HIV DRUG RESISTANCE

MEETING REPORT

WHO HIV DRUG RESISTANCE STEERING GROUP MEETING

OCTOBER 2013

World Health Organization

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1. BACKGROUND

In 2004, WHO and the United States Centers for Disease Control and Prevention (CDC), in collaboration with partners (HIVResNet), developed a global strategy for the assessment and prevention of HIV drug resistance (HIVDR). Between 2004 and 2010, 101 surveys to assess transmitted drug resistance were conducted in 30 countries, and forty surveys to assess acquired HIVDR were performed in 12 countries. These surveys have generated invaluable data, published in 2012 in *WHO's HIV Drug Resistance Report,* on the magnitude of HIVDR transmission and emergence in low- and middle-income countries and have put to rest concerns that the rapid scale up of ART would generate widespread drug resistance.

Nevertheless, lessons learned from this initial implementation phase and the evolution of ART programmes have highlighted important limitations of the first generation of surveillance methods. First, due to the limited coverage of antiretroviral therapy at that time, the first generation of HIVDR surveillance methods explicitly sought to monitor HIVDR levels in a circumscribed geographical area using conveniently selected sites to facilitate implementation. Although important as general markers of programme performance, the fact that results were derived from convenient samples in defined geographic areas limited the ability to inform national and global level decision making with respect to optimal treatment regimens at the population-level. Country experiences also made clear the challenges inherent to the prospective method used to assess acquired HIV drug resistance, particularly the high costs of maintaining a prospective cohort and issues with the quality and integrity of the clinical and demographic data collected.

In the light of these lessons, WHO launched in 2012 a consultative process to revise existing surveillance methods with a view towards simplifying their operational design and improving their feasibility and uptake. Revised methods were developed in consultation with a broad group of programme managers, technical experts and virologists.

In order to review the outcomes of this process, a meeting of the HIVDR Steering Group was held on 1-2 October, 2013 to discuss the draft revised methods and obtain the group's expert input and advice. The meeting also reviewed the governance arrangements of WHO's HIV Drug Resistance Network to optimize the Steering Group's functioning as WHO's key advisor on HIVDR issues.

2. MEETING OBJECTIVES

i. Review and provide feedback on the proposed revised methods for the surveillance of transmitted, pre-treatment and acquired drug resistance.
ii. Discuss governance arrangements of the WHO HIVDR area of work.

3. KEY EXPECTED OUTCOMES

The meeting's key expected outcomes were: (i) advice to WHO on the revised surveillance methods and (ii) agreement on the governance and structure of the HIVDR work.

4. MEETING PARTICIPANTS

WHO standard Declarations of Interest (DoI) forms were completed by Steering Group members. Four members declared potential conflicts of interest. Sergio Carmona has received research support from Roche for a research unit developing an assay that is still under validation and that has currently no commercial value. Annemarie Wensing received research and unrestricted educational grants belonging to the university as well as subsidized travel to international conferences and workshops, paid for by BMS, Gilead, Janssen, MSD, ViiV healthcare and Virology Education. Jonathan M Schapiro has served within the past four years as a consultant, advisor and has received honorarium and research support from Abbot, BMS, GSK, ViiV Healthcare, Pfizer, Janssen-Cilag, Roche, Gilead, Teva, Virology Education and Merck. Robert Shafer received and still receives remuneration for consulting from Celera and Siemens Health Care. He also received and still receives research funding from Hoffman LaRoche, Gilead Sciences, Bristol-Myers Squibb, Celera and Siemans Health Care. As none of these interests were deemed substantively conflicting with the meetings purpose and topics, the individuals declaring those interests were allowed to fully participate in the meeting.

5. SUMMARY OF DISCUSSIONS

5.1 Opening and election of the Chair

Dr. Joseph Perriëns, Coordinator, HIV Commodities and Technologies (HIV Department, WHO), opened the meeting. Avelin Aghokeng (IMPM-IRD/CREMER, Yaounde, Cameroon), was nominated Chair of the meeting and was accepted without objections by the group.

5.2 Rationale and overview of revised methods

The group was briefed on the rationale for the introduction of revised methods. The original surveillance methods, developed in 2005, were designed for an early phase of ART scale-up characterized by low ART coverage and limited number of individuals on ART. At that stage, ART was available only at a few selected sites, mostly in urban areas. To reflect this reality, the original HIVDR surveillance and monitoring strategy focused on sentinel sites and relied on convenient sampling to select sites where enrolment would be possible. The focus was on clinic functioning, and results were area/region-specific. Survey findings were designed as an alert that would trigger more in depth investigations.

However, availability and coverage of antiretrovirals have increased dramatically in low- and middle-income countries since 2003. As of December 2012, almost 10 million people were receiving antiretroviral therapy in 149 low- and middle-income countries, with over 800,000 pregnant women receiving ARVs for MTCT. ART is now accessible across more than 30,000 ART facilities worldwide. The roles and uses of antiretrovirals are being increasingly expanded, both for treating and preventing HIV infection, and a number of countries have already approved their use in the context of pre-exposure prophylaxis for specific populations.

In addition to profound changes in the landscape of ART scale-up, it was highlighted that the limited geographic coverage of results derived from the application of original methods hampered their utilization for national policy making. Restricting surveys to specific geographic areas also rendered challenging the identification of sufficient numbers of specimens for genotyping. Furthermore, the original statistical method, which relied on Lot-Quality Assurance Sampling (LQAS), generated considerable confusion about its classification scheme and objectives and was applied inconsistently across countries.

In view of these changes and lessons learnt, the new generation of HIVDR surveillance methods were designed to simplify and standardize data collection, to be of greater relevance for decision making, while being sufficiently flexible to be implemented in multiple epidemiological settings. The ultimate goal is to obtain nationally representative results that can inform national programming.

Broadly, the HIVDR surveillance strategy elements tabled for discussion at the steering group included the following 5 elements:

1. TDR: transmitted drug resistance in populations likely to be naive and have been recently infected
2. PDR: Pre-treatment drug resistance in populations initiating ART
3. ADR: Acquired drug resistance in populations receiving ART at different time points
4. HIV drug resistance surveillance in ART-naive children less than 18 months recently diagnosed with HIV using Early Infant Diagnosis (EID) testing
5. EWI: Early Warning Indicators for HIVDR

Within this architecture, TDR survey results are particularly useful to inform the selection of optimal pre-exposure prophylaxis (PrEP), post exposure prophylaxis (PEP) regimens, and on ART programme functioning to minimize HIVDR emergence and its transmission; PDR survey results inform the selection of optimal first-line combinations; and ADR surveys results inform the selection of optimal second-line regimens.

It was highlighted that, under certain circumstances, routine HIVDR testing may also be used to assess HIVDR prevalence at the population level. However, it was stressed that losses along the cascade of viral load testing and genotyping can lead to biased estimates and inappropriate public health decision making (see section 5.14).

5.3 Antimicrobial Resistance

Antimicrobial resistance (AMR) is a critical item in WHO's agenda, and WHO leadership in this area was endorsed by several resolutions of the World Health Assembly. The group was briefed on the current status and future directions of WHO's Programme on AMR. The organization's work in this area is coordinated by a Task Force, created in November 2011, and an AMR Action Framework 2013–2017 is currently being implemented. More recently, a Strategic and Technical Advisory Group (STAG) was established to review and help shape a global strategy to tackle the growing challenge of antimicrobial resistance and advise WHO on the coordination role it should be playing in the fight against AMR. Its first

meeting took place on 19–20 September 2013. It is expected that AMR will be discussed at Ministerial level at WHO governing bodies meetings in 2014, including the Executive Board and the World Health Assembly.

5.4 Roles of WHO in a global approach to HIVDR

An effective and coordinated global HIVDR surveillance framework requires clarity with respect to the roles played by the various institutions and partners active in the field. WHO is currently engaged in the following key activities in the HIVDR landscape, including:

- 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

A number of participants expressed their satisfaction at the work done and spearheaded by the WHO since the launch of the first generation of surveillance methods. At the same time, concern was expressed regarding the availability of resources to adequately perform all current activities, particularly with respect to capacity building and the management of the laboratory network. It was deemed imperative to have in place a realistic framework to ensure it can be actually implemented. In this respect, the role of WHO in the development of global-level guidance and coordination was stressed.

In an environment of increasing financial constraints, participants 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 HIVDR is currently an issue of decreasing importance in the United States and Europe, greater involvement of low- and middle-income countries is necessary.

Key points and next steps

- The development of normative work (guidance, tools, standards) should remain a WHO priority.
- WHO should continue to advocate for HIVDR surveillance uptake and implementation, including in national-level decision making.
- WHO plays an important role as a knowledge center for HIVDR. It is critical that its ability to collate data and report of the development of HIVDR be maintained. This requires sustainable approaches to data collection, data management (incl. quality control) and analysis and report writing in HIVDR.
- WHO's support for capacity building is important, but should be pursued in collaboration with other partners given financial and human resource constraints in WHO.
- It is critical to enhance communications with partners. The secretariat's intent to update the HIVDR website regularly was noted and welcomed.

5.5 Governance of WHO HIVDR work

5.5.1 Overview of presentation

A discussion paper on governance arrangements of WHO/ResNet HIVDR was presented and discussed. Previous governance arrangements were perceived to be too complex, leading to a lack of clarity about the scope of work of institutions involved in global HIVDR work. Thus, revised governance arrangements needed to be simplified and WHO's roles and responsibilities for the promotion of survey implementation and uptake clarified.

A draft proposal, tabled by the Secretariat, envisaged three main advisory bodies: (i) Steering Group, and two standing working groups: (ii) Epidemiology Working Group, (iii) Laboratory Working Group. The Steering Group would remain as the principal advisory group to WHO on HIV Drug Resistance, while the Epidemiology and Laboratory Working Groups would be the loci of technical discussions on their respective fields.

5.5.2 Summary of discussion

A number of participants highlighted that it was critical to specify whether the Steering Group was an advisory or an oversight body. Greater clarity was also needed on the timing and method of the Group's interaction with the Secretariat.

It was noted that attendance requirements were needed to avoid disrupting the workflow and expedite proceedings, and that members unable to attend consecutive meetings should be replaced. A number of participants identified the need for a smaller Core Group, who would interact more frequently with the Secretariat, addressing technical questions as they arise on a real-time basis.

A number of participants expressed concern that the boundaries between the Steering Group and HIVResNet should be more clearly delineated. It was clarified that 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. However, it

was also noted that the "HIVResNet" "brand" was well-known, and that it should be kept, even without formal membership. Affiliation with WHO was highly valued, and HIVResNet provided a loose engagement mechanism that was nevertheless appreciated by the broad and diverse community of HIVDR professionals.

With respect to working groups, greater clarity was needed on their membership and what skills should be represented (e.g., lab, ART, monitoring and evaluation). Participants also emphasized the need to avoid having working group split in knowledge silos without cross cutting collaboration and interaction. The importance of linking the Epidemiology and Laboratory working groups was highlighted. The issue of data management and survey data analysis was raised as an important component that should be addressed in the future as countries implement surveys.

The importance of regional representation was stressed to ensure the relevance of methods for each region, as well as the need for greater integration of HIVDR within national HIV Monitoring and Evaluation (M&E) frameworks. Participants further noted the importance of clear communications with the Steering Group to sustain engagement. Short emails should be distributed informing members of meetings, goals and their participation.

It was clarified that the Steering Group is an advisory body to WHO, as WHO's only governing bodies are the Executive Board and the World Health Assembly. Given the high transaction costs involved, the group decided that standing working groups were not needed, and that communications between the Secretariat and the Steering Group should be take place on a quarterly basis.

Key points and next steps

- The Steering Group is an advisory body to WHO – not a governing board.
- The Steering Group should remain relatively small (not bigger than the group convened on 1–2 October).
- A Core Group with a maximum membership of 5 people (excluding Secretariat) will be established to be consulted on a regular basis; this group should include some members of the Steering Group. The secretariat will make a full proposal and nominations.
- The steering group and secretariat will be supported by ad hoc working groups - not standing working groups, given their operational complexity.
- HIVResNet brand should be kept and participation should remain open.

5.6 Consultation process to develop revised methods for HIVDR surveillance

The group was briefed on the consultation processes between October 2012 and September 2013 that underpinned the development of the revised draft surveillance methods, including:

i. 18–19 October, 2012: WHO experts consultation in Geneva to discuss epidemiological and statistical issues in HIV drug resistance surveillance
ii. 3-6 March, 2013: HIVResNet Statistical consultation
iii. March-July, 2013: Consultation of programme manager and protocol "users" in 5 regional workshops: 1 covering Latin America and the Caribbean, 1 covering Asia and 3 covering Africa (Eastern, Western and Southern Africa)
iv. Ongoing: electronic communication and ad hoc meetings with HIVResNet members on selected key technical issues

The five regional consultation meetings were attended by 147 participants from 43 countries, including country programme 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 on (i) prevalence of viral load suppression at different time points (e.g., 6,12, 18, 24, 36, 48 and 60 months) and on (ii) prevalence of HIVDR by duration of ART, were also commissioned to inform the review process.

5.7 TB Drug Resistance Surveillance

A staff of WHO's TB Department introduced the group to the surveillance methods used for TB drug resistance. TB drug resistance surveillance was launched in 1994, with two objectives: (i) to estimate the magnitude of drug resistance, and (ii) to determine trends over time. The achievement of these goals rests on three principles: (i) accurate sampling to ensure it represents the population of interest, (ii) quality-assurance of laboratory results and (iii) differentiation between new and previously treated cases.

TB drug resistance surveillance relies on two main sources of data: (i) programmatic data and (ii) surveys (ad hoc studies to measure DR among representative samples). In the first case, data are collected in the context of routine service provision, but are assessed with respect to their coverage of case detection rate (positive culture) and drug susceptibility testing coverage among positive cultures. Based on certain coverage thresholds established by expert

consultations, they are divided into two "data quality" categories, and only category "A" data are accepted for WHO publication and reporting.

The sampling approach relies on probability proportional to size (PPS) method to ensure representativeness, with a minimum of 30 clusters, and between 10–40 patients sampled per cluster. As of 2012, 63 countries rely on programmatic data and 72 countries have implemented periodic surveys.

5.8 Transmitted HIV Drug Resistance (TDR)

5.8.1 Overview of presentation

The draft concept note on surveillance of transmitted HIV drug resistance was presented.

The revised approach for TDR surveillance seeks to estimate a national prevalence of drug resistance in ARV-naïve populations likely to have been recently infected (approximately within the last 3 years) by integrating TDR surveillance into ongoing or planned HIV surveillance activities (e.g., Demographic and Health Surveys/AIDS Indicator Surveys, ANC or PMTCT sentinel surveillance, bio behavioral surveys, etc). No changes to patient eligibility criteria were envisaged from the previous protocol. The duration and sites would be the same as the ones envisaged for the national HIV surveillance activity. Knowledge about TDR prevalence in a country is useful as a broad marker of programme performance in minimizing the emergence and transmission of HIV drug resistance, and to inform the likely efficacy of regimens for pre- and post-exposure prophylaxis (PreP and PEP).

In order to have interpretable results and to assess trends over time, an increased sample size is necessary, ideally over 200 specimens. Survey is designed to yield a point prevalence of drug resistance (overall and by individual drug class) with a corresponding 95% plausibility interval.

5.8.2 Summary of discussion

A number of participants invited the Secretariat to explore alternatives to currently-recommended eligibility criteria, such as incidence assays and other lab-based criteria, as age and CD4 cell counts may not be reliable markers of recent infections in many settings. Nevertheless, participants stressed the importance of balancing specificity with feasibility, as laboratory criteria may overly restrict the number of eligible specimens, thus rendering the implementation of TDR surveillance impossible.

Current TDR prevalence thresholds for public health action (less than 5%, between 5%–15%, and over 15%) were discussed and it was suggested that their basis should be further clarified. In this context, it was suggested that trends should also inform public health actions along with individual surveys results.

Participants expressed the need for greater clarity with respect to the relative relevance and priority of the different protocols. A number of Steering Group members stressed that greater emphasis should be placed on the

Key points and next steps

TDR is especially relevant to inform programme decisions on PrEP and PEP and to assess ART programme performance in minimizing HIVDR emergence and its transmission.

- When high levels of pre-treatment HIVDR are observed or when PEP/PrEP is adopted in national policy TDR can have a place in the overall HIVDR surveillance framework.
- TDR is especially relevant to inform programme decisions on PrEP and PEP and to assess ART programme performance in minimizing HIVDR emergence and its transmission.
- Where PrEP and PEP are not part of national programming, implementing the TDR protocol should be considered a relative priority, and greater emphasis should be placed on the implementation of pre-treatment and acquired drug resistance surveys.
- The revised approach seeks to integrate TDR surveillance within ongoing national HIV surveillance activities (e.g ANC or PMTCT-based HIV serosurveillance, or in DHS).
- An appropriate sample size is necessary (ideally 200+) to obtain interpretable results and to assess trends over time.
- The decision on whether to implement TDR surveillance should be informed by a prior assessment of its feasibility and relevance in the national context.
- Given the urgency to publish the PDR and ADR protocols, amendments to this protocol should not be given priority before December 2013.

implementation of pre-treatment and acquired drug resistance surveys, given their roles in informing optimal first-line regimens and in assessing the performance of programmes in achieving and sustaining viral load suppression and therefore preventing HIVDR emergence. Nevertheless, TDR should be kept as an element of the overall HIVDR surveillance and monitoring strategy, and it could be triggered by PDR/ADR results or by the introduction of a particular policy (e.g., PrEP) (see section 5.15).

5.9 Pre-treatment Drug Resistance (PDR)

5.9.1 Overview of presentation

The draft concept note on surveillance of pre-treatment drug resistance was presented. The primary objective of the revised approach is to produce a nationally representative estimate of HIVDR in populations initiating ART through a cross-sectional sampling of patients during a predetermined period. PDR survey results support national and global decision making regarding optimal first-line regimens. Surveillance of PDR represents a new stand-alone element within the broader HIVDR Surveillance and Monitoring Strategy. Previously, PDR surveillance was assessed in the context of the original prospective "Monitoring" protocol.

Operationally, the revised method relies on a method known as a two-stage cluster design similar to the approach followed for the surveillance of TB drug resistance. In the first stage, 10–30 clinics are sampled from a list of all clinics which initiate ART in the country based on probability proportional to size (PPS) sampling (or probability proportional to proxy size, depending on data availability), with each clinic ideally contributing equally to the overall sample size. Consecutive eligible patients are then enrolled until the patient quota is reached at each clinic, and the proposed maximum survey enrollment period is six months.

Given the significant differences in HIVDR prevalence levels expected to be observed among individuals initiating ART with and without prior ARV exposure, it is important to differentiate these populations. Two potential approaches were proposed to address this issue:

i. At the design stage, whereby a questionnaire at enrollment would identify eligible patients with, without and/or unknown prior ARV exposure. Operationally, countries wishing to survey patients with as well as without prior ARV exposure would need to collect two distinct samples (this option was developed in the concept note).
ii. At the analysis stage, whereby all eligible ART initiators would be enrolled regardless of exposure. A questionnaire would be applied at enrollment to identify prior ARV exposure status, and such information would be used to stratify outcomes at the analysis stage. The sample size would be based on the estimated prevalence of HIVDR among patients never exposed to ART, which would then be inflated to account for the proportion of individuals with or unknown prior ARV exposure.

Additional issues presented include what to do in the case of survey under-enrollment or difficult to access clinics, and special sampling strategies for countries with few ART clinics or eligible patients.

5.9.2 Summary of discussion

Participants welcomed the addition of this tool to the WHO HIVDR monitoring and surveillance strategy as a critical component of effective ART programme management.

A number of Steering Group members stressed the need for clarity with respect to the use of survey results, in particular whether they could be used to influence or change national treatment guidelines. At the global level, the Secretariat clarified that survey results will provide critical data to inform future revisions of global treatment recommendations and that they could be modified depending on observed levels. Additional mathematical modeling is planned for the next 12 months to better clarify recommended prevalence thresholds for public health actions.

Key points and next steps

- The secretariat was requested to revise the PDR protocol, taking into account the approach of enrolling all clients starting treatment, and subsequent stratification of the analysis for no prior, prior and unknown prior exposure to ART.
- Sample size calculations should be based on the estimated prevalence of HIVDR among patients without prior ARV exposure. This figure should be increased to account for the estimated proportions of patients starting treatment with prior or unknown exposure to ART so that the sample can be disaggregated at the analysis stage and statistically relevant sub-analyses can be performed.
- Proposed survey eligibility criteria are all ART starters at the clinics sampled regardless of exposure. Nevertheless, prior ARV exposure status should be assessed through an enrollment questionnaire, and this information should be used to inform post-hoc sub-analyses.

The group also discussed the two approaches for differentiating patients with or without prior ARV exposure. The first one was deemed operationally complex and the group supported the adoption of the second approach. A number of participants stressed the inherent uncertainty of using a questionnaire to ascertain prior ARV exposure, while others highlighted that it has already been successfully applied in several research and programme settings.

As in earlier sessions, the potential role of VL and HIVDR data routinely collected in the context of regular service provision was stressed, and additional work should be conducted to identify a suitable and robust framework to assess the quality and coverage of routinely reported programme data.

5.10 Acquired Drug Resistance (ADR)

5.10.1 Overview of presentation

The draft concept note on surveillance of acquired drug resistance was presented. ADR surveillance provides an opportunity to assess levels of virological suppression at the national level and is critical to support selection of optimal second-line ART regimens. Originally, ADR surveillance was assessed in the context of the prospective "Monitoring" protocol. Given the operational challenges and the costs associated with the recruitment and maintenance of a prospective cohort, the new method is based on a cross-sectional sampling of patients receiving ART at different time points.

Two different time points were proposed in the revised approach:

i. "early stage of ART exposure": adults who have been on fist-line ART for 12–24 months (18 ± 6 months)
ii. "late stage of ART exposure": adults who have been on first-line ART for 48–60 months (54 ± 6 months), which approximates the median time to switch to second-line ART

Each time point would require a different sample, of distinct sizes. The proposed approach had five key outcomes of interest:

1. Prevalence of VL suppression (VL<1000 copies/mL) among individuals sampled
2. Prevalence of VL suppression among individuals sampled, adjusted for non-retention
3. Prevalence of HIVDR among individuals sampled
4. Prevalence of HIVDR among individuals sampled and failing (VL>1000 c/ml)
5. Upper estimate of prevalence of HIVDR

By the very nature of the cross-sectional method, outcomes 1, 3 (which is the basis for all sample size calculations) and 4 would be calculated taking into account only individuals still attending clinics. Outcomes 2 and 5 attempt to correct for this "survival" bias by incorporating national or global data on retention in care to produce adjusted outcomes that reflect the proportion of individuals who can no longer be sampled because they have died, have been lost to follow up or have stopped ART.

5.10.2 Summary of discussion

The group reviewed critically which outcome should drive the survey's sample size calculations. A number of participants highlighted that, while information on the prevalence of HIVDR among people failing first-line ART is important, given that cross-resistance between first- and second-line regimens recommended within the public health approach is limited, that most patients in low- and middle-income countries are still receiving first-line combinations and that coverage of VL testing is still limited in most countries, nationally representative data on viral load suppression among individuals receiving therapy may be of greater relevance to assess programme performance. As such, the group agreed that outcome 1 (prevalence of viral load suppression), instead of outcome 3, should serve as the basis for the survey's sample size calculations. Confidence intervals for outcomes 3 and 4, therefore, would be calculated ex-post.

The use of retention data – as suggested in outcomes 2 and 5 – was also discussed. Some Steering Group members expressed concern that the use of non-representative national or global retention data to adjust cross-sectional "on-treatment" estimates derived from rigorous statistical techniques was not advisable. It was important, nevertheless, to assess the possibility of developing a retention-adjusted outcome 2 by leveraging retention data from the specific clinics sampled. It was stressed that retention is an EWI as well, and that such an approach would support EWI roll-out. With respect to outcome 5, it was suggested that it should be dropped due to the dearth of evidence to inform the necessary assumptions regarding HIVDR among non-retained individuals.

The group also discussed the proposed patient eligibility criteria. Three options were raised: (i) include only patients on first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, (ii) include all patients on first-line regimens, regardless of whether NNRTI- or protease inhibitor (PI)-based, or (iii) include all individuals presenting to care, regardless of line or regimen. In cases (ii) and (iii), a questionnaire would be applied to obtain information on current and previous regimens, and these would be used to stratify results and perform necessary sub-analyses by regimen type and/or line. It was suggested

Key points and next steps

- Outcome 1 (VL suppression among individuals sampled) should be the main outcome of this survey and should drive sample size calculations. Sample size calculation should therefore be recalculated.
- The secretariat should assess the possibility of developing a retention-adjusted outcome 2 by leveraging retention data from the specific clinics sampled. The statistical implications of using sampled clinics to assess retention and methods of patients sampling within each clinic should be explored.
- The confidence intervals of outcomes 3 (prevalence of HIVDR among individuals sampled) and 4 (HIVDR among individuals sampled with viral loads above 1000 copies/mL) should be calculated ex-post at the analysis stage based on the available data.
- In case individual country data are insufficient to develop national prevalence estimates, aggregation across surveys at the regional and/or global levels can be performed to obtain a sample of sufficient size.
- The survey's eligibility criteria should be more clearly defined to clarify whether it will include only patients on NNRTI-based first line, any first-line regimen or on any regimen (including first and second lines). Consideration should be given to a proposition to include all patients on ART, irrespective of regimen and line. In this case, the sample size could be increased, in line with the approach adopted for PDR, to ensure sufficient statistical power for stratified analyses to be performed post-hoc.

that consideration be given to including patients receiving PI-based first-line regimens, as well as patients with second-line exposure. In this case, the sample size could be increased, in line with the approach adopted for PDR, to ensure sufficient statistical power for stratified analyses to be performed post-hoc.

Additional issues discussed include:

i. use of regular programme data on HIVDR from patients switching therapy: it was noted that although switchers are the ideal population in which to assess HIVDR, operational and logistical difficulties often hinder reliable and timely case reporting and thus prevent this option from being adopted for the time being. Nevertheless, further clarity was needed on the use of regular VL and HIVDR data for surveillance purpose.
ii. representativeness of the survey in very large and diverse countries: large countries with many clinics should sample at least 20 clinics, and preferably more. In order to evaluate the pertinence of implementation of area-specific surveys within one country, countries should review their national epidemiological dynamics and assess whether policy changes can be applied at sub-national level.
iii. surveillance in children: it was agreed that an approach for ADR surveillance in children will be developed and incorporated into the ADR protocol in 2014.

5.11 Early Warning Indicators (EWI)

The Steering Group was briefed on the ongoing effort, led by WHO's HIV Department, to develop consolidated guidance on strategic information for the HIV health-sector response, including EWI. It is envisaged that a consolidated Guide, to be published by the AIDS Conference in July 2014, will contain three main elements: (i) a framework for strategic information in the health sector, (ii) a core set of strategic information elements and indicators ("what"), and (iii) guidance on the management and use of strategic information ("how"), supported by annexes/ companion booklet with detailed information, including on each indicator. Early Warning Indicators, which are a core element of WHO's HIVDR Monitoring and Assessment Strategy, are being considered within this broad consolidation effort, and the Steering Group will be kept abreast of new developments.

Key points and next steps

- Consolidation of EWI with health-sector M&E is ongoing.
- EWI for HIVDR are key for HIVDR prevention. They must be included and prioritized in routine health sector M&E plans.
- Targets for EWI 5 (VL suppression) must be redefined considering WHO's 2013 ART guidelines.

5.12 HIVDR surveillance in children less than 18 months recently diagnosed with HIV

5.12.1 Overview of presentation

The Steering Group was briefed on the experiences and lessons learned from piloting the protocol for the surveillance of HIVDR in children less than 18 months in Swaziland and Zimbabwe in 2011 and 2012. This protocol is based on a retrospective cross-sectional survey using remnant DBS specimens from Early Infant Diagnosis. Its main goal is to assess the prevalence of NRTI and NNRTI resistance in HIV-infected children according to prior exposure to PMTCT (with, without or unknown history of exposure to PMTCT) to inform optimal ART regimen selection and the feasibility of PI-sparing strategies.

In Swaziland, overall prevalence of HIVDR was found to be 35.3% (31.8% to NNRTI and 3.5% to NRTI). In Zimbabwe, overall HIVDR prevalence was considerably higher, at 62.9% (62.% to NNRTI and 12.5% to NRTI). Overall, these findings lend support to WHO's 2013 recommendations to treat all children less than 3 years with LPV/r-based first-line ART regardless of PMTCT-exposure, and reinforce the need to gather data on the prevalence of NNRTI resistance to inform the feasibility of PI-sparing strategies at the national level. In addition to Swaziland and Zimbabwe, the protocol is currently being implemented in Uganda, Mozambique, Nigeria, DRC, Togo and Malawi.

Key lessons learned include the need for guidance when the sampling strategy involves many EID laboratories, issues with specimen storage (e.g., time spent at room temperature) that affected the genotyping amplification rate, the lack or low quality of the epidemiological data collected to inform post-hoc sub-analyses, and the collection of more than one specimen per patient.

5.12.2 Summary of discussion

The Steering Group welcomed the successful implementation of the protocol in Swaziland and Zimbabwe as it demonstrated the protocol's feasibility and value, particularly as many countries are currently assessing whether to move to a LPV-based first line regimen. It also highlighted the importance of aggregating data across countries when national data are insufficient for the development of relevant estimates, particularly with respect to NRTI and PI mutations.

A number of participants expressed concern that, some countries, particularly those with low level epidemics, may be unable to reach the required sample size. It was suggested that the protocol should include guidance on what to do when, in spite of enrolling all eligible specimens and performing a de facto census, a country is still unable to reach the required sample size.

The possibility of increasing the survey's confidence interval was also raised as a way to improve its feasibility, given the high levels of expected HIVDR. The group also discussed the relative prioritization of HIVDR surveillance in infants vis-a-vis other elements of the HIVDR monitoring and surveillance strategy, and agreed that further guidance was needed, in particular on the use of this protocol in areas with low and concentrated HIV epidemics, and areas with generalized epidemics with lower HIV prevalence.

Key points and next steps

- Country experiences in countries with generalized epidemics and very high HIV prevalence demonstrate the protocol's relevance and feasibility.
- Guidance should be provided on how to perform and interpret the survey when a census is conducted and the sample size cannot be reached.
- Guidance is needed on the sampling strategy for countries with many participating EID laboratories.

5.13 Laboratory Network

The Steering Group received an update on the achievements to date and current status of the Laboratory Network, ongoing challenges and future activities. The laboratory network underpins the implementation of HIVDR surveillance in low- and middle-income countries, as it ensures comparable and high quality genotyping data. As of September 2013, 33 laboratories have met accreditation criteria and received WHO designation (see table).

Table: List of WHO-designated laboratories for HIVDR (as of September 2013)

Region	National	Regional	Specialized	TOTAL
AFRO	6	3	0	9
SEARO	4	0	0	4
WPRO	4	3	0	7
EURO	0	0	5	5
AMRO	1	4	3	8
Total	15	7	8	33

Key points and next steps

- DBS testing capacity should continue to expand.
- Viral load measurement from DBS: cut-offs and methods need to be clarified to inform discussion on measuring the EWI on viral suppression, taking into account the cut-off defined by WHO to assess treatment failure.
- Guidance on streamlining post-testing QA of sequence data needs to be used by all accredited labs.
- Alternatives to DBS (e.g.ViveST) need to be assessed to increase the specimen volume for HIVDR genotyping and, at the same, time preserving the field-friendly characteristics of DBS.
- The secretariat should initiate a discussion on the options available to sustain and expand access to high quality VL and HIVDR testing for surveillance purpose with the laboratory working group.

As Dried Blood Spots (DBS) is the preferred specimen type recommended in revised surveillance methods, it is critical to expand the number of laboratories accredited for DBS, and this is one of the programme's major challenges. Three laboratories have already been accredited for DBS, and an additional ten are actively working towards it. Critical obstacles are amplification sensitivity and assay validation.

In addition to expanding DBS testing capacity, future priorities of the Laboratory Network include streamlining post-testing quality assurance of sequence data, reducing genotyping costs, exploring alternatives to DBS and developing an operational research agenda to improve viral load measurement from DBS. Within this context, the sustainability of the Laboratory Network is also an issue of increasing prominence, and it will necessitate a joint approach from all partners involved in HIVDR surveillance. A discussion on the options available to sustain and expand access to high quality VL and HIVDR testing is therefore needed.

5.14 Use of programme data for decision making

5.14.1 Summary of discussion

Some large middle-income countries already recommend routine VL and genotype testing, often at pre-determined intervals, to monitor patient outcomes. Given their ready availability, these routinely collected data could be used to assess programme performance and inform optimal regimen selection. However, in many cases, only a fraction of patients who should receive a viral load test actually receive one, and inadequate viral load amplification rates mean that the proportion with a successful viral load test is further reduced. The same applies to patients with detectable viral loads for whom genotyping is indicated in national policy: an important proportion often does not receive a test, and among those who do, not all are successfully genotyped. These losses along the VL and genotyping cascade can significantly impair the representativeness of results. In the light of these issues, it was recommended that the Secretariat should explore approaches to optimize the use of programme data for decision making, and to develop a set of key criteria and thresholds, drawing from the relevant literature and the experiences of other health programmes, to assess the quality and representativeness of routine country data to inform policy making.

Summary and next steps

- Programmatic data can be a valuable source of information for decision making.
- In 2014, the secretariat will convene an ad-hoc working group to explore optimal approaches for using and analyzing programmatic data and will present its proposals on how to go about the use of those data for surveillance purposes at next steering group meeting.

5.15 Prioritization of the different strategy elements

5.15.1 Summary of discussion

Programme managers must allocate limited resources to competing programmatic needs, and a number of Steering Group members suggested that clearer guidance should be made available to countries to assist them in most effectively prioritizing the various elements of the HIVDR surveillance and monitoring strategy.

Generally, countries should be encouraged to scale up early warning indicators to all clinics so that they can become part of routine patient and programme monitoring. However, it was recognized that EWI must be placed within the broader context of M&E and quality improvement

frameworks to ensure the necessary buy-in beyond the HIVDR community, particularly from programme managers and decision makers.

Among the various survey components, a number of participants considered the survey of pre-treatment drug resistance to be the most critical due to its role in informing the choice of optimal first-line regimen, followed by the surveillance of acquired drug resistance as a critical source of information to assess the performance of programmes in achieving and sustaining viral load suppression and resistance prevention.

The surveillance of HIVDR in infants was clearly considered a priority, but its implementation should be informed by a prior assessment of feasibility. TDR would have a more limited role, and would be particularly relevant in contexts where PrEP is being introduced, or as follow-up survey triggered by worrisome levels of PDR and/or ADR.

Finally, as the capacity for VL testing and genotyping increases, the amount of programmatic data potentially useful for surveillance purposes is also increasing. The secretariat should therefore convene an ad-hoc working group to explore approaches for using and analyzing programmatic data in HIVDR surveillance.

Summary and next steps

- WHO should develop and provide guidance on which HIVDR surveillance activities and surveillance protocols should be prioritized in which setting and convene an ad-hoc working group to explore approaches for using and analyzing programmatic data in HIVDR surveillance.
- It was suggested that :
  i. EWI should be routinely collected at all clinics.
  ii. greater emphasis should be placed on the implementation of pre-treatment and acquired drug resistance surveys.
  iii. TDR plays a more limited role in the overall HIVDR surveillance framework (e.g., triggered by high levels of pre-treatment HIVDR or when PrEP is adopted in national policy).

6. NEXT STEPS AND TIMELINES

The steering Group agreed on the following key immediate next steps:

i. Intensified effort should be devoted in October and November 2013 to finalizing the PDR and ADR concept notes. The Steering Group should convene a teleconference prior to December 1 to be updated on the revision process of PDR and ADR concept notes.

ii. A technical brief on the design and costing of the various HIVDR surveillance elements is currently being drafted for use by Global Fund grantees, to be developed by 31 October 2013.

iii. An ad-hoc working group will be convened by the Secretariat to address the use of programme data for decision making after the ICASA conference in December 2013.

iv. The laboratory working group will be convened to review viral load thresholds and define a workplan to address the Network's capacity constraints.

ANNEX 1: AGENDA

DAY ONE: 1 October 2013

Time	Session topic/Presenter
8:30–9:00	Registration
Opening session	
9:00–9:15	Opening remarks and introduction Designation of Chair Review of agenda *Joseph Perriëns, Coordinator, HIV/TCO*
Session 1: HIVDR programme in a changing landscape – Past/future functioning of ResNet	
9:15–9:40	Changing landscape of HIV treatment and implications for HIVDR surveillance *WHO*
9:40–9:50	WHO programme on Antimicrobial Resistance – update on current status and future directions *Carmem Pessoa Da Silva, HQ/AIP, Antimicrobial Resistance Team*
9:50–10:30	Role of WHO in a global approach to HIVDR *All*
10:30–11:00	Coffee Break
11:00–12:30	Governance of WHO/ResNet HIVDR work *WHO* Q&A and way forward *All*
12:30–14:00	Lunch Break
Session 2: HIVDR Strategy elements revision	
14:00–14:20	Consultation process to revise HIVDR guidance documents *WHO*
Session 3: Learning from the experience of TB DR surveillance	
14:20–14:30	TB Drug Resistance Surveillance *Anna Dean, TB Department, WHO*
Session 4: Transmitted drug resistance	
14:30–15:40	Presentation of draft revision *WHO* Q&A and way forward *All*
15:40–16:00	Coffee Break
Session 4: Transmitted drug resistance	
16:00–17:15	Presentation of draft revision *WHO* Q&A and way forward *All*
17:15	End of day one

DAY TWO: 2 October 2013

Time	Session topic/Presenter
Session 1: Acquired drug resistance	
9:00–10:30	Presentation of draft revision *WHO* Q&A and way forward *All*
10:30–11:00	Coffee Break
Session 2: Early warning indicators	
11:00–11:30	Integration of Early Warning Indicators in the consolidated guidelines on M&E for the health sector response to HIV *WHO* Q&A and way forward *All*
Session 3: HIV drug resistance in infants and children	
11:30–12:30	Update on ongoing activities and plans for revision *WHO* Q&A and way forward *All*
12:30–14:00	Lunch Break
Session 4: HIVDR Laboratory strategy	
14:00–15:00	Laboratory strategy, quality assessment – options for the future *WHO* Q&A and way forward *All*
Session 5: Planned activities 2014-2015	
15:00–16:00	Prioritization of the different strategy elements *WHO* Q&A and way forward *All*
16:00–16:30	Coffee Break
Session 6: Next steps	
16:30–17:00	Summary of the meeting key conclusions & Discussion *All*
17:00–17:15	Wrap up and close *Joseph Perriëns, Coordinator, HIV/TCO*
17:15	End of day two

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