Long-Term Monitoring of Treatment Related Adverse Events in the Resource Limited Setting

The Forum for Collaborative HIV Research
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www.hivforum.org

Forum for Collaborative HIV Research

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The Forum for Collaborative HIV Research is a public/private partnership including government agencies, industry, HIV researchers and clinicians, payors, foundations and the HIV patient advocacy community.

Our mission is to facilitate and enhance HIV research.

The Forum Executive Committee

- Government Agencies
  - US DHHS (NIH, CDC, FDA, HRSA), State Department (OGAC)
  - European Regulatory: EMEA
- Industries
  - Abbott, Bayer Diagnostic, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Monogram BioSciences, Roche Laboratories, Roche Molecular Systems, Pfizer, Schering-Plough, Tibotec, VIRxSYS
- Payors: Kaiser Permanente
- Academia
  - US and Europe
- Providers
- Patient Advocacy
  - US and Europe
- Foundations & Organizations (Gates, AmFAR, IAS)

Forum Projects on Treatment Associated Toxicities

- Lipodystrophy Roundtable Discussions (1998-2000)
  - www.hivforum.org – reports&publications/metabolic abnormalities
- Monitoring of long-term treatment associated toxicities Workshop I (April 2002)
  - AIDS 2003; 17:2407
- Assessing cardiovascular risk (May 2003)
  - www.hivforum.org – reports& publications/cardiovascular risk
- Regulatory issues in LD www.hivforum.org
- Long-term monitoring in resource limited settings (November 2005)

Project Planning Committee

Shabir Banoo	South African MCC/University of Witwatersrand
Ben Cheng	Forum for Collaborative HIV Research
David Cooper	NCHECR
Judith Currier	UCLA
Elly Katabira	Makerere University
Cissy Kityo	Joint Clinical Research Centre
Jens Lundgren	Copenhagen HIV Program/EuroSIDA
Veronica Miller	Forum for Collaborative HIV Research
David Pizzuti	Johnson & Johnson
Bill Powderly	Mater University Hospital
Ian Weller	Royal Free & University College Medical School

Roundtable Objectives

- Discuss rationale for monitoring of treatment associated toxicities in resource-limited settings
- Develop recommendations for the implementation of a monitoring plan

Agenda

13:00 – 13:15	Welcome and Introductions	Bill Powderly and Ben Cheng
13:15 – 13:30	Long-term monitoring of treatment related adverse events in adults	Elly Katibira
13:30 – 13:45	Regulatory considerations for long -term monitoring of treatment related adver se events	Shabir Banoo
13:45 – 14:45	Discussion	
14:45 – 15:00	Break	
15:00 – 15:15	Considerations for data collection	Veronica Miller
15:15 – 15:30	Use of Information Technology for Data Collection	Pamela Johnson
15:30 – 16:45	Discussion	
16:45 – 17:00	Wrap up and next steps	Bill Powderly and Ben Cheng

Agenda

- Welcome & Introductions
  - Ben Cheng & William Powderly
- Long Term Monitoring of Treatment Related Toxicities
  - Elly Katabira
- Regulatory Issues in South Africa
  - Shabir Banoo
- Discussion
- Novel Approaches for Monitoring
  - Pamela Johnson
- Considerations for Data Gathering
  - Veronica Miller
- Discussion & Wrap-Up
  - William Powderly

E Katabira

Region	On ART by June 05	% Coverage	On ART by Dec 04
Sub-Saharan Africa	500,000	11%	310,000
L. America + Caribbean	290,000	62%	275,000
E, S, SE Asia	155,000	14%	100,000
Europe + C. Asia	20,000	13%	15,000
N. Africa + M. East	4,000	5%	4,000

The scope of adverse events in RLS

- The burden of long -term adverse events in RLS is not well known
  - Not long enough experience with ART
- Commonly encountered events include:
  - Hematological disorders
  - Liver toxicity
  - Metabolic toxicity
  - Neurological complications
    - CNS and peripheral nerve toxicities

The Implications of adverse events

- Majority of patients initiated on ART are too sick
  - In 3315 DART pts, b/l median CD4+ 100
- Differentiating signs and symptoms due to HIV disease and drug toxicity may be difficult
  - Worse in less experienced health worker
- Delay in diagnosis and management of the toxicities

The Implications of adverse events

- Erosion of patient's confidence in ART
  - Due to real and assumed toxicity
- Decrease in patient adherence and development of resistance
  - Subsequently leading to treatment failure
- Negative impact on national programs
  - PMTCT – Nevirapine
  - ART scaling up programs
    - Resistance makes the programs too expensive

The challenges of monitoring adverse events in RLS

- Inadequate infrastructures
  - Laboratories poorly equipped + limited reagents
  - Referral services too few and too far
- Lack of trained personnel
  - To diagnose and investigate the adverse events
- Quality of services variable within and across countries
  - Implications on data sharing

The challenges of monitoring adverse events in RLS

- Variable health information systems
  - Electronic vs. manual data capture
  - Quality of data collected equally variable from unit to unit and country to country
- Difficulties of communication
  - Variable or non existence IT facilities and training
- Unwillingness to share information
  - Issues of data ownership

Conclusion

- As the ART access is rapidly scaled up:
  - There is urgent need to map out the burden of adverse events in the RLS
  - To monitor them
  - To share the results
  - To plan interventions jointly in order to minimize their negative impact on ART programs in RLS.

S Banoo

Long-Term Monitoring of ARV Treatment Related Adverse Events

Pharmacovigilance and Regulatory Considerations in the South African Programme

Meeting on Long -Term Monitoring of Treatment Related Adverse Events in Resource Limited Settings
Dublin, 13 th November 2005

Objectives

- To determine the burden of drug -related morbidity and mortality in patient with HIV/AIDS, particularly associated with ARV use.
- To identify and develop measures to minimize drug -related morbidity and mortality in patients with HIV/AIDS
- To provide information support to health personnel and patients on the safe use of antiretrovirals.
- To identify, assess and communicate any new safety concerns associated with the use of antiretrovirals.
- To support regulatory and public health decision -making through an efficient, national post -marketing surveillance system, monitoring the benefits and risk of harm associated with ARV's in particular but also of other drugs currently used in the health sector.
- To minimize the negative impact of misleading information or unproven associations between adverse events and ARV therapy.

Programme Activities

1. Enhanced national spontaneous reporting system with active feedback to decision -makers, prescribers , reporters, patients and the public.

2. Development of a sustainable, functional, user -friendly database to support the spontaneous reporting system.

3. Develop regulatory procedures to support the defined objectives

4. Provision of unbiased, evidence -based information on the safety profile of ARV's, the safe and effective use of ARV's and the management of potential complications.

5. To introduce targeted sentinel surveillance systems to evaluate signals of safety issues of potential public health importance (e.g. high risk groups such as pregnant women, infants, HIV -TB co - morbidity).

6. Develop novel pharmacovigilance methods to complement and support spontaneous reporting and sentinel surveillance systems.

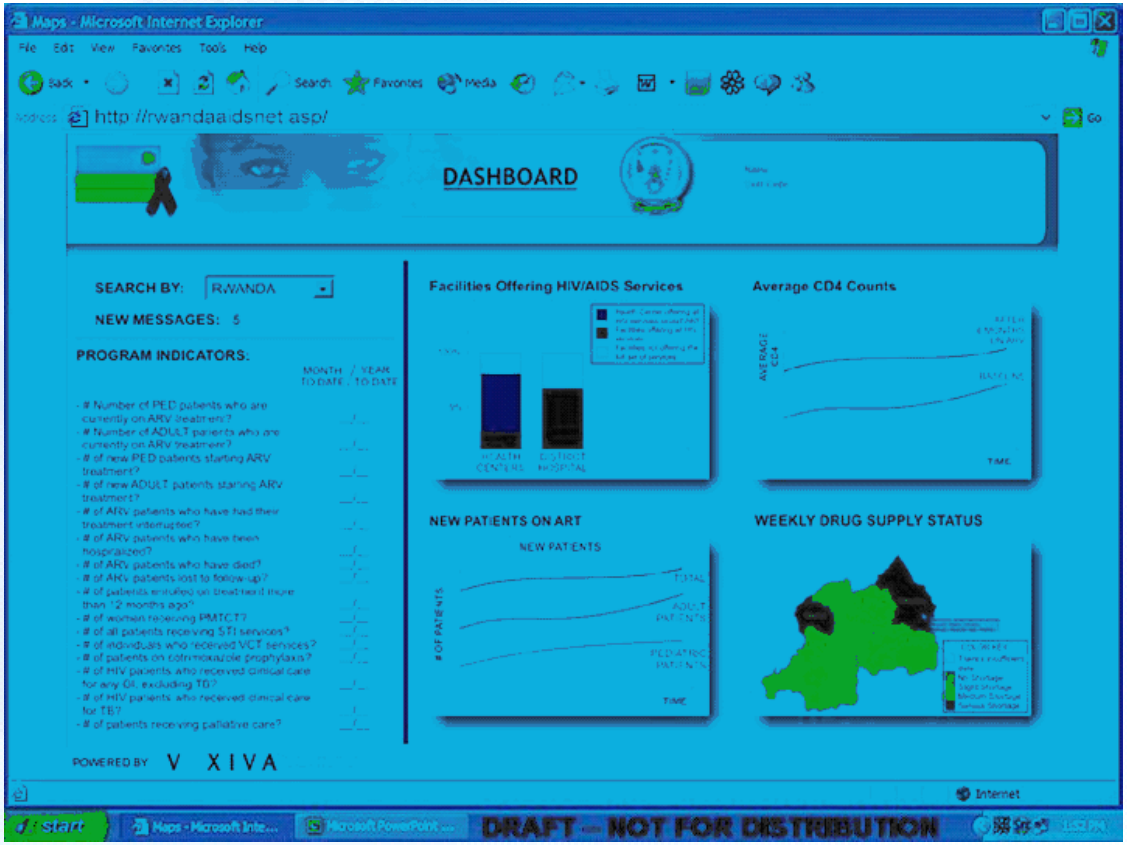
7. Develop key indicators for estimating the prevalence of drug -related morbidity and mortality.

Challenges

- How to integrate with ARV roll -out?
- Who are the partners likely to effectively support this process?
- Timing and prioritizing
- What is our role in actual training?
- Lessons learnt from other programmes (e.g. vaccines and malaria)
- Identifying critical success factors
- Relationship of programme versus regulatory pharmacovigilance activities
- Adequate resources and planning
- Collaboration and critical partnerships

Introduction

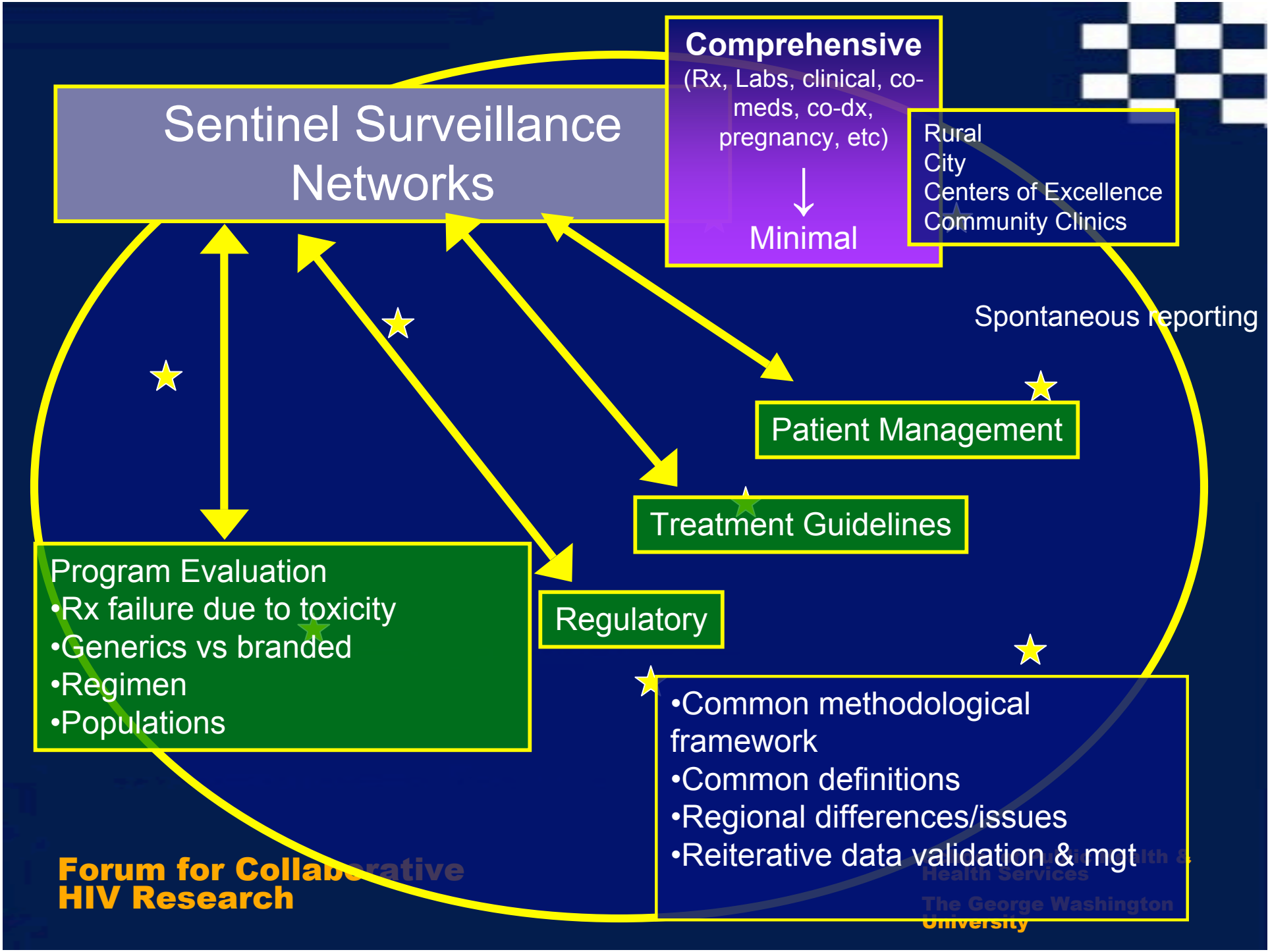
Rwanda: Monitoring the National ARV Program



- All ARV Sites
- Program Indicators
- Patient lab results, drug regimens
- Stock levels

Issue

- Major roll-out programs in progress without attention to monitoring of treatment toxicities


Sentinel Surveillance Networks
Comprehensive
(Rx, Labs, clinical, co-meds, co-dx, pregnancy, etc)
Minimal
Rural
City
Centers of Excellence
Community Clinics
Spontaneous reporting
Patient Management
Treatment Guidelines
Program Evaluation
•Rx failure due to toxicity
•Generics vs branded
•Regimen
•Populations
Regulatory
•Common methodological framework
•Common definitions
•Regional differences/issues
•Reiterative data validation & mgt
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Data collection basics

- Make use of various traditional & IT formats:
  - Cell & land-line phones, computers, paper
  - Clinician (nurse, physician) based reporting, patient based reporting
- Collection of data:
  - Expected toxicities relatively well known
    - Distribution & prevalence in populations with co-infections, presenting with advanced disease, nutritional status, traditional and complementary medicines, etc
  - Prioritize collection of data in pediatrics
    - Minimal experience available from developed world
  - Prioritize collection of data on life-threatening & treatment threatening toxicities

Approaches

- Work with existing programs, observational databases and cohorts
- Establish working group to develop a common framework:
  - Map existing data collection sites; identify gaps
  - Common definition & collection formats
  - Data validation, management & handling
- Define role of stakeholders:
  - Bilateral & multilateral treatment programs
  - Local government and regulatory agencies
  - Innovator & generic drug companies
- EARLY BUY-IN

Monitoring of Treatment Associated Toxicities -- Summary

- Role in development, review and revision of treatment guidelines
  - Regional factors
- Role in program evaluation
- Feedback to clinicians & patients
- Regulatory considerations

Monitoring of Treatment Associated Toxicities -- Summary 2

- Spontaneous reporting will generate some signal detection but not suitable for monitoring
- Regional sentinel sites
  - established reporting protocols
  - harmonization of protocols
  - representative of diverse treatment modalities
    - FDC's, diverse generics, centers-of-excellence, community health clinics
- Training & education of clinicians and patients