World Health Organization surveys to monitor HIV drug resistance prevention and associated factors in sentinel antiretroviral treatment sites

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The World Health Organization (WHO) estimates that >2 million people will have started antiretroviral therapy (ART) by the end of 2006. As the development of some HIV drug resistance (HIVDR) is inevitable in populations taking ART, the emergence of HIVDR must be balanced against the benefits of providing ART, including improved health outcomes and decreased HIV/AIDS-associated morbidity and mortality. ART programmes should operate to minimize the emergence of HIVDR in populations receiving therapy and HIVDR itself must be monitored to ensure ongoing regimen efficacy. ART regimens in resource-limited settings are usually selected at the national level following a public health approach: generally only one first-line regimen with alternate regimen(s) incorporating within-class drug substitutions are available in the public sector. The WHO has developed a population-based HIVDR assessment and prevention strategy, which includes standardized HIVDR monitoring surveys in populations receiving first-line ART at sentinel sites. The WHO surveys monitor HIVDR prevention in sentinel sites by utilizing a standardized, minimum-resource prospective survey methodology to assess the success of adult and paediatric ART sites in preventing HIVDR emergence during the first year of ART. The surveys also identify associated factors that can be addressed at the level of the ART site or programme. WHO HIVDR monitoring surveys are designed to be integrated easily into a country's ongoing, routine HIV-related evaluation activities. Performed regularly at representative sites, the data generated will inform evidence-based decision making regarding national and global ART regimen selection and minimize the emergence of HIVDR at a population level.

Introduction

In 2001, an analysis of resource needs prepared for the United Nations General Assembly Special Session on HIV/AIDS determined that, with optimal funding and technical capacity, access to life-saving antiretroviral therapy (ART) in developing countries could be achieved [1]. In the same year, the United Nations General Assembly Special Session on HIV/AIDS recommended that antiretroviral (ARV) drugs be made available in resource-limited countries to address the disparity in ART access between rich and poor countries. Following this recommendation, the World Health Organization (WHO) elaborated public health guidelines for the implementation of ART in resource-limited settings. Key components of these guidelines include the standardization and simplification of ARV regimens, the use of scientific evidence to support treatment protocols and avoidance of substandard regimens associated with treatment failure and HIV drug resistance (HIVDR) [2].

Treatment guidelines for most resource-limited countries are based on WHO guidelines. These guidelines specify one first-line ART regimen using two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) to support a non-nucleoside reverse transcriptase inhibitor (NNRTI) with one or two alternate regimens (single-drug substitutions for toxicity or drug–drug interactions); and generally, only one second-line regimen based on a boosted protease inhibitor. ART treatment is provided using a population-based approach rather than by individual patient management. International organizations, including non-governmental organizations, have agreed on a standard minimum set of information elements that are to be recorded for all ART patients to support care of the individual patient and population-based monitoring of ART scale-up [3,4]. By the end of 2006, the WHO estimated that 2.015 (1.795–2.235) million people with

HIV were receiving ART in low- and middle-income countries, representing around 28% of the estimated 7.1 million people in need of treatment [5].

Because of the error-prone nature of HIV replication, its high mutation rate in the presence of drug-selective pressure and the need for lifelong treatment, some HIVDR will occur among patients receiving treatment even when appropriate first-line regimens are provided and optimal adherence to therapy is supported [6]. As access to ART expands, it may be anticipated that HIVDR will emerge in populations receiving ART. Because ART prescribing in resource-limited countries is population-based rather than based on the model of individual patient management utilized in resource-rich countries, WHO's strategy to minimize HIVDR includes surveys at representative sentinel clinics to assess the extent to which HIVDR is being prevented at the population level and to identify potentially associated factors for which interventions can be made at the level of the site or programme. The surveys will provide information to evaluate the continued efficacy of standard regimens and pinpoint the areas of programme functioning requiring increased support to prevent HIVDR [7].

The WHO recommends that sentinel surveys be initiated in one to four pilot sites in a country under the direction of the Ministry of Health HIVDR working group. These surveys can then be expanded to representative sites throughout the country as part of routine public health activities. The assessment collects information on baseline characteristics, interim measures and outcomes of the first year of ART for a cohort of patients at each site. This data can be used to assess the extent to which each site is functioning to prevent the emergence of HIVDR and to evaluate the patterns of HIVDR that do emerge. The goal is to perform the surveys routinely with minimal disruption to the functioning of treatment programmes. After the pilot year, countries implement a rolling 3-year cycle of sentinel HIVDR prevention surveys. The plan should select 15–30 representative ART sites (fewer in countries with small numbers of ART patients). Five to 10 sites are surveyed yearly for each of the 3 years; in the fourth year, the cycle starts again with the sites surveyed in year 1. Site selection should not be made based on ease of availability of information, staff expertise in research or ease of collection and processing of specimens, because site characteristics may not be representative of the situation at other sites and, thus, are unlikely to yield results that can be generalized.

Potential survey funding comes from the country itself, the Global Fund, the WHO, the United States Centers for Disease Control and Prevention, and other international non-governmental organizations. A more detailed description of other aspects of the overall WHO strategy to minimize the emergence of HIVDR is found in the general strategy article published in this supplement [8].

Conducting WHO sentinel HIVDR prevention surveys

Objectives

The survey has several objectives: to estimate the proportion of patients starting ART at each site who achieve HIVDR prevention (defined by viral load suppression at 12 months after starting first-line ART); to identify specific HIVDR mutations and mutation patterns in populations not achieving prevention of HIVDR at 12 months or before the switch to second-line therapy; to collect and analyse data on factors potentially associated with the prevention or emergence of HIVDR that can be addressed at the ART site and programme level; and to report and disseminate results along with recommendations. Results permit a country's HIVDR working group to develop evidence-based recommendations to support optimal ART programme functioning at sentinel sites, to apply lessons learned to other ART sites, to suggest further studies or evaluations to provide additional information on factors associated with HIVDR emergence, or methods for optimizing programme functioning, and to support site-level and country-level decision making to optimize ART effectiveness. Sentinel survey time points and other concepts are defined in Box 1.

Patients

Starting on a randomly selected start date, 96 patients consecutively initiating ART at a sentinel site, together with a number of additional patients to reflect transfers out and deaths (specified as the number of transfers out and deaths in the previous year/100), are enrolled after an informed consent process. Patients eligible for the adult surveys are consenting patients who initiate an adult ART regimen at a participating site, regardless of age, unless the national policy specifies an age restriction. Paediatric surveys require consent of a parent or guardian; eligible participants are children initiating a paediatric regimen at a participating site.

Because it is important to assess the extent to which patients starting first-line ART have previous ARV experience, which could affect ART outcomes, patients who have had previous mono- or dual-therapy, have taken one or more ARV drugs for prevention of mother-to-child transmission (PMTCT) of HIV or who have acquired ARV drugs informally, are also included. The extent of previous ARV experience and its effect on outcomes is analysed [9,10].

Laboratory assessments

Sequencing of the relevant reverse transcriptase and protease regions of the HIV-1 *pol* gene is performed for

Box 1. Sentinel HIV drug resistance monitoring time points and definitions

Baseline
- Defined as the time of commencement of first-line ART. Baseline specimens should be collected within 1 month prior to starting ART.

Endpoint
- Defined as the time when the patient can be classified into one of the categories below; still on a first-line ART regimen 12 months after commencement of first-line ART; time of switch from a first-line to a second-line ART regimen during the first 12 months after commencement of first-line ART; time of stop of the first-line ART regimen during the first 12 months after commencement of first-line ART; time of first classification as lost to follow-up during the first 12 months after commencement of first-line ART; time of death during the first 12 months after commencement of first-line ART. An outcome evaluation is performed when a patient reaches an endpoint.

Switch
- Defined as the change from a first-line to a second-line ART regimen and is consequent on the failure of first-line therapy, as defined in national ART guidelines.

Substitution
- Substitution for reasons of toxicity or drug–drug interactions is defined as the change from the standard first-line ART regimen to an alternate first-line ART regimen: one drug is substituted for another within the same class. For the purposes of HIVDR monitoring, the new regimen instituted at time of substitution is recorded in the database and can be analysed, but this is not an endpoint; the patient will continue to be followed until an endpoint event.

Transfer out
- Defined as the transfer of HIV care from the HIVDR monitoring site to another identified ART delivery site for patients who have not stopped first-line ART at the time of transfer.

Death
- Death refers to the recorded death of a patient for which a date (at least month and year) is recorded within 12 months following the start of first-line ART.

Stop
- An ART stop for the purposes of HIVDR monitoring is defined as the complete cessation of ART by a patient who has not restarted ART by the time of the 12-month blood draw, although he or she remains in care at the site. Stops usually take place because of a patient decision or a decision by the clinical team. Stops generally reflect either a planned treatment interruption of ART or a decision based on poor adherence. Operationally, 'stop' is defined as the endpoint if a patient still attending the clinic has taken no ART in the 30 days before the 12-month blood draw.

On first-line ART at 12 months
- A patient is defined as still on first-line ART at 12 months.

Loss to follow-up
- A patient is defined as 'lost to follow-up' if he or she has not returned to the clinic or pharmacy for a scheduled appointment or drug pick-up >90 days after the missed appointment/drug pick-up and there is no information to classify the patient in one of the other endpoint categories, such as 'death' or 'transfer out.'

ART, antiretroviral therapy; HIVDR, HIV drug resistance.

all participants at baseline and HIV RNA quantification (viral load testing) and genotyping (HIVDR testing) is performed at the endpoint for patients who switch to second-line and those who remain on first-line ART at 12 months. Remnant specimens from blood drawn for clinical purposes are utilized whenever possible. Generally, residual blood from specimens drawn for routine $CD4^+$ T-cell counts at baseline, before switch as first-line failure is confirmed according to national guidelines, and at 12 months can be used. Either plasma specimens or dried blood spots are collected; a complete description of specimen collection, handling, and processing can be found in the generic survey protocol [9]. For WHO surveys to monitor HIVDR prevention, low, intermediate or high levels of resistance as determined by the Stanford algorithm are used to define HIVDR [11,12]. For survey purposes, successful viral suppression is defined as an HIV RNA level <1,000 copies/ml using a quality-assured viral load assay. A cut-off of 1,000 copies/ml is used because transient viraemia or blips are not typically associated with the development of HIVDR and, importantly, are not associated with virological or clinical failure of previously adequate ART [13]. Viral load and HIVDR testing should be performed at regional or national WHO accredited laboratories; additional information regarding the WHO laboratory strategy can be found in the laboratory document published in this supplement [14].

Data collection

Variables collected include only elements recommended in the internationally agreed list of basic ART patient information [3], with the addition of one standardized question on adherence in the past 30 days based on a visual analogue scale (VAS) to be asked at the endpoint

[15]. The minimum dataset for each participant includes several factors: information on previous ARV use (at sites where previous use is not collected routinely in a standard format, a short supplemental questionnaire is to be used at baseline to collect this information). Previous ARV use is assessed at endpoint using a standardized questionnaire; clinical status at ART start; regimens prescribed at start and at substitution or switch; appointment-keeping and drug pick-up regularity; adherence; and the endpoint category into which the patient can be classified 12 months after ART start or earlier. Paediatric surveys collect mother's ARV experience during pregnancy and breastfeeding. Data from individual laboratory assessments are also recorded. Weight is recorded in children so that the assessment of prescribing practices can include appropriateness of ARV doses for weight.

At the site-level, information is collected at the start and end of the assessment. The information includes standard regimens in use at the site, the numbers of patients, provider-to-patient ratio, cost to patient (if any) for clinical services including ARVs, other barriers to continuous ARV access and drug supply continuity.

Factors to be analysed for association with HIVDR prevention or emergence are listed in Box 2. Data routinely collected from medical records, pharmacy records and supplemental data are summarized in Box 3. As illustrated in Figure 1, HIV viral load testing, HIVDR testing and data extraction are performed at baseline and at endpoints. Major HIVDR outcomes are described in Box 4.

Surveys are supported by a simple shareware database application supplied by the WHO for data collection and analysis. The application includes demographic and clinical variables required for each survey, as well as a linked module that takes in, cleans and interprets HIV *pol* gene nucleotide sequences. At the regional level, the

Box 2. Patient factors assessed for association with HIV drug resistance prevention or emergence*

Patient factors

- Previous ARV experience (PMTCT, HIV mono- or dual-therapy, etc.) before first-line ART.
- Baseline HIVDR mutations.
- ARV drugs used.
- On-time drug pick-up as a percentage of the expected value (provides a surrogate marker of adherence to prescribed ARV regimen).
- On-time ART clinic attendance as a percentage of expected value (proivdes a surrogate marker of adherence to the prescribed ARV regimen).
- Adherence to first-line ART as measured by the visual analogue scale.
- Pill count (if routinely performed as part of routine clinic practice).

ART site factors

- Provider-to-patient ratio.
- Adherence support and follow-up.
- Factors affecting ARV access (drug, treatment and laboratory costs; distance and transport to clinic, clinic hours and waiting times).
- Drug supply continuity: pharmacy stock-outs.
- Prescribing guidelines and practices.
- Drug quality (if assessed as part of programme monitoring).

*Additional factors such as other clinical conditions or other medications may be collected if available. ART, antiretroviral therapy; ARV, antiretroviral; HIVDR, HIV drug resistance; PMTCT, prevention of mother-to-child transmission.

Box 3. Routinely collected data for HIV drug resistance sentinel monitoring: data sources and extracted variables

Medical records

- Previous ARV experience, start date, prescriptions, adherence, appointment scheduled and attended, death, loss to follow-up, transfer out on first-line regimen, stop, switch of regimen, new WHO stage 3 or stage 4 events and $CD4^+$ T-cell count.

Pharmacy records

- ARV regimens picked up and pick-up dates.

Supplemental data

- Viral load at endpoint.
- Genotyping of blood specimen at baseline and defined endpoints.
- Supplemental question at baseline (if data not routinely collected) and endpoints on pretreatment ARV use.
- Visual analogue scale [15] to assess 30-day adherence at endpoint.

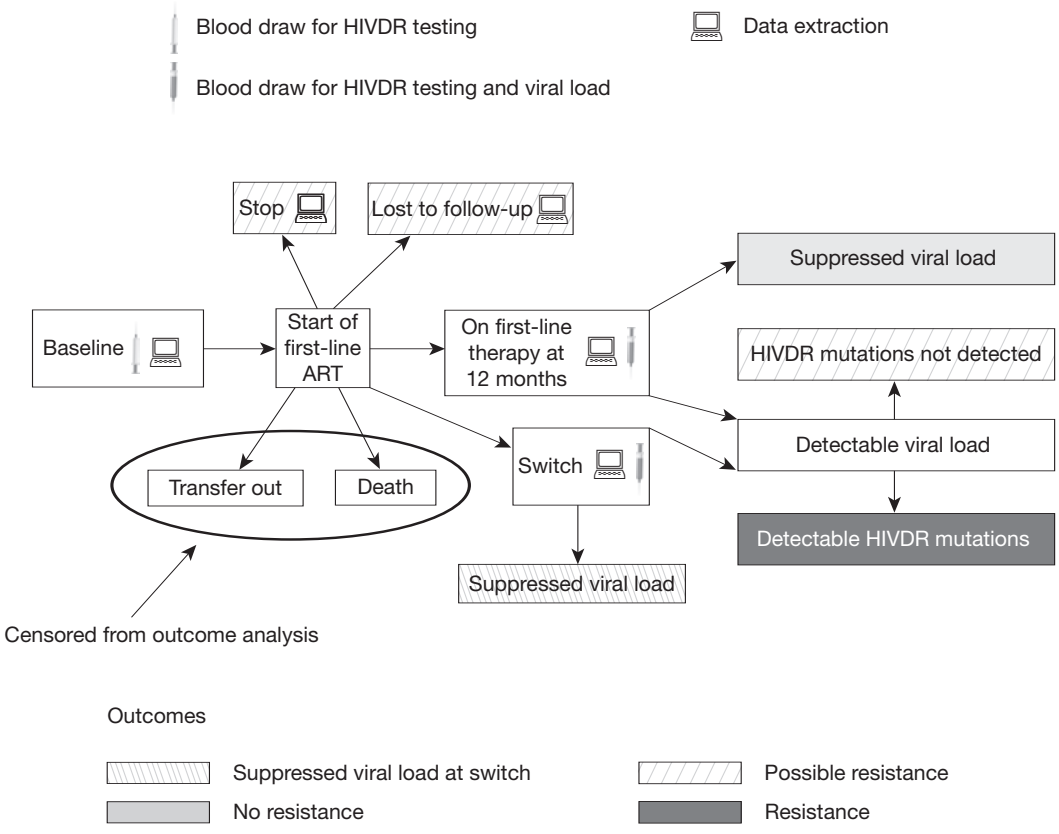
ARV, antiretroviral; WHO, World Health Organisation.

software automatically performs quality checks of sequence data as part of the laboratory quality assurance system; at the country-level, the software produces automated reports and exports more complex datasets for analyses to provide population-based HIVDR estimates linked to the ART program.

Classification of endpoints

At 12 months, or at time of switch to second-line ART, patients who began ART in the sentinel cohort are classified according to endpoint and laboratory results. Four possible outcomes are used: HIVDR prevention (viral load suppression), possible HIVDR, HIVDR and suppressed viral load at switch. The majority of patients will be on their first-line or alternative first-line regimen with undetectable viral load and their outcome is thus classified as HIVDR prevention. The outcome of patients who switch within the first year and are found to have a suppressed viral load at the time of switch is simply noted as suppressed viral load at time of switch. These switches are likely to have been clinically inappropriate and premature and may require programmatic review. Patients who have been lost to follow-up or who have stopped ART within the first 12 months and from whom no specimens are available for classification, are classified as having possible HIVDR. Outcomes of patients found to have detectable viral load and relevant HIVDR mutations are classified as HIVDR [11,12]. Because death in the first year of treatment is unlikely to be attributable to HIVDR and

Figure 1. WHO HIVDR prevention survey timepoints and outcomes



A schematic overview of the HIV drug resistance (HIVDR) prevention survey timepoints and outcomes. A cohort of approximately 100 patients is consecutively selected for HIVDR sentinel monitoring. Baseline data collection and HIVDR testing are performed. The vast majority of patients will be expected to be alive and still on first-line antiretroviral therapy (ART) at 12 months after initial start of ART, and thus eligible for viral load and genotypic testing. Data and specimen collection for viral load and genotypic testing are performed at the endpoints of switch and on first-line therapy at 12 months; data collection is also performed at the time of first lost to follow-up and stop. Efforts are made using existing defaulter tracking systems at ART delivery sites to properly identify and classify other endpoints. Patients with viral suppression at the endpoint on first-line therapy at 12 months are classified as having no HIVDR. Patients having an undetectable viral load at the endpoint switch are classified as suppressed viral load at switch. These switches are likely to have been clinically inappropriate and premature and may require programmatic review. Patients with detectable viral loads at the endpoint on first-line therapy at 12 months and with no HIVDR mutations are classified as having possible HIVDR. Likewise, patients who have stopped or have been lost to follow-up are classified as having possible HIVDR. Patients with detectable viral loads and HIVDR mutations at switch or on first-line therapy at 12 months are classified as having HIVDR.

because outcomes for patients transferring out cannot be used to assess the functioning of the ART sentinel site, patients with these endpoints are censored from the numerator and the denominator for the prevalence estimate of HIVDR prevention at 12 months (Box 4).

Analysis

HIVDR prevention

A target of ≥70% HIVDR prevention, as defined by viral suppression at 12 months, is a suggested target for each sentinel site. At the level of the site, factors associated with HIVDR prevention and emergence will be analysed. Examples of potentially associated patient factors include previous ARV experience, baseline HIVDR mutations, regimen taken, on-time drug pick-up and other surrogate measures of adherence (Box 2). Site characteristics potentially associated with HIVDR to be analysed include drug supply continuity and adherence support (Box 2). Patient- and site-associated factors will be scrutinized to generate hypotheses for planning of additional assessments to support interventions.

HIVDR resistance

At endpoint, resistance to specific drugs will be classified as low, intermediate or high according to the Stanford HIV Drug Resistance Database [11,12]. The association of patient factors and site characteristics with drug resistance levels and specific mutation patterns will be analysed.

Discussion

Because in resource-limited countries ART is usually delivered according to a public health approach [4], the prevention and emergence of HIVDR is best assessed at the population level. Sentinel HIVDR prevention surveys use a minimum resource methodology that easily integrates into countries' ongoing routine HIV surveillance and monitoring activities and make use of routinely collected clinical data supplemented by HIV genotyping and viral RNA quantification. To conserve resources, the WHO HIVDR sentinel monitoring strategy requires a single endpoint viral load and HIVDR evaluation at start of ART and 12 months after ART begins, or earlier if a switch to second-line therapy occurs before 12 months. WHO HIVDR prevention surveys assess factors that can be abstracted from patient information recorded routinely at most ART sites in resource-limited countries. On the basis of this information, public health action can be taken on an ART programme or on a multiprogramme basis at the country-level to address problems or difficulties revealed by assessment of these factors.

The rationale for a 1 year monitoring period is that although testing after 3–6 months of ART may be sufficient to evaluate the initial efficacy of an ART regimen, it is insufficient to evaluate programme effectiveness: that is, in retaining patients in care and successfully continuing to deliver ARVs to prevent emergence of

Box 4. Sentinel HIV drug resistance monitoring: HIV drug resistance outcomes

HIVDR

- Defined as the presence of one or more major mutations associated with resistance to one or more drugs in the standard first-line regimen(s) in use in a geographic setting or a combination of other mutations at baseline or at endpoint as specified by the Stanford HIV drug resistance database [11,12].

Possible HIV drug resistance

- Patients still taking their first-line or alternative first-line regimen 12 months after starting ART, with a viral load >1,000 copies/ml and no evidence of HIVDR on genotype testing at a defined endpoint, are classified as having possible drug resistance. This is because these patients likely had less than optimal adherence to their prescribed regimen and may have HIVDR mutations present at a level not detectable by standard genotypic analyses. Patients lost to follow-up or who stopped ART within the first 12 months of starting a first-line regimen, and from whom no specimens are available for testing, are also classified as having possible HIV drug resistance.

HIVDR prevention

- Defined as a patient with HIV RNA <1,000 copies/ml on viral load testing obtained from a patient still on first-line ART 12 months after initiating ART.

Suppressed viral load at time of switch

- Individuals having undetectable viral load at time of switch are classified as having 'suppressed viral load at time of switch.' These switches are likely to have been clinically inappropriate and premature and may require programmatic review.

HIVDR not classifiable

- Patients whose endpoint is transfer out or death cannot be classified with regards to HIVDR. Patients dying in the first year of ART are unlikely to have died due to drug-resistant HIV and patients who transfer out from one ART delivery site to another remain linked into care and therefore may be assumed to be receiving ART. Thus, transfers out and deaths are removed from the numerator and denominator before the estimation of the prevalence of HIVDR at a defined endpoint.

ART, antiretroviral therapy; HIVDR, HIV drug resistance.

HIVDR. Factors potentially influencing the emergence of HIVDR include rates of non-retention in care (losses to follow-up), irregularities with appointment keeping or drug pick-up and discontinuities in drug supply. Losses to follow-up and waning of patient adherence to prescribed regimens may also be more likely to occur after the first 6 months. The WHO believes the HIVDR prevention surveys provide the optimum information on ART programme functioning and its relationship to HIVDR, given limited resources. Where additional resources are available, the WHO survey methodology may be embedded in more extensive research-level studies: an example of successful integration of the WHO methodology is found within the Treat Asia Network's and PharmAccess' HIVDR monitoring strategy [18,19]. Additionally, WHO HIVDR prevention surveys may also be extended to encompass the second and third year of ART as national ART scale-up programmes evolve and look beyond the start-up phase.

Because populations achieving viral suppression, as measured by HIV RNA quantification (viral load testing), are less likely to develop HIVDR, viral suppression at the population level is an important measure of HIVDR prevention. Populations of patients achieving viral suppression during first-line ART at the time of the viral load evaluation are considered for the purposes of the survey to have no 'effective' HIVDR, that is, no HIVDR mutations that are currently compromising regimen efficacy [13]. Previous ARV experience and baseline drug resistance are key indicators that inform the interpretation of HIVDR prevention and HIVDR mutations present after 12 months of first-line ART. Given the limitation of HIVDR testing in detecting mutations present in viral quasispecies at low frequencies [20], a population with a history of experience to a specific drug (or drug class in the case of NNRTIs) is considered as having potential archived resistance to that drug or drug class, which in turn may influence patient and programmatic success of viral suppression.

The WHO-suggested standard for successful HIVDR prevention is site and programme achievement of ≥70% viral suppression in populations after 1 year of first-line ART. This standard represents a consensus of international experts and takes into account the literature demonstrating that well-functioning ART programmes can achieve ≥70% viral load suppression in resource-limited settings [16,17], which is comparable to that achieved in resource-rich settings. The 70% threshold for HIVDR prevention provides a benchmark against which ART programme function can be compared.

The use of the standardized WHO prospective survey methodology is recommended over the use of a cross-sectional methodology, which would not allow measurement of baseline mutations and the evaluation of previous ARV experience in all patients starting ART, including those who are lost to follow-up or those who stop ART before a cross-sectional survey takes place. Cross-sectional surveys also cannot evaluate drug resistance in patients with first-line treatment failure just before a switch to second-line ART. Additionally, this standardized methodology attempts to minimize biases introduced by cross-sectional studies of convenience samples, which may over- or underestimate HIVDR emergence and could lead to inappropriate public health action.

Surveys to monitor HIVDR prevention inform HIVDR working groups about site facts associated with the emergence of HIVDR in populations on treatment and about programme function. Results support working groups to take appropriate corrective action to minimize HIVDR. By virtue of providing actionable results, the sentinel HIVDR monitoring survey method distinguishes itself from observational studies of HIVDR and from other large international cohort studies evaluating regimen efficacy and/or in-depth analyses of the relationship of such factors as adherence and HIV-1 subtype to ART response. The WHO HIVDR prevention survey methodology is meant to complement rather than replace such research studies. Countries may contribute multisite survey results to meta-analyses that focus on such research questions, and survey results may also generate research hypotheses for more detailed study. If countries agree, some data elements will be contributed to the WHO global HIVDR database for use in a variety of analyses.

The factors assessed in the surveys are factors that are relatively easily collected from routine medical records and which have been demonstrated to be associated with the prevention or emergence of resistance. Adherence to prescribed ART has been shown to greatly influence the development of HIVDR [21,22]. In each sentinel ART site, several measures of adherence are used: patient self-report using the VAS and pill count (if performed routinely); the proportion of patients picking up their ART on time during the first 12 months of therapy with late refills as a marker of incomplete adherence [23]; and the proportion of patients keeping their regular appointments [23].

Additional site and programme factors include continuity of drug supply assessed using pharmacy stock records and drug shipment logs and the extent to which ARV prescribing practices differ from national prescribing guidelines, as determined from medical and pharmacy records. Although the distribution of ART may be difficult in many resource-limited countries [24], the continuity of ARV supplies is a crucial measure in ensuring uninterrupted ART and in preventing HIVDR [25]. Information on potential barriers to ART continuity, such as cost of treatment

and drugs and the extent to which patients must travel to reach the ART site, are also collected. Finally, national AIDS-coordinating authorities should promulgate treatment guidelines commensurate with international standards and monitor programmes to ensure their use [7,26]; therefore, prescribing practices are assessed to ensure that regimens that could create HIVDR are not used [7].

At survey sites achieving ≥70% HIVDR prevention, factors associated with successful prevention of HIVDR will be assessed. An analysis will also be performed to assess potentially associated factors among the survey population not achieving HIVDR prevention. Important lessons learned from sites achieving ≥70% HIVDR prevention may be qualitatively generalized to other similar ART sites.

At sites achieving <70% HIVDR prevention, the analysis will focus on the identification of factors that could have contributed to lack of HIVDR prevention in the survey cohort. A rapid assessment will take place at each site regarding further investigations, including research studies if necessary, and measures will be put in place to better support ART programme functioning and HIVDR prevention at both the effected survey site and other sites. Factors to be addressed could include drug supply discontinuities, non-standard prescribing practices, previous ARV experience among patients starting first-line ART or other factors associated with lack of access, non-adherence and loss to follow-up. Lessons learned at sites achieving <70% HIVDR prevention may be qualitatively generalized to other sites; this qualitative generalization of results permits a country's entire ART programme to benefit from the surveys. Specific recommendations for action depend upon mutations observed and their distribution patterns within the survey cohort. Examples of action may include the consideration of alternate regimens for patients with specific histories if, for example, specific mutations are associated with PMTCT or other previous ARV experience. Additionally, if specific mutations are associated with prescribing practices that differ from national prescribing guidelines, the national HIVDR working group may consider training or other measures to standardize the prescribing of ART.

The WHO HIVDR sentinel monitoring strategy has been well received by country working groups. Several countries including Burundi, Haiti, India, Malawi, Mozambique, Nigeria, Swaziland, Tanzania, Thailand, Vietnam and Zambia are planning or implementing HIVDR prevention surveys.

Both nationally and globally, implementation of plans for universal access to ART using a public health approach should include a systematic and standardized evaluation of HIVDR coupled with appropriate public health actions to limit its emergence. To achieve these goals all countries scaling-up ART should implement national HIVDR strategies before drug resistance becomes a widespread problem. Surveys to monitor HIVDR prevention make up one of the key three HIVDR assessment elements recommended by WHO to resource-limited countries, which also include HIVDR early warning indicators to be monitored at all ART sites and surveys of transmitted HIVDR. The WHO methodology to monitor HIVDR prevention at sentinel sites is a global standard that easily integrates into existing patient and programme monitoring activities in countries rapidly scaling-up ART delivery. Integration of these minimum resource surveys into national programme activities will provide important and crucially needed data.

Results from all three WHO assessment elements will provide national working groups and key decision makers with data to support evidence-based recommendations on ART delivery and HIVDR prevention. The results will also inform policy decisions at national and global levels regarding the durability and composition of first- and second-line regimens.

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