World Health Organization

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Sentinel surveys of acquired HIV resistance to dolutegravir among people receiving dolutegravir-containing antiretroviral therapy.

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ABBREVIATIONS AND ACRONYMS

ART	antiretroviral therapy
DTG	dolutegravir

DEFINITIONS

Adult: generally, people 18 years of age and older; however, the definition may vary from country to country.

Children and adolescents: generally, individuals younger than 18 years of age; however, the definition may vary from country to country.

Viral load testing coverage: the proportion of all people receiving antiretroviral therapy who have at least one annual viral load test with classifiable results. Viral load testing coverage rates are usually derived from programmatic data.

Detectable viral load: for the purposes of this survey, HIV RNA above the lower limit of detection of the assay used in a country for individuals receiving a dolutegravir-containing regimen.

Confirmed unsuppressed viral load: for the purposes of this survey, confirmed unsuppressed viral load among individuals receiving a dolutegravir-containing regimen is defined as HIV RNA >1000 copies/mL on a second or confirmatory viral load test obtained after a first viral load test showing detectable virus and after a period of enhanced adherence counselling or other recommended adherence support, as defined by the national antiretroviral therapy programme in the country in which the survey is being implemented.

EXECUTIVE SUMMARY

As dolutegravir (DTG)-based antiretroviral therapy (ART) for the treatment of people living with HIV expands globally, estimating the extent to which acquired DTG drug resistance emerges in populations receiving ART is important. Although DTG resistance did not emerge in ART-naive populations with failure to suppress viral loads in clinical trials, evidence suggests that DTG resistance can emerge among people taking DTG-containing regimens. WHO recommends that countries scaling up DTG-containing ART accompany its roll-out with routine drug resistance surveillance.

The primary outcome of this survey is the prevalence of DTG resistance among people receiving DTG-containing ART who have confirmed unsuppressed viral load. This survey uses a one-stage design, applied at select viral load testing laboratories that serve as sentinel sites. Eligible remnant viral load specimens are sampled at each sentinel laboratory. Countries may choose to implement the survey at one or more viral load testing laboratories. If more than one viral load testing laboratory is included, the eligible remnant specimens are sampled at each laboratory until the required target sample size is achieved at each laboratory.

Remnant viral load specimens are eligible for sampling if:

- the remnant specimen is from an individual receiving a DTG-containing ART regimen;
- the remnant specimen is from an individual with a previous detectable viral load who received enhanced adherence counselling for three months (a repeat confirmatory test); and
- the viral load test result of the corresponding remnant specimen has a high viral load (HIV RNA >1000 copies/mL), consequently classifying the individual as having confirmed unsuppressed viral load.

Consecutive sampling of eligible specimens continues until the target sample size of 139 eligible specimens is achieved or until the recommended three-month survey window ends, whichever occurs first. Remnant eligible specimens are genotyped. In assessing HIV drug resistance to antiretroviral drugs, sequences predicated to have low-, intermediate- or high-level resistance (according to the Stanford HIV drug resistance database) are classified as drug resistant.

This survey method is intended for easy and frequent (such as annual) implementation to gain insight into the prevalence and year-over-year trends of DTG resistance. This sentinel method is implemented complementary to WHO-recommended methods for estimating nationally representative levels of acquired HIV drug resistance. Given the rapidly evolving science and understanding of correlates of DTG-resistant HIV, prevalence estimates of DTG resistance generated using this sentinel survey method are not currently linked to recommend specific ART programmes or public health actions. Each survey should conclude with the dissemination of results and conversations within national ART programmes and between ART programmes and WHO to discuss the possible programmatic and public health implications of survey results in the context of the most up-to-date science.

1. INTRODUCTION

As dolutegravir (DTG)-based antiretroviral therapy (ART) for the treatment of people living with HIV expands, estimating the extent to which acquired DTG drug resistance emerges in populations receiving DTG-containing ART is important from a public health and ART programme perspective. The overarching purpose of this sentinel survey method is to generate precise prevalence estimates of DTG resistance among adults and among children and adolescents having confirmed unsuppressed viral load while receiving DTG-containing ART.

DTG is a well-tolerated and highly effective antiretroviral drug and is recommended by WHO in first- and second-line ART *(1)*. An important advantage of DTG is its high genetic barrier to the selection of drug resistance *(2)*. DTG resistance did not emerge among ART-naive participants in clinical trials *(3,4)* and, to date, has only been described in a few ART-naive people for whom DTG-based ART has failed as their first-line treatment *(5)*. However, DTG resistance can emerge, especially among people with previous exposure to first-generation integrase inhibitors with comparatively lower genetic barriers to the selection of drug resistance or when used as DTG monotherapy *(6)*. The risk of acquiring DTG-resistant virus may be increased by infection with a non-B HIV subtype, high viral load and low CD4 cell count at the time of treatment initiation, inadequate adherence to treatment and drug–drug interactions or malabsorption, which reduce DTG drug levels *(5)*.

Based on available information, the prevalence of acquired DTG resistance in populations receiving DTG-containing ART in low- and middle-income countries is anticipated to be low based on current evidence from clinical trials *(3,4)*; however, recent ART programme information from sub-Saharan Africa documents the emergence of DTG resistance in populations for which DTG-containing regimens have failed *(7)*, thus highlighting the need for routine population-level surveillance of drug resistance among people receiving DTG-containing regimens.

The overall goal of this survey is to monitor the potential emergence and trends over time of DTG-resistant HIV as DTG becomes the treatment of choice for many people living with HIV globally. Given the evolving science on what would be considered concerning (or high) population levels of DTG-resistant HIV, how signals of acquired DTG-resistant HIV detected using this or other survey methods would motivate guideline changes to promote alternate regimens is speculative. Thus, WHO does not currently suggest thresholds of DTG resistance above which it recommends specific actions at the country level. Nationally, surveys should conclude with conversations within and between ART programmes and WHO to define the programmatic and public health implications of survey results in the context of the most up-to-date science. Finally, survey results from various countries will be valuable at the global level as WHO and partners considers recommendations for drug-switching strategies for people for whom DTG-based ART has failed.

2. SURVEY METHODS

2.1 Overview

The survey is designed to precisely estimate the prevalence (±10% maximum confidence interval width) of DTG resistance among individuals who have confirmed unsuppressed viral load while receiving DTG-containing regimens for treating HIV infection. The approach described here may be used to estimate levels of resistance among adults or among children and adolescents. Because prevalence estimates of DTG resistance may differ between adults and children and adolescents, surveys should be conducted simultaneously with two separate samples, one for adults and one for children and adolescents.

The survey uses a one-stage design, applied at selected viral load testing laboratories that serve as sentinel sites. Each country selects one or more viral load testing laboratories that will serve as the sentinel sites (see subsection 2.3). The eligible remnant viral load specimens (see subsection 2.4) are sampled independently at each laboratory until the required target sample size is achieved at each laboratory. Thus, each selected laboratory will have its own prevalence estimate of DTG resistance among adults or among children and adolescents with confirmed unsuppressed viral load. Eligible remnant viral load specimens are sampled consecutively.

Consecutive sampling of remnant specimens continues until the target sample size of 139 eligible specimens is achieved or until the three-month sample enrolment window ends, whichever occurs first (see subsection 2.6). Since the focus of the survey is DTG resistance and co-administered antiretroviral drugs, genotyping and analysis of the HIV-1 integrase and reverse-transcriptase regions are generally given priority (see subsection 2.8).

This survey differs from standard WHO HIV drug resistance surveillance methods. This new DTG-focused approach is simple in its design and sample size determination, with straightforward strategies to identify and sample eligible specimens and simple-to-conduct analysis. This sentinel survey method is intended for easy and frequent (such as annual) implementation to gain insight into the prevalence of DTG resistance in populations receiving DTG for treating HIV infection – an emerging global concern for which there is currently little information to guide countries and global stakeholders. This survey should be implemented complementary to the standard methods for estimating nationally representative levels of acquired HIV drug resistance *(8,9)*.

The following are important points on implementing this survey method.

- In accordance with WHO guidelines, countries should routinely perform viral load testing to confirm unsuppressed viral load among people receiving DTG-containing ART after a first viral load test showing detectable virus and after a period of enhanced adherence counselling *(1,10)*. If there is no routine testing to confirm unsuppressed viral load in a country, the country should consult WHO regarding preferable options for estimating the prevalence of DTG in populations receiving DTG-containing ART.
- Unlike WHO's nationally representative acquired HIV drug resistance surveys, this sentinel method may be implemented regardless of the coverage of confirmatory viral load testing in a country; however, the coverage levels of confirmatory viral load testing – nationally and at the selected sentinel laboratories – should be reported alongside drug resistance results to provide insight on generalizability. Moreover, since this concept note does not stipulate a predefined threshold of confirmatory viral load testing in a given laboratory below which this survey method should not be implemented, the national ART programme and national working group implementing this survey should have sufficient confidence in available information to be willing to accept the result of this survey for ART programme and or public health decision-making.
- Viral load laboratory requisition forms or laboratories' automated data systems should enable eligible remnant specimens to be identified (see subsection 2.4).
- To ensure timely survey results, the recommended survey period is three months; the sampling of specimens stops early if the target of 139 eligible specimens is achieved before the three-month survey period ends.
- The required deidentified participant-level survey information is minimal (subsection 3.1). It is highly recommended that this information be collected from viral load laboratory requisition forms at the time specimens are collected but can also be obtained by interrogating electronic laboratory information systems if conditions allow.
- No identifying patient-level information is recorded for analysis. However, a link between a unique survey identification number, assigned by the viral load laboratory and the participants' ART number (available on the viral load requisition form or from the electronic laboratory information system), should be kept at the sentinel viral load testing laboratories to facilitate quality assurance of data and the return of drug resistance genotyping results.
- Other minimal demographic information may be collected but is used for descriptive analysis only.

2.2 Survey outcomes

The primary outcome of this survey is the annual prevalence of predicted DTG resistance among adults and among children and adolescents with confirmed viral non-suppression while receiving a DTG-containing regimen. Secondary analysis includes the prevalence of predicted resistance to co-administered and other antiretroviral drugs.

2.3 Sentinel sites

Viral load testing laboratories serve as sentinel sites. Countries may choose to implement the survey at one or more viral load testing laboratories. When selecting the sentinel sites, countries should assess whether adequate laboratory infrastructure and appropriate standard operating procedures for collecting, handling, transporting and storing specimens are in place *(11)*. To serve as sentinel sites, laboratories must have adequate capacity to store eligible remnant viral load specimens at –20°C or –80°C. If testing to confirm viral non-suppression is limited in a country, then the laboratories where most confirmatory testing is conducted should be given priority for inclusion as a sentinel site.

Countries must assess a laboratory's capacity to operationalize the remnant viral load specimen inclusion criteria defined in subsection 2.4.1 and the availability or ability of a laboratory to generate required variables as defined in subsection 3.1.1. Although this concept note does not stipulate a predefined threshold of confirmatory viral load testing in a given laboratory below which this survey method should not be implemented, the national ART programme and national working group implementing this survey must have sufficient confidence in available information to be willing to accept the result of this survey for ART programme and/or public health decision-making.

2.4 Eligibility criteria

Remnant viral load specimens eligible for the survey must meet inclusion criteria and not meet exclusion criteria. Fig.1 supports the identification of eligible remnant specimens.

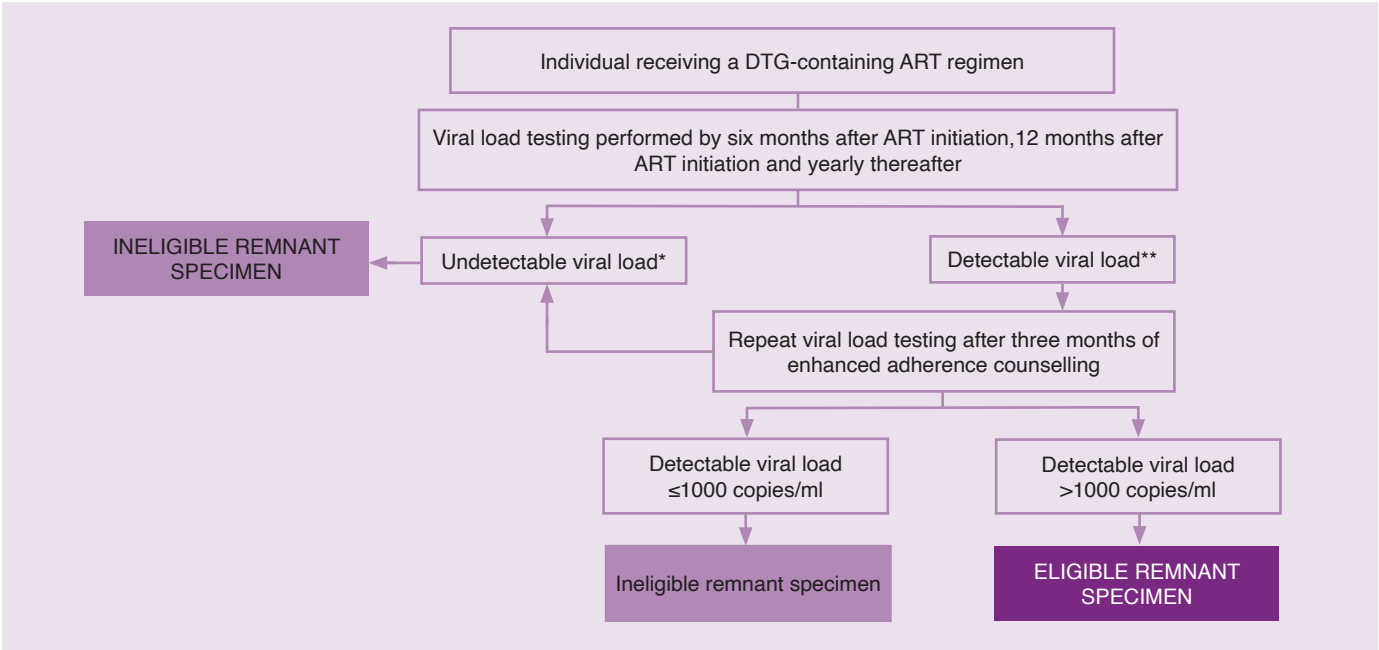
2.4.1 Inclusion criteria

- The remnant specimen is from an individual receiving a DTG-containing ART regimen.
- The remnant specimen is from an individual with a previous detectable viral load who received enhanced adherence counselling for three months (this is a repeat confirmatory test).
- The viral load test result of the corresponding remnant specimen has a high viral load (HIV RNA >1000 copies/mL), consequently classifying the individual as having confirmed unsuppressed viral load.

2.4.2 Exclusion criterion

- The remnant viral load specimen has an inconclusive test result.
- The remnant specimen is a "first" viral load test not obtained to confirm viral non-suppression.

Fig 1. Flow diagram for selecting the eligible specimens for the sentinel surveys of acquired HIV resistance to DTG among people receiving DTG-containing ART



* Undetectable viral load: HIV viral load is **below** the lower limit of detection of the viral load assay used in the country. In most countries, the lower limit of detection is 50 copies/ml.
** Detectable viral load: HIV viral load is **above** the lower limit of detection of the viral load assay used in the country. In most countries, the lower limit of detection is 50 copies/ml.

2.5 Survey sample size

2.5.1 Sample size design parameters

The required sample size (before accounting for genotyping failure) is determined with the goal of reporting the 95% confidence interval with a width restricted to ±10%. Because the prevalence of DTG resistance is uncertain, the anticipated prevalence is set at 50%, the point of maximum variability, which corresponds to the largest sample size. These assumptions yield a recommended sample size of 97 (Annex 1).

In nearly all cases, a sample size of 97 remnant specimens is sufficient to restrict the 95% confidence interval to ±10%, and in most cases, the confidence interval widths will be even narrower.

- Rarely is the observed prevalence equal to 50%, the point of maximum variability. Any prevalence different from 50% will result in more precise confidence intervals. For example, at a prevalence of 10%, the resulting confidence interval width is around ±6%.
- The finite population correction is used in the analysis (Annex 1) and restricts the confidence interval width to less than ±10%. However, to simplify the sample size calculations and the sentinel laboratory–specific details needed for calculating the sample size, the finite population correction is not used in the design.

If the sentinel viral load testing laboratories are unable to achieve the target sample size, all eligible specimens are included. Since the survey window is three months, the number of available eligible remnant viral load specimens is estimated to be one quarter of the total eligible population for a given 12-month period or year. This annual eligible population is used to determine the finite population in analysis (see Annex 1, section A1.3.2). With a prevalence of DTG resistance of 50% and incorporating the finite population correction, the confidence interval in the analysis is restricted to ±10% if 74 or more eligible specimens are sampled. At the more plausible 10% DTG resistance prevalence, the confidence interval in the analysis is restricted to ±10% if 27 or more eligible specimens are sampled for the survey.

2.5.2 Inflating the sample size for genotypic testing failure

Since not all remnant viral load specimens will be successfully genotyped, the required sample size is inflated to account for the genotyping failure. WHO recommends using an anticipated genotypic testing failure rate of 30% in this calculation. This 30% genotyping failure rate is recommended for plasma or dried blood spot sample types. This results in the recommended target sample size of 139 specimens per sentinel laboratory.

2.5.3 Allocating samples across sentinel sites

Each country must include at least one viral load testing laboratory as a sentinel site. Multiple laboratories may participate. If multiple laboratories are included, each laboratory serves as its own sentinel site, with a recommended target sample size of 139. Therefore, there are no stratification variables, and the recommended target sample size of 139 is not distributed across multiple laboratories.

2.6 Sampling procedures

Eligible specimens within a sentinel laboratory are sampled using consecutive sampling, stopping when the target sample size of 139 is reached. Sentinel laboratories should record the starting date and ending date of sampling and use the ending date to estimate the total size of the eligible population over the three-month survey window. This information is required for using the finite population correction (Annex 1). For example, if all eligible specimens were collected in the first 20 days (of 90 days), then the estimated total size of the eligible population during the survey window is 626 (139 times 90/20), and the estimated total size of the eligible population over the year is 2504 (626 times 4).

To maximize the feasibility of implementation, WHO does not recommend extending the duration of the survey beyond a three-month period. If a sentinel laboratory has not achieved its target sample size of 139 by the end of the recommended three-month survey window, all eligible specimens sampled during the window are included for drug resistance testing.

2.7 Survey of acquired DTG HIV drug resistance among children and adolescents

Surveys of acquired DTG HIV drug resistance among children and adolescents should be implemented separately from the adult survey, following the same procedures for design, specimen identification and sampling and analysis. Thus, although the surveys of adults and of children and adolescents each have separate samples of remnant specimens, the surveys in each population should be implemented simultaneously.

2.8 Laboratory procedures

The quality and quantity of viral load specimens coming from clinics to the selected viral load testing laboratories should be sufficient to enable both viral load testing and drug resistance testing if an eligible remnant specimen is identified.

Dried blood spots or plasma can be used as the specimen type for this survey. Dried blood spots are a reliable specimen type for HIV drug resistance testing *(12)*. Dried blood spots and plasma specimens should be collected and handled according to the 2020 WHO HIVResNet HIV drug resistance laboratory operational framework *(11)*.

Remnant specimens from people identified as having confirmed viral non-suppression (viral load >1000 copies/mL on a second or confirmatory test) are genotyped. Drug resistance genotyping should include sequencing of the integrase, reverse-transcriptase and protease regions of the HIV-1 *pol gene*. WHO recommends that drug resistance testing be performed in WHO-designated laboratories. Designated laboratories are members of the WHO HIVResNet Laboratory Network, undergo rigorous quality assurance processes and participate in annual proficiency panel testing *(11)*. Using WHO-designated laboratories ensures high-quality results for public health surveillance and programme decision-making. If a country does not have a WHO-designated HIV drug resistance testing laboratory, it is encouraged to send specimens to a WHO-designated regional or specialized laboratory. A list of WHO-designated laboratories is available at the WHO HIV drug resistance website (https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/laboratory-network). Countries planning HIV drug resistance surveys are strongly advised to collaborate with a WHO-designated laboratory in the survey planning stage to ensure that specimen collection, processing, handling, storage and shipment are optimized to yield high-quality HIV drug resistance test results.

2.9 Observed sample size

Not all sampled specimens will be successfully genotyped. The observed sample size is the number of sampled specimens that are successfully tested and for which HIV drug resistance test results are available for analysis. All these samples are included in the analysis.

Ideally, the observed sample size is at least as large, if not larger, than the sample size required to meet the constraints ($n = 97$). If the observed sample size is smaller than the required sample size because the genotypic testing failure rate exceeds 30%, then the confidence intervals may be wider than specified in the design. Importantly, the analysis below remains statistically correct, whether or not the observed sample size is larger or smaller than the required sample size.

2.10 Data analysis

When drug resistance is being interpreted, sequences classified as having predicted low-level, intermediate- or high-level resistance (according to the Stanford HIV drug resistance database *(13))* to a given antiretroviral drug should be classified as drug resistant. The frequency of drug resistance mutations contributing to a predicted antiretroviral drug resistance classification, as defined by the Stanford HIV drug resistance database algorithm, is reported.

The statistical analysis for the primary outcome accounts for the fact that samples are drawn from finite populations. Annex 2 provides full formulas and Stata code that automate these analyses. Prevalence estimates and corresponding 95% confidence intervals are calculated. The Stata code provided in Annex 2 also enables subgroup analysis and the combining of estimates across multiple sentinel viral load testing laboratories in a country.

1. To ensure reliable and reproducible results across a range of drug resistance testing assays and specimen types, only specimens with viral loads >1000 copies/ml are sent for amplification and sequencing.

3. IMPLEMENTATION CONSIDERATIONS

3.1 List of variables to be collected

This section lists the set of information that should be captured to ensure correct survey analysis.

3.1.1 Required -level information

- Participant ART number (clinic ID)[1]
- Participant survey ID (see Box 1 for identification conventions)
- Current ART regimen – the names of each currently prescribed antiretroviral drug
- Genotyping successful (successful, unsuccessful, not attempted or unknown)
- Laboratory specimen code – unique identifier assigned to a participant's specimen by the HIV drug resistance testing laboratory if different from the participant's survey ID (this variable is not required if the laboratory specimen code and the participant ID are identical)
- HIV drug resistance genotype (sequence in FASTA file format)

3.1.2 Optional participant-level information

- Date of initiation of a DTG-containing ART regimen
- Previous ART regimens – the names of each previously prescribed antiretroviral drug
- Gender (female, male or other)
- Date of birth (or age)

3.1.3 Required sentinel laboratory-level information

- Viral load testing laboratory name
- Viral load testing laboratory ID
- Survey type (that is, sentinel acquired HIV drug resistance, as defined in Box 1)
- Proportion of the survey window during which eligible specimens were sampled to achieve the target sample size. For example, if 20 of 90 days were needed to achieve the target sample size of 139, then this proportion is 20/90 = 0.222.

Box 1. Assigning a unique participant survey identification (SID) number, or unique survey ID

This box summarizes the convention for assigning unique SIDs to participants enrolled in this survey. The SID is used to identify the patient as well as the sequence generated by the genotyping assay. It is composed of the following five elements delimited by a hyphen ("-"):

- country abbreviation: the International Organization for Standardization's standard three-letter abbreviation;
- survey type: sentinel acquired HIV drug resistance (SADR);
- year the survey started;
- site abbreviation (a three-letter abbreviation for the site, unique within the country; by default, the first three letters of the name of the viral load laboratory unless this is not unique);
- a four-digit unique participant number: that is, a consecutive unique participant number assigned to a participant at that site; and
- a lower case "-a" denotes adults and a lower case "-c" denotes children and adolescents.

For example, if the "University HIV Clinic" is a site participating in a national survey of acquired HIV drug resistance among adults in South Africa in 2022, a participant's SADR-SID would look like this: ZAF-SADR-2022-UHC-0001-a. Using this unique survey identifier is required if using the WHO HIV drug resistance database, which supports cleaning and quality assurance of both deidentified participant data and HIV sequences, thus enabling data analysis and quality-assured results.

1. This variable is not used in analysis; however, a code linking the assigned participant survey identification code and the participant ART number (clinic ID) should be maintained at the sentinel viral load testing laboratory to facilitate quality assurance and return of results to participants' medical records, if desired.

3.2 Repeating the survey

This survey is designed to enable the assessment of trends in the prevalence of DTG drug resistance in populations with confirmed viral non-suppression while receiving DTG-containing regimens. Thus, it should be repeated annually or at least every other year as a complement to nationally representative acquired HIV drug resistance surveys *(8,9)*. Annex 3 presents an example of a budget.

3.3 Data extraction

The same unique survey identification number described in Box 1 is assigned to the deidentified survey participant-level data, the remnant viral load specimens used for drug resistance testing and the FASTA file header of the drug resistance genotype. All participant- and sentinel laboratory-level data should be entered into a spreadsheet-based data capture tool developed by WHO for this purpose (https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/surveillance-of-acquired-hiv-drug-resistance-in-populations-receiving-art).

3.4 Using WHO's HIV drug resistance database

Countries are encouraged to use the WHO HIV drug resistance database to clean and quality assure the deidentified participant information and to quality assure sequence information and generate standardized resistance interpretations. A spreadsheet-based data upload template into which deidentified participant information is uploaded for quality assurance is available for download from within the WHO HIV drug resistance database (https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance). A data upload template is also available at: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/surveillance-of-acquired-hiv-drug-resistance-in-populations-receiving-art.The HIV drug resistance testing laboratory or the country may upload sequence information directly into the database for the purpose of performing quality assurance and genotypic resistance scoring.

Use of the WHO HIV drug resistance database for data cleaning, sequence quality assurance, and drug resistance interpretation does not constitute reporting of data to WHO for the purpose of global dissemination or use in published analyses. Data uploaded into the database are kept private and may be used by WHO to support countries in generating quality-assured country reports and the development of country-specific ART programme or public health actions. Information uploaded into the WHO database is not reported by WHO in global reports or used in analyses without prior explicit authorization by a country.

For the purposes of global HIV drug resistance surveillance and for informing global and regional ART programme and planning decision-making, countries are encouraged to report to WHO a dataset consisting of (1) deidentified participant-level survey information, (2) viral load laboratory-level data and (3) HIV sequences in FASTA file format. It is recommended that data identifiers follow the WHO convention as defined in Box 1. Data may be reported using the WHO HIV Drug Resistance Database: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance. Country data are only included in WHO reports or published analyses with appropriate prior permissions obtained by WHO before global dissemination.

When HIV drug resistance is reported by a specified antiretroviral drug, sequences classified as having predicted low-level, intermediate- or high-level resistance (according to the Stanford HIVdb) should be classified as drug resistant.

3.5 Implementation overview: practical guide

This section provides a practical overview of implementation. In this example, a national HIV drug resistance working group meets on 1 January 2023 and plans to implement an acquired HIV drug resistance survey using this sentinel viral load testing laboratory method. Funding is available until December 2023, and the working group follows the steps outlined below:

1. The working group determines whether the available budget permits the implementation of a simultaneous survey among children and adolescents. This means planning for genotyping of 139 remnant viral load specimens from adults with confirmed viral non-suppression and 139 remnant viral load specimens from children and adolescents with confirmed viral non-suppression. Implementation of simultaneous surveys is strongly recommended, and sufficient funding to assess DTG resistance among children and adolescents and among adults should be planned for when developing national drug resistance surveillance budgets.

2. The working group decides whether the available funds are sufficient to enable the survey to be performed in one or more than one sentinel site (one or multiple viral load laboratories).

3. The working group verifies that the selected sentinel viral load laboratories are able to identify eligible remnant specimens (see subsection 2.4) and obtain minimum required survey variables from viral load requisition forms or from electronic databases. If obtaining minimum information is not feasible or confidence in available data is lacking, the country should contact WHO for advice and support.

4. The survey period is three months. The working group selects the survey start date. Viral load specimens coming to the selected sentinel viral load testing laboratories on or after the survey start date are screened for eligibility using the criteria defined in subsection 2.4.

5. For each selected laboratory, all eligible specimens are consecutively sampled until the target sample size of 139 is reached or until the three-month survey window ends, whichever occurs first. If the target of 139 specimens is reached before the survey window ends, the proportion of the survey window needed for specimen sampling (the amount of time passed since sampling began) must be recorded, since this information is required for the analysis.

6. Once the sample size of remnant specimens from people with confirmed viral non-suppression is achieved, all remnant specimens are sent for HIV drug resistance genotyping. For reasons of quality, WHO recommends using WHO-designated laboratories for HIV drug resistance testing.

7. The drug resistance testing laboratory performs drug resistance testing, and deidentified participant information is entered into upload templates provided by WHO (subsection 3.4) for use with the WHO HIV drug resistance database.

8. A national data coordinator uploads deidentified participant information and HIV drug resistance genotypes into the WHO HIV drug resistance database. Data and sequences undergo a process of quality assurance in the database. The database generates resistance interpretations using the set of quality-assured sequences.

9. Cleaned and quality-assured datasets including standardized drug resistance interpretations are downloaded from the database and are analysed by countries using Stata or other high-quality statistical packages.

10. The working group drafts a national report, and conversations take place within the national ART programme and between the ART programme and WHO to discuss possible programmatic and public health implications of the survey results in the context of the most up-to-date science.

11. The national reports are finalized, and the results are disseminated.

12. Countries are encouraged to report data to WHO for global dissemination and for use in global decision-making regarding optimal ART regimens.

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ANNEX 1. STATISTICAL METHODS

This annex provides the statistical details of the DTG-specific HIV drug resistance survey approach.

A1.1 Calculating required sample sizes

For moderate sample sizes and prevalence estimates away from the boundaries (prevalence estimates away from 0% or 100%), the method for calculating a confidence interval for individual-sample surveys uses a z-distribution. The required sample size formula is obtained by inverting the 95% Wald confidence interval with a z-distribution:

$$n = \frac{z_{0.975}^2 * p^{HIVDR} * (1 - p^{HIVDR})}{L^2},$$

where n is the required sample size; p^{HIVDR} is the anticipated prevalence of DTG-specific HIV drug resistance; L is the desired absolute precision; and $z_{0.975}$ is the 97.5th quantile of the z-distribution.

For this survey, in the absence of more conclusive and broad evidence on the prevalence of DTG drug resistance, p^{HIVDR} is set at 50%. This is the point of maximum variability and will yield the largest required sample size for this estimate. The target confidence interval width is ±10%, thus resulting in a required sample size of $n = 97$.

A1.2 Inflating the sample size for genotypic testing failure

The required sample size must be inflated to account for genotypic testing failure rates among specimens. Since not all specimens will have a HIV drug resistance test result to contribute to analysis, WHO recommends incorporating an anticipated genotypic testing failure rate of 30% into sample size calculations. WHO recommends this 30% failure rate for both plasma and dried blood spot specimen types. Thus, the target sample size will be 139 (=97/(1-0.3)).

A1.3 Statistics

This subsection describes the statistical details for primary outcome. Stata code is provided to automate this analysis (Annex 2).

A1.3.1 Notation

The following notation is used throughout this subsection.

l = subscript for induviduals

N = estimated total number of eligible specimens in a year

$n^{sampled}$ = number of sampled specimens

p_s = proportion of days in the survey window needed to achieve the target sample size

N_s = total number of eligible specimens in the three-month survey period, which is either: (a) $139p_s$, if the three-month survey window ends before achieving the target sample size of 139; or (b) estimated to be $139p_s$ if the target sample size is achieved before the end of the three-month window.

m^{geno} = number of sampled specimens with successful genotyping

Y_l = binary outcome of HIV drug resistance for specimen l

$\hat{p}^{HIVDR}$ = estimated prevalence of DTG-specific HIV drug resistance among eligible specimens

A1.3.2 Analysis

The primary survey outcome is the prevalence of DTG resistance among people with confirmed viral non-suppression while receiving a DTG-containing regimen.

Prevalence

An estimate of the prevalence of DTG drug resistance among all eligible specimens can be obtained as follows: the numerator is the number of tested specimens with DTG drug resistance, and the denominator is the total number of samples successfully genotyped.

Let Y_l denote the binary outcome variable for DTG drug resistance, equal to 1 if specimen l has DTG resistance and equal to 0 otherwise, and let m^{geno} denote the total number of sampled specimens with successful genotyping. The estimated prevalence of DTG resistance among all eligible specimens is given by:

$$\hat{p}^{HIVDR} = \frac{\sum_{l=1}^{m^{geno}} Y_l}{m^{geno}}$$

Variance

For the variance formula to apply the finite population correction, the total size of eligible specimens forming the finite population (N) must be estimated. In order to incorporate a finite population correction and accommodate uncertainty in extrapolating inference to the year period, the finite population is set to be the estimated annual number of eligible specimens rather than the estimated number over the three-month survey period. For each laboratory, if the three-month survey window ends before achieving the target sample size of 139, then the total number of eligible specimens within the three-month period (N_s) is known and is equal to the number of sampled specimens: $N_s = n^{sampled} < 139$, and the annual population is estimated by multiplying by four: $N = N_s * 4$. If the sampling ends early because the target sample size of 139 is achieved before the survey window ends, then N_s is not known and is estimated using the proportion of days in the survey window needed to achieve the sample size (p_s) : $N_s = n^{sampled} * 1/p_s = 139/p_s$. The annual population is once again estimated by multiplying by four: $N = N_s * 4$.

The resulting variance, using the normal approximation, is:

$$\widehat{\text{var}}\left(\hat{p}^{HIVDR}\right) = \left(1 - \frac{m^{geno}}{N}\right)\left(\frac{\hat{p}^{HIVDR} * \left(1 - \hat{p}^{HIVDR}\right)}{m^{geno} - 1}\right)$$

A 95% confidence interval is calculated using a standard Wald formula or a Wald formula transformed to the logit scale (default in Stata). If the number of eligible specimens is very small or if the prevalence of DTG drug resistance ($\hat{p}^{HIVDR}$) is very small, such that $m^{geno} * \hat{p}^{HIVDR} < 5$, then exact methods for the confidence interval should be used. In the instance of rare events, please consult a WHO statistician for the appropriate analysis.

ANNEX 2. STATA CODE

User-friendly instructions are provided below for data analysis in Stata. To use the code, the data must follow the format described in subsections 3.3 and 3.4, with participant-level and laboratory-level information following the configuration of the Excel data upload template, and HIV drug resistance sequences must be in FASTA file format. The same unique survey identification number must follow WHO convention and be assigned to the participant-level data, the remnant viral load specimen used for drug resistance testing and the FASTA file header of the drug resistance genotype.

In Stata, estimation and inference can be implemented using the svy package. The default variance estimation used is linearization (based on a first-order Taylor series linear approximation), which simplifies to the typical stratified variance formula for proportions. All variance computations include finite population corrections. Alternative statistical packages can be used to analyse data providing that they properly adjust for survey weights and stratification (if necessary). All statistical packages are expected to yield identical point estimates; however, not all statistical packages are expected to yield identical standard error estimates and confidence intervals. Statistical packages that do not allow users to specify the finite population correction at each stage of sampling will overestimate the standard error, especially in countries with small eligible populations.

Sections A2.1–A2.6 below provide Stata code for processing and combining the participant and laboratory datasets, and subsections A2.7–A2.10 provide code for analysing the survey outcomes. All code displayed can be found in a downloadable Stata do-file (https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/surveillance-of-acquired-hiv-drug-resistance-in-populations-receiving-art) that can run all pre-processing and analysis instructions at once.

A2.1 Importing participant- and laboratory-level data into Stata

Begin by importing participant- and laboratory-level data from the Excel data capture tool in subsection 3.3. The Excel file should be saved with the file name "patient_data_sentinel.xlsx".

1. To start, create a do-file so that commands can be saved and then run. Click on the notepad icon corresponding to NEW DO-FILE EDITOR on the top-left corner of the Stata viewer, then save the do-file that is created.

2. Clear any previous output and set the working directory to the directory containing the data files. For example, if the directory is C:/DOCUMENTS, run the following code:

```
clear
cd "C:/Documents"
```

3. Import each sheet of the Excel data capture tool file, storing the first row as headers, changing the header names to uppercase, and saving each sheet as its own .dta file using uppercase letters. Given the Excel file name "patient_data_sentinel.xlsx", run:

```
import excel using "patient_data_sentinel.xlsx", describe

forvalues sheet=1/`=r(N_worksheet)' {

        local sheetname = r(worksheet_`sheet')

        import excel using patient_data_sentinel, sheet("`sheetname'") firstrow case(upper)

        local sheetname = upper(subinstr("`sheetname'", " ", "_", .))

        save "`sheetname'", replace

        clear

}
```

The Excel file should contain five sheets entitled: (1) Survey information, (2) Configuration, (3) VL lab information, (4) Survey participants and (5) Participant treatments.

A2.2 Importing HIV drug resistance data into Stata

1. Import the HIV drug resistance data from the data capture tool described in subsection 3.4. The file name should be "FASTA_sentinel.xlsx". Store the first row as headers and change all header names to uppercase.

```
import excel using "FASTA_sentinel.xlsx", sheet("ResistanceSummary") firstrow case(upper)
```

The resistance data file should be an Excel file containing one sheet entitled "ResistanceSummary".

2. Rename SEQUENCENAME as PARTICIPANTID. Drop all cells without a subject ID. Drop all unnecessary variables. Replace NAs as missing.

```
rename SEQUENCENAME PARTICIPANTID
drop if missing(PARTICIPANTID)
drop *SCORE ALGORITHM* STRAIN GENES PI* NRTI* NNRTI* INSTI*
destring, ignore("NA") replace
```

3.For each of the resistance-level variables, reclassify the variable as a binary resistance indicator, with levels 1–2 corresponding to susceptible (no HIV drug resistance) and levels 3–5 corresponding to HIV drug resistance. Rename the resistance type variables.

```
ds *LEVEL
local plist = r(varlist)
foreach i of local plist {

        replace `i' = 0 if `i' < 3 & !missing(`i')

        replace `i' = 1 if `i' >= 3 & !missing(`i')

}

rename *LEVEL *_RES
```

4. Generate variable for DTG-specific resistance.

```
gen DTG_ADR = DTG_RES
```

5. Save the modified HIV drug resistance data as a .dta file. In this example, we save the data as "RESISTANCE_SUMMARY.dta".

```
save RESISTANCE_SUMMARY, replace
```

A2.3 Preparing viral load laboratory data

1. Remove the previous dataset, then load the viral load laboratory data, stored as "VL_LAB_INFORMATION.dta", and rename the variables for viral load laboratory name, viral load laboratory code, and proportion of survey window needed to achieve the target sample size.

```
clear
use VL_LAB_INFORMATION.dta
rename NAME* LABNAME
rename SITECODE* LABCODE
rename PROP* PROPWINDOW
```

2. Exclude observations missing a laboratory code.

```
drop if missing(LABCODE)
```

3. Save the modified data as a .dta file. In this example, we save the data as "VL_LAB_INFORMATION.dta".

```
save VL_LAB_INFORMATION, replace
```

A2.4 Preparing participant-level data on ART regimen

1. Remove previous dataset, then load the treatment regimen data, stored as "PARTICIPANT_TREATMENTS.dta".

```
clear
use PARTICIPANT_TREATMENTS.dta
```

2. Exclude observations missing a subject ID or corresponding to past ART. Drop unnecessary variables and rename antiretroviral drug types so that all variable names begin with a letter.

```
drop if missing(PARTICIPANTID) | upper(CURRENTARTYN) == "N"
drop OTHERARVDRUG CURRENTARTYN
replace ARVDRUG = "ARV_" + ARVDRUG
```

3. Generate an indicator variable of DTG-based ART, equal to 1 if a person is receiving a DTG-containing regimen and 0 if a person is receiving a non-DTG-containing regimen.

```
gen TEMP_DTG = cond(inlist(ARVDRUG, "ARV_DTG", "ARV_TLD", "ARV_JUL"), 1, 0)
by PARTICIPANTID, sort: egen DTG = max(TEMP_DTG)
drop TEMP_DTG
```

4. Reformat the ARVDRUG variable so that each antiretroviral drug type is created as a new binary variable, set to 1 if the person's regimen includes the drug and 0 if not.

```
gen ON = 1
reshape wide ON, i(PARTICIPANTID) j(ARVDRUG) string
rename ON* *
```

5. Save the modified data as a .dta file. In this example, we save the data as "PARTICIPANT_TREATMENTS.dta".

```
save PARTICIPANT_TREATMENTS, replace
```

A2.5 Preparing participant-level data on other variables

1. Remove the previous dataset and then load the participant-level data, stored as "SURVEY_PARTICIPANTS.dta". Drop observations with missing subject ID or ones that do not pertain to adult participants.

```
clear
use SURVEY_PARTICIPANTS.dta
drop if missing(PARTICIPANTID) | substr(PARTICIPANTID, -1, .) != "a"
```

If analysis is for children and adolescents, drop observations that do not pertain to children and adolescents instead. Replace the last line of code above with the following line.

```
drop if missing(PARTICIPANTID) | substr(PARTICIPANTID, -1, .) != "c"
```

2. Rename VL laboratory variable and other variables for brevity.

```
rename SITECODE* LABCODE
rename DATEOFINITIATION* DATEINIT
rename AGE* AGE
rename DATEOFBIRTH* DATEOFBIRTH
rename GENDER* GENDER
rename LABSPEC* LABSPECIMENCODE
```

3. Recode unknown values as missing.

```
recode DATE* (9999 = .)
recode AGE (-9 = .)
```

4. Save the modified data as a .dta file. In this example, we save the data as "SURVEY_PARTICIPANTS.dta".

```
save SURVEY_PARTICIPANTS.dta, replace
```

A2.6 Merging all datasets

1. Use a many-to-one merge to merge the viral load laboratory data.

```
merge m:1 LABCODE using VL_LAB_INFORMATION, keep(match) nogenerate
```

2. Merge in the treatment regimen data by subject ID.

```
merge 1:1 PARTICIPANTID using PARTICIPANT_TREATMENTS, keep(match) nogenerate
```

3. Merge in the HIV drug resistance data by subject ID.

```
merge 1:1 PARTICIPANTID using RESISTANCE_SUMMARY, keep(match) nogenerate
```

4. Save the combined and reorganized data as a .dta file. In this example, we save the data as "ALL_DATA.dta".

```
save ALL_DATA.dta, replace
```

A2.7 Creating finite populations and other necessary variables for survey design

1. Remove the previous dataset and load in the combined data.

```
clear
use ALL_DATA.dta
```

2. Generate the variable for the total eligible specimens forming the finite population for each laboratory. This is equal to $\frac{n_{sampled}}{p_s} * 4$

```
bysort LABCODE: gen FINITE_POP = _N / PROPWINDOW * 4
```

3. Generate the sampling weights, calculated as the stratum totals divided by the number of sampled case specimens per stratum.

```
bysort LABCODE: gen WEIGHTS = FINITE_POP / _N
```

4. Stratify the data by laboratory.

```
egen STRATA = group(LABCODE)
```

A2.8 Analysis for obtaining outcome estimates combined across multiple laboratories or sentinel sites

1. To combine estimates across multiple laboratories, each laboratory will be treated as a stratum, and estimates will be combined assuming a stratified one-stage survey design with finite population correction. If there exists a stratum or multiple strata with only one unit sampled, sampling errors cannot be estimated for all strata independently, and Stata will report a missing standard error. This situation is addressed by setting the standard errors for single-unit strata to be the average of the standard errors for other strata and is represented by the single unit (scaled) term in the code below.

```
svyset [pweight = WEIGHTS], strata(STRATA) fpc(FINITE_POP) singleunit(scaled)
```

2. Obtain estimates and confidence intervals for the prevalence of DTG drug resistance among people receiving DTG-containing regimens and with confirmed viral non-suppression. In the output, the point estimate, standard error and 95% confidence interval of interest are located in the row labelled "1".

```
svy, subpop(if DTG==1): proportion DTG_ADR
```

This command gives confidence intervals expressed on the logit scale. For Wald confidence intervals, simply add citype(wald) to the end:

```
svy, subpop(if DTG==1): proportion DTG_ADR, citype(wald)
```

If the number of eligible specimens is very small or if the prevalence of DTG drug resistance is very small, then exact methods for the confidence interval should be used. In the instance of rare events, please consult a WHO statistician for the appropriate analysis.

A2.9 Analysis for obtaining outcome estimates for a single laboratory or sentinel site

1. Subset data to the desired laboratory. For instance, if the laboratory code of the desired laboratory is "HOS", run the following code.

```
keep if LABCODE == "HOS"
```

2. Set the one-stage survey design with finite population correction.

```
svyset [pweight = WEIGHTS], strata(STRATA) fpc(FINITE_POP) singleunit(scaled)
```

3. Obtain estimate and confidence interval for the prevalence of DTG drug resistance among people receiving DTG-containing regimens and with confirmed viral non-suppression

```
svy, subpop(if DTG==1): proportion DTG_ ADR
```

This command gives confidence intervals expressed on the logit scale. For Wald confidence intervals, simply add citype(wald) to the end:

```
svy, subpop(if DTG==1): proportion DTG_ADR, citype(wald)
```

If the number of eligible specimens is very small or if the prevalence of DTG drug resistance is very small, then exact methods for the confidence interval should be used. In the instance of rare events, please consult a WHO statistician for the appropriate analysis.

4. Restore the full dataset for additional analyses

```
clear
use ALL_DATA.dta
```

A2.10 Secondary analysis

Some examples of secondary analysis are given below. Before running, be sure to set the correct survey design corresponding to analysis for a single laboratory or combined across multiple laboratories, as described above.

1. Obtain prevalence and variance estimates of DTG drug resistance among people receiving DTG-containing regimens who are older than 40 years of age.

```
svy, subpop(if DTG == 1 & AGE > 40): proportion DTG_ADR
```

2. Obtain prevalence and variance estimates of efavirenz (EFV) drug resistance among all individuals. Prevalence and variance estimates of drug resistance for any specific antiretroviral drug can be obtained by replacing 'EFV_RES' below with the column name corresponding to the antiretroviral drug of interest.

```
svy: proportion EFV_RES
```

ANNEX 3. BUDGET CONSIDERATIONS

Below is an example budget for countries implementing a survey following this sentinel method. In this example, the country is implementing a survey among children and adolescents and a survey among adults. The target sample size in each group is 139, and the country has chosen one sentinel viral load testing laboratory. Note that if the country were to have chosen to implement the survey in two sentinel laboratories, the target sample size in each laboratory and each population would remain 139, thus bringing the total number of specimens sampled for genotyping to 556 (278 for the survey among children and adolescents and 278 for the survey among adults).

Example	Number of sentinel viral load laboratories: 1	Target sample size for adults: 139	Target sample size for children and adolescents: 139

					Shared survey costs	Survey among adults	Survey among children and adolescents
Protocol development and training							
	Number of staff per site	**Transportation costs**	**Per diem cost**	**Number of nights**	**Total US$**		
Training of site staff (1-day training)	2	200.00	150.00	2	1 000.00		
Production of protocol and training materials					2 000.00		
				Subtotal	**3 000.00**		
Survey coordination							
	Number of staff	**Cost per staff/month**	**Number of months**		**Total**		
National coordination	1	1000.00	3		3 000.00		
Data management	1	800.00	4		3 200.00		
Viral load laboratory survey coordinator	1	800.00	3		2 400.00		
				Subtotal	**8 600.00**		
Laboratory							
				Cost per Unit	**Total**	**Total**	
Genotyping for reverse transcriptase and integrase; costs including labour				150[a]		20 850.00	20 850.00
Shipment of specimens to a WHO-designated laboratory (outside the country)					5 000.00		
				Subtotal	**5 000.00**	**20 850.00**	**20 850.00**
Technical support							
					Total		
Consultant for protocol development, data analysis and report writing (US$ 550 for 10 days and daily per diem US$ 200 for 7 days); international flight US$ 3000					9 900.00		
Statistical consultant – support statistical analysis (US$ 550 per day for 7 days)					3 850 .00		
				Subtotal	**13 750.00**		
Report production, printing and distribution							
					Total		
Report production and distribution					4 400.00		
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)					10 000.00		
				Subtotal	14 000.00		
				Total US$	**86 050.00**		

[a] The cost of HIV drug resistance testing should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test). All costs in this table are estimated in United States dollars.

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