Monitoring Toxicity of ARVs

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- Why Pharmacovigilance
- Methods of monitoring
- WHO International Programme for Adverse Drug Reaction reporting

Why is pharmacovigilance necessary?

- Efficacy is the major focus of drug clinical trials; short duration of clinical trials and risk of long term adverse effects
- Early detection of unknown safety problems
- Identifying risk factors
- Ultimately leading to rational use of drugs

Why pharmacovigilance in resource-limited settings?

- Medicine regulatory systems inadequate
- Absence of local product stewardship by the pharmaceutical companies.
- Local health care delivery systems do not have the necessary training, knowledge or expertise.

Why pharmacovigilance necessary for antiretrovirals in resource –limited settings?

- Available data on drug toxicity are mainly from industrialized countries - different clinical and operational context of developing countries
- Drug toxicity is common with antiretrovirals causing switching specific drugs
- Co-morbidity: TB and other infections,
- Use of alternative therapies, medicine interactions, socio-cultural-educational background is different; conditions such as malnutrition.

HIV Clinic 2005

Prescription

Dr A. Who

31 December 2005

Re: Mr Joseph Bloggs

R/

1) **abacavir + lamivudine + zidovudine 1 BD**
2) **atenolol 100 mg/d**
3) **acetylsalicylic acid 150mg/d**
4) **simvastatin 10 mg/d**
5) **bezafibrate 200 mg/d**
6) **metformin 500 mg/d**
7) **fluoxetine 50 mg/d**
8) **sildenafil**

What?

- All ARVs in use in the country
- All ARVs used in HIV/AIDS programmes
- New combination products
- Other medicines used in treatment of opportunistic infections
- Medicines used in treatment of adverse events

Methods of Monitoring

- Spontaneous reporting
- Cohort event monitoring
- Special Phase IV studies for specific toxicities
- Pregnancy registers
- A special study on patients with TB co-infected with HIV
- Special studies for paediatric populations

Spontaneous ADR reporting

Spontaneous reporting depends on encouraging health workers to report **suspicions** of ADRs

Spontaneous reporting can play a major role in identifying signals after a drug is marketed

Spontaneopus reports should be sent to national PV centre and then sent to global database

Spontaneous ADR reporting

advantages

- large population
- all medicines
- hospital and out-patient care
- long perspective
- patient analyses possible
- non-interventional
- low cost

Spontaneous ADR reporting

disadvantages

- under-reporting
- difficult to detect
  - delayed reactions
  - reactions with high background
  - incidence
- number of exposed unknown

Partners in reporting

- Minister of health
- Regulatory authority
- National pharmacovigilance centre
- Professional organizations
- Health professionals who are to participate
- Pharmaceutical companies
- Patients
- Patient support groups where these exist
- General public.

What to report?

- Adverse reactions
  - Type A
  - Type B
- Lack of effect
  - counterfeiting
  - resistance
  - interaction
- Quality problem http://mednet3.who.int/prequal/
- Dependence and abuse

What to report?

- Allopathic medicines
  - Prescription
  - OTC
- Traditional medicines

Special Phase IV studies for specific toxicities

- Abacavir and nevirapine hypersensitivity reactions (important to know what is the real prevalence of this problem in developing countries)
- Tenofovir nephrotoxicity risk, particularly in Africans, which can be more prone to this kind of toxicity
- Tenofovir bone toxicity, which should be particularly evaluated in children under 5 years of age.

Special Phase IV studies for specific toxicities (cont.)

- Prevalence of stavudine associated neuropathies (not restricted to peripheral forms).
- Prevalence of HIV-related lipodystrophy in patients using stavudine containing regimens.
- Nevirapine and saquinavir/r associated hepatotoxicity particularly when used concomitantly with TB drugs and also in presence of Hep B co-infection, which is probably high in Asian and African context but not well evaluated.

Special Phase IV studies for specific toxicities (cont.)

- Zidovudine associated anaemia, particularly in high prevalence malaria regions.
- Occurrence of birth defects in patients which have used efavirenz during 1st trimester of pregnancy.
- Occurrence of didanosine-related pancreatitis and its association with the use of other drugs.
- Problems with lopinavir/r or ritonavir capsules (related to ambient temperature in some African settings).
- Occurrence of lactic acidosis and other severe acute metabolic toxicity associated to NRTIs, particularly with stavudine and didanosine.

Proposed study

An evaluation of the impact of early initiation of HAART on TB treatment outcomes for TB patients co-infected with HIV

Trial Drugs

TB

All patients will receive anti-TB chemotherapy as recommended by the WHO treatment GL (4FDC/2FDC)

HIV

All patients will receive HAART as currently recommended by the WHO treatment GL: 2FDC *Combivir* (zidovudine + lamivudine)+efavirenz

Outcome measure: Primary

- **The primary outcome measure is the composite endpoint of treatment failure or death evaluated at 6 months after initiation of short course chemotherapy.**

Outcome measure: Secondary

- TB relapse in the 24 months after initiation of short course chemotherapy.
- A composite endpoint of treatment failure, relapse and death evaluated at 24 months after TB treatment initiation.
- Safety parameters. These will include biochemical and haematological parameters and all Adverse events (AE) and serious adverse events (SAE) occurring during treatment.
- Time to Relapse / treatment failure /death up to 24 months after initiation of anti-TB treatment.
- All occurrences of other opportunistic infections (as defined according to WHO staging system) and any event which alters clinical staging (e.g. extrapulmonary TB).
- Impact of early HAART on all-cause mortality
- Early response rate as measured by sputum smear conversion at the end of the intensive phase of treatment.
- Impact of early HAART on Immunological reconstitution (assessed through CD4 count measurements) of TB co-infected patients

WHO structure at headquarters

Director-General

Dr Jong-wook Lee

Representatives of the Director-General

Polio Eradication

Health Action in Crises

HIV/AIDS, TB and Malaria

Sustainable Development and Healthy Environments

Evidence and Information for Policy

Communicable Diseases

Health Technology and Pharmaceuticals

External Relations and Governing Bodies

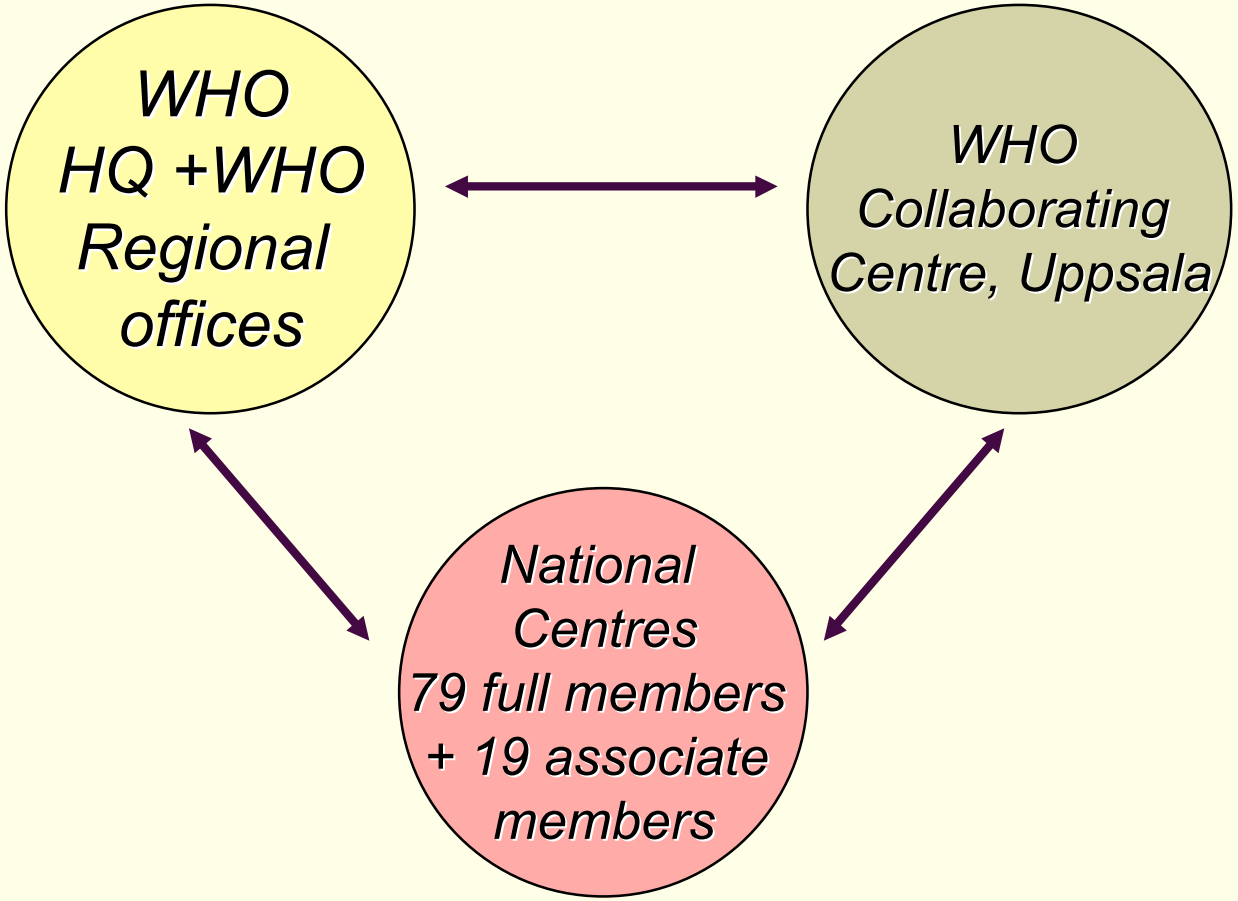
Link to Regional Offices

Noncommunicable Diseases and Mental Health

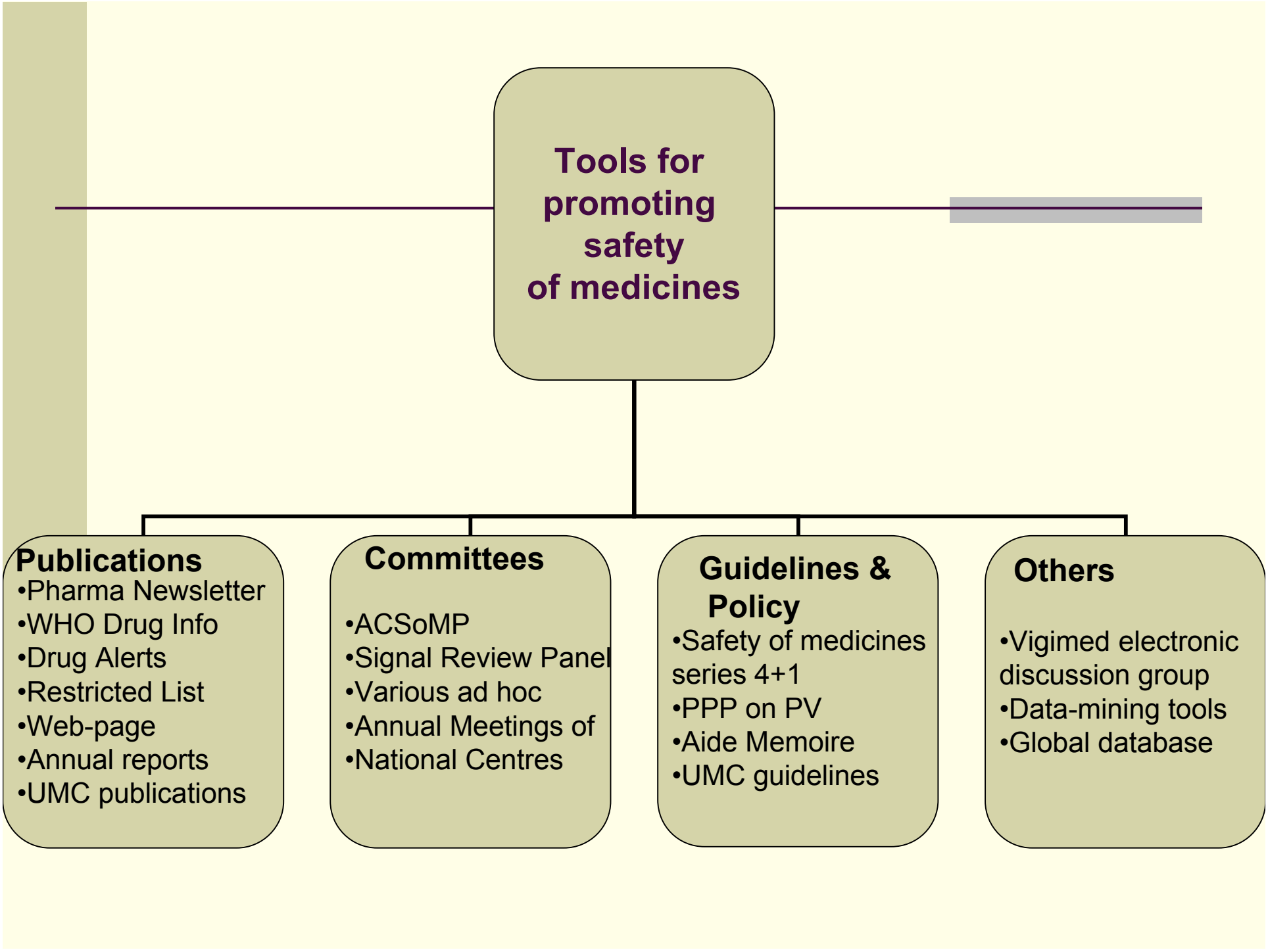
Family and Community Health

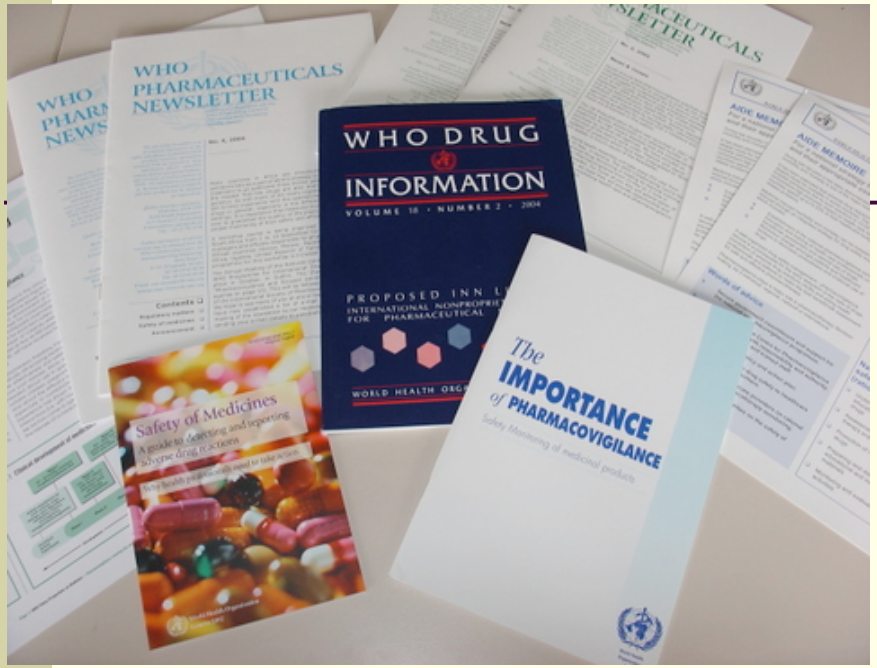
General Management

WHO Programme for International Drug Monitoring




Full members of the WHO Programme
Associate members of the WHO Programme
Non members of the WHO Programme


Tools for promoting safety of medicines
Publications
•Pharma Newsletter
•WHO Drug Info
•Drug Alerts
•Restricted List
•Web-page
•Annual reports
•UMC publications
Committees
•ACSoMP
•Signal Review Panel
•Various ad hoc
•Annual Meetings of
•National Centres
Guidelines & Policy
•Safety of medicines series 4+1
•PPP on PV
•Aide Memoire
•UMC guidelines
Others
•Vigimed electronic discussion group
•Data-mining tools
•Global database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Safety of Medicines
A guide to detecting and reporting adverse drug reactions
The IMPORTANCE of PHARMACOVIGILANCE
Safety Monitoring of medicinal products


Consolidated List of Products
United Nations
PHARMACEUTICALS: RESTRICTIONS IN USE AND AVAILABILITY
April 2003


New Delhi, India,
Report of the
Twenty-seventh Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring
Dublin, Ireland, 4 - 6 October 2004
December 2004

Training courses

- 2004 Pretoria, South Africa
- 2005 Uppsala, Sweden
- 2006 Caribbean