Overview of current knowledge of ARV-related adverse events and existing definitions

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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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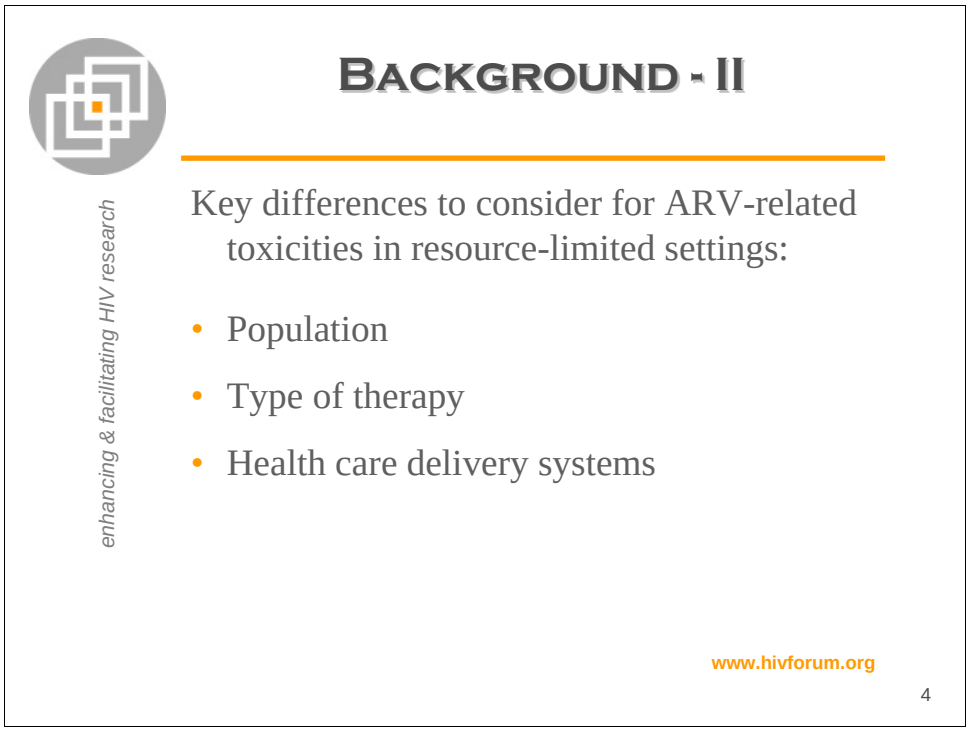
BACKGROUND - I

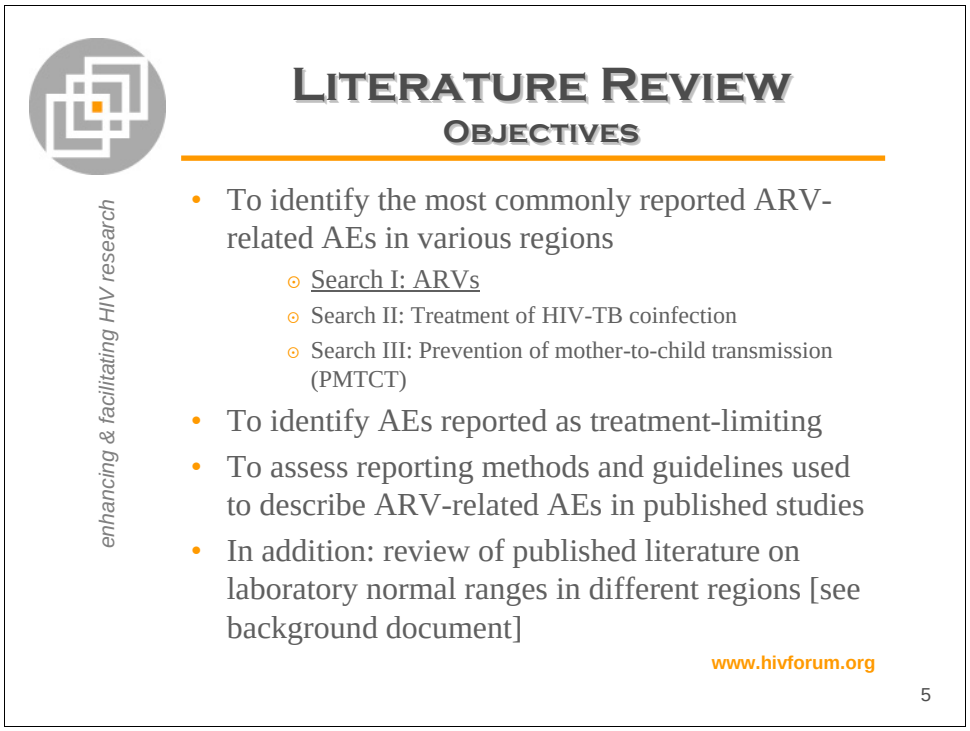
- Majority of existing data on ARV-related toxicities comes from resource-rich settings
- Public health approach to treatment now being implemented in resource-limited settings focused initially on access
- Information on ARV-related AEs is critical for the continued success of programs



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



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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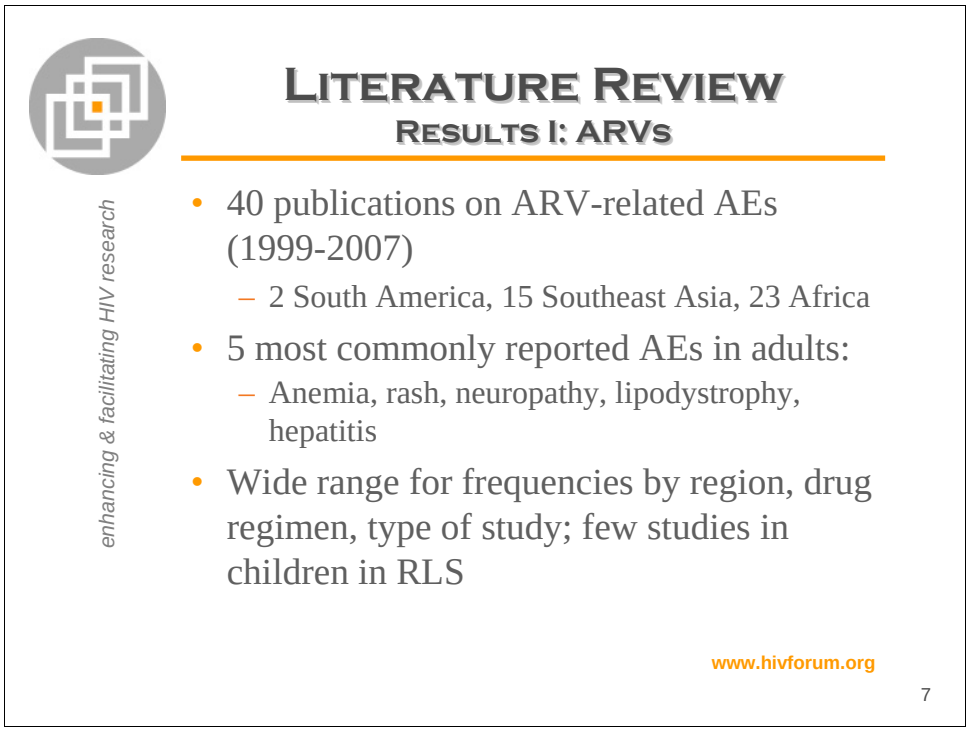
Literature Review

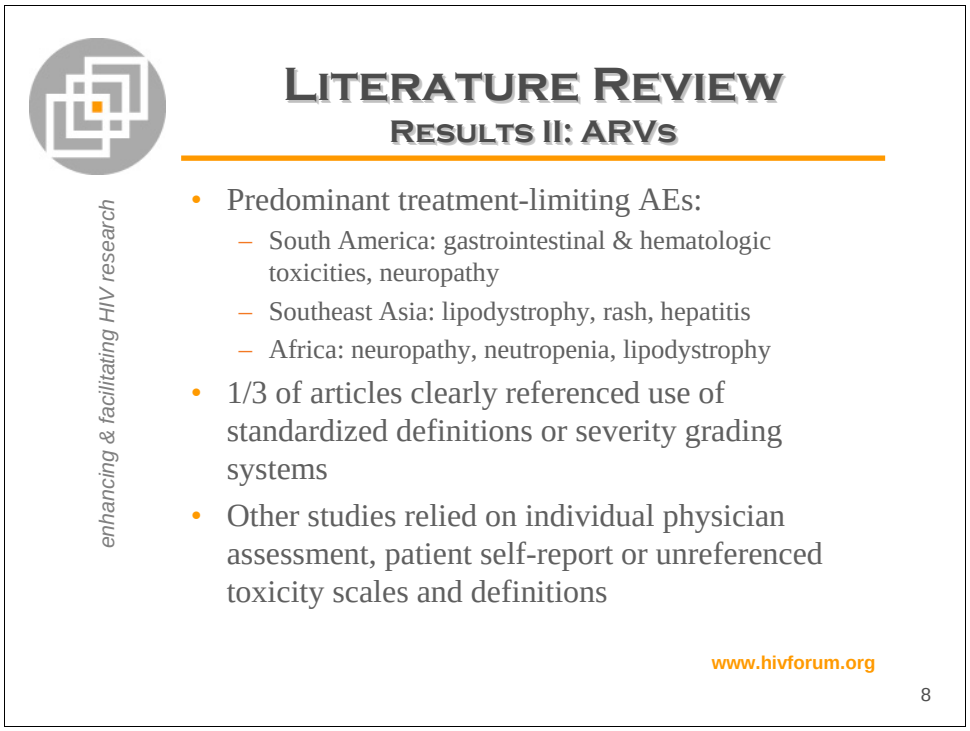
Methods

- 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



Few reports found from Eastern Europe, China

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



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

Forum-IeDEA Collaboration*

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- 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

IeDEA Site Survey

Objectives

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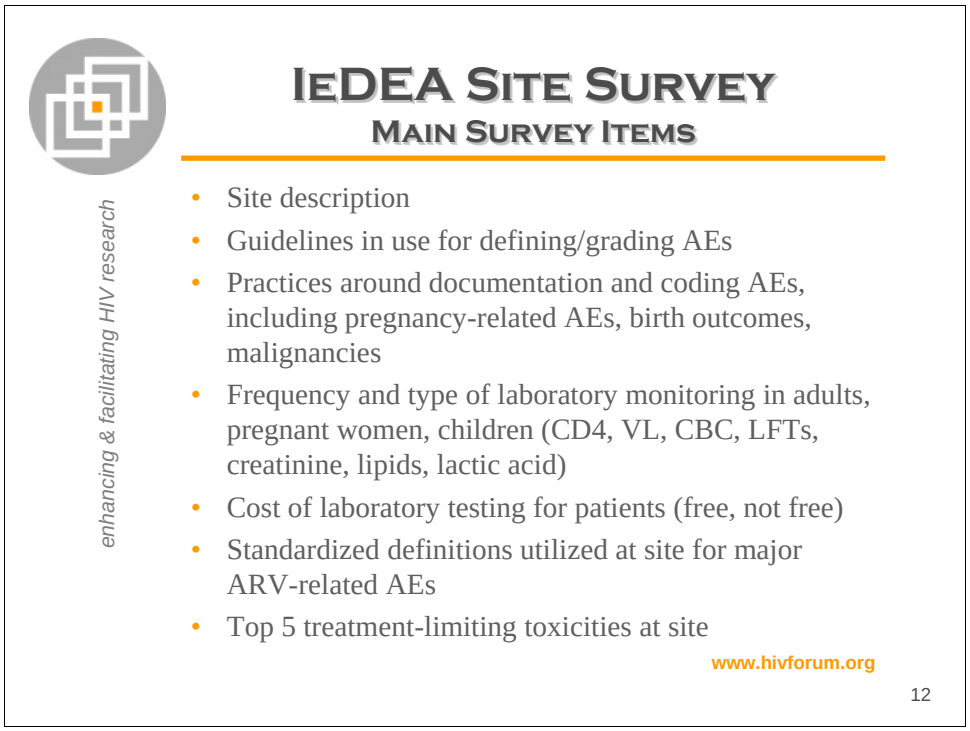
- To describe monitoring and reporting practices for ARV-related toxicities at various sites in the network
- To assess the use of standardized definitions for reporting of ARV-related AEs
- To determine which sites/regions have developed normative reference ranges for laboratory parameters based on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



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

IeDEA Site Survey

Results - I

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- 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

IeDEA Site Survey

Results - II

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- 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

IeDEA Site Survey
Results - III

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- 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

IeDEA Site Survey
Results - IV

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- 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

IeDEA Site Survey

Results – V: Lab testing in adults

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	CBC		LFT		Creatinine		Lactic acid		Lipids	
Sites	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

IeDEA Site Survey
Results - VI

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

Site Survey Feedback

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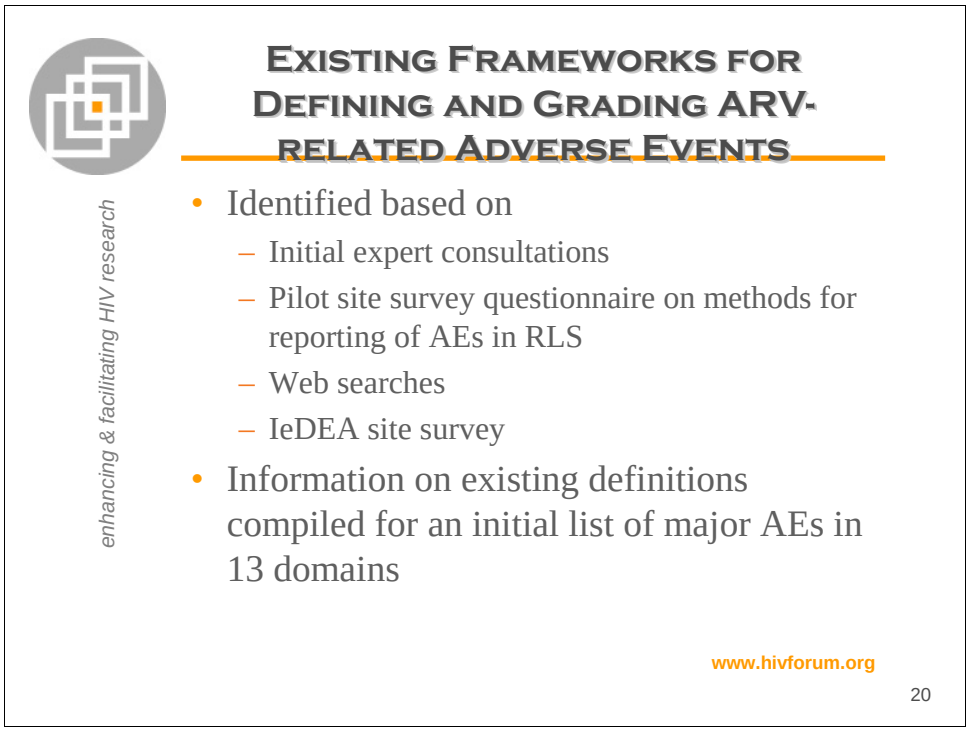
- From the pilot site survey:

"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



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

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Existing Frameworks

Classification and coding of terms	•MedDRA •WHO-ART •ICD-10
Definitions and coding, HIV clinical trials groups	•AACTG TOX-EG •PACTG Appendix 40 •ACTG Appendix 60
Definitions and coding, HIV cohorts	•TAHOD data specifications •HICDEP
Definitions, for pharmacovigilance	•CIOMS/ MSSO SMQs •CIOMS 1999
Severity grading and terminology criteria in different patient populations	•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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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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