Surveillance for drug toxicities in people living with HIV-experience in South Africa

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Outline

• Targeted spontaneous reporting (TSR)
  – Western Cape ARV and TB pharmacovigilance programme

• Sentinel cohorts in South Africa

• South African pharmacovigilance workshop
Context

• 20% of people living with HIV infection are in South Africa

• largest ARV treatment programme in the world (2.5 million people on ART)

• Pharmacovigilance included in national HIV strategic plan from inception
Western Cape ARV and TB pharmacovigilance programme

• Started in 2005, collaboration:
  – Western Cape Provincial Health Department
  – Medicines Information Centre (University of Cape Town)

• Targeted spontaneous reporting system

• Goals:
  – Increase drug safety awareness
  – Identify signals
  – Inform policy and training

• TB included from 2012
Western Cape ARV and TB pharmacovigilance programme

• Methods:
  – Serious ADR reporting form
  – Case definitions for specific events
  – Follow up by pharmacist
  – Panel for causality assessment of deaths

• Feedback
  – Reports
  – Newsletters

• Training

• Reports forwarded
  – Regulatory pharmacovigilance unit
  – National DOH
Example of reporting form
ART scale up and ADR reports received

**Patients receiving ART**
- **2004**: 0
- **2005**: 0
- **2006**: **50000**
- **2007**: 0
- **2008**: 5000
- **2009**: 10000
- **2010**: 15000
- **2011**: 20000
- **2012**: 25000

**Number of reports**
- **2004**: 0
- **2005**: 0
- **2006**: **100**
- **2007**: 0
- **2008**: 150
- **2009**: 300
- **2010**: 500
- **2011**: 700
- **2012**: 900

**Year**

- **2004**
- **2005**
- **2006**
- **2007**
- **2008**
- **2009**
- **2010**
- **2011**
- **2012**

**Submitting:**
- **2006**: 35/49 facilities (71%) 34% of reports from primary care
- **2012**: 38/200 facilities (19%) 80% of reports from primary care

**Healthcare workers reporting:** 72% doctors, 19% nurses, 8% pharmacists
Trends in reported ADRs

<table>
<thead>
<tr>
<th>Year (total ADRs)</th>
<th>Number of ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>(140)</td>
</tr>
<tr>
<td>2006</td>
<td>(453)</td>
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<tr>
<td>2007</td>
<td>(320)</td>
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<td>2008</td>
<td>(200)</td>
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<td>2009</td>
<td>(287)</td>
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<tr>
<td>2010</td>
<td>(353)</td>
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<tr>
<td>2011</td>
<td>(296)</td>
</tr>
<tr>
<td>2012</td>
<td>(273)</td>
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</table>

- Skin reactions
- Hepatotoxicity
- Nephrotoxicity
- Hyperlactataemia/ lactic acidosis
Challenges in the W Cape TSR system

• Reduced reporting rates with scale up
• “Reporter fatigue”

Addressing challenges:

• Prioritising reporting of toxicities for current policy questions
• Optimal use of “reporting champions”
• Improving system responsiveness
  – Prompt, individualised feedback and clinical support
  – Telephonic reporting, immediate answers to questions
• Strengthening of data collection and analysis
  – Preventability, assessment of clinical management
• Training
Sentinel cohorts

- Several sentinel cohorts in South Africa
- Valuable resource for toxicity surveillance
- Robust denominator data
  - Can determine incidence
  - Can identify risk factors
South African sentinel cohort toxicity data

A high incidence of nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidosis in HIV-infected patients in a South African context

Rosemary Geddes, Stephen Knight, Mahomed Yunus Suleman Moosa, Anand Reddi, Kerry Uebel, Henry Sunpath

A High Incidence of Lactic Acidosis and Symptomatic Hyperlactatemia in Women Receiving Highly Active Antiretroviral Therapy in Soweto, South Africa

M. G. Bolhaar and A. S. Karstaedt

- Higher incidence than reported in clinical trials
- Women, particularly obese, at risk
Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort

Andrew Boulle¹*, Catherine Orrell², Richard Kaplan³, Gilles Van Cutsem⁴, Matthew McNally², Katherine Hilderbrand¹, Landon Myer¹, Matthias Egger⁵, David Coetzee¹,³, Gary Maartens⁶ and Robin Wood² for the International Epidemiological Databases to Evaluate Aids in Southern Africa (IeDEASA) Collaboration

Adults first-line ART in 2 Western Cape cohorts (Khayelitsha and Gugulethu)

Antivir Ther 2007;12:753
SA response to stavudine toxicity reports

• Meta-analysis:
  – lower stavudine doses equally effective & less toxic

• Interventions 2007:
  – lower dose stavudine (30mg all weight bands)
  – point of care lactate meters
  – educate HCWs
  – avoid stavudine in obesity

Hill A Expert Opin Pharmacother 2007;8:679
Perez EH Int J Infect Dis. 2008; 553
Impact of policy changes

Reduced referral and case fatality rates for severe symptomatic hyperlactataemia in a South African public sector antiretroviral programme: a retrospective observational study

Charlotte Schutz¹,², Andrew Boulle³, Dave Stead¹,², Kevin Rebe¹,², Meg Osler³ and Graeme Meintjes¹,²,⁴

GF Jooste Hospital, Cape Town

Referral rate
- 2005 20.4/1000py on ART
- 2008 1.3/1000py on ART

Acidosis
- 2003 67% of cases
- 2008 13% of cases

Case fatality rate
- 2004 33%
- 2008 0%

National pharmacovigilance workshop (Aug 2012)

• More cohesive national system
  – Programmatic, regulatory, institutional PV

• Address important policy issues; improve patient care

• Multiple methodologies encouraged, prioritising:
  – Spontaneous reporting
  – TSR for public health programmes
  – Active surveillance: sentinel cohorts
  – Pregnancy exposure registry

• Investment in capacity building & training

• Feedback & communication to stakeholders
# Current SA pharmacovigilance priorities

(National pharmacovigilance workshop Aug 2012)

<table>
<thead>
<tr>
<th>HIV/AIDS Priorities</th>
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<tbody>
<tr>
<td>• Safety of tenofovir- nephrotoxicity, bone/skeletal toxicity risk</td>
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<td>• Safety in pregnancy of ARVs –particularly efavirenz (EFV)</td>
</tr>
<tr>
<td>• Safety of medicines for common co-morbidities in HIV-infected patients (e.g. diabetes)</td>
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<tr>
<td>• Serious skin reactions with tuberculosis (TB) and HIV meds</td>
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<th>Tuberculosis</th>
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<tr>
<td>• Safety of drugs used to treat MDR and XDR TB</td>
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<tr>
<td>• Drug-drug interactions with HIV drugs and treatments for co-morbidities</td>
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<tr>
<td>• Deafness (ototoxicity) due to aminoglycosides</td>
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<tr>
<td>• Hepatotoxicity associated with with first- and second-line TB regimens</td>
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<th>Maternal Child Health</th>
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<tr>
<td>• Risk of medicine-related harm to pregnant woman and fetus e.g. PMTCT regimens, cotrimoxazole, fluconazole, TB medicines and novel vaccines</td>
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<tr>
<td>• Ethambutol and ocular toxicity in children with TB</td>
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<tr>
<td>• Long term effects of first-line protease inhibitors in children</td>
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<tr>
<td>• Safety of recommended antiretroviral (ARV) regimens in children</td>
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<tr>
<td>• Safety of nevirapine (NVP) and tenofovir (TDF) in children</td>
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<tr>
<td>• EFV and neurodevelopmental effects with in utero exposure</td>
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<th>Immunization and vaccines</th>
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<tbody>
<tr>
<td>• Efficacy and safety of vaccines in HIV/immuno-compromised patients</td>
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<tr>
<td>• BCG vaccinated neonates of HIV-infected mothers</td>
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<tr>
<td>• Improved detection of serious events such as intestinal intussusceptions</td>
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<th>Cross-cutting issues</th>
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<tr>
<td>• Poorly tolerated medicines and their impact on adherence</td>
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<td>• Drug resistance – early warning indicators</td>
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<tr>
<td>• Safety of traditional medicines</td>
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Mehta et al, SAMJ (in press)
Conclusions

- Toxicity surveillance methodology-selection based on priority questions
- Existing resources
- Different methods provide complementary data
- Communication and feedback are key
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Health care workers who submit reports

CDC & PEPFAR