TESSy - The European Surveillance System

HIV Drug Resistance Reporting Protocol and Analysis Plan 2019

HIV drug resistance surveillance data for 2018 and historical data

February 2019

Contents

Introduction

This reporting protocol is for the 2019 data call for transmitted HIV drug resistance (HIVDR) diagnoses made in 2018. Acquired drug resistance is out of scope for this surveillance data collection and reporting protocol. The objective of HIVDR data collection are:

1. Monitoring the prevalence of and trends in HIV drug resistance in newly diagnosed HIV patients, when they start antiretroviral treatment (ART) for the first time, to inform national treatment policies in the EU/EEA Member States;
2. Identification of at-risk populations for transmission of drug-resistant HIV;
3. Identification of high-risk geographical areas;
4. Reporting emerging trends in resistance to learned societies and professional associations to help guide their treatment protocol updates.

This reporting protocol covers the 31 European Union/European Economic Area (EU/EEA) countries. The reporting of HIVDR is voluntary. Reporting protocols are data collection guidelines for data managers in reporting countries.

The TESSy website contains additional generic technical information for each data collection in the general technical annex and surveillance protocol. Additional information on the HIV and AIDS data collection is available in *TESSy HIVAIDS reporting protocol*.

How to use this document

This reporting protocol has three main sections:

- *Reporting to TESSy* – contains guidelines on how to prepare data for submission to TESSy, deadlines for data submission, subject-specific information (e.g. new changes to metadata), and links to further information.
- *Annex 1 HIVDR metadata* – contains the metadata set for the subject(s) covered by this reporting protocol.
- *Annex 2 HIVDR-specific material* – contains subject-specific material relevant for distribution with the reporting protocol:
    - Case definitions.
    - Analysis plan.

Finding further information

Paragraphs denoted by the information icon tell where you can find further information.

Updated links to all the schedules, documentation and training materials mentioned in this reporting protocol are included in the technical annex on the TESSy website, including:

- Metadata sets and history.
- Tutorials for data transformation using respectively Excel and Access.
- TESSy user documentation.
- CSV and XML transport protocols.

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Reporting to TESSy

This section provides both an overview of the TESSy reporting process and tips on where you can find useful information.

The overall process is:

1. *Familiarise yourself with the data collection deadlines*.
2. *Prepare (export and transform) your data*.
3. *Check that your data comply with the metadata*.
4. *Check that your data source profile is up-to-date*.
5. *Submit your file(s) to TESSy*.
6. *Finalise and approve your submission*.

Checking the data collection schedule

An updated link to the current data collections schedule is provided in the technical annex.

The 2018 HIV/AIDS surveillance data collection opens in March 2019 and closes on **15 September 2019. Please inform us as soon as possible if you are unable to meet the 15 September deadline,** and on a case-by-case basis, we will determine whether countries reporting later can be included in the 2018 data report planned to be published in Q1 in 2020.

Table 1. Indicative timeframe for 2018 HIVDR data collection.

Description of process	Date
Data call for submission of HIVDR data	Open from March 2019
Data submission for HIVDR closes	15 September 2019
Validation of data tables	Within two-three weeks of country data upload
Data analysis and report drafting	October 2019
Validation of draft report by countries	October-November 2019
Publication of the surveillance report	Q1/2020

Preparing data

After you have exported the data from your national database, you need to ensure that the data are in a format that TESSy can accept. This applies both to the type of file submitted to TESSy (only CSV and XML files can be submitted) and to the format of the data in certain fields.

Tutorials covering how you can transform your data to the correct TESSy format using Excel or Access are available on the TESSy documents website. Information on the file formats is available in the CSV Transport Protocol and XML Transport Protocol.

Annex 1 HIVDR metadata describes the HIV/AIDS variables for reporting to TESSy, including a detailed *description of HIVDR variables in the TESSy metadata set*.

The data will be submitted in aggregate format.

Denominator data

The total number of patients tested for HIVDR needs to be collected as denominator for calculation of the overall transmitted drug resistance (TDR) prevalence.

Historical HIVDR data

It is recommended that historical data are updated every time data are submitted to TESSy. If historical data for HIVDR exist, you may upload such data since year 2000.

Checking metadata

The TESSy metadata define the fields and data formats that are valid as input to TESSy for a given subject. The metadata set is the set of standard variables that is applied for reporting to TESSy across all diseases under EU surveillance and hence defines all details of each variable and its coding. New versions reflect changes in one or more disease areas.

As surveillance requirements change, the data changes needed to support the new requirements are identified and agreed upon by nominated surveillance contact points in countries and are then implemented as changes to the TESSy metadata.

In order to ensure that your data can be saved correctly in TESSy, you therefore need to check that your data are correctly formatted according to the most recent metadata set.

It is especially important to focus on:

- **Field formats**

  Many fields require that data are formatted in a specific way. For example, dates must be in the YYYY-MM-DD format; dates in the DD/MM/YYYY format will be rejected.

- **Coded values**

  Some fields only permit the use of specific values (coded values). For example, MSM, HETERO, IDU and OTH are the coded values for *Transmission* and any other value in a *Transmission* field will be rejected.

The metadata file contains all the definitions and rules you need to comply with to format your data correctly for every subject (usually a disease). The file can be downloaded as an Excel file from the TESSy documents website.

By filtering the fields in the file by subject, you can see the fields required for your subject and the rules applying to these fields.

The technical annex provides an overview of how you work with the metadata file, and the TESSy user documentation provides in-depth details on metadata.

Checking your data source profile

Before submitting your file(s), please review the profile for your data source(s) in TESSy (go to **Data sources**), and update the information for record type HIVDRAGGR.

Complete and up-to-date data source information for each subject is important for improving interpretation of data - each surveillance system has different features that need to be taken into account when comparing data at international level.

If your data source information is out-of-date and you do not have access rights to update it, please request your National Focal Point for Surveillance or National Coordinator to do so.

In-depth information on the data source variables is available in the TESSy user documentation.

Submitting your data

Data are submitted through the TESSy web interface (go to **Upload**).

The *Technical Annex* provides an overview of how you submit files to TESSy, and the TESSy user documentation provides in-depth descriptions of all the upload methods.

Finalising your submission

The compliance of your data with the validation rules in the metadata is checked automatically during the data upload.

The result of your upload – i.e. rejected or validated – is displayed immediately after the conclusion of the check in the **Validation details** webpage. Please review the result carefully:

- If your file has been rejected, there will be a message explaining each instance of non-compliance with the metadata that you need to correct.
- If your file has been validated, there might be warnings and remarks relating to possible data quality issues or to potential overwriting of existing records that you should consider.

When your file has been validated and you are satisfied that all corrections have been made, please ensure prompt approval – unapproved uploads can block the approval of other uploads.

HIVDR verification reports are available online to check if data in TESSy are the same data the user has submitted. The data are presented either by date used for statistics or date of diagnosis. Information on the "data source" is displayed as well for countries to keep information on their national surveillance systems updated.

The TESSy user documentation provides information on reviewing validation results and adjusting reporting periods to avoid overwriting existing records.

TESSy HelpDesk

Email:	*TESSy@ecdc.europa.eu*
Telephone number:	**+46-(0)8-5860 1601**
Availability:	9:00 – 16:00 Stockholm time, Monday to Friday (except ECDC Holidays)

Changes to current metadata

HIVDRAGGR is a new record type and no changes have yet been applied.

Information on changes to the metadata for other subjects is available on the TESSy documentation website.

Annex 1 HIVDRAGGR metadata

This section describes:

- *The HIVDRAGGR metadata set*
- *Dataset structure: HIVDR aggregated record type*

Available record types

Different record types are available for European level reporting of HIV/AIDS surveillance data. HIVDR data are reported **in aggregate in the HIVDRAGGR record type**.

The dataset structure for HIVDR is provided in this section. For all the other record types related to HIV epidemiological reporting, please refer to *HIV/AIDS reporting protocol*.

Current record type version

Table 2 shows the record type available for reporting 2018 HIVDR surveillance data to TESSy.

Table 2. HIVDRAGGR record version type for 2018 data.

Subject	Record type	Aggregated record type version
HIVDR	HIVDRAGGR	HIVDRAGGR 1

Description of dataset: HIVDRAGGR, aggregated record type

The variables used for aggregate reporting include drug class, transmission, country of origin, reporting country and the number of cases. All variables are mandatory, unless otherwise specified.

1. RecordType

The record type defines the structure and the format of the data reported. It is defined by ECDC and specifies what data values TESSy expects to receive. The record type is related to the 'subject'. Only valid combinations of record type, subject and data source will be accepted. For aggregated HIVDR data, the record type is **HIVDRAGGR**.

2. RecordTypeVersion (not mandatory)

The version of the record type defines the current structure of the data reported. If the original dataset for any particular disease changes, the version number increases. All record types started at version 1 with the launch of TESSy. This variable can be omitted if a valid metadata set is provided.

*Coding for HIVDRAGGR value =**1**.*

3. Subject

The subject describes the disease or related health topic under surveillance: ***HIVDR***.

4. DataSource

The data source specifies the surveillance system from which the data on this particular disease originate. The list of available surveillance systems per country is an integral part of TESSy and will be

generated and revised/updated in collaboration with the nominated contact points for surveillance in each MS.

5. ReportingCountry

The country reporting the record.

Coding: Country = ISO 3166-1 alpha-2 (two-letter code).

6. DateUsedForStatistics

This is the date used by the national surveillance institute or organisation in the national and other official statistics to indicate the period for which HIVDRAGGR data are reported. The date is expressed as a year and should have the following format:

Coding: YYYY

7. ResistanceDrugClass

This variable specifies the drugs under HIVDR surveillance. Only low, intermediate and high-level resistance as defined by the Stanford HIVdb susceptibility algorithm should be reported. 'Potentially low' resistance will be considered as not clinically relevant and therefore be excluded.

When reporting HIVDR by drug class, the following categorisation should be used:

Nucleoside reverse transcriptase inhibitor (NRTI) class refers to any NRTI. Examples include abacavir (ABC), emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), zidovudine (ZDV);

Non-nucleoside reverse transcriptase inhibitors (NNRTI) class refers to any NNRTI. Examples include: efavirenz (EFV), etravirine (ETV), nevirapine (NVP), rilpivirine (RIL);

Protease inhibitor (PI) class refers to any PI such as atazanavir (ATV), darunavir (DRV), fosamprenavir (FPV), lopinavir/ritonavir (LPV/r), ritonavir (RTV), saquinavir (SQV), tipranavir (TPV);

Integrase inhibitor (INI)[1] class refers to any INI such as dolutegravir (DTG), raltegravir (RAL).

It is possible to code resistance to one or multiple classes of drugs. When reporting resistance against a combination of different drug classes, the resistance level can vary between the drug classes, e.g. being low for one and intermediate or high for another.

Each case should be categorised only once. If a case is reported as resistant to a combination of drug classes, the same case should not be reported again under the individual drug classes.

Coding:

NRTI

NNRTI

PI

INI

NRTI + NNRTI

PI + NRTI

PI + NNRTI

PI + NRTI + NNRTI

[1] Also referred to as integrase strand transfer inhibitors (INSTI)

8. NumberDetected

Total number of patients with laboratory-detected HIVDR against any of the existing NRTI, NNRTI, INI and PI or their combination (see ResistanceDrugClass).

Coding: *Number = Min:0; Max:999999999*

9. NumberTested

This variable specifies the number of newly diagnosed HIV patients tested during the reporting period for susceptibility upon ART initiation by route of transmission. It is required as denominator for calculation of the overall TDR prevalence.

Coding: *Number = Min:0; Max:999999999*

UNK *Unknown*

10. Transmission

Describes the most probable route of HIV transmission. 'Heterosexual contact' is used for cases for which heterosexual transmission is highly probable and which do not fit into another category. Cases not fully documented should be coded as UNK.

Coding:

HETERO	*heterosexual contact*
IDU	*ever injected drugs*
MSM	*MSM/homo or bisexual male*
OTH	*Other route of transmission (haemophiliac patient, mother-to-child transmission, nosocomial or transfusion recipient)*
UNK	*Unknown or undetermined*

11. Origin

Origin of the patient.

Coding:

REPCOUNTRY	*Case is born in/from the reporting country*
ABROAD	*Case is from abroad (not from the reporting country)*
UNK	*Unknown*

Table 3. Variables and coded values for HIVDRAGGR record type.

Variables for HIVDRAGGR	Coded values
1. RecordType	HIVDRAGGR
2. RecordTypeVersion	1
3. Subject	HIVDR
4. DataSource	Country-specific code
5. ReportingCountry	2-letter code

6. DateUsedForStatistics	YYYY
7. ResistanceDrugClass	NRTI; NNRTI; PI; INI; NRTI+NNRTI; PI+NRTI; PI+NNRTI; PI+NRTI+NNRTI
8. NumberDetected	Number of patients fulfilling the HIVDR case definition
9. NumberTested	Number of patients tested
10. Transmission	MSM, HETERO, IDU, OTH, UNK
11. Origin	REPCOUNTRY, ABROAD, UNK

Annex 2 Case definition and analysis plan

Introduction

Robust surveillance data are critical to monitor and inform the public health response to the European HIV epidemic in an accurate and timely fashion. HIV surveillance within Europe has been coordinated jointly by the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe since 2008.

ECDC is implementing a surveillance system for HIV drug resistance (HIVDR) in European Union/European Economic Area (EU/EEA) countries. Increasing the number of people receiving antiretroviral treatment (ART) among those living with HIV is critical to reduce HIV incidence and AIDS-related morbidity and mortality in the region. Preventing and managing the emergence of HIVDR is a key component of a comprehensive and effective HIV response and should be integrated into broader efforts to ensure sustainability and greatest impact. It is essential that actions to monitor, prevent and respond to HIVDR are implemented at the clinical, programme and policy levels to address the many drivers of HIVDR. To this end, WHO published a Global action plan on HIV drug resistance in July 2017[2].

HIVDR surveillance data are submitted to The European Surveillance System (TESSy); this platform enables countries to upload and also performs an automated validation to improve data quality.

This document is a practical reference guide for countries reporting HIVDR data to ECDC. It specifies the dataset for HIVDR reporting at the European level, and provides detailed definitions and guidelines for coding each variable. It also provides an analysis plan to show how the data will be used.

HIVDR is a new record type and will be tested for feasibility of reporting in 2019 with voluntary countries. The record type will be reviewed and discussed at the European HIV Surveillance Network meeting in 2020. Revisions based on network feedback will be implemented and further countries invited for reporting in 2020 to achieve larger representation of the countries of countries who collect HIVDR data.

The HIVDR record type will first be tested in an aggregate format. A pilot study on implementation of a HIVDR data collection was performed in 2017-2018 (pending publication, provided upon request).

Each country should examine the contents of the dataset in detail. All fields are mandatory and must be completed, even if the information is 'unknown'.

HIVDR case definition

HIVDR case definition:

Any **newly diagnosed treatment-naïve** HIV patient[3] tested prior to initiating HIV treatment for susceptibility to any of the 22 available antiretroviral drugs in the four main drug classes.

In context of this data collection, pre-exposure prophylaxis (PrEP) is not considered treatment and cases on PrEP are included.

Low-level, intermediate and high-level resistance will all be coded as "resistant".

Required laboratory analysis:

Sequencing of HIV protease and reverse transcriptase and/or integrase genes.

2 World Health Organization. Global action plan on HIV drug resistance 2017–2021. Geneva: WHO; 2017. Available from: *http://apps.who.int/iris/bitstream/10665/255883/1/9789241512848-eng.pdf*.

3 Commission Implementing Decision (EU) 2018/945: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018D0945&from=EN

HIVDR interpretation algorithm:

HIVDR is defined as any mutation or combination of mutations that produces low, intermediate or high-level resistance to any relevant NRTI, NNRTI, PI or INI. Potential low-level resistance is not included (see below).

Since 2000, the Stanford University has maintained a free, publicly available drug resistance mutation (DRM) interpretation system that can be accessed via an HTML or an automated web service, the Stanford HIV Drug Resistance Database (HIVdb)[4]. HIVdb is an expert system that accepts user-submitted HIV-1 sequences in FASTA data format and returns inferred levels of resistance to 22 ARV drugs including 8 PI, 7 NRTI, 4 NNRTI, and 3 INI. In the HIVdb system, each drug resistance mutation is assigned a drug penalty score and a comment; the total score for a drug is derived by adding the scores of each DRM associated with resistance to that drug. Using the total drug score, the programme reports one of the following 5 levels of inferred drug resistance: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance. The scores are the sum of each mutation penalty score for a drug. Scores of less than 10 indicate susceptibility; scores between 10 and 14 indicate potential low-level resistance; scores between 15 and 29 indicate low-level resistance; scores between 30 and 59 indicate intermediate resistance. Scores of 60 or above indicate high-level resistance. For TESSy HIVDR reporting, cases with scores of 15 and higher were defined as HIVDR.

These results are aggregated per drug class, transmission route and origin.

[4] *https://hivdb.stanford.edu/page/release-notes/*

Draft analysis plan (for information only)

Description of surveillance data

Data are presented in aggregated format, indicating number of cases per main drug class and overall resistance by main route of transmission and country of origin.

The overall HIVDR prevalence is defined as the percentage of drug-naïve newly diagnosed patients infected with an HIV virus carrying any mutation indicative of pre-treatment drug resistance. The denominator is the total number of persons tested for each risk group ("NumberTested").

Data cleaning

- Data submitter is contacted in case of lack of clarity or detected inconsistencies;
- Assessment of data completeness; minimum 30% data completeness is required for any variable to be included in any further analysis.

Calculation of specific indicators

HIVDR prevalence

Prevalence estimates will be calculated: (1) overall; (2) in each transmission group (MSM, HETERO, IDU, OTH); (3) per drug class; and (4) by reporting country and origin.

Other indicators include:

- Number of newly diagnosed HIV cases (and proportion of tested cases) with any HIVDR mutations.
- Newly diagnosed HIV infections tested for HIVDR, compared to the numbers of new HIV diagnoses reported to TESSy in 2018, by country.
- Number of HIVDR cases, by country, EU/EEA, 2018
- Number of HIVDR cases, by drug class resistance, EU/EEA, 2018
- Number of HIVDR cases, by country and drug class resistance, EU/EEA, 2018
- Number of HIVDR cases, by drug class resistance and transmission mode, EU/EEA, 2018
- Number of HIVDR cases, by country of origin, EU/EEA, 2018

Principles of analysis

Geographical grouping of countries

Data are presented for the European Union (EU) and European Economic area (EEA) countries: the EU consists of 28 Member States and the EEA consists of Norway, Liechtenstein, and Iceland. Data for country of origin are grouped by "reporting country" and "abroad" (excluding unknown).

Absolute numbers

Data are presented in absolute numbers and proportions of cases resistant to a selected drug class, where appropriate. In addition, data are presented by year, reporting country, route of transmission and origin. Due to variations in coverage, completeness and representativeness of the data, direct comparisons of absolute numbers must be done with caution.

The tables in the report use absolute numbers. Denominators are based on data collected from 'NumberTested' variable.

Reporting delays

Data are provisional due to reporting delays, and because previously reported data are subject to regular updates (e.g. detection and deletion of duplicate cases, inclusion of new information about cases already reported).

Outputs

Data presentation

The report will include tables, figures, maps, annexes.

Example of tables:

Table 1. Number and proportion of newly diagnosed HIV cases with transmitted drug resistance and number of new HIV diagnoses reported by country, EU/EEA, 2018.

Reporting country	HIVDR cases (% out of HIVDR tested cases)	New HIV diagnoses in HIV surveillance system
Austria	n (%)	n
Belgium		
…		
Total	n (%)	n

Table 2. Number and proportion of newly diagnosed HIV cases with transmitted drug resistance by transmission route, EU/EEA, 2018.

Characteristics	Number	(%)
Total number of reported HIVDR diagnoses		
Main route of transmission		
Men who have sex with men		
Heterosexual contact		
Injecting drug use		
Other		
Unknown		

Table 3. Number and proportion of newly diagnosed HIV cases with transmitted drug resistance by drug class and transmission route, EU/EEA, 2018.

Transmission route	Nr of MSM (%)	Nr of HETERO (%)	Nr of IDU (%)	Nr of UNK (%)	Nr of OTH (%)	Total
NRTI	n (%)					
NNRTI						
PI						
INI						
NRTI+NNRTI						
PI+NRTI						
PI+NNRTI						
PI+NRTI+NNRTI						

Table 4. Number and proportion of newly diagnosed HIV cases with transmitted drug resistance by reporting country and origin, EU/EEA, 2018.

Reporting country	Number of local cases (%)	Number of cases from abroad (%)	Number of cases with unknown origin (%)
Austria	n (%)	n (%)	n (%)
Belgium			
…			
Total	**n (%)**	n (%)	n (%)

Examples of figures:

Figure 1. Prevalence of HIVDR by drug class, EU/EEA, 2018.

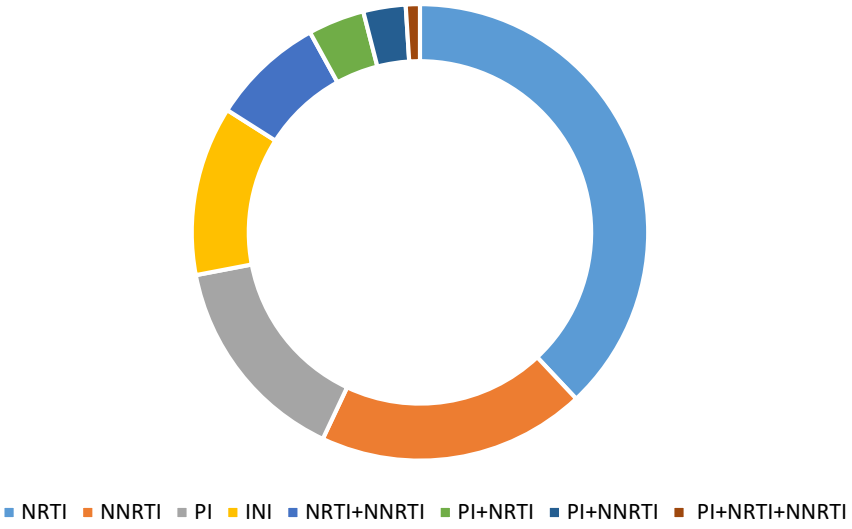
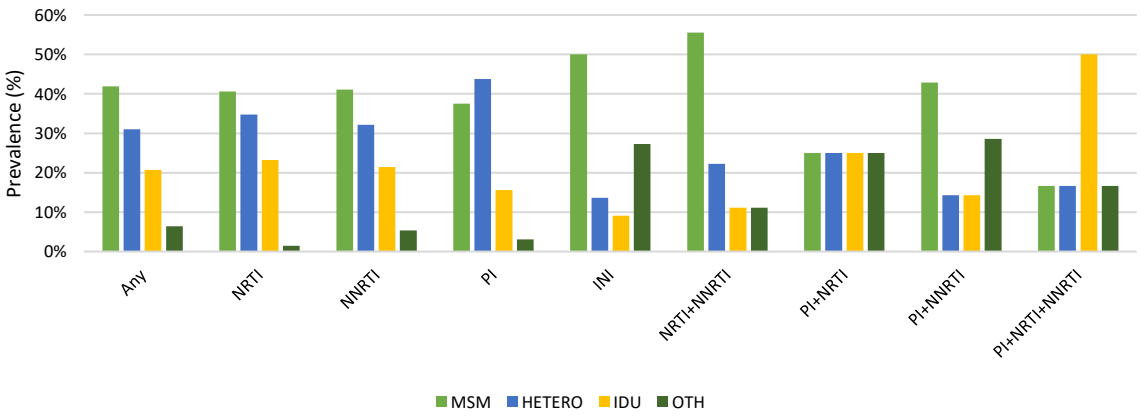


Figure 2. Prevalence of HIV drug resistance by drug class and transmission route, EU/EEA, 2018.



Output

These results will be reflected in surveillance reports or journal articles.