WHO HIV Drug Resistance Strategy

Boston, 27 February 2011

Background

Global ART scale-up has been a remarkable achievement benefiting over 5.2 million individuals in resource limited settings

Maintaining this achievement requires a comprehensive approach to assess emergence and transmission of HIVDR at population level

WHO has developed and implemented a population based strategy for surveillance of HIVDR

Goal of the WHO HIVDR Surveillance Strategy

Promote the long-term effectiveness of available regimens, improve quality of care, and optimize program efficiency

Using standardized methods

- Inform population-based selection of first- and second-line ART regimens
- Support national programs in minimizing the emergence and transmission of HIVDR

Gilks et al. Lancet, 2006

Elements of the HIV Drug Resistance Strategy

A. Monitor HIVDR "Early Warning Indicators" from ART clinics (adult and paediatric versions)

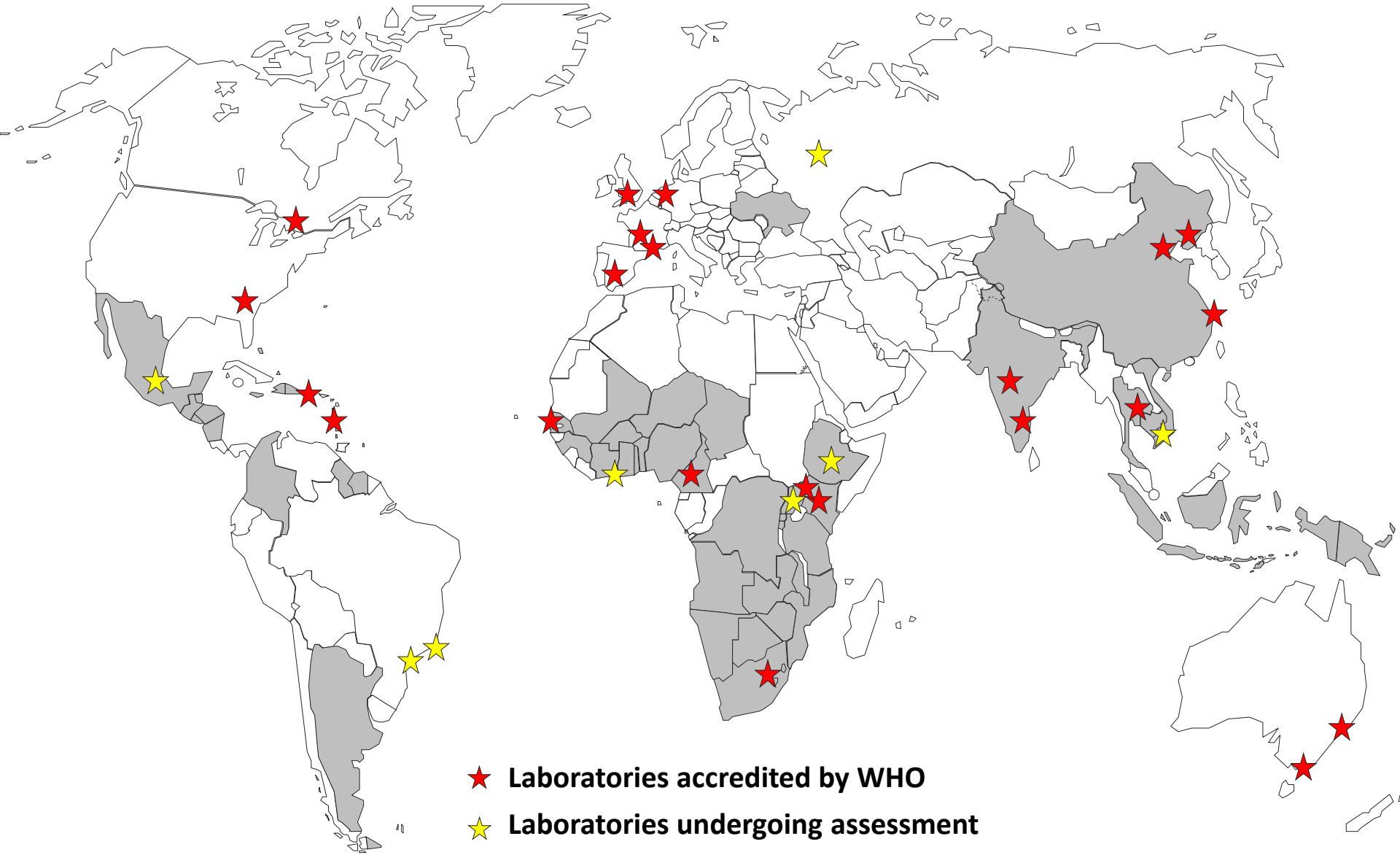
B. Surveys to assess acquired HIVDR (adult and paediatric versions)

C. Surveillance of HIVDR transmission

D. Surveillance of HIVDR in children < 18 months

E. Development of a network of accredited genotyping laboratories

Countries Implementing One or More WHO HIVDR Surveys (Feb 2011)



Early Warning Indicators (EWI)

What are EWI?

- EWI assess factors at individual clinics which are known to create situations favourable to the development of HIVDR
- HIVDR EWIs exist for adults and children
- Unlike many program indicators, WHO HIVDR EWIs provide clinic specific information which empower clinics and programmes to take action to optimize population based care to minimize situations which favour the development of HIVDR leading to optimization of patient care

Bennett DE et al., Antivir Ther 2008

High-priority element

Early Warning Indicators (EWI)

How EWI are monitored?

- From all ART sites, or large number of representative sites
- Generally, data abstraction is performed annually by teams lead by Ministries of Health
- EWI are reported on a site-by-site basis
- Results are returned to sites, best practices are identified and lessons applied to all sites
- The spirit is never to be punitive; rather to identify and support best programmatic practices

Bennett DE et al., Antivir Ther 2008

WHO-recommended HIVDR EWIs

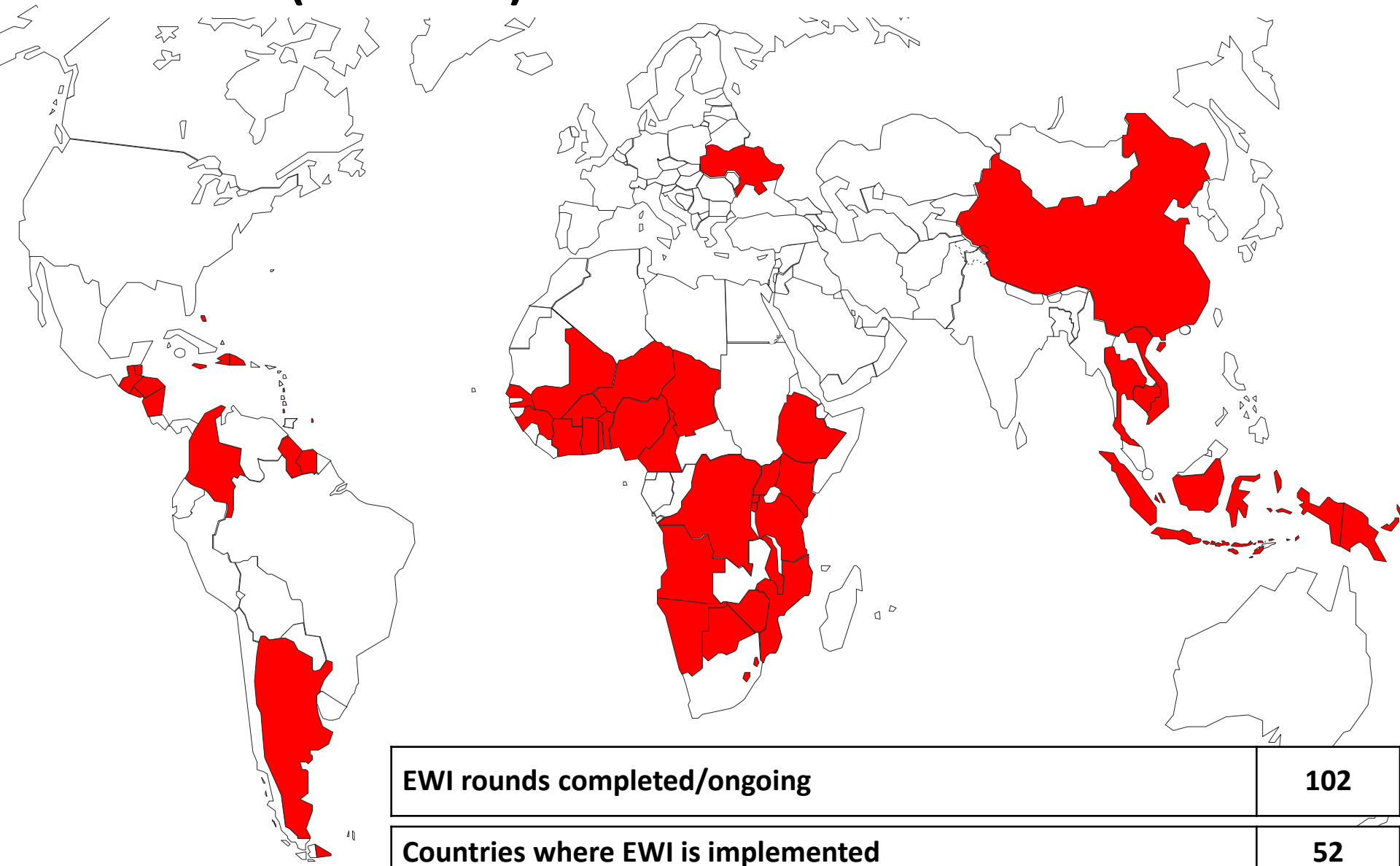
EWI	EWI Target
Prescribing practices	100%
Lost to follow-up at 12 months	≤ 20%
Retention on first-line ART at 12 months	≥ 70%
On-time drug pick up	≥ 90%
On-time appointment keeping	≥ 80%
Drug supply continuity	100%
Viral load <1000 copies/ml at 12 months	≥ 70%

Bennett DE et al., Antivir Ther 2008

Example of EWI Site-based Report

Site	EWI 1: % appropriate prescriptions of initial ART regimen Target 100%	EWI 2: % patients initiating 1° line ART lost to follow up at 12 months Target ≤ 20%	EWI 4: % patients on ART attending all clinical consultations on time Target ≥ 80%	EWI 5: % patients on ART picking up all ARV drugs on time Target ≥ 90%	EWI 6: % of months with no ARV drug stockouts Target 100%
1	144/145 (99%)	2/145 (1%)	140/ 160 (88%)	145/ 160 (91%)	12/12 (100%)
2	122/ 130 (94%)	6/130 (5%)	100/145 (69%)	131/145 (90%)	10/12 (84%)
3	75/75 (100%)	14/75 (19%)	68/ 100 (68%)	79/ 100 (79%)	10/12 (84%)
4	100/ 100 (100%)	9/ 100 (9%)	88/ 120 (73%)	99/ 120 (83%)	12/12 (100%)
5	179/ 180 (99%)	6/180 (3%)	166/ 200 (83%)	166/ 200 (83%)	12/12 (100%)
6	145/145 (100%)	9/145 (6%)	141/ 160 (88%)	150/ 160 (94%)	10/12 (84%)
7	130/130 (100%)	19/130 (15%)	111/ 145 (77%)	121/ 145 (83%)	12/12 (100%)
8	144/145 (99%)	26/145 (18%)	118/175 (67%)	138/175 (79%)	12/12 (100%)
9	101/110 (92%)	25/110 (23%)	88/ 130 (68%)	83/ 130 (64%)	11/12 (92%)
10...	75/75 (100%)	4/75(5%)	59/100 (59%)	81/100 (81%)	12/12 (100%)
173	40/40 (100%)	3/40 (8%)	34/ 110 (31%)	47/ 110 (43%)	12/12 (100%)
174	158/160 (99%)	33/ 160 (21%)	144/ 180 (80%)	171/ 180 (95%)	12/12 (100%)
175	110/110(100%)	14/110 (13%)	100/130 (77%)	114/130 (88%)	12/12 (100%)

Countries Monitoring WHO HIVDR Early Warning Indicators (Feb 2011)



EWI rounds completed/ongoing	**102**
Countries where EWI is implemented	**52**

Elements of the HIV Drug Resistance Strategy

A. Monitor HIVDR "Early Warning Indicators" from ART clinics (adult and paediatric versions)

B. Surveys to assess acquired HIVDR (adult and paediatric versions)

C. Surveillance of HIVDR transmission (adult only)

D. Surveillance of HIVDR in children < 18 months

E. Development of a network of accredited genotyping laboratories

Surveys of Acquired HIVDR: Goals

At sentinel clinics in countries scaling-up ART:

To describe HIVDR in cohorts at start and 12 months after ART initiation

To estimate viral load suppression 12 months after ART initiation at the clinic level

Jordan et al *Antivir Ther* 2008

Protocol Summary

- Cohorts of approximately ~ 130 adults or **children** initiating ART at the sentinel site followed during first 12 months of ART

- Baseline assessment of HIVDR
  - Genotyping, ARV history, PMTCT history of mother and child

- Endpoint assessment 12 months after start of ART or at switch to second-line
  - Viral load
  - Genotype (if applicable)

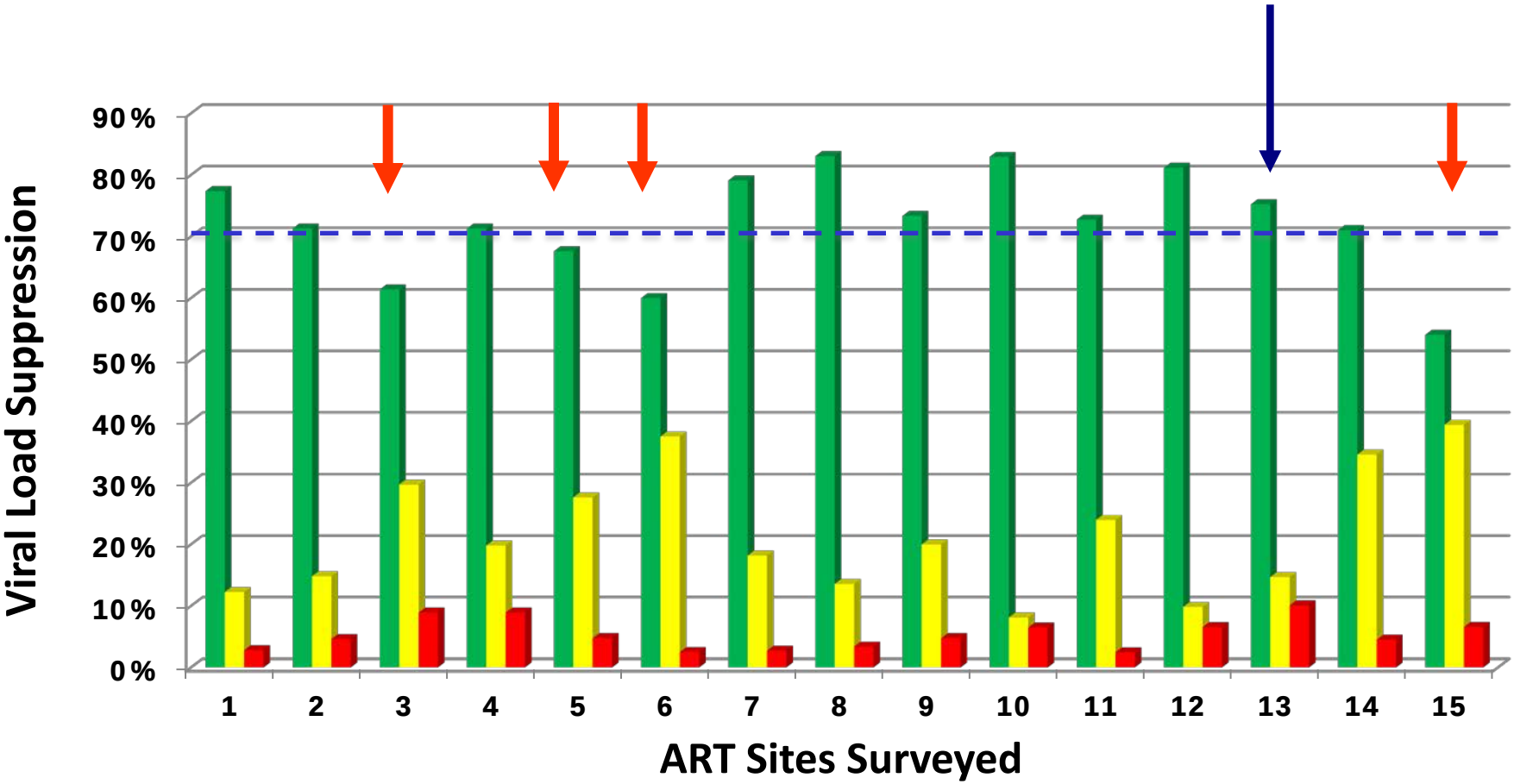
- Site profile (baseline + endpoint)

Jordan et al *Antivir Ther* 2008

VL Suppression by Site 12 months after ART Start

Clinic	Setting	Type of facility	VL Suppression(Per protocol analysis)	VL suppression (On treatment analysis)
Burundi 1	Urban	Public	77%	84%
Burundi 2	Urban	NGO	71%	81%
India 1	Urban	Public	61%	86%
India 2	Urban	Public	71%	89%
Malawi 1	Peri-urban	Public/NGO	67%	92%
Malawi 2	Urban	Public/NGO	60%	96%
Malawi 3	Urban	Public/NGO	79%	97%
Malawi 4	Rural	Public/NGO	83%	94%
Malawi 5	Peri-urban	Public/NGO	73%	93%
Malawi 6	Urban	Public/NGO	82%	92%
Malawi 7	Urban	Public/NGO	72%	94%
Malawi 8	Rural	Public/NGO	81%	92%
Mozambique	Urban	Public/NGO	75%	87%
Nigeria 1	Urban	Public	71%	90%
Nigeria 2	Urban	Public	54%	89%

Viral Load Suppression by Site 12 months



VL Suppression (<1,000 c/ml; "HIVDR prevention")

Possible HIVDR: VL >1000 c/ml and no HIVDR + Lost to follow up + Stop

Detected HIVDR: VL > 1000 c/ml and DR mutations detected

Denominator = Patients enrolled – (death + transfer out + unclassifiable)

Jordan et al Antiviral Ther 2008

Cross-sectional Surveys of HIVDR at Representative ART Clinics

Summary of Survey (1)

- Two components:
  - Monitoring the ability of representative ART sites to achieve virologic suppression in patients retained on ART at 12-15 months and ≥ 24 months
  - Determining best practices or appropriate interventions to maximize prevention of HIVDR at all ART sites
    - supplemental to widespread monitoring of Early Warning Indicators (EWI)

Summary of Survey (2)

- Cumulative dataset of DRMs in patients failing first-line ART created in participating countries
- Frequency, patterns, and trends of DRMs, may provide information for programmatic decision-making

Methodology (1)

- *Population and patient selection criteria*:
  - Survey of patients with "early" virologic failure:
    - adult or pediatric on ART for 12-15 months attending a participating site for a routine visit
  - Survey of patients with "later" virologic failure:
    - Adult or pediatric on ART for > 24 months attending a participating site for a routine visit

Methodology (3)

- Specimen types
  - DBS are desirable as specimen type as can be obtained from all sites
  - Sites with existing infrastructure for plasma specimen preparation and storage may use plasma or DBS (2 specimen types may complicate shipment)

- Development of a sampling plan using LQAS
  - Small sample size
  - Allows for classification above or below threshold for virological failure

Proposed Thresholds: Adult surveys

- Survey of patients with early virologic failure:
  - Viral Suppression rates for patients retained in care 12-15 months after ART initiation:
    - 85% upper threshold
    - 70% lower threshold
- Survey of patients with later virologic failure:
  - Viral Suppression rates for patients retained in care ≥ 24 months after ART initiation:
    - 80% upper threshold
    - 65% lower threshold
- For both surveys the CPE = 0.1 and the PPE = 0.05
  - Lower PPE limits risk for misclassification of true low suppression rates as above upper threshold

Anticipated Results

- Cumulative dataset of HIVDR in patients not achieving viral load suppression at specific time points
- Assessment of sentinel clinic success in maintaining population level viral load suppression at different time points

Protocol for Surveillance of initial drug-resistant HIV-1 among children ≤ 18 months of age newly diagnosed with HIV

Hypothesis

As ARV use for PMTCT increases, there will be a relatively small proportion of children who become infected with HIV despite PMTCT prophylaxis. However, among those infected, an increasing proportion will harbor drug-resistant strains of HIV.

Purpose

Assess initial drug-resistant HIV among children ≤ 18 months of age newly diagnosed with HIV to inform selection of first-line ART regimens for this population in each participating country and global decision-making on regimens

Objectives

- To describe the prevalence of initial NNRTI and NRTI resistance in newly-diagnosed children ≤ 18 months of age

- To describe the prevalence of initial NNRTI and NRTI resistance in children newly diagnosed with HIV who are ≤ 18 months of age and whose previous ARV exposure is recorded as “none” or “unknown

Survey Design

Retrospective cross-sectional survey of DR-HIV prevalence among children diagnosed with HIV by PCR methodology using remnant DBS specimens.

Data will be abstracted from laboratory requisition forms that accompany DBS samples

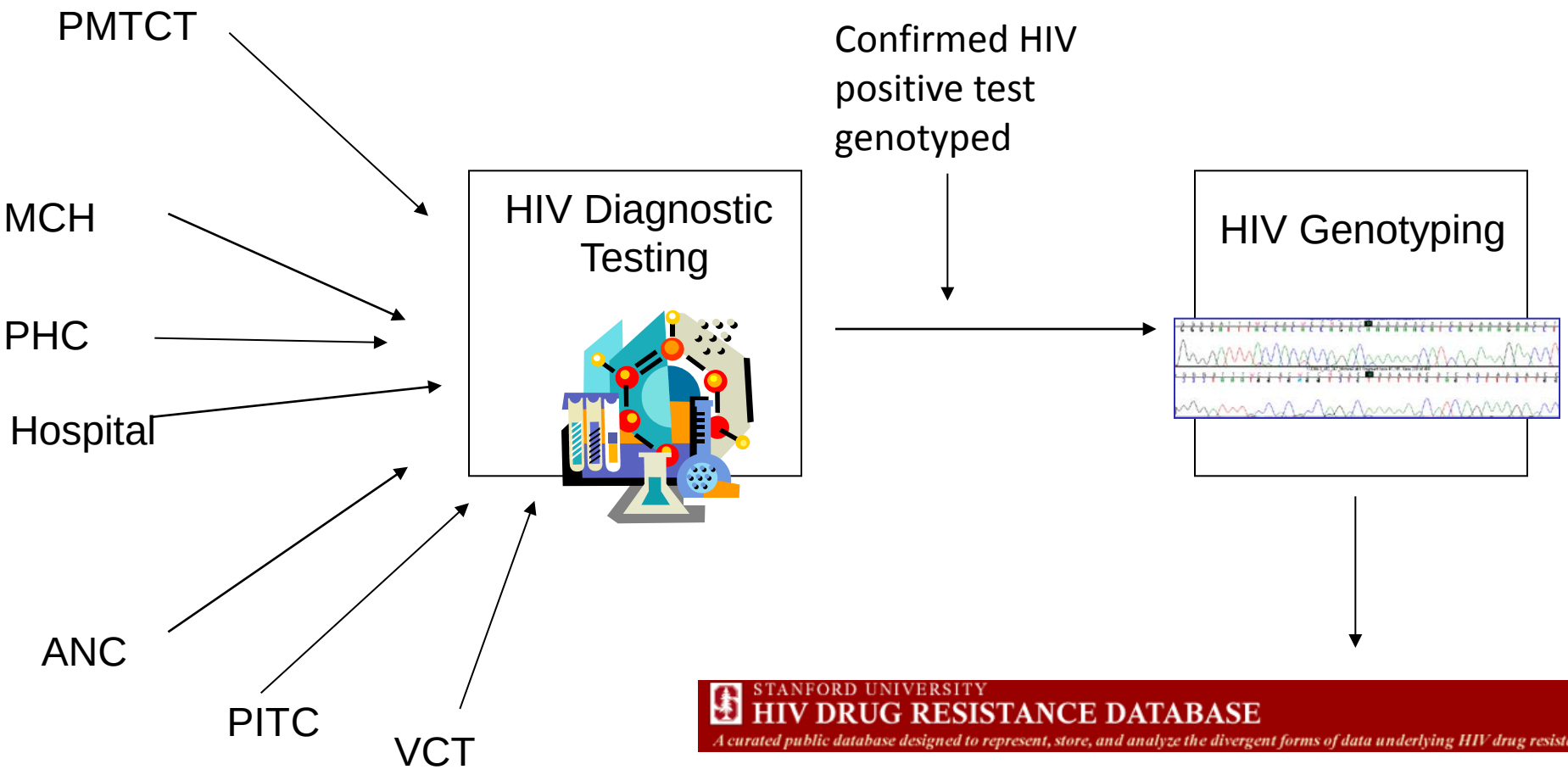
Inclusion/Exclusion Criteria

- Included:
  - DBS collected from an infant ≤ 18 months of age
  - The DBS specimen tested **HIV-positive** by DNA PCR
  - Maternal and infant ARV drug exposure, non-exposure, or "unknown" recorded on the laboratory requisition form for the DBS or routinely recorded in other accessible records
  - At least one viable remnant DBS available
  - DBS specimen has been or will be stored following WHO HIVDR DBS collection and storage guidelines
- Excluded:
  - Child on HAART (not PMTCT) at time of blood draw

Minimum Required Variables

- Gender
- Site where DBS was collected
- Facility type where DBS was collected
- Date of blood draw (heel stick)
- Date freezing DBS at -20 C or -70 C
- Is child on HAART (not PMTCT) at time of blood draw? (exclusion criteria)
- Date of PCR assay

Protocol for Surveillance of Initial drug-resistant HIV-1 among children ≤ 18 months of age newly diagnosed with HIV



Sample Size calculations based on:

- "true DR-HIV prevalence" of 50%
- 95% confidence intervals (CI) +/- 5%
- Power = 0.80
- non-amplification rate of 20%

These "conservative" assumptions yield the largest sample size and the most precise estimates of prevalence with the most narrow confidence intervals

Sample Size Examples

In country X there is one diagnostic lab:

4350-5000 (N) infants < 18 months are diagnosed as HIV-infected by PCR in the target year.

The sample size would be **490**.

In Country Y there are two laboratories:

Lab A where 2530-3200 (N_A) infants $\leq$ 18 months are diagnosed as HIV-infected by PCR in the target year,

Lab B where 490-510 (N_B) infants $\leq$ 18 months are diagnosed as HIV-infected by PCR in the target year

The sample size would be **463 for Lab A and 299 for Lab B**

Overall Conclusions

- As rollout continues at a blistering pace with a decentralized ART delivery system and evolving regimens, a global approach to assessing HIVDR is needed

- The lack of accessible individual HIVDR testing need never limit optimization of global efforts to minimize HIVDR

Overall Conclusions

- ART programs must be informed by robust programmatic evaluation of factors associated with HIVDR
- Routine, standardized, population-based surveillance of HIVDR is imperative, and should be integrated into routine national Monitoring and Evaluation programmes
- "Protocols are meaningless without investing resources to ensure high-quality implementation [of HIVDR surveillance] and continuous quality management"[1]
- Funders and national governments must steps up to support and sustain population based HIVDR surveillance

[1]B Hedt., et al. Am J Trop Med. Hyg 2011

Thank You !