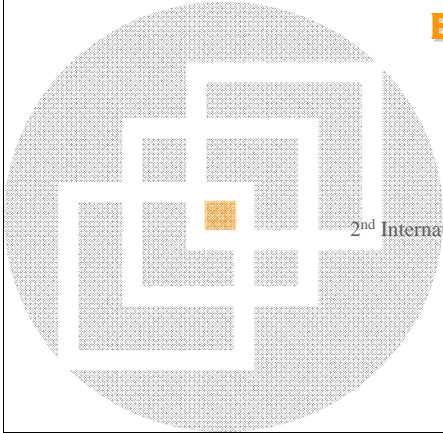




Forum for
Collaborative HIV Research

CASE DEFINITION AND SEVERITY GRADING FOR TREATMENT-RELATED ADVERSE EVENTS



Nyasha Bakare, MD, MPH
Forum for Collaborative HIV Research

2nd International Workshop on HIV Treatment, Pathogenesis and
Prevention Research in Resource-Poor Settings

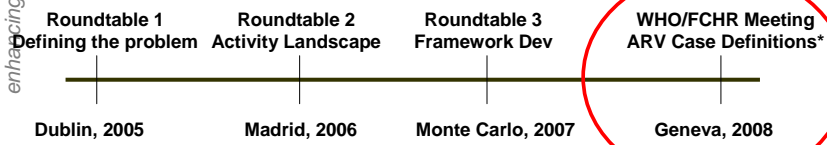
Dakar
May 2008



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BACKGROUND

- Information on ARV-related AEs is critical for the continued success of programs
- Lack of consistency in reporting of AEs across regions and data sources
- First step: develop a common framework for defining and grading AEs
- Forum/WHO Collaboration established to address this gap



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EXISTING FRAMEWORKS FOR DEFINITION AND SEVERITY GRADING OF AEs

Classification and coding of terms	<ul style="list-style-type: none">•MedDRA•WHO-ART•ICD-10
Definitions and coding, HIV clinical trials groups	<ul style="list-style-type: none">•AACTG TOX-EG•PACTG Appendix 40•ACTG Appendix 60
Definitions and coding, HIV cohorts	<ul style="list-style-type: none">•TAHOD data specifications•HICDEP
Definitions, for pharmacovigilance	<ul style="list-style-type: none">•CIOMS/ MSSO SMQs•CIOMS 1999
Severity grading and terminology criteria in different patient populations	<ul style="list-style-type: none">•DAIDS Table for severity grading•ANRS Table for severity grading•WHO treatment guidelines, adults and adolescents•WHO treatment guidelines: infants and children•CTCAE criteria for adverse events•DMID Toxicity tables•TAHOD data specifications v2.1

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EXISTING FRAMEWORKS FOR DEFINITION AND SEVERITY GRADING OF AEs

- Majority of existing frameworks developed for resource-rich settings
- Definitions may require laboratory testing or other diagnostic procedures that are not widely available
- Severity grades for laboratory parameters are based on normal values in Western populations

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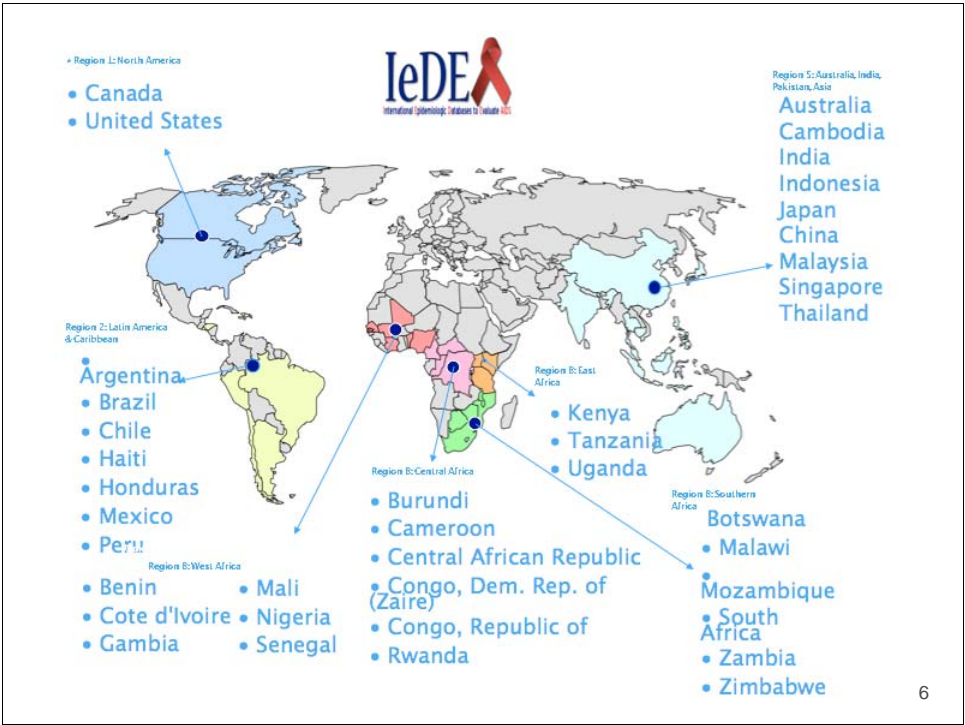
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FORUM/IEDEA SITE SURVEY

- IeDEA is a network of cohort studies in regions around the world
- The Forum collaborated with the IeDEA Pharmacovigilance Working Group* in the design of site and regional database surveys
- Goal: to assess current practices around ARV-related toxicity evaluation and reporting at IeDEA sites in various regions

*Co-chairs: N Kumarasamy & P Braitstein

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FORUM/IEDEA SITE SURVEY RESULTS - I

- 31 clinics responded
 - 11 Asia, Australia
 - 5 Central Africa
 - 9 East Africa
 - 1 West Africa
 - 3 Southern Africa
 - 6 Caribbean/Central America/South America
- All active research sites, 10 primary care clinics, 21 referral level
- Represents total of 147,178 patients, of which 57,820 are on ARVs

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FORUM/IEDEA SITE SURVEY RESULTS - II

- Less than 50% of sites use standardized definitions for AEs
- Major sources for classifying and defining adverse events:
 - WHO treatment guidelines
 - DAIDS toxicity tables
 - TAHOD data specifications
 - Clinical experience
- Toxicities assessed at all visits, by a variety of providers
- All sites document maternal exposure, birth outcomes and malignancies
 - Few sites with normal lab reference ranges based on local population

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FORUM/IEDEA SITE SURVEY RESULTS - III

- Main treatment-limiting AEs encountered by sites:
 1. Anemia
 2. Rash
 3. Peripheral neuropathy
 4. Lipodystrophy
 5. Hepatotoxicity
 6. Lipoatrophy
 7. Dyslipidemia
 8. IRIS
 9. Nausea /Vomiting
 10. Hypersensitivity

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SITE SURVEY - FEEDBACK

- From the pilot site survey:

“Protocols should include a step wise approach or algorithm, in response to the abnormal results, to assist clinicians in the appropriate management of toxicities.”

- Johannesburg, South Africa

“In carrying out research in international settings, it is important to study and define normal value ranges for infants and children as well as adults by country setting as there are clear age related and race-ethnicity differences for international sites compared to US for a number of measures (CD4, hemoglobin, neutrophil count, TLC, creatinine, etc).”

- Kampala, Uganda

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CONCLUSIONS

- These findings illustrate need for a common methodological framework to harmonize definition and reporting of ARV-related AEs
- Existing frameworks provide a useful basis for deriving standardized definitions for ARV-related AEs but may require adaptation to generate appropriate definitions applicable in a variety of settings
- Normal laboratory reference ranges need to be established by region to allow appropriate severity grading of toxicities

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**“ARV DRUGS ADVERSE EVENTS, CASE DEFINITION,
GRADING, LABORATORY DIAGNOSIS AND TREATMENT
MONITORING”**

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**World Health
Organization**



**Forum for
Collaborative HIV Research**

**A meeting of experts,
jointly organized by WHO/HIV and WHO/PSM Departments
and the Forum for HIV Collaborative Research**

28-29 February, 2008, Geneva

With support from the Bill and Melinda Gates Foundation

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MEETING OBJECTIVE

- To bring together the pharmacovigilance and HIV treatment communities to establish a common language with agreed terms to harmonize AE case definitions, and hence the detection, recording, reporting and analysis of AE data related to the use of ARVs

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POINTS OF CONSENSUS AND RECOMMENDATIONS

- Priority list of major ARV-related AEs for surveillance
- Confirmation of the need for AE terms and definitions applicable at all levels of health care delivery
- Expert panels to further develop specific case definitions
 - severity grading based on clinical and laboratory findings as needed
- Sentinel surveillance sites for active reporting of AEs
 - linked to both national and international networks
 - representative of different levels of the health care system.
- Further strengthening of pharmacovigilance systems for spontaneous reporting of known and unexpected AEs in countries where these are already established

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NEXT STEPS

- WHO will set up working groups, including HIV clinicians and pharmacovigilance experts to develop standardized definitions of major ARV-related AEs
- A meeting of experts will be convened to obtain a consensus on the final definitions, reporting forms, protocols and systems to report AEs
- Operational linkages will be made with existing systems, the cohort implementers and existing national PV programs

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 - Caroline Williams
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