HIV Drug Resistance in Ireland, 2017

v1.0
March 2019

Key Facts

- Drug resistance testing was performed on 283 persons diagnosed with HIV-1 in Ireland in 2017, 58% of all HIV diagnoses that year. Testing was not possible on the remainder mainly due to low viral load, indicating that these patients were likely to already be on treatment.
- Of those tested, 66% were antiretroviral therapy (ART)-naïve, 7% were ART-experienced, and prior exposure to ART was unknown for 27%.
- Of those tested, 16 ART-naïve individuals (9%; 95% CI 5.3%-13.5%) had HIV transmitted drug resistance (TDR) mutations.

Among those with TDR:

- By drug class, the prevalence of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (8%; n=14) was higher than nucleoside-analogue reverse transcriptase inhibitor (NRTI) resistance (1%; n=2) and protease inhibitor (PI) resistance (2%; n=3). No individuals were identified to have integrase inhibitor resistance.
- By HIV-1 subtype, the majority of TDR cases was subtype B (31%), followed by subtype C (25%), and subtype CRF02_AG (19%).
- By region of origin among those tested, the prevalence of resistance to any drug class was highest in individuals born in sub-Saharan Africa (13%), followed by those born in Ireland (10%), and Latin America (9%).
- By probable route of transmission among those tested, the prevalence of resistance to any drug class was higher among men who have sex with men (MSM) (9%) and heterosexual females (8%), compared to heterosexual males (3%).
- This was the first year of TDR surveillance using combined epidemiological and drug resistance data, which improves the accuracy of the findings. Nonetheless, when compared with laboratory based TDR data in recent years, the trends appear stable.

Suggested citation: HSE-Health protection surveillance centre and UCD-National Virus Reference Laboratory. HIV drug resistance in Ireland, 2017. Dublin: HSE HPSC; 2019.

Background

Currently all HIV antiretroviral (ARV) drugs are at risk of becoming ineffective due to the emergence of resistant virus [1]. HIV drug resistance (HIVDR) arises due to genetic mutations in the virus and can be either acquired (ADR) or transmitted (TDR). ADR arises in individuals receiving (suboptimal) antiretroviral treatment (ART), whereas TDR occurs in individuals never previously exposed to ART who become infected with a virus that has pre-existing drug resistance mutations. As therapies are used more widely, the potential for drug resistance increases. TDR is of public health concern due to implications at both the individual and population level [2]. At an individual level, persons with TDR begin ART with a lower genetic barrier to resistance and a higher risk of virological failure. At a population level TDR carries significant implications for national treatment guidelines and first line treatment options. Population surveillance of TDR is recommended by the World Health Organization (WHO), both in order to preserve ART options, and to control future HIV epidemics [3].

A pilot study was undertaken by the HSE-Health Protection Surveillance Centre (HPSC) in partnership with the UCD National Virus Reference Laboratory (NVRL) in 2018. Oversight of the project was provided by a multidisciplinary steering group, comprising investigators from NVRL and HPSC, as well as patient representatives and advocates, representatives of the Public Health HIV STI Special Interest Group, the Society for the Study of Sexually Transmitted Diseases in Ireland (SSSTDI), the Infectious Disease Society of Ireland (IDSI), the Gay Men's Health Service (GMHS) and NGOs (see Appendix 1 for membership). The study analysed data from individuals diagnosed with HIV-1 in Ireland during 2017 to determine TDR prevalence, to conduct demographic analyses, and to determine the feasibility of sustained national TDR surveillance. For the first time, epidemiological data from the national Computerised Infectious Diseases Reporting system (CIDR) were linked to HIVDR data from the NVRL in order to produce more accurate population TDR prevalence rates. This report presents the results of the analysis for 2017; a report describing the methodological issues in linking the data and recommendations on implementing sustained national TDR surveillance will be published separately.

Methods

Criteria for inclusion in surveillance

The criteria for inclusion in HIVDR surveillance were: a person aged ≥18 years, who was diagnosed with HIV-1 in Ireland in 2017, and tested prior to commencing their first ART regimen in Ireland for susceptibility to any of the 22 available ARV drugs in the four main drug classes; nucleoside-analogue reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and integrase inhibitors (INI). Cases were identified as having TDR using information on prior exposure to ART, available in CIDR, in combination with genotypic antiretroviral resistance testing results.

Prior exposure to antiretroviral therapy

A high proportion of people diagnosed with HIV in Ireland (39%) has been previously diagnosed with HIV abroad and exposed to ART prior to arrival in Ireland [4]. Information on prior ART is collected by clinicians, GPs, consultants in infectious disease and genitourinary medicine, microbiology laboratories, clinical nurse specialists, health advisors and clinical staff using an HIV surveillance form, and entered in CIDR by Departments of Public Health. HIV data were extracted from CIDR on 16th November 2018, and were correct at the time of publication. ART refers to treatment of HIV infection and does not include pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP).

Genotypic antiretroviral testing

The NVRL undertakes all HIV genotypic antiretroviral testing (GART) in Ireland. Nested RT-PCR and Sanger sequencing were used to generate viral genome sequences, which were entered into the Stanford University online bioinformatics tool to identify the presence or absence of ARV drug resistance mutations (https://hivdb.stanford.edu). Of 492 individuals diagnosed with HIV in Ireland in 2017, GART could be conducted for 283 (58%). For the remaining 209 cases (42%) GART could not be conducted. The reasons for this were:

- The viral load was too low for analysis (n=192)
- The plasma sample was unavailable simultaneous to the serum sample having exceeded the sample retention time (n=15)
- The sample could not be linked to a CIDR event (n=2).

Integrase sequences were generated for 278 individuals, but could not be generated for five.

Data linkage

GART data and epidemiological data from CIDR were linked using the CIDR Event ID.

Genotypic definition of transmitted HIV-1 drug resistance

To compare TDR rates across geographic regions and times, WHO recommended in 2009 the adoption of a consensus genotypic definition of transmitted HIV-1 drug resistance, comprising a list of 93 surveillance drug resistance mutations (SDRMs) (https://hivdb.stanford.edu/page/who-sdrm-list/) [2]. In this study, NRTI, NNRTI and PI associated TDR were defined as the presence in ART-naïve individuals of one of more mutations from the WHO 2009 SDRM list. INI-associated TDR, which is not included in the WHO 2009 definition, was defined as the presence in ART-naïve individuals of one or more major INI-resistance mutations identified using the Stanford University online bioinformatics tool.

Statistical analysis

Ninety-five percent confidence intervals (CI) were computed using the Wilson score interval for binomial proportions, with OpenEpi software version 3.01 [5]. CIs for TDR prevalence during the periods 2004-2008, 2015 and 2016 were computed using data from a study on documented prevalence of HIV type 1 antiretroviral TDR in Ireland from 2004 to 2008, and using data from annual HIV reports in 2015 and 2016 [6-8].

Results

Prior exposure to antiretroviral therapy

Prior exposure to ART could be determined for 371 (75%) of HIV diagnoses in 2017 and could not be determined for 121 (25%) due to incomplete or missing forms. Of those with information on prior ART, 205 (55%) were ART-naïve and 166 (45%) were ART-experienced. Of those with GART data (n=283), 66% were ART-naïve, 7% were ART-experienced and 27% were ART-unknown. Of those not suitable for GART (n=209), 9% were ART-naïve, 70% were ART-experienced and 21% were ART-unknown. The majority (92%) of those not suitable for GART had a viral load that was too low for analysis, suggesting viral suppression due to being on ART among these individuals.

HIV drug resistance

In total, 30 individuals were identified with one or more SDRM from the WHO 2009 list, corresponding to a crude prevalence of 11% (95% CI 7.5%-14.7%) HIVDR among individuals

tested. SDRMs were detected for three of the four main drug classes; there were no major INI-resistance mutations detected. INI-accessory mutations, which have minimal or no effect on susceptibility to integrase inhibitors, were detected in nine individuals, these are listed in Appendix 2.

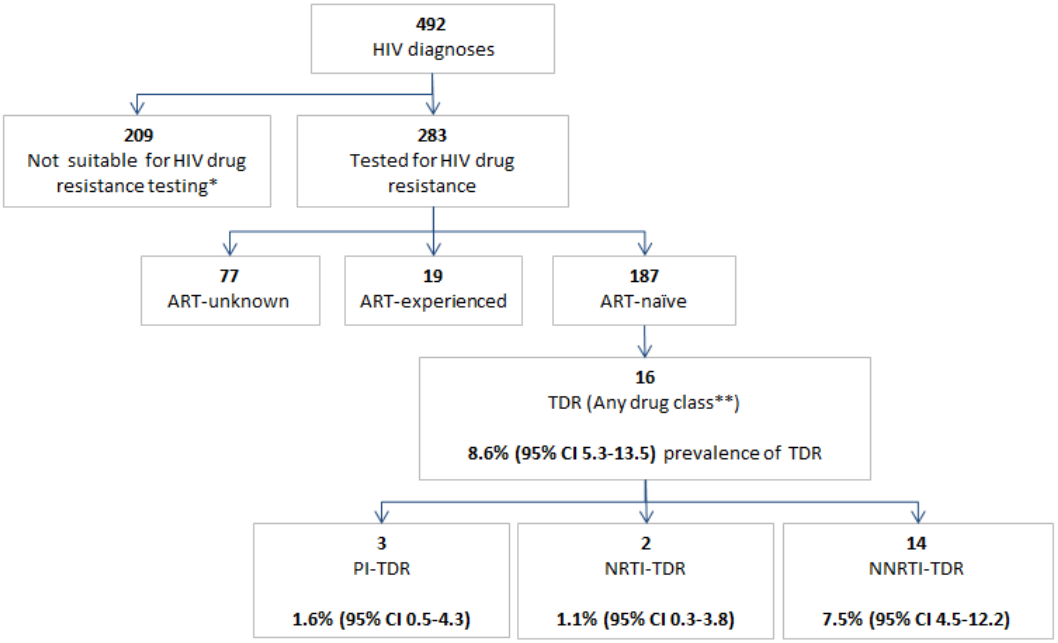
Of those who were known to be ART-naïve, 16 individuals were identified with one or more SDRM, corresponding to a TDR prevalence of 9% (95% CI 5.3%-13.5%). Of those who were ART-experienced, four were detected with ≥1 SDRM, an HIVDR prevalence of 21% (95% CI 8.5%-43.3%), and of those whose history of prior ART was unknown, 10 were detected with ≥1 SDRM, an HIVDR prevalence of 13% (95% CI 7.2%-22.3%). Table 1 presents the frequency of resistance to each drug class, for all individuals tested and by prior exposure to ART.

Table 1 Frequency of HIV drug resistance (≥1 SDRM from the WHO 2009 list) by drug class and prior exposure to ART among HIV diagnoses in Ireland, 2017

Drug class	All individuals tested (N=283)	ART-naïve (N=187)	ART-experienced (N=19)	ART-unknown (N=77)
PI	4	2	1	1
NRTI	3	0	0	3
NNRTI	17	11	1	5
NRTI + NNRTI	4	2	1	1
PI + NRTI + NNRTI	1	0	1	0
PI + NNRTI	1	1	0	0
Total	30	16	4	10

Transmitted HIV drug resistance

The categorisation of cases and prevalence of TDR among individuals diagnosed with HIV in Ireland in 2017 is presented in Figure 1. Whilst TDR to any drug class was 9%, TDR to the different drug classes varied; NNRTI resistance was 8% and was significantly higher than PI resistance (2%) and NRTI resistance (1%). Thirteen individuals were detected with transmitted resistance to a single drug class and three with dual class resistance (Table 1). Twenty seven SDRMs were detected in total; these are listed by drug class and HIV-1 subtype in Appendix 3.



*Viral load too low (n=192), plasma sample unavailable simultaneous to the serum sample having exceeded the sample retention time (n=15), or sample could not be not linked to CIDR event (n=2). **One or more surveillance drug resistance mutation from the WHO 2009 list (13 individuals had single-class drug resistance and three had dual-class resistance).

Figure 1 Categorisation, prevalence and 95% CIs of HIV transmitted drug resistance (TDR) in Ireland, 2017

The available data on TDR prevalence in Ireland prior to 2017 are presented in Figure 2 [6-8]. There were no significant differences in TDR prevalence during 2004-2008 and 2015-2017, however trends should be interpreted with caution due to different methods used to categorise individuals as having TDR prior to 2017.

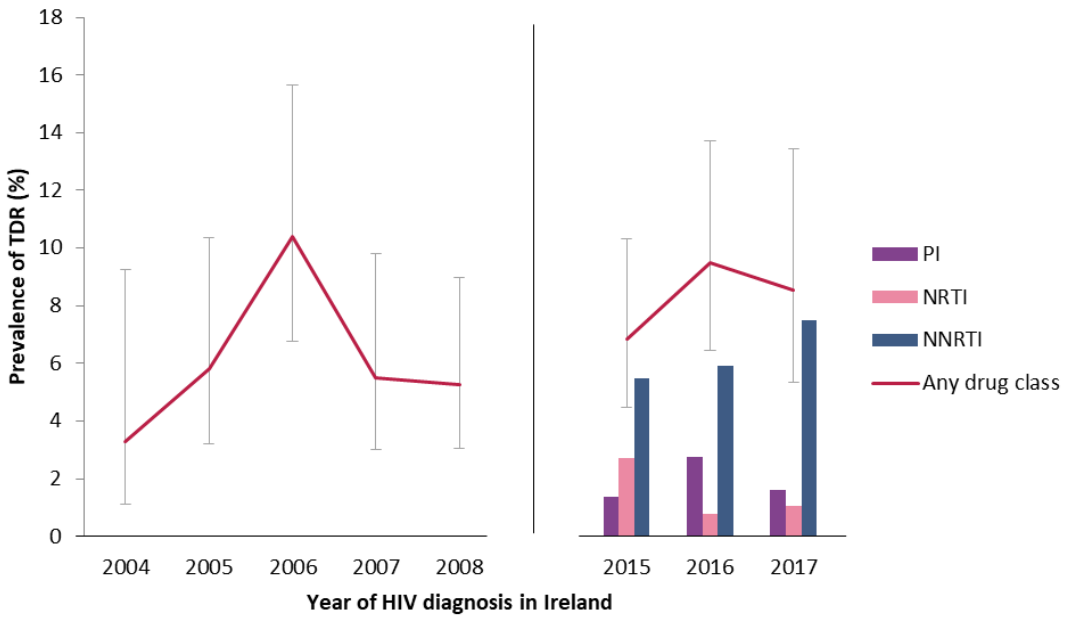


Figure 2 Prevalence (%) of HIV transmitted drug resistance (TDR) among HIV diagnoses in Ireland, 2004-2008 and 2015-2017. 95% CIs are shown for resistance to at least one (any) drug class. Prevalences for each year were calculated using different methodologies and may not be comparable.

Demographic characteristics of all ART-naïve individuals tested for drug resistance in 2017, and of those with TDR, are presented in Table 2. Prevalence of TDR among the subgroups presented in Table 2 should be interpreted with caution due to wide confidence intervals caused by the small sample size.

The proportion of TDR cases (any drug class) was highest among individuals born in Ireland (n=8; 50%), however among those tested the prevalence of TDR was highest in individuals born in sub-Saharan Africa (13%), followed by those born in Ireland (10%), and Latin America (9%).

The median age among all individuals tested was 35 years (range 19-71 years). Among those with TDR, the median age was 38 years (range 27-70 years); the median age among males was also 38 years and among females it was 41 years.

With regard to HIV-1 subtype, the commonest subtype among TDR cases was subtype B (n=5), followed by subtype C (n=4), and subtype CRF02_AG (n=3). MSM accounted for the majority (n=4) of subtype B TDR cases, and all subtype CFR01_AG TDR cases. Heterosexual females accounted for the majority (n=3) of subtype C TDR cases.

Table 2 Demographic characteristics and prevalence (%) of TDR (any drug class) among ART-naïve individuals tested for drug resistance, HIV diagnoses in Ireland, 2017

		Total ART-naïve population tested	Individuals with TDR	Prevalence of TDR	95% CI
		N	N	%	% - %
Total		187	16	8.6	5.3 - 13.5
Sex	Male	145	12	8.3	4.8 - 13.9
	Female	42	4	9.5	3.8 - 22.1
Age group (years)	15-24	18	0	0.0	n/a
	25-34	70	8	11.4	5.9 - 21.0
	35-44	57	2	3.5	1.0 - 11.9
	45+	42	6	14.3	6.7 - 27.8
Region of origin	Ireland	77	8	10.4	5.4 - 19.2
	Sub-Saharan Africa	40	5	12.5	5.5 - 26.1
	Latin America	22	2	9.1	2.5 - 27.8
	Europe	40	1	2.5	0.4 - 12.9
	Other	8	0	0.0	n/a
	Unknown	0	0	0.0	n/a
Region of infection	Ireland	75	9	12.0	6.4 - 21.3
	Sub-Saharan Africa	29	4	13.8	5.5 - 30.6
	Latin America	15	1	6.7	1.2 - 29.8
	Europe	24	0	0.0	n/a
	Other	18	1	5.6	1.0 - 25.8
	Unknown	26	1	3.8	0.7 - 18.9
Probable route of transmission	MSM/bisexual	100	9	9.0	4.8 - 16.2
	Heterosexual male	31	1	3.2	0.6 - 16.2
	Heterosexual female	40	3	7.5	2.6 - 19.9
	PWID	7	1	14.3*	2.6 - 51.3
	Other	2	0	0.0	n/a
	Unknown	7	2	28.6	8.2 - 64.1
CD4 count (median, range)		314 (2-1368)	251 (9-944)	-	
HIV subtype	A	15	0	0.0	n/a
	B	83	5	6.0	2.6 - 13.3
	C	46	4	8.7	3.4 - 20.3
	CRF01_AE	11	1	9.1	1.6 - 37.7
	CRF02_AG	14	3	21.4	7.6 - 47.6
	CRF06_cpx	1	1	100.0	20.7 - 100.0
	F	7	1	14.3	2.6 - 51.3
	G	6	1	16.7	3.0 - 56.4
	Other	4	0	0.0	n/a

PWID; People who inject drugs, *interpret prevalence with caution due to low numbers tested.

Transmitted HIV drug resistance by drug class

The number of HIV diagnoses with TDR by drug class and demographic characteristics is presented in Table 3; data should be interpreted with caution due to low numbers.

Table 3 Number of HIV diagnoses with transmitted HIV drug resistance by drug class and demographic characteristics, Ireland, 2017

		NNRTI	PI	NRTI + NNRTI	PI + NNRTI	Total
		N	N	N	N	N
Sex	Male	7	2	2	1	12
	Female	4	0	0	0	4
Age group	15-24	0	0	0	0	0
	25-34	6	1	0	1	8
	35-44	2	0	0	0	2
	45+	3	1	2	0	6
Region of origin	Ireland	6	1	1	0	8
	Sub-Saharan Africa	4	0	1	0	5
	Latin America	1	0	0	1	2
	Europe	0	1	0	0	1
Probable route of transmission	MSM	6	1	1	1	9
	Heterosexual males	0	1	0	0	1
	Heterosexual females	3	0	0	0	3
	PWID	1	0	0	0	1
	Unknown	1	0	1	0	2

Discussion

The findings of this report indicate a 9% (95% CI 5.3%-13.5%) prevalence of TDR among individuals diagnosed with HIV who underwent GART testing in Ireland during 2017. Prevalence of NNRTI TDR (8%) was significantly higher than NRTI TDR (1%) and PI TDR (2%). In the past three years, the trend in TDR has been stable, with the caveat of acknowledging the differences in methodologies used this year compared with previous years.

The higher prevalence of TDR among MSM and heterosexual women in Ireland is important in the context of the high proportion of HIV diagnoses among these two groups in recent years [4].

Information on TDR prevalence in other countries is limited. Latest data from the United Kingdom shows a TDR prevalence of 7% and a NNRTI TDR prevalence of 3% in 2014 [9]. Information on TDR at the European level is not currently available; however European level surveillance of TDR will commence in 2019, according to an HIVDR Reporting Protocol and Analysis Plan that was recently published by the European Centres for Disease Prevention and Control (ECDC) [11]. At a global level, WHO conducts surveillance of pre-treatment drug resistance (PDR), which is detected in ARV drug-naïve people initiating ART or people with prior ARV drug exposure(s) initiating or reinitiating first-line ART [10]. Latest data for the period 2014-2016 shows that levels of PDR and NNRTI PDR have exceeded 10% in several African and South American countries; with increasing NRTI PDR in some low and middle income countries (LMIC) and increasing NNRTI PDR in all LMIC [12]. The high level of PDR in LMIC is important in the context of the increasing rate of HIV diagnoses among migrants in recent years in Ireland and the high proportion (50%) of TDR cases in 2017 that were born abroad [4]. WHO currently recommends that countries in which the prevalence of NNRTI PDR among people initiating first line ART, regardless of previous ARV drug exposure, is ≥10%, should urgently consider an alternative first-line ART regimen that does not contain NNRTIs [12]. This report did not analyse PDR, however the possibility of analysing PDR as part of future HIVDR surveillance in Ireland will be explored.

Modelling predicts that as more people receive treatment, fewer HIV transmissions will occur, but a higher prevalence of HIVDR will be observed [10]. Thus, early engagement in care and immediate initiation of effective ART is critical for clinical benefits to individuals and to prevent onward transmission of TDR. It is recommended in Ireland and internationally that ART is offered to all people living with HIV (PLHIV) irrespective of immunological status [13]. In Ireland, guidelines from the British HIV Association (BHIVA) and the European AIDS Clinical Society (EACS) are used in combination with guidelines from the US Department of Health and Human Services (DHHS) and WHO, to make decisions regarding first line therapy [13]. BHIVA and EACS guidelines currently recommend that ART-naïve PLHIV start combination therapy comprising two NRTIs plus one of the following: ritonavir-boosted PI, NNRTI or INI, depending on factors such as risk of poor adherence [14, 15]. Clinically relevant TDR to currently recommended first line HIV drugs (excluding NNRTIs) remains low in Ireland.

The findings of this study highlight the importance of TDR surveillance in Ireland and, for the first time, demonstrate that epidemiological data and drug resistance data from separate Irish

reporting systems can be combined to determine TDR prevalence, and be used to guide future treatment guidelines, or indeed preferred medicine strategies for the management of HIV. There were some limitations; 58% of HIV diagnoses in 2017 were excluded from the study, either due to unsuitability for GART (42%) or lack of information on prior ART (16%); however the majority (92%) of those unsuitable for GART had low viral loads, suggesting viral suppression due to being on ART among these individuals. Whilst it may be possible to perform proviral DNA sequencing in these individuals to identify latent HIVDR, it will not be possible to ascertain whether any resistance identified in the provirus constitutes TDR or ADR. Of those excluded due to lack of information on prior ART, 10 were detected with SDRMs; therefore the number of individuals with TDR may be underestimated. Furthermore, potential biases may exist among particular subgroups due to better testing access and uptake in these groups.
This report does not include NRTI, NNRTI or PI drug resistance mutations detected by the Stanford University bioinformatics tool that are not on the WHO 2009 SDRM list. Expanding the protocol to include these mutations in future reports is currently under review.

Acknowledgements

We would like to thank all of the data providers and all who have contributed to this report including the NVRL; Microbiology laboratories; Departments of Public Health; Consultants in Infectious Disease/Genitourinary Medicine; Infectious Disease Unit, GPs; HIV clinical nurse specialists; Health Advisors and all other clinical staff involved. We would also like to thank the Developments in HIV surveillance Steering Group for study oversight and review of this report.

Report prepared by

This report was prepared by Melissa Brady, Kate O'Donnell and Derval Igoe (HPSC), Martha Neary, Joanne Moran, Aoife Ronayne, Suzie Coughlan and Cillian De Gascun (NVRL), on behalf of the Developments in HIV Surveillance Steering Group.

References

1. World Health Organization, Global action plan on HIV drug resistance 2017–2021. 2017: Geneva
2. Shafer, R.W., et al., HIV-1 protease and reverse transcriptase mutations for drug resistance surveillance. AIDS, 2007. 21(2): p. 215-23
3. World Health Organization, Global Strategy for the surveillance and monitoring of HIV drug resistance. 2012, WHO: Geneva
4. HSE Health Protection Surveillance Centre. HIV in Ireland, 2017. Dublin: HSE HPSC; 2018
5. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed 2019/01/30
6. De Gascun CF., et al., Documented prevalence of HIV type 1 antiretroviral transmitted drug resistance in Ireland from 2004 to 2008. AIDS Research and Human Retroviruses. 2012 Mar;28(3):276-81
7. HIV in Ireland, 2015 Report. Health Protection Surveillance Centre, 2016
8. Annual Reference Virology Report 2017. UCD-National Virus Reference Laboratory, 2017
9. http://www.hivrdb.org.uk/hiv-drug-resistance-uk; accessed 2019/02/05
10. HIV drug resistance report 2017. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO
11. HIV Drug Resistance Reporting protocol and Analysis Plan 2019. TESSy-The European Surveillance System. European Centres for Disease Prevention and Control, February 2019.
12. World Health Organization, Guidelines on the public health response to pretreatment HIV drug resistance, July 2017 WHO Geneva. License: CC BY-NC-SA 3.0 IGO
13. HSE Position on Antiretroviral Therapy for all people living with HIV. July 2017 Health Service Executive
14. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update), August 2016
15. The European AIDS Clinical Society guidelines version 9.1. October 2018

Appendices

Appendix 1 Membership of the Developments in HIV Surveillance Steering Group

Name	Organisation
Derval Igoe	HSE Health Protection Surveillance Centre
Melissa Brady	HSE Health Protection Surveillance Centre
Kate O'Donnell	HSE Health Protection Surveillance Centre
Jeff Connell	National Virus Reference Laboratory
Cillian De Gascun	National Virus Reference Laboratory
Suzie Coughlan	National Virus Reference Laboratory
Martha Neary	National Virus Reference Laboratory
Joanne Moran	National Virus Reference Laboratory and HSE Health Protection Surveillance Centre
Sarah Doyle	Public Health STI HIV Special Interest Group
Orla Ennis	Public Health STI HIV Special Interest Group
Fionnuala Cooney	Public Health STI HIV Special Interest Group
Shay Keating	Society for the Study of Sexually Transmitted Diseases in Ireland
Erin Nugent	HIV Ireland (formerly Dublin AIDS alliance)
Siobhan O'Dea	Gay Men's Health Service
Lysander Preston	Positive Now
Helen Tuite	Infectious Disease Society of Ireland and Society for the Study of Sexually Transmitted Diseases in Ireland

Appendix 2 Integrase accessory drug resistance mutations in individuals diagnosed with HIV by HIV-1 subtype, Ireland, 2017

	All	B	C	CRF06_cpx	F	G
H51HY	1		1			
E157Q	5	2		2		1
S230R	2	2				
T97A	1				1	

Appendix 3 Surveillance drug resistance mutations (WHO 2009 list) in individuals diagnosed with transmitted HIV drug resistance by HIV-1 subtype, Ireland, 2017

	All	B	C	CRF01_AE	CRF02_AG	CRF06_cpx	F	G
Number of ART-naïve individuals tested for NRTI/NNRTI/PI resistance	187	83	46	11	14	1	7	6
Number of individuals with TDR (any drug class)	16							
Number of SDRMs detected	27	7	6	1	3	1	4	5
NRTI mutations (n)								
D67E	1	1						
T215F	1							1
T215I	1							1
T215S	1							1
NNRTI mutations (n)								
K101E	3	1					1	1
K103N	7	2	4				1	
Y181C	2			1				1
Y188C	1	1						
Y188L	1	1						
G190A	2		1				1	
G190E	1		1					
P225H	3				3			
PI mutations (n)								
M46I	1					1		
M46L	2	1					1	