Pharmacovigilance for antiretrovirals in resource−poor countries

World Health Organization

Health Technology
and Pharmaceuticals

Medicines Policy
and   Standards

Printed by the WHO Document Production Services, Geneva, Switzerland

Contents

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
- patient support groups where these exist
- general public.

Medicine safety should be seen as part and parcel of the global fight against HIV/AIDS.

Cohort event monitoring

Cohort event monitoring is often referred to as prescription event monitoring (PEM), but this terminology is inappropriate where individual prescriptions with subsequent dispensing are not part of the process. Examples of users of this methodology are the Intensive Medicines Monitoring Programme (IMMP) in New Zealand and PEM run by the Drug Safety Research Unit in England. A similar method is being used successfully in China to monitor contraceptives and includes monitoring in rural areas. Cohort event monitoring is an adaptable and powerful method of getting good comprehensive data. It is essentially a phase IV study.

There are two basic requirements for the collection of data for cohort event monitoring:
- − establishing a cohort of patients for each medicine and/or medicine combination;
- − recording adverse events for patients in the cohort(s) for a defined period.

Establishing cohorts

Cohorts

Cohorts are normally built up prospectively from prescription records, but this would not apply in an HIV/AIDS programme in most countries in Africa. In China, patients are automatically enrolled as they are seen in the contraceptive clinics and it would seem that a similar approach could be used for monitoring ARVs. Patients should be entered into a cohort when they report or enrol for the provision of ARVs in the HIV/AIDS clinics.

The cohort needs to be as complete and as representative as possible. Decisions will be required on how to select patients. Two options are available. The first is to enrol all patients in selected, representative regions until the number of patients in the cohort reaches the target figure. The second is a method of systematically sampling patients from the whole country e.g. all patients seen at clinics on a Thursday. This option may lead to bias in areas where the day chosen is special e.g. if the day is a "market day" or "no farming" day or "no fishing" day. It is therefore important to choose a day on which the full range of patients in the community are likely to attend the clinic. If the number of HIV/AIDS clinics is small, it may be possible to enrol all patients as they begin treatment until the target figure is reached. Monitoring for adverse events should commence from the time patients are enrolled in the cohort. The monitoring is thus prospective, free of selection bias, inceptional (each patient is monitored from the beginning of treatment), dynamic (new patients are added as the programme proceeds) and longitudinal (effects are studied over a known time period).

If the monitoring study is to be multicentred and international, then a similar approach to selection of patients should be undertaken in all the study areas.

Numbers

The number of persons taking the medicines being studied needs to be carefully considered. Some risks occur so infrequently that they become apparent only after thousands or tens of thousands of patients have been exposed to the medicine in question. For example, if the "true" frequency of a particular adverse event is 1/1000, then administering the medicine to 3000 people should result in a 95% chance of detecting at least one instance of that event. Therefore in order to achieve sufficient statistical power for comparisons, the normal aim is to have cohorts of 10 000 patients. This number however is likely to be inadequate for subgroup analyses in the HIV/AIDS programme and a cohort with approximately 20 000 patients for each of the main medicine combinations may be needed. The actual number will depend on the requirements of the programme in respect of subgroup analyses and should ideally be discussed with a biostatistician. However, the estimated numbers depend on knowledge of the incidence of the factors under consideration and these are often unknown. A review of the results with a cohort size of 10 000 will allow a better evidence-based decision on the final numbers required.

Duration

The duration of monitoring will again depend on the requirements of the programme. Long-term effects are of particular importance and it would seem desirable to monitor at least a sample of patients indefinitely.

Patients

Initially, all patients should be monitored without selection, in particular, to determine any age- and gender-related differences. At a certain point it could be decided to continue enrolling only women of childbearing age and/or children or another group of particular interest e.g. patients with TB, in order to increase numbers to obtain sufficient statistical power. The special groups of interest should not be monitored in the absence of data on the full range of patients because the "standard" patients are needed for comparison.

Special categories
As a natural part of the process of cohort event monitoring a pregnancy register will be established. All women of childbearing age should be checked for pregnancy at follow-up visits. For those who fail to attend the HIV/AIDS clinic for a scheduled visit, or perhaps all women of childbearing age, it is desirable to organize a system of information sharing with antenatal clinics or birthing units where these exist. Domiciliary visits may be necessary for some women.

Similarly, children, or patients with TB, or patients in other categories of interest from the general cohort can be given specific follow-up to meet the requirements of the programme.

Patient identification
Some acceptable means of identifying patients in the cohort database needs to be established for the purposes of follow-up and linking records. Options include one or more of the following:
- programme ID number for the patient;
- name, if confidentiality can be assured by limiting access to the information or by other means;
- date of birth and sex;
- town or village with street address, where this exists, or identifying landmarks understandable by participants and/or the monitoring team;
- name of clinic;
- community or village health workers;
- village head who might be the best means of contact.

It is desirable to record several means of identification to compensate for missing or incomplete data. If patients cannot be accurately identified the resulting statistics will have little meaning.

A unique ID number has advantages if insufficient privacy rules out using names. Also, if a unique code can be applied consistently, there should be less room for error. Names can easily be mis-spelled or spelt inconsistently and this may create two or more patients in the database when there is in fact only one. In the cultures that are being considered here, people often have more than one name, such as an English name as well as their indigenous name and they may quote either. They may also have a shortened name or change their names.

Demographic and other background data
The following should be recorded (see sample baseline recording form)
- date of birth and sex;
- ethnicity;
- weight and height – for body mass index;
- other medications administered or being taken;
- other morbidity e.g. TB, anaemia, malnutrition, depression, alcohol and/or substance abuse.

The details to be recorded will depend on the requirements of the programme and the population from which the patients come (i.e. background morbidity, cultural characteristics).

Ethical approval
Ethical standards may not be well developed in countries where the HIV/AIDS programme is undertaken. Nevertheless, appropriate consideration needs to be given to this aspect.

In the IMMP in New Zealand the following patient data are used and stored indefinitely: name, address, national patient identification number, date of birth and sex. In addition, there is medical information, some of which is very sensitive (e.g. on sexually transmitted disease). The recording of these types of data has been approved by ethics committees on a national basis with the requirement that patients are informed that their data are being stored and why, and that they have the opportunity to opt out. The IMMP does not require patient consent. Approval by the ethics committees has been given repeatedly after recent reviews of the methodology. The ethics committees regard the safety of the patients as paramount. This is also the viewpoint of patients who, given basic standards of confidentiality, regard safety as having greater priority than privacy.

In 27 years, only two patients opted out of the IMMP and only one of these did so because of privacy concerns. Local ethics committees would need to review the protocols.

Increasingly medicines are released on condition that they are monitored, and participation by health professionals and patients is required if they are to receive the medicine. This is in line with the International Committee on Harmonisation ICH E2E *Guideline on pharmacovigilance planning*. It may be appropriate to seek conditional approval from the regulatory authority with the requirement that satisfactory monitoring must be undertaken before full approval is granted. This is an approach that could be considered by those running the programme. Voluntary systems are preferred, but there are circumstances which can be envisaged with a new, potentially toxic medicine for which safety information is very limited and which is likely to be used quite widely, where it would be ethically irresponsible to approve and use the medicine in a public health programme unless it was carefully monitored. This would have to be a decision of the regulatory authority made in consultation with the programme director and the supplier of the medicine. It would depend in part on local attitudes and ethos. It would not be appropriate to have mandatory monitoring for only one medicine. For scientific reasons and for reasons of equity, all ARVs being used in the programme would need to be monitored under the same conditions. Mandatory monitoring can be instituted without any penalty so that health professionals do not feel under duress. If monitoring is made mandatory by law, this could allay any fears health professionals may have over privacy considerations, and improve their compliance.

Long-term storage of data is essential for the identification and assessment of long-term effects and the authorities and patients need to understand this from the outset.

Database

The programme organizers will need to decide which software to use. Appropriate software may already be available, or choice can be guided by the experience of other WHO public health programmes. The WHO Programme for International Drug Monitoring (the Uppsala Monitoring Centre) is an excellent resource for assistance in this area. The IMMP uses SAS which is also used widely by pharmaceutical companies. Any system should be evaluated in the field before the programme commences to make sure that data entry and transmission, and the desired level of data retrieval can be achieved at all sites.

The database should have all the fields necessary for adequate case assessment, accurate analyses and possible follow-up. These should include:

- location of origin of the report;
- identity of the reporter;
- patient identification – to avoid duplication and enable follow-up if necessary (the patient must be identified in such a way as to ensure patient confidentiality);
- date of birth and sex of patient;
- information concerning the medicine, including name (generic and brand names) and formulation, manufacturer, mode of administration, dose and dates of administration;
- indication for use;
- other morbidity and relevant history;
- concomitant medications with doses, dates and indications;
- details of the event(s) with date of onset and details of any investigations;
- adverse reaction terms from a recognized dictionary, e.g. the WHO Adverse Reaction Terminology (WHOART);
- assessment of seriousness and severity;
- management and outcome.

The fields should, of course, match the fields on the recording forms.

Data recording

Data required routinely should be recorded on standard forms (questionnaires) by support staff before the patient is seen by the clinician. All the clinician should need to do is to record any clinical adverse events. Ideally, if an electronic database of patients is available locally, the forms

with the desired details can be computer generated and printed out automatically (similar to a "mail merge"). Further details of the logistics are given below.

Controls
The inclusion of control or comparator groups may be logistically impossible and would add to the cost. It should be sufficient to be able to compare patients on different treatment regimens and to make comparisons with known morbidity statistics of the population. However, should another public health programme operating in parallel undertake cohort event monitoring, this could provide useful data for comparison.

In the absence of control groups, it is a considerable advantage to have each patient monitored for adverse events for a period before commencing ARV therapy. The protocol for the programme may include an assessment period prior to the commencement of treatment. Ideally, from the epidemiological point of view, this should be a minimum of one month, but a longer control period would be better if it fitted in with the local protocol and the clinical condition of the patient. Adverse events occurring in this period should be recorded and this can serve as a control period.

Recording adverse events

Definition
The WHO definition of an adverse event is, "*Any untoward medical occurrence that may appear during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment.*"

Recording of events
Practical guidance for reporting adverse events may be given along the following lines.

Please record:
- all new events even if minor;
- change in a pre-existing condition;
- abnormal changes in laboratory tests;
- accidents;
- **all deaths** with date and cause;
- possible interactions:
    − pharmaceutical or traditional medicines;
    − remember oral contraceptives, tobacco, alcohol or other commonly ingested products which the patient may not realize are "medicines".

When providing guidance for clinicians and other prescribers (e.g. medical attendants and medical assistants), the simplest advice is to request that any clinical event that is recorded in the patient record should also be recorded as an adverse event on the questionnaire. A brief description of each event is usually all that is necessary. These event descriptions will be reviewed later by pharmacovigilance staff and standard adverse event terminology applied. The clinician does not need to know the standard event terminology. If clinical details are recorded electronically, then they could be sent to a central point where they could be reviewed and transcribed for the HIV/AIDS study.

It is important that non-serious adverse events are recorded, particularly if they are likely to affect adherence e.g. nausea or impotence. In addition, if only known adverse reactions are reported, unexpected adverse reactions will not be identified. Previously unrecognized adverse reactions are always found when using new medicines. It is important to identify them, understand their importance, determine their incidence and identify the risk factors as quickly as possible.

The events recorded should not be restricted or pre-defined. There are two basic reasons for this.
- Assuming one of the reasons for monitoring is to detect signals of previously unidentified adverse reactions, it is not logical to specify the types of events to be recorded. Recording

all events offers the best chance of detecting the unexpected. Unexpected reactions cannot be identified by specifying the known or expected.

- Specifying the events to be recorded is also likely to cause confusion. In the middle of a busy clinic, it is difficult for clinicians to remember what should or should not be recorded. As a result, events are often not reported. If clinicians understand that all events should be recorded, that problem is removed. In addition, at the analytical stage, the programme can be reasonably sure that it has a source of events data to return to and also to help answer questions raised in the preliminary analysis. This may avoid the necessity for a further specific study.

It is important that every contact with the patient is recorded and if there are no events, this should be stated.

Other attendance at a medical facility
Reasons for attendance at primary health care centres, village clinics, hospital emergency services or clinics as well as hospital admissions need to be recorded. Consideration should be given to the supply of the questionnaires or spontaneous reporting forms to be completed for all patients on ARVs. These attendances or admissions should be reported by the patients at their regular follow-up, but the dates and reasons for attendance may not be recalled accurately if at all.

Recording forms (questionnaires)
Sample questionnaires are attached at the end of this document (Annex 1). These would need to be adapted to suit the protocols of the HIV/AIDS programme by changing, deleting or adding particular entries. They are based on the format of the IMMP questionnaires. The forms are self explanatory. Hand-held personal digital assistants (PDAs), if available would be ideal for recording and downloading data.

Baseline questionnaire Ideally, this should be completed one month prior to treatment. However, there may be circumstances where it would be inappropriate and unethical to delay treatment.

Pre-treatment questionanire with a record of adverse events that have occurred since the baseline assessment. If feasible, a pregnancy test at this stage would be useful, because many women may not know they are pregnant until fetal movements are felt.

Current review questionnaire with a record of changes or events since the previous visit. The investigations performed will depend on the protocol and some may not be done at every visit, but there is a space for recording if they are done. If they are not done, this should be indicated by putting a stroke through the date and result boxes. A new form needs to be completed at each visit.

Pregnancy questionnaire the details recorded on the pregnancy form will be entered into the pregnancy register and will most likely be added in stages as progress of the pregnancy and the outcome is monitored. All women of childbearing age who have treatment should be followed up if possible, even to the extent of a domiciliary visit. It is possible that a woman may become pregnant and have a miscarriage without attending an antenatal clinic, or hospital, or making her scheduled visit to the HIV/AIDS clinic. Follow-up procedures for these women need to be established and written into the protocol.

There are some general features that should characterize all forms:
- All dates should be in a standard format that is noted on the form (e.g. dd-mm-yyyy).
- Names (generic or brand) or abbreviations for medicines should be standardized. Drop-down lists would be ideal if electronic recording is available.
- The forms should include units for all laboratory values. The organizers should ensure that all clinics use the same units for recording the results of a given test. If this is not the case, the forms will have to have an option that allows the local site staff to indicate the unit

being used (e.g. mmol/l versus mg/dl), and the data centre can make the conversion. Using a central laboratory would minimize difficulties and avoid variations between laboratories, but this may not be feasible.
- Definitions for medical conditions will be needed e.g. malnutrition (preferably body mass index), or anaemia (haemoglobin level).

Data processing and review
New data from the forms need to be entered into the database. Possible processes for this include:
- Direct computer entry into the database at the clinic. This is the ideal. If the clinics cannot be linked to the central database, then it may be possible to enter data into a local database and for these data to be transmitted electronically to the central database e.g. on a memory stick (pen drive).
- Sending the forms to regional or country centres where data entry will take place. The forms could be picked up by a visiting supervisor, or they could be faxed or delivered by some other reliable means.
- If a pharmacovigilance centre is functioning in the country, then it is desirable to invite them to collaborate and use their expertise in reviewing the data, applying the adverse event terminology, coding the medicines and their indications, coding concomitant diseases and performing assessments on the relationship of the event to the medicine or medicine combination (causality assessment). The centre would need additional resources to cope with the extra workload. In the absence of a pharmacovigilance centre, the programme would need to appoint staff to do this work and have them trained. Possible scenarios and responsibilities for reviewing the adverse events recorded are outlined in the document, *The safety of medicines in public health programmes: pharmacovigilance an essential tool.* If more than one country in a multicountry study has a National Centre, then the Programme Director and the National Centres would need to discuss the possibility of one Centre taking responsibility for reviewing the events and being provided with the resources to do so for the HIV/AIDS programme. This would be the optimum situation, but compromises may be necessary.

The process of data entry can be made very efficient. Drop-down lists can be used where appropriate e.g. for medicines, laboratory tests and recording sex. These will reduce error. After baseline data have been entered, it should not be necessary to re-enter patient details for subsequent visits. The patient's unique ID number can be typed in to bring up the previous records and only new data need be entered. Sometimes there may be none, but in this case an entry should still be made with the visit date and an entry for "no change". If the medicines and doses have not changed, there should be no need to re-enter these. The results of new laboratory tests (if any) would need to be entered. Drop-down lists can also be used for selecting the tests.

Entry of events, concomitant medicines and their indications and other morbidity should be done centrally for familiarity with the terminology and for consistency. The events may be recorded as a description, a clinical term or a change in laboratory values. A description would require interpretation and the allocation of adverse event terms. If a clinical term is not present in the adverse events dictionary, then an appropriate event dictionary term would need to be applied. "Clinical reviewers" with some kind of clinical background (e.g. physicians, nurses or pharmacists) would be needed at the central site to review the events and determine the event terms.

Terminology
- *Adverse event terminology.* There are two systems of adverse reaction terminology in widespread use, WHOART and MedDRA. The latter is used by pharmacovigilance centres in most developed countries and by pharmaceutical companies. WHOART is used by most (mainly developing) countries participating in the WHO International Drug Monitoring Programme. It is likely to be easier to base the adverse event terminology on WHOART, which is more adaptable and cost-effective. The high cost of MedDRA may be a

disincentive to its use in resource-constrained environments. New event terms will be needed for monitoring the ARVs. The Uppsala Monitoring Centre (UMC) can advise on this.

- *The WHO Drug Dictionary* should be used for coding medicines.
- *ICD 10* (the International Classification of Diseases version 10) should be used for the coding of diseases.

Relationship (causality) assessment
This is summarized in the WHO/UMC booklet, *Safety Monitoring of Medicinal Products: A guide to setting up and running a pharmacovigilance centre.* Relationship assessment is of considerable value in cohort event monitoring. It is essential to examine the relationship of a group of events before establishing causality. When analysing data to establish risk factors, it is most useful to include only those events with a strong relationship (definite or probable). Other events of the same type with a weak or unlikely relationship may be unrelated to the medicine and inclusion of data on these may weaken or mask otherwise significant statistical relationships. Relationship assessment should be performed centrally by suitably trained people, preferably in a pharmacovigilance centre.

Data analysis
There are many advantages in undertaking regular interim analyses, say, at monthly intervals. These analyses will provide results of value to help with management early in the programme. More data will be available more quickly than with spontaneous reporting.

- *Collation of events.* The computerized events data can be collated into clinical strata using the structured events dictionary. Profiles of events prepared by system organ class, or at lower levels if desired, can be constructed comparing different treatment regimens. Any clinical patterns emerging can be seen at a glance by viewing tabulated data.
- *Rates.* These can be calculated for individual events, or groups of related events, for the different treatment regimens and relative risks comparing different treatments can be calculated.
- *Multiple logistic regression.* This can be used for identifying risk factors taking into account concomitant medicines, concomitant morbidity, age, sex, duration of therapy and other factors as desired. The expertise of a biostatistician would be necessary for these analyses.

Quality control

Quality checks are important, but quality control should begin at the point of data entry and as far as possible, restricted parameters should be set for data fields (e.g. number of digits for age not >2; standard formats for dates). It is important to prevent duplication of patients. At intervals, a computer analysis can be made of patients of the same sex and date of birth to see if they come from the same site, have the same medicines and/or the same visit dates and to verify that they have not been mistakenly recorded as more than one individual. The data manager at the central site should be responsible for these quality checks and should be responsible to the study director. In addition, at central (and, where possible, local) data entry level, the action of bringing up the previous entry for a patient in order to add new data, should be used to check the consistency of the basic data e.g. sex. Experience from settings where similar programmes have been successfully implemented shows that this approach provides very clean data.

Personnel

What staff are required depends on the intensity of data flow, particularly during the stage of establishing the cohorts. Another complication is the intention to undertake multicentre monitoring in different countries. There would seem to be advantages in having one central agency (preferably located in a pharmacovigilance centre) that would manage all the data from the different regions and/or countries.

Presuming a lack of previous experience, it would be advisable to allocate the personnel time as follows:
- − a full-time physician who will undertake the clinical review of the events
- − a full-time analyst/programmer
- − a full-time clerical assistant
- − three half-time data processors
- − a full-time coder.

In addition to the above staff working in a central agency, national or regional supervisors would be needed. Pharmacists are likely to have a suitable background for this role. Their role would be largely one of support, communication and promotion. This could be a key role which should be specific, and integrated with the administrative structure of the programme. The number of supervisors required in each country would depend on the number of HIV/AIDS clinics, the local administrative set-up, availability of transport and costs of travel.

Spontaneous reporting

Methodology

A spontaneous report is an unsolicited communication by health care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Spontaneous reports play a major role in the identification of safety signals once a medicine is marketed. Spontaneous reports can also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known serious ADRs.

Spontaneous reporting is dependent on encouraging clinicians and other health professionals to report details of suspected adverse reactions in patients on ARV treatment. Under-reporting is a serious problem with this method, but reporting can be intensified in selected units e.g. hospitals.

There is no standard global reporting form for spontaneous reports as the needs of countries differ and it is important that they are involved in developing their own form. However, the form from Ghana (Annex 1) for use in monitoring ARVs is a good example. The completed reports can be mailed individually or in bulk, faxed, sent electronically (if forms are available on the Internet or by email) or reports can be made by telephone. If a national pharmacovigilance system is in place, then consideration should be given to using the reporting form already in use or adapting it as necessary.

Health professionals will need advice on what types of suspected adverse reactions to report. Most pharmacovigilance programmes request reports of all serious events (which include death) and fetal abnormalities and in addition, all suspected reactions to new medicines. In general, deaths are very poorly reported. The special requirements for ARV monitoring would need to be specified e.g. those reactions that affect adherence; reactions of special interest; all suspected reactions in children.

All spontaneous reports should first be sent to the pharmacovigilance centre in the country for evaluation. The processing of data will be the same as for cohort event monitoring. Spontaneous reporting for ARVs should be integrated with the national pharmacovigilance programme and regarded as an ongoing monitoring method continuing after any special studies are completed.

The reports should then be forwarded to the WHO Collaborating Centre for International Drug Monitoring for entry into a global database that uses systematic methods for the detection of safety signals from spontaneous reports. These methods include the use of Bayesian Confidence Propagating Neural Networks (BCPNN) and other techniques for signal detection. Data-mining techniques should always be used in conjunction with, and not in place of, analyses of single case-reports. Data-mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. Confounding factors that

influence reporting of spontaneous adverse events are not removed by data-mining. The results of data-mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate for different medicines and countries and the many potential biases inherent in spontaneous reporting. All signals should be evaluated while recognizing the possibility of false-positives. In addition, the absence of a signal does not mean that a problem does not exist.

Personnel

The volume of work will be less than for cohort event monitoring. It is suggested that the following personnel would be adequate:

- − a full-time physician or pharmacist
- − a half-time analyst/programmer
- − a half-time clerical assistant
- − a half-time data processor
- − a half-time coder.

Special studies

Discussion to date has indicated the need to:

- − establish pregnancy registers
- − monitor for specific toxicities
- − monitor special populations such as children.

These cannot be accomplished as an integral part of a spontaneous reporting programme and special studies would therefore be needed. However, adequate data in these important areas should be recorded in the normal course of events when using cohort event monitoring and special studies should be unnecessary.

If special studies are to be undertaken, then the same principles will apply as outlined for cohort monitoring. Special forms would need to be designed to provide the information needed, and advice and training given on what is required and the appropriate data flow.

For reliable pregnancy registers to be established, collaboration and sharing of information with antenatal and birthing clinics would be needed. If feasible, a pregnancy test just prior to commencement of ARV therapy would be desirable. A potential gap in data collection results when women who become pregnant, have a spontaneous abortion without having attended a clinic or when women die (e.g. as a result of bleeding following abortion or pelvic inflammatory disease). It would be important to follow up all women of childbearing age who fail to attend the HIV/AIDS clinic.

The major issues requiring evaluation are as follows:

- Abacavir (ABC) and nevirapine (NVP) hypersensitivity reactions. (It is important to find out the real prevalence of this problem in developing countries, to establish specific management algorithms and to try to assess whether any specific genetic test can be used to identify high-risk individuals.)

- Tenofovir (TDF) nephrotoxicity risk, particularly in African people, who can be more prone to this kind of toxicity (not related exclusively to TDF, but to any potential nephrotoxic medicine), according to some anecdotal information from experts working in Africa.

- TDF bone toxicity, in particular in children younger than 5 years of age.

- Prevalence of stavudine (d4T)-associated neuropathies (not restricted to peripheral forms).

- Prevalence of HIV-related lipodystrophy in patients using regimens containing d4T. There is a possibility that the prevalence of this problem may be lower than expected because of lower dosage related to the lower mean body weight generally observed in people in developing

countries (generally less than 60 kg, which means a predominant use of 30-mg tablets instead of the 40-mg tablets which are usual in developed countries).

- Hepatotoxicity associated with NVP and saquinavir-soft-gelatin capsule/ritonavir (SQV/r), particularly when used concomitantly with TB medicines, and also in the presence of hepatitis B co-infection, which is probably high in the Asian and African context, but has not been well evaluated. In Mozambique, Angola and Malawi, in particular, there have been reports of the use of NVP and rifampicin (RMP) together because of the unavailability of efavirenz (EFV) and the high cost of ABC, but the information is not well documented.

- Zidovudine (AZT)-associated anaemia, particularly in regions with a high prevalence of malaria.

- Occurrence of birth defects in the offspring of patients who have used EFV during the first trimester of pregnancy.

- Occurrence of didanosine (ddI)-related pancreatitis and its association with the use of other medicines.

- Problems with lopinavir/ritonavir (LPV/r) or ritonavir (RTV) capsules (related to the ambient temperature in some African settings).

- Occurrence of lactic acidosis and other severe acute metabolic toxicity associated with nucleoside reverse transcriptase inhibitors (NRTIs), particularly stavudine and didanosine.

Other considerations

The following important topics are considered in detail in the WHO document *The safety of medicines in public health programmes: pharmacovigilance an essential tool* and hence are not described in detail here.

Relationship with national pharmacovigilance system

It will be beneficial to the HIV/AIDS programme to collaborate with the national pharmacovigilance system if there is one. The expertise and networks of such a centre should facilitate the safety monitoring and evaluation considerably and such collaboration would represent the ideal situation.

Training

Training courses in pharmacovigilance for key personnel would be essential. WHO, in collaboration with the Uppsala Monitoring Centre, has run several such courses both in Africa for the HIV/AIDS and malaria programmes and in the Caribbean for HIV/AIDS programmes.

Promotion

Good promotion of the safety monitoring aspect of the programme will enhance people's confidence and adherence with the requirements of the programme. This needs to be given strong emphasis before the programme begins as well as when it is put into operation. It should entail:
- meetings with significant opinion leaders, influential people and groups as outlined in the section on communication;
- information leaflets for health professionals and patients on the monitoring methods to be used;
- items in the media, including newspapers, radio and television.

Costing

The main items specifically related to pharmacovigilance are likely to be as follows. In general, these would form components additional to those already included in the programme.
- staff
- training
- communication
- computer hardware and software

- production of promotional literature
- production of reporting forms.
-

Comparative advantages and disadvantages of the monitoring methods

Cohort event monitoring
Advantages
- It has the ability to produce rates.
- It enables the production of a complete adverse event and/or adverse reaction profile for the medicines of interest.
- It is very effective in identifying signals at an early stage.
- Reactions can be characterized in relation to age, sex and duration to onset and thus produce risk factors. Other relevant data may be collected, such as weight, or co-morbidity, to enable other risk factors to be determined.
- It enables accurate comparisons to be made between medicines.
- It allows a pregnancy register to be established; this can be used to define and calculate rates of any abnormalities.
- The routine follow-up enables confident detection of reduced or failed therapeutic effect and thus raises suspicion of inaccurate diagnosis of disease, programme failure, or poor quality or counterfeit medicines.
- It enables details of all deaths to be recorded and examined and provides rates of death.
- It has the ability to produce rapid results in a defined population.
- It enables the collection of comprehensive and near-complete data that will provide for the special needs of the programme including effects in pregnancy, specific toxicities and safety in children.
- Because the method looks intensively at new medicines of great interest in a specific area of need, and provides clinically significant results rapidly, it stimulates interest in medicine safety in general.
- The method provides sound evidence with which to deal with any medicine scares.

Disadvantages
- This method is more labour intensive and more costly than spontaneous reporting.
- It will be new to health professionals and pharmacovigilance centres.

Spontaneous reporting
Advantages
- It is administratively simpler and less labour intensive than cohort event monitoring.
- It is less costly.
- It is the method most commonly used in pharmacovigilance.
- National pharmacovigilance centres and health professionals (to a certain extent) will be familiar with the method.

Disadvantages
- The data are incomplete. In developed countries less than 5% of reactions are reported. A report from the WHO filariasis programme suggests that reporting compliance in resource-poor countries is much less than this, leaving many unanswered questions.
- Reliable rates cannot be calculated and therefore risks cannot be measured and risk factors cannot be established with confidence.
- There are strong biases in reporting.
- Deaths are poorly reported.
- Special studies will need to be set up to collect accurate information on areas of particular interest e.g. pregnancy, children and the elderly. These special studies add to the overall cost and reduce the cost advantage of spontaneous reporting.

LOGO

Antiretroviral therapy: Cohort Event Monitoring
Baseline questionnaire

Treatment centre/Clinic: .... **Contact person:** ....

A. Patient: Name: ………………………………………….. Clinic Number:………………

Contact details: ……………………………………………………………………………….

Date of birth: ..../..../....   Sex: Male ☐   Female ☐

Weight: ……………….   Height: …………….

B. HIV/AIDS: stage at first screening:……………………………………

C. Current medicines

D. Laboratory tests *(Blank row is for other tests)*

Test	Date	Result	Test	Date	Result
CD4 count			Cholesterol		
Viral load			Triglyceride		
ALT			Glucose		
FBC					

E. Current conditions (background morbidity) *(Blank spaces for "other")*

Problem	Tick	Problem	Tick	Problem	Tick
Malnutrition		Depression		Heart disease	
Anaemia		Tuberculosis		Hepatomegaly	
Alcohol abuse		Renal disease		Splenomegaly	
Substance abuse		Liver disease		Significant bacterial infection	

F. Past conditions of significance *(Might include some of above problems, but not currently present)*

Date	Event(s)

Continue on other side of form if necessary
PLEASE SEND THIS FORM TO:....
Recorder: Name……………………….Signature:…………………………….Date…./…./…..

Pre-treatment questionnaire

Treatment centre/Clinic: .... Contact person: ....

A. Patient: Name: ……………………………………………….. Clinic Number:………………
    Contact details: ……………………………………………………………………………….
    Date of birth: ..../..../....   Sex: Male ☐   Female ☐

B. HIV/AIDS: stage at current review:………………………………………

C. Medicines taken over treatment readiness assessment period

Medicines	Daily dose	Date begun	Date stopped

D. Laboratory tests *(Blank row is for other tests)*

Test	Date	Result	Test	Date	Result
CD4 count			Cholesterol		
Viral load			Triglyceride		
ALT			Glucose		
FBC					

E. Any new events or worsening problems over the period since last seen

Date	Event(s)

Continue on other side of form if necessary
PLEASE SEND THIS FORM TO:....

Recorder: Name……………………….Signature:……………………………….Date…/…/…..

Current review questionnaire

Treatment centre/Clinic: ………………………… **Contact person:** ……………………………..

A. Patient: Name: ………………………………………………….. Clinic Number:………………

Contact details: ………………………………………………………………………………….

Date of birth: ..../..../….   Sex: Male ☐   Female ☐

B. HIV/AIDS: stage at current review ……………………………………………

C. Medicines

ARV medicines	Daily dose	Date begun	Date stopped
1.			
2.			
3.			
4.			

Reason(s) for stopping ARV medicines

Poor compliance ☐; lost to follow-up ☐; death ☐ (give date & cause below in section E); Suspected adverse reaction ☐ (describe in E); lack of effect ☐; other ☐ (describe)

Comment on efficacy:

Other medicines (in review period)			

D. Laboratory tests *(blank row is for other tests)*

Test	Date	Result	Test	Date	Result
CD4 count			Cholesterol		
Viral load			Triglyceride		
ALT			Glucose		
FBC					

E. Any new events or worsening problems over the period since last seen

Date	Event(s)

Continue on other side of form if necessary

G. Has the patient become pregnant? Yes ☐ No ☐ If yes, complete pregnancy questionnaire
PLEASE SEND THIS FORM TO:....

Recorder: Name:………………………….Signature:…………………………………….Date:/…/…..

Pregnancy questionnaire

Treatment Centre/Clinic: …………………………. **Contact person:** ………………………….

A. Woman's details: Name: ……………………………………………Clinic Number:……………

Contact details: ……………………………………………………………………………….

Date of birth: …./…./….

B. Stage of pregnancy at exposure

LMP if known: …../…./……   Estimated weeks of pregnancy at current examination: ……….weeks

At what stage was she exposed to the antiretrovirals? (*Tick all if applicable, or as many as necessary*)

1st trimester □; 2nd trimester □; 3rd trimester □; at term □

Was she on treatment when she became pregnant?   Yes □; No □

Was treatment withdrawn when pregnancy was diagnosed?   Yes □;   No □
          Date of withdrawal ……/……/……..

C. Outcome of pregnancy
          Date of birth □;   Not yet born □
1. Abnormalities of pregnancy: None □   Don't know □   Miscarriage□
date:……/……/……..   Therapeutic abortion □

Date	Description

2. Abnormalities of labour (*describe*)   None □   Don't know □

3. Abnormalities of fetus or infant   Don't know □   Fetal death □ date …../…../……
None identified at birth □; None identified at 3 months □;   None identified at 1 year □

Date identified	Description of any abnormalities

D. Breastfeeding
1. Did the mother breastfeed the infant while on treatment? Yes □; No □; Don't know □
2. If yes, when was the baby first exposed with the mother on treatment?
     From birth □; From age …………………..; Don't know □
3. Was there any effect on the infant? Yes □; No □; Don't know □
4. If yes, please describe:

PLEASE SEND THIS FORM TO: ....

Recorder: Name………………………….Signature:………………………….Date…./…./…..

Adverse Event Form for
Anti-Retroviral Medicines.

Please complete as much as possible, regardless of any missing details

PATIENT DETAILS

Folder Number:		Patient initials:		Sex: [M] [F]

Residential Address: Town/City:
District   Region:

Date of birth __/___/____   Age:____ years____ months   Weight (kg):_____

Type of Treatment	□ HAART □ PMTCT □ PEP

DRUG DETAILS

	Drug 1	Drug 2	Drug 3	Drug 4
1st Line Drugs	Combivir / Nevirapine Dose: Date Started: __/__/__	Combivir / Efavirenz Dose: Date Started: __/__/__	Stavudine / Lamivudine /Nevirapine Dose: Date Started: __/__/___	Stavudine / Lamivudine /Efavirenz Dose: Date Started: __/__/___
2nd Line Drugs	Abacavir/ Didanosine/ Nelfinavir Dose: Date Started: __/__/__	Abacavir/ Didanosine/ Kaletra Dose: Date Started: __/__/__		
CONCOMITANT DRUG	Co-trimoxazole prophylaxis Dose: Date Started: __/__/___	Drug: Dose: Date Started: __/__/__	Drug: Dose: Date Started: __/__/__	Drug: Dose: Date Started: __/__/__

DETAILS OF ADVERSE EVENT

Date event started:____/____/____   Date event stopped:____/____/____

Adverse reaction observed (*please tick all that apply*)
□Vomiting   □Nausea   □Itching   □Skin rashes   □Diarrhoea   □Headache   □Mouth sores   □Abdominal pains
□Dizziness   □Insomnia   □Dark-coloured urine   □Other (please specify):

Description of event (*Continue on back page if necessary*):

Treatment or action taken (*Continue on back page if necessary*):

Outcome (please tick all that apply)
□Change of therapy   □ Recovered without change of therapy   □Death
□Required / prolonged hospitalisation   □Ongoing   □ Other outcome (please specify)

REPORTER DETAILS

Profession   □Doctor   □Pharmacist   □Nurse   □Other (please specify)

Last Name:	Other Name(s):		Title

Address: Tel No.   Email:

Signature   Date:

Please return this form to: YOUR ART FOCAL PERSON:
Forms MAY also be sent to The Centre for Pharmacovigilance, CTCPT, UGMS, 2nd Floor Medical Block Building, Korle-Bu Teaching Hospital, Box 4236, Accra, Ghana Tel: 021-675885/668219; Fax: 668219

Please note: Completion of this form is not an admission of causation by, or contribution to the suspected adverse event by the suspected drug(s) or the reporting healthcare professional. The information does help to ensure the safety of all patients taking anti-retroviral medications in Ghana.
GAC/MSHAP/CTCPT-UGMS