Drug Safety Considerations and Pharmacovigilance Approaches in HIV Care

Thomas Mertenskoetter MD
T.O.M. Life Science Consulting
Hamburg, Germany
Transparency: Clients

• WHO HIV/AIDS Department
• WHO Reproductive Health and Research
• German Parliament
• Gilead
• MSD
• Janssen
• Viiv
• AstraZeneca
• Mylan
Outline

• Shift from Efficacy to Longterm-Outcome
• Prevalent Safety Issues
• Drug Safety Research
• Approaches to PV
Evolution of ART Regimens: From Efficacy to Safety and Tolerability

• Initial focus on improving antiviral efficacy and immune-restoration
  – Introduction of new drug classes and drug combinations
  – Strategy to treat patients early with a highly potent regimens

• High incidence of drug safety issues as e.g.
  – Lipodystrophy and Lactate Acidosis
  – Hyperlipidemia
  – Liver and renal toxicity

• The further evolution of treatment strategies was strongly driven by
  – Need to understand the safety profile of long-term antiretroviral combination therapies better
  – Delineate the contribution of the various drugs and the specific role of the HIV-disease in the observed safety issues.
Importance of PV in ART

• As ART is
  – A life-long therapy
  – Not only for adults, but also for children of all ages
  – Pregnant and breast-feeding women
  – Population with co-morbidities

• Innovative HIV treatment and prevention strategies
  – Earlier initiation of ART in people with relatively good immune status and limited immediate risk of disease progression
  – Use of ARVs in HIV negative populations
Shift focus to the risk-benefit ratio of ART

- Longterm observation of treatment outcome
  - Capture the
    - effects of ART on: HIV progression and overall morbidity and mortality
    - vs. ART associated harm induced
  - Broad and diverse population scope
  - Various health aspects
  - Teratogenicity questions
  - Very long-term perspective

- Analyse both risk and benefit
  - In specific populations
  - In specific settings

- Deep and rich data sets wanted
Challenges of PV

• Pharmacovigilance systems need to
  – Detect relevant safety signals against a background of clinical noise
  – Provide robust information on frequency and risk factors for adverse effects of ART
  – Follow-up patients through different parts of the health care system
    • Out-patient / In-patient / various locations /

• ART roll-out is putting a significant burden on the healthcare systems
  – Decentralization
  – Task shifting
Drug safety issues requiring further investigation

• Safety profile of TDF and other ARVs in children
  – E.g. renal toxicity, bone toxicity

• Effect of EFV in pregnant women and their offspring, as well as in adolescents

• Potential drug-drug interactions
  – HIV-TB co-infections
  – Non-communicable diseases
Figure 2

ARV discontinuation according to current eGFR level

- **TDF** 21,899 persons on TDF at baseline or start during follow up, 9,141 stop during 63,698 PY
- **ATV/r** 7,857 persons on ATV/r at baseline or start during follow up, 4,709 stop during 19,371 PY
- **LPV/r** 8,038 persons on LPV/r at baseline or start during follow up, 5,387 stop during 20,449 PY

Same pattern for ATV and other PI/r as for LPV/r. Models adjusted for CD4 nadir, gender, ethnicity, HIV transmission risk, enrolment cohort and prior AIDS (all at baseline) and HBV, HCV, smoking status, hypertension, diabetes, cardiovascular events, age and CD4 as time-updated values.
Data on stavudine toxicity from sentinel cohorts informed policy

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

2007: 30 mg for all weights, point of care lactate meters, avoidance in obesity, education HCW
Dramatic decrease referral rates, severity at admission, mortality

ENCORE Study
Optimizing Efavirenz Dose: 400 mg vs. 600 mg

Mean change from baseline to week 48 pVL

Effavirenz adverse events*

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Mean change</th>
<th>95%CI</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Intention to treat (last observation carried forward)</td>
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<tr>
<td>EFV 400mg</td>
<td>321</td>
<td>-3.00</td>
<td>-3.09</td>
<td>-2.91</td>
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<tr>
<td>EFV 600mg</td>
<td>309</td>
<td>-2.94</td>
<td>-3.03</td>
<td>-2.84</td>
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</table>

Puls et al, IAS Kuala Lumpur 2013 WELBB02
Treatment Failure through Counterfeit Medicines

- Estimation of medicines on sale being counterfeit vary between 30% to less than 10% (1)
- Fake medicines market is estimated to be worth $ 75 billion in 2011 (3)
- Over 700,000 deaths from Malaria and TB through counterfeit medicines alone (2)
- Need to be suspicious and report possible cases

2 Kennedy V. Consumer Health: Internet drug scams can make you sick. 2011
So Many Questions – Collaboration Needed

• Various countries have employed a combination of different pharmacovigilance approaches as
  – Targeted spontaneous reporting
  – Together with long-term sentinel cohorts and registries

• Large cohort studies and international collaborations can
  – Provide information on the safety profile of drug classes or single compounds
  – Allow for analysis of additional risk factors for adverse effects as well as the disease progression
  – Provide a deeper insight into the risk-benefit ratio of ART in various populations
South African Approach

- South Africa: 20% of PLWH globally
- Largest ARV treatment program in the world
  - 2.4 million people on ART
- Pharmacovigilance included in national HIV strategic plan from inception
- National pharmacovigilance workshop 2012
  - Most priority surveillance issues are HIV-related
- Top priorities
  - Tenofovir
  - Safety of ARVs in pregnancy
  - Toxicities of TB treatment
  - Drug toxicities in HIV and TB co-infected patients

Mehta et al. SAMJ 2014
Targeted spontaneous reporting
Western Cape ARV and TB pharmacovigilance programme

• Started in 2005; TB included from 2012
• Collaboration: WC DoH & Medicines Information Centre (UCT)
• Goals:
  – Increase drug safety awareness
  – Identify signals
  – Inform policy and training
• Methods:
  – Serious adverse drug reaction (ADR) reporting form
  – Case definitions
  – Follow up by pharmacist
  – Panel for causality assessment of deaths
• Feedback: reports and newsletters
• Reports forwarded to Regulatory PV unit & National DoH
Trends in reported ADRs

<table>
<thead>
<tr>
<th>Year</th>
<th>Total ADRs</th>
</tr>
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<td>2005</td>
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<tr>
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<tr>
<td>2011</td>
<td>296</td>
</tr>
<tr>
<td>2012</td>
<td>273</td>
</tr>
</tbody>
</table>

Number of ADRs:
- **Hyperlactataemia/ lactic acidosis**
- **Skin reactions**
- **Hepatotoxicity**
- **Nephrotoxicity**
ART scale up and ADR reports received

Facilities submitting reports:
• 2007: 39/59 facilities (66%)
• 2012: 38/200 (19%)
Sentinel cohorts

• Several sentinel cohorts in South Africa
  – Set up by researchers to assess outcomes
• Valuable resource for toxicity surveillance
  – Requires fewer resources than setting up cohorts solely for toxicity surveillance
• Can determine toxicity incidence, identify risk factors
• Cohort collaborations- increase study power
Pregnancy registries

- **USA FDA**
  - Reporting through physicians and manufacturers

- **Launched in KwaZulu Natal province Oct 2013**
  - Assesses both maternal and neonatal outcomes
  - Prospective registry collecting data on all drug exposures during pregnancy
  - Birth defect surveillance at referral centre
  - Plan to expand to other provinces

Mehta et al.; BMC Pregnancy Childbirth 2012
Key points

• Identify priority questions
• Different PV methods can provide complementary data
• Create systems that can address multiple questions
• Data on incidence is key to inform policy
• Strengthen existing cohorts and cohort collaborations
• Create a culture of communication and feedback
Summary

• Greater adherence and subsequently better ART outcome through:
  – Improving the safety profile and tolerability of ART
  – Understanding and managing drug associated adverse effects proactively

• To scale up and maintain long-term PV
  – Integrate traditional reporting systems, cohort studies, registries
  – Deeper collaboration with the innovative pharmaceutical industry as well as generic manufactures
Acknowledgements

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