Cross-sectional survey of acquired HIV drug resistance to ARV drugs in children, adolescents and adults receiving antiretroviral treatment in *[country name], [year of the survey implementation]*

* **Generic Protocol Version 1.0, January 6, 2025**
* **Nationally representative ART clinic-based method**

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# **Resources**

## **Collaborating Institutions**

*[Complete as appropriate]*

## **Funding Sources**

*[Complete as appropriate]*

# **Abbreviations and Acronyms**

|  |  |
| --- | --- |
| ART | Antiretroviral therapy |
| ARVs | Antiretroviral (drugs) |
| DTG | Dolutegravir |
| HIV | Human immunodeficiency virus |
| INSTI | Integrase strand transfer inhibitors |
| NNRTI | Non-nucleoside reverse transcriptase inhibitors |
| NRTI | Nucleoside reverse transcriptase inhibitors |
| PI | Protease inhibitors |
| PPPS | Probability proportional to the proxy size |
| PrEP | Pre-exposure prophylaxis |
| WHO | World Health Organization |

# **Definitions**

* **Adults:** individuals at least 18 years of age *[adjust if needed for the country context]*.
* **Children and adolescents:** individuals under 18 years of age *[adjust if needed for the country context]*.
* **Acquired HIV drug resistance:** develops when HIV mutations emerge due to viral replication in individuals receiving ARV drugs.
* **Viral load suppression:** defined for this survey as viral loads <1000 copies/ml.

# **Introduction**

HIV drug resistance emerges and is selected when the virus replicates in the presence of antiretroviral (ARV) drugs. HIV resistance to ARV drugs affects the ability of these drugs to block viral replication, negatively affecting the effectiveness of antiretroviral therapy (ART) programmes. HIV drug resistance to ARV drugs decreases the efficacy and options of ART regimens. In addition, it may reduce the prevalence of viral suppression in people with HIV receiving ART, increase the number of new HIV infections and deaths associated with advanced HIV infection, and increase ART program costs (1, 2). Therefore, WHO recommends monitoring HIV resistance to ARV drugs as a key component of a comprehensive and effective HIV response (3, 4). Surveillance of acquired HIV drug resistance provides critical information for evaluating the performance of ART programs in achieving viral suppression goals and describes patterns of HIV drug resistance among individuals receiving ART (3).

Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) drug. Since 2018, WHO has recommended using DTG-containing ART as a first-line regimen for adults and as a second-line preferred regimen for those receiving a non-DTG-containing ART regimen with unsuppressed VL (5). As of July 2023, DTG-based ART has been adopted as the primary first-line ART for adults and adolescents by 91% of the 127 reporting countries. Additionally, 77% of the 116 reporting countries have included DTG as part of their second-line ART for adults and adolescents (6). WHO also recommends using DTG-containing ART for children with ≥3 kg and aged ≥4 weeks. As of July 2023, DTG-containing ART regimens are preferred for initiating treatment among infants and children in 69% of the 114 reporting countries (6).

In clinical trials, the prevalence of emergent INSTI-associated drug-resistance mutations remained low among previously INSTI-naive individuals receiving DTG-containing ART regimens with unsuppressed viral load. Among ART-experienced people living with HIV on an NNRTI-containing regimen who were switched to DTG plus two NRTIs, the prevalence of acquired INSTI-associated mutations reached 1.6% by weeks 48/96. By contrast, among ART-naive individuals initiating DTG-based ART and ART-experienced individuals with suppressed viral load who were switched to a DTG-based regimen, the prevalence of INSTI-associated drug-resistance mutations was ≤0.1% (7).

The prevalence of ADR to DTG may be higher in populations that are less closely monitored than in clinical trials. Therefore, WHO recommends monitoring HIV drug resistance to INSTIs as part of the HIV drug resistance surveillance (3). According to the 2024 WHO HIV Drug Resistance Report, populations receiving DTG-containing ART have achieved high levels of HIV VL suppression (>90%) (7). However, the report highlights that levels of HIVDR to DTG observed in country-generated survey data are higher than those seen in clinical trials (7). Four cross-sectional surveys of acquired HIV drug resistance to DTG, supported by the United States President’s Emergency Plan for AIDS Relief (PEPFAR), have been conducted in Malawi, Mozambique, Uganda, and Ukraine (7, 8). These surveys found that the prevalence of DTG resistance among individuals receiving DTG-based ART with unsuppressed VL (≥1,000 copies/mL) ranged from 3.9% to 19.6%. The highest prevalence was observed among ART-experienced people who transitioned to TLD while having high HIV viral loads (7, 8).

In *[name of country]*, *[national estimate]* people are living with HIV. As of *[indicate corresponding year]*, *[national estimate]* adults and *[national estimate]* children and adolescents received ART. According to current national ART guidance, for adults and adolescents, the preferred first-line ART scheme in *[country name]* is *[include ART regimen]*, and the standard second-line scheme is *[include ART regimen]*. The preferred first-line scheme for children weighing <20kg is *[include ART regimen],* 20 to 30kg is *[include ART regimen],* and >30kg is *[include ART regimen]*.

# **Justification**

HIV drug resistance may compromise the efficacy of ARV drugs in reducing HIV incidence and morbidity (1, 2, 9). Even in contexts where ART programs are optimally managed, drug resistance to ARVs can emerge and be transmitted (10). As the number of people receiving ARVs for HIV prevention or treatment expands, levels of resistance to ARVs will likely increase (11-13).

To minimise the emergence and spread of HIV drug resistance, WHO recommends that ART and pre-exposure prophylaxis programmes be accompanied by measures to monitor the quality of ART and pre-exposure prophylaxis services, as well as surveillance of resistance to ARV drugs (3, 4), including surveillance of acquired HIV drug resistance (14).

The results of surveys of acquired HIV drug resistance will be used to inform the national ART guideline and the national action plan to prevent and control HIV drug resistance.

# **Objectives**

## **Primary Objectives**

* To estimate the prevalence of viral suppression (viral load <1000 copies/mL) in adults, children, and adolescents receiving ART, irrespective of their specific ART regimen.
* To estimate the prevalence of HIV drug resistance to ARV drugs in adults, children, and adolescents who are receiving ART and are not virally suppressed (viral load ≥1000 copies/mL), irrespective of their specific ART regimen.

## **Secondary Objectives**

* To estimate the prevalence of viral suppression (viral load <1000 copies/mL) in adults receiving ART, stratified by ART regimen with or without DTG.
* To estimate the prevalence of viral suppression (viral load <1000 copies/mL) in children and adolescents receiving ART, stratified by ART regimen with or without DTG.
* To estimate the prevalence of HIV drug resistance to ARV drugs in adults without viral suppression (viral load ≥1000 copies/mL) and receiving ART, stratified by ART regimen with or without DTG.
* To estimate the prevalence of HIV drug resistance to ARV drugs in children and adolescents without viral suppression (viral load ≥1000 copies/mL) and receiving ART, stratified by ART regimen with or without DTG.

# **Methodology**

## **Survey Design**

A nationally representative cross-sectional survey will be conducted following WHO-recommended methods for clinic-based acquired HIV drug resistance surveys (15). The sample size was calculated following the WHO-recommended approach (**Section 7.2**).

The survey method uses a two-stage cluster design. *[Optional: Very small ART clinics, which together represent ≤10% of the national cohort of adults on ART, were excluded from the sampling frame.]* ART clinics were randomly sampled for inclusion, using probability proportional to proxy size (PPPS) sampling (**Section 7.3**).

During a 3-month period, individuals who meet the survey eligibility criteria (**Section 7.4**) will be enrolled consecutively in the selected ART clinics and, as part of the survey, receive a viral load test and an HIV drug resistance test if their viral load is ≥1000 copies/mL (**Section 7.7**).

Because the prevalence of acquired HIV drug resistance, its determinants and public health actions may differ for adults and children and adolescents, these populations will be assessed separately in simultaneous surveys. Therefore, the calculation of the sample size, the enrolment in the survey and the data analysis will be stratified for adults and, separately, for children and adolescents.

## **Sample Size Calculation**

The sample size was calculated following the WHO-recommended method for clinic-based ADR surveys (15), using the WHO sample size calculator (web tool available at: <https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/>) and adjusting the parameters to the context of *[country name]* (**See Annex 1**).

The total sample for the survey of acquired HIV drug resistance to be conducted among adults is *[include the number generated by the WHO sample size calculator generated for the country context:* [*https://worldhealthorg.shinyapps.io/ADR\_ClinicBasedMethod/*](https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/)*]*. The sample size for the survey to be conducted among children and adolescents is *[include the number generated by the WHO sample size calculator generated for the country context:* [*https://worldhealthorg.shinyapps.io/ADR\_ClinicBasedMethod/*](https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/)]. **Table 1** shows the breakdown of the sample size required by type of population (adults and children and adolescents) and by ART regimen (with or without DTG-based ART).

***Table 1.*** *Sample size of individuals to be enrolled in the acquired HIV drug resistance surveys in [country name] in [year]*

|  |  |  |  |
| --- | --- | --- | --- |
| **Population** | **Individuals taking ART with DTG** | **Individuals taking ART without DTG** | **Total sample** |
| **Sample by clinic** | **Country sample** | **Sample by clinic** | **Country sample** | **Sample by clinic** | **Country sample** |
| Adults | *[complete]* | *[complete]* | *[complete]* | *[complete]* | *[complete]* | *[complete]* |
| Children and adolescents | *[complete]* | *[complete]* | *[complete]* | *[complete]* | *[complete]* | *[complete]* |

DTG: dolutegravir; ART: antiretroviral treatment

## **Sampling Procedures**

### **ART Clinic Selection**

ART clinics were randomly sampled using systematic sampling using PPPS; the probability of a clinic being sampled is the proportion of adults (or of children and adolescents) on ART at the clinic divided by the total number of adults (or of children and adolescents) on ART.

The design assumes that the proportion of people receiving DTG-containing ART is consistent across clinics, which is why this is considered probability proportional to the proxy size. The updated weights used in the analysis will reflect the fact that these proportions can, and likely do, vary by clinic.

* + - 1. **Survey of Acquired HIV Drug Resistance Among Adults**
* A sampling frame was constructed including ART clinics serving adults (adults only and adults + children and adolescents) using the number of adults on ART by clinic in prior year. The sampling frame was constructed as follows:
	+ First column: name of ART clinics
	+ Second column: the total number of adults receiving ART in the previous year at each clinic
	+ Each ART clinic was listed in a row
* Starting at the top of the sampling frame, in a new column, the cumulative eligible population size for each row was calculated. The cumulative eligible population size of the clinic (the total number of adults receiving ART in the previous year) plus the size of all ART clinics listed in the previous rows in the sampling frame.
* The sampling interval was determined by dividing the total number of adults receiving ART (final cumulative frequency) according to the sampling frame, by the total number of clinics to be sampled.
	+ **The total number of clinics to be sampled =** the number automatically generated by the WHO sample size calculator for adults (<https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/>).
	+ **Sampling interval=** the total number of adults receiving ART in the sampling frame was *[include the corresponding number for the country]* and the total number of clinics to be sampled is *[include the corresponding number for the country]*. Therefore, the sampling interval is *[include the numerator]*/ *[include the denominator]* = *[include sample interval]* rounded to *[include rounded sample interval without decimals]*.
* A random number was selected to initiate systematic sampling. A random number between 1 and the sampling interval *[include rounded sampling interval without decimals]* was generated using the random number generator available at <https://openepi.com/Random/Random.htm>. The random number obtained to initiate sampling was *[include the random number obtained]*.
* The first ART clinic to be selected was one in which the cumulative frequency of adults receiving ART was greater than or equal to the random number generated.
* To select the second ART clinic, the initial random number and sampling interval were added (*[include the random number obtained]* + *[include the rounded sampling interval without decimals]* = *[include the result of the sum of the random number and the sampling interval]*). Subsequently, the first clinic on the list in which the cumulative frequency was greater than or equal to this number was selected (*[include the result of the sum of the random number and the sampling interval]*). To select the next ART clinic, the sampling interval was added to the previous result obtained. This procedure was repeated until all the required ART clinics were selected.

Using this method, larger ART clinics (i.e., those that serve large cohorts of adults receiving ART) may be selected more than once. For the survey to be conducted in *[name of country] in [year],* *[indicate number of clinics]* clinics were selected *[indicate number of times such clinics were selected]* times.

 **Annex 2** includes the sampling frame used for the survey of acquired HIV drug resistance among adults.

* + - 1. **Survey of Acquired HIV Drug Resistance Among Children and Adolescents**
* A sampling frame was constructed including ART clinics serving children and adolescents. That is, both ART clinics that serve only children and adolescents and ART clinics that serve adults, children and adolescents. The sampling frame was constructed as follows:
	+ First column: name of TAR clinics
	+ Second column: the total number of children and adolescents receiving ART in the previous year at each clinic
	+ Each ART clinic was listed in a row
* ART clinics serving adults, children, and adolescents that were selected for the adult survey were excluded from the sampling frame (**section 7.3.1.1**). This was done because these clinics will automatically also be used for the survey in children and adolescents and it is no longer necessary to select them again in this procedure.
* Starting at the top of the sampling frame, in a new column, the cumulative eligible population size for each row was calculated. The cumulative eligible population size of the clinic (the total number of adults receiving ART in the previous year) plus the size of all ART clinics listed in the previous rows in the sampling frame.
* The sampling interval was determined by dividing the total number of children and adolescents receiving ART (final cumulative frequency) according to the sampling frame, by the number of clinics to be sampled.
	+ **The total number of clinics to be sampled =** the number automatically generated by the WHO sample size calculator for children and adolescents (<https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/>).
	+ **The number of clinics to be sampled =** the total number of clinics to be sampled for children and adolescents minus the number of clinics serving adults, children and adolescents that were selected for the adult survey **(section 7.3.1.1**)
	+ **Sampling interval =** the total number of children and adolescents receiving ART in the sampling frame was *[include the corresponding number for the country]* and the number of clinics to be sampled is *[include the corresponding number for the country]*. Therefore, the sampling interval is *[include numerator]*/ *[include denominator]* = *[include sample interval]* rounded to *[include rounded sample interval without decimals]*.
* A random number was selected to initiate systematic sampling. A random number between 1 and the sampling interval *[include rounded sampling interval without decimals]* was generated using the random number generator available at <https://openepi.com/Random/Random.htm>. The random number obtained to initiate sampling was *[include the random number obtained]*.
* The first ART clinic that was selected was the one in which the cumulative frequency of children and adolescents receiving ART was greater than or equal to the random number generated.
* To select the second ART clinic, the initial random number and sampling interval were added (*[include the random number obtained]* + *[include the rounded sampling interval without decimals]*= *[include the result of the sum of the random number and the sampling interval]*). Subsequently, the first clinic on the list in which the cumulative frequency was greater than or equal to this number was selected (*[include the result of the sum of the random number and the sampling interval]*). To select the next ART clinic, the sampling interval was added to the previous result obtained. This procedure was repeated until all the required ART clinics had been selected.

Using this method, larger ART clinics (i.e., those that serve large cohorts of children and adolescents receiving ART) may be selected more than once. For the survey to be conducted in *[name of country] in [year],* *[indicate number of clinics] clinics* were selected *[indicate number of times such clinics were selected]* times.

**Annex 3** includes the sampling frame used for the survey of acquired HIV drug resistance among children and adolescents.

**Annex 4** includes the list of clinics randomly selected to participate in the surveys of acquired HIV drug resistance among adults and children and adolescents.

### **Selection of individuals**

Eligible individuals (**section 7.4**) will be enrolled consecutively until the ART clinic sample size is reached according to the ART regimen (with or without DTG) (**section 7.2**).

## **Eligibility Criteria**

### **Survey of Acquired HIV Resistance to ARVs in Adults**

**Inclusion criteria:**

* Adults, 18 years of age or older *[adjust for country context]*, with confirmed HIV diagnosis;
* Adults who have received ART for ≥3 months and who are taking ART at the time of enrolment, regardless of the ART clinic at which they started treatment and regardless of the ART regimen they are receiving; and
* Provide informed consent.

### **Survey of Acquired HIV Resistance to ARVs in Children and Adolescents**

**Inclusion criteria:**

* Children and adolescents, under 18 years of age *[adjust according to country context]*, with a confirmed HIV diagnosis;
* Children and adolescents who have received ART for ≥3 months and who are taking ART at the time of enrolment, regardless of the ART clinic in which they started treatment and regardless of the ART regimen they are receiving; and
* Provide informed consent and assent *[adjust for country context]*.

## **Participant Enrolment**

The survey enrolment period will be months, *[indicate the starting month and the end month corresponding to the 3-month period]*. Eligible individuals will be enrolled consecutively until the sample size is reached. The staff of each ART clinic participating in the survey will be responsible for inviting eligible individuals to participate in the survey, obtaining informed consent, and collecting the blood specimen (**section 7.7**) and the data (**section 7.8**). A unique survey identifier will be used to identify the data and blood specimen collected from each patient (**section 7.6**).

## **Participant Survey Identifier**

No personally identifiable information will be collected. Participants enrolled in the survey will be assigned a unique survey identifier. The unique survey identifier that will be assigned to each participant consists of the following five components separated by a hyphen (-):

* Country abbreviation: The International Organization for Standardization’s standard 3-letter abbreviation[[1]](#footnote-1) for *[country name],* which is *[three-letter ISO code]*
* Survey type: ADR (*acquired drug resistance)*
* Year survey will start: *[indicate year]*
* Site abbreviation: Three-letter code identifying the participating ART clinic (**Annex 4**)
* 4-digit unique patient number: This is a consecutive unique patient number assigned to a participant at that site
* Population: **a** for adults and **c** for children and adolescents

For example, if the “University HIV Clinic” *[change this example to the name of a clinic that will participate in the survey]* is selected to participate in the survey to be conducted among adults in Venezuela *[change this example to the name of the country]* in 2025 *[change this year to the year in which the survey will be conducted]*, the survey ID for the first adult enrolled would be VEN-ADR-2025-UHC-0001-a *[change this example accordingly]*.

## **Laboratory procedures**

The specimens will be collected, handled, stored and processed following WHO-recommended procedures for the surveillance of will be carried out in a laboratory designated by the WHO for this purpose. These laboratories are members of HIVResNet and operate under the operational framework of the WHO HIV Drug Resistance Laboratory, providing timely and quality-assured results (16).

### **Blood Specimen Collection**

Peripheral venous blood samples will be collected from each participant enrolled in the survey. Two 5mL tubes containing EDTA as an anticoagulant will be used for each collection. This procedure will be carried out following universal biosafety precautions for blood collection. The specimens will be identified using the survey ID (**section 7.6**).

### **Handling of Specimens**

Centrifugation, pipetting and aliquot preparation will follow standard biosafety precautions in the laboratory. The plasma will be separated as soon as possible within 6 hours of specimen collection.

Whole-blood specimens will be kept as cold as possible without freezing, at 4°C or on ice, between collection and separation. They may also be stored at room temperature (15–30°C) for short periods, preferably less than six hours. If the room temperature exceeds 30°C, an isothermal box will be used to maintain the specimens at 15–30°C.

Blood specimens will be centrifuged at room temperature at 800-1600 x g for 20 minutes. The plasma will be separated using sterile transfer pipettes, generating at least three aliquots of plasma of 1 to 1.5 ml in cryotubes labelled with the corresponding survey ID. After separation, plasma specimens will be constantly refrigerated (4°C) until the aliquots are frozen.

### **Storage and Transport of Specimens**

Plasma aliquots will be frozen as soon as possible within 48 hours after the blood is drawn. Plasma aliquots will be stored at -80°C *[alternative: -20]* in the *[name of laboratory]* (16). Freezing and thawing plasma samples will be avoided to avoid damaging the viral RNA, which could lead to failures in HIV amplification and sequencing (16).

Specimens from individuals without viral suppression (viral load ≥1000 copies/mL) will be sent for HIV drug resistance testing to the *[name of laboratory]* in a cold chain using dry ice and avoiding thawing (16). Specimens will be packed using triple packaging. The shipment of specimens (packaging, classification, and labelling) will be carried out according to the regulations of the International Air Transport Association. Import and export permits will be obtained before sending the samples.

### **HIV Viral Load Testing**

HIV viral load will be performed at *[the name of laboratory]* by RT-qPCR using the *[name of platform for HIV viral load]* platform according to the manufacturer's instructions. Viral load results will be identified using the survey ID (**section 7.6**).

### **HIV Drug Resistance Testing**

Specimens from individuals without viral suppression (viral load ≥1000 copies/mL) will be tested in WHO-designated HIV drug resistance genotyping laboratories. HIV drug resistance testing will follow WHO recommendations (16) at *[name of laboratory]*, a laboratory designated by WHO for the surveillance of HIV drug resistance. Drug resistance testing will include sequencing of the integrase, reverse-transcriptase and protease regions of the HIV-1 *pol* gene (16). The sequences will be identified using the survey ID (**section 7.6**).

The sequences will be assembled using ReCall (British Columbia Centre for Excellence in HIV/AIDS, BCCfE, Vancouver, BC) (17). The sequence quality control will be done using the WHO/BCCfE HIVDR quality control tool: <https://recall.bccfe.ca/who_qc/> (18). If pairs or groups of viral sequences with a small genetic difference (<0.5%) are identified, the HIV genotyping process will be repeated to rule out contamination errors, and the WHO-designated laboratory will link with the country to ascertain for possible epidemiological linkages of sequence pair(s).

## **Data Collection and Management**

Demographic and clinical data (**section 7.9**) will be extracted from clinical records by trained healthcare workers. The data collection form provided in **Annex 5** will be utilised for this purpose. If additional information is required, it may be supplemented through interviews with the enrolled patients.

Forms will be identified using the survey ID (**section 7.6**). At each ART clinic, designated staff will use a paper-based link log to record the survey ID with the corresponding participant ART number (clinic ID) to support data quality assurance and allow the results to be returned to the clinics for clinical management. The study coordinator at each survey site will be responsible for securely maintaining the link log in a locked file cabinet at each participating ART clinic. Access to the link log will be restricted to authorised personnel, managed by the study coordinator at each ART clinic participating in the survey. This paper-based link log will be retained for the duration of the study to ensure data integrity and will be destroyed by shredding immediately after the final data analysis is completed and all necessary validations have been performed.

Data collection forms will be sent to *[name of the institution that will be entering the data]*, where forms will be electronically registered. A survey coordinator will evaluate the quality of the data. Discrepancies, such as inconsistent or out-of-range responses and missing data, will be reported to the clinics participating in the survey. Each clinic will be contacted, as needed, to review the patient's clinical records, clarify discrepancies, or fill in missing information.

The WHO HIV drug resistance database will be the primary platform for managing survey data, ensuring robust epidemiological and sequence data quality assurance (19). Deidentified data will be entered using a standardised Excel-based upload template (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>), and corresponding HIV drug resistance genotypes in FASTA format will also be submitted to the WHO HIV drug resistance database (19). This web-based system consolidates survey-level and deidentified participant-level data, performing automated quality checks on epidemiological and sequence information before analysis. The WHO HIV drug resistance database reviews sequence data following the WHO HIV drug resistance laboratory operational framework (16).

## **Variables to be collected**

### **Patient Information**

* ART Clinic ID (**Annex 4**)
* Participant survey ID (**Section 7.6**)
* Date of birth (DD/MM/YYYY). If unknown, the age will be recorded in completed years
* Gender (male, female, transgender)
* Date when ART was first initiated (DD/MM/YYYY)
* Current ART line (first line/second line/third line/unknown)
* Current ART regimen (list the names of each ARV drug)
* Viral load testing successful and results available? (IRQ=In range; BLQ=Below lower limit of quantitation; AUQ=Above upper limit of quantitation; UNK=Result not available)
* VL result (copies/mL) from survey blood draw (VL is entered as copies/mL if the result is within assay quantitation limits. If the result is below the lower limit of quantitation, the
* lower limit is entered. If result is above the upper limit of quantitation, the upper limit is entered.)
* If VL ≥1000 copies/mL, were reverse transcriptase and protease (RT/PR) regions of HIV-1 pol gene successfully sequenced? (Indicates whether the viral genotype was successfully sequenced, and data are available. Possible values: SUC=Sequencing successful; UNS=Sequencing unsuccessful; SNA=Sequencing not attempted; UNK=Sequencing status unknown).
* If VL ≥1000 copies/mL, was the INI region of pol gene successfully sequenced? (Indicates whether the viral genotype was successfully sequenced, and data are available. Possible values: SUC=Sequencing successful; UNS=Sequencing unsuccessful; SNA=Sequencing not attempted; UNK=Sequencing status unknown).

**Optional patient-level information**

* ART history: list the name of each ARV drug
* Breastfeeding status (patient is currently breastfeeding: Y=Yes/N=No/UNK=Unknown)
* Pregnancy status (patient is currently pregnant: Y=Yes/N=No/UNK=Unknown).

### **Clinic-level Information**

* Clinic name
* ART Clinic ID (**Annex 4**)
* Date survey started (DD/MM/YYYY)
* Date sampling Completed (DD/MM/YYYY)
* Number of adults receiving DTG-containing ART who attended the ART clinic during the survey period. ***Note:*** *This variable is essential to perform the statistical analysis adjusted with statistical weights according to the survey design.*
* Number of adults receiving non-DTG-containing ART who attended the ART clinic during the survey period. ***Note:*** *This variable is essential to perform the statistical analysis adjusted with statistical weights according to the survey design.*
* Number of children and adolescents receiving DTG-containing ART who attended the ART clinic during the survey period. ***Note:*** *This variable is essential to perform the statistical analysis adjusted with statistical weights according to the survey design.*
* Number of children and adolescents receiving non-DTG-containing ART who attended the ART clinic during the survey period. ***Note:*** *This variable is essential to perform the statistical analysis adjusted with statistical weights according to the survey design.*

## **Statistical Analysis**

Viral suppression will be defined as viral load <1000 copies/ml. The WHO/BCCfE HIVDR quality control tool (18) will be used to assess the quality of the HIV sequences. If pairs or groups of viral sequences with a genetic difference <0.5%, with no apparent epidemiological link, are identified, only one sequence from that group will be included in the data analysis.

HIV resistance to ARV drugs will be predicted using the Stanford University HIVdb (20, 21). The virus will be considered resistant when the HIVdb assigns a score ≥15 to a given ARV drug. HIV resistance disaggregated by ARV drugs will be reported.

Statistical analysis will be performed according to the WHO guidelines to analyse clinic-based surveys of acquired HIV drug resistance (15), using STATA (StataCorp, College Station, TX, USA). The statistical analysis for the viral suppression outcomes will account for clustering by the selection of clinics, stratification by individuals receiving DTG-containing or non-DTG-containing regimens, the sampling weights reflecting the true sampling probability (correcting for the fact that PPPS sampling was used instead of probability proportional to size (PPS)), nonresponse due to laboratory failure, and the fact that samples are drawn from finite populations.

The statistical analysis for the ADR outcomes will use a partially weighted analysis to account for stratification by individuals receiving DTG-containing or non-DTG-containing regimens and nonresponse due to genotyping failure.

The statistical analysis will be performed separately for children and adolescents and for adults. Proportions and their 95% confidence intervals will be calculated.

## **Ethical considerations**

*[Select the appropriate option and edit accordingly:*

*Option A: This protocol has been evaluated and approved by the ethics committee [insert name of committee].*

*Option B: This protocol describes a surveillance activity for HIV resistance to ARV drugs. Therefore, local regulations have approved this protocol as a surveillance activity, and informed consent will not be required.]*

Staff participating in the survey will be trained on the purpose and appropriate procedures for enrolling participants to participate in the HIV drug resistance survey. The training will address maintaining the confidentiality of the survey participants and how to use the survey ID (**section 7.6**).

Non-identifiable demographic and clinical information will be extracted from existing medical records for the purposes of HIV antiretroviral resistance surveys. A link log will be maintained in each clinic, allowing the unique survey identifier to be associated with the patient's medical record registration number. This log will be accessible only to the clinic's health personnel, enabling them to connect the results of viral load testing and HIV genotyping to the corresponding patients in the survey. The log will be securely stored within the clinic to ensure patient confidentiality and data security.

Patients will be informed that participation in the HIV drug resistance survey is entirely voluntary (**Annexes 7–10**). They will be assured that their decision to participate or not will not affect the quality of care they receive at the ART clinic. No monetary compensation or material incentives will be provided to survey participants. However, the results of viral load testing and HIV genotyping will be beneficial for managing and enhancing the medical care they receive, though these results may take some time to become available. Additionally, the data collected from these surveys will provide valuable insights at the public health level.

For children aged 7 and above, as well as adolescents, informed consent from the parents or guardians (**Annex 8**) and the child's or adolescent's informed assent (**Annex 9** or **10**) will be required. If children or adolescents are aware of their HIV diagnosis, the informed assent in **Annex 9** will be used; if they are unaware of their diagnosis, the informed assent in **Annex 10** will be utilised. For children under 7 years of age, only the informed consent of the parents or guardians is required (**Annex 8**).

### **Risks to Participants**

The risk associated with participating in these surveys is minimal. The primary risk involves collecting blood samples through phlebotomy, which may result in a minor possibility of bruising or discomfort at the injection site. In the event of any issues arising from the blood draw, clinic staff will be available to provide the necessary medical support and care. Trained professionals will conduct all procedures to minimise any potential risks.

### **Benefits for Participants**

The results of HIV resistance tests for antiretroviral drugs will be provided to the ART clinic, enabling healthcare personnel to update the patient's clinical record with these laboratory findings. A secure link log will be maintained at each clinic, allowing the unique identifier from the survey to be linked to the patient's medical record registration number. This link log will be accessible only to the clinic's health personnel, ensuring that the laboratory results can be accurately associated with each patient participating in the survey. The link log will be securely stored within the clinic and will be available until the laboratory test results are received.

These findings may assist the treating physician in making informed decisions for the patient's clinical management, adhering to national guidelines.

# **Dissemination of results**

A comprehensive report will be prepared detailing the findings of the survey. These findings will be reviewed within the Ministry of Health and utilized to develop or update the national action plan for the prevention and control of HIV drug resistance, as well as to refine the national ART guidelines.

The report will be disseminated to various entities within the Ministry of Health and relevant partners in the national HIV response. The survey findings may also be published in scientific journals, as determined appropriate by the Ministry of Health. Additionally, demographic, clinical, and laboratory data from the survey will be shared with WHO for inclusion in regional and global analyses.

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# **Annexes**

## **Annex 1: Parameters used for sample size calculation**

**Survey of Acquired HIV Drug Resistance in Adults**

|  |  |
| --- | --- |
| **Assumptions** | **Value** |
| Expected prevalence of viral load suppression in adults receiving a DTG-based ART regimen  | 90% |
| Expected prevalence of viral suppression in adults receiving ART (overall, regardless of ART regimen) | 85% |
| Desired absolute precision (95% CI half-width) | ±5% |
| Total number of ART clinics providing ART to adults in the country (included in the sampling frame) | *[include the corresponding country number]* |
| The national percentage of adults receiving ART who receive dolutegravir-containing regimens (%)? | *[include the corresponding country number]* |
| Number of clinics to be sampled | *[include the number recommended by the WHO app for the country context:* [*https://worldhealthorg.shinyapps.io/ADR\_ClinicBasedMethod/*](https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/)*]* |
| Intracluster correlation coefficient | *[include the number generated by the WHO app for the country context:* [*https://worldhealthorg.shinyapps.io/ADR\_ClinicBasedMethod/*](https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/)*]* |
| Design effect due to imperfect weights | 1.5 |
| Viral load testing failure rate | 10% |

DTG: dolutegravir; ART: antiretroviral therapy

**Survey of Acquired HIV Drug Resistance in Children and Adolescents**

|  |  |
| --- | --- |
| **Assumptions** | **Value** |
| Expected prevalence of viral load suppression in children and adolescents receiving a DTG-based ART regimen  | 90% |
| Expected prevalence of viral suppression in children and adolescents receiving ART (overall, regardless of ART regimen) | 85% |
| Desired absolute precision (95% CI half-width) | ±5% |
| Total number of ART clinics providing ART to children and adolescents in the country (included in the sampling frame) | *[include the corresponding country number]* |
| The national percentage of children and adolescents receiving ART who receive dolutegravir-containing regimens (%)? | *[include the corresponding country number]* |
| Number of clinics to be sampled | *[include the number recommended by the WHO app for the country context:* [*https://worldhealthorg.shinyapps.io/ADR\_ClinicBasedMethod/*](https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/)*]* |
| Intracluster correlation coefficient | *[include the number generated by the WHO app for the country context:* [*https://worldhealthorg.shinyapps.io/ADR\_ClinicBasedMethod/*](https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/)*]* |
| Design effect due to imperfect weights | 1.5 |
| Viral load testing failure rate | 10% |

DTG: dolutegravir; ART: antiretroviral therapy

## **Annex 2: ART Clinic Sampling Frame — Adults**

*[The table below is included for illustrative purposes. Please replace with the table corresponding to the country]*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Clinic Name | Number of adults receiving ART in the previous year | Cumulative frequency | Selection | Selected clinic |
| Clinic A | 300 | 300 |  |   |
| Clinic B | 111 | 411 |  |   |
| Clinic C | 53 | 464 |  |   |
| Clinic D | 20 | 484 |  |   |
| Clinic E | 16 | 500 | 500\* (random start) | Clinic 1 |
| Clinic F | 356 | 856 |  |   |
| Clinic G | 353 | 1209 | 500+683\*\*=1183 | Clinic 2 |
| Clinic H | 125 | 1334 |  |   |
| Clinic I | 45 | 1379 |  |   |
| Clinic J | 604 | 1983 | 1183+683=1866 | Clinic 3 |
| Clinic K | 600 | 2583 | 1866+683=2549 | Clinic 4 |
| Clinic L | 400 | 2983 |  |   |
| Clinic M | 383 | 3366 | 2549+683=3232 | Clinic 5 |
| Clinic N | 201 | 3567 |  |   |
| Clinic O | 115 | 3682 |  |   |
| Clinic P | 105 | 3787 |  |   |
| Clinic Q  | 99 | 3886 |  |   |
| Clinic R | 25 | 3911 |  |   |
| Clinic S | 687 | 4598 | 3232+683=3915 | Clinic 6 and 7 (selected 2 times so twice as many adults must be enrolled) |
| 3915+683=4598 |
| Clinic T | 633 | 5231 |  |   |
| Clinic U | 585 | 5816 | 4598+683=5281 | Clinic 8 |
| Clinic V | 651 | 6467 | 5281+683=5964 | Clinic 9 |
| Clinic W | 517 | 6984 | 5964+683=6647 | Clinic 10 |
| Clinic X | 353 | 7337 | 6647+683=7330 | Clinic 11 |
| Clinic Y | 330 | 7667 |  |   |
| Clinic Z | 279 | 7946 |  |   |
| Clinic AA | 167 | 8113 | 7330+683=8013 | Clinic 12 |
| Clinic BB | 630 | 8743 | 8013+683=8696 | Clinic 13 |
| Clinic CC | 464 | 9207 |  |   |
| Clinic DD | 158 | 9365 |  |   |
| Clinic EE | 33 | 9398 | 8696+683=9379 | Clinic 14 |
| Clinic FF | 688 | 10086 |  |   |
| Clinic GG | 598 | 10684 | 9379+683=10062 | Clinic 15 |
| Clinic HH | 556 | 11240 | 10062+683=10745 | Clinic 16 |
| Clinic II | 465 | 11705 | 10745+683=11428 | Clinic 17 |
| Clinic JJ | 399 | 12104 |  |   |
| Clinic KK | 285 | 12389 | 11428+683=12111 | Clinic 18 |
| Clinic LL | 181 | 12570 |  |   |
| Clinic MM | 143 | 12713 |  |   |
| Clinic NN | 668 | 13381 | 12111+683=12794 | Clinic 19 |
| OO Clinic OO | 285 | 13666 | 12794+683=13477 | Clinic 20 |
| \*500=random start generated using <https://openepi.com/Random/Random.htm> \*\*683=sampling interval (13666/20) |

## **Annex 3: ART Clinic Sampling Frame — Children and Adolescents**

*[Please replace with the table corresponding to the country]*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Clinic Name | Number of children and adolescents receiving ART in the previous year | Cumulative frequency | Selection | Selected clinic |
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| \* *[include the number selected for the random start]*=random start generated using <https://openepi.com/Random/Random.htm> \*\* *[include rounded sampling interval without decimals]*=sampling interval (/) |

## **Annex 4: Selected ART clinics**

*[Please complete the table with the data corresponding to the country]*

|  |  |  |  |
| --- | --- | --- | --- |
| **ART Clinic Name** | **ART Clinic ID (3 letters)** | **Sample: number of adults eligible to enrol** | **Sample: number of children and adolescents eligible to enrol** |
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## **Annex 5: Demographic and Clinical Data Collection Form**

**Acquired HIV Drug Resistance Survey Data Collection Form**

*Note: please ensure that the informed consent has been signed before filling out this form.*

1. ART Clinic Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
2. ART Clinic ID (3-letter code): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
3. Unique Participant Survey Identifier:

ADR

(ART Clinic ID:

3-letter code)

(4-digit consecutive patient number)

(A = Adult; C = Child or Adolescent)

(3-digit country code)

(Year)

1. Date of birth: \_\_\_\_/\_\_\_\_/\_\_\_\_\_\_\_ (DD/MM/YYYY)
2. Age: \_\_\_\_\_ years old
3. Gender: ❑ F (Female) ❑ M (Male) ❑ O (Other)
4. Date when ART was first initiated: \_\_\_\_/\_\_\_\_\_/\_\_\_\_\_\_\_\_\_ (DD/MM/YYYY)
5. Current ART line:

❑ First-line ❑ Second-line ❑ Third-line ❑ Unknown

1. Current ART regime:

|  |  |
| --- | --- |
| ❑ TLD (TDF + 3TC + DTG)  | ❑ CBV (ZDV + 3TC) + LPV/r |
| ❑ TLE (TDF + 3TC + EFV)  | ❑ PTO + 3TC + LPV/r |
| ❑ ATR (TDF + FTC + EFV)  | ❑ Other (please indicate):  |
| ❑ CBV (ZDV + 3TC) + EFV |

1. ART history. Please select all the corresponding options (This variable is optional):

*[Adapt this section with the current and historical regimes used in the country – see annex 6]*

|  |  |
| --- | --- |
| ❑ TLD (TDF + 3TC + DTG)  | ❑ CBV (ZDV + 3TC) + LPV/r |
| ❑ TLE (TDF + 3TC + EFV)  | ❑ PTO + 3TC + LPV/r |
| ❑ ATR (TDF + FTC + EFV)  | ❑ Other (please indicate):  |
| ❑ CBV (ZDV + 3TC) + EFV |

**Instructions: Demographic and Clinical Data Collection Form**

| **No.** | **Variables** | **Description** | **Comment** |
| --- | --- | --- | --- |
| 1 | ART Clinic Name | Health facility where the participant was enrolled in the survey.  |  |
| 2 | ART Clinic ID | Unique identifier (3-letter code) of the health facility where the participant was enrolled in the survey. | Use the code described in this protocol in **Annex 4** |
| 3 | Unique Participant Survey Identifier | Unique identifier of the survey that is assigned to each participant who is enrolled in the survey.  | Use the format in **section 7.6** |
| 4 | Date of birth | Date of birth of the participant enrolled in the survey. | Format: DD/MM/YYYYIf the exact date is unknown, but the month and year are known, you can report partial dates. If the information is not available, report '9999'. |
| 5 | Age | Age (in years completed) of the participant enrolled in the survey. |  |
| 6 | Gender | The gender of the participant enrolled in the survey | * Female
* Male
* Other
 |
| 7 | Date when ART was first initiated | It corresponds to the date on which the participant started ART for the first time, regardless of the health service in which he or she started ART. | Format: DD/MM/YYYYIf the exact date is unknown, but the month and year are known, you can report partial dates. If the information is not available, report '9999'. |
| 8 | Current ART line | It indicates the ART line that the patient is taking at the time of being enrolled in the survey. | * First-line
* Second-line
* Third-line
 |
| 9 | Current ART Regime | Indicate which ARVs the participant is taking, at the time of the survey enrolment, as part of their current ART regimen | List the names of each ARV drug |
| 10 | ART history | Providing history of previous ART regimens is optional. | Please select all the options that apply |

## **Annex 6: ARV codes**

| **Code** | **Label** | **Description** |
| --- | --- | --- |
| STB | elvitegravir + cobicistat + tenofovir + emtricitabine | elvitegravir + cobicistat + tenofovir + emtricitabine is a 4 drug combination pill commonly known as Stribild or the Quad pill |
| ZLN | zidovudine + lamivudine + nevirapine | zidovudine + lamivudine + nevirapine is a triple combination pill known commonly as Duovir-N or Zidovex-LN |
| ATR | efavirenz + tenofovir + emtricitabine | efavirenz + tenofovir + emtricitabine is a triple drug pill commonly known as Atripla |
| TRI | nevirapine + stavudine + lamivudine | nevirapine + stavudine + lamivudine is a triple drug pill commonly known as Triomune |
| CMP | rilpivirine + tenofovir + emtricitabine | rilpivirine + tenofovir + emtricitabine is a triple drug pill commonly known as Complera or Eviplera |
| TLE | tenofovir + lamivudine + efavirenz |  tenofovir + lamivudine + efavirenz is a triple drug pill |
| TLD | tenofovir+lamivudine+dolutegravir |  tenofovir + lamivudine + dolutegravir is a triple drug pill |
| BIK | bictegravir+ emtricitabine+tenofovir alafenamide | bictegravir+ emtricitabine+tenofovir alafenamide is a triple drug pill commonly known as Biktarvy |
| GEN | emtricitabine+tenofovir alafenamide+elvitegravir | emtricitabine+tenofovir alafenamide+elvitegravir is a triple drug pill commonly known as Genvoya |
| ODE | emtricitabine+rilpivirine+tenofovir alafenamide | emtricitabine+rilpivirine+tenofovir alafenamide is a triple drug pill commonly known as Odefsey |
| SYM | darunavir+cobicistat+emtricitabine+tenofovir anafenamide | darunavir+cobicistat+emtricitabine+tenofovir anafenamide is a four drug pill commonly known as Symtuza |
| MVC | maraviroc | maraviroc is CCR5 antagnonist commonly known as Selzentry or Celsentry |
| ENF | enfuvirtide | enfuvirtide is an HIV fusion inhibitor commonly known as Fuzeon or T20 |
| EVG | elvitegravir | elvitegravir is an HIV integrase inhibitor sometimes known as GS-9137 |
| RAL | raltegravir | raltegravir is an HIV integrase inhibitor sometimes known as Isentress or MK-0518 |
| DTG | dolutegravir | dolutegravir is an HIV integrase inhibitor known as Tivicay |
| BIC | bictegravir | bictegravir is an HIV integrase inhibitor know as bictegravir |
| NVP | nevirapine | nevirapine is an NNRTI known as Viramune |
| DOR | doravirine | doravirineisn an NNRTI known as Pifeltro |
| DLV | delavirdine | delavirdine is an NNRTI known as Rescriptor |
| EFV | efavirenz | efavirenz is an NNRTI know as Sustiva, Stocrin or Efavir |
| ETR | etravirine | etravirine is an NNRTI formerly known as TMC-125 |
| RPV | rilpivirine | rilpivirine is an NNRTI known as Edurant |
| ZDV | zidovudine | zidovudine is an NRTI also known as AZT or retrovir |
| ddI | didanosine | didanosine is an NRTI known as Videx or Videx EC |
| d4T | stavudine | stavudine is an NRTI known as zerit |
| 3TC | lamivudine | lamivudine is an NRTI known as 3TC or epivir |
| ABC | abacavir | abacavir is an NRTI known as ziagen |
| TDF | tenofovir DF | tenofovir DF is an N(t)RTI known as viread |
| TAF | tenofovir alafenamide | tenofovir alafenamide |
| DES | emtricitibine + tenofovir alafenamide | emtricitibine + tenofovir alafenamide is a two drug pill commonly knonw as Descovy |
| SYF | lamivudine +tenofovir disoproxil+ efavirenz | lamivudine +tenofovir disoproxil+ efavirenz is a triple dug pill commonly known as Symfil or SymfiLo |
| FTC | emtricitabine | emtricitabine is an NRTI known as Emtriva  |
| CBV | zidovudine + lamivudine | zidovudine + lamivudine is a 2 drug combination pill known as combivir |
| EPV | abacavir + lamivudine | abacavir+lamivudine is a 2 drug combination pill known as kivexa or epzicom |
| JUL | rilpivirine+dolutegravir | rilpivirine+dolutegravir is a 2 drug pill commonly known as Juluca |
| TRV | tenofovir + emtricitabine | Fosamprenavir is a protease inhibitor known as telzir or lexiva |
| DEL | lamivudine +tenofovir disoproxil+doravirine | lamivudine +tenofovir disoproxil+doravirine is a 3 drug pill known as Delstrigo |
| TZV | zidovudine + lamivudine + abacavir | zidovudine + lamivudine + abacavir is a triple drug combination pill known as trizivir |
| SQV | saquinavir | saquniavir is a protease inhibitor known as invirase |
| IDV | indinavir | indinavir is a protease inhibitor known as crixivan |
| RTV | ritonavir | ritonavir is a protease inhibitor given in combination with other HIV protease inhibitors to boot their activity. The drug is also known as norvir |
| NFV | nelfinavir | nelfinavir is a protease inhibitor known as viracept |
| FPV | fosamprenavir | fosamprenavir is a protease inhibitor known as telzir or lexiva |
| APV | amprenavir | amprenavir is a protease inhibitor |
| ATV | atazanavir | atazanavir is a protease inhibitor known as reyataz  |
| ATV/r | atazanavir + ritonavir | atazanavir is a protease inhibitor co-formulated with ritonavir |
| TPV | tipranavir | tipranavir is a protease inhibitor known as aptivis |
| DRV | darunavir | darunavir is a protease inhibitor known as Prezista  |
| LPV/r | lopinavir + ritonavir | lopinavir+ritonavir are 2 co-formulated protease inhibitors known as kaletra or aluvia |
| OTH | Other ARV Drugs not listed above | Move to the next column and type the drug name |
| UNK | Unknown ARV Drug | Unknown ARV Drug exposure or ARV initiated |

## **Annex 7: Informed consent for adults**

*[Please adapt as required for the local context]*

**Survey on HIV Drug Resistance: Informed Consent**

**Introduction:**

Hello, my name is \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_. I work at this clinic and would like to invite you to participate in a survey about how well HIV medicines are working. Below, I'll explain what the survey involves, any possible risks, and the benefits of taking part. I'll also describe how we'll protect your privacy. Please feel free to ask any questions you have.

**Why is this survey being conducted?**

Thanks to national and international efforts, many people now have access to HIV medicines. However, sometimes these medicines stop working as well as they used to. This is known as HIV drug resistance, which can lead to treatment failure. If your treatment stops working, you may need to switch to different medicines that could be more expensive or harder to take. Understanding HIV drug resistance helps us protect your treatment options.

**What is the purpose of this survey?**

This survey aims to find out how many people in the country are experiencing HIV treatment failure. We'll also check if these failures are due to HIV drug resistance. The results will help doctors make better decisions about your treatment.

**How many people will participate in this survey?**

The survey will include *[insert number]* adults and *[insert number]* children and adolescents from across the country.

**What will happen if I participate?**

If you agree to join the survey, we'll record some basic information about you and your medical history. We'll also take a small blood sample, about the amount in two teaspoons. We use new, sterile equipment for this.

The lab results will come back to this clinic in the next few months, and your doctor will use them to evaluate your HIV treatment.

**What are the benefits of participating?**

By participating, you'll help the Ministry of Health understand how well HIV medicines are working for people like you. This information may also help us decide if your treatment needs to be adjusted.

**What are the risks of participating?**

The risks are minimal. You might feel a little pain or get a small bruise where the blood is taken. Some people may feel faint or weak, but our clinic staff will be here to help if that happens.

**Do I have to pay anything to participate?**

No, there is no cost to you for participating in this survey.

**Will I be paid for participating?**

No, you won’t receive payment for participating. However, you will receive your lab results for free.

**How will my privacy be protected?**

Your participation is confidential. Your name will not appear in any of the survey reports.

**What if I don’t want to participate?**

Your participation is entirely voluntary. If you choose not to take part, it will not affect the quality of care you receive at this clinic.

**Questions or Concerns:**

If you have any questions or concerns about the survey, or if you need to report a problem, please call *[include name and contact number]*.

**Consent:**

By signing below, you agree to participate in this survey voluntarily.

**DECLARATION OF CONSENT:**

I have read this form, or it has been read to me. I have discussed it with the clinic staff, and my questions have been answered. I agree to participate in this survey.

**Patient's Name and Signature/Fingerprint:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Name) (Signature/Fingerprint) (Date: dd/mm/yyyy)

**Health Personnel Who Explained the Survey:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Name) (Signature) (Date: dd/mm/yyyy)

## **Annex 8: Informed consent for parents (or guardians) of children and adolescents**

*[Please adapt as required for the local context]*

**Survey on HIV Drug Resistance: Informed Consent for Parents/Guardians**

**Introduction**

Hello, my name is \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_. I work at this clinic and would like to invite your child to participate in a survey to assess how well HIV medicines are working. Below, I'll explain what the survey involves, any possible risks, and the benefits of your child's participation. I'll also describe how we'll protect your child's privacy. Please feel free to ask any questions you have. You are free to decide whether or not you want your child to participate.

**Why is this survey being conducted?**

Thanks to national and international efforts, many people now have access to HIV medicines. However, sometimes these medicines stop working as well as they used to. This is known as HIV drug resistance, which can lead to treatment failure. If treatment stops working, your child may need to switch to different medicines that could be more expensive or harder to take. Understanding HIV drug resistance helps us protect your child's treatment options.

**What is the purpose of this survey?**

This survey aims to find out how many people in the country are experiencing HIV treatment failure. We'll also check if these failures are due to HIV drug resistance. The results will help doctors make better decisions about your child's treatment.

**How many people will participate in this survey?**

The survey will include *[insert number]* adults and *[insert number]* children and adolescents from across the country.

**What will happen if my child participates?**

If you agree to have your child participate in this survey, we'll record some basic information about them and their medical history. We'll also take a small blood sample, about the amount in two teaspoons. We use new, sterile equipment for this.

The lab results will come back to this clinic in the next few months, and your child's doctor will use them to evaluate their HIV treatment.

**What are the benefits of participating?**

By participating, your child will help the Ministry of Health understand how well HIV medicines are working for children and adolescents in the country. This information may also help us decide if your child's treatment needs to be adjusted.

**What are the risks of participating?**

The risks are minimal. Your child might feel a little pain or get a small bruise where the blood is taken. Some children may feel faint or weak, but our clinic staff will be here to help if that happens.

**Do I have to pay anything for my child to participate?**

No, there is no cost to you or your child for participating in this survey.

**Will my child or I be paid for participating?**

No, you and your child won’t receive payment for participating. However, your child will receive their lab results for free.

**How will my child's privacy be protected?**

Your child's participation is confidential. Their name will not appear in any of the survey reports.

**What if I don’t want my child to participate?**

Your child's participation is entirely voluntary. If you choose not to have your child take part, it will not affect the quality of care they receive at this clinic.

**Questions or Concerns:**

If you have any questions or concerns about the survey, or if you need to report a problem, please call *[include name and contact number]*.

**Consent:**

By signing below, you agree that your child will participate in this survey voluntarily.

**DECLARATION OF CONSENT:**

I have read this form, or it has been read to me. I have discussed it with the clinic staff, and my questions have been answered. I agree that my child will participate in this survey.

**Name and Signature of Parent/Guardian:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Name) (Signature/Fingerprint) (Date: dd/mm/yyyy)

**Health Personnel Who Explained the Survey:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Name) (Signature) (Date: dd/mm/yyyy)

## **Annex 9: Informed assent for children and adolescents (7 to <18 years old) who know their HIV diagnosis**

*[Please adapt as required for the local context]*

**Survey on HIV Medicines: Informed Assent for Children and Adolescents**

**(7 to <18 Years Old)**

**Introduction**

Hello, my name is \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_. I work at this clinic and would like to invite you to take part in a survey to see how well HIV medicines are working. I'll explain what we'll do, the possible risks, and the benefits of joining the survey. I'll also tell you how we'll keep your information private. If you have any questions, feel free to ask. You can decide if you want to participate or not.

**Why are we doing this survey?**

Thanks to important efforts, many people can now get medicines to treat HIV. But sometimes, these medicines don't work as well as they did at first. This is called drug resistance. When this happens, we might need to use other medicines that could be more expensive and harder to take.

**What is the purpose of this survey?**

We want to find out how many people in the country are having problems with their HIV treatment and if those problems are because of drug resistance. This will help doctors choose the best treatments.

**How many people will participate?**

This survey will include *[insert number]* adults and *[insert number]* children and teenagers from across the country.

**What will we do?**

If you decide to participate, we will write down some information about you and your health. We'll also take a small blood sample, about the amount in two teaspoons. We will use clean, new equipment. The results of the blood tests will come back to this clinic in the next few months, and we will use them to check your HIV treatment.

**What are the benefits of participating?**

The information we get will help doctors understand how well HIV medicines are working for you and others. It will also help us know if we need to change your medicine.

**What are the risks?**

The risk is low. You might feel a little pain or get a small bruise where the blood is taken. Some people might feel faint or weak, but our clinic staff will be here to help if that happens.

**Do you have to pay anything to participate?**

No, there is no cost for you to participate.

**Will you get paid for participating?**

No, you won’t receive any money or prizes for participating. But your doctor will get the results of your blood tests for free.

**How will we protect your privacy?**

All the information from the survey is private. Your name won't be on any reports.

**What if you don’t want to participate?**

It’s your choice whether to participate. If you decide not to join, it won't change the care you get at this clinic.

**Questions or Concerns:**

If you have any questions or concerns about the survey, or if you need to report a problem, you can talk to *[include reasonable/feasible contact details]*.

**Consent:**

By signing below, you agree to participate in this survey.

**DECLARATION OF ASSENT:**

I have read this form, or it has been read to me. I have talked to the clinic staff and my questions have been answered. I agree to participate in this survey.

**Participant's Name and Fingerprint:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Name) (Fingerprint) (Date: dd/mm/yyyy)

**Health Personnel Who Explained the Survey:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Name) (Signature) (Date: dd/mm/yyyy)

## **Annex 10: Informed assent for children and adolescents (7 to <18 years old) who do NOT know their HIV diagnosis**

*[Please adapt as required for the local context]*

**Survey on How Medicines Work: Informed Assent for Children and Adolescents**

**(7 to <18 Years Old)**

**Introduction:**

Hello, my name is \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_. I work at this clinic and would like to invite you to join a survey to see how well medicines work against illnesses. I'll explain what we'll do, the possible risks, and the benefits of taking part in the survey. I'll also tell you how we'll keep your information private. If you have any questions, feel free to ask. You can decide if you want to participate or not.

**Why are we doing this survey?**

Thanks to important efforts, many people can now get the medicines they need to treat their illnesses. But sometimes, these medicines don't work as well as they did at first. This is called drug resistance. When this happens, we might need to use other medicines that could be more expensive or harder to take.

**What is the purpose of this survey?**

We want to find out how many people in the country are having problems with their treatment and if these problems are because of drug resistance. This will help doctors choose the best treatments.

**How many people will participate?**

This survey will include *[insert number]* adults and *[insert number]* children and teenagers from all over the country.

**What will we do?**

If you decide to participate, we'll write down some information about you and your health. We'll also take a small blood sample, about the amount in two teaspoons. We will use clean, new equipment. The results of the blood tests will come back to this clinic in the next few months, and we'll use them to check how well your treatment is working.

**What are the benefits of participating?**

The information we get from the survey will help doctors understand how well medicines are working for you and others. It will also help us know if we need to change your medicine.

**What are the risks?**

The risk is low. You might feel a little pain or get a small bruise where the blood is taken. Some people might feel faint or weak, but our clinic staff will be here to help if that happens.

**Do you have to pay anything to participate?**

No, there is no cost for you to participate.

**Will you get paid for participating?**

No, you won’t receive any money or prizes for participating. But your doctor will get the results of your blood tests for free.

**How will we protect your privacy?**

All the information from the survey is private. Your name won't be on any reports.

**What if you don’t want to participate?**

It’s your choice whether to participate. If you decide not to join, it won't change the care you get at this clinic.

**Questions or Concerns:**

If you have any questions or concerns about the survey, or if you need to report a problem, you can talk to *[include reasonable/feasible contact details]*.

**Consent:**

By signing below, you agree to participate in this survey.

**DECLARATION OF ASSENT:**

I have read this form, or it has been read to me. I have talked to the clinic staff and my questions have been answered. I agree to participate in this survey.

**Participant's Name and Fingerprint:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Name) (Fingerprint) (Date: dd/mm/yyyy)

**Health Personnel Who Explained the Survey:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Name) (Signature) (Date: dd/mm/yyyy)

## **Annex 11: Timeline**

*[Adjust as required]*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Activity** | **Month 1** | **Month 2** | **Month 3** | **Month 4** | **Month 5** | **Month 6** | **Month 7** | **Month 8** | **Month 9** | **Month 10** | **Month 11** | **Month 12** | **Month 13** |
| **Preparatory phase** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Protocol development | X | X |   |   |   |   |   |   |   |   |   |   |   |
| Protocol approval  |   |   | X |   |   |   |   |   |   |   |   |   |   |
| Procurement of supplies |   |   |   | X | X |   |   |   |   |   |   |   |   |
| Printing of required documents (protocol, registration forms, consents, etc.) |   |   |   | X |   |   |   |   |   |   |   |   |   |
| Training |   |   |   |  | X |   |   |   |   |   |   |   |   |
| Management of export and import permits for biological samples |   |   |   | X | X |   |   |   |   |   |   |   |   |
| **Survey phase** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Enrolment of participants  |   |   |   |   |   | X | X | X |   |   |   |   |   |
| Transport of biological samples to the national laboratory for storage |   |   |   |   |   | X | X | X |   |   |   |   |   |
| Shipment of biological samples to the reference laboratory |   |   |   |   |   |   |   | X |   |   |   |   |   |
| HIV viral load testing |   |   |   |   |   |   |   |   | X | X |   |   |   |
| HIV drug resistance testing |   |   |   |   |   |   |   |   | X | X |   |   |   |
| Delivering results at the clinic level |   |   |   |   |   |   |   |   |   | X | X |   |   |
| Data analysis and reporting |   |   |   |   |   |   |   |   |   |   |   | X | X |
| Report and data disemination |   |   |   |   |   |   |   |   |   |   |   |   | X |

1. ISO 3166 Country Codes: <https://www.iso.org/obp/ui/#search/code/> [↑](#footnote-ref-1)