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<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AMPATH</td>
<td>Academic Model Providing Access to Healthcare</td>
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<tr>
<td>ART</td>
<td>antiretroviral treatment</td>
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<tr>
<td>ARV</td>
<td>antiretroviral</td>
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<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
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<tr>
<td>CD4</td>
<td>T-lymphocyte cell bearing CD4 receptor</td>
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<tr>
<td>Global Fund</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>PDR</td>
<td>People’s Democratic Republic (Lao)</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHO/EMP</td>
<td>Essential Medicines and Pharmaceutical Policies Department, WHO</td>
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WHO convened a technical review meeting in Geneva on 7 and 8 November 2013, on surveillance of antiretroviral (ARV) drug toxicity within antiretroviral treatment (ART) programmes. The aim was to review progress and lessons learnt from country experiences and identify solutions.

Implementation of ARV drug toxicity monitoring surveillance has become particularly critical for HIV programmes in the context of the recent WHO consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection (1), as more people start ART earlier and remain on treatment for a longer period on a wider scale. The WHO guidelines highlight some key toxicity concerns associated with the use of ARVs. They also emphasize the need to strengthen toxicity surveillance as a key component of the continuum of care, and to stimulate research to inform future guidelines. A WHO technical brief – *Surveillance of antiretroviral drug toxicity within antiretroviral treatment programmes* (2) – was released in October 2013; it describes approaches that address the particular needs of HIV/AIDS treatment programmes to monitor the toxicity of ARVs.

The meeting brought together countries from various regions where the following approaches have been implemented:

- cohort event monitoring for ARV drugs in Belarus and the United Republic of Tanzania;
- targeted spontaneous reporting in Côte d’Ivoire, Kenya, Lao People’s Democratic Republic (PDR), South Africa and Viet Nam;
- targeted monitoring of key toxicities within existing cohorts in South Africa and Viet Nam; and
- retrospective chart reviews in Côte d’Ivoire and Ukraine.

These experiences covered national project implementation, e.g. as in South Africa since early 2003 or pilot project implementation as initiated in 2011 under a collaborative project between WHO and the Bill and Melinda Gates Foundation [BMGF] in Côte d’Ivoire, Kenya, Lao PDR, Ukraine, United Republic of Tanzania and Viet Nam.

Progress and lessons learnt from the various approaches to toxicity surveillance were reviewed during the meeting. Despite the many challenges identified, there was clear evidence that the various approaches increased the collection of toxicity data within ART programmes, and that the data arising from these surveillance approaches could meaningfully inform treatment policies and improve patient care. The key recommendations from the meeting are given below.

**Recommendations for optimizing ARV toxicity surveillance approaches**

WHO technical guidance will be updated on the basis of the following outcomes:

- nesting ARV cohort event monitoring in a few centres of excellence, where the necessary resources would be available;
- taking advantage of targeted spontaneous reporting for capturing and reporting on severe reactions with all ARVs delivered at selected sentinel sites;
- investing in reporting champions for integrating toxicity surveillance within existing treatment cohorts;
- including recruitment of patients at different points in ART in the surveillance programmes, to monitor both short- and long-term toxicity;
- strengthening surveillance of hospitalizations due to ARV toxicity at selected hospitals;
- making use of and reviewing patient charts for retrospective or prospective toxicity data analysis; and
- investing in an HIV monitoring and evaluation systems to deliver on key indicators of toxicity surveillance.
Recommendations for integrating ARV toxicity surveillance into HIV monitoring and evaluation

The forthcoming WHO *Consolidated strategic information guide for HIV in the health sector* (to be released in July 2014) will provide a framework that countries can use to integrate toxicity surveillance within a national monitoring and evaluation system, using a combination of routine monitoring and special surveys or studies.

The following indicator will be integrated into core indicators for national programme monitoring:

- percentage of ART patients with treatment-limiting toxicity by ART cohort;
- numerator – that is, the number of treatment-limiting toxicities in ART patients; and
- denominator – that is, the number of ART patients, disaggregated by drug or regimen, at time of toxicity; sex; age; pregnant women; key populations; and tuberculosis (TB)/HIV.

Treatment-limiting toxicity is defined as life-threatening illness, death, hospitalization, disability or effects resulting in treatment discontinuation or substitution.

The HIV patient card, ART register and reporting forms will be updated to report on the core indicator. The link to specific regimens or drugs will be monitored. Where available, an electronic patient-monitoring system is expected to facilitate monitoring. Other priority toxicity questions will be addressed through special studies and surveys, using approaches reviewed during the meeting.

Recommendations for conducting operational research

The main challenge arising from the meeting was to generate more reliable data on the incidence of treatment-limiting toxicity within national HIV programmes. Generating such data appears to require additional methods that source the data directly from the emerging electronic patient-monitoring systems, and from networks of sentinel hospitals that agree to report on all severe adverse drug reactions that require hospitalization. Even in settings with electronic patient-monitoring systems, there may be insufficient capacity to ensure full reporting on all toxicities that require treatment substitution, switching or stopping. It is unclear how best to implement these more engaged approaches; therefore, the meeting recommended a focus on operational research into optimization of implementation modalities.

Next steps

It is a complex task to develop effective ARV toxicity monitoring systems that are contextually feasible. The efforts to establish a combination of approaches should continue and be strengthened. Integrating toxicity surveillance into the HIV monitoring and evaluation system will strengthen the generation of data within ART programmes. There is a need to explore additional approaches that can be incorporated into the menu of relevant methods available for surveillance, and to explore how, where and when such methods may be feasible and appropriate. This includes making use of the emerging electronic patient-monitoring systems, and building on networks of sentinel hospitals. The decision to explore and expand on existing approaches comes with a significant agenda for operational research.

WHO will incorporate the identified priority questions for optimizing implementation modalities of toxicity monitoring into an operational research agenda for the strategic use of ARVs. The WHO technical brief – *Surveillance of antiretroviral drug toxicity within antiretroviral treatment programmes* (2) – will be updated in light of key outcomes of the meeting, and the forthcoming WHO Consolidated strategic information guide for HIV in the health sector will incorporate the findings and suggestions of the meeting for integrating ARV toxicity surveillance into HIV monitoring and evaluation systems. WHO will continue building country capacities for the implementation of toxicity surveillance systems, and will support the generation of toxicity data as part of the consolidated guidelines on the use of ARVs and other initiatives.
1 INTRODUCTION

In July 2013, WHO published consolidated guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection (1). These guidelines recommend implementing toxicity surveillance within antiretroviral treatment (ART) programmes, to assess the short- and long-term toxicities associated with the use of ARV drugs (1). Results from such surveillance should be used to improve performance of ART clinics and programmes, and inform revisions of future guidelines. Currently, ARV toxicity issues are intermittently monitored and are not systematically reported in most low- and middle-income countries.

To address the gap in toxicity data, WHO produced technical guidance, and since 2011 it has supported pilot projects in toxicity surveillance for ARV drugs in six low- and middle-income countries (2, 3). Two approaches have been field-tested: a targeted spontaneous reporting approach in four countries (Côte d’Ivoire, Kenya, Lao People’s Democratic Republic [PDR] and Viet Nam), and a cohort event monitoring approach in the United Republic of Tanzania. In addition, in Ukraine, capacity-building in pharmacovigilance for ARV drugs was undertaken, to strengthen ARV toxicity reporting. The pilot projects in these six countries are part of a collaborative project between WHO and the Bill and Melinda Gates Foundation (BMGF). The aim of the collaboration is to produce technical guidance and build country capacity on the surveillance of toxicity of ARV drugs.

WHO organized a technical review meeting in Geneva on 7 and 8 November 2013, to review progress and lessons learnt from the country experiences. In addition to the six countries involved in the pilot projects, two other countries were invited: South Africa to present its experience of a public health approach for surveillance of ARV toxicities within an ART programme that started in 2003, and Belarus to present a cohort event monitoring programme for ARV drugs. The meeting brought together staff from national AIDS programmes and national pharmaceutical regulatory authorities responsible for implementing the relevant projects, WHO responsible officers from piloting country offices, and national and international experts from partner organizations.

Dr Joseph Perriëns, Coordinator of the HIV Technologies and Commodities Unit, HIV/AIDS Department (WHO/HIV), welcomed the participants on behalf of the Director of the HIV/AIDS Department, and presented the main objectives of the meeting, which were to:

- share results, and review progress and lessons learnt in the pilot projects and in other low- and middle-income countries; and

- highlight the challenges, and discuss solutions for improving the capture of ARV toxicity data in low- and middle-income countries, to inform future ARV guidelines.

The outcomes of the meeting are expected to be used to update technical guidance on ARV toxicity surveillance developed by WHO, and support the expansion of strengthened surveillance activities in resource-limited settings.

This report summarizes the presentations given by country representatives and key technical experts and partners. All presentations and background documents are available on the toxicity monitoring link of the HIV/AIDS Department.1 The report also summarizes the discussions from the plenary sessions and working group sessions.

1 http://www.who.int/hiv/topics/arv_toxicity/en/index.html
During this session, the following were presented:

The 2013 *WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (1). The new recommendations in these guidelines will result in more people on treatment, with an earlier and more prolonged exposure to ARV drugs, in populations with comorbidities and concomitant exposure to other drugs. The guidelines note that more data are needed to improve understanding of the frequency and clinical relevance of ARV-associated toxicities. These guidelines are discussed in Section 2.1.

Technical guidance on the surveillance of ARV drugs within ART programmes recently produced by WHO (2). This technical brief provides programmatic and technical guidance to national AIDS programme managers for optimizing and implementing strengthened surveillance, using three approaches: targeted spontaneous reporting, active surveillance for specific toxicities within sentinel cohorts and cohort event monitoring. These approaches are discussed in Section 2.2.

Experience and results from a public health approach for surveillance of ARV toxicities, implemented in South Africa since 2003 within an ART programme and using a mix of approaches. This is discussed in Section 2.3.

### 2.1 WHO 2013 consolidated ARV guidelines – evolving landscape for HIV treatment and prevention

The consolidated guidelines (1), which were released in July 2013, include new clinical recommendations that promote expanded eligibility for ART, with a CD4 threshold for treatment initiation of 500 cells/mm$^3$ or less for adults, adolescents and children (1). For certain populations, ART is recommended to be initiated regardless of CD4 count, including for people with active tuberculosis (TB) who are living with HIV, people with both HIV and hepatitis B virus infection with chronic severe liver disease, partners with HIV in serodiscordant couples, pregnant and breastfeeding women, and children under 5 years of age.

The guidelines emphasize that ART should be used within a broad continuum of HIV care. They provide updated guidance on key aspects along that continuum of care, and for ensuring that the continuum is maintained; aspects covered include monitoring and managing ARV toxicities, and drug substitution for ARV drug toxicities (See Figure 1).

**Figure 1 Monitoring ARV toxicity: a key aspect of the ART continuum of care**

Source: WHO 2013 (1)
The guidelines also emphasize that preventing or minimizing any serious drug reactions will help to avoid treatment discontinuation, will prolong first-line or second-line regimens (provided that treatment failure has not occurred), and will reduce morbidity and mortality related to rare but severe drug reactions. Thus, monitoring and managing ARV toxicities will contribute to improved treatment adherence and retention, and better treatment outcomes.

In developing the guidelines, evidence on a number of toxicities of concern was updated through systematic reviews. Also, a public health approach was recommended for monitoring and managing drug toxicities and drug substitution. The guidelines follow two main principles:

• the availability of laboratory monitoring is not required for initiating ART; and

• symptom or directed laboratory monitoring for safety and toxicity can be used for those receiving ART.

The systematic reviews highlighted knowledge gaps in toxicities that had been identified previously, and potential toxicities related to earlier and prolonged exposure to ARV drugs. Although the most important toxicities associated with ARV drugs have been well described, information on the incidence of such toxicities from low- and middle-income countries remains limited. In addition, the extent to which the occurrence of toxicities affects the ability of treatment programmes to retain people on ART, and affects the implementation costs of such programmes, remains poorly documented. More data are needed on whether routine or periodic laboratory monitoring for specific types of toxicity is required for all individuals or only for those at higher risk. To assess the toxicities associated with ARV drugs in both the short and long term, the guidelines recommend the implementation of strengthened toxicity surveillance within ART programmes (See Box 1).

2.2 WHO technical brief on surveillance of ARV drug toxicity within ART programmes

In October 2013, WHO produced a technical brief to assist programme managers and implementing partners with the implementation of strengthened surveillance of the toxicity of ARV drugs (2).

The goal of a toxicity surveillance system is to improve patient care, and inform national guidelines and global policies. Specific objectives include the following:

• determine and minimize the incidence of ARV drug toxicities;

• monitor the impact of toxicities on treatment outcomes, including treatment discontinuation or substitution;

• determine risk factors (comorbidities, drug association) and nature or severity of ARV toxicity; and

• identify rare toxicities or toxicities associated with long-term ARV drug use.

Three surveillance approaches are described for assessing ARV toxicity:

• Targeted spontaneous reporting – This approach elicits reports of specified toxicities with one or few ARV drugs; is implemented at selected ART sites, geographical regions or all ART sites; determines the nature and seriousness or severity of adverse reactions; and is not expected to produce incidence rates because the size of the population exposed to ARV drugs remains unknown, and underreporting may occur.

Box 1 Toxicity concerns

The WHO consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection (1) identified the need for more data on:

• renal and bone toxicity with long-term use of tenofovir;

• renal and bone toxicity of tenofovir in children and adolescents;

• toxicities associated with efavirenz, such as adverse reactions affecting the central nervous system;

• safety of the use of efavirenz- and tenofovir-containing regimens during pregnancy and in breastfeeding mothers (4);

• severe skin rash and hypersensitivity reactions associated with nevirapine;

• 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. Chapter 7 of the WHO 2013 guidelines (1) – titled Clinical guidance across the continuum of care: antiretroviral therapy – describes evidence from the systematic reviews conducted on the toxicity of ARV drugs.
• **Active surveillance for specific toxicities within sentinel cohorts** – This surveillance is nested within existing ART cohorts; focuses on few or one ARV drug and few toxicities; builds on a reliable system for capturing clinical and toxicity data; and determines incidence, provided there is a reliable denominator.

• **Cohort event monitoring** – This approach uses a prospective observational cohort study; reports on all adverse events collected for all ARV drugs; produces rates of events and early detection of signals; and presents fewer missing data. Its inclusion in existing HIV cohorts may be reasonably cost–effective (3).

The technical brief highlights a number of important considerations when developing a surveillance system; in particular, the need to link the system to the local context, priorities and use of resources. Ensuring continual feedback and communication with patients and communities, healthcare staff, and district or national health authorities is key to a successful surveillance.

WHO encourages countries to include ARV toxicity surveillance activities under the monitoring and evaluation component in the new financing model of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), to mobilize funding to support ARV toxicity surveillance within programmes for ART and prevention of mother-to-child transmission (5).

### 2.3 ARV toxicity surveillance through a public health programme in South Africa

**Presented by Dr K. Cohen, University of Cape Town, South Africa**

Dr Cohen presented a pioneering experience of a public health approach for surveillance of ARV toxicities within an ART programme that started in South Africa in 2003. The system has been using a mix of approaches, including targeted spontaneous reporting, active surveillance of specific toxicities in existing sentinel cohorts, and prospective and retrospective hospital studies, as discussed below.

#### 2.3.1 Multiple strategies providing complementary data

The South African government has incorporated ARV toxicity surveillance into its national strategic plan for HIV/AIDS since the plan’s inception in 2003. As an integral part of the strategic plan, a targeted spontaneous reporting system – called at the time of initiation “strengthened spontaneous reporting” – was initiated in Western Cape Province in 2005. The system is a collaboration between the Medicines Information Centre based at the University of Cape Town, and the Provincial Government of the Western Cape. Importantly, the project was funded by the Global Fund under the Western Cape’s HIV monitoring and evaluation budget.

The targeted spontaneous reporting system is designed to prioritize information collection on serious adverse drug reactions (including those that warrant a drug substitution) occurring in all patients receiving ART. The focus was made on severe reactions, rather than on specific regimens or drugs. This approach aimed to reduce the likelihood of missed reports compared to a passive spontaneous reporting system. Case definitions of specific adverse reactions known to be associated with ART and TB drugs were included in the reporting form. Any request for further information or feedback was conducted by a pharmacist housed at the Medicines Information Centre.

Several sentinel cohorts of patients on ART already existed in South Africa at the time when active surveillance for specific toxicities was introduced. These cohorts are considered as valuable approaches for toxicity, because they produce a robust denominator that makes it easier to determine toxicity incidence and identify risk factors. Prospective or retrospective hospital studies were also implemented as part of the ARV toxicity surveillance system. Publications about stavudine toxicity arising from data analysed from these sentinel cohorts and from hospital studies have been useful in assessing national treatment policies for HIV, and in shifting from stavudine to first-line regimens containing tenofovir.

A national pharmacovigilance workshop for strengthening the development of a cohesive and integrated national system was held in August 2012. The workshop encouraged the use of multiple methodologies to inform important policy issues and improve patient care. The integrated system will prioritize four approaches:

- a regulatory pharmacovigilance spontaneous reporting system;
- a targeted spontaneous reporting approach for public health programmes (e.g. HIV, TB and immunization);
- active surveillance of toxicities using existing cohorts of patients; and
- a national pregnancy exposure registry.

Although the potential value of a cohort event monitoring approach was recognized, it was not prioritized. In South Africa, two cohort event monitoring programmes for ARV drugs were suspended because they were found to be too
costly and labour intensive; also, they were less efficient than building surveillance elements into existing sentinel cohorts of patients taking ART.

2.3.2 Main results

One of the major achievements has been the ability of the reporting system to generate changes in the reported toxicity profiles of the ART regimen with changes in treatment policy (e.g. when stavudine was removed and tenofovir introduced).

There has been a move towards decentralizing the reporting system by involving district specialist teams in the review of the reports arising from their districts. However, there is a concern that this approach may delay the submission of reports to the provincial and national levels.

Quarterly reports from the system are submitted to the National Department of Health, and copies of all reports are submitted to the National Regulatory Pharmacovigilance Centre. In addition, an annual newsletter is distributed to all treatment sites.

2.3.3 Key challenges and solutions

There is a major challenge in terms of scaling up the reporting system, as evidenced by the fact that the reporting rate has remained steady, despite a massive scale-up of ART. The rate of toxicity reporting did not keep pace with the evolution of treatment, but plateaued – suggesting that scale-up of approaches may yield different results than initial pilots.

Solutions considered in South Africa to overcome challenges included:

• prioritizing the reporting of toxicities of current interest;
• selecting toxicity surveillance methodology based on the priority toxicities;
• centring cohorts around champions who are consistent at reporting;
• providing clinical support and real-time feedback to reporters by instituting a telephonic reporting system via the Medicines Information Centre; and
• optimizing existing resources for data collection (e.g. investing in existing cohorts and reporting champions) to ensure sustainability of these programmes.

2.4 Main points of discussion

The attribution of toxicity to a specific ARV drug can be difficult because patients are receiving triple therapy (Ukraine). The solution is to substitute a single ARV drug, to make it easier to measure and resolve the toxicity. In most cases, patients are shifted from a fixed-dose combination to a dual or triple combination.

It was suggested that interventions be even more strongly targeted; for example, by investing in reporting champions and creating mini-cohorts (which might be under the responsibility of pharmacist managers). These suggestions would require further investigation to ensure that the approach is feasible and yields reliable results (WHO/HIV).

In commenting on the presentation from South Africa, two countries – Côte d’Ivoire and Ukraine – also reported retrospective review of data from their patient-monitoring systems. A particular suggestion was that the emerging electronic patient-monitoring system be used in a more systematic way for toxicity surveillance. WHO is already working on integrating the monitoring of treatment-limiting toxicities into the routine HIV monitoring system (WHO/HIV).

The presenter acknowledged that most reports in their systems come from doctors (as is the case in Côte d’Ivoire and Kenya). She expressed concern that, with task shifting, monitoring of toxicity may become a greater challenge. The use of nurses and other cadres in toxicity surveillance would need to be supported (through mentoring) and researched, to ensure that it does not increase the risk of underreporting.

The importance of causality assessment and early feedback was highlighted (Côte d’Ivoire). In South Africa, causality assessment is conducted on individual cases by the pharmacist, and by a group of experts in situations where fatal drug reactions are reported. Feedback is provided to reporters individually when requested, when preventable adverse drug reactions have been identified, or when a report indicates inappropriate management of adverse drug reactions.

The representative of the WHO Essential Medicines and Pharmaceutical Policies Department (WHO/EMP) made a final comment that terminology is important, and that the terminology of “spontaneous” within a “targeted spontaneous reporting” approach could be questioned (i.e. it is no longer actually spontaneous).
3 COUNTRY EXPERIENCES WITH COHORT EVENT MONITORING AND OTHER EXPERIENCES

In this session, experiences and pilots were presented; these are summarized below in Table 1. Under the collaborative WHO–BMGF project, Ukraine has strengthened its spontaneous reporting system (mainly by investing in the training of clinicians on ARV toxicity monitoring and reporting). The United Republic of Tanzania has engaged in the piloting of a cohort event monitoring programme for ARV drugs. Both countries reported on achievements, challenges and proposed pathways for improving methods. The experience from Belarus, invited to present another cohort event monitoring programme for ARVs, demonstrated both the resources required for cohort event monitoring and this approach’s capacity to generate data when functioning well. However, sustainability of such an enterprise remains a concern in resource-limited settings.

3.1 Presentations of country experiences with strengthening a pharmacovigilance system, and implementing cohort event monitoring for ARVs

Table 1 summarizes the presentations made by Belarus, Ukraine and the United Republic of Tanzania.

3.2 Main points of discussion

A cohort event monitoring approach requires significant investment because it is expensive and labour intensive. In settings with huge workloads and where reporting capacity is limited, the approach may not be feasible (United Republic of Tanzania). However, cohort event monitoring may be more feasible if nested within existing cohort studies that document a series of outcomes, because the cost of reporting adverse drug reactions would be marginal in this situation (WHO/HIV).

Cohort event monitoring can produce toxicity data and rates; this was particularly clear from the Belarus experience, which provided intermediary results. The vast majority of adverse reactions reported were non-serious and expected; such results are of limited interest for ART optimization, are expensive to obtain and create a high workload for the health system – requiring a lot of paper work and time for recording data (Belarus, United Republic of Tanzania). The issue of incentives for prescribers and reporters was raised because of the addition to the staff workload (Belarus, United Republic of Tanzania). The dedication of staff was acknowledged, and was considered key to the project (WHO/EMP).

The retrospective review of patient charts conducted in Ukraine showed the system’s capacity to document toxicity and severe adverse drug reactions (Ukraine). The same method was applied in Côte d’Ivoire using paediatric charts, and led to the identification and documentation of severe cases that were not reported from a spontaneous notification system (Côte d’Ivoire).

The transmission of data from the sites to the Drug Information Center or Pharmacovigilance Center was experimented with and found difficult in other settings. The terminology used in CemFlow appeared to be complicated, requiring prescribers to enter the data to avoid misreporting (Viet Nam).

It can be challenging to record a cohort of sufficient size to assess the incidence of adverse drug reactions, when patients may not be willing to give their consent for inclusion, especially if written informed consent is needed, and populations have low literacy rates (Lao PDR). In other settings, it was reported that inclusion was completed through oral consent (South Africa).

Cohort event monitoring was found to be a long process to implement, and the long-term use of the programme once established and its financial sustainability was questioned (South Africa).
Table 1 Experiences from Belarus, Ukraine and the United Republic of Tanzania

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<th>Country</th>
<th>Surveillance approaches</th>
<th>Challenges and limitations</th>
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| BELARUS               | **Cohort event monitoring of ZDV+3TC+EFV/NVP and TDF+3TC+EFV/NVP** (Monitoring Medicines Programme7)** Five sentinel sites recruited, with 450 of 800 HIV-infected individuals initiating treatment enrolled (October 2013). Recruitment and baseline data at start of treatment and follow-up data collected at 4 weeks, 8 weeks and every further 12 weeks for 1 year. Sites selected based on staff willingness, feasibility of the site based on predefined criteria, and staff appreciation of the importance of safety monitoring of ART. Clinicians reimbursed for their contribution to the cohort event monitoring project. Individual case causality assessment at the national PV centre. Data capture and analysis via CemFlow. Intermediate toxicity data: 36% patients experienced adverse drug reactions, with most reported reactions being non-serious and expected, common (very common), correctable or reversible. Regimen substitution due to toxicity 4%. Eight cases of serious adverse drug reactions expected (i.e. 5% of total adverse drug reactions). | • Significant additional workload  
• Challenges with follow-up of certain patients, particularly drug and alcohol abusers  
• Staff changes affect continuity  
• Challenge of sustaining beyond pilot period  
• Recruitment at initiation of treatment results in only early toxicities detected, and longer term effects missed  
• Lack of drugs for substitution after toxicity is encountered        |
| UKRAINE               | **Ukraine has made significant efforts in improving the spontaneous reporting of adverse drug reactions associated with ART** The national PV system comprised a national centre (the State Expert Center) and 27 regional offices. Reporting rates for ARV-related adverse drug reactions increased, as did reporting for all medicines, from 1996 to 2012. Training course for HIV specialists resulted in an increase in reporting rates among those regions where training occurred. **Initial findings of a retrospective chart review conducted on 831 patients who were on TDF-based regimens but were switched from TDF highlighted the potential value of this approach and of the collection of data from electronic medical records.** **TSR system is now being piloted in Ukraine.** | • Underreporting  
• Reporter fatigue  
• Low motivation towards reporting  
• Inadequate feedback and lack of reciprocal communication with health-care providers and other key stakeholders        |
| UNITED REPUBLIC OF TANZANIA | **Cohort event monitoring for AZT+3TC+NVP/EFV started in April 2013** 32 enrolment sites in eight regions. Zonal PV centres acted as coordinating centres. Sites selected based on accessibility and willingness of health-care providers to assist in data collection and patient monitoring. Approximately 1500 of 3000 patients recruited; sample size unlikely to be reached in time. Oral consent obtained from all patients who are willing to participate. Intermediate toxicity data: 220 treatment initial forms collected, and 310 treatment review forms (220 for first follow-up visit and 90 for second follow-up visit). Data entered in CemFlow. | • High staff turnover rates in some settings require ongoing investment in training and capacity-building initiatives  
• Losses to follow-up due to regimen changes, and difficulties with patients failing to adhere to required follow-up schedule  
• Longer term toxicities will be missed  
• Inadequate funding to continue or complete the project  
• Inclusion of only those who are willing to participate may bias the sample |

3TC, lamivudine; AIDS, acquired immunodeficiency syndrome; ARV, antiretroviral treatment; ART, antiretroviral; AZT, zidovudine; EFV, efavirenz; HIV, human immunodeficiency virus; NVP, nevirapine; PV, pharmacovigilance; TDF, tenofovir; TSR, targeted spontaneous reporting; ZDV, zidovudine
4 COUNTRY EXPERIENCES WITH TARGETED SPONTANEOUS REPORTING

This session covered findings from targeted spontaneous reporting of ARV toxicity. Three countries – Côte d’Ivoire, Lao PDR and Viet Nam – reported on progress, lessons learnt and intermediary data from pilot projects. A fourth country, Kenya, reported on findings from operational research that compared five different points for collecting toxicity data from Ministry of Health–AMPATH (Academic Model Providing Access to Healthcare) clinic sites. The presentations and the discussion that followed acknowledged that a variety of targeted approaches to toxicity surveillance can be integrated into different points of care, and can facilitate a more comprehensive understanding of ARV toxicity and its impact on care.

4.1 Presentations of country experiences with targeted spontaneous reporting of adverse drug reactions for ARV drugs

Table 2 summarizes the presentations made by Côte d’Ivoire, Kenya, Lao PDR and Viet Nam.

4.2 Main points of discussion

The pilot projects used a hybrid approach involving integration of reporting into routine care and the set-up of a cohort of selected ART patients. In all projects, all patients were ART naive or newly receiving one or more targeted ARV drugs, meaning that it was not possible to capture long-term toxicity associated with ARV drugs (Côte d’Ivoire, Lao PDR, Viet Nam). Including patients initiating one or more targeted ARV drugs, or receiving the drugs from earlier stages of ART, would make it possible to capture both short- and long-term toxicity (WHO/HIV).

Targeted reporting systems need to ensure that only clinically significant toxicities are reported, rather than all symptoms (Viet Nam). This would avoid the reporting and management of numerous unnecessary data. Another suggestion was to optimize the surveillance by reporting on severe reactions of all ARV drugs instead of only one or two regimens or drugs (Lao PDR).

The issues of underreporting, poor quality and incompleteness of data were raised. Also highlighted was the importance of training, supervision and triangulation using different sources of data and different modes of reporting (South Africa).

The importance of a systematic causality assessment – particularly in the case of fixed-dose combinations or drug associations – was acknowledged. The need for technical assistance to build capacity in this area was highlighted (Lao PDR).

In some situations, the population under surveillance can be well characterized, allowing an estimated incidence of specific toxicities associated with specific drugs to be obtained from a targeted spontaneous reporting approach. In such situations, it may be more cost efficient to capture data on all types of ARV drugs rather than only one regimen (Viet Nam).

The feasibility of various toxicity surveillance approaches can be assessed through pilot studies before national scale-up of these systems. Lessons learnt from pilot studies can be valuable to other countries embarking on similar initiatives; hence, there is a need for a network of communication and collaboration between targeted spontaneous reporting systems across countries (WHO/HIV).
### Table 2 Experiences from Côte d’Ivoire, Kenya, Lao People’s Democratic Republic and Viet Nam

<table>
<thead>
<tr>
<th>Country</th>
<th>Surveillance approaches</th>
<th>Challenges and limitations</th>
<th>Lessons learnt</th>
</tr>
</thead>
<tbody>
<tr>
<td>CÔTE D'IVOIRE</td>
<td>Cohort study with TSR of nephrotoxicity associated with TDF</td>
<td>• Limitations of follow-up and the need to reimburse patients to encourage them to return for care</td>
<td>• It is important to support reporting staff with diagnostic algorithms and appropriate laboratory capacity</td>
</tr>
<tr>
<td></td>
<td>TDF prioritized because it is recommended as first-line treatment in patients with anaemia, hepatitis B or TB, and as second-line treatment.</td>
<td>• Poor culture of reporting</td>
<td>• TSR relies on a good reporting culture (as with any spontaneous reporting system)</td>
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<td></td>
<td>Cohort identified from three hospital ART centres with 674 patients currently receiving TDF.</td>
<td>• Inadequate resources for routine renal-function testing</td>
<td>• The challenges in ensuring retention in care affect the ability to detect toxicities</td>
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<tr>
<td></td>
<td>Inclusion of patients initiating TDF (naive or substituting from a non-TDF-based regimen).</td>
<td></td>
<td>• In resource-limited settings, toxicity surveillance systems need to be designed within the context of priority national safety concerns, and clinical and laboratory capacity</td>
</tr>
<tr>
<td></td>
<td>Sites selected based on volume of cohort, experience in HIV case management, and ability to detect and manage adverse drug reactions.</td>
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<td></td>
<td>Nephrotoxicity spontaneously reported, based on diagnostic algorithms provided to staff.</td>
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<td></td>
<td>Baseline renal-function tests will be conducted on patients.</td>
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<td></td>
<td>The data will be reviewed by a multidisciplinary expert committee. Recruitment will be initiated from November 2013 and will continue until February 2015.</td>
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<tr>
<td></td>
<td>ARV toxicity surveillance system is one of the eight pillars of new national ART plan.</td>
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## KENYA

**Surveillance approaches**

A pilot study was undertaken; the study was aimed at assessing the feasibility and challenges encountered when various TSR approaches were used in the collection of adverse drug reaction data in patients on ART.

Surveillance comprised a multipronged approach to soliciting adverse drug reaction information from patients on ART; the approach involved:

- reporting adverse drug reactions using the national spontaneous reporting system;
- recording adverse drug reactions in a routine clinical encounter form that prompts for adverse drug reaction information;
- peer-led interviews of patients on ART, which obtained information using standardized forms (including a symptom form, adherence form, quality-of-life assessment form, pregnancy questionnaire, and PV encounter form);
- pharmaceutical technician-led interviews (3 and 4 = 1000 patients); and
- pharmacy dispensing data that prompted for reasons of drug substitution, including the presence of toxicities.

Data were entered into the REDCap database and the outputs of the various approaches were compared.

Preliminary results: Interim analysis demonstrated that there were differences in the frequency and nature of adverse drug reaction data derived from the various approaches. Pharmacy data indicated that, in over 583 cases of change in ART, 389 (67%) were due to toxicity.

**PV activities for ARV toxicity**

Various capacity-building initiatives in place, including integrating PV into ARV guidelines and into the integrated HIV training curriculum.

Continuous support and training at 12 sentinel sites across the country on adverse drug reaction reporting; sensitization using HIV-PV handbook for health workers and pharmacists.

Cohort event monitoring of 10,000 patients on ART in eight sites planned to start in 2014.

Treatment outcome monitoring plan (2014–2018) – HIV DR, toxicity surveillance will be included.

### Challenges and limitations

- Underreporting is still present even in a highly targeted, stimulated environment where toxicity surveillance is integrated into M&E
- Incomplete data and underreporting or underdetection with TSR1 using spontaneous reporting forms
- Few symptoms reported with routine clinical encounter forms (TSR2)
- Pharmacy encounter forms (TSR5) do not provide clinical information to document the toxicity; need to combine with another source of data
- Interviews by peers (TSR3) or technicians (TSR4) add value of close personal interaction with patients, which increases treatment quality outcome (beyond adverse drug reaction reporting)

### Lessons learnt

- The type of toxicity information depends on the diagnostic capacity of the reporters at the point of data collection and the mode of data collection (spontaneous reporting, solicited information on regimen changes, patient interviews), and the cadre of health worker (doctors, pharmacists, nurses, etc.) targeted for the reporting
- Using pharmacy records for quality control (e.g., flagging of treatment discontinuation or change due to severe adverse drug reactions)
- Need:
  - a way to make optimal use of the electronic medical records
  - a focal point at the facility to improve completeness of data in the spontaneous notification forms
  - a proper infrastructure to address poor data in the clinical encounter forms
- Establishing phone-based care improves management of adverse drug reactions and ART adherence
<table>
<thead>
<tr>
<th>Country</th>
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<th>Challenges and limitations</th>
<th>Lessons learnt</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAO PDR</td>
<td>Pilot of TSR in five ART sites in three provinces ZDV and NVP, preferred first-line options, were targeted for toxicity surveillance for anaemia (ZDV) and for skin reactions, including rash and Stevens–Johnson syndrome, and hepatotoxicity (NVP). A key goal of the TSR system was to serve as a pathfinder for a more comprehensive national PV system. Case definitions and severity grading of the targeted toxicities provided to the reporting sites. Ten clinicians trained in five ARV hubs on SOPs and reporting forms, with adverse drug reactions now routinely reported. The country registered to the WHO International Drug Monitoring Programme. Intermediate toxicity data: 421 new patients have been put on ART in the five sites, with 64 cases of adverse drug reactions reported. Reporting of all grades of toxicities was completed (including grade 4), with eight severe cases of anaemia and six with NVP (four rash and two hepatotoxicity).</td>
<td>Need to: • improve efficiency of reporting system • build national capacity for validation and analysis of data, and assessment of causality of individual reported cases • develop appropriate response and feedback to reporters and reporting sites • develop a mechanism to conduct further investigations and follow-up on important cases • secure ongoing funding to ensure sustainability of the reporting system</td>
<td>• TSR was found to be useful for generating evidence on targeted toxicity, and improving treatment adherence and safety, by providing early warnings on adverse drug reactions • Increased awareness and capacity in reporting in settings where there are no systems • Clear case definitions and severity grading improves quality of reports • Individual assessment of cases is a critical part of the analysis of data. Even though targeted reactions are known to be associated with the drugs under surveillance, the individual case may not be attributable to the drugs under surveillance • In settings where the TSR sites are confined to certain centres that have robust denominator data, reporting rates could be calculated</td>
</tr>
<tr>
<td>Country</td>
<td>Surveillance approaches</td>
<td>Challenges and limitations</td>
<td>Lessons learnt</td>
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<td>VIET NAM</td>
<td>Two pilots of TSR approach:</td>
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<td>– TSR within a TasP clinical trial among serodiscordant couples – study conducted in 11 clinics in 98 patients in two provinces</td>
<td>• The lower reporting rates observed in the TasP study suggest that the recording of other information for the purposes of the study may compromise the recording and reporting of toxicity data</td>
<td>• TSR was found to be applicable and relevant for countries with a concentrated epidemic and limited resources</td>
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<td>– TSR in patients newly treated with TDF and with EFV – pilot was conducted in seven outpatient clinics in 558 patients in Hanoi</td>
<td>• Incomplete and inaccurate information on adverse drug reactions reported</td>
<td>• Feasible with well-structured reporting form, resulting in increased number of reports</td>
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<td>Both pilots targeted collection of TDF- and EFV-related toxicities.</td>
<td>• Delays in reporting via postal system; email reporting may be preferable</td>
<td>• Importance of ensuring that reporters are not overwhelmed by their reporting requirements</td>
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<td></td>
<td>TSR reporting form with case definitions and guidelines for reporting developed and health staff trained.</td>
<td>• The high number of non-serious adverse drug reactions reported (making up the majority of reports) consume time and resources, but have limited relevance for surveillance</td>
<td>• Technical assistance and close monitoring increase the number of adverse drug reaction reports</td>
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<td></td>
<td>Staff trained to elicit toxicity experiences from patients at all follow-up visits, and to assess serum creatinine levels periodically.</td>
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<td>• Training on detecting, recoding and reporting skills is vital for success</td>
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<td>Doctors trained to complete the toxicity section, and nurses the remaining sections.</td>
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<td>• TSR can include reporting rates when reliable denominator data are available from sites</td>
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<td>Reports transmitted to the national drug information and adverse drug reaction centre on a monthly basis.</td>
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<td>• Key to success is close communication and feedback between the national drug information centre, national ART programme and ART sites</td>
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<td>Intermediate toxicity data: 22% of all patients in the TasP study experienced adverse events, all of which were related to EFV; about 40% of patients in the Hanoi pilot study experienced an adverse drug reaction, with most reactions due to EFV. In both pilots, the vast majority of reports were non-serious.</td>
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<td>TSR was able to include reporting rates due to the availability of reliable denominator data (number of patients receiving TDF or EFV) from the clinics.</td>
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<td>Way forward: Scale-up to five high-burden provinces planned. Training and guidelines needed for implementation and scale-up.</td>
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<td></td>
<td>A pilot cohort event monitoring for ARV drugs project was conducted in five sentinel sites from October 2011 to June 2013; 645 patients were recruited and followed up for an average of 11.4 months.</td>
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<td></td>
<td>Useful data on adverse drug reaction rates and risk factors were identified.</td>
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<td>The programme was found to be too costly, and too time and labour intensive to be sustainable or suitable for national expansion.</td>
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<td></td>
<td>Public health PV system has been incorporated into HIV, TB and immunization programmes.</td>
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<tr>
<td></td>
<td>Spontaneous reporting has been mandatory for ARV drugs since 2005, but has had little impact on reporting rates, particularly of adverse drug reactions related to ART.</td>
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</tbody>
</table>

AMPATH, Academic Model Providing Access to Healthcare; ART, antiretroviral treatment; ARV, antiretroviral; DR, drug resistance; EFV, efavirenz; HIV, human immunodeficiency virus; M&E, monitoring and evaluation; NVP, nevirapine; PDR, People’s Democratic Republic; PV, pharmacovigilance; SOP, standard operating procedure; TasP, treatment as prevention; TB, tuberculosis; TDF, tenofovir; TSR, targeted spontaneous reporting; ZDV, zidovudine
5 INTEGRATION OF TOXICITY SURVEILLANCE INTO HIV MONITORING AND EVALUATION PROGRAMME

5.1 ARV toxicity surveillance within HIV monitoring and evaluation framework

WHO is preparing a consolidated approach to monitoring and evaluation – the WHO Consolidated strategic information guide for HIV in the health sector – that will be released in July 2014. Under the treatment and care section, this approach is organized along the cascade of HIV care, and integrates toxicity surveillance within routine national monitoring and evaluation activities. The approach recommends toxicity surveillance as a key component of strategic information that needs to be collected and evaluated by the HIV programme. As ART is scaled up – meaning that more people start ART earlier and remain on treatment for a longer period – implementation of toxicity surveillance becomes even more critical for HIV programmes.

The question arises of how best to implement a toxicity monitoring system in a given country (beyond special studies in sentinel sites) by integrating selected components into routine monitoring systems. Toxicity surveillance indicators need to be included in the list of monitoring and evaluation indicators.

The monitoring and evaluation approach requires clarity on which adverse reactions are worth collecting routinely at all sites, the form and minimum set of data elements to be reported on, and the criteria or conditions that need to be met for this to be achieved. Various monitoring and evaluation data collection tools would prompt the collection of data on toxicity, such as:

- the HIV patient card – one card or file per individual;
- the ART register – a summary of key variables to facilitate data aggregation and reporting (6);
- the ART cohort reporting form – a report on the status of a group of patients at a specific time after initiation, which is routinely collected from treatment sites;
- the cross-sectional reporting form; and
- a special toxicity reporting form – capturing severe reactions with all ARV drugs and including standardized definitions and reporting guidance.

The proposed key indicator for toxicity monitoring is:

- percentage of ARV drug patients with treatment-limiting toxicity

It will use the patient clinic record to assess the number of ART patients with treatment-limiting toxicity over the total number of patients on ART (6).

Treatment-limiting toxicity is defined as life-threatening illness, death, hospitalization, disability or resulting in treatment discontinuation or substitution.

The data could be included in the paper-based system (where a small and simple set of toxicity data is reported, on a monthly or quarterly basis) or electronically (where a core set of data for toxicity monitoring are identified for routine reporting). Alternatively, data could be extracted retrospectively, based on various inclusion or exclusion criteria, disaggregation of data, or identification of a target population of interest whose records are reviewed.

This approach to monitoring and evaluation is systematic and widespread and, if conducted correctly, will provide information on incidence of serious toxicities and their relative impact on patient health outcomes and patient care. Compared to other approaches, the approach provides more data from a larger number of facilities and patients, and allows comparison of data across sites, countries and regions. It also provides a potentially more representative characterization of toxicities, and could be less expensive than dedicated research studies.

As with other approaches, a number of challenges would need to be addressed; for example, underreporting remains a risk; training and supervision may not be as rigorous as more targeted or site-specific approaches; and, in the absence of a separate reporting form, the actual clinical details of individual reactions may be more limited.
5.2 Main points of discussion

The need for a roadmap with minimum requirements and changes to integrate to HIV monitoring and evaluation tools was highlighted (Côte d’Ivoire). The possibility of specificities in relation to key populations, drug associations or risk factors would need to be addressed (Ukraine).

The practicalities of this approach would need to be tested in various settings. For instance, experience from Western Cape, South Africa suggests that reminders on a monthly basis do not necessarily encourage reporting of adverse drug reactions, although in Belarus such monthly reminders were found to be helpful.

In many countries, there are efforts to integrate TB, HIV and maternal child health services. Thus, the monitoring and evaluation system may need to take this into consideration, to avoid parallel reporting systems for each of these areas (South Africa).

Collaboration between the ART programme and the national pharmacovigilance programme would ensure that the data informs the HIV programme, the drug regulatory agency and clinical institutions. Also, collaboration is in line with the need for data standardization within a national and global perspective (WHO/EMP).
6 SOLUTIONS TO IMPROVE APPROACHES AND ENHANCE THE CAPTURE OF ARV TOXICITY DATA (WORKING GROUPS)

The value of a national toxicity surveillance system lies in its ability to inform policy and improve clinical care. The success of the system in achieving these objectives relies on its ability to generate a reasonable amount of high-quality data.

Three working groups, comprising country and international experts, were formed to discuss key challenges of ARV toxicity surveillance programmes identified in previous discussions. The focus was on how to address the challenges, improve quantity and quality of toxicity data generation, and integrate ARV toxicity surveillance into HIV monitoring and evaluation programmes.

Working group participants identified some solutions to support ARV toxicity surveillance programmes; these are described in Table 3 below.

Table 3 Challenges of and solutions to support ARV toxicity surveillance programmes (working groups)

<p>| Theme 1: Key challenges of ARV toxicity surveillance programmes and how to address them |</p>
<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences in the level of capacity for surveillance and in toxicity priorities among countries</td>
<td>• Tier the expectations, based on where the countries are and how they can contribute to data on an international level</td>
</tr>
<tr>
<td>Lack of awareness of the need for monitoring of ARV toxicity, and its relevance to treatment quality outcomes</td>
<td>• Create a global platform for sharing experiences</td>
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<tr>
<td>Objectives of toxicity surveillance systems are not SMART</td>
<td>• Increase communication and advocacy-building efforts among professionals, patients and the public</td>
</tr>
<tr>
<td>Underuse of existing sources of toxicity data</td>
<td>• Invest more time and effort in generating outputs from the surveillance system (e.g. feedback to providers and policy-makers)</td>
</tr>
<tr>
<td>Difficulties in pooling and comparing data across sites and countries</td>
<td>• Develop global SMART objectives for toxicity surveillance that countries can adapt</td>
</tr>
<tr>
<td>Sustainability and reliance on external resources</td>
<td>• Identify all potential sources of national toxicity data:</td>
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<tr>
<td></td>
<td>-- patient records</td>
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<tr>
<td></td>
<td>-- existing registers and cohorts</td>
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<tr>
<td></td>
<td>-- HIV M&amp;E system</td>
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<tr>
<td></td>
<td>-- existing national PV system</td>
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<td>-- research data</td>
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<td></td>
<td>• WHO to provide guidance on case definitions, core data sets and so on</td>
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<td></td>
<td>• Integrate toxicity surveillance into the treatment programme so that it is not seen as separate to or vertical from the programme of providing access to treatment</td>
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<td>• Incorporate toxicity surveillance in all funding applications</td>
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</table>

<p>| Theme 2: Improving the quantity and quality of toxicity data generation |</p>
<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task shifting from doctors to nurses for patient care</td>
<td>• Build capacity of the data “collectors”, through training, mentorship and other initiatives</td>
</tr>
<tr>
<td>Data sets differ between systems (even those with shared objectives), and definitions are not standardized among countries</td>
<td>• Improve access to laboratories, to assist in verification of specific toxicities</td>
</tr>
<tr>
<td>Too much information collected, of limited usefulness</td>
<td>• Define priority toxicities, develop indicators, define core data set, provide case definitions and develop user-friendly forms and training materials</td>
</tr>
<tr>
<td>Poor infrastructure for laboratory monitoring</td>
<td>• Collect strategic information on treatment-limiting toxicities</td>
</tr>
<tr>
<td>High risks of loss to follow-up and disengagement of care</td>
<td>• Perform retrospective analysis of adverse drug reactions from clinical settings</td>
</tr>
<tr>
<td>Underreporting</td>
<td>• Improve laboratory capacity for toxicities, particularly at higher levels of care</td>
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<tr>
<td></td>
<td>• Improve retention in care by engaging with recommended approaches, including counselling patients on expected toxicities that may affect adherence</td>
</tr>
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<td></td>
<td>• Identify all points of patient contact as opportunities to collect data on toxicities in a way that is integrated into routine practice</td>
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<td>• Trigger a simple system using providers and PLHIV to identify ARV toxicity</td>
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<td></td>
<td>• Telephonic reporting, or submission of reports via email</td>
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</tbody>
</table>
### Theme 3: Integrating ARV toxicity surveillance into monitoring and evaluation

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unclear priorities and objectives in ARV toxicity monitoring</td>
<td>• Countries to select toxicity priorities and design or adapt tools or system to collect these toxicities</td>
</tr>
<tr>
<td>• Inefficient reporting mechanisms</td>
<td>• Integrate reporting system into routine care and training</td>
</tr>
<tr>
<td>• Lack of simple collection tools for toxicity within routine monitoring</td>
<td>• Tier approach for ARV toxicity surveillance, within M&amp;E of system</td>
</tr>
<tr>
<td>• Absence of link between toxicities and treatment discontinuation or substitution in routine registers</td>
<td>• Provide technical feedback to the clinicians</td>
</tr>
<tr>
<td>• Inadequate validation of data for internal consistency</td>
<td>• Adapt or update generic M&amp;E tools</td>
</tr>
<tr>
<td>• Delayed reporting</td>
<td>• Collect data on treatment discontinuation and deaths associated with toxicities by ART cohort</td>
</tr>
</tbody>
</table>

**ART, antiretroviral treatment; ARV, antiretroviral; HIV, human immunodeficiency virus; M&E, monitoring and evaluation; PLHIV, people living with human immunodeficiency virus; PV, pharmacovigilance; SMART, specific, measurable, achievable, realistic and time-based**
Implementation of ARV drug toxicity surveillance becomes even more critical for HIV programmes in the context of the recent WHO Consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection (1), as more people start ART earlier and remain on treatment for a longer period on a wider scale. The WHO guidelines highlight some key toxicity concerns associated with the use of ARV drugs. They also emphasize the need to strengthen toxicity surveillance as a key component of the continuum of care, and to stimulate research to inform future guidelines. A WHO technical brief – Surveillance of antiretroviral drug toxicity within antiretroviral treatment programmes (2) – was released in October 2013; it describes approaches that address the particular needs of HIV/AIDS treatment programmes to monitor the toxicity of ARV drugs.

This meeting brought together countries from various regions where the following approaches have been implemented (with other methods):

- cohort event monitoring in Belarus and the United Republic of Tanzania;
- targeted spontaneous reporting in Côte d’Ivoire, Kenya, Lao PDR, South Africa and Viet Nam;
- targeted monitoring of key toxicities within existing cohorts in South Africa and Viet Nam; and
- retrospective chart reviews in Côte d’Ivoire and Ukraine.

These experiences covered national project implementation (e.g. as in South Africa since early 2003) or pilot project implementation (as initiated in 2011 under a collaborative WHO/BMGF project in Côte d’Ivoire, Kenya, Lao PDR, Ukraine, United Republic of Tanzania and Viet Nam).

Progress, challenges and lessons learnt from the various approaches of toxicity surveillance were reviewed during the meeting. Despite the many challenges identified, there was clear evidence that the various approaches increased the collection of toxicity data within ART programmes, and that the data arising from these surveillance approaches could meaningfully inform treatment policies and improve patient care. Solutions to improving approaches and interventions were discussed. The outputs of these discussions are summarized below. They will serve as the basis for updating technical guidance and strengthening country capacity in monitoring toxicity in order to directly improve patient care and inform policies.

7.1 Building on current successes

The surveillance approaches have successfully demonstrated their usefulness in:

- enhancing reporting of adverse reactions associated with ARV drugs;
- documenting key toxicities that influence drug substitution rates and affect morbidity;
- determining rates of key toxicities that are risk drivers of specific drug regimens;
- building capacity and confidence among health professionals in reporting, with clear case definitions and reporting guidelines;
- optimizing the analysis and use of data through the collaborative expertise of the pharmaceutical sector and public health programmes; and
- disseminating findings and providing relevant feedback to reporters and those who support the surveillance system.

7.2 Addressing shared challenges across countries

Common and persistent challenges met by countries in achieving the objectives of a toxicity surveillance system include:

- a limited capacity to conduct surveillance programmes, including the capacity to diagnose, report and analyse data;
- inadequate clinical record keeping, high rates of staff turnover and poor retention of patients in care;
- reporter fatigue, leading to underreporting and incompleteness of data;
- lack of incidence and risk-factor data on key toxicities;
- inadequate analysis and use of the data to directly improve the care of patients at participating sites;
- inadequate feedback and other communication initiatives; and
- limited funding, and political and resource investment for sustaining surveillance systems.
7.3 Recommendations for optimizing ARV toxicity surveillance approaches

WHO technical guidance will be updated on the basis of the following outcomes:

- nesting ARV cohort event monitoring in a few centres of excellence, where the necessary resources would be available;
- taking advantage of targeted spontaneous reporting for capturing and reporting on severe reactions with all ARVs delivered at selected sentinel sites;
- investing in reporting champions for integrating toxicity surveillance within existing treatment cohorts;
- including recruitment of patients at different points in ART, to monitor both short- and long-term toxicity;
- strengthening surveillance of hospitalizations due to drug toxicity at selected hospitals;
- making use of and reviewing patient charts for retrospective or prospective toxicity data analysis; and
- investing in HIV monitoring and evaluation systems to deliver on key indicators of toxicity surveillance.

7.4 Recommendations for integrating ARV toxicity surveillance into HIV monitoring and evaluation

Although toxicity monitoring is key to the success of ART programmes, limited strategic information has been collected and evaluated through the HIV programmes. The forthcoming WHO Consolidated strategic information guide for HIV in the health sector (to be released in July 2014) will provide a framework that countries can use to integrate toxicity surveillance within a national monitoring and evaluation system, using a combination of routine monitoring and special surveys or studies.

The following indicators will be integrated into core indicators for national programme monitoring:

- percentage of ART patients with treatment-limiting toxicity by ART cohort;
- numerator; that is, the number of treatment-limiting toxicities in ART patients; and
- denominator; that is, the number of ART patients, disaggregated by drug or regimen, at time of toxicity; sex; age; pregnant women; key populations; and TB/HIV.

The HIV patient card, ART register and reporting forms will be updated to report on core indicators. The link to specific regimens or drugs will be monitored. Where available, an electronic patient-monitoring system is expected to facilitate monitoring.

It was considered that other priority toxicity questions would be addressed through special studies and surveys, using approaches reviewed during the meeting:

- targeted spontaneous reporting at “champion reporting” sites;
- active surveillance of toxicity in existing sentinel cohorts;
- retrospective or prospective review of clinical charts abstracted from (electronic) patient-monitoring systems;
- hospital surveys on hospitalizations due to ARV-related toxicity; and
- cohort event monitoring at sites of excellence.

7.5 Recommendations for conducting operational research

The main challenge arising from the meeting was to generate more reliable data on the incidence of treatment-limiting toxicity within national HIV programmes. Generating such data appears to require additional methods that source the data directly from the emerging electronic patient-monitoring systems, and from networks of sentinel hospitals that agree to report on all severe adverse drug reactions that require hospitalization.

Even in settings with electronic patient-monitoring systems, there may be insufficient capacity to ensure full reporting on all toxicities that require treatment substitution, switching or stopping. It is unclear how best to implement these more engaged approaches; therefore, the meeting recommended a focus on operational research into optimization of implementation modalities.
8 NEXT STEPS

It is a complex task to develop effective ARV toxicity monitoring systems that are contextually feasible. The efforts to establish a combination of approaches should continue and be strengthened. Integrating toxicity surveillance into the HIV monitoring and evaluation system will strengthen the generation of data within ART programmes. There is a need to explore additional approaches that can be incorporated into the menu of relevant methods available for surveillance, and to explore how, where and when such methods may be feasible and appropriate. This includes making use of the emerging electronic patient-monitoring systems, and building on networks of sentinel hospitals. The decision to explore and expand on existing approaches comes with a significant agenda for operational research.

WHO will incorporate priority questions for optimizing implementation modalities of toxicity monitoring into an operational research agenda for the strategic use of ARV drugs. The WHO technical brief – *Surveillance of antiretroviral drug toxicity within antiretroviral treatment programmes* (2) – will be updated in light of key outcomes that arose from the meeting, and the forthcoming WHO *Consolidated strategic information guide for HIV in the health sector* will incorporate the findings and suggestions of the meeting for integrating ARV toxicity surveillance into HIV monitoring and evaluation systems. WHO will continue building country capacities for the implementation of toxicity surveillance systems, and support the generation of toxicity data as part of the consolidated guidelines on the use of ARV drugs and other initiatives.
# MEETING AGENDA

## DAY ONE: 7 November 2013

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| 9:00–9:15     | **Wrap up from Day One**  
**Dr J. Perriëns, WHO, Coordinator HIV Technologies and Commodities** |
| 9:15–10:45    | **VI. Solutions to improve approaches and enhance the capture of ARV toxicity data**  
**Moderation: Dr U. Mehta, Medicines Control Council, South Africa**  
1. Working group session: Split into three groups:  
   1) Identifying key challenges of toxicity surveillance programmes and how to address them – Suite 104  
   2) Improving quantity and quality of toxicity data generation – Room St. Moritz  
   3) Integrating ARV toxicity surveillance into HIV monitoring and evaluation programme – Suite 106 |
| 10:45–11:15   | Coffee Break                                                                          |
| 11:15–12:15   | **VI. Solutions to improve approaches and enhance the capture of ARV toxicity data (contd.)**  
**Moderation: Dr U. Mehta, Medicines Control Council, South Africa**  
2. Feedback from working groups in plenary:  
   Presentation by rapporteur from each group (15 min)  
   Discussion (15 min) |
| 12:15–12:30   | **VII. Closing**  
Wrap up and concluding remarks, **Dr J. Perriëns, WHO, Coordinator HIV Technologies and Commodities** |
| 12:30–14:00   | Lunch Break                                                                            |
| 14:00–16:00   | **Individual meetings between WHO officers and country delegations**  
Possible topics for discussion:  
• Publication of protocols and experience in peer review journals, planning of conference presentations  
• Actions to anchor toxicity monitoring in routine monitoring and evaluation of national ART programmes |
| 16:00–16:30   | Coffee Break                                                                            |
| 17:30         | End of Day Two                                                                          |
LIST OF PARTICIPANTS

COUNTRIES

AFRO

Côte d’Ivoire
Pr Eric Balayssac
Service de Pharmacologie Clinique
UFR des Sciences Médicales de Cocody
Abidjan
Email: ebalayssac@yahoo.fr

Dr Regina Nee Koko Konan
Directeur de la Prise en Charge Thérapeutique du SIDA
Programme National de lutte contre le VIH/Sida
Abidjan
Email: dpects_infos@yahoo.fr

Kenya
Dr Caroline A. Olwande
Program Pharmacist
National AIDS and STI Control Program
KNH grounds
PO Box 19361-00202
Nairobi
Email: colwande@nascop.or.ke

South Africa
Dr Karen Cohen
Division of Clinical Pharmacology
Department of Medicine
University of Cape Town
K floor, Old Main Building
Groote Schuur Hospital Observatory
Cape Town 8001
South Africa
Email: karen.cohen@uct.ac.za

Dr Ushma Mehta (Rapporteur)
Chairperson Pharmacovigilance Committee, Medicines
Control Council
130C Pearson Park, Rosmead Avenue
Kenilworth, 7708
South Africa
Email: ushmaza@yahoo.com

United Republic of Tanzania
Dr Alex Nkayamba
Clinical Trials Control and Pharmacovigilance
Tanzania Food and Drugs Authority
PO Box 77150
Dar es Salaam
United Republic of Tanzania
Email: alexnkayamba@yahoo.com

EURO

Belarus
Dr Setkina Sviatlana
Chief Specialist
Republican Unitary Enterprise
Center for Expertise and Testing
In Health Care
2a Tovarishchesky Lane
Minsk 220037
Belarus
Email: rcpl@rceth.by

Ukraine
Dr Valentyna Yaichenia
Head – Department of Information and Analysis
State Expert Center
Ministry of Health of Ukraine
Kyiv
Ukraine
Email: valja@dec.gov.ua

WPRO

Lao People’s Democratic Republic
Dr Lamphone Syhakhang
Deputy Director
Food and Drug Department
Ministry of Health
Vientiane
Lao PDF
Email: syhakhangl@yahoo.com

Dr Bounpheng Philavong
Director
National Centre for HIV/AIDS and STI
Ministry of Health
Vientiane
Lao PDR
bounphengphilavong@yahoo.com

Viet Nam
Dr Le Thi Huong
Deputy Head of HIV/AIDS Care and Treatment
Viet Nam Administration of HIV/AIDS Control
Hanoi
Viet Nam
Email: lehuongmoh@yahoo.com
Dr Nguyen Hoang Anh  
Deputy Director  
National Drug Information & Adverse Drug Reaction Centre  
Hanoi University of Pharmacy  
Hanoi  
Viet Nam  
Email: anh90tk@yahoo.com

RESEARCH INSTITUTIONS, NGOS AND PARTNER AGENCIES

Dr Christopher Duncombe  
(not able to attend)  
Senior Program Officer HIV  
Global Health Program  
Bill & Melinda Gates Foundation  
Seattle  
United States of America (USA)  
chris.duncombe@gatesfoundation.org

Dr Mercy Wangechi Maina  
Pharmacovigilance-Pharmacist  
USAID-AMPATH Partnership  
AMPATH Centre, MTRH/MU  
Nandi Road - PO Box 4606  
Eldoret 30100  
Kenya  
Email: mwmercy@gmail.com

WHO REGIONAL AND COUNTRY OFFICES

AFRO

Dr Marie-Catherine Barouan  
National Professional Officer  
HIV/TB  
WHO Country Office  
PO Box 01  
Abidjan  
Côte d’Ivoire  
Email: barouanm@ci.afro.who.int

WHO/HQ SECRETARIAT

Department of HIV/AIDS

Dr Gottfried Hirnschall  
Director  
World Health Organization  
Avenue Appia 20  
CH-1211 Geneva 27  
Switzerland  
Email: hirnschallg@who.int

EURO

Dr Ihor Perehinets  
National Professional Officer  
WHO Country Office  
30, Borychiv Tik Street  
Kiev 04070  
Ukraine  
Email: pei@euro.who.int

WPRO

Dr Van Thi Thuy Nguyen  
National Professional Officer  
HIV Care and Treatment  
WHO Country Office  
PO Box 52-63 Tran Hung Dao  
Hanoi  
Viet Nam  
Email: nguyenva@who.int

Dr Dominique Ricard  
Medical Officer and Team Leader for HIV/STI  
WHO Country Office  
PO Box 343  
Vientiane  
Lao PDR  
Email: ricardd@who.int

Dr Brian Pazvakavambwa  
HIV Medical Officer  
WHO Country Office  
Nairobi  
Kenya  
Email: pazvakavambwab@who.int

Dr Joseph Perriëns  
Coordinator  
HIV Technologies and Commodities Unit  
World Health Organization  
Avenue Appia 20  
CH-1211 Geneva 27  
Switzerland  
Email: perriensj@who.int
Dr Meg Doherty
Coordinator
HIV Treatment and Care
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: dohertym@who.int

Dr Gundo Weiler
Coordinator
Strategic Information and Planning
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: weilerg@who.int

Dr Françoise Renaud
Technical Officer
HIV Technologies and Commodities
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: renaudf@who.int

Dr Marco Vitoria
Medical Officer
HIV Treatment and Care
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: vitoriam@who.int

Dr Chika Hayashi
Technical Officer
Strategic Information and Planning
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: hayashic@who.int

Dr Nathan Ford
Technical Officer
HIV Treatment and Care
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: fordn@who.int

Department of Essential Medicines and Pharmaceutical Policies

Dr Lembit Rago
(not able to attend)
Head
Quality Assurance and Safety: Medicines
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: ragol@who.int

Dr Shanti Pal
Technical Officer
Quality Assurance and Safety: Medicines
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
Email: pals@who.int
REFERENCES


Useful links and documents:


For more information, contact:

World Health Organization
Department of HIV/AIDS
20, avenue Appia
1211 Geneva 27
Switzerland

E-mail: hiv-aids@who.int

www.who.int/hiv