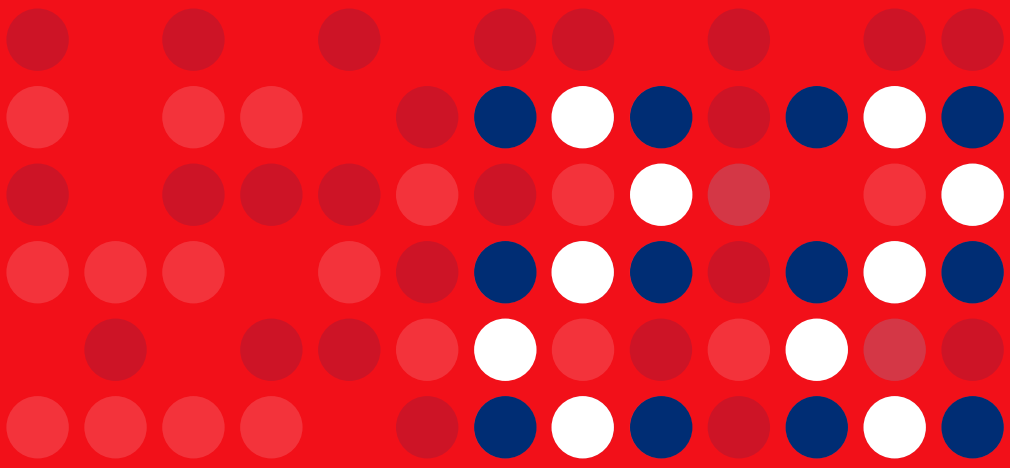
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2022

Chapter 2: Response to combination antiretroviral therapy



2. Response to combination antiretroviral therapy

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Introduction

Since the introduction of combination antiretroviral therapy (ART) in 1996, there have been substantial advances in the use of antiretroviral drugs for the treatment and prevention of HIV infection. The primary goals of ART are to prevent HIV disease progression, improve clinical outcomes, and limit transmission[1,2]. Treatment guidelines across the globe recommend the initiation of ART as soon as possible in all people newly diagnosed with HIV, regardless of CD4 cell count. The decision to initiate ART should always include consideration of a person's comorbid conditions and willingness and readiness to initiate therapy[3-7]. In general, the guidelines of the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) follow the US Department of Health and Human Services guidelines[8].

Besides preventing clinical events, including tuberculosis and AIDS, the immediate start of ART is also more effective at preventing transmission of HIV than deferral of treatment until the CD4 cell count has dropped to a level equal to or below 350 cells/mm^3 [9,10]. People with HIV on ART with an undetectable viral load in their blood have no risk of onward sexual transmission of HIV, (i.e. undetectable equals untransmittable, or U = U[11-16]). Depending on the drugs employed, it may take as long as six months for the viral load to become undetectable. Sustained HIV suppression requires selection of appropriate treatment and adherence to treatment. HIV viral suppression should therefore be monitored and documented to ensure both personal health and public health benefits.

Treatment with ART generally results in sustained suppression of HIV viral load to levels below the reported threshold. Nevertheless, drug resistance mutations may develop if a given drug, even when combined with other drugs, cannot sufficiently prevent the selective pressures driving resistance. Over time, accumulation of mutations in the HIV genome that are associated with drug resistance can prevent sustained viral suppression, thereby increasing the risk of poor clinical outcomes[17-23].

In this chapter, we describe trends over time in the use of ART, and trends in the virological and immunological responses to ART, in adults registered by stichting hiv monitoring (SHM) and enrolled in the ATHENA cohort[24]. We also analyse the presence of transmitted and acquired HIV drug resistance. *Box 2.1* gives an overview of the number of people included in the various analyses described in this chapter.

***Box 2.1:** Outline of the ATHENA cohort in the Netherlands.*

Between 1996 and the end of 2021, a cumulative total of 29,128 individuals (aged 15 years or older at the time of diagnosis) were registered by SHM as with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   27,604 people were known to have initiated ART between January 1996 and December 2021.

2. **In care and on ART in the Netherlands in 2021**
   Of the 27,604 people who initiated ART between January 1996 and December 2021,
   ➔ 20,804 were in care by the end of 2021.

3. **Changes in the use of the initial ART regimen**
   Of the 27,604 people who initiated ART between January 1996 and December 2021,
   ➔ 4,767 initiated ART between January 2016 and December 2021.
   ➔ The most frequently used guideline-recommended initial regimens in 2016-21 were:

   - ABC/3TC/DTG (20.8%)
   - TAF/FTC/BIC (16.7%)
   - TDF/FTC/DTG (14.5%)
   - TAF/FTC/EVG/c (14.2%)
   - TDF/FTC/EFV (3.9%)
   - TDF/FTC/EVG/c (3.6%)
   - TAF/FTC/DRV/c (3.3%)
   - TDF/FTC/DRV/b (3.2%)
   - TAF/FTC/DTG (3.0%)

4. Virological response

Of the 27,604 people who initiated ART between January 1996 and December 2021,

➔ 23,443 people were ART-naïve, not pregnant at ART initiation, and had an HIV viral load result within six months (plus or minus three months) of ART initiation.

5. HIV drug resistance

Transmitted HIV drug resistance

As of December 2021, 8,637 HIV-1 sequences had been obtained from 8,327 ART-naïve people prior to initiation of ART in 2003-21.

➔ 8,627 reverse transcriptase sequences were available from 8,320 individuals.
➔ 8,133 protease sequences were available from 7,835 individuals.
➔ 202 integrase sequences were available from 201 individuals.

Acquired HIV drug resistance

As of December 2021, 4,587 HIV-1 sequences had been obtained from 2,757 people who received ART for at least four months in 2000-21.

➔ 3,225 sequences were from 2,021 people who had been ART-naïve before initiating ART.
➔ 4,511 reverse transcriptase sequences were available from 2,731 individuals.
➔ 4,343 protease sequences were available from 2,616 individuals.
➔ 371 integrase sequences were available from 295 individuals.

6. Immunological response

Of the 27,604 people who initiated ART between January 1996 and December 2021,

➔ 26,561 had CD4 cell count data available after initiating ART.

Legend: *ART = combination antiretroviral therapy (defined as a combination of three antiretroviral drugs from two different antiretroviral drugs classes, or the use of selected combinations of two antiretroviral drugs for which there is sufficient efficacy data to support its use); 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; /b = booster; /c = cobicistat; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

Starting combination antiretroviral therapy

In total, 27,604 individuals ever registered by SHM and monitored in the ATHENA cohort were aged 15 years or above at the time of HIV-1 diagnosis and were known to have initiated ART between January 1996 and December 2021 (*Box 2.1*). In *Table 2.1*, we have grouped people by calendar year of ART initiation: 9,578 started in 1996-2005, 6,084 in 2006-10, 7,175 in 2011-15, and 4,767 in 2016-21.

Of the 27,604 people known to have initiated ART since January 1996, 22,541 (81.7%) were men, of whom 16,760 (74.4%) were men who have sex with men (MSM). Overall, 15,123 (54.8%) originated from the Netherlands. Whereas the proportion of people from the Netherlands was stable over time, the region of origin for non-Dutch people changed. From 1996 onwards, there was a slight but steady increase in people from eastern and central Europe; from 2-3% prior to 2010, to 5.5% in 2011-15, and 10.3 in 2016-21. Simultaneously, the number of people from western Europe/North America/Australia decreased slightly from 10.0% in 1996-2005, to 5.4% in 2016-21. This was also true for sub-Saharan Africa; the number declined from 17.9% in 1996-2005, to 10.0% in 2016-21.

Prompt initiation of ART following the first seropositive HIV test has increased over time, reflecting implementation and uptake of evolving HIV treatment guidelines (*Figure 2.1A*). Among people with an accurate date of HIV diagnosis and who started ART in the Netherlands, the median time between an HIV-positive diagnosis and ART initiation shifted from 142 days (interquartile range [IQR] 33-731) for those who entered care in 2011, to:

- 36 days (IQR 17-83) in 2015;
- 25 days (IQR 11-48) in 2018;
- 23 days (IQR 9-47) in 2019;
- 19 days (IQR 8-42) in 2020; and
- 19 days (IQR 7-38) in 2021.

The time between entering care and starting ART decreased over time (*Figure 2.1B*). The majority of newly diagnosed ART-naïve people entering care in the Netherlands initiated ART within one month. In 2021, 78.1% of this group initiated ART within one month, while the remainder of newly diagnosed, ART-naïve individuals who initiated ART in the Netherlands did so (*Figure 2.1A*):

- between 1 and 5 months after their HIV diagnosis (17.6%);
- between 6 and 12 months after diagnosis (1.7%); and
- more than one year after diagnosis (2.6%).

People originating from sub-Saharan Africa, the Caribbean, and central and eastern Europe were overrepresented among those starting more than six months after HIV diagnosis. The delay between testing HIV-positive and initiating ART was mostly driven by a long period between HIV diagnosis and entering care, as 94.9% of people initiating ART in 2021 did so within one month of entering care (*Figure 2.1B*). All designated HIV treatment centres in the Netherlands have a policy to arrange for the first consultation within a couple of days; usually just a single working day after being contacted by the newly diagnosed person or their referring healthcare provider.

Table 2.1 Characteristics of people starting combination antiretroviral therapy in 1996–2021.

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	1996–2021
Number of individuals		9,578	6,084	7,175	4,767	**27,604**
DEMOGRAPHIC						
Age at ART initiation (years)	Median	37.5	40.14	39.23	37.54	38.47
	Q1	31.76	32.85	30.79	29.15	31.3
	Q3	44.59	47.31	48.18	49.09	46.86
Male sex (at birth)	n	7,357	4,952	6,192	4,040	22,541
	%	76.7	81.4	86.4	85.1	81.6
Transmission risk group						
Missing	n	8	9	13	19	49
	%	0.1	0.1	0.1	0.3	0.1
Men who have sex with men	n	5,029	3,730	4,932	3,069	16,760
	%	52,5	61.3	68.7	64.4	60.7
Heterosexual contact	n	3,302	1,872	1,777	1,229	8,180
	%	34.5	30.8	24.8	25.8	29.6
Injecting drug use	n	539	110	44	35	728
	%	5.6	1.8	0.6	0.7	2.6
Blood or blood products*	n	170	48	61	54	333
	%	1.8	0.8	0.9	1.1	1.2
Vertical transmission	n	2	4	3	6	15
	%	0.02	0.1	0.04	0.1	0.1
Unknown	n	528	311	345	355	1,539
	%	5.5	5.1	4.8	7.5	5.6

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	1996–2021
Region of origin						
Missing	n	45	18	28	56	147
	%	0.5	0.3	0.4	1.2	0.5
The Netherlands	n	5,168	3,408	4,207	2,340	15,123
	%	54.0	56.0	58.6	49.1	54.8
Western Europe/North America/Australia	n	952	504	500	254	2,210
	%	9.9	8.3	7.0	5.3	8.0
Eastern/central Europe	n	179	210	391	483	1,263
	%	1.9	3.5	5.5	10.1	4.6
Latin America and the Caribbean	n	1,035	714	928	769	3,446
	%	10.8	11.7	12.9	16.1	12.5
Sub-Saharan Africa	n	1,705	881	671	469	3,726
	%	17.8	14.5	9.4	9.8	13.5
Other	n	494	349	450	396	1,689
	%	5.2	5.7	6.3	8.3	6.1
CLINICAL						
Recent infection (tested HIV-negative	n	580	939	1,721	1,146	4,386
<12 months before diagnosis)	%	6.1	15.4	24.0	24.0	15.9
Ever having tested HIV-negative	n	1,987	2,471	3,909	2,542	10,909
	%	20.8	40.6	54.5	53.3	39.5
CD4 cell count at start of ART	Median	190	243	353	379	270
	Q1	80	140	220	180	130
	Q3	320	330	500	570	410
HIV RNA (log_{10}) at start of ART	Median	4.9	5.0	4.8	4.8	4.9
	Q1	4.3	4.4	4.3	4.2	4.3
	Q3	5.3	5.4	5.3	5.5	5.4
(Prior) AIDS at start of ART	n	2,965	1,153	933	656	5,707
	%	31.0	19.0	13.0	13.8	20.7
Prior mono- or dual-NRTI treatment	n	2,027	54	26	31	2,138
at start of ART**	%	21.2	0.9	0.4	0.7	7.8
Hepatitis B status at start of ART						
HBV-negative (HBsAg-negative)	n	8,642	5,623	6,715	4,417	25,397
	%	90.2	92.4	93.6	92.7	92.0
HBV-positive (HBsAg-positive)	n	596	323	216	115	1,250
	%	6.2	5.3	3.0	2.4	4.5
Unknown	n	340	138	244	235	957
	%	3.6	2.3	3.4	4.9	3.5

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	1996–2021
Hepatitis C status at start of ART						
HCV-negative	n	8,669	5,773	6,903	4,509	25,854
	%	90.5	94.9	96.2	94.6	93.7
HCV RNA-positive	n	172	135	104	70	481
	%	1.8	2.2	1.5	1.5	1.7
HCV Ab seropositive	n	196	46	44	25	311
	%	2.1	0.8	0.6	0.5	1.1
Unknown	n	541	130	124	163	958
	%	5.7	2.1	1.7	3.4	3.5
ART started during pregnancy	n	403	231	140	85	859
	%	4.2	3.8	2.0	1.8	3.1

Legend: ART = combination antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NRTI = nucleoside analogue reverse transcriptase inhibitor.

* *In recent years, the category 'blood or blood products' mainly contains people who have reported coming into contact with blood from other people (via fights, biting or tattoo shops) as the only possible risk factor for HIV acquisition, although this has rarely been proven by HIV testing of the purported source. Iatrogenic transmission of HIV through contaminated blood or blood products in the Netherlands is extremely rare.*

** *In recent decades, most cases of pre-treatment with mono- or dual-NRTI therapy prior to initiation of ART occurred in people who were diagnosed and started ART abroad before migrating to the Netherlands, and in people who inadvertently used PEP or PrEP while being HIV-positive, or because of medication errors.*

Figure 2.1A: Time between HIV diagnosis and initiation of combination antiretroviral therapy (ART) in people starting ART in 2012–21.

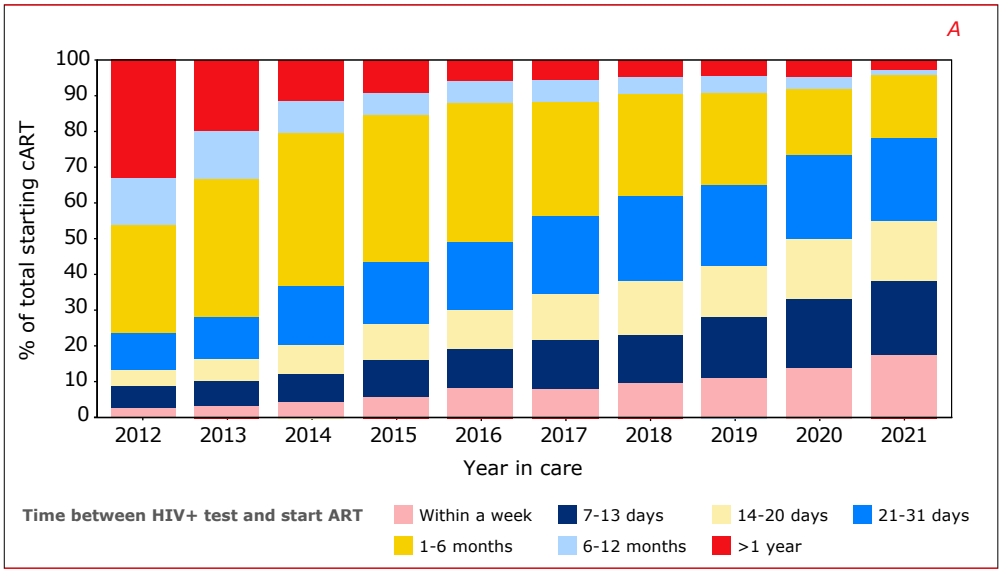
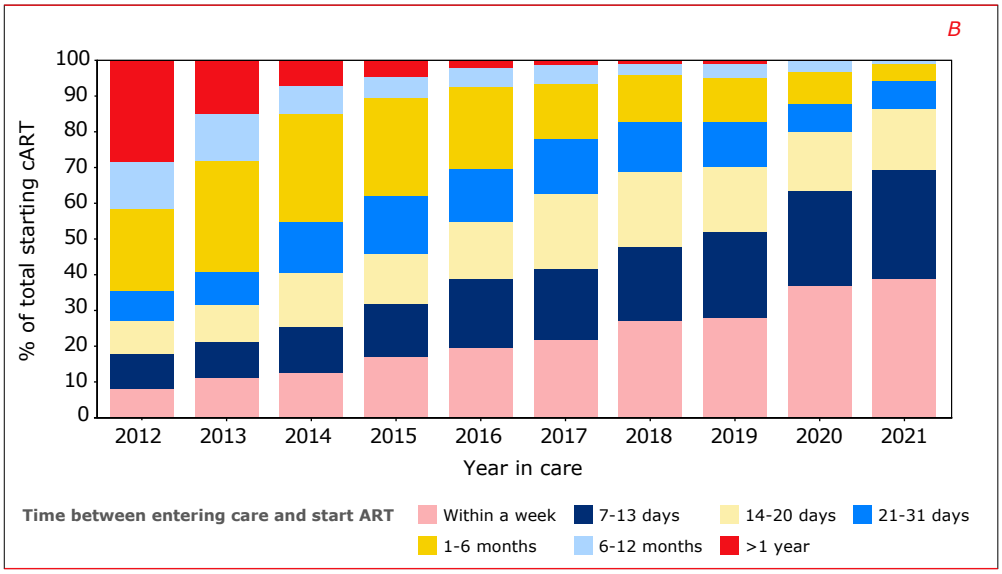


Figure 2.1B: Time between entry into HIV care and initiation of combination antiretroviral therapy (ART) for people starting ART in 2012–21.



Legend: ART = combination antiretroviral therapy.

The proportion of individuals newly diagnosed with HIV who have a known previous negative HIV test, has increased over the years, reaching:

- 20.8% in the period 1996-2005;
- 40.6% in 2006-10;
- 54.5% in 2011-15; and
- 53.3% in 2016-21.

In addition, an increasing proportion of those starting ART showed evidence of recent infection (i.e. within 12 months of a last negative HIV test). The percentage of 6.1% in 1996-2005 rose to 15.4% in 2006-10, 24.0% in 2011-15, and 24.0% in 2016-21.

Over the same time period, there was an increase in the median CD4 cell count at the start of ART:

- 190 cells/mm^3 (IQR 80-320) in 1996-2005;
- 243 cells/mm^3 (IQR 140-330) in 2006-10;
- 353 cells/mm^3 (IQR 220-500) in 2011-15;
- 379 cells/mm^3 (IQR 180-570) in 2016-21

In 2015, the median CD4 cell count at ART initiation peaked at 415 (IQR 220-600) and has since continued to decrease slightly each year to 309 cells/mm^3 (IQR 130-551) in 2021. This trend is likely due to the substantial group already in care but not on ART (because of their high CD4 cells counts), who subsequently initiated ART en masse in 2015 and 2016, when the 2015 guideline change recommended ART for all, irrespective of CD4 count. In the period 2016-2021, at the start of ART, 14.6% of individuals had already been diagnosed with an AIDS-defining condition; 92.2% of those with prior AIDS diagnosis had a CD4 cell count below 350 cells/mm^3, and 84.5% had a CD4 cell count below 200 cells/mm^3.

Chapter 1 provides more detailed information on changing trends in the CD4 cell count at the start of ART, and additional aspects of the continuum of HIV care.

In care and on ART in the Netherlands in 2021

Of the 27,604 people known to have initiated ART between January 1996 and December 2021, 20,804 (75.4%) were alive, still receiving ART, and had a recorded visit for HIV care in the Netherlands in 2021. A total of 238 people were still alive but (temporarily, and for various reasons) no longer on ART, and have therefore been excluded from the analyses in this section. Most of these individuals had medical, psychiatric, and/or psycho-social issues that temporarily prevented them from continuing ART. They are expected to re-start ART once those issues are sufficiently resolved.

Table 2.2 shows the treatment and clinical characteristics of all 20,566 individuals on ART at the last clinic visit in 2021. Overall, 16,916 (82.3%) were men, and 13,236 (64.4%) were MSM. Their median age on 31 December 2021 was 52.2 (IQR 42.4-59.9) years. The majority (58.2%) originated from the Netherlands, followed by Latin America / the Caribbean (12.4%) and sub-Saharan Africa (11.7%).

Table 2.2: Characteristics of people receiving combination antiretroviral therapy and known to be in care in 2021.

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	All
Total	n	5,770	4,593	5,980	4,223	**20,566**
	%	**28.1**	**22.3**	**29.1**	**20.5**	**100**
Male sex	n	4,381	3,761	5,191	3,583	**16,916**
	%					
Age on 31 December 2021	Median	58.3	53.4	48.1	41.3	**52.2**
	Q1	52.4	46.3	39.5	32.8	**42.4**
	Q3	64.5	60.0	56.8	52.5	**59.9**
Transmission risk group						
No data	n	5	5	9	16	**35**
	%	0.1	0.1	0.2	0.4	**0.2**
Men who have sex with men	n	3,260	2,988	4,236	2,752	**13,236**
	%	56.5	65.1	70.8	65.2	**64.4**
Heterosexual contact	n	2,000	1,335	1,433	1,080	**5,848**
	%	34.7	29.1	24.0	25.6	**28.4**
Injecting drug use	n	163	49	17	20	**249**
	%	2.8	1.1	0.3	0.5	**1.2**
Blood or blood products	n	101	33	46	51	**231**
	%	1.8	0.7	0.8	1.2	**1.1**
Vertical transmission	n	1	3	2	5	**11**
	%	0.0	0.1	0.0	0.1	**0.1**
Other/unknown	n	240	180	237	299	**956**
	%	4.2	3.9	4.0	7.1	**4.6**
Region of origin						
No data	n	20	11	25	50	**106**
	%	0.3	0.2	0.4	1.2	**0.5**
The Netherlands	n	3,316	2,785	3,711	2,155	**11,967**
	%	57.5	60.6	62.1	51	**58.2**
Western Europe/North America/Australia	n	445	284	342	**193**	**1,264**
	%	7.7	6.2	5.7	4.6	**6.1**
Eastern/central Europe	n	101	141	291	396	**929**
	%	1.8	3.1	4.9	9.4	**4.5**
Latin America/the Caribbean	n	623	526	729	677	**2,555**
	%	10.8	11.5	12.2	16.0	**12.4**
Sub-Saharan Africa	n	938	568	508	399	**2,413**
	%	16.3	12.4	8.5	9.4	**11.7**
Other	n	327	278	374	353	**1,332**
	%	5.7	6.1	6.3	8.4	**6.5**

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	All
ART regimen						
TDF/FTC/EFV	n	365	484	316	51	**1,216**
	%	6.3	10.5	5.3	1.2	**5.9**
TDF/FTC/NVP	n	461	267	171	9	**908**
	%	8.0	5.8	2.9	0.2	**4.4**
TDF/FTC/RPV	n	114	84	248	27	**473**
	%	2.0	1.8	4.1	0.6	**2.3**
TDF/3TC/DOR	n	245	309	411	328	**1,293**
	%	4.2	6.7	6.9	7.8	**6.3**
TDF/FTC/DRV/b	n	105	108	129	51	**393**
	%	1.8	2.4	2.2	1.2	**1.9**
TDF/FTC/ATV/b	n	49	51	37	10	**147**
	%	0.8	1.1	0.6	0.2	**0.7**
TDF/FTC/LPV/r	n	7	8	1	.	**16**
	%	0.1	0.2	0.0	.	**0.1**
TDF/FTC/EVG/c	n	80	93	276	76	**525**
	%	1.4	2.0	4.6	1.8	**2.6**
TDF/FTC/DTG	n	111	89	181	356	**737**
	%	1.9	1.9	3.0	8.4	**3.6**
TDF/FTC/RAL	n	42	37	46	26	**151**
	%	0.7	0.8	0.8	0.6	**0.7**
ABC/3TC/DTG	n	417	424	721	598	**2,160**
	%	7.2	9.2	12.1	14.2	**10.5**
TAF/FTC/RPV	n	213	210	425	90	**938**
	%	3.7	4.6	7.1	2.1	**4.6**
TAF/FTC/DRV/c	n	342	296	372	226	**1,236**
	%	5.9	6.4	6.2	5.4	**6.0**
TAF/FTC/EVG/c	n	431	477	830	532	**2,270**
	%	7.5	10.4	13.9	12.6	**11.0**
TAF/FTC/DTG	n	110	102	133	154	**499**
	%	1.9	2.2	2.2	3.6	**2.4**
TAF/FTC/BIC	n	630	561	700	1,066	**2,957**
	%	10.9	12.2	11.7	25.2	**14.4**
TAF/FTC/NVP	n	386	219	89	4	**698**
	%	6.7	4.8	1.5	0.1	**3.4**
ABC/3TC/NVP	n	191	61	41	.	**293**
	%	3.3	1.3	0.7	.	**1.4**

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	All
DTG/3TC	n	308	300	520	441	**1,569**
	%	5.3	6.5	8.7	10.4	**7.6**
DTG/RPV	n	65	25	21	8	**119**
	%	1.1	0.5	0.4	0.2	**0.6**
CAB/RPV injectables *	n	16	14	22	28	**80**
	%	0.3	0.3	0.4	0.7	**0.4**
2DR: NNRTI + INST	n	7	.	2	1	**10**
	%	0.1	.	0.0	0.0	**0.0**
2DR: PI + INSTI	n	253	63	50	29	**395**
	%	4.4	1.4	0.8	0.7	**1.9**
2DR: NRTI + INSTI	n	3	1	.	.	**4**
	%	0.1	0.0	.	.	**0.0**
Other: 2NRTI + NNRTI	n	156	85	42	19	**302**
	%	2.7	1.9	0.7	0.4	**1.5**
Other: 2NRTI + PI	n	108	76	56	6	**246**
	%	1.9	1.7	0.9	0.1	**1.2**
Other: 2NRTI + INST	n	83	55	60	25	**223**
	%	1.4	1.2	1.0	0.6	**1.1**
Other: 2DR	n	55	14	12	7	**88**
	%	1.0	0.3	0.2	0.2	**0.4**
Other: NRTI + PI + INSTI (3ARVs)	n	48	2	4	3	**57**
	%	0.8	0.0	0.1	0.1	**0.3**
Other: NRTI + PI + INSTI (4ARVs)	n	129	35	27	32	**223**
	%	2.2	0.8	0.5	0.8	**1.1**
Other	n	240	43	37	20	**340**
	%	4.2	0.9	0.6	0.5	**1.7**
CD4: CD8 ratio						
No data	n	730	585	824	645	**2,784**
	%	12.7	12.7	13.8	15.3	**13.5**
<0.50	n	874	554	624	915	**2,967**
	%	15.1	12.1	10.4	21.7	**14.4**
≥0.50 to <1.00	n	2,458	2,078	2,635	1,586	**8,757**
	%	42.6	45.2	44.1	37.6	**42.6**
≥1.00	n	1,708	1,376	1,897	1,077	**6,058**
	%	29.6	30.0	31.7	25.5	**29.5**

Year of ART initiation		1996–2005	2006–2010	2011–2015	2016–2021	All
CD4 count (cells/mm³)						
No data	n	22	17	21	37	**97**
	%	0.4	0.4	0.4	0.9	**0.5**
<50	n	6	8	7	22	**43**
	%	0.1	0.2	0.1	0.5	**0.2**
50–199	n	92	51	46	172	**361**
	%	1.6	1.1	0.8	4.1	**1.8**
200–349	n	362	235	257	428	**1,282**
	%	6.3	5.1	4.3	10.1	**6.2**
350–499	n	899	671	697	628	**2,895**
	%	15.6	14.6	11.7	14.9	**14.1**
500–749	n	2,020	1,666	1,991	1,287	**6,964**
	%	35.0	36.3	33.3	30.5	**33.9**
≥750	n	2,369	1,945	2,961	1,649	**8,924**
	%	41.1	42.3	49.5	39	**43.4**
Viral load <50 copies/ml						
No data	n	1	4	3	11	**19**
	%	0.0	0.1	0.1	0.3	**0.1**
Yes	n	5,596	4,425	5,796	3,900	**19,717**
	%	97.0	96.3	96.9	92.4	**95.9**
No	n	173	164	181	312	**830**
	%	3.0	3.6	3.0	7.4	**4.0**
Viral load <200 copies/ml						
No data	n	1	4	3	11	**19**
	%	0.0	.0.1	0.1	0.3	**0.1**
Yes	n	5,695	4,527	5,902	4,059	**20,183**
	%	98.7	98.6	98.7	96.1	**98.1**
No	n	74	62	75	153	**364**
	%	1.3	1.3	1.3	3.6	**1.8**

Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ATV = atazanavir; ARVs = antiretroviral drugs; BIC = bictegravir; ART = combination antiretroviral therapy; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LPV = lopinavir; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; INSTI = integrase inhibitor.*

** Some patients using this combination were participating in a clinical trial.*

Among the 20,566 people in HIV care and on ART in 2021, the vast majority (85.9%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either:

- an integrase inhibitor (INSTI) (46.3%);
- a non-nucleoside reverse transcriptase inhibitor (NNRTI) (29.7%); or
- a protease inhibitor (PI) (9.9%).

The distribution of ART use among the population in care in 2021 is presented in *Figure 2.2*. The most frequently used regimens (used by at least 5% of the population) were:

- tenofovir alafenamide (TAF)/emtricitabine (FTC)/bictegravir (BIC) (14.4%);
- tenofovir alafenamide (TAF)/ emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (11.0%);
- abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (10.5%);
- dolutegravir (DTG)/lamivudine (3TC) (7.6%);
- tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/doravirine (DOR) (6.3%);
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (6.0%); and
- tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz (EFV) (5.9%).

The proportion of the population in care using TDF has slowly decreased in the last couple of years, with a percentage of:

- 46.4% in 2017;
- 35.3% in 2018;
- 31.9% in 2019;
- 30.8% in 2020;
- 29.7% in 2021.

The proportion of the population in care using TAF meanwhile, continued to slowly increase, with:

- 24.4% in 2017;
- 33.2% in 2018;
- 42.1% in 2019;
- 43.7% in 2020;
- 44.5% in 2021.

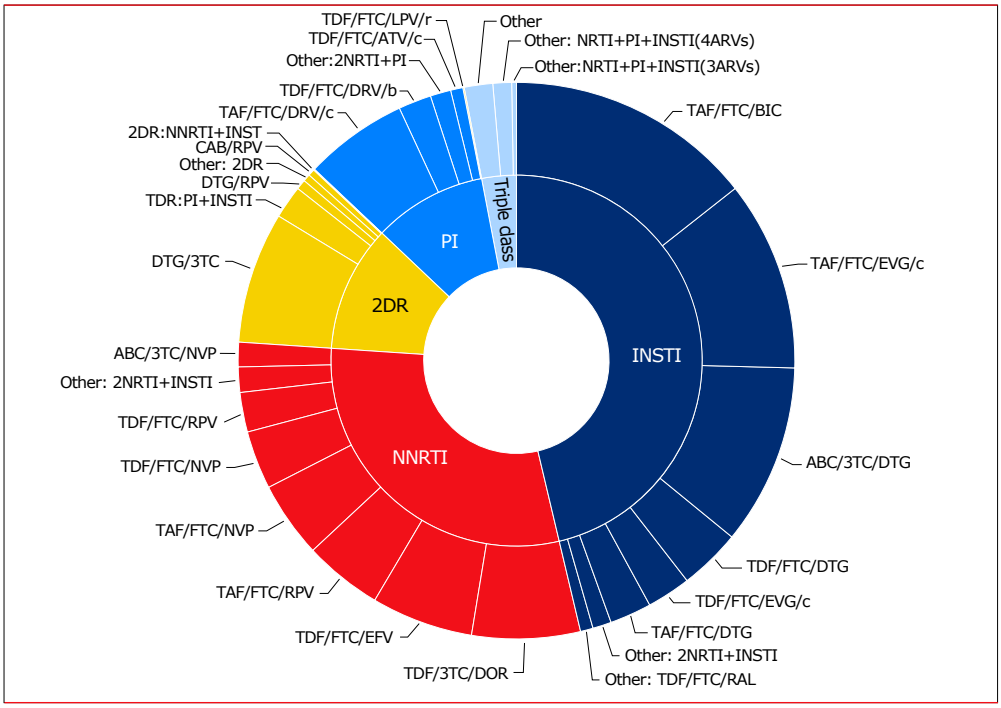
Zidovudine was still used by 97 individuals (0.5%, mostly in combination with lamivudine).

In 2021 the use of regimens not consisting of two NRTIs plus a third 'anchor drug' (an NNRTI, PI, or INSTI), continued to increase. In total, 745 (3.6%) individuals used an ART regimen without any NRTI and 1,748 (8.5%) individuals used one with just a single NRTI. There were 2,265 (11.0%) individuals who used a two-drug regimen (excluding pharmacological boosters). The most common of these regimens were a combination of:

- NRTI + INSTI (n=1,573 people or 69.5%) of which
  - 99.8% used lamivudine
  - 0.2% used TDF
  - 100% used dolutegravir;
- PI + INSTI (n=395 people, or 17.4%) of which
  - 98.2% used darunavir plus either dolutegravir (89.4%) or raltegravir (10.6%);
- NNRTI + INSTI (n=209 people, or 9.2%) of which
  - 95.2% used rilpivirine
  - 61.2% used dolutegravir
  - 38.3% used cabotegravir (intramuscularly);
- NNRTI + PI (n=22 people, or 1.0%).

Of those with a plasma HIV RNA measurement in 2021, 89.0% had a viral load below 50 copies/ml, and 98.1% had a viral load below 200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-21, 77.3% had a CD4 cell count of 500 cells/mm^3 or higher, and 29.5% had a CD4: CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (ART) use in 2021.



Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ATV = atazanavir; ARVs = antiretroviral drugs; BIC = bictegravir; ART = combination antiretroviral therapy; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LPV = lopinavir; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; INSTI = integrase inhibitor.*

Changes in the use of initial ART regimen

Data from recent clinical trials on new antiretroviral drugs have shown good outcomes in terms of viral suppression, convenience, tolerability, and toxicity. Over the past years, these new antiretroviral drugs and new, once-daily, fixed-dose combination regimens have been approved in the Netherlands (*Box 2.2*). In this section, we evaluate the post-approval implementation of these new drugs/regimens in HIV treatment.

***Box 2.2:** Approval dates of new antiretroviral drugs/regimens for HIV treatment in the Netherlands in 2013–21.*

Medicine	Authorisation date
TDF/FTC/EVG/cobicistat (Stribild®)	24 May 2013
DTG (Tivicay®)	16 January 2014
ABC/3TC/DTG (Triumeq®)	01 September 2014
DRV/cobicistat (Rezolsta®)	19 November 2014
TAF/FTC/EVG/cobicistat (Genvoya®)	19 November 2015
TAF/FTC (Descovy®)	21 April 2016
TAF/FTC/RPV (Odefsey®)	21 June 2016
TAF (Vemlidy®)	09 January 2017
TAF/FTC/DRV/cobicistat (Symtuza®)	21 September 2017
DTG/RPV (Juluca®)	21 May 2018
TAF/FTC/BIC (Biktarvy®)	25 June 2018
Doravirine (Pifeltro®)	22 November 2018
TDF/3TC/Doravirine (Delstrigo®)	22 November 2018
3TC/DTG (Dovato®)	03 July 2019
Cabotegravir (Vocabria®)	17 December 2020
Rilpivirine (Rekambys®)	17 December 2020
Fostemsavir (Rukobia®)	04 February 2021
Lenacapavir (Sunlenca®)	17 August 2022

***Legend:** 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; DTG = dolutegravir; DRV = darunavir; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; RPV = rilpivirine.*
***Source:** Medicines Evaluation Board http://english.cbg-meb.nl/ and European Medicines Agency http://www.ema.europa.eu/*

Initial ART regimen

Of the 27,604 people known to have initiated ART between 1996 and 2021, 4,767 (17.3%) started ART between January 2016 and December 2021. *Figures 2.3* and *2.4* show the trends over time in third-drug additions to the NRTI backbone used as part of the initial ART regimen. The use of integrase inhibitors in combination with a dual-NRTI backbone as initial therapy, increased, with percentages reaching:

- 70.5% in 2016;
- 77.2% in 2017;
- 71.2% in 2018;
- 78.5% in 2019;
- 82.5% in 2020; and
- 80.8% in 2021 (90.9% including other INSTI-containing regimens).

Cobicistat-boosted elvitegravir was used in 25.2%, 30.7% and 23.8% of the initial regimens in 2016, 2017, and 2018, respectively, before its use dropped sharply to 3.2% in 2019, 1.3% in 2020, and 1.2% in 2021. Dolutegravir was used in:

- 50.7% of initial regimens in 2016;
- 50.7% of initial regimens in 2017;
- 43.8% of initial regimens in 2018;
- 35.1% of initial regimens in 2019;
- 43.5 of initial regimens in 2020; and
- 47.5% of initial regimens in 2021.

Bictegravir was introduced in the Netherlands in 2018 and was used in 7.0%, 44.3%, 44.5, and 41.1% of the initial regimens in 2018, 2019, 2020, and 2021, respectively. The use of NNRTIs in the initial regimen decreased from 13.6% in 2016 to:

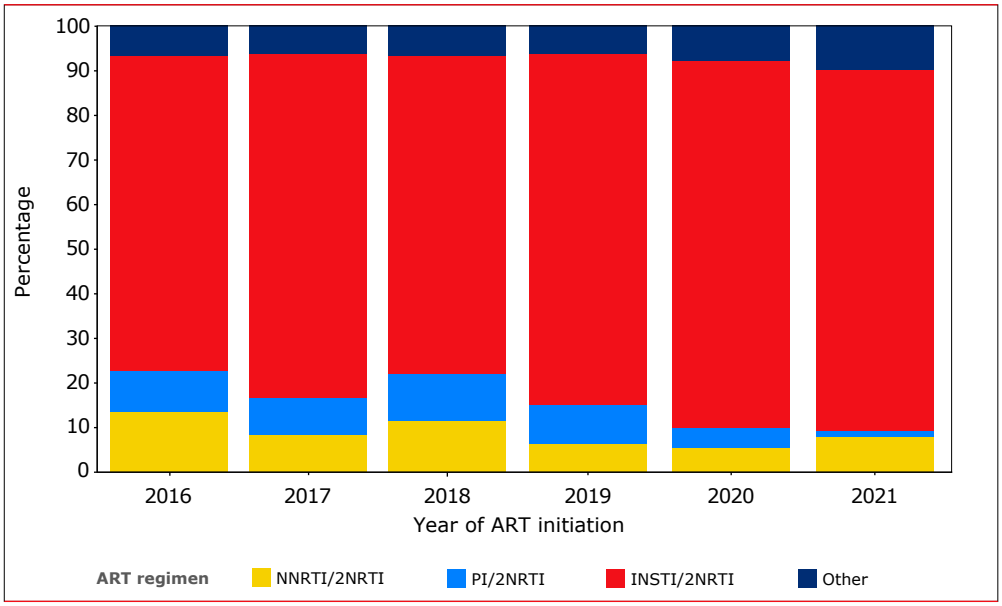
- 8.4% in 2017;
- 11.4% in 2018;
- 5.7% in 2019;
- 5.1% in 2020; and
- 7.6% in 2021.

The use of PIs in the initial regimen also decreased from 9.2% in 2016 to:

- 8.3% in 2017;
- 10.7% in 2018;
- 9.5% in 2019;
- 4.8% in 2020; and
- 1.5% in 2021.

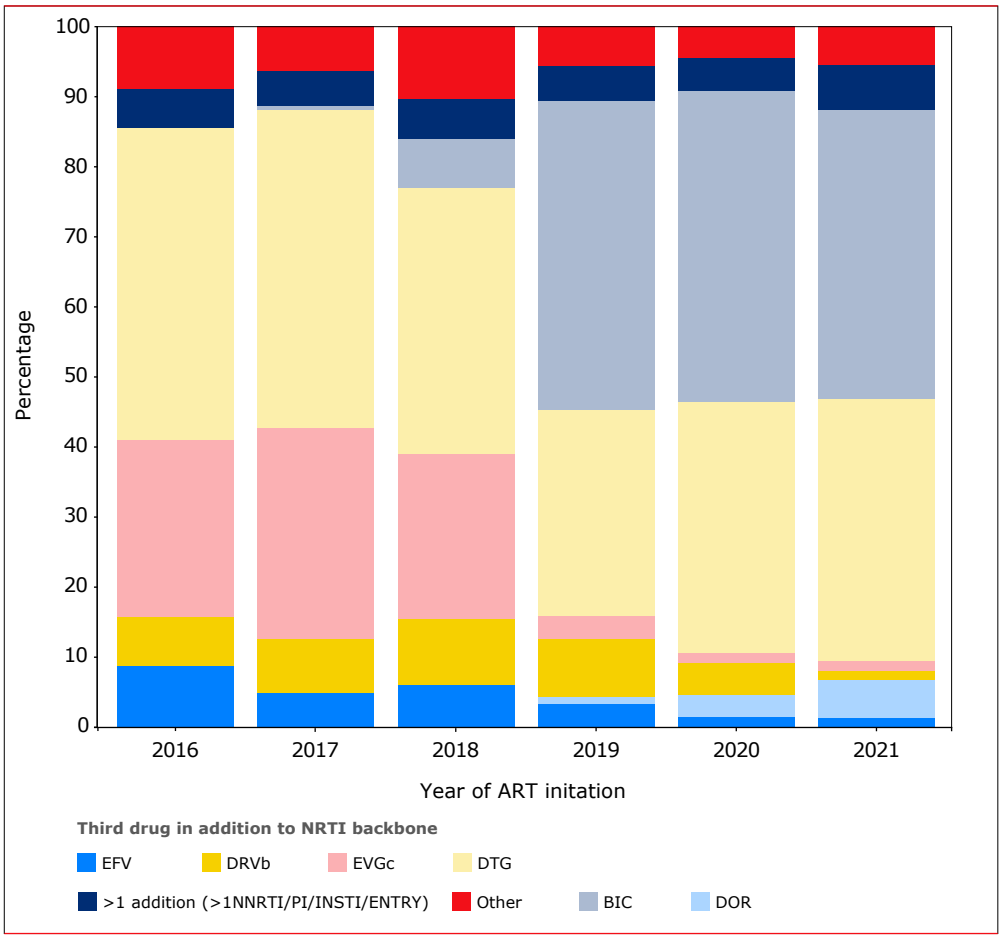
In the period 2016-21, 5.3% of individuals received more than one third-drug addition to the NRTI backbone in their initial ART regimen. The majority of these were people initiating ART during an acute HIV infection, with the regimen consisting of a PI (mainly boosted darunavir) plus an INSTI (mainly dolutegravir), plus two NRTIs. *Figure 2.4* shows all third-drug additions to the nucleoside reverse transcriptase backbone that were used in at least 5% of individuals for one or more years as part of the initial regimen during the period 2016-21. The use of nevirapine, rilpivirine, atazanavir, lopinavir, and raltegravir as third-drug additions to initial regimens did not exceed 5% in any year in the period 2016-21. As a result, those regimens have been included in the category 'other' in *Figure 2.4*.

Figure 2.3: *Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2016-21.*



Legend: *ART = combination antiretroviral therapy; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.*

Figure 2.4: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2016–21.



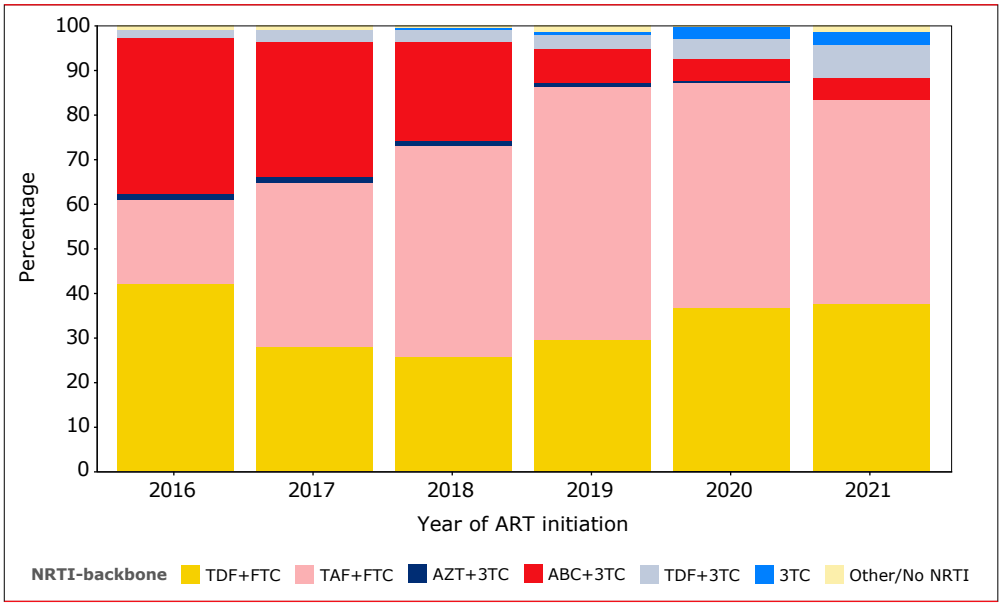
Legend: ART = combination antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; ENTRY = entry inhibitor; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Figure 2.5 provides an overview of the NRTI backbone components of the initial ART regimens used in 2016-21. The combination of tenofovir (TDF or TAF) and emtricitabine was the predominant backbone prescribed. Following its introduction at the end of 2015, TAF was prescribed in:

- 18.9% of the initial regimens in 2016;
- 37.2% of the initial regimens in 2017;
- 47.3% of the initial regimens in 2018;
- 57.1% of the initial regimens in 2019;
- 50.7% of the initial regimens in 2020; and
- 46.1% of the initial regimens in 2021.

At the same time, TDF use decreased from 43.6% in 2016 to 28.4% in 2018, before increasing to 33.1% in 2019, 41.4% in 2020, and 45.3% in 2021. The use of abacavir (in combination with lamivudine) decreased from 35.4% of all initial regimens in 2016 to 30.9% in 2017, and 22.3% in 2018, after which there was a sharp decrease to 8.1% in 2019, 4.8% in 2020, and 5.2% in 2021. The combination of zidovudine and lamivudine, which is still sometimes used by migrants who initiated ART before arriving in the Netherlands, has further decreased to less than 1% since 2017 (n=0 in 2021).

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2016-21.*



Legend: *ART = combination antiretroviral therapy; 3TC = lamivudine; ABC = abacavir; AZT = zidovudine; FTC = emtricitabine; NRTI = nucleoside analogue reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

The ART regimens initiated in 2016-21 are presented in *Figure 2.6* and *Table 2.3*. In 2021, the most frequently used initial regimen was TAF/FTC/bictegravir (41.1%). Dolutegravir-containing initial regimens were used in 38.4% of cases. Additionally, 5.4% initiated a doravirine-containing once-daily, fixed-dose combination with lamivudine and tenofovir (TDF). Elvitegravir/c, darunavir/b, or raltegravir use in an initial regimen was 1.2%, 1.5%, and 0.7%, respectively, in 2021. *Table 2.3* provides more detail on the 'other' initial regimens that are not further specified in *Figures 2.4-2.6*.

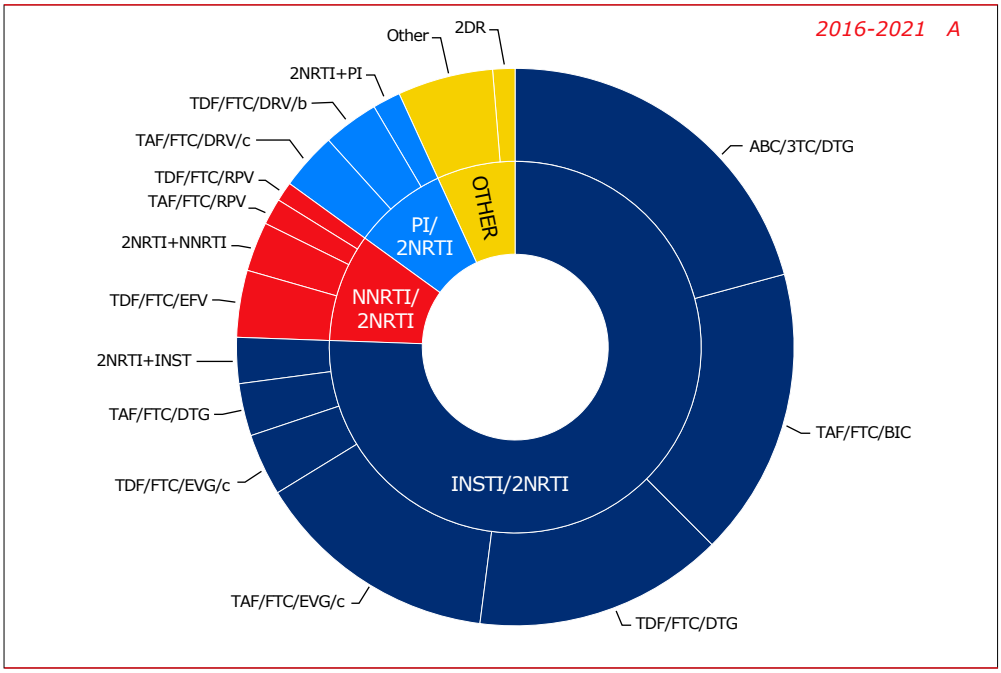
***Table 2.3:** Initial regimens in 2016–21.*

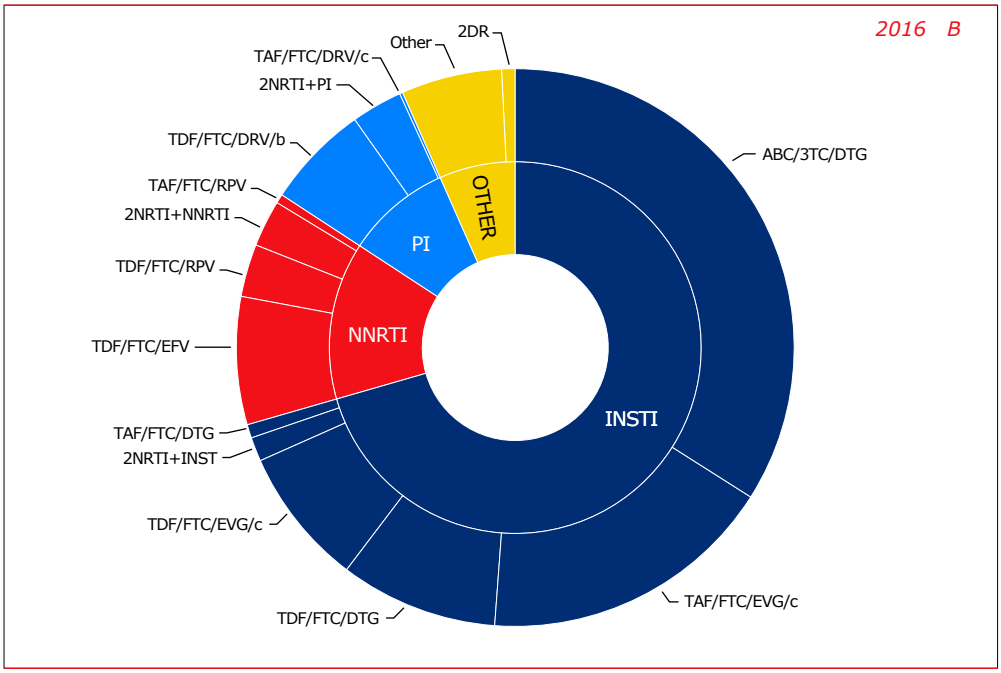
		2016	2017	2018	2019	2020	2021	2016–21
N		1,147	1038	900	750	526	406	4,767
Regimen								
TDF/FTC/EFV	n	85	33	39	19	6	3	185
	%	7.41	3.18	4.33	2.53	1.14	0.74	3.88
TDF/FTC/NVP	n	9	2	2	1	.	1	15
	%	0.78	0.19	0.22	0.13	.	0.25	0.31
TDF/FTC/RPV	n	35	10	4	3	.	2	54
	%	3.05	0.96	0.44	0.4	.	0.49	1.13
TDF/3TC/DOR	n	.	.	.	5	16	22	43
	%	.	.	.	0.67	3.04	5.42	0.9
TDF/FTC/DRV/b	n	69	42	15	16	9	3	154
	%	6.02	4.05	1.67	2.13	1.71	0.74	3.23
TDF/FTC/ATV/b	n	17	5	6	6	1	.	35
	%	1.48	0.48	0.67	0.8	0.19	.	0.73
TDF/FTC/LPV/r	n	2	1	.	.	.	.	3
	%	0.17	0.1	.	.	.	.	0.06
TDF/FTC/EVG/c	n	92	56	16	6	.	2	172
	%	8.02	5.39	1.78	0.8	.	0.49	3.61
TDF/FTC/DTG	n	105	92	92	132	152	118	691
	%	9.15	8.86	10.22	17.6	28.9	29.06	14.5
TDF/FTC/RAL	n	9	7	14	11	3	3	47
	%	0.78	0.67	1.56	1.47	0.57	0.74	0.99
ABC/3TC/DTG	n	390	311	190	56	25	19	991
	%	34	29.96	21.11	7.47	4.75	4.68	20.79
ABC/3TC/NVP	n	1	1	1	.	.	.	3
	%	0.09	0.1	0.11	.	.	.	0.06
TAF/FTC/RPV	n	6	20	37	6	3	1	73
	%	0.52	1.93	4.11	0.8	0.57	0.25	1.53

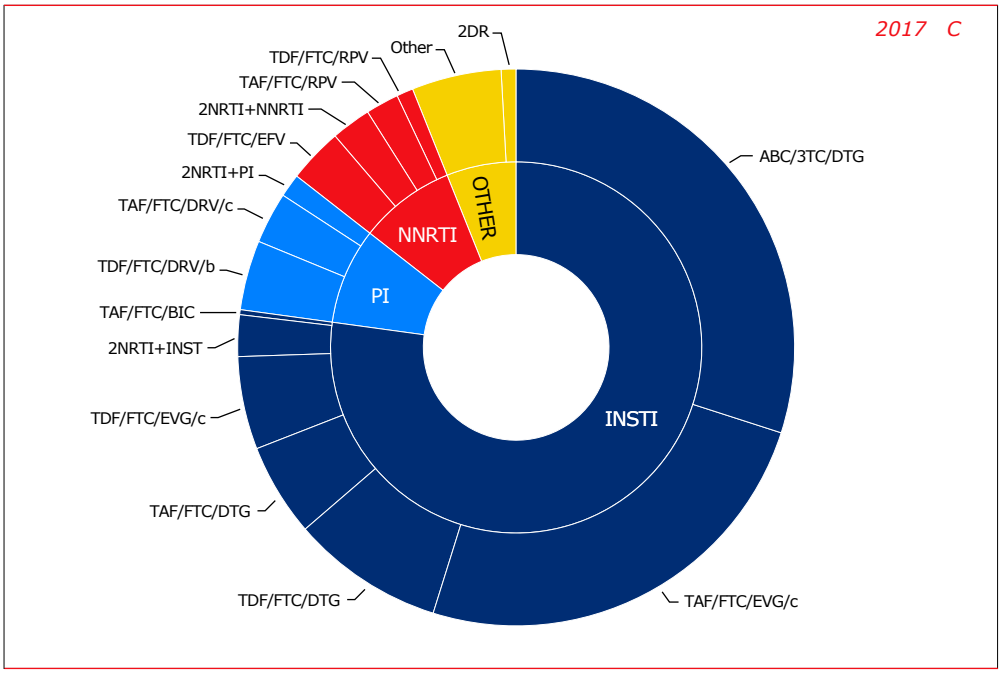
		2016	2017	2018	2019	2020	2021	2016–21
N		1,147	1038	900	750	526	406	4,767
Regimen								
TAF/FTC/DRV/c	n	2	31	65	46	12	3	159
	%	0.17	2.99	7.22	6.13	2.28	0.74	3.34
TAF/FTC/EVG/c	n	197	258	195	18	7	3	678
	%	17.18	24.86	21.67	2.4	1.33	0.74	14.22
TAF/FTC/DTG	n	9	56	48	18	6	8	145
	%	0.78	5.39	5.33	2.4	1.14	1.97	3.04
TAF/FTC/BIC	n	.	3	63	331	234	167	798
	%	.	0.29	7	44.13	44.49	41.13	16.74
DTG/3TC	n	1	1	3	4	13	11	33
	%	0.09	0.1	0.33	0.53	2.47	2.71	0.69
DTG/RPV	n	.	.	1	1	.	.	2
	%	.	.	0.11	0.13	.	.	0.04
2DR: PI + INSTI	n	8	8	3	3	1	3	26
	%	0.7	0.77	0.33	0.4	0.19	0.74	0.55
Other: 2NRTI + NNRTI	n	21	21	20	10	2	2	76
	%	1.83	2.02	2.22	1.33	0.38	0.49	1.59
Other: 2NRTI + PI	n	15	8	10	3	3	.	39
	%	1.31	0.77	1.11	0.4	0.57	.	0.82
Other: 2NRTI + INST	n	7	18	23	17	7	8	80
	%	0.61	1.73	2.56	2.27	1.33	1.97	1.68
Other: 2DR	n	.	.	1	.	.	.	1
	%	.	.	0.11	.	.	.	0.02
Other: NRTI + PI + INSTI (3ARVs)	n	1	1	1	1	.	1	5
	%	0.09	0.1	0.11	0.13	.	0.25	0.1
Other: NRTI + PI + INSTI (4ARVs)	n	57	52	50	33	24	23	239
	%	4.97	5.01	5.56	4.4	4.56	5.67	5.01
Other	n	9	1	1	4	2	3	20
	%	0.78	0.1	0.11	0.53	0.38	0.74	0.42

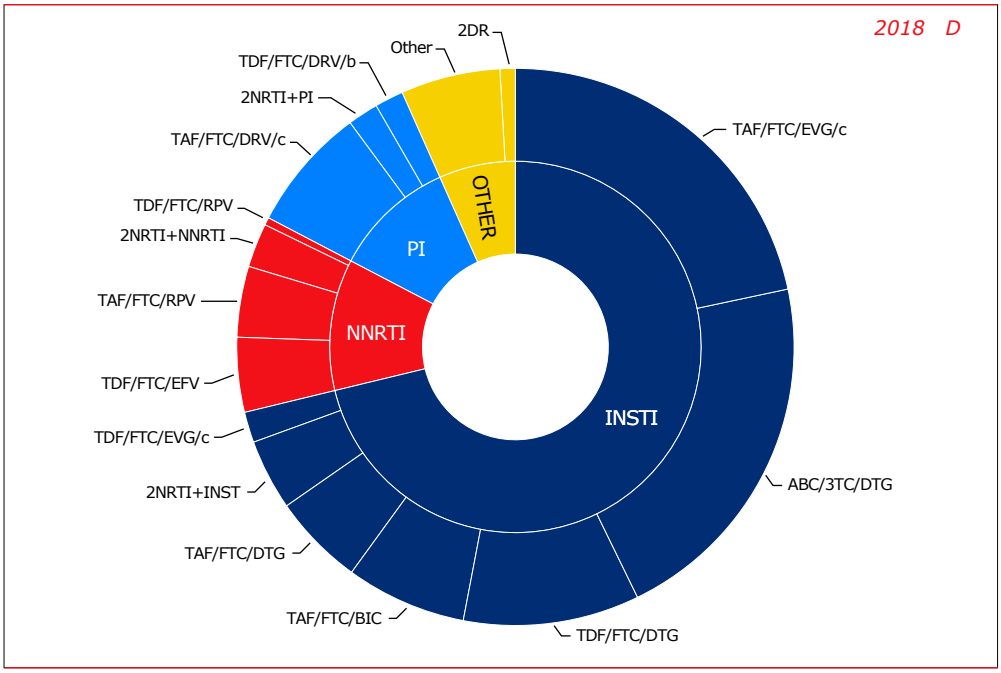
Legend: *ARVs = antiretroviral drugs; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CI = confidence interval; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LPV = lopinavir; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RPV = rilpivirine; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

Figure 2.6: The initial combination antiretroviral therapy regimens given in 2016–21 A) in total and B) by year.






2017 C
2DR
Other
TDF/FTC/RPV
TAF/FTC/RPV
2NRTI+NNRTI
TDF/FTC/EFV
2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TAF/FTC/BIC
2NRTI+INST
TDF/FTC/EVG/c
TAF/FTC/DTG
TDF/FTC/DTG
ABC/3TC/DTG
TAF/FTC/EVG/c
OTHER
NNRTI
PI
INSTI


2018 D
2DR
Other
TDF/FTC/DRV/b
2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/RPV
2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/EVG/c
2NRTI+INST
TAF/FTC/DTG
TAF/FTC/BIC
TDF/FTC/DTG
TAF/FTC/EVG/c
ABC/3TC/DTG
OTHER
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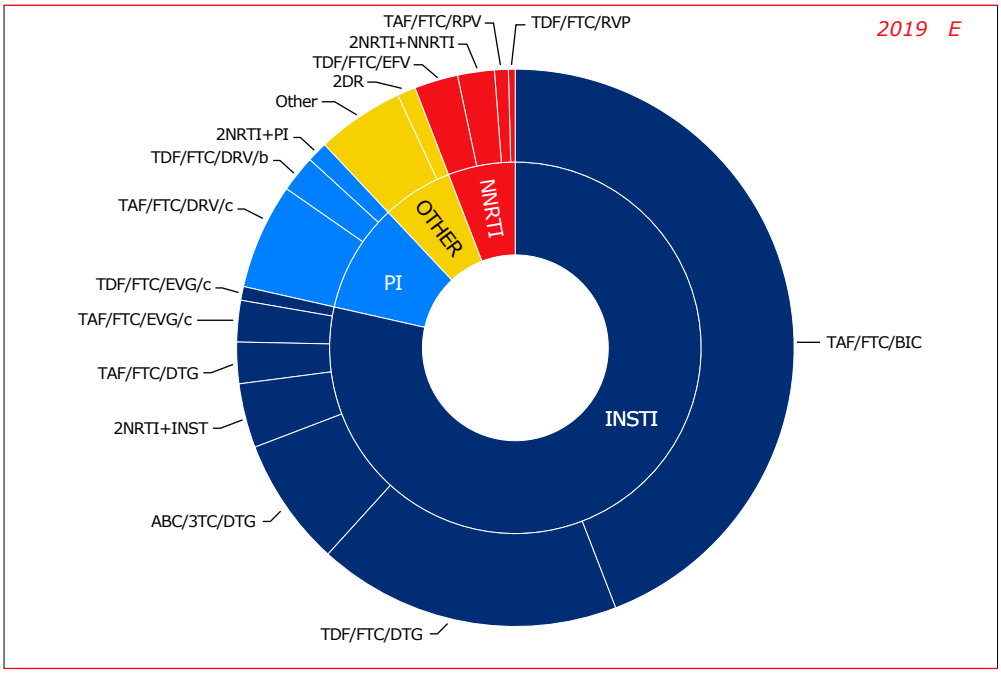
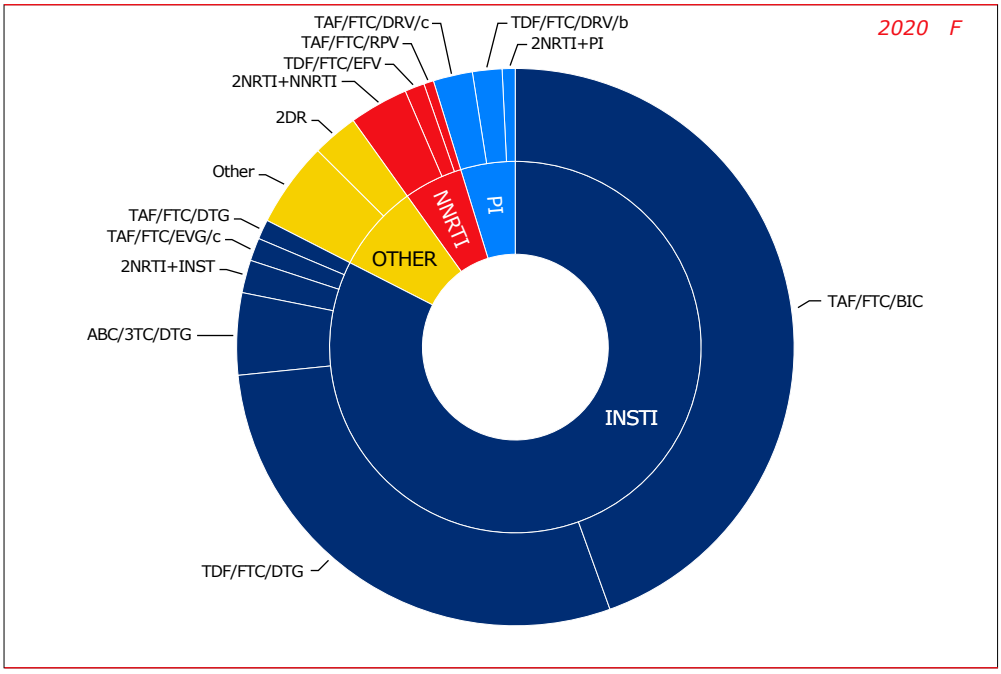
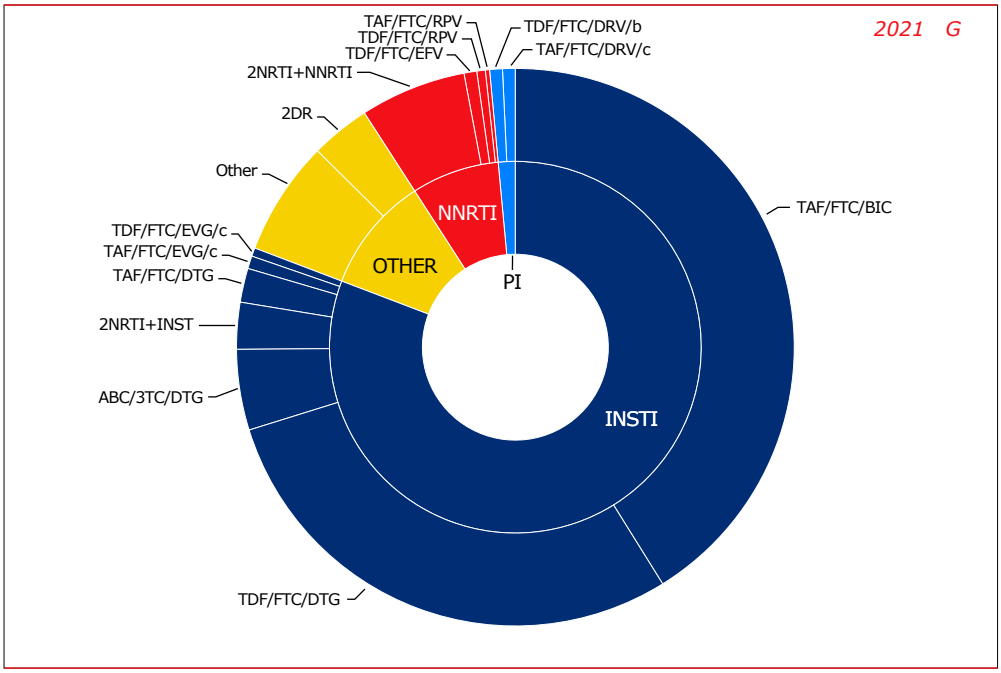

2019 E
TAF/FTC/RPV
TDF/FTC/RVP
2NRTI+NNRTI
TDF/FTC/EFV
2DR
Other
2NRTI+PI
TDF/FTC/DRV/b
TAF/FTC/DRV/c
TDF/FTC/EVG/c
TAF/FTC/EVG/c
TAF/FTC/DTG
2NRTI+INST
ABC/3TC/DTG
TDF/FTC/DTG
TAF/FTC/BIC
NNRTI
OTHER
PI
INSTI


2020 F
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TAF/FTC/RPV
2NRTI+PI
TDF/FTC/EFV
2NRTI+NNRTI
2DR
Other
TAF/FTC/DTG
TAF/FTC/EVG/c
2NRTI+INST
ABC/3TC/DTG
TDF/FTC/DTG
TAF/FTC/BIC
NNRTI
PI
OTHER
INSTI



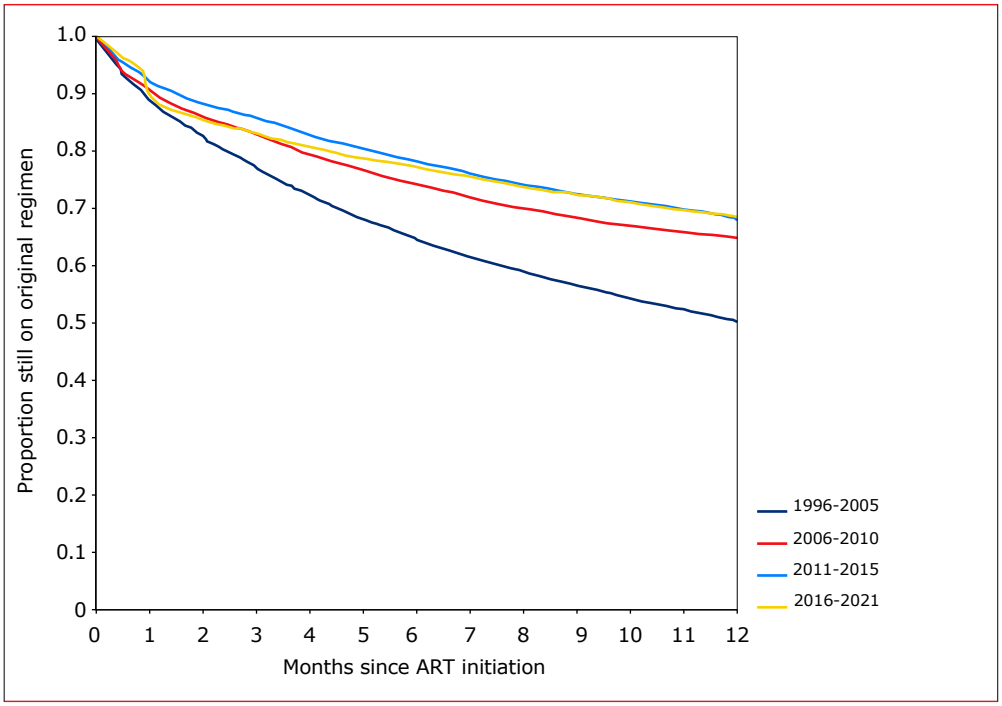
Legend: *3TC = lamivudine; ABC = abacavir; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

Discontinuation of the initial ART regimen

For the 27,604 people who started ART between 1996 and 2021, we assessed the time spent on that initial ART regimen. Discontinuation was defined as a change in, or discontinuation of, one or more of the drugs included in the regimen. Simplification to a fixed-drug combination formulation containing the same drugs was not considered a discontinuation. Likewise, the breakup of a (more expensive) single tablet regimen (STR) into (cheaper) generic components of the original STR, was also not considered a switch. A switch from one booster to another was also ignored; for example, a switch from efavirenz (EFV) with fixed-dose TDF/FTC to the fixed drug combination EFV/TDF/FTC was not considered discontinuation of the initial regimen, however, a change from EFV/TDF/FTC to EVG/c/TDF/FTC was. One-year discontinuation rates are based on the Kaplan-Meier estimates.

In the period 1996-2021, 38.7% of individuals discontinued their initial regimen within one year; the length of time they remain on it has improved over the years: in 1996-2005, 49.9% discontinued it within a year, compared to 35.0% in 2006-10, 31.9% in 2011-15, and 31.0% in 2016-21. *Figure 2.7* shows the time to the first modification of the initial regimen during the first year of ART, stratified by five-year calendar periods.

Figure 2.7: *Kaplan–Meier estimate of the time on initial regimen, by calendar year period of initiation (log-rank test p<0.001).*



Legend: *ART = combination antiretroviral therapy.*

Discontinuation of the initial ART regimen: 2016–21

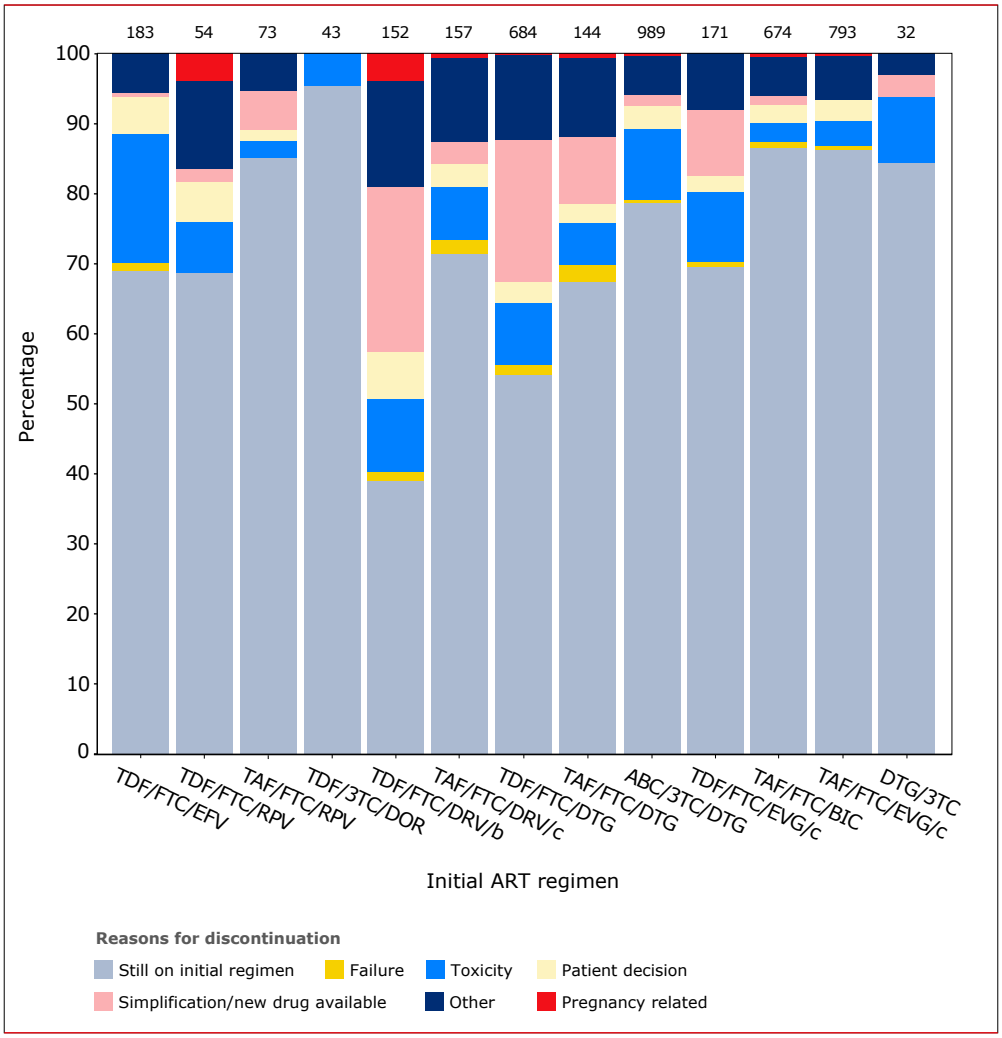
We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 4,149 people who started 'common' and guideline-recommended initial regimens in 2016-21. The regimens considered in this analysis were:

- tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV, 4.1%);
- tenofovir disoproxil fumarate/emtricitabine/rilpivirine (TDF/FTC/RPV, 1.3%);
- tenofovir disoproxil fumarate/emtricitabine/ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b, 3.7%);
- tenofovir disoproxil fumarate/emtricitabine/cobicistat-boosted elvitegravir (TDF/FTC/EVG/c, 4.1%);
- tenofovir disoproxil fumarate/emtricitabine/dolutegravir (TDF/FTC/DTG, 16.5%);
- tenofovir disoproxil fumarate/lamivudine/doravirine (TDF/3TC/DOR, 1.0%);
- abacavir-lamivudine/dolutegravir (ABC/3TC/DTG, 23.8%);
- tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir (TAF/FTC/EVG/c, 16.2%);
- tenofovir alafenamide/emtricitabine/rilpivirine (TAF/FTC/RPV, 1.8%);
- tenofovir alafenamide/emtricitabine/dolutegravir (TAF/FTC/DTG, 3.5%);
- tenofovir alafenamide/emtricitabine/cobicistat-boosted darunavir (TAF/FTC/DRV/c, 3.8%);
- tenofovir alafenamide/emtricitabine/bictegravir (TAF/FTC/BIC, 19.1%); and
- dolutegravir/lamivudine (DTG/3TC, 0.8%).

One year after ART initiation, 1,052 (25.4%) of the 4,149 individuals using one of these initial regimens had discontinued it. The main reason for this discontinuation was toxicity (306, 29.1%), followed by simplification and/or availability of new drugs (243, 23.1%). The availability of new, once-daily, fixed-dose combinations contributed to an increase in initial regimen discontinuation due to simplification and/or availability of new drugs, especially for those receiving TDF/FTC/DTG, and TDF/FTC/DRV/b (*Figure 2.8*).

The nature and severity of toxicities leading to discontinuation have changed considerably over time. Because of the availability of a large number of potent and well-tolerated recommended and alternative regimens, as well as the very low risk of viral breakthrough following a switch, the threshold for modifying the initial (or any) regimen has become much lower over the years. Furthermore, in recent years, the regimens TDF/FTC/DTG and TDF/FTC/DRV/b have frequently been used as an initial 'induction' regimen in treatment-naïve patients because of their potent antiretroviral activity and high genetic barrier to resistance, with the explicit intention to quickly switch to a single tablet 'maintenance' regimen after the plasma HIV-1 viral load has become undetectable.

Figure 2.8: *Reasons for discontinuation of the initial regimen during the first year of treatment in 2016–21, by regimen. Numbers above the bars represent the total number of individuals using that particular regimen.*

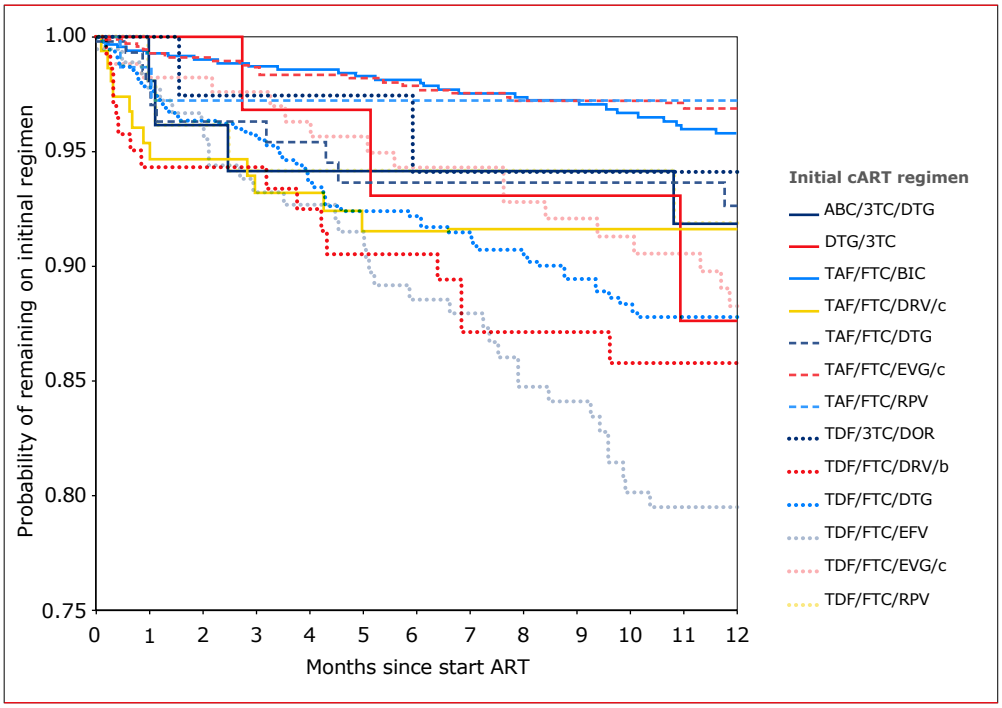


Legend: *ART = combination antiretroviral therapy; /b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

Discontinuation of the initial ART regimen due to toxicity

The time until discontinuation of the initial regimen due to toxicity during the first year of treatment, by regimen, is presented in *Figure 2.9*.

Figure 2.9: *Kaplan-Meier estimate of the time on initial regimen until modification due to toxicity in 2016-21, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).*



Legend: *ART = combination antiretroviral therapy; /b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

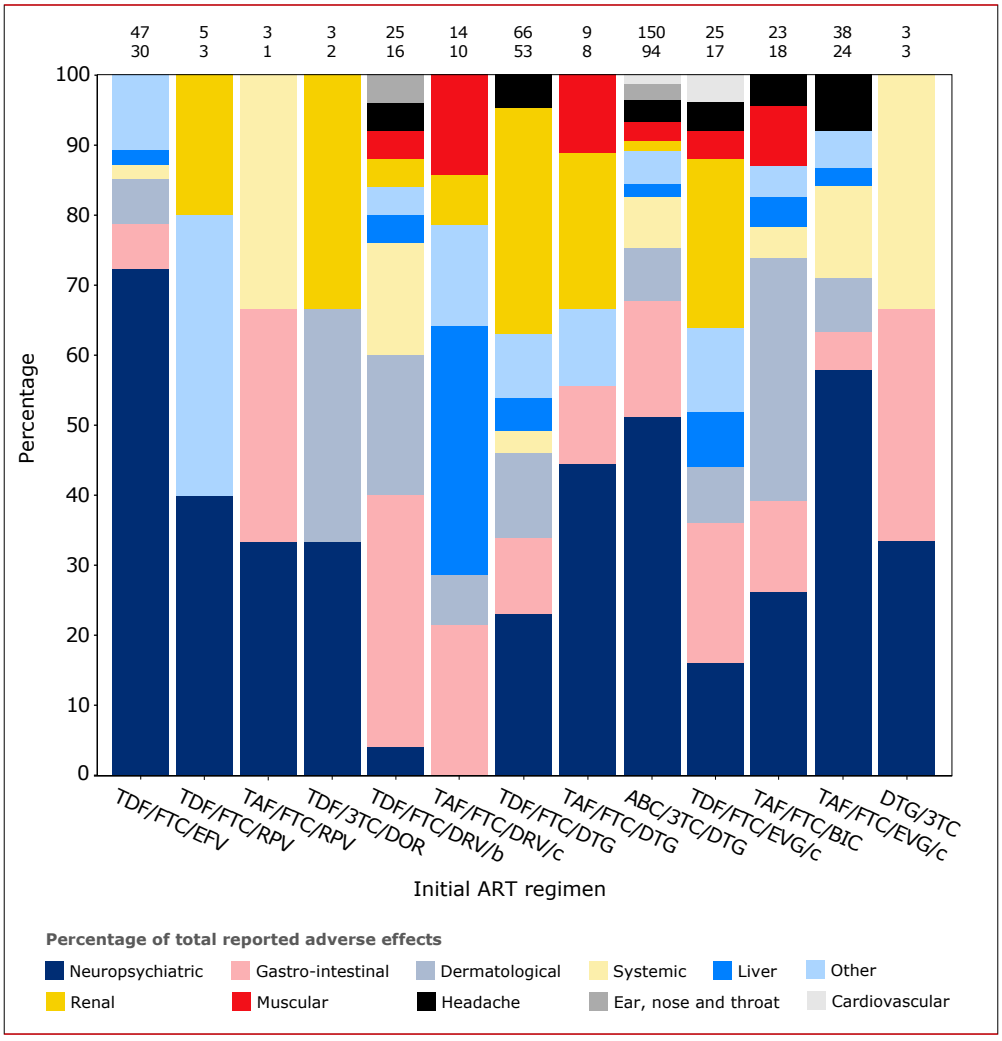
Adverse effects

Among the 306 individuals who discontinued their initial ART regimen within a year due to toxicity, 411 adverse effects were recorded. The predominant adverse effects were:

- neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression) 40.6%;
- gastrointestinal (mainly diarrhoea and nausea) 14.6%;
- dermatological (rash due to medication, itching) 10.2%;
- renal (renal insufficiency and increased serum creatinine) 8.5%; and
- systemic (tiredness, apathy, and loss of appetite) 6.6%.

These adverse effects are stratified by ART regimen in *Figure 2.10*. Neuropsychiatric effects were associated with regimens containing efavirenz and dolutegravir, and, to a lesser extent, rilpivirine and elvitegravir. Renal effects were mainly, but not exclusively, reported by people who discontinued tenofovir disoproxil fumarate-based ART.

Figure 2.10: *Adverse effects associated with initial regimen discontinuation due to toxicity, during the first year of treatment in 2016–21. The bars represent the distribution of 411 reported effects among 306 individuals, by regimen. Numbers above the bars represent 1) the number of adverse events reported as reasons for discontinuing that particular regimen (top row), and 2) the number of individuals using that particular regimen who experienced those events (bottom row).*



Legend: *ART = combination antiretroviral therapy; 3TC = lamivudine; ABC = abacavir; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EGV = elvitegravir; FTC = emtricitabine; NRTI = nucleoside analogue reverse transcriptase inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

Note: *The discontinuation rates and reasons for discontinuation are descriptive by nature and should be interpreted with caution. The choice of the initial ART regimen depends on personal characteristics, which might explain differences in discontinuation that are unrelated to the regimen (i.e. confounding by indication). Furthermore, follow-up time for some of the newer ART regimens was fairly short, which also influences discontinuation rates.*

Virological response

In the Netherlands, a total of 27,604 adults started ART between January 1996 and December 2021. For the analysis of virological outcomes in this section, we have focused on the 23,443 adults who were ART-naïve and not pregnant at the time of ART initiation (because ART may have been interrupted at the end of the pregnancy). We have also excluded people without an appropriate viral load test result within at least three months of ART initiation. The main definitions for virological outcomes used in this chapter are summarised in *Box 2.3*.

***Box 2.3:** Definitions of virological response and HIV drug resistance.*

Virological response

Initial virological success
HIV viral load below 100 copies/ml within six months of starting combination antiretroviral therapy (ART).
The viral load measurement closest to six months (plus or minus three months) after ART initiation was included in the analysis, irrespective of the viral load level.

Viral suppression
Any viral load measurements below 200 copies/ml, after at least three months of ART initiation.

HIV drug resistance

Transmitted HIV drug resistance
At least one resistance-associated mutation detected among individuals who had never received antiretroviral drugs and had not started ART.
The 2019 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[25].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving ART for at least four months.
The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.9-1) was used to infer antiretroviral drug susceptibility and resistance scores[26,27].

Initial virological success

Of the 23,443 individuals with a viral load test result within at least three months of ART initiation, 20,207 (86.2%) had a viral load measurement six months (plus or minus three months) after ART initiation. Of these people, 17,155 (84.9%) achieved initial virological success (i.e. a plasma viral load below 100 HIV RNA copies/ml [*Box 2.3*]). That percentage has improved over time, from 68.3% in those starting ART between 1996 and 2005, to 87.9% in 2006-10, 92.3% in 2011-20, and 93.3% in those starting in 2021.

Initial virological success of common initial ART regimens (2013–21)

We analysed initial virological success among the 5,867 adults who started a common or guideline-recommended ART regimen in 2013-21, which was used frequently enough to allow for a meaningful analysis (TDF/FTC/EFV; TDF/FTC/RPV; TDF/FTC/DRV/b; TDF/FTC/DTG; TDF/FTC/EVG/c; TAF/FTC/RPV; TAF/FTC/DRV/c; TAF/FTC/BIC; TAF/FTC/DTG; TAF/FTC/EVG/c; and ABC/3TC/DTG), and had a viral load result within six months (plus or minus three months) of ART initiation. In total, 94.0% (95% confidence interval [CI] 93.4-94.6) of individuals achieved initial virological suppression, after a mean of 178 (standard deviation [SD] 39) days. Overall, people receiving an integrase inhibitor or NNRTI-based regimen showed significantly higher rates of initial virological success: 94.8% (CI 94.1-95.5) of those on an integrase inhibitor-based regimen and 94.0% (92.7-95.4) on a NNRTI-based regimen, compared to 89.4% (87.1-91.7) on a protease inhibitor-based regimen.

Using logistic regression analysis, we further evaluated the initial virological success rates stratified by viral load at ART initiation (below, as well as equal to or above, 100,000 copies/ml), ART regimen, and regimen class. Stratified analysis of initial virological success based on viral load at ART initiation, showed superior virological outcomes for INSTI-based regimens, compared to both NNRTI-based and protease inhibitor-based regimens in people with a viral load at or above 100,000 copies/ml at ART initiation (*Table 2.4*). However, there were no significant differences between the three regimen classes in people with a viral load below 100,000 copies/ml at ART initiation. Population characteristics, which may be associated with the initial prescribed regimen, were not taken into account in this analysis.

Table 2.4: *Initial virological success rates (see definition in Box 2.3), by initial regimen and initial viral load at ART initiation in 2013–2021.*

	Total		By initial viral load at ART initiation					
					<100,000 copies/ml			
	n	%	n	%	Initial viral success	95% CI low	95% CI high	p-value
ART regimen								
TDF/FTC/EFV	640	10.9	352	9.8	97.7	96.2	99.3	Ref.
TDF/FTC/RPV	465	7.9	465	12.9	95.3	93.4	97.2	0.070
TDF/FTC/DRV/b	549	9.4	226	6.3	95.6	92.9	98.3	0.15
TDF/FTC/EVG/c	769	13.1	531	14.8	97.4	96.0	98.7	0.73
TDF/FTC/DTG	711	12.1	338	9.4	96.5	94.5	98.4	0.32
ABC/3TC/DTG	1,254	21.4	839	23.4	97.0	95.9	98.2	0.50
TAF/FTC/RPV	52	0.9	52	1.5	100	100	100	0.99
TAF/FTC/DRV/c	122	2.1	54	1.5	100	100	100	0.99
TAF/FTC/EVG/c	561	9.6	348	9.7	97.4	95.7	99.1	0.79
TAF/FTC/DTG	105	1.8	48	1.3	95.8	90.2	100	0.44
TAF/FTC/BIC	639	10.9	340	9.5	98.2	96.8	99.6	0.64
Regimen class								
NNRTI/2NRTI	1,157	19.7	869	24.2	96.5	95.3	97.8	Ref.
PI/2NRTI	671	11.4	280	7.8	96.4	94.3	98.6	0.92
INSTI/2NRTI	4,039	68.8	2,444	68.0	97.2	96.6	97.9	0.32
All regimens	**5,867**	**100**	**3,593**	**61.2**	**97.0**	**96.4**	**97.6**	

Legend: *ART = combination antiretroviral therapy; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; CI = confidence interval; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil.*

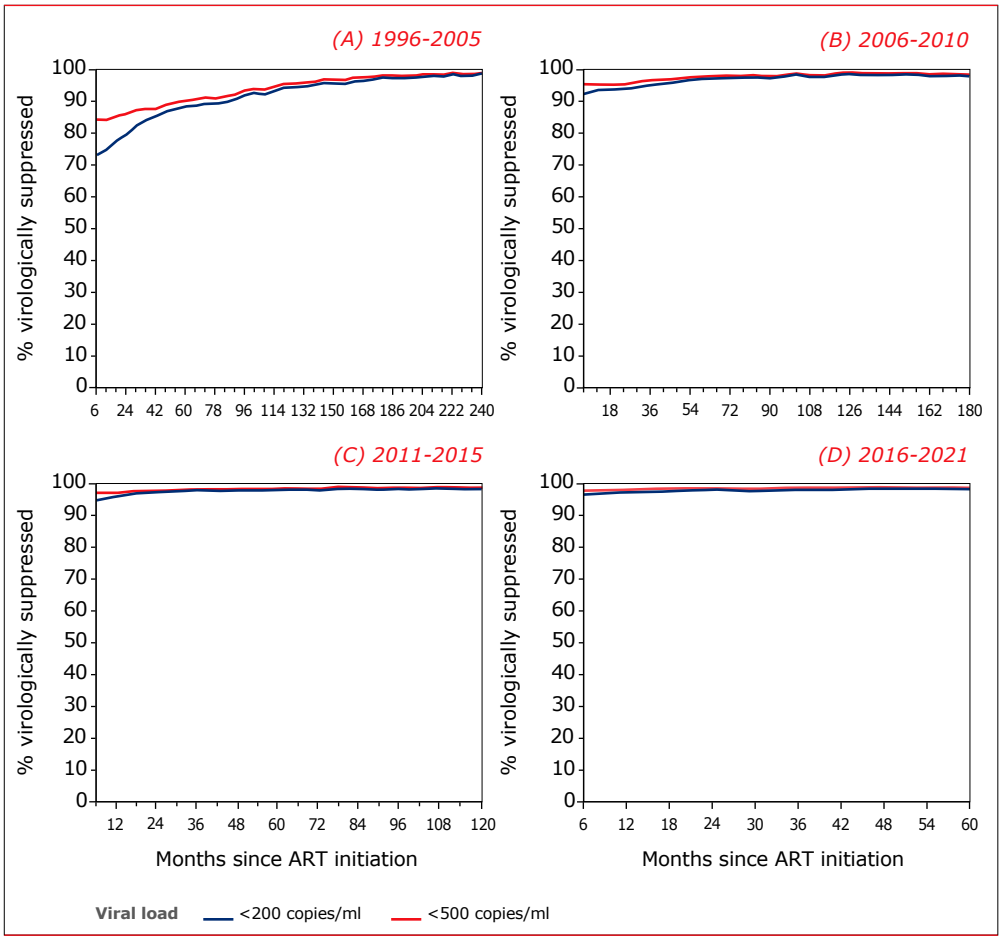
Viral suppression

We assessed long-term viral suppression rates (i.e. viral load below 200 copies/ml), during six-month intervals among adults on ART with a viral load test result after ART initiation. The viral load measurement after at least three months of ART, closest to each six-month time point (plus or minus three months), was included in the analysis, irrespective of the viral load.

Figure 2.11 shows viral suppression rates by calendar period of ART initiation: 1996-2005, 2006-10, 2011-15, and 2016-21. In line with the initial virological success rates, the long-term viral suppression rates improved over time. In people initiating ART in, or after 2016, suppression rates ranged from 97.4% (95% CI 96.8-97.9) after one year of ART use, to 98.4% (97.9-99.0) after four years.

		By initial viral load at ART initiation					
		≥100,000 copies/ml					
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	ART regimen						
	TDF/FTC/EFV	288	12.7	86.5	82.5	90.4	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	323	14.2	84.5	80.6	88.9	0.50
	TDF/FTC/EVG/c	238	10.5	89.5	85.6	93.4	0.29
	TDF/FTC/DTG	373	16.4	90.1	87.0	93.1	0.15
	ABC/3TC/DTG	415	18.3	92.0	89.4	94.7	0.017
	TAF/FTC/RPV	not recommended					
	TAF/FTC/DRV/c	68	3.0	83.8	75.1	92.6	0.57
	TAF/FTC/EVG/c	213	9.4	91.1	87.3	94.9	0.11
	TAF/FTC/DTG	57	2.5	91.2	83.9	98.6	0.33
	TAF/FTC/BIC	299	13.2	92.0	88.9	95.1	0.033
	Regimen class						
	NNRTI/2NRTI	288	12.7	86.5	82.5	90.4	Ref.
	PI/2NRTI	391	17.2	84.4	80.8	88.0	0.45
	INSTI/2NRTI	1,595	70.1	91.0	89.6	92.4	0.017
	All regimens	**2,274**	**38.8**	**89.3**	**88.0**	**90.6**	

Figure 2.11: *Viral suppression following combination antiretroviral therapy (ART) initiation, by calendar period of therapy initiation; A) 1996–2005, B) 2006–10, C) 2011–15, and D 2016–21.*



Legend: *ART = combination antiretroviral therapy.*

Note: *To some extent, the rising trend in viral suppression after starting ART, may reflect a bias towards those who do well and remain in follow up (i.e. survivor bias).*

HIV drug resistance

Box 2.3: Definitions of virological response and HIV drug resistance.

HIV drug resistance

Transmitted HIV drug resistance
At least one resistance-associated mutation detected among individuals who had never received antiretroviral drugs and had not started ART. The 2019 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[25].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving ART for at least four months. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.0) was used to infer antiretroviral drug susceptibility and resistance scores[26,27].

Preventing, monitoring and responding to HIV drug resistance is a key component of comprehensive and effective HIV care. When antiretroviral therapy does not result in complete suppression of viral replication, HIV drug resistance can occur; mutations in the genetic structure of HIV detrimentally affect the ability of a particular drug, or combination of drugs, to block replication of the virus. All current antiretroviral drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant HIV virus[28].

We assessed the occurrence of HIV drug resistance in the Netherlands among adults for whom genotypic test results were available. The genotypic test results presented in this section relate to the HIV-1 reverse transcriptase and protease gene. HIV-1 sequences of the integrase gene were relatively rare, therefore results of testing for integrase inhibitor resistance are described separately. It is worth noting that SHM does not receive drug resistance data from all HIV treatment centres and laboratories, hence presented figures may not be representative of the entire population in HIV care.

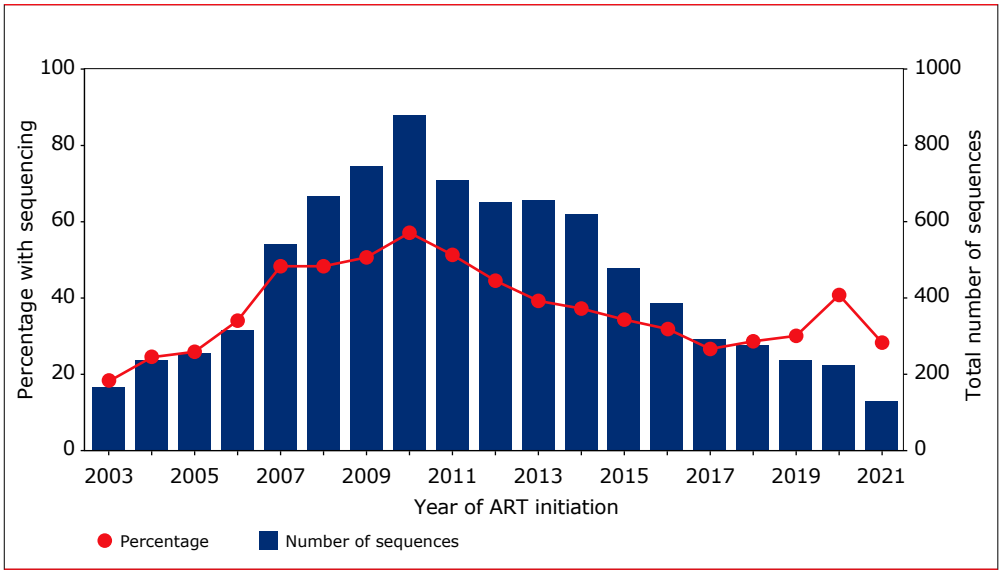
We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2019 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[25]. Furthermore, we assessed the association between these mutations and the susceptibility to antiretroviral drugs. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.0) was used to infer antiretroviral drug susceptibility scores for each sequence according to a five-level scheme: susceptible; potential low-level resistance; low-level resistance; intermediate resistance; and high-level resistance[26,27]. The definitions of transmitted and acquired-HIV drug resistance used in our analyses are summarised in *Box 2.3*. The number of sequences and people included in each of the analyses is outlined in *Box 2.1*.

Screening for drug-resistant HIV before treatment initiation

Since 2003 Dutch treatment guidelines have included a recommendation to screen for HIV drug resistance at the time of entry into care. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistant mutations. Drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[29-31]. These dormant mutant variants may not be detected, which can make it difficult to distinguish between drug-susceptible and drug-resistant strains[32]. Ideally, the presence of transmitted resistance should be identified as close as possible to the moment of infection in people who are antiretroviral (ARV)-naïve before initiating ART.

In total, 8,637 HIV-1 sequences were obtained between 2003 and 2021 from 8,327 ARV-naïve people before they initiated ART. The number of sequences and the percentage of ARV-naïve people with sequencing before ART initiation peaked in 2010 and have steadily declined since then (*Figure 2.12*). The decline in the number of sequences in 2021 is likely due to a backlog in relaying sequence data to SHM. If someone had more than one sequence available before ART initiation, we selected the first available sequence (closest to the date of HIV-1 diagnosis) for our analysis, to limit the effect of back mutation. Of those with pre-treatment drug-resistance data, the majority were MSM (67.4%), while (14.9%) were women. Most people with an available pre-treatment sequence originated from the Netherlands (59.5%), or sub-Saharan Africa (11.1%). The main HIV-1 subtype was B (74.7%), followed by non-B subtypes (25.3%), including recombinant form CRF_02AG (6.7%), subtype C (5.0%), and CRF_01AE (3.7%).

Figure 2.12: The annual number of sequences and the percentage of ARV-naïve people with sequencing before ART.

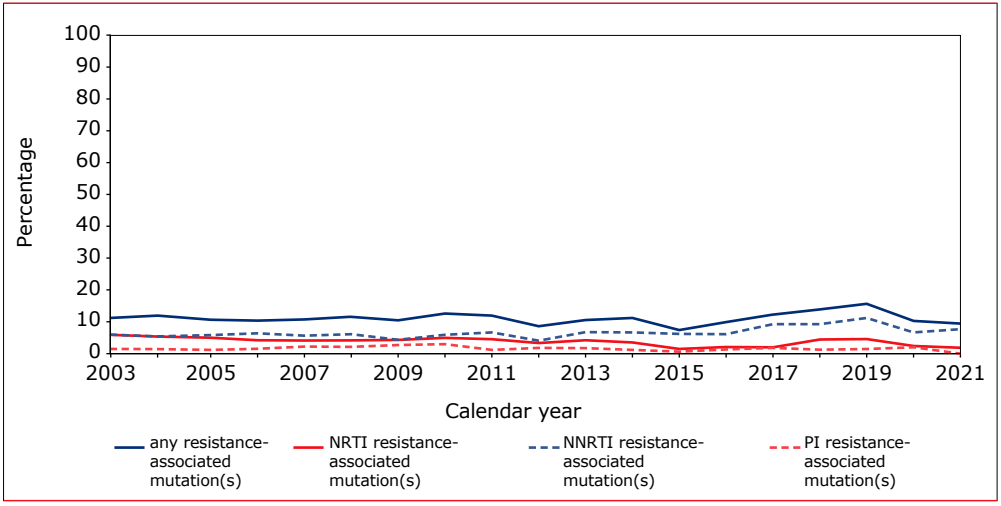


Legend: ART = combination antiretroviral therapy.

Transmitted HIV drug resistance

In total, at least one or more major resistance-associated mutation[25] was found in 909 (10.9%) of the people tested for resistance, including 334 (4.0%) with NRTI-associated resistance mutations, 509 (6.1%) with NNRTI-associated resistance mutations, and 144 (1.7%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2021 (*Figure 2.13*).

Figure 2.13: *The annual percentage of people with evidence of transmitted HIV drug resistance over time. Transmitted drug resistance was defined as the presence of at least one resistance-associated mutation detected before initiation of ART. The 2019 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[25].*



Legend: *NRTI = nucleotide/nucleoside reverse transcription inhibitor, NNRTI = non-NRTI, PI = protease inhibitor, RAS = resistance associated substitution.*

In total, 247 (3.0%) individuals screened for transmitted drug resistance harboured high-level resistance[26,27] to at least one antiretroviral drug: 45 (0.5%) to at least one NRTI; 182 (2.2%) to at least one NNRTI; and 34 (0.4%) to at least one PI. More information on transmitted resistance to NRTI and pre-exposure prophylaxis (PrEP) for HIV can be found in the special report on prior use of PrEP in this year's Monitoring Report. On the basis of the available resistance data, more than 97% were fully susceptible to all antiretroviral drugs: 2.6% (n=212) harboured high-level resistance in one drug class; 0.3% (n=24) in two drug classes; and less than 0.1% (n=5) to three drug classes (i.e. NRTIs, NNRTIs and PIs).

It should be emphasised that this does not mean that entire drug classes are rendered unsuitable for use in antiretroviral combinations. Even for people with resistance to all three classes, it often remains possible to construct fully efficacious ART combinations.

Integrase inhibitor resistance before HIV treatment initiation

In total, 201 people had an integrase sequence available prior to ART initiation, of whom all but three were ARV-naïve. No major or minor integrase resistance-associated mutations were detected in these individuals.

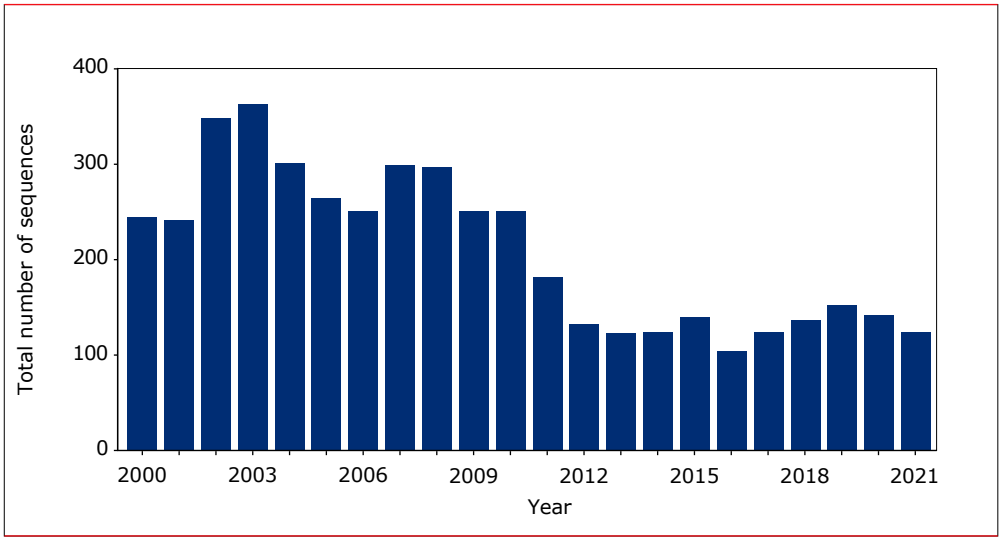
Acquired HIV drug resistance

The overall viral suppression rates of people receiving ART are very high and continue to improve in the Netherlands (see section *Virological response*). However, acquired-HIV drug resistance is still detectable in a subset of people receiving ART.

In this section, we describe the level of acquired drug resistance detected among the treated population with a viral load above 500 copies/ml, and resistance test results available after at least four months of ART in 2000-21. If ART had been interrupted more than two weeks before the test, the sequence was excluded from the analysis.

In total, 4,587 HIV-1 sequences were obtained from 2,757 people who received ART for at least four months. The number of sequences and people included in each subsequent analysis are outlined in *Box 2.1*. The number of sequences in this group was consistently above 200 between 2000 and 2010, substantially declined in 2011, then remained at the same level until 2021 (*Figure 2.14*). The median time between initial start of ART and resistance testing was 5.7 years (IQR 3.1-9.2). The main HIV-1 subtype was B (67.5%), followed by recombinant form CRF_02AG (11.2%), and subtype C (5.7%).

Figure 2.14: *The annual number of HIV-1 sequences in people who received ART for at least four months.*



Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,362 (29.7%) sequences were obtained from 736 (26.7%) pre-treated people, and 3,225 (70.3%) sequences were obtained from 2,021 (73.3%) ARV-naïve people. However, over time this difference became less distinct: in 2000, 73.0% of sequences were obtained from pre-treated people, compared with 36.0% in 2005, and less than 14% from 2010 onwards.

Of the 4,587 sequences obtained when the HIV RNA was above 500 copies/ml, 2,828 (61.7%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,849 (62.1%) sequences; of those, 2,440 (85.6%) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,793 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2021, 1,179 (65.8%) were still on ART containing lamivudine or emtricitabine, of whom 883 (74.9%) had undetectable HIV-RNA at their last visit. In addition, 1,693 (37.5%) harboured high-level resistance to at least one NNRTI, and 1,033 (23.8%) to at least one PI.

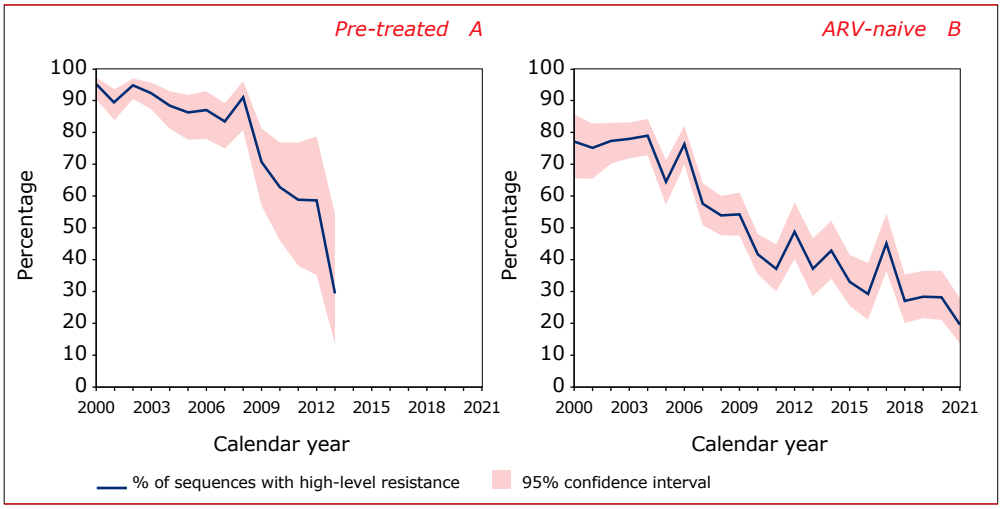
Previous antiretroviral drug exposure

The occurrence of acquired resistance was different for sequences obtained from people with mono NRTI therapy or dual NRTI therapy, than for those from people who were ARV-naïve before initiating ART.

Among pre-treated people, the annual percentage of sequences harbouring high-level resistance to at least one drug was 94.9% (95% CI 90.6-97.4) in 2000, 62.9% (46.0-77.1) in 2010, and 29.4% (12.8-54.2) in 2013 (*Figure 2.15A*). The availability of new drugs, both in existing and new drug classes, largely explains the decline since 2008[33]. In recent years (2014-21), both the number of pre-treated people, and the number of sequences from pre-treated people, were too low to provide meaningful percentages.

Among previously ARV-naïve people, high-level resistance to at least one drug was detected among 77.3% (95% CI 65.7-85.8) of sequences in 2000, 49.1% (40.2-58.2) in 2012, and 19.7% (13.4-27.9) in 2021 (*Figure 2.15B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naïve people has disappeared.

Figure 2.15: *The annual percentage of sequences with evidence of high-level resistance to any antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (ART), by prior antiretroviral (ARV) drug exposure, among A) people who were pre-treated with mono or dual nucleoside-analogue RT inhibitors (NRTIs), and B) previously antiretroviral drug-naïve people. The shaded area represents the 95% confidence interval.*



Note: *The number of sequences from pre-treated people in 2014-21 was too low to give meaningful percentages.*

Acquired HIV drug resistance among previously ARV-naïve people

In the remainder of our analysis, we focus solely on the 2,021 people who were ARV-naïve before ART initiation. Overall, 1,849 (57.3%) of the 3,225 sequences from previously ARV-naïve people receiving ART harboured at least one major resistance mutation, which were associated with resistance to NRTI (n=1,461, or 45.3%), NNRTI (n=1,143, or 35.4%), or PI (n=370, or 11.5%).

In *Figure 2.16A*, the annual percentage of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000:

- 77.3% (95% CI 65.7-85.8) of sequences harboured high-level resistance to at least one NRTI;
- 27.7% (18.2-39.7) harboured high-level resistance to at least one NNRTI; and
- 49.2% (37.3-61.2) harboured high-level resistance to at least one PI.

The percentage of sequences with high-level resistance declined over time for all drug classes, and in 2011:

- 37.1% (95% CI 30.0-44.9) of sequences harboured high-level resistance to at least one NRTI;
- 25.2% (19.0-32.5) harboured high-level resistance to at least one NNRTI; and
- 1.9% (0.6-5.8) harboured high-level resistance to at least one PI.

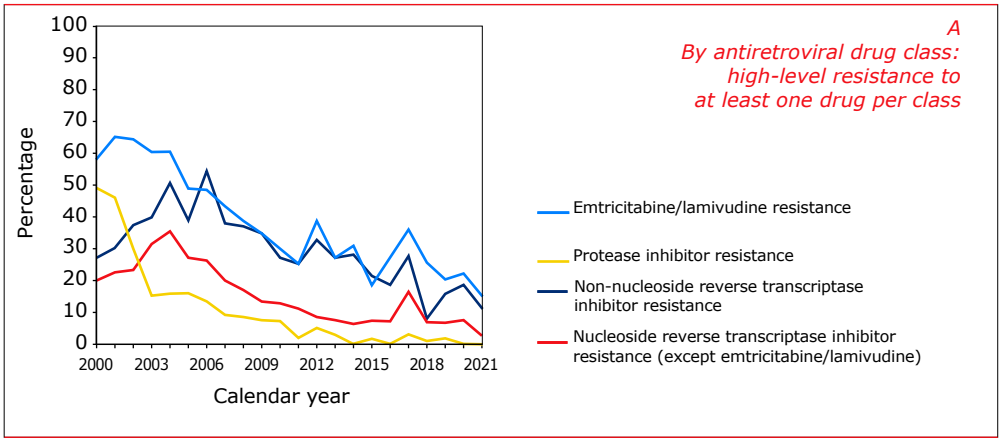
By 2021, these percentages were down to:

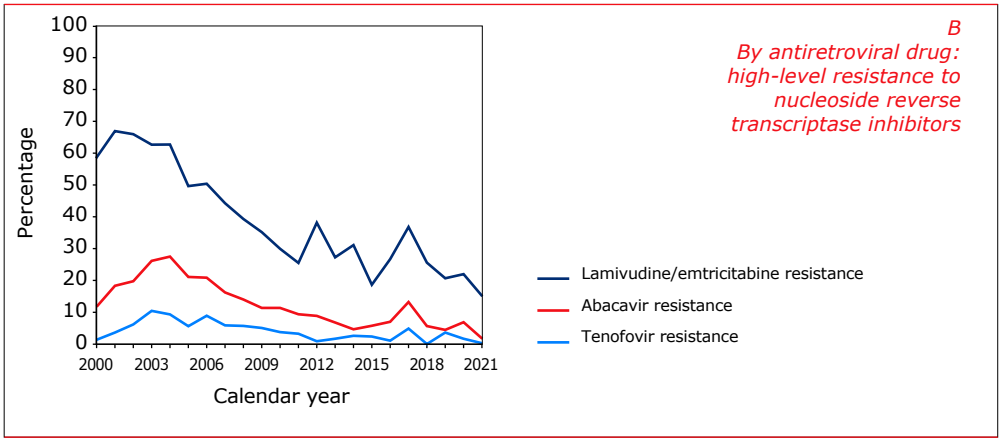
- 19.7% (95% CI 13.4-27.9) of sequences harbouring high-level resistance to at least one NRTI;
- 11.4% (6.6-19.1) harbouring high-level resistance to at least one NNRTI; and
- 0% harbouring high-level resistance to at least one PI.

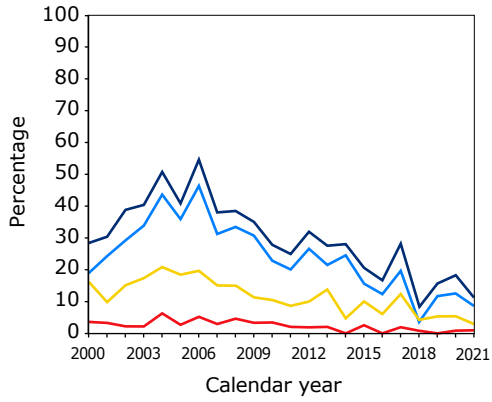
The percentage of sequences with at least one resistance mutation to all three drug classes (i.e. NRTI, NNRTI and PI) also declined over time: from 9.0% (4.1-18.8) in 2000 to 0% in 2014.

The annual percentage of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 2.16B-D*. The annual percentage of sequences harbouring major resistance mutations to specific drugs are outlined in *Appendix Table 2.1A-C*. *Figure 2.16E,* meanwhile, shows the annual percentage of sequences harbouring at least one high-level resistance mutation to all three drug classes. It should be pointed out that drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed, but instead remains viably archived in the viral reservoir.

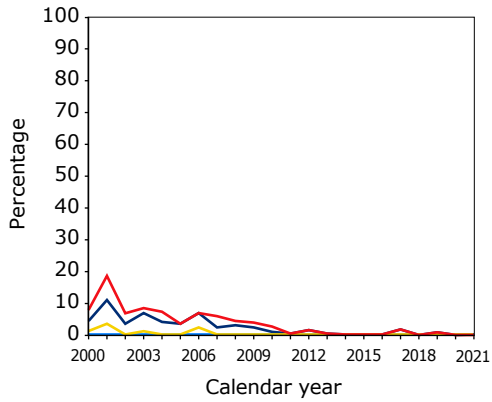
Figure 2.16: *The annual percentage of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (ART), among previously antiretroviral drug-naïve people. Results are shown by A) antiretroviral drug class: high-level resistance to at least one drug within class, B) antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors, C) antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors, D) antiretroviral drug: high-level resistance to protease inhibitors, and E) high-level resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.*



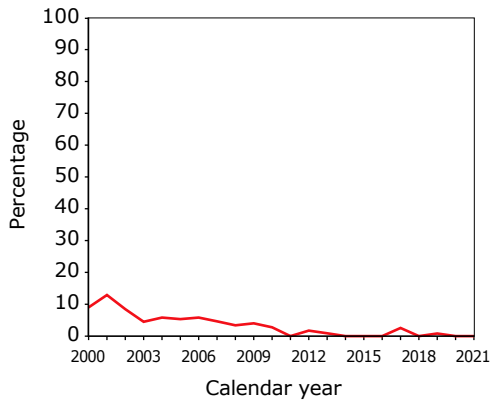




C
By antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors



D
By antiretroviral drug: high-level resistance to protease inhibitors



E
High-level triple class resistance to nucleoside reverse transcriptase inhibitors (NRTI), non-NRTIs and protease inhibitors

Legend: *NRTIs = nucleoside analogue reverse transcriptase inhibitors; NNRTIs = non-nucleoside reverse transcriptase inhibitors; PIs = protease inhibitors.*

Note: *The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.0) was used to infer antiretroviral drug susceptibility scores for each sequence, according to a five-level scheme: susceptible; potential low-level resistance; low-level resistance; intermediate resistance; and high-level resistance*[26,27].

Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on ART was relatively rare. The available 371 integrase sequences originated from 295 people who received ART for at least four months; 32 were pre-treated with monotherapy or dual NRTI therapy before initiating ART, and 263 were ARV-naïve before initiating ART. Of the 295 people who received ART for at least four months and had integrase gene sequencing available, 288 (97.6%) had been treated with an INSTI-containing regimen. Most people had initiated ART years before; the median time between initial ART initiation and testing for integrase inhibitor resistance was 10.4 years (IQR 4.6-15.7). For each person, we used the most recent sequence in our analysis.

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 46 of the 295 individuals, which resulted in high-level resistance to at least one integrase inhibitor[25,26]. Among the 46, the following major INSTI resistance mutations were detected (numbers are given in parenthesis):

- N155H (n=16) and N155H/N (n=3);
- R263K (n=6) and R263R/K (n=3);
- E92Q (n=5) and E92E/Q (n=2);
- Y143R (n=2) and Y143Y/C (n=1);
- T66I (n=2) and T66T/I (n=1);
- Q148H (n=1) and Q148R (n=1); and
- S147G (n=1) and S147S/G (n=1).

Minor mutations detected were at position:

- T97 (any, n=6; T97A, n=6);
- T66 (any, n=5; T66T/A, n=3; T66T/K, n=1; T66K, n=1);
- L74 (any mutation, n=3; L74I/L/M, n=1; L74L/M, n=1; L74I/M, n=1);
- G140 (any, n=2; G140S, n=1; G140G/S, n=1); and
- E138 (any, n=1; E138K, n=1).

The 46 individuals who harboured major INSTI resistance mutations had been treated with the following INSTI drugs: raltegravir (n=23), elvitegravir (n=16), dolutegravir (n=33), and bictegravir (n=5). Seven of these 46 individuals had ever received INSTI-monotherapy.

Immunological response

After initiation of ART, most people suppress HIV RNA to levels below the limit of detection, and this is accompanied by an increase in CD4 cell count. Failure to suppress viremia is associated with poorer recovery of CD4 cell count[34,35]. However, incomplete recovery of CD4 cell count (i.e. a CD4 cell count persistently below 350 cells/mm^3) may also occur, despite sustained viral suppression. This is a situation reported to be associated with an increased risk of progression to AIDS and development of non-AIDS-related diseases[36]. Normal CD4 cell counts in people without HIV are on average approximately 800 cells/mm^3, but this varies according to factors such as age, ethnicity, sex, and smoking behaviour[37]. Furthermore, although the CD4 cell count is considered the key prognostic factor for mortality and AIDS-defining endpoints, some, but not all studies have suggested that the CD4: CD8 ratio may have additional prognostic value[38-43]. The clinical benefit of ART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[44-48].

Immunological response by calendar year

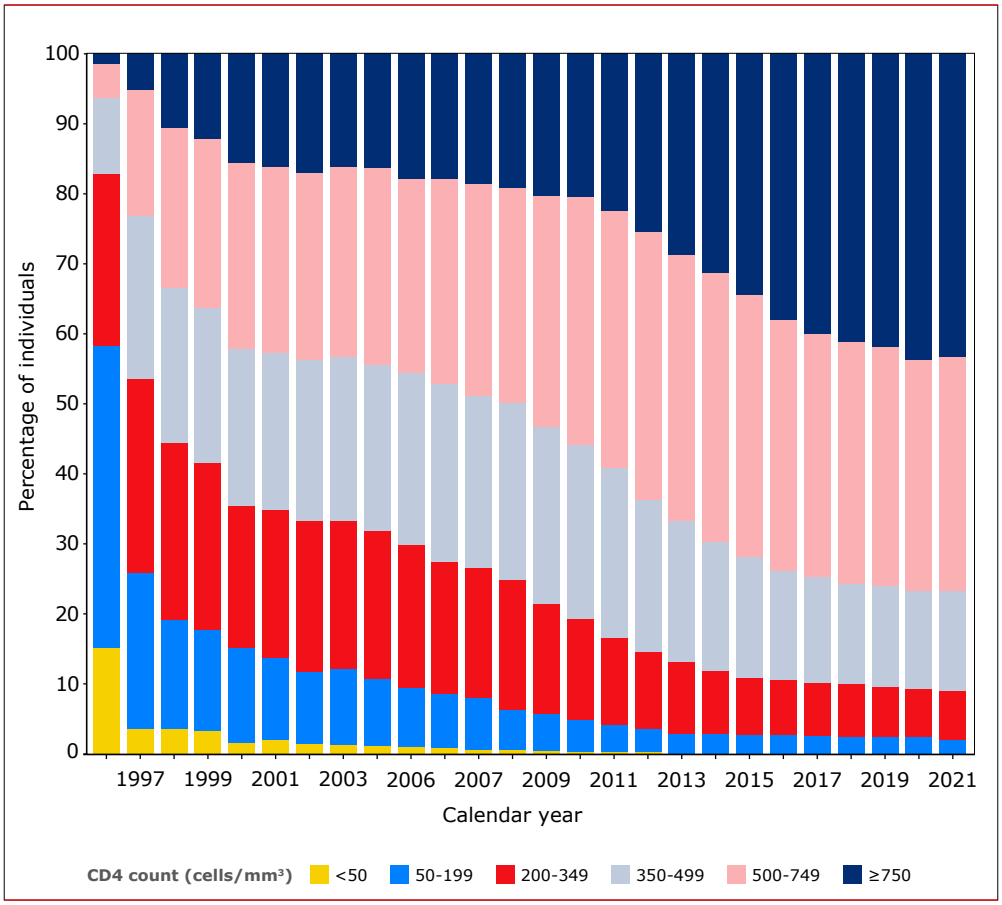
Of the 27,604 people known to have initiated ART between January 1996 and December 2020, CD4 cell count data after ART initiation were available for 26,561 (96.2%). *Figures 2.17* and *2.18* show the last known CD4 cell count and CD4: CD8 ratio of all people in HIV care for each calendar year. After starting ART, the percentage of people with CD4 cell counts below 350 cells/mm^3 dropped from 53.3% in 1997 to (*Figure 2.17*):

- 29.7% in 2005;
- 19.2% in 2010;
- 11.0% in 2015;
- 9.2% in 2020, and
- 8.9% in 2021.

The decrease in the percentage of people with low CD4 cell counts at the end of each calendar year is a consequence of:

- the trend of starting ART at higher CD4 cell counts;
- a more pronounced immune recovery with longer ART use;
- continually-declining virological failure rates; and
- attrition by the higher mortality rates in those with low CD4 counts.

Figure 2.17: Last available CD4 cell count of the treated population by calendar year (missing measurements/ data were not taken into account). Figures for 2021 may change slightly as data collection is not yet complete.



The percentage of those with a CD4: CD8 ratio of one or above increased from 1.2% in 1997 to (*Figure 2.18*):

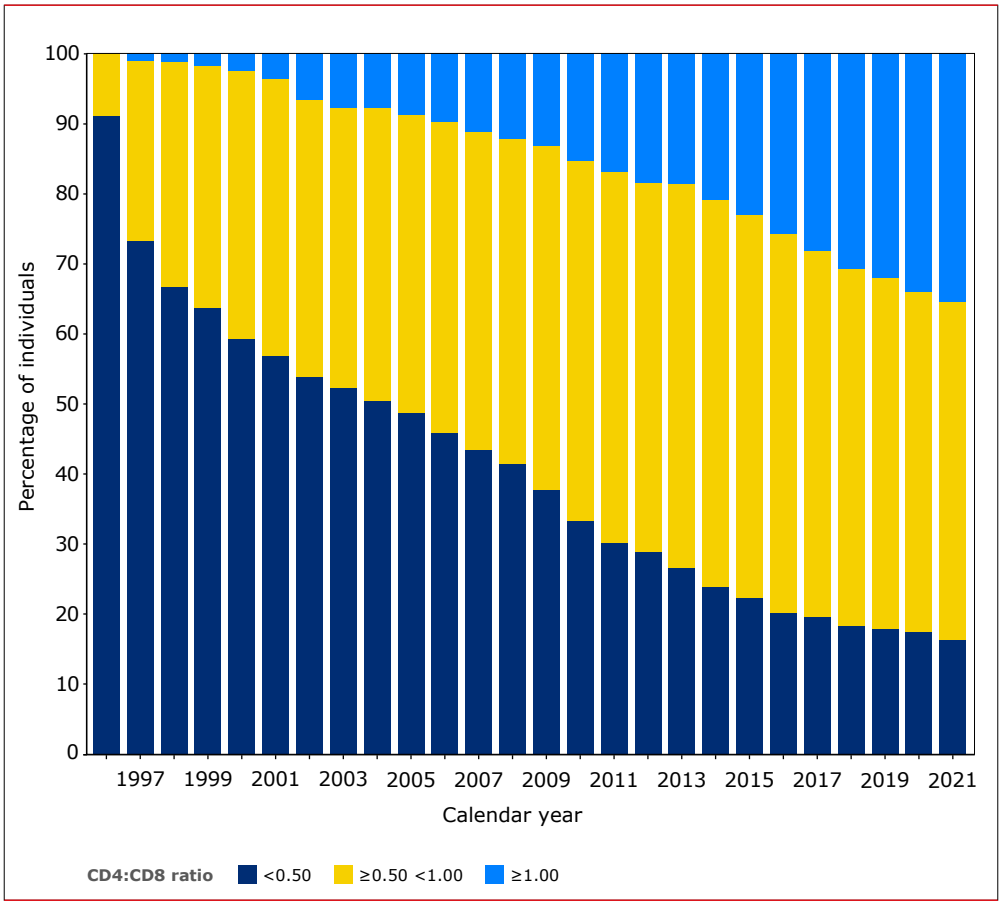
- 2.7% in 2000;
- 8.8% in 2005;
- 15.3% in 2010;
- 23.1% in 2015;
- 34.3% in 2020; and
- 35.6% in 2021.

Of all CD4: CD8 ratio measurements equal to or above one:

- 10.1% had a CD4 cell count of less than 500 cells/mm^3;
- 31.6% had a CD4 cell count between 500-749 cells/mm^3; and
- 58.2% had a CD4 cell count equal to or above 750 cells/mm^3.

When the CD4: CD8 ratio was equal to or above one, the median CD4 cell count was 802 cells/mm^3 (IQR 630-1,010).

Figure 2.18: Last available CD4: CD8 ratio in each calendar year after the start of combination antiretroviral therapy (ART).



Immunological response after ART initiation (2016–21)

We also assessed the immunological response in people who started ART more recently (i.e. in 2016-21), and had CD4 cell count data available at, and after ART initiation. The level of viral suppression and treatment interruptions after initiating ART were not taken into account in this analysis. Of the 3,690 people who started ART in 2016-21 and had sufficient immunological data available:

- 10.9% had CD4 cell counts below 50 cells/mm^3;
- 16.5% had CD4 cell counts between 50-199 cells/mm^3;
- 19.3% had CD4 cell counts between 200-349 cells/mm^3;
- 20.5% had CD4 cell counts between 350-499 cells/mm^3; and
- 32.8% had CD4 cell counts equal to or above 500 CD4 cells/mm^3 at the time of ART initiation.

The average CD4 cell count at ART initiation has decreased slightly in recent years (*Appendix Table 2.2*).

The CD4 cell count and CD4: CD8 ratio trajectories following ART initiation are plotted in *Figures 2.19* and *2.20* by CD4 cell count at ART initiation. The median CD4 cell counts and CD4: CD8 ratios increased after ART initiation. Both depended on the CD4 cell count at ART initiation and did not converge among the five baseline CD4 cell count strata. These observations are in line with a study by the Antiretroviral Therapy Cohort Collaboration (ART-CC), which included ATHENA data. It showed that the likelihood of normalisation of the CD4: CD8 ratio is strongly related to baseline CD4 cell count[49].

Figure 2.19: *CD4 cell count over time after the start of combination antiretroviral therapy (ART) in 2016–21.*

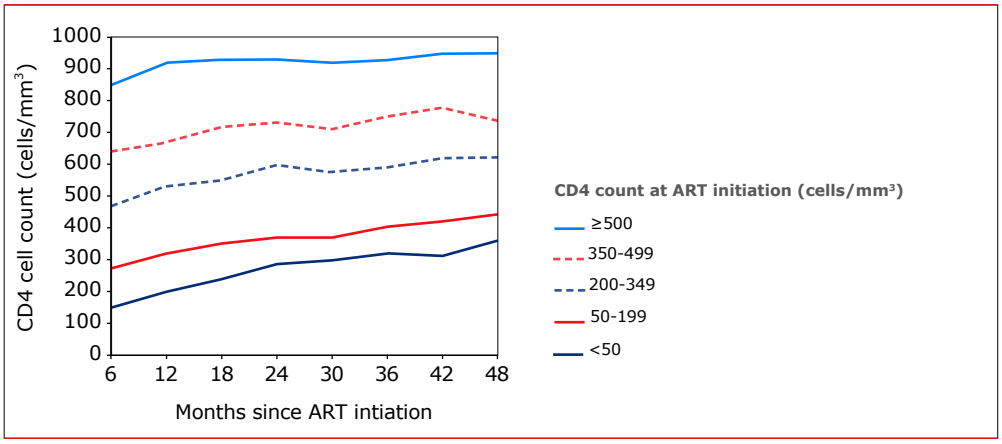
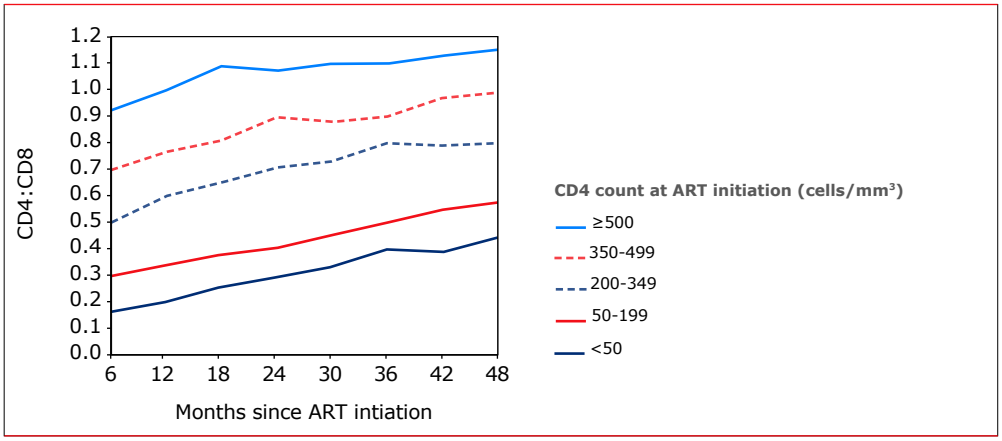


Figure 2.20: CD4: CD8 ratio over time after the start of combination antiretroviral therapy (ART) in 2016-21.



Note: The presented immunological outcomes are based on available test results. For people with a low-to-moderate CD4 cell count (below 350 cells/mm³), CD4 cell count testing is recommended at least twice a year[60]. When a person has a CD4 cell count above 350 cells/mm³, the testing frequency may be reduced. Therefore, CD4 data from people achieving higher CD4 cell counts are disproportionally underrepresented, and their true CD4 responses may be even better.

Summary and conclusions

Starting ART and the initial regimen

- Rapid initiation of ART following a diagnosis of HIV infection, irrespective of CD4 cell count, has generally resulted in a shorter median time to initiation of ART following diagnosis.
- The CD4 cell count at ART initiation initially increased over time, peaking in the year 2015 at a median of 414 cells/mm³ (IQR 220-600). This was when new guidelines were issued that recommended rapid initiation of ART at any CD4 cell count. Those guidelines resulted in substantial numbers of individuals with preserved CD4 cell counts, who had postponed starting ART, deciding to initiate treatment. Since then, the median CD4 cell count at the start of ART has continued to decrease. Among individuals with HIV starting ART in 2021, the median CD4 cell count was 200 cells/mm³ (IQR 51-398). *Chapter 1* explores in greater detail the changes in the proportion of people with HIV (PWH) who are late presenters at the time of HIV diagnosis. It also considers possible reasons for the observed trends. Immunological recovery was better when ART was started at a higher CD4 cell count.

- In 2021, 90.9% of initial regimens contained an integrase inhibitor. The most frequently used initial regimen was bictegravir/emtricitabine/tenofovir alafenamide (41.1%). Dolutegravir-containing initial regimens were used in 47.5% of cases.
- Compared to the first decade of the ART era, discontinuation of the initial regimen has become less common over time. In the past decade, the discontinuation rate has remained stable. However, the reasons for switching have continued to change, with virological failure a very rare event nowadays. In recent years, many switches were driven by the wish for regimen simplification and pre-emptive modifications because of the availability of new regimens that are perceived to have better long-term safety profiles.
- Toxicity-associated discontinuations of the initial regimen were often related to neuropsychiatric problems, problems involving the gastrointestinal tract or liver, or a rash due to medication.

In care and receiving ART in 2021

- ART containing two NRTIs plus an integrase inhibitor has been implemented on a large scale in the Netherlands and was used by 46.3% of all individuals. Integrase inhibitors were used by 59.4% of the total population receiving ART, if other integrase inhibitor-containing regimens are also considered.
- The nucleoside analogue backbone used contained TDF in 29.7% of cases, ABC in 13.8%, and TAF in 44.5% of cases.
- In 2021, 11.0% used a two-drug regimen.
- Of those receiving ART for at least 12 months (who had a plasma HIV RNA measurement in 2021) 98.1% had a viral load below 200 copies/ml, and 95.9% had a viral load equal to or below 50 copies/ml.

Virological response and drug resistance

- The overall viral suppression rates of the population with HIV receiving ART is high and has continued to improve. Among the limited number of individuals who experienced virological failure, the annual percentage with acquired drug resistance remained low; this is in line with findings in other high-income settings[51,52].
- Transmitted drug resistance was rare, and the overall prevalence was low and stable over time, in line with rates reported by other European countries[53].
- Integrase inhibitor resistance data remain limited. No transmitted integrase inhibitor resistance was detected among the 201 people tested by the end of 2021. Detected rates of acquired integrase inhibitor resistance among available sequences remained very low, with only a few cases of significant resistance to dolutegravir.

- The number of sequences available in 2020 and 2021 were comparabe to other years, suggesting that the restricted capacity at virology departments during the COVID-19 pandemic did not affect sequencing for drug resistance.

Immunological response

- In individuals receiving ART, the percentage of people with CD4 cell counts below 350 cells/mm^3 dropped from 53.3% in 1997 to:
  - 29.7% in 2005;
  - 19.2% in 2010;
  - 11.0% in 2015;
  - 9.0% in 2020; and
  - 8.9% in 2021.
- The percentage of those with a CD4: CD8 ratio of one or above increased from 1.2% in 1997 to:
  - 8.8% in 2005;
  - 15.3% in 2010;
  - 23.1% in 2015;
  - 34.6% in 2020; and
  - 35.6% in 2021.

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APPENDIX

Appendix Table 2.1A–C: *Acquired drug resistance: annual percentage of available sequences with major resistance mutations after virological failure by antiretroviral drug, associated with people who received combination antiretroviral therapy and were previously antiretroviral drug-naïve. Results are shown by A) major resistance mutations to nucleoside reverse transcriptase inhibitors, B) major resistance mutations to non-nucleoside reverse transcriptase inhibitors, and C) major resistance mutations to protease inhibitors.*

A

	Calendar year									
	2017		2018		2019		2020		2021	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Emtricitabine/lamivudine										
K65R, E or N	5	4.8	4	3.3	3	2.3	5	4.5	1	1.1
M184V or I	39	37.1	31	25.8	27	20.9	25	22.7	14	15.9
Abacavir										
K65R, E or N	5	4.8	4	3.3	3	2.3	4	3.8	1	1.2
L74V	4	3.8	2	1.7	2	1.6	3	2.8	0	0
Y115F	4	3.8	1	0.8	2	1.6	3	2.8	0	0
M184V	36	34.6	26	21.7	20	15.6	18	17	8	9.4
Tenofovir										
K65R, E or N	5	4.9	0	0	4	3.1	2	1.9	0	0
K70R	0	0	1	0.9	1	0.8	0	0	1	1.2

B

	Calendar year									
	2017		2018		2019		2020		2021	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Nevirapine										
L100I	1	1.0	1	0.8	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	11	10.5	4	3.3	12	9.1	11	10.3	6	6.8
V106A or M	6	5.7	0	0	1	0.8	5	4.7	0	0
V108I	6	5.7	1	0.8	5	3.8	4	3.7	0	0
Y181C or I	12	11.4	5	4.2	7	5.3	8	7.5	4	4.5
Y188L, C or H	0	0	0	0	2	1.5	1	0.9	0	0
G190A	9	8.6	0	0	0	0	2	1.9	1	1.1
M230L	0	0	0	0	1	0.8	0	0	1	1.1
Etravirine										
L100I	0	0	0	0	0	0	0	0	0	0
L101P	0	0	0	0	0	0	0	0	0	0
Y181C, I or V	2	2.1	1	0.9	0	0	0	0	1	1.2
Efavirenz										
L100I	1	1.0	1	0.9	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	12	12.5	4	3.5	12	9.5	11	10.8	6	7.1
V106M	2	2.1	0	0	1	0.8	2	2.0	0	0
V108I	5	5.2	0	0	2	1.6	1	1.0	0	0
Y181C or I	7	7.3	1	0.9	1	0.8	2	2.0	1	1.2
Y188L	0	0	0	0	1	0.8	0	0	0	0
G190S or A	8	8.3	0	0	0	0	2	2.0	1	1.2
P225H	0	0	0	0	1	0.8	0	0	1	1.2
M230L	1	1.0	1	0.9	0	0	0	0	1	1.2
Rilpivirine										
L100I	1	1.0	1	0.9	0	0	0	0	0	0
K101E or P	4	3.8	1	0.9	1	0.8	2	1.9	1	1.2
E138A, G, K, Q or R	7	6.7	6	5.1	7	5.5	10	9.7	4	4.7
V179L	1	1.0	0	0	0	0	0	0	0	0
Y181C, I or V	9	8.7	3	2.6	4	3.1	3	2.9	2	2.3
Y188L	0	0	0	0	1	0.8	0	0	0	0
H221Y	2	1.9	1	0.9	3	2.3	2	1.9	1	1.2
F227C	0	0	0	0	0	0	0	0	0	0
M230I or L	0	0	0	0	1	0.8	0	0	1	1.2

C

	Calendar year									
	2017		2018		2019		2020		2021	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Atazanavir										
I50L	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	1	1.0	0	0	0	0
N88S	0	0	0	0	0	0	0	0	0	0
Darunavir										
I47V	0	0	0	0	0	0	0	0	0	0
I50V	0	0	0	0	0	0	0	0	0	0
I54M or L	0	0	0	0	0	0	0	0	0	0
L76V	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	0	0	0	0	0	0
Lopinavir										
V32I	1	1.1	1	1.1	0	0	0	0	0	0
I47V or A	0	0	0	0	0	0	0	0	0	0
I50V	0	0	0	0	0	0	0	0	0	0
I54V, L or M	2	2.1	0	0	1	1.0	0	0	0	0
L76V	0	0	0	0	1	1.0	0	0	0	0
V82A, F, T or S	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	1	1.0	0	0	0	0
Tipranavir										
I47V	0	0	0	0	0	0	0	0	0	0
Q58E	1	1.1	0	0	0	0	2	2.4	1	1.6
T74P	0	0	0	0	0	0	0	0	0	0
V82L or T	0	0	0	0	0	0	0	0	0	0
N83D	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	0	0	0	0	0	0

Appendix Table 2.2: *CD4 cell count at combination antiretroviral therapy (ART) initiation by calendar year in 2016–21.*

Year of ART initiation	2016	2017	2018	2019	2020	2021	2016–2021
CD4 cell count available at ART initiation	936	843	710	605	404	192	**3,690**
CD4 cell count, median cells/mm³ (IQR)	410 (240–580)	380 (200–560)	376 (167–580)	360 (169–570)	300 (126–545)	200 (51–398)	**370 (173–566)**
CD4 cell count (cells/mm³)							
<50	8.9%	8.4%	11.1%	10.6%	14.3%	24.5%	**10.0%**
50–199	12.1%	16.3%	16.9%	18.5%	19.1%	25.5%	**16.0%**
200–349	18.3%	19.6%	18.6%	19.0%	22.3%	19.8%	**19.4%**
350–499	23.3%	22.8%	19.4%	19.5%	16.6%	13.0%	**21.0%**
≥500	37.5%	33.0%	33.9%	32.4%	27.7%	17.2%	**33.5%**

Legend: *ART = combination antiretroviral therapy; IQR = interquartile range.*