cohort event monitoring in the United Republic of Tanzania**

The United Republic of Tanzania has started cohort event monitoring for ARV drugs, with 300 people being monitored at each of 10 implementing sites. Data-collection tools have been developed and introduced to various sites, with development of a cohort event monitoring manual and standard operating procedures and training of health care providers. Health care staff at participating sites have been trained on the use of CemFlow (a tool for collecting cohort event monitoring) for data management, and continuous monitoring and site supervision are now taking place.

**Important considerations when developing a surveillance system**

Surveillance priorities should be chosen for the local context, in consultation with national or regional clinical and epidemiological experts and WHO guidance. It is very important to choose surveillance approaches that are appropriate for these objectives and to integrate toxicity surveillance into routine monitoring and evaluation activities to efficiently use of resources. Targeted spontaneous reporting and active surveillance for specific types of toxicity within cohorts are complementary approaches and, where resources permit, adopting both approaches should be considered. Cohort event monitoring could be pursued when cohort studies with very large scope are planned or ongoing.

Individual monitoring for toxicity should be integral to delivering high-quality care. Facility-based records can

---

28. 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).
provide valuable information, if regular and accurate records are kept of key aspects of the care and treatment offered. Patient-monitoring systems also record information on clinical and laboratory toxicity monitoring for individual case management. When electronic medical record systems for people receiving ARV regimens are implemented, they will enable data extraction and aggregated reports generated through these systems could contribute towards documenting the impact of ARV-related toxicity on treatment outcomes (6).

Data arising from spontaneous reports, other regulatory data and investigator-initiated research often 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. Programme managers, drug regulators, academic researchers and pharmaceutical manufacturers therefore need to develop platforms that facilitate the exchange of information on the efficacy and safety of medicines used.

Table 13.1. Surveillance challenges and how to address them

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underreporting, poor quality of reports and reporter “fatigue” will occur within targeted spontaneous reporting systems</td>
<td>Solicit reports of important types of toxicity for a specific window in time. Field-test reporting forms and procedures before implementation. Provide training and information on why reporting priority types of toxicity is important. Give feedback so that stakeholders can appreciate that their reports are of value to the programme. Provide reporting guidelines, clinically appropriate case definitions and simple reporting procedures to all staff.</td>
</tr>
<tr>
<td>Poor quality of the denominator within sentinel cohorts</td>
<td>Provide necessary resources, to ensure accurate data for calculation of incidence. Use triangulation of approaches – use patient cohort data, pharmacy records and clinic registers to estimate denominators.</td>
</tr>
<tr>
<td>Wide differences among facilities in the ability to conduct both laboratory and clinical monitoring</td>
<td>Assess the availability of laboratory monitoring and diagnostic capacity at candidate sentinel sites. Match the surveillance approach to laboratory and clinical monitoring capacity.</td>
</tr>
<tr>
<td>Obtaining reliable and standardized causality assessment and decisions about the implications of findings for policy</td>
<td>Adopt an internationally recognized standardized and systematic approach to causality assessment. Establish a panel with the necessary expertise to review individual and collective data.</td>
</tr>
<tr>
<td>Sustainability</td>
<td>Provide frequent and relevant feedback to all stakeholders. Identify and address site staff concerns about the system on an ongoing basis. Limit reporting requirements (such as with electronic management systems).</td>
</tr>
</tbody>
</table>

Improving 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 (Fig. 13.1). This can be achieved by ensuring continual feedback and communication with relevant stakeholders, including patients and their communities, health care staff, district, state, provincial and national authorities, the medicines regulatory agency, pharmaceutical manufacturers, the media and the national and international scientific community.

All public communication with stakeholders needs to be skilfully prepared and relevant expertise used to ensure that messages are clear, informative, contextual and delivered in the appropriate format and 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 already be in place on how to handle such issues.

**Table 13.1. Surveillance challenges and how to address them**

**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 developing and implementing ARV toxicity surveillance and its inclusion into the monitoring and evaluation effort of antiretroviral therapy programmes.29

WHO is convening a Steering Group on ARV Toxicity Surveillance, comprising 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 funding model, to mobilize funding to support ART toxicity surveillance within ART programmes and programmes for preventing mother-to-child transmission (7).

Pilot projects on toxicity surveillance that WHO has supported in several countries since 2011 informed the content of this briefing note. More information on these projects can be found at: [http://www.who.int/hiv/topics/arv_toxicity/en/index.html](http://www.who.int/hiv/topics/arv_toxicity/en/index.html).

---

29. WHO is working on a consolidated HIV monitoring and evaluation framework and global reporting that will include ARV toxicity monitoring as a key component. Technical consolidated guidance for monitoring and evaluation in HIV programmes will be available in 2014.
14. SUPPORTING THE DEVELOPMENT OF NATIONAL STRATEGIES FOR SURVEILLANCE OF HIV DRUG RESISTANCE

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 11 – Monitoring and evaluation

Key messages

- Preventing and assessing HIV drug resistance should be integrated into every national HIV programme. WHO recommends that countries put in place a comprehensive strategy to monitor the emergence and transmission of HIV drug resistance.

- Each element of the overall HIV drug resistance monitoring and surveillance strategy has been designed to support optimal programme management at every step along the treatment cascade, from treatment initiation to long-term viral load suppression. HIV drug resistance data should ideally be available to support global and national decision-making as ART guidelines for adults and children are regularly updated.

- Grants from the United States President’s Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria can be used to facilitate the establishment or expansion of a national HIV drug resistance strategy. Investments in HIV drug resistance surveillance and monitoring should fall well within the monitoring and evaluation budget for ART programmes.

- Early-warning indicators for HIV drug resistance should be monitored at all facilities where ARV drugs are provided in the country.

- In the first quarter of 2014, WHO will release tools to assist programme managers design and cost HIV drug resistance surveillance adapted to their country contexts and needs.

Context

The 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection provide clinical and programmatic recommendations for scaling up antiretroviral therapy. Chapter 11 – “Monitoring and evaluation” – describes adaptations to monitoring and evaluation frameworks and systems that are needed to track the implementation and impact of these recommendations.

Surveillance of HIV drug resistance provides critical information to assess the performance of HIV treatment and prevention programmes, to support effective regimen selection and to optimize patient monitoring protocols. Specifically, HIV drug resistance surveillance is essential to predict the population-level efficacy of current and future first- and second-line therapy and pre- and post-exposure prophylaxis; reduce unnecessary switches to more costly and less well-tolerated regimens; optimize strategies for monitoring the people receiving treatment (such as frequency of viral load monitoring); and implement targeted interventions to improve care, treatment adherence and minimize HIV drug resistance.

The WHO global strategy for the surveillance and monitoring of HIV drug resistance comprises five key elements (Fig. 14.1):

- monitoring early-warning indicators;
- surveillance of HIV drug resistance in recently infected populations;
- surveillance of pre-treatment HIV drug resistance in populations initiating ART;
- surveillance of acquired HIV drug resistance in populations receiving ART; and
- surveillance of HIV drug resistance among children younger than 18 months of age.

Components of a comprehensive HIV drug resistance surveillance and monitoring strategy

Early-warning indicators

Early-warning indicators are indicators of the quality of care that assess factors associated with the emergence of HIV drug resistance. Early-warning indicators are designed to
be monitored at all ART clinics as part of routine monitoring and evaluation. Early-warning indicators can alert clinics and ART programmes to situations favouring the emergence of HIV drug resistance and provide an opportunity for corrective action to be taken. In 2011, the number of HIV drug resistance early-warning indicators was reduced from eight to five: (1) on-time pill pick-up, (2) retention in care, (3) pharmacy stock-outs, (4) dispensing practices and (5) viral load suppression (if viral load is routinely monitored). Standardized definitions and performance targets have been developed for each indicator, along with a colour-based scorecard system (Table 14.1).

Table 14.1. List of early-warning indicators and associated clinic-level targets

<table>
<thead>
<tr>
<th>Early-warning indicator</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. On-time pill pick-up</td>
<td>Red: &lt;80%</td>
</tr>
<tr>
<td></td>
<td>Amber: 80–90%</td>
</tr>
<tr>
<td></td>
<td>Green: &gt;90%</td>
</tr>
<tr>
<td>2. Retention in care</td>
<td>Red: &lt;75% retained after 12 months of ART</td>
</tr>
<tr>
<td></td>
<td>Amber: 75–85% retained after 12 months of ART</td>
</tr>
<tr>
<td></td>
<td>Green: &gt;85% retained after 12 months of ART</td>
</tr>
<tr>
<td>3. Pharmacy stock-outs</td>
<td>Red: &lt;100% of a 12-month period with no stock-outs</td>
</tr>
<tr>
<td></td>
<td>Green: 100% of a 12-month period with no stock-outs</td>
</tr>
<tr>
<td>4. Dispensing practices</td>
<td>Red: &gt;0% dispensing of mono- or dual therapy</td>
</tr>
<tr>
<td></td>
<td>Green: 0% dispensing of mono- or dual therapy</td>
</tr>
<tr>
<td>5. Viral load suppression at 12 months</td>
<td>Red: &lt;70% viral load suppression after 12 months of ART</td>
</tr>
<tr>
<td></td>
<td>Amber: 70–85% viral load suppression after 12 months of ART</td>
</tr>
<tr>
<td></td>
<td>Green: &gt;85% viral load suppression after 12 months of ART</td>
</tr>
</tbody>
</table>
Among individuals without previous ARV exposure. This survey and will be used to separately assess the resistance drugs will be collected from everyone enrolled in the initiating ART. Information on previous exposure to ARV calculate a nationally representative prevalence estimate Pre-treatment drug resistance surveys are designed to resistance in populations initiating ART.

Surveillance of transmitted drug resistance in recently infected populations

This surveillance is designed to provide a national prevalence of transmitted HIV drug resistance among individuals likely to have been recently infected with HIV (within about three years of diagnosis) and unlikely to have been exposed previously to ARV drugs. The prevalence of transmitted drug resistance should be reported by individual drug class and overall. Data on transmitted HIV drug resistance to the classes of drugs being used in a country, together with data on HIV drug resistance in people for whom ART is failing, are essential to predict the likely efficacy of regimens used for pre- and post-exposure prophylaxis at the time of the survey.

For cost and feasibility reasons, WHO suggests that countries integrate transmitted drug resistance surveillance into pre-existing HIV surveillance systems or routine diagnostic testing activities (if the reporting system is centralized and the reporting rate exceeds 90%) to ensure the widest possible geographical reach. Examples of routine nationwide HIV surveillance activities designed to estimate HIV prevalence into which the surveillance of transmitted drug resistance may be integrated include: surveillance of HIV in men and women performed as part of a national household survey (such as Demographic and Health Surveys), surveillance of HIV prevalence among women attending antenatal clinics (antenatal surveillance), surveillance of HIV among people newly diagnosed with HIV infection (women and men) attending voluntary counselling and testing sites, or special populations, such as sex workers, men who have sex with men and people who inject drugs, often conducted as part of bio-behavioural surveys. A sample size of at least 200 specimens meeting eligibility criteria is recommended to provide the precision needed for adequate planning and programming.

Surveillance of pre-treatment drug resistance in populations initiating ART

Pre-treatment drug resistance surveys are designed to calculate a nationally representative prevalence estimate of HIV drug resistance among ARV-naive populations initiating ART. Information on previous exposure to ARV drugs will be collected from everyone enrolled in the survey and will be used to separately assess the resistance among individuals without previous ARV exposure. This distinction is justified by the fact that higher levels of HIV drug resistance are anticipated among ART initiators with previous ARV exposure. The results of pre-treatment drug resistance surveys inform the selection of optimal first-line regimens to maximize population-level impact.

Pre-treatment drug resistance surveillance is based on a cross-sectional survey, which involves observing a representative subset of a population at one specific point in time and uses a method known as a two-stage cluster design. In the first stage, 15–40 clinics are sampled from a list of all clinics that initiate ART in the country. In the second stage, consecutive eligible people initiating ART on or after a predefined survey start date are sampled and their specimens genotyped. The number of people to be sampled varies according to several factors. For budgeting purposes, countries can use 350 as an approximate number of specimens to be genotyped. It is recommended that the duration of sampling be limited to six months to ensure that the results are available in a timely fashion.

Surveillance of acquired drug resistance in populations receiving ART

The objective of surveys of acquired drug resistance is to calculate nationally representative point prevalence estimates (with associated confidence intervals) of viral load suppression and prevalence of HIV drug resistance in populations receiving antiretroviral therapy for 12 (±3) months and ≥48 months. According to programme needs and the feasibility of patient sampling, countries can decide whether to sample only populations receiving ART for 12 (±3) months or also sample people who have received ART for ≥48 months.

Acquired drug resistance surveillance is based on a cross-sectional survey, which involves observing a representative subset of a population at one time and uses a method known as a two-stage cluster design. First, 17–40 clinics are sampled from a list of all clinics dispensing ART in the country. Second, once clinics have been selected, consecutive eligible people receiving ART for 12 (±3) months and/or ≥48 months on or after a predefined survey start date are sampled. The specimens of those individuals for whom ART is found to be failing (defined as having a viral load above 1000 copies/ml) are subsequently genotyped. To correct for any potential survivor bias and to improve comparability across countries and over time, a representative estimate of retention, developed by reviewing a predefined number of patient files at the participating clinics, will be used to adjust the prevalence of viral load suppression among observable people for the proportion of individuals who have been lost to care. It is recommended that the duration of sampling be limited to six months to ensure that the results are available in a timely fashion.
Surveillance of HIV drug resistance among children younger than 18 months of age

The purpose of this survey is to calculate nationally representative point prevalence estimates (with associated confidence intervals) of initial drug-resistant HIV among children younger than 18 months of age and newly diagnosed with HIV. As ARV use for preventing mother-to-child transmission increases, the proportion of children who become infected with HIV despite prophylaxis for preventing mother-to-child transmission tends to decrease. However, among those infected, an increasing proportion is expected to harbour drug-resistant HIV. Data on HIV drug resistance among this population are therefore critical to inform the selection of optimal first-line ART regimens for children.

The default survey method is retrospective, since stored remnant dried blood spot samples collected for PCR diagnosis of children will be used for genotyping. In contrast to surveys of pre-treatment drug resistance and acquired drug resistance, the sampling unit in this case is the diagnostic laboratory and not the clinic where specimens were collected. When possible, all early infant diagnostic laboratories in the country should participate in the survey and thus contribute to the overall sampling.

The main survey outcome is the prevalence of HIV drug resistance, along with 95% confidence intervals, of relevant mutations and combinations of mutations leading to classifications of high, intermediate or low resistance to relevant drug classes and drugs. A generic protocol has been developed and is already available for country review and adaptation. It is available at http://apps.who.int/iris/bitstream/10665/75202/1/WHO_HIV_2012.17_eng.pdf.

Identifying the target populations

Each survey targets a specific population:

- transmitted drug resistance surveys: ARV-naive individuals likely to have been recently infected;
- pre-treatment drug resistance surveys: ARV-naive and ARV-exposed individuals initiating first-line ART (for their own health, preventing mother-to-child transmission, etc.);
- acquired drug resistance surveys: populations receiving ART at different time points (such as 12 (±3) months and/or ≥48 months); and
- surveys of children: children living with HIV younger than 18 months of age newly diagnosed with HIV by early infant diagnosis testing.

In concentrated epidemics with well-identified key populations at higher risk for HIV infection, such as men who have sex with men, sex workers and people who inject drugs, activities for preventing and assessing HIV drug resistance could be planned to target specific populations.

Strategy review and development

HIV drug resistance surveillance and monitoring should be integrated into every national HIV programme. Grants from the United States President’s Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria can be used to facilitate the establishment of a national HIV drug resistance strategy, to maintain or expand existing programme activities or to add new programme components.

Country priorities may differ depending on their type of epidemic and on the status and coverage of their national ART programmes. Countries may also choose to stagger the implementation of the various survey components. Nevertheless, it is desirable that all ART clinics annually report early-warning indicators, although this can be accomplished in stages as clinic capacity is built. HIV drug resistance data should ideally be available to support national decision-making as ART guidelines for adults and children are regularly updated to ensure the delivery of the most effective interventions to everyone in need.

The development of a robust plan involves (1) performing situation analysis to take stock of the country’s existing HIV drug resistance monitoring and assessment strategy, (2) reviewing available data describing the prevalence and patterns of transmitted, pre-treatment drug resistance in adult and infants, and acquired drug resistance among adults and children, (3) identifying any data gaps that must be addressed given the country’s programmatic priorities and (4) developing a costed strategy, aligned with the broader national HIV strategy, outlining how the various elements of the HIV drug resistance strategy will be implemented and how they will be funded.

Various factors influence the cost of an HIV drug resistance survey, such as the number of specimens to be genotyped, the number of sites included in the survey as well as the prices of genotyping and, when applicable, viral load tests. However, it should fall well within the accepted proportion of an ARV programme’s budget that should be allocated to monitoring and evaluation activities. A more detailed briefing note, with budget examples, has been developed to assist countries as they prepare their national strategies and will be available online on the WHO website.

Table 14.2 provides a summary of HIV drug resistance surveys and their relevance for optimal programme management.
## Table 14.2. Summary of drug resistance surveys

<table>
<thead>
<tr>
<th>Type of survey</th>
<th>Population of interest</th>
<th>Measure</th>
<th>Programmatic relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmitted drug resistance</td>
<td>ARV-naive, recently infected individuals</td>
<td>National estimate of level and patterns of transmitted HIV drug</td>
<td>Transmitted drug resistance can compromise the effectiveness of ARV drugs in preventing HIV transmission among uninfected individuals and may compromise the efficacy of first-line ART when recently infected populations require it.</td>
</tr>
<tr>
<td>Pre-treatment drug resistance</td>
<td>ARV-naive individuals initiating ART</td>
<td>Nationally representative estimates of HIV drug resistance among ARV-naive individuals about to start ART</td>
<td>The presence of HIV drug resistance before ART initiation can compromise both the therapeutic as well as the prevention benefits of first-line ART.</td>
</tr>
<tr>
<td></td>
<td>ARV-exposed individuals initiating ART</td>
<td>Regional or global estimates of HIV drug resistance among ARV-exposed individuals about to start ART</td>
<td></td>
</tr>
<tr>
<td>Acquired drug resistance</td>
<td>Individuals receiving antiretroviral therapy for 12 (±3) months and/or ≥48 months</td>
<td>Nationally representative estimate of viral load suppression and levels and patterns of HIV drug resistance among individuals receiving treatment at 12 (±3) and/or ≥48 months</td>
<td>Acquired drug resistance may compromise the effectiveness of second-line ART among individuals receiving ART and may, if transmitted, negatively affect the effectiveness of first-line ART among individuals starting first line in the future, as well as that of pre-exposure prophylaxis and post-exposure prophylaxis.</td>
</tr>
<tr>
<td>HIV drug resistance among children younger than 18 months</td>
<td>Children living with HIV younger than 18 months newly diagnosed with HIV by early infant diagnosis testing</td>
<td>Estimate of HIV drug resistance among newly infected children undergoing early infant diagnosis</td>
<td>As ARV drug use for preventing mother-to-child transmission increases, the proportion of children who become infected with HIV despite prophylaxis for preventing mother-to-child transmission tends to decrease. However, among those infected, an increasing proportion is expected to harbour drug-resistant HIV strains. HIV drug resistance data are thus essential to select optimal first-line ART regimens for children.</td>
</tr>
</tbody>
</table>