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TECHNICAL REPORT

Developing a reporting system for the surveillance of HIV drug resistance in Europe

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Developing a reporting system for the surveillance of HIV drug resistance in Europe

A pilot study

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Abbreviations

ADR	Acquired drug resistance
ART	Antiretroviral treatment
ARV	Antiretroviral
CD4	Cluster of differentiation 4 (immune system marker)
DRM	Drug-resistant mutation
EU/EEA	European Union/European Economic Area
HIV	Human immunodeficiency virus
HIVdb	HIV drug resistance database (at Stanford University)
HIVDR	Human immunodeficiency virus drug resistance
HSX	Heterosexual contact
IDU	Injecting drug use
INI	Integrase inhibitor
MSM	Men who have sex with men
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PI	Protease inhibitor
PrEP	Pre-exposure prophylaxis
RT	Reverse transcriptase
SPREAD	Strategy to control the spread of HIV drug resistance
SDRM	Surveillance drug resistance mutations
TDR	Transmitted drug resistance
TESSy	The European Surveillance System (at ECDC)
VL	Viral load
WHO	World Health Organization

1. Introduction

1.1 Goal

ECDC seeks to design and implement a pilot reporting system for surveillance of HIV drug resistance (HIVDR) in the European Union/European Economic Area (EU/EEA) countries. One of the priorities identified in ECDC's molecular surveillance roadmap [1] is to focus on the molecular characterisation of HIV, starting with HIVDR. ECDC intends to develop a sustainable HIVDR surveillance system that complements the overall structure of European HIV surveillance. Earlier information on HIVDR in the EU/EEA came from time-limited research projects such as SPREAD, which collected data from 29 European countries [2], though according to a recent ECDC survey, only 11/21 countries shared sequences with SPREAD [3]. The goal of the pilot project is to make recommendations for a future HIVDR surveillance system at the European level.

The epidemiological surveillance of HIV in the EU/EEA is based on the reporting of newly diagnosed HIV infections by all Member States. The system is considered to identify a very high proportion of new HIV diagnoses in the EU/EEA [4]. It has, however, a considerable lag, because European surveillance reports are usually published with an average delay of 1.5 years after the date of notification to the national surveillance system.

Increasing the number of people receiving antiretroviral treatment (ART) among those living with HIV is critical to reduce the 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 address this issue, WHO published a *Global action plan on HIV drug resistance* in July 2017 [5]. Increasing the proportion of people who achieve viral suppression during treatment will also reduce HIV transmission rates [6].

The global scale-up of ART has led to dramatic reductions in HIV-1 mortality and incidence. However, HIVDR poses a potential threat to the long-term success of ART and is emerging as a threat to the elimination of HIV/AIDS [7]. In this context, it is important to be aware that individuals who initiate triple-drug ART need to critically rely on adequate, timely information on drug resistance. So far, no systematic surveillance system for HIVDR has been established in the EU/EEA.

1.2 Surveillance of HIV drug resistance

The objectives of HIVDR surveillance are to monitor the prevalence of, and trends in, HIV drug resistance in newly diagnosed HIV patients at initiation of antiretroviral treatment in order to inform treatment policies in the EU/EEA Member States.

Due to its impact on public health and treatment guidelines, transmitted drug resistance (TDR) is the focus of HIVDR surveillance at the European level and therefore the focus of this pilot project. The prevalence of TDR is an important indicator to inform national and EU guidance on therapy initiation for newly diagnosed HIV patients [2]. Acquired drug resistance (ADR) is expected to be monitored at the clinical level in individual patients under treatment because ADR may lead to therapeutic changes.

Surveillance reports are expected to describe trends of HIVDR complemented with periodic or need-based risk assessments informing Member States on the prevalence and emergence of resistant HIV strains. These insights are expected to be an important element of future prevention policies, including treatment guidelines and public health prevention programs.

Routine surveillance will provide data on trends of HIVDR, including resistance mutations against the currently available four main drug classes: non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI) and the relatively new integrase inhibitors (INI).

1.3 Pilot project objectives

The pilot project was carried out to investigate the feasibility of HIVDR surveillance in EU/EEA countries and to make recommendations for the design and implementation of a potential future HIVDR surveillance system at the European level.

The objectives of the pilot project were to:

- design and implement a dataset on HIVDR monitoring for three reporting options;
- conduct data collection in a select number of countries;
- evaluate the surveillance mechanism (simplicity, acceptability, workload);

- assess the completeness of reporting (variables, coverage) and estimate the representativeness of national HIVDR prevalence estimates through interviews with data providers; and
- recommend options for design and implementation of HIVDR surveillance at the European level.

2. Methods

2.1 Pilot data collection

All EU/EEA countries were invited to participate in the voluntary HIVDR surveillance pilot study. Prerequisite was the submission of 2015 epidemiological data to The European Surveillance System (TESSy). Pilot data collection was scheduled for October–November 2017. The selection of countries was based on the ability to submit most of the requested HIVDR-related variables for the HIV/AIDS cases reported in 2015, data on geographical distribution in the EU/EEA, and the existence of a surveillance system for HIVDR. Participating countries appointed a designated contact point for the pilot HIVDR surveillance who communicated directly with the project team.

2.1.1 Population under surveillance

The population of interest for the HIVDR surveillance pilot was: newly diagnosed treatment-naïve HIV patients tested prior to initiating HIV treatment for susceptibility to any of the 22 available ARV drugs in the four main drug classes. In the context of this pilot, pre-exposure prophylaxis (PrEP) was not considered treatment but cases who at some point in time received PrEP were included.

The total number of patients tested for HIVDR was determined so that it could be used as denominator for the calculation of the overall HIVDR prevalence. The overall HIVDR prevalence was defined as the percentage of newly diagnosed drug-naïve patients infected with an HIV virus carrying any mutation indicative of TDR.

2.1.2 Definition of drug resistance

HIVDR is defined as any mutation or combination of mutations that produces low, intermediate, or high-level resistance to NRTI/NNRTI, PI or INI.

The presence of HIV-1 genotypic resistance prior to the start of ART is a strong predictor of the failure of that treatment. Genotypic resistance testing using DNA sequencing is often used before patients start ARV. Interpreting HIV-1 genotypic resistance tests is difficult because there are many different drug-resistant mutations (DRM), which occur in complex patterns and which have diverse effects on the ARVs within each drug class.

Since 2000, Stanford University has maintained a free, publicly available DRM interpretation system that can be accessed online, the Stanford HIV Drug Resistance Database (HIVdb) [8,9]. The DRM interpretation system of the Stanford HIVdb has been integrated into the workflows of the World Health Organization's HIV drug resistance network.

The pilot surveillance project used the Stanford HIVdb DRM interpretation algorithm for the interpretation of drug resistance [10,11]. HIVdb is an expert system that accepts user-submitted HIV-1 sequences and returns inferred levels of resistance to 22 ARV drugs, including eight protease inhibitors (PI), seven nucleoside RT inhibitors (NRTI), four non-nucleoside RT inhibitors (NNRTI), and three integrase inhibitors (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 calculated by adding the scores of each DRM associated with resistance to that drug. Using the total drug score, the system reports one of the following five 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 below 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. In this project, cases with scores of 15 and higher were defined as HIVDR. Alternatively, without using the Stanford algorithm, sequence data can also be translated into resistance mutations and resistance types as described in Bennet et al. [12].

Submitted sequences from participating countries were exported from the HIVDR project database using a standard text file in FASTA file format, with each sequence coded by a unique surveillance record identifier in the FASTA header. These files were uploaded to the Stanford HIVdb in batches of 1 000 or fewer. HIVdb returned the record identifiers with the identified DRMs per sequence, along with the penalty scores per drug. Results were then uploaded back to the HIVDR project database, using the unique surveillance record identifier to allow comparison with the original submissions.

2.1.3 Reporting options

For the HIVDR surveillance pilot project on newly diagnosed HIV patients upon initiation of ART, three reporting options were assessed.

Option A: case-based reporting with sequence data. This option provided the highest flexibility in the analysis and interpretation of data because it allows for repetition of analyses and comparisons of results as more resistance

mutations emerge over time. Sequence data can be translated into resistance mutations and resistance types as described in the *Surveillance drug resistance mutations list* [13].

Option B1: case-based reporting without sequence data but with resistance mutation coding: this option was selected when sequence data were not available or when laboratories could not provide the sequencing. Mutation code data were translated into resistance types as described in the updated *Surveillance drug resistance mutations list*.

Option B2: case-based reporting without sequence data or mutation coding but with interpretation of resistance results against the main drug classes (NNRTI, NRTI, PI, INI). Results are presented as susceptible (Stanford score <15), low resistance (Stanford score 15–29), intermediate resistance (Stanford score 30–59), and high resistance (Stanford score 60+).

Option C: aggregate reporting: if case-based reporting was not possible, the number of cases for every main drug class was reported, along with main route of transmission and overall resistance interpretation by gender.

2.1.4 Selection of HIVDR variables

The reporting protocol was developed in collaboration with experts from participating countries and included a detailed description of the variables. The following categories were included in the pilot data collection; all 28 variables are described in Annex 1.

- Diagnosis: date of diagnosis, date of notification, HIV type, main mode of transmission
- Demographics: age, gender, country of birth, reporting country
- Clinical: CD4 count at date of diagnosis, viral load, prior ART (where pre-exposure prophylaxis (PrEP) is not considered as treatment)
- Resistance: date of sampling, sequence, resistant mutation, HIV subtype, DR interpretation.

For resistance-specific data, the list of surveillance drug resistance mutations (SDRM) [12,14] was used, which has 93 mutations, including 34 NRTI-resistance mutations at 15 RT positions, 19 NNRTI-resistance mutations at 10 RT positions, and 40 PI-resistance mutations at 18 protease positions. For major integrase inhibitor mutations, consensus was developed as published in the Stanford list. The SDRM list and major integrase inhibitor mutations are available from HIVdb [15,16].

2.1.5 Data collection and analyses

Data (CSV files) were electronically submitted to a secure data exchange platform (Voozanoo, EpiConcept, Paris, France), which ensured that data handling met European security requirements for health data processing. It was agreed with the participating countries that submitted data would be removed from the server and all data permanently deleted after the pilot. For reporting options A and B, the countries needed to process the datasets, based on individual, anonymised, patient data, including the relevant sequence coding (option A) and/or resistance mutation or interpretation (option B). For reporting option C, the pilot country performed data aggregation steps in accordance with the guidelines in the reporting protocol.

Uploaded files were manually checked for the correct format and merged into a single Microsoft Excel worksheet. Records containing sequence data were exported to a TXT file (FASTA) which only contained the unique record ID and the sequence. These files were uploaded through the HIVdb web page (as described above) and output was merged into the Excel worksheet, using a unique record ID.

In order to get information about the population denominators, options A, B1 and B2 required countries to submit all case records of patients that had been tested for drug resistance, irrespective of outcome. This resulted in 'total population tested' as denominator. For option C, the aggregate number of total persons tested was required for each risk group.

2.1.6 Completeness and irregular data submission

At the data field level, 'completeness' was defined as the number of correctly formatted submissions, divided by the total number of records provided. In addition to completeness, we looked at irregularities in data collection, defined as 'interpretation problems' (answers that suggest multiple interpretations of the protocol instructions), 'formatting errors' (using a format that deviates from the protocol), and double records.

Countries that used case-based reporting with sequence reporting (option A), also reported the resistance mutation code for NRTI (option B1). We studied the congruence between the reported resistance mutation codes and the results of parsing the sequences through the Stanford HIVdb to confirm the mutation coding.

2.2 Country interviews

Semi-structured interviews were conducted with representatives of participating countries to capture their views on data collection and hear about their experiences with regard to data processing. Findings are presented in Annex 2. Participating countries were interviewed by telephone between 14 and 21 November 2017. Participants received the questionnaire in advance so they could prepare. Completed questionnaires were returned before the interview took place. Individual summary reports with the information from the questionnaire and the interviews were validated by all countries.

2.2.1 Objectives

First, the aim of the interviews was to elicit feedback in order to evaluate the pilot reporting system for HIVDR surveillance in the participating countries and understand whether a European-wide system would be both feasible and useful. Second, based on the feedback, data comparability between the different European countries could be assessed and testing coverage estimated. Finally, the interviews pointed out limitations, barriers and challenges and indicated the amount of resources needed to case reporting in accordance with the draft surveillance protocol.

2.2.2 Surveillance attributes

During the interviews, a number of surveillance attributes were addressed, such as:

- Simplicity: to understand the country's user experiences with regard to the structure of the system, the reporting process, and the way it operates
- Acceptability: to assess the willingness of EU countries to use an HIVDR surveillance system and share data with other EU countries
- Representativeness: to assess whether the reported data reflect the actual HIVDR situation in Europe and to evaluate the geographical distribution of cases across the region
- Workload: amount of time spent to process and submit data; may serve as a proxy for the timeliness of data reporting
- Barriers for DR testing and reporting: to understand the potential magnitude of underreporting and its biases, to assess the limitations of the reporting process and explore potential solutions
- Challenges: a thorough evaluation of the challenges for each country is imperative to understand what further steps need to be taken for the establishment of a sustainable HIVDR surveillance system in Europe.
- Suggestions for changes: To collect feedback and suggestions to modify HIVDR reporting for the requested dataset, variables, and the reporting protocol.

Additional detailed information was collected on the data sources for HIVDR data and the estimated coverage. The data source for HIVDR may be a different source from the one for epidemiological HIV/AIDS surveillance. The process of diagnosis and sequencing was investigated as well as the processing of test results (individual laboratories or central authorities).

3. Results

3.1 Pilot data collection

Nine countries participated in the pilot: Belgium, Denmark, France, Germany, Hungary, Ireland, the Netherlands, Slovenia, and Sweden. Countries contributed to the reporting protocol and agreed on the final version of the protocol.

3.1.1 Data submissions per country

Countries could select up to three reporting options (see above). Five countries submitted sequence data for all case-based records (option A), six countries submitted mutation codes (option B1), six submitted DRM interpretations (option B2), and three submitted aggregate data (option C), as specified below. One country (Sweden) submitted data to options B1, B2 and C, and partially to option A, since sequence data were not available for all cases. Table 1 provides an overview of the reporting options selected by the participating countries.

Table 1. Reporting options per country, HIVDR pilot surveillance, 2017

Country	Case based			Aggregate
	Sequence (A)	Mutation codes (B1)	DRM interpretation (B2)	C
Belgium	Y	Y	Y	
Denmark				Y
France				Y
Germany	Y	Y	Y	
Hungary	Y	Y	Y	
Ireland				Y
Netherlands	Y	Y	Y	
Slovenia	Y	Y	Y	
Sweden	(Y)	Y	Y	Y

In total, the nine participating countries submitted 1 790 individual records: 1 680 case-based records from six countries, 110 aggregate data records from three countries (representing 695 people tested); one country submitted two tables with aggregate data (707 people tested).

Table 2 presents the number of records on newly diagnosed HIV infections tested for HIVDR (case-based and aggregate) reported by the participating countries, compared with the number of new HIV diagnoses reported to TESSy in 2015 by the same countries. The data submitted for this pilot represent a proportion of the total number of new HIV diagnoses (diagnosed in 2015) in the participating countries, ranging from 5% to 60%. The amount of records submitted in the aggregate data option is much lower (110 records to report on 1 402 cases) compared with the case-based option, though countries commented that the workload to create aggregate records is high.

Table 2. Number of records submitted per country, HIVDR pilot surveillance, 2017

Country	Reported records for HIVDR pilot surveillance (year 2015)		New HIV diagnoses in 2015*** (% included in HIVDR surveillance pilot)
	Case-based records	Aggregate data records (no. of patients)	
Belgium	472		1001 (47%)
Germany*	618		3674 (16%)
Hungary*	14		271 (5%)
Netherlands*	277		802 (35%)
Slovenia	15		48 (31%)
Sweden	284	31 (284)	447 (60%)
France		0** (707)	3943 (18%)
Ireland		15 (293)	486 (60%)

Country	Reported records for HIVDR pilot surveillance (year 2015)		New HIV diagnoses in 2015*** (% included in HIVDR surveillance pilot)
	Case-based records	Aggregate data records (no. of patients)	
Denmark		64 (118)	277 (43%)
Total	**1 680**	**110 (1402)**	

** Germany, Hungary and the Netherlands indicated that the data source for national HIV surveillance is the same as for national HIVDR data.*
*** Data were excluded from analysis as submission was not in accordance with the reporting protocol.*

**** Data were extracted from European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 20152016 6 July 2018. Available from:*
https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/HIV-AIDS-surveillance-Europe-2015.pdf

3.1.2 Completeness of reporting and data quality

The six countries that submitted case-based data for a total of 1 680 records also reported data for all variables. The completeness of the variables is presented in Annex 3. The completeness appeared to be higher for demographical variables than for specific epidemiological and virological variables such as CD4 count, latest viral load and sequence data.

Double records

The 1 680 reported case records included four double record IDs (from one country). These appeared to be updates of previously missing information. For the purpose of this pilot, these records were kept in the datasets and subsequent analysis; this did not affect the TDR prevalence in this report.

Formatting errors

Variables were not always reported in accordance with the formats specified in the final reporting protocol. Such formatting errors would routinely be captured by automated data uploads and data checks in TESSy. Occasionally, the formatting errors were the result of errors and ambiguity in the reporting protocol (can be improved for future usage). Also, in drafting the reporting protocol, it was not foreseen that an individual case could have more than one mutation for the same antiviral drug class (only one variable field was available). When this became apparent, the participating countries agreed to report the additional mutation in the comment fields or in the mutation code fields, using comma-separated values.

Interpretation problems

Variable 10 (HIVStatus) was frequently misinterpreted. In 472 records from one single country, variable 10 was coded as 'POS' – a code not listed in the reporting protocol. This variable provides information on previous positive test results, prior to the current episode of reporting (PREVPOS).

The largest problem regarding interpretation was observed in the variables on resistance interpretation (variables 24–27, Annex 1), which are part of option B2. Only in a very small number of records, these were correctly interpreted (i.e. in accordance with the protocol: H, I, L, or S); the majority of record fields were left blank.

3.1.3 Congruence between option A and option B1

Eighty-four cases of all cases reported with sequences (option A) were also reported with the resistance mutation code for NRTI (option B1). The sequences were re-submitted to the Stanford sequence analysis tool to confirm the mutation coding. It appeared that in 80 cases (95%) the submitted mutation code was identical to the one generated by the (repeated) Stanford sequence analysis. In three cases, however, the submitted sequence could not be constructed by the Stanford HIVdb[1]; in another three cases, T215-Y was reported while a Stanford analysis produced 'N/A'. For 17 cases (20%) with a submitted mutation code for NRTI, additional NRTI mutation codes were produced by the Stanford HIVdb.

Of all cases reported with sequences (option A), 96 were also reported with the resistance mutation code for NNRTI (option B1). In 92 cases (96%), the mutation code was identical to the repeated sequence analysis. In four cases, the submitted sequence could not be processed by the Stanford HIVdb[1]. In 14 cases with a reported NNRTI mutation code, additional NNRTI mutation codes were produced by the repeated sequence analysis. This is consistent with the comment from countries that they had used the Bennet list (2009) for reporting mutation codes, while the Stanford HIVdb is more up to date and also includes polymorphisms.

Of all cases reported with sequences (option A), 20 were reported with a mutation code for PI (option B1). In 19 cases (95%), the mutation code was identical to the one found through repeated sequence analysis. In one case,

[1] Reasons for failure to process are unclear and discussed in Section 4.1.2.

the repeated sequence analysis yielded a single mutation code ('M46L') from the Stanford HIVdb while the country submitted two mutation codes ('M46L, A71V').

In 1 of 20 cases with a reported PI mutation code, additional NRTI mutation codes were produced through repeated sequence analysis. In five cases, the country reported a mutation code for PI (4 x I85-V; 1 x F53-L) while the Stanford HIVdb did not produce any mutation code.

Due to the low number of cases, reporting on INI resistance between options A and B1 could not be compared.

These results suggest a high level of congruence between a) self-reported mutation codes in the submitted HIVDR surveillance data and b) the results from processing sequences through the Stanford HIVdb. The dissimilarity of the results in 5% of the cases is most likely due to the use of the SDRM list ('Bennett list') instead of the Stanford HIVdb that was used in the pilot project.

3.1.4 Congruence between option A and option B2

When comparing variables for option B2 (Annex 1; variables 24–27) with the results of the sequence analysis (option A), a high level of congruence was found. Results are presented for NRTI, NNRTI and PI interpretation resistance levels with repeated automated sequence analysis.

Table 3. Comparison of NRTI resistance levels from sequence data and reported interpretation, HIVDR surveillance pilot, 2017

NRTI resistance level resulting from sequence analysis (score)	NRTI resistance interpretation (var 24)						Congruence
	H	I	L	S	(empty)	Total	
No level/no sequence		3		3	302	308	n.a.
1 Susceptible: 0-9		5	1	**287**	1001	1294	99.5%
2 Potential low level: 10-14[2]		3	2	**1**		6	n.a.
3 Low level: 15-29		14	**26**			40	65.0%
4 Intermediate level: 30-59	4	**8**				12	66.7%
5 High level: 60+	**17**	2			1	20	85.0%
Total	**21**	**35**	**29**	**291**	**1304**	**1680**	**98.0%**

For 308 cases, the NRTI resistance interpretation level could not be calculated from the sequence analysis because 45 sequences from three countries could not be processed[3], and one country did not submit sequences for 263 cases. For 1 304 cases, no information on resistance interpretation was submitted but the majority of those cases (n=1 001) appeared to be 'susceptible' according to the results of the sequence analysis. This lack of reporting may be due to a misunderstanding because countries erroneously thought that this variable should only be reported for penalty scores of 15 and higher (L, I, and H). For the collection of pilot data, it was agreed to report scores from 10 to 14 as 'susceptible'. The automated (repeated) sequence analysis identified six cases with NRTI scores between 10 and 14, which were classified by countries as 'susceptible' (1), 'low level' (2) and 'intermediate' (3). The mutation codes for NRTI reported by the countries, however, were all confirmed (with 100% similarity) by the (repeated) sequence analysis. Some interpretations were dissimilar: 14/40 cases, categorised as 'low-level' resistance for NRTI, were reported by one country as 'intermediate'; 4/12 cases, categorised as 'intermediate level' resistance, were reported by one country as 'high level', and 2/20 cases, categorised as 'high-level' resistance, were reported either as 'intermediate' or 'empty'.

Table 4. Comparison of NNRTI resistance levels from sequence data and reported interpretation, HIVDR surveillance pilot, 2017

NRTI resistance level resulting from sequence analysis (score)	NNRTI resistance interpretation (var 25)						Congruence
	H	I	L	S	(empty)	Total	
No level	3		1	4	300	308	n.a.
1 Susceptible: 0-9		1		**284**	947	1232	99.9%
2 Potential low level: 10-14		3	13			16	n.a.
3 Low level: 15-29		2	**41**			43	95.3%
4 Intermediate level: 30-59	7	**4**				11	36.4%
5 High level: 60+	**70**					70	100.0%
Total	**80**	**10**	**55**	**288**	**1247**	**1680**	**99.3%**

[2] Due to an omission in the reporting protocol, we did not include this option in the pilot. However, we could comply with the resistance level in the (repeated) sequence analysis.
[3] Reasons for failure to process are unclear, see discussion in Section 4.1.2.

In 308 cases, no NNRTI resistance level could be calculated from the sequence analysis because 45 sequences from three countries could not be processed[4], and one country did not submit sequences for 263 cases. For 1 247 cases, no information was available: the majority of those (947) were categorised as 'susceptible'. One case with a sequence analysis result of 'susceptible for NNRTI' was reported as 'intermediate'; however, no DRM codes were reported by the country and no codes could be identified through the sequence analysis. The sequence analysis identified 16 cases with NNRTI scores between 10 and 14. One country reported DRM codes under variable 26 (three 'I' cases). One country reported four DRM codes as 'additional DRM codes' under comments (variable 28) for four 'L' cases, and one country did not report any DRM codes for nine 'L' cases. Two of 43 cases, categorised as 'low resistance' for NNRTI, were reported by one country as 'intermediate'. Seven of 1 cases, categorised as 'intermediate resistance', were reported by one country as 'high'. All 70 cases that were categorised as 'high resistance' were coded correctly by the countries.

Table 5. Comparison of PI resistance levels from sequence data and reported interpretation, HIVDR surveillance pilot, 2017

PI resistance level resulting from sequence analysis (score)	PI resistance interpretation (var 26)						Congruence
	H	I	L	S	(blank)	Total	
no level				8	366	374	n.a.
1 Susceptible: 0-9				**230**	1028	1258	100%
2 Potential low level: 10-14			10		4	14	n.a.
3 Low level: 15-29	1		**8**		7	16	50%
4 Intermediate level: 30-59	1	**10**				11	90.9%
5 High level: 60+	**3**		1		3	7	42.9%
Total	**5**	**10**	**19**	**238**	**1408**	**1680**	99.0%

For 374 cases, no PI resistance level could be calculated from the sequence analysis because 42 sequences from three countries could not be processed, 69 sequences from one country contained only RT sequences (no PR), and one country did not submit sequences for 263 cases. For 1 408 cases, no information was available, but the majority of these cases (1 028) were categorised as 'susceptible' according to the results of a sequence analysis. The automated sequence analysis identified 14 case sequences with PI scores between 10 and 14. The countries classified 10 of these as 'L'. Seven of 16 cases, categorised as 'low resistance' for PI based on the submitted sequence, had an empty score. One case was reported as 'H', although the highest penalty score was 20. One of 11 cases, categorised as 'intermediate resistance', was reported as 'high', though the highest penalty score for a PI drug was 30. One of seven cases, categorised as 'high resistance' for PI, was reported as 'L', and for three the value was missing.

We did not analyse the submitted INI sequences during this pilot.

The results of comparing the submitted resistance interpretation in option B2 (variables 24–27) with the results of the repeated Stanford sequence analysis show an overall congruence of 98.8%, yet with a wide range. The lowest observed congruence was among the 11 cases with intermediate NNRTI resistance according to sequence analysis: only four (36.4%) were reported as intermediate, and seven as 'high'.

3.1.5 Congruence between option A and option C

Sweden supplied both case-based data (option A) and aggregate data (option C), which made it possible to compare both methods. The mutation codes (interpretation) from the 284 case-based records were compared with the data for 284 tested people reported in 31 aggregate records. Tables 6 and 7 show the differences between the results in mutation coding between reported aggregate numbers and the aggregated case records. In the case-based surveillance, 21 individuals had sequences with drug resistance mutations, according to the Stanford HIVdb. Of those, three mutations were not clinically relevant, so Sweden excluded them from aggregate reporting and labelled them as 'resistant'.

Table 6. Overview of TDR cases by sex and transmission route, aggregate reporting, Sweden, HIVDR surveillance pilot, 2017

	Male					Female				TOTAL
Transmission	MSM	HSX	IDU	UNK	OTH	HSX	IDU	OTH	UNK	
Number tested	85	65	9	18	3	83	0	2	19	284
NRTI			1			1			1	3
NNRTI	3	3				3				9
PI						1				1

[4] Reasons for failure to process are unclear and discussed in Section 4.1.2.

	Male					Female				TOTAL
INI										0
NRTI+NNRTI				1		4				5
PI+NRTI										0
PI+NNRTI										0
PI+NRTI+NNRTI										0
TDR overall	3	3	1	1	0	9	0	0	1	18
%	(3.5%)	(4.6%)	(1.1%)	(0.6%)	(0%)	(10.8%)	(0%)	(0%)	(5.3%)	(6.3%)

Table 7. Overview of TDR cases by sex and transmission route, case-based reporting, Sweden, HIVDR surveillance pilot, 2017

	Male					Female				TOTAL
Transmission	MSM	HSX	IDU	UNK	OTH	HSX	IDU	OTH	UNK	
Tested	85	65	9	18	3	83	0	2	19	284
NRTI			1	1		1		1	1	5
NNRTI	2	3		1		2				8
PI	2									2
INI										0
NRTI+NNRTI	1					4				5
PI+NRTI						1				1
PI+NNRTI										0
PI+NRTI+NNRTI										0
TDR overall	5	3	1	2	0	8	0	1	1	21
%	(5.9%)	(4.6%)	(1.1%)	(1.1%)	(0%)	(9.6%)	(0%)	(50%)	(5.3%)	(7.4%)

Table 7 uses Swedish surveillance data (option B1/B2). To verify the validity of the Swedish B1/B2 data, they were compared to results returned by HIVdb for sequence data submitted with option A. The results were identical, fully validating the B1/B2 data.

3.1.6 HIVDR prevalence and submitted sequences

The basic surveillance tables below present newly diagnosed HIV cases with TDR. The nine participating countries used either case-based (five countries) or aggregate reporting (three countries), or a combination of both (one country). Several tables present data from a subset of countries. In total, the nine participating countries provided information on 2 798 cases. Table 8 presents epidemiological characteristics of the submitted HIV cases. Annex 4 also lists the region of origin, CD4 counts and HIV types for case-based reporting.

Table 8. Characteristics of newly diagnosed HIV cases in nine EU/EEA countries, HIVDR surveillance pilot, 2017

Characteristics	Number	(%)
Total number of reported HIV diagnoses	2798	(100%)
Total number of male/female cases (%)	2248/515	(81%/19%)
Main route of transmission		
Men who have sex with men	1497	54%
Heterosexual contact	672	24%
Injecting drug use	84	3%
Other [5]	123	4%
Unknown	387	14%

Tables 9 and 10 present reported HIVDR data in newly diagnosed HIV patients tested prior to initiating HIV treatment in the year 2015. Table 9 presents data from four countries that provided aggregate HIVDR data, whereas Table 10 presents similar data from six countries that provided case-based surveillance data. Sweden is included in both tables.

[5] Note: France could not submit data on heterosexual transmission and categorised 108 women as 'other'.

The TDR prevalence is significantly different between the two tables. This is most likely due to using the SDRM-list, as compared to the Stanford HIVdb that was used for this pilot project.

Table 9. Prevalence of HIVDR[6] by gender and transmission route, aggregate reporting from four countries, HIVDR pilot surveillance, 2017

Gender/transmission	Male					Female				Total
	MSM	HSX	IDU	UNK	OTH	HSX([21])	IDU	OTH([21])	UNK	
Number tested	717	206	43	112	5	150	11	110	48	1402
NRTI	22	2	1	5	1	1	0	5	2	39
NNRTI	30	10	3	3	0	9	0	3	1	59
PI	13	4	0	2	0	1	0	2	1	23
INI[7]	1	1	0	0	0	0	0	0	0	2
NRTI+NNRTI	4	2	0	4	0	5	0	4	0	19
PI+NRTI	2	0	0	0	0	0	0	0	0	2
PI+NNRTI	1	0	0	0	0	0	0	0	0	1
PI+NRTI+NNRTI	3	1	0	0	0	1	0	1	0	6
TDR overall	76	20	4	14	1	17	0	15	4	151
%	10.6	9.7	9.3	12.4	16.6	11.3	0	13.8	8.3	10.8

Table 10. Prevalence of HIVDR[8] by gender and transmission route, case-based reporting from six countries, HIVDR pilot surveillance, 2017

Gender/transmission	Male					Female				Total
	MSM	HSX	IDU	UNK	OTH	HSX	IDU	OTH	UNK	
Number tested	865	208	34	231	7	256	5	6	62	1674
NRTI	35	4	2	9		4			3	57
NNRTI	57	12	4	26	1	15			3	118
PI	17	1		9		4				31
INI	4			1		4				9
NRTI+NNRTI	12	1		5		6			2	26
INI+PI	1									1
PI+NRTI	1									1
PI+NNRTI										0
PI+NRTI+NNRTI	1									1
TDR overall	128	18	6	50	1	33	0	0	8	244
%	14.8	8.7	17.6	21.6	14.3	12.9	0.0	0.0	12.9	14.6

Six countries that provided case-based surveillance data also submitted sequence data: 1 417/1 680 records included one or more sequences for protease or reverse transcriptase resistance. All countries submitted sequences for all individual records, except for Sweden, which provided sequences for TDR cases only. Table 11 presents the number of submitted sequences and the overall reported TDR (low, intermediate, and high) for NRTI, NNRTI, PI and INI combined.

Table 11. Reported sequences, mutation codes and proportion with TDR, case-based reporting from six countries, HIVDR surveillance pilot, 2017

Country	Records submitted	Sequences submitted	Any mutation code	% TDR	95% CI
Belgium	472	472	74	15.7%	(12.5 - 19.3)
Germany	618	618	114	18.4%	(15.5 – 21.7)
Hungary	14	14	1	7.1%	(0.2 – 33.9)
Netherlands	277	277	34	12.3%	(8.7 – 16.7)
Sweden*	284	21	21	7.4%	(4.6 – 11.1)

[6] As these are aggregate data results, there is no detailed information available about resistance levels. As per protocol, countries considered scores over 15 as 'resistant' (thus grouping low, intermediate, and high resistance).

[7] For integrase inhibitor resistance, only 403 cases were tested in one country. Three countries did not test for INI.

[8] No detailed information is available about the level of resistance in aggregate reports: scores > 15 as 'resistant' (grouping low, intermediate, and high resistance)

Country	Records submitted	Sequences submitted	Any mutation code	% TDR	95% CI
Slovenia	15	15	0	0.0%	(0 – 21.8)
Total	**1680**	**1417**	**244**	**14.5%**	**(12.9-16.3)**

** Sweden only submitted sequences for TDR cases*

The submitted records per country represent a proportion of the total amount of newly diagnosed HIV cases in 2015 reported by the countries, ranging from 5% to 60% (Table 2). Participants consider the data to be relatively representative for the country, except France and Hungary, as no bias was introduced in the sampling frame for HIVDR testing. Even with fully representative samples, the confidence intervals for TDR in countries with less than 20 observations are expected to be wide (see Table 11). The observed TDR prevalence for some countries is higher than expected, based on previous publications. For example, Belgium reported 9.9% overall TDR (42 cases with at least one DRM among 425 tested people) in 2015 [18]. This is significantly lower than the 15.7% observed in this pilot surveillance, among 472 tested individuals. This is most likely due to using the surveillance drug resistance mutation (SDRM) list instead of the Stanford HIVdb that was used for the purpose of this project. Seventy-four people were reported with either L, I or H levels of resistance for at least one DRM. For eight of these 74, a mismatch was detected when comparing the original results with the results returned by Stanford HIVdb, which classified them as 'susceptible' or 'potential low resistance', i.e. not 'resistant' as defined by this pilot. For 6 of the 74 cases with reported TDR, the sequence could not successfully be processed through the Stanford HIVdb[9]. Even if these 14 cases were excluded, TDR prevalence would still be higher than previously reported (12.7%; 60/472).

In addition, observed TDR prevalence in Germany (18.4%) was higher compared to previous reports: 10–11% TDR reported in Germany between 2013 and 2014 [19]. Recent data from Sweden (2010–2016) show results comparable to our findings [20]. In the German data we detected a discrepancy between reported resistance interpretation and calculated resistance level (through sequence analysis) in 25 of the 114 reported cases. The reported interpretation was 'resistant' for at least one relevant DRM: the sequence analysis resulted in 'susceptible' (9) or 'potential low resistance' (16). However, when discarding these 25 observations, the overall TDR remains higher than expected (14.4%). This too may be explained by the fact that Germany used the SDRM list (2009) in previous HIVDR reports while the pilot project used the Stanford HIVdb (2017). In addition, HIV sequences in Germany were, until recently, only obtained from recent infections.

Table 12 provides an overview of reported TDR in case-based (six countries) and aggregate surveillance (three countries). TDR in the case-based surveillance was calculated from reported resistance mutation codes and resistance interpretations, combining low, intermediate and high resistance for each of the four drug classes. TDR in the aggregate surveillance is as reported by the countries. The overall TDR is 14.5% among case-based surveillance and appears to be higher than the overall TDR reported in aggregate format (11.9%).

The overall TDR prevalence in this pilot (14.5%) appears to be higher than previously reported for European countries [2].

Table 12. Number of cases (and proportion of tested cases) with TDR mutations in newly diagnosed HIV cases, HIVDR pilot surveillance, 2017

Drug class	Case-based surveillance (six countries) N (%)	Aggregate surveillance (three countries) N (%)	Total (combined for nine countries) N (%)
Total number tested	1674	1118	2792
TDR any class[10]	244 (14.5%)	133 (11.9%)	377 (13.5%)
NRTI	85 (5.1%)	58 (5.2%)	143 (5.1%)
NNRTI	145 (8.6%)	71 (6.4%)	216 (7.7%)
PI	34 (2.0%)	31 (2.8%)	64 (2.3%)
INI	10 [11]	2	12 (n.a.)

Table 13 presents an overview of reported TDR as calculated from reported resistance mutation codes (option B1) and resistance interpretations (option B2), combining low, intermediate and high resistance for each of the four drug classes.

[9] Reasons for failure to process are unclear, see Section 4.1.3.

[10] At least 1 DRM reported as L, I or H in any of the groups (NRTI, NNRTI, PI, or INI)

[11] It is unknown how many individuals were tested for integrase inhibitor resistance, so no percentage is calculated

Table 13. Prevalence of TDR mutations in newly diagnosed HIV cases in six EU/EEA countries, HIVDR pilot surveillance, 2017

Mutation	Year of diagnosis = 2015
NRTI mutations	
T215rev [12]	42
M41L	14
D67N	4
K219Q	1
Other	38
NNRTI mutations	
E138Ab	13
K103N	47
G190A	4
Y181C	4
Y188L	4
Other	73
PI mutations	
L90M	2
I85-V	4
M46L	4
V82L	5
other	19
INI mutations	
157E – Q	4
163G – R	1
97T - A	5

The most frequently observed NRTI mutations T215 and M41L were seen in HIV-1 subtypes B and C, respectively. The distribution of NNRTI mutation K103N seemed to be independent of HIV-1 subtype (see Table 14). Other variations in distribution of DRM among subtypes are too small to interpret in the current dataset.

Table 14. Prevalence of mutations in newly diagnosed HIV cases with TDR, by HIV subtype in six EU/EEA countries, HIVDR pilot surveillance, 2017

Subtype	A (n=131), %	B (n=905), %	C (n=148), %	CRF 01_AE (n=97), %	CRF 02_AG (n=156), %
NRTI mutations					
T215rev	0.0	**3.8**	**0.0**	0.0	0.6
M41L	1.5	1.0	**7.4**	0.0	0.0
D67N	0.0	0.3	0.7	0.0	0.0
K219Q	0.0	0.1	0.0	0.0	0.0
L210W	0.0	0.3	0.0	0.0	0.0
M184V	0.0	0.2	0.0	0.0	0.6
NNRTI mutations					
E138A	1.5	0.3	0.0	0.0	0.6
K103N	2.3	2.8	2.7	2.1	2.6
Y181C	0.0	0.2	0.7	1.0	0.0
G190A	0.0	0.0	0.7	1.0	0.0
K101E	0.0	0.2	0.0	0.0	0.0
K103S	0.0	0.0	0.0	0.0	0.6
PI mutations					
L90M	0.0	0.1	0.0	0.0	0.0
I85-V	1.5	0.3	0.7	0.0	0.0

[12] T215rev represent revertant mutations (S/D/C/E/I/V) that can occur at position 215

Subtype	A (n=131), %	B (n=905), %	C (n=148), %	CRF 01_AE (n=97), %	CRF 02_AG (n=156), %
M46L	0.0	0.4	0.0	1.0	0.0
V82A	0.0	0.0	0.0	0.0	0.0
I54V	0.0	0.0	0.0	0.0	0.0
V82-L	0.0	0.6	0.0	0.0	0.0

3.2 Country interviews

Telephone interviews were conducted with all nine pilot countries. Persons interviewed were identical to the persons participating to the pilot surveillance project. Results are summarised below and in Annex 2.

3.2.1 Data source and national coverage

In three countries (Germany, Hungary, the Netherlands), the national data source for HIVDR test results is the same as for epidemiological HIV surveillance. For six countries, the data source is different because HIVDR samples and test results are mostly obtained through a collaboration between clinics and laboratories. Dedicated HIVDR surveillance (research) projects exist in four countries (Germany, Denmark, France, Slovenia).

Annex 2 shows that the sampling frame for HIVDR testing is 'comprehensive' (all newly diagnosed HIV patients) for six countries, 'sentinel' for one country (Denmark) and 'other' for two countries (Netherlands, Slovenia). In the interviews, estimates for the coverage of HIVDR sampling and testing range from 5% to 80% of the total population of newly diagnosed HIV patients, while a comparison of the pilot project data with the 2015 TESSy data suggests a coverage of between 5 to 60% (Table 2). Two countries (France and Hungary) did not describe all newly diagnosed patients that were tested for HIVDR; coverage was therefore too low to produce reliable prevalence rates. All other countries argued that the sampling framework or selected reference laboratories did not introduce bias towards certain transmission groups or drug classes.

The epidemiological surveillance systems in six countries (Belgium, Denmark, France, Hungary, the Netherlands, Slovenia) can link the results of HIVDR testing to individual HIV diagnoses; in most cases, this is achieved with a unique identifier (code) that requires validation from a public health institute. In some countries, linking to individual diagnoses is either explicitly forbidden by data protection laws and patient safety regulations (Germany, Sweden) or has not been explored (Ireland). Ireland is currently reviewing its procedures.

Countries use different internal procedures to organise and carry out HIVDR testing: six countries (Denmark, Germany, Hungary, Ireland, Slovenia, Sweden) report that HIVDR testing is carried out at the central level; this includes analysis and interpretation. In Belgium, France and the Netherlands, HIVDR test results are collected and analysed at the central level, but the actual sequences are obtained from regional centres or laboratories. In seven countries, sequences are directly submitted to a common national database. Barriers for HIVDR testing were mentioned by three countries (Denmark, the Netherlands, Slovenia): the lack of financial resources made it difficult to increase the coverage and accessibility of HIVDR testing.

3.2.2 HIVDR surveillance at the EU level

Five countries have the capacity to submit HIVDR test results together with epidemiological HIV surveillance data by the second quarter of the following year, while four countries reported that they would need more time to gather the required information and link the epidemiological and laboratory data.

With regard to future HIVDR surveillance datasets, all countries, except Belgium, recommend collecting case-based data with sequences. Some argue that this would be the easiest way as no additional work for recoding is required. However, experts from five countries (Belgium, Denmark, France, Germany, Ireland) argue that aggregated datasets would in fact be sufficient at the EU level. This would require an agreement on a standard protocol with regard to methods (definitions of resistance levels, attribution of resistance mutation coding and penalty scores) and procedures (data aggregation). The other experts did not agree that aggregated data collection would suffice at the EU level because information would be lost, repeated analyses could not be carried out, and comparisons across countries would not be possible.

All countries state that patient confidentiality, data protection, data ownership and data sharing were major difficulties, especially for case-based data with sequences, which needed to be discussed. Access to sequence data by third parties must be controlled. Sharing of sequence data should be restricted, based on signed agreements and surveillance protocols and agreements. Collection of aggregate datasets may help with issues of patient confidentiality and diminish data protection issues, but would also make it more difficult to analyse the data and compare them across countries. An alternative would be to collect only the mutation codes or resistance interpretations, provided that all countries could agree on common resistance interpretation rules and submit case-

based data. The results of this pilot suggest that even if common resistance interpretation rules were applied, there would still be errors in up to 5% of all results.

Countries voiced different opinions regarding the added value of internationally shared HIVDR data for public health. Most agree that there is an added value for public health while two countries question the overall strategy and purpose of HIVDR surveillance. Topics that need further discussion are the purpose and objectives of such a system, the added value of collecting HIVDR data for European surveillance, and the strategy behind the use of HIVDR surveillance data.

The pilot countries stated that any future HIVDR surveillance system in Europe should be part of the existing HIV surveillance reporting to TESSy. The pilot participants also recommended that countries investigate the possibility to align their HIVDR data collection with other international partners. For instance, countries can already upload epidemiological and sequence data to the WHO HIVDR database through standardised templates.

3.2.3 Attributes of the pilot surveillance system

Acceptability. The overall experience with the proposed HIVDR pilot surveillance system was good. The required operations were not unnecessarily complex. Countries reported that data preparation took some time because variables had to be recoded in accordance with the reporting protocol, but this only had to be done once.

Simplicity. The upload of CSV data was considered easy and simple. The reporting protocol clearly explained how to code variables, and the instructions for data submission were considered clear and simple. Suggestions were made to add DRM codes to be fully aligned with the Stanford mutation output for RT, PR, and INI. In addition, it was suggested that multiple resistance mutations should be collected (as a repeated field). The instructions for data submission should be improved because some descriptions were inconsistent between the template and the protocol or not completely clarified in the protocol.

In some countries, HIVDR datasets had to be combined with epidemiological or clinical information and required intense communication between different centres in the country (Belgium, Ireland, Slovenia).

Workload. Preparation of the dataset took between 3 and 16 hours. One country mentioned the cumbersome process of manually editing the typing differences in the dataset because HIV subtypes were spelled differently in the national systems. On average, five to six hours were needed to process the datasets. The actual upload was easy and fast (average time: 5 to 15 minutes).

Barriers for HIVDR testing and reporting. Not all requested variables could be submitted. Countries mentioned that data for the following variables were difficult to obtain: latest viral load, latest viral load date, and integrase sequence. The main barriers that require further discussions and clarification are patient confidentiality, data ownership and data protection. Some countries mentioned that extensive legal clarifications would be needed before individual sequence data could be shared, even though sharing case-based sequence data linked to epidemiological data is considered the best option from a surveillance perspective.

Comparability. All countries except France used the Stanford HIVdb database for the recoding the individual sequences into mutation codes and DR interpretation. Despite a common method for all participants, we observed differences in interpretations. France used its own algorithm. It was also pointed out that the existing SDRM list has not been updated since 2009.

4. Discussion and conclusion

4.1 Discussion

4.1.1 Strengths of the protocol

The results of the pilot project demonstrate that each of the three options for data collection is feasible and acceptable. All nine countries could provide the required data, though not all managed to produce the results in the required format. All collected data could be used to generate results and surveillance tables as specified in the reporting protocol. Submitting the data to the online system was considered easy and effortless by all participants. Preparing the datasets for submission in accordance with the reporting protocol was a challenge but acceptable and seen as a one-time chore.

The acceptability of the system was high, as was the score for simplicity in terms of submitting the data. The workload to process the dataset ranged from 3 to 16 man-hours and may reflect the lack of a European terminology standard for coding HIV resistance details in common laboratory information management systems. Developing terminology standards should be considered because terminology affects all laboratory-based surveillance.

From a surveillance perspective, the availability of sequence data in case-based reporting (option A) offers a higher degree of freedom; for option B, all information can be derived from sequence data and the system should use a single interpretation frame for all sequences in the database. This improves the comparability of TDR data and reduces methodological variation. In this pilot, sequence data were transformed to mutation codes and resistance interpretations in a series of manual batch processes, but this could be easily automated through algorithms. In addition, discrepancies observed in the congruence analysis between reported susceptibility categories in all drug classes and Stanford HIVdb categorisation results for the submitted sequences were unidirectional and consisted in minor errors (misclassification as H, I or L for S or I or L) and no major errors (misclassification as S for H, I or L).

Collecting mutation codes (option B1) and resistance interpretations (option B2) are also viable alternatives to the collection of sequences. This would be easier to implement than sequence-based reporting which requires more analytical steps. However, this pilot has demonstrated that the interpretation of sequences varies between countries, depending on which reference list is used (e.g. SDRM or HIVdb). When the reported resistance interpretation in option B2 was compared with the results of a sequence analysis, overall congruence was 98.8%. According to the results of a sequence analysis, the lowest observed congruence was among the 11 reported cases with intermediate NNRTI resistance.

4.1.2 Weaknesses and limitations of the protocol

The four countries submitting aggregate data (option C) encountered some difficulties in preparing and recoding the dataset. One country was unable to submit aggregate records as specified in the reporting protocol and submitted the aggregated outcome table as a spreadsheet. The aggregate submissions of three countries varied as some provided aggregate records to report 'zero (susceptible)' as an outcome, while others only provided aggregate records when resistance ('any mutation code') was found.

Coding ambiguities in the protocol were identified for two HIV surveillance variables, 'VLLatest' and 'HIVStatus'. Although these ambiguities may be easily corrected, it remains to be seen how feasible these variables are for EU-level case-based HIVDR surveillance.

As to the completeness of reporting and the interpretation of the reporting protocol, the variables on resistance interpretation were poorly addressed as part of option B2. Variables on resistance interpretation were rarely interpreted in accordance with the protocol (H, I, L, or S) and a majority of fields was left blank. In the future, such omissions could be avoided by an automated check on data submissions.

In addition, significant variation was found in the congruence between the resistance interpretations and the Stanford HIVdb results for the submitted sequences. It is not possible to determine from the current dataset if this variation was caused by errors in sequence data processing, or if it was the result of misclassified resistance levels at the country level. Although technically possible, there was no opportunity to design a fully automated analytical algorithm for sequence data. This will be a relevant question for future surveillance systems which use molecular diagnostics, including whole genome sequencing, that replace traditional typing methods. Some countries expressed reluctance to use the Stanford HIVdb systematically.

For any future HIVDR surveillance, three factors seem to impact feasibility and comparability more than the differences in tools and methods for molecular surveillance: differences across countries with respect to the sampling frame, the estimated coverage, and the possibility to link data to epidemiological surveillance information. The submitted data per country represent a proportion of the total amount of newly diagnosed HIV cases, ranging

from 5% to 60%. It would be useful to include an assessment of the representativeness before (and during) participation in the HIVDR surveillance system. Communication and training sessions would have to be developed for the participating countries in order to teach the proper use and interpretation of the reporting protocol.

Some countries reported that their national HIVDR analysis had resulted in different prevalence of DR than in the pilot. Perhaps this is linked to the observation that a number of countries mentioned having used the SDRM list (2009) [12] for all interpretations instead of the more up-to-date Stanford database in the pilot.

4.1.3 Errors identified in the protocol

Six countries provided case-based surveillance data for options A, B1 and B2, which allowed comparison of the different options. An error was detected in the surveillance protocol: 'potential low resistance' as a resistance level with a score ranging from 10 to 14 was not included. This contributed to the misclassification of those cases that then became ascribed to other levels of resistance within option B. This error could be corrected for by including an analysis of sequence data.

For this pilot, sequences were analysed in a semi-automatic manner: manual extraction in batches and processing through the Stanford HIVdb web interface. This worked well, and only a small portion of sequences could not be processed. It is not clear why some sequences could not be batch-processed. In some instances, the Stanford HIVdb reported that the sequence was too short, but sequence length could not explain all failures.

It was recommended that a variable should be added to aggregate reporting for those who transfer care. Another recommendation was to focus on a consistent terminology for mutations because of the spelling variations for INI mutations. The mutation code variables contained a relatively large number of formatting errors. The final protocol should correct these errors.

4.1.4 General observations

In some of the participating countries, the HIVDR pilot project found levels of TDR prevalence that were higher than expected. This could be due to selection of non-representative samples for this pilot, different methods for calculating and interpreting the resistance mutations (Stanford HIVdb yields more mutations than the SDRM list), or different cut-off values. The higher-than-reported TDR prevalence could also reflect the true TDR prevalence in the participating countries. There is also the possibility of misclassification, as discussed above, which could have contributed to the higher TDR prevalence. In addition, we observed that the total numbers of cases reported by countries differed from previously reported denominators for TDR. This suggests that the cases reported for this pilot represent different samples than those that were published previously.

This pilot demonstrates that case-based HIVDR surveillance data allow for a broader range of surveillance analysis, compared with aggregate surveillance data. In principle, option A can be considered superior, as it allows the application of a single interpretation framework to submitted sequences in order to automatically generate the variables for options B1 and B2. The pilot demonstrates that this is technically possible. However, the pilot also shows a discrepancy between the results of the sequence analysis and the variables for B1 and B2 as submitted by the countries. The reasons for these discrepancies have not become apparent in this pilot yet and deserve further investigation. Based on the current results, it is not possible to say which data are more reliable.

All countries seem to agree that case-based surveillance provides the best information for surveillance of HIVDR at the EU level, with detailed information on transmission routes, CD4 status, and a wide range of mutation codes. From that perspective, further work on addressing the barriers to submitting case-based datasets is needed, especially since several countries expressed concerns in this regard.

It may be argued that data on viral load could be omitted from the dataset to simplify the process, i.e. reduce the number of variables for HIVDR surveillance that need to be collected for, and included in, the surveillance tables.

Routine surveillance tables should include a valid DRM interpretation.

As of now, data on CD4 counts are not sufficiently complete to provide insights into the stage of the infection.

4.2 Conclusions and suggestions

Based on the results of this pilot, and considering the above discussion, the following can be concluded:

- All nine pilot EU countries have the capacity to participate in EU-wide surveillance of HIVDR.
- There are no technical obstacles for countries to submit either case-based or aggregate data of newly diagnosed HIV cases with available information on drug resistance testing.
- Individual countries may encounter legal or political barriers to the submission of case-based HIV sequence data because health data are considered sensitive information, and data protection may be insufficient or

perceived as insufficient to protect patient anonymity. Data protection appears to be a major obstacle for data submission in some countries.

- Over the duration of the pilot project, no legal or political barriers were encountered with regard to the submission of aggregate surveillance data for HIVDR.
- Countries use similar tools and methods for HIVDR testing and categorisation methods that produce categorical phenotypic data that are fairly congruent with current interpretation standards and WHO-endorsed reference database.
- System disease coverage and the possibility to link data with epidemiological information affects the feasibility of HIVDR surveillance.
- Aggregate reporting may be sufficient, provided there is a concise and agreed-upon protocol, including adherence to WHO protocol for sequence analysis and inferred ARV susceptibility phenotype characterisation for all countries; this approach, however, may pose a higher burden on the staff preparing the data.

Apart from the above conclusions, the following should be taken into account by ECDC when planning the next steps:

- The development and roll-out of an EU-wide HIVDR surveillance system, based on the three options that were piloted in this project. The case-based approach appears to pose a lower burden on the countries than the use of aggregated data. Surveillance objectives have to be carefully considered. Also needed is a review what each of the surveillance options can deliver and what not.
- The need to take into account the legal restrictions imposed on the submission of case-based sequence data in EU Member States. This implies that ECDC should also provide guidance on data protection issues for countries that want to participate in a future HIVDR surveillance network. Of particular importance is the addition of data privacy guidance to the general terms for data submission to TESSy.
- There is a need for reliable denominator information for prevalence calculation for the submitted HIVDR data and how this relates to the reported cases for HIV surveillance.
- There needs to be more work on linking data on HIVDR test results with relevant epidemiological data to achieve sufficient levels of surveillance data completeness.
- The participating countries analysed their own final surveillance dataset in order to validate the results of the semi-automatic sequence analysis. This may explain the differences between observed and assumed TDR prevalence.

Annex 1a. Variables for pilot HIVDR data collection

Variables case-based reporting	TESSy report type	Included in HIVDR pilot (all variables optional)
System-related variables		
1. RecordID	Mandatory	+
2. ReportingCountry	Mandatory	+
Diagnosis Information		
3. DateOfDiagnosis	Mandatory	+
4. DateOfNotification	Mandatory	+
5. HIVType	Mandatory	+
6. Transmission	Mandatory	+
7. FirstCD4Count	Mandatory	+
8. FirstCD4Date	Mandatory	+
9. VLLatest	Optional	+
10. VLLatestDate	Optional	+
Demographics		
11. Gender	Mandatory	+
12. Age	Mandatory	+
13. CountryOfBirth	Mandatory	+
14. RegionOfOrigin	Optional	+
HIVDR-related variables		
15. DateOfDRSampling	-	+
16. HIVSubType	-	+
17. PriorART	-	+
18. SequenceHIV	-	+
19. ResistanceMutationCodeNRTI	-	SDRM list
20. ResistanceInterpretationNRTI	-	S; L; I; H [13]
21. ResistanceMutationCodeNNRTI	-	SDRM list
22. ResistanceInterpretationNNRTI	-	S; L; I; H
23. ResistanceMutationCodePI	-	SDRM list
24. ResistanceInterpretationPI	-	S; L; I; H
25. ResistanceMutationCodeINI	-	Stanford HIVdb
26. ResistanceInterpretationINI	-	S; L; I; H
Variables, aggregated	**TESSy report type**	**Included in HIVDR pilot**
1. DateUsedForStatistics	Mandatory	YYYY=2015
2. ReportingCountry	Mandatory	+
3. Gender	Mandatory	+
4. Transmission	Mandatory	+
5. ResistanceTested	-	Number of patients tested
6. ResistanceDrugClass	-	NRTI; NNRTI; PI; INI; NRTI+NNRTI; PI+NRTI; PI+NNRTI; PI+NRTI+NNRTI
7. Number of cases	Mandatory	+

[13] 'S; L; I; H' refer to 'susceptible, low, intermediate and high-level' resistance

Annex 1b. Description of variables: case-based reporting

There are 28 variables for HIVDR case-based reporting, divided into diagnosis information, demographics, clinical information, and sequence information or resistant mutation.

Note: Sequences are only required for cases with any type of resistance mutation.

1. RecordID

The identifier should be provided by the country, it should be unique and, preferably, be the same as the identifier used for the epidemiological surveillance of HIV diagnosis in TESSy (if available). If this is not possible, another unique identifier should be selected, e.g. the laboratory identification number of the sample.

Coding:

- Text max. 80 characters
- UNK Unknown

2. ReportingCountry

This variable identifies the country that participates in the pilot and reports the case. A list of ISO country codes is provided. This variable should be included by the Member State by default.

Coding:

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

3. DateOfDiagnosis

The date of first HIV diagnosis in the reporting country; clinical or laboratory diagnosis. Date should be provided as exact date.

Coding:

- Date YYYY-MM-DD (preferred)

Incomplete date: YYYY-MM, YYYY, YYYY-WW, YYYY-Q

4. HIVType

This variable specifies the type of HIV infection.

Coding:

- HIV1 HIV1 only
- HIV12 HIV1 and HIV2 (co-infection)
- HIV2 HIV2 only
- UNK Unknown

5. Transmission

Describes the most probable route of transmission of HIV. It is classified by sexual transmission: sex between men or heterosexual contact. The other categories refer to those who ever injected drugs, mother-to-child transmission, transfusion recipients, nosocomial infection. Nosocomial infection includes patients infected in healthcare settings. Cases of occupational exposure should be classified as 'exposure unknown' or 'undetermined'. Cases which are not fully documented should also be coded as 'unknown' or 'undetermined'.

Coding:

- HAEMO haemophiliac patient
- HETERO heterosexual contact
- IDU ever injected drugs
- MSM men who have sex with men
- MTCT mother-to-child-transmission
- NOSO nosocomial infection
- TRANSFU transfusion recipient
- UNK unknown or undetermined

6. FirstCD4Count

The first CD4 cell count recorded following HIV diagnosis. The variable specifies the first CD4 cells count taken. Dates during the year following the reporting year are acceptable (i.e. CD4 cell count in January 2016 for a person diagnosed in November 2015).

Coding:

- Numeric value 0–6000
- -9 Unknown

7. FirstCD4Date

Date of first available CD4 cell count. The exact date is preferred; incomplete dates (e.g. week, quarter, month, year) are allowed as well.

Coding:

- Date YYYY-MM-DD
- Incomplete date YYYY-MM, YYYY, YYYY-WW, YYYY-Q
- 11-11-1911 Unknown

8. VLLatest

Last known viral load. Enter the numeric value of the last viral load. If viral load is 'undetectable' (i.e. no numeric value is provided by the test), code as '0'. If the latest viral load is unknown, code as 'UNK'.

Coding:

- Numeric value (up to seven digits)
- 0 Low or Undetectable
- -9 Unknown

9. VLLatestDate

Date of last known viral load assessment (date of blood test if available). The exact date is preferred and should be provided if available; incomplete dates are also accepted.

Coding:

- Date YYYY-MM-DD
- Incomplete date YYYY-MM, YYYY, YYYY-WW, YYYY-Q
- 11-11-1911 Unknown

10. HIVStatus

This variable provides information on previous positive test results, prior to the current episode of reporting. This variable distinguishes cases that are 'newly diagnosed' from cases who had a positive HIV test in the past but were tested and/or reported for the first time in another country (e.g. transfer of care).

- Coding: NEG Not known to have been previously tested positive
- PREVPOS Previously tested, HIV positive
- UNK Unknown i.e. no previous confirmed test result on record

11. Gender

Gender of the infected person. Transsexual persons should be coded as 'Other'.

Coding:

- M Male
- F Female
- O Other (e.g. transsexual)
- UNK Unknown (default value)

12. Age

This is the age (in years) of the person at the time of diagnosis.

Coding:

- Num 0–100
- -9 Unknown (default value)

13. CountryOfBirth

Birth country of patient. Defines the country of birth and codes it in ISO (ISO country codes are provided). If country of birth cannot be determined, report 'region of origin' (variable 14).

Coding:

- Country ISO 3166-1 alpha 2
- UNK Unknown

14. RegionOfOrigin

Region from which the case originates. If the case is from the reporting country, it should be coded as REPCOUNTRY. CountryOfBirth is the preferred variable. If not available, submit RegionOfOrigin.

Coding:

- ABROAD Born abroad but location unknown
- AUSTNZ Australia and New Zealand
- CAR Caribbean
- CENTEUR Central Europe
- EASTASIAPAC East Asia and Pacific
- EASTEUR Eastern Europe
- EUROPE If a case cannot be classified as west, central or eastern European, report as 'Europe, subregion unknown'
- LATAM Latin America
- NORTHAFRMIDEAST North Africa and Middle East
- NORTHAM North America
- REPCOUNTRY Same as reporting country
- SOUTHASIA South and south-east Asia
- SUBAFR Sub-Saharan Africa
- UNK Unknown
- WESTEUR Western Europe

15. DateOfDRSampling

Date of sequencing and resistance testing (date of blood test if available). The exact date is preferred and should be provided if available.

Coding:

- Date YYYY-MM-DD
- Incomplete date YYYY-MM, YYYY, YYYY-WW, YYYY-Q
- 11-11-1911 Unknown

16. HIVSubType

This variable specifies the subtype of HIV infection, in accordance with the national protocol.

Coding:

- Text A, B, C, G, F, 01_AE, 01_AG; up to six characters
- UNK Unknown

17. PriorART

This variable specifies whether the newly diagnosed case has ever received medication for HIV/AIDS with any combination of antiretroviral drugs.

Coding:

- PREP PrEP (patient received pre-exposure prophylaxis)
- Y Yes, any combination of ARV drugs
- N No
- UNK Unknown

18. prrtSequenceHIV

This variable codes the PR-RT sequence of HIV virus; see Annex 1 for an example of the sequence format.

Coding:

- Characters (max. 3000 characters)
- UNK Unknown

19. intSequenceHIV

This variable lists the integrase sequence of HIV virus used to detect integrase resistance; see Annex 1 for an example of the sequence format.

Coding:

- Characters (max 3000 characters)
- UNK Unknown

20. ResistanceMutationCodeNRTI

This variable specifies the mutations related to resistance to drugs in drug class NRTI. The updated SDRM list has 93 mutations, including 34 NRTI resistance mutations at 15 RT positions [15]. Enter the identified mutation code here. In the (rare) event that more than one mutation code is identified for NRTI, please indicate in field 28 ('comment') which additional mutation codes were identified.

The information in this field is still useful for pilot surveillance even if fields 18 or 19 are already filled in because it validates that our interpretation of the sequence is similar to that of the reporting country.

Coding: based on the SDRM worksheet [15]:

M41-L, K65-R, D67-N, D68-G, D69-E, T69-D, T70-Ins, K70-R, K71-E, L74-V, L75-Ins, V75-M, V76-T, V77-A, V78-S, F77-L, Y115-F, F116-Y, Q151-M, M184-V, M185-I, L210-W, T215-Y, T216-F, T217-I, T218-S, T219-C, T220-D, T221-V, T222-E, K219-Q, K220-E, K221-N, K222-R

21. ResistanceMutationCodeNNRTI

This variable specifies the mutations related to resistance to drugs in drug class NNRTI. The updated SDRM list has 93 mutations, including 19 NNRTI resistance mutations at 10 RT positions [15]. Enter the identified mutation code here. In the (rare) event that more than one mutation code is identified for NNRTI, please indicate in field 28 ('comment') which additional mutation codes were identified.

The information in this field is still useful for pilot surveillance even if fields 18 or 19 are already filled in because it validates that our interpretation of the sequence is similar to that of the reporting country.

Coding: based on the SDRM worksheet [15]:

L100-I, K101-E, K102-P, K103-N, K104-S, V106-M, V107-A, V179-F, Y181-C, Y182-I, Y183-V, Y188-L, Y189-H, Y190-C, G190-A, G191-S, G192-E, P225-H, M230-L, K222-R

22. ResistanceMutationCodePI

This variable specifies the mutations related to resistance to drugs in drug class PI. The updated SDRM list has 93 mutations including 40 PI resistance mutations at 18 protease positions [15]. Enter the identified mutation code here. In the (rare) event that more than one mutation code is identified for PI, please indicate in field 28 ('comment') which additional mutation codes were identified.

The information in this field is still useful for pilot surveillance even if fields 18 or 19 are already filled in because it validates that our interpretation of the sequence is similar to that of the reporting country.

Coding: based on the SDRM worksheet [15]:

L23-I, L24-I, D30-N, V32-I, M46-I, M47-L, I47-V, I48-A, G48-V, G49-M, I50-V, I51-L, F53-L, F54-Y, **I54-V, **I55-L, **I56-M, **I57-A, **I58-T, G73-S, G74-T, G75-C, L76-A, V82-A, V83-T, V84-F, V85-S, V86-C, V87-M, V88-L, N83-D, I84-V, I85-A, I86-C, I85-V, N88-D, N89-S, L90-M

23. ResistanceMutationCodeINI

This variable specifies the mutations related to resistance to drugs in drug class INI. The SDRM worksheet lists the most common clinically significant INI resistance mutations [15].

Enter the identified mutation code here. In the (rare) event that more than one mutation code is identified for INI, please indicate in field 28 ('comment') which additional mutation codes were identified.

The information in this field is still useful for pilot surveillance even if fields 18 or 19 are already filled in because it validates that our interpretation of the sequence is similar to that of the reporting country.

Coding: based on the SDRM worksheet [15]:

66T-A, 66T-I, 66T-K, 92E-Q, 138E-K, 138E-A, 138E-T, 140G-S, 140G-A, 140G-C, 143Y-R, 143Y-C, 143Y-H, 147S-G, 148Q-H, 148Q-R, 148Q-K, 155N-H, 148Q-K, 155N-H

24. ResistanceInterpretationNRTI

This variable specifies the level of resistance to drugs in drug class NRTI. This field is required if fields 18 and 19 are both blank, i.e. no sequence reported.

The information in this field is still useful for pilot surveillance even if fields 18 or 19 are already filled in because it validates that our interpretation of the sequence is similar to that of the reporting country

Coding:

- S Susceptible
- L Potentially low and low-level resistance
- I Intermediate

- H High-level resistance
- NA Not applicable/not tested for this drug class

25. ResistanceInterpretationNNRTI

This variable specifies the level of resistance to drugs in drug class NNRTI. This field is required if fields 18 and 19 are both blank, i.e. no sequence reported.

The information in this field is still useful for pilot surveillance even if fields 18 or 19 are already filled in because it validates that our interpretation of the sequence is similar to that of the reporting country.

Coding:

- S Susceptible
- L Potentially low and low-level resistance
- I Intermediate
- H High-level resistance
- NA Not applicable/not tested for this drug class

26. ResistanceInterpretationPI

This variable specifies the level of resistance to drugs in drug class PI. This field is required if fields 18 and 19 are both blank, i.e. no sequence reported.

The information in this field is still useful for pilot surveillance even if fields 18 or 19 are already filled in because it validates that our interpretation of the sequence is similar to that of the reporting country.

Coding:

- S Susceptible
- L Potentially low and low-level resistance
- I Intermediate
- H High-level resistance
- NA Not applicable/not tested for this drug class

27. ResistanceInterpretationINI

This variable specifies the level of resistance to drugs in drug class INI. This field is required if fields 18 and 19 are both blank, i.e. no sequence reported.

The information in this field is still useful for pilot surveillance even if fields 18 or 19 are already filled in because it validates that our interpretation of the sequence is similar to that of the reporting country.

Coding:

- S Susceptible
- L Potentially low and low-level resistance
- I Intermediate
- H High-level resistance
- NA Not applicable/not tested for this drug class

28. Comment

This variable is an open text field and allows for the sharing of comments on reported cases with ECDC (for the purpose of this pilot).

Coding:

- Open text

Annex 1c. Description of variables: aggregate reporting

There are seven variables for aggregate reporting in HIVDR surveillance.

1. DateOfStatistics
The date of first HIV diagnosis; must be 2015.

2. ReportingCountry
This variable identifies the country that participates in the pilot project and reported the case. A list of ISO country codes is provided. This variable should be included by the Member State by default.

Coding:

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

3. Gender
Gender of the infected person. Transsexual persons should be coded as 'Other'.

Coding:

- M Male
- F Female
- O Other (e.g. transsexual)
- UNK Unknown (default value)

4. Transmission
Describes the most probable route of transmission of HIV. It is classified by sexual transmission: sex between men, heterosexual contact, or those who ever injected drugs. The other category refers to mother-to-child transmission, transfusion recipients, or nosocomial infection. Cases of occupational exposure should be classified as 'exposure unknown' or 'undetermined'.

Coding:

- HETERO Heterosexual contact
- IDU Ever injected drugs
- MSM Men who have sex with men
- OTHER Other includes: mother-to-child-transmission, haemophiliac patient, nosocomial infection, transfusion recipient
- UNK Unknown or undetermined

5. ResistanceTested
This variable specifies the number of newly diagnosed HIV patients tested for susceptibility upon ART initiation. This variable is reported as aggregate numbers by gender and route of transmission.

Coding:

- Number
- UNK Unknown

6. ResistanceDrugClass
This variable specifies the drugs for which resistance (low, intermediate or high level) was detected in the tests.

Coding:

- NRTI
- NNRTI
- PI
- INI
- NRTI + NNRTI
- PI + NRTI
- PI + NNRTI
- PI + NRTI + NNRTI

7. NumberOfCases
Total number of cases by drug class, gender and route of transmission.

- Coding: Number (0 minimum – 999 999 maximum)

Annex 2. Overview of country interviews

Country	Submitted	What is the national data source for HIVDR data?	Same data source as for HIV surveillance?	Describe the sampling frame for HIVDR surveillance in your country	National procedure for obtaining sequence data from reference centres
Belgium	Case based	Database for HIV reference centers	No	Comprehensive	National database Central analysis NVRL
Denmark	Aggregated	SERO project database (clinics)	No	Sentinel (7 HIV clinics)	Central testing SSI
France	Aggregated	HIV surveillance network (labs)	No	Comprehensive	Central analysis
Germany	Case based	National HIV database	Yes	Comprehensive	Central testing RKI
Hungary	Case based	National HIV database	Yes	Comprehensive	Central testing
Ireland	Aggregated	National Virus Reference Laboratory	No	Comprehensive	Central testing NVRL
Netherlands	Case based	National HIV database (clinical)	Yes	Other - labs submit sequences	Central analysis
Slovenia	Case based	National HIV Reference Center	No	Other - half of samples are selected for DR testing	Central testing HRL
Sweden	Case based Aggregated	National HIV clinical database	No	Comprehensive	National database - Central testing

Country	Link HIVDR test to an HIV case	Coverage – TDR prevalence	Timeline for submission	Future data collection Format	Aggregated data sufficient at EU level	Display of individual country submissions	Further steps
Belgium	Yes	Yes, 40% coverage (increasing)	Q4	Aggregate	Yes	Yes	Data protection
Denmark	Yes	Yes, 65-70% coverage	Q2-Q4	Case based	Yes	Yes, agreement	Data protection
France	Yes	No, 70% coverage	Q2	Case based	Yes	Yes, agreement	Data protection
Germany	No	Yes, 60% coverage	Q3-Q4	Case based	Yes	Yes, agreement	Data protection
Hungary	Yes	No, 5% coverage	Q2	Case based	No	Yes	Data protection
Ireland	No	Yes, 65-70% coverage	Q3	Case based	Yes	Yes, agreement	Data protection
Netherlands	Yes	Yes, 35% coverage	Q2	Case based	No	Yes	Data protection
Slovenia	Yes	Yes, 50% coverage	Q2	Case based	No	Yes	Data protection
Sweden	No	Yes, 80% coverage	Q2	Case based	No	Yes	Data protection

Annex 3. Completeness of HIVDR pilot reporting

Variable no.	Variable name	Correct and complete reports	All data completeness	Min	Max
1	RecordID	1680	100.0%	100,0%	100,0%
2	Reportingcountry	1680	100.0%	100,0%	100,0%
3	DateOfDiagnosis	1678	99.9%	85,7%	100,0%
4	HIVType	1680	100.0%	100,0%	100,0%
5	Transmission route	1674	99.6%	98,7%	100,0%
6	FirstCD4Count	942	56.1%	51,3%	100,0%
7	FirstCD4Date	713	42.4%	0,0%	100,0%
8	VLLatest	1279	76.1%	64,9%	100,0%
9	VLLatestDate	805	47.9%	0,0%	100,0%
10	HivStatus	1208	71.9%	0,0%	100,0%
11	Gender	1680	100.0%	100,0%	100,0%
12	Age	1652	98.3%	97,5%	100,0%
13	CountryOf Birth	1674	99.6%	98,6%	100,0%
14	RegionOfOrigin	738	67.0%	30,6%	100,0%
15	DateOfDRSampling	1673	99.6%	98,5%	100,0%
16	HIVSubType	1653	98.4%	90,5%	100,0%
17	PriorART	1680	100.0%	100,0%	100,0%
18	prrtSequencehiv	1504	89.5%	7.4%	100.0%
19	intSequenceHIV	354	21.1%	0.0%	100.0%
20	ResistanceMutationCodeNRTI	n.a.			
21	ResistanceMutationCodeNNRTI	n.a.			
22	ResistanceMutationCodePI	n.a.			
23	ResistanceMutationCodeINI	n.a.			
24	ResistanceInterpretationNRTI	376	22.4%		
25	ResistanceInterpretationNNRTI	433	25.8%		
26	ResistanceInterpretationPI	272	16.2%		
27	ResistanceInterpretationINI	311	18.5%		
28	Comment	n.a.			

Annex 4. Additional results: Region of origin, CD4 and HIV subtypes for HIV cases, case-based reporting

Table A-1 presents the region of origin of reported HIV cases, as recorded by six EU/EEA countries (case-based surveillance data). More than half of the cases (58%) come from Europe. Fifteen per cent come from sub-Saharan Africa, and for 16% of the reported cases the region of origin is unknown.

Table A-1. Region of origin of newly diagnosed HIV cases (six countries), HIVDR surveillance pilot

Region of origin	Number	(%)
EUROPE	970	58%
SUBAFR	247	15%
OTHER	196	12%
UNKNOWN	267	16%

The first CD4 count after HIV diagnosis was submitted for 936 of the 1 680 (56%) cases (Table A-2). Almost half of these cases (47%) were diagnosed with CD4 counts < 350 cells per microliter, which is classified as late stage. Thirty-one per cent of the reported individuals were classified as 'advanced stage'.

Table A-2. CD4 counts of newly diagnosed HIV cases (six countries), HIVDR surveillance pilot, 2017

Reported CD4-counts	936
Median	363 cells/µL
Late stage (<350 cells/µL) (no. of cases; %)	438 (47%)
Advanced stage (<200 cells/µL) (no. of cases; %)	238 (31%)
CD4 >350 cells/µL (no. of cases; %)	260 (28%)

HIV subtype was submitted for 95% of all reported cases (see Table A-3). Subtype B infection was the most common subtype in more than half of the cases (54%).

Table A-3. HIV subtypes of newly diagnosed HIV cases (six countries), HIVDR surveillance pilot, 2017

HIV subtype	Percentage
A	131 (7.8%)
B	905 (54%)
C	148 (8.8%)
01_AE	97 (5.8%)
02_AG	156 (9.3%)
Other CRF	39 (2.3%)
D	13 (0.8%)
F	72 (4.3%)
G	32 (1.9%)
H	2 (0.1%)
J	1 (0.1%)
Unknown	84 (5.0%)

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