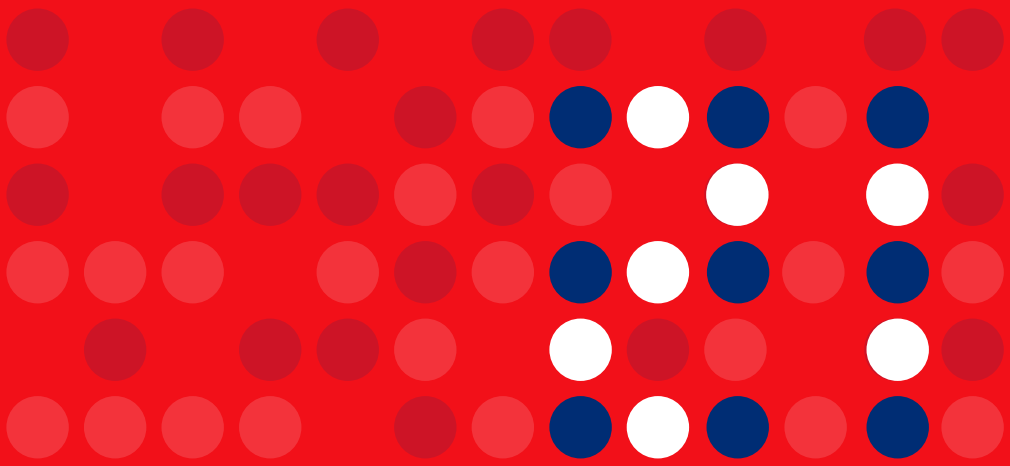
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2021

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 (cART) 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 cART are to prevent HIV disease progression, improve clinical outcomes, and limit transmission[1,2]. Treatment guidelines across the globe recommend the initiation of cART as soon as possible in all people newly diagnosed with HIV, regardless of CD4 count. The decision to initiate cART 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 cART is also more effective at preventing transmission of HIV than deferral of treatment until the CD4 count has dropped to a level equal to or below 350 cells/mm^3 [9,10]. People living with HIV on cART 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 cART generally results in sustained suppression of HIV viral load to levels below the reported threshold. Nevertheless, drug resistance mutations may develop if a given agent, even when combined with other agents, 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 cART, and trends in the virological and immunological responses to cART, 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 2020, a cumulative total of 28,745 individuals (aged 15 years or older at the time of diagnosis) were registered by SHM as living with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   26,806 people were known to have initiated cART between January 1996 and December 2020.

2. **In care and on cART in the Netherlands in 2020**
   Of the 26,806 people who initiated cART between January 1996 and December 2020,
   ➔ 20,479 were in care by the end of 2020.

3. **Changes in the use of the initial cART regimen**
   Of the 26,806 people who initiated cART between January 1996 and December 2020,
   ➔ 5,389 initiated cART between January 2015 and December 2020.
   ➔ The most frequently used guideline-recommended initial regimens in 2015-20 were: ABC/3TC/DTG (25.8%), TDF/FTC/DTG (12.5%), TAF/FTC/EVG/c (12.3%), TAF/FTC/BIC (10.8%), TDF/FTC/EVG/c (7.1%), TDF/FTC/EFV (5.0%), TDF/FTC/DRV/b (4.3%), TAF/FTC/DRV/c (2.7%), TDF/FTC/RPV (2.5%), and TAF/FTC/DTG (2.5%).

4. **Virological response**
   Of the 26,806 people who initiated cART between January 1996 and December 2020,
   ➔ 22,675 people were ART-naive, not pregnant at cART initiation, and had an HIV viral load result within six months (plus or minus three months) of cART initiation.

5. HIV drug resistance

Transmitted HIV drug resistance

As of December 2020, 8,158 HIV-1 sequences had been obtained from 7,863 ART-naive people prior to initiation of cART in 2003-20.

➔ 8,149 reverse transcriptase sequences were available from 7,857 individuals.

➔ 7,758 protease sequences were available from 7,473 individuals.

➔ 42 integrase sequences were available from 42 individuals.

Acquired HIV drug resistance

As of December 2020, 4,298 HIV-1 sequences had been obtained from 2,596 people who received cART for at least four months in 2000-20.

➔ 2,959 sequences were from 1,868 people who had been ART-naive before initiating cART.

➔ 4,248 reverse transcriptase sequences were available from 2,578 individuals.

➔ 4,132 protease sequences were available from 2,495 individuals.

➔ 208 integrase sequences were available from 168 individuals.

6. Immunological response

Of the 26,806 people who initiated cART between January 1996 and December 2020,

➔ 26,330 had CD4 cell count data available after initiating cART.

Legend: *ART=antiretroviral therapy; cART=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, 26,806 individuals ever registered by SHM and followed in the ATHENA cohort were 15 years or older at the time of HIV-1 diagnosis, and were known to have initiated cART between January 1996 and December 2020 (*Box 2.1*). Of these, 2,135 (8.0%) had prior exposure to mono- or dual- nucleoside-analogue antiretroviral therapy (ART) at the start of cART, and 24,671 (92.0%) were ART-naive. The proportion of pre-treated people starting cART has decreased over time to less than 1%, and nowadays mostly consists of people who were diagnosed and started on ART abroad. In *Table 2.1*, we have grouped people by calendar year of cART initiation: 9,562 started in 1996-2005, 6,066 in 2006-10, 7,081 in 2011-15, and 4,097 in 2016-20.

Table 2.1 Characteristics of people starting combination antiretroviral therapy in 1996-2020.

Year of cART initiation		1996-2005	2006-2010	2011-2015	2016-2020	1996-2020
Number of individuals		9,562	6,066	7,081	4,097	**26,806**
DEMOGRAPHIC						
Age at cART initiation (years)	Median	37.5	40.2	39.4	37.7	38.6
	Q1	31.8	32.9	30.9	29.1	31.4
	Q3	44.6	47.3	48.3	49.0	46.9
Male sex (at birth)	n	7,338	4,936	6,120	3,485	21,879
	%	76.7	81.4	86.4	85.1	81.6
Transmission risk group						
Missing	n	8	8	12	13	41
	%	0.1	0.1	0.1	0.3	0.1
Men who have sex with men	n	5,010	3,722	4,877	2,664	16,273
	%	52.4	61.4	68.9	65.0	60.7
Heterosexual contact	n	3,306	1,870	1,750	1,053	7,979
	%	34.6	30.8	24.7	25.7	29.8
Injecting drug use	n	538	108	42	27	715
	%	5.6	1.8	0.6	0.7	2.7
Blood or blood products*	n	170	49	67	51	337
	%	1.8	0.8	1.0	1.2	1.3
Vertical transmission	n	2	4	3	4	13
	%	0.02	0.1	0.04	0.1	0.05
Unknown	n	528	305	330	285	1,448
	%	5.5	5.0	4.7	7.0	5.4
Region of origin						
Missing	n	48	18	27	42	135
	%	0.5	0.3	0.4	1.0	0.5
The Netherlands	n	5,162	3,405	4,202	2,095	14,864
	%	54.0	56.1	59.3	51.1	55.5
Western Europe/North America/Australia	n	945	499	485	213	2,142
	%	9.9	8.2	6.9	5.2	8.0
Eastern/central Europe	n	177	201	374	377	1,129
	%	1.9	3.3	5.3	9.2	4.2
Latin America and the Caribbean	n	1,030	717	892	631	3,270
	%	10.8	11.8	12.6	15.4	12.2
Sub-Saharan Africa	n	1,706	879	658	407	3,650
	%	17.8	14.5	9.3	10.0	13.6
Other	n	494	347	443	332	1,616
	%	5.2	5.7	6.3	8.1	6.0

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	1996–2020
CLINICAL						
Recent infection	n	581	932	1,704	1,044	4,261
(within 12 months of diagnosis)	%	6.1	15.4	24.1	25.5	15.9
Ever having tested HIV-negative	n	1,986	2,468	3,883	2,248	10,585
	%	20.8	40.7	54.8	54.9	39.5
CD4 cell count at start of cART	Median	190	244	355	381	270
	Q1	80	140	220	190	130
	Q3	320	330	500	570	410
HIV RNA (log_{10}) at start of cART	Median	4.9	5.0	4.8	4.8	4.9
	Q1	4.3	4.4	4.3	4.1	4.3
	Q3	5.3	5.4	5.3	5.4	5.3
(Prior) AIDS at start of cART	n	2,961	1,149	924	543	5,577
	%	31.0	18.9	13.1	13.3	20.8
Prior mono- or dual-NRTI treatment	n	2,030	54	26	25	2,135
at start of cART	%	21.2	0.9	0.4	0.6	8.0
Hepatitis B status at start of cART						
HBV-negative (HBsAg-negative)	n	8,584	5,576	6,460	3,455	24,075
	%	89.8	91.9	91.2	84.3	89.8
HBV-positive (HBsAg-positive)	n	596	321	208	100	1,225
	%	6.2	5.3	2.9	2.4	4.6
Unknown	n	382	169	413	542	1,506
	%	4.0	2.8	5.8	13.2	5.6
Hepatitis C status at start of cART						
HCV-negative	n	8,631	5,751	6,803	3,892	25,077
	%	90.3	94.8	96.1	95.0	93.6
HCV RNA-positive	n	171	134	103	63	471
	%	1.8	2.2	1.5	1.5	1.8
HCV Ab seropositive	n	194	45	43	21	303
	%	2.0	0.7	0.6	0.5	1.1
Unknown	n	566	136	132	121	955
	%	5.9	2.2	1.9	3.0	3.6
cART started during pregnancy	n	404	229	137	73	843
	%	4.2	3.8	1.9	1.8	3.1

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 cART 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.*

Legend: *cART=combination antiretroviral therapy; cART=combination antiretroviral therapy; HBV=hepatitis B*

Of the 26,806 people known to have initiated cART since January 1996, 21,879 (81.6%) were men, of whom 16,273 (74.4%) were men who have sex with men (MSM). Overall, 14,864 (55.5%) 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 5.3% in 2011-15, and 9.2% in 2016-20. Simultaneously, the number of people from western Europe/North America/Australia decreased slightly from 9.9% in 1996-2005, to 5.2% in 2016-20. This was also true for sub-Saharan Africa; the number declined from 17.8% in 1996-2005, to 9.9% in 2016-20.

Prompt initiation of cART 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 cART in the Netherlands, the median time between an HIV-positive diagnosis and cART initiation shifted from 141 days (interquartile range [IQR] 34-729) for those who entered care in 2011, to 36 days (IQR 17-83) in 2015; 25 days (IQR 11-47) in 2018; 22 days (IQR 9-46) in 2019; and 18 days (IQR 8-37) in 2020. The time between entering care and starting cART decreased over time (*Figure 2.1B*), with the majority of newly diagnosed ART-naïve people entering care in the Netherlands initiating cART within one month. In 2020, 77.5% of individuals initiated cART within one month, while 15.2%, 3.3% and 4.1% of newly diagnosed ART-naïve individuals who initiated cART in the Netherlands did so either 1-5 months, 6-12 months, or more than one year after their HIV diagnosis, respectively (*Figure 2.1A*). 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 cART was mostly driven by a long period between HIV diagnosis and entering care, as 92.0% of people initiating cART in 2020 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.

Figure 2.1A: Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) in people starting cART in 2011–2020.*

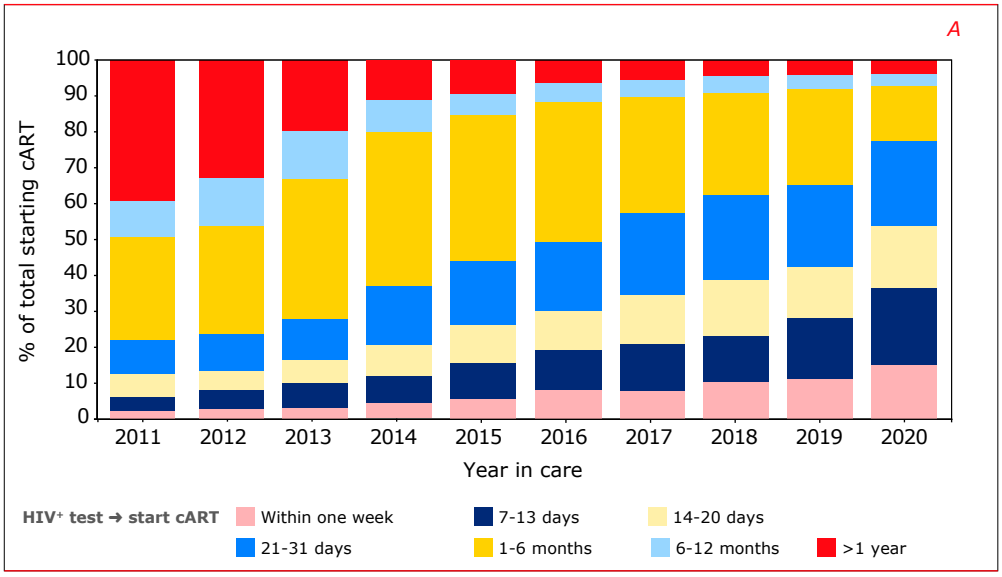
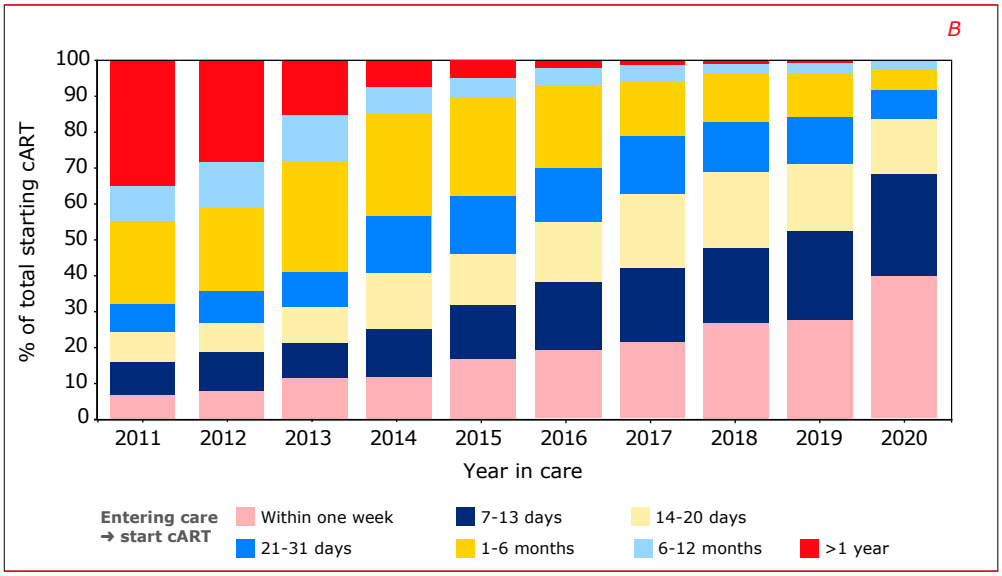


Figure 2.1B: Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) for people starting cART in 2011–2020.*



Legend: cART=combination antiretroviral therapy.

The proportion of individuals newly diagnosed with HIV who have a known previous negative HIV test has increased over the years, from 20.8% in the period 1996-2005, to 40.7% in 2006-10, 54.8% in 2011-15, and 54.9% in 2016-20. In addition, an increasing proportion of those starting cART 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, 24.1% in 2011-15, and 25.5% in 2016-20. Over the same time period, there was an increase in the median CD4 cell count at the start of cART: from 190 cells/mm^3 (IQR 80-320) in 1996-2005, to 244 cells/mm^3 (IQR 140-330) in 2006-10, 355 cells/mm^3 (IQR 220-500) in 2011-15, and 381 cells/mm^3 (IQR 190-570) in 2016-20. In 2015, the median CD4 cell count at cART initiation peaked at 412 (IQR 270-560) and has since continued to decrease slightly each year to 344 cells/mm^3 (IQR 160-560) in 2020. This trend is likely due to the substantial group already in care but not on cART (because of their high CD4 cells counts), who subsequently initiated cART en masse in 2015 and 2016, when the 2015 guideline change recommended ART for all, irrespective of CD4 count. At the start of cART, 20.8% of individuals had already been diagnosed with an AIDS-defining condition; 90.9% had a CD4 cell count below 350 cells/mm^3, and 76.5% 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 cART, and additional aspects of the continuum of HIV care.

In care and on cART in the Netherlands in 2020

Of the 26,806 people known to have initiated cART between January 1996 and December 2020, 20,251 (75.6%) were alive, still receiving cART, and had a recorded visit for HIV care in the Netherlands in 2020. A total of 228 people were still alive but (temporarily, and for various reasons) not on cART anymore and have therefore been excluded from the analyses in this paragraph – most of these individuals had medical, psychiatric, and/or psycho-social issues that temporarily prevented them from using their cART, and expected to re-start cART once those issues were sufficiently resolved. *Table 2.2* shows the treatment and clinical characteristics of all individuals on ART at the last clinic visit in 2020. Overall, 16,651 (82.2%) were men, and 13,033 (64.4%) were MSM. Their median age on 31 December 2020 was 51.5 (IQR 42.0-59.3) years. The majority (58.9%) originated from the Netherlands, followed by Latin America / the Caribbean (12.1%) and sub-Saharan Africa (11.8%).

Table 2.2: Characteristics of people receiving combination antiretroviral therapy and known to be in care in 2020.

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	All
Total	n	5,886	4,663	6,007	3,695	**20,251**
	%	29.1	23.0	29.7	18.3	**100**
Male sex	n	4,469	3,809	5,215	3,158	**16,651**
	%	75.9	81.7	86.8	85.5	**82.2**
Age on 31 December 2019	Median	57.4	52.5	47.3	40.9	**51.5**
	Q1	51.5	45.4	38.7	32.0	**42.0**
	Q3	63.6	59.1	56.0	51.7	**59.3**
Transmission risk group						
No data	n	5	5	7	12	**29**
	%	0.1	0.1	0.1	0.3	**0.1**
Men who have sex with men	n	3,309	3,030	4,256	2,438	**13,033**
	%	56.2	65.0	70.9	66.0	**64.4**
Heterosexual contact	n	2,043	1,359	1,438	934	**5,774**
	%	34.7	29.1	23.9	25.3	**28.5**
Injecting drug use	n	170	54	19	16	**259**
	%	2.9	1.2	0.3	0.4	**1.3**
Blood or blood products	n	108	36	49	47	**240**
	%	1.8	0.8	0.8	1.3	**1.2**
Vertical transmission	n	1	3	2	4	**10**
	%	0.02	0.06	0.03	0.1	**0.05**
Other/unknown	n	250	176	236	244	**906**
	%	4.3	3.8	3.9	6.6	**4.5**
Region of origin						
No data	n	22	12	23	36	**93**
	%	0.4	0.3	0.4	1.0	**0.5**
The Netherlands	n	3,383	2,834	3,759	1,958	**11,934**
	%	57.5	60.8	62.6	53.0	**58.9**
Western Europe/North America/Australia	n	453	287	351	174	**1,265**
	%	7.7	6.2	5.8	4.7	**6.3**
Eastern/central Europe	n	101	136	288	313	**838**
	%	1.7	2.9	4.8	8.5	**4.1**
Latin America and the Caribbean	n	639	541	708	563	**2,451**
	%	10.9	11.6	11.8	15.2	**12.1**
Sub-Saharan Africa	n	956	575	503	348	**2,382**
	%	16.2	12.3	8.4	9.4	**11.8**
Other	n	332	278	375	303	**1,288**
	%	5.6	6.0	6.2	8.2	**6.4**

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	All
cART regimen						
TDF/FTC/EFV	n	404	551	375	42	**1,372**
	%	6.9	11.8	6.2	1.1	**6.8**
TDF/FTC/NVP	n	515	303	189	9	**1,016**
	%	8.8	6.5	3.2	0.2	**5.0**
TDF/FTC/RPV	n	132	124	325	29	**610**
	%	2.2	2.7	5.4	0.8	**3.0**
TDF/3TC/DOR	n	157	200	239	172	**768**
	%	2.7	4.3	4.0	4.7	**3.8**
TDF/FTC/DRV/b	n	123	131	166	53	**473**
	%	2.1	2.8	2.8	1.4	**2.3**
TDF/FTC/ATV/b	n	68	69	55	11	**203**
	%	1.2	1.5	0.9	0.3	**1.0**
TDF/FTC/LPV	n	8	9	1	1	**19**
	%	0.1	0.2	0.02	0.03	**0.1**
TDF/FTC/EVG/c	n	89	98	304	92	**583**
	%	1.5	2.1	5.1	2.5	**2.9**
TDF/FTC/DTG	n	125	92	193	331	**741**
	%	2.1	2.0	3.2	9.0	**3.7**
TDF/FTC/RAL	n	44	47	57	29	**177**
	%	0.8	1.0	1.0	0.8	**0.9**
ABC/3TC/DTG	n	499	500	883	684	**2,566**
	%	8.5	10.7	14.7	18.5	**12.7**
TAF/FTC/RPV	n	211	225	420	90	**946**
	%	3.6	4.8	7.0	2.4	**4.7**
TAF/FTC/DRV/c	n	338	287	356	216	**1,197**
	%	5.7	6.2	5.9	5.9	**5.9**
TAF/FTC/EVG/c	n	475	526	919	561	**2,481**
	%	8.1	11.3	15.3	15.2	**12.3**
TAF/FTC/DTG	n	118	115	145	147	**525**
	%	2.0	2.5	2.4	4.0	**2.6**
TAF/FTC/BIC	n	523	465	621	873	**2,482**
	%	8.9	10.0	10.3	23.6	**12.3**
TAF/FTC/NVP	n	378	223	94	4	**699**
	%	6.4	4.8	1.6	0.1	**3.5**
ABC/3TC/NVP	n	231	73	48	1	**353**
	%	3.9	1.6	0.8	0.03	**1.7**

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	All
DTG/3TC	n	198	194	275	222	**889**
	%	3.4	4.2	4.6	6.0	**4.4**
DTG/RPV	n	60	19	20	4	**103**
	%	1.0	0.4	0.3	0.1	**0.5**
CAB/RPV*	n	3	2	2	9	**16**
	%	0.05	0.04	0.03	0.2	**0.1**
2DR:NNRTI+INST	n	6	.	2	.	**8**
	%	0.1	.	0.03	.	**0.04**
2DR:PI+INSTI	n	2	1	1	1	**5**
	%	0.03	0.02	0.02	0.03	**0.02**
2DR:NRTI+INSTI	n	180	85	40	11	**316**
	%	3.1	1.8	0.7	0.3	**1.6**
Other:2NRTI+NNRTI	n	143	103	75	8	**329**
	%	2.4	2.2	1.3	0.2	**1.6**
Other:2NRTI+PI	n	94	63	61	23	**241**
	%	1.6	1.4	1.0	0.6	**1.2**
Other:2NRTI+INST	n	94	63	61	23	**241**
	%	1.6	1.4	1.0	0.6	**1.2**
Other:2DR	n	52	14	15	4	**85**
	%	0.9	0.3	0.3	0.1	**0.4**
Other:NRTI+PI+INSTI(3ARVs)	n	57	5	5	4	**71**
	%	1.0	0.1	0.1	0.1	**0.4**
Other:NRTI+PI+INSTI(4ARVs)	n	141	32	24	22	**219**
	%	2.4	0.7	0.4	0.6	**1.1**
Other	n	270	48	45	17	**380**
	%	4.6	1.0	0.8	0.5	**1.9**
CD4:CD8 ratio						
No data	n	742	575	847	553	**2,717**
	%	12.6	12.3	14.1	15.0	**13.4**
<0.50	n	915	607	691	887	**3,100**
	%	15.6	13.0	11.5	24.0	**15.3**
≥0.50 <1.00	n	2,542	2,147	2,632	1,365	**8,686**
	%	43.2	46.0	43.8	36.9	**42.9**
≥1.00	n	1,687	1,334	1,837	890	**5,748**

Year of cART initiation		1996–2005	2006–2010	2011–2015	2016–2020	All
	%	28.7	28.6	30.6	24.1	**28.4**
CD4 count (cells/mm³)						
No data	n	18	12	18	26	**74**
	%	0.3	0.3	0.3	0.7	**0.4**
<50	n	10	7	4	21	**42**
	%	0.2	0.2	0.1	0.6	**0.2**
50–199	n	101	52	60	152	**365**
	%	1.7	1.1	1.0	4.1	**1.8**
200–349	n	377	243	278	370	**1,268**
	%	6.4	5.2	4.6	10.0	**6.3**
350–499	n	888	676	732	577	**2,873**
	%	15.1	14.5	12.2	15.6	**14.2**
500–749	n	2,047	1,703	1,969	1,080	**6,799**
	%	34.8	36.5	32.8	29.2	**33.6**
≥750	n	2,445	1,970	2,946	1,469	**8,830**
	%	41.5	42.3	49.0	39.8	**43.6**
Viral load <50 copies/ml						
No data	n	25	31	66	460	**582**
	%	0.4	0.7	1.1	12.5	**2.9**
Yes	n	5,203	4,121	5,277	2,677	**17,278**
	%	88.4	88.4	87.9	72.5	**85.3**
No	n	658	511	664	558	**2,391**
	%	11.2	11.0	11.1	15.1	**11.8**
Viral load <200 copies/ml						
No data	n	25	31	66	460	**582**
	%	0.4	0.7	1.1	12.5	**2.9**
Yes	n	5,749	4,556	5,840	3,055	**19,200**
	%	97.7	97.7	97.2	82.7	**94.8**
No	n	112	76	101	180	**469**
	%	1.9	1.6	1.7	4.9	**2.3**

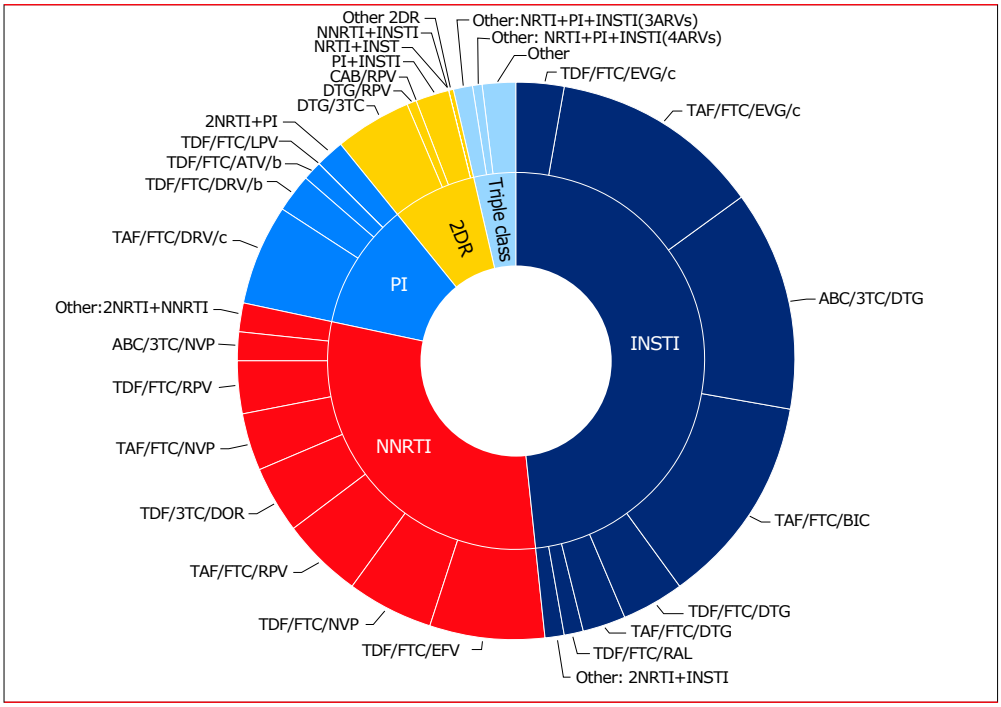
** All patients using this combination were participating in a clinical trial.*

Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; ARVs=antiretroviral drugs; BIC=bictegravir; cART=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.*

Among the 20,251 people in HIV care and on cART in 2020, the vast majority (89.4%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either an integrase inhibitor (INSTI) (48.4%), a non-nucleoside reverse transcriptase inhibitor (NNRTI) (30.0%), or a protease inhibitor (PI) (10.9%). The distribution of cART use among the population in care in 2020 is presented in *Figure 2.2A*. The most frequently used regimens (used by at least 5% of the population) were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (12.7%), tenofovir alafenamide (TAF)/FTC/bictegravir (BIC) (12.3%), tenofovir alafenamide (TAF)/FTC/elvitegravir (EVG)/cobicistat (12.3%), tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz (EFV) (6.8%), tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (5.9%), and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/nevirapine (NVP) (5.0%). The proportion of the population in care in 2020 using TDF declined over time (from 46.4% in 2017, to 35.3% in 2018, 31.9% in 2019, and 30.8% in 2020), while the proportion using TAF continued to increase (from 24.4% of the population in care in 2017, to 33.2% in 2018, 42.1% in 2019, and 43.7% in 2020). Zidovudine was still used by 128 individuals (0.6%, mostly in combination with lamivudine). In total, 650 (3.2%) and 1,099 (5.4%) individuals used a cART regimen without any NRTI or with just a single NRTI. There were 1,484 (7.3%) individuals who used a two-drug regimen (excluding pharmacological boosters): the most common two-drug regimens were a combination of NRTI+INSTI (894, 60.2%, of which 99.6% used lamivudine and 99.8% dolutegravir); PI+INSTI (378, 25.5%, of which 98.4% used darunavir plus either dolutegravir (87.8%), or raltegravir (12.2%)); NNRTI+INSTI (127, 8.6%, of which 93.7% used rilpivirine, 86.6% used dolutegravir, and 12.6% used cabotegravir); NNRTI+PI (16, 1.1%).

Of those with a plasma HIV RNA measurement in 2020, 87.8% had a viral load below 50 copies/ml, and 97.6% had a viral load below 200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-20, 77.5% had a CD4 cell count of 500 cells/mm^3 or higher, and 32.8% had a CD4:CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (cART) use in 2020.



Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; ARVs=antiretroviral drugs; BIC=bictegravir; cART=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 the initial cART 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 2013–2020.

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

Legend: *3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DTG=dolutegravir; DRV=darunavir; EVG=elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.*

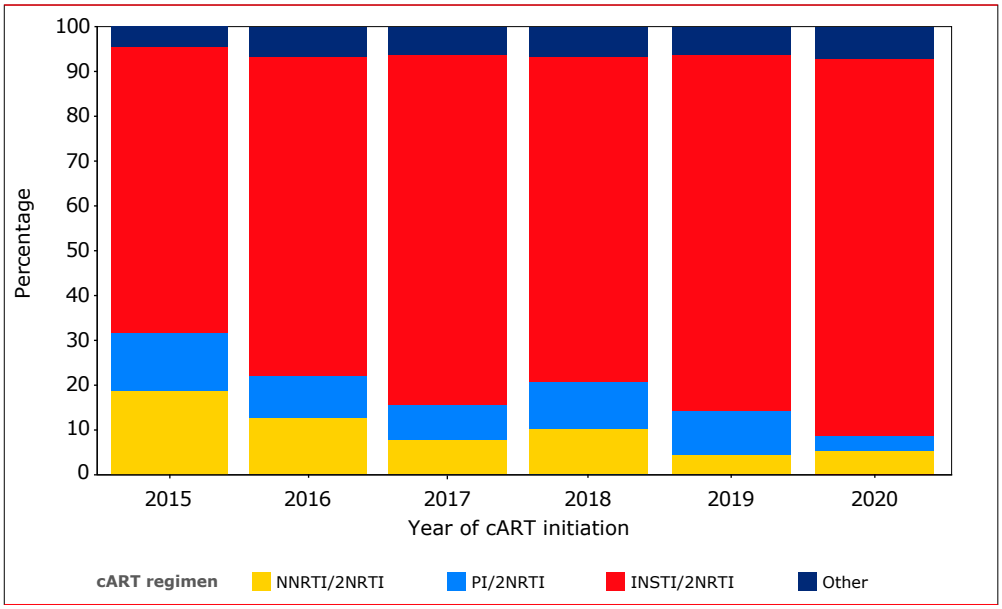
Source: *Medicines Evaluation Board http://english.cbg-meb.nl/ and European Medicines Agency http://www.ema.europa.eu/*

Initial cART regimen

Of the 26,806 people known to have initiated cART between 1996 and 2020, 5,389 (20.1%) started cART between January 2015 and December 2020. *Figures 2.3* and *2.4* show the trends over time in third-drug additions to the NRTI backbone used as part of their initial cART regimen. The use of integrase inhibitors in combination with an NRTI backbone as initial therapy, continued to rise from 63.8% in 2015, to 71.0% in 2016, 78.0% in 2017, 72.1% in 2018, 79.0% in 2019, and 83.7% in 2020 (89.4% including other INSTI-containing regimens). EVG/c was used in 17.2%, 25.2%, 30.5% and 24.1% of the initial regimens in 2015, 2016, 2017, and 2018, respectively, before its use dropped sharply to 3.2% in 2019 and 1.6% in 2020. Dolutegravir was used in 49.4%, 51.4%, 51.5%, 44.3%, 33.7%, and 42.7% of the initial regimens in 2015, 2016, 2017, 2018, 2019, and 2020, respectively. Bictegravir was introduced in the Netherlands in 2018 and was used in 7.1%, 46.4%, and 45.9% of the initial regimens in 2018, 2019, and 2020, respectively. The use of NNRTIs in the initial regimen

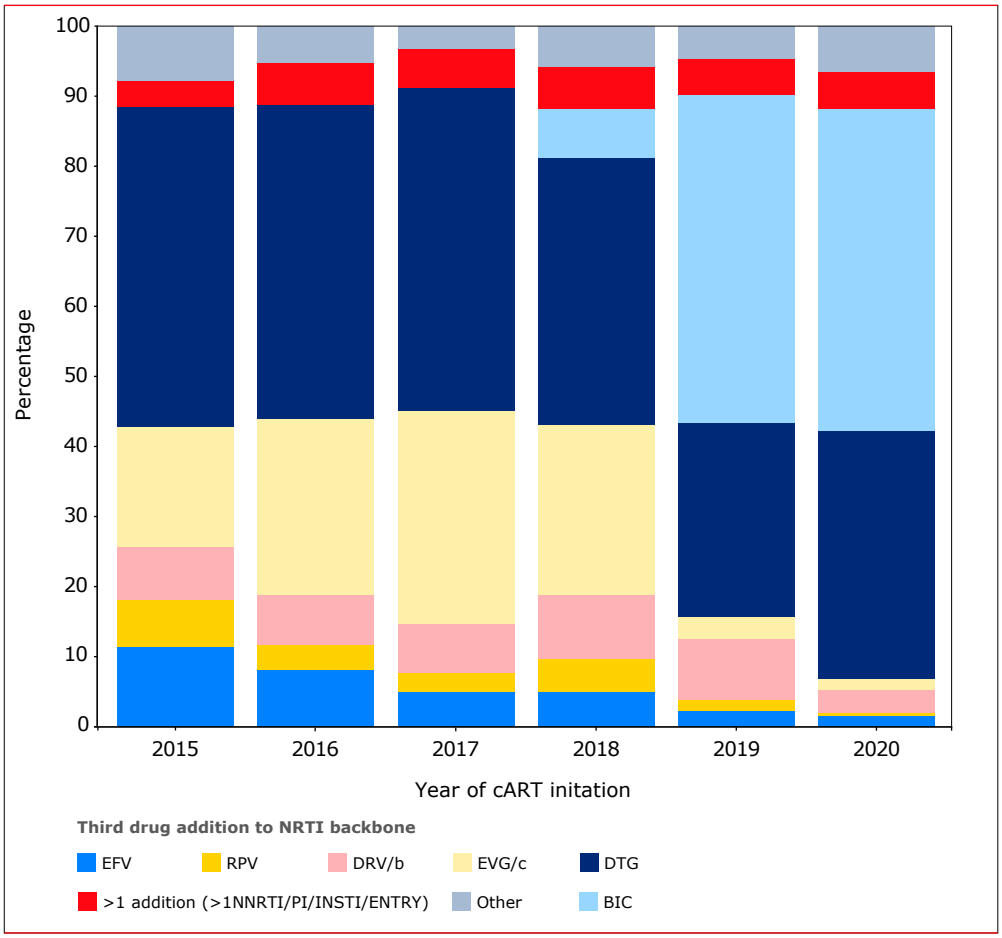
decreased from 18.9% in 2015 to 12.9% in 2016, 7.9% in 2017, 10.4% in 2018, 4.6% in 2019, and 5.5% in 2020. The use of PIs in the initial regimen decreased from 12.9% in 2015 to 9.2% in 2016, 7.8% in 2017, 10.5% in 2018, 9.9% in 2019, and 3.4% in 2020. In 2015-20, 4.9% of individuals received more than one third-drug addition to the NRTI backbone in their initial cART regimen, the majority of whom were people initiating cART 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 2015-20. The use of nevirapine, atazanavir, lopinavir, raltegravir, and doravirine as third-drug additions to initial regimens did not exceed 5% in any year in the period 2015-20. 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 2015-2020.*



Legend: *cART=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 2015-2020.

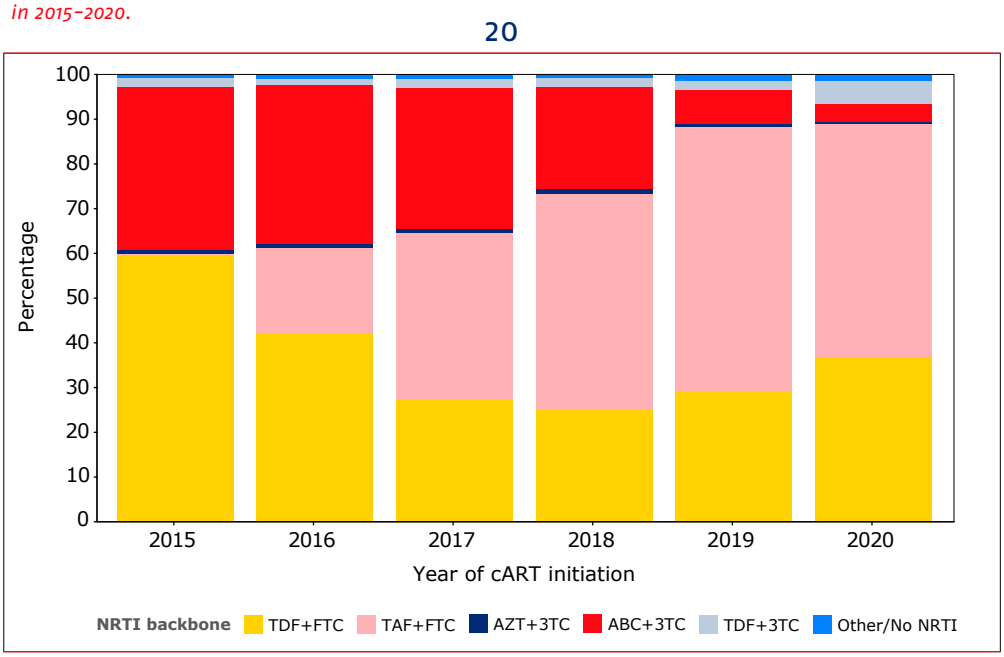


Legend: cART=combination antiretroviral therapy; b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside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

Figure 2.5 provides an overview of the NRTI backbone components of the initial cART regimens used in 2015-20. 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 19.0%, 37.6%, 48.3%, 59.4%,

and 52.0% of the initial regimens in 2016, 2017, 2018, 2019, and 2020, respectively. At the same time, TDF use decreased from 61.2% in 2015 to 27.0% in 2018, and then increased to 31.4% in 2019 and 41.7% in 2020, probably because of a sharp decrease in the use of abacavir-containing NRTI backbones in 2019 and 2020. The use of abacavir in combination with lamivudine decreased from 36.5% of all initial regimens in 2015 to 35.8% in 2016, 31.6% in 2017, and 22.9% in 2018, after which there was a sharp decrease to 7.7% in 2019 and 4.1% in 2020. The combination of zidovudine and lamivudine, which is still sometimes used by migrants who initiated cART before arriving in the Netherlands, has further decreased to less than 1% since 2016 (n=1 in 2020).

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2015–2020.*



Legend: *cART=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 cART regimens initiated in 2015-20 are presented in *Figure 2.6* and *Table 2.3*. In 2020, the most frequently used initial regimen was TAF/FTC/bictegravir (45.9%). Dolutegravir-containing initial regimens were used in 35.8% of cases: combined with either abacavir and lamivudine as part of the once-daily, fixed-dose

combination (1.2%), or provided with emtricitabine and tenofovir separately (TDF 29.1%/TAF 1.9%). Additionally, 4.1% 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 1.6%, 4.2%, and 0.7%, respectively, in 2020. *Table 2.3* provides more detail on the 'other' initial regimens that are not further specified in *Figures 2.4-2.6*.

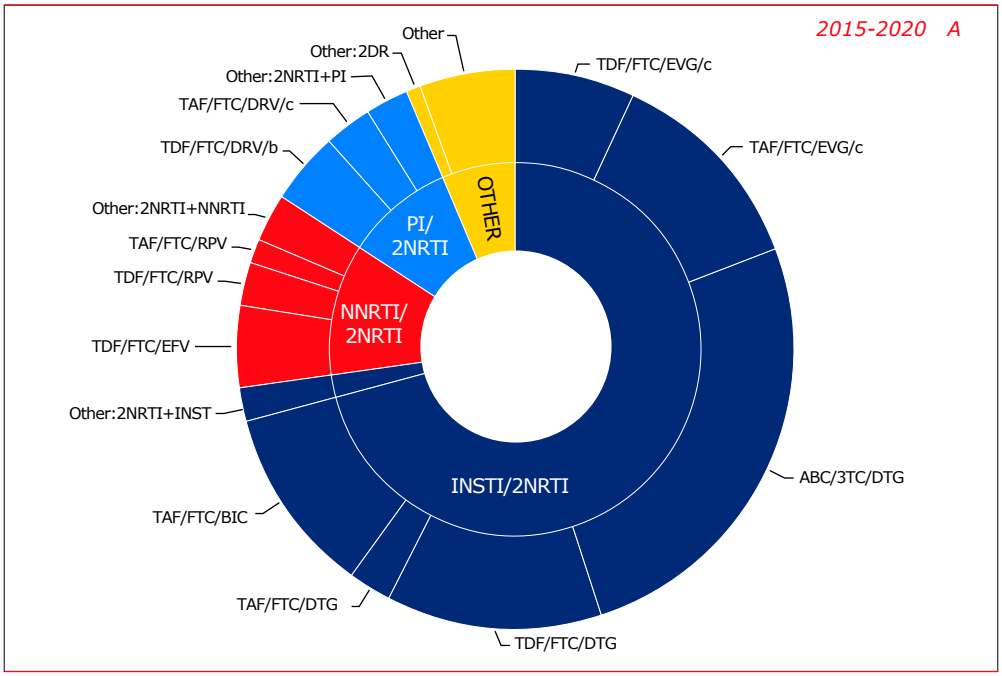
***Table 2.3:** Initial regimens in 2015–2020.*

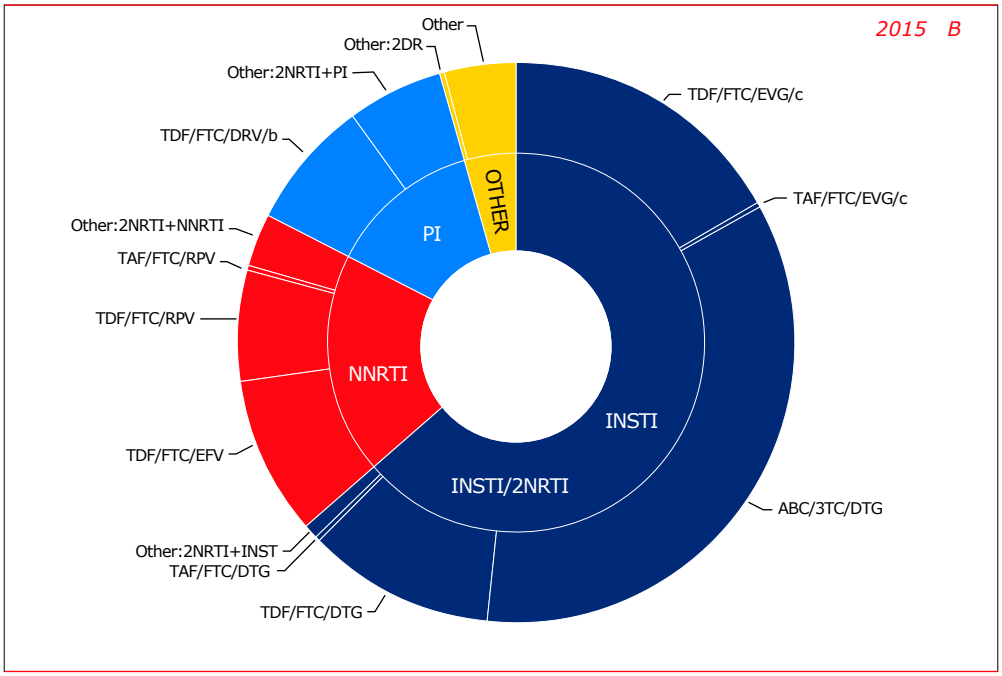
		2015	2016	2017	2018	2019	2020	2015–2020
n		1,292	1,119	998	855	689	436	5,389
Regimen								
TDF/FTC/EFV	n	117	75	29	30	12	4	267
	%	9.06	6.7	2.91	3.51	1.74	0.92	4.95
TDF/FTC/NVP	n	7	9	2	2	1	.	21
	%	0.54	0.8	0.2	0.23	0.15	.	0.39
TDF/FTC/RPV	n	85	34	8	3	3	.	133
	%	6.58	3.04	0.8	0.35	0.44	.	2.47
TDF/3TC/DOR	n	.	.	.	.	4	16	20
	%	.	.	.	.	0.58	3.67	0.37
TDF/FTC/DRV/b	n	94	69	36	13	16	6	234
	%	7.28	6.17	3.61	1.52	2.32	1.38	4.34
TDF/FTC/ATV/b	n	45	17	4	6	6	.	78
	%	3.48	1.52	0.4	0.7	0.87	.	1.45
TDF/FTC/LPV/r	n	8	2	1	.	.	.	11
	%	0.62	0.18	0.1	.	.	.	0.2
TDF/FTC/EVG/c	n	217	88	54	17	5	.	381
	%	16.8	7.86	5.41	1.99	0.73	.	7.07
TDF/FTC/DTG	n	143	105	90	85	122	127	672
	%	11.07	9.38	9.02	9.94	17.71	29.13	12.47
TDF/FTC/RAL	n	10	8	6	13	8	3	48
	%	0.77	0.71	0.6	1.52	1.16	0.69	0.89
ABC/3TC/DTG	n	446	386	305	186	48	18	1,389
	%	34.52	34.5	30.56	21.75	6.97	4.13	25.77
ABC/3TC/NVP	n	1	1	1	.	.	.	3
	%	0.08	0.09	0.1	.	.	.	0.06
TAF/FTC/RPV	n	1	6	18	38	6	2	71
	%	0.08	0.54	1.8	4.44	0.87	0.46	1.32
TAF/FTC/DRV/c	n	.	1	31	62	43	8	145
	%	.	0.09	3.11	7.25	6.24	1.83	2.69

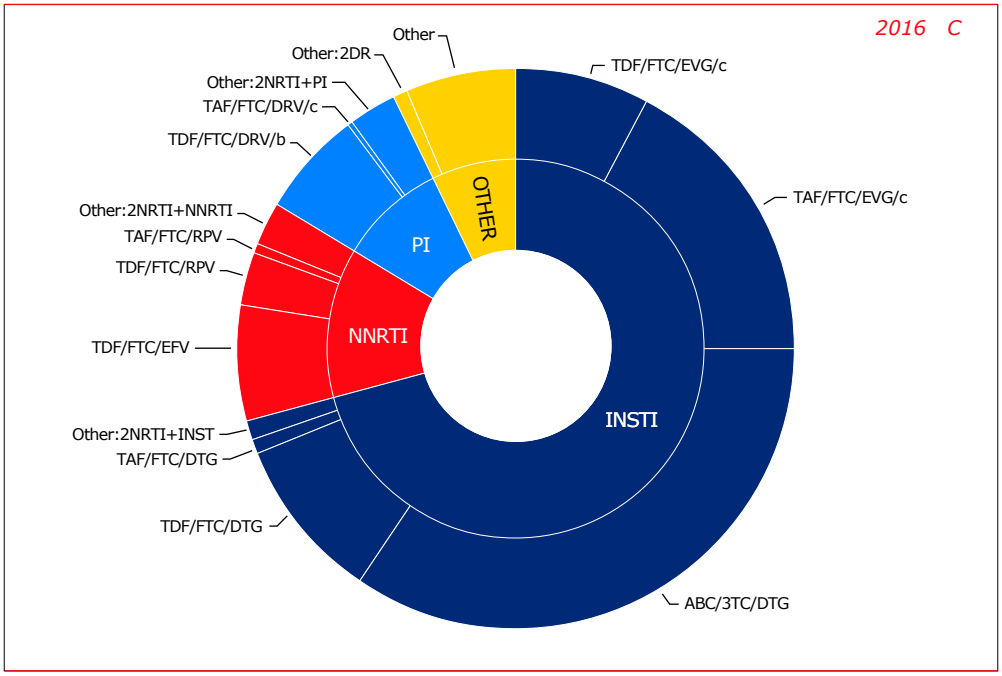
		2015	2016	2017	2018	2019	2020	2015–2020
n		1,292	1,119	998	855	689	436	5,389
Regimen								
TAF/FTC/EVG/c	n	5	194	250	189	17	7	662
	%	0.39	17.34	25.05	22.11	2.47	1.61	12.28
TAF/FTC/DTG	n	1	9	56	47	14	5	132
	%	0.08	0.8	5.61	5.5	2.03	1.15	2.45
TAF/FTC/BIC	n	.	.	2	61	320	200	583
	%	.	.	0.2	7.13	46.44	45.87	10.82
DTG/3TC	n	.	1	1	2	3	6	13
	%	.	0.09	0.1	0.23	0.44	1.38	0.24
DTG/RPV	n	.	.	.	.	1	.	1
	%	.	.	.	.	0.15	.	0.02
2DR: PI+INSTI	n	5	8	7	4	2	2	28
	%	0.39	0.71	0.7	0.47	0.29	0.46	0.52
Other: 2NRTI+NNRTI	n	34	19	21	16	7	2	99
	%	2.63	1.7	2.1	1.87	1.02	0.46	1.84
Other: 2NRTI+PI	n	19	14	7	9	3	1	53
	%	1.47	1.25	0.7	1.05	0.44	0.23	0.98
Other: 2NRTI+INST	n	2	4	15	19	10	5	55
	%	0.15	0.36	1.5	2.22	1.45	1.15	1.02
Other: NRTI+PI+INSTI (3ARVs)	n	2	1	1	1	1	.	6
	%	0.15	0.09	0.1	0.12	0.15	.	0.11
Other: NRTI+PI+INSTI (4ARVs)	n	42	57	52	49	33	23	256
	%	3.25	5.09	5.21	5.73	4.79	5.28	4.75
Other	n	8	11	1	3	4	1	28
	%	0.62	0.98	0.1	0.35	0.58	0.23	0.52

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 2015–2020 A) in total and B) by year.






2016 C
Other
Other:2DR
Other:2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
Other:2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
Other:2NRTI+INST
TAF/FTC/DTG
TDF/FTC/DTG
TDF/FTC/EVG/c
TAF/FTC/EVG/c
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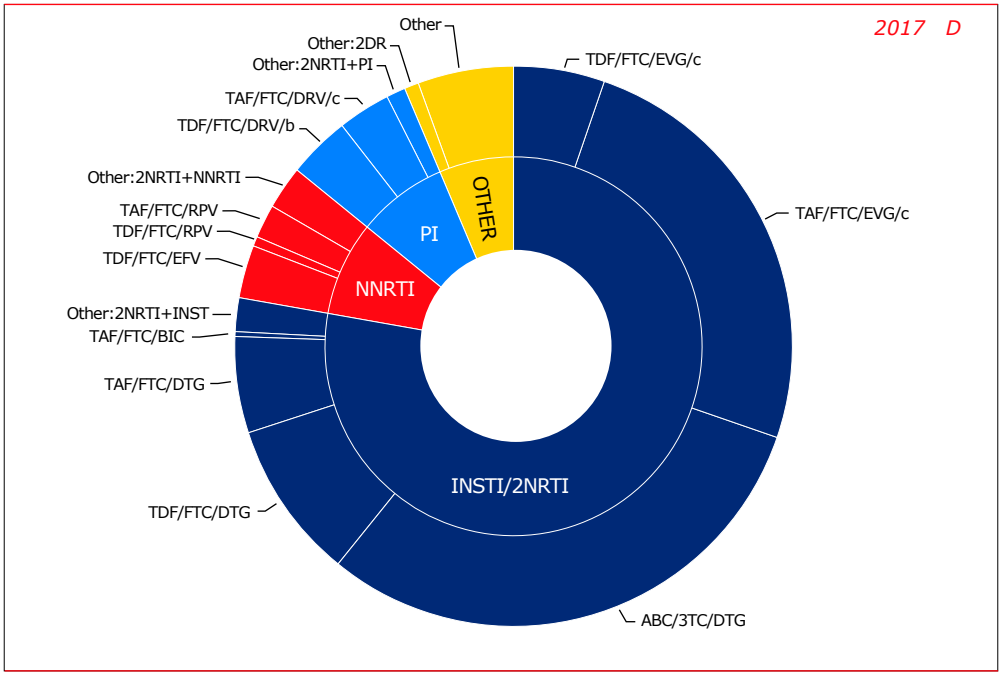
2017 D
Other
Other:2DR
Other:2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
Other:2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
Other:2NRTI+INST
TAF/FTC/BIC
TAF/FTC/DTG
TDF/FTC/DTG
TDF/FTC/EVG/c
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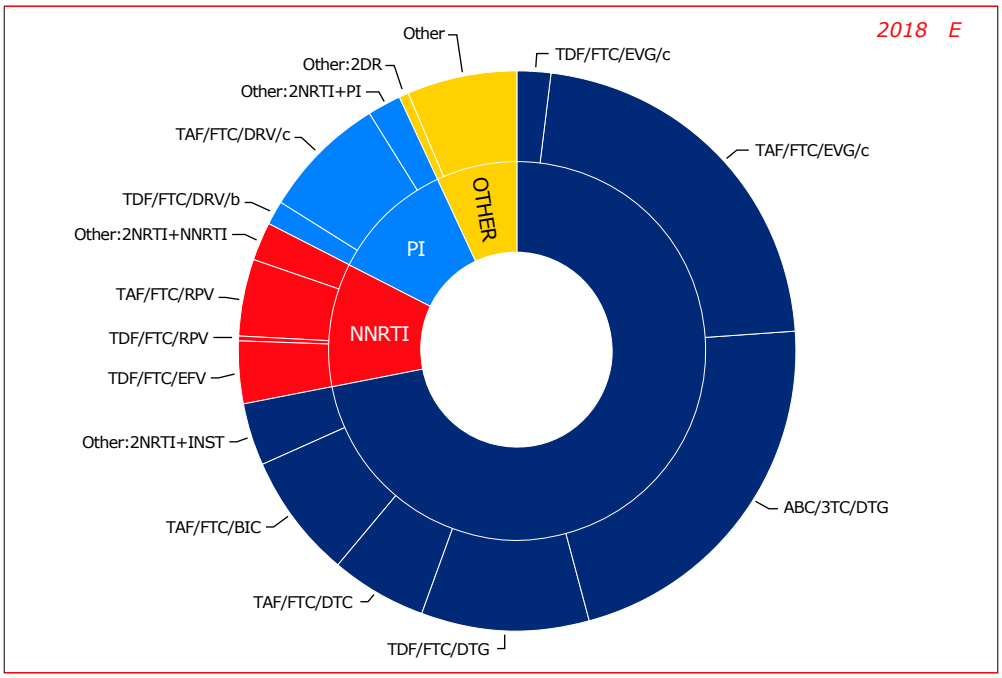
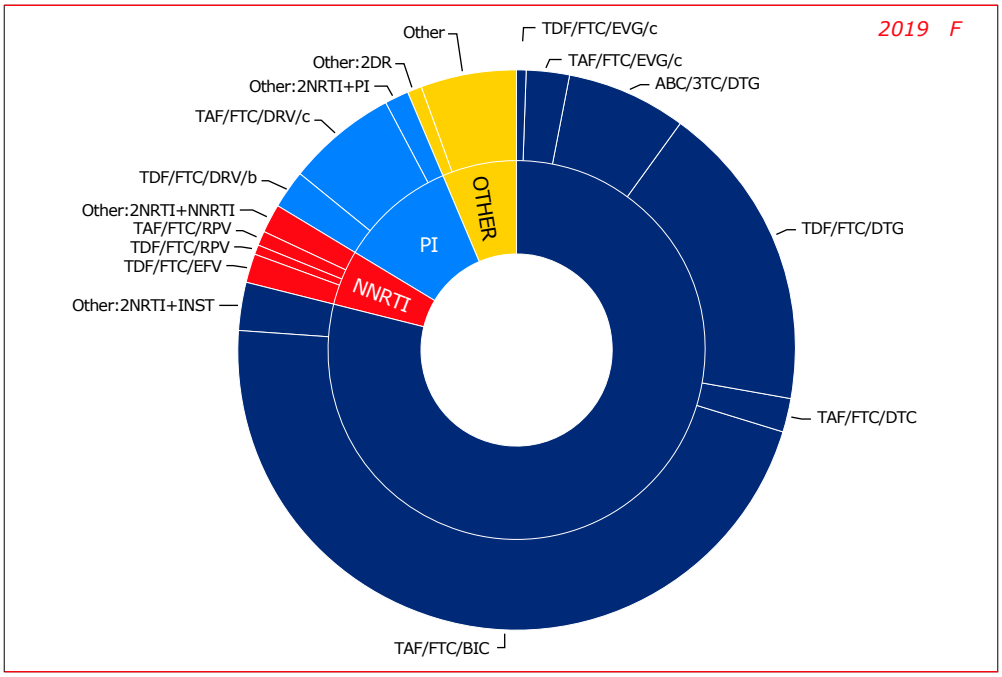

2018 E
Other
Other:2DR
Other:2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
Other:2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
Other:2NRTI+INST
TAF/FTC/BIC
TAF/FTC/DTC
TDF/FTC/DTG
TDF/FTC/EVG/c
TAF/FTC/EVG/c
ABC/3TC/DTG
OTHER
PI
NNRTI


2019 F
Other
Other:2DR
Other:2NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
Other:2NRTI+NNRTI
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
Other:2NRTI+INST
TAF/FTC/BIC
TDF/FTC/EVG/c
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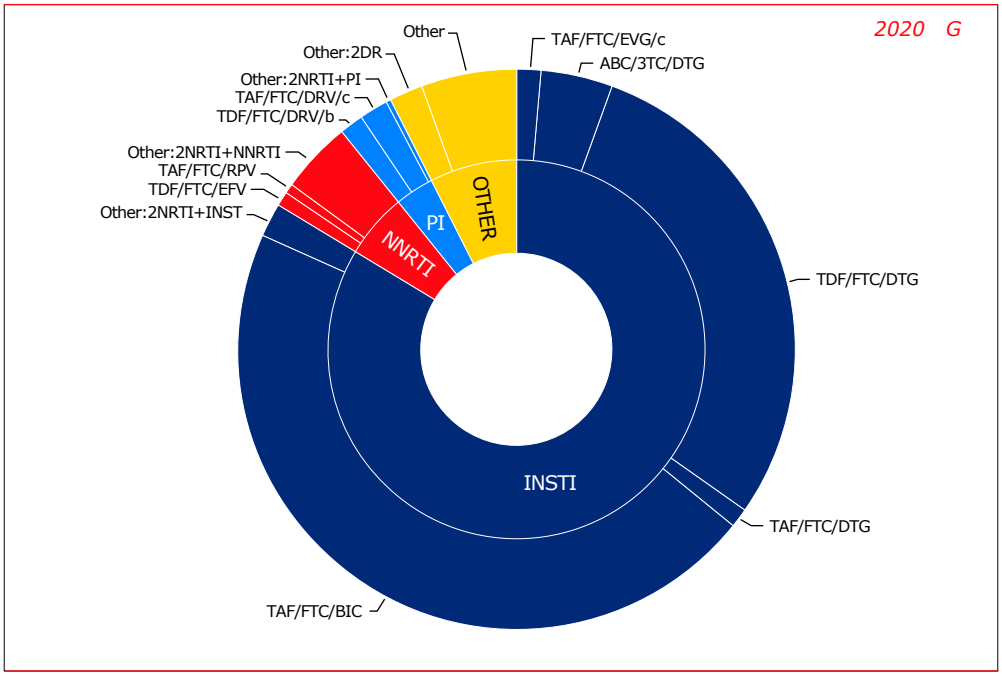
PI
NNRTI



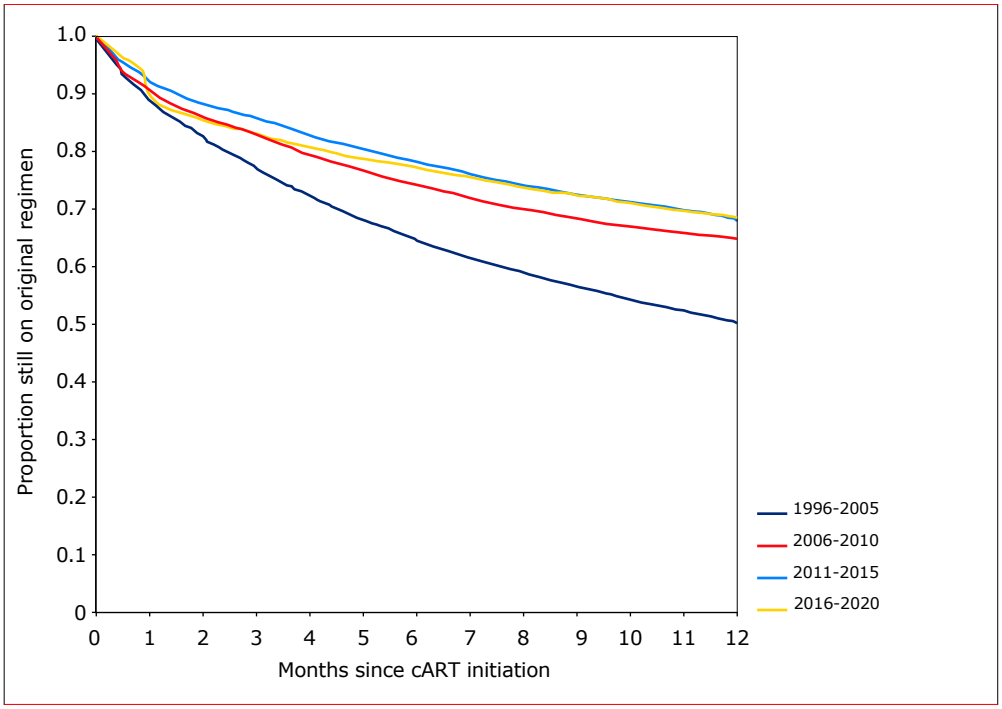
Legend: *3TC=lamivudine; ABC=abacavir; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor;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

Discontinuation of the initial cART regimen

For the 26,806 people who started cART between 1996 and 2020, we assessed the time spent on that initial cART 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 1996-2020, 38.9% 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 35.1% in 2006-10, 32.0% in 2011-15, and 30.6% in 2016-20. *Figure 2.7* shows the time to the first modification of the initial regimen during the first year of cART, 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).*



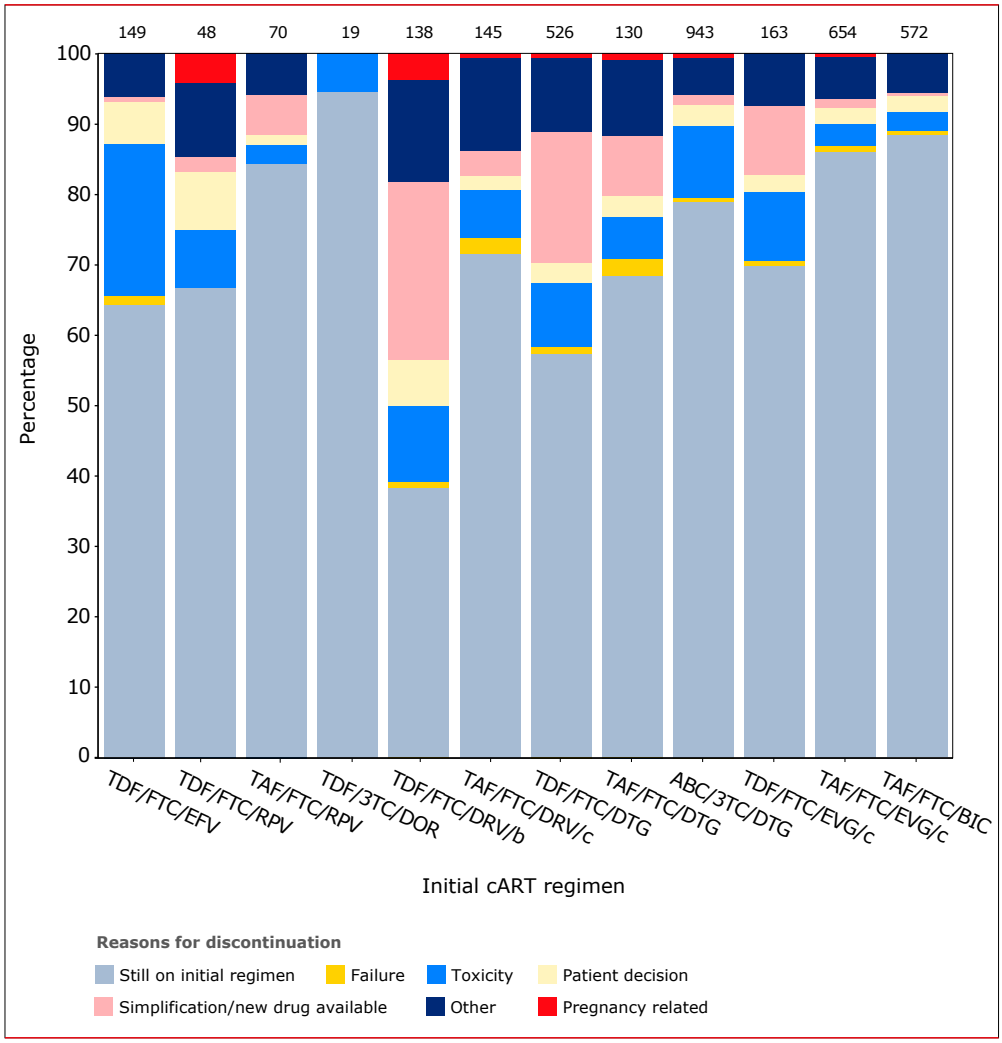
Legend: *cART=combination antiretroviral therapy.*

Discontinuation of the initial cART regimen: 2016–2020

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 3,557 people who started 'common' and guideline-recommended initial regimens in 2016-20. The regimens considered in this analysis were: tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (TDF/FTC/EFV, 4.2%); rilpivirine (TDF/FTC/RPV, 1.4%); ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b, 3.9%); cobicistat-boosted elvitegravir (TDF/FTC/EVG/c, 4.6%); dolutegravir (TDF/FTC/DTG, 14.8%); tenofovir disoproxil fumarate/lamivudine combined with doravirine (TDF/3TC/DOR, 0.5%); abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG, 26.5%); tenofovir alafenamide/emtricitabine combined with cobicistat-boosted elvitegravir (TAF/FTC/EVG/c, 18.4%); rilpivirine (TAF/FTC/RPV, 2.0%); dolutegravir (TAF/FTC/DTG, 3.7%); cobicistat-boosted darunavir (TAF/FTC/DRV/c, 4.1%); and bictegravir (TAF/FTC/BIC, 16.1%).

One year after cART initiation, 874 (24.6%) of the 3,557 individuals using one of these initial regimens, had discontinued it. The main reason for this discontinuation was toxicity (267, 30.6%), followed by simplification and/or availability of new drugs (192, 22.0%). 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*). In total, 23.4% of all discontinuations were for reasons of simplification and/or availability of new drugs in 2016, 20.0% in 2017, 18.6% in 2018, 23.5% in 2019, and 28.4% in 2020. The nature and severity of toxicities leading to discontinuation have changed considerably over the decades. 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, (typically a single tablet 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 2016–2020, by regimen. Numbers above the bars represent the total number of individuals using that particular regimen.

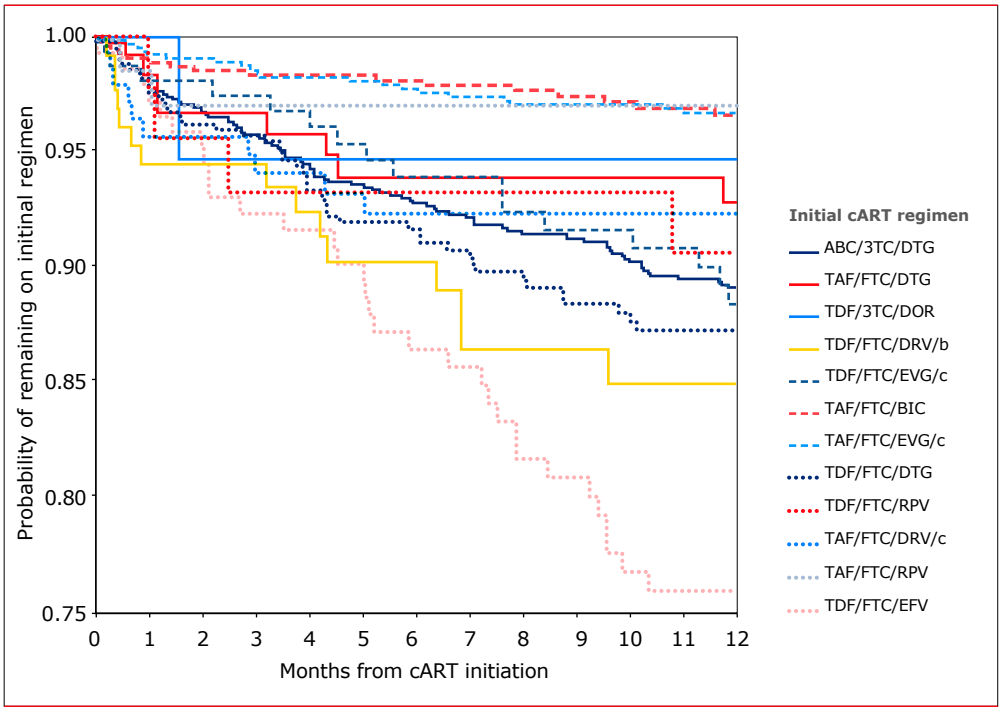


Legend: cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DOR=doravirine; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide;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

Discontinuation of the initial cART 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 2016-2020, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).*



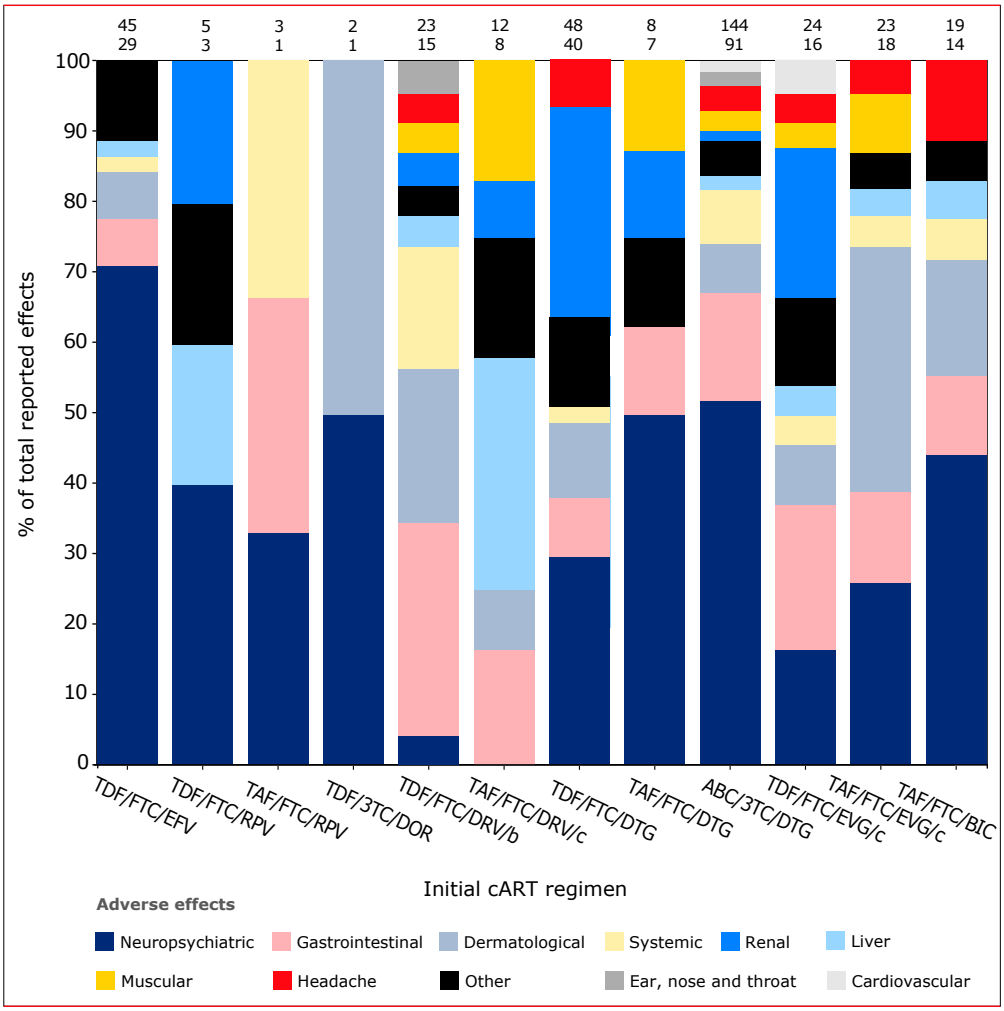
Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir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

Adverse effects

Among the 267 individuals who discontinued their initial cART regimen within a year due to toxicity, 356 adverse effects were recorded. The predominant effects were: 41.6% neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression), 14.0% gastrointestinal (mainly diarrhoea and nausea), 10.7% dermatological (rash due to medication, itching), 7.0% renal (renal insufficiency and increased serum creatinine), and 5.9% systemic (tiredness, apathy, and loss of appetite). These adverse effects are stratified by cART 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 TDF-based cART.

Figure 2.10: Adverse effects associated with initial regimen discontinuation due to toxicity, during the first year of treatment in 2016–2020. The bars represent the distribution of 356 reported effects among 267 people, 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).



Note: The discontinuation rates and reasons for discontinuation are descriptive by nature and should be interpreted with caution. The choice of the initial cART 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 cART regimens was fairly short, which also influences discontinuation rates.

Legend: *cART=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.*

Virological response

In the Netherlands, a total of 26,806 adults started cART between January 1996 and December 2020. For the analysis of virological outcomes in this section, we have focused on the 23,290 adults who were ART-naive and not pregnant at the time of cART initiation (because cART 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 cART initiation. Results are therefore restricted to the remaining 22,675 individuals. 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 (cART).
The viral load measurement closest to six months (plus or minus three months) after cART 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 cART 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 cART.
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 cART 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 22,675 individuals with a viral load test result within at least three months of cART initiation, 19,692 (86.8%) had a viral load measurement six months (plus or minus three months) after cART initiation. Of these people, 16,678 (84.7%) 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 68.2% in those starting cART between 1996 and 2004, to 87.9% in 2005-10, 92.3% in 2011-19, and 93.9% in those starting in 2020.

Initial virological success of common initial cART regimens (2013–2020)

We analysed initial virological success among the 5,454 adults who started a common or guideline-recommended cART regimen in 2013-20, who used it 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 cART initiation. In total, 94.1% (95% confidence interval [CI] 93.5-94.7) of individuals achieved initial virological suppression, after a mean of 179 (standard deviation [SD] 39) days. Overall, people receiving an integrase inhibitor or NNRTI-based regimen showed significantly higher rates of initial virological success: 94.1% (95% CI 92.7-95.4) of those on an integrase inhibitor-based regimen and 95.0% (95% CI 94.2-95.7) on a NNRTI-based regimen, compared to 89.6% (95% CI 87.2-91.9) on a protease inhibitor-based regimen.

Using logistic regression analysis, we further evaluated the initial virological success rates stratified by viral load at cART initiation (below, as well as equal to or above 100,000 copies/ml), cART regimen, and regimen class. Stratified analysis of initial virological success based on viral load at cART 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 cART 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 cART 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 cART initiation in 2013–2020.*

	Total		By initial viral load at cART initiation					
					<100,000 copies/ml			
	n	%	n	%	Initial viral success	95% CI low	95% CI high	p-value
cART regimen								
TDF/FTC/EFV	633	11.6	346	10.1	98.0	96.5	99.5	Ref.
TDF/FTC/RPV	463	8.5	463	13.5	95.2	93.3	97.2	0.045
TDF/FTC/DRV/b	545	10.0	225	6.6	95.6	92.9	98.2	0.10
TDF/FTC/EVG/c	765	14.0	528	15.4	97.3	96.0	98.7	0.55
TDF/FTC/DTG	564	10.3	290	8.5	97.2	95.4	99.1	0.54
ABC/3TC/DTG	1,223	22.4	820	24.0	97.0	95.8	98.1	0.33
TAF/FTC/RPV	52	1.0	52	1.5	100	100	100	0.99
TAF/FTC/DRV/c	116	2.1	51	1.5	100	100	100	0.99
TAF/FTC/EVG/c	551	10.1	340	9.9	97.4	95.6	99.1	0.59
TAF/FTC/DTG	98	1.8	48	1.4	95.8	90.2	100	0.36
TAF/FTC/BIC	444	8.1	256	7.5	97.7	95.8	99.5	0.78
Regimen class								
NNRTI/2NRTI	1,148	21.1	861	25.2	96.6	95.4	97.8	Ref.
PI/2NRTI	661	12.1	276	8.1	96.4	94.2	98.6	0.84
INSTI/2NRTI	3,645	66.8	2,282	66.7	97.2	96.5	97.9	0.41
All regimens	**5,454**	**100**	**3,419**	**62.7**	**97.0**	**96.4**	**97.6**	

Legend: *b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; cART=combination antiretroviral therapy; 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.*

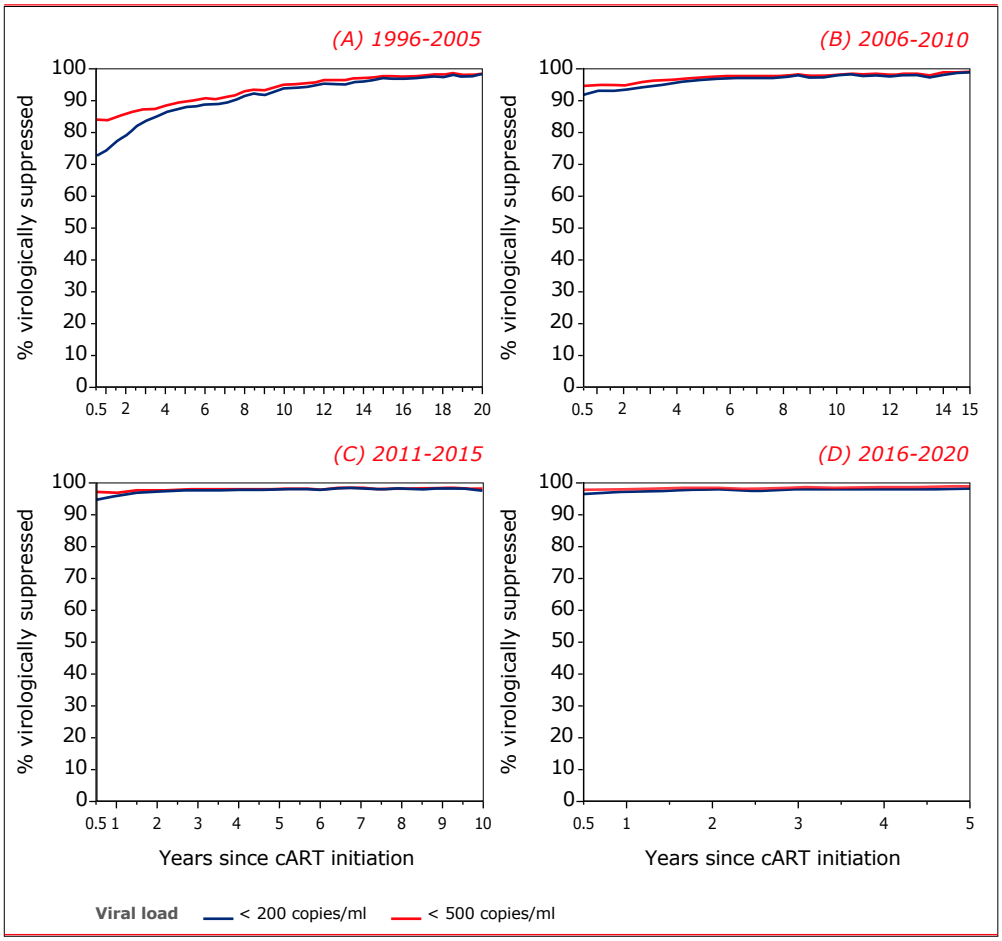
		By initial viral load at cART initiation					
		≥100,000 copies/ml					
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	cART regimen						
	TDF/FTC/EFV	287	14.1	86.4	82.4	90.4	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	320	15.7	85.0	81.1	88.9	0.62
	TDF/FTC/EVG/c	237	11.7	89.9	86.0	93.7	0.23
	TDF/FTC/DTG	274	13.5	90.1	86.6	93.7	0.17
	ABC/3TC/DTG	403	19.8	92.1	89.4	94.7	0.017
	TAF/FTC/RPV	not recommended					
	TAF/FTC/DRV/c	65	3.2	83.1	74.0	92.2	0.49
	TAF/FTC/EVG/c	211	10.4	91.5	87.7	95.2	0.082
	TAF/FTC/DTG	50	2.5	92.0	84.5	99.5	0.28
	TAF/FTC/BIC	188	9.2	92.0	88.1	95.9	0.062
	Regimen class						
	NNRTI/2NRTI	287	14.1	86.4	82.4	90.4	Ref.
	PI/2NRTI	661	18.9	84.7	81.1	88.3	0.53
	INSTI/2NRTI	3,645	67.0	91.2	89.7	92.7	0.013
	All regimens	**2,035**	**37.3**	**89.3**	**87.9**	**90.7**	

Viral suppression

We assessed long-term viral suppression rates (i.e., viral load below 200 copies/ml), during six-month intervals among adults on cART with a viral load test result after cART initiation. The viral load measurement after at least three months of cART, 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 cART initiation: 1996-2005, 2006-10, 2011-15, and 2016-20. In line with the initial virological success rates, the long-term viral suppression rates improved over time. In people initiating cART in, or after 2015, suppression rates ranged from 97.4% (95% CI 96.8-97.9) after one year of cART use, to 98.3% (95% CI 97.4-99.1) after four years.

Figure 2.11: *Viral suppression following combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation; A) 1996-2005, B) 2006-2010, C) 2011-2015, and D 2016-2020.*



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

Legend: *cART=combination antiretroviral therapy.*

HIV drug resistance

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

HIV drug resistance

Transmitted HIV drug resistance
At least one major resistance-associated mutation detected among individuals who had never received antiretroviral drugs and had not started cART.
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 cART 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].

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 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 in separate sections. Of note, SHM does not receive drug resistance data from all HIV treatment centres and laboratories; therefore, presented figures might not be representative of the full population in HIV care.

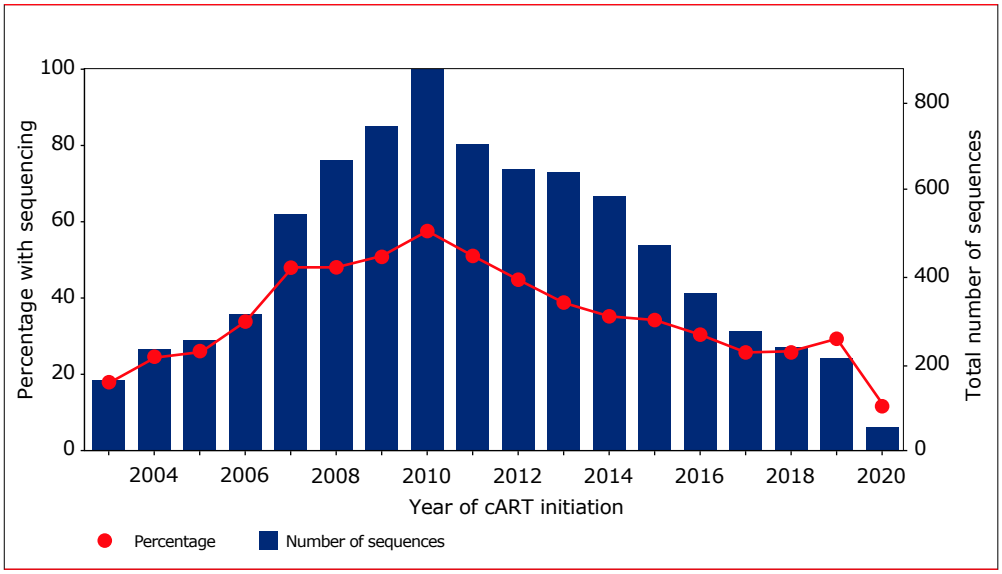
We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2019 International Antiviral Society-USA (IAS-USA) HIV drug resistance mutation list was used to score major resistance-associated mutations[25]. Furthermore, we assessed the association between these mutations and the susceptibility to antiretroviral drugs. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.9-1) 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, the 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)-naive before initiating cART.

In total, 8,158 HIV-1 sequences were obtained between 2003 and 2020 from 7,863 ARV-naive people before they initiated cART. The number of sequences and the percentage of ARV-naive people with sequencing before cART initiation peaked in 2010 and have steadily declined since then (*Figure 2.12*). The decline in the number of sequences in 2020 is likely due to a backlog in relaying sequence data to the SHM; it is too early to determine whether the reduced capacity at virology departments across the Netherlands during the COVID-19 pandemic had any influence. If someone had more than one sequence available before cART 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 (67.7%), while (14.8%) were women. Most people with an available pre-treatment sequence originated from the Netherlands (60.0%), or sub-Saharan Africa (11.1%). The main HIV-1 subtype was B (75.3%), followed by non-B subtypes (24.7%), including recombinant form CRF_02AG (6.6%), subtype C (5.1%), and CRF_01AE (3.4%).

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

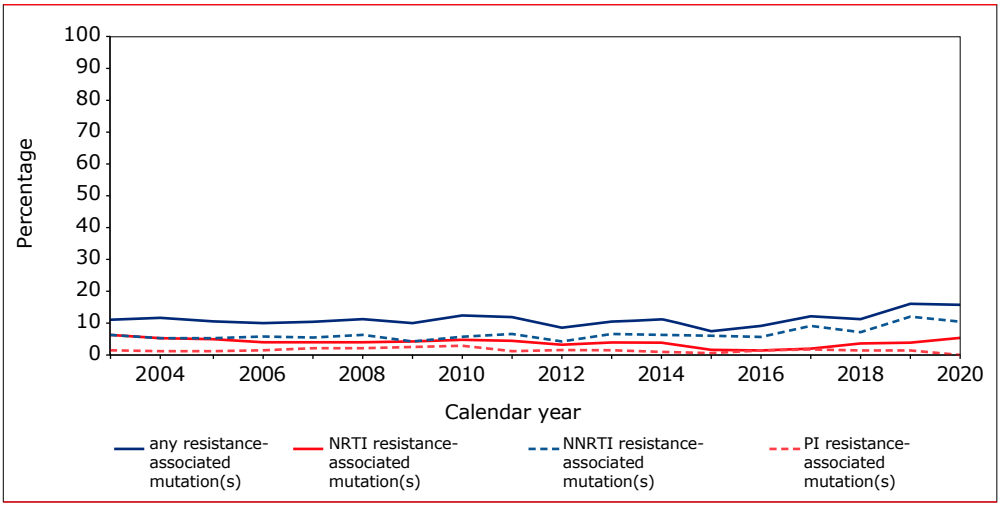


Legend: cART=combination antiretroviral therapy.

Transmitted HIV drug resistance

In total, at least one or more major resistance-associated mutation[25] was found in 859 (10.9%) of the people tested for resistance, including 321 (4.1%) with NRTI-associated resistance mutations, 474 (6.0%) with NNRTI-associated resistance mutations, and 140 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2020 (*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 cART. 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, 225 (2.9%) individuals screened for transmitted drug resistance harboured high-level resistance[26,27] to at least one antiretroviral drug; 41 (0.5%) to at least one NRTI, 166 (2.1%) to at least one NNRTI, and 34 (0.5%) to at least one PI. On the basis of the available resistance data, more than 97% were fully susceptible to all antiretroviral drugs; 2.5% (195) harboured high-level resistance in one drug class, 0.3% (22) in two drug classes, and less than 0.1% (five) 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, fully efficacious cART combinations can still often be constructed.

Integrase inhibitor resistance before HIV treatment initiation

Forty-two people had an integrase sequence available prior to cART initiation; all of them were ARV-naive. No major or minor integrase resistance-associated mutations were detected.

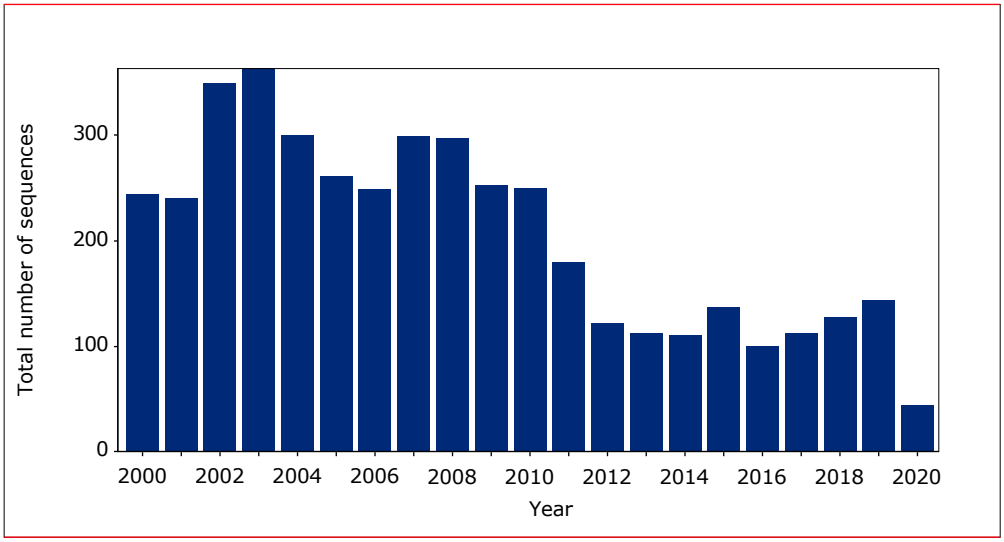
Acquired HIV drug resistance

The overall viral suppression rates of people receiving cART 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 cART.

In this section, we describe the level of acquired drug resistance detected among the treated population with both a viral load above 500 copies/ml, and resistance test results available after at least four months of cART in 2000-20. If cART had been interrupted more than two weeks before the test, the sequence was excluded from the analysis.

In total, 4,298 HIV-1 sequences were obtained from 2,596 people who received cART 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 continued to decline slightly until 2019 (*Figure 2.14*). There was a considerable decline in 2020. The median time between initial start of cART and resistance testing was 5.5 years (IQR 3.0-8.8). The main HIV-1 subtype was B (67.8%), followed by recombinant form CRF_02AG (10.9%), and subtype C (5.8%).

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



Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,339 (31.2%) sequences were obtained from 728 (28.0%) pre-treated people, and 2,959 (68.8%) sequences were obtained from 1,868 (72.0%) ARV-naive people. However, over time this difference became less distinct: in 2000, 73.0% of sequences were obtained from pre-treated people, compared with 36.4% in 2005, and less than 16% from 2010 onwards.

Of the 4,298 sequences obtained when the HIV RNA was above 500 copies/ml, 2,735 (63.6%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,750 (64.0%) sequences; of those, 2,368 (86.1%) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,721 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2020, 1,158 (67.3%) were still on cART containing lamivudine or emtricitabine, and 908/1,158 (78.4%) had undetectable HIV-RNA at their last visit. In addition, 1,640 (38.6%) harboured high-level resistance to at least one NNRTI, and 1,027 (24.9%) to at least one PI.

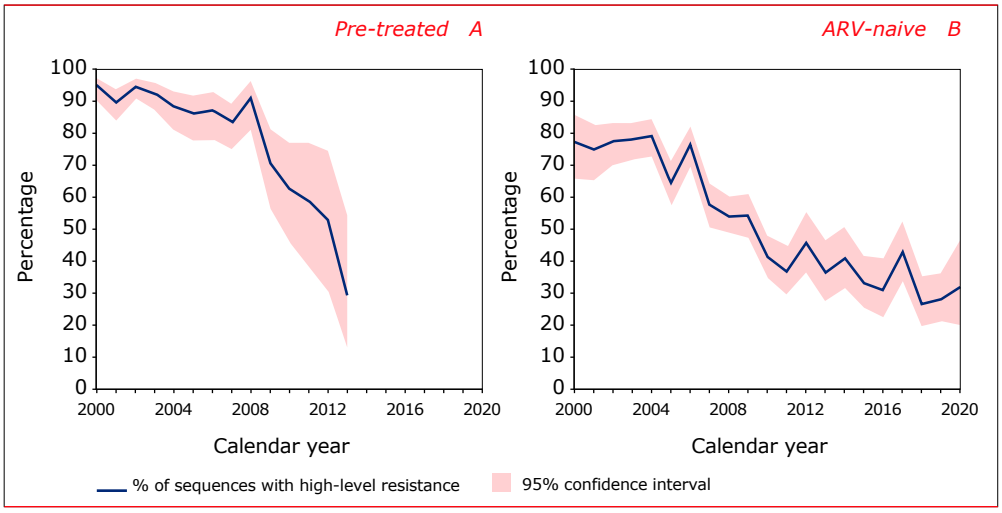
Previous antiretroviral drug exposure

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-naive before initiating cART.

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, 88.5% (95% CI 81.2-93.2) in 2004, 62.9% (95% CI 46.0-77.1) in 2010, and 29.4% (95% CI 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 (2014-20), 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-naive people, high-level resistance to at least one drug was detected among 77.3% (95% CI 65.7-85.8) of sequences in 2000, 76.5% (95% CI 69.5-82.2) in 2006, 45.7% (95% CI 36.4-55.3) in 2012, and 31.8% (95% CI 19.8-46.8) in 2020 (*Figure 2.15B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naive 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 (cART), 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-naive people. The shaded area represents the 95% confidence interval.



Note: The number of sequences from pre-treated people in 2014-2020 was too low to give meaningful percentages.

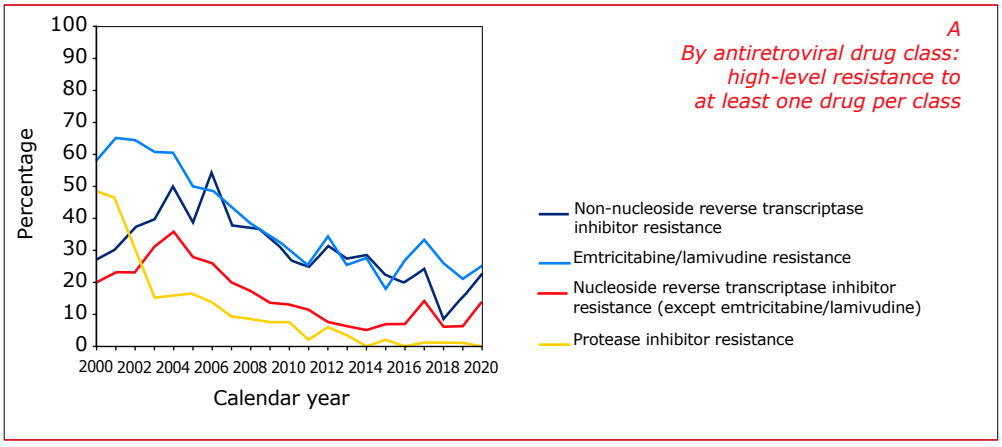
Acquired HIV drug resistance among previously ARV-naive people

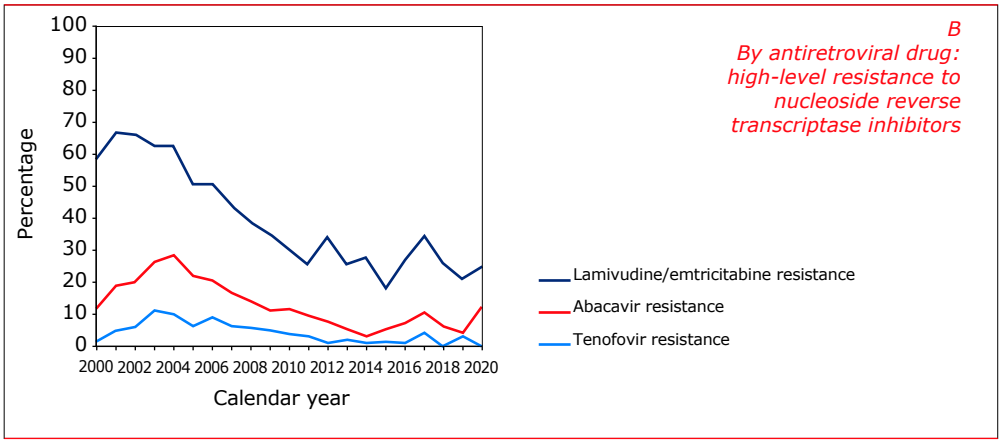
In the remainder of our analysis, we focus solely on the 1,868 people who were ARV-naive before cART initiation. Overall, 1,743 (58.9%) of the 2,959 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation, associated with resistance to NRTI (1,388; 46.9%), NNRTI (1,080; 36.5%), or PI (363; 12.3%).

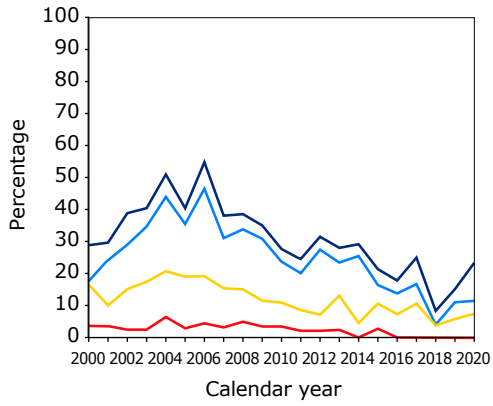
In *Figure 2.16A* and *Table 2.5*, the annual percentage of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000, 67.7% (95% CI 55.5-78.9), 27.7% (95% CI 18.2-39.7), and 48.5% (95% CI 36.7-60.4) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. The percentage of sequences with high-level resistance declined over time for all drug classes. In 2009, 36.8% (95% CI 30.4-43.7), 34.8% (95% CI 28.6-41.7), and 7.5% (95% CI 4.5-12.0) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. In 2020, 25.0% (95% CI 14.4-39.7), 22.7% (95% CI 12.7-37.3), and 0% of sequences harboured high-level resistance to at least one NRTI, NNRTI or PI, respectively. 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 9.1% (95% CI 4.1-18.8) in 2000 to 0% in

2014. The annual percentages of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 2.16B-D* and *Appendix Table 2.1A-C*, and annual percentages of sequences harbouring at least one high-level resistance mutation to all three drug classes in *Figure 2.16E*. Of note, drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed, but instead remains viably archived in the viral reservoir.

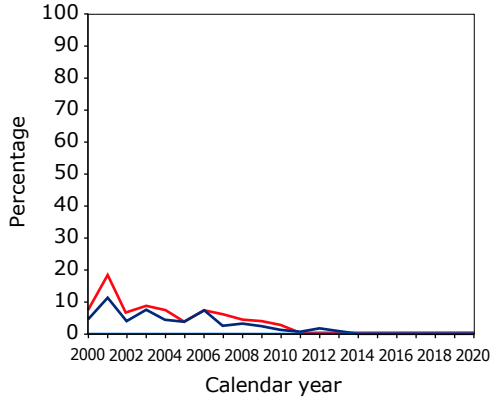
Figure 2.16: *The annual percentages of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (cART), among previously antiretroviral drug-naive people. Results are shown by 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.*



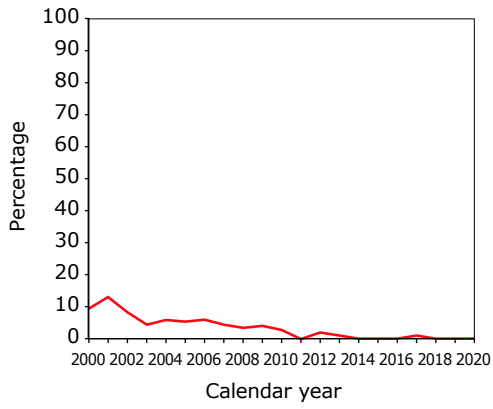




C
By antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors



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



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

Note: *The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.9-1) 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].
Legend: *NRTIs=nucleoside analogue reverse transcriptase inhibitors.*

Table 2.5: Acquired drug resistance: the annual percentage of available sequences with evidence of high-level resistance to at least one antiretroviral drug class after virological failure from people who received combination antiretroviral therapy and were previously antiretroviral drug-naive. See Appendix Table 2.1 for antiretroviral drug-specific results.

Drug class	Nucleoside analogue reverse transcriptase inhibitors			Non-nucleoside reverse transcriptase inhibitors			Protease inhibitors		
		95% confidence interval			95% confidence interval			95% confidence interval	
Calendar year	%	low	high	%	low	high	%	low	high
2000	67.7	55.5	77.9	27.7	18.2	39.7	48.5	36.7	60.4
2001	72.8	62.9	80.9	29.3	21.0	39.4	46.2	36.2	56.4
2002	71.6	64.0	78.2	37.4	30.2	45.3	30.3	23.6	38.0
2003	69.2	62.4	75.2	39.8	33.3	46.7	15.1	10.7	20.7
2004	69.0	62.0	75.2	50.3	43.1	57.4	16.0	11.4	22.0
2005	56.6	49.0	64.0	38.6	31.5	46.2	16.3	11.4	22.7
2006	57.6	50.1	64.9	54.1	46.6	61.5	13.6	9.2	19.7
2007	48.7	41.8	55.7	37.9	31.4	45.0	9.2	5.9	14.2
2008	43.1	37.0	49.5	37.2	31.3	43.5	8.4	5.5	12.6
2009	36.8	30.4	43.7	34.8	28.6	41.7	7.5	4.5	12.0
2010	31.6	25.8	38.1	27.0	21.5	33.3	7.5	4.6	11.9
2011	27.2	20.8	34.7	24.7	18.6	32.0	1.9	0.6	5.8
2012	34.3	25.9	43.8	31.4	23.3	40.9	5.7	2.6	12.1
2013	26.3	18.4	36.1	27.4	19.4	37.2	3.4	1.1	9.9
2014	28.6	20.5	38.3	28.6	20.5	38.3	0		
2015	20.3	14.0	28.6	22.0	15.5	30.4	1.9	0.5	7.4
2016	26.7	18.5	37.1	19.8	12.7	29.5	0		
2017	37.4	28.4	47.3	24.2	16.8	33.6	1.2	0.2	7.8
2018	25.9	18.6	34.8	8.0	4.2	14.7	1.2	0.2	7.9
2019	22.4	15.9	30.5	15.2	9.9	22.6	1.0	0.1	7.0
2020	25.0	14.4	39.7	22.7	12.7	37.3	0		

Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was relatively rare. The available 208 integrase sequences originated from 168 people who received cART for at least four months; 17 were pre-treated with monotherapy or dual NRTI therapy before initiating cART, and 151 were ARV-naive before initiating cART. Most people had initiated cART years before; the median time between initial cART initiation and testing for integrase inhibitor resistance was 10.4 years (IQR 3.7-15.0). 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 29 of the 168 individuals, which resulted in high-level resistance to at least one integrase inhibitor[25,26]. Among the 29, the following major INSTI resistance mutations were detected (numbers are given in parenthesis): N155H (14) and N155H/N (two); Y143R (three) and Y143Y/C (one); T66I (one); E92Q (four) and E92E/Q (one); Q148H (one, in combination with the G140S minor mutation); and R263K (one). Minor mutations detected were at position L74: any mutation (six); L74I (five); L74M (one); T97 (any, four; T97A, four); T66 other than T66I (any, three; T66T/A, two; T66T/K, one); and G140S (one). Six of the 29 patients who harboured a high-level resistance mutation to INSTI had ever received INSTI-monotherapy.

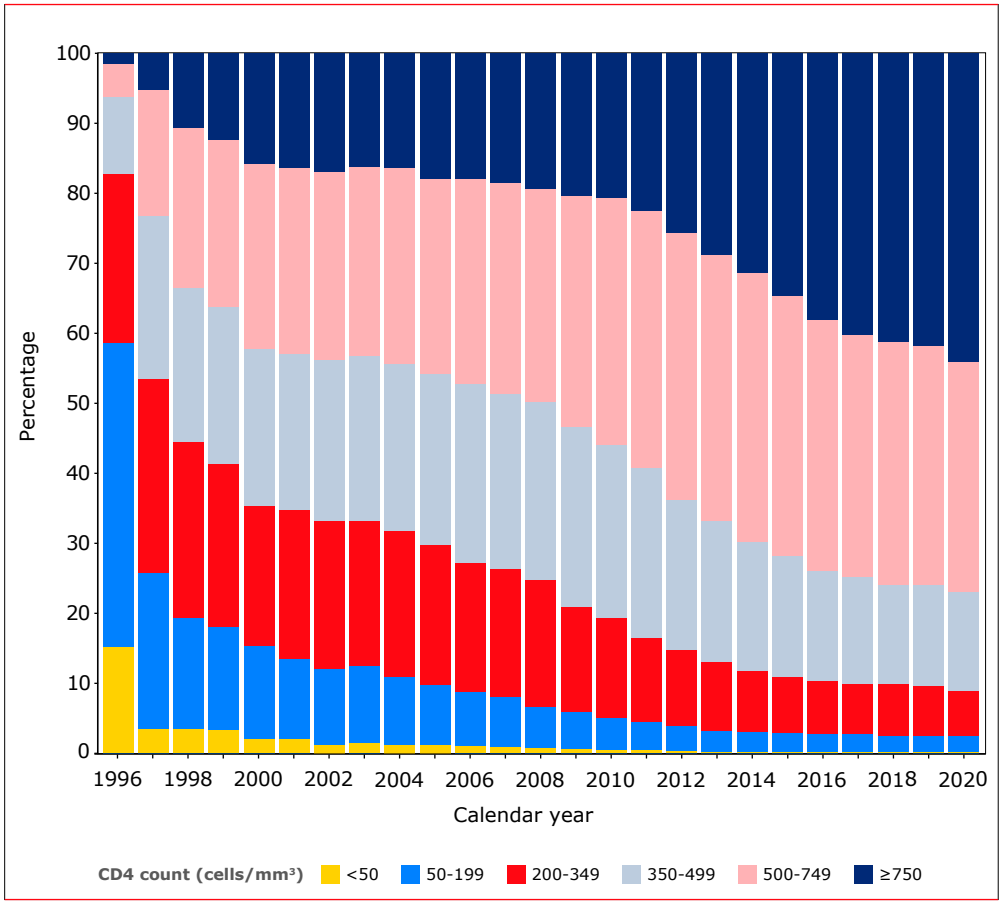
Immunological response

After initiation of cART, 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., having a CD4 count persistently below 350 cells/mm^3), may also occur, despite sustained viral suppression, 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 vary 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 cART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[44-48].

Immunological response – by calendar year

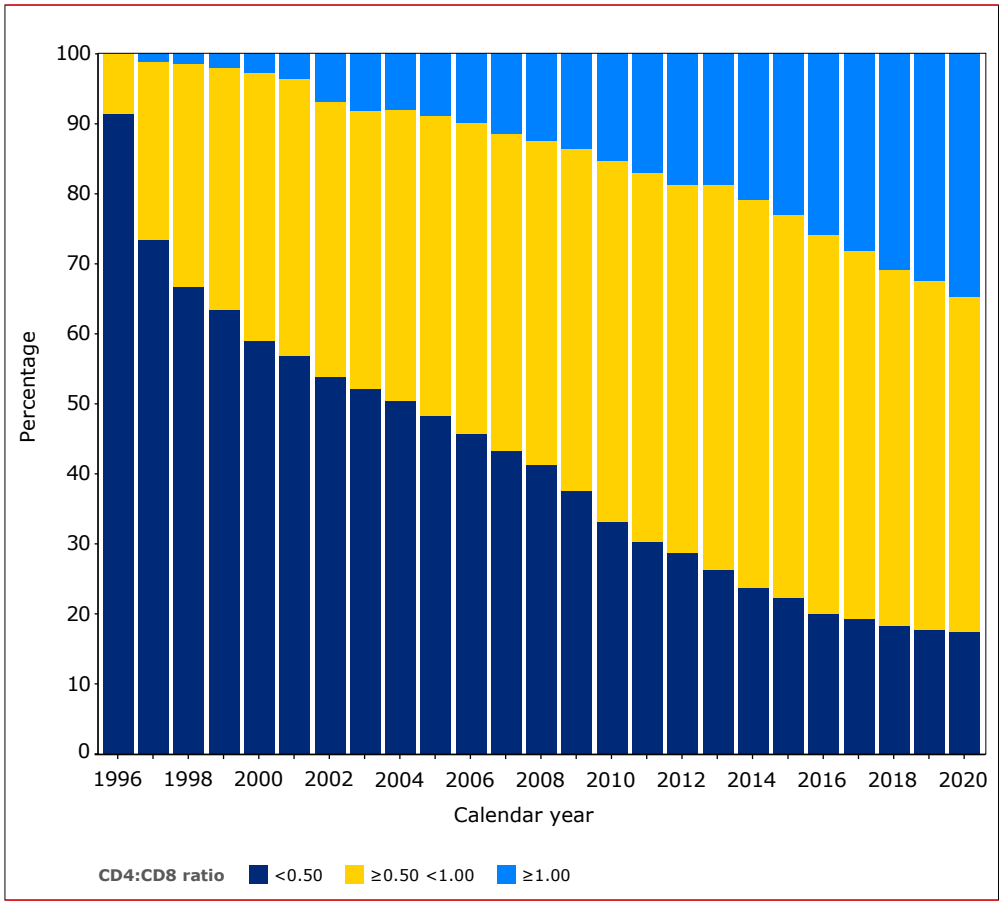
Of the 26,806 people known to have initiated cART between January 1996 and December 2020, CD4 cell count data after cART initiation were available for 26,330 (98.2%). *Figures 2.17* and *2.18* show the last known CD4 cell count and CD4:CD8 ratio of all people in HIV care for each calendar year. After starting cART, 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, and 9.0% in 2020 (*Figure 2.17*). The decrease in the percentage of people with low CD4 cell counts at the end of each calendar year results from the trend of starting cART at higher CD4 cell counts, more pronounced immune recovery with longer cART 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 2020 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 2.8% in 2000, 8.8% in 2005, 15.3% in 2010, 23.1% in 2015, and 34.6% in 2020 (*Figure 2.18*). Of all CD4:CD8 ratio measurements equal to or above one, 10.4% had a CD4 count of less than 500 cells/mm^3, 32.1% had a CD4 count between 500-749 cells/mm^3, and 57.5% had a CD4 count equal to or above 750 cells/mm^3. When the CD4:CD8 ratio was equal to or above one, the median CD4 count was 800 cells/mm^3 (IQR 621-1,000).

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



Immunological response – after cART initiation (2016–2020)

We also assessed the immunological response in people who started cART more recently (i.e., in 2016-20), and had CD4 cell count data available at, and after cART initiation. The level of viral suppression and treatment interruptions after initiating cART were not taken into account in this analysis. Of the 3,210 people who started cART in 2016-20 and had sufficient immunological data available, 10.0% had CD4 counts below 50 cells/mm^3, 16.0% 50-199 cells/mm^3, 19.4% 200-349 cells/mm^3, 21.0% 350-499 cells/mm^3, and 33.5% equal to or above 500 CD4 cells/mm^3 at the time of cART initiation. The average CD4 cell count at cART initiation has decreased slightly in recent years (*Appendix Table 2.2*).

The CD4 cell count and CD4:CD8 ratio trajectories following cART initiation are plotted in *Figures 2.19* and *2.20* by CD4 cell count at cART initiation. The median CD4 cell counts and CD4:CD8 ratios increased after cART initiation. Both depended on the CD4 cell count at cART initiation and did not converge among the five baseline CD4 cell count strata. These observations are in line with a study by the Antiretroviral TherapyCohort 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 (cART) in 2016–2020.*

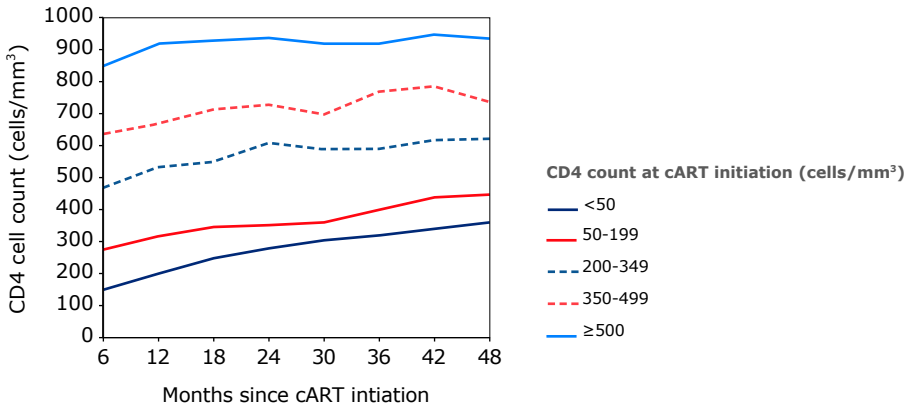
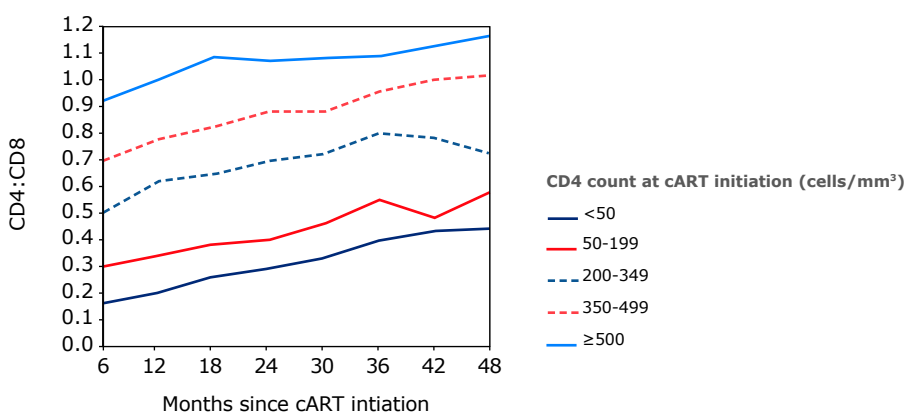


Figure 2.20: *CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART) in 2016–2020.*



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[50]. 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 cART and the initial regimen

- Rapid initiation of cART following a diagnosis of HIV infection, irrespective of CD4 cell count, has generally resulted in a shorter median time to initiation of cART following diagnosis.
- The CD4 cell count at cART initiation initially increased over time, peaking in the year 2015 at a median of 414 cells/mm^3 (IQR 220-600). This was when new guidelines were issued that recommended rapid initiation of cART at any CD4 count. Those guidelines resulted in substantial numbers of individuals with preserved CD4 counts, who had postponed starting cART, deciding to initiate treatment. Since then, the median CD4 count at the start of cART has continued to decrease. Among individuals living with HIV starting cART in 2020, the median CD4 cell count was 286 cells/mm^3 (IQR 99-500). Immunological recovery was better when cART was started at a higher CD4 cell count.
- In 2020, 89.4% of initial regimens contained an integrase inhibitor. The most frequently used initial regimen was bictegravir/emtricitamine/tenofovir alafenamine (45.9%). Dolutegravir-containing initial regimens were used in 42.7% of cases.
- Compared to the first decade of the cART 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 cART in 2020

- Integrase inhibitor-based cART has been implemented on a large scale in the Netherlands and was used by 48.4% of all individuals.
- The nucleoside analogue backbone used contained TDF in 30.8% of cases, ABC in 16.8%, and TAF in 43.7% of cases.
- In 2020, 7.3% used a two-drug regimen.
- Of those receiving cART for at least 12 months, who had a plasma HIV RNA measurement in 2019, 97.6% had a viral load below 200 copies/ml, and 96.9% had a viral load equal to or below 50 copies/ml.

Virological response and drug resistance

- The overall viral suppression rates of the population living with HIV receiving cART 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 168 people tested by the end of 2020. Detected rates of acquired integrase inhibitor resistance among available sequences remained very low, with almost no significant resistance to dolutegravir.
- There was a considerably lower number of sequences available in 2020 than in other years; this could be due to restricted capacity at virology departments during the COVID-19 pandemic. The effect of limited sequencing should be evaluated in the future.

Immunological response

- In individuals using cART, 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, and 9.0% in 2020.
- 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, and 34.6% in 2020.

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Appendix

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

A)

Calendar year	Number of sequences	Emtricitabine/ lamivudine	Zidovudine	Stavudine	Abacavir	Didanosine	Tenofovir
2000	65	58.5	14.8	10.7	11.7	12.3	1.7
2001	92	66.7	15.0	17.7	18.8	16.7	4.8
2002	155	66.2	12.4	15.2	19.9	18.6	6.3
2003	201	62.9	18.4	24.0	26.4	26.5	11.2
2004	187	62.8	18.8	22.1	28.3	28.7	10.1
2005	166	50.6	13.6	18.1	22.1	21.2	6.5
2006	170	50.9	10.8	16.8	20.5	22.1	9.0
2007	195	44.3	10.2	13.5	16.8	14.0	6.5
2008	239	39.1	7.6	11.5	14.3	15.1	5.9
2009	201	35.2	6.8	9.5	11.5	11.3	5.2
2010	215	30.4	5.4	8.4	11.7	12.1	3.9
2011	158	25.6	2.6	4.8	9.7	9.7	3.3
2012	105	34.3	0.0	2.0	7.9	7.8	1.0
2013	95	25.5	0.0	2.2	5.5	5.5	2.2
2014	98	27.8	1.0	3.1	3.2	4.1	1.1
2015	118	18.3	0.9	2.7	5.3	6.8	1.8
2016	86	26.7	1.2	2.5	7.1	4.9	1.2
2017	99	34.4	2.0	6.3	10.5	12.4	4.3
2018	112	25.9	0.0	0.0	6.3	5.4	0.0
2019	125	21.1	1.6	4.9	4.1	5.7	3.2
2020	44	25.0	2.3	2.3	12.2	9.8	0.0

B)

Calendar year	Number of sequences	Nevirapine	Efavirenz	Etravirine	Rilpivirine
2000	65	28.6	17.5	3.7	16.1
2001	92	29.7	24.4	3.5	9.9
2002	155	38.9	29.2	2.3	15.3
2003	201	40.4	34.2	2.4	17.5
2004	187	50.8	44.0	6.4	20.6
2005	166	40.3	35.3	2.8	18.9
2006	170	54.8	46.3	4.6	19.3
2007	195	38.0	31.1	3.1	15.2
2008	239	38.7	33.9	4.8	15.0
2009	201	35.0	30.7	3.4	11.4
2010	215	27.6	22.9	3.6	10.7
2011	158	24.5	20.1	2.1	8.7
2012	105	31.4	27.3	2.1	7.1
2013	95	28.0	23.3	2.4	12.9
2014	98	29.2	25.5	0.0	4.3
2015	118	21.2	16.1	2.8	10.5
2016	86	17.9	13.6	0.0	7.2
2017	99	25.0	16.9	0.0	10.5
2018	112	8.0	3.7	0.0	3.7
2019	125	15.2	10.9	0.0	5.7
2020	44	23.3	10.8	0.0	7.3

C)

Calendar year	Number of sequences	Nelfinavir	Saquinavir	Indinavir	Atazanavir	Fosamprenavir	Lopinavir	Tipranavir	Darunavir
2000	66	48.5	9.4	6.6	7.9	7.7	4.8	1.6	0.0
2001	91	46.7	21.3	18.2	18.8	14.0	11.5	3.5	0.0
2002	155	30.7	10.9	7.8	6.9	5.6	4.0	0.7	0.0
2003	199	15.7	8.3	8.9	8.7	6.7	7.2	1.6	0.0
2004	187	15.2	6.7	6.9	7.7	5.5	4.5	0.6	0.0
2005	166	16.3	3.9	6.5	3.8	3.2	3.8	0.6	0.0
2006	169	13.1	6.1	7.8	7.3	5.5	7.1	2.4	0.0
2007	195	9.4	4.8	4.3	6.2	3.1	2.6	1.0	0.0
2008	239	6.8	3.4	4.7	4.7	4.7	3.5	0.4	0.0
2009	201	7.1	3.5	4.1	4.1	4.1	2.6	1.0	0.0
2010	214	6.2	2.9	3.9	2.8	3.8	1.5	0.0	0.0
2011	156	1.9	0.6	0.6	0.6	0.6	0.6	0.0	0.0
2012	105	5.7	2.0	2.0	1.9	1.9	1.9	0.0	0.0
2013	89	3.4	0.0	1.1	1.1	2.2	1.1	0.0	0.0
2014	83	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2015	103	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2016	75	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2017	86	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2018	85	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2019	97	1.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
2020	44	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Appendix Table 2.2: *CD4 cell count at combination antiretroviral therapy (cART) initiation by calendar year in 2016–2020.*

Year of cART initiation	2016	2017	2018	2019	2020	2016–2020
CD4 cell count available at cART initiation	926	822	687	540	235	**3,210**
CD4 cell count, median cells/mm³ (IQR)	410 (237–580)	380 (200–560)	373 (167–580)	354 (154–560)	286 (99–500)	**380 (185–570)**
CD4 cell count (cells/mm³)						
<50	8.9%	8.3%	11.5%	10.2%	16.2%	**10.0%**
50–199	12.2%	16.1%	16.6%	20.0%	20.4%	**16.0%**
200–349	18.4%	20.3%	18.6%	18.9%	23.4%	**19.4%**
350–499	23.1%	22.6%	19.5%	19.8%	14.5%	**21.0%**
≥500	37.5%	32.7%	33.8%	31.1%	25.5%	**33.5%**

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