MEETING REPORT

Technical Consultation on HIV Drug Resistance Surveillance in Latin America and the Caribbean Region

Brasilia, Brazil, 19-21 March 2013

MEETING REPORT

Table of Contents

Executive Summary

In March of 2013, a group of experts from Latin America and the Caribbean (LAC), the United States and Canada came together in Brasilia, Brazil, for a three days Technical Consultation to discuss and advance key recommendations towards scale up of surveillance of HIV drug resistance (HIVDR) based on quality controlled genotyping and harmonized methodology and with the ultimate goal of improving the Region's response to the HIV epidemic.

The consultation included 30 experts from 14 countries, including 15 representatives from national HIV programs in Pan American Health Organization (PAHO) member States, 4 representatives of the World Health Organization (WHO) accredited HIVDR laboratories in the Region, and 11 international experts on HIVDR from the Region.

During this meeting, the participants were presented global and regional HIVDR data, were familiarized with the revised WHO Global Strategy for HIVDR Surveillance and Monitoring, and discussed priorities, challenges and recommendations to support HIVDR surveillance in Latin America and the Caribbean.

The main consensus areas and recommendations defined through plenary discussion and work-group sessions are presented below.

Priorities for HIVDR surveillance

HIVDR surveillance should be tailored to the epidemiological context of Latin America and the Caribbean, mostly countries with concentrated epidemics in most- at-risk populations (MARPS), and integrated within HIV surveillance activities already being planned and implemented. In addition, methodological adaptations should be considered for small countries.

WHO pre-treatment and acquired resistance surveillance protocols are considered as priority for HIVDR surveillance and identified as more practically relevant for National Programs in the Region, since they provide complementary strategic information for the assessment of ART program effectiveness, which may inform public health actions with immediate impact on the quality of treatment and care of people living with HIV.

Surveillance of transmitted drug resistance is less feasible and was not prioritized, but could be integrated into existing HIV surveillance activities, if relevant in specific countries.
Initial HIVDR surveillance in children with less than 18 months was also considered less of a priority in the Region, considering that, in line with the Elimination Initiative, cases of vertical transmission are declining in many countries. On the other hand, countries with installed HIV genotyping capacity could consider performing baseline resistance test in all HIV+ children, as part of the recommended clinical monitoring, and use those data for surveillance purpose.

Considering the variety of epidemiological profiles in LAC, availability of human and financial resources and laboratory capacity, organization of lab and health service networks and other country specific logistic issues, the approach to HIVDR surveillance implementation should be flexible, as long as the analytical framework is standardized for comparability among countries and over time. In addition, HIVDR surveillance should be implemented guaranteeing national representativeness of data to support effective use of data for decision-making at National Program level.

WHO Early Warning Indicators for HIVDR prevention should continue to be monitored in each country as program monitoring and evaluation tools and to support interpretation of HIVDR surveillance data.

Challenges and recommendations

Genotyping and lab capacity building

HIVDR surveillance should be supported by reference laboratories that have the capacity to perform high quality HIV genotyping, in order to provide reliable information for decision takers.

Technical assistance should be provided to build lab capacity for the implementation of HIV genotyping at country level, including regular training of laboratory personnel on HIV genotyping. In addition assistance should be provided to access external quality assurance programs for HIV genotyping.

Considering the high costs of commercial kits and reagents for HIV genotyping, countries should be supported to negotiate better prices or reduce costs through international procurement mechanisms (ex. PAHO Strategic Fund).

Considering that some countries still experience limitations in scaling up viral load monitoring, technical assistance should be provided to scale up and optimize viral load testing (universal access, turnaround time, use of Dried Blood Spots, etc.).

WHO accredited laboratories in the region should support countries with limited lab capacity to perform HIV genotyping and viral load measurement in the context of HIVDR surveillance activities.

In addition, training activities on interpretation of genotyping results for clinical monitoring purpose. This should include regional networks to discuss difficult and unusual cases.

Political and financial issues

Advocacy is still necessary to convince funders and policy makers of the importance of HIVDR surveillance as a way to monitor and address the sustainability of national treatment programs. Economic analysis could demonstrate the long-term economic benefits of implementing HIVDR surveillance.

Considering the limited use of data for decision-making at program level, as well as the limited knowledge on HIVDR surveillance data interpretation and on how to translate it into public health actions (ex. guidelines adaption, drug procurement issues, personnel training, adherence and follow up in care), training and capacity building activities on epidemiological analysis, interpretation and use of HIVDR surveillance data for public health decision-making should be promoted.

The disconnection between national HIVDR experts (Universities, Laboratories and other research institutions) and HIV programs is a challenge for the implementation of HIVDR surveillance and use of HIVDR data at country level. National programs should create and coordinate national intersectoral working or advisory groups (Ministry of Health, Universities, Laboratories, Specialized societies, UN Agencies, etc.) to discuss technical issues, including HIVDR, to strengthen collaboration, communication and timely sharing of information between HIVDR experts and program managers.

Considering the dependency on external financial support and the limited integration of HIVDR surveillance activities within National Program work-plans and budgets, Ministries of Health should identify resources, from national budget or external cooperation, to support the implementation of HIV genotyping, maintain equipment, buy kits and reagents, and train lab personnel. HIVDR surveillance should be integrated within routine HIV surveillance activities.

Technical cooperation

WHO should finalize all reference documents for HIVDR surveillance protocols. WHO protocols should include clear guidance on use of data for public health actions, possibly presenting the cost-benefit aspect of HIVDR surveillance for enhanced sustainability of national programs.

The Latin American and Caribbean Region is rich in technical capacity and human resources to support HIVDR surveillance, although still presents important disparities among countries. Therefore, technical cooperation should be made available to assist countries with limited capacity and resources in protocol development and implementation of HIVDR surveillance based on quality controlled genotyping and harmonized methodology.

Technical cooperation for the implementation of HIVDR surveillance could be provided through International collaborative initiatives of transfer of technology, based on a horizontal technical cooperation approach. This could be done by creating regional, or sub-regional, working groups that may operate as knowledge hubs or networks, with the objective of discussing HIVDR surveillance issues from a regional perspective and supporting HIVDR surveillance implementation by mobilizing technical capacity in a more coordinated and efficient way. Term of reference of such working groups, including memberships and roles, should be developed. PAHO/WHO could have a coordinating role, but it is fundamental that these working groups liaise with regional/sub-regional coordination mechanisms (ex. Horizontal Technical Cooperation Group – GCTH in Latin America). The GCTH, not only should be a prominent partner for technical cooperation, but a space to meet and discuss FRHIV policies in a systematic manner. In the Caribbean, CARPHA and PANCAP will be important partners in the sub-regional coordination mechanisms.

Additional key consideration:

Participants also recommended that follow up activities with the participation of National Program Directors should be organized at sub-regional level to present the new WHO HIVDR surveillance protocols and these recommendations.

Background

The emergence and transmission of HIV drug resistance (HIVDR) in the context of Universal Access to antiretroviral therapy (ART) is a major challenge, not only from the point of view of individual effectiveness of treatment, but also for the population based effectiveness of national ART programs and their sustainability.

Since 2004, the World Health Organization (WHO) and HIV-ResNet partners have been developing a public health strategy to prevent and assess HIV Drug Resistance in resource-limited countries and in the context of accelerated ART scale up.[1]

Since then, through the implementation of WHO recommended protocols worldwide, a considerable amount of data on transmitted and acquired HIV drug resistance has been produced and recently published in the Global HIVDR Report.[2] As presented in the report, a recent systematic literature review performed by WHO suggests that, in selected low- and middle-income countries, the prevalence of transmitted drug resistance to any antiretroviral (ARV) drug increased between 2003 and 2010, reaching a peak of 6.6% in 2009 (95% confidence interval 5.1%-8.3%). A significant increase in prevalence of transmitted resistance to any ARV class was observed in Latin America and the Caribbean between 2003 (4,7%) and 2009 (9,8%).

Pooled analysis of data from WHO surveys, which target people who have been recently infected, indicates that there appears to be increasing levels of resistance to NNRTI, particularly in the areas surveyed in Africa, where the prevalence of NNRTI resistance reached 3.4% (95% CI 1.8%–5.2%) in 2009. There is no clear evidence of increasing HIV drug resistance levels for other drug classes, with persistent low prevalence (<5%) between 2003 and 2010 (Figure 1).

Figure 1.

Table 3.2 Estimated prevalence of HIV drug resistance among ARV-naive individuals from the published literature, 2003-2010

	% with at least one drug resistance mutation (95% confidence interval)								
	2003	2004	2005	2006	2007	2008	2009	2010	P-value[a]
Any	3.6 (2.3-5.2)	4.5 (2.3-7.3)	1.9 (0.9-3.3)	2.5 (1.2-4.1)	3.1 (1.6-5.0)	4.9 (3.6-6.3)	6.6 (5.1-8.3)	2.1 (0.3-5.8)	0.03
NRTI	2.0 (0.9-3.4)	2.3 (1.0-4.0)	0.7 (0.1-1.5)	0.9 (0.1-2.2)	1.2 (0.4-2.4)	1.9 (1.1-2.9)	2.0 (0.8-3.5)	0.0 (0.0-1.4)	0.46
NNRTI	0.9 (0.2-2.0)	1.0 (0.2-2.1)	1.1 (0.4-2.0)	1.2 (0.3-2.7)	1.2 (0.5-2.2)	1.8 (1.3-2.4)	3.3 (2.3-4.4)	0.9 (0.0-4.8)	<0.001
PI	0.3 (0.0-1.0)	0.9 (0.2-2.0)	0.0 (0.0-0.1)	0.0 (0.0-0.3)	0.2 (0.0-0.6)	0.7 (0.3-1.4)	0.9 (0.2-1.9)	0.0 (0.0-1.4)	0.48

a Statistical methods are described in Section 3, Annex 1.

Source: WHO. WHO HIV Drug resistance Report 2012.

[1] Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. Antivir Ther. 2008;13(Suppl 2):1–13.
[2] WHO. WHO HIV Drug resistance Report 2012. Available at: http://www.who.int/hiv/pub/drugresistance/report2012/en/index.html

Of 72 WHO surveys of transmitted drug resistance conducted between 2004 and 2010, 20 (28%) were classified as having moderate (between 5% and 15%) prevalence of resistance. The proportion of surveyed areas reporting moderate levels of transmitted drug resistance increased from 18% in 2004-2006 to 32% in 2007-2010 (Figure 2). These findings deserve particular attention. If confirmed and documented in multiple areas of the same country, immediate investigation is recommended to understand their determinants and policy implications from the point of view of prevention and treatment interventions.

Figure 2.

Table 1 Frequency of WHO surveys reporting moderate prevalence of transmitted HIV drug resistance, by period (before or after 2007)[a]

		Number (%) of surveys with moderate (5–15%) prevalence			
Year	Total surveys	Any drug class	NNRTI	NRTI	PI
2004-2006	22	4 (18%)	1 (5%)	3 (14%)	0 (0%)
2007-2010	50	16 (32%)	11 (22%)	7 (14%)	2 (4%)

a Mid-point period.

Source: WHO. WHO HIV Drug resistance Report 2012.

In addition, according to data from 36 WHO surveys of acquired HIV drug resistance assessing more than 5000 people in 12 low- and middle-income countries between 2007 and 2010, the prevalence of HIV drug resistance to any drug among people starting antiretroviral therapy ranged from 4.8% (95% CI 3.8%–6.0%) in 2007 to 6.8% (95% CI 4.8%–9.0%) in 2010. About 90% of patients alive and on therapy at 12 months (as treated analysis) achieved treatment success (viral load suppression). Among people with virological failure, 72% had resistance, mostly to nucleoside reverse transcriptase inhibitors (NRTI) and NNRTI drugs. The remaining 28% had no resistance mutations and therefore experienced treatment failure for other reasons, such as very poor adherence or extended treatment interruptions, and may have been switched to costlier second-line regimens unnecessarily.

Since the launching of the HIVDR strategy, WHO recommended protocols for HIVDR monitoring and surveillance have been implemented mostly in countries with generalized epidemics. In Latin America and the Caribbean (LAC) HIVDR Monitoring surveys are currently ongoing in Haiti and Guyana, while threshold surveys for transmitted resistance have been implemented in Mexico (2004), Brazil (2007/8) and Panama (2008/2010) - in Brazil and Panamá with partially adapted WHO methodology. The most relevant challenge for the implementation of WHO surveys in LAC is the epidemiological context of low prevalence and concentrated epidemic which has important implications for the feasibility of the sampling methods of WHO recommended generic protocols. Nevertheless, evidence of transmitted resistance in LAC is available from a wide amount of scientific literature, as recently reported by WHO, but the overall regional prevalence does not consider subregional and national variability within LAC, as well as gaps in information for a number of countries in the Latin American region and very limited data for the Caribbean.

As observed in literature reviews,[3][4][5] HIVDR monitoring and surveillance methodologies in LAC are heterogeneous and present a number of limitations:

- convenience sampling or undefined sampling frame and/or method;
- long sampling periods;
- heterogeneous populations (recently infected; recently diagnosed; pre-ART; mixed);
- heterogeneous definitions (e.g. recently infected);
- different TDR reference (IAS, Stanford, WHO, ANRS, etc.);

Considering these methodological limitations generalizability of results, regional metanalysis, trend analysis and comparisons among countries should be taken with caution for programmatic actions.
To improve feasibility of implementation of HIVDR surveillance and monitoring, the WHO HIVDR strategy is currently under revision with the development of new surveillance tools:

- TDR threshold surveillance (Bennett et al. 2008);
- Baseline pre-ART surveillance;
- Cross sectional monitoring survey;
- Initial resistance surveillance (pediatric patients <18 months) (Bertagnolio et al. 2012)

In addition, in countries where HIV genotyping is already available, acquired resistance data from patients failing ART could be used for programmatic actions regarding strategic use of ARV armamentarium and inclusion of new ARV drugs.

Considering the challenges faced by National HIV/Aids Programs in the Region, in the context of limited resources and urgent need for optimization, efficiency and effectiveness of ART programs, PAHO/WHO, with the support of partner institutions, convened a technical consultation of program managers and regional experts to discuss current HIVDR evidence in the region, public health priorities for HIVDR surveillance and most appropriate methodologies.

[3] Gupta R et al. Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource limited settings: a global collaborative study and meta-regression analysis. Lancet. 2012 Oct 6; 380(9849):1250-8.
[4] Frentz DF et al. Temporal changes in the epidemiology of transmission of drug resistant HIV-1 across the world. AIDS Rev. 2012; 14: 17-27.
[5] Pineda-Peña AC et al. HIV-1 Transmitted drug resistance in Latin America and the Caribbean: What do we know? AIDS Rev. 2012; 14:256-67.

Purpose, Objectives and Expected Outcomes

Purpose

The purpose of this technical consultation was to support future implementation of harmonized and quality controlled HIVDR surveillance in the LAC region, and guide the development of a technical cooperation agenda to support HIVDR surveillance implementation.

Through plenary discussions and work groups this technical consultation addressed:

- priorities for HIVDR surveillance, based on use of information for public health decision-making at National Program level;
- relevance and feasibility of implementation of WHO recommended HIVDR surveillance generic protocols in LAC; and
- regional agenda of technical cooperation to support HIVDR surveillance in LAC.

Objectives

-
- To review global and regional evidence of HIVDR;
- To discuss priorities for HIVDR surveillance and use of HIVDR data for decision-making from the point of view of National Programs in LAC;
- To review the WHO HIVDR surveillance strategy, and discuss the relevance and feasibility of each surveillance tool in the LAC region;
- To develop a set of recommendations for HIVDR surveillance in LAC.
- To discuss priorities and roles for a regional agenda of technical cooperation to support HIVDR surveillance in LAC.

Expected Outcomes

- Consensus on priorities for HIVDR surveillance and use of HIVDR data for decision-making from the point of view of National Programs in LAC;
- Consensus on relevance and feasibility of implementation of WHO recommended HIVDR surveillance tools in LAC, and recommendations for harmonized methodologies of HIVDR surveillance in LAC.
- Consensus on priorities and roles for a technical cooperation agenda to support HIVDR surveillance in the LAC region, including the formation of a regional HIVDR working group.

Session Overview

Session 1: Overview of HIV Drug Resistance (HIVDR) at global and regional level.

The objective of this first session was to review current evidence of HIVDR from global to regional perspective.

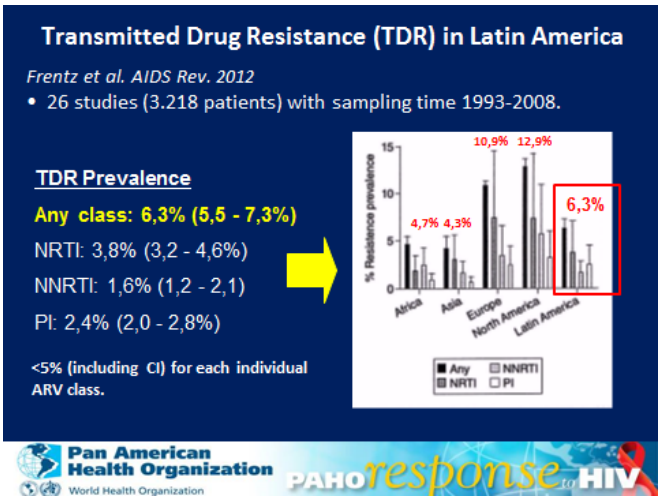
Summary results of HIVDR surveys performed globally between 2004 and 2010 using WHO recommended protocols were presented.).

Conclusions:

- Transmitted resistance (particularly to NNRTI) in recently infected people is increasing over time in areas surveyed in Africa, but still within the expected levels (3.4% in 2009).
- In 2010, HIVDR in pre-treatment population: 5.4% (3.7-7.4) to NNRTI; 6.8% (4.8-9.0) overall.
- Currently recommended first-line ART regimens still effective for most people initiating treatment.
- Response to first-line ART is excellent at 12 month (90% OT, 76% ITT).
- Attention to: unnecessary switch for about 30% of people failing ART with wild type; "possible" drug resistance in about 18% of people at 12 months from ART start (lost to follow up).
- At 12 month, drug resistance patterns largely preserve NRTIs for second line.
- Second line ART is still effective (12 month endpoint) despite partially active NRTI-backbone.

Complete data were published by WHO in the Global HIV Drug Resistance Report in 2012 (http://www.who.int/hiv/pub/drugresistance/report2012/en/index.html

Evidence of HIV Drug resistance in Latin America and the Caribbean was presented, based on recent literature reviews. [6][7][8]



[6] Gupta R et al. Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource limited settings: a global collaborative study and meta-regression analysis. Lancet. 2012 Oct 6; 380(9849):1250-8.

[7] Frentz DF et al. Temporal changes in the epidemiology of transmission of drug resistant HIV-1 across the world. AIDS Rev. 2012; 14: 17-27.

[8] Pineda-Peña AC et al. HIV-1 Transmitted drug resistance in Latin America and the Caribbean: What do we know? AIDS Rev. 2012; 14:256-67.

TDR prevalence in Latin America and the Caribbean.

Pineda-Peña AC et al AIDS Rev, 2012

50 articles + 27 abstracts (1996-2009)

Any ARV: 7,7% (6,54 - 8,98)

NRTI: 4,4% (3,5 - 5,4)

NNRTI: 2,3% (1,7 – 3,1)

PI: 2,1% (1,5 – 2,8)

NRTI/NNRTI: 0,4%

NRTI/PI: 0,5%

Frentz et al. AIDS Rev. 2012

(1993-2008)

Any ARV: 6,3% (5,5 -7,3%)

NRTI: 3,8% (3,2 - 4,6%)

NNRTI: 1,6% (1,2 - 2,1)

PI: 2,4% (2,0 - 2,8%)

Pan American Health Organization
World Health Organization
PAHO response to HIV

TDR prevalence (any ARV drug) in Latin America and the Caribbean.

Pineda-Peña AC et al. AIDS Rev, 2012.

TDR prevalence (1996-2009):

ALC: 7,7% (6,54 - 8,98)

Caribbean: 4,3% (1,87 – 8,29)

Mexico: 3,9% (1,87 – 8,29)

Brazil: 9,4% (7,68 – 11,3)

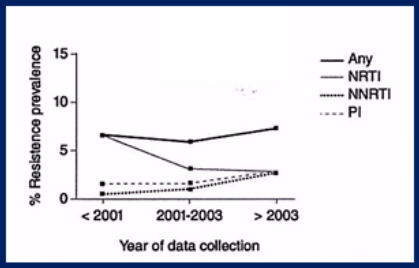
Andean Region: 10% (6,03 – 16,82)

Southern Cone: 4,9% (3,2 – 7,24)

Central America (not available)

Pan American Health Organization
World Health Organization
PAHO response to HIV

Transmitted Drug Resistance (TDR) in Latin America



Time trends (<2001 vs. >2003): NRTI decreased 6,6 to 2,8% (p<0,001)

NNRTI increased 0,6 to 2,7% (p<0,001)

Frentz et al. AIDS Rev. 2012

PI increased 1,6 to 2,7% (p=0,01)

Pan American Health Organization
World Health Organization
PAHO response to HIV

Conclusions:

- Published data on HIVDR in ARV naïve show that prevalence and patterns of resistance vary across subregions and overtime.
- Can we really compare and perform trend analysis with data obtained with such different surveillance methodologies?
- Methodological limitations, especially regarding national representativeness of survey population, are a challenge for the programmatic use of HIVDR data by National Programs.
- HIVDR surveillance should be done using standardized methodology overtime in nationally representative populations.
- HIVDR surveillance should be part of routine national HIV surveillance activities and repeated overtime (as HIV sero-prevalence and behavioral surveys).
- HIVDR prevention activities should be supported and strengthened at country level (Treatment 2.0 – optimization, simplification, improved program efficiency and quality of care; HIVDR early warning Indicators and stock-out monitoring; prevention for positives, etc.).
- Strengthen program monitoring and evaluation of access, coverage, retention and effectiveness (including VL suppression indicators).

The plenary discussion of this first session highlighted the importance of tailoring HIVDR surveillance to the epidemiological context of Latin America and the Caribbean, mostly countries with concentrated epidemics in most- at-risk populations (MARPS), and integrating HIVDR surveillance within HIV surveillance activities already being planned and implemented. Methodological adaptations should also be considered for small countries.

The use of HIVDR data, including viral load suppression analysis, is important for program monitoring and evaluation and decision-making on antiretroviral treatment, but remains a challenge.

Session 2: HIVDR Surveillance from a public health perspective in the context of T 2.0.

The objective of this session was to review the WHO HIVDR Strategy and discuss its linkage to the Treatment 2.0 initiative at regional level, as well as discuss the public health purpose and use of HIVDR surveillance information for decision making.

The WHO Global Strategy for the Surveillance and Monitoring of HIV Drug Resistance, recently revised in 2012, was presented and discussed. The WHO strategy is based on 5 tools:

- Surveillance of transmitted drug resistance (TDR) in recently infected populations.
- Surveillance of HIVDR in populations initiating ART.
- Surveillance of HIVDR in children <18 months of age.
- Surveillance of acquired resistance in populations on ART for >12 and >24 months.
- The pillar of the strategy is the monitoring of HIVDR early warning indicators (EWI).

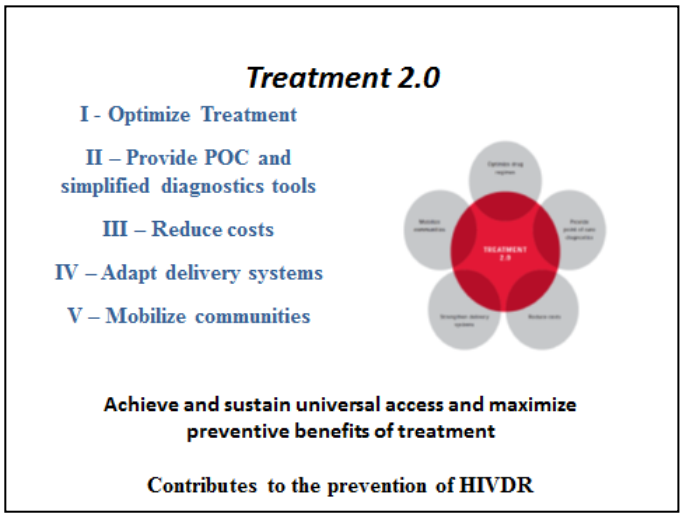
The complete WHO HIVDR strategy has been recently published and is available at:
http://www.who.int/hiv/pub/drugresistance/drug_resistance_strategy/en/index.html

The new 2012 HIVDR EWI guidance is available at:
http://www.who.int/hiv/pub/meetingreports/ewi_meeting_report/en/index.html

More information on the WHO Global HIVDR strategy are available at:
http://www.who.int/hiv/topics/drugresistance/general_info/en/index.html

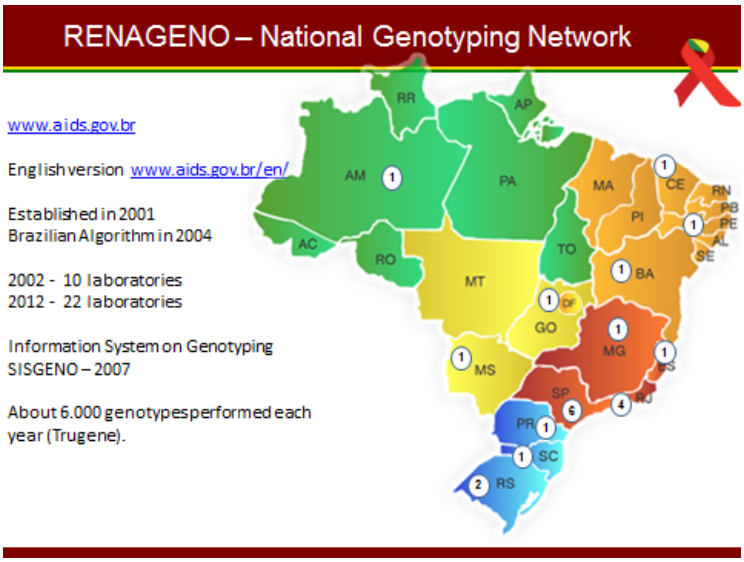
Conclusions:
HIVDR surveillance should aim at providing nationally representative results and generate data for enhanced program and public health decision making.
The new WHO strategy is based on increased flexibility to provide HIVDR surveillance methods that are more relevant in low-prevalence and concentrated HIV epidemics, as well as generalized epidemics.

The Treatment 2.0 initiative and its adaptation for the Latin American and Caribbean Region was then presented, highlighting its linkage to HIVDR surveillance considering the use of HIVDR data to support the ART program optimization process and programmatic monitoring according to the cascade framework of the continuum of care.



Treatment 2.0 is based on five pillars. Complete documents on the Treatment 2.0 strategy are available at: http://www.who.int/hiv/topics/treatment2/en/.

Two National HIVDR strategies from Brazil and Guyana were then presented to support the discussion on setting priorities for HIVDR control at country level and on feasibility of the WHO HIVDR strategy in the Latin American and Caribbean Region.



In Guyana the HIVDR strategy is based on two pillars: EWI monitoring (ongoing since 2008); and HIVDR monitoring survey based on the WHO HIVDR Monitoring protocol (2008 version), currently ongoing and

expected to be finalized in 2013. In addition, the country is assessing quality of care, patient involvement and satisfaction, which provides relevant information for HIVDR prevention.

The plenary discussion highlighted that HIVDR surveillance should aim at generating nationally representative results and should not be area-specific (e.g. one capital city only, one province or health district), since nationally representative data better inform decision making for national policies. For the same reason, HIVDR surveillance sites, as well as EWI monitoring sites, should not be selected for convenience.

Considering the variety of epidemiological profiles in LAC, availability of human and financial resources and laboratory capacity, organization of lab and health service networks and other country specific logistic issues, the approach to HIVDR surveillance implementation should be flexible, as long as the analytical framework is standardized for comparability.

Session 3: Surveillance of transmitted drug resistance (TDR) in recently infected individuals.

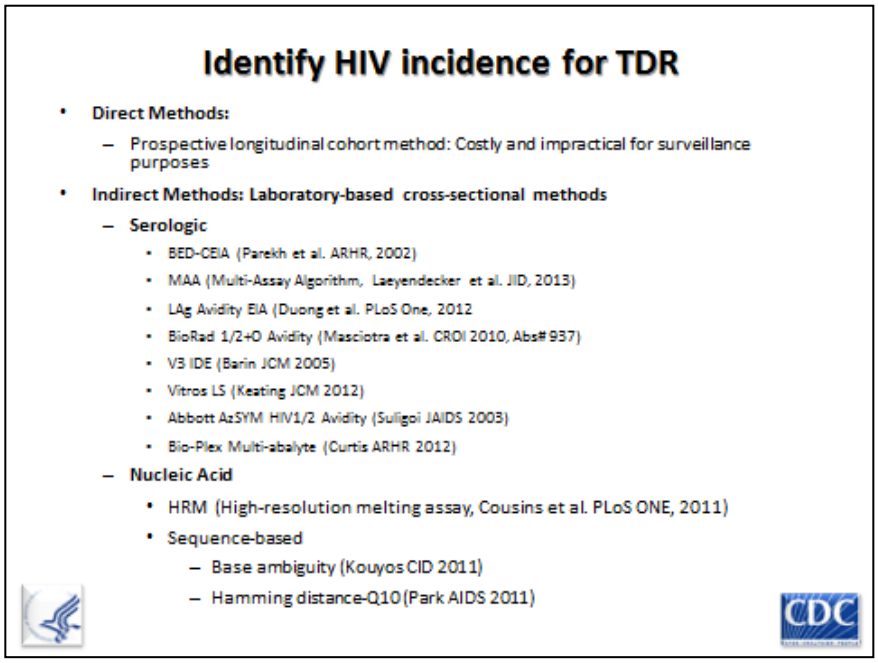
The objective of this session was to review the WHO protocol for TDR surveillance in recently infected individuals and discuss its relevance and feasibility in the LAC region.

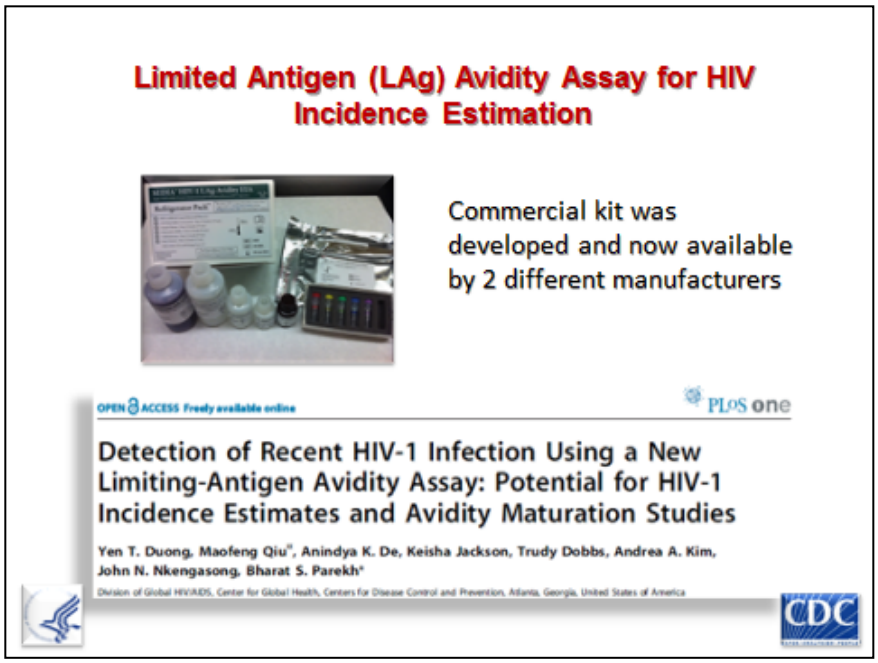
The main elements of the WHO generic protocol for TDR surveillance were presented.
The goal of TDR surveillance is to estimate the national prevalence of drug resistance in a recently infected population by integrating drug resistance testing into a pre-existing HIV surveillance system or routine diagnostic testing.

Examples of Sampling Frames for TDR surveillance:
- Primigravida women <25 years of age included in antenatal care (ANC) surveys;
- Individuals <25 years of age newly diagnosed with HIV at voluntary counseling & testing (VCT) sites (if women, no previous pregnancies);
- Bio-behavioral surveys (BBS) of key populations (MSM, IDU/DU, SW, transgender) <25 years of age;
- HIV case reporting (ex. centralized in a national reference lab): <25 yrs and/or CD4 >500, and no previous pregnancies if female.

The revised WHO protocol for TDR surveillance is available at:
http://www.who.int/hiv/topics/drugresistance/protocols/en/index.html

TDR surveillance is based on the identification of recently infected populations. A summary of direct and indirect methods that can be used to identify incident cases of HIV infection was presented.





Conclusions:

With more accurate incident detection assays at a misclassification rate of <1%, LAg Avidity EIA or MAA combining with CDC low cost HIVDR assay we would be able to:

- Identify recently HIV-infected populations to conduct TDR surveys in regions/countries with concentrated/generalized HIV epidemics using samples collected from sentinel surveys.
- Provide more efficacious treatment regimens to those populations with high level of TDR and mitigate the emergency and transmission of HIVDR.
- Improve care and treatment effectiveness and reduce the cost for program implementation.

Two country experiences of TDR surveillance in recently infected populations (Panama) and in MARPs (Honduras) were presented to support the discussion on the feasibility of TDR surveillance in recently infected in LAC and programmatic use of data.

Once again, the plenary discussion highlighted the importance of performing surveys in nationally representative populations, integrating TDR surveillance within HIV prevalence surveillance activities (ex. ANC surveys, BBS surveys, HIV incidence studies, etc.), or by centralized selection of samples for TDR surveillance at National Reference Labs.

Considering that the ideal samples size (ex. 200) of HIV positive samples in recently infected subjects for TDR point prevalence estimation represents a challenge in the context of low- and concentrated epidemics, feasibility of TDR surveys in LAC was discussed.

Considering integration of TDR surveillance within HIV prevalence activities, the smaller the foreseen sample size of HIV positive samples in recently infected subjects, the larger will be the uncertainty of the survey results (wide confidence interval). It is a country decision to accept the uncertainty of TDR surveillance results, based on national priority and expected use of data. No matter the result, it is part of a larger picture to describe the HIV epidemic and HIVDR. In general, use of confidence intervals is recommended, when analyzing and interpreting survey results.

From the point of view of inclusion criteria for TDR surveillance, the following options were discussed to improve feasibility of TDR surveillance in LAC:

- **Option 1 (ANC setting): Age<25; and no previous pregnancies**
- **Option 2 (other settings): Age<25 or >500 CD4 count; and no previous pregnancies, if female.**
- **Option 3 (any setting): HIV incidence lab assay (MAA or Lag), if available.**

Since the "no previous pregnancy" criterion is used to avoid the risk of inclusion of individuals with previous exposure to PMTCT, if "previous ARV exposure" can be excluded through national information systems/databases/records, the criterion could be dropped.

In case of TDR surveillance implemented through centralized sampling at a National Reference Lab (ex. samples sent for confirmatory HIV test, CD4 or VL) is important to assess the loss between diagnosis and sampling to avoid selection bias.

Session 4: Surveillance of resistance in patients initiating HAART.

The objective of this session was to review WHO protocol for surveillance of resistance in patients initiating ART and discuss its relevance and feasibility in the LAC region.

The WHO generic protocol for surveillance of resistance in patients initiating antiretroviral treatment is currently being revised and its main elements were presented.

The goal of surveillance in patients initiating antiretroviral treatment is to produce a nationally representative estimate of the prevalence of HIVDR in the population initiating treatment, including individuals who may have had prior exposure to antiretroviral drugs (ex. PMTCT).
The primary outcomes are estimated prevalence of HIVDR mutations by drug class among patients initiating therapy. Proposed survey is designed for a confidence interval width of ±4%.

Proposed Survey:
Two-stage cluster survey where countries randomly sample:
1. 10-20 clinics from a list of all clinics in the country, and
2. Consecutive eligible patients within clinics during a predefined three-month period

Sampling Clinics:
The selection of clinics can involve stratification on site type, region, or urban/rural location, if desired.
For the optimal design (smallest confidence interval width for a given sample size), clinics are sampled proportionally to the number of treatment initiators observed at that clinic (Information from a prior time period can be used). If information on treatment initiators is unavailable, clinics can be sampled proportionally to the total number of patients on ART at each clinic.

Extremely Small Clinics:
Countries may have some clinics with extremely small patient populations. The definition of small will be country-specific. If less than 10% of the patient population attends extremely small clinics, these clinics can be ignored without incurring too much bias. Otherwise, countries should take a small representative sample of these clinics

Sampling Clinics Strategies:
- Probability Proportional to Size (PPS) Sampling: Sample clinics proportional to the number of treatment initiators at each clinic.
- Probability Proportional to Proxy Size (PPPS) Sampling: Sample clinics proportional to total number of patients on ART at each clinic.

Sampling Patients from Clinics:
Clearly define enrollment period, such as a three-month period.
Screen consecutive patients for eligibility at each sampled site.
Eligible patients are sampled until the patient quota is achieved or the enrollment period ends.

Goal is to construct a nationally representative estimate of the prevalence of HIVDR in population initiating ART. Countries with few clinics can adjust their sample size requirements to reflect the total eligible population size.

Three country experiences of surveillance of resistance in patients initiating ART (Brazil, Mexico and Trinidad and Tobago) were presented to support the discussion on the feasibility of surveillance of resistance in patients initiating ART in LAC and programmatic use of data.

The plenary discussion supported the feasibility of implementation of these surveys in the vast majority of countries in the region and with nationally representative survey design and consecutive sampling of individuals initiating first line ART at selected site. Different approaches may be required in countries with large number of clinics vs. small number of clinics and/or very small clinics.
These surveys may include participants with previous exposure to ARVs (ex. PMTCT, ART in private sector, migrant subjects with previous ARV exposure abroad, etc.).
For the interpretation of results the WHO mutation list is recommended (to be updated in 2013)[9] as well as the Stanford Score (http://hivdb.stanford.edu).

[9] Bennet *et al*. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS One. 2009;4(3):e4724.

Session 5: Surveillance of acquired resistance in patients on HAART.

The objective of this session was to review WHO protocol for surveillance of acquired drug resistance (ADR) in patients on HAART and discuss its relevance and feasibility in the LAC region.

The main elements of the WHO generic protocol for surveillance of acquired resistance in patients on HAART (all patients on ART for more than 6 months) were presented.

The goal of ADR surveillance is:

- Measure nationally representative outcomes relating to viral load suppression and HIVDR;

In addition, viral load suppression outcome will inform program functioning, and observed HIVDR will support selection of second-line ART.

The Primary Outcomes are:

1. Using cross-sectional data from patients on therapy for more than 6 months, describe the prevalence of viral load suppression as a function of the length of time on ART.
2. Produce a nationally representative estimate of the prevalence of viral load failure and HIVDR in the population on ART for more than 6 months.

Proposed survey is designed for a confidence interval width of ±5%.

Proposed Survey:
Two-stage cluster survey where countries randomly sample

1. 10-20 clinics from a list of all clinics in the country (sampling proceeds in the same manner described for the pre-treatment survey), and
2. consecutive eligible patients within clinics during a predefined three-month period.

Countries with routine viral load testing can use existing data to construct the viral load suppression curve. Countries with routine genotyping among patients with viral load failure can use existing data to construct the prevalence of HIVDR/Viral Load Failure.

The revised WHO protocol for ADR surveillance is available at:
http://www.who.int/hiv/topics/drugresistance/protocols/en/index.html

One country experience of ADR surveillance (viral load suppression rates and resistance profile at first failure using existing data from Brazil) was presented to support the discussion on the feasibility of ADR surveillance in LAC and programmatic use of data.

The plenary discussion mainly focused on feasibility of ADR surveillance using existing data (ex. Brazil), especially considering that many countries in the region are scaling up viral load monitoring and some countries have access to HIV genotyping at treatment failure.

In countries with existing data (viral load and/or genotyping) the WHO analytical framework could be applied, provided viral load (or genotyping) monitoring is scaled up at national level, and therefore data may be considered nationally representative.

Limited viral load scale up at country level and fragmented data in separate information systems were also highlighted as common challenges for ADR surveillance using existing data.

Countries that wish to use existing data to apply WHO analytical framework for ADR surveillance should assess viral load coverage to make sure that program data are acceptable and reliable for national representativeness. Performing a national survey and comparing results with existing data could be used as a validation process for future ongoing ADR surveillance with national program data.

Session 6: Surveillance of initial resistance in pediatric patients <18 months of age.

The objective of this session was to review the WHO recommended protocol for surveillance of initial resistance in pediatric patients <18 months of age and discuss its relevance and feasibility in the LAC region.

The main elements of the WHO generic protocol for surveillance of initial resistance in pediatric patients <18 months of age were presented.[10]

The objectives of initial resistance surveillance are:

- To describe the prevalence of initial NNRTI and NRTI resistance in newly-diagnosed children < 18 months receiving Early Infant Diagnosis for whom previous ARV exposure is recorded as "known", "none" or "unknown.
- To evaluate the impact of PMTCT scale up on the pattern of resistance acquired by infants acquiring the infection despite PMTCT.
- Inform the identification of the best strategy to treat HIV infected infants (LPV/r vs NVP-based).

These are retrospective cross-sectional surveys of HIV drug resistance prevalence among children diagnosed with HIV by Early Infant Diagnosis methodology using remnant DBS specimens.

The revised WHO protocol for initial resistance surveillance is available at:
http://www.who.int/hiv/topics/drugresistance/protocols/en/index.html

Two country experiences of HIVDR surveillance in children (Brazil and Panama) were presented to support the discussion on the feasibility of initial resistance surveillance in LAC and programmatic use of data.

Considering the regional progress towards elimination of vertical transmission of HIV, many countries have very low numbers of HIV cases diagnosed in children less than 18 months of age. In addition, use of single dose Nevirapine for prevention of mother to child transmission, associated with higher risk of resistance, is not common in this region.

In most countries the surveillance plan is more likely to be a census of all cases. In case of sample size calculation, finite population correction should be used in this region.

Some countries in the region already perform HIV genotyping in this population (ex. Brazil) and may use existing data for surveillance purpose.

[10] Bertagnolio S *et al*. World Health Organization Generic Protocol to Assess Drug-Resistant HIV Among Children <18 Months of Age and Newly Diagnosed With HIV in Resource-Limited Countries. Clinical Infectious Diseases 2012; 54(S4):S254–60.

Session 7: Work group discussion on HIVDR surveillance and consensus building session.

This was a break-out session for working groups. The working groups were organized as follows:

Group 1	Group 2	Group 3
Michael Jordan	Giovanni Ravasi	Noreen Jack
Gustavo Reyes Terán	Silvia Bertagnolio	Natalie Exner
Rosangela Ribeiro	Eddie Antonio León Juárez	Chris Archibald
Carlos Rafael Genovez	Emiliano Bissio	Shanti Singh
Rodrigo Tobar	José Ledesma	Gerard Joseph
Juan Pascale	José Carlos Couto Fernandez	Ayanna Sebro
Anderson Pereira	Luis Bonilla	George Dos Santos
Amilcar Tanuri	Ricardo Diaz	Glavia Delva
Horacio Salomon	Unaí Tupinambá	Chunfu Yang
Juan Pascale	Ivette Lorenzana	Paul Sandstrom
	Santiago Ávila	

Groups discussed and answered to the following 4 questions:

1. Which HIVDR surveillance protocols should be prioritized, based on identified public health priorities at National Program level and feasibility in the LAC region?
2. Which are the most relevant challenges for the implementation of harmonized and quality controlled HIVDR surveillance in the region?
3. Which are the most relevant challenges for the programmatic use of HIVDR surveillance data to support decision making at National Program level?
4. Recommendations from the group about technical cooperation needs to support harmonized and quality controlled HIVDR surveillance in the region.

The answers from the three groups are included in the Annex 2 of this report.

Session 8: Consensus building session on prioritization of HIVDR surveillance protocols in the LAC region.

Recommendations from the groups are presented in the following chapter “Recommendations and Proposals from the Meeting”.

Session 9: Perspectives of technical cooperation to support HIVDR surveillance in the LAC region.

The objective of this session was to discuss priorities and roles for a technical cooperation agenda to support HIVDR surveillance in the region.

The session was opened by a presentation on the WHO HIVDR Laboratory Network with highlights on the status of accreditation of labs in the region of the Americas. As of 2013, the region has two Specialized Drug Resistance Labs (Atlanta, USA; Ottawa, Canada); two Regional Drug Resistance Labs (Ponce, Puerto Rico; Fort-de-France, Martinique); and one National Drug Resistance Lab in Rio de Janeiro, Brazil. In addition, two regional labs (Mexico City, Mexico; Rio de Janeiro, Brazil) and one national lab (São Paulo, Brazil) are in the process of evaluation.

Complete information on the WHO HIVDR Laboratory Network is available at:
http://www.who.int/hiv/topics/drugresistance/laboratory/en/index.html

The plenary discussion stressed on the importance of guaranteeing quality controlled genotyping for HIVDR surveillance in countries with or without WHO accredited labs. The WHO HIVDR Lab network should support countries with no genotyping capacity or no accredited labs in the implementation of quality controlled HIVDR surveys.

Considering the newly revised WHO HIVDR surveillance protocols and their increased feasibility in the context of concentrated epidemics, it is expected that more countries will start planning and implementing HIVDR surveillance in LAC. Countries wishing to implement quality controlled HIVDR surveillance according to WHO methodological standards could refer to the WHO network, or apply for accreditation of a national reference lab, provided compulsory criteria are met.
Although the WHO accreditation process was perceived lengthy and bureaucratic by some countries, it was recognized the importance of WHO accreditation and of quality controlled genotyping to support the use of HIVDR surveillance data by decision makers at National Program level.

The group recognized that the Latin American and Caribbean Region is rich in technical capacity and human resources to support HIVDR surveillance, although still presents important disparities among countries. International collaborative initiatives that are based on horizontal technical cooperation and transfer of technology should be promoted to support quality controlled genotyping and a harmonized methodological approach to HIVDR surveillance.

Based on recommendations from the groups, participants also discussed the possibility of creating regional, or sub-regional, working groups that may operate as knowledge hubs or networks with the objective of discussing HIVDR surveillance issues from a regional perspective and supporting HIVDR surveillance implementation by mobilizing technical capacity in a more coordinated and efficient way.

Term of reference of such working groups, including memberships and roles, should be developed. PAHO/WHO could have a coordinating role, but it is fundamental that these working groups should liaise with regional/sub-regional coordination mechanisms for horizontal technical cooperation (ex. Horizontal Technical Cooperation Group - HTCG in Latin America). The HTCG, not only should be a prominent partner for technical cooperation, but a space to meet and discuss FRHIV policies in a systematic manner. In the Caribbean, CARPHA and PANCAP will be important partners in this process.

Priorities, Challenges and Recommendations

The following priorities, challenges and recommendations are based on consolidated common answers across the three groups and based on the four key questions of the work group session.

Question 1 - Which HIVDR surveillance protocols should be prioritized, based on identified public health priorities at National Program level and feasibility in the LAC region?

Across the groups, WHO pre-treatment and acquired resistance surveillance protocols were prioritized and identified as more practically relevant for National Programs in the Region, since they provide complementary strategic information for the assessment of ART program effectiveness, which may have an immediate impact on the quality of treatment and care of people living with HIV. These surveys may be implemented in both adult and pediatric populations (according to country specific definitions of pediatric population).

1. **Pre-treatment Resistance Surveillance**
   Surveillance of pre-HAART resistance is generally feasible in all countries, even in small countries, where all treatment initiators can be sampled and small clinics included for representativeness.
   Inclusion of specific variables could enable analysis of pre-HAART resistance in special populations (e.g. pregnant women, migrant, etc.), and inclusion of baseline CD4 count analysis of pre-HAART resistance in individuals in different CD4 count intervals.

2. **Acquired Resistance Surveillance**
   Surveillance of acquired resistance (HIV viral load suppression rate, % of individual with detectable viral load with or without evidence of acquired resistance) mat be implemented both in countries with or without systematic viral load monitoring. At country level, it is important to assess, identify and address the challenges and logistic difficulties to scale up access to viral load.
   This surveillance may promote the expansion and decentralization of viral load monitoring at country level, and will provide a standardized framework to assisting countries in making recommendations on switch to second line and appropriate second line regimens.

3. **Surveillance of Transmitted Drug Resistance**
   Even though in some countries could be identified as a priority, based on the many methodological limitations and challenges identified during the discussion, surveillance of transmitted drug resistance was not considered as a regional priority for HIVDR surveillance.
   Countries which identify TDR surveillance as a priority should integrate it into existing surveillance activities (either special surveys or HIV case-based surveillance systems).

4. **Surveillance of Initial Resistance in Children with less than 18 months**
   Initial surveillance in children was also considered less of a priority in the Region, considering that, in line with the Elimination Initiative, cases of vertical transmission are declining in many countries. On the other hand, countries with installed HIV genotyping capacity could consider performing a baseline resistance test in all HIV+ children, as part of the recommended clinical monitoring, and use those data for surveillance purpose, provided the representativeness of the sample.

Additional considerations on Question 1:

- For any type of surveillance, it is desirable to guarantee national representativeness.
- In addition it is important to reinforce the implementation EWI in each country.
- Apart from the main outcomes of HIVDR surveillance, surveys could include additional tests to provide information on HIV subtypes, phenotype, immunological characterization at population level, etc.

Question 2 - Which are the most relevant challenges for the implementation of harmonized and quality controlled HIVDR surveillance in the region?

1. Genotyping, viral load and other laboratory related issues

- Limited national laboratory capacity to perform quality controlled HIV genotyping and limited access to external quality assurance programs.
- Limited human resources trained on HIV genotyping and need for harmonized training and regular refresher training.
- The process of accreditation to the WHO HIVDR Lab Network guarantees quality controlled results and may give more credibility at national level, but the process is lengthy, bureaucratic, and depends on political will and support.
- High costs of commercial genotyping kits, as well as differences in cost among countries in the region. In House methods are cheaper, but require homologation of methodology and quality control.
- In certain settings (Caribbean) transportation of samples is an issue and dried blood spots (DBS) could be a solution. Very few labs in the WHO network are accredited for DBS (CDC, France, Kenya).
- Countries still experience limitations in scaling up viral load monitoring, especially in case of centralized access. Some Caribbean countries (OECS) do not have viral load capacity and access viral load testing from countries with national capacity.

2. Funding issues

- Dependency on external financial support.
- Limited integration of HIVDR surveillance activities within National Program work-plans and budgets. Ministries of Health should identify resources, from national budget or external cooperation, to support the implementation of HIV genotyping, maintain equipment, buy kits and reagents, and train lab personnel.

3. Political issues

- Changes in personnel and priorities at national program level.
- Advocacy. It is necessary to convince funders and policy makers of the importance of HIVDR surveillance as a way to monitor and address the sustainability of national treatment programs. Economic analysis could demonstrate the long-term economic benefits of implementing HIVDR surveillance.
- Integration of HIVDR surveillance within routine HIV surveillance activities.

4. Technical cooperation issues

- Need to have reference documents on new WHO generic standardized protocols as soon as possible.
- Need of external technical support for protocol adaptation and implementation of HIVDR surveillance.

Question 3 - Which are the most relevant challenges for the programmatic use of HIVDR surveillance data to support decision making at National Program level?

1. Genotyping and HIVDR surveillance related issues

- Laboratories must perform high quality HIV genotyping information for decision takers.
- HIVDR surveillance studies need to generate nationally representative results.

2. Public Health issues

- Limited culture of evidence based decision-making and use of data at program level.
- Limited knowledge on HIVDR surveillance data interpretation and how to translate it into decisions and public health actions (ex. guidelines adaption, drug procurement issues, personnel training, adherence and follow up in care).
- Need of empowerment of decision makers on interpretation and efficient use of HIVDR surveillance data is needed.
- Need of local and regional technical assistance for the analysis of HIVDR surveillance data.
- Disconnection between national HIVDR experts (Universities, Laboratories and other research institutions) and programs. National programs should create and coordinate national intersectoral working or advisory groups (Ministry of Health, Universities, Laboratories, Specialized societies, UN Agencies, etc.) to discuss technical issues, including HIVDR, to strengthen collaboration, communication and timely sharing of information between HIVDR experts and program managers.

Question 4 - Recommendations from the group about technical cooperation needs to support harmonized and quality controlled HIVDR surveillance in the region.

1. Lab capacity building

- Technical assistance should be provided to build lab capacity for the implementation of HIV genotyping at country level, including access to external quality assurance programs.
- Countries should be supported to negotiate better prices for kits and reagents for viral load, CD4 count and genotyping (ex. Strategic Fund).
- Countries should be supported in the scale up and optimization (universal access, turn around time, use of DBS, etc.) of viral load testing.
- WHO accredited laboratories in the region should support countries with limited lab capacity to perform HIV genotyping and viral load measurement in the context of HIVDR surveillance activities.

2. Training activities

- Training and capacity building activities on epidemiological analysis, interpretation and use of HIVDR surveillance data for public health decision-making.
- Training activities on interpretation of genotyping results for clinical monitoring purpose. This should include regional networks to discuss difficult and unusual cases.

3. Technical cooperation

- WHO should finalize all reference documents for HIVDR surveillance protocols. WHO protocols should include clear guidance on use of data for public health actions, possibly presenting the cost-benefit aspect of HIVDR surveillance for enhanced sustainability of national programs.
- Technical cooperation should be made available to assist countries in HIVDR surveillance protocol development and implementation, for example through the conformation of technical groups and networks at regional/subregional level to provide technical cooperation and support countries in the implementation of quality controlled and harmonized HIVDR surveillance.
- Follow up activities with the participation of National Program Directors should be organized at subregional level to present the new WHO HIVDR surveillance protocols and these recommendations.

Annex 1. Meeting agenda

Technical Consultation on HIV Drug Resistance Surveillance in Latin America and the Caribbean Region -19-21/3/2013 - Brasilia, Brazil

Day 1,		
8:00 - 8:30	Registration	
8:30 – 9:00	Welcome remarks	PAHO/WHO, Dep DST/aids/HV
9:00 – 9:15	Introduction and Objectives	PAHO
Session 1: 9:30 – 10:30 **Overview of HIV Drug Resistance (HIVDR) at global and regional level.** Objective: review current evidence of HIVDR from global to regional perspective. Chair: **Chris Archibald** Rapporteur: **Noreen Jack**		
20 min	WHO Global HIVDR report 2012	WHO
20 min	HIVDR in Latin America and Caribbean	PAHO
20 min	Q/A – Discussion: evidence of HIVDR resistance in LAC	
10:30 – 10:50	**Coffee Break**	
Session 2: 10:50 – 12:30 **HIV Drug Resistance Surveillance from a public health perspective in the context of Treatment 2.0.** Objective: review the WHO HIVDR Strategy and discuss its link to the Treatment 2.0 initiative at regional level. Discuss the public health purpose and use of HIVDR surveillance information for decision making (ex. ART guidelines development/update, use of genotyping, etc.). Chair: **Chris Archibald** Rapporteur: **Noreen Jack**		
20 min	WHO HIVDR Strategy 2012 and public health actions based on HIVDR surveillance	WHO
10 min	Treatment 2.0: Regional adaptation and strategies of implementation in LAC	PAHO
20 min	National HIVDR Strategy. Country experiences (10 minutes each): ▪ Brazil ▪ Guyana	 Dirceu Greco Shanti Singh
50 min	Q/A – Discussion and Consensus building session: Setting regional priorities for HIVDR surveillance and use of HIVDR data for decision-making from the point of view of National Programs in LAC (ex. Decision making for ART guidelines development/update, use of genotyping, etc.)	

12:30-14:00	**Lunch**	
<u>Session 3: 14:00 – 15:15</u> **Surveillance of transmitted drug resistance (TDR) in recently infected individuals** Objective: review WHO protocol for TDR surveillance in recently infected individuals and discuss its relevance and feasibility in the LAC region and adaptation at country level. Chair: **Silvia Bertagnolio** Rapporteur: **Noreen Jack**		
15 min	Surveillance of transmitted drug resistance (TDR) in recently infected individuals	WHO
15 min	Defining recent HIV infection for TDR surveillance	CDC
20 min	Country experiences (10 minutes each): ▪ Panama ▪ Honduras	Juan Pascal Ivette Lorenzana
25 min	Q/A – Discussion: feasibility of TDR surveillance in recently infected in LAC and programmatic use of data.	
15:15 – 15:30	**Coffee Break**	
<u>Session 4: 15:30 – 16:50</u> **Surveillance of resistance in patients initiating HAART.** Objective: review WHO protocol for surveillance of resistance in patients initiating ART and discuss its relevance and feasibility in the LAC region and adaptation at country level. Chair: **Silvia Bertagnolio** Rapporteur: **Noreen Jack**		
20 min	WHO protocol for surveillance of resistance in patients initiating HAART.	WHO
30 min	Country experiences (10 minutes each): ▪ Brazil ▪ Mexico ▪ TRT	Amilcar Tanuri Santiago Àvila TRT
30 min	Q/A – Discussion: feasibility Surveillance of resistance in patients initiating HAART in LAC and programmatic use of data.	
16:50 – 17:00	Closing of first day	

Day 2,		
8:30 – 9:00	Review of first day	Rapporteurs 1st day
Session 5: 9:00 – 10:30 **Surveillance of acquired resistance in patients on HAART** Objective: review WHO protocol for surveillance of acquired resistance in patients on HAART and discuss its relevance and feasibility in the LAC region and adaptation at country level. Chairs: **Chunfu Yang** Rapporteur: **Giovanni Ravasi**		
20 min	WHO cross sectional surveys for acquired resistance	WHO
20 min	Country experiences (10 minutes each): ▪ Brazil ▪ WHO (Country simulation exercise)	Marcelo Freitas Michael Jordan
50 min	Q/A – Discussion: ▪ How to measure the clinical impact of HIVDR in patients on HAART. ▪ Feasibility of cross sectional surveys for acquired resistance in LAC and programmatic use of data.	
10:30 – 10:45	**Coffee Break**	
Session 6: 10:45 – 12:30 **Surveillance of initial resistance in pediatric patients <18 months of age** Objective: review WHO recommended protocol for surveillance of initial resistance in pediatric patients <18 months of ageand discuss its relevance and feasibility in the LAC region and adaptation at country level. Chairs: **Chunfu Yang** Rapporteur: **Giovanni Ravasi**		
20 min	WHO recommended protocol for surveillance of initial resistance in pediatric patients <18 months of age	WHO
20 min	Country experiences (10 minutes each): ▪ Brazil ▪ Panama	Rodrigo Zilli Juan Pascal
50 min	Q/A – Discussion: feasibility of surveillance of initial resistance in pediatric patients <18 months of age in LAC and programmatic use of data.	
12:15 – 14:00	**Lunch**	
Session 7: 14:00 – 16:45 **Work group discussion on HIVDR surveillance**		
14:00 – 14:30	Work group formation (3 groups). Each group will discuss the relevance of WHO protocols for the LAC region, considering regional public health priorities and their feasibility in the context of concentrated epidemics. The groups should respond to the following questions:	

	1. Which HIVDR surveillance protocols should be prioritized, based on identified public health priorities at National Program level and feasibility in the LAC region? 2. Which are the most relevant challenges for the implementation of harmonized and quality controlled HIVDR surveillance in the region? 3. Which are the most relevant challenges for the programmatic use of HIVDR surveillance data to support decision making at National Program level ? 4. Recommendations from the group about technical cooperation needs to support harmonized and quality controlled HIVDR surveillance in the region.	
14:30 - 16:45	Group work	
16:45 – 17:00	Closing of second day	
Day 3,		
8:30 – 9:00	Review of second day	Rapporteurs 2nd day
Session 8: 9:00 – 10:30 **Consensus building session on prioritization of HIVDR surveillance protocols in the LAC region.** Objective: building consensus on recommendations for HIVDR surveillance based on identified public health priorities, challenges for implementation of harmonized protocols with quality control and use of data for public health actions in LAC Chairs: **Paul Sandstrom** Rapporteurs: **Michael Jordan, Pamela Bermúdez**		
9:00 – 09:45	Presentation of groups (15 min presentation for each group)	
09:45 – 10:30	Consensus building session on prioritization of HIVDR surveillance protocols in the LAC region.	
10:30 – 10:45	**Coffee Break**	
Session 9: 10:45 – 12:15 **Perspectives of technical cooperation to support HIVDR surveillance in the LAC region** Objective: Discuss priorities and roles for a technical cooperation agenda to support HIVDR surveillance in the region. Chairs: **Paul Sandstrom** Rapporteurs: **Michael Jordan, Pamela Bermúdez**		
10:45 – 11:00	▪ WHO HIVDR Lab Network Update	WHO

11:00 – 11:45	Plenary session to discuss areas of technical cooperation to support HIVDR surveillance in LAC: ▪ Technical cooperation for lab capacity building for genotyping, including quality assurance; ▪ Technical support to implement HIVDR surveillance in LAC; ▪ Development of a regional HIVDR working group.	
11:45-12:15	Consensus building session on priorities and roles for a technical cooperation agenda to support HIVDR surveillance in the region.	
12:15 – 12:30	Closing remarks	
12:30 – 14:00	**Lunch**	

Annex 2. Working groups results

Question 1 - Which HIVDR surveillance protocols should be prioritized, based on identified public health priorities at National Program level and feasibility in the LAC region?

Group 1

1. **Pre-treatment**
2. **Acquired resistance**
3. **TDR**
4. **Pediatric (mininos)**

In addition it is important to reinforce the implementation EWI in each country, something that can be done by the National Programs without great expenses

Group 2

Los siguientes dos protocolos se consideraron igualmente prioritarios, por que proporcionan informaciones complementares para informar sobre efectividad de los programas de TAR:
Resistencia pre tratamiento (con foco en poblaciones específicas: mujeres embarazadas, migrantes y deportados – incluir variables para identificar estas poblaciones); y
Resistencia adquirida (tasa de supresión de carga viral, % de casos con carga viral con y sin evidencia de resistencia)
Resistencia pediátrica: considerada la baja cantidad de casos en la mayoría de los países de la región, se recomienda realizar genotipaje en todos los casos y utilizar los datos del censo para vigilancia.
Resistencia transmitida: considerados los criterios estrictos, la tendencia de diagnóstico tardío, y la posible complejidad de implementación de pruebas de incidencia, entre otras limitaciones, estos protocolos se consideraron importantes, pero menos prioritarios.
En general es deseable utilizar un muestreo representativo nacional.
Integrar en estudios de vigilancia otras evaluaciones (subtipos, fenotipos, aplotipos, etc.).

Group 3

1. **Pre-treatment Drug Resistance**

More practically relevant
Small countries can sample all treatment initiators, as data on treatment initiators are available.
Proposed sample sizes are feasible for other countries.
Might be interested in analyzing the relationship between treatment resistance and CD4 at the time of presentation- stratifying the CD4 at the initiation (sub population for the TDR)

Many countries patients presenting for the first time have low CD4 (<200)- there should be the interest in effective viral suppression of this population- hence the importance of the Pre treatment survey.
For small countries, sample from all clinics. Do not want to exclude small clinics

2. Acquired Drug Resistance

Provide the Public Health Approach vs Individual care approach
Provide the framework and a Standardise way assisting countries in making recommendations on switch to second line- appropriate regimens.
This would push programmes to strengthen it VL monitoring
For countries without VL testing
For countries with VL testing – logistic challenges in making VL accessible to all (eg special days for blood draw etc). With some of the logistic difficulties- important to better understand how to treat with VL samples (storage, shipping etc). Decentralising of VL?

3. Transmitted Drug Resistance

Greater interested in pre-treatment strategy and acquired than transmitted drug resistance.
In a limited resource setting, do not have the luxury to collect information for use in the future vs the need to collect information that can impact patient treatment now.
Challenging to achieve the numbers necessary for this survey(especially in terms of applying the epidemiological criteria)
Because of this- possibility of 2 countries (Haiti and the DR). If done then the results could be shared with the wider Caribbean.
Proposals for moving forward:
Integrate into existing surveillance. Existing surveillance is recommended case-based surveillance system (follow patients over time).
Integrate any planned special surveys.

4. Pediatric Drug Resistance

Least priority.
Numbers are extremely small in the Caribbean, with some countries reporting 0 MTCT.
In line with the Elimination Initiative- the numbers will continue to decline.
Proposal – Include paediatric cases (country specific definitions) in the Acquired Drug Resistance Survey.

Question 2 - Which are the most relevant challenges for the implementation of harmonized and quality controlled HIVDR surveillance in the region?

Group 1

- **Genotyping**

QA process
Accreditation system: slow, bureaucratic, painful

- **Funding**

Diversion of resources from clinical care to surveillance

Dependency of external support
Identification of funding resources within the country

- **Political issues**

Changes in personnel and priorities
Examples: Ecuador

- **Public Health issues**

External TAs to help with methodology and implementation
Efficient use of the data generated

Group 2

- Abogacía. OPS/OMS debería seguir impulsando el tema a nivel de la región y apoyar a los PN para la implementación de estudios de vigilancia de la FR en los países.
- Contar con documentos de referencia sobre los protocolos de vigilancia (en español, ingles, etc.)
- Asesoría técnica para el desarrollo/adaptación de los protocolos a nivel nacional.
- Integración en presupuestos nacionales (Ministerio de Salud). Los Programas Nacionales deberían identificar recursos, propios o de cooperación, para implantar genotipaje, mantener equipamientos, comprar reactivos y capacitar recurso humanos.
- Integración de la vigilancia de la resistencia en las practicas rutinarias de vigilancia en la redes de servicios y de laboratorios. Capacitación de recursos humanos de las redes.
- Apoyo técnico para implantación de genotipaje (estructura del laboratorio, flujos de trabajo, conservación de muestras, SOPs, etc.)
- Laboratorio: carencia de recursos humanos capacitados en genotipificación. Necesidad de entrenamiento armonizado y regular .
- Diferencias de precios de los kits de genotipificación (kits comerciales). In House es más económico, pero necesitaría homologar la metodología y establecer control de calidad.
- Participación en programas externos de control de calidad.

Group 3

- Convincing funders/policy makers on the importance of the surveys and address the sustainability (integrating into case base surveillance)- Suggested a cost analysis/ cost benefit study to demonstrate the long term economic benefits of conducting these surveys. Important to convince the policy makers.
- Protocol- there is a need for a standardized protocol (design, implementation, reporting, data analysis and reporting) as early as possible so that the momentum is not lost.
- Cost - genotyping and transportation- Suggestion that we could use dried blood spots

- Limited access to laboratory testing- Labs need to be quality assured by WHO- Only 4 laboratories in the Region- Associated logistics in regards to shipping of samples (in addition to cost)
- Even fewer labs approved to do genotyping for dried blood spots. 3 labs presently (CDC, France, Kenya).
- VL- there is more access- difficulties in a centralized system in some case and in others no VL capacity in country.

Question 3 - Which are the most relevant challenges for the programmatic use of HIVDR surveillance data to support decision making at National Program level ?

Group 1

- **Public Health issues**

Representation of the information a the national level
Efficient use of the data generated
Support a local and regional technical assistance system for the analysis of the data obtained
Importance of the data for decision takers?

- **Integrate expertise within the country**

Disconnection between experts inside the country

- **Genotype use**

Generate high quality information for decision takers
Assure an efficient system for interpretation of the results

Group 2

- Empoderamiento de los PN en el tema de la vigilancia de la FR y uso de la información.
- Conformación de una "mesa técnica" sobre antirretrovirales, coordinada por el Programa Nacional (miembros: PN, Agencias, Sociedades Especializadas, Laboratorios, Universidades, etc.) para discusión de temas técnicos.
- Fortalecimiento de la comunicación entre universidades y programas (Ex. para proyectos de investigación: producción de informes regulares – updates - sobre avances de implementación de los estudios enviados al MS y coordinaciones locales).
- Desarrollo de una base de datos Global/Regional para análisis de datos de vigilancia producidos con metodologías estandarizadas y con calidad

Group 3

- How we transitioned the necessary actions based on the findings?
- Guidelines adaption
- Procurement issues.
- Training.
- Adherence
- Follow up in care.
- Cost for the changes.
- TWGs existing in countries – capacity to use the data?
- Proposal: The protocol has to include the areas for actions

Question 4 - Recommendations from the group about technical cooperation needs to support harmonized and quality controlled HIVDR surveillance in the region.

Group 1

Genotyping
Implement in each country a ARV drug resistance testing system
Training about interpretation of genotyping results
Regional network to discuss difficult and unusual cases
Public health
Workshops in epidemiological analysis and use of the information
Sell the results to decision takers (lobby)
If the person/s in charge do not recognize the importance of the information nothing will be done to implement necessary changes
What we should not do
Invest in activities that do not promote technology transference and capacity building: Example the CA HIV Reference Lab

Group 2

- Diagnostico situacional en los países (capacidad de laboratorio, acceso a geno/carga viral, bases de datos/sistemas de información, etc.).
- Desarrollar documentos de referencia para la vigilancia de la resistencia.
- Garantizar el acceso a programas externos de control de calidad.
- Conformación de un Grupo Técnico Regional en red para apoyar a los países en las necesidades identificadas. Se propone la posibilidad de coordinación de OPS/GCTH.
- Incluir el tema en la pauta de una próxima reunión de Directores de Programa

Group 3

- Protocol development and implementation
- Capacity building for the interpretation of the results.
- Capacity building for action based on the results- Defined in the protocol.
- In country capacity building along the way
- Optimization of the VL testing (internal issue that countries should address)
- - For countries that have VL- turn around time?
- -For countries who don't have how do they get access to this. (This issue be raised at an upcoming regional meeting)
- Inventory of Labs in the Caribbean needed- VL (Caribbean Med Labs- PANCAP/GF). PT needs to be addressed in these labs. (CARPHA).
- Possibility to build capacity for DBS testing for VL- because of the logistics in some countries.
- Genotyping- Coordinating laboratory centers within the Caribbean to do QA (centers of Excellence) and that these labs would then have international PT.
- Capacity of a regional laboratory to do culture
- EWI and the HIVDR surveys.

Annex 3. List of Participants

Name	Country	Agency/Institution	e-mail
Dirceu Greco	Brazil	Ministry of Health	dirceu.greco@aids.gov.br
Marcelo Freitas	Brazil	Ministry of Health	marcelo.freitas@aids.gov.br
Rodrigo Zilli	Brazil	Ministry of Health	rodrigo.zilli@aids.gov.br
Rosangela Ribeiro	Brazil	Ministry of Health	rosangela.ribeiro@aids.gov.br
Ana Flávia Nassif P. Coelho Pires	Brazil	Ministry of Health	ana.pires@aids.gov.br
Anderson Pereira	Brazil	Ministry of Health	anderson.pereira@aids.gov.br
Francisco Viegas	Brazil	Ministry of Health	francisco.viegas@aids.gov.br
Emiliano Bissio	Argentina	Ministry of Health	ebissio@gmail.com
Rodrigo Tobar	Ecuador	Ministry of Health	rtobar_99@yahoo.com
Carlos Rafael Genovez	El Salvador	Ministry of Health	crgenovez@gmail.com
Eddie Antonio León Juárez	Mexico	Ministry of Health	edyleon_64@hotmail.com
Shanti Singh	Guyana	Ministry of Health	fsjaanthony@gmail.com
Ayanna Sebro	Trinidad and Tobago	Ministry of Health	asebro@yahoo.com
Joseph Gerard	Haiti	Ministry of Health	gerardajo944@gmail.com
Jose Ledesma Baez	Dominican Republic	Ministry of Health	drjoseledesma@gmail.com
José Carlos Couto Fernandez	Brazil	IOC/Fiocruz	coutofer@ioc.fiocruz.br
George Dos Santos	Martinique	CHU	Georges.Dos-Santos@chu-fortdefrance.fr
Chunfu Yang	USA	CDC	cxy0@cdc.gov
Luis Bonilla	Dominican Republic	CDC	wlx6@cdc.gov
Paul Sandstrom	Canada	PHAC	paul.Sandstrom@phac-aspc.gc.ca
Amilcar Tanuri	Brazil/RJ	UFRJ	atanuri@biologia.ufrj.br
Ricardo Diaz	Brazil/SP	UNIFESP	rsdiaz@catg.com.br
Unaí Tupinambá	Brazil/MG	UFMG	unaitupi@gmail.com
Horacio Salomon	Argentina	National AIDS Reference Centre/UBA	hsalomon@fmed.uba.ar
Gustavo Reyes Terán	Mexico	CIENI/INER	gustavo.reyesteran@gmail.com
Santiago Àvila	Mexico	CIENI/INER	santiago.avila@cieni.org.mx
Juan Pascale	Panama	Gorgas Institute	jmpascal@yahoo.com
Ivette Lorenzana	Honduras	UNAH	ivettelorenzana@yahoo.com
Glavia Delva	Haiti	GHESKIO	delvagreatdia@gmail.com
Chris Archibald	Canada	PHAC	Chris.Archibald@phac-aspc.gc.ca
Pamela Bermudez	Brazil	PAHO	bermudex@paho.org
Giovanni Ravasi	Brazil	PAHO	ravasigi@paho.org
Noreen Jack	Trinidad	PAHO	jackn@trt.paho.org
Michael Jordan	Geneva	WHO	mjordan@tuftsmedicalcenter.org
Silvia Bertagnolio	Geneva	WHO	bertagnolios@who.int
Natalie Exner	USA	Harvard University	nmexner@gmail.com