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

A Project of the Forum for Collaborative HIV Research

September 25, 2006

Forum for Collaborative HIV Research

School of Public Health & Health Services

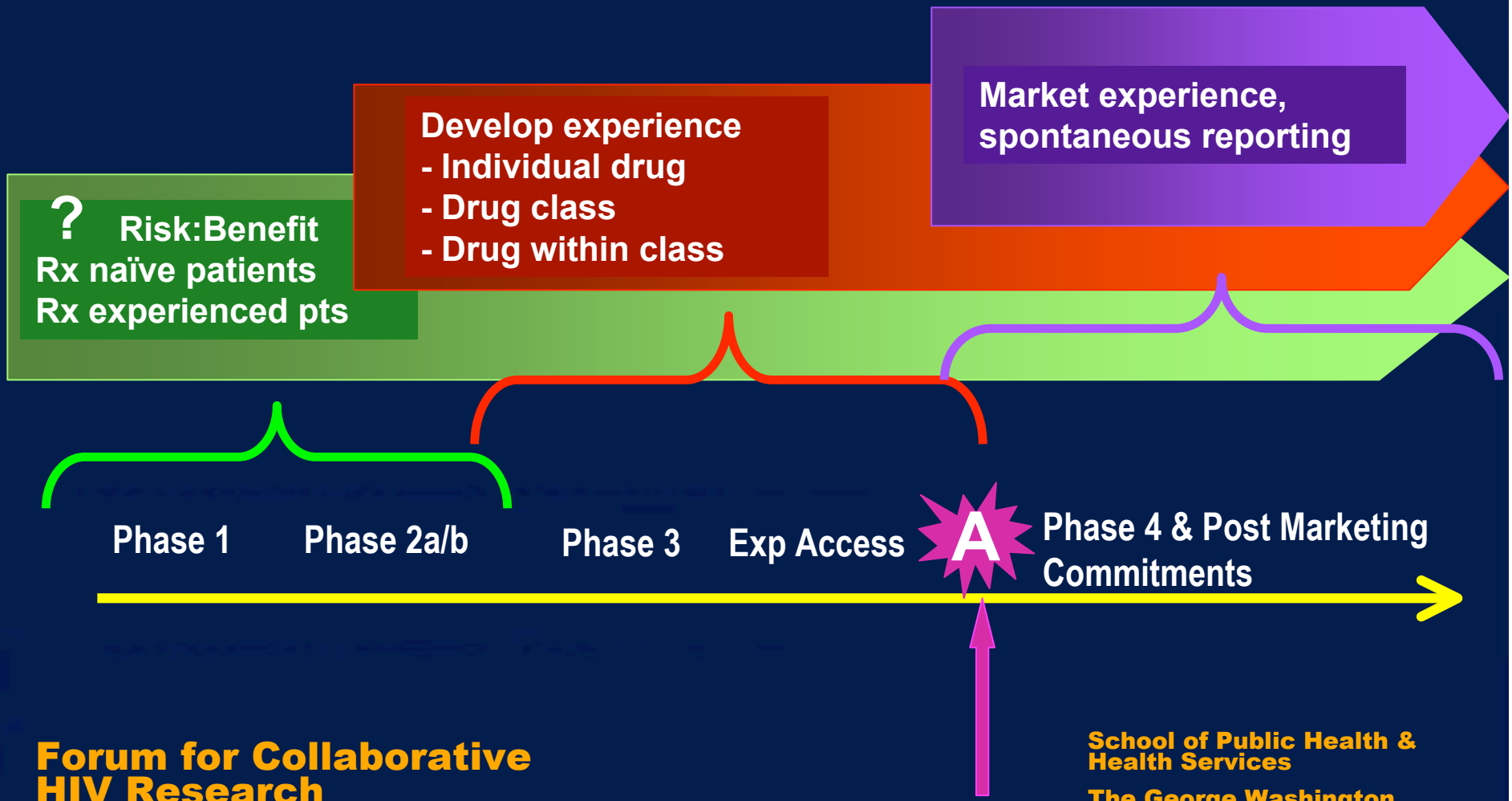
The George Washington University

Why is monitoring of toxicities needed in resource constrained 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

Drug Development Timeline



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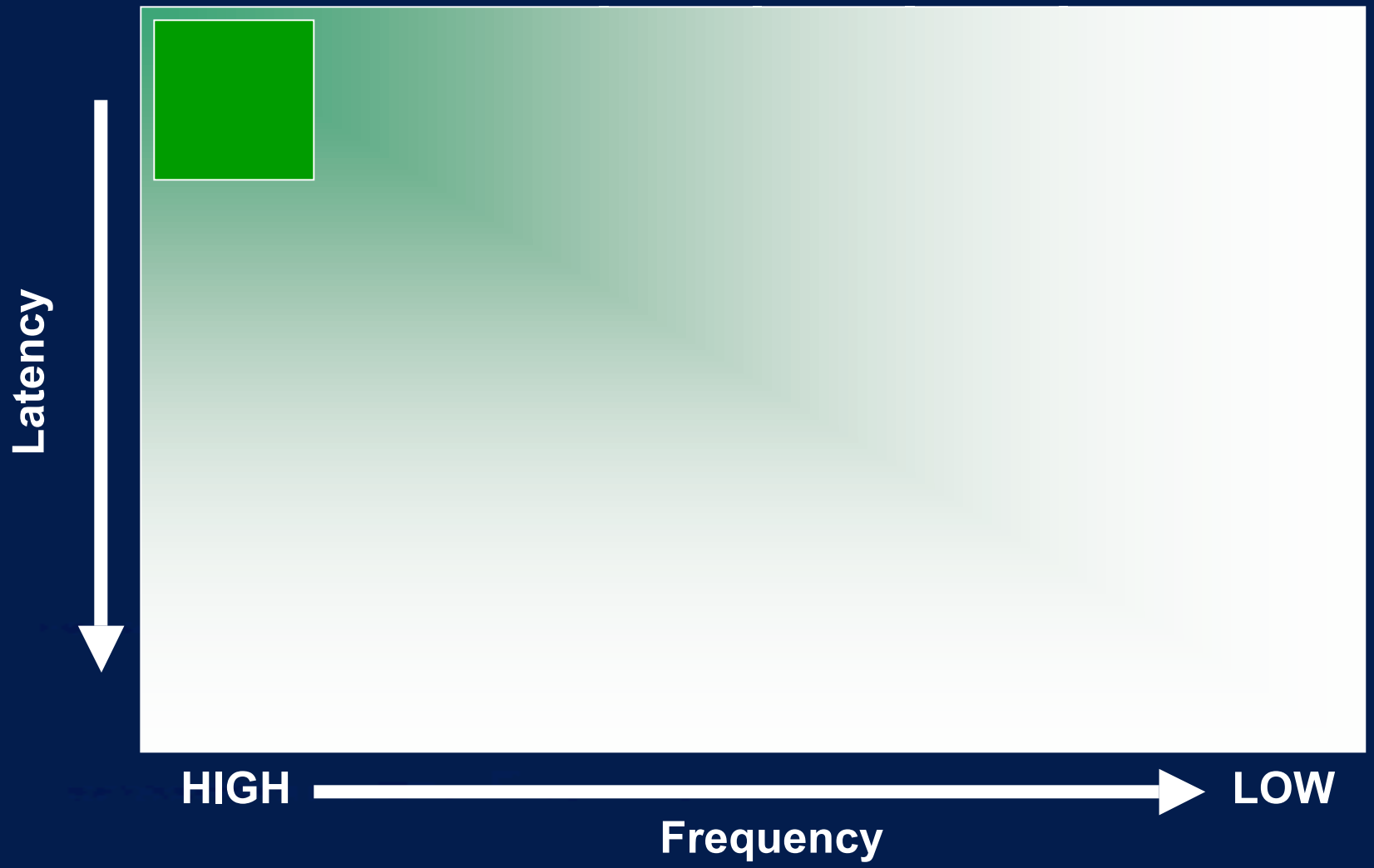
Adverse Event Field

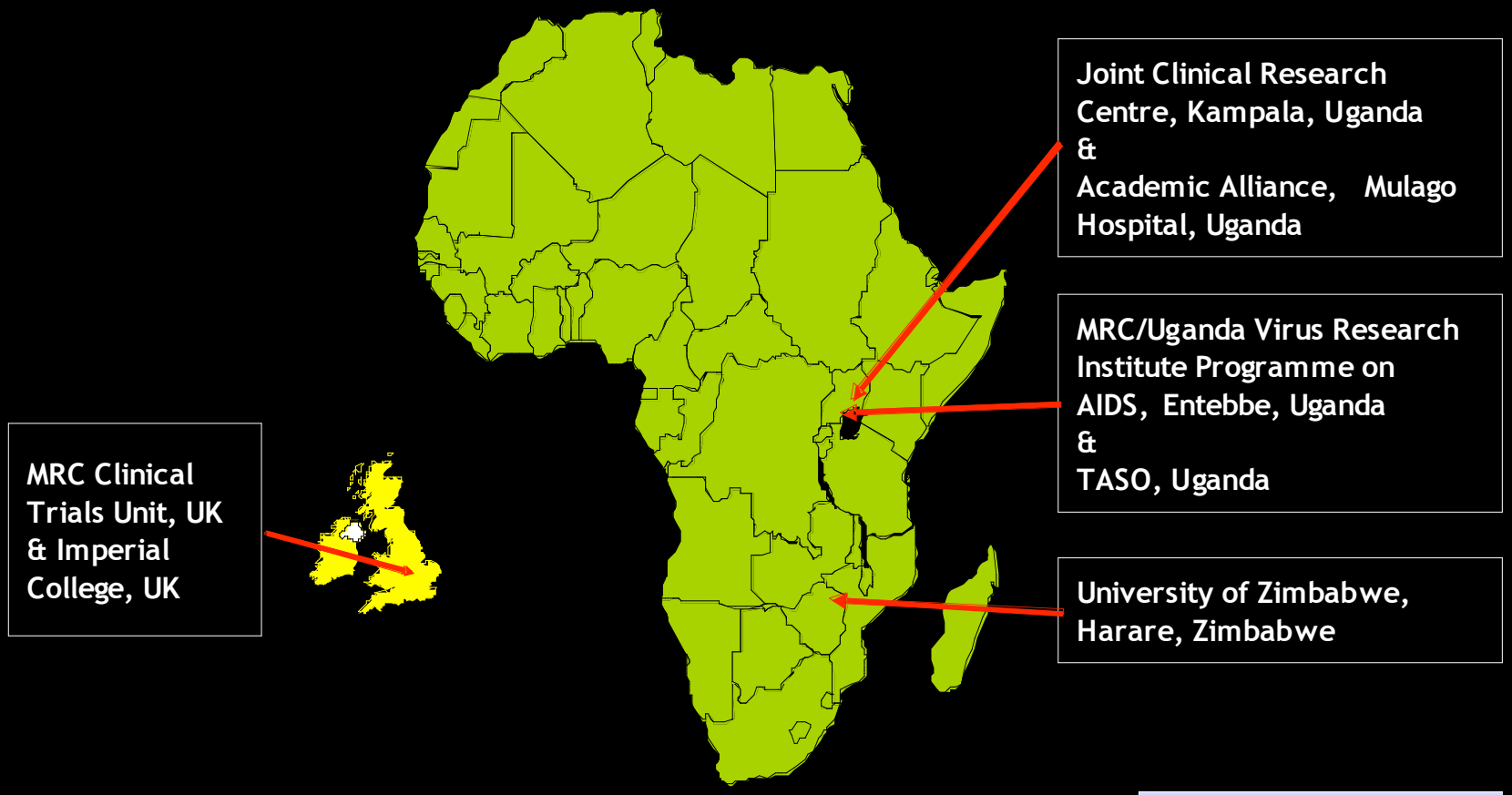
Adapted from Evans and Waller, MCA 2002



Pharmacoviligance

- Randomized clinical trials
- Cohort studies and observational databases
- Spontaneous reporting

Development of AntiRetroviral Therapy In Africa: DART



Rockefeller Foundation

MRC, UK

DFID, UK

GlaxoSmithKline
Gilead
Boehringer -Ingelheim

Issue

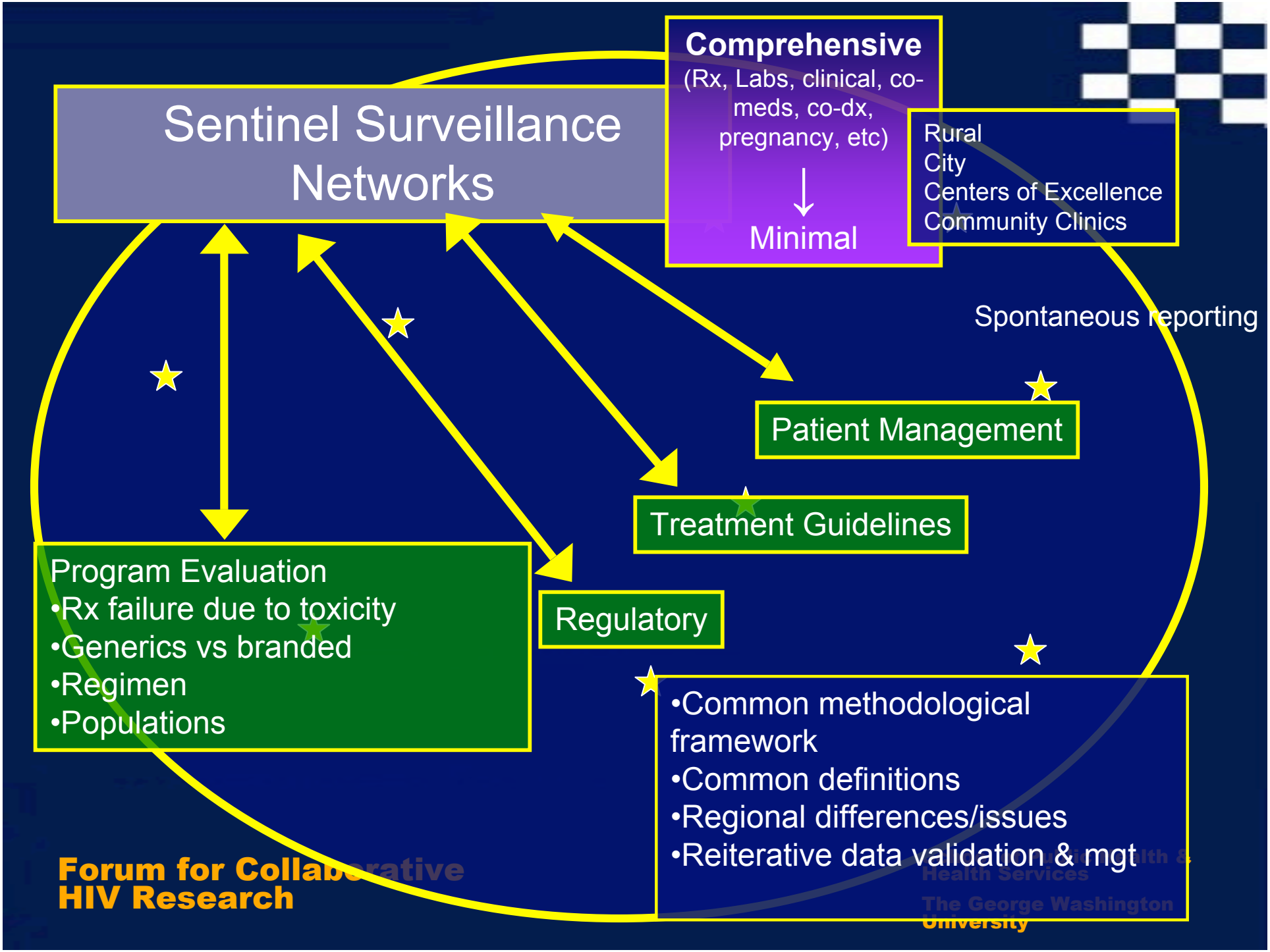
- Pharmacovigilance activities low priority
  - WHO, regional, country levels
- Major antiretroviral treatment roll-out programs in progress without attention to monitoring of treatment toxicities

Forum Rountable #1, November 2005 (Dublin)

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

Monitoring of Treatment Associated Toxicities

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


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

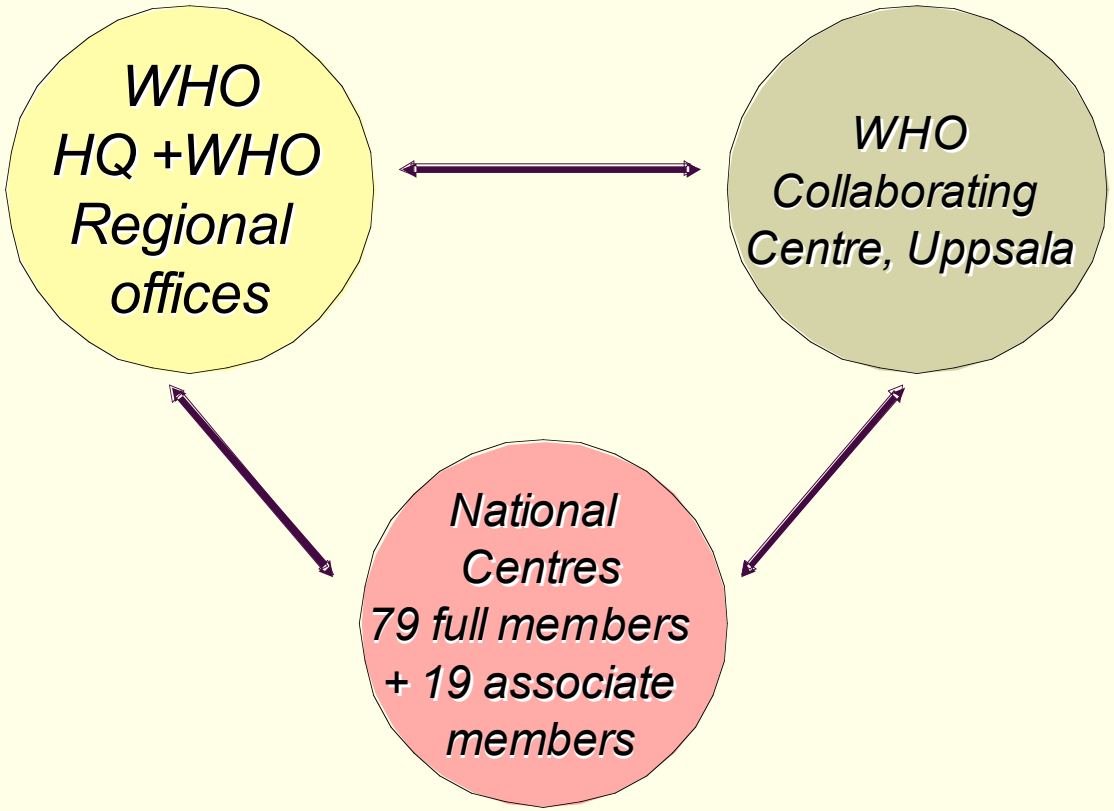
Roundtable #2: Sentinel Surveillance Working Group (Madrid, March 2006)

- Map current surveillance activities
- Develop a basic plan for a common framework
- Participants:
  - WHO (HIV, Pharmacovigilance)
  - In country pharmacovigilance programs
  - Industry
  - Cohort studies (including pediatric cohorts)
  - PEPFAR, NIH, CDC
  - Large clinical trials (DART)

WHO – commitment to pharmacovigilance for ARVs

- Adverse reactions
- Lack of effect
  - counterfeiting
  - resistance
  - interaction
- Quality problem http://mednet3.who.int/prequal/
- Dependence and abuse
- Proposed specific phase IV studies to address toxicities, for example hypersensitivity, nephrotoxicity, bone toxicity, etc

WHO Programme for International Drug Monitoring



Challenges for PV in Resource Constrained Setting

- a scarcity of physicians, with many clinical tasks being undertaken by other cadres of health workers
- rapid implementation of a complex health intervention on an unprecedented scale
- weak management and clinical oversight
- protocolised treatment regimens with limited access to diagnostic and laboratory technologies
- a scarcity or absence of electronic patient information systems
- difficulties in ascertainment and accurate recording of adverse events

Challenges in RLS

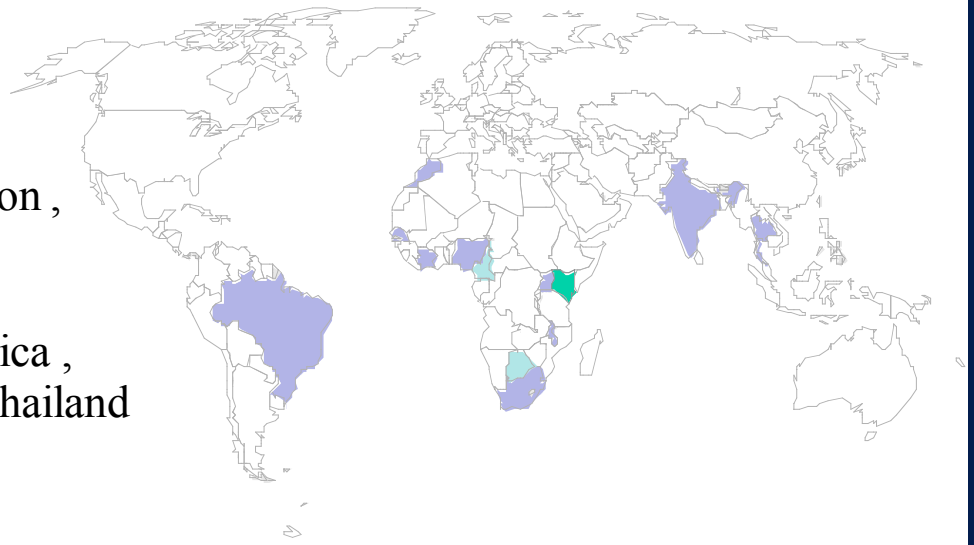
- Absence of funding for data enhancement activities
- High loss to follow up in cohort studies in absence of national registration systems and national unique identifiers
- Requires investment in patient tracing
  - Will be restricted by resources – consider sentinel system

Challenges in patient follow-up

- Inherent problem of scale up programs:
  - Patients initiate treatment at central site, then referred to other centers for continuing care

Results from 1st data merger (1996-2003)

- 8734 patients
- 23 centres
- 16 countries
  - Botswana, Burundi, Cameroon, DRC, Côte d'Ivoire, Kenya, Malawi, Morocco, Nigeria, Rwanda, Senegal, South Africa, Uganda, Brazil, India, and Thailand

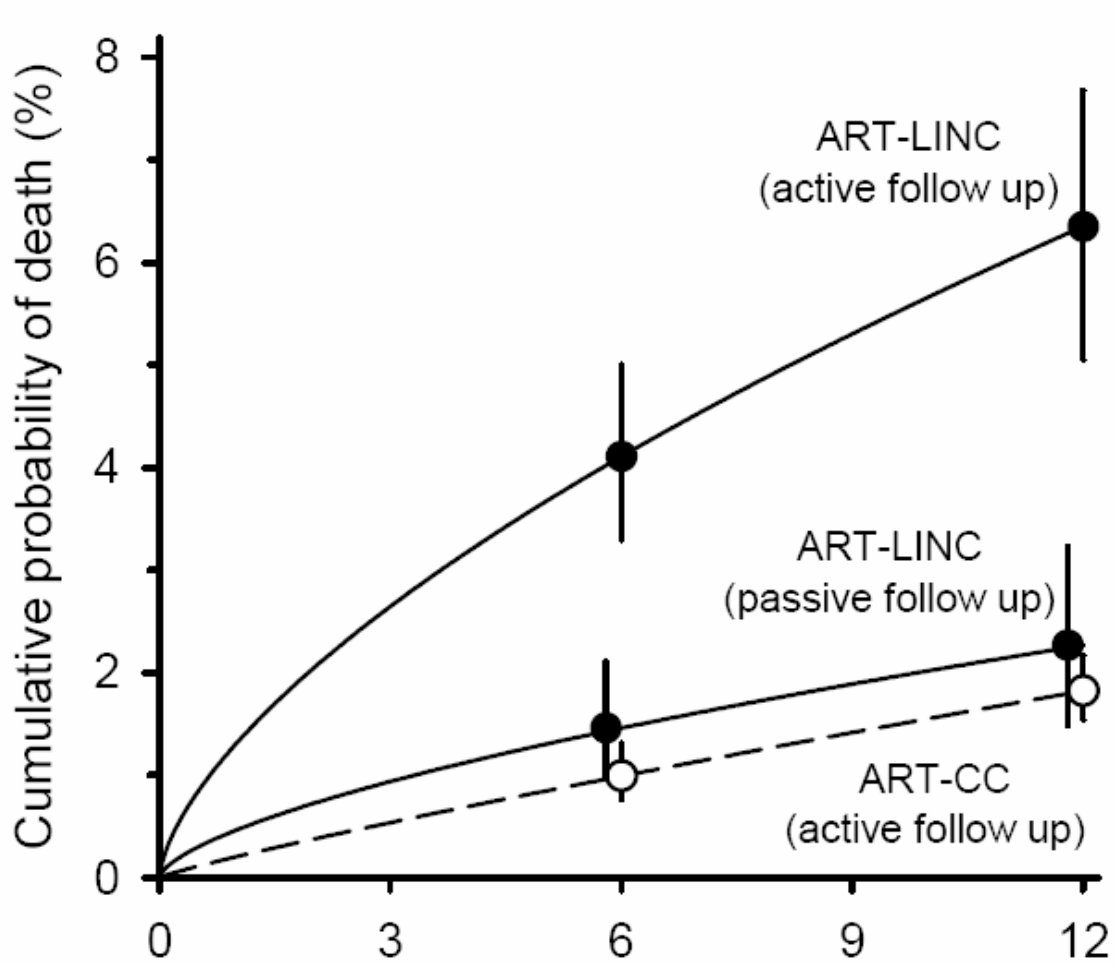


- Characteristics of centres
  - 9 public, 4 private for-profit, 10 private not-for-profit (NGO)
  - 18 provided VCT
  - 15 provided PMTCT
  - 13 had specialised TB clinic

ART-LINC Collaboration

ART-LINC Collaboration *Int J Epidemiol* 34:979-986; 2005

Cumulative mortality in first year



ART-LINC Collaboration

Losses to Follow-up (LTFU)

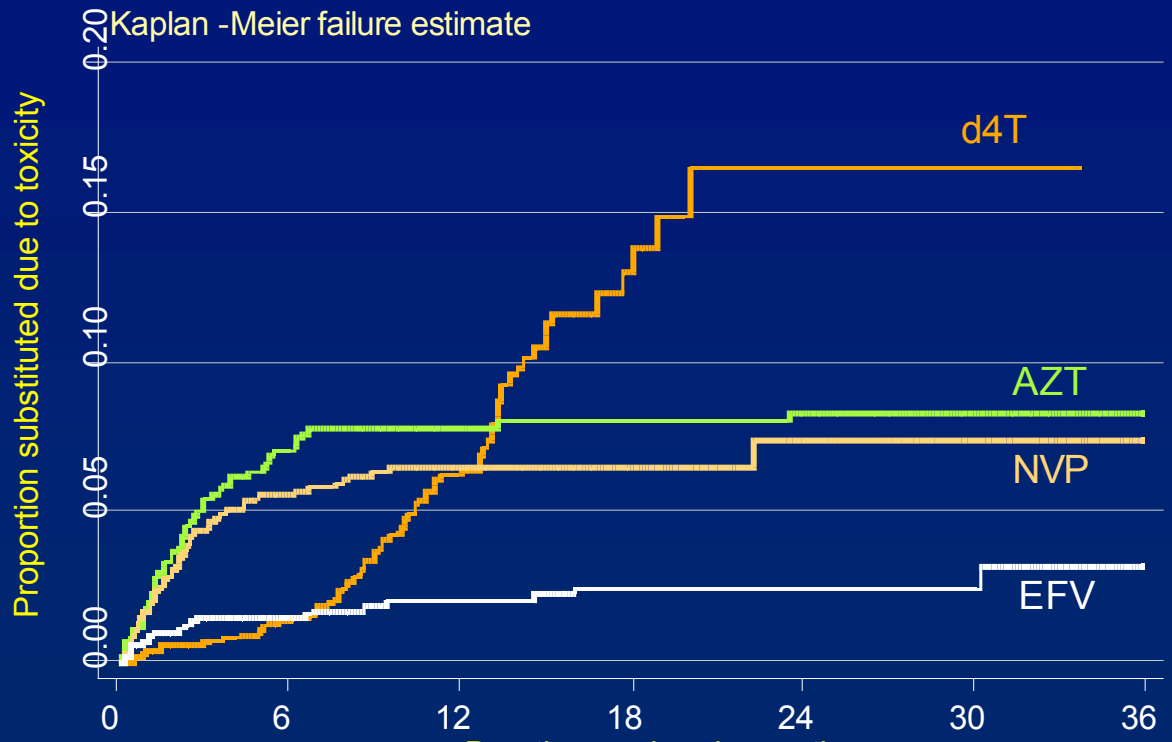
- 727 (15%) patients LTFU in ART -LINC (range 0 -44%)
- ART-LINC centres with active follow -up:
  - LTFU: 12%
  - Median baseline of LTFU: 115 cells/ μL vs. 123 cells/ μL in those followed
- ART-LINC centres with passive follow -up:
  - LTFU: 19%
  - Median baseline of LTFU: 64 cells/ μL vs. 123 cells/ μL in those followed

ART-LINC Collaboration

Proposed data collection approach

- Use treatment limiting toxicity
  - Document each treatment switch

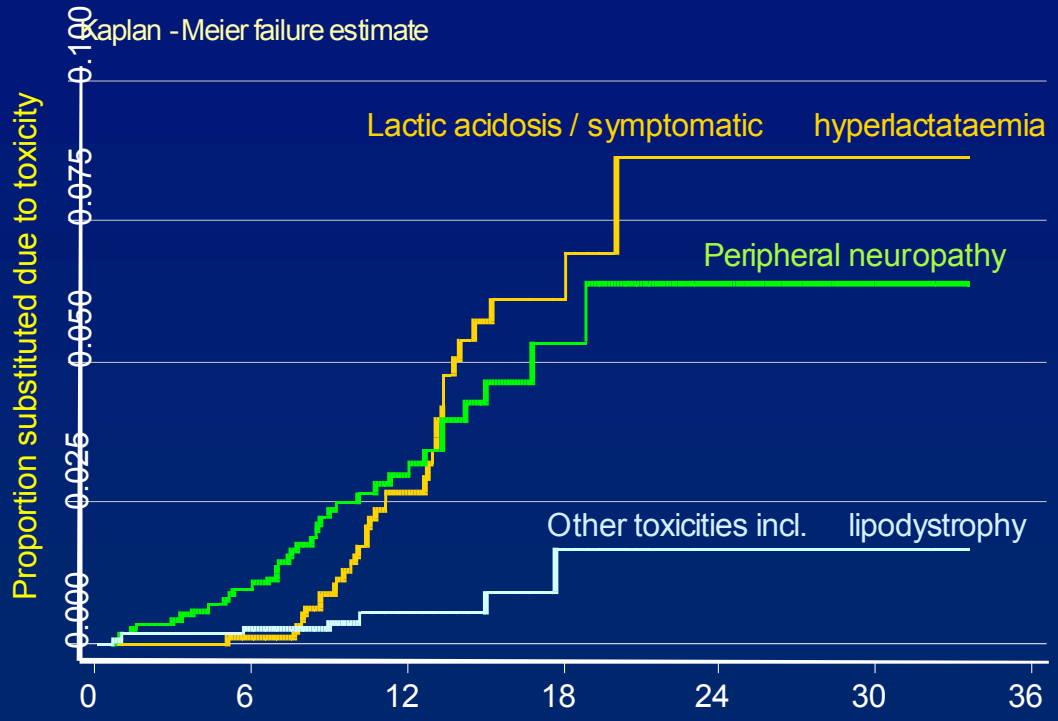
Cohort example - Substitutions due to toxicity by drug



	n							Changed by 36 months (%, 95% CI)
d4T	1228	1065	471	113	18	9	5	16.5 (12.0 -22.6)
AZT	639	497	442	417	306	205	132	8.3 (6.3 -10.9)
NVP	977	828	385	129	104	89	63	7.4 (5.4 -10.1)
EFV	967	790	558	423	245	139	81	3.1 (1.8 -5.5)

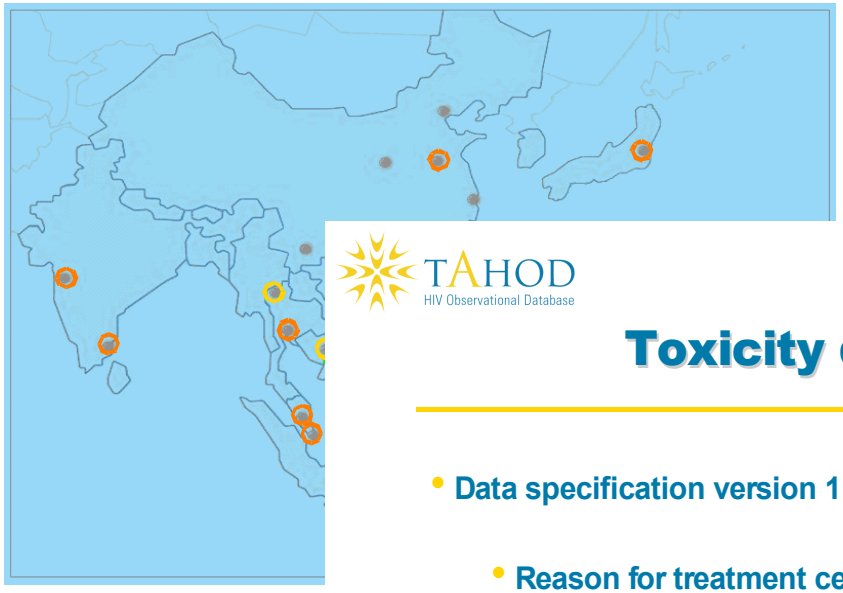
A Boule, W Cape Prov

Cohort example - Causes of toxicity -driven substitutions in patients on stavudine



Reason for subst.	n							Changed by 36mo (%, 95% CI)
Hyperlactataemia /LA	1228	1074	484	118	20	11	6	8.7 (5.3 -14.0)
Peripheral Neuropathy	1228	1068	486	120	19	9	5	6.4 (4.0 -10.2)
Other	1228	1073	495	123	21	11	6	1.7 (0.6 -4.6)
Combined	1228	1065	471	113	18	9	5	16.5 (12.0 -22.6)

TAHOD
HIV Observational Database



March 2006

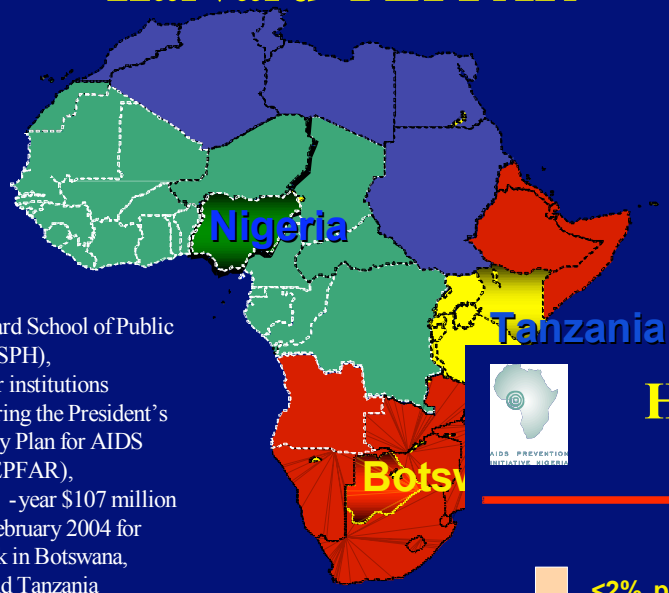
TAHOD
HIV Observational Database

Toxicity data collection

- Data specification version 1
  - Reason for treatment cessation
  - Laboratory tests
    - Haemoglobin, ALT
- Data specification version 2 (beginning March 2006)
  - Grade 3 -4 clinical adverse events
    - AACTG criteria
  - Additional laboratory tests
    - When collected according to local site practice

Therapeutics Research • Education • AIDS Training
TREATASIA

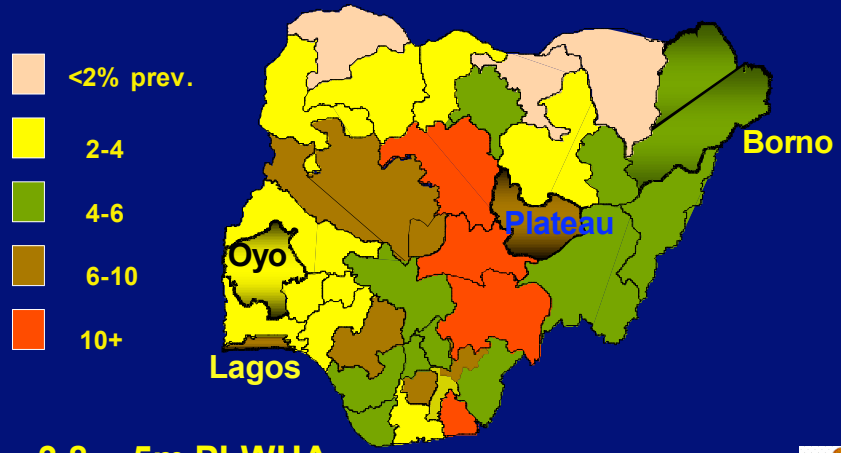
Harvard PEPFAR



The Harvard School of Public Health (HSPH), one of four institutions administering the President's Emergency Plan for AIDS Relief (PEPFAR), won a five -year $107 million grant in February 2004 for relief work in Botswana, Nigeria and Tanzania

Harvard PEPFAR Nigeria

Target states



3.8 – 5m PLWHA

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Harvard PEPFAR Nigeria

Patient monitoring

Evaluation	Pre-Entry	Entry	3	6	9	12	18	24	Every 6 mo.
Informed Consent		X							
Documentation of HIV-1/HIV-2	X								
Medical/Medication History		X		X		X		X		X
Complete Physical Exam	X	X		X		X		X	X	X
Pulmonary radiograph Referral for TB tx		X							
OI dx and tx		X				X			X	
Hematology		X	X	X		X		X	X	X
Blood Chemistries		X	X	X		X		X	X	X
Hepatic enzymes and bilirubin		X	X	X		X		X	X	X
CD4+ cell count		X	X	X		X		X	X	X

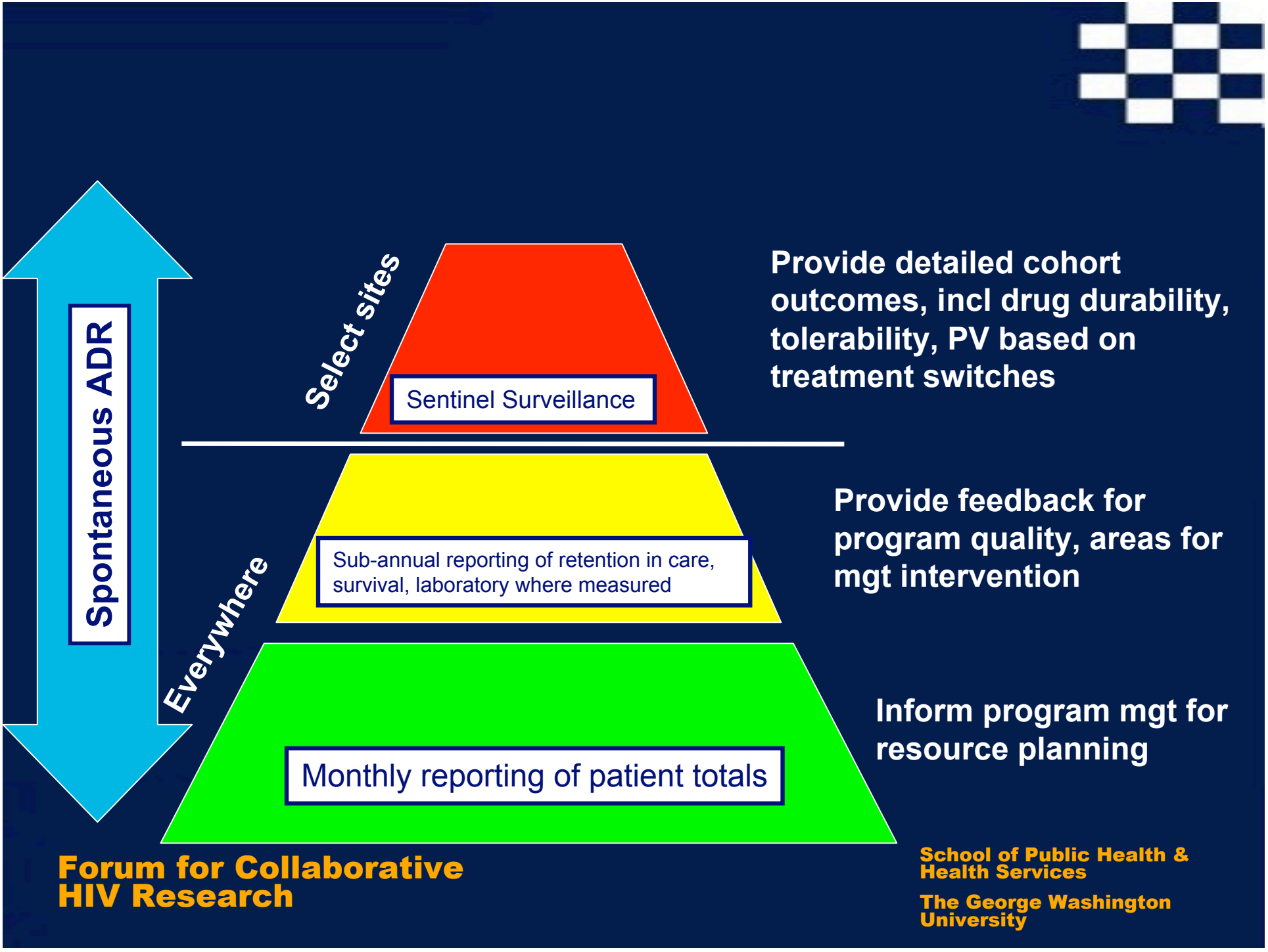
Harvard PEPFAR Nigeria

Monitoring & Evaluation

- **Toxicity, Efficacy and deaths reporting in real time to country coordinator**
- **Weekly submission of all electronic records and weekly summary to country coordinator**
- **Submission of country summary to Boston biweekly.**
- **Covers all parameters of PEPFAR monthly report**

Framework

- Stratified approach is the only option
- Primary goal of programs is to establish basic minimum (survival & retention)
- Electronic systems (often with academic partners)
  - Quality is an issue
  - Validation is not resourced
- Sentinel sites with extra resourced invested to ensure long term cohort data


Spontaneous ADR
Select sites
Sentinel Surveillance
Provide detailed cohort outcomes, incl drug durability, tolerability, PV based on treatment switches
Everywhere
Sub-annual reporting of retention in care, survival, laboratory where measured
Provide feedback for program quality, areas for mgt intervention
Monthly reporting of patient totals
Inform program mgt for resource planning
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Next steps

- Comparison and standardization of data collection
- Mapping of populations
- Developing a common framework
  - Within programs
    - E.g. PEPFAR
    - E.g. IDEA

Special Acknowledgments

- All participants of surveillance working group!
  - (www.hivforum.org)
- Bill Powderly, Ben Cheng (RT#1)
- Boulle A, Couper M, Dodoo A, Lapierre D, Lundgren J, Reiss P, Sevene E, Vitoria M, Weller I (RT#2)