

# **"ARV drugs adverse events, case definition, toxicity grading and laboratory diagnosis"**

**Meeting**

**WHO Geneva**

**28 -29 February 2008**

**A meeting jointly organized by WHO/HIV, PSM and the Forum for Collaborative HIV Research**

## **Report summary**

Considerable progress has been made in providing global access to antiretroviral therapy, with three million people currently on antiretroviral drugs around the world. However, the effectiveness of treatment programs, particularly in low and middle income countries, risks being compromised by problems related to toxicity, intolerance and drug-drug interactions. These adverse events, be they acute or chronic, mild or severe, are relatively common phenomena affecting both individual patients and public health, but are being only intermittently identified and scarcely systematically reported in low and middle income settings. Adverse reactions related to the use of antiretroviral drugs may severely jeopardize confidence in the safety of these medicines and alter patient adherence to antiretroviral therapy, not only reducing the treatment efficacy with increased morbidity and mortality, but also reducing treatment programme effectiveness and increasing the risk for emergence of secondary drug resistance. New adverse events and toxicities are identified, as people live longer on ART. The availability of numerous new drugs and drug combinations makes it critical to monitor more systematically adverse events linked to ARVs.

*For these reasons, there is an urgent need to strengthen the science of pharmacovigilance for antiretroviral drugs.*

The WHO Departments of HIV and Medicines Policy and Standards together with the Forum for Collaborative HIV Research, and with the support of the Bill and Melinda Gates Foundation, jointly organized a meeting in Geneva on February 28-29, 2008. This meeting was attended by 65 experts in pharmacovigilance, clinical HIV medicine and laboratory science, with representatives from governments and academia, international pharmacovigilance networks and cohorts, pharmaceutical companies, international and non-governmental organizations.

The primary objective of the meeting was to bring together the pharmacovigilance and HIV treatment communities to establish a common language with agreed terms to harmonize the adverse event case definitions, and hence the detection, recording, reporting and analysis of adverse event data related to the use of antiretroviral drugs. This is a prerequisite for improving patient safety and the effectiveness of treatment programs, for guiding national policies and for stimulating research. The ultimate goal is to develop a thesaurus of definitions of these adverse events of ARVs and contribute to improving global pharmacovigilance for antiretroviral drugs, with particular focus on resource-limited settings, children and special populations.

With the support of a network of experts, WHO is committed to further developing a mechanism to harmonize the assessment, reporting and analysis of antiretroviral drug-related adverse events, with a view to informing global and country specific treatment programs and improving the science of pharmacovigilance for antiretroviral drugs.

The meeting resulted in the generation of a list of major adverse events for surveillance related to the use of antiretroviral drugs, including those relevant to adult, pediatric and special populations (e.g. pregnant women).

Consensus was reached on the need to make available terms and definitions for adverse events that are applicable at all levels of health care delivery. The criteria for presenting these terms were agreed upon. Meeting participants endorsed a process for the development of a priority list of specific case definitions by expert panels that can be operationalized in treatment settings. In addition, it was recommended that expert panels develop severity grading of adverse events based on clinical and laboratory findings as needed. Drug-drug interactions and co-morbidities are to be considered for specific population subgroups, such as children, pregnant women and patients affected by tuberculosis, malaria and hepatitis. Treatment outcomes, such as death, life threatening or disabling adverse events including treatment limitations should be considered in patients management.(such as hospitalization, referral, treatment substitution or interruption.

Participants agreed on the principle of establishing sentinel surveillance sites for active reporting of adverse events in all countries including countries where pharmacovigilance systems for antiretroviral drugs still need to be developed. These sentinel surveillance sites will be linked to both national and international networks and need to be representative of the different levels of the health care system.

In addition, spontaneous reporting should be further strengthened in countries where pharmacovigilance systems have already been established, and where training and feedback is sustained. Known and unexpected adverse events will continue to be captured through existing passive pharmacovigilance reporting mechanisms. Where spontaneous reporting and PV systems are in place, strengthening existing PV mechanisms for stimulating spontaneous reporting will help to capture emerging problems and new toxicities.

## **Points of consensus**

### **1. The thesaurus of adverse events linked to antiretroviral drugs**

#### **Will be**

- A compilation of commonly agreed terms and definitions of adverse events related to antiretroviral drugs, to be used in clinical settings, cohort surveys and special studies.
- Developed based on existing and commonly agreed terms and definitions where available and by filling gaps when identified.

#### **Will not be**

- linked to causality.
- related to specific drugs, nor limited to adverse events linked to antiretroviral drugs.

## **2. Definition of adverse events linked to antiretroviral drugs (AE/ARVs): diagnosis classification and applicable levels<sup>1</sup> (required for each definition)**

- Presumptive<sup>2</sup>: symptomatic description mainly based on clinical findings  
1<sup>st</sup> level
- Presumptive or confirmed: symptomatic description confirmed by simple (1<sup>st</sup> level) or more complex laboratory test results  
1<sup>st</sup> and 2<sup>nd</sup> level
- Confirmed: symptomatic confirmed by laboratory; other diagnostic procedures  
3<sup>rd</sup> level

## **3. Criteria of terms and definitions of AE/ARVs:**

Existing AE/ARVs terms and definitions, will be reviewed updated or improved as needed and new terms and definitions of AE/ARVs will be developed as appropriate against the following criteria:

AE/ARVs terms and definitions should be :

- simple and descriptive, relating:
  - the nature of adverse events linked to ARVs, and
  - specific features (identified as biochemical, clinical, anatomical), and
  - differentiating features (from similar conditions)
- clinically relevant,
- simple, short, self-explanatory, and straightforward as possible,
- clear and understandable,
- specific and unambiguous,
- applicable (across health system structures) taking into account
  - the language of recording (preferred terms)
  - the level of education and training of service provider,
- consistent with the international standard pharmacovigilance terminology such as MedDRA (Medical Dictionary for Regulatory Activities), based as much as possible on pre- existing definitions, and
- applicable to the general pharmacovigilance system as well as to trials and observational studies.

## **4. Organization of the thesaurus of AE/ARVs**

The definitions of AE/ARVs were presented as classified by categories/domains; the organization as proposed in the background document (based on MedDRA) was accepted.

- No further stratification of definitions is needed (symptoms, syndromes, diseases, should be listed one by one)
- Working groups provided a list of definitions with various additions and deletions<sup>3</sup>
- There is a need to prioritize (see listing) development of definitions for a limited number of major adverse events.
- Additional terms may have to be provided in thesaurus format where MedDRA terms are not easily applicable at point of care.

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<sup>1</sup> Refers to the various levels of the health care system:

- a. Tier 1 – Definition based on clinical signs and symptoms only-basic facility.
- b. Tier 2 – Definition based on clinical signs and symptoms, and simple laboratory testing or diagnostic procedures -first reference clinical level-
- c. Tier 3 – Definition based on clinical signs and symptoms, supported by more extensive laboratory testing or diagnostic procedures such as referral laboratory, highest referral level-

<sup>2</sup> Presumption, confirmation and necessary tests to be defined by expert panels.

<sup>3</sup> See full report

## List of Priority Definitions (Classified according to MeDRA and WHO-ART SOC<sup>4</sup>)

<ol style="list-style-type: none"> <li>1. Skin disorders: severe cutaneous adverse reaction (SCAR), SJS</li> <li>2. Bone toxicity : <b>osteopenia, osteoporosis, osteonecrosis</b></li> <li>3. <i>Peripheral neuropathy</i></li> <li>4. Neuro-psychiatric toxicity (terms TBD<sup>5</sup>)</li> <li>5. Gastro-intestinal disorders; diarrhea;</li> <li>6. Hepatitis</li> <li>7. <i>Lactic acidosis;</i></li> <li>8. <b>Glucose intolerance;</b> <i>hyperglycemia;</i></li> <li>9. <i>Dyslipidemia, lipo-atrophy; lipohypertrophy</i></li> <li>10. Pancreatitis</li> <li>11. Cardiac diseases (to include further terms TBD, e.g. Cardiomyopathy, coronary heart disease, cardiac failure, arrhythmia.</li> </ol>	<ol style="list-style-type: none"> <li>12. Respiratory (TBD)</li> <li>13. Anaemia, Neutropenia,</li> <li>14. Urinary system disorders, <i>Renal disorders</i> (further terms TBD)</li> <li>15. Reproductive health, female. <b>eclampsia.</b></li> <li>16. <b>Congenital disorders</b></li> <li>17. Neonatal and infancy disorders: <b>premature birth; low birth weight;</b></li> <li>18. Neoplasms <i>malignant neoplasms.</i></li> <li>19. <b>Hypersensitivity</b></li> <li>20. <b>IRIS?</b></li> </ol>
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Existing definition; *definition in development*; **definition to be developed**, as published March 1 2008

### 5. Consensus was reached on the case definition content:

- Clinical findings
- Laboratory testing and other exploration as needed for confirmatory diagnosis
- Positive and negative signs
- Severity grading where applicable
- Special characteristics:
  - Onset (acute, delayed)
  - Appearance (naked eye , histological)
  - Intermittent, constant, variable
- Outcome:
  - Reversible
  - Self-limiting
  - Debilitating
  - Death
- Treatment management.
  - Hospitalization, referral etc.
  - Treatment limitation: substitution within the same line regimen, switching to another ARV regimen, treatment stopping.

<sup>4</sup> <sup>4</sup> **The complete list of system-organ classes and codes (WHO-ART SOC):**

0100.Skin and appendages disorders; 0200.Musculo-skeletal system disorders; 0300. Collagen disorders, 0410. Central & peripheral nervous system disorders; 0420. Autonomic nervous system disorders; 0431. Vision disorders; 0432. Hearing and vestibular disorders; 0433. Special senses other disorders; 0500 Psychiatric disorders; 060. Gastro-intestinal system disorders; 070. Liver and biliary system disorders; 080. Metabolic and nutritional disorders; 090. Endocrine disorders, 1010. Cardiovascular disorders, general; 1020. Myo-, endo-, pericardial & valve disorders; 11030. Heart rate and rhythm disorders; 1040. Vascular (extracardiac) disorders; 110. Respiratory system disorders; 11210. Red blood cell disorders; 1220. White cell and RES\* disorders; 1230. Platelet, bleeding & clotting disorders, 1300. Urinary system disorders, 1410. Reproductive disorders, male; 1420.Reproductive disorders, female; 1500.Foetal disorders; 1600. Neonatal and infancy disorders; 1700.Neoplasms; 1810. Body as a whole - general disorders; 1820.Application site disorders; 1830. Resistance mechanism disorders; 2000.Secondary terms - events; 2100Poison specific terms;

<sup>5</sup> TBD: specific terms to be identified by respective experts panels

## Remaining issues

**Severity grading:** more questions than answers:

- Which grades are to be used? (mild, moderate, severe, life threatening)?
- Should only serious events be reported?
- Should a severity threshold be defined to enable comparability?

Recommendation: expert panels should be convened to decide which qualified adverse events linked to antiretroviral therapy apply to specific population subgroups and to develop toxicity grading recommendations. The meeting participants will be consulted through the process.

## Next steps

The review of the listing of terms and definitions (priority and extended lists as proposed by the group) will be carried out in small working groups based on the System Organ class (SOC)<sup>6</sup> classification of WHO- ART. These expert teams identified by WHO HIV and PSM Departments, will include clinicians and pharmacovigilance experts.

Based on the meeting recommendations, expert panels will decide which qualified adverse events linked to antiretroviral drugs apply to specific populations subgroups and develop toxicity grading recommendations.

Once the thesaurus is completed, the PSM and HIV Departments will convene a meeting of experts to establish a consensus on

- the thesaurus, final document
- reporting forms, protocols and systems to report recorded adverse events linked to antiretroviral therapy
- coding, data compilation, analysis and management,
- compliance with current International Standards, and
- operational linkages with existing systems (MedDRA, International Drug Monitoring Programme), the cohort implementers and existing national PV programmes.