WHO recommendations for HIVDR surveillance and their application in Latin America and the Caribbean

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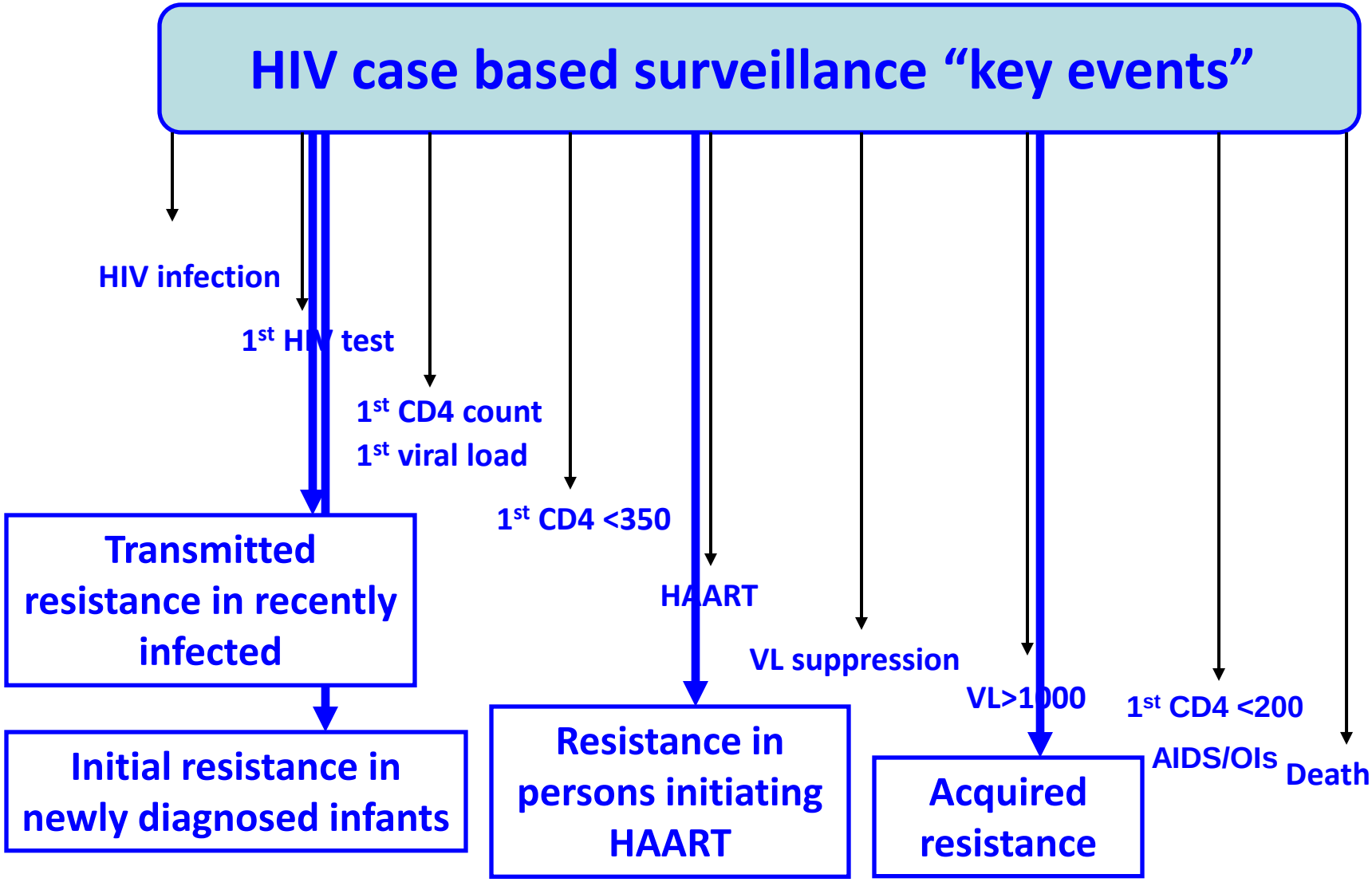
Background

- National programs in LAC are scaling-up antiretroviral treatment (ART) (ART coverage 70% LA; 67% Caribbean – Dec 2011).
- Emergence of HIV drug resistance (HIVDR) and its transmission are concerns in the context of increased coverage and ART as prevention (TasP).
- Some degree of emergence of HIVDR is inevitable in patients on ART (acquired resistance).
- Resistance to ARVs can be transmitted and detected in recently infected subjects without previous exposure to ARV drugs (transmitted resistance).
- Resistance in subjects initiating ART (pre-ART resistance) may impact on early virological failure of first-line treatment.

HIVDR Surveillance



World Health Organization HIV Drug Resistance Prevention and Assessment Strategy (2008)

A. D… pl…

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C. Su… A…

D. H… ha…

E. H…

F. D… ge…

G. R…

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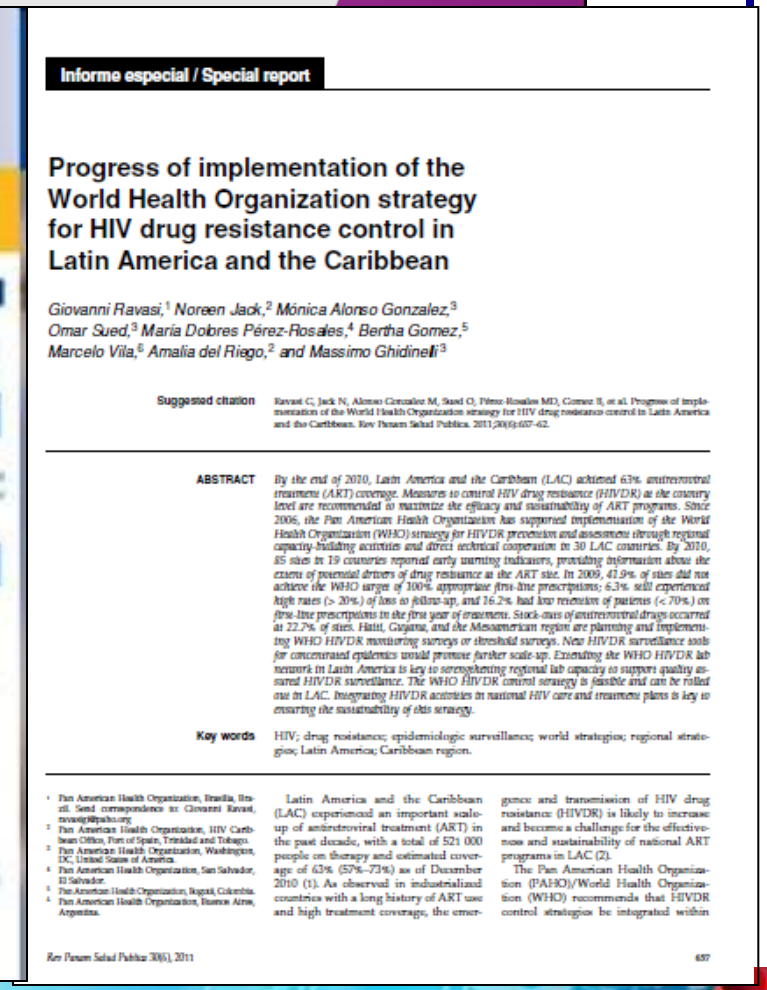

Informe especial / Special report

Progress of implementation of the World Health Organization strategy for HIV drug resistance control in Latin America and the Caribbean

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ABSTRACT *By the end of 2010, Latin America and the Caribbean (LAC) achieved 63% antiretroviral treatment (ART) coverage. Measures to control HIV drug resistance (HIVDR) at the country level are recommended to maximize the efficacy and sustainability of ART programs. Since 2006, the Pan American Health Organization has supported implementation of the World Health Organization (WHO) strategy for HIVDR prevention and assessment through regional capacity-building activities and direct technical cooperation in 30 LAC countries. By 2010, 85 sites in 19 countries reported early warning indicators, providing information about the extent of potential drivers of drug resistance at the ART site. In 2009, 41.9% of sites did not achieve the WHO target of 100% appropriate first-line prescriptions; 6.3% still experienced high rates (> 20%) of loss to follow-up, and 16.2% had low retention of patients (< 70%) on first-line prescriptions in the first year of treatment. Stock-outs of antiretroviral drugs occurred at 22.7% of sites. Haiti, Guyana, and the Mesoamerican region are planning and implementing WHO HIVDR monitoring surveys or threshold surveys. New HIVDR surveillance tools for concentrated epidemics would promote further scale-up. Extending the WHO HIVDR lab network in Latin America is key to strengthening regional lab capacity to support quality assured HIVDR surveillance. The WHO HIVDR control strategy is feasible and can be rolled out in LAC. Integrating HIVDR activities in national HIV care and treatment plans is key to ensuring the sustainability of this strategy.*

Key words HIV; drug resistance; epidemiologic surveillance; world strategies; regional strategies; Latin America; Caribbean region.

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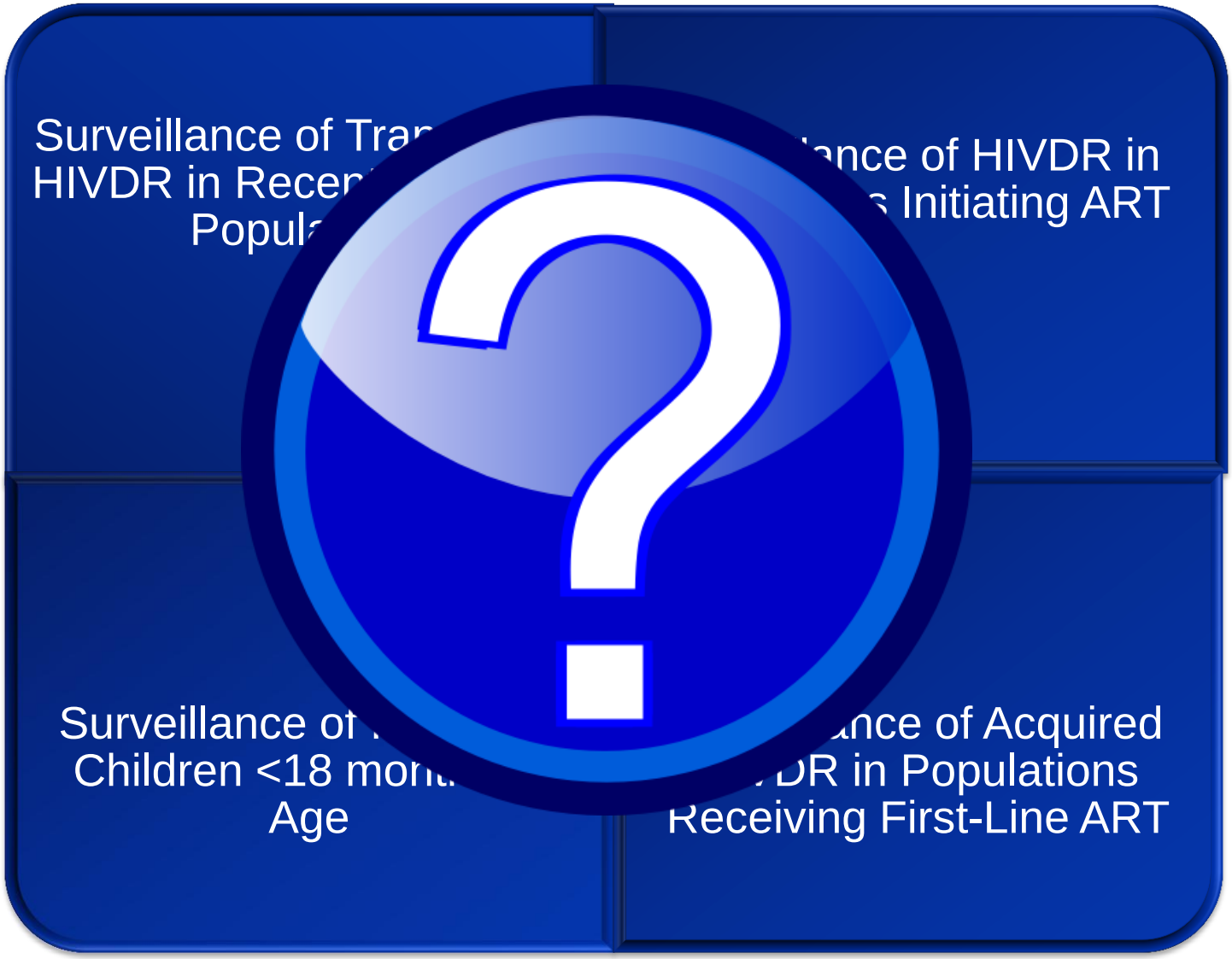
Latin America and the Caribbean (LAC) experienced an important scale-up of antiretroviral treatment (ART) in the past decade, with a total of 521 000 people on therapy and estimated coverage of 63% (57%–73%) as of December 2010 (1). As observed in industrialized countries with a long history of ART use and high treatment coverage, the emergence and transmission of HIV drug resistance (HIVDR) is likely to increase and become a challenge for the effectiveness and sustainability of national ART programs in LAC (2).

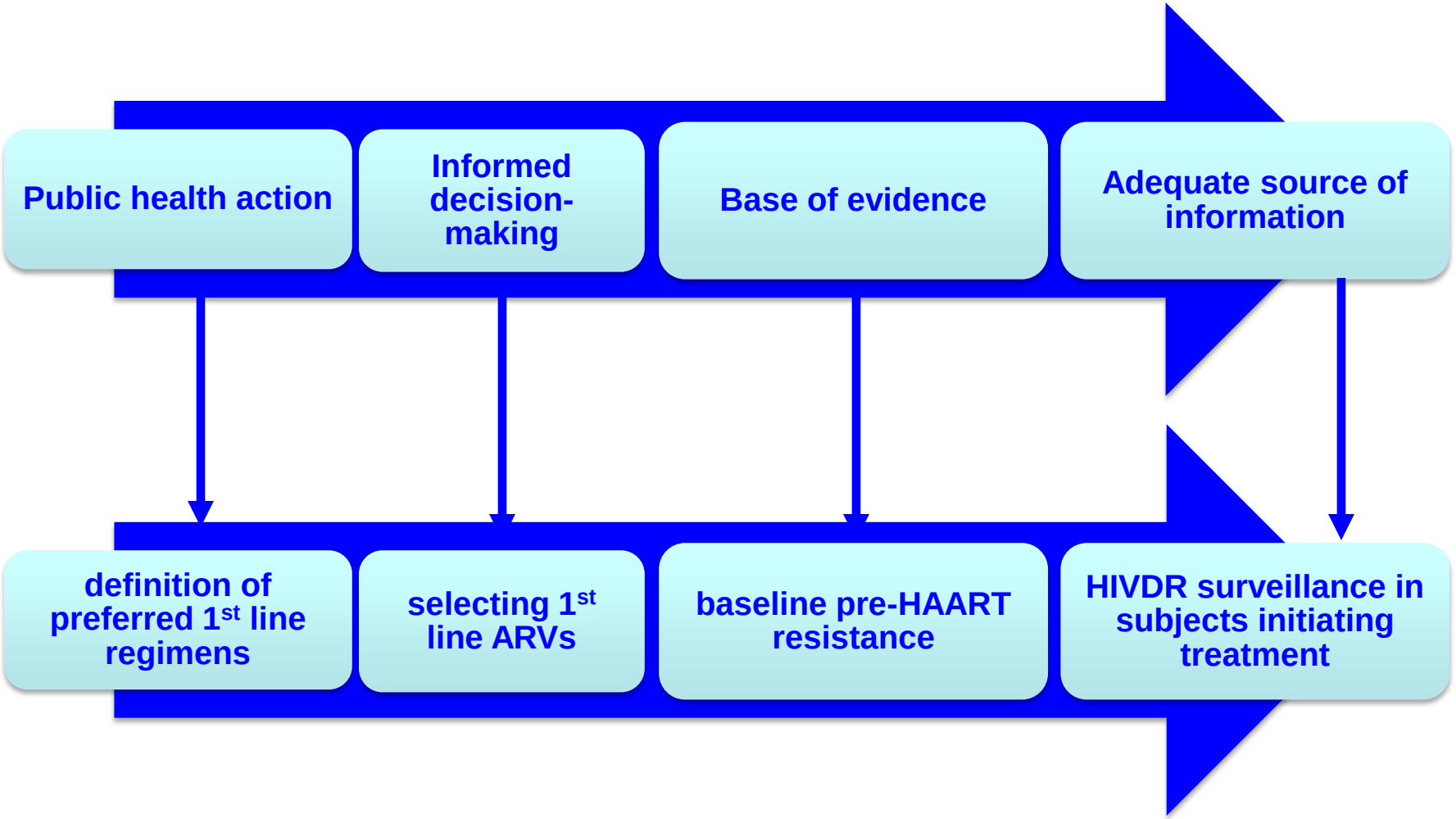
The Pan American Health Organization (PAHO)/World Health Organization (WHO) recommends that HIVDR control strategies be integrated within

Pan American Health Organization
World Health Organization
PAHO response to HIV

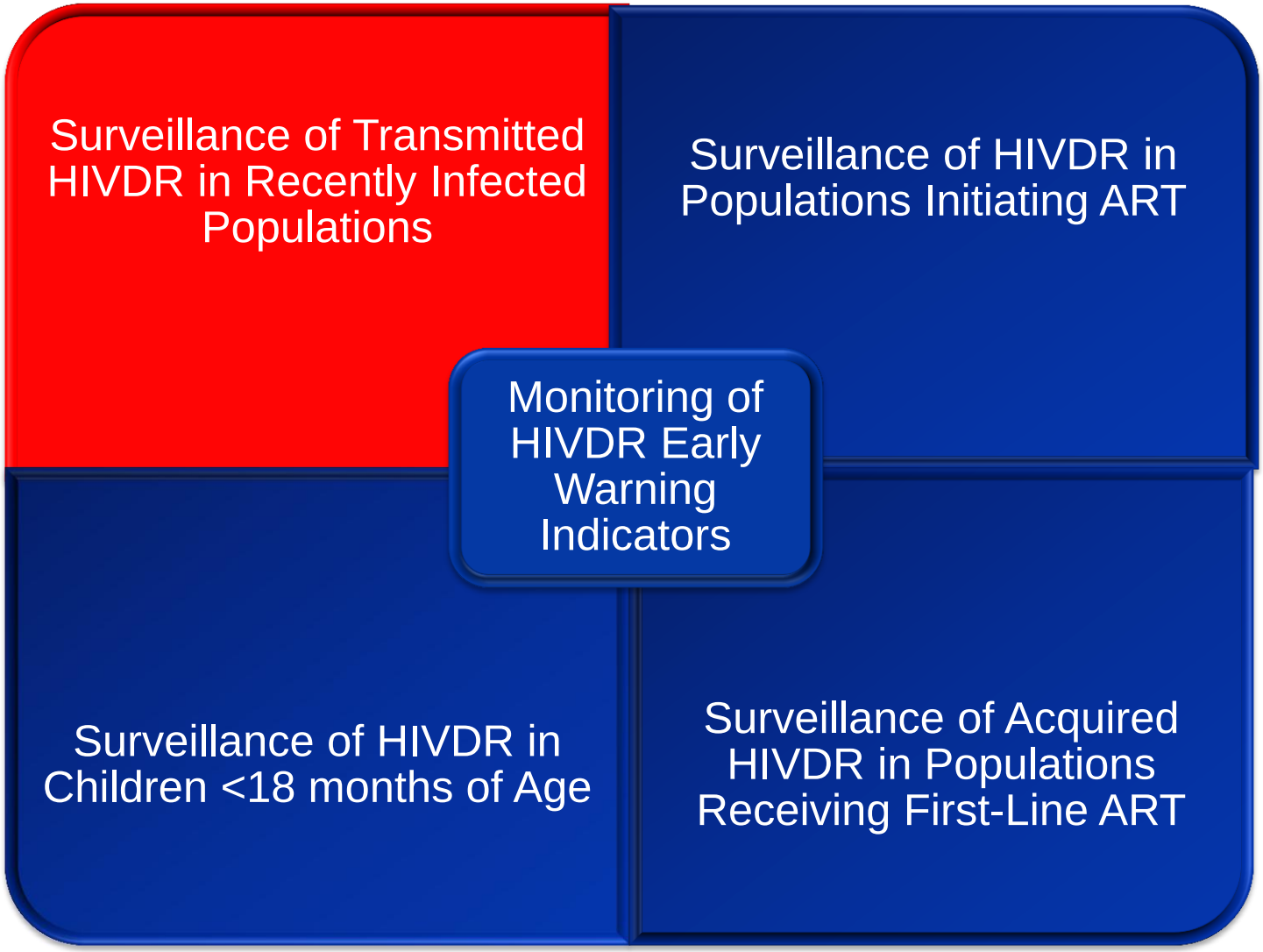
WHO HIVDR Surveillance and Monitoring Strategy (2012)



Generating HIVDR data for public health actions



WHO HIVDR Surveillance and Monitoring Strategy (2012)



Surveillance of transmitted drug resistance (TDR) in recently infected populations

Public Health Objectives:

- **Alert** about transmission of drug resistant HIV (TDR).
- **Inform on effectiveness of prevention strategies**, especially for patients receiving ART (*prevention for positives*).
- **Allow program planners time to react to future needs**: cost effectiveness analysis of baseline HIVDR testing, switch from NNRTI to PI/r based 1st-line regimen; planning for **future** 1st-line regimens.
- **Support planning for current PMTCT, PrEP, PEP regimens.**

WHO generic protocol under revision

TDR in “recently infected”

Inclusion criteria to identify subjects likely to have been recently infected should be selected and combined according to the type of population being surveyed.

- Newly diagnosed HIV+

AND

- < 25 years (22 years preferable)
- No previous pregnancy (if female)
- First exposure to risk behavior within 3 years (if MARPs)
- CD4 cell count >500 cells/mm^3 (if available)

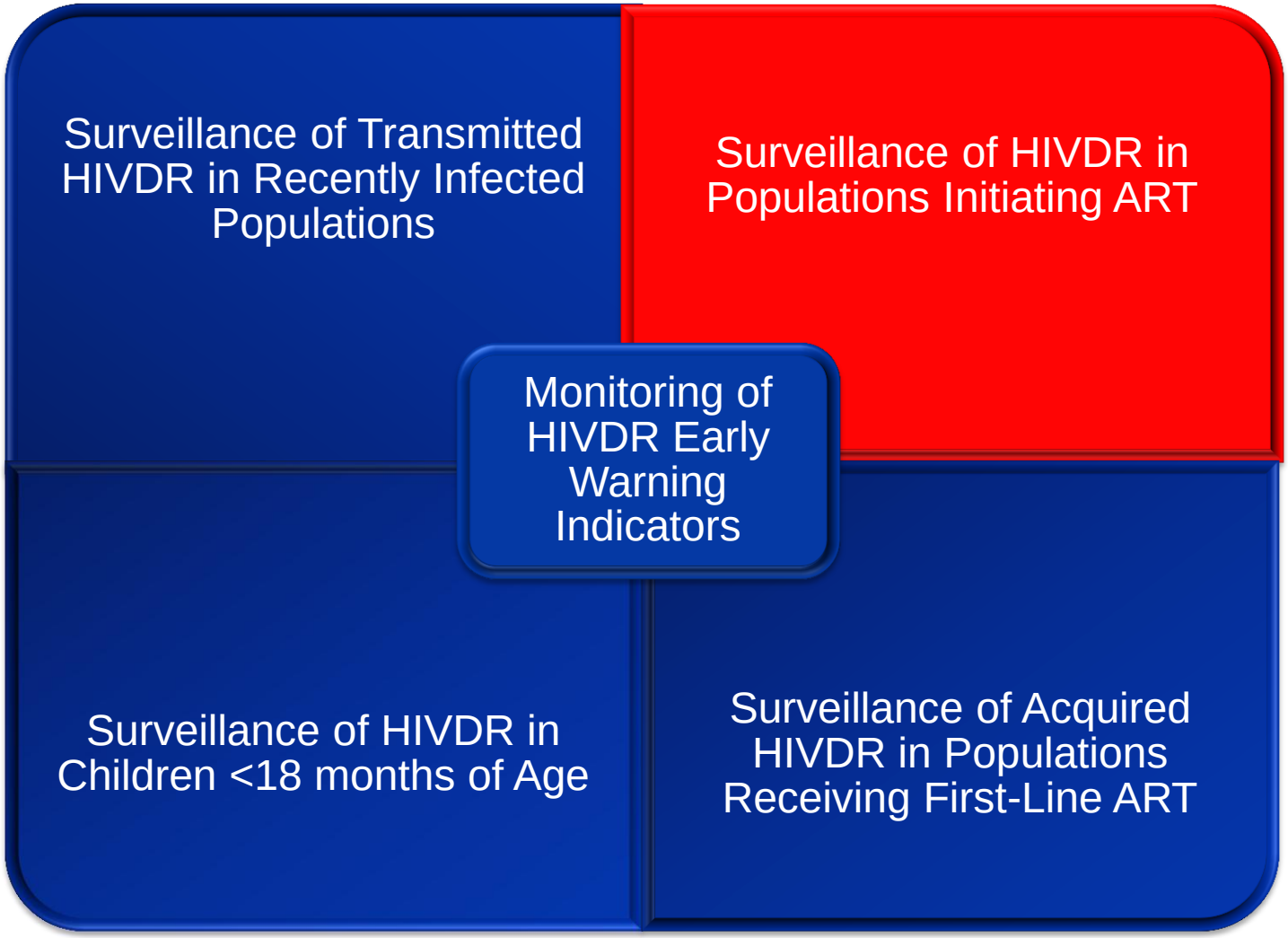
OR

- Laboratory methods: seroconversion or *Recent Infection Testing Algorithm* (RITA)
  http://www.who.int/hiv/pub/surveillance/sti_surveillance/en/index.html

Surveillance of TDR in recently infected populations

Objective	Estimate TDR prevalence in recently infected subjects.
Population	Recently infected subjects from general population, or pregnant women, or MARPs.
Survey design	Sample size calculation for point prevalence (confidence interval).
Surveillance type	▪ TDR surveys integrated in ANC surveys ▪ TDR surveys integrated in BBS for MARPs ▪ Cross sectional TDR surveys at sentinel ANC sites, VCT sites. ▪ *Lab based sample selection (National Reference lab)*
Result	National estimate of point prevalence of TDR (to any ARV drug as well as each ARV class) in general population, or pregnant women, or MARPs

WHO HIVDR Surveillance and Monitoring Strategy (2012)



Surveillance of HIVDR in Populations Initiating ART

Public Health Objectives:

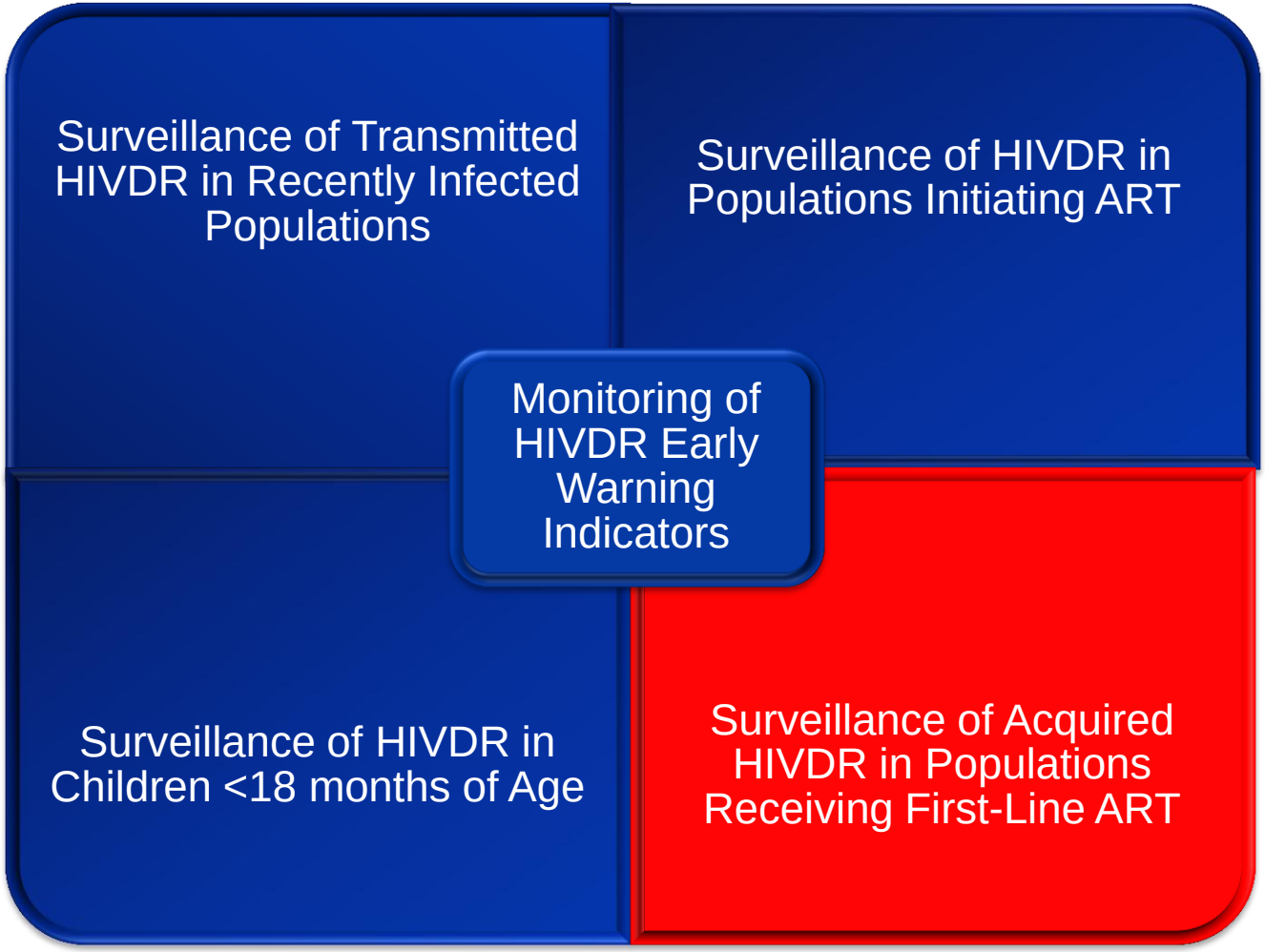
- **Select current first-line ARV drugs and preferred regimens.**
- **Inform cost effectiveness analysis** of **current** implementation of individual HIVDR testing, switch from NNRTI to PI/r based 1st-line.
- **Change current 1st-line:** from NNRTI-based to PI/r-based regimens;
- **Introduce individual baseline genotyping** to guide therapy;
- **Introduce/intensify viral load monitoring** to detect early failure presumably associated with pre-ART HIVDR.

WHO generic protocol under development

Surveillance of HIVDR in Populations Initiating ART

Objective	Estimate HIVDR in patients who are initiating ART.
Population	Any patient who is eligible to start ART according to national guidelines.
Survey design	Sample size calculation for point prevalence (confidence interval).
Surveillance type	Cross sectional surveys at sentinel ART sites (geographically representative sites with higher volume of patients initiating ART) *Lab based sample selection (National Reference lab)*
Result	National estimate of point prevalence of pre-ART resistance (to any ARV drug as well as each ARV class).

WHO HIVDR Surveillance and Monitoring Strategy (2012)



Surveillance of acquired HIVDR in population receiving first-line ART

Public Health Objectives:

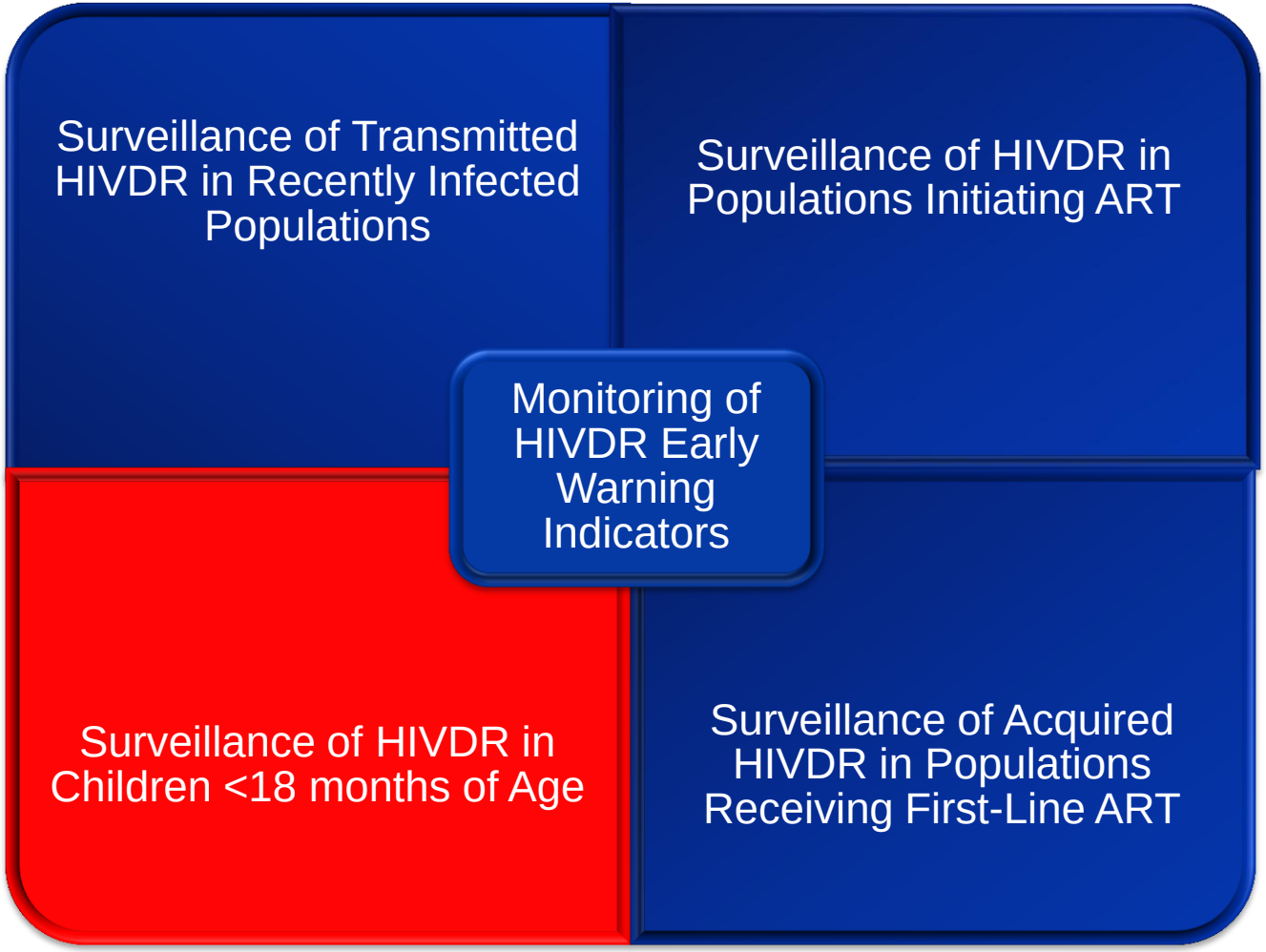
- Inform about population-level virological suppression at different time points (and occurring within different models of ART delivery)
- Support country decision making regarding optimal second-line regimen selection.

WHO generic protocol available (WHO HIVDR page)
http://apps.who.int/iris/bitstream/10665/75205/1/WHO_HIV_2012.15_eng.pdf

Surveillance of Acquired HIVDR

Scenario	No VL and no genotyping ↓	VL monitoring and no genotyping ↓	VL monitoring and genotyping ↓
Method	WHO Cross-sectional survey	VL data analysis (virological suppression at ART site) and cross sectional genotyping in patients with virological failure of 1st line ART.	VL and HIV genotype data analysis to calculate WHO survey outcomes.

World Health Organization HIV Drug Resistance Surveillance and Monitoring Strategy



Surveillance of HIVDR in children < 18 months of age

Public Health Objectives

- Inform selection of pediatric first-line ART and/or adoption of baseline genotyping in recently diagnosed infants.
- Evaluate the impact of PMTCT scale up on the pattern of resistance acquired by infants exposed to ARV drugs for PMTCT .

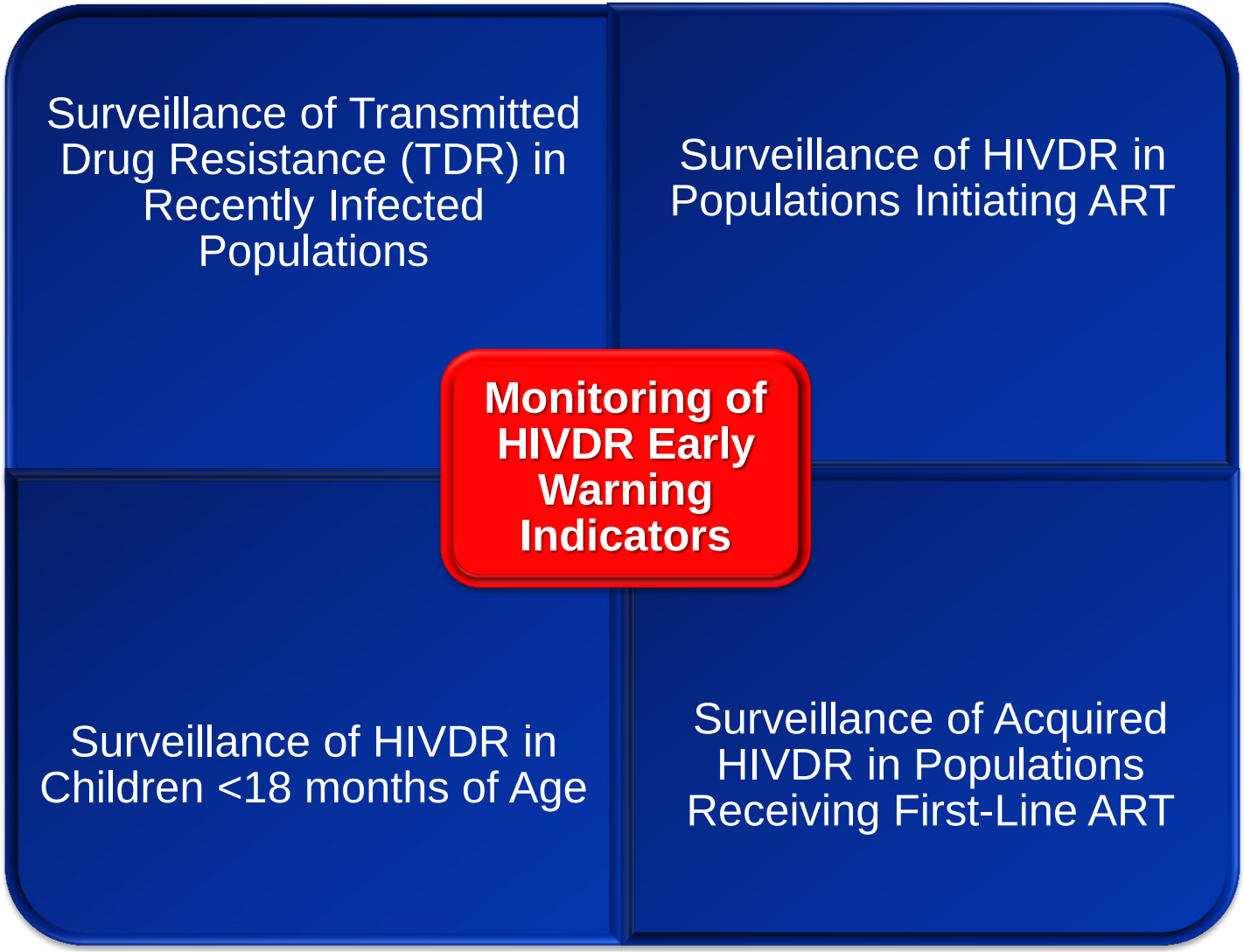
WHO generic protocol

http://apps.who.int/iris/bitstream/10665/75202/1/WHO_HIV_2012.17_eng.pdf

Surveillance of HIVDR in children < 18 months of age

Objective	Estimate initial resistance in newly diagnosed children <18 months of age.
Population	Newly diagnosed children <18 months of age.
Survey design	Sample size calculation for point prevalence (confidence interval).
Surveillance type	Retrospective cross sectional survey on stored samples at reference lab. Prospective survey on samples received at reference lab for virological diagnosis (ex. PCR DNA).
Result	National estimated prevalence of initial resistance (to any ARV drug and each ARV drug class) and characterization of mutations (overall and according to known or unknown PMTCT exposure)

WHO HIVDR Surveillance and Monitoring Strategy (2012)



Early Warning Indicators of HIV Drug Resistance

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- EWI
  ART
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- EWI
- Resi
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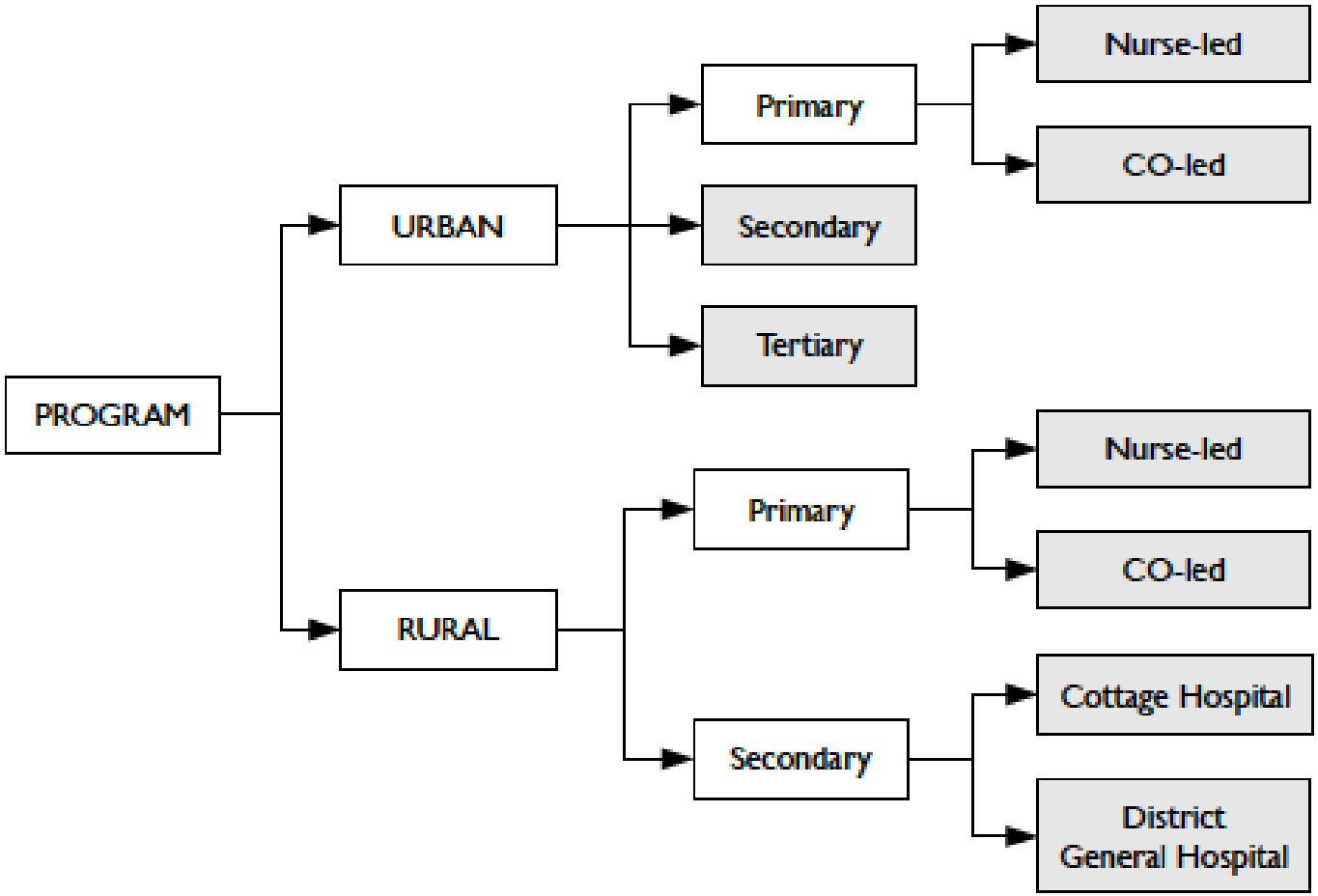

ART Site based indicators

WHO-recommended HIVDR EWIs (2004-2010)

EWI	EWI Target
1. % of patients starting appropriate first line ART regimens	100%
2. % of patients lost to follow-up at 12 months	≤ 20%
3. % patients retained on first-line ART at 12 months	≥ 70%
4. % picking up ARV drugs on-time	≥ 90%
5. % keeping appointments on-time	≥ 80%
6. % months without ARV stock-outs	100%
7. % with 100% adherence (ex. pill count)	≥ 90%
8. % with viral load <1000 copies/ml at 12 months	≥ 70%

TABLE 3. Summary of four HIV drug resistance early warning indicator results in Latin America and the Caribbean, 2007–2009[a]

HIVDR early warning indicator[b]	WHO target, %	Sites meeting WHO target, %		
		2007	2008	2009
EWI 1a: Percentage of patients initiating ART during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen	100	47.6 (20/42)	29.3 (12/41)	41.9 (18/43)
EWI 2: Percentage of patients initiating ART in a selected time period who are lost to follow-up during the 12 months after starting ART	≤ 20	78.6 (33/42)	62.5 (10/16)	93.7 (15/16)
EWI 3 a: Percentage of patients initiating ART during a selected time period who are taking an appropriate first-line ART regimen 12 months later	≥ 70	69.8 (30/43)	73.5 (25/34)	83.8 (31/37)
EWI 6b: Percentage of months in a designated year in which there were no ARV drug stock-outs	100	48.5 (16/33)	36.4 (4/11)	77.3 (17/22)
EWI 6a: Percentage of patients on first-line ART whose regimen was stopped, modified, or incompletely dispensed at the pharmacy due to ARV stock-outs or shortages during a designated year	0	80.0 (4/5)	100.0 (4/4)	100.0 (1/1)

HIVDR: HIV drug resistance, WHO: World Health Organization, EWI: early warning indicator, ART: antiretroviral treatment, ARV: antiretroviral.

[a] Summary results from 85 ART sites in 19 countries in Latin America and the Caribbean (Bahamas, Barbados, Belize, Colombia, Dominica, Dominican Republic, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Montserrat, Nicaragua, St. Kitts and Nevis, St. Vincent and the Grenadines, St. Lucia, Suriname) that reported EWI as of December 2010.

[b] EWI 2008 version.

- *Ravasi G. et al. Pan-American Journal Public Health, 2011.*

WHO HIVDR EWI - 2012 Revision

- New EWI guidance available (2012).
- EWIs were evaluated using GRADE method for association with HIVDR and definition of optimal target.
- EWIs without strong association with HIVDR were eliminated.
- Simplification and harmonization with other indicators (GARP).

http://www.who.int/hiv/pub/meetingreports/ewi_meeting_report/en/index.html

HIV Drug Resistance Early Warning Indicators (2012)

- EWI 1 (EWI 4, 2010) Percentage of patients that pick-up ART no more than two days late.
- EWI 2 (EWI 3, 2010) Percentage of patients known to be alive and on treatment 12 months after initiation of ART (GARP 4.2a)
- EWI 3 (EWI 6, 2010) Percentage of months in a year in which there were no ARV drug stock-outs
- EWI 4 (EWI 1, 2010) Percentage of patients being dispensed a mono or dual-drug regimen
- EWI 5 (EWI 8, 2010) Percentage of patients receiving ART at the site after the first 12 months of ART whose viral load is <1000 copies/ml.

2012 Revised EWI Reporting: Scorecard

Red	Poor performance, below desired level
Amber	Fair performance, progressing toward desired level
Green	Excellent performance, achieving desired level
Grey	Data not available

2012 Revised WHO HIVDR EWIs

Early Warning Indicator	Target
1. On-time pill pick-up	• Red: <80% • Amber: 80–90% • Green: >90%
2. Retention in care	• Red: <75% retained after 12 months of ART • Amber: 75–85% retained after 12 months of ART • Green: >85% retained after 12 months of ART
3. Pharmacy stock-outs	• Red: <100% of a 12-month period with no stock-outs • Green: 100% of a 12-month period with no stock-outs
4. Dispensing practices	• Red: >0% dispensing of mono- or dual therapy • Green: 0% dispensing of mono- or dual therapy
5. Viral load suppression at 12 months	• Red: <70% viral load suppression after 12 months of ART • Amber: 70–85% viral load suppression after 12 months of ART • Green: >85% viral load suppression after 12 months of ART

At-a-glance assessment of ART site performance

Clinic	EWI 1 On-time pill pick-up	EWI 2 Retention	EWI 3 Drug stock-outs	EWI 4 Dispensing practices	EWI 5 VL suppression
1	95%	77%	100%	95%	95%
2	70%	95%	100%	88%	98%
3	100%	82%	75%	0%	75%
4	85%	....	100%	0%	95%
5	97%	60%	95%	0%	50%
....	....	....	.....	....	....
....	....	....	....	....	....
100	100%	100%	100%	0%	100%

Scorecard facilitates:

- Reporting of results
- Interpretation at clinic and national levels
- Strategic allocation of resources

Conclusions

- HIVDR has potential to decrease effectiveness of ART and prophylactic regimens (PMTCT, PEP, PrEP).
- National Programs should optimize antiretroviral treatment use, improve quality of care, promote adherence and retention in care, and maximize effectiveness of ART and viral suppression (HIVDR prevention).
- A national HIVDR surveillance strategy provides strategic information for National ART Programs and ART clinics to support decision-making for quality improvement actions and to update national guidelines.
- HIVDR surveillance should be part of a comprehensive HIV surveillance plan at national level.
- Pilot surveys currently being implemented in a number of countries.
- New WHO HIVDR strategy guidance (2013)

Thank you

HIVDR regional technical consultation – Brasilia, 2013