WHO HIVDR-SMS PROGRAM REVIEW

Prepared by the Boston Consulting Group

June 13th, 2014

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EXECUTIVE SUMMARY

The BMGF has supported WHO HIV's drug resistance surveillance strategy since 2007. As the grant is coming to an end, and the BMGF is considering renewing it, the BMGF has hired the Boston Consulting Group to review the implementation of WHO's HIVDR surveillance strategy and identify potential areas for improvement. Past achievements and challenges were reviewed in so far as they can inform future implementation.

The scale up of ART in Low and Middle Income Countries initiated in 2003, raised concerns on the emergence of drug resistance for HIV, as low adherence, poor patient monitoring and limited drug stocks are commonly observed in resource limited settings and are known to favor emergence of drug resistance.

Therefore an initial strategy for surveillance of HIVDR was designed in 2004. The objective was to detect whether the resistance had emerged and was transmitted in resource limited settings where ARVs were dispensed. This strategy has been revised in recent years with a focus on quantifying the magnitude of resistance and transmission and to provide robust elements to inform global treatment guidelines and national treatment program management. A revised methodology has been launched and a revised organization is now in place. These changes are too recent to assess whether they fully address the concerns raised by various stakeholders regarding the previous methodology and organization.

The program was reviewed along three axes defined by WHO as the objectives of the initial strategy: 1/ Coordination and mobilization of partners, 2/ Implementation of surveys and database, 3/ Implementation of a genotyping laboratory network.

1/ Coordination and mobilization of partners

Key activities included under this objective are collecting input and generating buy-in from partners, advocating for HIVDR surveillance and prevention and coordinating and providing guidance for the surveillance and prevention of HIVDR.

Collecting input and generating buy-in

WHO has relied on HIV ResNet Steering Group to provide input and steer, to inform its strategy. This governance has faced challenges in the past and has been reported as unclear, complex and ineffective. A revision of the organization was implemented at the end of 2013 and is expected to address these challenges.

WHO and its advisory network HIV ResNet are granted legitimacy and credibility for standard-setting by the scientific community. Countries also highlight the international mandate and neutral status of WHO, perceived as facilitating access to country governments and data collection.

While the composition of WHO HIVDR ResNet Steering Group has been improved and is now representative of countries involved in the strategy and of the various types of stakeholders (e.g., donors, program managers, public health experts), some challenges remain. The Steering Committee is still perceived as focusing on scientific topics. Limited steer is provided to WHO on programmatic implications and advocacy aspects of the strategy. Procedures for gathering input from ResNet members and governance are still perceived as unclear by members, which poses a challenge to their sustained engagement.

In the future, WHO should continue to clarify and formalize the governance and ways of functioning for ResNet. For instance: the agenda for the Steering Group should be clarified to systematically include updates on all elements of WHO mandate for HIVDR (including advocacy), WHO should continue developing and specifying terms of reference for the Core Group and the Working Groups, as well as clarifying the process of consultation and feedback loops with WHO HIV ResNet members. These deliverables should be developed and discussed at the next Steering Group meeting in October.

Relations to donors may also require more coordination in the future as WHO is encouraged to seek for other donors to sustainably support the HIVDR surveillance strategy. This would require defining a clear strategic plan, in line with donors and partners, ensuring all areas are financially supported and reporting on implementation of the strategy. WHO should set up a mechanism to manage donor relations, with specific resources. A subgroup of the Steering Group, composed of donors, should be convened once or twice a year for this purpose.

Advocacy for HIVDR surveillance

Advocacy for HIVDR surveillance is needed (i) to help create interest at country level for HIVDR surveillance, and therefore ensure countries are willing to invest on it and (ii) to ensure donors understand why HIVDR surveillance is needed and are willing to fund it.

Advocacy for HIVDR is acknowledged to be a challenge given low levels of resistance found so far and the decreasing importance of the topic in high-income countries. WHO is recognized as the sole advocate of HIVDR and has shown significant efforts (publications, participation in conferences). No other organization has been mentioned in this field. However, HIVDR is still perceived as more relevant for scientific aspects than for programmatic ones. This is partly due to the fact that before 2014, most of the communication on HIVDR was separated from general communication on HIV (e.g. Treatment guidelines, Health Sector Strategy) and that communication on HIVDR was targeting the scientific community and HIVDR technical stakeholders (most documents were survey protocols and technical guidance).

A priority for the future would be to develop a communication strategy for HIVDR. Key elements of the strategy would be to define target audience, create clear and simple messages for non-technical stakeholders, identify partners and relays that could amplify the communication on HIVDR and could participate in Steering Group meetings, and develop specific documentation for HIVDR advocacy.

Coordination of surveillance and prevention

WHO has developed a strategy document and guidance documents for the initial and for the revised methodologies. These documents explain the various components of the strategy, with a first level of prioritization. They also explain how to implement the surveys targeting technical stakeholders in charge of implementation. However, feedback from countries shows that the lack of alignment of partners at country level is often an issue for the implementation of the strategy. Different partners would encourage countries to implement different elements of the strategy, hindering their ability to pursue a consistent strategy.

WHO should therefore work on creating partner alignment on what should be the priorities for countries. A shared high-level action plan with partners could serve this objective and be used as an advocacy tool, outlining how to translate the results of surveys and EWI into programmatic actions. This document would not target technical stakeholders but policy makers and donors, to help them understand the links with programmatic aspects.

2 / Implementation of surveys and database

Country participation and repeat rate are key steps in ensuring that quality surveillance data is produced and shared with WHO for Global Reporting and to inform policy making. From 2004 to 2014, 68 countries have participated in the HIVDR surveillance strategy. Out of the 68 countries, only 20 implemented all elements of the strategy. Repeat rate is low: on average 48% of countries implementing ADR surveys (43% for TDR) did it the recommended number of times.

Some challenges explain why the uptake and repeat rate have not been higher. Most of the challenges faced in the past are expected to be addressed by the revised methodology, in particular, the relevance for national decision-making, the adaptability to epidemic settings, the size of samples, the duration of the survey or the prioritization of the elements. However this should be closely monitored in the future. Other challenges are expected in the future and will require specific attention for successful implementation of the revised methodology:

- **Usefulness.** Countries consider surveys and EWI useful, but do not use them to their potential. Results are used for information purpose, awareness raising and sometimes to inform major decisions such as changes in drug regimen. Results are not yet used to contribute to program management improvement (for instance EWIs results are often not well cascaded at facility level).
- **Logistics challenges** are however still expected in the future, given the increased number of sites to be surveyed for surveys and EWIs.
- **Funding** is expected to be a major challenge both for surveys and EWIs. WHO and partners have initiated steps to ensure countries budget for these activities in their Global Fund applications and PEPFAR Country Operating Plans.
- **Need for Technical Assistance.** Significant technical assistance will be needed to ensure that countries appropriately plan for HIVDR in their national strategic plan, to support countries in designing the surveys and conducting the project and to support countries with specific expertise on data analysis.

A priority for the future would be to ensure that countries are engaged in the HIVDR strategy and repeat surveys at the recommended pace. Therefore, WHO should:

- Advocate HIVDR surveillance strategy and develop guidance targeting program managers, donors and ministries of health for prioritization of the strategy and for programmatic response
- Work with key donors to ensure countries get funding to implement the surveys: continue work with CDC/PEPFAR and with the Global Fund to encourage further inclusion of HIVDR)
- Create interest for countries in HIVDR surveillance by providing feedback on the quality of their data
- Reinforce the link with HIV programmatic activities
- Ensure feedback from countries on survey implementation and methodology is integrated for instance with a dedicated feedback process and form. This would ensure that the revised methodology addresses the challenges faced in the past as expected.
- Build capacity and support countries in accessing appropriate Technical Assistance

In addition, WHO should ensure that the HIVDR Global Report leverages all quality data available. WHO should define criteria for quality of laboratory and epidemiology data and present a process to the Steering Group during next Steering Group meeting in October, by which it would assess whether data can be included or not in the Global Report.

3/ Implementation of genotyping laboratory network

WHO, with the support from partners, has built a network of 33 laboratories, accredited with high quality standards, with presence in AFRO, AMRO and WPRO and capacity to cover the genotyping needs for HIVDR surveillance. The WHO accreditation process is recognized by countries as a key

element in building capacity at national level. WHO is also acknowledged to have played a leading role in supporting the introduction of quality genotyping performed on DBS, by developing the accreditation process, specific training materials and accrediting 8 laboratories to date.

Although the overall genotyping capacity is in theory sufficient to meet HIVDR surveillance needs, further expansion of the network may be needed: expansion of DBS capacity, expansion of national capacity.

In 2012, 23% of genotyping for HIVDR surveys has been performed on DBS. This number is expected to increase in the future as DBS is more cost-effective (due to transportation costs) and more convenient for logistics. Logistics becomes even more critical with the need to collect specimen from up to 40 sites randomly selected in the revised survey methodology. It is therefore a priority for the HIVDR strategy to encourage expansion of capacity to perform genotyping on DBS. WHO should continue to support countries in that field.

Countries are willing to build genotyping capacity at national level, some because of regulatory requirements preventing them from shipping specimens outside of the country, some because they view it as a key component of laboratory strengthening. Laboratories applying for the accreditation should receive support to ensure that the capacity they build is of quality. However, given resource constraints at WHO HQ, WHO should prioritize candidate laboratories. Prioritization criteria should be in line with WHO treatment guidelines and should be presented to the Steering Group during next meeting for information and advice on the messaging. They could include – but not be limited to – interest in HIVDR, current genotyping capacity, number of accredited laboratories in the country. WHO and regional / specialized laboratories would provide direct support to high-priority candidate, while lower-priority laboratories could receive support from partners through a stepwise process, in early stages of their applications. WHO would need to work with partners to define common standards and steps for the accreditation process.

The role of regional and specialized laboratories in capacity building should be reinforced by setting requirements for those laboratories to train and support candidate or national laboratories, acknowledging that they would need financial support. This would ensure a more consistent provision of technical assistance and build capacity at regional and national level.

In addition, as viral load is now recommended by WHO for routine monitoring of programs, scale up of viral load testing capacity is expected. Quality of this testing is critical for HIVDR surveillance as it is one of the EWIs and one step of the ADR survey. WHO has a role to play in the scale up of quality viral load testing, in synergy with existing capabilities in the network. This role is to be defined in the context of the broader HIV strategy and not focusing on HIVDR.

Key requirements

Strategic planning. WHO should develop in the coming year, a comprehensive strategic plan, detailing a target scale-up, a robust M&E plan, a communication plan, an action planas well as a plan for sustainable funding, to serve as a roadmap for WHO and a reference for donors and partners. This strategic plan would help WHO communicate around the roadmap, around the funding needs and the achievements and it would be a key element to support funding discussions. It should be shared and validated with partners and detail what is at stake, what is the funding needed, what can be done with the results and what should be the role of each stakeholder. This high-level document would serve for advocacy purpose at global and local level. It would be key in ensuring that partners at all levels are aligned on the priorities and ready to support countries in a coordinated way.

Sustainable funding. WHO has, at this stage, not managed to secure sustainable funding for HIVDR. It should continue to work on defining a plan for sustainable funding, as part of the development of the strategic plan. Three main levers can be activated: advocacy, donor relations and integration of HIVDR in HIV programs. WHO should therefore reinforce its advocacy with the appropriate staffing, tools and relays, targeting donors and ministries of health. It should reinforce its donor relations to provide donors with more visibility on the strategic plan, the achievements and the funding gaps. It should continue to work with donors supporting countries directly, such as CDC/PEPFAR and the Global Fund, to ensure HIVDR is considered a priority and supported. Eventually, it should continue to encourage countries to integrate HIVDR in HIV, so that the budget for surveillance activities would be integrated in regular M&E activities.

Funding needs. WHO should put together a proposal for funding in the coming months. Main cost buckets identified are the following:

- HQ team support estimated at 2.0M$ to cover the needs for coordination, expertise on surveys and laboratories, and new resources for donor relations and advocacy. This cost could be reduced depending on sourcing options for staff (secondment, etc.)
- Support to countries for survey implementation. Support for one country implementing the full strategy over 4 years is estimated at 261k$/year. The support needed, would depend on the scale up plan and the support already available from other donors (CDC/PEPFAR, the GF). WHO should work with them to validate scale up plan and identify funding gaps and potential redundancies.
- Capacity building would require a number of regional workshops to train TA providers on survey design and analysis, and a number of regional laboratory workshops conducted by regional and specialized laboratories.
- Other costs elements would have to be estimated by WHO based on expected volume of activities (number of Global reporting, number of Steering Group meetings, etc.).

Summary of recommendations

Recommendations	Indicative timeframe
Further develop WHO HIVDR strategic plan in line with main partners and donors • Define clear recommendations. for countries, aligning partners and allowing countries to prioritize elements of the strategy • Set targets for the scale up plan (timing, target countries for each element), in line with key donors / partners • Build robust M&E plan in line with donors' expectations	To be developed for April-June 2015
Reinforce advocacy for HIVDR and links with programmatic aspects	
• Define communication /advocacy strategy and identify relays in a communication plan *(part of the strategic plan described above)*	• To be developed for April-June 2015
• Develop a stakeholder alignment and engagement plan *(part of the strategic plan described above)* to serve as advocacy tool	• To be developed for April-June 2015
• Include Advocacy as a standing agenda point for the Steering Group, and invite advocacy experts	• For next Steering Group meeting, (October)
Reinforce relations with key stakeholders	
• Further formalize governance (advisory bodies ToRs meeting frequency and agenda, feedback process)	• For next Steering Group meeting (October)
• Reinforce the role of the Core group to get input on data quality issues, survey methodology revision	• For next Core Group meeting
Secure sustainable funding	

• Advocate for awareness of HIVDR strategy and integration of HIVDR in HIV	• Continuous effort
• Reinforce donor relations (organize regular donor meetings and ensure donor reporting)	• To be set-up in coming months
• Work with major donors on direct funding to countries and modalities to support the scale up plan through WHO	• Discussions with the Global Fund and CDC to be conducted as soon as possible (NFM/TRP and COP timelines)
Continue to support implementation of the strategy in priority countries and link with programmatic aspects	
• Support countries in finding funding *(see above)*	• Continuous effort
• Ensure country feedback on survey implementation is well integrated, including the development of a formal process and feedback form	• To be discussed during next Steering Group meeting
• Develop guidance for prioritization of the strategy and for response with clear, high-level guidance outlining how to prevent HIVDR based on results of the surveillance	• Continuous effort
• Continue to support laboratory expansion, focusing on HIVDR priorities and continue to be active in encouraging expansion of capacity to perform genotyping in DBS	• Process and candidate laboratories prioritization criteria to be discussed during next Steering Committee
• Coordinate and / or provide TA to build capacity for surveys and for laboratories	• Continuous effort - formal commitment of support from specialized and regional laboratories to be discussed during next Steering Group meeting in October

I. INTRODUCTION

1. PURPOSE OF CONSULTANCY

The Boston Consulting Group (BCG) has been retained by the Bill and Melinda Gates Foundation (BMGF) to review the implementation of the World Health Organization's (WHO) global HIVDR surveillance and monitoring strategy and identify potential areas of improvement and potential future models for sustainable funding. The foundation is considering a new grant to support the WHO global HIV Drug Resistance (HIVDR) surveillance and monitoring work globally after June 2014 but wishes to conduct an independent review of the past 7 years before considering a further investment. The review is intended to inform the Bill and Melinda Gates Foundation on whether, where and how to continue investing in the surveillance of HIV Drug Resistance surveillance. The scope of the work focuses on the assessment of the WHO HIVDR Surveillance and monitoring strategy regarding the program achievements, challenges faced and priorities for the future, as well as on the identification of future potential organizational and funding models.

This consultancy was conducted over a 12-week period from late March to early June 2014. It did not set out to evaluate the strategy's theory of change, nor claim to prove or disprove a causal link between the strategy's activities (implemented with the initial or revised methodology) and public health outcomes. Instead, it built on the premise that there is a consensus over the public health relevance of the strategy objectives, and reviewed its implementation to assess how these objectives can best be met going forward.

Past achievements and challenges were reviewed in so far as they can inform future implementation. They were reviewed relative to the 4 initial objectives of the strategy:

- Piloting of HIVDR transmission threshold surveys and sentinel surveys to monitor HIVDR emerging in treatment in sentinel antiretroviral treatment (ART) sites in 30 of 50 WHO focus countries
- Development and implementation of an HIVDR database application for national, regional and global use
- Implementation of a WHO global HIVDR genotyping laboratory network to support HIVDR surveillance and monitoring
- Coordination and mobilization of WHO staff and partners for successful global implementation of the HIVDR strategy

2. METHODOLOGY

The methodology relied on the triangulation of three main sources:

a) Desk research
b) 95 interviews including countries HIVDR focal points, CDC country offices, HIV program managers, laboratory focal points, WHO HIV ResNet Steering Committee members, content experts for instance academics, consultants, representative from CDC, PEPFAR, NIH involved in HIVDR, Partner organizations for instance implementers such as PASER, TREATAsia, Médecins sans Frontières. (see full list, interviewee selection criteria, approach to interview and interview guide in appendix)
c) Country visits

These different sources were used to check the information and provide more depth when possible. Hypotheses were also built, tested and refined with a variety of sources to ensure that all relevant perspectives were considered.

A Steering Committee for the project, composed of Gottfried Hirnschall Director of WHO HIV department and Joseph Perriens WHO Coordinator HIV Technologies and Commodities, Elliot Raizes ART Technical Advisor for the Center for Disease Control and Prevention (CDC) and Christopher Duncombe responsible of the WHO HIVDR grant for the BMGF reviewed the facts collected and the analysis conducted during the project. The Steering Committee discussed priorities for the future for HIVDR-SMS and crafted the recommendations summarized in this report.

3. HOW TO READ THIS DOCUMENT

This report is structure into 4 chapters, beginning with this introduction. Chapter 2 "Context and initial objectives of HIVDR SMS" provides a high-level contextual analysis with background information relevant to the following chapters. Chapters 3 and 4 of the document present the achievements, challenges and future priorities identified by the Steering Committee on each of the components of WHO's strategy.

We would like to respectfully remind the readers that our work is explicitly not evaluative in nature. For the most part, any qualitative assessments of HIVDR SMS performance are based on interviewees' quotes rather than a reflection of BCG's opinion. In the rare cases where we offer our own qualitative assessment of the strategy's performance, we will clearly indicate as much.

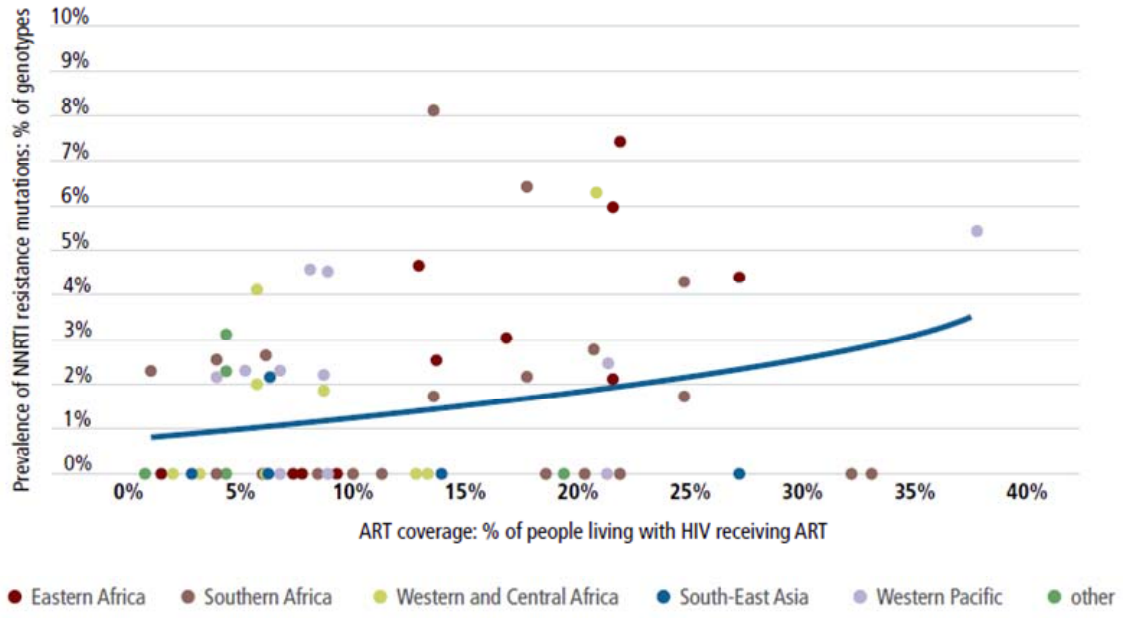
II. CONTEXT AND INITIAL OBJECTIVES OF HIVDR SMS

1. WHY IS HIVDR SURVEILLANCE NEEDED?

Drug resistance is a common challenge faced across most infectious diseases. With the increase in treatment coverage this threat has gained importance and has become a major public health concern (Fig.II.1.). It is even more a concern for a disease such as HIV, with lifelong treatments and fast replication of the virus. Low adherence to treatment reinforces the risk of drug resistance emergence.

HIV drug resistance (HIVDR) is expected to emerge in patients under antiretroviral treatment (ART), even when appropriate therapy is provided and a high level of adherence is achieved (Fig.II.1.). As for other infectious diseases, the risk of emergence is reinforced by lack of adherence which can be the result of program management (stock-outs, supply chain management issues) or patient behavior (not taking the right dosage, or not as prescribed, not coming on time to pick up the drugs at the pharmacy). Therefore, issues in program management are one of the factors favoring the emergence of drug resistance. There are two main categories of HIV drug resistance: acquired resistance and transmitted drug resistance.

FIG. II.1. Relationship between transmitted resistance to non-nucleoside reverse transcriptase inhibitor drugs and coverage of antiretroviral therapy



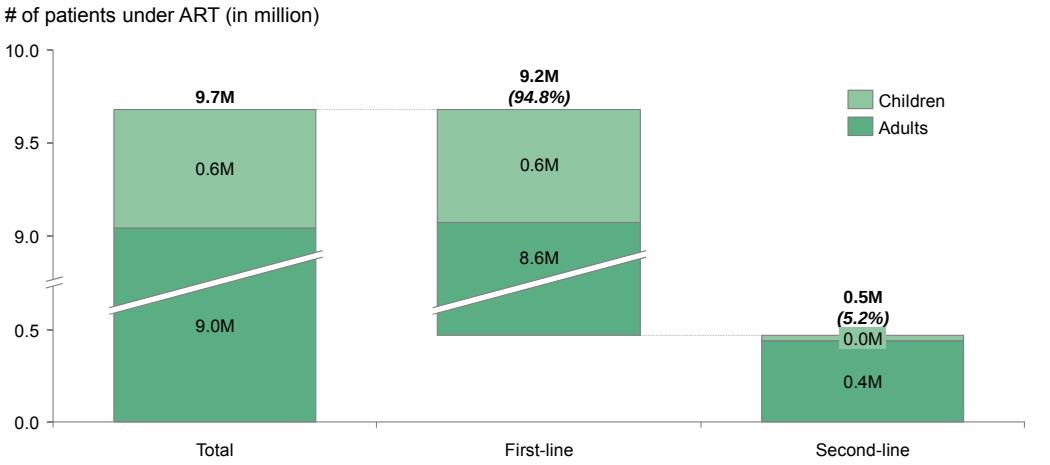
Note: p-value adjusted for region: 0.039 – Odds ratio = 1.4 (95% CI 1.07-1.073)
Source: WHO, UNICEF and UNAIDS, Global update on HIV Treatment 2013, Fig 3.18

Because of the link between HIVDR emergence and ART coverage, the plan to scale up ART starting in 2003 raised concerns. Concerns were even higher since some of the issues identified as factors favoring emergence of resistance (e.g., low level of adherence, poor patient monitoring or limited drug stocks) are often observed in resource limited settings. In 2003, the "3-by-5" strategy was launched by UNAIDS and WHO, with a global target to scale-up treatment from ~300k patients in 2003 to 3 million by 2005 in low-middle income countries, bringing ART coverage from ~1% of the infected population in LMIC to ~5% by 2005. Since 2005, massive scale-up has continued with a number of patients under ART reaching 9.7M people in LMIC.

Resistance rates observed to date and reported in WHO 2012 Report on HIVDR in LMIC range between 3.9%[1] and 6.8%[1] for pre-treatment drug resistance, 0.3%[1] and 3.4%[1] for transmitted drug resistance depending on the year of observation, and 4.3%[1] and 8.9%[1] for acquired drug resistance depending on the regions. These results have been perceived as reassuring by the overall community, who feared that treatment scale-up would be jeopardized by HIVDR. Based on the results, WHO has determined that no change in treatment guidelines has been warranted at this time and surveillance of DR levels should be maintained.

In 2012, second-line treatment (SLT) is only used by 4.4% of the 9.7M patients under ART in LMIC and third-line treatment (TLT) is still very marginal (Fig. II.2). The proportions of people receiving first- and second-line regimens vary substantially between regions, according to the latest WHO survey data[2] in 2011. In Latin America and the Caribbean in 2011, 77% of adults on ART were receiving first-line regimens and 21% second-line regimens (2% on third-line) vs. 96% and 4% in the other LMIC regions overall[2]. The variation can be explained by differences in the maturity of the ART cohorts, the availability of viral load testing to diagnose treatment failure and the availability of second-line ART. Each year, an estimated 2-3%[3] of FLT patients are switched to SLT treatments worldwide after treatment failure.

FIG. II.2. Distribution of patients under ART between first-line and second-line, 2012



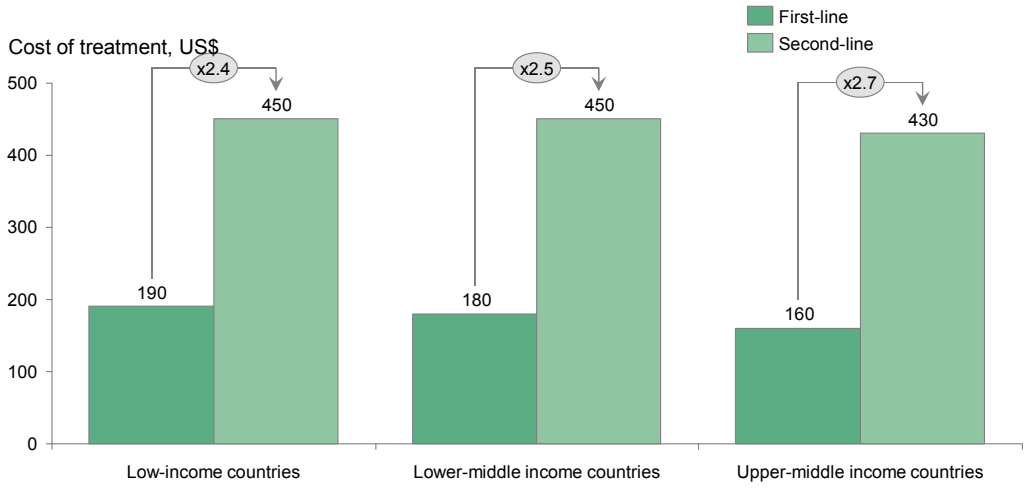
Source: WHO, Future Institutes and UNAIDS, Technical report on aids medicine and diagnostics service, Antiretroviral medicines in low-and middle-income countries – Forecast of global and regional demand for 2013-2016 , Figure 3

The potential implications of HIVDR at both the individual and public health levels are far greater in LMIC than in high-income countries. In most high-income countries, treatments are individualized and a wide range of drugs are available. When resistance occurs, patients are able to switch to a new personalized regimen adapted to their virus type. In LMIC, standardized first-line and second-line treatment regimens have been selected to enable treatment scale up and maximize cost-effectiveness of programs. The limited availability of treatment options in LMIC puts ART programs at risk with HIVDR. As a result, HIVDR should receive greater attention in LMIC.

[1]Note: 3.9% in 2008 and 6.8% in 2010 for PDR, 0.3% in 2005 and 3.4% in 2009 for TDR and 4.3% in Eastern Africa and 8.9% in South-East Asia for ADR
Source: WHO (Silvia Bertagnolio and others), WHO HIV Drug Resistance report, 2012, Table 4.4, Table 3.9 and Table 9
[2]Source: WHO, UNICEF and UNAIDS, Global update on HIV treatment: results, impact and opportunities, 2013, Page 91
[3]Source: UNITAID, Adult second-line HIV / AIDS project, 2012, http://www.unitaid.eu/en/secondline

HIVDR is a threat to efficiency and cost-effectiveness of HIV programs. Increase in HIVDR will require more patients to be switched to SLT or even TLT. The cost of SLT is on average 2-3 times the cost of FLD[4]. Options beyond second-line treatment remain even more costly. There are no WHO-prequalified generic versions of the drugs commonly used for third-line treatment (i.e. treatments including raltegravir, etravirine or darunavir), and prices remain extremely high. The lowest possible price for a third-line regimen is around US$ 2000 in low-income countries, almost 18 times more than the lowest price for first-line regimens. Some middle-income countries are paying much higher prices[4]. Currently TLT seems to be available only in 37 out of 112 low-middle income countries[5]. With higher levels of HIVDR, more resources would be needed to treat the same number of patients, or more likely, fewer patients could be treated with the same resources (Fig.II.3.).

FIG. II.3. Median prices per person in US dollars for first-line and second-line antiretroviral therapy regimens in low-, lower-middle- and upper-middle-income countries, 2012



Source: Global price reporting mechanism of the AIDS medicine and Diagnostic Service

Monitoring of HIV drug resistance levels and of conditions favoring the emergence of HIVDR is key to preserve the future effectiveness of antiretroviral therapy, and protecting the efficacy of the limited therapeutic options is essential for the sustainability of HIV programmes[6]. It provides countries and global decision makers with data to inform their decisions on selection of future first-line treatment regimens, the selection of second-line regimens for individuals failing first-line, and the optimal regimens to prevent mother-to-child transmission and pre/post-exposure prophylaxis. HIVDR monitoring also enable countries to identify program performance issues and take corrective actions for the prevention of emergence of HIVDR. HIVDR data can also be used as an advocacy tool at global and country level, to raise awareness and increase partner collaboration.

[4]Note: Containing raltegravir, etravirine or boosted darunavir
Source: WHO, UNICEF and UNAIDS, Global update on HIV treatment: results, impact and opportunities, 2013
[5]Sources: Global Fund, UNCEF, IDA, UNITAID and PEPFAR, Procurement dataset, 2013
WHO and Organization Panamericana de la Salud, Tratamiento Antirretroviral Bajo La Lupa: un análisis de salud pública en Latinoamérica y el Caribe, 2013
WHO, survey and procurement data, 2013
[6]Source: WHO, Antimicrobial resistance: Global report on surveillance, 2014

2. INITIAL STRATEGY

a. CONTEXT OF THE INITIAL STRATEGY

Given the concerns raised by the scale-up of ART initiated with the "3 by 5" strategy in 2003, WHO initiated global surveillance of HIV drug resistance in resource-limited settings in 2004. WHO was assisted in the development and implementation of the strategy by WHO HIV ResNet, a global advisory group composed of over 50 institutions, laboratories, clinicians, epidemiologists, virologists and other HIVDR experts. To develop the initial strategy, the WHO HIVDR team also gathered inputs from TB, malaria, influenza, measles, polio teams at WHO headquarters to understand their experience with surveillance of resistance and laboratory strengthening, as these programs had been initiated earlier (more details available in Appendix 4).

Although HIV drug resistance was feared, at the time the strategy was developed in 2004, no data were available on drug-resistance in LMIC countries to confirm whether there was an issue.

The scale-up of ART initiated by the "3 by 5" initiative was mostly targeting generalized epidemics to address the disparity between countries, regarding access to antiretroviral therapy (ART)[7]. Indeed in 2003, out of the ~27.8M people infected with HIV in LMIC and 0.4M people under ART, ~22.3M people were in generalized epidemics (~80%) and only 0.1M were under ART (~27%).

b. OBJECTIVES OF THE INITIAL STRATEGY

The initial objective of the HIV DR strategy was to provide an alert on whether the resistance was transmitted or has emerged in areas where ARVs were dispensed in resource limited settings. The strategy used a site-based approach focusing on clinic-functioning (i.e. ability of a clinic to maximize VL suppression and minimize HIVDR emergence) in countries with generalized epidemics and targeted a specific area of the country (usually the capital city) where, if resistance was ever transmitted, it was more likely to observe this phenomenon.

The strategy, as described in the proposal sent by WHO to the BMGF in 2006, intended to support ~50 countries with a focus on the following priorities[8]:

a) Implement surveys for surveillance of transmitted and acquired HIVDR
b) Develop and implement an HIVDR database application for national, regional, and global use
c) Implement a WHO global HIVDR genotyping laboratory network to support HIVDR SMS
d) Coordinate and mobilize WHO staff and partners for successful global implementation of the strategy

c. COMPONENTS OF THE INITIAL STRATEGY

The initial strategy as defined in 2004, consisted of two surveys, defined below. The strategy was later amended to include a set of Early Warning Indicators.

Acquired Drug Resistance (ADR) survey (also called HIVDR monitoring survey). The monitoring of HIVDR acquired is based on treated populations at sentinel ART sites, using specimens and data from ART clinics. The survey was population-based and for use in resource-limited settings where limited

[7]Source: WHO and UNAIDS, Progress on Global Access to HIV Antiretroviral Therapy: a report on "3 by 5" and beyond, March 2006, http://www.who.int/hiv/fullreport_en_highres.pdf

[8]Source: WHO, Proposal to BMGF, Global strategy to evaluate and limit HIV drug resistance emergence and transmission, 2006

ART regimens are selected on a population basis (not individualized). Analysis of data from the HIVDR ADR surveys in sentinel ART clinics was intended to provide estimates of HIVDR emerging in patients during their first year of ART therapy in order to inform on most effective initial and second-line ART regimens and factors that limit emergence of HIVDR.

Transmitted Drug Resistance (TDR) survey (also called threshold survey) focusing on recently infected patients. It uses specimens and data from sites where HIV is initially diagnosed. As the ADR survey, the TDR survey was population-based and for use in resource-limited settings. Analysis of data from the HIVDR TDR surveys was intended to provide an alert of the extent of drug resistance in newly acquired HIV infections in order to inform policy-making for ART regimens and to provide an indirect assessment of the overall programme performance.

Early Warning Indicators. The initial Early Warning Indicators (EWI) were composed of 8 indicators: prescribing practices, loss to follow-up, retention on first-line ART, on-time pill pickup, on-time clinic appointment keeping, drug supply continuity, adherence as measured by pill count and viral load suppression 12 months after ART initiation. Where feasible and where routinely available, indicators were measured at each ART site enrolled and compared to a target recommended by WHO.

Early warning Indicators of HIV drug resistance have been developed in order to monitor factors at individual clinics known to create situations favorable to the emergence of HIV drug resistance. The identification of clinics with suboptimal performance helps to target appropriate interventions that can potentially optimize care and this reduce the risk of HIV drug resistance emerging. Routine EWI monitoring was designed to alert national ART programme managers as well as clinic and district managers to specific areas which require attention and support overall optimization of patient care.

d. COSTS OF THE PROGRAM

In 2004, the total cost of the project was estimated in the initial grant proposal submitted by WHO to the BMGF at ~50M$[8]. WHO requested a 15.2M$ grant from the BMGF for 5 years initially, to cover for activities for which they had not yet identified contributions from other donors (Fig. II.4.). More details on what other donors have contributed is provided later in this section.

FIG. II.4. Distribution of the costs planned for the BMGF grant by priority and by type

Source: WHO, Proposal to BMGF, Global strategy to evaluate and limit HIV drug resistance emergence and transmission, 2006

e. INITIAL WHO HIV RESNET ORGANIZATION

At WHO Headquarter, a global HIVDR team was established between 2003 and 2005 to coordinate the global strategy and provide technical assistance. The initial team consisted of a Team Leader with epidemiological and clinical skills supported by PHAC, an HIV clinician supported by the Italian Ministry of Foreign Affairs, and a medical epidemiologist supported by CDC with experience in HIVDR surveillance, database development, and the formation of laboratory networks. The main activities of the team were to provide technical assistance to countries, coordinate activities, including the development of appropriate HIVDR guidance, standards, and policies related to implementation, scale-up, operations, monitoring and evaluation, analysis, reports, and recommendations[9]. In 2006, a virologist position was added, funded by the BMGF. The virologist was in charge of developing the laboratory network and to increase the laboratory capacity to support HIVDR surveillance activities.

In WHO regional offices, up to 5 FTEs, of which 3 regional advisors for HIVDR funded by the BMGF grant composed of epidemiologists as well as WHO consultants from WHO HIV ResNet, were identified to support the strategy, mainly along three activities: increase local capacity building, coordinate the regional activities (database development, laboratory networks, national trainings, quality assurance activities and regional analyses) and disseminate reports.

WHO has been assisted in the development of the HIVDR strategy by WHO HIV ResNet. WHO HIV ResNet consisted of a Steering Group to oversee implementation of the strategy, two Advisory Groups which included experts in the field who guided (i) the laboratory network and (ii) the epidemiology working group *(Please refer to the appendix for more details)*. Subsequently, the epidemiology working group was enlarged to include countries and institutions participating in surveillance and monitoring, working groups and individual consultants who provided technical assistance[9].

Other organizations have also been collaborating with WHO to develop, disseminate and implement strategies for ART scale-up, as well as fund part of the HIVDR-SMS program (more details in following pages).

3. REVISED STRATEGY

a. CONTEXT EVOLUTION SINCE 2004

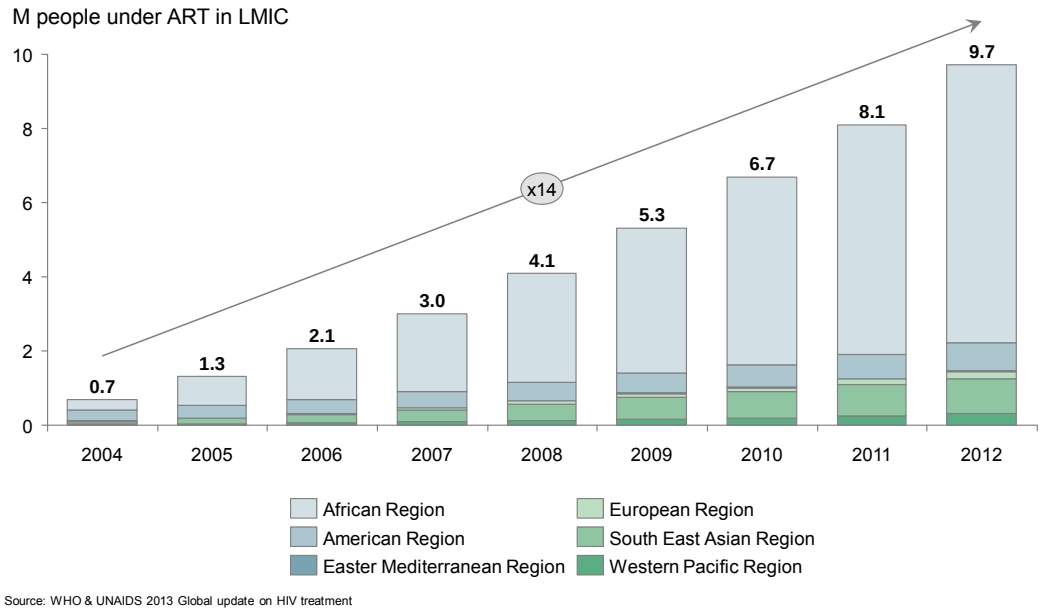
Significant scale-up of ART has happened since 2004, when the initial strategy was launched, and a new phase of scale-up is now starting. In 2012, there were in total ~14 times more people under treatment in LMIC than in 2004 (Fig.II.5). The scale-up of ART mostly occurred in generalized epidemics with ~77% of patients under ART in 2012 located in countries with generalized epidemics (7.5M patients) compared to ~44% in 2004. In 2011, the United Nations Member States set the goal to reach 15 million people with antiretroviral treatment by 2015[10]. In 2013, WHO launched new ARV treatment guidelines to continue and expedite scale-up towards universal access to treatment for the

[9]Source: WHO, Proposal to BMGF, Global strategy to evaluate and limit HIV drug resistance emergence and transmission, 2006

[10]Source: United Nations, Resolution adopted by the general assembly, Political Declaration on HIV and AIDS: Intensifying Our Efforts to Eliminate HIV and AIDS, 2011, http://www.unaids.org/en/media/unaids/contentassets/documents/document/2011/06/20110610_un_a-res-65-277_en.pdf

25.9 million people worldwide who need antiretroviral therapy[11]. These consolidated guidelines promote expanded eligibility for ART with a CD4 threshold for treatment initiation of 350 cells/mm3 or less for adults, adolescents and older children. These guidelines represent an important step towards achieving universal access to ARV drugs for treating and preventing HIV[12]. The expanded eligibility for ART and the inclusion of healthier patients (for prevention) may drive increase in resistance as more patients will be under ART and as adherence may be expected to be lower in healthier patients. Therefore it reinforces the need for resistance surveillance.

FIG.II.5. Number of patients under ART in low-middle income countries, 2004-2012



Source: WHO & UNAIDS 2013 Global update on HIV treatment

The evolution of ART programmes as well as lessons learned from initial implementation phase (to be detailed in next chapters), have highlighted important limitations of the first generation of surveillance methods and the need for a different objective (to be detailed in following chapters).

b. REVISED OBJECTIVES

Due to the limited coverage of ART in 2004, the first generation of HIVDR surveillance methods explicitly sought to monitor HIVDR levels in a limited geographical area using convenient sites to facilitate implementation. The original surveys design was not intended to generate results to inform national and global level decision making. Country experiences also revealed the challenges inherent to the prospective method used to assess acquired HIV drug resistance and particularly the difficulty to maintain a prospective cohort and the issues with the quality of the clinical and demographic data collected.

[11]Source: UNAIDS, Treatment 2015,
http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/JC2484_treatment-2015_en.pdf
WHO, Executive summary: Consolidated ARV guidelines, 2013,
http://www.who.int/hiv/pub/guidelines/arv2013/intro/executivesummary/en/
[12]Source: WHO, Executive summary: Consolidated ARV guidelines, 2013,
http://www.who.int/hiv/pub/guidelines/arv2013/intro/executivesummary/en/

The revision of the strategy was initiated in 2012. The new objective emphasizes the need to quantify the magnitude of resistance emergence and transmission, and to provide robust elements to inform global treatment guidelines and national treatment program management.

c. Revised Strategy

The revised strategy consists of four surveys and a set of five Early Warning Indicators.

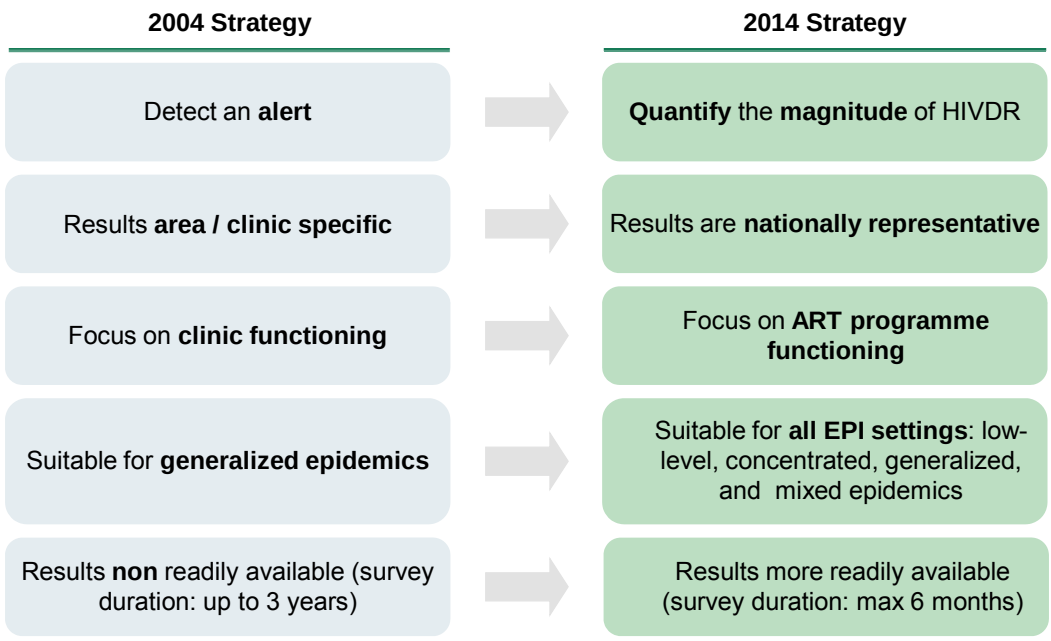
Early Warning Indicators revision process. The set of EWI was revised in 2011, through an advisory panel appointed by WHO. The objective of this revision was to simplify the indicators, revise the targets and align their definition with the ones used by UNGASS/PEPFAR. The number of indicators went from 8 indicators before 2011 to 5. WHO insisted repeatedly on the importance to include them in routine health sector M&E plans in different presentations and articles. The revised set of indicators is anticipated to require less data abstraction, facilitating wider uptake and reporting. Monitoring of early warning indicators is now based on a scorecard approach (Fig.II.6.). EWIs provide valuable program planning information about how well populations are adherent to ART, whether pharmacies which dispense regimens are likely to promote the emergence of HIVDR through the prescribing of mono-or dual therapy, whether stock-outs of ART occur, the extent to which patients on ART are retained in care and the level of viral load suppression, as well as enable program managers to identify clinic-level weaknesses that might facilitate the emergence of resistance. The objective of these changes is to facilitate the interpretation of programme data.

Fig. II.6. Revised set of Early Warning Indicators

EWI	Target
• **On-time pill pick-up**	• Red: <80% adherence in ≥90% of patients • Amber: 80-95% adherence in ≥90% of patients • Green: >95% adherence in ≥90% of patients
• **Retention in care**	• Red <75% retained after 12 months ART • Amber, 75-85% retained after 12 months ART • Green >85% retained after 12 months ART
• **Pharmacy stock-outs**	• Red <100% of a 12 months period with no stock-outs • Green 100% of a 12 months period with no stock-outs
• **Prescribing practices**	• Red >0% dispensing of mono or dual therapy • Green 0% dispensing of mono or dual therapy
• **Virological suppression**	• 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

Surveys revision process. WHO conducted a 2-year revision process of the survey methodology and launched new concept notes in March 2014 with the objective to simplify implementation of surveys (fostering increased participation) and enable national representativeness of results (Box 1). The methodology was revised to move from a localized alert detection mechanism to a system that quantifies the magnitude of HIVDR with nationally representative results, so as to inform national ART policies (selection of regimens for first-line, second-line or beyond, PrEP, PEP, PMTCT). While initial surveys were mainly suitable for generalized epidemics and, because of their prospective nature, could take up to 3 years, the revised approach is expected to suit all epidemics settings and provide results in no more than 6 months. (Fig.II.7) Public health decision makers would therefore be provided with more current results, and could implement containment measures more rapidly.

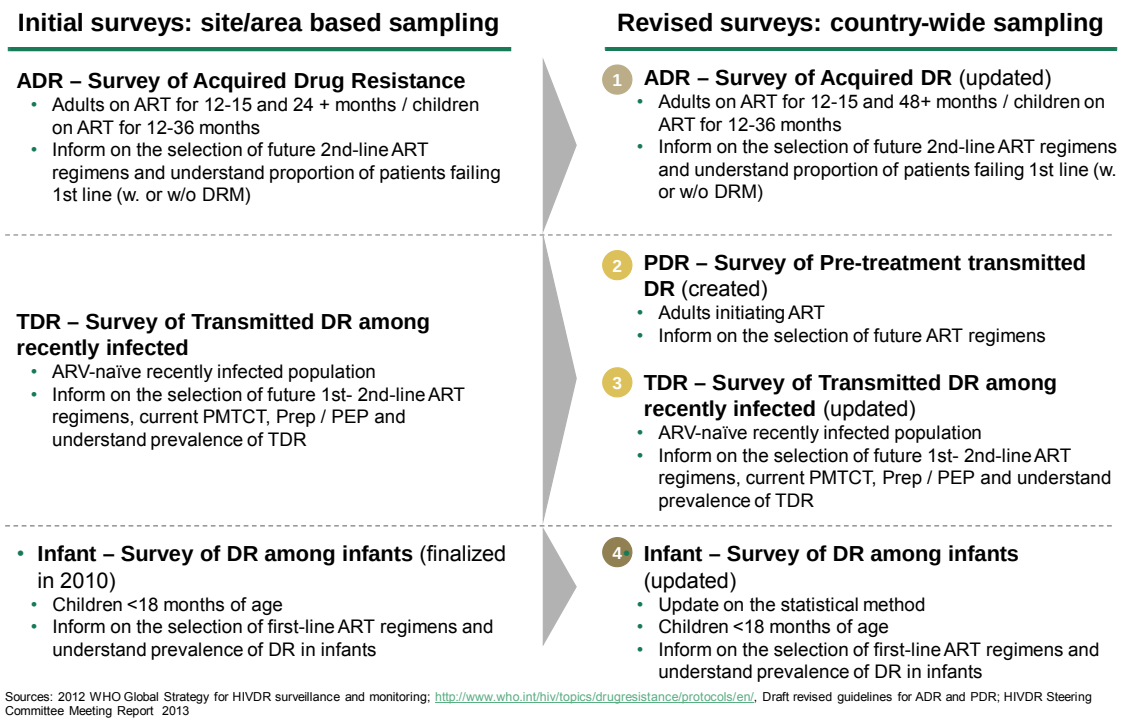
FIG. II.7. Revision of the strategy, 2004-2014



Source: WHO, ICAP web seminar, 20 March 2014

Revised surveys description. The HIVDR surveillance strategy moved from two different surveys (Acquired Drug Resistance survey and Transmitted Drug Resistance survey) to four surveys (Fig.II.8.). The Acquired Drug Resistance survey targets populations receiving ART at different time points. The other three surveys consist of one Transmitted Drug Resistance survey in populations likely to be naive and have been recently infected (TDR), one Pre-Treatment Drug Resistance survey (PDR) in populations initiating ART and one pediatric survey in ART-naive children less than 18 months recently diagnosed with HIV (Infant survey). See Box 1 for more details on the surveys.

FIG. II.8. Description of the revised surveys vs. the initial surveys



Sources: 2012 WHO Global Strategy for HIVDR surveillance and monitoring; http://www.who.int/hiv/topics/drugresistance/protocols/en/, Draft revised guidelines for ADR and PDR; HIVDR Steering Committee Meeting Report 2013

Priorities in survey implementation. The PDR survey and the ADR survey have been designated by WHO as priority elements to be repeated approximately every 3 years. The presence of HIVDR prior to ART initiation can compromise the therapeutic and prevention benefits of first-line treatment, and PDR survey results will inform the choice of drugs to be included in first-line treatment regimens, as well as PreP and Post-Exposure Prophylaxis (PEP). In the same way, ADR may compromise the effectiveness of second- and third-line ART, PREP and PEP. ADR surveys will inform on regimen effectiveness and program performance in maximizing viral load suppression. It was decided during the October 2012 Steering Committee meeting, that TDR would have a more limited role, and would be highlighted in guidance as particularly relevant in contexts where PrEP is being introduced, or as follow-up survey triggered by worrisome levels of PDR and/or ADR, and that infant survey should be prioritized only when there would be a need to inform guidance on infant treatment[13].

Status on revised surveys implementation. The revised methodology was officially launched at the Conference on Retroviruses and Opportunistic Infections (CROI) meeting in March 2014, guidance is expected to be communicated to countries in the very short term. Once TDR guidance is finalized, WHO will roll out the methodology to all countries willing to participate. The methodology had been communicated to 4 countries for piloting purposes: 3 pilot surveys were implemented in Kenya, Namibia and Tanzania using Lot Quality Assurance Sampling (LQAS) and one pilot was implemented in South Africa using Probability Proportional to Size (PPS).

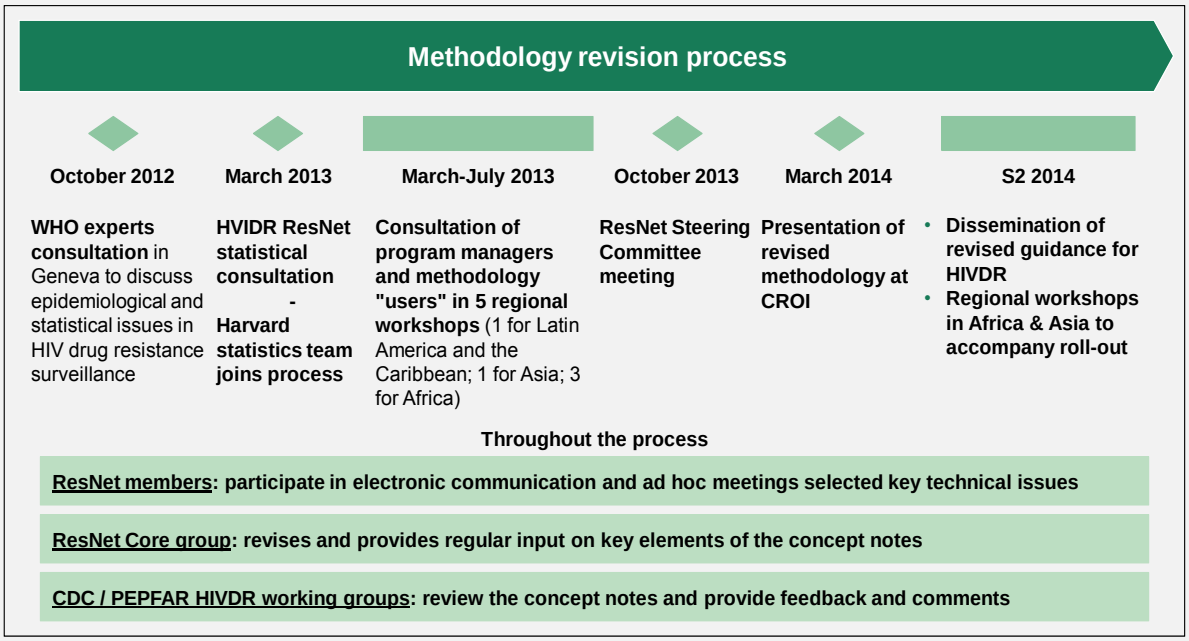
Box 1: Revision of the survey methodology

Drug resistance surveys

[13]Source: WHO, WHO HIV Drug Resistance Advisory Group Meeting, Meeting report, October 2013

Revision process[14]

WHO launched a 2-year revision process in 2012, based on the following consultation process:



The five regional consultation meetings were attended by 147 participants from 43 countries, including country program managers, technical experts and local and international partners. Participants shared experiences and lessons learnt from implementing the original HIVDR survey methods, were briefed on the revised draft methods, assessed feasibility and use of revised methods and discussed national surveillance plans. Special literature reviews were also commissioned to inform the review process.
The final revised methodology was presented at a ResNet meeting in March 2014. Revised surveys will be laid out in a set of 4 documents: the ADR and PDR concept notes were completed in March 2014, the infant survey guidance was finalized in 2010 and is currently being slightly amended and the TDR survey guidance is currently being finalized. Roll-out will be supported by two regional workshops to be held in Africa and Asia in the summer 2014.

Description of the four surveys in the revised methodology

1. **Acquired Drug Resistance (ADR).** The cross-sectional ADR survey aims at informing second-line (and beyond) regimen selection by estimating HIVDR national prevalence in populations receiving ART for 12 (+/-3) months and for ≥48 months. For each of those two populations, ~400-600 patients are selected in at least 17 randomly sampled clinics. HIVDR status is determined through genotyping for selected patients with a viral load of ≥1000 copies/mL. A concept note regarding ADR for infants is currently being developed by CDC and should be reviewed by WHO in May 2014. There will only be slight differences between the adults and infants ADR surveys.
2. **Pre-treatment Drug Resistance (PDR).** The cross-sectional PDR survey aims at informing first-line regimen selection by estimating HIVDR national prevalence among ART initiators. ~300-400

[14]Source: WHO, Concept note: Surveillance of HIV drug resistance in Adults receiving ART (acquired HIV drug resistance), 2014
WHO, Concept note: Surveillance of HIV drug resistance in Surveillance of HIV drug resistance in adults initiating antiretroviral therapy (pretreatment HIV drug resistance), 2014
WHO, Consultation process to inform the revision of the HIVDR strategy, 2012-2013

patients initiating ART are selected in at least 15 randomly sampled clinics, and their HIVDR status is determined through genotyping.

3. **Adult Transmitted Drug Resistance (TDR).** The adult TDR survey aims at informing PrEP, PEP and future first-line regimen selection, as well as informing on program quality, by estimating HIVDR national prevalence among ARV-naïve recently infected adults (details of survey not finalized).
4. **Infant Drug Resistance.** The infant TDR (or pediatric) survey aims at informing first-line pediatric regimen selection by estimating HIVDR national prevalence among ART-naïve infants below 18 months. Some or all laboratories that perform infant diagnosis select at least 245 existing DBS samples and determine HIVDR status through genotyping.

d. Revised WHO HIVResNet organization

The organization and governance of the WHO HIV ResNet was also revised at the end of 2013 to optimize the Steering Group's functioning as WHO's key advisor on HIV drug resistance issues and to support the strategy more effectively[15]. Previous governance arrangements were perceived by the WHO HIVDR Advisory Group to be too complex, leading to a lack of clarity regarding roles of main stakeholders and constituencies. The objectives of the revision are to:

- Simplify and clarify roles and responsibilities
- Optimize comparative advantages
- Promote implementation and uptake.

WHO HIV Secretariat. The role of WHO has been clarified around 6 key areas in HIVDR[15]:

- Global coordination and engagement of stakeholders
- Production of global-level guidance and tools
- Advocacy for the integration of HIVDR prevention and surveillance into national HIV strategies
- Capacity building, directly or with partner institutions
- Management of laboratory network
- Data collection, management, analysis and reporting

Steering Group. In 2013, the structure of the Steering Group has been changed and its role has been clarified. The HIVDR Steering Group in 2013 was reaffirmed as the principal advisory group to WHO on HIVDR, with a maximum of 20 members for 3 years. The scope of this group is to provide input on :

- WHO's strategy to tackle HIVDR consistent with WHO's mandate and comparative advantages and respective roles of partner organizations
- The majors issues and challenges to be addressed to monitor and contain HIVDR
- The engagement of partners, advocacy and outreach
- The long term sustainability of WHO's work on HIVDR
- The formulation of strategies for capacity building

Core Group. A Core Group, with a maximum membership of 5 people, was set up to interact more frequently with the WHO HIV Secretariat and address technical questions on a real-time basis.

Ad hoc working groups. It was also decided that the Steering group and Secretariat should be supported by ad hoc working groups (rather than standing working groups), in order to avoid working groups in silos and further enhance collaboration between the different topics (labs, treatment, M&E, epidemiology, etc.). Current working groups are Epidemiology, SDRM mutation list, Laboratory and DBS.

[15]Source: WHO, WHO HIV Drug Resistance Advisory Group Meeting, Meeting Report, October 2013

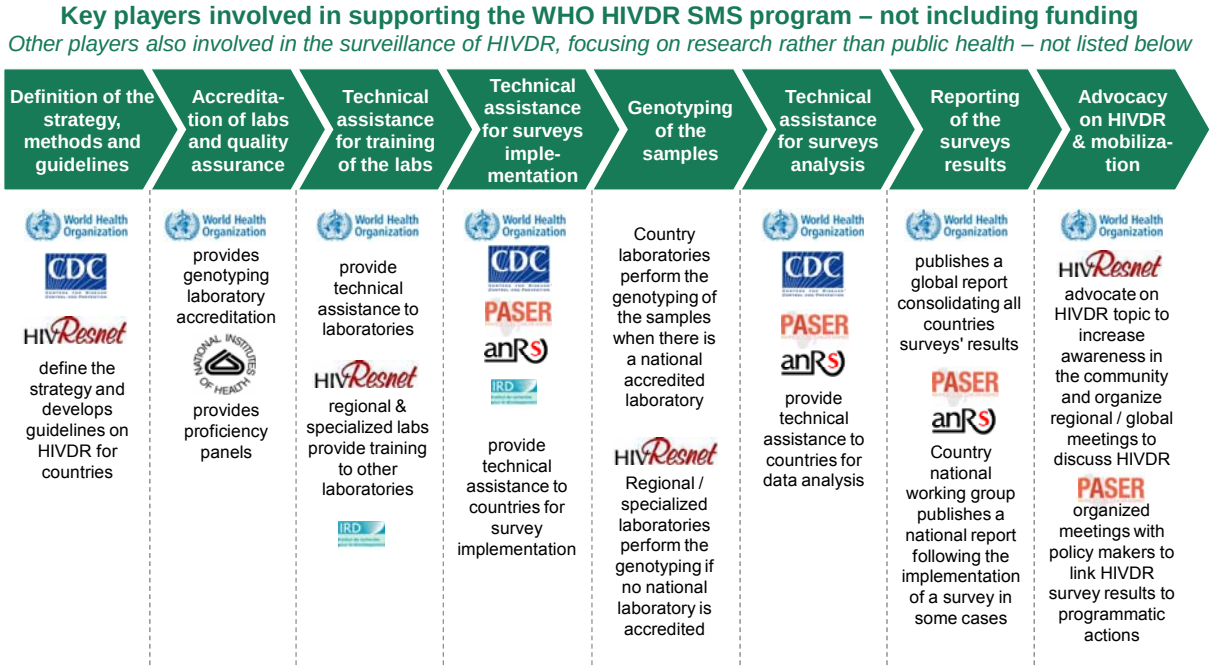
HIVResNet network. HIVResNet was broadly defined as institutions and experts interested in HIVDR that worked with WHO to develop the original strategy and who participated in its subsequent implementation and advocacy.

Members of each of these groups have been appointed, and the Steering Group Terms of Reference were presented during last Steering Committee in October 2013 and shared by email with the members. The other groups Terms of Reference have not yet been drafted and shared with participants. There have been various calls between the members of the Core group, but the Steering Group has not convened since October. In March 2014, the SDRM mutations list working group, the Laboratory working group and the HIVResNet network convened separate meetings.

4. KEY PARTNERS INVOLVED IN THE STRATEGY

Many organizations have been active in the implementation of the WHO HIVDR strategy since 2004, either at country level or directly to WHO. Their support has been financial, with grants or in-kind support, or operational through the provision of technical assistance. Support was provided for the implementation of the surveys, laboratory accreditation, technical assistance for data analysis, advocacy and social mobilization, and monitoring of the impact of drug resistance (Fig.II.9). Specific sources of support have been described in detail in various reports provided by WHO to the BMGF *(Please refer to appendix for more details)*.

FIG. II.9. Key partners involved in the WHO HIVDR strategy



At WHO HQ level, in addition to the support from the BMGF, support has been granted mostly through CDC/PEPFAR and the Public Health Agency of Canada. CDC / PEPFAR supported part of the implementation of the strategy through Country Operating Plans (COP) funding, CDC supported database development through Headquarter Operating Plans (HOP) funding and PEPFAR supported central coordination. The Canadian Government through the Public Health Agency of Canada, also contributed to the definition of the strategy through financial support for the salaries of a full time Public Health specialist and HIVDR consultants.

At country level, many organizations have supported the implementation of WHO surveys, either with funding or with technical assistance, either for the data collection and analysis parts or for the genotyping parts. CDC reports they have supported survey implementation in more than 20 countries both financially through PEPFAR Country Operating Plans (COP) money, and operationally with technical assistance from headquarters or CDC country offices. PASER supported survey implementation in six Sub-Saharan countries through a PharmAccess foundation's grant (The Netherlands Ministry of Foreign Affairs). Regional and specialized laboratories of the WHO HIVResNet network, such as the laboratories in Vancouver, in Ottawa or the CDC Atlanta facility, provided free genotyping for countries.

Laboratory support at country level has mostly been provided by WHO HIVResNet network of regional and specialized laboratories which provided training and technical assistance to national laboratories. NIH also supplied HIVDR genotyping proficiency panels to the accredited laboratories including candidate laboratories since 2007.

Other organizations also contributed on a smaller scale or more ad hoc basis to the implementation of WHO's HIVDR strategy *(Please refer to the appendix for more details regarding partners)*.

III. ACHIEVEMENTS, CHALLENGES AND PRIORITIES

1. COORDINATION AND MOBILIZATION OF PARTNERS

a. KEY ACTIVITIES

Coordination and mobilization of partners was one of the initial objectives set for WHO HIVDR SMS. Partners include: countries, donors, implementing partners, and other institutions involved in HIV prevention and treatment. Key activities undertaken to serve this objective can be broken down in three parts: collect input and generate buy-in from partners; advocate for HIVDR surveillance and prevention; and coordinate and provide guidance for the surveillance and prevention of HIVDR.

Although prevention was not explicitly cited in 2004 strategy, it is now included in the mandate of WHO as defined in Steering Group meeting in November 2013 (Advocating for the integration of HIVDR surveillance and prevention in HIV programs).

In the BMGF grant, these activities represent a budget of $6.1m (direct costs), including $1.4m of travel costs for regional meetings, trainings, consensus meetings and Steering Committee meetings; and $1m for document development & publication and meeting organizational costs. The remaining budget covered staff, consultants and contracted services.

b. COLLECTING INPUT AND GENERATING BUY-IN FROM PARTNERS

a) Achievements in collecting input and generating buy-in from partners

WHO granted with legitimacy, credibility and neutrality for standard-setting. Content experts and countries interviewed consider WHO as a legitimate coordination and standard-setting body for HIVDR surveillance. Its international mandate and neutral status are perceived to facilitate access to country governments and collection of sensitive data, which countries might not share with other parties. Countries interviewed have mentioned they were confident sharing their data with WHO. No other organization has been mentioned as having the ability and legitimacy to fulfill this role. WHO's methodology and results are key standards of reference in the field of HIVDR surveillance. Content experts and in particular academics interviewed reported that WHO has built a strong scientific credibility through publications; presence at scientific events, and information sharing through WHO HIV ResNet. WHO results are reported by one academic interviewed to be widely used to validate studies conducted using other methodologies.

Country representativeness of WHO's HIVDR advisory boards[16] (HIVDR ResNet). The network gathers a diverse range of stakeholders to ensure that different perspectives are reported and taken into account by WHO. The 18 current members of the Steering Group include representatives from AFRO (3 members), AMRO (7 members), EURO (5 members), SEARO (1 member) and WPRO (2 members). The Core Group shows a comparable make-up: its 4 current members represent CDC headquarters, two implementing countries from AMRO and AFRO and a European scientist (Andrea de Luca from the University of Siena). Interviewees, in particular countries HIVDR focal points, perceived as a key achievement the fact that WHO gathered input from all regions through the Steering Committee, as this facilitated adapting the strategy to settings such as Latin America. The initial methodology was reported not to be adapted to some regions specificities and would therefore have led to gaps in the global data used to inform global recommendations.

[16]Note: Steering Group and Core group membership provided in appendix

Thorough consultation process conducted by WHO to revise survey and EWI methodology. WHO gathered extensive input from its partners to revise the methodology of EWI (in 2011) and surveys (in 2012-2014) *(see Box 1 for more details on the survey and EWI revision process)*. The revision process of surveys took place over 2 years and involved the consultation of experts as well as program managers and end users of the methodology (5 regional workshops, 147 participants from 43 countries). Feedback from interviewed countries on the consultation process is very positive, which drives country engagement and support the revised methodology.

Challenges faced in the past by the organizational structure are expected to be solved by the new organization of WHO HIVDR ResNet. The objective of this reorganization was to simplify the network's structure, clarify roles and responsibilities and improve the effectiveness of the network. It was approved by WHO HIVDR ResNet Steering Committee in December 2013 *(see Chapter on Context and Objectives of the Strategy)*. Three advisory bodies were defined: a Steering Group; a Core Group; and a set of ad hoc Working Groups that will gather as needed to tackle specific topics.

b) Challenges in collecting input and generating buy-in from partners

Focus of WHO's HIVDR advisory boards perceived to be on scientific topics while limited steer is provided on programmatic implications and advocacy aspects of the strategy. According to its revised draft terms of reference[17], the Steering Group should advise WHO on all aspects of the strategy, including coordination of prevention and advocacy. However, according to interviewed members, discussions within the Group have tended in the past to focus on scientific considerations. This scientific focus has been critical in establishing the credibility of the program, strategy, methodology and quality of data reported, and is likely to have been required in recent years as the revision of the methodology was being conducted, but it is highlighted by participants that WHO receives limited steer and support on the other aspects of its mandate for HIVDR.

Lack of Steering Group meetings. Based on the initial terms of reference of the Steering Group, the group was supposed to meet at least two times each year. There have been annual Steering Group meetings in November 2008 and November 2009, but no Steering Group meeting was organized in 2010, 2011 and 2012. The last Steering Group meeting was held in October 2013. There have been some WHO HIVResNet meetings organized in 2011 and 2012 but a consequent number of members of the Steering Group did not participate. Lack of formal face-to-face meetings could lead to a decreased engagement of the Steering Group members.

Procedures for gathering input from ResNet members and governance still perceived as unclear by members and a challenge to sustained engagement. Interviewed network members reported that there is room to clarify the way participants arebrought in and consulted, as well as the process through which orientations are taken. The revised ResNet organization (Reviewed Steering Group membership, creation of Core Group) and the draft terms of reference for the revised Steering Group were communicated several times to all members since the end of 2013. Statements have been made to clarify the role of the Steering Group as an advisory board to WHO HIVDR. Yet, some participants, even within the Steering Group, do not have a clear understanding of the role of the Steering Group, and how the consultation process operates. This might be due to the fact that those changes are very recent. However, based on their experience with the survey methodology revision process, they highlighted it as a challenge to buy-in on decisions made by WHO and also to the participation of members (if they don't understand why some of their suggestions are not taken into account, their engagement in the WHO HIVDR work might decrease), even more since participation is on a voluntary basis.

[17]Source: WHO, Steering Group on HIV Drug Resistance Draft Terms of Reference,

Lack of donor coordination and/or reporting mechanisms. There is no formal mechanism to coordinate donors and provide a consolidated view of funding provided to WHO. (i) This has been highlighted by donors as a challenge for the definition of their strategy and support and (ii) may become even more relevant since WHO is expected to diversify funding sources.

- Some donors have reported it as a gap in the current functioning as it prevents them from accessing all the information they need to define their strategy. It could make it difficult to rapidly identify gaps in coverage, and ensure that all relevant activities are funded sustainably. If funding sources diversify further in the future, the need for visibility and coordination of donors' commitments will only increase.
- As WHO may have more donors in the future than in the past (in the past, focus was on the BMGF, while more recent donors include CDC and Canada), it will need to devote more time to defining strategies through bilateral discussions and report on grant activities.

Although this may be a minor challenge, it has been mentioned by interviewees from AFRO countries that the AFRO region may be under-represented in the Steering Committee relative to its importance in the global epidemics, ART caseload and risk of resistance emergence. The AFRO region represents 17% of Steering Committee members and 77% of patients under ART in LMIC in 2012.

c) Priorities for the future in collecting input and generating buy-in from partners

Ensure WHO receives support and steer from its advisory boards on issues related to advocacy and coordination of prevention. Currently the steer and support that WHO HIV receives on HIVDR comes from the WHO HIV ResNet Steering Group, which has focused its discussions and recommendations on scientific issues (e.g., guidance, survey methodology etc.). However, 8 members of the Steering Group have public health and policy expertise and the lack of steer on issues related to advocacy and coordination of prevention may be more a reflection of the agenda rather than the composition of the group. To ensure support on a broader range of aspects of the strategy, Steering Group meetings should feature recurring agenda points covering all aspects of WHO HIVDR mandate, in particular (in accordance with the Group's revised terms of reference)[18]: engagement of partners, advocacy and outreach efforts; long-term sustainability; approaches to ensure appropriate links with ART programming; formulation of strategies for capacity building. WHO could also present the Steering Group with specific issues related to those topic areas on an ad hoc basis, so as to receive more steer beyond scientific and technical questions. In addition, partners with expertise on advocacy could be brought in as Steering Group members (e.g., UNAIDS).

Further clarify exchanges and feedback loops with WHO HIV ResNet. ToR for each group or committee should be communicated and made available (at the moment, there are draft ToRs for the Steering Group, but not for the Core Group, ad hoc working groups, and ResNet network). These ToR should outline: roles, responsibilities, frequency of meetings, standing agenda points and since none of these groups is a decision-making body, the ToR should clarify how their input will be taken into account by WHO Secretariat (e.g., formal responses or responses during meetings or minutes of key meetings or others).

Create a mechanism to manage donor relations and coordination. Facilitating coordination between donors could help ensure the sustainable and efficient funding of all identified needs. Donors would be assigned a point of contact within WHO, who would provide consolidated information on the whole strategy's funding and provide progress information. Based on this information, donors would coordinate their actions to ensure that funding is targeted in the most effective way based on their

[18]Source: WHO, Steering Group on HIV Drug Resistance Draft Terms of Reference,

respective areas of focus and expertise, and that all needs are met sustainably. A subgroup of the Steering Group composed of donors should be convened on the side of Steering Group meetings once or twice a year.

C. ADVOCATING FOR HIVDR SURVEILLANCE AND PREVENTION

a) Achievements in advocating for HIVDR surveillance and prevention

Increased awareness of HIVDR at global and national levels. WHO is credited by most interviewees (content experts as well as countries) with raising awareness on the issue of HIVDR, both at global and national levels. WHO is recognized for having helped to clarify the stakes and put HIVDR on the agenda of the global HIV community with its strategy, but also with the many publications and participation in key scientific events.

- In 2012, WHO published the HIV Drug Resistance report.
- A large number of other publications has been produced as part of the strategy: in 2012 alone, 77 papers, presentations and posters were published or presented by WHO and its partners (in particular laboratories in the network)[19].
- WHO and its partners also participate and were invited speakers in high-profile scientific events such as CROI, IAS, Glasgow HIV Conference, International Resistance Workshop, INTEREST.
- WHO organized 27 regional workshops on HIVDR between 2007 and 2014[20] (for capacity building as well)
- The Chair of the WHO HIV ResNet Steering Committee called on the WHO Director General to alert donors on the importance of HIVDR in 2009, emphasizing the need for increased funding efforts[21]
- WHO has dedicated a webpage to HIV Drug Resistance surveillance strategy

Increasing integration of HIVDR surveillance in WHO HIV documents. Key HIV documents published by WHO increasingly integrate HIVDR considerations. The March 2014 supplement to the 2013 ARV guidelines features a summary of the HIVDR strategy[22], and the Global Health Sector Strategy on HIV/AIDS 2011-2015 interim progress report published on May 19th 2014 for World Health Assembly addresses HIVDR challenges[23]. These efforts are a starting point to provide increased visibility to HIVDR among other HIV priorities and emphasize the issue's relevance for HIV programming as a whole.

Increasing integration of HIVDR surveillance by key partners. As a result of bilateral discussions with partners, some partners are recently increasingly integrating HIVDR surveillance in their programs. In December 2013, the UNAIDS Program Coordinating Board recommended that countries monitor HIVDR according to the WHO global strategy[24]. Steps are being taken to ensure that HIVDR

[19]Source: WHO, Global Strategy to Evaluate and Limit HIV Drug Resistance Emergence and Transmission, Progress report, 2012

[20]Source: WHO, Email from Silvia Bertagnolio, May 19th 2014

[21]Source: Letter from Mark Wainberg to Margaret Chan, Hiroki Nakatani and Kevin DeCock, February 4th 2009

[22]Source: WHO, March 2014 Supplement to the 2013 Consolidated Guidelines on the Use of ARV drugs for treating and preventing HIV infection, 2014,
http://apps.who.int/iris/bitstream/10665/104264/1/9789241506830_eng.pdf?ua=1

[23]Source: WHO, The Global Health Sector Strategy on HIV/AIDS 2011-2015: An Interim Review of Progress, May 2014
http://apps.who.int/iris/bitstream/10665/112790/1/9789241507295_eng.pdf?ua=1

[24]Source: UNAIDS, 33rd Meeting of the UNAIDS Programme Coordinating Board, Decisions, Recommendations and Conclusions,

surveillance is integrated in funding requests to two key donors, the Global Fund and PEPFAR. The Global Fund Standard Grant Agreement (Article 19) reinforces the importance of drug resistance-related activities, and 68% of Round 7-9 funded grant proposals mentioned HIVDR (although only 15% of budget requests included specific funding for these activities). In 2012, WHO advocated with the Global Fund to take measures to encourage countries to take HIVDR into consideration in their applications, such as requiring documentation on an HIVDR plan, advocating HIVDR action, and modifying application materials to facilitate HIVDR surveillance fund requests[25]. In 2014, WHO published guidance to help countries budget for HIVDR surveillance and ensure that this activity is included in countries' Global Fund applications[26]. In the 2014 Country Operational guidelines, PEPFAR also now requests that countries present their HIVDR surveillance strategy as part of their COP[27]. These achievements are starting points and partners could engage more strongly. They are also very recent and their impact has not yet been assessed.

b) Challenges in advocating for HIVDR surveillance and prevention

Limited resources for HIVDR advocacy at WHO. WHO currently has limited resources for advocacy on HIVDR. The HIV department has 80% of an FTE (P4) for advocacy for HIV and 20% for Hepatitis. For HIVDR specifically, advocacy represents one of the activities of the only full staff position at WHO HQ (less than 20% of medical officer (P5)).

Need for more advocacy to ensure that countries secure funding. For countries to receive funding, both donors (e.g., the Global Fund, CDC/PEPFAR, other bilateral donors) and countries (e.g., HIV program managers defining National Strategic Plans and writing applications for grants, Ministries of Health deciding on allocation of budgets) need to be convinced of the importance of the issue. Content experts interviewed and HIVDR country focal points reported that this was a challenge at both levels, as countries and donors perceive HIVDR among competing priorities on the HIV agenda.

Low resistance levels detected to date. Surveillance results have not shown alarming levels of resistance in any of the countries surveyed so far, and fears that HIVDR might prevent the effective scale-up of ART have not yet materialized. As a result, it has been challenging to raise HIVDR and therefore HIVDR surveillance and prevention as a major issue.

Challenging context and financial constraints make the need for advocacy on HIVDR surveillance and prevention even greater. The WHO HIVDR ResNet Steering Committee reported that advocacy efforts face a particularly challenging context due to financial constraints and a decreasing attention to HIVDR in the high-income countries. "In an environment of increasing financial constraints, [Steering committee members] emphasized the need to adequately marshal and present convincing evidence about the importance of HIVDR to all those concerned, including technical partners and funders. It was highlighted that, as HIV drug resistance is currently an issue of decreasing importance in the United States and Europe, greater involvement of low- and middle-income countries is necessary"[28].

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http://www.unaids.org/en/media/unaids/contentassets/documents/pcb/2013/pcb33/agendaitems/20131220_Decisions_Recommendations_Conclusions_33PCB_meetingl.pdf

[25]Source: WHO, Email from Silvia Bertagnolio, May 19th 2014

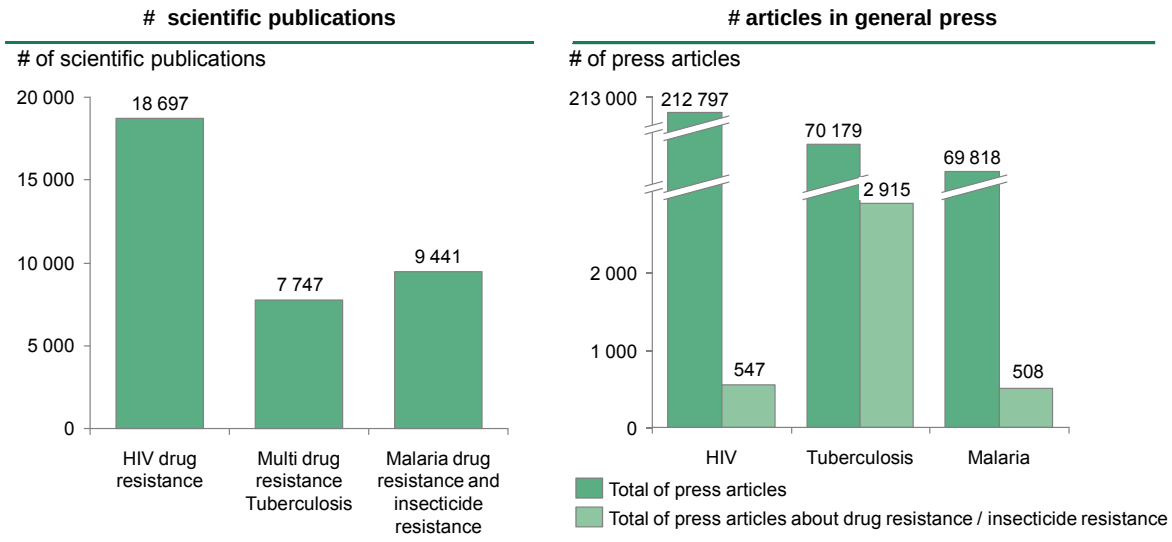
[26]Source: WHO and UNAIDS, Resource kit, Guidance note HIV drug resistance surveillance, March 2014

[27]Source: PEPFAR, Country Operating Plan (COP) Guidance, November 2013, http://www.pepfar.gov/documents/organization/217765.pdf

[28]Source: WHO, WHO HIV Drug Resistance Advisory Group Meeting, Meeting report, October 2013

HIVDR communication targeted to the scientific community and HIVDR technical stakeholders rather than donors and policy makers. Interviewees reported that HIVDR is often primarily viewed as a topic of research. ResNet focus has been mainly on scientific and technical issues, the documents that WHO has published on HIVDR have chiefly been aimed at a scientific audience: for instance survey protocols[29], concept notes[30], and the 2012 Global Report on HIV Drug Resistance[31]. While HIVDR is considered important in the scientific community, there has been less awareness of the extent of the issue and its practical relevance among donors, program managers and policy-makers, as well as in the general audience. This concern is reflected by the volume of publications on HIVDR, if compared with publications on tuberculosis and malaria drug resistance. Among scientific publications, there have been twice as many publications involving HIVDR as there has been for either TB drug resistance or malaria drug resistance. In the general press, however, HIV drug resistance has come up much less frequently than TB drug resistance, and about as frequently as malaria drug resistance, even though HIV as a whole obtains far more coverage than either of the two other diseases (Fig. III.1). This is consistent with a perception of HIVDR as a scientific issue with less practical relevance than resistance in other diseases.

FIG. III.1. Presence of drug resistance in scientific publications and the general press



1. DR stands for drug resistance -Note: keywords used on PubMed and Factiva for research on HIV drug resistance : HIV drug resistance and HIV drug resistant; on tuberculosis drug resistance : multi drug resistance tuberculosis, multi drug resistant tuberculosis; on Malaria drug resistance : artemisinin resistance, malaria insecticide resistance, artemisinin combination therapy resistance, malaria pyrethroids resistance
PubMed is linked to the US National Library of Medicine and the National institute of Health;Factiva is a business information and research tool owned by Dow Jones & Company
Source: PubMed website, Factiva, BCG analysis

Lack of supporting materials for advocacy purpose. The 2012 Global Report on HIVDR is recognized a key scientific achievement, but it was not designed to serve advocacy purpose. In addition to future editions of this scientific report, interviewees at global level suggested a need for another document that would focus on key, simple messages relevant for advocacy and targeting a broader audience (e.g., donors, policy makers). It could use some of the data included in the Global Report to show the extent of the problem through global and regional aggregate numbers for

[29]Source: WHO, WHO Generic Protocol for surveillance of initial drug-resistant HIV-1 among children < 18 months of age newly diagnosed with HIV, 2012, http://apps.who.int/iris/bitstream/10665/75202/1/WHO_HIV_2012.17_eng.pdf?ua=1

[30]Source: WHO, Concept note: Surveillance of HIV drug resistance in Adults receiving ART (acquired HIV drug resistance), 2014

[31]Source: WHO, WHO HIV Drug Resistance report, 2012

resistance level, outline the implications, underline what is at stake, summarize the roles of the main stakeholders in implementation of the strategy and in advocacy, and present funding needs. In the context of malaria, such documents have been developed jointly by WHO and Roll Back Malaria partnership, the Global Plan for Artemisinin Resistance Containment (GPARC)[32] and the Global Plan for Insecticide Resistance Management (GPIRM)[33] aimed at raising awareness among policy makers and potential donors beyond the research community (see details in Appendix).

Lack of advocating relays. No other organization either at global level or local level than WHO has been mentioned by interviewees as advocate of this cause. WHO lacks advocacy partners that would help craft the message, relay it, and coordinate communication. As a key player in awareness for HIV in general, UNAIDS has been mentioned as a potential partner by implementing partners or donors interviewed, but it has not been active on HIVDR advocacy at this stage. No report has been published by UNAIDS on HIV Drug resistance, the 2012 HIVDR report has not been further advertised by UNAIDS, anecdotally the official UNAIDS Twitter account did not issue any tweet related to HIVDR over the past 12 months (out of 564 tweets). By contrast, both Roll Back Malaria and Stop TB Partnership issue regular communications on resistance in their respective fields and often co-sign reports with WHO (e.g., The Global Plan to Stop TB 2011-2015, The Global Plan for Artemisinin Resistance Containment, The Global Plan for Insecticide Resistance Management), they communicated on resistance through Twitter (3.2% and 9% of their tweets mentioned it, respectively)[34].

c) Priorities for the future in advocating for HIVDR surveillance and prevention

Define a communication strategy for HIVDR. The strategy would include five key elements.

Define target audiences; outline objectives and communication channels. Key target audiences are funding instruments, country ministries of health and HIV programs, and technical partners. Donors / funding instruments and governments are particularly critical as their endorsement helps secure funding. Support from some donors and governments may also encourage the endorsement of others.

- **Donors / funding instruments**. In its communication with donors, WHO should emphasize the importance of funding HIVDR surveillance as a key element of HIV programs. It should be perceived by donors as an integral part of funding the general HIV program. One avenue to achieve this goal is to continue working with the Global Fund to ensure that countries include HIVDR in their plans (whether funded by the Global Fund or by other sources). Other donors should be approached for the same purpose.
- **Country ministries of health and HIV programs**. In countries, WHO should secure buy-in from Ministries of health and HIV program managers so that countries are willing to find and devote funding for HIVDR, implement the strategy, and share results with WHO. To do so, WHO could leverage meetings scheduled by the rest of the HIV department and ensure that time is dedicated to the HIVDR issue (e.g. presentation of the revised methodology, impact of survey results, case studies) and should ensure that regional and local WHO staff is provided with the right set of messages to convey to key interlocutors.
- **Technical partners**. WHO should engage with technical partners (e.g. implementers, NGOs) to ensure that they advocate for HIVDR surveillance and prevention with countries, and improve

[32]Source: WHO and Roll Back Malaria, Global Plan for Artemisinin Resistance Containment, 2011, http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf?ua=1
[33]Source: WHO and Roll Back Malaria, Global Plan for Insecticide Resistance Management in Malaria Vectors, 2012, http://apps.who.int/iris/bitstream/10665/44846/1/9789241564472_eng.pdf?ua=1
[34]Source: UNAIDS, STOP TB, Roll back Malaria official Twitter accounts, BCG analysis

coordination on HIVDR across agencies. WHO could reach them in major conferences (e.g. ICAAP, ICASA).

Create clear and simple messages. Messages should clearly link HIVDR surveillance with the outcome and the cost-effectiveness of the ART programs, by outlining how surveillance helps detect adherence problems, facilitates scale-up, improves treatment effectiveness and ultimately keeps more people healthy. To donors, HIVDR surveillance could also be presented as a sound investment: for comparatively limited funds, donors can use it to protect the effectiveness of ART programs.

Identify major events and milestones. Events and milestones can be leveraged both in the context of AMR (e.g. publication of WHO AMR global report on surveillance[35]) and the context of HIV (e.g. World AIDS Day) or other specific milestones (e.g., MDG progress update, updates on child mortality). Frequency of communication should be defined.

Identify relays for communication. Relays should be sought within WHO and with external partners.

- **Relays within WHO**. A first step is to continue integrating WHO HIVDR with HIV communication targeting a broad audience. The next set of guidelines to be published, or the next update to the Health Sector Strategy by WHO are opportunities to integrate HIV and HIVDR further. Similarly, advocacy for HIV should include advocacy for HIVDR more systematically.
- **External partners**. A further step is to explore ways to leverage existing partners on advocacy more strongly, for instance UNAIDS, the BMGF, and civil society and include some of them in Steering Group (e.g., UNAIDS).

Develop documentation. Appropriate documentation should be developed to convey the key messages to each target audience. Documents would show a high-level view of the HIVDR issue, underline the stakes, detail key actions for surveillance and prevention, explain the role of key stakeholders and funding needs.

d. COORDINATING SURVEILLANCE AND PREVENTION

a) Achievements in coordinating surveillance and prevention

WHO has created and relies on two main tools to communicate surveillance and prevention guidance as well as updates for coordination among HIVDR implementers and advisors.

- Guidance documents designed by WHO and disseminated during key scientific conferences (e.g., CROI) to countries and key stakeholders (e.g., HIVDR focal points, RestNet members, in-country laboratory focal points)
- Regular newsletter shared with over 450[36] WHO HIVDR ResNet members and stakeholders. The latest issue was published in November 2013. The newsletter provides updates on HIVDR surveillance activity, such as an overview of surveys conducted, and a updated list of accredited genotyping laboratories, and encloses the guidance documents/reports newly released by WHO HIVDR team. It also summarizes major network events, such as Steering Committee meetings, and announces upcoming ones.

WHO has developed guidance on surveillance of HIVDR. WHO has provided countries with guidance to implement its surveillance methodology since the strategy was launched in 2004. Most

[35]Source: WHO, Antimicrobial Resistance: Global Report on Surveillance, 2014
http://www.who.int/drugresistance/documents/surveillancereport/en/
[36]Source: WHO, newsletter mailing list, Email form Silvia Bertagnolio, May 1st 2014

interviewed countries value this guidance as it enables them to know how to implement the different surveys and EWIs following WHO methodology. Following the revision of the methodology, updated guidance is provided through six separate documents listed below:

- A strategy paper summarizing the new methodology[37]
- A meeting report outlining the revised guidance for monitoring through EWI[38]
- A protocol for the HIVDR survey in children < 18 months [39]
- A concept note detailing the revised ADR survey[40]
- A concept note detailing the revised PDR survey[41]
- A concept note detailing the revised TDR survey – not finalized to date

These documents provide detailed information for countries to understand how they can implement the surveys and EWIs. The revised ADR and PDR survey concept notes provide an overview of the methods employed as well as guidance on implementation and data analysis. For implementation, the concept notes specify the duration of the surveys; patient screening and sampling techniques, the list of variables to be collected and guidance to repeat the survey. They also provide excel tools to calculate sample sizes based on specific country settings and advice on how to implement both ADR and PDR surveys in the same clinics. For analysis, the concept notes include instructions on how to analyze survey results using STATA statistical software.

WHO also leverages relays at regional and national levels:

- WHO regional staff
- National HIVDR working groups
- Partners with local or regional presence

WHO regional offices leveraged in the initial organization of the strategy. In the first years of the implementation of the strategy, WHO relied on HIVDR focal points in regional offices to support local capacity building and coordinate activities at the regional level. Over the course of the strategy, a reorganization at WHO led to HIVDR focal point positions being "abolished in 3 AFRO regions (West, Eastern and Southern Africa) and SEARO, and multiple WHO country offices saw loss of HIV focal points"[42]. This resulted in regional offices having a lesser role in the implementation of the strategy, which relied on the headquarters team to a greater extent than initially planned.

Creation of National HIVDR working groups. With the support of WHO, over 60 onboarded countries have created a national HIVDR working group[42] within their Ministry of Health and developed a national HIVDR strategy to coordinate HIVDR surveillance. WHO has not assessed the functionality of these working groups to date. As per WHO's recommendations[43], the main tasks of the

[37]Source: WHO, WHO global strategy for the surveillance and monitoring of HIV Drug Resistance, 2012, http://apps.who.int/iris/bitstream/10665/77349/1/9789241504768_eng.pdf?ua=1

[38]Source: WHO, Assessment of WHO HIVDR EWI: Report of the EWI Advisory Panel Meeting, Meeting Report, August 2011, http://apps.who.int/iris/bitstream/10665/75186/1/9789241503945_eng.pdf?ua=1

[39]Source: WHO, WHO Generic Protocol for surveillance of initial drug-resistant HIV-1 among children < 18 months of age newly diagnosed with HIV, 2012,
http://apps.who.int/iris/bitstream/10665/75202/1/WHO_HIV_2012.17_eng.pdf?ua=1

[40]Source: WHO, Concept note: Surveillance of HIV drug resistance in Adults receiving ART (acquired HIV drug resistance), 2014

[41]Source: WHO, Concept note: Surveillance of HIV drug resistance in Surveillance of HIV drug resistance in adults initiating antiretroviral therapy (pretreatment HIV drug resistance), 2014

[42]Source: WHO, Global Strategy to Evaluate and Limit HIV Drug Resistance Emergence and Transmission, Progress report, 2012

[43]Source: WHO, Email from Silvia Bertagnolio, 19th May 2014

working group should include, the collection and assessment of indicators known to be related to HIVDR, the implementation of WHO HIVDR surveys, and the collation of any additional HIVDR-related information from projects or research being performed in the country. The working group also plans further evaluations to clarify issues raised by survey results and to address other country-specific issues, and is responsible for making public health recommendations and facilitating the development of national plans for action. In each country, the national HIVDR working group also coordinates funding requests and is supposed to develop a 5-year plan for HIVDR surveillance, even if all funding sources have not yet been identified. Participants generally include epidemiologists, clinicians, and laboratorians with expertise in HIV surveillance, HIV prevention, and ART-related laboratory issues as well as representatives from the government, academic institutions and other stakeholders.

b) Challenges in coordinating surveillance and prevention

Alignment of partners at country level has been reported by countries to be a challenge. Countries willing to implement HIVDR surveillance strategy have faced situations where partners would not encourage them in the same direction (for instance recommending implementation of TDR or not, recommending implementation of EWIs or not, recommending to follow WHO methodology or to adjust it). This makes it difficult for countries to implement a consistent strategy.

Integration of HIVDR surveillance guidance is expected in a single document and with other HIV documents. WHO's guidance for HIVDR surveillance is currently fragmented and published as 6 separate documents. However, one of WHO action points since December is to consolidate this guidance documents into one booklet. Moreover, guidance for surveillance has been separated from WHO HIV other documents in the past. For example, the 2013 consolidated guidelines on the use of ARV drugs[44] devote 1 of 272 pages to monitoring and surveillance of HIVDR; and similarly, the Global health sector strategy on HIV/AIDS[45] published in 2011 has no chapter on HIVDR. As a comparison, resistance surveillance and prevention in the field of TB and malaria is consolidated into unified documents ("Guidelines for surveillance of drug resistance surveillance"[46] for TB drug resistance; "Methods for surveillance of antimalarial drug efficacy"[47] for malaria drug resistance; "Test procedures for insecticide resistance monitoring"[48] for malaria insecticide resistance) (see appendix 4 for more details) and is included in strategy documents. However recently, WHO took a first step towards integrating surveillance guidance with treatment guidance by providing a summary of the HIVDR surveillance strategy in the March 2014 supplement to the 2013 ARV guidelines[49] and by addressing HIVDR challenges in the Global Health Sector Strategy on HIV/AIDS 2011-2015 interim progress report published on May 19th 2014 for World Health Assembly[50].

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[44]Source: WHO, Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, June 2013, http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1

[45]Source: WHO, Global health sector strategy on HIV/AIDS 2011-2015
http://whqlibdoc.who.int/publications/2011/9789241501651_eng.pdf?ua=1

[46]Source: WHO, Guidelines for surveillance of drug resistance in tuberculosis, fourth edition, 2009,
http://whqlibdoc.who.int/publications/2009/9789241598675_eng.pdf

[47]Source: WHO, Methods for surveillance of anti-malarial drug efficacy, 2009,
http://whqlibdoc.who.int/publications/2009/9789241597531_eng.pdf?ua=1

[48]Source: WHO, Test procedures for insecticide resistance monitoring in malaria vector mosquitoes, 2013,
http://apps.who.int/iris/bitstream/10665/80139/1/9789241505154_eng.pdf

[49]Source: WHO, March 2014 Supplement to the 2013 Consolidated Guidelines on the Use of ARV drugs for treating and preventing HIV infection, 2014,
http://apps.who.int/iris/bitstream/10665/104264/1/9789241506830_eng.pdf?ua=1

[50]Source: WHO, The Global Health Sector Strategy on HIV/AIDS 2011-2015: An Interim Review of Progress, May 2014
http://apps.who.int/iris/bitstream/10665/112790/1/9789241507295_eng.pdf?ua=1

In the interviews several countries mentioned that while they believed HIVDR was well integrated within the national HIV program, they perceived the organization at WHO headquarters as siloed with limited coordination between HIVDR unit and other HIV units.

More detailed and actionable guidance on HIVDR prevention is expected. 3 interviewed countries reported spontaneously the lack guidance on the appropriate response to HIVDR or measures to be undertaken for prevention was a challenge for the use of data. Content experts interviewed also identified this gap in guidance. As part of the previous version of the methodology, WHO has published guidance on how to translate drug resistance levels into treatment policy, but it does not exist anymore. When it existed, this guidance was included in survey protocols and was therefore targeting implementers of the strategy, while it could be used to help policy makers understand how HIVDR survey results can be used to support improvement of HIV program management.

As a comparison, resistance prevention in the field of TB and malaria is described in dedicated Global Action Plans and in general strategy documents. The Global Plan to Stop TB 2011-2015[51] includes one chapter on MDR-TB (41 pages) describing the current status target and progress as well as future objectives for surveillance and prevention, funding requirements, strategic framework. For malaria, the Global Plan for Artemisinin Resistance Containment[52] and Global Plan for Insecticide Resistance Management[53] are self-contained action plans which integrate policy options for resistance prevention (see appendix 4 for more details). In the context of malaria, the Global Plan for Artemisinin Resistance Containment and the Global Plan for Insecticide Resistance Management provide examples of such guidance[54]. They are non-technical documents, accessible to a wide range of stakeholders, in particular policy makers and donors. They provide prevention guidance based on national conditions such as epidemic types, and assist countries in understanding the local settings and defining their own prevention plans. They suggest examples of a broad range of concrete resistance prevention actions, ranging from changing drug regimens to combating counterfeit drugs or adapting the monitoring approach (see Appendix 4 for more details).

A model for translation of survey results into programmatic action is under development but not intended for direct use by countries. Under the lead of WHO, experts within the network are currently elaborating a cost-effectiveness model that would inform on the cost effectiveness of 5 policy options based on country-specific cost-effectiveness threshold and observed resistance levels (change the first-line regimen; introduce viral load monitoring; introduce one-off viral load testing after 6 months of ART; introduce individual-level drug resistance testing; or maintain treatment policies unchanged)[55]. However, the model is not yet operational, and it would require extensive additional analysis to be calibrated for each national setting, which means that countries will not be able to use it directly. Therefore this tool will not be a way for countries to easily understand how they can use their data. In addition, as reported by the interviewee involved in building this model, there is currently no plan or funding to perform those extra steps.

[51]Source: Stop TB Partnership, The Global Plan to Stop TB 2011-2015, 2011, http://www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011-2015.pdf
[52]Source: WHO and Roll Back Malaria, Global Plan for Artemisinin Resistance Containment, 2011, http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf?ua=1
[53]Source: WHO and Roll Back Malaria, Global Plan for Insecticide Resistance Management in Malaria Vectors, 2012, http://apps.who.int/iris/bitstream/10665/44846/1/9789241564472_eng.pdf?ua=1
[54]Note: See appendix on malaria
[55]Source: Interviews with content expert, April-May 2014

Translation of EWI results into programmatic action (jointly with other teams in WHO/HIV). Countries have also not been provided with specific guidance translating EWI results into follow-up actions. Interviewed experts fear that this lack of response guidance may also be an obstacle to the uptake and repeat of survey implementation at country level, since their impact on treatment programs may not be evident to policy makers, or key persons making investment and budget allocation decisions.

c) Priorities for the future in coordinating surveillance and prevention

Ensure surveillance guidance is further integrated into HIV general guidance (see paragraphs above)

Align partners at global and national level on the priorities for implementation of HIVDR surveillance and prevention. Such alignment could be worked out with an common high-level action plan shared with partners, detailing the priorities and roles of each stakeholders.

Develop guidance for prevention of HIVDR. Beyond surveillance guidance, WHO should provide countries with clear, high-level guidance outlining how to prevent HIVDR based on results of the surveillance. Such guidance in the context of HIVDR could for instance propose a set of surveillance and prevention actions based on the country settings (e.g., level of resources, cost-effectiveness of the program) and the level of resistance observed. It could provide countries with criteria to help define the relevant surveillance and prevention actions.

FIG. III.2. Key messages from the interviews on Coordination and mobilization

Perspectives	Key messages
Countries *(based on 14 countries and 19 interviewees – full list in appendix)*	**WHO is credited with legitimacy, credibility and neutrality** **More advocacy is needed at the Ministry of Health and program management levels, WHO could support advocacy at national level** **Partners at national level are often not aligned**
Content experts *(including WHO, BMGF, CDC/PEPFAR, academics – full list in appendix)*	**WHO is credited with legitimacy, credibility and neutrality** **Lack of clarity on the role and ways of working of ResNet (for instance processes for survey revision, decision-making)** **New organization of ResNet is not well known and people aware of it often don't find it clear** **More guidance should be provided to support countries in identifying actions to take based on surveillance results**
Steering Group *(15 members of the new Steering Group and 21 of the previous one interviewed)*	**Lack of formal procedures for gathering input from WHO HIVResNet identified as a weakness by several members**

Source: Interviews, March-June 2014

2. DATA FOR DECISION-MAKING - HIVDR SURVEYS AND DATABASES

a. KEY ACTIVITIES

From 2004 to 2013, the global HIVDR Surveillance and Monitoring Strategy has measured and collected data on HIVDR through 2 types of surveys (Acquired Drug Resistance ADR and Transmitted Drug Resistance TDR) and a set of Early Warning Indicators. There are three main activities undertaken: the definition ofsurvey methodology, the implementation of the surveys, the data storage and analysis of the results to support decision-making.

In the BMGF grant, these activities represent a budget of $5.1m for surveys and $0.6m for databases. $0.1m for FTE, $0.7m for consultants, $3.4m for testing costs for survey implementation viral load, genotyping and specimen transport)[56]. The $0.6m for database has not been fully spent and part is meant to cover for 2013-2014 database development.

Methodology is defined by WHO secretariat, supported by a consultation process that mobilizes WHO HIV ResNet (Resistance Network), WHO's network of partners involved in HIVDR. The initial methodology was defined and rolled out in 2004; a revision process started in 2011 and led to a revised set of indicators in 2011 (EWI) and the roll-out of a new methodology in 2014 (surveys, ongoing).

Implementation is conducted or overseen by countries. Implementation of surveys involves sampling, collecting specimens and shipping them to a laboratory for genotyping (national, regional or specialized laboratory). Implementation of EWIs involves the collection of ART monitoring indicators in care facilities. Over the reviewed period, WHO has funded survey implementation for 40 countries[57] (of which 26 are PEPFAR countries and 6 are in PEPFAR regions[58]) with the support from the BMGF, (amounts ranged from $20k to $200k per country depending on countries and needs).

Data storage and analysis at a national level is conducted by countries, with technical assistance from WHO consultants or other partners (such as CDC). Results are produced for national, regional and global use. They are disseminated nationally and used for national public health and programme decision making. They are also reported to WHO at the global level. Technical assistance may involve providing data management tools, supporting countries in analyzing data and producing reports. Global reporting and analysis is conducted by WHO and includes quality check of the data.

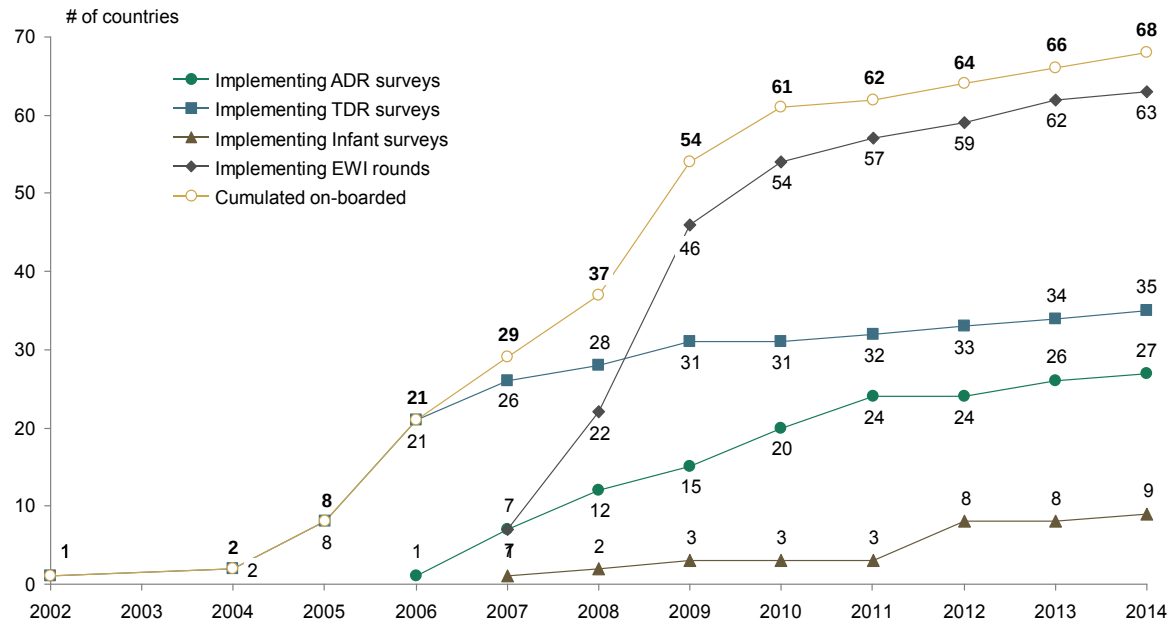
b. ACHIEVEMENTS

a) <u>Achievements in methodology definition and implementation</u>

Between 2004 and 2014, 68 countries implemented at least one survey or EWI round, compared to an initial target of 50 participating countries.

[56]Sources: WHO, Proposal to BMGF, Global strategy to evaluate and limit HIV drug resistance emergence and transmission, 2006,
WHO, 2012 HIV Drug Resistance Project Annual Report, 2013
[57]Source: WHO, Email form Silvia Bertagnolio, April 23rd, 2014
[58]Source: PEPFAR website
http://www.pepfar.gov/countries/

FIG. III.3. Number of countries participating in ADR surveys, TDR surveys and EWI 2002-2014[59]



Implementation of surveys. 115 ADR surveys, 178 TDR surveys and 13 infant surveys were implemented between 2004 and 2014. 41 countries implemented at least one survey and those 41 countries represent 90% of ART patients in LMIC.

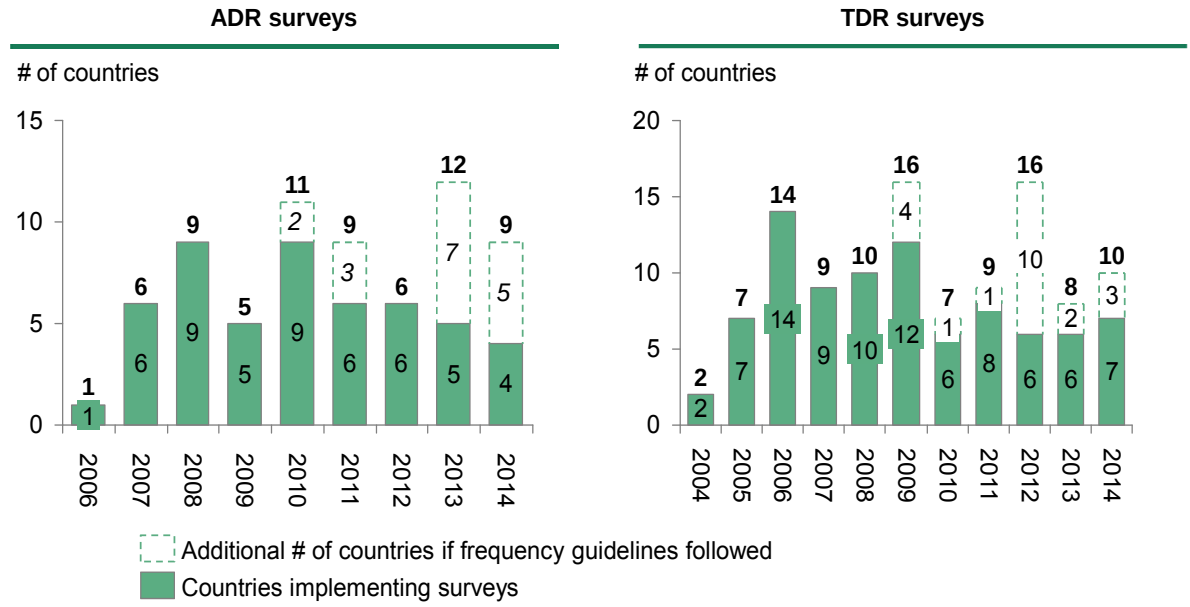
- 27 countries implemented ADR surveys, 13 of which implemented the recommended number of survey rounds[60] (those countries represent 31% of ART patients in LMIC). On average, countries implementing ADR surveys conducted them 1.9 times (different years) which means 37% of countries would have only one data point.
- 35 countries implemented TDR surveys, 15 of which implemented the recommended number of survey rounds[61] (those countries represent 45% of ART patients in LMIC). On average, countries implementing TDR surveys conducted them 2.5 times (different years). 11 countries (i.e. ~33% of countries implementing TDR) have only conducted TDR once while they should have conducted it at least a second time in the reviewed timeframe according to WHO recommendations.

[59]Source: WHO, Email from Silvia Bertagnolio, 19th May 2014
Note: Considered as the number of survey rounds they should have implemented if they had followed frequency guidelines and implemented one survey every three years

[60]Note: Considered as the number of survey rounds countries would have implemented if they had followed frequency guidelines and implemented one survey every three years. At this stage we have not found written guidelines on the number of sites to be surveyed, but this is still under review.

[61]Note: Considered as the number of survey rounds countries would have implemented if they had followed frequency guidelines and implemented one survey every three years.

FIG. III.4. Actual number of countries implementing ADR and TDR surveys vs. expected number if countries followed frequency guidance[62]

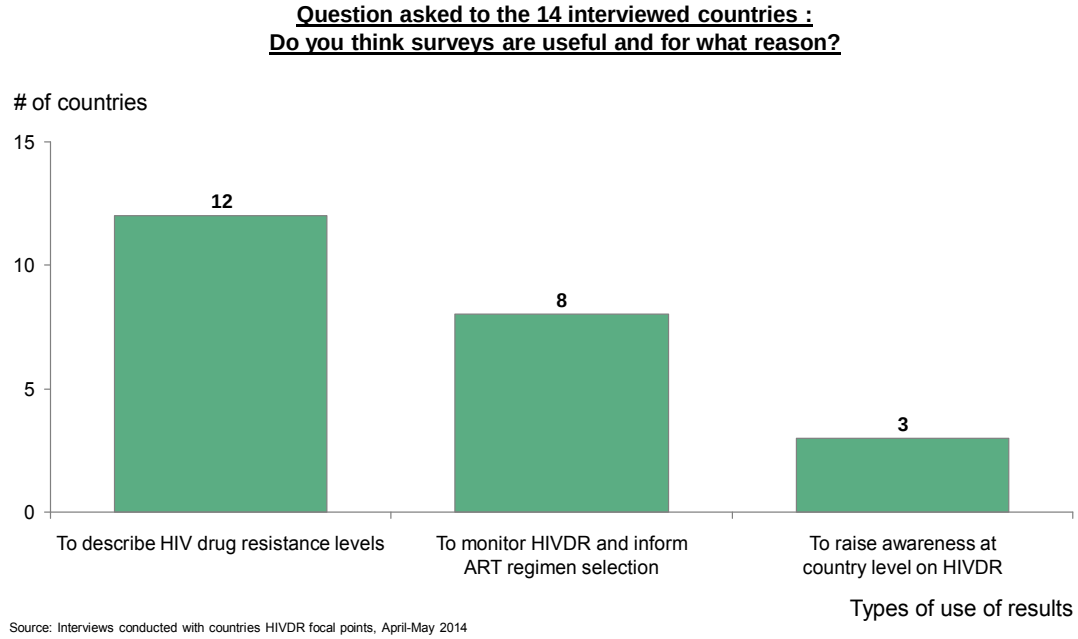


All 14 countries interviewed considered surveys useful to inform their HIV strategy. How countries use the results of the surveys differs from one country to the other (Fig.III.5.), but in most cases countries report during the interviews and in their HIVDR surveillance reports and strategy briefs that data is used for description purpose and to inform drug regimen selection decision-making processes (even though the end decision has always been not to change drug regimen).

- Most countries mention that surveys are useful to describe HIV drug resistance levels.
- Three countries mentioned they use the data to raise awareness at country level (e.g., Ministry of Health, program management) on HIVDR, ensure continued surveillance and decide whether further action is needed.
- Eight countries mentioned they use surveys to monitor HIVDR and inform ART regimen selection. At this stage, given levels of resistance found, survey results have not triggered changes to the regimen choices.
- Most countries did not have sufficient data points on the same sites / areas to perform trend analyses.

[62]Source: WHO, Email from Silvia Bertagnolio, 19th May 2014

FIG. III.5. Different uses of the survey data at country level



Source: Interviews conducted with countries HIVDR focal points, April-May 2014

Illustration 1: Use of the surveys in Zimbabwe

Zimbabwe – Illustration

Key figures 2012	• **Epidemic type:** Generalized • **# of patients under ART:** 565,675[1]	• **# of people living with HIV:** 1,400,000[2] • **Adult prevalence:** 14.7%[2]
HIVDR Strategy	• **EWI rounds:** 2007, 2008, 2009, 2010, 2013	• **TDR survey:** 2006, 2011 • **ADR survey:** 2008, 2009, 2010, 2012

Methodology

- Zimbabwe used the WHO recommended HIVDR prospective monitoring survey methodology to evaluate level of acquired drug resistance 12 month after the start of ART.
- The sites were selected in a phased approach to represent different levels of care, geographies, urban / rural settings.
- The survey also informs on the prevalence of HIVDR in patients initiating ART with no prior exposure to ARVs but it is acknowledged in the report that the prospective methodology is not comparable to the threshold survey methods recommended by WHO for TDR.

Results

# of sites	Baseline results	Endpoint results
• 2008: 3 sites • 2009: 5 sites • 2010: 4 sites	• **6.3%** with baseline HIVDR mutations (94 people) o 12 .1% for those with previous exposure o 5.7% for those with no previous exposure	• **3.3%** with HIVDR mutations at 12 months excluding those with baseline mutations (38 people)

Objectives of the study and prospective report *(as defined in the report on the national HIVDR monitoring at sentinel sites 2009-2011)*

- Highlight patterns of HIVDR at baseline and 12 month endpoint
- Raise awareness
- Guide programming in prevention of HIVDR for the national ART programme

The target audience of the report is health managers, health staff at all levels and partners in health

Recommendations highlighted in the national prospective report

- Consider genotyping for all patients starting ART who were previously exposed to ARVs
- Consider including viral load testing at baseline as cheaper alternative to monitor treatment success
- Carry out a TDR survey to inform the program better on options on the first-line drugs and get prevalence rate of transmitted drug resistance mutations
- Survey resistance in populations starting ART to collect resistance data in pretreatment populations and get information about the effectiveness of available regimens for each region

The results of the monitoring surveys were used to inform decision making on ART regimen and it was decided to remain with the same regimen given the results.
A TDR survey is planned to be implemented in 2014-2015 following the recommendation of the monitoring survey.

1. WHO, Number of patients under ART 2004-2012, Excel file
2. UNAIDS, UNAIDS Report on the Global AIDS Epidemic, 2013
Source: Report on the national HIVDR monitoring at sentinel sites, 2009-2011

Implementation of Early Warning Indicators. 63 countries monitored EWIs at least once between 2004 and 2014, and only one of them did so at the WHO-recommended frequency but it started to implement it in 2014 (once a year). 29% of countries monitoring EWIs conducted rounds once in the period considered; another 21% did so twice; 25% 3 times; 16% 4 times and 10% 5, 6 or 7 times. Since 2007, over 4850 ART sites were monitored[63] (39 sites in average per country. No data is available to determine how many sites were available in each country, as that information has not been collected by WHO to date). At this stage, countries implementing EWIs may have chosen to monitor only some of the EWIs indicators and not all of them.

EWIs are considered useful by countries interviewed as they provide information on the ART program implementation in each site monitored. Countries report in the interviews and in their HIVDR surveillance reports or strategy briefs that they use data to identify, analyze and address treatment delivery issues in care facilities, such as low adherence and retention. As EWIs have been implemented in selected ART facilities and with a low repeat rate, the use of results has been more on an ad hoc basis than a systematic one. It has mostly informed corrective actions in the specific sites surveyed and in few occasions, countries have mentioned that since the results have been considered a good indication of issues that other facilities may face (even though there was no statistical evidence of this) they have been used to trigger corrective actions at a wider scale.

[63]Source: WHO, Email from Silvia Bertagnolio, 19th May 2014

FIG. III.6. Actual number of countries implementing EWI rounds vs. expected number if countries followed frequency guidance[64]

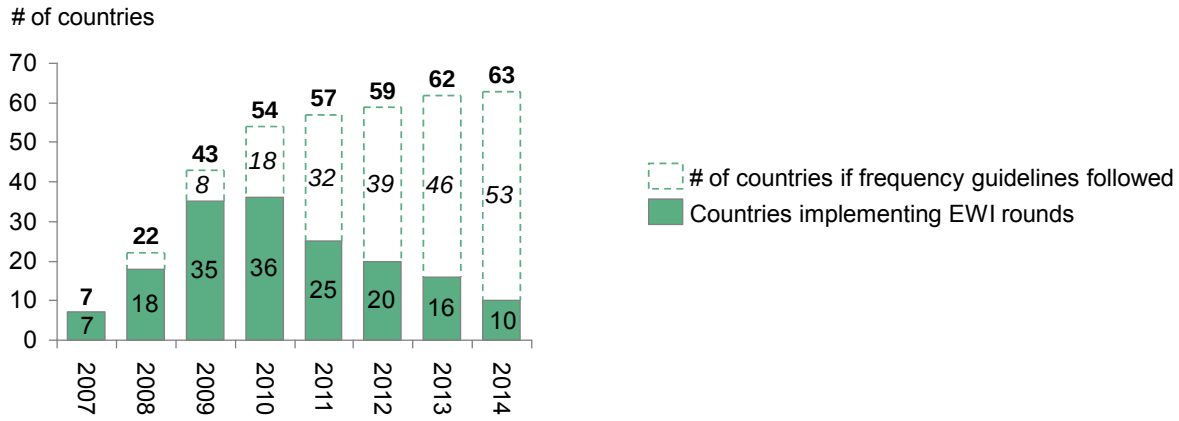


Illustration 2: Use of the Early Warning Indicators in Côte d'Ivoire

Côte d'Ivoire – Illustration

Key figures 2012	• **Epidemic type:** Generalized • **# of patients under ART:** 110,370[1]	• **# of people living with HIV:** 450,000[2] • **Adult prevalence:** 3.7%[3]
HIVDR Strategy	• **EWI rounds:** 2008, 2011, 2014	• **TDR survey:** 2008

[64]Source: WHO, 2012 HIV Drug Resistance Project Annual Report, 2013

Early Warning Indicators	2008 Results – Pilot study in 14 sites in Abidjan		2011 Results – 20 sites in Abidjan and inside the country	
	Measured?	# of sites achieving the target	Measured?	# of sites achieving the target
• Prescribing practices	✓	• 50% (7/14 sites)	✓	• 20% (4/20 sites)
• Loss to follow-up	✓	• 14% (2/14 sites)	✓	• 21% (4/19 sites)
• Retention on first-line ART	✓	• 100% (14/14 sites)	✓	• 11% (2/19 sites)
• On-time pill pick-up	✓	• 0% (0/14 sites)	✓	• 0% (0/19 sites)
• On-time clinic appointment keeping	✓	• 0% (0/14 sites)	✗	
• Drug supply continuity	✓	• 50% (5/10 sites)	✓	• 6% (1/18 sites)
• Adherence as measured by pill count	✗		✗	
• Viral load suppression at 12 months	✗		✗	

Example of recommendations / actions *(not exhaustive)*

Following the pilot phase
- Develop a new follow-up system for patients missing appointments
- Computerize data collection on-site to enable routine monitoring
- Repeat the survey in more sites including other cities' sites

To the program management
- Conduct regular sites supervisions
- Involve NGOs in ART sites activities
- Set-up quarterly self-assessment tools

To the technical working group
- Disseminate data to all stakeholders
- Repeat the survey each year

To Planning & Evaluation team
- Set-up on-site visits to counteract the low use of some tools

To national treatment program
- Ensure dissemination of guidelines
- Organize trainings of doctors
- Set-up on-site visits to ensure implementation of guidelines
- Develop a national system for LTFU[4]

Lessons learned / challenges from the 2011 EWI round
- Delay in implementation due to the socio-political environment
- Laborious data collection due to the diversity in patient files types
- Too high selectivity of the extraction tool
- Low consistency between paper and electronic files
- Low archiving quality of the data collection tools

The recommendations are being followed-up by the national surveillance technical working group regularly to ensure correct implementation of the different defined actions on the field.

1. Source: WHO, Number of patients under ART 2004-2012, Excel file
2. Source: UNAIDS, UNAIDS Report on the Global AIDS Epidemic, 2013
3. Source: National demographic and Health Study, Côte d'Ivoire, 2011-2012
4. Note: Lost-To-Follow-Up
Source: National reports on Early Warning Indicators, Côte d'Ivoire, 2008 and 2011

Challenges expected to be addressed by the revised methodology (see Box 1 for more details on the revised methodology). Challenges faced while implementing the initial methodology contributed to countries not participating in the strategy, or failing to repeat surveys or failing to extend surveys to more sites. As countries reported those challenges to WHO and implementing partners, this input was taken into account in the revision process. A survey conducted by WHO in 2012-2013 shows that 93% of countries surveyed (on a total of 14 countries) thought the new survey methodology represented an improvement compared to the previous one (7% did not respond)[65]. During the interviews, content

[65]Source: WHO, Consultation process to inform the revision of the HIVDR strategy (2012-2013), 2013

experts and countries have mentioned the following challenges and explained how they considered those would be addressed by the new methodology.

Relevance for national decision-making. The initial methodology was meant to produce local results that were relevant to detect the existence of resistance and raise alert. Treatment policy-making such as regimen choice is largely driven at the national level, however, and nationally representative data is necessary to inform country-wide decision-making. To meet this need, the revised methodology relies now on national sampling and is expected to produce nationally representative HIVDR estimates.

Adaptation to epidemics settings. The initial methodology was perceived to be most adapted to generalized epidemics settings, and difficult to apply to contexts of concentrated epidemics such as Latin America (only two Latin American countries, Haiti and Guyana, implemented surveys under the initial methodology from 2004 to 2012). WHO collected input from different regions in the definition phase of the revised methodology to ensure that it would be applicable to all regions and epidemics settings.

Feasible sample sizes in a given site. With the initial methodology, each site had to gather large samples to achieve valid results, which proved challenging in some countries. Typically 50 to 70 specimens would be collected for TDR surveys for a given area[66] and over 100 patients for ADR surveys[67]. Under the revised methodology, samples will be smaller for each site surveyed (and larger at national level). For instance, a PDR survey could require as few as 8 patients in each of 40 sites nationwide[68].

Suitable survey duration. The initial ADR methodology adopted a longitudinal follow-up of ART patients and could take up to 3 years to complete and produce results: resistance would be tested in the same cohort of patients before they initiate ART, and 12 to 15 months into treatment. By contrast, the revised ADR methodology prescribes a cross-sectional survey: at the same point in time, different groups of patients are to be tested for resistance (patients initiating ART, patients treated for ~12 months, patients treated for ≥ 48 months). As there is no need to follow the same cohort in time in the revised methodology, this methodology is expected to generate results in less than 6 months. It has not been piloted in full in its final form, however (pilots tested the methodology with a slightly different sampling approach).

Prioritization of the different elements of the strategy. The initial methodology let countries prioritize themselves the elements of the strategy they decided to implement in case they did not have the resources (financial and human) to implement all elements. Countries may for instance have decided to focus on one element of the strategy and repeat it regularly or to try to implement each of the elements at least once. WHO now recommends that EWI are implemented in all countries and at all eligible sites, and that PDR (Pre-treatment Drug Resistance) and ADR surveys are implemented in priority in all countries monitoring HIVDR, while TDR would be implemented as a second priority, to inform program decisions on PrEP and PEP and to assess ART program performance in minimizing HIVDR emergence and its transmission.

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[66]Source: WHO, Protocol for Surveillance of Transmitted HIV Drug Resistance, 2012 update http://apps.who.int/iris/bitstream/10665/75204/1/WHO_HIV_2012.16_eng.pdf?ua=1

[67]Source: WHO, Protocol for Population-based Monitoring of HIV Drug Resistance Emerging during Treatment and Related Program Factors at Sentinel Antiretrovial Therapy Clinics, 2012 update http://apps.who.int/iris/bitstream/10665/75205/1/WHO_HIV_2012.15_eng.pdf?ua=1

[68]Source: WHO, Concept note: Surveillance of HIV drug resistance in Surveillance of HIV drug resistance in adults initiating antiretroviral therapy (pretreatment HIV drug resistance), 2014

b) Achievements in data management and analysis

Production of global reporting. WHO published the HIV Drug Resistance Report in 2012. The report is regarded as a key achievement by the community (countries, content experts and WHO HIVResNet Steering Group members interviewed). It presented a global view of the state of HIVDR as of 2010, based on: 112 WHO surveys implemented in 30 countries; the monitoring of 2107 clinics with EWIs in 50 countries; and a literature review of other existing studies in LMIC and high-income countries.

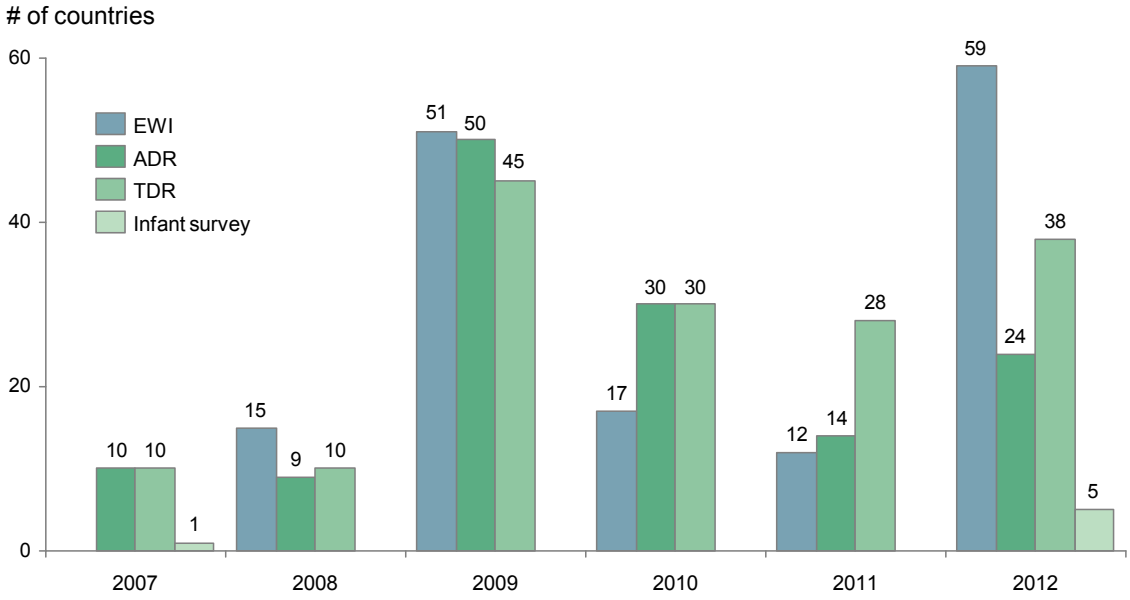
Implementation of a database (see Box 2 for more details on the new database and the revision process). In order to produce the 2012 Global Progress Report on HIVDR, WHO originally implemented a central data repository in the Microsoft content management product Sharepoint, for internal use. This repository has been fed with results from the national surveys and literature reviews, and used by WHO during the writing of the 2012 Global Progress Report on HIVDR. WHO also designed and rolled out a national-level data management system, CHIP (named after the Copenhagen HIV Program), which had both data storage and data analysis capabilities. CHIP database was expected to allow data storage at country level with subsequent export and reporting capabilities to WHO. Additionally, CHIP was intended to generate preformatted reports for countries and WHO. The preformatted reports were intended to report on survey outcomes. CHIP was designed to be available without an internet connection and was therefore suitable for local systems without reliable internet connection. 35 countries were trained on this tool and 9 countries used it for data storage[69]. However, due to technical issues (*see Box 3*), no country successfully used CHIP to report data to WHO or perform analyses.

An assessment of WHO's needs and current capacity at headquarters level was conducted by CDC. This assessment[70] highlights that "the current information system is cumbersome and not easily exploited. Information about country progress is gathered somewhat informally through [WHO HIVDR] staff communication with ministries of health and agencies providing funding. […] Further, the technical tools being used are limited in their ability to support the data needs". WHO, with the support of CDC, is currently devising a data management system to replace the one using MS Sharepoint, which involves a new database for data storage and the use of third party software for analysis at WHO. This system is designed to meet headquarters needs and may also be a starting point for those of country-level centralized data repository. The primary goal of the first phase of this database development is the reporting of completed and analyzed HIVDR survey data from countries to WHO for global reporting purposes. The first phase of rollout is expected in late 2014.

Capacity building for countries. WHO has also provided technical assistance to countries for data analysis (Fig.III.7). WHO staff and consultants have conducted individualized assistance visits, training sessions, and back-stopping to help countries analyze survey data and build self-reliant analysis capacity in the future. In 2012, in preparation for the Global Report, 50 countries (all countries providing data for the report) were provided remote assistance on data quality assurance and result analysis.

[69]Sources: WHO, 2012 HIV Drug Resistance Project Annual Report, 2013
WHO, Email from Silvia Bertognolio, April 4th, 2014
[70]Source: CDC, WHO HIV Drug Resistance Data Warehouse Assessment Version 1.1, January 18th 2013

FIG. III.7. Technical assistance provided and mobilized by WHO to support HIVDR strategy[71]



Source: WHO, Email for Sylvia Bertagnolio, 19th May 2014

C. FUTURE CHALLENGES

a) Challenges in methodology definition and implementation

Although the new methodology has not been rolled out yet, six main potential challenges are anticipated by the interviewees (in particular content experts and members of WHO HIV ResNet Steering Committee) in its implementation.

Engagement of countries compared with pace of ART scale-up. The WHO report on antimicrobial resistance states that surveillance of HIV drug resistance has not kept pace with the scale-up of treatment in many countries, limiting the ability to reliably identify levels and patterns of HIV drug resistance and to assess trends over time[72].

Readiness for roll-out. The new ADR methodology has not been tested in its final form before roll-out: four pilot surveys were implemented but they used a different sampling methodology. Three pilots were implemented in Kenya, Tanzania and Namibia using Lot Quality Assurance Sampling (LQAS) rather than Probability Proportional to Size (PPS) which is the recommended method for ADR. A fourth survey in South Africa used a different variant of PPS than the one prescribed by the final form of the revised methodology in order to obtain faster results. While all four pilots were considered successful and provided input to the revised methodology, data from the pilots has not been formally shared with the Steering Group and the finalized methodology has remained untested until roll-out. Yet, WHO considers that the methodology piloted is close enough to the final one and that challenges expected are mostly logistical, and well informed by the pilots.

EWI data collection process. Interviewees (mostly countries and content experts) reported that the implementation of EWI is a challenging process. Countries highlighted the fact that EWIs needed to be implemented in a large number of sites, which is a challenge, especially as some sites lacked resources

[71]Source: WHO, Email from Silvia Bertagnolio, 19th May 2014

[72]Source: WHO, Antimicrobial resistance: Global report on surveillance, 2014

and capacity to manage the data needed. Out of 14 countries interviewed, 12 implemented EWIs, of which 4 countries reported that EWIs were complicated to implement. Difficulties were faced in collecting data from a large number of facilities; content experts specified that it involves the collection of 'soft' data, which is not necessarily defined in a consistent way across all sites. As a result, aligning data collection method in a large number of monitored sites is a challenging and resource-intensive effort. This may stem from misunderstanding in the methodology, since, in theory EWI propose a standardized approach and rely mostly on data that are already available (for UNGAS/PEPFAR). These elements contribute to explaining the low repeat rate of EWIs despite interest in the results. Implementation challenges can be expected even stronger in the future as the new recommendation is that EWIs should be implemented in all sites and every year.

Sampling requirements. The revised methodology prescribes random sampling of survey sites at the national level. It is expected to be more challenging to implement than the initial methodology which allowed for the selection of convenient sites. Logistical and coordination challenges are also expected in reaching, collecting and transporting samples in a higher number of sites and potentially sites that are more remote. Typically with the new methodology, countries will be expected to collect samples in 15 to 40 different sites, while with the previous one, each survey was collecting samples in one site.

Implementation funding. For the time being, countries indicated they mostly relied on international funding to implement surveys and were thus willing to implement the strategy when funds were available. In the future, countries may increasingly be expected to secure funds for their own surveys. The cost of survey implementation is typically a small portion of HIV/AIDS national programs (~$150k to ~$350k per survey[73], see Fig.III.8) and has so far been supported by WHO seed money or full grant (from the BMGF grant), CDC/PEPFAR, Global Fund funding or other resources. Funding is the main challenge outlined by countries, in particular small countries, given the need to prioritize resource allocation for HIV between treatment, surveillance etc. 7 countries out of 14 mentioned it as a matter of worry for the future. Countries have to be convinced of the usefulness of the surveys to be willing to pay for it moving forward. One interviewed country mentioned they would not implement the strategy if they did not receive international funding because HIVDR was not top priority for the Ministry of Health. WHO should ensure that countries will still participate to the strategy even when international funding will decrease.

Regarding the cost of genotyping (which can represent ~10% to 50% of total survey costs based on examples of survey budgets[74] - see Fig.III.8), WHO and partners have created options to lower genotyping costs within the laboratory network. Three specialized laboratories have supported survey implementation by providing genotyping for free: the British Columbia Centre for Excellence in HIV/AIDS and the National HIV and Retrovirology Laboratory in Ottawa, which perform plasma testing, as well as the CDC laboratory in Atlanta, which is also accredited to perform DBS testing. However, countries willing to build their own national laboratory capacity or with restrictions on specimen shipping would not be able to use this opportunity.

WHO and CDC have taken actions to foster inclusion of HIVDR in countries request for funding. WHO has prepared guidance to help countries budget appropriately for the surveys (including technical assistance, travels, specimen transport costs) in their funding applications for instance to the Global Fund. WHO will participate in two workshops in the summer 2014 (in Africa and in Asia) to train countries on HIVDR and how to appropriately budget for it. PEPFAR has included HIVDR in the list of elements that countries should integrate in their COP to encourage appropriate budgeting.

[73]Source: WHO and UNAIDS, Resource kit, Guidance note HIV drug resistance surveillance, March 2014

[74]Source: WHO and UNAIDS, Resource kit, Guidance note HIV drug resistance surveillance, March 2014

FIG. III.8. Standard survey budget developed by WHO as an example for countries[75]

		PDR	ADR[1]	Infant	TDR
Key hypotheses	# sites	20	35	20	60
	# specimens sampled	460	1 020	490	200
	Average cost per genotyping test ($)	150	150	150	150
Budget / survey ($k)	Protocol Development & training	29	40	24	31
	Survey coordination	77	123		69
	Site support visits	12	18		
	Viral Load		61		
	Genotyping	69	36	74	30
	Other laboratory costs	8	16	5	9
	Technical support	23	23	23	23
	Report production, printing and distribution	21	21	21	21
	Total	**239**	**337**	**146**	**182**

1. ADR coordination and laboratory costs are higher than other surveys because two samples are collected and tested: patients on ART for ~12 months (460 specimens) and patients on ART for 48+ months (560 specimens)

Source: UNAIDS/WHO Resource Kit Guidance note on HIV drug resistance surveillance (March 2014)

Implementation delays. Some countries and partners have reported delays in the implementation of some of the surveys funded with CDC/PEPFAR support. When countries receive funding from PEPFAR for survey implementation, the survey methodology has to be approved by ethics committees, first at the CDC county office by a review board and then by the CDC headquarters in Atlanta. The length of the ethical clearance process depends on the number of exchange rounds between the country and the review boards. Based on interviews with CDC country offices, the regular process usually takes around 3 to 4 months. In some cases, countries have reported that the ethical clearance process took several years. This process is required even when countries use WHO methodology.

Clarity of guidance on survey repeat rate. Content experts and in particular WHO HIVResNet Steering Group members interviewed expressed a need to clarify guidance on survey repeat rates (expressed in the last Core Group call as well). While updated guidance for EWIs are clear (EWIs should be implemented in all sites every year), the revised ADR and PDR methodology concept notes only state that surveys should be repeated every three years or earlier. In the past, countries have interpreted time intervals differently (e.g. time between the start of two surveys, or between result publication and the start of the next survey). This would also help track implementation of surveys.

b) Challenges in data storage and analysis

Need for technical assistance and capacity building. Countries, even middle-income ones, face a continuous need for technical assistance in data management and analysis. 10 countries out of 11 countries that were asked if more technical assistance was required stated that they needed assistance in statistics and data analysis. Countries highlight the difficulties they are facing in identifying, training

[75]Source: WHO and UNAIDS, Resource kit, Guidance note HIV drug resistance surveillance, March 2014

and retaining qualified staff in this field (6 countries mentioned out of 8 who were asked). Such combination of data management skills and public health background is seen as rare at global level and even more at national level. Sustained capacity building efforts are required to enable national teams to analyze data and inform national decision-making independently in the future.

Need to take into account different sources of data in order to provide the most comprehensive set of information for decision-making and advocacy. Although the 2012 Drug Resistance Report presented unprecedented amounts of global HIVDR data, the set of data available at this stage and the nature of the data was not sufficient to inform fully HIVDR strategies and ART strategies at global and national level, and to be used for advocacy purposes, since it was not nationally representative (which was expected given the methodology).

In the coming years, data on HIVDR surveillance is expected to be available from a wider range of sources and methodologies as countries progress in developing their own strategies. Countries may use other quality sources of information to inform their decisions. Although in the 2012 Global Report WHO has included data that was collected with a different methodology (e.g., ANRS funded surveys with different inclusion criteria), there is a concern among content experts that these sources of information, even though the quality may be sufficient, would not be included in the WHO Global Report, while it could provide more quality data points.

Non-WHO surveys and other sources are expected to represent a larger part of overall HIVDR data available. The expected expansion of individualized testing in such countries as South Africa (though not recommended by WHO) will also produce additional HIVDR data outside of WHO survey methodology. As advised by the Steering Group, WHO would need to work further with appropriate statisticians and opinion leaders to develop ways to optimally use such data produced with non-WHO suggested methods, or with the initial WHO survey methods, including data from individual monitoring. The revised HIVDR database is expected by the revision team to have a flexible structure which would allow the capture of data from surveys and studies performed using those methods (although WHO highlights that this would require resources). It is not certain, however, according to statisticians interviewed and to the database revision team that this would allow establishing trends between the nationally representative data of the revised methodology (produced with national sampling) and the local data of the initial methodology (produced with convenience sampling).

FIG. III.9. Key elements from the interviews

Perspectives	Key messages
Countries *(based on 14 countries and 19 interviewees – full list in appendix)*	**Surveys and EWIs are considered useful (all countries) even though countries struggle to provide concrete examples of actions taken based on the results (used to describe the resistance by 12 countries and to inform decision-making process by 8 countries)** **Survey revision process has been perceived as inclusive and key country concerns are reported to be taken into account (in particular for Latin American countries)** **Strong need for Technical Assistance to implement the surveys (sampling and survey management – 6 countries mentioned difficulty with sampling and 1 country specifically requested TA) but also to analyze the data (statistics and analytics – 10 countries)** **Funding for surveillance is mentioned as a key challenge in the future (7 countries), linked to the perception at MoH and program management level that HIVDR is not a priority**

Content experts *(including WHO, BMGF, CDC/PEPFAR, academics – full list in appendix)*	**New methodology is expected to address most of the challenges faced in the past** **Next Global Report is expected to present trends, aggregate numbers and national representatives numbers** **WHO is expected to work with statisticians and countries to integrate as much quality nationally representative data (and, where relevant regionally representative data) as possible.**

Source: Interviews, March-June 2014

Box 3: Revision of the database

Lessons learned from past experience

- From WHO perspective of the data managed using MS SharePoint: the format of data transmitted by countries was often inconsistent, the data were often inconsistent (data transmitted by laboratories did not match survey data, making it hard to link sequences with epidemiological data), data were not always shared by countries or not at the right time, and was often of poor quality or incomplete. The process was found to be cumbersome, difficult and did not enable WHO to monitor the implementation of the program.
- From a country perspective of the survey data management application, CHIP (based on interviews): the database was hard to use from a technical standpoint and did not allow for customization, so countries were not able to store all variables they wanted to use for their analysis.

Revision of the database and milestones

An assessment was conducted by CDC in addition to WHO analysis to understand lessons learned and define the objectives of the new database.

A new project was launched with support from CDC, delivery expected to end of 2014 with milestones in September 2014. Project owners are Silvia Bertagnolio from WHO and the consultant Michael Jordan. Project sponsor is Linda Mattocks from CDC. Other contributors provide expertise on the subject (e.g., Neil Parkin, as well as country and laboratory representatives). At the end of 2013, a consultant was recruited to be the data management person for HIVDR at WHO.

Objectives of the new database (as set in the Project Database Document)

The overall objective of the WHO HIVDR database, is to provide a robust, flexible structure for WHO to manage information needs and to ensure the integrity of the submitted and captured data. The solution designed is therefore expected to:

- Engage countries and WHO-designated HIVDR genotyping laboratories participating in HIVDR surveillance to report all survey information in a consistent manner.
- Enable WHO to monitor implementation of HIVDR surveillance and EWIs, manage communication between WHO, countries and laboratories and track missions and remote TA to support the implementation of HIVDR surveillance strategy.
- Enable countries and accredited laboratories to request and receive feedback about the quality of HIV genotypes from WHO prior to final analysis.

The project will be implemented using existing WHO technical infrastructure and existing software licenses (Microsoft SQL, .NET framework and INETSOFT).

Priorities identified for the project are to design the database to manage information related to the four surveys defined by WHO, and also to manage historical data and integrate the system with Stanford database for genotyping interpretation.

The WHO HIVDR database model may be of interest to countries who wish to enhance their capacity to manage HIVDR surveillance data. When interviewed on the usefulness of a database and data management tools, countries mentioned that they do not necessarily need a new database provided by WHO. They are currently using their own data storage and management systems and tools such as STATA to perform their analyses. Some of them mentioned they would be interested in comparing their results with neighboring countries, which they felt a common database could allow them to do. However, at this stage the new tool is primarily designed to facilitate the reporting of survey data to WHO, and include the variables required by the WHO survey methodology. Creating additional variables would require programming and could not easily be done by end-users. While additional variables would not be needed for the purpose of reporting standard data to WHO, they could be

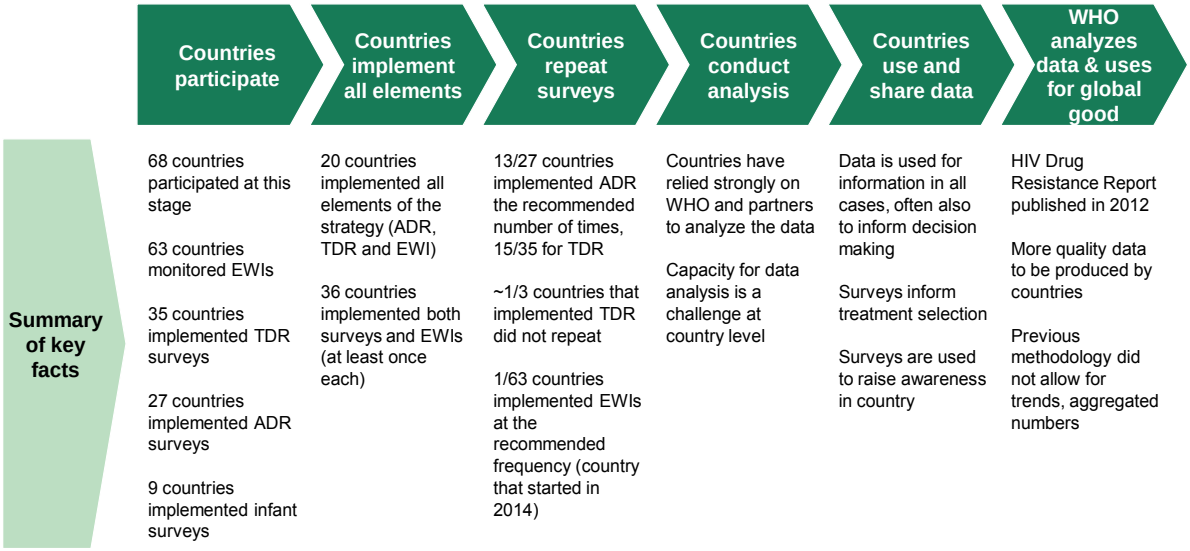
requested by countries if the new system were to be used at country-level as the main data storage system, rather than as a tool to report data to WHO in addition to other local data systems.

d. PRIORITIES FOR THE FUTURE

Summary of key objectives for future improvements.

In the cascade from enrolling countries into HIVDR Surveillance strategy to analyzing data and using it for global good, there are several critical steps to ensure that quality data is produced and used.

FIG. III.10. Critical steps to ensure quality data is produced, shared with WHO and used at global and national level



Ensure sustained country participation in the new methodology and adequate repeat rate. 68 countries have been on-boarded in the strategy since its inception, but in recent years, the uptake in countries participating has slowed down, partly because of the shift of focus on new methodology design. This engagement needs to be sustained as WHO rolls out the new methodology. Some countries have already expressed their interest in the new methodology. As the new methodology is rolled out with a focus on providing results that are nationally representative and can inform public health decisions it is increasingly important that countries are able to provide trends data. Therefore it is critical to address the bottlenecks explaining low repeat rate such as: lack of clarity in the repeat rate guidance, implementation difficulties, lack of funding, decreasing interest in HIVDR surveillance.

Ensure countries understand which elements of the strategy they should implement. In the past, only 20 countries implemented all elements of the strategy (ADR, TDR and EWI) because of resource constraints and difficulties of implementation. Limited guidance was provided to countries as to which element they should implement in priority given their context. More prescriptive guidance is expected from WHO in the future to help countries understand which elements they should prioritize. WHO has started prioritizing the surveys in the latest version of the methodology concept notes.

Ensure countries have the capacity to conduct analysis. National capacity for the analysis of the survey results is repeatedly mentioned as a challenge by countries and confirmed by content experts in interviews, even for the most advanced countries.

Ensure countries use data. Over the reviewed period, countries have mostly used the data to describe HIVDR, or to inform program management and or to raise awareness on HIVDR (see previous section on achievements). The new methodology is designed to provide national representative data and therefore support more strongly decision-making both in terms of program management and in terms of regimen selection. There is strong interest from countries in guidance describing how to translate the results of surveys into programmatic actions (*detailed in section III.3.d: Coordinating surveillance and prevention)*.

Ensure countries share data with WHO. Although this is a critical element to secure, there is no evidence at this stage that countries would not be willing to share their data with WHO, even in the case where their surveys are not funded by WHO anymore. Resistance for surveillance in other fields (for instance TB) is not necessarily funded by WHO and yet countries still share the data because it is understood as part of the mandate and because WHO provides feedback information (e.g., estimates based on the data, that countries use for their applications to grants, for decision-making etc.). WHO/HIV however underlines the fact that this will require more effort and more interactions with countries in the future if surveys are not funded through WHO anymore. Therefore, WHO has initiated work on data sharing agreements as part of the project on database revision.

Secure high quality data. Data provided in the 2012 report was considered a great achievement. More is expected in the future in order not only to understand whether there is a drug resistance issue, but also to qualify the magnitude of this issue and understand how it evolves over time. The objectives should therefore be to ensure that more quality data (quality criteria need to be defined) is produced at country level and to ensure that all quality data produced is integrated in the global reporting. Addressing the first point would be the result of the various objectives cited above. In addition, as quality data may be available from a wider range of sources than the WHO-surveys that data cannot be neglected, and as countries may increasingly fund surveys through other channels than WHO, it is critical to ensure that this data would meet minimum quality requirements and that countries would share it with WHO.

In order to ensure that the key objectives will be reached, several priority actions should be set-up.

Priority actions for the future

WHO has already initiated a number of actions in order to address these priorities, for instance:

- WHO has revised the survey concept notes and provided a first prioritization of the strategy
- WHO has publicized the new concept notes to country programmes and to major donors (PEPFAR and the Global Fund)
- WHO is participating in meetings in Asia and in Africa over the summer 2014 to share and explain the methodology to countries

Advocate HIVDR surveillance strategy. Further advocacy at national and global level is required to continue raising awareness on the importance of drug resistance surveillance and secure funding. This aspect is detailed in the specific chapter on Coordination and Mobilization of Partners.

Align strategy with key donors to ensure countries get funding to implement the surveys. WHO, as lead coordinator for HIVDR surveillance and monitoring, should align with key donors to make sure that the prioritization of activities for HIV is shared and that HIVDR is considered a priority. It should support countries in their applications for financial support for HIVDR surveillance. CDC/PEPFAR have already included HIVDR in the COP guidelines, a review should be performed to understand what the impact of this measure has been in helping countries plan and obtain funding for their strategies. Similarly, HIVDR could be integrated in the Global Fund's Strategic Investment Framework for HIV as part of good Monitoring and Evaluation practices for HIV programs. WHO should engage in

discussions with the Global Fund to understand if and how further support can be encouraged. WHO should continue developing guidance to support countries when they budget for their HIVDR strategies, with input from the roll-out of the new methodology (e.g., real life costs).

Provide feedback to countries. In order to encourage countries to participate in the strategy and to share their data with WHO, it appears important to make sure countries get something in return. Part of this would come from making sure countries understand why HIVDR is needed (via advocacy, see previous paragraph), and helping them understand how they can use the results of surveillance (guidance on use of the results, see chapter on Coordination and Mobilization). In addition WHO could provide individual feedback on the quality of the data countries share through a formalized mechanism. The resources required to perform this activity and whether this activity should be performed by WHO or by a partner should be discussed by the Steering Group.

Develop guidance for prioritization of the strategy and for response. The upcoming release of a new set of guidance for HIVDR surveillance provides the opportunity for WHO to help countries understand how they should prioritize the implementation of the strategy. A first step is provided in the current draft of the new concept notes to prioritize EWI, ADR and PDR surveys before TDR and to limit infant TDR surveys to countries considering changes in the pediatric regimens. However, further prioritization (for instance guidance on how to develop a situational analysis which would allow countries to identify their own set of priorities, clear repeat rate guidance) can be expected given that countries in the past have experienced difficulties implementing several surveys and EWIs at the same time. This is part of WHO's current plans and should be continued. This new guidance should also help countries understand how they can translate the results of surveillance intro programmatic action. This aspect is more detailed in the Chapter and Coordination and mobilization.

Set up a formal continuous improvement mechanism for survey methodology. In order to maintain countries engagement in the strategy, the methodology needs to be adapted to their challenges and needs. WHO has to ensure that feedback from countries and partners on survey methodology is collected and that the Core Group or a specific working group is leveraged to assess whether a revision of the methodology is required. For example, WHO could prepare a 1-page form that countries would fill after the implementation of a survey in order to give their feedback on the methodology, and summarize the findings for the WHO/ Core Group to review them. This would ensure that course corrections are made to secure country participation and country repeat rate, and that a right balance is reached between frequent update of the methodology which could be disturbing for countries and lag time without updates in the methodology which could lead to decreasing repeat rates. This needs to be developed as part of the M&E plan.

Build capacity and support countries with appropriate Technical Assistance. TA resources are required to support countries, in defining HIVDR surveillance strategy, designing survey protocols according to WHO guidance (e.g., sampling, site selection) and in analyzing and managing the data (e.g., data management, statistics and analytics), as well as in implementing the surveys (e.g., project management and coordination within the country). The skills required are diverse and often rare. Today this technical assistance is mostly provided by a limited number of individuals, which is not sustainable.

Support in defining National Strategy Plans. Countries will need support in defining their HIVDR surveillance strategy as part of the National Strategic Plan and in budgeting for it. This support can be provided through the regular channels of support for NSP. In addition to HQ support, WHO should work with partners providing that support (e.g., UNAIDS TSF or CDC) to ensure they have the appropriate briefing and knowledge of HIVDR to support countries.

Support in project management. Project management skills are often available at country level and should therefore be sourced in countries (local experts, in-country partners).

Support in designing and analyzing the surveys. Epidemiology, statistics and data management skills are often rare even at international level. For these specific skills, two main models of TA provisions can be envisioned. WHO should use a combination of those models to ensure sustainable capacity building, quality of TA provided and support to countries who need it the most.

WHO should provide back-stopping from headquarters to high-capacity countries. With back-stopping from HQ, countries would lead the process of survey design and data management and analysis, and request support from headquarters on an ad hoc basis as needs arise. Headquarters would provide support remotely or through short country visits, to address specific aspects of survey design and analysis. While this would help countries develop their own skills to a certain extent, the impact on capacity is expected to be relatively limited, as contact with headquarters experts would be short and infrequent.

WHO should work on transfer skills from headquarters to low-capacity countries. Local TA resources should always be mobilized in priority when they are available. However, when national resources are insufficient, additional support and training would be coordinated at a global level. Support would be provided through country-visits as well as national and/or regional workshops, which would develop local capacity to a greater extent than back-stopping. This scheme would require resources at headquarters for coordination and for training of TA providers. TA providers could be a pool of international consultants (similar to the model that TB[76] is using), and/or implementing partners (who would then be responsible for the quality of the TA). The skill transfer approach could be applied to countries that have lower established capacities, as the level of support provided by HQ and relays would ensure that the required skills are made available to countries.

A third model has been considered by the Steering Committee but not retained: Forming regional knowledge hubs for added local capacity in high-need areas (e.g. Africa). Implementing the scheme has substantial organizational requirements, as regional structures need to be set up to support it – either by creating new regional positions or by leveraging regional partners, or regional offices of international partners. At this stage, the Steering Committee does not recommend to implement this scheme, but it could be investigated if sustainable resources are identified.

Ensure the WHO HIVDR report leverages quality data in accordance with consistent standards. WHO should ensure that countries produce quality data to inform public health decisions, and that quality data is integrated in global reporting even if it is produced using different methods than the standard WHO survey methodology. For that purpose, WHO and its Steering Group should work with experts in statistics and epidemiology to 1/ proactively define a set of quality criteria to integrate non-standard data and 2/ examine reported data to ensure that it meets the criteria and may be used in global reporting in a rigorous way. The proposed process and criteria should be presented to the Steering Group.

Publish regular Progress Reports on HIVDR. Results should be shared in a regular progress report on HIVDR in order to maintain momentum and keep HIVDR issue on top of the agenda and allow for effective advocacy. Appropriate pace should be discussed by Steering Committee, in light of advocacy needs and availability of meaningful data, options include: Yearly update on partial information

[76] Source: content expert interviews, April-May 2014

(either a type of survey per year, e.g., ADR, or TDR, or EWI, or partial information every year, e.g., only new surveys conducted), Progress report every 3 years (in line with recommended repeat rate for surveys).

3. GLOBAL HIVDR GENOTYPING LABORATORIES NETWORK

a. KEY ACTIVITIES[77]

WHO has been accrediting and supporting a genotyping laboratory network since 2006. The purpose of the network is to provide high-quality genotype testing, so as to support HIVDR surveys and ensure the credibility of their results. All WHO survey specimens are expected to be tested by accredited laboratories within the network. Network laboratories are also expected to be able to perform viral load testing as required by the strategy. There is no WHO accreditation for viral load testing so non-WHO accredited laboratories can also perform viral load testing for EWI as well as for ADR surveys.

In the BMGF grant, these activities represent a budget of $2.4m (direct costs): $1.7m for staff and consultants, $0.3m for travel and $0.4m for supplies. Over the course of the project, NIH has provided in-kind support in the form of proficiency panels for quality assurance (see details below). This support was worth $150k in 2010 and $527k in 2012[78].

The targets defined in the initial grant proposal were to set up a network of more than 20 laboratories by the end of Year 1 accredited and annually tested, to ensure that genotyping for HIVDR surveys would be performed in these accredited laboratories and to ensure that proficiency panels and standards operating procedures would be available.

WHO defined three types of laboratories: national, regional and specialized laboratories. All three types perform genotyping tests; regional and specialized laboratories also have additional coordination and capacity building responsibilities (*see appendix for details on the roles of each of these laboratories*). WHO approaches expansion and support to the network through two main activities: 1/ accreditation and quality assurance and 2/ capacity building.

Accreditation and quality assurance are conducted by WHO staff and consultants, with the support of regional and specialized laboratories as well as NIH for proficiency panels. WHO bears the cost of the accreditation process and does not charge a fee to candidate laboratories. Candidates only face internal costs required to bring their laboratories to compliance. Candidate laboratories for accreditation are designated by their Ministry of Health and assessed by WHO in three steps: (i) a questionnaire and a checklist on laboratory capacity, experience and standard operating procedures, staff training and the existence of a national plan to implement the HIVDR surveillance strategy; (ii) a proficiency panel test; and (iii) an on-site assessment. Laboratories are specifically accredited for plasma and/or DBS specimen testing techniques. Once accreditation is obtained, a laboratory conducts annual proficiency panel testing: laboratories must pass two out of the last three tests to maintain accreditation.

Capacity building is also provided by WHO staff and consultants with the support of regional and specialized laboratories within the network. Candidate laboratories are assisted in the preparation of their accreditation. Once accredited, laboratories continue receiving support in the form of expert visits, local or regional trainings, and back-stopping.

b. ACHIEVEMENTS

a) <u>Achievements in network capacity and accreditation / quality assurance</u>

[77] Note: Key trends in laboratory technologies are presented in appendix.

[78]Sources: WHO, 2010 HIV Drug Resistance Project Annual Report, 2011
WHO, 2012 HIV Drug Resistance Project Annual Report, 2013

WHO accreditation standards referred to as gold standards by the HIVDR surveillance community (content experts interviewed and countries). Reasons that these interviewees mentioned are 1) the fact that WHO is a specialist in the field and the only accreditation body operating globally in this field. While other organizations provide accreditations for other types of tests, WHO focuses on HIVDR genotyping which is perceived as a sign of expertise; 2) WHO has strict requirements; 3) WHO relies on a single source for proficiency panel which means that the same criteria are applied in the same way to all labs, as it is implemented by WHO itself and uses a unique source of proficiency panels[79] (NIH) and standardized criteria to evaluate proficiency panels testing results (proficiency panels have mostly been invoked in interviews by content experts, not specifically by countries). These three elements provide credibility to accredited laboratories and the data they report.

Overall global genotyping capacity in line with current needs. The overall genotyping capacity achieved in the network is considered by content experts interviewed (laboratory specialists) sufficient to meet current demand of HIVDR surveillance. Over the 2003-2010 period, out of the 24 laboratories that were accredited in 2010, 9 did not perform genotype tests for WHO HIVDR surveys and no capacity issue was reported[80]. In 2012, the network genotyped over 8 200 specimens. Since 2006, 33 laboratories have been accredited in 22 countries, compared to an initial target of 20. There are 14 national laboratories, 11 regional laboratories (4 in AFRO, 4 in AMRO and 3 in WPRO) and 8 specialized laboratories (in AMRO and EURO). 14 LMIC have at least one accredited laboratory in their country, and those countries account for 53% of ART patients in LMIC. Out of all genotyping tests conducted for WHO HIVDR surveys between 2004 and 2010, 38% were performed in South Africa. Another 39% were performed by laboratories in four high-income countries.

Current global genotyping capacity considered sufficient to meet future needs. The revised survey methodology prescribes larger samples and therefore more tests per survey than the initial methodology, and improved survey feasibility may lead to more frequent implementation of surveys. If all 68 on boarded countries as of 2014 were to implement the revised methodology surveys in full compliance with WHO guidance, this would represent an upper limit of ~29,000 genotype tests per year[81] (vs. a total of 8,200 tests performed in 2012 in the network) to be compared to an average estimated capacity of thousands genotyping per week for a major laboratory (e.g. Canada laboratory) and around 50 per week for a small laboratory (>2000 per year) as reported by laboratory experts interviewed.

Development of DBS genotyping capacity. WHO and the network of laboratories have played a leading role in the development of DBS genotyping techniques. DBS is considered a more cost-effective technique than plasma specimen testing (testing seems to be as expensive for plasma as for DBS[82], but transport for DBS is much cheaper) and mostly simplifies survey logistics as it does not require refrigerated shipping. Specialized laboratories such as the PHAC laboratory in Ottawa, the IRD laboratory in Montpellier and the CDC laboratory in Atlanta have devoted operational research to develop this technology and assist in rolling it out in the network. In addition, WHO, specialized laboratories and the VQA (supported by NIH) have designed and implemented a specific accreditation program for DBS genotyping, and trained candidate countries towards accreditation. WHO also

[79] Note: Proficiency panels are test that all laboratories from a network have to pass every year. Results are then compared to a consensus sequence derived from all the individual results from the participating laboratories

[80]Sources: WHO, 2012 HIV Drug Resistance Project Annual Report, 2013

WHO, 2010 HIV Drug Resistance Project Annual Report, 2011

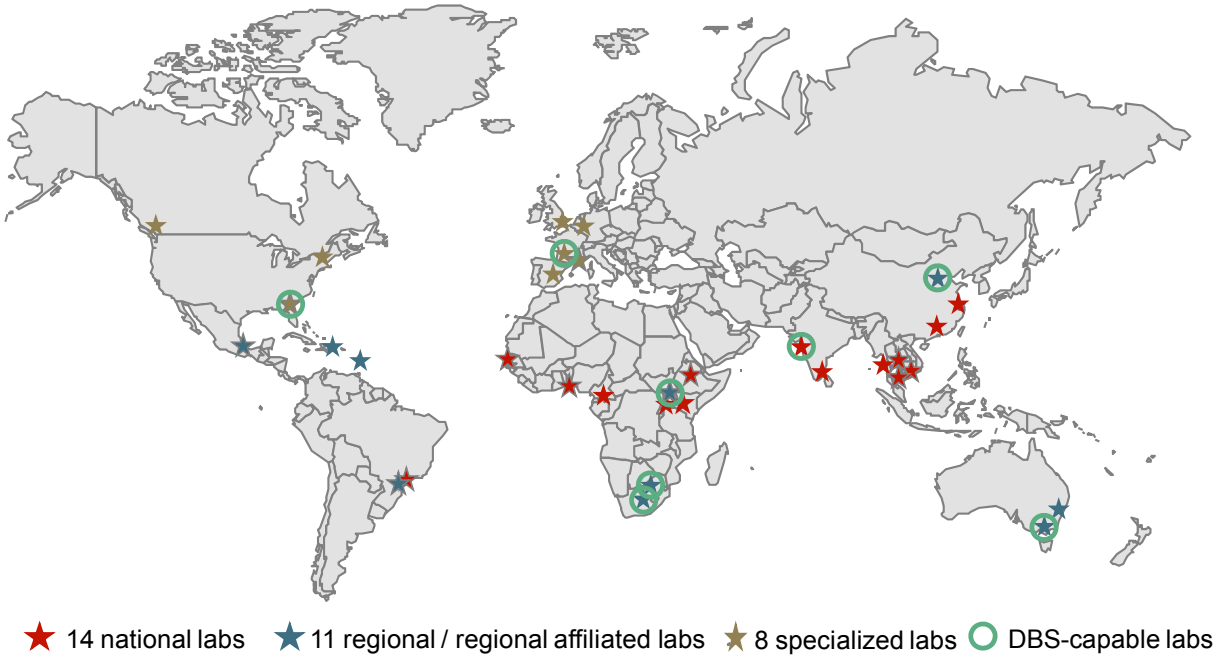
WHO, DBS Genotyping Capacity in the WHO HIVDR Genotyping Laboratory Network, 2013

[81] Note: see Appendix

[82] Note: See cost estimates in Appendix

developed a specific training module on DBS for laboratory technicians, and delivered it as part of two HIV genotyping training workshops. As a result, 8 accredited laboratories in the network have achieved genotyping capability on DBS (5 of which obtained DBS accreditation in 2014). In 2012, 23% of all specimens genotyped were DBS. 9 additional laboratories are currently in the late stage of the DBS accreditation process and 9 other laboratories are also working through DBS accreditation but will probably not achieve it in 2014.

FIG. III.11. HIVDR Genotyping network in 2014[83]



b) Achievements in capacity building

WHO has supported the capacity of laboratories in two main ways.

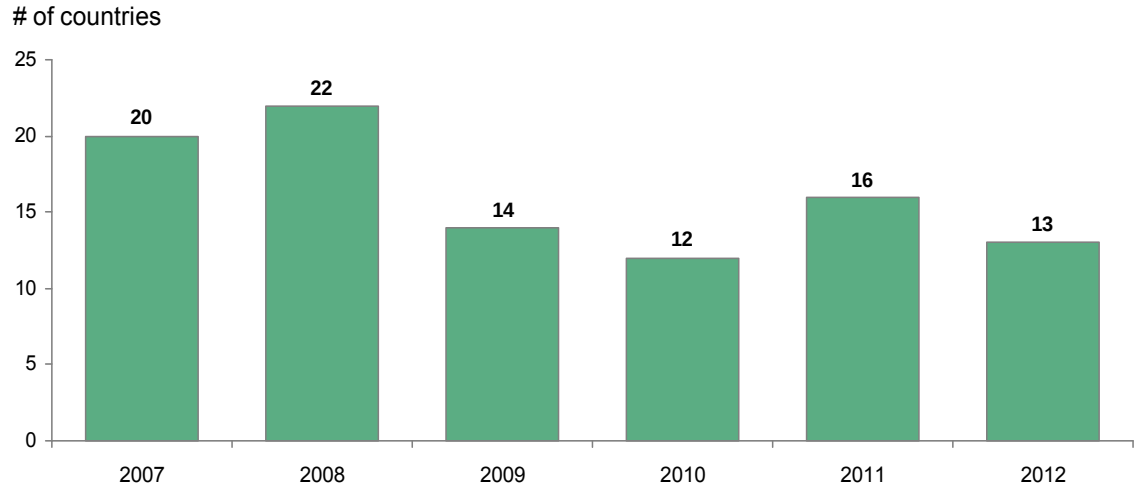
Capacity building through the accreditation process. Laboratories focal points interviewed report that the accreditation process itself is a significant capacity building opportunity. WHO and its partners (such as CDC Atlanta, IRD Montpellier, PHAC in Ottawa, etc.) provide support to candidates in strengthening and formalizing their standard operation procedures, which improves the laboratory's capacity regardless of accreditation outcome. Staff from candidate laboratories have also been trained at specialized laboratories in the run-up to accreditation. Laboratories failing the accreditation and willing to apply again can receive support from regional and specialized laboratories. As HIV genotyping is considered one of the most complex tests, developing genotyping capacity is expected to raise a laboratory's quality as a whole. Over 33 laboratories have benefited from this capacity building opportunity.

Training of network laboratories after the accreditation. WHO (in collaboration with the SDRL at CDC in Atlanta) specifically developed a 17-module training course for laboratories in the network, covering testing techniques as well as quality assurance, laboratory management and data management. It was made publicly available and was delivered twice in training workshops. Specialized and regional laboratories have contributed to capacity building through training sessions,

[83]Source: WHO, Emails from Silvia Bertagnolio, April 4th 2014 and May 14th, 2014

by hosting visiting staff from national laboratories, and by providing back-stopping to national laboratories in need of support. WHO facilitates an informal 'twinning program' that links laboratories with strong capacity with less experienced laboratories to facilitate technology transfer and knowledge sharing. In 2011 and 2012, specialized and regional laboratories leveraged training material developed by WHO and trained 84 laboratory professionals from 21 countries on practical and theoretical aspects of HIVDR genotyping[84]. The network also benefits from tools developed by specialized and regional laboratories. For instance, a Canadian laboratory developed a software application for result interpretation which other laboratories could use for free[85].

FIG. III.12. Technical assistance for laboratories provided and mobilized by WHO



Source: WHO, Email for Sylvia Bertagnolio, 19th May 2014

C. CHALLENGES

a) Challenges in network capacity

Although global genotyping capacity may be sufficient in the future, the mix of plasma genotyping vs. DBS genotyping and national capacity requirements in certain countries may be challenges.

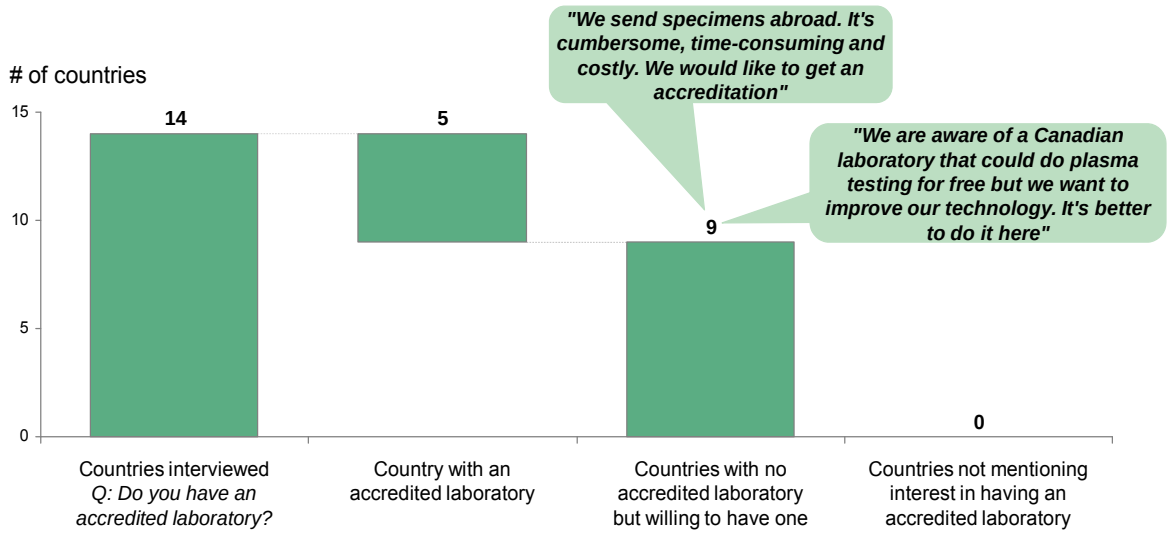
Need for increased laboratory capacity to perform quality genotyping on DBS given need to survey more and potentially remote sites in the revised methodology. Data show an imbalance between the share of DBS-capable laboratories in the network and the share of DBS genotype tests performed. In 2012, 23% of all specimens genotyped were DBS and were treated by 9% of the network's laboratories. Many countries rely on DBS specimen collection (and more can be expected to do so in the future given that new methodology prescribes to survey more sites than in the past and that DBS allows for easier and cheaper transportation), especially in settings with limited logistics infrastructure. Therefore, a large volume of specimens are shipped to the DBS-accredited laboratories while other laboratories are less utilized. WHO now makes DBS capacity a condition to maintain accreditation as a regional or specialized laboratory, and 9 laboratories are currently working towards

[84]Sources: WHO, 2011 HIV Drug Resistance Project Annual Report, 2012
WHO, 2012 HIV Drug Resistance Project Annual Report, 2013
[85]Source: Interview of a country focal point, April-May 2014

DBS accreditation. This should partially address the gap in capacity as over 50% of the network would have DBS capability if all 9 laboratories obtain accreditation.

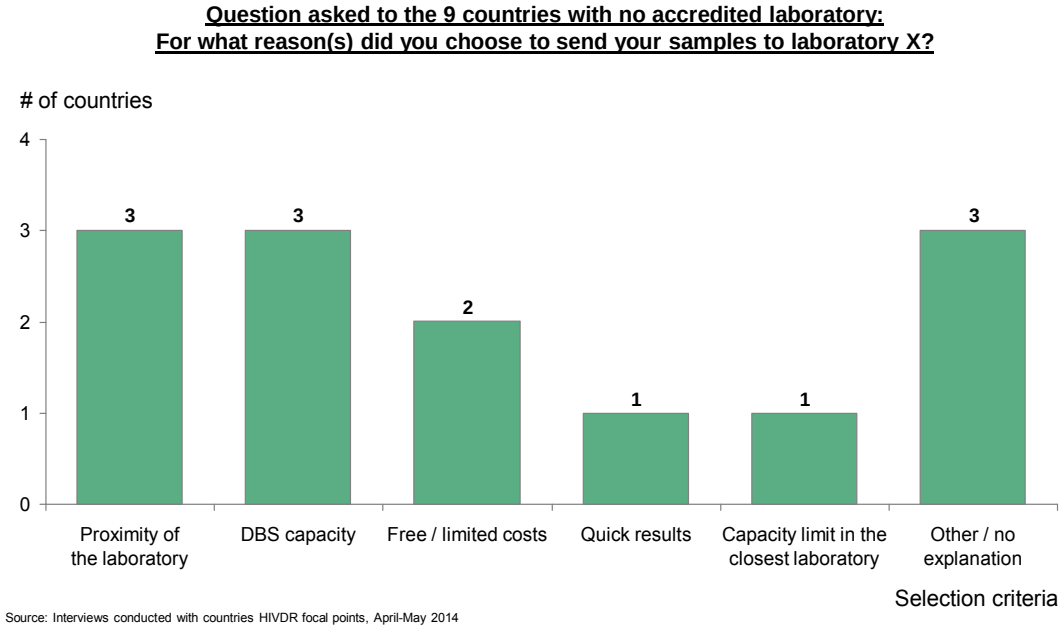
National requirements may push for increased laboratory capacity. National considerations may also drive a further expansion of the network. Some countries such as Russia, Zambia and Uzbekistan reportedly do not ship specimens to foreign laboratories as a matter of policy. Out of 14 countries interviewed, one mentioned such policies slowed down the shipping of samples, though they did not prevent it. As a result they require their own laboratories, regardless of available global capacity. Out of the 14 interviewed countries, 9 do not have an accredited lab in the country but all of them would like to get one (Fig.III.13.). Countries also see the development and accreditation of a laboratory as an important element in building national scientific and public health capacity. Even though the British Columbia Centre for Excellence in HIV/AIDS offered to perform plasma genotyping free of charge for any survey conducted in the network, 9 countries reported that they would rather set up their own laboratories (out of 9 countries interviewed that do not currently have accredited laboratories). Proximity, DBS capacity and low costs appear as the main selection criteria mentioned in interviews for countries with no accredited laboratory, for the choice of a network laboratory outside the country to test the samples (Fig.III.13.)

FIG. III.13. Interest in having an accredited laboratory



Source: Interviews conducted with countries HIVDR focal points, April-May 2014

FIG. III.14. Key laboratory selection criteria for countries with no national accredited laboratory



Source: Interviews conducted with countries HIVDR focal points, April-May 2014

Support in scaling-up quality viral load capacity. The demand for additional viral load testing capacity is also expected to increase significantly in coming years as viral load is now recommended by WHO over CD4 count to routinely monitor ART, and it is required for ADR surveys and EWI which are now recommended in more sites. Scaling up viral load testing is considered a priority among content experts and countries interviewed but established capacity remains limited given high costs. As per a MSF / UNAIDS survey conducted in 2012[86] in 23 LMIC (representing 83% of ART patients in LMIC), 19 countries showed limited or no availability of routine VL testing for ART patients. Those 19 countries represent 49% of ART patients in LMIC. As viral load is adopted at a larger scale and becomes not only for HIVDR surveys (EWI and ADR), but a critical monitoring tool for ART programming, there is a need for consistent, high quality data. At the moment there are no WHO-recommended standards for viral load testing quality assurance, but some laboratories interviewed have indicated working on it (e.g., Ottawa). WHO has a role to play in ensuring quality viral load testing.

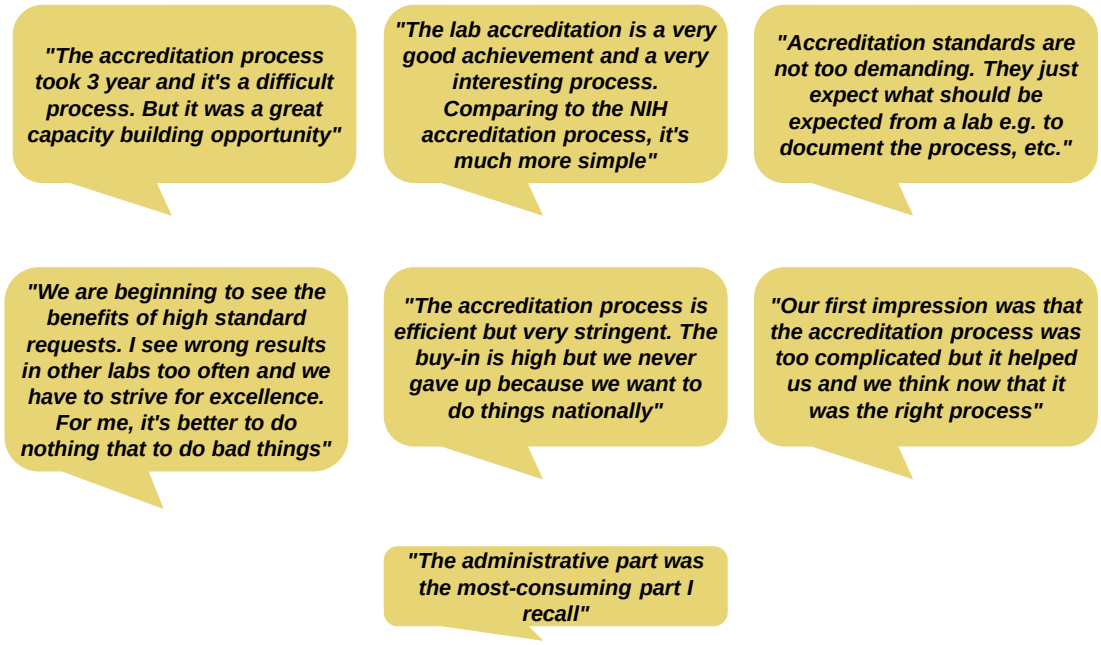
b) Challenges in accreditation and quality assurance

Demanding accreditation process. Accreditation is often perceived by countries and content experts as a demanding process: out of 19 country and laboratory focal points interviewed, 7 reported that the process was long and/or difficult. However most countries found it useful that requirements were high and did not wish it was different (Fig III.15). It has taken laboratories up to three years to complete it, and administrative aspects were reported as a particular challenge. Laboratories cannot use certifications obtained in other contexts to fast-track WHO accreditation process. Some content experts interviewed fear that qualified laboratories may be reluctant to apply for accreditation, or fail to obtain it, limiting the potential expansion of the network but this has not been confirmed by

[86]Source: UNAIDS and MSF, Speed Up Scale-Up: Strategies, tools and policies to get the best HIV treatment to more people, sooner, 2012
http://www.msfaccess.org/content/speed-scale-strategies-tools-and-policies-get-best-hiv-treatment-more-people-sooner

countries interviewed (neither countries with an accredited laboratory nor countries seeking to obtain accreditation for a laboratory).

FIG. III.15. Selected country quotes on the WHO laboratory accreditation process



Source: Interviews conducted with countries HIVDR focal points, April-May 2014

Limited resources at WHO headquarters devoted to laboratory support. WHO's approach currently faces resource constraints that may limit the development of the network's capacity. This work is conducted by a small team of WHO staff and consultant (part of the time of 2 persons in total) who handle laboratory applications and analyze proficiency panel results. No other institution is currently mandated to deliver accreditation, concentrating this responsibility at WHO HQ. This ensures consistency across laboratories but might limit the size of the network in the future to a scale that remains manageable for the team. At this stage, however, this has not been considered a limiting factor by WHO.

Supply of proficiency panels from a single provider. Specialized and regional laboratories do not produce proficiency panels for quality assurance, as was initially envisaged. All panels are provided by a single partner, the VQA (Rush University, Chicago), under contract from NIH, which has been reported to be a bottleneck to network expansion as panel delivery did not always keep up with demand[87]. In the interest of consistency, the WHO HIVDR Steering Committee nonetheless opted to maintain VQA as the sole provider of proficiency panels. NIH has recently informed WHO that VQA had increased its capacity as a panel provider and would be able to serve more labs in the future, funded by NIH.

c) Challenges in capacity building

[87]Source: WHO, 2012 HIV Drug Resistance Project Annual Report, 2013

Turnover in laboratories is a challenge for sustained capacity building. Staff turnover is identified by interviewees as a key obstacle to sustained capacity building, as trained technicians reportedly often leave laboratories within a few years of their training. This is especially problematic as genotyping is a complex and specialized activity that requires substantial training. Turnover limits the ability to build sustainable capacity at country level and also to leverage this capacity to train other neighboring countries.

Role of regional and specialized laboratories in capacity building could be reinforced. The involvement of specialized and regional laboratories in capacity building is not a requirement, it is on a voluntary basis: laboratories have to "be willing" to participate in capacity building. Therefore, the involvement has varied from laboratory to laboratory. For instance, the Atlanta CDC laboratory has been active in training national laboratories. It has delivered most of its training to PEPFAR countries as part of CDC programming. There are no specific requirements or monitoring system regarding the capacity building effort contributed by regional or specialized laboratories. Limited available funding is perceived by content experts interviewed to constrain capacity building activities between laboratories, including technical assistance and twinning programs. Moreover, the capacity building role is more aligned to the mandate of some laboratories such as CDC laboratories, which makes it easier for them to support it financially.

FIG. III.16. Key messages from the interviews on Laboratory network

Perspectives	Key messages
Countries *(based on 14 countries and 19 interviewees – full list in appendix)*	**The WHO accreditation process is considered as stringent by countries, but helpful in building capacity (4 out of 4 countries with an accredited laboratory)** **Countries are interested in having their own laboratories even if cheaper options exist for genotyping of surveys (e.g., genotyping performed for free by some international laboratories) – 8 countries out of 9 with no accredited lab to date** **Countries priorities are to develop viral load capacity and then genotyping on DBS capacity**
Content experts *(including WHO, BMGF, CDC/PEPFAR, academics – full list in appendix)*	**The set-up of the laboratory network is considered a great WHO achievement** **Experts expect that the accreditation process can be streamlined leveraging existing organizations active in the field** **WHO HQ limited human resources is feared to be a bottleneck for further network expansion** **Regional and specialized laboratories are expected to be more leveraged in the future, in particular during the accreditation process and in continuous training for capacity building**
Laboratory experts *(7 experts interviewed)*	**Overall genotyping capacity is considered sufficient for current and future needs (not taking into account national / global mix or DBS/ plasma mix)** **Expansion of genotyping based on DBS capacity is considered the priority for the networks in the future**

Source: Interviews, March-June 2014

d. PRIORITIES FOR THE FUTURE

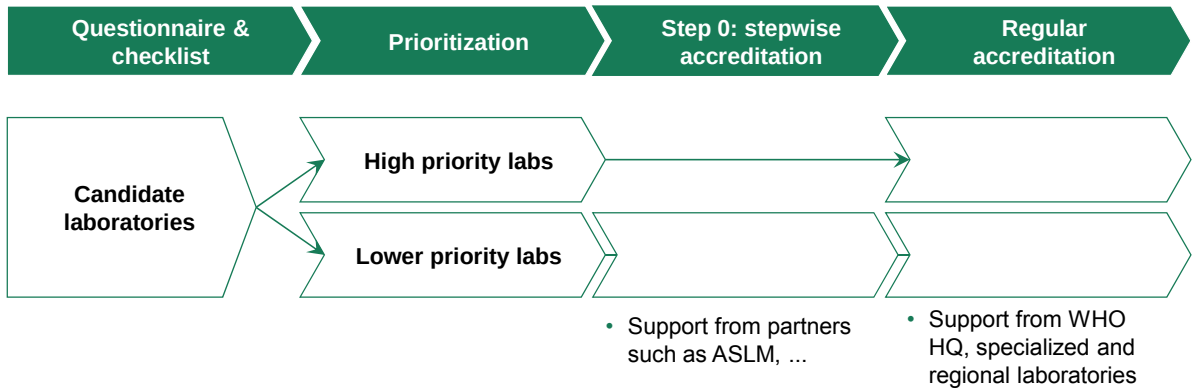
a) Network capacity, accreditation process and quality assurance

As DBS has been identified as a priority for HIVDR, WHO should continue be active in encouraging expansion of capacity to perform genotyping in DBS. As the new methodology prescribes to survey more sites than in the past and that DBS allows for easier and cheaper transportation, WHO should continue to be active in encouraging laboratories accredited for plasma genotyping and laboratories seeking to obtain accreditation for plasma genotyping to apply for the DBS genotyping accreditation. In order to support this expansion, WHO has developed an accreditation for genotyping on DBS, sets of training materials and has already made it mandatory for regional and specialized laboratories to be accredited for DBS. To further encourage DBS expansion, WHO could survey laboratories accredited for genotyping on plasma to understand what would be the hurdles for the accreditation and how WHO and its partners could further support them.

WHO should continue to support the expansion of HIVDR genotyping laboratory capacity while prioritizing the allocation of its resources. WHO should accompany further expansion of the genotyping laboratory network to facilitate the implementation of surveys in countries and support laboratory strengthening, which is considered a priority for HIV in general. Given resource constraints at WHO HQ however, WHO should prioritize countries they would directly support, and seek and organize relays for other countries. Prioritization criteria must be in line with WHO treatment guidelines. They could include - but should not be limited to - the number of accredited laboratories already in the country and the region, country-specific regulation (e.g. legal obstacles to shipping specimens overseas), number of patients under ART, perspectives of sustainable funding for laboratories, demonstrated interest in HIVDR surveillance, prevention strategy, number of genotype tests performed, and established or planned DBS capability in the candidate laboratory. The criteria should be presented to the Steering Group for information and advice on the messaging.

The process could be as follows (Fig. III.17). Candidate laboratories identified as high-priority, would enter the regular WHO accreditation process, conducted by WHO HQ and specialized and regional laboratories. Lower-priority candidate laboratories would be invited to work towards accreditation with partners, such as ASLM or TREATAsia (acknowledging that such partners would need support). A stepwise accreditation approach would allow such laboratories to build capacity and validate pre-accreditation steps that recognize specific achievements (e.g. administrative organization of the laboratory; formalization of standard operating procedures). Once the candidate laboratory has reached the highest step in the process, it would become a priority candidate and its application is considered by WHO for accreditation. This ensures that qualified candidates can eventually obtain the accreditation, while WHO's capacity is focused on priority laboratories which will bring the largest contribution to the surveillance strategy. For example, a candidate laboratory might be assigned a lower priority because it has conducted few genotyping tests at the time of application. It could benefit from the support of a partner that would play the role of an 'incubator' until it has built additional capacity and gained genotyping experience.

FIG. III.17. Proposed process to support candidate countries for WHO HIVDR genotyping accreditation



Define role of WHO in the scale-up of quality viral load testing, leveraging potential synergies with existing genotyping laboratory network. WHO has a role to play in supporting the expansion of quality viral load capacity. The topic is broader than HIVDR and should therefore be discussed in the appropriate setting. Options can range from providing a framework of good practices to laboratories, to defining standards for VL testing or setting up an accreditation process for viral load testing.

b) Capacity building

Capacity building in laboratories is a priority for HIVDR but it faces resource constraints. Interviewees have mentioned the current participation of specialized and regional laboratory in capacity building activities is valuable and much appreciated by countries, but variable and rather on an informal and voluntary basis. There is therefore an opportunity to leverage more regional and specialized laboratories so that they would provide national laboratories and applicant laboratories with the support they need (instead of relying on WHO HQ and consultants).

WHO should enforce a formal commitment of support from specialized and regional laboratories. The TB Supranational Reference Laboratory Network has recently updated ToRs for their laboratories and now provides examples of such requirements[88]: members of the network commit to establishing formal links with at least two national laboratories; providing at least three Technical Assistance visits every two years; and reporting at least one activity per supported country per year.

In the future, specialized and regional laboratories should formally commit to specific targets of TA provision. For instance, they could establish, in collaboration with WHO, which laboratories they will mentor, and formalize what this entails: a certain number of TA visits / year; a number of technicians trained; a commitment to respond to requests from the mentored laboratories within a certain timeframe; etc. For specialized and regional laboratories, maintaining their accreditation would be conditioned to meeting the commitment targets each year. This would ensure that the expertise of all laboratories is leveraged for TA, and would help increase the capacity of the network as a whole. Coordinating and tracking TA commitments at global level could also guarantee that every laboratory that needs it is assigned a mentor laboratory. This model would require funding to support the additional costs (mostly travels).

[88] Note: See Appendix on tuberculosis

IV. KEY REQUIREMENTS

1. STRATEGIC PLAN

A key requirement for successful implementation of the strategy is to develop a comprehensive strategic plan and get alignment on it, to serve as a roadmap for WHO and a reference for donors and partners at a global level and at country level. Such plan would likely take 6 to 9 months to develop and should be developed as soon as possible, in order to ensure coordinated action to achieve the objectives of the HIVDR strategy.

The revised WHO strategy for HIVDR surveillance and monitoring details recommendations on what countries should to do to monitor HIVDR. The next step is to define WHO strategic plan, including:

- A scale-up plan: Prioritization of the elements of the strategy for countries and target countries for implementation of the strategy in the medium term
- An action plan: Priority actions and agreed role of each stakeholder at global level and country level
- A plan for sustainable funding: Summary of funding needs, mapping of potential sources of funding for country level activities and HQ level activities, donor mapping
- A communication and advocacy plan: Summary of key messages, target audience, identified milestones for communication, key relays for communication
- An M&E plan: Indicators and monitoring process to track the successful implementation of the strategy

Scale-up plan. Key targets to be set in the scale-up plan would include:

- Target number of countries to be enrolled in surveillance
- Target list of countries to focus on, based on criteria such as geographic representativeness, programmatic aspects, and epidemiological aspects
- Target number of ART patients covered by the data provided by each type of survey
- Target number of countries implementing EWIs
- Target coverage of EWI facilities

Action plan. WHO should also work with partners through consultation to develop a stakeholder alignment and engagement plan, in order to mobilize partners, align on priority actions at country level and global level. Key elements of such plan would be:

- Prioritization of surveillance actions at global level and country level
- Key prevention actions to be taken based on surveillance results
- Expected role of each stakeholder at global level and country level for advocacy, implementation of the strategy, participation in strategy definition, fundraising etc.

Communication and advocacy plan. WHO should work with partners to define the communication and advocacy plan for HIVDR. This would include

- Defining key messages and target audience for advocacy and communication
- Identifying key milestones linked to HIV or AMR
- Defining the role of each stakeholder at global and country level (linked to action plan)

M&E plan. As part of its oversight role over HIVDR SMS, WHO should collect and consolidate indicators agreed upon with donors and key stakeholders, and use them in reporting to other stakeholders of the strategy, in particular the Steering Group and donors.

Plan for sustainable funding. WHO should develop a plan summarizing the funding needs for the future, continue working with key partners to identify funding gaps and be able to develop a donor mapping (clear view of funding gaps and potential redundancies).

2. ORGANIZATION

Implementing identified priorities would require four main evolutions over the existing organization, as listed in the report.

Reinforce WHO HQ team.

- **Advocacy**. Ramping up the advocacy effort and developing a communication strategy would require additional resources and skills. The resources are estimated to ~0.5 FTE and should be well integrated with the HIV Advocacy team *(please refer to "Advocating for HIVDR surveillance and prevention", challenges and priorities for the future sections)*.
- **Donor relations**. Engaging with donors on a sustained basis and providing them with the information they need would require additional resources estimated at ~0.5 FTE *(please refer to "Collecting input and generating buy-in from partners", priorities for the future section)*.

Further clarify and formalize functioning of existing advisory bodies. Terms of reference with clear functioning mode (meeting frequency, agenda, decision-making process etc.) should be developed for all advisory bodies: Steering Group, Core Group and Working Group function *(please refer to "Collecting input and generating buy-in from partners", priorities for the future section)*.

Create a formal process for Survey Methodology Improvement (e.g., create a working group or add it as a standing agenda point for the Core Group)**,** to ensure that feedback on survey methodology is continuously provided by countries rolling out the surveys, examined by a group of experts. This group could advise WHO on potential revisions needed *(please refer to "Data for decision-making", priorities for the future section).*

Convene a Donor Group on the side of Steering Group meetings. The objective of this group would be to align donor strategies and to increase funding visibility and improve coordination *(please refer to "Collecting input and generating buy-in from partners", priorities for the future section)*.

3. SUSTAINABLE FUNDING

a. REMINDER ON INITIAL COST OF THE PROGRAM

In 2006, the total cost of the HIVDR SMS program was estimated at 50M$ based on a projected extensive roll-out of the program, given the global economic context at that time and the higher available resources for health. WHO requested a 5-year 15M$ grant from the Bill and Melinda Gates Foundation based on WHO planned activities, in order to cover ~30% of the budget share.

The 35M$ gap between the estimated cost and the amount of the BMGF grant was expected to be mobilized with other donors. At that time, other donors such as CDC / PEPFAR, Canada or Spain had already committed ~21M$ to fund a part of the program through WHO. ~22M$ additional potential funding to WHO was also pending at the time of the Grant application.

Due to the global economic crisis, funding availability became less likely and WHO scaled down the HIVDR program. The total budget of the program was consequently less important than originally planned, but the total cost of the program is not available.

b. SUSTAINABILITY

The initial BMGF grant was not designed to be renewed and WHO was expected to find other sources of funding after five years. WHO benefited from two no-cost extensions from BMGF in 2012 and 2013.

For the moment, WHO has not been successful at securing enough funding for the next 3 years and may seek funding from BMGF again. WHO is planning to develop a detailed budget in the coming months including a funding request to BMGF.

This report details several initiatives and paths summarized below, that WHO could follow in order to secure sustainable funding for the future, for HQ level funding and for country level funding. Three main types of levers can be used: advocacy, specific donor relations and integration of HIVDR activities in HIV program activities.

a) HQ level activities - Normative work (incl. HQ staff, coordination and guidance roll-out workshops)

In order to ensure sustainable funding in the coming years at HQ level for the staff positions, the coordination and normative activities and the capacity building for survey implementation and laboratory network extension, WHO should take different actions along three major dimensions: reinforce advocacy, structure donor relations and further integrate the strategy to HIV program.

Reinforce advocacy. To ensure HIVDR is considered a priority topic for donors, WHO should reinforce advocacy through broader communications to emphasize the importance of funding HIVDR surveillance as a key element of HIV programs.

Structure donor relations. To identify potential sources of funding among existing or new donors, WHO should better highlight its needs for support, mapped to a clear strategic plan. This would enable donors to understand the envisioned outputs of the strategy and decide on the elements they would be willing to support.

Further integrate the strategy to HIV program. Better integrating the HIVDR strategy to the HIV program could enable WHO to identify additional potential donors supporting HIV activities. For example, positioning the network expansion as a mean to increase capacity building and strengthen laboratory capabilities at country level could enable WHO to be funded by a broader range of partners, including donors from the HIV field.

b) Country level activities – Implementation of surveys and EWIs (incl. country level project management, genotyping, analysis and TA)

To ensure sustainable funding at country level to support survey and EWI implementation, WHO should take different actions along the three major dimensions.

Reinforce advocacy. Moving forward, WHO should better highlight the need and value of surveys and EWI for HIVDR, including for improvement of program quality, especially among participating countries and among donors. Improving the perceived usefulness of the surveys and EWI could ensure better uptake and more sustainable funding in the future.

Structure donors relations. CDC / PEPFAR has been one of the key donors at country level for survey / EWI implementation and has included HIVDR in the list of elements that countries should integrate in their COP to encourage appropriate budgeting. Moving forward, WHO should continue to work with CDC / PEPFAR to understand the impact the changes in COP guidelines have had on countries' requests for funding. In the same way, WHO should work with the GFATM to encourage them to prioritize HIVDR and include it in their strategic framework and grant applications forms, as it is currently not the case.

Further integrate the strategy to HIV program. The revised guidance for EWI developed by WHO, encourages countries to integrate the EWI to their routine M&E plans, as a key component of the HIV

program. This action will enable specific funding for EWIs to decrease, as the implementation costs could be supported by the HIV program funds. Other diseases such as TB and malaria which set-up drug resistance surveillance programs in the 1990's have different funding mechanisms from the HIVDR strategy especially because both surveillance programs mostly rely on funding from GFATM and are much more integrated to global TB and Malaria programs. Most of the grant applications for both surveillance programs are submitted conjointly with the global TB and malaria programs, as drug resistance appears as a key component, and not as a distinct stream. An assessment carried out on funding requests to the GFATM for tuberculosis program indicated that ~60% of round 4–8 proposals for TB funds requested specific funding for surveillance of drug resistant TB[89] whereas only 22% specifically documented DRS as a grant-funded activity *(please refer to the Appendix section for more details)*. Indeed, regarding HIV, most grant applications for HIVDR are done separately from the grant applications of the global program and the donors are often not the same. Fostering integration of country-level funding for survey and EWI implementation in HIV funding streams would enable more sustainable funding moving forward.

c) Proficiency panels activities

Since 2007, the provision of proficiency panels and logistical support for the genotyping external quality assurance program was supported by a grant from NIH. NIH has agreed to continue to fund proficiency panels for the laboratories, both for plasma and DBS and will remain the main donor in this field until 2019 at least.

C. HIGH-LEVEL ESTIMATE OF FUNDING NEEDS FOR THE FUTURE

The following estimates are based on WHO input and aim at indicating the order of magnitude of funding needs. Refining these estimates would be a key element that WHO should work on in order to prepare for grant proposals and to develop the strategic plan.

a) HQ level activities

Funding for HQ staff. WHO considers that it would need 6-7 FTE at HQ level (4 FTE and 4 part-time resources) to ensure successful implementation of the strategy. In addition, 1 FTE (2 part-time resources) would be needed for advocacy and donors relations.

To date, WHO resources include :

- 1 WHO staff for coordination of the strategy,
- 3 WHO consultants (2.7 FTE) in charge of normative guidance, data gathering, analysis and reporting, as well as coordination and quality assurance of laboratory network,
- 1 statistician consultant from Harvard to support data analysis for global report and country survey data,
- 1 consultant for data management
- 1 WHO staff (0.7 FTE) for administration (supported by WHO core funds)

In addition, WHO considers that part-time IT staff (0.3FTE) would be needed to assist with data management and reporting.
Based on this program review, 1 additional part-time staff would be needed for advocacy (to be integrated in HIV advocacy team) and 1 additional part-time staff for donor relations.

[89]Source: WHO & GFATM, K. F. Kelley and others, Are Countries Using Global Fund Support to Implement HIVDRug Resistance Surveillance? A Review of Funded HIV Grants, November 2012

Based on WHO assumptions, a first estimate of the total costs of these positions at HQ level would be ~1.5-2.0M$[90] annually depending on staff sourcing options. The new positions could either be sourced directly at WHO HQ, or WHO consultants could be hired, or a secondment from a partner organization could also be envisioned.

Funding for supplies and meeting costs.

Global reporting. Based on past budgets, the expenses for one HIVDR report, as the one published in 2012, are ~45k$[90] (for layout, editing and publication, as well as a two-months full-time work from a consultant). Additionally, funding for the editing and dissemination of the normative guidance, the production and printing of technical updates as well as the regular update of the WHO HIVDR newsletter and the WHO websites should also be accounted and a first WHO estimate of these costs is ~70k$[90] per year.
Development of the stakeholder alignment and engagement plan. A high-level document highlighting the HIVDR strategy would support advocacy and partner alignment. Based on the cost of the 2012 HIVDR Global Report, layout, editing and publication of this document would require ~45k$[90].
Meetings organization. WHO HQ will continue to organize an annual meeting with the Steering Group and meetings with other advisory groups, and to participate in meetings organized by the HIV department with countries. Such activity is estimated by WHO to represent an annual budget of ~105k$[90].

A first estimate of the total costs for supplies and travel would be ~0.3M$ per year.

Funding for capacity building activities to roll out the guidance. Technical assistance to countries for implementation of a specific survey is integrated in the budget of each survey. Additional efforts are required to train countries and build capacity on HIVDR strategy. WHO should put together a plan confirming the unit cost assumptions listed below and indicating how many of each type of support (workshops, visits) they consider necessary.

For survey implementation, there are three types of activities: regional workshops (average unit cost ~25k$[90]), technical visits to priority countries (average unit cost ~5k$[90]) and training workshop for consultants (average unit cost ~50k$[90]).
For support to laboratory expansion, there are two types of activities: on-site visits (average unit cost ~5k$[90] per visit, to be conducted by WHO or by specialized laboratories) and regional workshops to be organized by regional and specialized laboratories (estimated at ~120k$[90] for one annual workshop).

Based on preliminary assumptions of how much each of these types of support would be needed, a first estimate of the total costs for capacity building in the future would be ~0.4M$ per year (not including proficiency panels).

b) Country level activities for survey / EWI implementation

The survey costs presented below are based on the guidance developed by WHO to help countries budget appropriately for the surveys in their funding applications, and include the costs for protocol development and training, the survey coordination staff, the travels for site support visits, the laboratory analyses (viral load, genotyping, labor costs), the costs for technical assistance as well as the

[90]Source: WHO, Email from Silvia Bertagnolio, May 23rd 2014
Note: The 1.7M$ include the costs of the staff for administration already covered by WHO core funds

reporting costs. The required costs for survey implementation at country level could be lower than described if, for example, the genotyping was done for free in a country with no national accredited laboratory or if countries used home-brew assays.

- **PDR survey.** Cost is estimated by WHO at 216-246k$ depending on the sample size required.
- **ADR adult and paediatric survey.** Cost is estimated by WHO at 322-342k$ (two time points at 12 months and 48+ months) depending on the sample size required.
- **TDR and infant survey.** Cost is estimated by WHO at 164-172k$ and 109-146k$ respectively depending on the sample size required.

Evaluation of potential future costs. Based on these assumptions 261k$ per year, over 4 years, would be needed to support a country doing all the priority surveys and either one infant or one TDR survey.

FIG. IV.2. Cost simulation for survey implementation

	PDR	Adults ADR	Paed. ADR	TDR	Infant	Total
Cost per survey (k$)	216-246	322-342	322-342	164-172	109-146	
Frequency	1 every 4 years	1 every 4 years	1 every 4 years	1 every 4 years		
Total average cost per year per country	**58k$**	**83k$**	**83k$**	**37k$**		**261k$**

EWI. EWI implementation costs could be integrated to HIV M&E budget as WHO advises countries to integrate the collection of the indicators routinely as part of the global M&E health sector plans. Training regarding EWI abstraction and data analysis would have to be performed to support implementation. The estimated cost of a training is ~50k$[91] and based on WHO assumption.

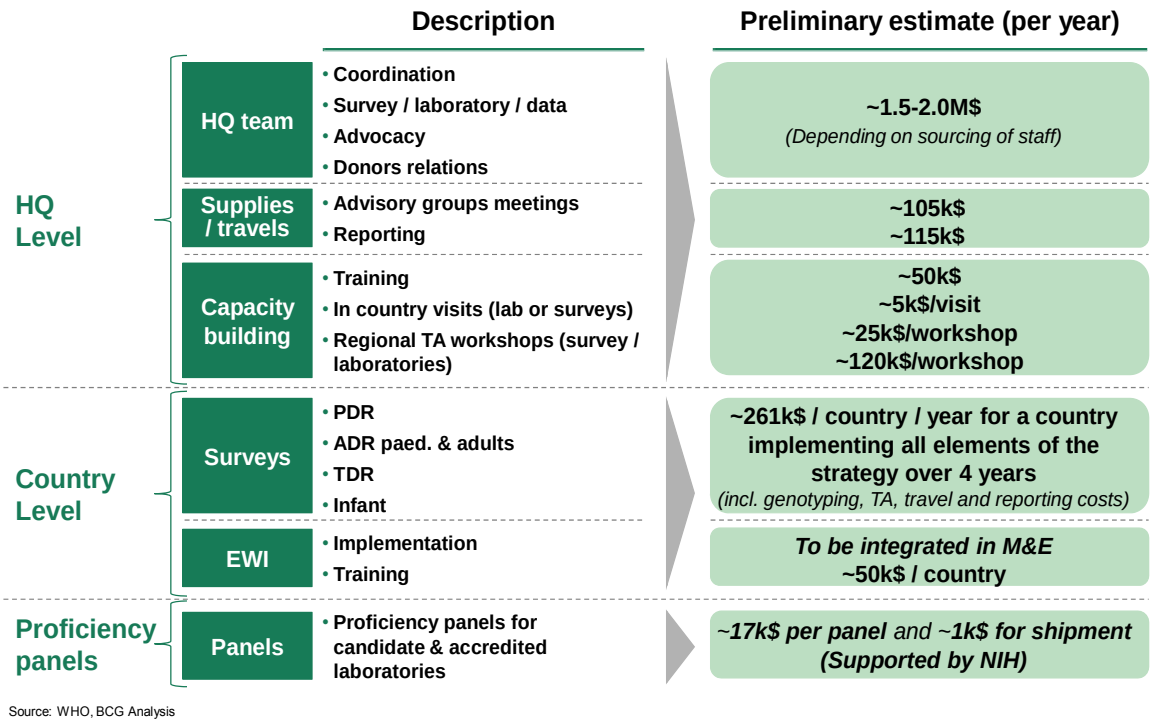
c) Proficiency panels

The cost of a proficiency panel is estimated at ~17k$[91] per panel and 1k$[91] for shipment. NIH will continue to fund proficiency panels for the laboratories through VQA, both for plasma and DBS in the future.

d) Summary of funding needs for the future

[91]Source: WHO, Email from Silvia Bertagnolio, May 23rd 2014

FIG. IV.3. Summary of funding needs by cost bucket, per year



Source: WHO, BCG Analysis

LIST OF APPENDICES

APPENDIX 1: METHODOLOGY

a) Desk research

Desk research was performed based on the following source types (listed in appendix):

- Publicly available data (e.g. WHO HIV Drug Resistance report, UNAIDS global report…)
- Internal BMGF documents (e.g. initial proposal, progress reports…)
- Internal WHO documents (e.g. WHO HIV ResNet presentations, draft methodology concept notes…)
- Other non-public documents provided by interviewees (e.g. country HIVDR strategy briefs, data on NIH laboratory network…)

Desk research was used to gather background information on HIVDR, and also to gather perspectives from the fields of tuberculosis (TB) and malaria drug resistance surveillance in order to guide the interviews. Research attempted to inform what is of interest for our work, identify what lessons learn in other fields could be relevant for the HIVDR strategy as well as guide interviews by testing ideas or hypothesis with the interviewees.

There are limits to this approach. The nature of the malaria and tuberculosis epidemics are different, as are the levels of resistance measured to date and their potential impacts on treatment programs. The DR surveillance strategies are organized differently, mobilize differing types of testing and are at various stages of maturity, with both TB and malaria strategies active for a decade longer than the HIV strategy.

Therefore, TB and malaria drug resistance strategies were not used as models, but helped generate hypotheses and stimulate discussion during the interviews or with the Steering Committee. Adopting this frame of reference helped interviewees approach the HIVDR surveillance strategy from a different perspective and generate further insight.

b) Interviews

- *Interviewee selection*

110 interviewees were selected to obtain a comprehensive perspective on the HIVDR strategy and gather all relevant input. The selection was not intended as statistically representative.

Interviewees comprise stakeholders who defined and/or implemented the strategy, as well as end users of the strategy. They are composed of the following groups (*see full list in appendix*), and are referred to in the rest of the report with these groups:

- Countries
- WHO HIV ResNet Steering Committee members (Steering Committee members would also belong to other groups of interviewees as they would be country HIVDR focal points, or representatives from partner organizations, donors or content experts)
- Content experts (for instance academics, consultants, representative from CDC, PEPFAR, NIH involved in HIVDR)
- Partner organizations (for instance implementers such as PASER, TREATAsia, Médecins sans Frontières)

Interviewees were selected along the following criteria:

- Country focal points *(see full list in appendix)*:

  - 5 WHO regions represented (except European region)
  - Both concentrated and generalized epidemics represented
  - Wide range of ART program sizes represented
  - Wide range of degrees of involvement in HIVDR surveillance represented (some countries implemented surveys, some Early Warning Indicators, some both)
- Other stakeholders:
  - All WHO HIV ResNet Steering Committee members included
  - All relevant stakeholders identified by the program review's Steering Committee included

The country perspective was represented by HIV DR country focal points, and complemented in many cases also by laboratory focal points, ART program managers and CDC country offices in order to triangulate information and generate the most comprehensive view possible.

FIG.APP.1.1. List of countries interviewed

	Country	HIVDR Focal point	ART program focal point	CDC Country office focal point	Laboratory focal point
15 focus countries	Argentina	✓	✓		
	Brazil	✓	No response		
	Burkina Faso	✓	✓		
	Indonesia	✓	✓		
	Malawi	✓	No response	✓	
	Mexico	✓	✓		
	Mozambique	✓	No response		
	Namibia	✓	✓	✓	✓
	Nigeria	✓	No response	✓	
	Rwanda	✓	✓	✓	
	South Africa	✓	No response		✓
	Uganda	✓	✓		
	Ukraine	No response	No response		
	Vietnam	✓	✓	✓	✓
	Zimbabwe	✓	✓	✓	
Other	Angola			No response	
	Botswana			✓	
	Côte d'Ivoire			✓	
	France				✓
	Haiti			✓	
	India			✓	✓
	Kenya				✓
	Martinique				✓
	Tanzania			✓	
	Togo	✓			
	Zambia			✓	

- *Interview approach*

Interviews were conducted by phone or in person, and lasted on average 1 hour. On occasions and as needed, follow-up interviews have been scheduled or further email exchanges with interviewees have happened. Interviews served to gather information, compare perspectives and test hypotheses.

Each interview followed the general structure below (*see interview guide*):

- Introduction on interviewee's background and involvement with the HIVDR strategy
- Discussion of overall achievements and challenges of the HIVDR strategy
- Review of the achievements, challenges and priorities for the future along the four initial objectives (surveys, databases, laboratories and awareness & mobilization)

- Discussion of funding and sustainability, with the objectives of determining the current funding landscape and outlining future perspectives

The emphasis on and duration of each section differed based on each interviewee's expertise. Whenever relevant and available, interviewees were asked to provide tangible sources and data to back up the information provided (e.g., reports, analysis).

c) Country Visits

- *Country visit selection*

Two country visits were conducted over the course of the assessment. Namibia and Vietnam were selected as they are the most familiar with the new survey methodologies: Namibia piloted the ADR survey in 2013, Vietnam started implementing it in May 2014. The choice of countries having piloted the new methodology is of particular importance as the new survey methodology has significant differences with the previous one and is expected to address many of the challenges faced in the past. This program review is a forward looking exercise, attempting to assess what may be the future challenges and identify priorities accordingly.

In addition, the two countries present different characteristics, which made visits complementary. Namibia is a Southern African country with a generalized epidemic and 53% ART coverage (based on number of ART patients in 2012[92] on total estimated number of people living with HIV[93]); Vietnam is a Southeast Asian country with a concentrated epidemic and 28% ART coverage. There are 2 WHO accredited laboratories in Vietnam and none in Namibia.

- *Country visit approach*

The objective of the visits was to build an in-depth understanding of the HIVDR surveillance strategy in-country, and to inform the review of the strategy in a concrete way. Visits consisted of interviews and site visits:

- Interviews with key stakeholders at national level : WHO representative, members of the HIV DR national working group, MoH representative, M&E focal point, ART program manager, HIV DR focal point
- Visit of ART clinics involved in EWI monitoring or surveys
- Visit of WHO accredited laboratory

- *Country visit planning*

FIG.APP.1.2. Planning of the country visits

[92]Source: WHO & UNAIDS, Global Update on Treatment, 2013
[93]Source: UNAIDS, Report on the Global AIDS Epidemic: HIV estimates with uncertainty bounds 1990-2012, 2013

Visit 1: 27-28 May 2014

Tuesday 27th May	
10:00 – 11:00	WHO - Country Office HIV Team Leader - M. Kato
11:15 – 12:00	CDC - Country Office focal point - S. Lyss
13:30 – 14:30	Laboratory focal point - N. Thi Lan Anh
15:00 – 16:00	WHO - Consultant - V. Quoc Dat

Wednesday 28th May	
09:00 – 09:45	MOH Representative - B. Duc Duong
10:00 – 11:30	MOH - HIV Treatment Program Management and HIVDR Focal point - N. Thi Nhan
13:30 – 15:00	MOH - M&E focal point & HIV surveillance focal point - N. Bui Duc

1. NIP: Namibia Institute of Pathology
2. MOHSS: Ministry of Health and Social Services
3. MSH: Management Sciences for Health
4. SIAPS: Systems for Improved Access to Pharmaceutical and Services

Visit 2: 3-4 June 2014

Tuesday 3rd June	
08:30 – 09:30	MSH / MOHSS - Research and Surveillance Officer, M&E and HIVDR Focal Point - T. Nakanyala, M. De Klerk and A. Jonas
11:00 – 12:00	MOHSS - Treatment program managers - F. Kaindjee Tjituka and N. Taiwo

Wednesday 4th June	
08:30 – 09:30	MSH / MOHSS - Senior Technical Advisor and ART logistics pharmacist - G. Njabulo Mazibuko, S. Mwsinga and E. Ugbim
09:30 – 10:30	NIP – Laboratory focal points – E. Gaeb and A. Shiningavamwe
11:00 – 12:00	WHO - Country office disease prevention control officer and WHO representative - D. Tiruneh and M. Islam

APPENDIX 2: CONTRIBUTORS TO THE REPORT

Names in italic represent members / observers of the 2012 WHO HIVResNet Steering Committee.

Stakeholder group	Institution / role	Name
Countries	Nigeria - CDC country focal point	Ahmed, Mukhtar
	Vietnam - Head of Immunology and Molecular Biology Dpt, NIHE	Ahn, Nguyen Thi Lan
	Mexico - HIVDR focal point	Avila, Santiago
	Malawi - HIVDR focal point	Bello, George
	Botswana - CDC country focal point	Bile, Ebi
	Argentina - HIVDR focal point	*Bissio, Emiliano*
	South Africa - HIVDR focal point	*Carmona, Sergio*
	Malawi - HIVDR focal point	Chipeta, Skhona
	Togo - Leader of the HIVDR working group	Dagnra, Claver Anouma
	Nigeria - CDC country focal point	Dalhatu, Ibrahim
	Namibia - MSH / MOHSS M&E focal point	De Klerk, Michael
	Burkina Faso - Treatment program focal point	Dioma, Solange
	Martinique - Laboratory focal point	Dos Santos, Georges
	Vietnam - Deputy Head of M&E Department	Duong, Bui Duc
	Zimbabwe - HIVDR focal point	Dzangare, Janet
	Cote d'Ivoire - CDC country focal point	Ekra, Kunomboa Alexandre
	Namibia - Laboratory focal point	Gaeb, Esegiel
	Zimbabwe - CDC country focal point	Gonese, Elizabeth
	Burkina Faso - HIVDR focal point	Guire, Abdoulaye
	South Africa - Laboratory focal point	Hunt, Gillian
	Namibia, WHO country representative	Islam, Monir
	Mozambique - HIVDR focal point	Jani, Ilesh
	Namibia - HIVDR focal point	Jonas, Anna

India - CDC country focal point	Joshi, Deepika
Namibia - MOH Treatment program manager	Kaindjee-Tjituka, Francina
Uganda - HIVDR focal point	Kaleebu, Pontiano
Tanzania - CDC country focal point	Kibona, Mary
Vietnam - WHO HIV Team Leader	Kato, Masaya
Uganda - Vice chair TWG for HIVDR, Ministry of Health	*Kirungi, Wilford*
India - Laboratory focal point	Kurle, Swarali
Cote d'Ivoire - CDC country focal point	Legre Roger, Lobognon
Mexico - Treatment focal point	Leon Juarez, Eddie Antonio
Indonesia - HIVDR focal point	Lingga, Janto
Vietnam - CDC country focal point	Liss, Sheryl
Haiti - CDC country focal point	Louis, Yves Frantz Jean
Vietnam - CDC country focal point	McConnell, Michelle
Zimbabwe - HIVDR focal point	Mhangara, Mutsa
Rwanda - HIVDR focal point	Mutagoma, Mwumvaneza
Zambia - CDC country focal point	Mwale, Jonas
Namibia - MIS Senior Technical Advisor at MSH	Mwsinga Sam
Namibia - MSH / MOH Research and Surveillance Officier	Nakanyala, Tuli
Uganda - Treatment focal point	Namagala, Elizabeth
Nigeria - HIVDR focal point	Ndembi, Nicaise
Vietnam - Treatment focal point	*Nhan, Nguyen Thi*
India - Laboratory focal point	Paranjape, Ramesh
Namibia - Senior Technical Advisor at MSH	Njabulo Mazibuko, Greatjoy
France - Laboratory focal point	Peeters, Martine
Namibia, Senior Technical Advisor at MSH/SIAPS	Phulu, Bayobuya
Mexico - HIVDR focal point	Reyes Teran, Gustavo

	Rwanda - Treatment focal point	Ribakare, Mpundu
	Uganda - Treatment focal point	Riolexus, Alex
	Namibia – Laboratory focal point	Shiningavamwe, Andreas
	Namibia - CDC country focal point	Taffa, Negussie
	Namibia - MOH Treatment program manager	Taiwo, Nathaniel
	Brazil - HIVDR focal point	Tanuri, Amilcar
	Burkina Faso - HIVDR focal point	Tiendrebeogo, Sylvestre
	Namibia - WHO focal point	Tiruneh, Desta
	Zimbabwe - HIVDR focal point	Tsitsi, Apollo
	Namibia - ART logistic pharmacist MOH	Ugbim, Emmanuel
	Malawi - CDC country focal point	Wadonda-Kabondo, Nellie
	Indonesia - HIVDR focal point	Wiweko, Nadia
	Kenya - Laboratory focal point	Zeh, Clement
Partner organizations	*Global Fund - Senior advisor HIV / AIDS*	*Abdelfadil, Lee*
	PHAC - Director of Surveillance and Risk Assessment Division	*Archibald, Chris*
	Global Fund - Senior advisor HIV / AIDS	*Fakoya, Ade*
	Médecins Sans Frontières - HIV Medical Epidemiologist	Maman, David
	UNAIDS - Senior Advisor in Epidemiology	Sabin, Keith
	PHAC - Director of National HIV and Retrovirology Laboratories	Sandstrom, Paul
	Treat Asia - AmfAR's vice president for global initiatives and director of Treat Asia	Sohn, Annette
	UNITAID - Director, Market Dynamics	Waning, Brenda
Content expert: Academics	*IMPM/IRD Laboratory Cameroon - Virologist*	*Aghokeng, Avelin*
	Universitaria Senese Infectious Diseases Division - Director	De Luca, Andrea
	Harvard University - Department of Biostatistics	*Exner, Natalie*
	PASER - Co-funder and Project Manager	Hamers, Raph
	Columbia University, Mailman School of Public Health - Professor of Public Health	Hammer, Scott

	University of California - Professor of Medicine	Havlir, Diane
	Tufts Medical Center - WHO Consultant with experience on survey implementation	Hong, Steven Y.
	Tufts University - WHO Consultant responsible of data management project	*Jordan, Michael*
	CHIP – Director	Lundgren, Jens
	University of Rochester School of Nursing - WHO Consultant with experience on survey implementation	McMahon, James
	Harvard University - Professor of Statistical Computing	*Pagano, Marcello*
	Johns Hopkins University School of Medecine - Associate Professor	Persaud, Deborah
	CHAI - Chair of ASLM	Peter, Trevor
	UCL - Professor of Epidemiology and Biostatistics	Philips, Andrew
	UCL - Professor of Virology	Pillay, Deenan
	Pharm Access - Director Research and Business development	Rinke de Wit, Tobias
	AIDS Service National Hemophilia Center Sheba Medical Center in Tel Aviv – Director	*Schapiro, Jonathan*
	University of Utrecht - Virologist	Schuurman, Rob
	Stanford University - Associate Professor	*Shafer, Bob*
	Rega Institute and University Hospitals - Head of Division Clinical and Epidemiological Virology	Vandamme, Anne-Mieke
	HIV Researcher and AIDS Activist	Wainberg, Mark
	University of Utrecht - Virologist	*Wensing, Anne-Marie*
	National Centre for AIDS/STD Control & Prevention, CCDC China – Doctor	*Zhang, Fujie*
Content expert: BMGF	BMGF - Responsible of the WHO HIVDR grant	Duncombe, Christopher
	BMGF - Program Officer, HIV diagnostics initiative	Rousseau, Christine
Content expert: CDC / PEPFAR / USG	CDC - Center for Global Health Director	De Cock, Kevin
	US OGAC - Senior Medical Advisor at Office of U.S. Global AIDS Coordinator	*Dierberg, Kerry*
	CDC - Health Scientist	Mattocks, Linda
	CDC - Chief of DGHA International Laboratory Branch	Nkengasong, John
	CDC - Medical Officer Adult Care and Treatment	*Raizes, Elliot*
	PEPFAR - Branch Chief	Sangrujee, Nalinee

	CDC – Surveillance	*Teeraratkul, Achara*
	CDC - International Laboratory Branch	*Yang, Chunfu*
Content expert: Laboratory expert	NIH - Director of DAIDS	Dieffenbach, Carl
	NIH – Microbiologist	Fitzgibbon, Joe
	Data First Consulting - WHO Consultant specialist of laboratory network	*Parkin, Neil*
	NIH - Chief of Drug Development and Clinical Sciences Branch	Read, Sarah
	NIH - Director of Therapeutics Research Program (DAIDS)	Ussery, Mike
	NIH - Chief at NIAID	Williams, Carlie
Content expert: WHO	*WHO - HIV Department*	*Barcarolo, Jhoney*
	WHO - HIVDR Project Leader	*Bertagnolio, Silvia*
	WHO - HIV treatment optimization	Ford, Nathan
	WHO - Director of HIV Department	Hirnschal, Gottfried
	WHO - Coordinator HIV Technologies and Commodities	*Perriens, Jos*
	WHO - Team Leader of Antimicrobial Resistance Program	*Pessoa Da Silva, Carmem Lucia*
	WHO - HIV care and treatment programs	Vitoria, Marco
	WHO - Coordinator HIV Program Development & Implementation	Weiler, Gundo
	WHO - Medical Officer, TB Monitoring and Evaluation, Global TB Programme	Zignol, Matteo

APPENDIX 3: GENERAL INTERVIEW GUIDE

Preliminary question

Please briefly describe your role in or experience with or understanding of the HIVDR SMS program.

1. Overall impact of global HIVDR SMS

1.1 Program achievements

From your point of view, what are the main achievements of the program, and the key challenges it has faced?

- In general;
- More specifically, in terms of
    - Providing a framework for standardized implementation of HIVDR surveys at country level *(WHO-HIV, academics, country level);*
    - Filling a gap in data on HIVDR and ART program effectiveness in countries scaling up ART;
    - How the network supports HIV DR in low and middle income countries and how it complements other HIV DR monitoring programs in resource rich countries
    - Contributing to an increased awareness of the importance of monitoring HIVDR in countries scaling up ART (at country level, at global level)

How has the program affected WHO's reputation as a global actor in the international arena of HIVDR?
(Academics, global institutions / selected NGOs)

Are you aware of the 2012 progress report published by WHO? Have you read it? Are you satisfied with the content? (e.g., the amount of data)

1.2 Challenges and future priorities

How has WHO monitored and evaluated the HIVDR network over the past 6 years? Has WHO elicited any feedback from end users of the HIVDR data?
What course corrections have there been based on M&E and feedback for the global community?

What are, in your view, the key challenges and priorities moving forward?

- Do you think the current number of countries enrolled is appropriate? Should WHO include surveillance in high-income countries?
- What drives country enrollment? (in surveys, in EWI)
- What drives country sustained engagement?

2. Surveys

2.1 Usefulness of the surveys / data for decision-making

Do you consider the surveys (ADR, TDR, EWI) useful?

How have you used the results of the surveys so far? (e.g., to inform decision making

Did you write / publish a report on HIV DR in your country? *(Countries)*

2.2 Methodology features

The surveys for HIVDR Surveillance have been very recently revised and new protocols have been launched. How familiar are you with this?

What are the main strengths of the methodology adopted in terms of relevance and impact - in particular regarding the newly recommended methods?
(WHO-HIV, BMGF, Global institutions / selected NGOs, academics, country-level)

When you have implemented surveys, did you follow the WHO methodology? *(Country-level)* If you have made changes, what kind of changes, why? Did you validate the changes with WHO? Did you implement other surveys than the WHO ones?

How does the WHO methodology differ from that of others running HIV DR networks (like the US, Europeans, the AmFAR resistance network in Asia)? What is the consequence of those differences?

How actionable for countries and at global level do you think this methodology is? When you implemented it, did you have troubles understanding how to apply the strategy in your country?
What are the key implementation challenges at country level? (C*ountry-level*)

How are the results of the HIVDR surveys disseminated, to whom are and how effective do you think the dissemination is?

2.3 Methodology design and revision process

Have you been involved in the revision of the methodology? What has been the process to revise the survey methodology?
What is your feedback? For instance on

- The forum used to define the methodology
- Who was involved
- How the final decision was made
- …

2.4 Capacity building

From your point of view, to what extent has national program capacity been supported to implement HIVDR surveys?

Did you receive support (TA) to implement the surveys? To design the surveys, to conduct the surveys, to analyze the data? *(Country-level)*

What challenges has HIVDR SMS faced in building national capacity? Is staff turnover at country level a major challenge?
How could capacity building be improved in the future? Do you have examples of other ways to provide TA that are more effective?

2.5 Priorities for the future

Could some surveys be prioritized over others in the face of resource constraints? Would it help countries to have a more prescriptive prioritization based on resources and national priorities?

Could surveys be further adapted to different national / local contexts?

Should survey methodology evolve regularly, or should it remain fixed to the extent possible? What would you consider the right pace of revision for survey methodology?

When consolidating data, there is a trade-off between collecting a lot of data generated with different methodologies and collecting less data generated with the exact same methodology. Do you feel the right trade-offs are being made on HIV DR?

2.5 Funding challenges

Where would you expect countries to find funding for surveillance activities in the future? For survey implementation & testing? For technical assistance?
Where you expect to get funding from in the future for surveys? Specifically to fund the technical assistance on design and analyses of the surveys? to fund the genotyping? to fund the project management? *(Country-level)*

Do you expect that changes in funding sources will drive challenges in compliance with the methodology or willingness to share the data with WHO? How can we ensure countries will still comply with WHO guidelines and share their data with WHO? (Similar question at country level)

3. Databases

3.1 Purpose / usefulness at country and global levels

From your experience, how useful are these databases? What are they used for at country level? At global level?

What are the features of a database that would be useful: ability to prepare reports? Comparison with data from other countries?

Did you use CHIP in the past? *(Country level)* Do you use your own tools?

3.2 Challenges

What are the challenges faced in the past?

The database is currently being revised. Are you familiar with this revision process? If yes, how will, in your view, the new database address the new challenges?

What is the role of WHO in database design and management? How do you see it evolve in the future?

4. Laboratories

4.1 Accreditation process

Do you consider the accreditation process efficient? How could it be improved?
As a laboratory, did you have to go through several accreditations? *(Country level)*
What is the role of WHO in this process? How do you see it evolve in the future?

4.2 Current network

What is your view on the current laboratory network?

Does it have appropriate footprint, capacity (e.g., number of genotypes), capabilities (e.g. DBS), staffing?
Do you see the value of specialized labs, regional labs? Do you think they play the appropriate role?

What has been the support provided by WHO to develop labs?

4.3 Priorities for the future

Do you consider the laboratory network sufficient? What evolutions are needed: geographical coverage expansion? Increase in capacity of existing labs? Expansion of their capabilities?

5. Awareness & mobilization

5.1 Awareness raising efforts at national and global levels

What actions did WHO and its partners take to raise awareness of the HIVDR issue at national and global levels? What challenges were faced?

How do you view the level of awareness of the scientific community on HIVDR surveillance? of the program managers?

How integrated is the HIVDR with the HIV treatment program?

Are you aware of WHO Newsletter? Do you read it? Find it useful? *(Country level)*

5.2 Mobilization through networks

How familiar are you with the organization of HIVDR and ResNet?
In October, changes in organization were decided (reinforcement of the HIVDR Steering Group, set up of a core group etc.). Have you participated in this reorganization? What is your feedback?

What are the strengths of this mode of organization?
What are some of the challenges it faces?
How could it be improved? *(WHO-HIV, BMGF, Global institutions / selected NGOs, country level)*

Are there other organizations that should be involved? Or that should have a stronger role?

5.3 Lessons learnt in other programs

How did other global public health programs increase awareness of critical issues? (e.g. PMTCT for HIV; artemisinin resistance for malaria…)

How did other programs ensure integration of resistance surveillance with routine program management?

6. Funding and sustainability

6.1 Achievements and challenges in funding current activities

What funding support does WHO receive for the HIVDR network other than that from BMGF?
What attempts have there been to diversify funding for the HIVDR network beyond the current support from BMGF and how successful have these been?

6.2 Perspectives for future sustainable funding

How could HIVDR surveillance be sustainably funded in the future?
What actors may provide funding and/or partnership? for which activities?
Through what mechanism?
(WHO-HIV, BMGF, Global institutions/selected NGOs)

APPENDIX 4: COUNTRY INTERVIEW GUIDE

Preliminary question

Please briefly describe your role in or experience with or understanding of the HIVDR SMS program.

1. Surveys

1.1 Usefulness of the surveys / data for decision-making

Do you consider the surveys (ADR, TDR, EWI) useful?

How have you used the results of the surveys so far? (e.g., to inform decision making?)

Did you write / publish a report on HIV DR in your country? If yes, could you send it to us?

EWI specifically: how many are monitored vs. eligible?

1.2 Methodology features

The surveys for HIVDR Surveillance have been very recently revised and new protocols have been launched. How familiar are you with this?

What are the main strengths of the methodology adopted in terms of relevance and impact - in particular regarding the newly recommended methods?

When you have implemented surveys, did you follow the WHO methodology? If you have made changes, what kind of changes, why? Did you validate the changes with WHO? Did you implement other surveys than the WHO ones?

How actionable for countries and at global level do you think this methodology is? When you implemented it, did you have troubles understanding how to apply the strategy in your country?
What are the key implementation challenges at country level?

How are the results of the HIVDR surveys disseminated, to whom are and how effective do you think the dissemination is?

1.4 Capacity building

From your point of view, to what extent has national program capacity been supported to implement HIVDR surveys?

Did you receive support (TA) to implement the surveys? To design the surveys, to conduct the surveys, to analyze the data?

What challenges has HIVDR SMS faced in building national capacity? Is staff turnover at country level a major challenge?

How could capacity building be improved in the future? Do you have examples of other ways to provide TA that are more effective?

1.5 Priorities for the future

Would it help countries to have a more prescriptive prioritization based on resources and national priorities?

Could surveys be further adapted to different national / local context?

When consolidating data, there is a trade-off between collecting a lot of data generated with different methodologies and collecting less data generated with the exact same methodology. Do you feel the right trade-offs are being made on HIV DR?

1.6 Funding challenges

Where do you expect to get funding from in the future for surveys? Specifically to fund the technical assistance on design and analyses of the surveys? to fund the genotyping? to fund the project management?

Will you share data with WHO even if they do not fund the surveys?

2. Databases

2.1 Purpose / usefulness at country and global levels

From your experience, how useful are these databases? What are they used for at country level? At global level?

What are the features of a database that would be useful: ability to prepare reports? Comparison with data from other countries?

Did you use CHIP in the past? Do you use your own tools?

2.2 Challenges

What are the challenges faced in the past?

Do you have the feeling you have enough capacity at national level to analyze the data?

3. Laboratories

3.1 Accreditation process

Do you consider the accreditation process efficient? How could it be improved?

As a laboratory, did you have to go through several accreditations?

Are you currently working towards DBS?

For countries w/o accredited labs:

- Would you prefer to use cheap / free foreign lab rather than getting a national lab accredited? Are you aware of the lab in Canada?
- Where did you ship the samples to? Why? Did you use plasma or DBS?

How many labs in your country monitor viral load?

3.2 Current network

What has been the support provided by WHO to develop labs?

3.3 Priorities for the future

What evolutions are needed: geographical coverage expansion? Increase in capacity of existing labs? Expansion of their capabilities? simplify accreditation process?

4. Awareness & mobilization

4.1 Awareness raising efforts at national and global levels

What actions did WHO and its partners take to raise awareness of the HIVDR issue at national and global levels? What challenges were faced?

How integrated is the HIVDR with the HIV treatment program?

Are you aware of WHO Newsletter? Do you read it? Find it useful? *(Country level)*

Are you aware of the 2012 progress report published by WHO? Have you read it? Are you satisfied with the content? (e.g., the amount of data)

4.2 Mobilization through networks

How familiar are you with the organization of HIVDR and ResNet?
In October, changes in organization were decided (reinforcement of the HIVDR Steering Group, set up of a core group etc.). Have you participated in this reorganization? What is your feedback?

What are the strengths of this mode of organization?
What are some of the challenges it faces?
How could it be improved? *(WHO-HIV, BMGF, Global institutions / selected NGOs, country level)*

Are there other organizations that should be involved? Or that should have a stronger role?

5. Funding and sustainability

5.1 Perspectives for future sustainable funding

How could HIVDR surveillance be sustainably funded in the future?

What actors may provide funding and/or partnership? for which activities?

Through what mechanism?

6. Overall impact of global HIVDR SMS

6.1 Program achievements

From your point of view, to summarize, what are the main achievements of the program, the key challenges it has faced and the priorities moving forward?

CDC Country Offices specific questions

What support in terms of funding was granted to the country? Since when?

Regarding surveys, could you explain us the ethical clearance process (duration, etc)?

Were there some changes to the WHO methodology?

What TA was brought to the country? From the country office only or also international support from the CDC?

What level of integration is there in the country?

What is your view on the utility and visibility of the program?

APPENDIX 5: WHO HIVRESNET INITIAL ORGANIZATION[94]

WHO HIVResNet is comprised both of a network of countries and affiliated institutions implementing the WHO HIVDR strategy, and a network of accredited laboratories that perform quality assured genotyping to support HIVDR surveillance and monitoring in those countries.

Initially, WHO HIV ResNet consisted of a Steering Committee to oversee implementation of the strategy, two Advisory Groups which included experts in the field who guided (i) the laboratory network and (ii) the epidemiology working group.

The WHO HIV ResNet Steering Committee was convened by the WHO Secretariat and the initial Grant proposal stated it was supposed to meet at least twice a year. Its membership consisted of a maximum of 20 people excluding the WHO secretariat.

The WHO HIVResNet Laboratory Network was overseen by the WHO HIVResNet Laboratory Network Advisory Group, which was made up of a maximum of 15 representatives of accredited regional and specialized laboratories supported by a WHO secretariat and which was supposed to meet at least once annually in person, and monthly in telephone consultations. Its functions were the following:

- Reports to the WHO HIVResNet SC on the functioning of the laboratory network;
- Recommends agenda items and suggests issues to the WHO HIVResNet Laboratory Working Group;
- Oversees the accreditation process for laboratories;
- Oversees the functioning of the proficiency panel system;
- Recommends to WHO and provides oversight for the technical assistance to be provided to genotyping laboratories in countries and regions;
- Reviews guidance produced by the HIVDR Laboratory Working Group reports from consultants providing technical laboratory-related assistance to countries;
- Recommends special studies to WHO to be undertaken by network laboratories;
- Makes recommendations for and oversees the development of training materials and the implementation of training related to the WHO HIVDR Laboratory Strategy;
- Oversees the production of laboratory-related guidance by working groups;
- Produces a report to the Steering Committee twice yearly, including a summary of consultant reports.

The WHO HIVResNet Surveillance and Monitoring Advisory Group was supposed to meet at least twice annually, to have monthly telephone consultations, and to communicate electronically through a list-serv. It had the following functions:

- Reports to the WHO HIVResNet SC on the functioning of the global HIVDR Surveillance and Monitoring Network;
- Recommends agenda items and suggests issues to the HIVDR surveillance and monitoring and the HIVDR Information Working Groups;
- Reviews guidance produced by the HIVDR Surveillance and Monitoring and the HIVDR Information Working Group and reports from consultants providing technical assistance;
- Advises WHO, national Ministries of Health, and WHO regions in collecting, compiling, interpreting, and reporting on HIVDR data;

[94]Source: WHO, HIV Drug Resistance Project Annual Report, 2010

- Assists WHO in advising countries in making public health recommendations based on their HIVDR data, implementing these recommendations, and monitoring and evaluating the functioning of national HIVDR prevention and assessment systems;
- Oversees the production of HIVDR surveillance and monitoring-related guidance by working groups and individual consultants;
- Produces a report to the Steering Committee twice yearly, including a summary of consultant reports.

Additionally, three HIVDR working groups were convened by WHO and the Steering Committee to serve specific functions. These included the production of guidance documents, the provision of technical assistance to the WHO or to countries, performing research or assessments as part of the WHO HIVDR Strategy, and providing training. Because working groups may have had several subgroups focusing on different projects, the membership number was not limited. Working groups were supposed to meet through telephone conferences; consultative meetings might have been as well planned to take advantage of group members' presence at international conferences and special meetings may have been arranged for subgroups to facilitate a specific piece of work. The three working groups were the HIVDR Surveillance and Monitoring Working Group, the HIVDR Laboratory working group and the HIVDR Information Working Group.

APPENDIX 6: LIST OF WHO HIVRESNET STEERING GROUP MEMBERS

Name	Institution, Role	Region	Category
Archibald, Chris	Director, Surveillance and Risk Assesment Division, Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada	AMRO (Canada)	Donor / partner
Avelin, Aghokeng	Doctor and research worker, Virology Laboratory IMPM-IRD/CREMER of Yaounde	AFRO (Cameroon)	Laboratory expert
Bissio, Emiliano	Coordinator, Department of AIDS and STI, National Ministry of Health of Argentina	AMRO (Argentina)	National HIV program representative
Carmona, Sergio	Pathologist, National Health Laboratory Services, General Hospital of Johannesburg	AFRO (South Africa)	Laboratory expert
Duncombe, Chris	Senior Program Officer, Bill and Melinda Gates Foundation	AMRO (USA)	Donor / partner
Fakoya, Ade	Senior Technical Advisor HIV, The Global Fund to fight AIDS, Tuberculosis and Malaria	EURO (Switzerland)	Donor / partner
Kirungi, Wilford	Senior Epidemiologist, Ministry of Health of Uganda	AFRO (Uganda)	HIVDR surveillance representative
Nhan, Do thi	Director, Care and Treatment Department, Vietnam Authority of HIV/AIDS Prevention and Control, Ministry of Health of Vietnam	WPRO (Vietnam)	National HIV program representative
Nizova, Natalya	Director, Ukrainian Center for Socially Dangerous Disease Control, Ministry of Health	EURO (Ukraine)	National HIV program representative
Raizes, Elliot	Medical Officer, Adult Care and Treatment, Center for Disease Control and Prevention (CDC) Headquarters, Atlanta	AMRO (USA)	Donor / partner
Rinke de Wit, Tobias	Director Research and Business development, PharmAccess Foundation, Amsterdam Institute for Global Health and Development (AIGHD)	EURO (The Netherlands)	Donor / partner
Schapiro, Jonathan	Director, AIDS Service, National Hemophilia Center Sheba Medical Center, Tel Aviv	EURO (Israel)	Scientist / academic
Shafer, Robert	Professor of Medicine and Pathology, Division of Infectious Diseases, Stanford University	AMRO (USA)	Scientist / academic
Stabinski, Lara	Clinical Research Fellow, Office of the US Global AIDS Coordinator (OGAC), US department of State	AMRO (USA)	Donor / partner
Teeraratkul, Achara	Epidemiologist, Center for Disease Control and Prevention (CDC), Asia Regional Office	SEARO (Thailand)	HIVDR surveillance representative
Wensing, Annemarie M.J	Virologist, University Medical Center Utrecht	EURO (The Netherlands)	Scientist / academic
Yang, Chunfu	Team Leader, Drug Resistance Unit, International Laboratory Branch, Division of Global HIV/AIDS, CGH, Centers for Disease Control and Prevention	AMRO (USA)	Laboratory expert
Zhang, Fujie	Doctor, National Center for AIDS/STD Control and Prevention, China	WPRO (China)	National HIV program representative

APPENDIX 7: LIST OF KEY PARTNERS INVOLVED IN THE HIVDR STRATEGY

WHO has been involved in every step of the process. Currently, it has one dedicated staff position for HIV DR SMS. However, in the latest years (after the reprogramming of the BMGF's grant), the grant has supported two staff at HQ and two staff (20-30% FTE each), one in PAHO and one in WPRO. There has been no dedicated staff in Africa after 2010.

The US Government has been involved in the strategy since the beginning and is part of the WHO ResNet organization (CDC/PEPFAR). It has provided subsequent funding and technical assistance for the implementation of the strategy (for instance surveys) since 2004 and for the development of the laboratory network. The USG has been the biggest contributor beyond the BMGF. The Centers for Disease Control and Prevention (CDC) uses funding to implements its Global AIDS Program (GAP) through two specific mechanisms described below.

- **Country Operating Plans** (**COP**). Country Operating Plans serve as the vehicle for documenting US Government annual investments and anticipated results in HIV/AIDS and are the basis for approval of annual USG bilateral HIV/AIDS funding in most countries[95]. At local level, CDC / PEPFAR supports countries through COP funding to implement surveys. Along with the funding of the implementation, CDC / PEPFAR also provides countries that have developed a COP with technical assistance. In 2013, 31 countries and 4 regions (composed of 26 countries) developed a Country Operating Plan with CDC / PEPFAR support.
- **Headquarter Operating Plans** (**HOP**). At global level, CDC also supports WHO HQ through HOP funding for the implementation of the strategy, for example regarding the database development.

The CDC / GAP laboratory network also supports the development of the WHOResNet genotyping laboratory network.

Below are some examples of the support granted by the CDC / PEPFAR.

- **Support provided by the CDC laboratory network.**
  - The CDC laboratory supplied training and back-up genotyping for several countries, using the WHO methods and training package. For example in 2010, 154,000$[97] were provided for laboratory capacity building and back-up genotyping.
  - CDC supported HIVDR laboratory training activities, in particular through its specialized lab in Atlanta and developed in partnership with WHO a standardized laboratory training package for HIV drug resistance testing[96].
- **Support provided through the COPs.**
  - US CDC provided an epidemiologist (0.25 FTE) for developing and implementing Threshold Survey in PEPFAR countries, as well as two Care and Treatment Officers (0.25 FTE each). In 2010, this support amounted to 150,000$[97].
  - US CDC supported WHO activities on HIV Drug Resistance Surveillance and Monitoring in more than 20 countries including technical assistance. In 2010, 23 countries received support for HIVDR as part of the PEPFAR COP implementation for an estimated amount of 3M$[97].
- **Support provided through the HOP.**
  - US CDC provided HIVDR database support to WHO including 30,000$[97] in 2010 and 50,000$[98] in 2012 for the needs assessment and specifications definition of the new

[95]Source: PEPFAR, Country Operating Plan (COP) Guidance, October 2012, http://www.pepfar.gov/documents/organization/198957.pdf
[96]Source: PEPFAR and CDC, CDC Laboratory Factsheet, December 2012 http://www.cdc.gov/globalaids/publications/laboratory_factsheet.pdf
[97]Source: WHO, HIV Drug Resistance Project Annual Report, 2010

database. HOP also supported the development of the CHIP database, and produced a training manual regarding the use of this database. Additionally, 400,000$ were committed for the coming years regarding the development and implementation of the new database along with the development of a mirror database at CDC.

The PharmAccess foundation, through the PharmAccess African Studies to Evaluate Resistance (PASER) program and the TREATAsia Asian Studies to Evaluate Resistance (TASER) program, funded by the Netherlands Ministry of Foreign Affairs, have supported the implementation of HIVDR monitoring surveys and laboratory strengthening since 2006. Both programs share three objectives which are 1) to build capacity on monitoring and surveillance of HIVDR including a clinical observational database and a quality assurance network for resistance testing, 2) to conduct studies on HIVDR in patients on ART and in recently infected patients, and 3) to increase the scientific knowledge on HIVDR patterns in order to effectively inform policy on optimal treatment practices. PASER has supported the implementation of the WHO HIVDR surveillance surveys in countries. TREATAsia developed its own protocols, as their work was most centered around monitoring than surveillance,

PASER supported the implementation of the strategy in six countries in Sub-Saharan Africa (Nigeria, Kenya, South Africa, Uganda, Zambia and Zimbabwe). In 2010, ~2.0M$[97] was used by PASER for the implementation of the strategy. In 2012, the PASER contribution was about 1,5M$[98]. PASER contributed to 10% of the overall number of surveys reported in the WHO report, and 25% of the ADR surveys[99]. In the future, PASER has indicated to WHO that they may be supported for 3 additional years by the Netherlands Ministry of Foreign Affairs to support 5 countries for HIVDR surveillance (Angola, Mozambique, Namibia, Zambia, Zimbabwe), but this has not yet been confirmed.

TASER supported the implementation of the strategy in most Asian countries. In 2010, ~6.5M$[100] was used by TASER for the implementation of the strategy. TREATAsia's approach slightly differs from the WHO HIVDR surveillance approach. It consists of clinics studies and focuses on monitoring resistance at individual level (vs. WHO's population based approach). TREATAsia also provides lab certifications for quality assessment for genotyping. This certification process is said to be less stringent than WHO's[101].

Three *specialized laboratories* have provided genotype testing for free to support the implementation of the strategy:

- The British Columbia Center for Excellence of HIVAIDS has offered to perform plasma testing for free for all countries implementing WHO HIVDR surveys. They are currently in the process of being accredited for DBS and will also offer free testing on DBS. In addition, the laboratory developed a freely accessible sequence analysis tool enabling automatic HIVDR genotyping called RECall for an estimated amount of 50,000$[98] in 2012.
- The PHAC National HIV and Retrovirology laboratory in Ottawa has been testing plasma specimens for free for other countries without a national accredited laboratory.
- The CDC Atlanta facility has alos been providing free testing, for both plasma and DBS specimens.

The African Society for Laboratory Medicine (ASLM) is a pan-African professional body working to advocate the critical role and needs of laboratory medicine and networks throughout Africa and to develop a laboratory accreditation program. It is headquartered in Addis Ababa, Ethiopia, and serves

[98]Source: WHO, Global Strategy to Evaluate and Limit HIV Drug Resistance Emergence and Transmission, Progress report, 2012
[99]Source: Interview with Silvia Bertagnolio, May 2014
[100]Source: WHO, HIV Drug Resistance Project Annual Report, 2010
[101]Source: Interview with a member of TASER, April 2014

all African countries. It is composed of African Ministries of Health and sub-Sahara African laboratorians as well as other local, national, and international leaders, and partners, who will serve as the accrediting body for the laboratory accreditation program. CDC was instrumental in establishing this organization in collaboration with support from WHO, Ministries of Health, the African Union, and other partners.

The goals set by ASLM to be achieved by 2020 are the following: strengthening laboratory workforce by training and certifying laboratory professionals and clinicians through standardized frameworks, transforming laboratory testing quality by enrolling laboratories in quality improvement programmes to achieve accreditation by international standards, developing strong, harmonized regulatory systems for diagnostic products as defined by the Global Harmonization Taskforce and building a network of national public health reference laboratories to improve early disease detection and collaborative research.

ASLM implements WHO's Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA) in Africa[102]. This process guides medical laboratories through successive steps of quality improvement that prepare them for ISO 15189 accreditation[103]. Concerning HIV laboratory testing specifically, ASLM does not provide accreditation for viral load nor for genotyping at this stage. ASLM has been involved in organizing two HIVDR meetings in 2013 and paid by WHO. These two meetings were part of a series of meetings held between February and July 2013 to maximize country input into revised HIVDR surveillance concept notes through a transparent and collaborative effort involving country programme managers, technical experts and local and international partners. ASLM is now working with several partners including WHO, on convening two additional meetings around the mutations for determining ARV Resistance in Low and Middle Income Countries and around laboratory strengthening (not specifically on HIVDR).

Other organizations provided grants for HIVDR surveillance, not all through WHO, but on a smaller scale. Their support amounted to ~3M$[100] in 2010 and ~1.2M$[98] in 2012. Key organizations are listed below:

- *The Canadian Government*, through the Public Health Agency of Canada, contributed to the full time work of a Public Health Specialist as well as HIVDR consultants and laboratory consultant for country visit including travel expenses. The amount received in 2010 was about 710,000$[100].
- *The Italian government* funded the position of an HIVDR clinical specialist at WHO and provided clinical and epidemiological support both at WHO and in the field.
- *The Spanish government* though the Ministry of Foreign Affairs supported the implementation of the strategy in selected African countries. In 2010, they supported the work in Namibia, Angola and Senegal for a total amount of 1,125,000$[100].
- *The European Union*, through the CHAIN project provided technical contributions for the work on mathematic modeling, looking at policy actions based on cost-effectiveness threshold and drug resistance prevalance (for example: 66,417$[100] in 2010 and 50,000$[98] in 2012).
- *The National Institute of Health (NIH)*, supplied HIVDR genotyping proficiency panels to the WHO HIVDR accredited laboratories since 2007. In 2010, the amount received for the proficiency panels was about 150,000$[100] and in 2012, it amounted to 527,000$[98] corresponding to the preparation and distribution of the panels to the 31 accredited labs by Virology Quality Assurance (VQA).

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[102]Source: ASLM, What We Do, http://www.aslm.org/what-we-do/slipta/

[103]Source: WHO, WHO Guide for the Stepwise Laboratory Improvement Process Towards Accreditation in the African Region, 2011, http://www.afro.who.int/en/clusters-a-programmes/hss/blood-safety-laboratories-a-health-technology/blt-highlights/3859-who-guide-for-the-stepwise-laboratory-improvement-process-towards-accreditation-in-the-african-region-with-checklist.html

- *The Global Fund*, funded HIVDR activities in several countries including 6 countries in 2010 as part of the rounds 7 and 8 amounting to 1,000,000$[100].
- *The World Bank*, supported HIVDR activities, among other HIV activities, in 3 countries (Ghana, Mozambique and Burkina Faso).
- *The Atomic Energy Agency*, supported HIVDR activities in selected countries of the AFRO region.
- *OPEC countries* also committed to support HIVDR activities in selected countries.
- *The Tufts Medical School University fellows* indirectly supported survey implementation in Namibia, Vietnam, Indonesia, Cameroon, and Nepal in 2012, by supporting a portion of the salary of three infectious disease fellows, for a total amount of 100,000$[98].
- *The WHO HIVResNet network of laboratories* contributed to the costs of genotyping and training of the laboratories which were not reimbursed by other sources, amounting to 300,000$[98] in 2012.
- *The HIV ResNet members* volunteered their time for the HIVDR strategy, corresponding to about 250 person-days in 2012 for an estimated amount of 200,000$[98].

APPENDIX 8: KEY EVOLUTIONS IN HIVDR LABORATORY TECHNOLOGIES

Genotyping on DBS. Genotyping can be performed on Dried Blood Samples (DBS) as well as plasma samples. While laboratory costs are similar for both methods[104], DBS samples are easier to collect and ship as they do not require refrigeration. This makes the method more cost-effective and more feasible, in particular in settings with remote sites and limited logistics capacity. Therefore DBS genotyping facilitates the implementation of HIVDR surveys. However, this is a specific capability that requires training, equipment and accreditation in each laboratory. WHO's specialized laboratories contributed operational research to the development of DBS genotyping technique[105], but only 8 WHO HIVDR ResNet laboratories are currently accredited for it.

Laboratory testing of viral load. In its 2013 ART guidelines, WHO recommends viral load as the preferred method to monitor ART failure, as it allows detection of treatment failure earlier and more accurately than CD4 count[106]. Viral load is also a key indicator for drug resistance surveillance: it is an Early Warning Indicator and is required in the ADR survey. In 2013, WHO defined virological failure using a threshold of 1,000 copies/mL based on two consecutive viral load measurements after 3 months, down from a threshold of 5,000 copies/mL in its 2010 guidelines. The updated guidance thus requires reliable testing at low viral load threshold. The test can be performed on plasma or DBS samples but, at low thresholds, DBS is not considered as reliable as plasma at this stage[107]. As DBS is logistically easier and more cost-effective to collect, the improvement of DBS viral load technology could facilitate the expansion of viral load testing. Interviewed experts reported that more research is needed to assess existing technology and develop improved techniques. The new WHO guideline as well as the development of viral load on DBS may drive the expansion of viral load testing and therefore facilitate the implementation of EWIs and ADR surveys.
The implementation of viral load raises quality challenges. If the integrity of specimens is impaired through manipulation, viral load can generate false undetectable results. At this stage, CDC uses proficiency panels to assess viral load quality, though has no formal accreditation system. The PHAC laboratory in Ottawa currently runs a leading program in CD4 enumeration quality assurance, serving 1,500 laboratories globally, and is investigating the possibility of running a quality assurance program for viral load as well.

Point-of-care testing of viral load. Experts interviewed indicated that point-of-care testing of viral load is in development and will become available in 2014. Although it cannot be ascertained at this stage, the example of CD4 testing suggests that this new technology could lead to a relative decrease in the role of laboratories in viral load testing.

Technologies from other disease fields. New ways of sequencing are being developed and could be used in LMIC. During the March 2012[108] WHO Laboratory network meeting, participants recommended that WHO investigate the potential new technologies developed for other diseases to understand whether it is possible to develop HIVDR genotyping assays that can be adapted to run on the same system. Two examples were mentioned during the meeting. The first example discussed was about MDR-TB and the GeneXpert instrument and Xpert MTB/RIF cartridges which have enabled simpler diagnosis and have been endorsed by WHO in 2010. At the end of 2011, 21 countries

[104]Note: See Appendix for overview of costs
[105]Source: Interview of a laboratory expert, April-May 2014
[106]Source: WHO, Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, June 2013, http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1
[107]Source: Interview of a content expert, April-May 2014
[108]Source: WHO, WHO ResNet Annual Meeting, Meeting report, Annex 1, March 2012

implementing the HIVDR surveillance strategy had ordered those new MDR-TB diagnostic instruments. The second example discussed was the switch from full sequencing to point mutation assays (PMA), also being considered for public health surveillance purposes. Cost-effectiveness plays an important role in the definition of the current strategy (reliance on surveys vs. individual monitoring for instance). This kind of changes could impact the cost-effectiveness of surveillance and could therefore call for a revision of the strategy.

APPENDIX 9: DBS VS. PLASMA COSTS ANALYSES

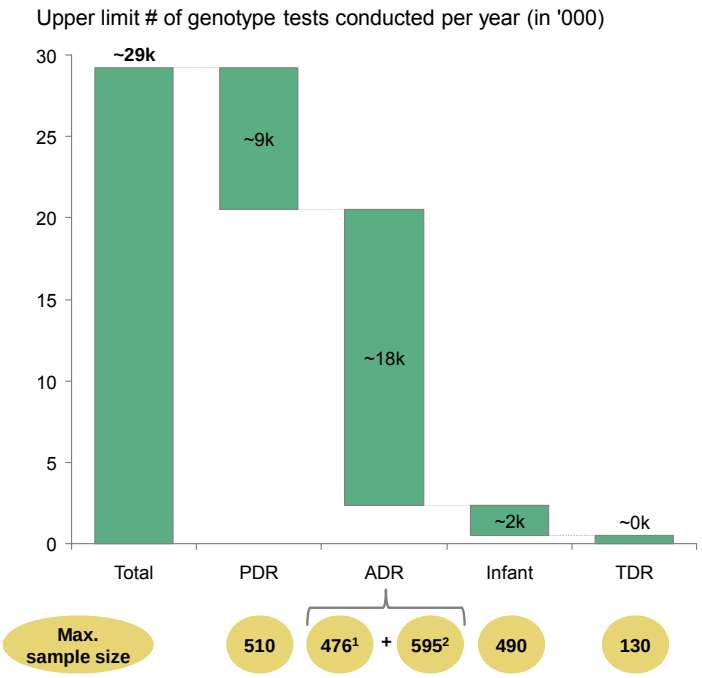
Based on the genotyping costs available online on WHO website[109], there is an average 14% difference between DBS and plasma genotyping costs excluding transport costs, in the WHO accredited laboratories.

City (country)	Cost 2012 (DBS)	Cost 2012 (plasma)	Delta plasma vs. DBS
Sydney (Australia)	250-350$	250-350$	-
Ottawa (Canada)	70$	95$	+25$
Beijing (China)	55$	65$	+10$
Bordeaux (France)	77$	77$	0
Montpellier (France)	129$	155$	+26$
Chennai (India)	180$	220$	+40$
Pune (India)	180$	220$	+40$
Kisumu (Kenya)	120$	120$	-
Utrecht (the Netherlands)	245$	271$	+26$
Ponce (Puerto Rico)	50-250	60-250	-
Dakar (Senegal)	129$	155$	+26$

[109]Source: WHO, HIVDR genotyping price list
http://www.who.int/hiv/topics/drugresistance/HIVDR_genotype_pricelist.pdf?ua=1

APPENDIX 10: UPPER LIMIT OF GENOTYPE TESTS CONDUCTED PER YEAR

FIG.APP.10.1. Upper limit of the number of genotype tests conducted per year if 68 countries implement the strategy under the revised methodology[110]



1. Sample of patients who have been on ART for ~12 months
2. Sample of patients who have been on ART for 48+ months
Source: WHO, BCG Analysis

Key hypotheses

# of countries implementing the strategy based on onboarded countries as of 2014
- 68 countries

Survey selection based on WHO prioritization recommendation
- All countries implement high-priority surveys (PDR & ADR)
- 1/4 of countries implement other surveys (infant & TDR) (WHO estimate)

Surveys are implemented within 6 months based on WHO expectations of revised methodology

Repeat frequency based on WHO guidelines
- 3-4 years on average after end of previous survey for PDR & ADR
- Every 4 years on average after end of previous survey for infant & TDR

Sample sizes required based on upper limits of WHO guidelines

[110]Sources: WHO, Concept note: Surveillance of HIV drug resistance in Adults receiving ART (acquired HIV drug resistance), 2014
WHO, Concept note: Surveillance of HIV drug resistance in Surveillance of HIV drug resistance in adults initiating antiretroviral therapy (pretreatment HIV drug resistance), 2014
WHO, Generic Protocol for surveillance of initial drug-resistant HIV-1 among children < 18 months of age newly diagnosed with HIV, 2012
WHO, Email from Silvia Bertagnolio, April 30th 2014

APPENDIX 11: LABORATORY TYPE DEFINITION[111]

WHO defines three tiers of accredited laboratories within the HIVDR genotyping laboratory network. Laboratories are national institutions designated by the MOH (except for specialized laboratories for which MoH designation is not a requirement) and accredited by WHO.

National HIVDR laboratories

There is usually one national laboratory per country. As of 2014, there are 14 national laboratories in 10 countries and 4 regions (AFRO, AMRO, SEARO, WPRO).

The national laboratory's main responsibilities are to

- Support HIVDR surveys by performing genotyping and viral load testing
- Comply with WHO's quality assurance program
- Report survey results to the national HIVDR Working Group and WHO
- Assist the country in analyzing survey data

Regional HIVDR laboratories

WHO recommends that there should be at least one regional laboratory in each WHO region. As of 2014, there are 11 regional laboratories in 9 countries and 3 regions (AFRO, AMRO and WPRO).

The regional laboratory may serve at the national laboratory in its own country.
In addition, it has regional responsibilities to

- Support HIVDR surveys by performing genotyping and viral load testing in the region, where capacity is needed
- Provide technical assistance to national laboratories within the region
- Facilitate capacity building of national laboratories and candidate laboratories within the region
- Participate in national laboratory assessment
- Participate in the WHO HIV ResNet Laboratory Network regional meetings

Specialized HIVDR laboratories

There should be a limited number of specialized laboratories worldwide, selected for their capacity and motivation. As of 2014, there are 8 specialized laboratories in 6 countries and 2 regions (AMRO and EURO).

The specialized laboratory may serve as a national and/or regional laboratory in its own country/region.
In addition, it has global responsibilities to

- Provide technical assistance to regional and national laboratories
- Be represented in the WHO HIV ResNet Laboratory Network Advisory Group and contribute actively to the development of the network
- Actively participate in the development and management of one or more of the following core activities: quality assurance system; capacity building/training; operational research; dried fluid spot activities

[111] Source: WHO, HIV / ResNet HIV Drug Resistance Laboratory Strategy, July 2010

APPENDIX 12: RESISTANCE SURVEILLANCE AND PREVENTION IN TB

Perspectives from the fields of tuberculosis (TB) and malaria drug resistance surveillance are used in this report to identify the lessons learned in those fields and understand how and if they could be relevant for the HIVDR strategy.

The natures of the malaria and tuberculosis epidemics are different, as are the levels of resistance measured to date and their potential impacts on treatment programs. The DR surveillance strategies are consequently organized differently, mobilize differing types of testing and are at various stages of maturity, with both TB and malaria resistance strategies active for a decade longer than the HIV drug resistance strategy.

1. CHARACTERISTICS OF DRUG RESISTANCE FOR TB

Drug resistance for TB. There were an estimated 450,000 new cases of MDR-TB worldwide in 2012112. Two types of drug resistance appear for TB: drug resistance in a new TB case referred as primary resistance and drug resistance in a previously treated TB case referred as secondary or acquired resistance. Drug-resistant TB in all its variations is found throughout the world. High-burden areas of the world include China, India, and the Eastern European region. 3.6% of newly diagnosed TB cases and 20% of previously treated for TB appear to have MDR-TB.

Nature of epidemics. Drug resistant tuberculosis arises in areas with weak TB control programs, as suboptimal treatment regimens or poor treatment adherence allow for the proliferation of drug-resistant populations.

History of the program. The program for drug resistance was launched in 1994 by WHO, International Union Against Tuberculosis and Lung Disease (IUATLD) and other partners due to lack of standardized data on anti-tuberculosis drug resistance and in an effort to estimate the global prevalence of resistance. Four editions of guidelines for surveillance of drug resistance have been published since 1994. Results were published on a regular basis in ad-hoc reports until 2010. Since 2012, results have been published annually in the global TB report. An MDR-TB Response plan "The Global MDR-TB and XDR-TB Response Plan 2007-2008" was published in 2007.

Funding of the program. In 2015, it is estimated that about 20% of the USD 8 billion that low-and middle-income countries require for TB care and control will be needed for the treatment of MDR-TB[113]. The Global Fund to Fight AIDS, Tuberculosis and Malaria plays a crucial role in funding programs for diagnosing and treating TB in low and middle-income countries, and it accounts for almost 90% of international TB funding[114]. To date, out of 22 high TB burden countries six are totally reliant on funding from the Global Fund (100% of financing) and for another 15 high burden countries two thirds (60%) of their budget come from Global Fund financing[114]. An assessment carried out on funding requests for tuberculosis indicated that ~60% of round 4–8 proposals for TB funds requested specific funding for surveillance of drug resistant TB[115]. Other partners also funded some specific elements of the strategy. The Global Laboratory Initiative (GLI), created by WHO and the

[112]Source: WHO, Global tuberculosis report, 2013
http://www.who.int/tb/publications/global_report/en/
[113]Source: WHO, Multidrug resistant tuberculosis: update 2013, 2013
[114]Source: All-Party Parliamentary Group on Global Tuberculosis, Drug resistant tuberculosis: old disease, new threat, April 2013
[115]Source: WHO & GFATM, K. F. Kelley and others, Are Countries Using Global Fund Support to Implement HIVDRug Resistance Surveillance? A Review of Funded HIV Grants, November 2012

STOP TB Partnership in 2007[116] to expand "access to quality-assured laboratory services in response to the diagnostic challenges of TB, notably HIV-associated and drug-resistant TB", has received funding from UNITAID. The EXPAND-TB (Expanding Access to New Diagnostics for TB) Project initiated in 2009 to accelerate access to diagnostics for patients at risk of MDR-TB in 27 low- and middle-income countries has been funded by the World Health Organization (WHO) and the Global Laboratory Initiative (GLI), the Stop TB Partnership's Global Drug Facility (GDF), UNITAID and the Foundation for Innovative New Diagnostics (FIND).

Monitoring features. Two types of monitoring resistance exist depending on country capacity: continuous surveillance based on routine drug susceptibility testing of all patients in countries with sufficient capacity, and periodic surveys of a specially designed sample of patients representative of the entire population of TB cases for countries lacking capacity.

Testing. The most common approach for testing is phenotyping drug susceptibility tests which consist in the culture of TB strain. Diagnosing TB using culture takes on average four weeks to get a definite test result, with another four to six weeks to then get the drug susceptibility results. In order to decrease length of diagnosis and since resistance arises from genetic mutations, another approach using molecular methods has been developed and is increasingly being used.

Potential outcomes. Cost of 2nd line treatment for TB is more than 10 times more expensive than cost of 1st line treatment[117] which emphasizes the need to measure drug-resistant TB and contain it. Moreover, 2nd line treatment appears longer than 1st line with at least a 9 months treatment for 2nd line (and often a 20 months treatment) vs. a 6 months treatment for 1st line. Second line drugs are frequently associated with very high rates of adverse drug reactions (damage to the kidneys, liver, or heart, loss of vision or hearing, changes in behavior or mood, etc.), needing frequent interruption and change of regimen and are thus more restricting for patients[118]. Very few actual trials have been carried out of the third-line to see how effective they actually are in the treatment of drug resistant TB.

2. The TB Global Laboratory Initiative[119]

In 2001, Stop TB Partnership was created and now operates with ~1100 partners. The Global Laboratory Initiative (GLI) is a Working Group of the Stop TB Partnership. It gathers international partners to expand "access to quality-assured laboratory services in response to the diagnostic challenges of TB, notably HIV-associated and drug-resistant TB". This translates into efforts to develop a TB Supranational Reference Laboratory Network; accelerate laboratories' access to relevant technologies; and provide tools for laboratories to implement quality management systems and obtain ISO accreditation.

a) The TB Supranational Reference Laboratory Network (SRLN)

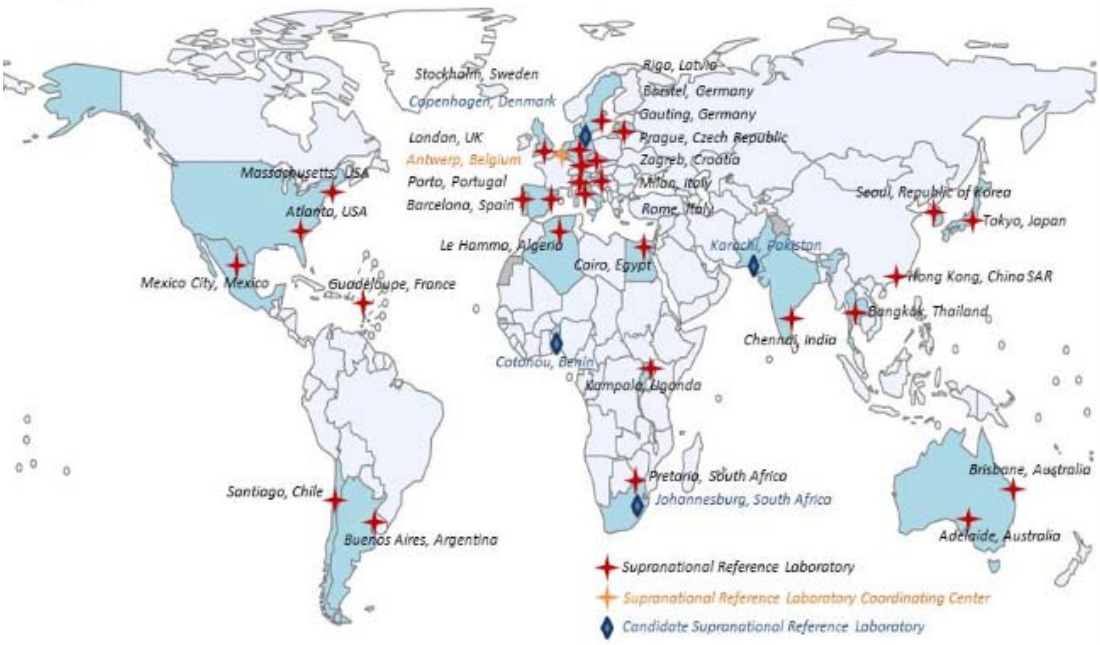
[116]Note: Please refer to appendix for more details
[117]Source: Resch et al., Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis, Table 3 Treatment costs, 2006
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0030241
[118]Source: Verma & Mahajan, Multiple Side Effects Of Second Line Antitubercular Therapy In A Single Patient, 2008
http://ispub.com/IJPM/9/2/10588
[119]Source: Stop TB Partnership, Global Laboratory webpage
http://www.stoptb.org/wg/gli/

The SRLN is a sub-group of the GLI. It is a network of 29 supranational reference laboratories (SRL) and 4 candidates SRLs under mentorship. Their role is to support and build capacity in national reference laboratories (NRLs), though no accreditation is provided to NRLs through the network. They also provide resistance testing services to countries where national laboratory capacity has not yet been established.

SRLs take the following commitments as part of network membership[120]:

- Establish formal links with at least two NRLs
- Provide at least 3 Technical Assistance visits every two years
- Report at least one activity per supported country per year

FIG.APP.12.1. The TB Supranational Reference Laboratory Network in 2013



b) ACCELERATE ACCESS TO TECHNOLOGIES

With funding by UNITAID, the GLI is accelerating access to diagnostic and assay technologies through the EXPAND-TB and TBXpert projects. From 2009 to 2013, new TB diagnostic technologies were made available to 77 reference laboratories, allowing the diagnosis of over 53,000 MDR-TB cases over the period. Recent efforts have focused over the roll-out of the Xpert MTB/RIF assay. EXPAND-TB also involved market shaping interventions which led to price reductions of up to 80% for diagnostic equipment and supplies.

c) PROVIDE TOOLS FOR QUALITY MANAGEMENT AND ISO ACCREDITATION THROUGH THE 'GLI TOOL'

The GLI tool is a website that provides a stepwise plan to guide TB laboratories towards ISO 15189 accreditation. Accreditation itself is provided by an independent accreditation body which also

[120]Source: Global Laboratory Initiative, Eligibility and Inclusion criteria for GLI TB Supranational TB Reference Laboratories,
http://www.stoptb.org/wg/gli/assets/documents/Eligibility%20Criteria%20SRL%20Final.pdf

operates to a standard (ISO 17011) and is an affiliate/member of the International Laboratory Accreditation Cooperation (ILAC).

The tool organizes the steps to accreditation in 4 phases:

- Ensure that the primary process of the laboratory operates correctly and safely
- Control and assure quality and create traceability
- Ensure proper management, leadership and organization
- Create continuous improvement and prepare for accreditation

For each of these phases, a roadmap is provided that outlines the steps involved. In following the recommended phasing, a laboratory can improve its quality even if it does not implement the whole plan or achieves accreditation.

In 2014, WHO launched a similar tool for any type of medical laboratory: the Laboratory Quality Stepwise Implementation tool (LQSI)[121].

3. Technical Assistance (TA) model for TB drug resistance surveillance[122]

WHO organizes TA for TB DR through 3 avenues.

Direct provision for high-priority countries. WHO fully funds and directly provides TA on an annual basis to countries it has identified as high-priority (typically 5 or 6). TA covers survey design, implementation and analysis.

Pool of consultants available for other countries. Lower-priority countries can call upon a pool of 10 international consultants that WHO has selected and trained. Consultants are typically from the US (CDC in particular) or Europe, as the required skill set is difficult to find in LMIC. Countries usually fund their interventions with Global Fund, CDC, or national funding.

Regional workshops to build national capacity. WHO HQ and regional offices organize 2 series of 3 capacity building workshops each year: one on survey design, the other on survey data analysis. Each workshop lasts 3 days and trains 2 persons from each of 5 to 6 countries. For data analysis, participating countries are invited to work on their own data.

[121]Source: WHO, Laboratory Quality Stepwise Implementation Tool webpage https://extranet.who.int/lqsi/

[122] Source: WHO, interviews, May 2014

APPENDIX 13: RESISTANCE SURVEILLANCE AND PREVENTION IN MALARIA

Resistance for malaria. Two types of resistance exist in the field of malaria: artemisinin resistance referred as drug resistance and pyrethroids resistance referred as insecticide resistance.

1. ARTEMISININ DRUG RESISTANCE

Nature of epidemics. Drug resistant malaria arises in areas with weak malaria control programmes and are mainly due to the uncontrolled use of artemisinin-based combination therapy (ACT), the continued use of oral artemisinin-based monotherapy[123], the use of subtherapeutic levels of artesiminin, substandard and counterfeit drugs, high treatment cost, and co-use of artemisinin derivates.

History of the program. The protocol for drug resistance was launched in 1996 by WHO for assessing antimalarial drug efficacy in high transmission areas. A Global Plan for Artemisinin Resistance Containment (GPARC) was published in 2011, in a conjoint effort from WHO and RBM Partnership. The GPARC was developed in consultation with members of each of the constituencies of the Roll Back Malaria Partnership and the work was coordinated by the World Health Organization (WHO) Global Malaria Programme, with the funding from the Bill & Melinda Gates Foundation.

Funding of the program. Several partners funded the artemisinin surveillance program including the BMGF and CDC / PEPFAR. WHO initiated a response to artemisinin resistance in November 2008, partly supported by some funding from the BMGF. These efforts were expanded with the initiation of the GPARC in 2011 and numerous international donors and organizations made contributions to these efforts such as PEPFAR through the President's Malaria Initiative. The first Global Fund's regional grant targets malaria drug resistance surveillance program. A $100-million grant to avert the spread of artemisinin resistance in five malaria endemic countries in the Greater Mekong sub-region has been signed by the Global Fund in December 2013. This constitutes the first regional grant under the Global Fund's new funding model (NFM).

Monitoring features. There are two types of monitoring for drug resistance which are the routine treatment monitoring on sentinel sites that does not enable to have national representativeness but enable to test efficacy of treatment on site patients, and the intensified treatment monitoring based on area typology which tailors treatment monitoring to local needs, in addition to sentinel site surveys.

Levels of resistance. Highest level of artemisinin drug resistance is found in the greater Mekong sub region. $100 million has been granted by the Global Fund in December 2013[124] to avert the spread of artemisinin resistance in five malaria endemic countries in the Greater Mekong sub-region. This is the first regional application under the Global Fund's new funding model (NFM). In most other countries, less than 5% treatment failure rate for artemisinin has been reported.

Testing. Testing of artemisinin resistance is done through clinical monitoring of therapeutic response.

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[123]Sources: WHO, Withdrawal of oral artemisinin-based monotherapies
http://www.who.int/malaria/areas/treatment/withdrawal_of_oral_artemisinin_based_monotherapies/en/
Chrubasik and Jacobson, The development of artemisinin resistance in malaria reasons and solutions, 2010
http://www.ncbi.nlm.nih.gov/pubmed/20578122

[124]Source: Global Fund, Flash issue #36, Joining forces in Mekong, January 2014,
http://www.theglobalfund.org/en/blog/2014-01-23_Global_Fund_News_Flash_Issue_36/

Potential outcomes. No drugs are currently available to replace artemisinin if it should cease to be effective which contributes to reinforce the urgency of monitoring drug resistance for malaria.

Prevention and response guidance[125]. GPARC provides recommendations based on a typology of target areas. Three tiers are defined, depending on the evidence of artemisin resistance detected:

- Tier I: areas for which there is credible evidence of artemisinin resistance
- Tier II: areas with significant inflows of people from tier I areas, including those immediately bordering tier I areas
- Tier III: areas with no evidence of artemisinin resistance and limited contact with tier I areas

For each tier, GPARC provides an integrated set of concrete recommendations for potential solutions in 5 categories:

- Stop the spread of resistant parasites – example: provide malaria interventions at the work site to control for mobile and migrant populations
- Increase monitoring and surveillance – example: consider adding new sentinel sites near foci of artemisinin resistance
- Improve access to diagnostics and artemisinin-based combination therapies – examples: ensure consistent availability of quality-assured therapies in the public sector by improved financing, procurement and distribution; take immediate regulatory action to stop the manufacture and wholesale purchase of counterfeit drugs
- Invest in research on artemisinin resistance – example: develop new diagnostic tools
- Motivate action and mobilize resources – example: raise funds for malaria control

2. INSECTICIDE RESISTANCE

History of the program. WHO first recommended the use of a standard bioassay technique to detect insecticide resistance in the early 1960s[126]. To ensure containment of the resistance and the implementation of the surveillance guidelines, a Global Plan for Insecticide Resistance Management (GPIRM) was published in 2012 by WHO in consultation with members of each of the constituencies of the Roll Back Malaria Partnership.

Monitoring features. Surveys rely on 2 steps to identify and understand resistance mechanisms: first the tests on sentinel sites to detect potential resistance as part of the routine monitoring and secondly laboratory-based analysis to understand mechanisms of resistance in the sample. The surveys do not provide national prevalence estimates.

Levels of resistance. For insecticide resistance, data are still limited but in 2012, resistance to at least one insecticide had been identified in 64 countries with ongoing malaria transmission.

Testing. The testing for the first step of the monitoring is done through susceptibility testing by exposing mosquitoes to insecticide, whereas the second step requires biochemical assays and molecular testing to understand the resistance.

[125]Source: WHO and Roll Back Malaria, Global Plan for Artemisinin Resistance Containment, 2011, http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf?ua=1
[126]Source: WHO, Insecticide resistance and vector control, Tenth Report of the Expert Committee on Insecticides, 1960
https://extranet.who.int/iris/restricted/bitstream/10665/40455/1/WHO_TRS_191.pdf

Potential outcomes. Long-lasting insecticidal nets and indoor residual spraying are the two tools mostly used currently. The combination of all the tools available enables to prevent further spread of resistant malaria.

Prevention and response guidance[127]. The GPIRM recommends that countries define Insecticide Resistance Management strategies and provides initial working proposals to be adapted to national settings, based on different types of geographical areas:

- Areas with unknown levels of resistance
- Areas in which indoor residual spraying (IRS) is the main form of vector control
- Areas in which long-lasting insecticidal nets (LLINs) are the main form of vector control
- Areas in which LLINs and IRS are already used in combination

For each area type, the GPIRM defines scenarios to help countries respond to their specific insecticide resistance situations. Fig. 5.2. provides an example of such guidance for areas controlled primarily by the use of LLINs. Four cases are defined, depending on whether resistance is detected, and whether confirmed malaria cases are increasing. For each of those four scenarios, the GPIRM outlines:

- The scenario at hand (e.g. resistance is reported but no increased malaria cases)
- How to interpret the situation (e.g. vector control is working well despite resistance)
- Recommended monitoring actions (e.g. check and reinforce epidemiological surveillance)
- Recommended vector control actions (e.g. ensure system for timely replacement of worn-out nets)

In this way, in a single document, the GPIRM provides simple, high-level guidance that helps countries understand the situation at hand and adjust both their monitoring and vector control policies to respond to it.

[127]Source: WHO and Roll Back Malaria, Global Plan for Insecticide Resistance Management in Malaria Vectors, 2012
http://apps.who.int/iris/bitstream/10665/44846/1/9789241564472_eng.pdf?ua=1

FIG.APP.13.1. Recommendations for areas in which vectors are controlled primarily by use of long-lasting insecticidal nets (LLINs)

Status	No increase in confirmed malaria cases	Increase in confirmed malaria cases
Susceptbility	**Scenario:** no foci of possible resistance identified, according to WHO test procedures [a] **Interpretation:** resistance is not an immediate threat; vector control is still effective **Monitoring action:** • conduct frequent [b] monitoring of vector mortality rates through susceptibility tests to determine that there is no resistance emerging **Vector control action:** • no change	**Scenario:** no reports of resistance but evidence of an increase in the number of malaria cases and no other clear cause **Interpretation:** insecticide resistance is not an immediate threat and is probably not the cause of the increase in the number of cases **Monitoring action:** • conduct frequent monitoring of vector mortality rates through susceptibility tests to confirm that there is no resistance emerging • monitor closely the quality and coverage of vector control interventions, which could be responsible for the increase in malaria cases **Vector control action:** • ensure system for timely replacement of worn-out nets and assure the quality and extent of LLIN coverage
***Kdr* resistance only**	**Scenario:** *kdr* resistance reported but no evidence of increase in malaria cases **Interpretation:** vector control working well despite *kdr-based* resistance **Monitoring action:** • conduct frequent and extensive susceptibility tests to monitor any increase and spread in resistance • check for metabolic resistance using bio-chemical and molecular testing methods • check and if necessary reinforce epidemiological surveillance **Vector control action:** • continue to promote the use of LLINs • ensure system for timely replacement of worn-out nets and assure the quality and extent of LLIN coverage	**Scenario:** resistance has been confirmed based on bioassays according to WHO test procedures, or genotypic data show rapid increase in resistance, with confirmation of *kdr* only; also evidence of an increase in the number of malaria cases and no other clear cause. **Interpretation:** resistance is an immediate threat and might already be contributing to the increase in malaria cases making it a serious and current public health problem **Monitoring action:** • conduct frequent and extensive susceptibility tests to monitor any increase in resistance • check whether metabolic resistance is present using bio-chemical and molecular testing methods **Vector control action:** • continue to promote the use of LLINs • introduce, in addition, focal IRS with a non-pyrethroid insecticide, preferably on annual rotations . Best practice is to do this in all areas of resistance, good practice is to do it at least in the areas of greatest concern [c]

ADVOCACY STRATEGY

The Malaria Advocacy Working Group. The Roll Back Malaria Partnership created the Malaria Advocacy Working Group (MAWG) in 2007[128] to convene, co-ordinate and facilitate communication among RBM partners involved in advocacy. The MAWG is chaired by two elected co-chairs, and the RBM Secretariat acts as the MAWG Secretariat. The MAWG develops and implements a biennium work plan and budget, which highlight the necessary interaction with other RBM Partnership bodies. The MAWG holds bi-annual ordinary meetings and bi-monthly conference calls (as well as ad hoc meetings as needed).

[128]Source: Roll Back Malaria Partnership, Malaria Advocacy Working Group (MAWG) TOR, November 2013 http://www.rollbackmalaria.org/partnership/wg/wg_advocacy/docs/tor.pdf

Strategic objectives. The MAWG led the revision of RBM's Advocacy Framework in 2012[129]. In order to maintain malaria as an international development priority, RBM defines four strategic objectives, one of which specifically relates to resistance:

- Position the malaria response as a key driver in promoting the Millennium Development Goals (MDGs) including maternal and child health
- Decisively strengthen country ownership
- Increase financial commitments, both from donor and endemic countries, by demonstrating malaria control benefits in economic development
- In coordination with WHO, inform stakeholders of the growing threat of insecticide and drug resistance

Roles and responsibilities. The Advocacy Framework assigns specific roles and responsibilities for advocacy to different stakeholders within the RBM Partnership: the RBM Board Chair, the RBM Executive Director, the Resource Mobilization Sub-Committee, the Malaria Advocacy Working Group and the Secretariat.

Messaging. The Advocacy Framework outlines the messaging strategy in three ways. First, the key messages are defined. They correspond to the messages announced for World Malaria Day 2012: "Sustain Gains, Save Lives: Invest in Malaria". Second, each major audience in donor and endemic countries is assigned key messages areas (see Fig. 5.3.). The rationale for the message is explained, as well as potential issues and obstacles faced in advocacy in addressing those audiences. Finally, an activity framework identifies advocacy activities that can be mobilized to address program priorities (see Fig. 5.4). For instance, the launch of GPIRM is identified as an opportunity to advocate for sustained funding, and call for improved access to key supplies (e.g. insecticidal nets).

FIG.APP.13.2. Audiences and Selected Messages

Donor Countries	Why	Key Message Area	Issues and Obstacles
Governments: development agencies	To sustain commitment and funding	ROI, malaria control link to development and progress across a range of MDGs including maternal & child health, support for other issues (eg health system strengthening)	Economic downturn, domestic agendas
Civil Servants	Need to build support for subject area and its key for Africa's development to provide policy support	ROI, malaria control link to development and progress across a range of MDGs including maternal & child health, support for other issues (eg HSS)	Economic downturn, domestic agendas
Parliamentarians	Need to build support for subject area and its key for Africa's development to provide policy support	ROI, malaria control link to development and progress across a range of MDGs including maternal & child health, support for other issues (eg HSS)	Under appreciation of ROI and link to development
General public	Need to build support for subject area and its key for Africa's development and global benefits, to provide support for policy decisions	Importance of malaria in Africa's and the world's prosperity, especially for women & children in ten priority countries	Economic downturn, lack of perceived relevance
Potential donors (foundations, corporations etc)	To increase funding by showing why malaria should be in their portfolios	ROI, malaria control link to development and progress across a range of MDGs including maternal & child health, support for other issues (eg HSS)	Under appreciation of ROI and link to development
Endemic Countries			
Governments: MoH, HoS	To prioritise malaria funding/commitment, drive ownership of the issue and facilitate activities	ROI, malaria control essential for development and maternal & child health, support for other issues (eg HSS), country's essential role for success, decision to implement new interventions	Under appreciation of ROI, link to development and its role for success
Governments: MoF	To prioritise malaria	ROI, malaria control value for development and maternal & child health, and to support other sectors, key issues eg resistance financing for new interventions	Lack of engagement so far, need to present a solid business case
Parliamentarians	To educate on why malaria is a priority issue for support	ROI, malaria control essential for development and progress across a range of MDGs including maternal & child health, support for other issues (eg HSS), key issues eg resistance	Under appreciation of ROI and link to development
Private and other sector new-type potential partners (non-commodity producers)	For increased domestic/continent support (funding and other forms of involvement such as provision expertise and capacities)	To see protection against malaria as business-critical and a key element for community support, and that the RBM Partnership is the most effective umbrella for action	Lack of evidence/data on business impact, who can influence them? What does it take to convince them?
General public	Time is right to create demanders of services, not passive recipients	A life free from risk of malaria is our right (malaria control and elimination), key issues to reach this goal eg resistance, access to interventions	Acceptance of malaria as part of life
Influencers/multipliers	To lend credibility, to magnify messages		Time limitations, choice of influencers

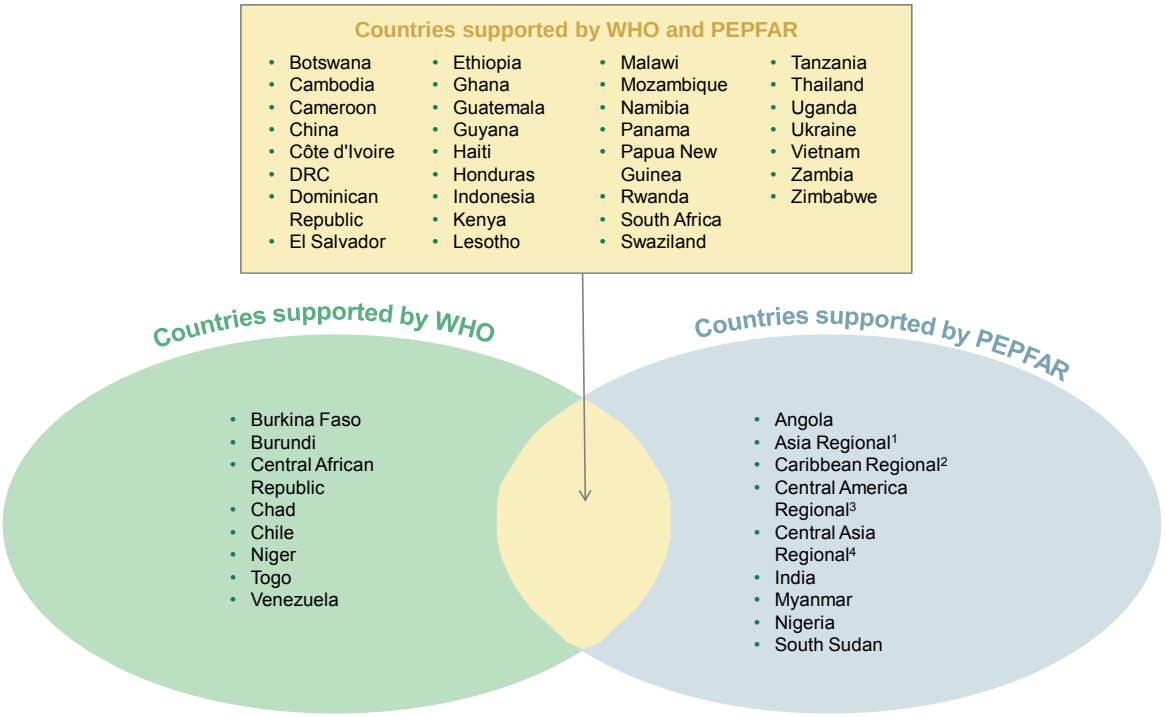
[129]Source: Roll Back Malaria Partnership, The Roll Back Malaria Advocacy Framework, 2012 http://www.rollbackmalaria.org/partnership/wg/wg_advocacy/docs/GlobalAdvocacyStrategy-Update-2012.pdf

FIG.APP.13.3. Proposed Activity Framework with Corresponding Messaging

		Activity Category	Leverage content from reports, surveys etc eg P&I Series, GPIRM, GPARC & initiatives, with media relations & advocacy plan			Media relations (trad'l & elect), incl for events	Joint initiatives with health p'ships fpr donor & endemic countries	Expand no./Utilise sp'people:	Joint initiatives targeting countries via the UN	Leverage assets eg World Malaria Day, Nadel exh'n,
		Identified Opp'ties	P&I Outside Africa	GPIRM launch	WMR	Plan calendar of activities	eg UN, AU, EU, US, parlit'ns, G20, WEF	EXD, GWAs, Board m'brs	AU briefings: Gva, Paris, London, NYC	Events, joint initiatives: Ldon, Paris, Brussels
		Potential Partners	WB, China, APMEN, MAWG	WHO, MAWG	WHO, MAWG	WHO, UN SE, GF, MAWG	AU, ALMA, MAWG	health p'ships, GF, MAWG	MAWG	MC, UK Gov, French Gov, MAWG
Priorities	**Topics**	***Why?***								
Funding - from donor & endemic countries	Attract new Donors	To increase funding	■		■	■	■	■	■	■
	Competitive environ't/Need to differentiate	To sustain and increase funding	■		■	■		■	■	■
	Economic Downturn	To sustain funding	■			■	■	■	■	■
	GF issues shadow	To distance from issues	■			■	■	■	■	■
Resource effi'cies	Disease diagnostics	For greater efficiencies				■				
Commod Access	Taxes & Tariffs elimination	Drops price of vector control				■		■		
	Pricing/AMFm	Access to medicines				■				
	Supply issues	Improves access		■		■				
Resist'ce (Drug & insect'de)	Client compliance & case mang't	Improve uptake	■	■		■	■		■	
	Counterfeits/monotherapies	Improve GPARC action	■			■	■	■	■	■
Surveill'ce	Funding	Increase as a priority	■			■				
	Tech Difficulties	New partners needed		■		■				
	Product performance	Cost effectiveness		■		■				
Elim'n & Resurg'ce	Sustained funding	Avoid future bigger issue	■	■		■		■		■
	Priority spending	Future scenarios to be clear	■	■		■	■	■		■

APPENDIX 14: LIST OF PEPFAR / WHO COUNTRIES

Over the reviewed period, WHO has funded survey implementation for 40 countries, of which 26 are PEPFAR countries and 6 are in PEPFAR regions (supported through COP money)



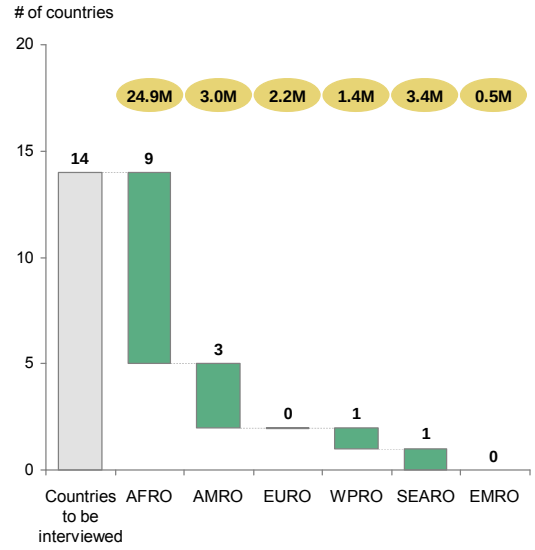
1. China, Laos and Thailand – China is also supported by WHO
2. Antigua and Barbuda, Bahamas, Barbados, Dominica, Grenada, Jamaica, St. Kitts and Nevis, St. Lucia, St. Vincent, Suriname, and Trinidad and Tobago
3. Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama – El Salvador, Guatemala, Honduras and Panama are also supported by WHO
4. Kazakhstan, Kyrgyz Republic, Tajikistan, Turkmenistan, and Uzbekistan

Source: PEPFAR, List of Countries, 2013, http://www.pepfar.gov/countries/ - Email from Silvia Bertagnolio, WHO, 23rd April 2014

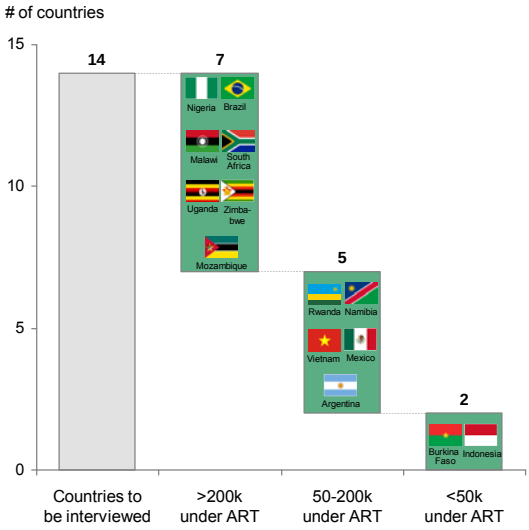
APPENDIX 15: SELECTION CRITERIA FOR COUNTRIES INTERVIEWED

Interviewed countries provide a view of all situations. Key selection criteria are geography, epidemics, number of ART patients and involvement in the strategy.

Balance between geographies

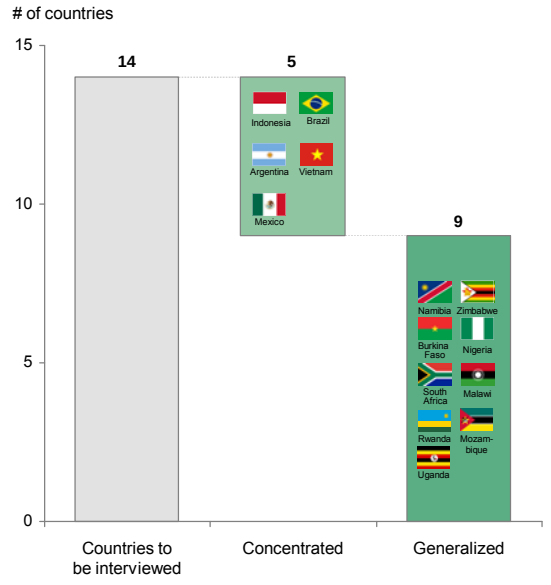


Balance between # of people under ART

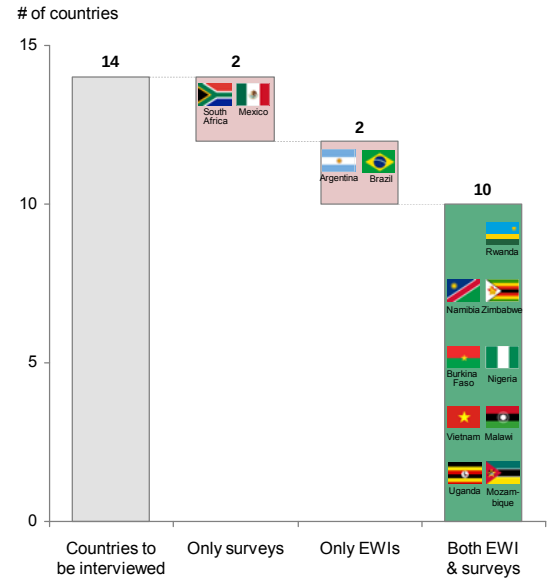


Source: WHO HIVDR 2013 Progress report, WHO HIV public database, BCG Analysis

Balance between epidemics types



Balance between HIVDR strategy involvement



Source: WHO HIVDR 2013 Progress report, WHO HIV public database, BCG Analysis

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APPENDIX 17: LIST OF ACRONYMS

ADR	Acquired Drug Resistance
ARV	Antiretroviral
ART	Antiretroviral Therapy
BMGF	Bill & Melinda Gates Foundation
CDC	Centers for Disease Control and Prevention
CHAI	Clinton Foundation HIV/AIDS Initiative
DBS	Dried Blood Spots
DFID	UK department for international development
DOTS	The Basic Package that Underpins the Stop TB Strategy
DRAM	Drug Resistance Associated Mutations
DRM	Drug Resistance Mutation
EWI	Early Warning Indicator
GLC	Green Light Committee
HAART	Highly active retroviral therapy
HSS	Health Systems Strengthening
IPT	Intermittent Preventative Treatment
IRS	Indoor residual spraying
ITN	Insecticide-Treated Nets
LIC	Low Income Country
LLIN	Long-Lasting Insecticidal Nets
LMIC	Lower-Middle Income Country
LPV/r	Lopinavir/ritonavir
LTFU	Lost To Follow-Up
M&E	Monitoring and Evaluation
M&ESS	Monitoring and Evaluation Systems Strengthening
MARPs	Most at Risk Populations
MDG	Millennium Development Goal
MDR-TB	Multidrug-Resistant Tuberculosis
MoH	Ministry of health
MOU	Memorandum Of Understanding
MTCT	Mother to Child Transmission of HIV
NAC	National AIDS committee
NAP	National AIDS programme
NDRL	National HIV Drug Resistance Laboratory
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PDR	Pre-treatment Drug Resistance
PEP	Post-exposure prophylaxis
PEPFAR	President's Emergency Plan For Aids Relief
PI	Protease Inhibitor
PMTCT	Prevention of Mother-to-Child Transmission
PrEP	Pre Exposure Prophylaxis
RBM	Roll Back Malaria
RDRL	Regional HIV Drug Resistance Laboratory
ResNet	WHO global HIVDR genotyping laboratory network (created in 2004)
SDRL	Specialized HIV Drug Resistance Laboratory
STB	Stop Tuberculosis
TB	Tuberculosis
TDR	Transmitted Drug Resistance
WHO	World Health Organization