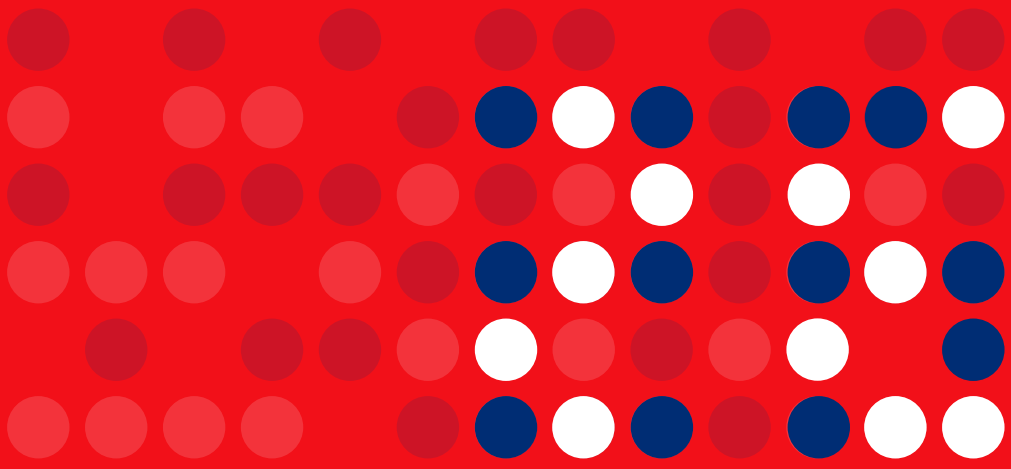
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

hiv Monitoring

HIV Monitoring Report 2026

Chapter 5: HIV drug resistance



5. HIV drug resistance

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Key findings

Baseline drug resistance

- Between 2016 and 2025, 45.5% of individuals with newly diagnosed HIV in the Netherlands and no known history of pre-exposure prophylaxis use underwent baseline screening for HIV drug resistance. The proportion of screened participants increased from 36.6% in 2016 to 58.8% in 2025.
- Low-level or greater resistance was detected in 8.4% of screened participants; intermediate-level or greater resistance was detected in 6.1%. The prevalence of intermediate-level or greater baseline drug resistance increased from 4.2% in 2016 to 7.1% in 2025.
- Between 2016 and 2025, the overall prevalence of low-level or greater integrase inhibitor resistance was 0.7%. When the resistance-associated integrase polymorphism IN L74I in participants with subtype A6 was included in the analysis, baseline integrase resistance increased to 8.0%.
- In 2025, two cases of intermediate- and high-level baseline resistance to all available integrase inhibitors was identified in the Netherlands for the first time.
- We found no differences in the rate of virological suppression at 48 weeks following ART initiation between participants with and without baseline drug resistance.

Acquired drug resistance

- Of 27,703 participants in HIV care between 2016 and 2025, 3,873 (14.0%) had at least one genotype performed after initiating antiretroviral therapy.
- Low-level or greater acquired resistance was identified in 7.3% of participants in care. Intermediate-level or greater resistance was identified in 7.1%, and was most frequently due to the cytidine analogue mutations RT M184V/I.
- Low-level or greater resistance to rilpivirine and doravirine was identified in 2% and 3% of patients in care, respectively. Low-level or greater resistance to bictegravir, dolutegravir, or darunavir was identified in <1% of patients in care.
- Of 1,154 participants ever treated with long-acting cabotegravir/rilpivirine (CAB/RPV), 27 had a genotype performed after treatment initiation. Of these, 19 (70.4%) had low-level or greater resistance to CAB, RPV, or both.

Introduction

Monitoring HIV drug resistance is integral to HIV prevention and care. In this chapter, we describe trends in the prevalence of baseline and acquired HIV drug resistance in the Netherlands.

Baseline resistance refers to the detection of antiretroviral resistance-associated mutations (RAMs) prior to the initiation of antiretroviral therapy (ART). Baseline resistance may occur due to transmission of a drug-resistant HIV strain and/or due to naturally occurring polymorphisms associated with specific HIV subtypes. Acquired resistance may emerge in the setting of incomplete virological suppression during antiretroviral treatment. People who acquire HIV while taking pre-exposure prophylaxis (PrEP) may develop drug resistance due to selective pressure exerted by antiretroviral agents (ARVs) used in HIV prevention. Drug resistance among people with a history of PrEP use is discussed in Chapter 2 of this report.

Dutch guidelines[1] recommend baseline drug resistance screening in all people with newly HIV at entry to care. Testing for acquired resistance is recommended in the setting of loss of virological control or virological failure during antiretroviral treatment.

Methods

We used data from 27,703 ATHENA participants with HIV-1 infection who had at least one HIV care visit between 2016 and 2025 and were 15 years of age or older at HIV diagnosis.

Stanford HIV Drug Resistance Database penalty scores (HIVdb version 10.2) were used to calculate predicted resistance for each antiretroviral agent, based on all relevant RAMs identified in each genotype[2]. Relevant RAMs were defined as those conferring resistance to ARVs currently used in the management of HIV (for a list of excluded drugs, see Appendix Table 1). We used the HIVdb drug resistance interpretation rubric to convert drug penalty scores into estimated resistance levels, as follows: 0-9, susceptible; 10-14, potential low-level resistance; 15-29, low-level resistance; 30-59, intermediate resistance; >= 60, high-level resistance.

We determined the resistance level for each antiretroviral class by taking the maximal resistance score across agents within that class. We assessed for resistance to the following antiretroviral drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs). In 2025, the International AIDS Society-USA added the integrase (IN) L74I RAM in

subtype A6 as the first subtype-specific major mutation[3]. The IN L74I RAM is a potential mediator of the increased risk of virological failure on long-acting cabotegravir/rilpivirine (LA CAB/RPV) observed in people with subtype A6[4-6]. Since IN L74I is considered a facilitator of the evolution of cabotegravir resistance in HIV-1 subtype A6 rather than a RAM that directly reduces cabotegravir susceptibility, analyses including this polymorphism are discussed separately in this year's report.

Findings

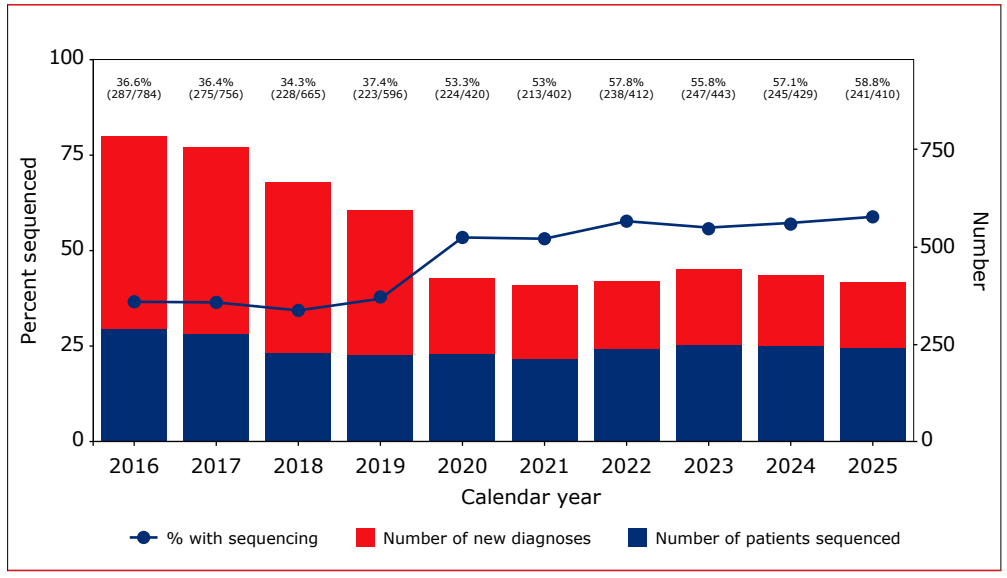
Baseline resistance

In our analysis of baseline resistance, we include participants who (in addition to the criteria described above), were diagnosed with HIV in the Netherlands between 2016 and 2025, had a genotype performed prior to initiating ART, and had no known history of PrEP use.

Screening for baseline resistance

Between 2016 and 2025, 5,317 individuals were diagnosed with HIV-1 in the Netherlands, of whom 2,421 (45.5%) were screened for baseline drug resistance. A total of 2,411 reverse transcriptase, 1,997 protease, and 980 integrase sequences were available for analysis. Baseline screening increased over time (*Figure 5.1*).

Figure 5.1: Proportion of newly diagnosed participants screened for baseline resistance, 2016-2025 (n=5,317).



Of the 2,421 participants screened for baseline resistance, 1,375 (56.8%) were MSM, 1,946 (80.4%) were cisgender men, and 1,205 (49.8%) were born in the Netherlands. The demographic characteristics of screened and unscreened participants are shown in *Table 5.1*.

***Table 5.1:** Characteristics of participants with newly diagnosed HIV in the Netherlands, by baseline resistance screening, 2016–2025 (n=5,317).*

	Not screened (N=2,896)	Screened (N=2,421)
Transmission group		
MSM	1679 (55.0%)	1375 (45.0%)
MSW	444 (56.5%)	342 (43.5%)
WSM	390 (50.6%)	380 (49.4%)
Other	383 (54.2%)	324 (45.8%)
Gender		
Cisgender man	2373 (54.9%)	1946 (45.1%)
Cisgender woman	438 (50.5%)	429 (49.5%)
Transgender woman	82 (65.1%)	44 (34.9%)
Transgender man	3 (60.0%)	2 (40.0%)
Age at first HIV visit		
Mean (range)	41.0 (16.0 - 79.7)	41.2 (15.3 - 80.6)
Birth region		
Netherlands	1704 (58.6%)	1205 (41.4%)
Latin America and Caribbean	319 (47.3%)	355 (52.7%)
Central and Eastern Europe	289 (53.8%)	248 (46.2%)
Sub-Saharan Africa	251 (50.1%)	250 (49.9%)
South and East Asia	132 (51.4%)	125 (48.6%)
W Eur, N America, Australia	85 (41.7%)	119 (58.3%)
N Africa and Middle East	81 (48.2%)	87 (51.8%)
Unknown	35 (52.2%)	32 (47.8%)

MSM, men who have sex with men; MSW, men who have sex with women; WSM, women who have sex with men; W Eur, Western Europe; N America, North America; N Africa, Northern Africa.

In a multivariable model adjusted for age at first HIV visit, transmission group, and birth region, we found no association between transmission group or age on the odds of baseline screening. The odds of baseline screening were higher in people born in all regions other than the Netherlands.

Integrase sequencing was performed in 980 (40.5%) of 2,421 participants with baseline screening. People born in Central and Eastern Europe (CEE), had 1.7 (95% CI 1.3-2.3) times the odds of integrase sequencing compared to people born in the Netherlands. Participants belonging to "Other" transmission groups had 2.2 times the odds (95% CI 1.7-2.8) of baseline screening than MSM; no other differences by transmission group were noted.

HIV-1 subtypes

Among 2,421 participants with baseline genotypes, 1,366 (56.4%) had HIV-1 subtype B. Subtypes A1 and A6 (including circulating recombinant forms, CRFs) were identified in 112 (4.6%) and 104 (4.3%) individuals, respectively. An additional 317 participants (13.1%) had other subtype-A associated CRFs, predominantly CRF01_AE and CRF02_AG. HIV-1 subtype differed significantly by region of birth (*Table 5.2*). Subtype A6 was identified in 27.8% of participants born in CEE, compared with 2.2% of those born in the Netherlands[7, 8].

Table 5.2: HIV subtype by region of birth among people screened for baseline drug resistance, 2016–2025 (n = 2,421).*

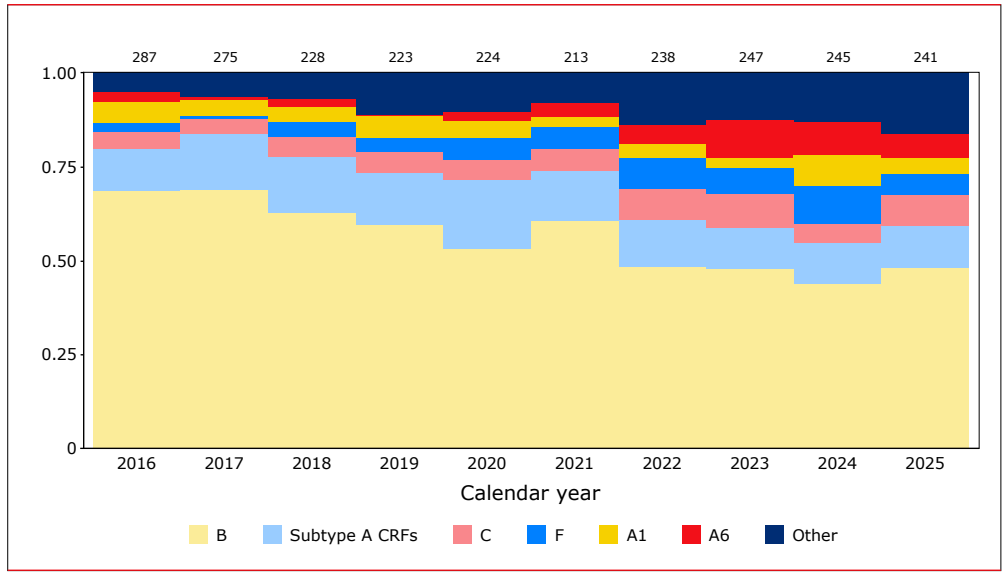
	B (N=1366)	A CRFs (N=317)	C (N=149)	F (N=124)	A1 (N=112)	A6 (N=104)	Other (N=249)
Netherlands	760 (63.1%)	144 (12.0%)	44 (3.7%)	76 (6.3%)	48 (4.0%)	26 (2.2%)	107 (8.9%)
Latin America and Caribbean	276 (77.7%)	23 (6.5%)	10 (2.8%)	12 (3.4%)	7 2.0%)	2 (0.6%)	25 (7.0%)
Sub-Saharan Africa	15 (6.0%)	83 (33.2%)	68 (27.2%)	5 (2.0%)	23 9.2%)	1 (0.4%)	55 (22.0%)
Central and Eastern Europe	113 (45.6%)	7 (2.8%)	6 (2.4%)	23 (9.3%)	8 (3.2%)	69 (27.8%)	22 (8.9%)
South and East Asia	54 (43.2%)	40 (32.0%)	7 (5.6%)	0 (0.0%)	9 (7.2%)	2 (1.6%)	13 (10.4%)
W Eur, N America, Australia	83 (69.7%)	7 (5.9%)	2 (1.7%)	5 (4.2%)	6 (5.0%)	4 (3.4%)	12 (10.1%)
N Africa and Middle East	46 (52.9%)	10 (11.5%)	10 (11.5%)	2 (2.3%)	9 (10.3%)	0 (0.0%)	10 (11.5%)
Unknown	19 (59.4%)	3 (9.4%)	2 (6.2%)	1 (3.1%)	2 (6.2%)	0 (0.0%)	5 (15.6%)

**HIV subtyping in the ATHENA database is performed using the COMET algorithm. A CRF: subtype A-related circulating recombinant forms; W Eur, Western Europe; N America, North America; N Africa, Northern Africa.*

We observed notable shifts in the distribution of HIV-1 subtype over time (*Figure 5.2*). Over the past decade, a decrease in the proportion of subtype B was complemented by an increase in A subtypes and recombinant forms. In 2016, subtype B accounted for 68.6% of new infections compared to 48.1% in 2025 ($p < 0.001$ for trend).

Subtype A6, which has been associated with increased risk of virological failure on long-acting CAB/RPV (see Introduction) was detected in 104 (4.3%) screened individuals. The proportion of participants with subtype A6 increased over time, from 2.8% in 2016 to 6.6% in 2025 ($p < 0.001$), peaking at 10.1% in 2023.

Figure 5.2: Changes in HIV-1 subtype identified in baseline genotypes, 2016–2025 (n = 2,421).



Prevalence of baseline resistance

Of 2,421 individuals screened for baseline resistance, 1,859 (76.8%) were fully susceptible to all ARVs included in the analysis while 358 (14.8%) had potential low-level resistance, 57 (2.4%) had low-level, 38 (1.6%) had intermediate-level, and 109 (4.5%) had high-level resistance to at least one ARV. *Table 5.3* shows the proportion of participants with low-level or greater and intermediate-level or greater resistance by drug class.

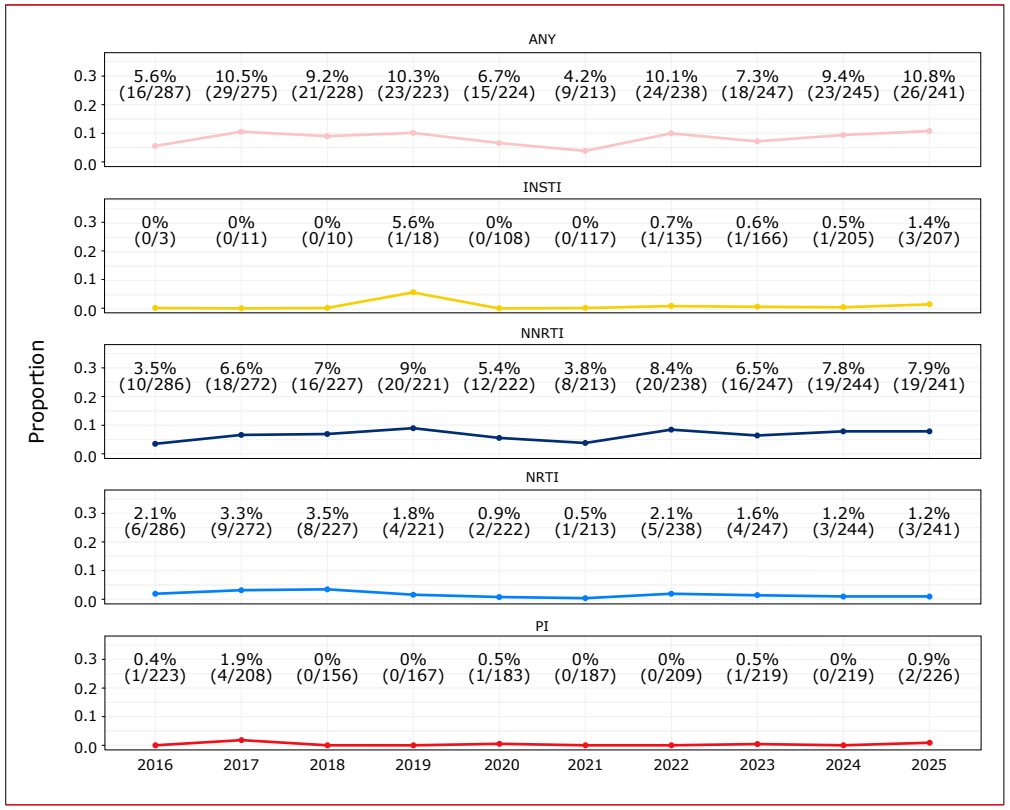
Table 5.3: Prevalence of baseline resistance by drug class, 2016–2025 (n = 2,421).

Drug class	Low-level or greater	Intermediate-level or greater
Any	8.4% (204/2421)	6.1% (147/2421)
NRTI	1.9% (45/2411)	0.8% (20/2411)
NNRTI	6.6% (158/2411)	5.2% (126/2411)
PI	0.5% (9/1997)	0.3% (6/1997)
INSTI	0.7% (7/980)	0.3% (3/980)

Intermediate-level or greater resistance to multiple drug classes was observed in eight participants: seven had evidence of NRTI and NNRTI resistance and one had INSTI and NNRTI resistance.

Figure 5.3 shows changes in the prevalence of baseline resistance between 2016 and 2025. The proportion of participants with low-level resistance or greater to any drug class increased from 5.6% in 2016 to 10.8% in 2025. The proportion of participants with any intermediate-level or greater resistance increased from 4.2% in 2016 to 7.1% in 2025 over the past decade.

Figure 5.3: *Proportion of participants with low-level or greater baseline resistance, by drug class, 2016–2025 (n = 2,421).*



Class- and drug-specific resistance patterns

Figures 5.4A and 5.4B show the proportion of participants with low-level or greater baseline resistance and intermediate-level or greater baseline resistance, respectively, by drug and drug class over time. *Table 5.4* shows the most frequently identified baseline RAMs.

Figure 5.4A: *Low-level or greater baseline resistance to antiretroviral agents, 2016–2025 (n = 2,421).*

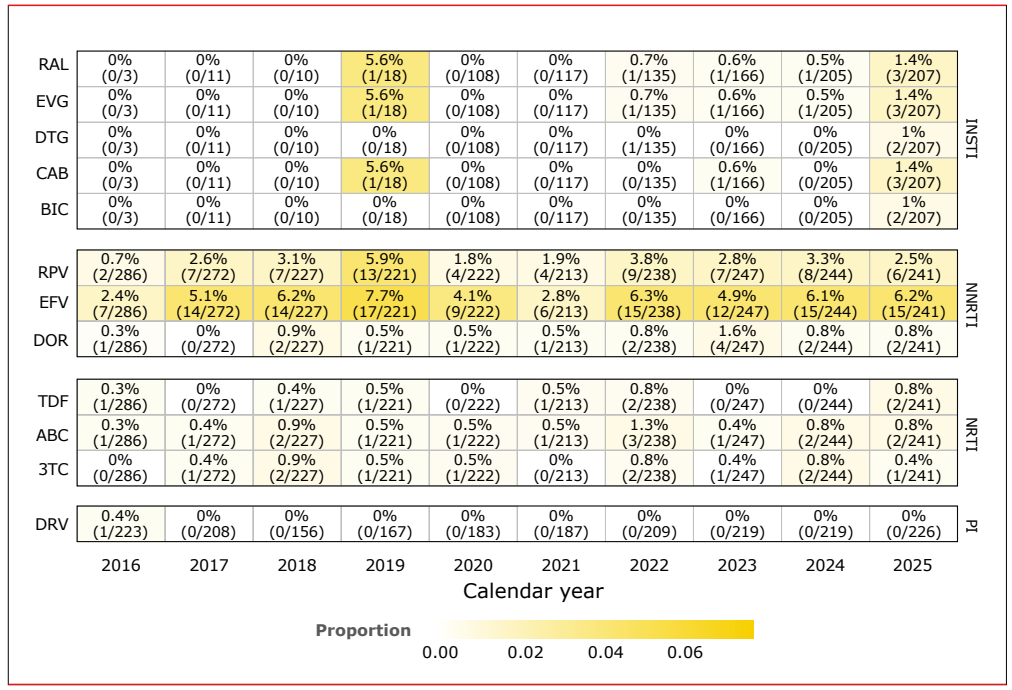
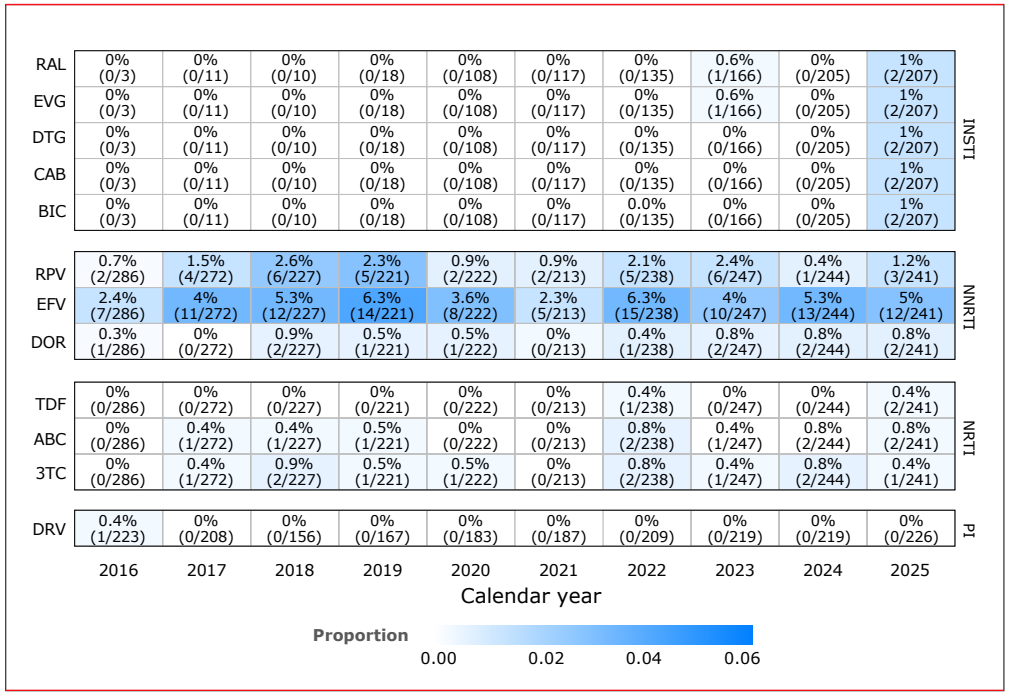


Figure 5.4B: Intermediate-level or greater baseline resistance to antiretroviral agents, 2016–2025 (n = 2,421).



Within each cell, the numerator represents the number of sequences with RAMs, and the denominator represents the number of available sequences.

Table 5.4: Most frequent RAMs identified on baseline resistance screening, 2016–2025.*

RAM	Class	Number	Percent
K103N	NNRTI	66	32.4
V108I	NNRTI	18	8.8
K101E	NNRTI	16	7.8
M41L	NRTI	14	6.9
K103S	NNRTI	11	5.4
Y181C	NNRTI	11	5.4
E138G	NNRTI	11	5.4
K238T	NNRTI	10	4.9
G190A	NNRTI	10	4.9
M184V	NRTI	9	4.4
E138K	NNRTI	7	3.4
L210W	NRTI	6	2.9
P225H	NNRTI	5	2.5
E138Q	NNRTI	5	2.5
V82A	PI	4	2.0
D67G	NRTI	4	2.0
A98G	NNRTI	4	2.0
K70N	NRTI	3	1.5
D67N	NRTI	3	1.5
T215I	NRTI	3	1.5
E138K	INSTI	3	1.5
M184I	NRTI	3	1.5

**IN L74I in subtype A6 not included in tabulation.*

Integrase resistance

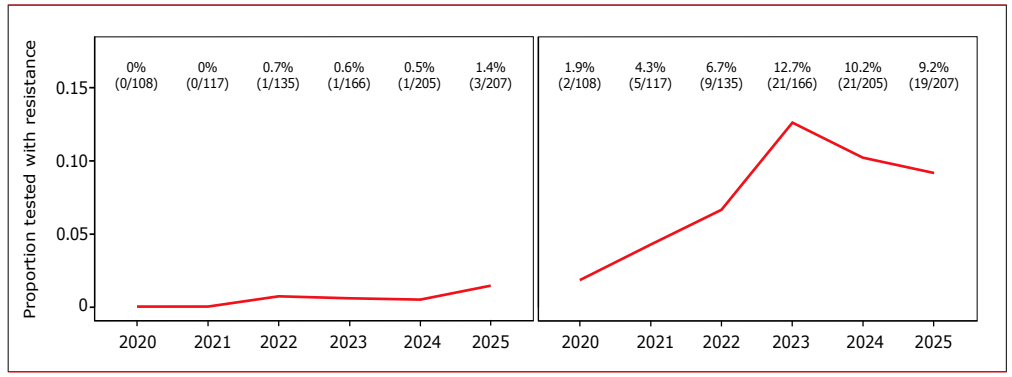
Of 980 participants with baseline integrase sequencing, low-level or greater resistance was identified in seven (0.7%), and intermediate-level or greater resistance was identified in three.

In 2025, two cases of intermediate to high-level baseline resistance to all available INSTIs were identified in the Netherlands for the first time. Both participants had subtype B infection. One participant harboured RAMs IN G140S and IN Q148H, and the second harboured RAMs IN E138K and IN Q148K. These RAMs confer intermediate resistance to bictegravir (BIC) and dolutegravir (DOL), and high-level resistance to cabotegravir (CAB), raltegravir (RAL), and elvitegravir (EVG). The second participant also harboured NNRTI RAMs K101E, Y181C and H221Y, conferring high-level resistance to rilpivirine (RPV). Neither participant reported a history of oral or injectable PrEP use prior to HIV diagnosis. A detailed description of the two cases has been published previously[9].

An additional 5 participants harboured single low- or intermediate-level INSTI RAMs: 2 had an E138K conferring low-level resistance to CAB, EVG and RAL; 2 had G163R conferring low level resistance to EVG and RAL, 1 had a G140S conferring low-level CAB and intermediate level EVG and RAL resistance.

Of 104 participants with subtype A6, integrase sequencing data was unavailable in 32 (30.8%). Among the remaining 72 participants, 68 had substitution IN L74I, 3 had IN L74LI mixture, and 1 participant had wild-type IN L74. *Figure 5.5* compares the prevalence of low-level or greater baseline integrase resistance with and without IN L74I subtype A6 resistance-associated polymorphism included in the analysis. Due to the low number of integrase sequences available prior to 2020, the analysis is restricted to the years 2020-2025.

Figure 5.5: Prevalence of baseline integrase inhibitor resistance, with and without IN L74I in subtype A6, 2020–2025.



NRTI resistance

Of 2,411 participants with baseline reverse transcriptase (RT) sequencing, low-level or greater NRTI resistance was detected in 45 (1.9%) participants; intermediate-level or greater resistance was detected in 20 participants. RAMs RT M184V/I, conferring high-level resistance to the cytidine analogues lamivudine and emtricitabine (3TC/FTC), were identified in 11 participants (0.5%) of which 7 had M184V/I as the sole RAM. Low-level tenofovir RAMs RT Y115F and RT K70ENT were identified in 1 and 6 participants respectively; a single participant had a RT K65R, conferring intermediate resistance to tenofovir.

NNRTI resistance

Low-level or greater NNRTI resistance was identified in 158 (6.6%) participants; intermediate-level or greater resistance was identified in 126 (5.2%). The most frequent NNRTI RAMs occurred at codon position RT 103 (n = 76) followed by RT 138 (n = 23).

Seventy-two participants had resistance to efavirenz only (49.7%). Low-, intermediate- and high-level resistance to rilpivirine was identified in 31, 23, and 5 participants, respectively. Low-, intermediate- and high-level resistance to doravirine was identified in 4, 8 and 4 participants respectively. Three participants had intermediate- or high-level resistance to both RPV and DOR.

Protease inhibitor resistance

Low-level or greater resistance to protease inhibitors was detected in nine participants and intermediate-level or greater resistance was detected in six. Only one participant had intermediate-level or greater resistance to the protease inhibitor darunavir.

Predictors of resistance and impact on treatment response

Table 5.5 shows the demographic and clinical characteristics of participants with any low-level or greater drug resistance, by drug class.

***Table 5.5:** Demographic and clinical characteristics of participants screened for baseline resistance, by type of resistance identified, 2016–2025 (n=2,421).*

	Any 204/2421	INSTI 7/980	NNRTI 158/2411	NRTI 45/2411	None 2217/2421
Transmission group					
MSM	90 (44.1%)	3 (42.9%)	62 (39.2%)	23 (51.1%)	1285 (58.0%)
WSM	42 (20.6%)	1 (14.3%)	35 (22.2%)	10 (22.2%)	338 (15.2%)
MSW	29 (14.2%)	2 (28.6%)	25 (15.8%)	4 (8.9%)	313 (14.1%)
Other	43 (21.1%)	1 (14.3%)	36 (22.8%)	8 (17.8%)	281 (12.7%)
Gender					
Cisgender man	146 (71.6%)	6 (85.7%)	108 (68.4%)	34 (75.6%)	1800 (81.2%)
Cisgender woman	48 (23.5%)	1 (14.3%)	41 (25.9%)	10 (22.2%)	381 (17.2%)
Transgender woman	10 (4.9%)	0 (0.0%)	9 (5.7%)	1 (2.2%)	34 (1.5%)
Transgender man	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Age at first HIV visit (mean, years)	41.5	38.3	40.6	42.1	41.1
Birth region					
Netherlands	94 (46.1%)	2 (28.6%)	70 (44.3%)	23 (51.1%)	1111 (50.1%)
Latin America and Caribbean	38 (18.6%)	4 (57.1%)	29 (18.4%)	6 (13.3%)	317 (14.3%)
Sub-Saharan Africa	29 (14.2%)	0 (0.0%)	24 (15.2%)	10 (22.2%)	221 (10.0%)
Central and Eastern Europe	13 (6.4%)	0 (0.0%)	13 (8.2%)	0 (0.0%)	235 (10.6%)
South and East Asia	10 (4.9%)	0 (0.0%)	9 (5.7%)	1 (2.2%)	115 (5.2%)
W Eur, N America, Australia	9 (4.4%)	0 (0.0%)	7 (4.4%)	2 (4.4%)	110 (5.0%)
N Africa and Middle East	9 (4.4%)	1 (14.3%)	4 (2.5%)	2 (4.4%)	78 (3.5%)
Unknown	2 (1.0%)	0 (0.0%)	2 (1.3%)	1 (2.2%)	30 (1.4%)

MSM, men who have sex with men; MSW, men who have sex with women; WSM, women who have sex with men; W Eur, Western Europe; N America, North America; N Africa, Northern Africa.

In a multivariable model adjusted for transmission group, age at first visit, and region of birth, participants in "Other" risk groups had higher odds of any intermediate-level or greater resistance compared to MSM (aOR 2.4, 95% CI 1.5-3.8), driven by higher odds of NNRTI resistance in this heterogenous group. Participants born in Sub-Saharan Africa had higher odds of NRTI resistance than those born in the Netherlands (aOR 5.0, 95% CI 1.5-16.0). When L74I in subtype A6 was included as a RAM in the analysis, participants born in CEE had 19.0 (95% CI 10.9, 34.0) times the odds of integrase resistance than those born in other regions.

Viral load data at 48 weeks post-ART initiation was available in 1,989 (82.2%) of 2,421 participants with baseline genotyping. Of these, 115 (5.6%) had intermediate-level or greater resistance to any antiretroviral agent. Viral suppression was observed in 84.2% of participants without baseline resistance and in 84.1% of participants with intermediate-level or greater baseline resistance (p = 1).

Acquired resistance

In the following sections, we describe patterns of acquired drug resistance in ATHENA participants with genotyping performed more than 14 days after their first ART initiation date.

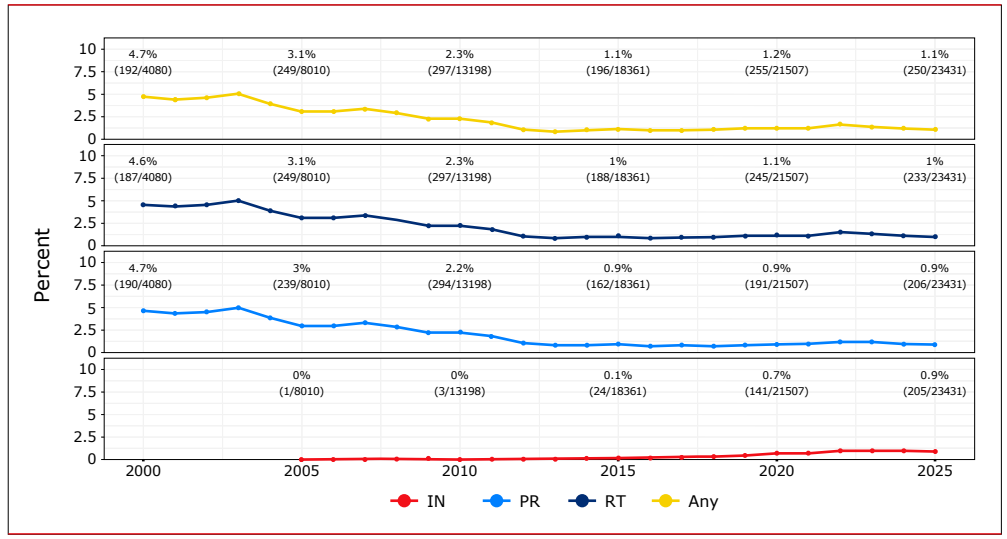
Because RAMs may be retained as integrated ("archived") proviral sequences in host cells, data from all available genotypes was used to determine the impact of cumulative RAMs in each participant. We included genotypes performed between cohort inception in 1996 and database closure on December 31, 2025. The cabotegravir resistance-associated polymorphism INL74I was not included in the overall analysis but is reported in the section on treatment-emergent CAB/RPV resistance.

Testing frequency and baseline characteristics

Between 1996 and 2025, 6,833 HIV-1 sequences were obtained in 3,873 participants. The mean number of sequences per participant was 1.8 (range 1-16) and the mean time from ART initiation to first sequence was 6.1 years (range 14 days – 32 years). Reverse transcriptase, protease, and integrase sequencing was obtained in 6,678, 6,150, and 1,443 samples, and 3,832, 3531, and 1,073 participants, respectively.

The number of sequences obtained per year, and the proportion of participants sequenced per year is shown in Figure 5.6. The proportion of sequences performed annually as a fraction of the number of participants in care has decreased, from 4.7% in 2000 to 1.1% in 2025.

Figure 5.6: *Number and proportion of participants in care tested for acquired drug resistance annually, 2000–2025.*



Of 3,873 participants evaluated for acquired RAMs, 2,759 (71.2%) were cis-gender men; 1,894 (48.9%) were MSM, 910 (23.5%) were WSM, 563 (14.5%) were MSW and 506 (13.1%) belonged to other transmission groups. One thousand six-hundred and eighty-eight participants (43.6%) were born in the Netherlands, 809 (20.9%) were born in Sub-Saharan Africa, and 713 (18.4%) in Latin America and the Caribbean. HIV-1 subtype B was identified in 2,649 (68.4%) participants.

Prevalence of acquired resistance

Among 27,703 participants in care over the past decade, low-level or greater acquired resistance was identified in 7.3%; intermediate-level or greater resistance was identified in 7.1%

Of the 6,833 genotypes obtained in 3,873 participants, 3,412 (50.0.%) sequences from 2,019 (52.1%) individuals had low-level or greater resistance to at least one ARV; 1,926 sequenced participants (49.7%) had intermediate-level resistance or greater to at least one ARV.

The most frequent patterns of low-level or greater resistance observed were dual-class NRTI + NNRTI resistance (n = 710, 35.2%), single class NRTI resistance (n = 482, 23.9%), single class NNRTI resistance (n = 293, 14.5%), and triple class NRTI, NNRTI and PI resistance (n = 252, 12.5%); similar patterns were observed for intermediate-level or greater resistance. Five participants had low-level or greater resistance to all four treatment classes and three participants had intermediate-level or greater resistance to all four treatment classes.

Figures 5.7A and 5.7B show the proportion of sequences with low-level or greater and intermediate-level or greater acquired resistance, respectively, by class and drug.

Figure 5.7A: *Proportion of sequences with low-level acquired resistance or greater, by class and drug, 2015–2026.*

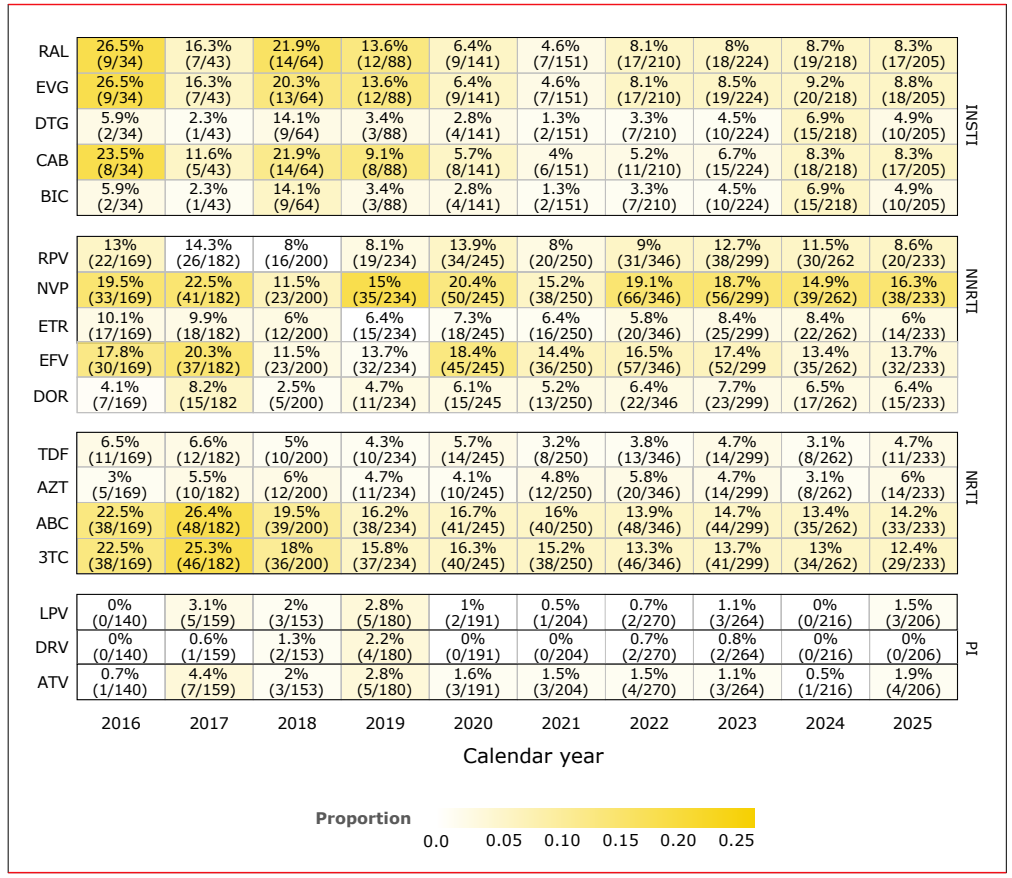
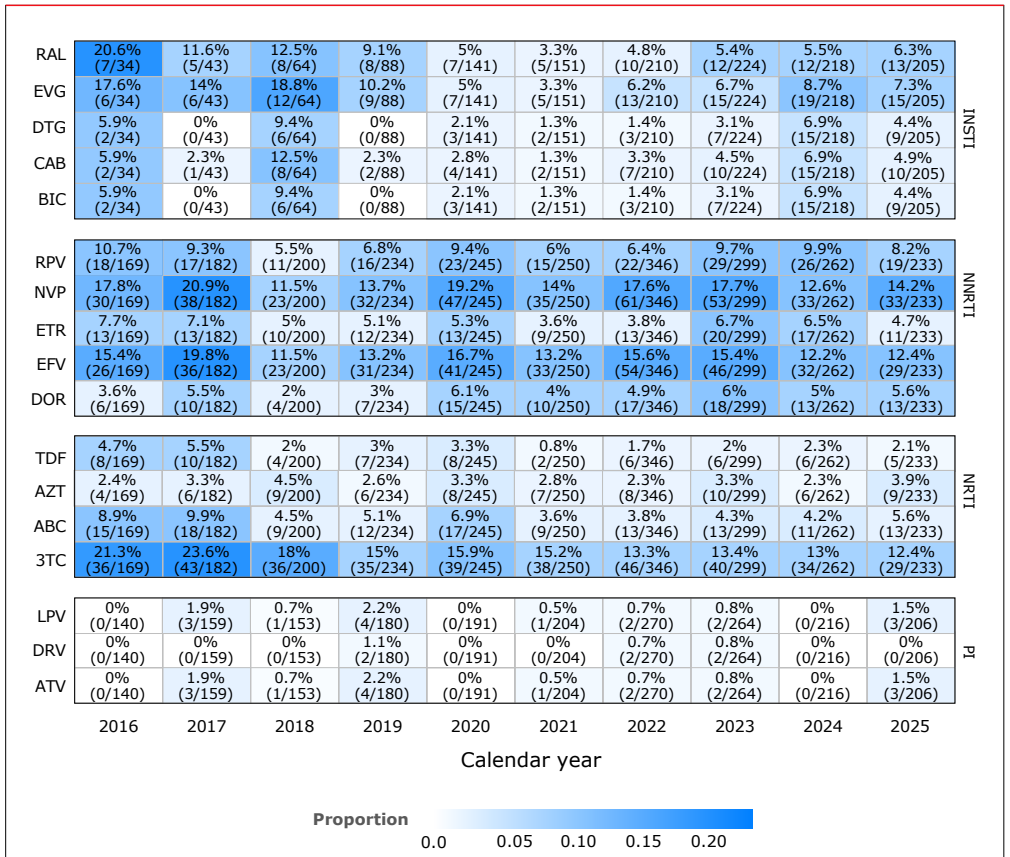


Figure 5.7B: *Proportion of sequences with intermediate-level acquired resistance or greater, by class and drug, 2015–2026*



Within each cell, the numerator represents the number of sequences with resistance, and the denominator represents the number of available sequences for the associated enzyme.

Table 5.7 shows the proportion of participants with low-, intermediate-, and high-level resistance to the main antiretroviral agents used in current HIV management. Resistance to 3TC/FTC was most frequent. Of 3,832 participants with RT sequencing, 36.0% had high-level 3TC/FTC resistance, representing 5.0% of 27,703 participants in care.

RPV and DOR resistance was identified in 3.2% and 2.1% of participants in care, respectively. DTG, BIC, and DRV resistance was identified in <1% of patients in care.

Table 5.7: *Acquired resistance to key antiretroviral agents among participants in care (n = 27,703).*

Class	Seq (n)	Drug	Resistance	Resistant	Resistant (% seq)	Resistant (% care)	Total (n)	Total (% care)
INSTI	1073		Low	15	1.4	0.05		
		BIC	Intermediate	33	3.1	0.12	59	0.21
			High	11	1.0	0.04		
			Low	15	1.4	0.05		
		DTG	Intermediate	28	2.6	0.1	59	0.21
			High	16	1.5	0.06		
NNRTI	3832		Low	170	4.4	0.61		
		DOR	Intermediate	185	4.8	0.67	590	2.13
			High	235	6.1	0.85		
			Low	199	5.2	0.72		
		RPV	Intermediate	238	6.2	0.86	891	3.22
			High	454	11.8	1.64		
NRTI	3832		Low	94	2.5	0.34		
		3TC/FTC	Intermediate	13	0.3	0.05	1485	5.36
			High	1378	36.0	4.97		
			Low	200	5.2	0.72		
		TDF/TAF	Intermediate	322	8.4	1.16	764	2.75
			High	242	6.3	0.87		
PI	3531		Low	117	3.3	0.42		
		DRV	Intermediate	36	1.0	0.13	163	0.59
			High	10	0.3	0.04		

Seq = number of participants with available sequences; % care, proportion of participants in care with resistance.

Resistance to long-acting regimens

A total of 1,154 ATHENA participants received at least one dose of the long-acting injectable INSTI/NNRTI combination agent LA CAB/RPV. Of these, 27 (2.3%) underwent genotyping at least 14 days after starting LA CAB/RPV and within a year of the last recorded LA CAB/RPV dose. Of these, pre-treatment RT sequencing data was available in seven and IN sequencing data in six.

Post-treatment CAB/RPV RAMs were detected in 19 participants (*Table 5.8*). Of these, one had pre-treatment RPV resistance (RT Y188L). Among the six participants with pre-treatment IN sequencing, no RAMs were identified. Post-treatment CAB resistance was identified in ten participants and RPV resistance in 18; nine had resistance to both CAB and RPV. Two participants with subtype A6 had an IN L74I polymorphism.

An analysis of predictors of virological failure on LA CAB/RPV within the ATHENA cohort has been published previously[10].

Table 5.8: RAMs observed in participants with genotypes performed after LA CAB/RPV initiation (n = 27).

Index	Subtype	RPV pre-treatment	CAB pre-treatment	RPV post-treatment	CAB post-treatment
1	02_AG	--	--	None	Q148R
2	02_AG	--	--	K101P	Q148R
3	02_AG	None	None	E138K	None
4	43_02G	--	--	None	None
5	A1	None	None	None	--
6	A6	--	--	E138K	L74I
7	A6	--	--	K101E	L74I, Q148R
8	B	--	--	E138K	Q148R
9	B	--	--	E138K, K101E, M230L	None
10	B	--	--	None	--
11	B	--	--	K101P	G118R, Q148R
12	B	--	--	E138K	None
13	B	--	--	E138K	None
14	B	--	--	K101E, Y181C	None
15	B	--	--	E138K, K101E	Q148R
16	B	--	--	E138K	None
17	B	--	--	None	None
18	B	--	--	K101E	None
19	B	None	--	--	None
20	B	None	None	None	None
21	C	--	--	Y181C	R263K
22	C	None	None	None	None
23	C	Y188L	None	Y188L	Q148R
24	REC	--	--	E138K	None
25	REC	--	--	Y181C	F121C
26	REC	--	--	K101E	None
27	REC_B	None	None	--	None

RPV, rilpivirine; CAB, cabotegravir; --, No sequence available; REC, circulating recombinant form, not otherwise specified.

Conclusions

Over the past decade, intermediate-level or greater baseline HIV drug resistance in the Netherlands increased from 4.2% to 7.1%. Most baseline resistance was due to NNRTI mutations. In 2025, two cases of intermediate-level or greater baseline resistance to all available INSTIs were identified for the first time, highlighting the need for continued monitoring of baseline INSTI resistance in the Netherlands. To date, baseline drug resistance has had no impact on treatment response.

Acquired drug resistance to core antiretroviral drugs used in the current management of HIV remains low in the Netherlands. Among the small number of participants who experienced treatment failure on long-acting CAB/RPV, the proportion with acquired resistance to CAB/RPV was 70%. Ongoing evaluation of predictors of long-acting CAB/RPV treatment failure is needed.

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Appendix

***Appendix table 5.1:** Drugs excluded from the resistance analysis*.*

Drug name	Class
Fosamprenavir	PI
Indinavir	PI
Nelfinavir	PI
Saquinavir	PI
Tipranavir	PI
Stavudine	NRTI
Zalcitabine	NRTI
Didanosine	NRTI
Dapivirine	NNRTI

**RAMs and RAM combinations conferring resistance exclusively to drugs in this table were not included in the analysis.*