Considerable progress has been made in providing global access to antiretroviral therapy (ART), with three millions people currently on antiretroviral drugs around the world. The effectiveness of such treatment programmes risks being compromised by problems related to toxicity, intolerance and drug-drug interactions. These adverse events are relatively common affecting both individual patients and public health, but are being only intermittently identified and scarcely reported in low and middle income settings. Countries implementing ART programmes should consider the need for strengthening pharmacovigilance for ARVs (ARV/PV).

Rationale for including ARV/PV in the proposal

- To strengthen patients safety and improve adherence and treatment outcome, management of adverse reactions, treatment guidelines, norms and standards.
- To improve ART programme effectiveness through improved management and informed policies, and drug safety monitoring (post marketing).
- To improve programmes cost effectiveness, drug forecasting, procurement.
- To strengthen health system through improved pharmacovigilance system.

Elements concerning the ARV/PV treatment area to be considered in the situation analysis

- The situation analysis should include the epidemiological and situation background with specific information regarding:

  EPIDEMIOLOGY
  - Prevalence of HIV among the general population
  - Number of ART sites
  - Number of people on ART.

  PROGRAMME REVIEW
  - Existence of a national PV programme and database.
  - Existing capacity in country and identified needs.
  - Existence of an active specific ARV/PV programme.
  - Number, type and quality of reported adverse events: known and unknown.
  - Whether the country is member of the International Drug monitoring Centre (and sending reports).
  - Which methodologies are in place (spontaneous reporting, cohort surveys? Others?)
  - If cohort surveys and specific studies and research on adverse events linked to the use of ARVs are currently undertaken in the country.
  - The need for implementing a new ARV/PV programme, or for strengthening, sustaining existing ones.

  SERVICES
  - ART national (governmental) services: 1st, second and tertiary levels;
o ART services implementers others (NGOs, private sector)
o Laboratory capacity to monitor drug toxicities
o PV network in country, in the region.
o PV reporting mechanisms; methodologies data analysis.
o Training

NORMS and STANDARDS
o Training tools
o Reporting forms and reporting guidelines
o Management of adverse events: guidelines for service providers

LOGISTICS
o Computer based system: existing resources and gaps (soft and hardware)
o Laboratory resources

HUMAN RESOURCES
o Informaticians
o Pharmaceutical and clinicians experts in PV
o Services providers, including laboratory technicians
o Regulatory authorities
o Programme managers
o Training needs in country and abroad
o Integration of PV into national curricula

Target populations
• Patients on ART and projected needs.
• Patients on first and second line regimen and projected needs (level of drug resistance; importance of identified adverse events.
• Specific sub groups (children, women, patients with co-morbidities, TB, Hepatitis)

Steps in setting up PV system
Appropriate indications for initiating or sustaining ARV/PV work

• Based on situation assessment
  1. Establishment or revision of a national ARV/PV plan (its integration in both drug policy and ART programmes)
  2. Mapping of existing and type of activities related to ARV/PV: procurement plans, staff training; monitoring and evaluation;
  3. Evaluation of needs based on the national planning (see A)

• National planning

E. 1 Where there is no pre-established PV system in the country
  1. Contact the WHO and International Drug Monitoring Programme (contact data below)
  2. Prepare a pilot phase based on few sentinel sites
  3. Establish a research agenda
  4. Identify and consult with implementing partners, stakeholders in countries and other countries with established ARV/PV system
5. Prepare norms and standards, reporting methodologies and support (see resources, logistics) training and implementing guidelines and policies.

E.2 Where PV exists in the country and no ARV/PV programme
1. Same as above + review and evaluation of existing data
2. Consider stimulating passive reporting
3. Consider strengthening the research agenda
4. Consider introducing, in a phased manner, methods that complement spontaneous reporting

E.3 Where PV exists with ARV/PV programme
1. Evaluation of the programme
2. Strengthening of key points
3. Research agenda,
4. Consider piloting regional training and guidance reference centre to support countries that do not have established programmes

- Policy and guidelines
  1. Establish a national expert working group
  2. Establish linkages with the International Drug Monitoring Centre
  3. Prepare:
     a. national policy including resource planning, training,
     b. national ARV/PV network and reporting forms
     c. national guidelines on AE ARV reporting, analysis of data and integration in national policies and guidelines on training

Proposed activities
1. Staff recruitment
2. Training, initial and refreshment training of the IT, programme managers, services providers.
3. set up the communication network and mechanisms.
4. Provide necessary tools forms, registers, communication tools
5. Start implementing at delivery level
6. Update and manage information through appropriate communication supports: newsletters, letters, mails, web posting; ensure a feedback system to providers; to the regulatory authorities; pharmaceutical industry;
7. Monitor evaluate prepare reports; adapt and update the PV programme.
8. Integrate results of PV in treatment programme management.

Some key indicators
- Number of quality reports of adverse effects linked to ARVs (to national database, to global database) (with a baseline value- percentage/total number of reports annually or by centre)
- Number of ART centers accurately reporting ARV AE/existing ART centres.
- Number of new ART centres beginning to report ARV AE
- Number of program managers, health workers trained in ARV PV/given (monthly, quarterly) period of time,(Percentage of ART services providers trained in ARV/PV)
- Number of national or regional registries established for specific population subgroups
- Number of targeted studies performed in specific populations
- No. of bulletins prepared / shared that include information on ARV-AEs
G. Approach to (or tools for) costing these activities.

- Evaluation of the number of training programmes within and outside (delete: in and out the country.
- Number of staff to be trained, recruited.
- IT needs, computers are critical tools (and an advocacy work needs to be done as exceptional measure for PV assessment, mapping costs and gaps of existing pharmacovigilance programme in countries. Hardware as well as software should be considered.
- Evaluation of the existing normative tools to be created, updated and tested.
- Mapping of existing ART centres to be selected as sentinel sites, equipped, monitored and evaluated.
- Evaluation and cost of existing work by other organizations leading cohort surveys in country/region, to be expanded, supported.
- Costs around information sharing (websites, bulletins, publications, circulars)

Linkages with other services?

- PMTCT
- PEP
- Antiretroviral therapies programme (ART)
- Drug supply programme

How gender, human rights and equity issues should be addressed

Women have or should have equal access to care and treatment. Regarding adverse events linked to the use of antiretroviral drugs, children and women represent populations sub groups who are exposed to specific, yet insufficiently reported and known, drug toxicities. In particular, most data on adverse events of ARVs are provided by treatment programmes in industrialized countries where a very limited number of children are treated.

Specific studies, cohorts surveys should be implemented to ensure that appropriate management of adverse reactions of antiretroviral drugs strengthen patients safety in these specific groups.

Key implementing partners to be considered

WHO HIV and PSM Departments
UPSALA International Drug Monitoring Centre
Cohort surveys implementers
Academicians and researchers

Type and sources of technical assistance which might be required during implementation

Professionals in ART treatment and care; professionals in pharmacovigilance, national regulatory authorities who have experience in delivering PEP services and working in developing countries are key technical assistance resources., at country and globally.

Contacts in WHO Geneva:
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Documents: Pharmacovigilance for antiretrovirals in resource-poor countries. www.who.int/entity/medicines/publications/PhV_for_antiretrovirals.pdf
The safety of medicines in public health programmes: www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf