



Forum for
Collaborative HIV Research

**OVERVIEW OF CURRENT KNOWLEDGE OF
ARV-RELATED ADVERSE EVENTS
AND EXISTING DEFINITIONS**

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WHO/Forum Joint Meeting
February 28, 2008



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OUTLINE

- Background
- Review of literature reports of ARV-related adverse events (AEs) in resource-limited settings
- Forum-IeDEA collaboration: site survey*
- Overview of existing frameworks for defining and grading ARV-related AEs
- Conclusion

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BACKGROUND - I

- Majority of existing data on ARV-related toxicities comes from resource-rich settings
- Public health approach to treatment now being implemented in resource-limited settings focused initially on access
- Information on ARV-related AEs is critical for the continued success of programs

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BACKGROUND - II

Key differences to consider for ARV-related toxicities in resource-limited settings:

- Population
- Type of therapy
- Health care delivery systems

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Population: Women, pregnancy, children, co-morbidities, nutritional status, host genetics

Therapy: Standardized regimens, fixed-dose combinations, generics, spectrum of drug interactions, traditional/alternative therapies

Health care delivery systems: Human resources, monitoring and diagnostic procedures, regulatory environment



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LITERATURE REVIEW OBJECTIVES

- To identify the most commonly reported ARV-related AEs in various regions
 - Search I: ARVs
 - Search II: Treatment of HIV-TB coinfection
 - Search III: Prevention of mother-to-child transmission (PMTCT)
- To identify AEs reported as treatment-limiting
- To assess reporting methods and guidelines used to describe ARV-related AEs in published studies
- In addition: review of published literature on laboratory normal ranges in different regions [see background document]

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I will focus in this presentation on Search I, the most extensive, or ARV-related AEs. Refer to background doc for results of searches II and III.

Main focus here is on the adverse events reported, causality assessment linking to specific drugs not included here, though drug regimens are listed in full tabulation of data in background document. Aim here is to determine who is reporting what and how.



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LITERATURE REVIEW

METHODS

- Primary electronic literature searches of published peer-reviewed clinical trials, cohort and cross-sectional studies reporting adverse events data from RLS in Africa, South America, Asia
- Additional web searches of recent HIV conferences
- Articles included if specific cases of drug toxicities reported and counted

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LITERATURE REVIEW

RESULTS I: ARVs

- 40 publications on ARV-related AEs (1999-2007)
 - 2 South America, 15 Southeast Asia, 23 Africa
- 5 most commonly reported AEs in adults:
 - Anemia, rash, neuropathy, lipodystrophy, hepatitis
- Wide range for frequencies by region, drug regimen, type of study; few studies in children in RLS

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Few reports found from Eastern Europe, China

Refer to background doc for details on drug regimens by region/study



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LITERATURE REVIEW

RESULTS II: ARVs

- Predominant treatment-limiting AEs:
 - South America: gastrointestinal & hematologic toxicities, neuropathy
 - Southeast Asia: lipodystrophy, rash, hepatitis
 - Africa: neuropathy, neutropenia, lipodystrophy
- 1/3 of articles clearly referenced use of standardized definitions or severity grading systems
- Other studies relied on individual physician assessment, patient self-report or unreferenced toxicity scales and definitions

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DAIDS most frequently referenced for severity grading



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LITERATURE REVIEW

CONCLUSIONS

- A considerable amount of data has been published on ARV-related AEs in different RLS
- ARV-related AEs are not consistently reported; often not specified whether reported AEs were treatment-limiting
- The lack of a uniform reporting style for defining and grading AEs complicates extraction of data for comparison across sites, regions and populations

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FORUM-IEDEA COLLABORATION*

- 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 assessing current practices around ARV-related toxicity evaluation and reporting at IeDEA sites in various regions

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IEDEA SITE SURVEY OBJECTIVES

- To describe monitoring and reporting practices for ARV-related toxicities at various sites in the network
- To assess the use of standardized definitions for reporting of ARV-related AEs
- To determine which sites/regions have developed normative reference ranges for laboratory parameters based on the local/regional HIV uninfected population

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IEDEA SITE SURVEY

MAIN SURVEY ITEMS

- Site description
- Guidelines in use for defining/grading AEs
- Practices around documentation and coding AEs, including pregnancy-related AEs, birth outcomes, malignancies
- Frequency and type of laboratory monitoring in adults, pregnant women, children (CD4, VL, CBC, LFTs, creatinine, lipids, lactic acid)
- Cost of laboratory testing for patients (free, not free)
- Standardized definitions utilized at site for major ARV-related AEs
- Top 5 treatment-limiting toxicities at site

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Description: type of facility, # patients on ARVs, location, PI



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IEDEA SITE SURVEY RESULTS - I

- 31 clinics have 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 www.hivforum.org

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IEDEA SITE SURVEY RESULTS - II

- 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; visit schedules varied according to national policies
- All sites document maternal exposure, birth outcomes and malignancies; limited use of registries to record this information

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IEDEA SITE SURVEY RESULTS - III

- Standardized definitions: Less than 50% of sites had standardized definitions for terms in the following AE categories:
 - Musculoskeletal/connective tissue disorders
 - Skin disorders
 - Respiratory disorders
 - Gastrointestinal disorders
 - Nervous system disorders & psychiatric disorders
 - Reproductive disorders
 - Perinatal conditions and congenital disorders
 - General disorders (constitutional symptoms)
 - IRIS

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IEDEA SITE SURVEY RESULTS - IV

- Laboratory testing schedules
 - Schedules vary greatly by region
 - In general, more frequent lab testing in Asia, CCASA, less frequent in Africa
 - Few sites with normal lab reference ranges based on local population
 - Costs of lab tests for patients vary:
 - Free in West, Central Africa for all tests listed
 - Free at many sites in CCASA, East, Southern Africa,
 - Usually not free at sites in Asia
 - However tests may not be conducted at many visits even if free for patients

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IEDEA SITE SURVEY

RESULTS – V: LAB TESTING IN ADULTS

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| Sites | CBC | | LFT | | Creatinine | | Lactic acid | | Lipids | |
|----------|-----|----|-----|----|------------|----|-------------|----|--------|----|
| | BL | Sx | BL | Sx | BL | Sx | BL | Sx | BL | Sx |
| CCASA | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Asia | ✓ | ✗ | ✓ | ✗ | ✓ | ✗ | ✗ | ✓ | ✗ | ✓ |
| W Africa | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ |
| C Africa | ✗ | ✓ | ✗ | ✓ | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ |
| S Africa | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✓ | ✗ | ✓ |
| E Africa | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |

✓: ≥50% of sites ✗: <50% of sites

BL-ARV baseline, Sx-symptoms



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IEDEA SITE SURVEY RESULTS - VI

- Top 10 treatment-limiting AEs listed 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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EXISTING FRAMEWORKS FOR DEFINING AND GRADING ARV- RELATED ADVERSE EVENTS

- Identified based on
 - Initial expert consultations
 - Pilot site survey questionnaire on methods for reporting of AEs in RLS
 - Web searches
 - IeDEA site survey
- Information on existing definitions compiled for an initial list of major AEs in 13 domains

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Expert consultations included ACTG, ANRS, industry, WHO, TAHOD, HICDEP



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EXISTING FRAMEWORKS

| | |
|--|---|
| 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 |



CONCLUSIONS

- Data is available from clinical trials and cohorts on ARV-related AEs in various settings
- A common methodological framework is needed to harmonize definition and reporting of ARV-related AEs
- Normal laboratory reference ranges need to be established for each region to allow appropriate severity grading of toxicities
- Existing frameworks provide a useful basis for deriving standardized definitions for ARV-related AEs but require adaptation for this purpose to generate appropriate definitions applicable in a variety of settings

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ACKNOWLEDGEMENTS

- Forum for Collaborative HIV Research
 - Ben Cheng
 - Abigail Wilkes
 - Linda Onaga
 - Veronica Miller
- IeDEA Pharmacovigilance Working Group
- WHO/HIV

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