Technical Guidance for Round 8 Global Fund Proposals

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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)**

A. Elements concerning the ARV/PV treatment area to be considered in the situation analysis (both the epidemic and response) existing resources and identified gaps.

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

**EPIDEMIOLOGY**
- Prevalence of HIV in the general population; in specific vulnerable groups
- 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 WHO International Drug Monitoring Programme (and sending quality reports)
- Which methodologies are in place (spontaneous reporting, cohort surveys? Others?)
- Existence of cohort surveys, specific studies and researches on adverse events linked to the use of ARVs in the country.
- Major gaps; specific need for implementing a new ARV/PV programme, or for strengthening, sustaining existing ones.

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

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

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

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

B. 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

C. Links between ARV/PV and the proposal objective: improved antiretroviral treatment and prevention.
- Patients safety and improved treatment outcome.
- Effectiveness of national programme;
- Cost effectiveness of procurement for ARVs.

D. How to define and quantify the 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)

E. Main (important) activities to be considered
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 national 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

->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.

->Where PV exists in the country and there is no active 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, such as active surveillance.
   5. Consider working in collaboration with existing cohorts in the country at sub-regional and regional level

-> Where PV exists with ARV/PV programme
   1. Evaluation of the programme
   2. Strengthening of key points
   3. Research agenda, (what area the key questions to improve patients safety, adherence, or re new drug regimen)
   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, data analysis and integration in national policies and guidelines.

- Implementation
   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.

F. Some key indicators (select only few)

- 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 centers.
- 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 information bulletins prepared and shared with clinicians and PV experts disseminating 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 the GFATM is most often not funding these: as critical tools for PV pharmacovigilance programme in countries. Hardware as well as software should be considered. Mobile phones, telephone lines, others)
- Evaluation of the existing normative tools; add update and testing costs: need for new tools to be created, adapted from existing ones. (WHO)
- 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 of communication (websites, bulletins, publications, circulars)

H. Linkages with other SDAs/programmes?

- PMTCT
- PEP
- Antiretroviral therapies programme (ART)
- Drug supply programme
- Malaria
- Opportunistic infections (including TB)
- Drug resistance
- Nutrition
I. How gender, human rights and equity issues should be addressed in implementing this SDA

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.

J. Key implementing partners to be considered

UPSALA International Drug Monitoring Centre
Cohort surveys implementers
Academicians and researchers
Other donors: PEPFAR, Clinton Foundation, EC.

K. 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.

In WHO:
Contacts in the WHO AFR, Bz: Dr Thomas Lapnet-Moustapha, lapnett@afro.who.org

Contacts in WHO Geneva:
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  Dr M Couper, PSM, couperm@who.int
  Dr S. PAL, PSM, pals@who.int

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


A practical handbook for the pharmacovigilance of antiretroviral medicines
WHO to be published 2009
Clinical Management of adverse events linked to antiretroviral medicines
WHO to be published 2010