Monitoring HIV Treatment Associated Toxicities
A WHO-Forum Collaboration

2nd International Workshop on HIV Treatment, Pathogenesis and Prevention Research
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Why is monitoring of toxicities needed in resource limited settings?

Compared to developed world:

- **Rapid scale-up of antiretroviral treatment**
  - Limited expertise, experience among clinicians and patients

- **Difference in populations**
  - Race
  - More women and children, pregnancy
  - Presenting with advanced disease
  - High level of co-morbidities and co-infections
  - Nutritional status
  - Use of traditional medicines

- **Difference in drugs**
  - Standardized first line, 2nd line
  - FDC’s, generics
  - Treatment of co-infections
Policy Information Gap

- Data on ARV toxicity is needed for
  - Development, review and revision of global, regional and national treatment guidelines
  - Program planning (supply of 1\textsuperscript{st} and 2\textsuperscript{nd} line drugs)
  - Program evaluation
  - Feedback to clinicians and patients
  - Regulatory considerations
FCHR Monitoring Toxicities Working Group & WHO Meetings

- Roundtable 1: Defining the problem
- Roundtable 2: Activity Landscape
- Roundtable 3: Framework Dev
- WHO/FCHR Meeting: ARV Case Definitions*

- Dublin, 2005
- Madrid, 2006
- Monte Carlo, 2007
- Geneva, 2008

*with support from the Bill & Melinda Gates Foundation

http://www.hivforum.org/projects/LTM.htm
http://www.hivforum.org/projects/PV.html

www.hivforum.org
Adverse Event Field

Adapted from Evans and Waller, MCA 2002
Monitoring Toxicities & Pharmacovigilance

Clinical Trials &/or Observational Cohorts:
- Active, prospective reporting
- Numerators, denominators
- Lack of standardization of definitions, grading and data format
- Multiple sponsors
- Pharmacoepidemiology  ◦ causality

Pharmacovigilance:
- Passive reporting/under-reporting
- Lack of numerators/denominators
- Standardized definitions & protocols
- MOH/Regulatory Agency based
- Experience in data mining

New approach: take the best of both worlds into one system
Major Recommendations from Forum Roundtables

• Use sentinel-site based methodology for collecting toxicity data in a standardized format
• Make best use of currently ongoing observational cohort studies (Bakare presentation)
• Engage all stakeholders (including program sponsors and pharmaceutical industry) in the effort
Regional distribution of ARV reports

ICH = EU, US, JP + NZ, AUS, CAN

ICH: 21,697 (95%)
Non-ICH: 1,088 (5%)

Report year 2001-2005

The WHO Collaborating Centre for International Drug Monitoring

ARV reports by product category

ICH
- Originator: 14,572 (67%)
- Generic: 5,040 (23%)
- X: 2,085 (10%)

Non-ICH
- Originator: 202 (19%)
- Generic: 790 (72%)
- X: 96 (9%)

Marie Lindquist
Uppsala Monitoring Center
Heterogeneity of Reports

- Regional differences observed in Uppsala Monitoring Center*:
  - 900/1138 reaction terms in ICH countries only
  - 8/1138 in non-ICH countries only
  - Skin and GI reactions most common in non-ICH countries

- FCHR literature survey of treatment limiting toxicities**
  - South America: gastrointestinal & hematologic toxicities, neuropathy
  - Southeast Asia: lipodystrophy, rash, hepatitis
  - Africa: neuropathy, neutropenia, lipodystrophy

From K Johnson 2008: Survey of published studies in 4 countries (51 studies: >31,000 pts)
Adult Treatment Regimen Distribution Based on Published Studies

Thailand
- TDF/3TC/SQV
- d4T/PI based
- d4T/3TC/NVP
- d4T/3TC/EFV

India
- AZT/3TC based
- Other
- d4T/3TC/NVP
- d4T/3TC/EFV

South Africa
- Other
- d4T/3TC/NVP
- d4T/3TC/EFV
- AZT/3TC based

Kenya
- Kaletra based
- Other
- d4T/3TC/NVP
- d4T/3TC/EFV
- AZT/3TC based

V Miller May 08
From K Johnson, 2008
Regional Heterogeneity

- Several explanations possible:
  - True differences in populations
  - Differences in reporting frequencies
  - Differences in definitions used
  - Differences in regimen used
- The lack of a uniform reporting style for defining and grading AEs complicates extraction of data for comparison across sites, regions and populations
Discussion

• Toxicity monitoring/pharmacovigilance effort includes *all* stakeholders:
  – Bi and multi-lateral scale up programs
  – National MOH’s and regulatory agencies
  – Pharmaceutical sector
    ￮ Generic
    ￮ Innovator
  – Clinicians and clinical researchers
Discussion - 2

- HIV treatment scale-up provides a unique opportunity to improve data gathering mechanisms for toxicity monitoring
  - Ultimately, this should extend beyond HIV/AIDS treatment
- Many opportunities exist for reducing the disease specific ‘silto approach’ and to energize the traditional pharmacovigilance approach