

HIV DRUG RESISTANCE

**GUIDANCE FOR SAMPLING
ART CLINICS IN COUNTRIES
COMBINING SURVEILLANCE
OF PRE-TREATMENT HIV
DRUG RESISTANCE AND
ACQUIRED HIV DRUG
RESISTANCE AT 12 AND 48+
MONTHS**

NOVEMBER 2017



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Guidance For Sampling ART Clinics In Countries Combining Surveillance Of Pre-Treatment HIV Drug Resistance And Acquired HIV Drug Resistance At 12 And 48+ Months.

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ACRONYMS

ADR	Acquired HIV drug resistance
ADR 12	Acquired HIV drug resistance at 12 (\pm 3) months
ADR 48+	Acquired HIV drug resistance at 48+ months
ART	Antiretroviral therapy
HIVDR	HIV drug resistance
PDR	Pre-treatment HIV drug resistance
PPPS	Probability proportional to proxy size
WHO	World Health Organization

BACKGROUND

Countries may choose to simultaneously implement HIV drug resistance (HIVDR) surveys to assess pre-treatment HIVDR (PDR) and acquired HIVDR (ADR). Simultaneous implementation quickly provides the maximum amount of information, while optimizing resources and available capacity.¹ The guidance in this technical update describes how to design a HIVDR survey to assess PDR, as well as ADR at the recommended time points: 12 (± 3) months and 48+ months. It is designed to be used as a companion to the 2014 World Health Organization (WHO) PDR and ADR concept notes.^{2,3} It provides detailed instructions on how to use “Calc 5” of the sample size calculators to design PDR and ADR surveys, available at:

<http://www.who.int/hiv/topics/drugresistance/protocols/en/>.

¹ HIV drug resistance surveillance guidance 2015 update. World Health Organization. World Health Organization, Geneva, Switzerland. 2015. Available at:

<http://www.who.int/hiv/pub/drugresistance/hiv-drug-resistance-2015-update/en/>.

² Surveillance of HIV drug resistance in adults initiating antiretroviral therapy (pre-treatment HIV drug resistance): Concept note. World Health Organization. World Health Organization, Geneva, Switzerland. 2014. Available at:

<http://www.who.int/hiv/pub/drugresistance/pretreatment/drugresistance/en/>.

³ Surveillance of HIV drug resistance in adults receiving ART. Concept note. World Health Organization. World Health Organization, Geneva, Switzerland. 2014. Available at:

http://www.who.int/hiv/pub/drugresistance/acquired_drugresistance/en/.

INTRODUCTION

In order to assess PDR, as well as ADR at 12 (± 3) months (“ADR 12”) and ADR at 48+ months (“ADR 48+”), a stratified design must be used. This means that the clinics must be selected from two distinct lists or sampling tables: one listing the “old” clinics (i.e. clinics in operation for more than 48 months) and one listing the “new” clinics (i.e. clinics in operation for less than 48 months). A nationally representative estimate of PDR and ADR 12 is calculated by combining data from the old and new clinics. It is assumed that new clinics will be unable to enrol patients on antiretroviral therapy (ART) for more than 48 months; therefore, a nationally representative estimate of ADR 48+ is calculated using data from the old clinics only.

In the first step, the country identifies the ART clinics in the country, and classifies them into two lists based on how long they have been in operation. In the second step, the country determines how many clinics to sample from each list using an Excel-based calculator. In the third step, the country selects the predetermined numbers of clinics from each list using systematic sampling.

STEP 1: PREPARE SAMPLING TABLES

1. Prepare a list of all the ART clinics in the country.
2. You may choose to exclude from this list the clinics that are excessively small or difficult to access (because they are located in a conflict zone or because they are too remote to reach); if you do so, ensure that the population excluded is less than 10% of the total population receiving ART in the country.
3. Separate the list into two distinct lists (sampling tables): one for old clinics and one for new clinics.
 - The **first sampling table** is the list of all clinics in the country that have been in operation for more than 48 months (old clinics). Clinics in this table will be able to enrol patients for PDR, ADR 12 and ADR 48+.
 - The **second sampling table** is the list of all clinics in the country that have been in operation for less than 48 months (new clinics). Clinics in this table will be able to enrol patients for PDR and ADR 12, but are expected to have too few patients eligible for ADR 48+.

STEP 2: SAMPLE SIZE CALCULATION

An Excel-based calculator has been developed to help countries determine the number of clinics to sample and the number of patients per clinic required to achieve the desired

confidence interval for each time point (see Section 9.5 of the ADR concept note).

The tool is available on the WHO HIVDR website:

<http://www.who.int/hiv/topics/drugresistance/en/>.

When implementing PDR, ADR 12 and ADR 48+ surveys simultaneously, use the “Calc 5 - PDR+ADR 12&≥48,” tab on the Excel calculator. Detailed instructions on the use of this tab are found in the tab labelled “Guide 5-PDR+ADR12&≥48, subset”.

In brief, sample size calculation is achieved by following the steps below.

1. Open tab for PDR, ADR 12 and ADR 48+ (Calc 5-PDR+ADR12&≥48, subset) of the Excel calculator.
2. Specify in the calculator the total number of old clinics (cell C33) and new clinics (cell C34) in the sampling table (after removing the small or hard-to-reach clinics).
3. In the calculator, enter the number of people on ART attending old clinics (cell D33) and the number of people on ART attending new clinics (cell D34).
4. In the calculator, enter other key parameters as specified in the green cells (column C, rows 6–20) and yellow cells (column C, rows 23–28) (e.g. desired precision, proportion of patients with prior antiretroviral drug exposure, etc.).
5. Decide how many old clinics will be selected to achieve the desired ADR 48+ outcomes. Enter a proposed number of clinics (e.g. 15) into the orange cell E33. Evaluate the feasibility of this design by assessing whether clinics can easily enrol the required sample size for outcomes at 48 months (row 33, columns L and M).

A minimum of 15 clinics should be sampled from the “old” sampling table.

6. Decide how many additional new clinics to include. Enter a proposed number of clinics (e.g. 15) into the orange cell E34. Evaluate the feasibility of this design by assessing whether new clinics can easily enrol the required sample sizes for outcomes at baseline and 12 months (row 34, columns F, G, H and I). The required number of new clinics will depend on how many patients attend these clinics. If few patients attend new clinics, few additional clinics may be required. Examples are shown below. A minimum of two clinics should be sampled from the “new” stratum. The total number of clinics sampled from both lists (cell F38) should not exceed 40.
 - a. **Example 1:** 10 000 patients attend old clinics, and 10 000 patients attend new clinics. The country decides to sample 15 clinics from the “old” table, based on the sample size calculations for ADR 48+. A suggested starting point is to sample 15 clinics from the table of new clinics. The country may then modify the number of new clinics sampled up or down, depending on logistical/financial constraints and their ability to achieve the necessary per-clinic sample size at new clinics.
 - b. **Example 2:** 30 000 patients attend old clinics, and 10 000 patients attend new clinics. The country decides to sample 18 clinics from the old table, based on the sample size calculations for ADR 48+. A

suggested starting point is to sample six clinics from the table of new clinics. This number can be calculated as: $(30\ 000/10\ 000)*(18) = 6$
 The general formula can be expressed as:
 $(\text{number of patients at old clinics} / \text{number of patients at new clinics}) * (\text{number of old clinics to be sampled}) = (\text{number of new clinics to be sampled})$

STEP 3: CLINIC SELECTION

Step 2 provided guidance on how to determine the number of old and new clinics for selection. To identify the old and new clinics to be included in the survey, a systematic sampling approach is used to select clinics from the two lists. (The systematic sampling approach is defined in Annex 1.1 of the PDR and ADR concept notes.) Countries should select clinics using probability proportional to proxy size (PPPS) sampling. PPPS is a random sampling method, in which clinics are sampled in proportion to the total number of patients receiving ART at each clinic. Clinics with more patients receiving ART are more likely to be sampled than clinics with fewer patients receiving ART.

In brief, clinic selection is achieved by following the steps below.

1. From the list of old clinics, follow the steps outlined in Annex 1.1 (PDR and ADR concept notes) to sample the predetermined number of old clinics using PPPS systematic sampling.

2. From the list of new clinics, follow the same steps to sample the predetermined number of new clinics using PPS systematic sampling.
3. As outlined in Figure 1, old clinics enrol patients for PDR, ADR 12 and ADR 48+, while new clinics enrol patients for PDR and ADR 12 only.
4. To construct nationally representative estimates of PDR and ADR 12 outcomes, clinic-level results are combined across old and new clinics, weighting for the size of each relevant population. For example, if 50% of patients initiate ART at old clinics and 50% of patients initiate ART at new clinics, the nationally representative estimate of PDR is the average of the PDR estimates from each population. In this example, the “old” and “new” populations are given equal weight.
5. To construct nationally representative estimates of ADR 48+ outcomes, clinic-level results are only combined among old clinics.

Figure 1. ART Clinic Sampling For Countries Simultaneously Implementing PDR Surveys And ADR Surveys at the 12 And 48+ Month Time Points

