MEETING REPORT

SURVEILLANCE OF ANTIRETROVIRAL TOXICITY

TECHNICAL REVIEW MEETING ON COUNTRY EXPERIENCES IN ANTIRETROVIRAL TOXICITY SURVEILLANCE

SHARING PRELIMINARY RESULTS AND LESSONS LEARNT, IDENTIFYING SOLUTIONS

7–8 NOVEMBER 2013, GENEVA, SWITZERLAND

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ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
AMPATH	Academic Model Providing Access to Healthcare
ART	antiretroviral treatment
ARV	antiretroviral
BMGF	Bill and Melinda Gates Foundation
CD4	T-lymphocyte cell bearing CD4 receptor
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HIV	human immunodeficiency virus
PDR	People's Democratic Republic (Lao)
TB	tuberculosis
WHO	World Health Organization
WHO/EMP	Essential Medicines and Pharmaceutical Policies Department, WHO
WHO/HIV	HIV/AIDS Department, WHO

EXECUTIVE SUMMARY

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

2 SETTING THE STAGE: DEFINING THE NEED AND STRENGTHENING TOXICITY SURVEILLANCE

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

Presented by Dr M. Doherty, Coordinator Treatment and Care, HIV/AIDS Department, WHO

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