Pharmacovigilance in HIV/AIDS Public Health Programmes: Luxury or Priority?

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WHO HIV/AIDS ATC
Launching a Three-Year Initiative

- Developing pharmacovigilance (PV) for antiretroviral medicines (ARVs)
- integrated in HIV Public Health programmes.

- Crucial for:
  1. Patient safety
  2. Treatment development and effectiveness

- Focus: post marketing
Launching an initiative based on a three-Year project

- WHO PV project funded by the Bill and Melinda Gates Foundation for three years
- Four components:
  1. Consensus building
  2. Capacity building
  3. Development of research agenda to respond to key questions
  4. Coordination and information sharing
1. Consensus Building

development and adoption of

- **Common language** around
  - Definitions
  - Case definition, toxicity grading
  - Clinical management algorithms AE

- **Simplified, standardized reporting tools, methods, and training.**

- Single system for pooling and analysing data: WHO drug monitoring programme

- Common platform for gathering information from and sharing it with all stakeholders
2. Capacity Building

• Proposing a "model" for building pharmacovigilance in HIV Public Health programmes

• Collaborating with 6 focus country to develop the strategy, test and implement tools (Brazil, Cote d'Ivoire, Tanzania, Zambia, Ukraine, Vietnam)
2. Capacity Building

Need to find innovative strategies for building PV in ART

• Creating a culture of “drug safety”
• Training and supporting service providers without burdening them (use of new technologies)
• Addressing issues around integration of PV surveillance into existing patient monitoring
• Stimulating interest, incentives, commitment, and ownership of service providers
3. Development of Research Agenda

• Establishment of a **project advisory group**
• Identifying (and selecting the most urgent) **key questions** re: pharmacokinetics, co-morbidities, contextual specificities, and rapid data gathering
• Doing a **cohort mapping** to identify ongoing research and resources.
Key questions. 1

When to start?

• Increased risk of nevirapine toxicity (hepatic and hypersensitivity) if CD4>250; BMI>
• Should we start ART in HIV/TB patients if CD4>350?
• What is "as soon as possible for initiating ART in TB infected HIV people? in children? In pregnant women?
• What is the increased risk of IRIS in early ART initiation?
Key questions. 2

What to start?

• Efficacy and level of toxicity of a reduced dose of stavudine D4T 20mg? A plan to safely phase out d4T based on cumulated toxicities??
• Teratogenicity of Efavirenz in first pregnancy trimester?
• Adverse events linked to TDF in children exposed in utero?
• Safety of first line regimen in pregnant women?
• Safety of rifabutin in HIV positive individuals?
• Pharmacokinetics of RFM and NVP?
Key questions. 3

Use of new drugs in LMIS: piloting pharmacovigilance studies of 3d line regimen in LMIS

• Darunavir?
• Hypersensitivity of etravirine?
• Use of these drugs in pregnancy?
4. Coordination and Information Sharing

- Project management and coordination at three levels of WHO
- Staffing
- Sensitization
- Resources mobilization
- Country support
- WHO website and a database
Challenges

In country programmes: finding a "model" and the right balance between:

- Long-term "systems strengthening" and the need for urgent and targeted information
- **Passive** versus **active** surveillance systems and integration of the two
- **Coordination** with cohort implementers and country ownership

- Protecting country ownership:
  - Database
  - Decision-making
Challenges

• Ensuring **sustainability** by **integrating** this project-driven initiative into:
  
  ➢ **Treatment management** of a chronic infectious disease with built in toxicities
  
  ➢ **Health systems strengthening**

• Within WHO: preventing “verticalism” by collaborating with other programmes, EMP, TB, Malaria, TDR, MPS.

• Ensuring widespread **information sharing**, including the pharmaceutical industry, brand and generic companies

• **Mobilising resources** and ensuring financial sustainability at all levels, supporting countries to access funding (e.g., Global Fund)
Challenges

• Building a supportive network involving multiple partners with diverse interests

• Convening partners to pool their strengths and interests:

  ➢ A consortium
THANK YOU!
Shanthi Pal

Quality Assurance and Safety of Medicines

Essential Medicines and Pharmaceutical Policies

WHO
A Tripartite Programme

HQ-WHO + 6 Regional offices

WHO Collaborating Centre, Uppsala

National Centres

Others
TDR
HIV/AIDS
Malaria
MPS

Others

World Health Organization
WHO International Drug Monitoring Programme
126 members
PV in Public health Programmes

- Modelling on WHO structure

Essential medicines programme
Norms, Standards, Techniques for Safety of Medicines

Public health programmes
HIV AIDS, Malaria, TB

Treatment norms policies; patient monitoring and care
Pharmacovigilance

- Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems
- Includes active and passive surveillance
- Encompasses a continuous benefit/harm evaluation
- Involves communications with regulators, industry, prescribers and patients
WHO Methods (1)

- Routine PV = Spontaneous reporting
- Cohort Event Monitoring
- Registers, especially pregnancy registers
ADR Supply Chain

Patient-HW

Suspicion of ADR

Hand delivery

PV Unit/Coordinator

Reporting ADR

Fax - mail courier

PV Unit/MoH

NDA

Web upload

Analyze global ADRs

Botswana
<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>• Large population</td>
<td>• Underreporting</td>
</tr>
<tr>
<td>• All medicines</td>
<td>• Quality variable</td>
</tr>
<tr>
<td>• hospital and outpatients</td>
<td>• No rates</td>
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<tr>
<td>• Analyses of data possible</td>
<td>• Difficult to detect reactions with high background incidence</td>
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<tr>
<td>• Long-term perspective; rare, unknown adverse effects</td>
<td>• Reporting varies with seriousness of reaction, time from market introduction, promotional claims and publicity of suspected reaction</td>
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<tr>
<td>• INEXPENSIVE</td>
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WHO Methods (2)
Cohort Event Monitoring CEM principles

• Prospective, observational method
• Enroll a cohort of patients (prospectively)
• Actively pursue all patients
• Collect ALL adverse events (‘Hot pursuit’)

World Health Organization
What CEM can do (1)

1. Characterise known reactions
   - Mean age, Gender, Mean dose, Treatment duration, Time to onset, Seriousness profile, Incidence, Outcomes, Effect on treatment (% withdrawals)

2. Detect signals of unrecognised reactions

3. Interactions with
   - Other medicines
   - Complementary and alternative medicines
   - Foods

4. Identify risk factors
5. Assess safety in pregnancy & lactation

6. Estimate risk (including comparative)

7. Provide evidence for effective risk management
   - Safer prescribing
   - Benefit / harm assessment
   - Regulatory changes
8. Detect inefficacy due to
   • Faulty administration, Poor storage conditions, Out of date, Poor quality product, Counterfeit, Interactions

9. Hypothesis generation

10. Cohorts for study
CEM - disadvantages

• Training needed
• Dedicated person
• Difficult to capture rare reactions
• EXPENSIVE
Where are we with CEM?

- Pharmacovigilance for antiretrovirals in resource-poor countries. WHO, 2007
- A Practical Handbook on the pharmacovigilance of antiretroviral medicines.
Reporting management

• Adverse events dictionary being developed
• CEMFlow: data entry / management tool for CEM
• CEMFlow-Events dictionary interface being developed
• To be tested (and adapted) in practice
Implementing CEM in countries

- Training
- 8 countries trained (Dar es Salaam 2009)
WHO Methods (3)
Pregnancy register

• A systematic enrollment of women during pregnancy to determine, at birth, the fetal effects from infections, medications taken or other exposures that occurred or other maternal factors.
• A protocol has been developed
• pilot study underway
Benefit of Pharmacovigilance—beyond Safety

**Benefit of PV**

- Safety
- Quality
- Resistance

**Impact on PH**

- Improves Quality of Care
- Improves Compliance
- Reduces Drop Out Rates

**Impact on Supply Chain**

- Good quality drugs
- More variety of drugs (less loss to resistance)

*World Health Organization*