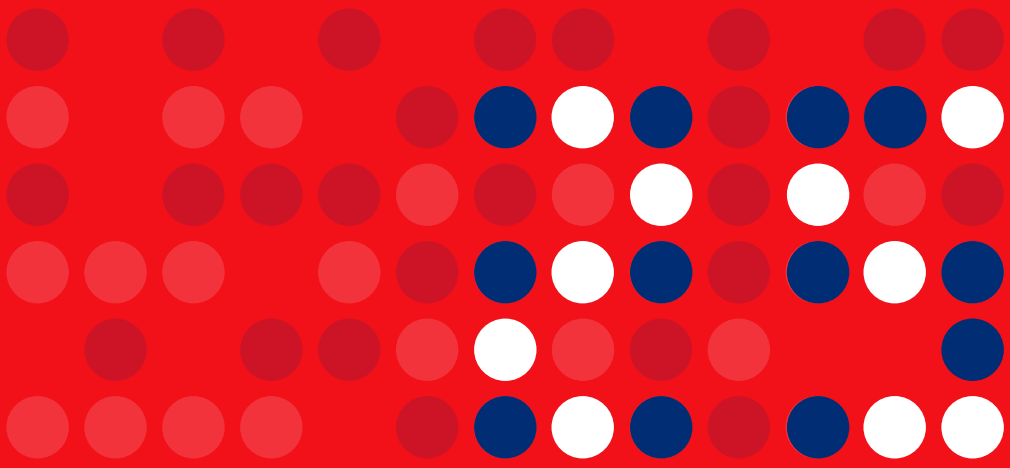
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2025

Chapter 5: HIV drug resistance



5. HIV drug resistance

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Key findings

Baseline drug resistance

- Between 2015 and 2024, 39% of individuals newly diagnosed with HIV in the Netherlands underwent baseline screening for HIV drug resistance. Clinically significant drug resistance was identified in 11.4%.
- The rate of baseline drug resistance increased from 5% in 2015 to 20% in 2024. This increase was largely driven by HIV-1 subtype A6 IN L74I resistance-associated polymorphism, impacting cabotegravir susceptibility only.
- To date, baseline drug resistance has had no observed impact on antiretroviral treatment response. We found no differences in rates of virological suppression between participants with and without baseline drug resistance.

Acquired drug resistance

- Of 24,028 participants in HIV care through 2024, 3,022 (12.6%) were tested for acquired HIV drug resistance. Clinically significant resistance was identified in 1,633 (6.8%) participants.
- Between 2000 and 2024, the proportion of sequences with clinically significant resistance associated mutations decreased from 78.1% to 31.1%.
- Resistance to newer treatment strategies, including second-generation integrase inhibitors and long-acting cabotegravir/rilpivirine, has been documented and requires future monitoring.
- Participants with a history of acquired drug resistance were less likely to be virologically suppressed at last observation than participants without a history of acquired drug resistance (92% vs 83%, respectively), attesting to the ongoing importance of adherence support.

Introduction

Monitoring for HIV drug resistance is integral to HIV surveillance and care. In this chapter, we describe trends in the prevalence of baseline and acquired HIV drug resistance in the Netherlands. In this year's report, we include participants who were alive and in care at year end 2024. For an analyses of HIV drug resistance in the ATHENA cohort since its inception, please refer to prior SHM monitoring reports.

We identified resistance-associated mutations [RAMs] using Stanford University's HIV Drug Resistance Database mutation analysis algorithm (version 9.5) [HIVdb] and the International Antiviral Society-USA HIV drug resistance mutation chart[1,2]. We used the HIVdb to calculate cumulative drug penalty scores for each antiretroviral agent, based on all RAMs identified in each sequence. We converted this score into a five-point drug resistance scale: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance. We designated all intermediate- and high-level resistance as clinically significant. Due to the increasing importance of long-acting cabotegravir/rilpivirine [CAB/RPV] in HIV treatment, we also considered the cabotegravir resistance-associated polymorphism IN L74I in HIV-1 subtype A6 and low-level resistance to RPV clinically significant[3,4]. We use the term "RAM" to refer to both naturally occurring polymorphisms and to mutations acquired due to selective antiretroviral pressure; when relevant, the polymorphic nature of the RAM is discussed.

The distribution HIV-1 subtypes among newly diagnosed individuals has become increasingly important, due to subtype-specific polymorphisms conferring clinically significant drug resistance. The most common of these polymorphisms are RT E138A in non-B subtypes (reducing susceptibility to rilpivirine) and the IN L74I in subtype A6 (reducing susceptibility to cabotegravir)[1,5]. We discuss the impact of HIV-1 subtype on antiretroviral resistance in detail throughout the chapter.

Baseline resistance

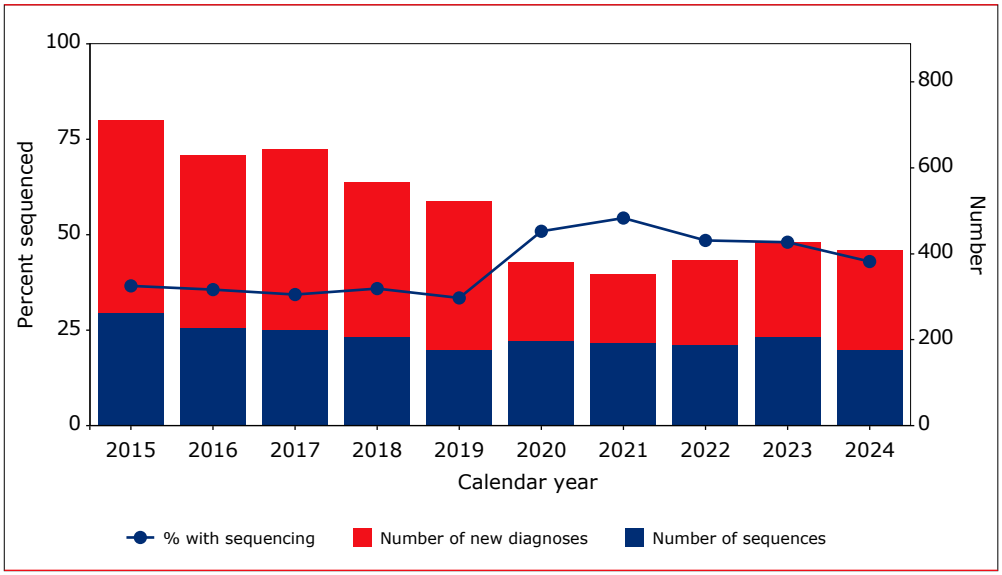
Baseline resistance refers to the detection of RAMs prior to the initiation of antiretroviral treatment. Baseline resistance may occur due to transmission of a drug-resistant HIV strain or due to naturally occurring polymorphisms associated with specific HIV-1 subtypes. Since 2003, Dutch guidelines recommend baseline resistance screening in all newly diagnosed individuals entering HIV care[6]. Implementation of these guidelines has been partial, varying significantly by treatment centre.

In our analysis of baseline resistance trends, we include ATHENA participants who met the following criteria: diagnosed with HIV between 2015 and 2024 while living in the Netherlands; screened within 60 days of HIV diagnosis and before initiating antiretroviral therapy; remained in care at year-end 2024; and reported no history of PreP use. Pre-treatment drug resistance associated with PrEP use is discussed elsewhere in this report (see Prior use of pre-exposure prophylaxis).

Screening frequency and baseline characteristics

Between 2015 and 2024, 5,197 individuals were diagnosed with HIV-1 in the Netherlands, of whom 2,039 (39.2%) were screened for baseline drug resistance. Baseline screening increased over time (Figure 5.1).

Figure 5.1: Proportion of newly diagnosed participants screened for baseline resistance, 2015–2024 (n=5,197).



In 2,039 individuals with baseline resistance screening, 2,028 reverse transcriptase, 1,671 protease, and 640 integrase sequences were available for review. Eighty-two percent of individuals undergoing baseline screening were male, 59.7% were MSM, and 53.1% were born in the Netherlands.

We observed notable shifts in the distribution of HIV-1 subtypes among newly diagnosed participants. Over the past decade, a decrease in the proportion of HIV-1 subtype B was complemented by an increase in HIV-1 subtypes A, C and recombinant forms. HIV-1 subtype varied significantly by mode of transmission (Figure 5.2)[7].

Figure 5.2: HIV-1 subtypes identified at baseline resistance screening, by transmission group, 2015–2024 (n=2,039).

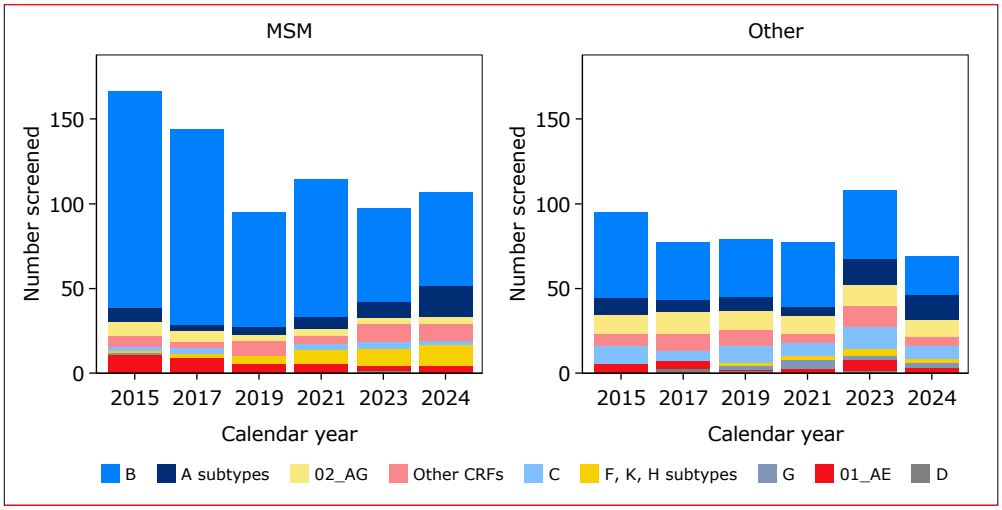


Figure 5.3 shows the region of birth of individuals with HIV-1 B and A subtypes. Since 2019, a greater proportion of individuals with HIV-1 subtype A were born in Central and Eastern Europe[8,9]. The proportion of subtype A6 as a fraction of all subtype A strains identified at baseline screening (n=170) has increased over the past decade (Figure 5.4). Sixty-three percent of participants with subtype A6 were born in Central and Eastern Europe and 28.6% were born in the Netherlands. Conversely, of 5,197 participants diagnosed with HIV between 2015 and 2024, 448 (8.6%) were born in Central and Eastern Europe; of these, 183 underwent baseline drug resistance testing and 49 (27.8%) had subtype A6 detected.

Figure 5.3: HIV-1 subtype by region of birth in participants screened for baseline resistance, 2015–2024 (n=2,039).

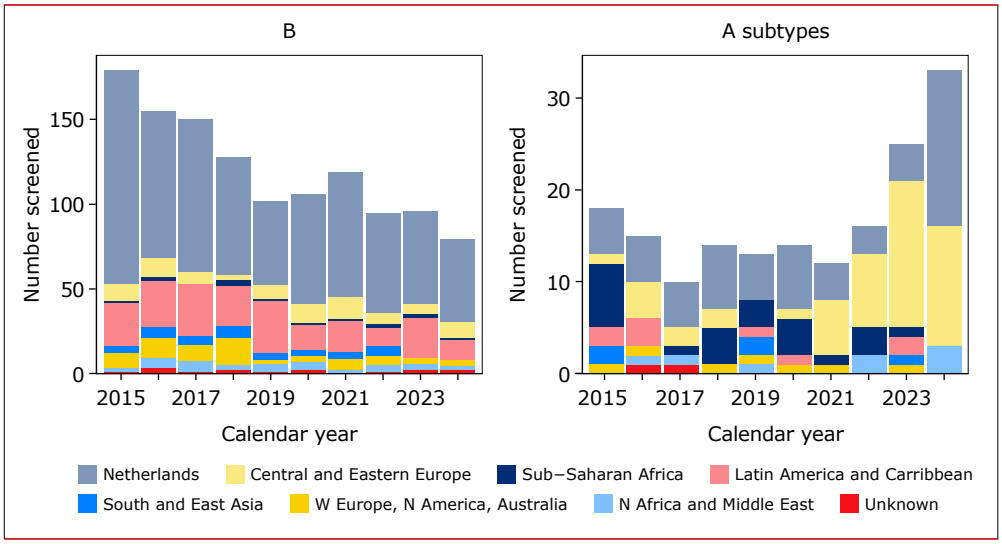
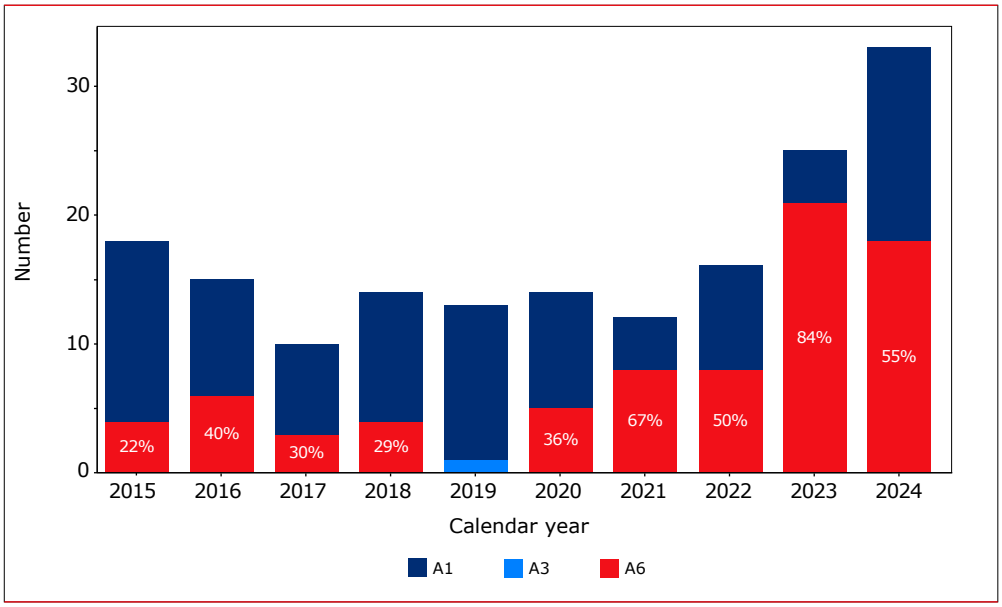


Figure 5.4: Distribution of HIV-1 A sub-subtypes in participants with subtype A identified at baseline resistance screening, 2015–2024 (n=170).



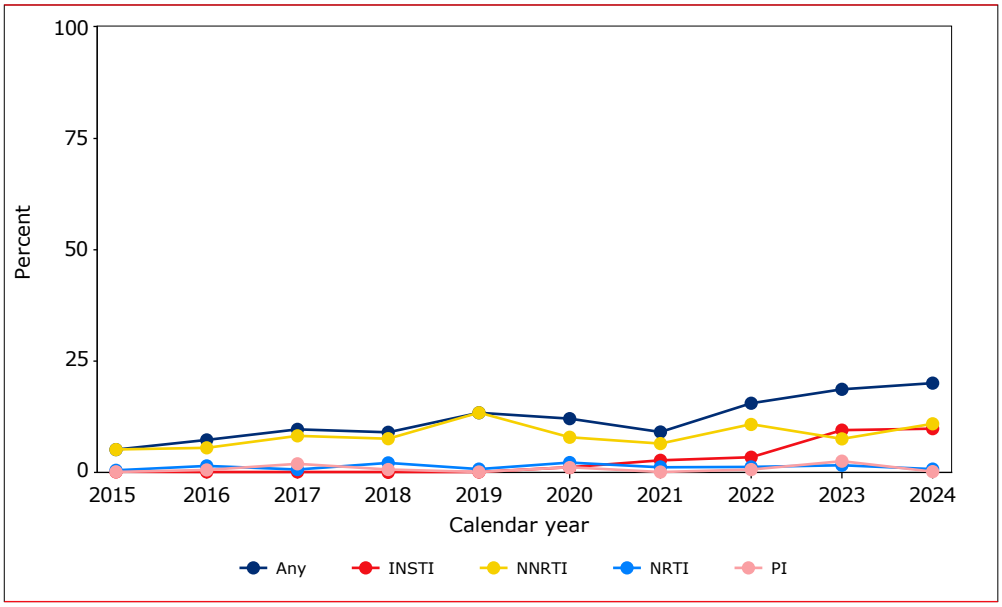
Patterns of baseline resistance

Of 2,039 individuals undergoing baseline screening, 233 (11.4%) had evidence of clinically significant resistance. The proportion of participants with clinically significant baseline resistance fluctuated between 5% and 20% over the past decade, with a pronounced increase after 2020 (Table 5.1 and Figure 5.5). This temporal increase coincides with the increasing prevalence of HIV-1 subtype A6 in the Netherlands and is discussed in further detail below. Baseline RAMs conferring resistance to NNRTIs, NRTIs, PIs, and INSTIs were observed in 162 (7.9%), 22 (1.1%), 14 (0.7%) and 49 (2.4%) of screened participants, respectively. Of 233 participants with baseline RAMs, 220 (94.4%) had one RAM, 12 (5.1%) had two RAMs, and 1 (<1%) had three RAMs.

Table 5.1: *Proportion of participants with clinically significant RAMs detected at baseline screening, by affected drug class, 2015–2024 (n=2,039).*

Year	Any	NRTI	NNRTI	PI	INSTI
2015	5	0.4	5	0	0
2016	7.1	1.3	5.3	0.4	0
2017	9.5	0.5	8.1	1.8	0
2018	8.8	2	7.4	0.5	0
2019	13.2	0.6	13.2	0	0
2020	11.9	2.1	7.7	1	1
2021	8.9	1	6.3	0	2.6
2022	15.4	1.1	10.6	0.5	3.2
2023	18.5	1.5	7.3	2.4	9.3
2024	19.9	0.6	10.8	0	9.7

Figure 5.5: Baseline HIV-1 drug resistance by antiretroviral class, 2015–2024 (n=2,039).



Of 640 participants with baseline integrase sequencing, 49 (7.6%) had integrase RAMs detected; 48 had HIV-1 subtype A6. All 48 participants with integrase sequencing and subtype A6 harboured the cabotegravir-associated IN L74I RAM; four of these participants also had RAMs conferring NNRTI resistance (two with RT K103N; one with RT G190S, K101E, and E138A; and one with RT E138A). An additional participant had HIV-1 subtype B with IN G140S, conferring resistance to the first-generation integrase inhibitors raltegravir and elvitegravir. No baseline resistance to dolutegravir or bictegravir was detected. Overall, 44 of 49 (90%) participants with baseline INSTI resistance harboured the subtype A6 IN L74I polymorphism only.

Baseline NNRTI resistance was detected in 162 participants. Of these, 56 (34.3%) had RT E138A only and 33 (20.2%) had RT K103N only; other NNRTI RAMs and RAM combinations occurred at a frequency of less than 5%. Of the 56 participants with RT E138A alone, 32 (57.1%) had HIV-1 subtype B; the remaining 24 (42.9%) had non-B subtypes and recombinant forms in which the RT E138A may be considered polymorphic.

Substitutions RT M184V/I, conferring resistance to the cytidine analogues lamivudine and emtricitabine [3TC/FTC], were identified in 6 participants. In three, 3TC/FTC resistance was accompanied by additional NRTI mutations, including one individual with the tenofovir-associated RAM RT K65R. In 3 participants with RT M184V/I, PrEP use history was not documented; the remaining 3 participants (including the individual with RT K65R) were documented to have not used PrEP.

Forty-four percent of people with clinically significant baseline resistance were born in the Netherlands, 11.2% in Latin America and the Caribbean, 11.2% in Sub-Saharan Africa and 22.7% in Central and Eastern Europe. Seventy-three percent of participants with the subtype A6 L74I RAM were born in Central and Eastern Europe and 23% were born in the Netherlands. Compared to people born in the Netherlands, people born in Central and Eastern Europe had 3.9 [CI 2.7 - 5.7] times the odds of any clinically significant RAMs and 15.6 [CI 7.9 - 32.9] times the odds of INSTI RAMs, driven by the high prevalence of HIV-1 subtype A6 in these regions (see Baseline characteristics). People born in Sub-Saharan Africa had higher odds of NNRTI-associated RAMs compared to people born in the Netherlands (unadjusted OR 1.8 [95%CI 1.1- 2.9).

Table 5.2 shows the number and proportion of RAMs occurring in at least 1% of participants with baseline resistance.

Table 5.2: Most frequent RAMs identified at baseline screening, 2015–2024 (n=233).

RAM	Class	Number	Percent^
E138A	NNRTI	63	27
L74I	INSTI	48	20.6
K103N	NNRTI	44	18.9
K101E	NNRTI	12	5.2
E138G	NNRTI	9	3.9
K103S	NNRTI	9	3.9
K238T	NNRTI	8	3.4
G190A	NNRTI	8	3.4
Y181C	NNRTI	7	3
E138K	NNRTI	6	2.6
M184V	NRTI	4	1.7
P225H	NNRTI	4	1.7
E138Q	NNRTI	4	1.7
Y318F	NNRTI	2	0.9
V106M	NNRTI	2	0.9
H221Y	NNRTI	2	0.9
G190E	NNRTI	2	0.9
G190S	NNRTI	2	0.9
M184I	NRTI	2	0.9

^Because participants could have more than one RAM, total adds up to greater than 100%.

Impact on antiretroviral therapy

Among participants with baseline resistance, NNRTI RAMs were observed in 162 (69.5%), INSTI RAMs in 49 (21%), NRTI RAMs in 22 (9.4%) and PI RAMs in 14 (6%). Table 5.3 shows commonly used ART drug classes affected by baseline resistance, by order of impact.

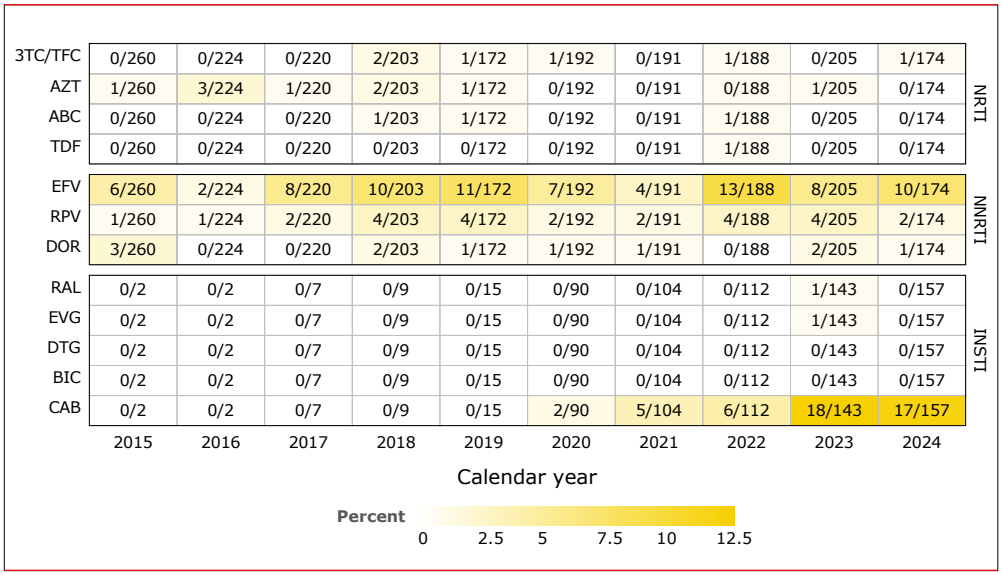
Table 5.3: Number and proportion of individuals with baseline resistance by drug class, 2015–2024 (n=233).

Class	Agents	Number	Percent^
2nd gen NNRTI	ETR, RPV	106	45.5
1st gen NNRTI	EFV, NVP	88	37.8
2nd gen INI	CAB	48	20.6
3rd gen NNRTI	DOR	11	4.7
Cytidine analogues	3TC, FTC	6	2.6
2nd gen PIs	ATV, FPV, LPV, TPV	5	2.1
1st gen INI	EVG, RAL	1	0.4
Tenofovir prodrugs	TDF	1	0.4

^Because participants could be resistant to more than one class, totals add up to greater than 100%.

Figure 5.6 shows the proportion of sequences with baseline resistance by drug and drug class, restricted to commonly used therapy. Within each cell, the numerator represents the number of sequences with RAMs and the denominator represents the number of available sequences.

Figure 5.6: Baseline HIV-1 drug resistance for commonly used antiretroviral agents, 2015-2024 (n=2,039).



To date, we observe no impact of baseline resistance on rates of virological suppression. Restricting the analysis to those who started antiretroviral therapy in 2023, the proportion of participants with virological suppression at year end 2024 in individuals with and without transmitted RAMs was 93.4% and 93%, respectively.

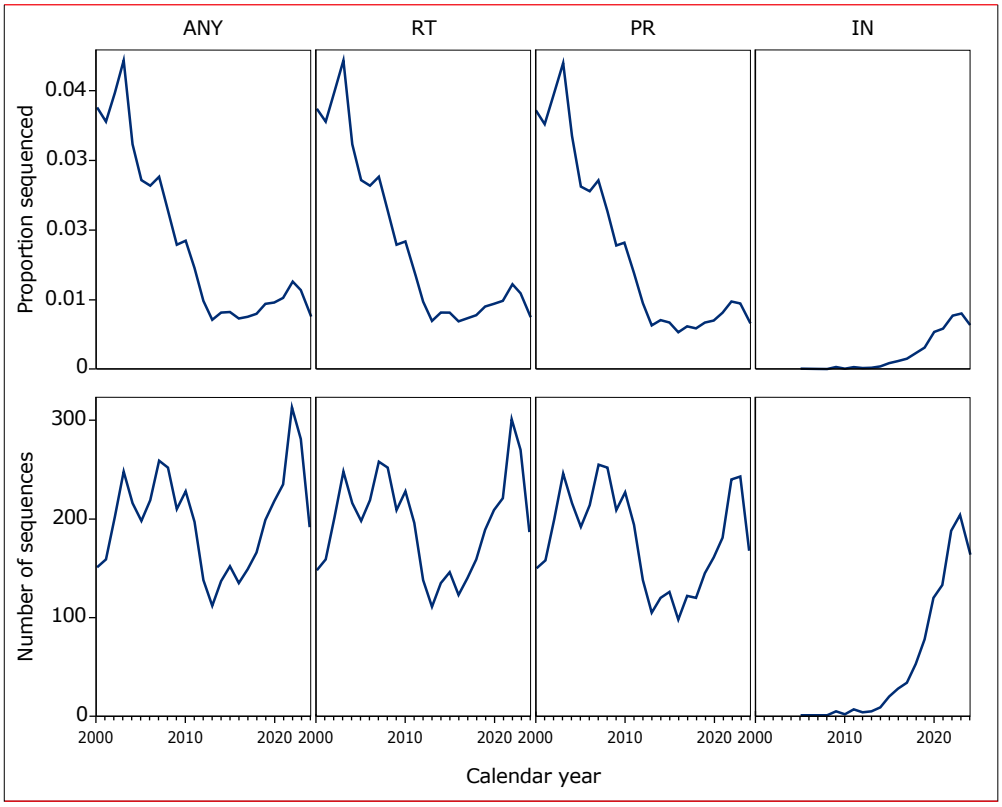
Acquired resistance

Acquired HIV drug resistance emerges in the setting of incomplete virological suppression during antiretroviral treatment. In the Netherlands, rates of virological suppression have improved significantly over time (see chapter 4 Response to combination antiretroviral therapy), leading to lower rates of RAMs detected at treatment failure. In the following sections, we describe patterns of acquired drug resistance in ATHENA participants who had at least one genotype performed more than 14 days after starting antiretroviral therapy and who were in care at year end 2024 . Antiretroviral therapy was defined as receipt of any antiretroviral agent or agent combination.

Testing frequency and baseline characteristics

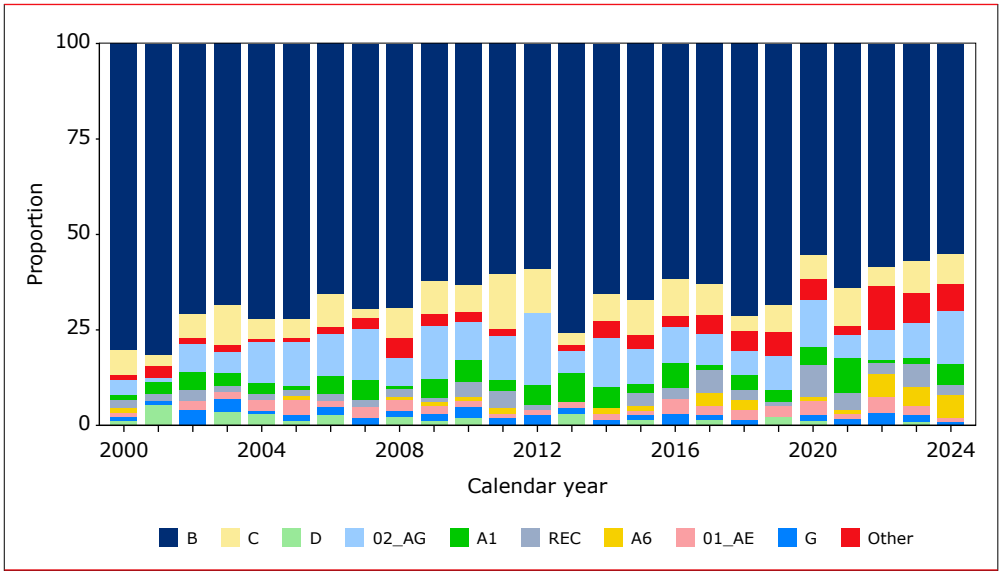
Between 1990 and 2024, 5,258 HIV-1 sequences were obtained from 3,022 people at least 14 days after first ART initiation. The mean number of sequences per participant was 3 (range 1-16) and the mean time from ART initiation to first sequence was 7.7 years (range 14 days – 33 years). Reverse transcriptase, protease, and integrase sequencing was obtained in 5,143, 4,764 and 1,059 samples, and 2,991, 2,777, and 788 participants, respectively. The number of sequences and the proportion of participants sequenced per year is shown in Figure 5.7. The proportion of sequences performed per year as a fraction of the number of participants in care has steadily decreased, from 4.4% in 2000 to 0.8% in 2024.

Figure 5.7: Proportion of participants in care undergoing drug resistance testing and number of sequences performed (n=24,028).



Of 3,022 participants tested for acquired RAMs, 2,193 (72.6%) were men, 1,475 (48.8%) were MSM and 1,182 (39%) heterosexual. One thousand three hundred and twenty-five participants (43.8%) were born in the Netherlands, followed by 658 (21.8.%) born in Sub-Saharan Africa, and 547 (18.1%) in Latin America and the Caribbean. HIV-1 subtype B was detected in 2,056 (68%) participants; an increase in the proportion of non-B subtypes was observed over time (Figure 5.8).

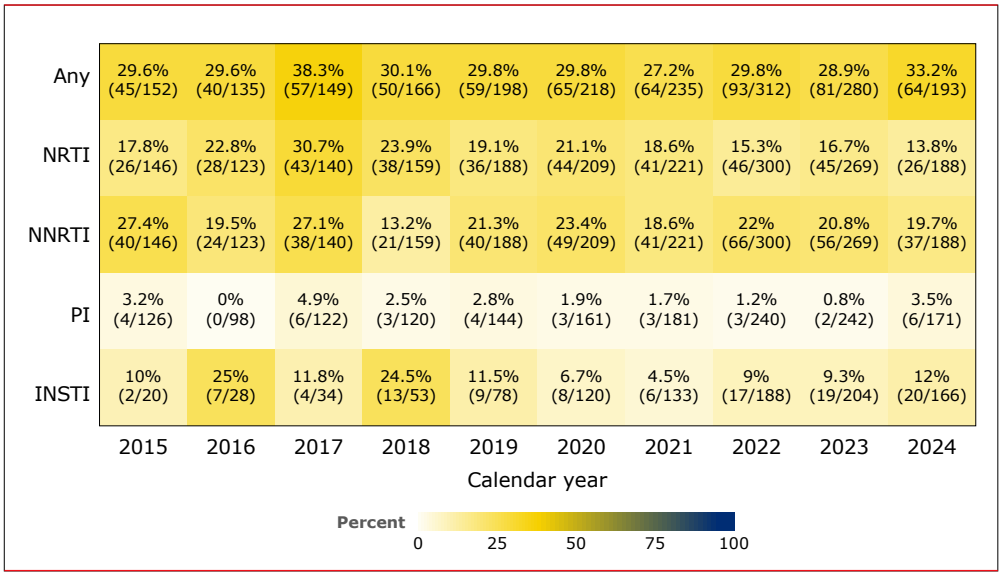
Figure 5.8: HIV-1 subtype in participants tested for acquired resistance (n=3,022).



Patterns of acquired resistance

Of the 5,258 samples obtained, 2,649 (50.4%) sequences from 1,633 individuals had at least one clinically significant RAM detected. NRTI, NNRTI, PI, and INSTI RAMs were detected in 2062 (39.2%), 1,622 (30.8%), 712 (13.5%), and 114 (2.2%) sequences, respectively. Single, dual, and triple class resistance was detected in 1,158 (22%), 1,121 (21.3%), 370 (7%) sequences, respectively; no single sequence contained RAMs to all four main treatment classes. Between 2000 and 2024, the proportion of sequences with any clinically significant RAMs decreased from 78.1% to 33.1%. Figure 5.9 shows the proportion of sequences with RAMs detected over the past decade, by drug class.

Figure 5.9: Proportion of sequences with HIV-1 RAMs, by drug class, 2015–2024 (n=5,258).



Numbers in parentheses represent the number of sequences with RAMs/number of available sequences.

Impact on antiretroviral therapy

Because RAMs may be retained as integrated ("archived") proviral sequences in host cells, data from sequential genotypes is needed to determine the impact of cumulative RAMs in individual participants[10]. In the remainder of this chapter, we present data on cumulative resistance patterns in 1,633 participants with any acquired RAMs. We begin with an overview of resistance by drug class. We then proceed to discuss drug-specific scenarios of particular relevance to current antiretroviral management.

Overview

At year end 2024, 24,028 participants were in care; of these, 1,633 (6.8%) had a history of acquired RAMs. Of 1,633 individuals with acquired RAMs, 1,310 (80%) had any NRTI resistance, 1,067 (65.3%) had NNRTI resistance, 375 (23%) had PI resistance, and 96 (5.9%) had integrase resistance. Resistance to an entire drug class was less frequent and varied by class: complete class resistance to NRTIs, NNRTIs, PIs and INSTIs occurred in 253 (15.5%), 212 (13%), 24 (1.5%) and 20 (1.2%) participants, respectively.

Six hundred and sixty-three participants (40.6%) had evidence of single class resistance, 728 (44.6%) had dual class resistance, 240 (14.7%) had triple class resistance, and two individuals had quadruple class resistance. The two participants with quadruple class resistance had a history of mono- or dual-NRTI exposure. The most frequent pattern of class resistance observed was dual-class NRTI + NNRTI resistance (n=558, 34.1%), followed by single class NRTI resistance (n=355, 21.7%) and single-class NNRTI resistance (n=253, 15.5%) (Table 5.4).

Table 5.4: Patterns of acquired resistance, by drug class (n = 1,633)

ART Drug Class	Number	Percent
NNRTI, NRTI	558	34.2
NRTI	355	21.7
NNRTI	253	15.5
NNRTI, NRTI, PI	212	13
NRTI, PI	135	8.3
INSTI	35	2.1
INSTI, NNRTI, NRTI	26	1.6
INSTI, NRTI	20	1.2
PI	20	1.2
INSTI, NNRTI	11	0.7

Resistance to antiretroviral "anchor" drugs used in current HIV management varied widely. Clinically significant resistance to doravirine was observed in 364 (22.2%) participants with a history of acquired RAMs; resistance to darunavir was observed in 34 participants (2.1%); resistance to the second-generation oral integrase inhibitors dolutegravir and bictegravir was detected in 32 (2%). These data represent resistance patterns observed irrespective of antiretroviral treatment history.

Participants with a history of acquired drug resistance were less likely to be virologically suppressed at last observation than participants without a history of acquired drug resistance (92% vs 83%, respectively).

Cytidine analogues

The cytidine analogues lamivudine and emtricitabine [3TC/FTC] form part of most first-line antiretroviral regimens and of oral PrEP. Resistance to 3TC/FTC emerges early in antiretroviral treatment failure and is almost universally caused by RT M184V/I RAMs[11]. Among 1,633 participants with acquired resistance, 1,108 (67.8%) had RT M184V/I identified on any sequence. One hundred and eighty-seven (11.5%) harboured the RT M184V/I as the sole RAM.

Among 1,108 participants with a history of RT M184V/I, we found no differences in rates of virological suppression by presence or absence of cytidine analogues in the current regimen (83.5% and 84.5%, respectively). Twenty patients with a history of RT M184V/I were treated with the dual-agent single tablet regimen dolutegravir/lamivudine; all twenty (100%) were virologically suppressed at last viral load measurement.

Integrase inhibitors

Understanding the emergence of INSTI resistance is important, given their central role in current HIV management[12]. Integrase inhibitors form the base ("anchor") of current antiretroviral regimens in 1,206 (73.9%) people with any acquired resistance.

Of 788 participants with integrase sequencing, 96 (12.2%) had INSTI RAMs detected. The most frequent INSTI RAMs identified were IN N155H (n=25, 26%), followed by the subtype A6 IN L74I (n=24, 25%) and IN R263K (n=16, 16.7%) (Table 5.5). In fifteen of twenty-four participants with the HIV-1 subtype A6 IN L74I polymorphism, no additional RAMs were identified. Excluding these 15 individuals from the analysis, only 81 participants had acquired INSTI resistance (10.3% of participants with INSTI sequencing, 0.3% of participants in care at year end 2024).

Table 5.5: INSTI RAMs detected in participants with post-treatment integrase resistance (n=96).

RAM	N	Percent^
N155H	25	26
L74I*	24	25
R263K	16	16.7
Q148R	9	9.4
E92Q	8	8.3
E138K	7	7.3
S147G	6	6.2
T66I	5	5.2
N155S	3	3.1
G140S	3	3.1
G118R	3	3.1
Y143C	3	3.1
Y143R	3	3.1
T66A	3	3.1
E138A	3	3.1
T66K	2	2.1
G140A	2	2.1
Q148H	1	1
E92G	1	1
F121C	1	1

**Considered a RAM in HIV-1 subtype A6 only. ^Percent represents proportion of participants with INSTI resistance harbouring each RAM; because participants could have more than one RAM, proportions exceed 100%.*

At time of first INSTI failure, 41 (42.7%) participants had been previously exposed to NNRTI and PI based therapy, 15 (15.6%) had been exposed to PI-based therapy only and 13 (13.5%) had been exposed to NNRTI-based therapy only; 23 (24%) had been treated with INSTI-based therapy only prior to the detection of INSTI RAMs (Table 5.6). Fifty-one (57.2%) participants with INSTI RAMs had no previously documented acquired resistance to either NNRTIs or PIs.

Forty-nine participants (50.5%) with INSTI RAMs had been treated with second generation INSTIs but not with a first generation INSTI. Nine participants had been treated with CAB prior to first integrase failure (CAB/RPV resistance is discussed in detail in the following section). Three participants with no documented history of INSTI treatment had INSTI-associated RAMs; none had been screened for transmitted drug resistance. Two of these participants had HIV-1 subtype A6 with IN L74I; the other participant had HIV-1 subtype B, a history of PI-based treatment only, and harboured IN L74IM and IN Y143C.

Five participants with INSTI RAMs had been screened for baseline drug resistance; four had no resistance and one had HIV-1 subtype A6 IN L74I detected.

Table 5.6: *Treatment characteristics of participants with acquired INSTI RAMs (n=96).*

	Number (precent)
Drug class exposure prior to INSTI resistance	
NNRTI, PI	41 (42.7%)
INSTI only	23 (24.0%)
PI	15 (15.6%)
NNRTI	13 (13.5%)
Unknown	4 (4.2%)
Type of integrase exposure	
Second generation only	47 (49.0%)
First generation only	34 (35.4%)
Both first and second generation	12 (12.5%)
No history of integrase exposure	3 (3.1%)
History of cabotegravir use	
No	87 (90.6%)
Yes	9 (9.4%)
History of dolutegravir monotherapy	
No	88 (91.7%)
Yes	8 (8.3%)
History of mono- or dual-NRTI therapy	
No	80 (83.3%)
Yes	16 (16.7%)

	Number (precent)
Birth region	
Netherlands	30 (31.2%)
Central and Eastern Europe	25 (26.0%)
Latin America and Caribbean	17 (17.7%)
Sub-Saharan Africa	17 (17.7%)
N Africa and Middle East	4 (4.2%)
W Europe, N America, Australia	3 (3.1%)
Gender	
Male	65 (67.7%)
Female	31 (32.3%)
Transmission group	
Heterosexual	38 (39.6%)
MSM/W	36 (37.5%)
Unknown	10 (10.4%)
IVDU	5 (5.2%)
Sexual transmission NOS	4 (4.2%)
Other	3 (3.1%)
HIV-1 subtype	
B	44 (45.8%)
A6	24 (25.0%)
02_AG	13 (13.5%)
REC	5 (5.2%)
C	4 (4.2%)
A1	3 (3.1%)
01_AE	2 (2.1%)
06_cpx	1 (1.0%)

Long-acting agents

The long-acting injectable combination CAB/RPV was introduced as a treatment option in the Netherlands in 2021. Nine-hundred and seventy ATHENA participants have received treatment with CAB/RPV. Of these, 17 (1.8%) participants underwent sequencing at least 14 days after starting CAB/RPV and within a year of discontinuing CAB/RPV.

CAB/RPV RAMs were detected in 14 participants treated with long-acting therapy. Pre-treatment reverse transcriptase sequencing was available in 9 and integrase sequencing in 3; 2/9 participants had NNRTI RAMs prior to CAB/RPV treatment and 0/3 had INSTI RAMs detected prior to treatment. The pre-treatment clinical characteristics of participants with CAB/RPV resistance at treatment failure are shown in Table 5.7.

Table 5.7: Select pre-treatment characteristics in participants with CAB/RPV resistance (n=14).

	Number (%)
Prior class resistance	
NNRTI	1 (7.1%)
NNRTI, NRTI	1 (7.1%)
None	12 (85.7%)
RT RAMs	
K103R, M184V, D67N, A98G	1/9 (11.1%)
Y188L	1/9 (11.1%)
None	7/9 (77.8%)
INSTI RAMs	
None	3/3 (100.0%)
History of INSTI treatment	
No	1 (7.1%)
Yes	13 (92.9%)
History of first generation INSTI treatment	
No	7 (50.0%)
Yes	7 (50.0%)
History of NNRTI treatment	
No	7 (50.0%)
Yes	7 (50.0%)
History of first generation NNRTI treatment	
No	8 (57.1%)
Yes	6 (42.9%)

In post-treatment sequencing, all 14 participants had NNRTI RAMs and 10 participants had INSTI RAMs (Table 5.8). One participant with HIV-1 subtype A6 IN L74I polymorphism did not have pretreatment sequencing available; this participant had an acquired IN N155S detected in post-CAB/RPV sequencing.

Table 5.8: Pre- and post-treatment RAMs in participants with acquired resistance to CAB/RPV (n=14).

HIV-1 Subtype	RT RAMS pre	INSTI RAMs pre	RT RAMs post	INSTI RAMs post
A6	Not performed	Not performed	E138K	N155S, L74I
B	None	Not performed	K101EQ, E138K, M230L, K238N	N155H
B	Not performed	Not performed	K101N, E138K, M184IV	None
B	None	Not performed	E138K	None
B	None	Not performed	K101E, K103R, V179D, Y181C	None
B	Not performed	Not performed	K101E, E138K	E138K, Q148R
B	None	Not performed	E138K, V90I	E138D
B	None	None	K101E	None
C	Y188L	None	V179I, Y188L	E138A, G140A, Q148R
C	Not performed	Not performed	K103N, Y181C, T215YSC, H221Y, A98S	E138A, S147G, N155H, R263K, T97A
02_AG	K103R, M184V, D67N, A98G	None	K103R, E138K, A98G	S147G, N155H
02_AG	None	Not performed	V106A, E138A, V179I	E138K, Q148R
02_AG	None	Not performed	K101P, V90I	E138K, Q148R
REC	Not performed	Not performed	Y181C, H221Y	F121C

Conclusions

Over the past decade, the rate of baseline drug resistance has increased from 5% in 2015 to 20% in 2024. This increase was driven largely by the HIV-1 subtype A6 IN L74I polymorphism, impacting cabotegravir susceptibility. Given the increasing prevalence of non-B subtypes in the Netherlands, baseline sequencing is required to identify both transmitted RAMs and subtype-specific polymorphisms that may impact HIV treatment efficacy. To date, baseline drug resistance has had no appreciable impact on treatment response.

Rates of acquired drug resistance have decreased substantially over the past twenty-five years. Improved antiretroviral efficacy and a higher barrier to the emergence of resistance have led to fewer RAMs detected at treatment failure. Nonetheless, resistance to second-generation INSTIs and long-acting CAB/RPV have been observed and require close monitoring. Participants with a history of acquired drug resistance had lower rates of virological suppression, attesting to the ongoing importance of adherence support.

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