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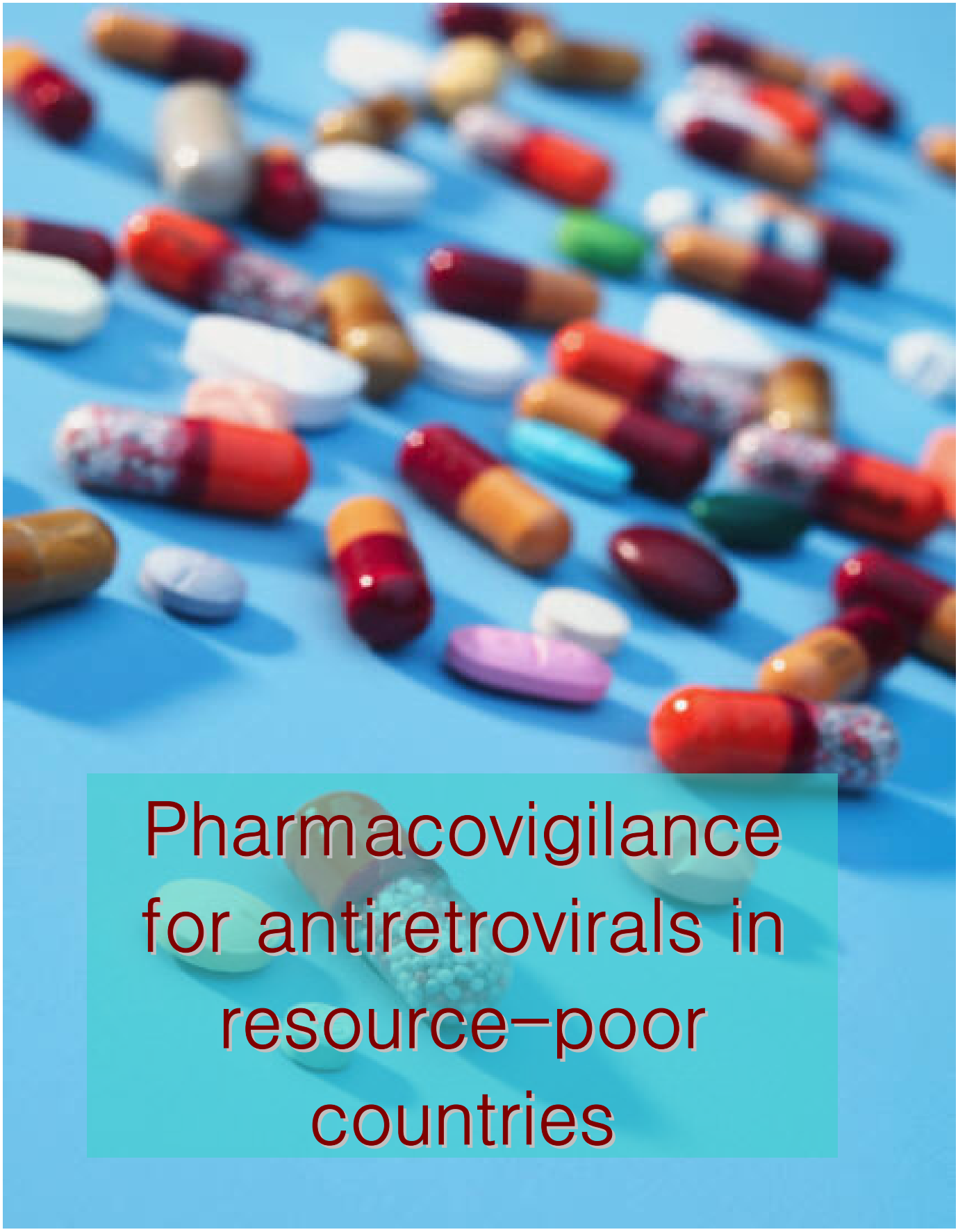

Pharmacovigilance for antiretrovirals in resource-poor countries

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Introduction

There is considerable experience in the developed world with the use of antiretroviral medicines (ARVs). They are associated with significant safety concerns including serious adverse reactions to medicines (ADRs), with both short- and long-term effects. The outcome of these long-term adverse effects is unknown. The reactions include altered body fat distribution (lipodystrophy), hypersensitivity reactions, hepatic disorders, acute pancreatitis, muscle damage (myopathy) of the newborn and lactic acidosis. These and other reactions may damage confidence in any national ARV programme and affect patient adherence. With the erosion of confidence in the safety of medicines and of the programme, patients may stop taking these life-prolonging medicines leading to problems for themselves and for society as a whole. Poor adherence is known to lead to failure of therapy in the patient (he or she will not get well and may die) and development of resistance by the virus leading to reduced efficacy of these life-prolonging medicines.

Little is known about the toxicity profile of ARVs in developing countries. These countries have special factors and conditions that are very different from those of the developed world and medicine use and safety may therefore vary considerably. The relevant factors and conditions include the existence of comorbid conditions such as tuberculosis (TB), malaria and other infections; malnutrition; heavy reliance on traditional and/or alternative therapies; insufficient numbers of trained doctors and pharmacists; abuse of prescription-only medicines; and likelihood of medicine interactions. In addition, the local systems for the delivery of health care will rely on people who may not have the necessary training, knowledge or expertise, and medicine regulatory systems are either nonexistent or are not adequately equipped to deal with medicine safety issues.

The monitoring of ARVs in these populations is therefore of paramount importance, and methods of monitoring are the subject of this article. This document should be considered in conjunction with a detailed assessment of the WHO publication, *The safety of medicines in public health programmes: pharmacovigilance an essential tool*, which includes much information that is not repeated here.

Aims of monitoring

The organizers of an adverse event monitoring programme for medicines used to treat HIV/AIDS must have a clear sense of the questions they want to answer before developing their plan. It is only with clear goals in mind that one can design a proper data collection instrument and an analytical plan.

The following are the potential outcomes of monitoring which can be prioritized for goal-setting and selecting the most appropriate method(s) of safety surveillance in the programme:

- Identify signals of previously unidentified adverse reactions to medicines.
- Quickly identify events that are likely to affect adherence to treatment; determine their rates and the risk factors that make these events more likely.
- Estimate rates of events so that:
  - risk can be measured;
  - the safety of medicines can be compared and informed choices made;
  - risk factors can be clearly identified.
- Determine safety in pregnancy.
- Determine safety in children.
- Monitor for specific toxicities:
  - establish rates and risk factors;
  - characterize the reactions.

The following descriptions of monitoring methods should clarify which methods are likely to meet the specific needs of the programme.

Methods of monitoring

Broadly speaking there are three major methods of monitoring:

- cohort event monitoring
- spontaneous reporting
- special phase IV studies.

If cohort event monitoring is selected as the principal means of monitoring, there are distinct advantages to encouraging spontaneous reporting as well. It should be seen as an option for reporting in the programme and reporting cards should be made widely available whether or not a spontaneous reporting programme is in existence. If a pharmacovigilance system is already operational, the same reporting card should be used and these cards should be processed in the established way, the information being channelled to the HIV/AIDS programme by the pharmacovigilance centre.

Cost considerations

There will be costs associated with monitoring, but monitoring should be seen as a cost-effective and essential component of the HIV/AIDS programme. Effective monitoring will:

- provide the means to make evidence-based decisions on medicine selection;
- produce sound data with which to respond to any medicine scares in an informed manner;
- minimize adverse effects which might affect patient safety and adherence by determining risk factors and the means for risk prevention;
- allow early identification of inefficacy or treatment failure;
- identify medicine–medicine, medicine–disease or medicine–food interactions.

The value of these types of data is immense in terms of the success of the programme and needs to be adequately budgeted for.

Communication

Whatever type of safety monitoring is undertaken, broad consultation is necessary to avoid problems and ensure success. A group should meet early in the planning phase to determine the activities to be undertaken. This group should involve all stakeholders and include representatives of the following:

- minister of health
- regulatory authority
- national pharmacovigilance centre (if there is one)
- academia – schools of medicine, pharmacy and nursing
- professional organizations
- health professionals who are to participate
- pharmaceutical companies
- patients
- media