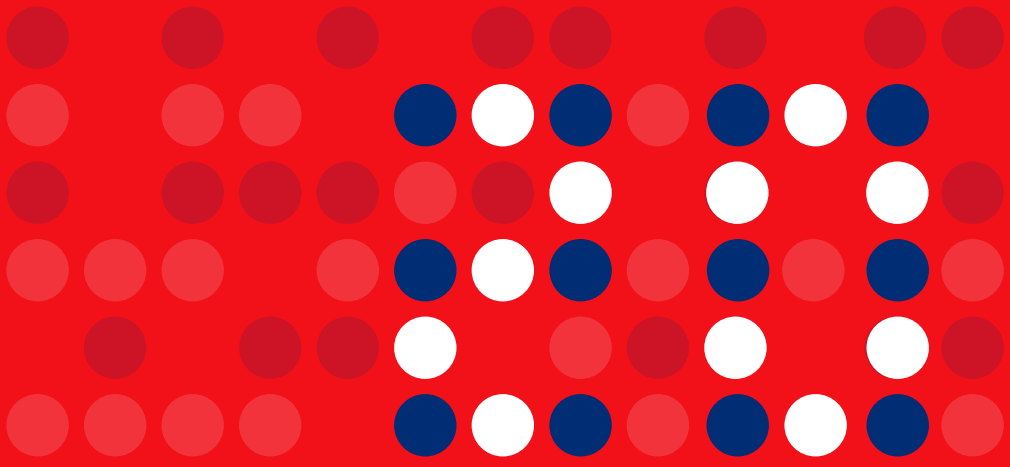
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2020



2. Response to combination antiretroviral therapy

Ferdinand Wit, Anders Boyd, Ard van Sighem, Kees Brinkman, Kees van Nieuwkoop, Anne Wensing, Peter Reiss

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 to initiate cART as soon as possible for 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, https://richtlijnhiv.nvhb.nl/index.php/Inhoud) follows the US Department of Health and Human Services guidelines.

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 ≤350 cells/mm^3 [8,9]. 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[10–15]). 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.

Most guidelines list an unboosted integrase inhibitor as the third agent of preferred first-line cART regimens. Further treatment options, which are recommended in certain clinical situations, include elvitegravir as a boosted integrase inhibitor; darunavir or atazanavir as a boosted protease inhibitor; or doravirine, efavirenz, or rilpivirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI, the latter only if viral load is <100,000 copies/ml). All aforementioned agents are used in combination with a double nucleoside backbone (either tenofovir/emtricitabine

or abacavir/lamivudine)[16]. Additionally, tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are two forms of tenofovir approved by the European Medicines Agency (EMA). TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. TDF use should be avoided in people with reduced renal function and in people with osteoporosis, or a risk of osteoporotic fractures[17,18]. The two-drug regimen of dolutegravir and lamivudine (co-formulated as Dovato®), has also recently been licensed by the US Food and Drug Administration (FDA) and EMA. It is now a recommended regimen for ART-naïve individuals with viral load below 500,000 copies/mL, without chronic HBV co-infection, and for whom a baseline HIV genotype is available to exclude the presence of transmitted resistance to lamivudine. Safety, ease of use, food effects, and potential for significant drug-drug interactions are among the factors to consider when choosing between regimens. Finally, although still frequently used, efavirenz is no longer recommended as the preferred first-line cART regimen in the Netherlands, but remains an alternative[3,7,16].

Treatment with cART generally results in sustained suppression of HIV viral load to levels below the reported threshold. Nevertheless, drug resistance mutations could develop if a given agent, even when combined with other agents, cannot sufficiently prevent the selective pressures driving resistance (i.e., low genetic barrier to 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[19–25].

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. 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 in Chapter 2.

There were a cumulative 27,097 adults (≥18 years at the time of diagnosis) registered by SHM as living with HIV-1 in the Netherlands by the end of 2019

1. **Starting combination antiretroviral therapy**
   25,587 people were known to have initiated cART between January 1996 and December 2019.

2. **In care and on cART in the Netherlands in 2019**
   Of the 25,587 people who initiated cART between January 1996 and December 2019,
   ➔ 19,498 were in care and had a clinical visit in 2019.

3. **Changes in the use of the initial cART regimen**
   Of the 25,587 people who initiated cART between January 1996 and December 2019,
   ➔ 4,581 initiated cART between January 2015 and December 2019.
   ➔ The most frequently used 'common' guideline-recommended initial regimens in 2015-19 were: ABC/3TC/DTG (28.9%), TAF/FTC/EVG/c (13.6%), TDF/FTC/DTG (11.0%), TDF/FTC/EVG/c (8.2%), TAF/FTC/BIC (6.7%), TDF/FTC/EFV (5.0%), TDF/FTC/DRV/b (4.7%), TDF/FTC/RPV (2.7%), TAF/FTC/DTG (2.5%), TAF/FTC/DRV/c (2.4%), TDF/FTC/ATV/b (1.6%), TAF/FTC/RPV (1.2%), and TDF/FTC/RAL (0.9%).

4. **Virological response**
   Of the 25,587 people who initiated cART between January 1996 and December 2019,
   ➔ 21,644 people were ART-naive, not pregnant at cART initiation, and had a viral load result within six months (±three months) of cART initiation.

5. HIV drug resistance

Transmitted HIV drug resistance

As of January 2020, 7,567 HIV-1 sequences had been obtained from 7,292 ART-naive people before they initiated cART in 2003-19.

➔ 7,559 reverse transcriptase sequences were available from 7,287 individuals.
➔ 7,184 protease sequences were available from 6,918 individuals.
➔ 27 integrase sequences were available from 27 individuals.

Acquired HIV drug resistance

As of January 2020, 3,899 HIV-1 sequences had been obtained from 2,402 people who received cART for at least four months in 2000-19.

➔ 2,610 sequences were from 1,691 people who had been ART-naive before initiating cART.
➔ 3,853 reverse transcriptase sequences were available from 2,384 individuals.
➔ 3,732 protease sequences were available from 2,298 individuals.
➔ 167 integrase sequences were available from 138 individuals.

6. Immunological response

Of the 25,587 people who initiated cART between January 1996 and December 2019,

➔ 25,088 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).*

Starting combination antiretroviral therapy

In total, 25,587 adults ever registered by SHM and followed in the ATHENA cohort were 18 years or older at the time of HIV-1 diagnosis, and were known to have initiated cART between January 1996 and December 2019 (*Box 2.1*). Of these, 2,100 (8.1%) had prior exposure to mono or dual nucleoside-analogue antiretroviral therapy (ART) at the start of cART, and 23,487 (91.8%) were ART-naive. The proportion of pre-treated people starting cART has decreased over time to <1%. In *Table 2.1*, we grouped people according to calendar year of cART initiation: 8,475 started in 1996-2004, 5,468 in 2005-09, 7,063 in 2010-14, and 4,581 in 2015-19.

Table 2.1: Characteristics of people starting combination antiretroviral therapy in 1996–2019.

Year of cART initiation		1996–2004	2005–2009	2010–2014	2015–2019	1996–2019
Number of individuals		8,475	5,468	7,063	4,581	**25,587**
DEMOGRAPHIC						
Age at cART initiation (years)	Median	37.6	39.9	40.0	38.0	**38.7**
	Q1	31.9	33.0	31.8	29.5	**31.7**
	Q3	44.6	47.0	48.3	49.1	**46.9**
Male gender (at birth)	n	6607	4,347	6,099	3,927	**20,980**
	%	78.0	79.5	86.4	85.7	**82.0**
Transmission risk group						
Missing	n	7	5	9	12	**33**
	%	0.1	0.1	0.1	0.3	**0.1**
Men who have sex with men	n	4,576	3,157	4,859	3,041	**15,633**
	%	54.0	57.7	68.8	66.4	**61.1**
Heterosexual contact	n	2,799	1,827	1,767	1,157	**7,550**
	%	33.0	33.4	25.0	25.3	**29.5**
Injecting drug use	n	495	117	57	27	**696**
	%	5.8	2.1	0.8	0.6	**2.7**
Blood or blood products	n	146	54	62	43	**305**
	%	1.7	1.0	0.9	0.9	**1.2**
Vertical transmission	n	.	.	4	2	**6**
	%	.	.	0.1	0.0	**0.0**
Other/unknown	n	452	308	305	299	**1,364**
	%	5.3	5.6	4.3	6.5	**5.3**
Region of origin						
Missing	n	41	15	14	31	101
	%	0.5	0.3	0.2	0.7	0.4
The Netherlands	n	4,743	2,974	4,272	2,474	14,463
	%	56.0	54.4	60.5	54.0	56.5
Western Europe/North America/Australia	n	856	443	478	272	2,049
	%	10.1	8.1	6.8	6.0	8.0
Eastern/central Europe	n	140	159	343	345	987
	%	1.7	2.9	4.9	7.5	3.9
Latin America and the Caribbean	n	889	669	835	672	3,065
	%	10.5	12.2	11.8	14.7	12.0
Sub-Saharan Africa	n	1,414	900	708	433	3,455
	%	16.7	16.5	10.0	9.5	13.5
Other	n	392	308	413	354	1,467
	%	4.6	5.6	5.9	7.7	5.7

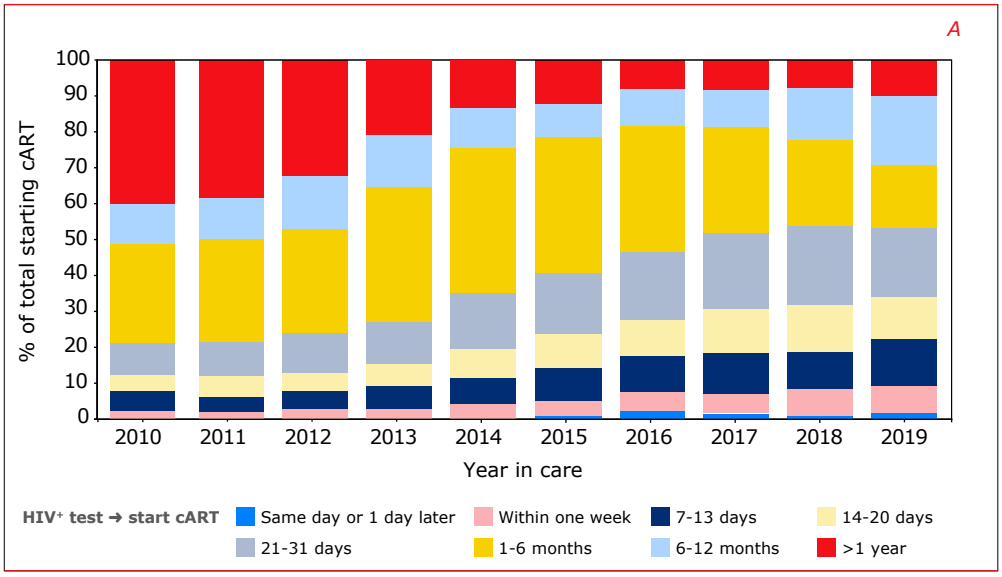
Year of cART initiation		1996–2004	2005–2009	2010–2014	2015–2019	1996–2019
CLINICAL						
Recent infection	n	479	729	1,607	1,194	**4,009**
(within 12 months of diagnosis)	%	5.7	13.3	22.8	26.1	**15.7**
Ever having tested HIV-negative	n	1,723	1,993	3,786	2,578	**10,080**
	%	20.3	36.5	53.6	56.3	**39.4**
CD4 cell count at start of cART	Median	190	230	330	400	**270**
	Q1	80	120	210	200	**130**
	Q3	320	306	458	585	**410**
HIV RNA (log_{10}) at start of cART	Median	4.9	5.0	4.9	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	2,635	1,164	1,010	567	**5,376**
	%	31.1	21.3	14.3	12.4	**21.0**
Prior mono or dual NRTI treatment	n	1,987	65	25	23	**2,100**
at start of cART	%	23.5	1.2	0.4	0.5	**8.2**
Hepatitis B status at start of cART						
HBV-negative (HBsAg-negative)	n	7,627	5,016	6,571	4,206	**23,420**
	%	90.0	91.7	93.0	91.8	**91.5**
HBV-positive (HBsAg-positive)	n	524	312	254	109	1,199
	%	6.2	5.7	3.6	2.4	**4.7**
Unknown	n	324	140	238	266	**968**
	%	3.8	2.6	3.4	5.8	**3.8**
Hepatitis C status at start of cART						
HCV-negative	n	7,613	5,152	6,741	4,309	**23.815**
	%	89.8	94.2	95.4	94.1	**93.07**
HCV RNA-positive	n	143	129	117	69	458
	%	1.7	2.4	1.7	1.5	1.8
HCV Ab seropositive	n	183	44	40	22	289
	%	2.2	0.8	0.6	0.5	1.1
Unknown	n	536	143	165	181	1,025
	%	6.3	2.6	2.3	4.0	4.0
cART started during pregnancy	n	306	255	121	77	759
	%	3.6	4.7	1.7	1.7	**3.0**

Legend: *cART=combination antiretroviral therapy; cART=combination antiretroviral therapy; HBV=hepatitis B virus; HCV=hepatitis C virus.*

Of the 25,587 people who had initiated cART since January 1996, 20,980 (82.0%) were men, of whom 15,633 (74.5%) were men who have sex with men (MSM). Overall, 14,433 (56.5%) 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 2009, to 4.9% in 2010-14, and 7.5% in 2015-19. Simultaneously, the number of people from western Europe/North America/Australia decreased slightly from 10.5% in 1996-2004, to 5.9% in 2015-19. This was also true for sub-Saharan Africa; the number declined from 16.7% in 1996-2004, to 9.5% in 2015-19.

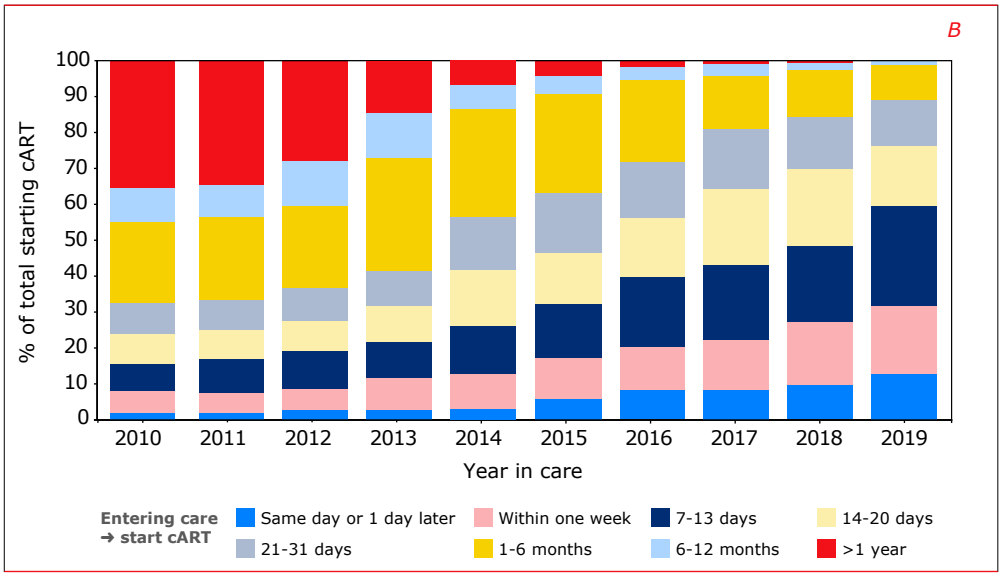
Prompt initiation of cART following an HIV-positive diagnosis has increased over time, reflecting implementation and uptake of evolving HIV treatment guidelines (*Figure 2.1A*). Among people with a known date of HIV diagnosis who started cART in the Netherlands, the median time between an HIV-positive diagnosis and cART initiation shifted from 136 days (interquartile range [IQR] 33-714) for those who entered care in 2011, to 110 days (IQR 30-519) in 2012; 66 days (IQR 27-293) in 2013; 42 days (IQR 21-117) in 2014; 36 days (IQR 17-82) in 2015; 30 days (IQR 14-55) in 2016; 28 days (IQR 14-49) in 2017; 25 days (IQR 11-46) in 2018; and 21 days (IQR 8-44) in 2019. The proportion of subjects initiating cART on the same day they were diagnosed HIV-positive increased from 0.3% in 2010, to 1.0% in 2015, 2.3% in 2016, 1.5% in 2017, 1.1% in 2018, and 1.6% in 2019. Likewise, the time between entering care and starting cART decreased over time (*Figure 2.1B*), with the vast majority of people newly entering care initiating cART within six months. In 2019, 19.0% and 10.2% of individuals initiating cART did so either 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. In 2018 and 2019, of those born outside the Netherlands who initiated cART more than six months after testing HIV-positive, 48.1% first tested HIV-positive after they migrated to the Netherlands, 29.8% tested HIV-positive before they migrated to the Netherlands, and, for 22.1%, the migration date was unknown. Among those who entered care in 2018 and 2019 and who had started ART more than 6 months after HIV diagnosis, 79.4% were migrants, mainly from European countries, North and sub-Saharan Africa and Asia, who were already diagnosed with HIV and on ART before they migrated to the Netherlands. This proportion increased from just 8.5% in 2010, to 40.8% in 2015, to 86.7% in 2019. In recent years, late initiation of ART has become rare in individuals who were first diagnosed with HIV while living in the Netherlands.

Figure 2.1A: Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) in people starting cART in 2010–19.



Legend: cART=combination antiretroviral therapy.

Figure 2.1B: Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) for people starting cART in 2010–19.



Legend: cART=combination antiretroviral therapy.

The proportion of those with a known previous negative HIV test increased over the years, rising from 20.3% in the period 1996-2004, to 36.5% in 2005-09, 53.6% in 2010-14, and 56.3% in 2015-19. In addition, an increasing proportion of those starting cART had evidence of recent infection (i.e., within 12 months of a last negative HIV test); the percentage of 5.7% in 1996-2004, rose to 13.3% in 2005-09, 22.8% in 2010-14, and 26.1% in 2015-19. Over the same time period, there was an increase in the median CD4 cell count at the start of cART, followed by a stabilisation, and then a slight decrease: from 190 cells/mm^3 (IQR 80-320) in 1996-2004, to 230 cells/mm^3 (IQR 120-306) in 2005-09, 330 cells/mm^3 (IQR 210-458) in 2010-14, and 400 cells/mm^3 (IQR 200-585) in 2015-19 (p for trend <.0001). In 2019, the median CD4 cell count at the start of cART was 370 cells/mm^3 (IQR 180-570). Since 2016, fewer people have initiated cART per calendar year and the median CD4 cell count at cART initiation has continued to decrease. This trend is likely due to the substantial group already in care but not on cART (because of their high CD4 cells counts), which subsequently initiated cART in 2015 and 2016, when the 2015 guideline change recommended ART for all, irrespective of CD4 count.

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.

1. In care and on cART in the Netherlands in 2019

Of the 25,587 people known to have initiated cART between January 1996 and December 2019, 19,489 (76.2%) were alive, receiving cART, and had a recorded visit for HIV care in the Netherlands in 2019. *Table 2.2* shows their treatment and clinical characteristics at their last clinic visit in 2019. Overall, 16,093 (82.6%) were men, and 12,615 (64.7%) were MSM. Their median age on 31 December 2019 was 51 (IQR 42-59) years. The majority (60.0%) originated from the Netherlands, followed by Latin America / the Caribbean (11.8%) and sub-Saharan Africa (11.7%).

Table 2.2: Characteristics of people receiving combination antiretroviral therapy and known to be in care in 2019.

Year of cART initiation		1996–2004	2005–2009	2010–2014	2015–2019	All
Total	n	5,244	4,160	5,952	4,133	**19,489**
	%	26.91	21.4	30.5	21.2	**100**
Male sex	n	4,049	3,319	5,172	3,553	**16,093**
	%	77.2	79.8	86.9	86.0	**82.6**
Age on 31 December 2019	Median	57.0	52.2	47.7	41.3	**51.0**
	Q1	51.4	45.6	39.4	32.4	**41.9**
	Q3	63.3	58.7	55.7	52.2	**58.6**
Transmission risk group						
No data	n	6	2	7	9	**24**
	%	0.1	0.1	0.1	0.2	**0.1**
Men who have sex with men	n	3,04	2,563	4,235	2,782	**12,615**
	%	57.9	61.6	71.2	67.3	**64.7**
Heterosexual contact	n	1,747	1,317	1,423	1,022	**5,509**
	%	33.3	31.7	23.9	24.7	**28.3**
Injecting drug use	n	152	56	31	17	**256**
	%	2.9	1.4	0.5	0.4	**1.3**
Blood or blood products	n	95	40	46	41	**222**
	%	1.8	1.0	0.8	1.0	**1.1**
Vertical transmission	n	.	.	3	2	**5**
	%	.	.	0.1	01	**0.0**
Other/unknown	n	209	182	207	260	**858**
	%	4.0	4.4	3.5	63	**4.4**
Region of origin						
No data	n	18	9	14	29	**70**
	%	0.3	0.2	0.2	0.7	**0.4**
The Netherlands	n	3,126	2,470	3,802	2,308	**11,706**
	%	59.6	59.4	63.9	55.8	**60.1**
Western Europe/North America/Australia	n	415	251	338	223	**1,227**
	%	7.9	6.0	5.7	5.4	**6.3**
Eastern/central Europe	n	80	99	258	290	**727**
	%	1.5	2.4	4.3	7.0	**3.7**
Latin America and the Caribbean	n	543	493	666	588	**2,290**
	%	10.4	11.9	11.2	14.2	**11.8**
Sub-Saharan Africa	n	787	598	520	374	**2,279**
	%	15.0	14.4	8.7	9.1	**11.7**
Other	n	275	240	354	321	**1,190**
	%	5.2	5.8	6.0	7.8	**6.1**

Year of cART initiation		1996–2004	2005–2009	2010–2014	2015–2019	All
cART regimen						
TDF/3TC/DOR	n	21	23	49	22	**115**
	%	0.4	0.6	0.8	0.5	**0.6**
TDF/FTC/EFV	n	368	563	544	91	**1,566**
	%	7.0	13.5	9.1	2.2	**8.0**
TDF/FTC/NVP	n	517	311	284	14	**1,126**
	%	9.9	7.5	4.8	0.3	**5.8**
TDF/FTC/RPV	n	134	130	373	59	**696**
	%	2.6	3.1	6.3	1.4	**3.6**
TDF/FTC/ATV/r	n	68	88	101	17	**274**
	%	1.3	2.1	1.7	0.4	**1.4**
TDF/FTC/DRV/b	n	137	118	227	66	**548**
	%	2.6	2.8	3.8	1.6	**2.8**
TDF/FTC/LPV/r	n	9	9	5	.	**23**
	%	0.2	0.2	0.1	.	**0.1**
TDF/FTC/DTG	n	121	105	170	306	**702**
	%	2.3	2.5	2.9	7.4	**3.6**
TDF/FTC/EVG/c	n	93	92	280	174	**639**
	%	1.8	2.2	4.7	4.2	**3.3**
TDF/FTC/RAL	n	42	50	77	27	**196**
	%	0.8	1.2	1.3	0.7	**1.0**
ABC/3TC/NVP	n	26	106	65	2	**428**
	%	4.9	2.6	1.1	0.1	**2.2**
ABC/3TC/DTG	n	489	551	846	1,151	**3,037**
	%	9.3	13.3	14.2	27.9	**15.6**
TAF/FTC/NVP	n	347	183	148	6	**684**
	%	6.6	4.4	2.5	0.2	**3.5**
TAF/FTC/RPV	n	189	226	463	140	**1,018**
	%	3.6	5.4	7.8	3.4	**5.2**
TAF/FTC/DRV/c	n	280	232	337	226	**1,075**
	%	5.3	5.6	5.7	5.5	**5.5**
TAF/FTC/BIC	n	327	257	389	584	**1,557**
	%	6.2	6.2	6.5	14.1	**8.0**
TAF/FTC/DTG	n	116	116	161	179	**572**
	%	2.2	2.8	2.7	4.3	**2.9**
TAF/FTC/EVG/c	n	459	505	984	843	**2,791**
	%	8.8	12.1	16.5	20.4	**14.3**
2DR: NNRTI+INSTI	n	52	15	20	9	**96**
	%	1.0	0.4	0.3	0.2	**0.5**
2DR: PI+INSTI	n	204	55	58	29	**346**
	%	3.9	1.3	10.0	0.7	**1.8**

Year of cART initiation		1996–2004	2005–2009	2010–2014	2015–2019	All
2DR: NRTI+INSTI	n	41	33	55	59	**188**
	%	0.8	0.8	0.9	1.4	**1.0**
Other:2NRTI+NNRTI	n	184	90	47	13	**334**
	%	3.5	2.2	0.8	0.3	**1.7**
Other:2NRTI+PI	n	147	133	104	22	**406**
	%	2.8	3.2	1.8	0.5	**2.1**
Other:2NRTI+INSTI	n	85	63	75	35	**258**
	%	1.6	1.5	1.3	0.9	**1.3**
Other: 2DR	n	55	14	15	5	**89**
	%	1.1	0.3	0.3	0.1	**0.5**
Other: NRTI+PI+INSTI (3ARVs)	n	65	9	8	5	**87**
	%	1.2	0.2	0.1	0.1	**0.5**
Other: NRTI+PI+INSTI (4ARVs)	n	132	32	25	30	**219**
	%	2.5	0.8	0.4	0.7	**1.1**
Other	n	307	51	42	19	**419**
	%	5.9	1.2	0.7	0.5	**2.2**
CD4:CD8 ratio						
No data	n	636	521	779	603	**2,539**
	%	12.1	12.5	13.1	14.6	**13.0**
<0.50	n	834	551	699	960	**3,044**
	%	15.9	13.3	11.7	23.2	**15.6**
≥0.50 <1.00	n	2,343	2,005	2,740	1,622	**8,710**
	%	44.7	48.2	46.0	39.3	**44.7**
≥1.00	n	1,431	1,083	1,734	948	**5,196**
	%	27.3	26.0	29.1	23.0	**26.7**
CD4 count (cells/mm^3)						
No data	n	12	6	14	33	**65**
	%	0.2	0.1	0.2	0.8	**0.3**
<50	n	11	10	4	20	**45**
	%	0.2	0.2	0.1	0.5	**0.2**
50–199	n	98	53	58	154	**363**
	%	1.9	1.3	1.0	3.7	**1.9**
200–349	n	351	241	293	430	**1,315**
	%	6.7	5.8	4.9	10.4	**6.8**
350–499	n	817	616	750	578	**2,761**
	%	15.6	14.8	12.6	14.0	**14.2**
500–749	n	1,817	1,584	2,121	1,235	**6,757**
	%	34.7	38.1	35.6	29.9	**34.7**
≥750	n	2,138	1,650	2,712	1,683	**8,183**
	%	40.8	39.7	45.6	40.7	**42.0**

Year of cART initiation		1996–2004	2005–2009	2010–2014	2015–2019	All
Viral load <50 copies/ml						
No data	n	5	4	3	9	**21**
	%	0.1	0.1	0.1	0.2	**0.1**
Yes	n	4,696	3,685	5,345	3,522	**17,248**
	%	89.6	88.6	89.8	85.2	**88.5**
No	n	543	471	604	602	**2220**
	%	10.4	11.3	10.2	14.6	**11.4**
Viral load <200 copies/ml						
No data	n	5	4	3	9	**21**
	%	0.1	0.1	0.1	0.2	**0.1**
Yes	n	5,147	4,080	5,855	3,957	**19,039**
	%	98.2	98.1	98.4	95.7	**97.7**
No	n	92	76	94	167	**429**
	%	1.8	1.8	1.6	4.0	**2.2**

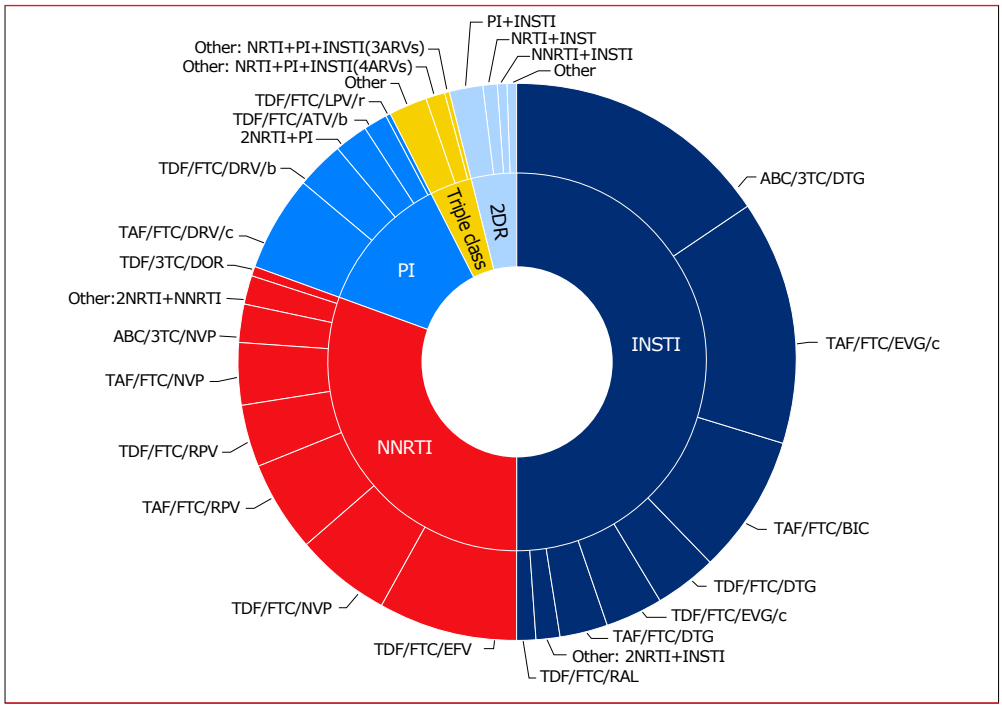
Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; ARVs=antiretroviral drugs; BIC=bictegravir; cART=combination antiretroviral therapy; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; 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 19,720 people in HIV care and on cART in 2019, the vast majority (92.5%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either an integrase inhibitor (INSTI) (50.0%), an NNRTI (30.6%), or a protease inhibitor (PI) (11.9%). The distribution of cART use among the population in care in 2019 is presented in *Figure 2.2*. The most common regimens were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (15.6%), tenofovir alafenamide (TAF)/FTC/elvitegravir (EVG)/cobicistat (14.3%), tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz (EFV) (8.0%), tenofovir alafenamide (TAF)/FTC/bictegravir (BIC) (8.0%), and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/nevirapine (NVP) (5.8%). The proportion of the population in care in 2019 using TDF continued to decline (from 46.4% in 2017, to 35.3% in 2018, and 31.9% in 2019), while the proportion using TAF continued to increase (from 24.4% of the population in care in 2017, to 33.2% in 2018, and 42.1% in 2019). Zidovudine was still used by 167 individuals (0.9%, mostly in combination with lamivudine). In total, 606 (3.1%) and 422 (2.2%) individuals used a cART regimen without any NRTI or with just one. There were 719 (3.6%) individuals who used a two-drug regimen (excluding pharmacological boosters): the most common two-drug regimen were a combination of PI+INSTI (346, 48.1%, of which 98.3% used

darunavir plus either dolutegravir (87.6%), or raltegravir (12.4%)); NRTI+INSTI (188, 26.1%, of which 97.3% used lamivudine and 99.5% dolutegravir); NNRTI+INSTI (96, 13.4%, of which 92% used rilpivirine and 93.8% used dolutegravir); and NRTI+PI (57, 7.9%, of which 77.2% used lamivudine, 5.3% used emtricitabine, 10.5% used TDF, 86.0% used darunavir, 7.0% used atazanavir, and 5.3% used lopinavir).

Of those with a plasma HIV RNA measurement in 2019, 88.5% had a viral load <50 copies/ml, and 97.6% had a viral load <200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-19, 76.7% had a CD4 cell count of 500 cells/mm^3 or higher, and 26.7% had a CD4:CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (cART) use in 2019.



2. Changes in the use of the initial cART regimen

Data from recent clinical trials on new antiretroviral drugs, such as bictegravir, dolutegravir, EVG/c, and TAF, 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 2013–19.*

Medicine	Authorisation date
TDF/FTC/EVG/cobicistat (Stribild®)	24 May 2013
Cobicistat (Tybost®)	19 September 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

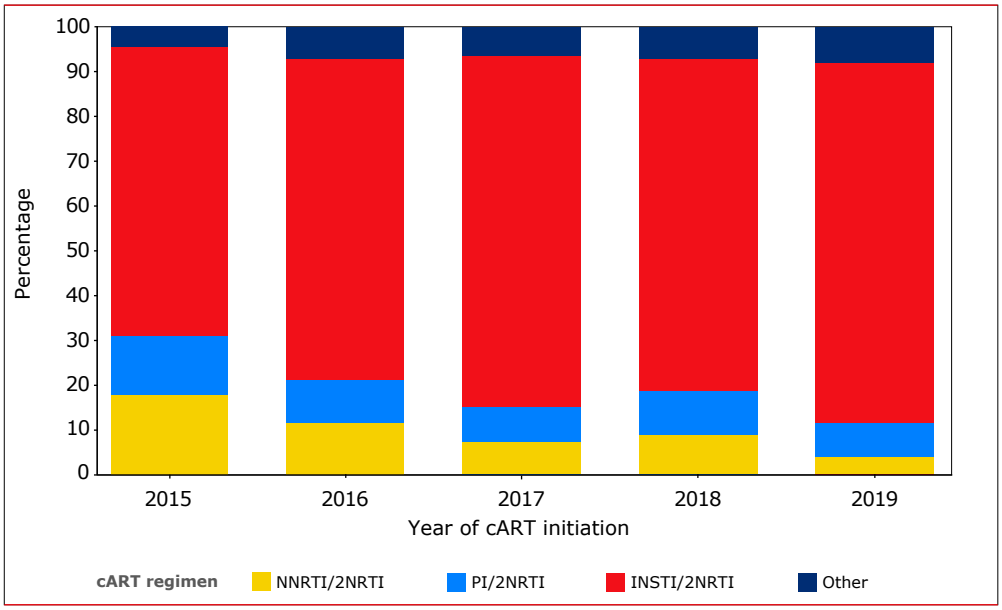
***Legend:** 3TC=lamivudine; ABC=abacavir; BIC = bictegravir; DTG=dolutegravir; DRV=darunavir; EVG=elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.*

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

Initial cART regimen

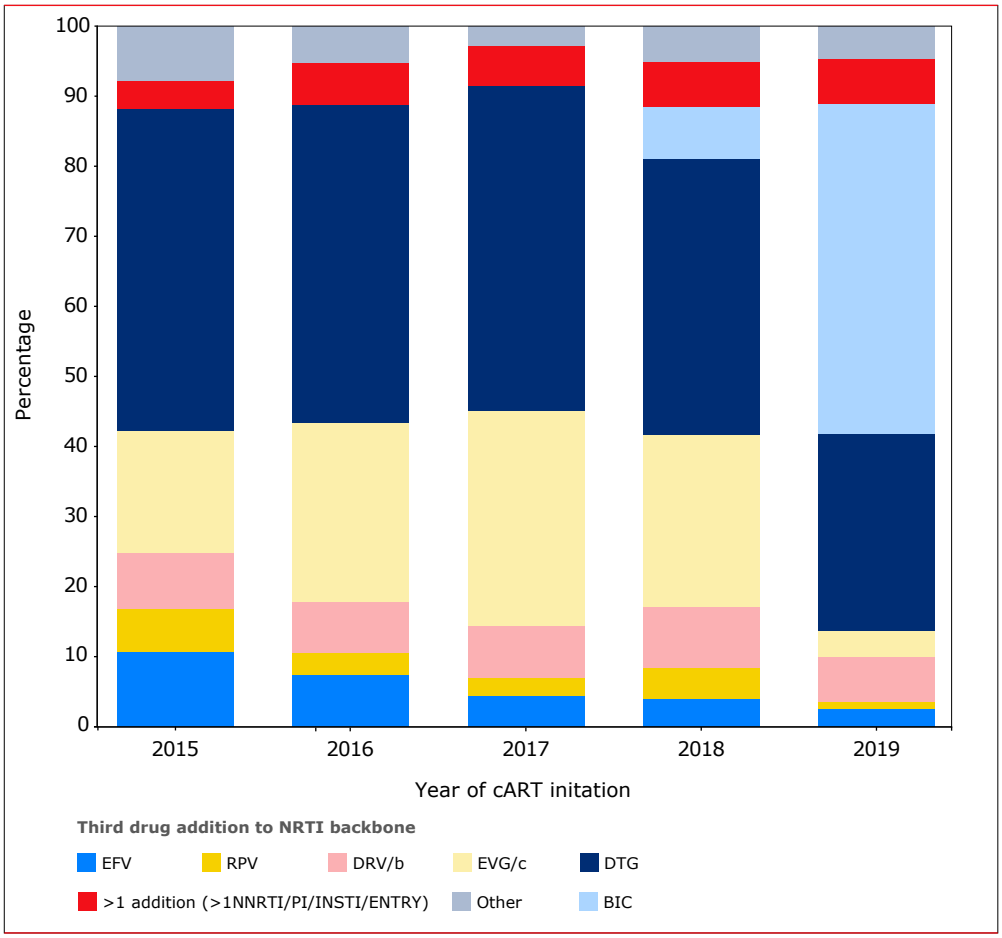
Of the 25,587 people known to have initiated cART between January 1996 and December 2019, 4,581 (17.9%) started cART between January 2015 and December 2019. *Figures 2.3 and 2.4* show the trends over time in third-drug additions to the NRTI backbone used as part of the initial cART regimen in these individuals. The use of integrase inhibitors in combination with an NRTI backbone as initial therapy, continued to rise from 64.4% in 2015, to 71.7% in 2016, 78.4% in 2017, 74.0% in 2018, and 80.7% in 2019. EVG/c was introduced in the Netherlands at the end of 2013 and was used in 17.4%, 25.6%, 31.0%, and 24.4% of the initial regimens in 2015, 2016, 2017, and 2018, respectively, before use dropped sharply to 3.6% in 2019. Dolutegravir was introduced in the Netherlands in 2014 and was used in 46.1%, 45.4%, 46.2%, 39.5%, and 28.2% of the initial regimens in 2015, 2016, 2017, 2018, and 2019, respectively. Bictegravir was introduced in the Netherlands in 2018 and was used in 7.4%, and 47.1% of the initial regimens in 2018 and 2019, respectively. The use of NNRTIs in the initial regimen decreased from 18.0% in 2015 to 11.8% in 2016, 7.4% in 2017, 8.9% in 2018, and 4.2% in 2019. The use of protease inhibitors in the initial regimen decreased from 13.1% in 2015 to 9.4% in 2016, 7.9% in 2017, 10.0% in 2018, and 7.4% in 2019. In 2015-19, 5.4% 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), with or without the addition of NRTI. *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 2015-19. The use of nevirapine, atazanavir, lopinavir, raltegravir, and doravirine as "third additions" to initial regimens did not exceed 5% in any year in the period 2015-19. As a result, those regimens are not shown in figure 2.4. Instead, these agents are categorised in the 'other' group. Dual therapy initial regimens were used too infrequently to be included as a separate category in figure 2.4: in this period, only 60 initial regimens containing fewer than three agents were recorded, 42 of which contained an integrase inhibitor as monotherapy, or combined with either one NRTI or one boosted PI.

Figure 2.3: Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2015–19.



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

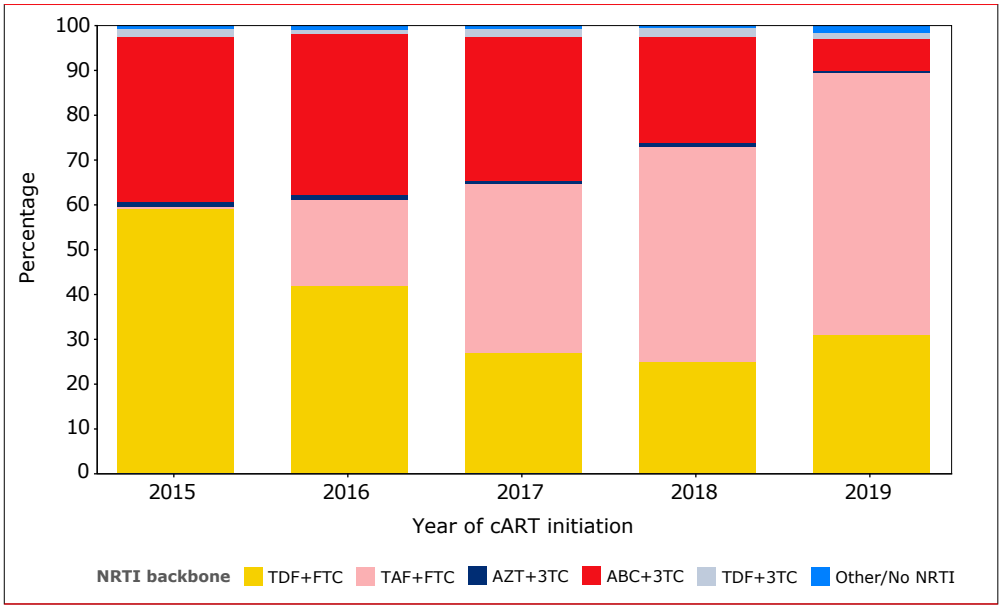
Figure 2.4: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2015-19.



Legend: cART=combination antiretroviral therapy; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /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 between 2015 and 2019. 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 19.3%, 37.8%, 48.2%, and 58.4% of the initial regimens in 2016, 2017, 2018, and 2019, respectively. At the same time, TDF use decreased from 60.9% in 2015 to 26.5% in 2018, and then increased to 32.5% in 2019, probably because of a sharp decrease in the use of abacavir-containing NRTI backbones in 2019. The use of abacavir in combination with lamivudine decreased from 36.8% of all initial regimens in 2015 to 23.7% in 2018, after which there was a sharp decrease to 6.9% in 2019. The combination of zidovudine and lamivudine, often used by migrants who initiated cART before arriving in the Netherlands, has further decreased to <1% since 2016.

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2015–19.*



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 between 2015 and 2019 are presented in *Figure 2.6* and *Table 2.3*. In 2019, the most frequently used initial regimen was TAF/FTC/bictegravir (47.1%). Dolutegravir-containing initial regimens were used in 27.3% of cases: combined with either abacavir and lamivudine as part of the once-daily, fixed-dose combination (6.9%), or provided with emtricitabine and tenofovir separately (TDF 18.5%/TAF 1.9%). Additionally, 3.6% initiated an EVG/c-containing once-daily, fixed-dose combination with emtricitabine and tenofovir (TDF 1.0%/TAF 2.7%). Raltegravir use in an initial regimen was 1.3% in 2019. The combination of ritonavir or cobicistat-boosted darunavir with tenofovir and emtricitabine was used in 6.5% of initial cART regimens in 2019: 1.7% based on TDF and 4.8% on the once-daily, fixed-dose combination with TAF. *Table 2.3* provides more detail on the 'other' initial regimens that are not further specified in *Figures 2.4-2.6*

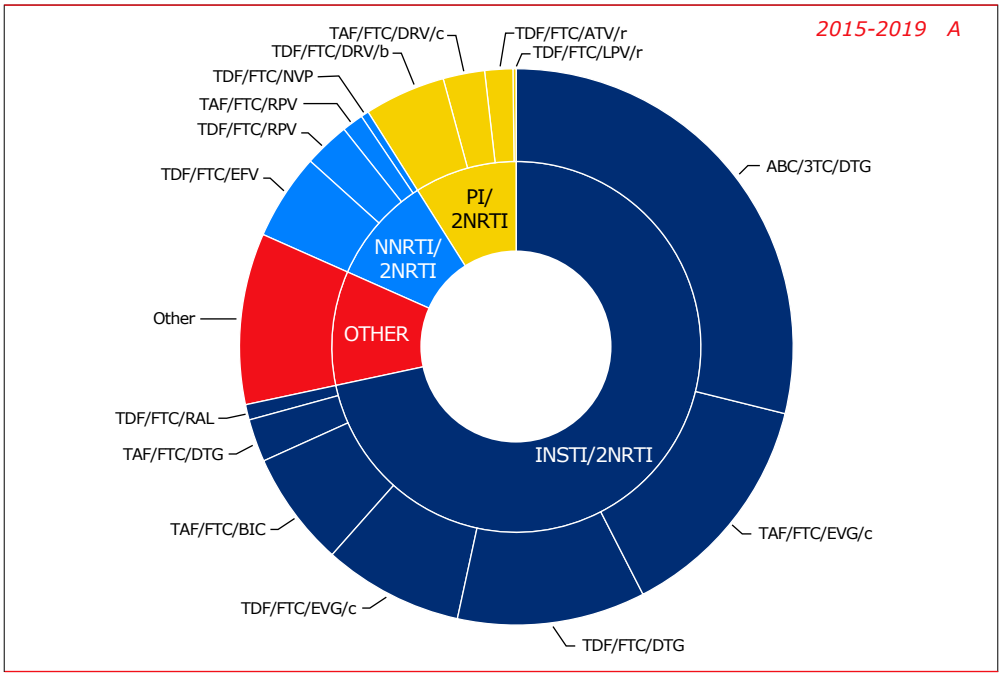
***Table 2.3:** Initial regimen in 2015–19.*

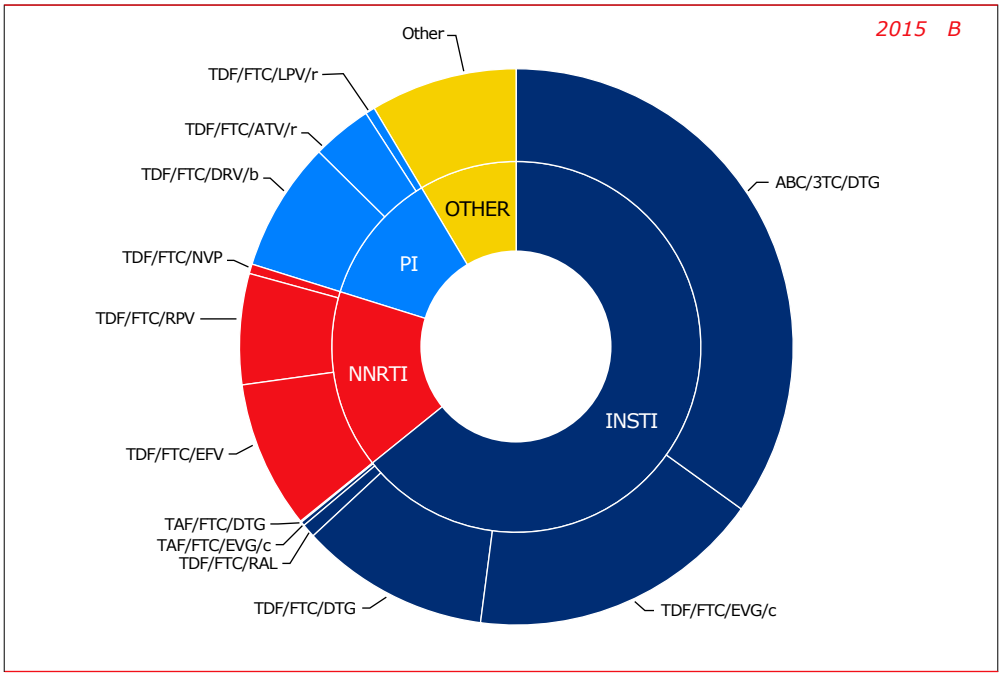
Regimen		2015	2016	2017	2018	2019	2015–2019
Total	n	1,258	1,065	950	784	524	**4,581**
TDF/FTC/EFV	n	108	65	25	23	9	230
	%	8.6	6.1	2.6	2.9	1.7	5.0
TDF/FTC/NVP	n	7	9	2	2	1	21
	%	0.6	0.9	0.2	0.3	0.2	0.5
TDF/FTC/RPV	n	81	30	8	1	2	122
	%	6.4	2.8	0.8	0.1	0.4	2.7
TDF/FTC/DRV/b	n	95	67	35	11	9	217
	%	7.6	6.3	3.7	1.4	1.7	4.7
TDF/FTC/ATV/b	n	44	17	4	6	4	75
	%	3.5	1.6	0.4	0.8	0.8	1.6
TDF/FTC/LPV	n	7	1	1	.	.	9
	%	0.6	0.1	0.1	.	.	0.2
TDF/FTC/EVG/c	n	216	85	53	15	5	374
	%	17.2	8.0	5.6	1.9	1.0	8.2
TDF/FTC/DTG	n	139	103	82	82	97	503
	%	11.1	9.7	8.6	10.5	18.5	11.0
TDF/FTC/RAL	n	10	7	5	12	7	41
	%	0.8	0.7	0.5	1.5	1.3	0.9
ABC/3TC/DTG	n	439	370	297	180	36	1322
	%	34.9	34.7	31.3	23.0	6.9	28.9
TAF/FTC/RPV	n	.	5	16	33	3	57
	%	.	0.5	1.7	4.2	0.6	1.2

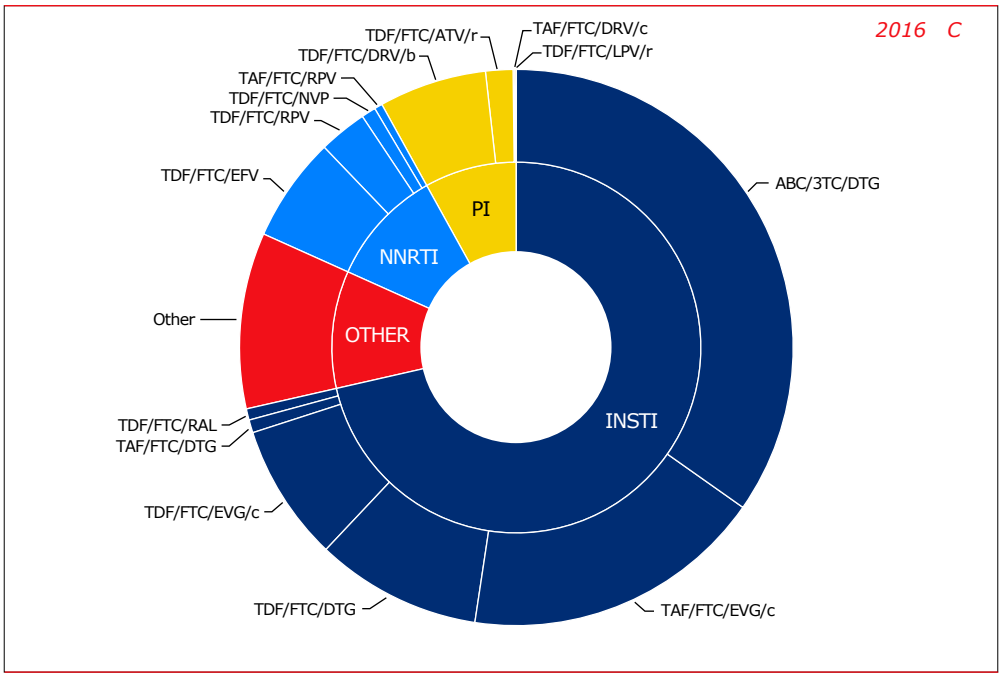
TAF/FTC/DRV/c	n	.	1	30	55	25	111
	%	.	0.1	3.2	7.0	4.8	2.4
TAF/FTC/EVG/c	n	3	188	241	176	14	622
	%	0.2	17.7	25.4	22.5	2.7	13.6
TAF/FTC/DTG	n	1	8	54	41	10	114
	%	0.1	0.8	5.7	5.2	1.9	2.5
TAF/FTC/BIC	n	.	.	2	58	247	307
	%	.	.	0.2	7.4	47.1	6.7
Other: 2NRTI+NNRTI	n	30	17	19	11	7	84
	%	2.4	1.6	2	1.4	1.3	1.8
Other: 2NRTI+PI	n	19	14	5	6	1	45
	%	1.5	1.3	0.5	0.8	0.2	1.0
Other: 2NRTI+INST	n	2	3	11	16	7	39
	%	0.2	0.23	1.2	2.0	1.3	0.9
Other: NNRTI+INST	n	.	.	.	.	1	1
	%	.	.	.	.	0.2	0.0
Other: PI+INSTI	n	5	7	7	3	2	24
	%	0.4	0.7	0.7	0.4	0.4	0.5
Other: NRTI+PI+INSTI (3ARVs)	n	2	.	1	1	1	5
	%	0.2	.	0.1	0.1	0.2	0.1
Other: NRTI+PI+INSTI (4ARVs)	n	42	58	52	48	32	232
	%	3.3	5.5	5.5	6.1	6.1	5.1
Other	n	8	10	.	4	4	26
	%	0.6	0.9	.	0.5	0.8	0.6

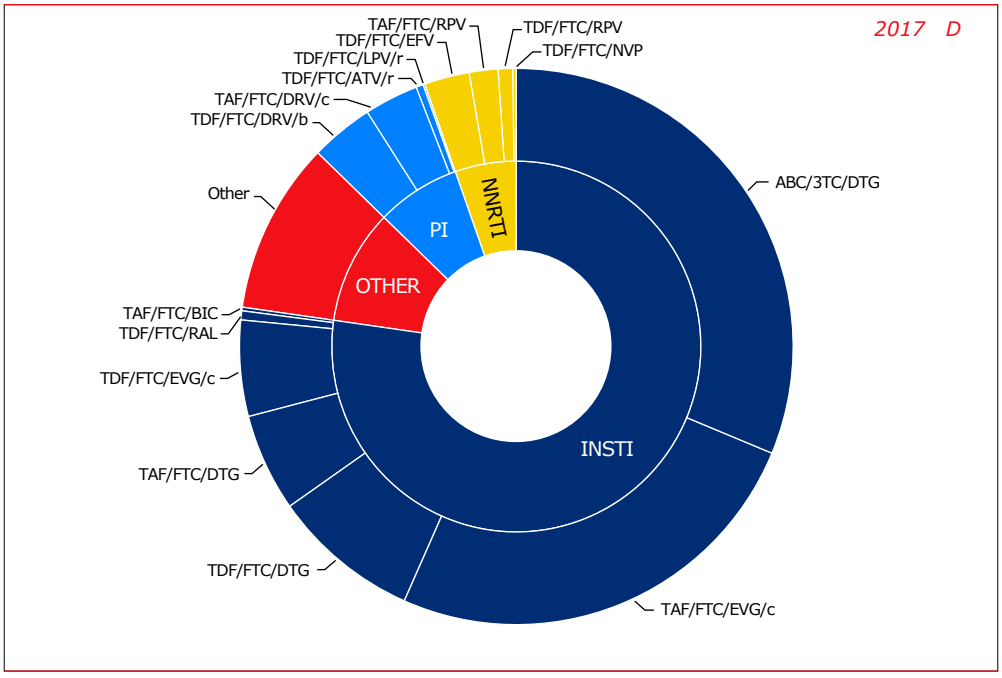
Legend: *ARVs=antiretroviral drugs; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; ATV= atazanavir; BIC=bictegravir; CI=confidence interval; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV=lopinavir; 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.*

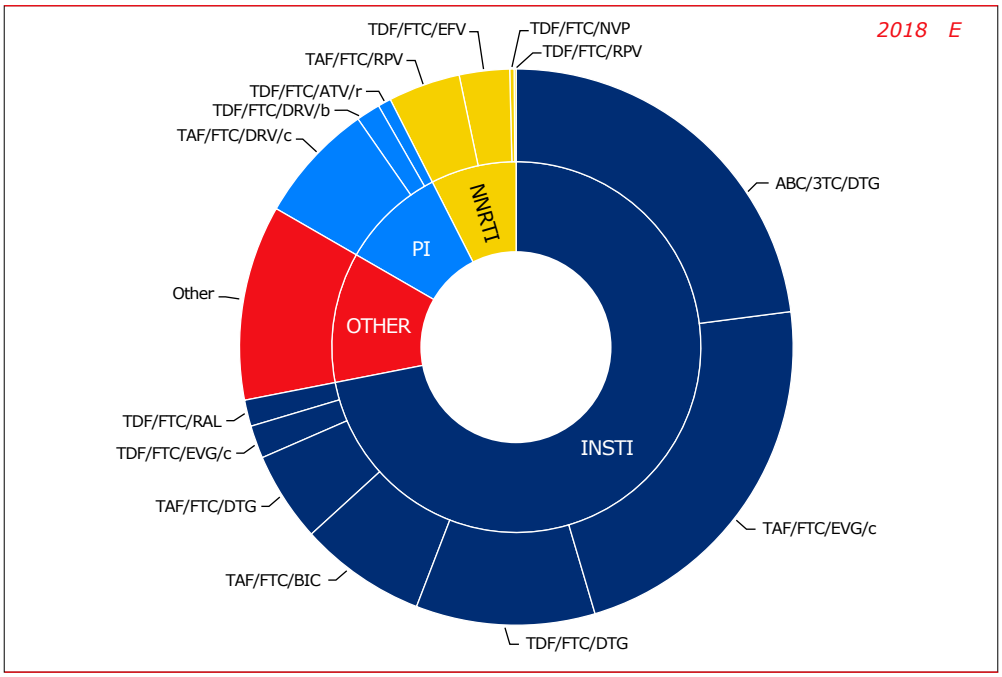
Figure 2.6A–F: Initial combination antiretroviral therapy regimens in 2015–19.

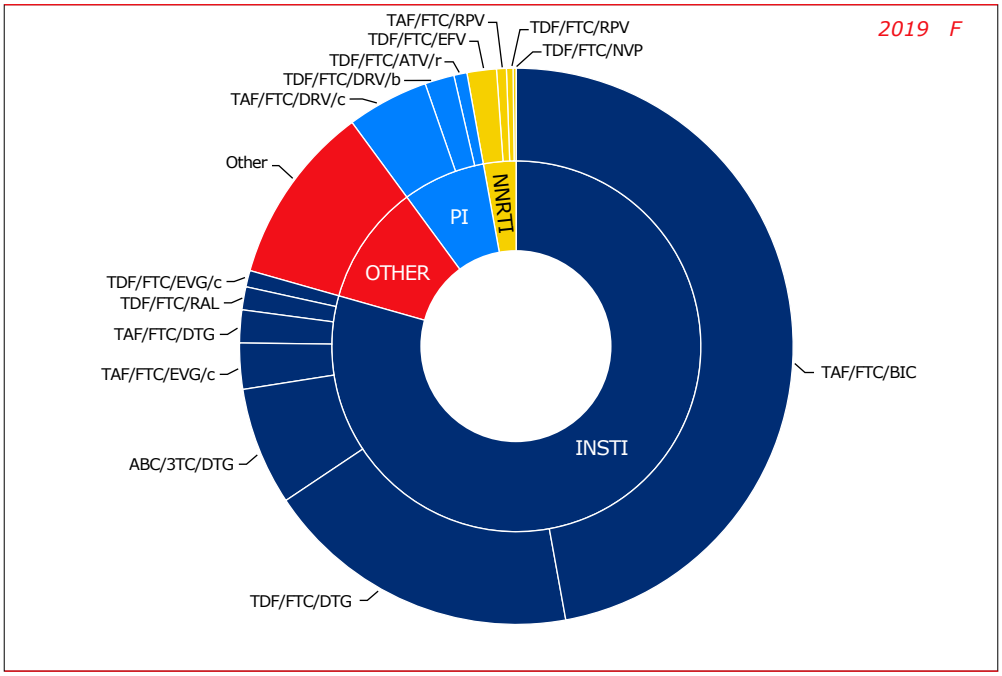





2016 C
TDF/FTC/ATV/r
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TDF/FTC/LPV/r
TAF/FTC/RPV
TDF/FTC/NVP
TDF/FTC/RPV
TDF/FTC/EFV
ABC/3TC/DTG
PI
NNRTI
Other
OTHER
INSTI
TDF/FTC/RAL
TAF/FTC/DTG
TDF/FTC/EVG/c
TDF/FTC/DTG
TAF/FTC/EVG/c


2017 D
TAF/FTC/RPV
TDF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/NVP
TDF/FTC/LPV/r
TDF/FTC/ATV/r
TAF/FTC/DRV/c
TDF/FTC/DRV/b
ABC/3TC/DTG
Other
PI
NNRTI
OTHER
TAF/FTC/BIC
TDF/FTC/RAL
TDF/FTC/EVG/c
INSTI
TAF/FTC/DTG
TDF/FTC/DTG
TAF/FTC/EVG/c





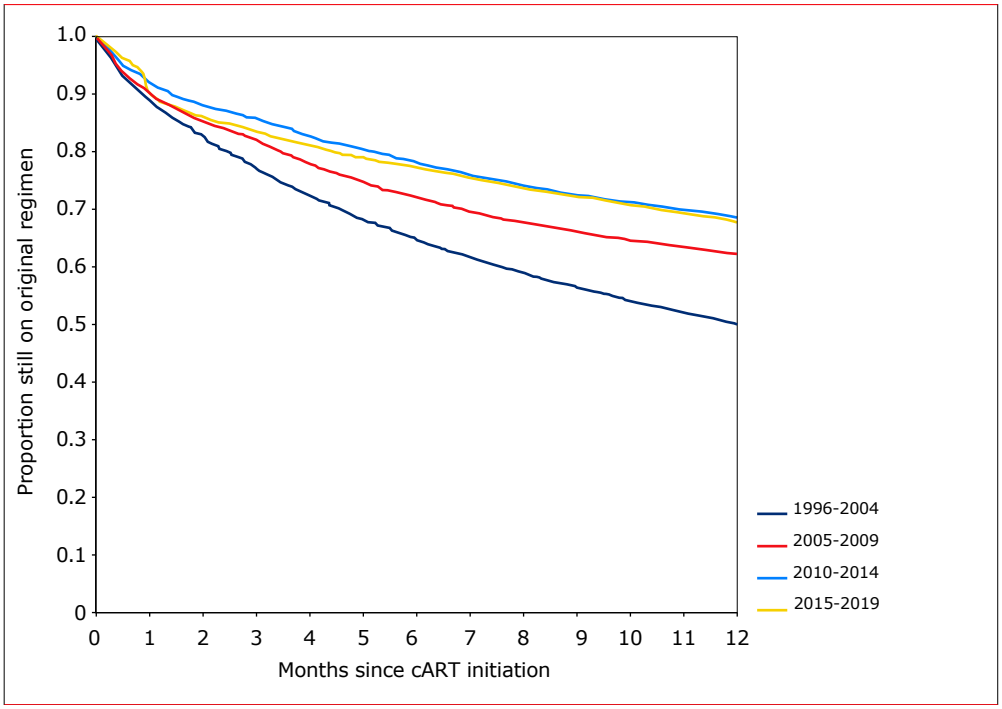
Legend: *3TC=lamivudine; ABC=abacavir; ATV=atazanavir; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; LPV=lopinavir; NNRTI=non-nucleoside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

Discontinuation of the initial cART regimen

For the 25,587 people who started cART between 1996 and 2019, we assessed the time spent on the initial cART regimen. Discontinuation of the initial cART regimen was defined as a change in, or discontinuation of ≥one 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 1996-2019, 38.9% of individuals discontinued their initial regimen within one year. The time remaining on the initial regimen improved over the years: in 1996-2004, 50.0% discontinued their original regimen within a year, compared to approximately a third in 2000-19. The time spent on the initial regimen during the first year of cART stratified by five-year periods is shown in *Figure 2.7*.

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



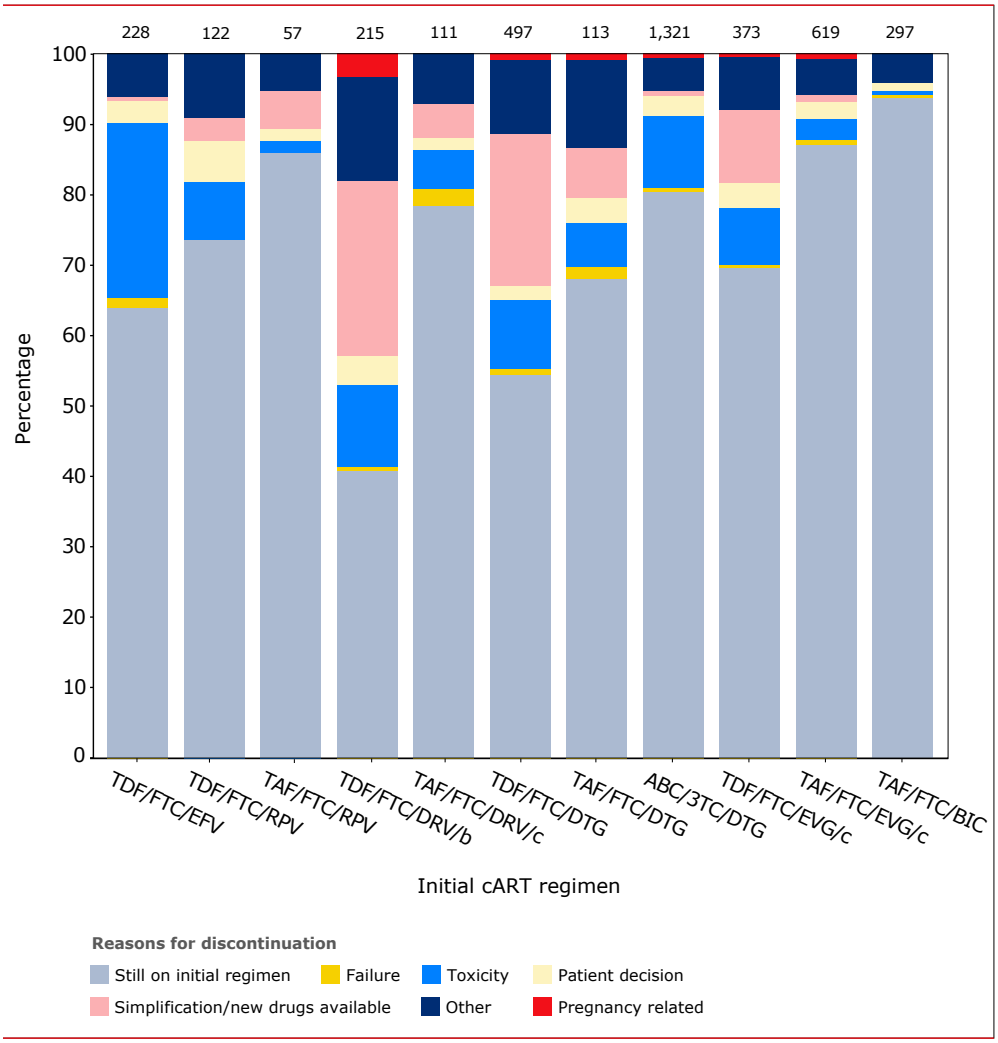
Legend: *cART=combination antiretroviral therapy*

Discontinuation of the initial cART regimen: 2015–19

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 3,953 people who started 'common' and guideline-recommended initial regimens in 2015-19. The regimens considered in this analysis were: tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (TDF/FTC/EFV, 5.7%); rilpivirine (TDF/FTC/RPV, 3.1%); ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b, 5.4%); cobicistat-boosted elvitegravir (TDF/FTC/EVG/c, 9.4%); dolutegravir (TDF/FTC/DTG, 12.6%); abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG, 33.4%); tenofovir alafenamide/emtricitabine combined with cobicistat-boosted elvitegravir (TAF/FTC/EVG/c, 15.7%); rilpivirine (TAF/FTC/RPV, 1.4%); dolutegravir (TAF/FTC/DTG, 2.9%); cobicistat-boosted darunavir (TAF/FTC/DRV/c, 2.8%); and bictegravir (TAF/FTC/BIC, 7.5%).

One year after cART initiation, 999 (25.3%) of the 3,953 individuals using one of these initial regimens, had discontinued it. The main reason for this discontinuation was toxicity (342, 34.2%), followed by simplification and/or availability of new drugs (232, 23.2%). 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, 27.9% of all discontinuations were for reasons of simplification and/or availability of new drugs in 2015, 24.0% in 2016, 20.2% in 2017, 18.2% in 2018, and 15.7% in 2019.

Figure 2.8: Reasons for discontinuation of the initial regimen during the first year of treatment 2015–19, by regimen. Numbers above the bars represent the total number of individuals using that particular regimen.

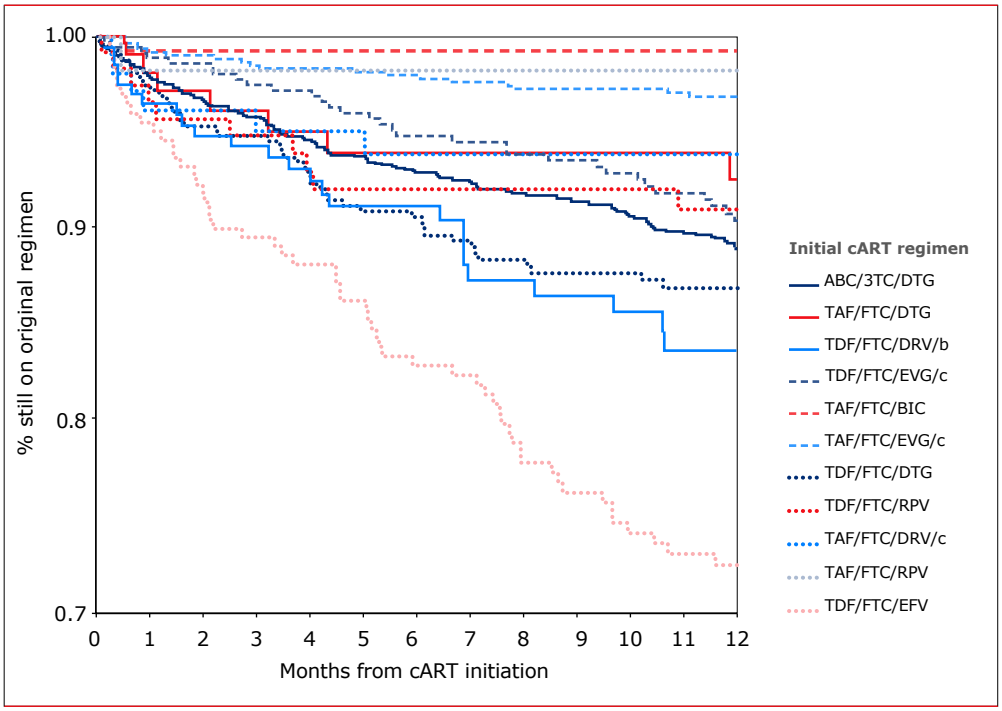


Legend: cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil 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 2015-19, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).*

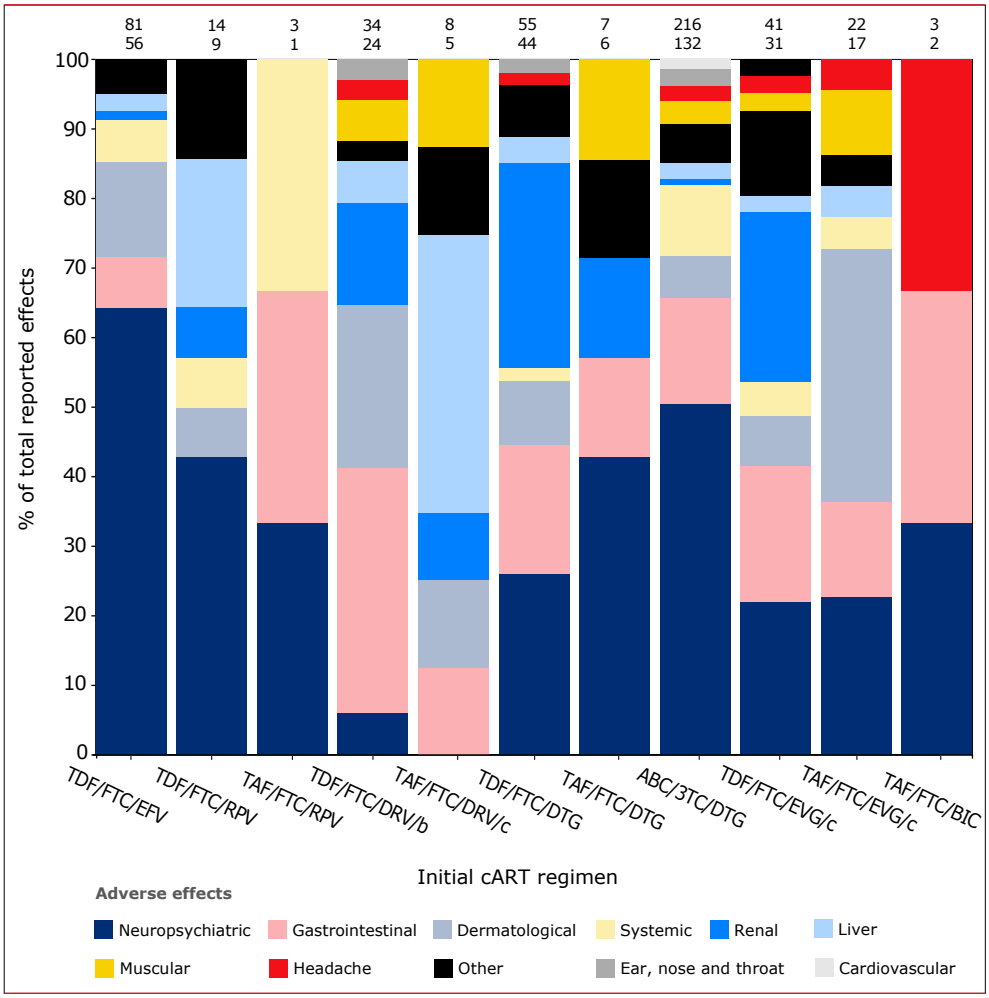


Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir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

Adverse effects

Among the 342 individuals who discontinued their initial cART regimen within a year due to toxicity, 484 adverse effects were recorded. The predominant effects were: 41.7% neuropsychiatric (mainly insomnia, mood changes, dizziness and depression), 15.7% gastrointestinal (mainly diarrhoea and nausea), 10.3% dermatological (rash due to medication, itching), 7.9% systemic (tiredness, apathy, loss of appetite), and 7.0% renal (renal insufficiency and increased serum creatinine). 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 2015–19. The bars represent the distribution of 484 reported effects among 342 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).



Legend: cART=combination antiretroviral therapy; 3TC=lamivudine; ABC=abacavir; b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 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 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.

Virological response

In the Netherlands, a total of 25,587 adults started cART between January 1996 and December 2019. For the current analysis of virological outcomes, we have focused on the 22,227 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 in the following section on viral response to cART are therefore restricted to the remaining 21,644 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 <100 copies/ml within six months of starting combination antiretroviral therapy (cART).
The viral load measurement closest to six months (±three months) after cART initiation was included in the analysis, irrespective of the viral load level.

Viral suppression

Any viral load measurements <200 copies/ml, within 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 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[26].

Acquired HIV drug resistance

High-level resistance to at least one antiretroviral drug, detected at the time of HIV viral load >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[27,28].

Initial virological success

Of the 21,644 individuals with a viral load test result after at least three months of cART initiation, 18,964 (87.6%) had a viral load measurement six months (±three months) after cART initiation. Of these people, 16,031 (84.5%) achieved initial virological success (i.e., a plasma viral load <100 HIV RNA copies/ml (*Box 2.3*)). The percentage of people with initial virological success has improved over time, from 61.1% in those starting cART between 1996 and 2003, to 88.0% in those starting between 2004 and 2010, 92.3% in those starting between 2011 and 2018, and 94.0% in those starting in 2019.

Initial virological success of common initial cART regimens (2015–19)

We analysed initial virological success among the 4,944 adults who started a common or guideline-recommended cART regimen in 2015-19, 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); described under 'Changes in use of initial antiretroviral therapy 2015-19'), and had a viral load result within six months (±three months) of cART initiation. In total, 94.1% (95% CI 93.5-94.8) 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: 94.3% (95% CI 94.1-95.8) of those on an integrase-inhibitor-based regimen and 94.0% (95% CI 92.6-95.4) on a NNRTI-based regimen had initial virological success, compared to 89.7% (95% CI 87.3-92.1) 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 (</≥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 ≥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 <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.

	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	627	12.7	346	11.0	97.7	96.1	99.3	Ref.
TDF/FTC/RPV	458	9.3	458	14.7	95.4	93.5	97.3	0.093
TDF/FTC/DRV/b	534	10.8	218	7.0	95.9	93.2	98.5	0.23
TDF/FTC/DTG	440	8.9	220	7.0	97.3	95.1	99.4	0.75
TDF/FTC/EVG/c	760	15.4	524	16.8	97.3	96.0	98.7	0.74
ABC/3TC/DTG	1,171	23.7	787	25.2	97.2	96.1	98.4	0.64
TAF/FTC/RPV	43	0.9	43	1.38	100	100	100	0.99
TAF/FTC/DRV/c	87	1.8	36	1.2	100	100	100	0.99
TAF/FTC/BIC	210	4.3	125	4.0	96.8	93.7	99.9	0.59
TAF/FTC/DTG	88	1.8	42	1.3	95.2	88.8	100	0.35
TAF/FTC/EVG/c	526	10.6	324	10.4	97.5	95.8	99.2	0.89
Regimen class								
NNRTI/2NRTI	1,128	22.8	847	27.1	96.6	95.4	97.8	Ref.
PI/2NRTI	621	12.6	254	8.1	96.5	94.2	98.7	0.92
INSTI/2NRTI	3,195	64.6	2,022	64.9	97.2	96.5	97.9	0.35
All regimens	**4,944**	**100 .0**	**3,123**	**63.2**	**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; Ref=Reference group.

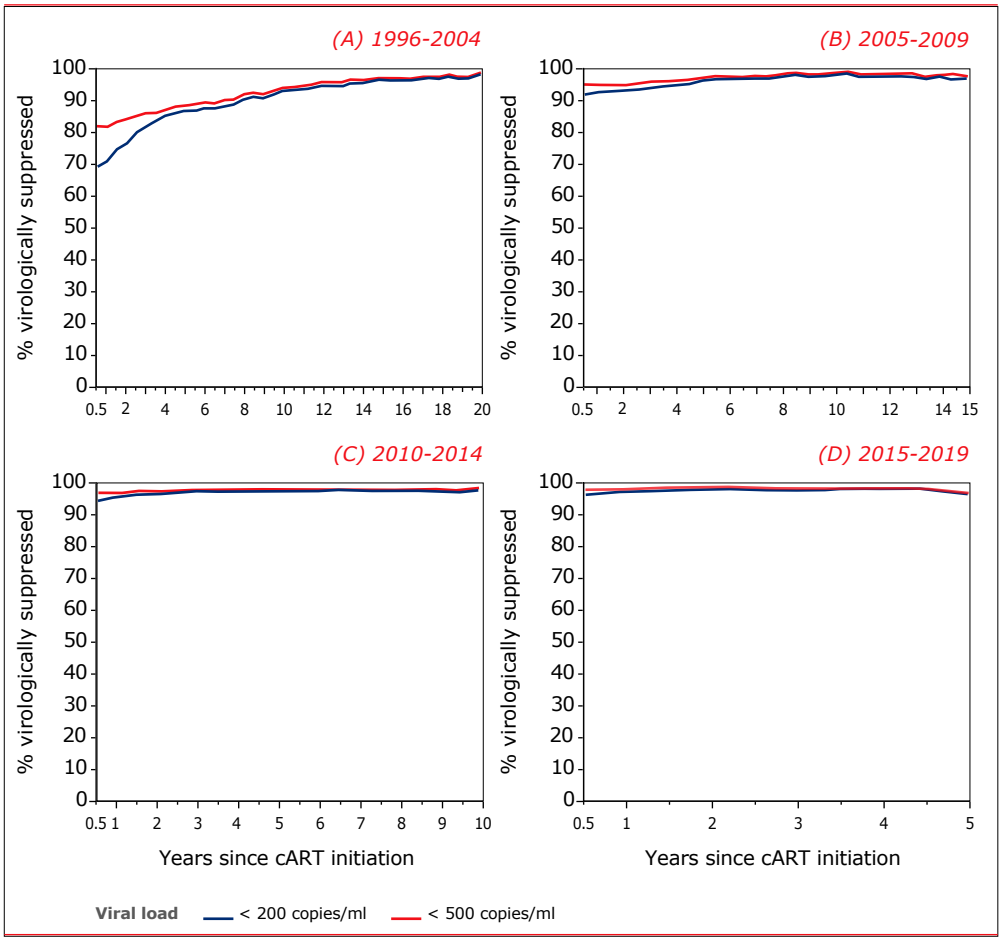
		By initial viral load at cART initiation					
		≥100,000 copies/ml					
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	cART regimen						
	TDF/FTC/EFV	281	15.4	86.1	82.1	90.2	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	316	17.4	85.4	81.6	89.3	0.81
	TDF/FTC/DTG	220	12.1	90.0	86.0	94.0	0.19
	TDF/FTC/EVG/c	236	13.0	89.8	86.0	93.7	0.20
	ABC/3TC/DTG	384	21.1	92.7	90.1	95.3	0.0061
	TAF/FTC/RPV	not recommended					
	TAF/FTC/DRV/c	51	2.8	82.3	71.9	92.8	0.48
	TAF/FTC/BIC	85	4.7	90.6	84.4	96.8	0.28
	TAF/FTC/DTG	46	2.5	93.5	86.3	100	0.18
	TAF/FTC/EVG/c	202	11.1	91.6	87.8	95.4	0.067
	Regimen class						
	NNRTI/2NRTI	281	15.4	86.1	82.1	90.2	Ref.
	PI/2NRTI	367	20.1	85.0	81.4	88.7	0.69
	INSTI/2NRTI	1,173	64.4	91.3	89.7	92.9	0.009
	All regimens	**1,821**	**36.8**	**89.2**	**87.8**	**90.7**	

Viral suppression

We assessed long-term viral suppression rates (i.e., viral load <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 (±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: 1996-2004, 2005-09, 2010-14, and 2015-19. 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 97.3% (95% CI 96.8-97.9) after one year of cART use to 97.9% (95% CI 97.0-98.7) after four years.

Figure 2.11A–D: *Viral suppression following combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation.*



Legend: *cART=combination antiretroviral therapy.*

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

HIV drug resistance

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 by the selection of mutations in the genetic structure of HIV that detrimentally affects 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[29].

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 part 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 for the full population in care.

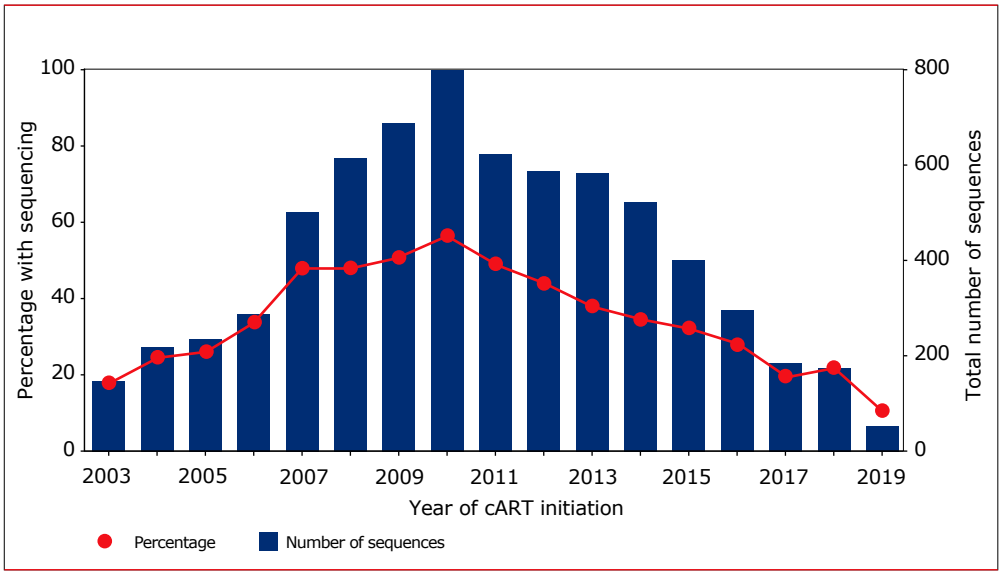
We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2019 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[26]. Furthermore, we assessed the association between these mutations and the susceptibility to 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[27,28]. 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

In the Netherlands, screening for HIV drug resistance at the time of entry into care has been incorporated in the treatment guidelines since 2003. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistance mutations. Drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[30–32]. These dormant mutant variants might not be detected, which could make it difficult to distinguish between drug-susceptible versus drug-resistant strains[33]. Therefore, ideally, the presence of transmitted resistance should be identified as close to the moment of infection as possible in people who are antiretroviral (ARV)-naive before initiating cART.

In total, 7,567 HIV-1 sequences were obtained between 2003-19 from 7,292 ARV-naive people before they initiated cART. The number of sequences and proportion of ARV-naive people with sequencing before cART initiation peaked in 2010 and have steadily declined since then (*Figure 2.12*). 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 (68.5%), while (14.4%) were women. Most people with an available pre-treatment sequence originated from the Netherlands (60.5%) or sub-Saharan Africa (11.3%). The main HIV-1 subtype was B (76.2%), followed by non-B subtypes (23.8%), including recombinant form CRF_02AG (6.6%), subtype C (4.8%), and CRF_01AE (3.4%).

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

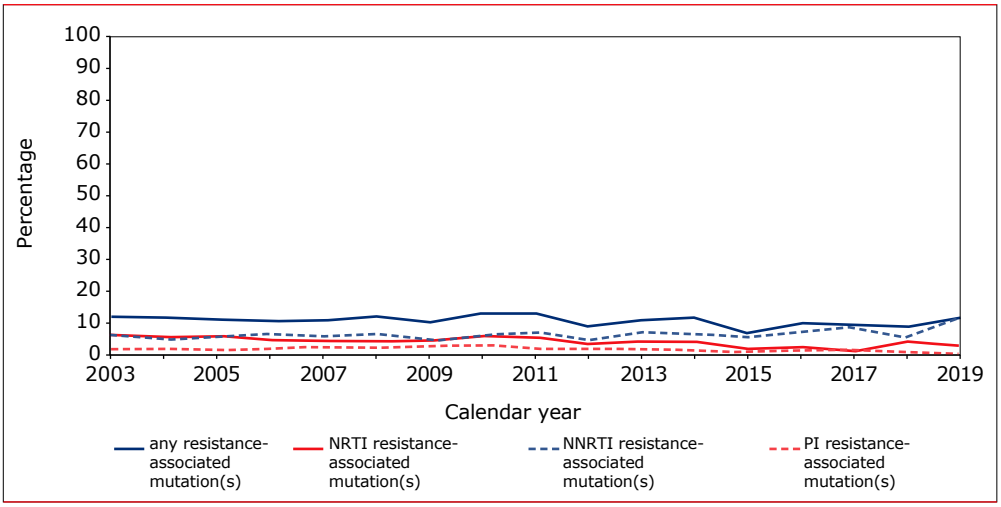


Legend: *cART=combination antiretroviral therapy.*

Transmitted HIV drug resistance

In total, ≥one resistance-associated major mutation[26] was found in 782 (10.7%) of the people tested for resistance, including 301 (4.1%) with NRTI-associated resistance mutations, 423 (5.8%) with NNRTI-associated resistance mutations, and 131 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2019 (*Figure 2.13*).

Figure 2.13: The annual proportion 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[26].



Legend: NRTI=nucleotide/nucleoside reverse transcription inhibitor, NNRTI=non-NRTI, PI=protease inhibitor.

In total, 195 (2.7%) individuals screened for transmitted drug resistance harboured high-level resistance[27,28] to at least one antiretroviral drug; 37 (0.5%) to at least one NRTI, 143 (2.0%) to at least one NNRTI, and 31 (0.5%) to at least one PI. On the basis of the available resistance data, >97% were fully susceptible to all antiretroviral drugs; 2.3% (166) harboured high-level resistance in one drug class, 0.3% (20) in two drug classes, and <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 often still be constructed.

Integrase inhibitor resistance before HIV treatment initiation

Twenty-seven 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.

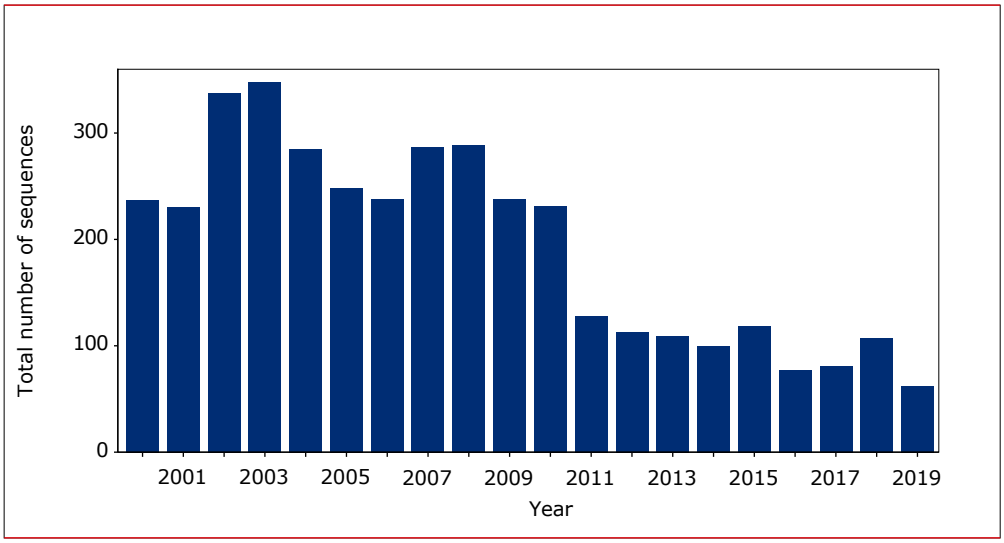
Acquired HIV drug resistance

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 can still be detected 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 >500 copies/ml and resistance test results available after at least four months of cART in 2000-19. If cART had been interrupted >two weeks before the test, the sequence was excluded from the analysis.

In total, 3,899 HIV-1 sequences were obtained from 2,402 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*). The median time between initial start of cART and resistance testing was 5.3 years (IQR 2.9-8.4). The main HIV-1 subtype was B (69.4%), followed by recombinant form CRF_02AG (10.1%), and subtype C (5.8%).

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



***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[27, 28].*

Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,289 (33.1%) sequences were obtained from 711 (29.6%) pre-treated people, and 2,610 (66.9%) sequences were obtained from 1,691 (70.4%) ARV-naive people. However, over time this difference became less distinct: in 2000, 73.2% of sequences were obtained from pre-treated people, compared with 36.8% in 2005, and less than 16% from 2010 onwards.

Out of the 3,899 sequences obtained at the time of HIV RNA >500 copies/ml, 2,590 (66.4%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,235 (58.0%) sequences; of those, 1,851 (82.8% of 2,235) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,595 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2019, 1,055 (66.1%) were still on cART containing lamivudine or emtricitabine, and 834/1055 (79.1%) had undetectable HIV-RNA at their last visit. In addition, 1,549 (40.2%) harboured high-level resistance to at least one NNRTI and 1,002 (26.9%) to at least one PI.

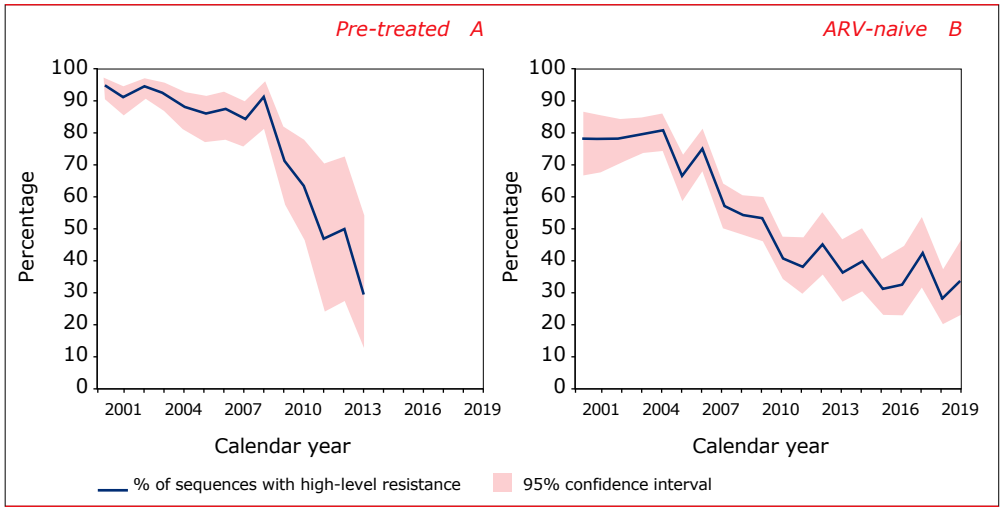
Previous antiretroviral drug exposure

The occurrence of acquired resistance was different for sequences obtained from pre-treated people than for those from people who were ARV-naive before initiating cART.

Among pre-treated people, the annual proportion of sequences harbouring high-level resistance to at least one drug was 94.9% (95% CI 90.4-97.3) in 2000, 88.1% (95% CI 80.5-93.0) in 2004, 63.6% (95% CI 46.2-78.1) 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[34]. In recent years (2014-19), both the number of pre-treated people, and the number of sequences from pre-treated people, were too low to provide meaningful proportions.

Among previously ARV-naive people, high-level resistance to at least one drug was detected among 78.1% (95% CI 66.4-86.6) of sequences in 2000, 75.3% (95% CI 68.1-81.3) in 2006, 45.5% (95% CI 35.9-55.3) in 2012, and 34.5% (95% CI 23.4-47.5) in 2019 (*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 proportion 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.*



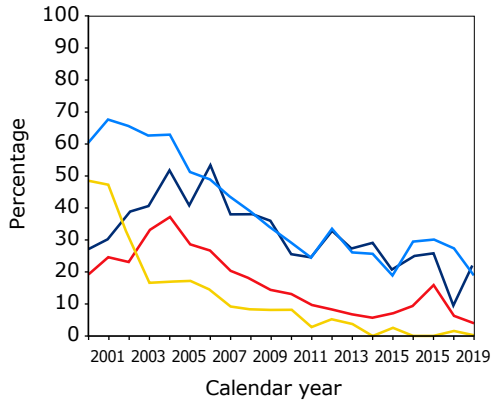
Note: *The number of sequences from pre-treated people in 2014-19 was too low to give meaningful proportions.*

Acquired HIV drug resistance among previously ARV-naive people

In the remainder of our analysis, we focus solely on the 1,691 people who were ARV-naive before cART initiation. Overall, 1,581 (60.6%) of the 2,610 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation, associated with resistance to NRTI (1,271, 48.7%), NNRTI (986, 37.8%), or PI (343, 13.1%).

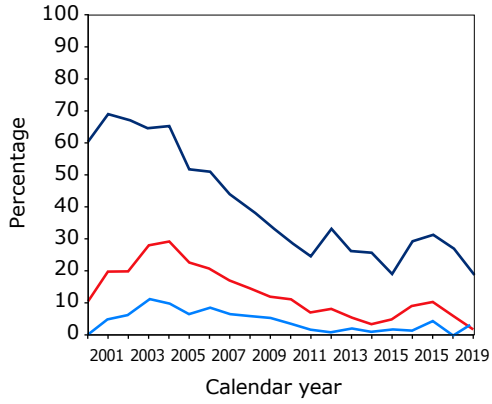
In *Figure 2.16A* and *Table 2.5*, the annual proportion of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000, 68.3% (95% CI 55.8-78.5), 27.0% (95% CI 17.5-39.2), and 48.4% (95% CI 36.5-60.5) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. The proportion of sequences with high-level of resistance declined over time for all drug classes. In 2009, 35.8% (95% CI 29.3-42.9), 35.8% (95% CI 29.3-42.9), and 7.9% (95% CI 4.8-12.7) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. In 2019, 20.8% (95% CI 11.9-33.7), 22.6% (95% CI 13.3-35.8), and 0% of sequences harboured high-level resistance to at least one NRTI, NNRTI or PI, respectively. The proportion of sequences with at least one resistance mutation to all three drug classes (i.e., NRTI, NNRTI, and PI) also declined over time: from 7.8% (95% CI 3.3-17.4) in 2000 to 0% in 2014. The annual proportions of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 2.16B-D* and *Appendix Table 2.1*, and annual proportions 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 2.16A-E: *The annual proportions 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 inhibitor, and protease inhibitors.*



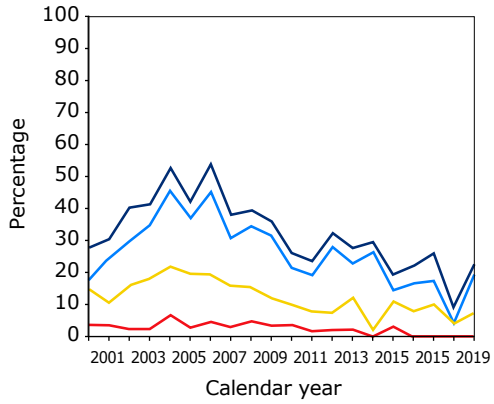
A
By antiretroviral drug class: high-level resistance to at least one drug per class

- Non-nucleoside reverse transcriptase inhibitor resistance
- Emtricitabine/lamivudine resistance
- Nucleoside reverse transcriptase inhibitor resistance (except emtricitabine/lamivudine)
- Protease inhibitor resistance

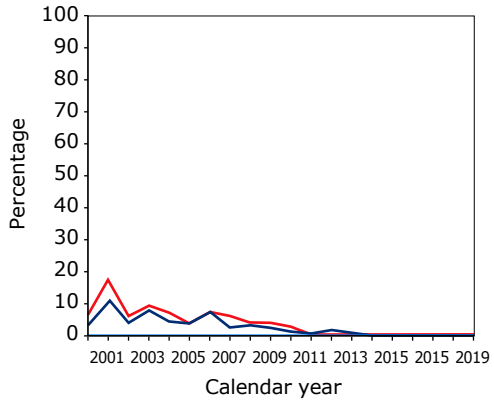


B
By antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors

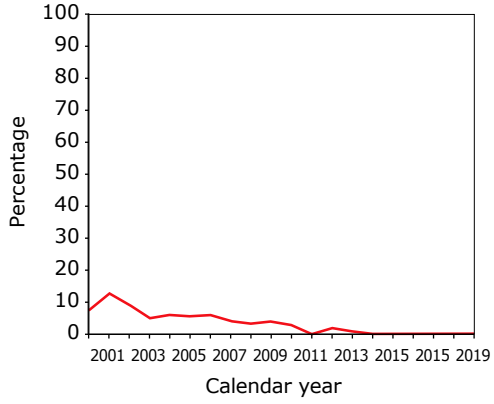
- Lamivudine/emtricitabine resistance
- Abacavir resistance
- Tenofovir resistance



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



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



E
By antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors (NRTI), non-NRTIs and protease inhibitors

Legend: *ABC=abacavir; ATV=atazanavir; DRV=darunavir; EFV=efavirenz; ETR=etravirine; FTC/3TC=emtricitabine/lamivudine; NRTIs=nucleo(s/t)ide-analogue reverse transcriptase inhibitors; NNRTIs=non-nucleoside reverse transcriptase inhibitors; NVP=nevirapine; LPV=lopinavir; PIs=protease inhibitors; RPV=rilpivirine; TDF=tenofovir disoproxil fumarate.*

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*[27,28].

Table 2.5: *Acquired drug resistance: the annual proportion 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 2.2 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	68.3	55.8	78.5	27.0	17.5	39.2	48.4	36.5	60.5
2001	75.6	65.4	83.5	30.2	21.5	40.7	47.1	36.7	57.6
2002	72.3	64.5	78.9	38.5	31.0	46.6	29.7	22.9	37.6
2003	70.8	64.0	76.8	40.6	33.9	47.7	16.3	11.7	22.3
2004	71.9	64.9	78.0	51.7	44.4	58.9	16.9	12.0	23.1
2005	58.2	50.4	65.7	40.5	33.1	48.3	17.1	12.0	23.8
2006	58.0	50.3	65.4	53.1	45.4	60.6	14.3	9.7	20.6
2007	48.7	41.6	55.8	38.0	31.3	45.1	9.1	5.7	14.1
2008	43.5	37.3	50.0	37.9	31.9	44.3	8.2	5.3	12.5
2009	35.8	29.3	42.9	35.8	29.3	42.9	7.9	4.8	12.7
2010	30.5	24.5	37.2	25.5	19.9	32.0	8.0	5.0	12.7
2011	27.0	19.6	35.8	24.3	17.4	33.0	2.7	0.9	7.9
2012	33.3	24.8	43.2	32.3	23.9	42.1	5.1	2.1	11.6
2013	27.2	19.1	37.1	27.2	19.1	37.1	3.4	1.1	10.2
2014	26.7	18.6	36.7	28.9	20.5	39.1	0		
2015	21.6	14.6	30.6	20.6	13.8	29.5	2.3	0.6	8.7
2016	29.2	19.5	41.4	24.6	15.7	36.5	0		
2017	35.7	25.4	47.5	25.7	16.8	37.2	0		
2018	27.3	19.4	36.9	9.1	4.8	16.6	1.4	0.2	9.5
2019	20.8	11.9	33.7	22.6	13.3	35.8	0		

Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was relatively rare. The available 167 integrase sequences originated from 138 people who received cART for at least four months; 15 were pre-treated with monotherapy or dual NRTI therapy before initiating cART, and 123 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 9.4 years (IQR 3.0-13.8). For each person, we used the most recent sequence for further analysis.

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 27 of the 138 individuals, which resulted in high-level resistance to at least one integrase inhibitor[27,35]. Among the 27, the following major INSTI resistance mutations were detected (numbers are given in parentheses): N155H (12) 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, three; T97A, three); T66 (any, three; T66T/A, two; T66T/K, one); and G140S (one). Four of the 27 patients who harboured major INSTI resistance mutations had ever received INSTI-monotherapy.

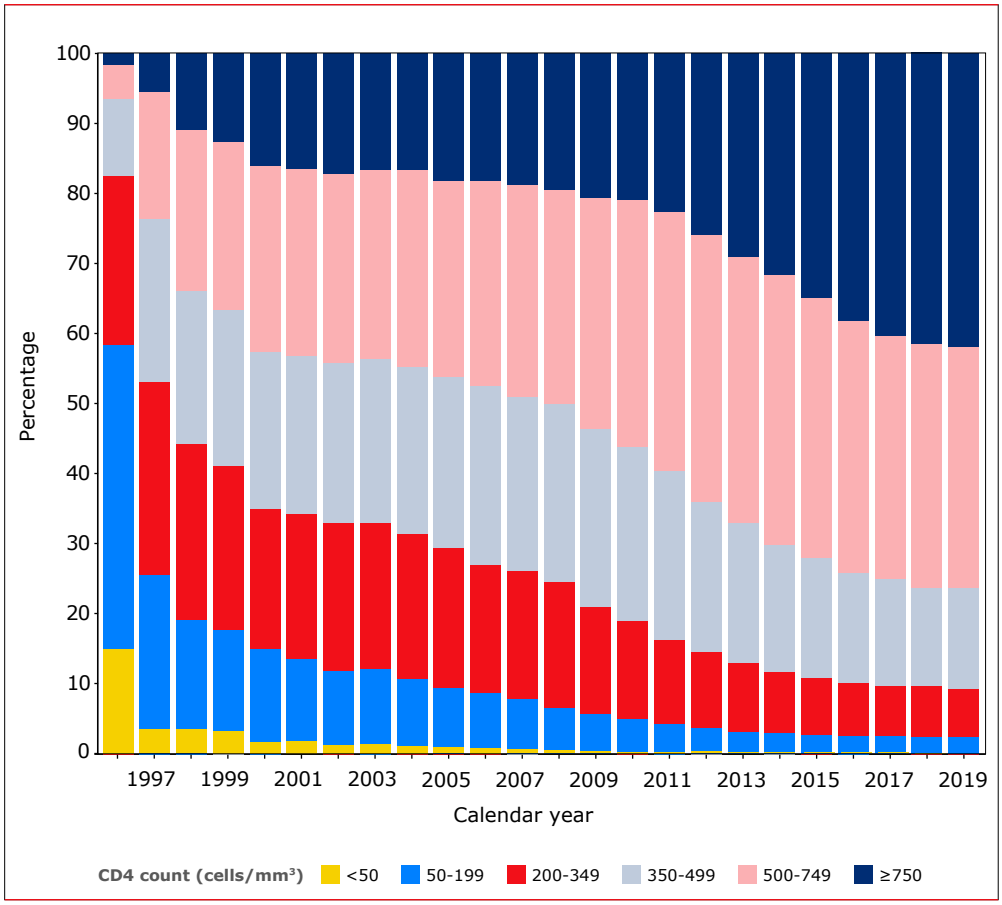
Immunological response

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 viraemia is associated with poorer recovery of CD4 cell count[36,37]. However, incomplete recovery of CD4 cell count 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[38]. 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[39]. 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[40–45]. The clinical benefit of cART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[46–50].

Immunological response – by calendar year

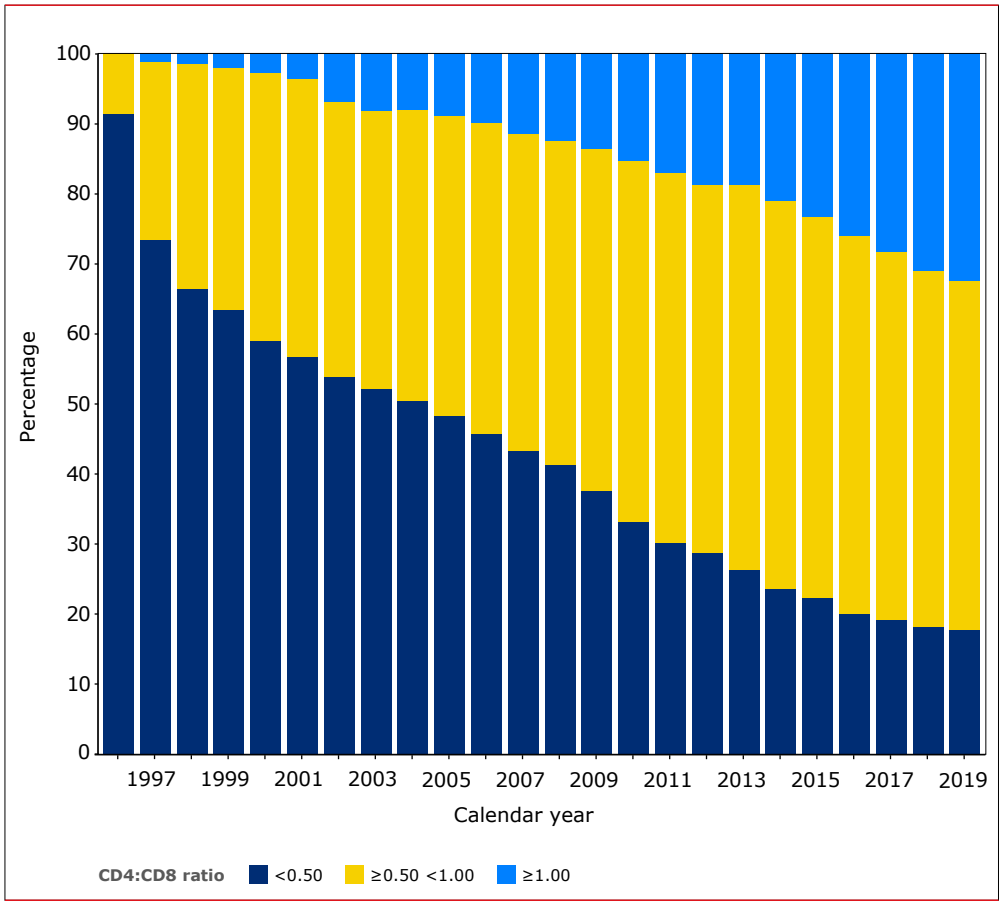
Of the 25,587 people known to have initiated cART between January 1996 and December 2019, CD4 cell count data after cART initiation were available for 25,088 (98.1%). *Figures 2.17* and *2.18* show the last known CD4 cell count and CD4:CD8 ratio of all people in HIV care for each calendar year. After starting cART, the percentage of people with CD4 cell counts <350 cells/mm^3 dropped from 53.1% in 1997 to 29.5% in 2005, 19.1% in 2010, 10.9% in 2015, and 9.4% in 2019 (*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 2019 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, 8.9% in 2005, 15.3% in 2010, 23.2% in 2015, and 32.4% in 2019 (*Figure 2.18*). Of all CD4:CD8 ratio measurements ≥one, 10.9% had a CD4 count of less than 500 cells/mm^3, 32.6% had a CD4 count between 500-749 cells/mm^3, and 56.5% had a CD4 count of ≥750 cells/mm^3. When the CD4:CD8 ratio was ≥one, the median CD4 count was 790 cells/mm^3 (IQR 620-1,000), and remained fairly stable over time, with a median of 760 cells/mm^3 (IQR 590-1,000) in 1996-2004, 750 cells/mm^3 (IQR 570-960) in 2005-09, 740 cells/mm^3 (IQR 580-940) in 2010-14, and 830 cells/mm^3 (IQR 653-1,030) in 2015-19.

***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 (2015–19)

We also assessed the immunological response in people who started cART more recently: 3,627 people started cART in 2015-19, and CD4 cell count data were 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 3,627 people who started cART in 2015-19 and had sufficient immunological data available, 9.3% had CD4 counts <50 cells/mm^3, 15.7% 50-199 cells/mm^3, 18.1% 200-349 cells/mm^3, 21.8% 350-499 cells/mm^3, and 35.0% ≥500 CD4 cells/mm^3 at the time of cART initiation. The CD4 cell count at cART initiation has decreased slightly in recent years (*Appendix Table 2.1*).

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 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[51].

Figure 2.19: CD4 cell count over time after the start of combination antiretroviral therapy (cART) in 2015–19.

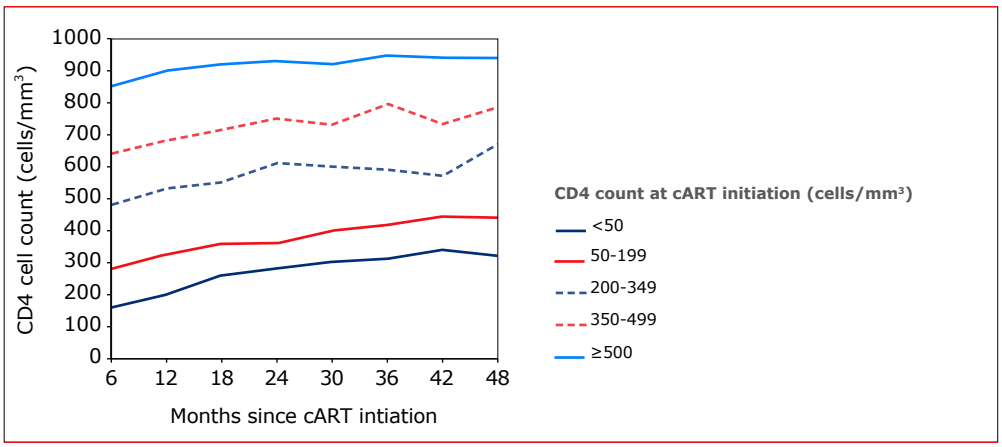
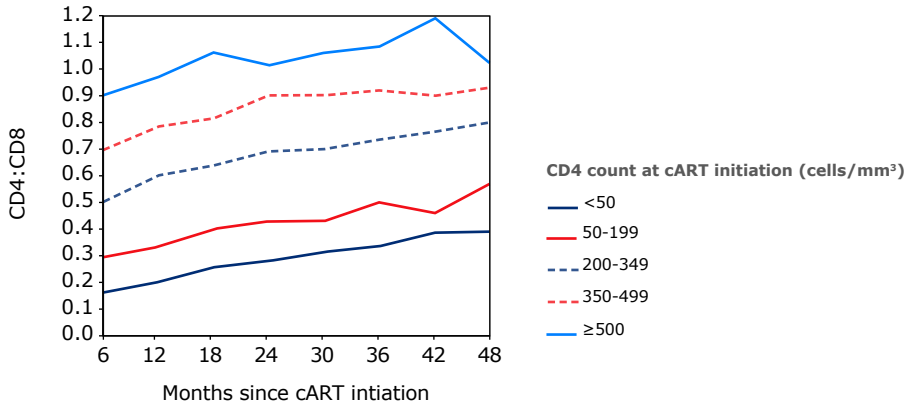


Figure 2.20: CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART) in 2015–19.



Note: The presented immunological outcomes are based on available test results. For people with a low to moderate CD4 cell count (<350 cells/mm³), CD4 cell count testing is recommended at least twice a year[52]. When a person has a CD4 cell count >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. However, despite this overall improvement, the proportion of HIV-positive individuals starting cART after six to 12 months, or more than 12 months after HIV diagnosis, increased in 2018 and 2019 to 29.2% of individuals initiating cART more than six months after HIV diagnosis. This increase was caused by a growing proportion of migrants who newly entered into care in the Netherlands while already being diagnosed with HIV and on ART before they migrated to the Netherlands, reflecting the increased availability of ART in their countries of origin. Late initiation of ART has become rare in individuals who were first diagnosed with HIV while living in the Netherlands.

- The CD4 cell count at cART initiation has increased over time, peaking in the year 2015 at a median of 414 cells/mm3 (IQR 220-600). This was when new guidelines came out recommending rapid initiation of cART at any CD4 count, which 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 decreased somewhat. Among HIV-positive individuals starting cART in 2019, the median CD4 cell count was 370 cells/mm3 (IQR 180-570). Immunological recovery was better when cART was started at a higher CD4 cell count.
- In 2019, 80.7% of initial regimens contained an integrase inhibitor. The most frequently used initial regimen was bictegravir/emtricitamine/tenofovir alafenamine (47.1%). Dolutegravir-containing initial regimens were used in 27.3% of cases; combined with either abacavir and lamivudine as part of the once-daily, fixed-dose combination (6.9%), or emtricitabine and tenofovir separately (TDF 18.5%/TAF 1.9%).
- Discontinuation of the initial regimen has become less common over time. Regimen switches were mainly due to intolerance, simplification, or the availability of new drugs.
- 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 2019

- Integrase inhibitor-based cART has been implemented on a large scale in the Netherlands and was used by 50.0% of all individuals.
- The nucleoside analogue backbone used by 31.9% contained TDF; 20.7% ABC and 42.1% TAF.
- Only 3.6% used a two-drug regimen.
- Of those receiving cART for at least 12 months, who had a plasma HIV RNA measurement in 2019, 97.5% had a viral load <200 copies/ml, and 95.1% had a viral load ≤50 copies/ml.

Virological response and drug resistance

- The overall viral suppression rates of the HIV-positive population receiving cART is high and has continued to improve. Among the limited number of individuals who experienced virological failure, the annual proportion of people with acquired drug resistance remained low; this is in line with findings from other high-income settings[53,54].
- Transmitted drug resistance was rare, and the overall prevalence was low and stable over time, in line with reported rates from other European countries[55].

- Integrase inhibitor resistance data remain limited. No transmitted integrase inhibitor resistance was detected amongst 27 people tested by the end of 2019. Detected rates of acquired integrase inhibitor resistance among available sequences continued to remain very low, with almost no significant resistance to dolutegravir.

Immunological response

- In individuals using cART, the percentage of people with CD4 cell counts <350 cells/mm3 dropped from 53.1% in 1997 to 29.5% in 2005, 19.1% in 2010, 10.9% in 2015, and 9.4% in 2019.
- The percentage of those with a CD4:CD8 ratio of one or above increased from 1.2% in 1997 to 2.8% in 2000, 8.9% in 2005, 15.3% in 2010, 23.2% in 2015, and 32.4% in 2019.

References

1. Cole SR, Hernan MA, Robins JM, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *Am J Epidemiol*. 2003;158(7):687-694. doi:10.1093/aje/kwg206
2. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171-181. doi:10.1001/jama.2016.5148
3. European AIDS Clinical Society. European AIDS Clinical Society (EACS) Guidelines. *Version 9*. 2017;(October):72. doi:10.1002/oby.21371.
4. Shilaih M, Marzel A, Yang WL, et al. Genotypic resistance tests sequences reveal the role of marginalized populations in HIV-1 transmission in Switzerland. *Sci Rep*. 2016;6(May):27580. doi:10.1038/srep27580
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Published 2016. Accessed July 14, 2016.http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf
6. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection.*; 2016.
7. Ryom L, Boesecke C, Bracchi M, et al. Highlights of the 2017 European AIDS Clinical Society (EACS) Guidelines for the treatment of adult HIV-positive persons version 9.0. *HIV Med*. Published online 2018:1-7. doi:10.1111/hiv.12600

8. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis*. 2014;14(4):281-290. doi:10.1016/S1473-3099(13)70692-3
9. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N Engl J Med*. 2011;365(6):493-505. doi:10.1056/NEJMoa1105243
10. Prevention Access Campaign. Consensus Statement: Risk of sexual transmission of HIV from a person living with HIV who has an undetectable viral load - Messaging Primer & Consensus Statement. 2017.
11. Nederlandse Vereniging van HIV Behandelaren. Het risico om hiv over te dragen is verwaarloosbaar klein indien de infectie goed behandeld wordt. May 3. Published 2017. http://nvhb.nl/2017/05/03/wetenschappelijk-onderzoek-toont-aan-dat-het-risico-om-hiv-over-te-dragen-verwaarloosbaar-klein-is-indien-de-infectie-goed-behandeld-wordt/
12. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000;342(13):921-929. doi:10.1056/NEJM200003303421303
13. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr*. 2002;29(3):275-283.
14. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. 2011;25(4):473-477. doi:10.1097/QAD.0b013e3283437c2b
15. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171-181. doi:10.1001/jama.2016.5148
16. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services.
17. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: Two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615. doi:10.1016/S0140-6736(15)60616-X
18. Nederlandse Vereniging van HIV Behandelaren. 2.2. Keuze van antiretrovirale therapie bij naïeve volwassen patiënten. Published 2019. http://richtlijnhiv.nvhb.nl/index.php/2.2._Keuze_van_antiretrovirale_therapie_bij_naïeve_volwassen_patiënten

19. Raboud JM, Rae S, Woods R, et al. Consecutive rebounds in plasma viral load are associated with virological failure at 52 weeks among HIV-infected patients. *AIDS*. 2002;16(12):1627-1632. doi:10.1097/00002030-200208160-00008
20. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS*. 2004;18(7):981-989. doi:10.1097/01.aids.0000125906.75228.f5
21. Hughes RA, Sterne JAC, Walsh J, et al. Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. *HIV Med*. 2011;12(10):583-593. doi:10.1111/j.1468-1293.2011.00929.x
22. van Lelyveld SF, Gras L, Kesselring A, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS*. 2012;26(4):465-474.
23. Zhang S, van Sighem A, Gras L, et al. Clinical significance of transient HIV type-1 viraemia and treatment interruptions during suppressive antiretroviral treatment. *Antivir Ther*. 2010;15(4):555-562.
24. Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to < 400 copies/ml. *AIDS*. 2002;16(11):1521-1527. doi:10.1097/00002030-200207260-00009
25. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr*. 2004;37(1):1147-1154. doi:00126334-200409010-00005 [pii]
26. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2019 update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2019;27(3):111-121.
27. Stanford University. HIV Drug Resistance Database - Release Notes.
28. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis*. 2006;42(11):1608-1618. doi:10.1086/503914
29. World Health Organization. *HIV Drug Resistance Report 2017*. World Health Organization; 2017.
30. Barbour JD, Hecht FM, Wrin T, et al. Persistence of primary drug resistance among recently HIV-1 infected adults. *AIDS*. 2004;18(12):1683-1689.
31. Little SJ, Frost SDW, Wong JK, et al. Persistence of Transmitted Drug Resistance among Subjects with Primary Human Immunodeficiency Virus Infection. *J Virol*. 2008;82(11):5510-5518. doi:10.1128/JVI.02579-07
32. Bezemer D, De Ronde A, Prins M, et al. Evolution of transmitted HIV-1 with drug-resistance mutations in the absence of therapy: Effects on CD4+ T-cell count and HIV-1 RNA load. *Antivir Ther*. 2006;11(2):173-178.

33. Boukli N, Boyd A, Collot M, Meynard J-L, Girard P-M, Morand-Joubert L. Utility of HIV-1 DNA genotype in determining antiretroviral resistance in patients with low or undetectable HIV RNA viral loads. *J Antimicrob Chemother*. 2018;73(11):3129-3136. doi:10.1093/jac/dky316
34. Lange JM, Ananworanich J. The discovery and development of antiretroviral agents. *Antivir Ther*. 2014;19 Suppl 3:5-14. doi:10.3851/IMP2896
35. Wensing AM, Calvez V, Günthard HF, et al. 2017 update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2017;24(4):132-133.
36. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm3 or greater. *J Acquir Immune Defic Syndr*. 2007;45(2):183-192. doi:10.1097/QAI.0b013e31804d685b
37. Hughes RA, Sterne JAC, Walsh J, et al. Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. *HIV Med*. 2011;12(10):583-593. doi:10.1111/j.1468-1293.2011.00929.x
38. van Lelyveld SF, Gras L, Kesselring A, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS*. 2012;26(4):465-474.
39. Tsegaye A, Messele T, Tilahun T, et al. Immunohematological reference ranges for adult Ethiopians. *Clin Diagn Lab Immunol*. 1999;6(3):410-414.
40. Serrano-Villar S, Moreno S, Fuentes-Ferrer M, et al. The CD4:CD8 ratio is associated with markers of age-associated disease in virally suppressed HIV-infected patients with immunological recovery. *HIV Med*. 2014;15(1):40-49. doi:10.1111/hiv.12081
41. Serrano-Villar S, P??rez-El??as MJ, Dronda F, et al. Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. *PLoS One*. 2014;9(1). doi:10.1371/journal.pone.0085798
42. Serrano-Villar S, Sainz T, Lee SA, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. *PLoS Pathog*. 2014;10(5):e1004078. doi:10.1371/journal.ppat.1004078
43. Lo J, Abbara S, Shturman L, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2010;24(2):243-253. doi:10.1097/QAD.0b013e328333ea9e
44. O'Connor J, Smith C, Lampe FC, et al. Durability of viral suppression with first-line antiretroviral therapy in patients with HIV in the UK: an observational cohort study. *Lancet HIV*. 2017;3018(17):1-8. doi:10.1016/S2352-3018(17)30053-X

45. The Antiretroviral Therapy Cohort Collaboration (ART-CC). Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV*. 2017;3018(17). doi:http://dx.doi.org/10.1016/
46. Effros RB, Fletcher C V, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis*. 2008;47(4):542-553. doi:10.1086/590150
47. Baker J V, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. 2008;22(7):841-848. http://www.ncbi.nlm.nih.gov/pubmed/18427202
48. Baker J V, Peng G, Rapkin J, et al. Poor initial CD4+ recovery with antiretroviral therapy prolongs immune depletion and increases risk for AIDS and non-AIDS diseases. *JAIDS J Acquir Immune Defic Syndr*. 2008;48(5):541-546. doi:10.1097/QAI.0b013e31817bebb3
49. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372(9635):293-299. doi:10.1016/S0140-6736(08)61113-7
50. Lanoy E, May M, Mocroft A, et al. Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements. *AIDS*. 2009;23(16):2199-2208. doi:10.1097/QAD.0b013e3283305a00
51. Hughes RA, May MT, Tilling K, et al. Long-term trends in CD4 cell counts, CD8 cell counts, and the CD4. *Aids*. 2018;32:1361-1367. doi:10.1097/QAD.0000000000001848
52. Nederlandse Vereniging van HIV Behandelaren. 4.1. Controles HIV-patiënten (polikliniek). Richtlijn HIV.
53. Scherrer AU, von Wyl V, Yang W-L, et al. Emergence of acquired HIV-1 drug resistance almost stopped in Switzerland: A 15-year prospective cohort analysis. *Clin Infect Dis*. 2016;62(10):1310-1317. doi:10.1093/cid/ciw128
54. Buchacz K, Baker R, Ward DJ, et al. Trends in decline of antiretroviral resistance among ARV-experienced patients in the HIV outpatient study: 1999-2008. *AIDS Res Treat*. 2012;2012. doi:10.1155/2012/230290
55. Hofstra LM, Sauvageot N, Albert J, et al. Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe. *Clin Infect Dis*. 2016;62(5):655-663. doi:10.1093/cid/civ963

Appendix

Appendix Table 2.1: CD4 cell count at combination antiretroviral therapy (cART) initiation by calendar year 2015–19.

Year of cART initiation	2015	2016	2017	2018	2019	2015–2019
CD4 cell count available at cART initiation	1,088	890	779	598	272	**3,627**
CD4 cell count, median cells/mm^3 (IQR)	420 (220–600)	410 (230–580)	380 (190–560)	365 (150–580)	322 (128–532)	**393 (199–580)**
CD4 cell count (cells/mm^3)						
<50	87 (8.0)	80 (9.0)	66 (8.5)	72 (12.0)	33 (12.1)	**338 (12.1)**
50–199	163 (15.0)	110 (12.4)	130 (16.7)	107 (17.9)	59 (21.7)	**569 (21.7)**
200–349	181 (16.7)	162 (18.2)	155 (19.9)	106 (17.7)	54 (19.9)	**658 (18.1)**
350–499	252 (23.2)	209 (23.5)	170 (21.8)	111 (18.6)	50 (18.4)	**792 (18.4)**
≥500	405 (37.2)	329 (37.0)	258 (33.1)	202 (33.8)	76 (27.9)	**1,270 (35.0)**

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

Appendix Table 2.2A–C: *Acquired drug resistance: annual proportion 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) High-level resistance to nucleoside reverse transcriptase inhibitors.

Calendar year	Number of sequences	Emtricitabine/ lamivudine	Zidovudine	Stavudine	Abacavir	Didanosine	Tenofovir
2000	63	60.3	13.6	9.3	10.3	10.9	0.0
2001	86	69.0	16.0	18.9	20.0	17.8	5.2
2002	148	67.4	12.2	15.8	20.1	19.3	6.6
2003	192	64.5	19.4	24.9	28.2	27.9	11.2
2004	178	65.5	19.9	23.2	29.3	29.7	10.1
2005	158	51.9	14.3	19.0	22.7	21.7	6.8
2006	162	51.0	11.3	16.8	20.9	22.6	8.8
2007	187	44.0	10.6	13.9	17.0	14.5	6.8
2008	232	39.5	7.8	11.8	14.7	15.6	6.1
2009	190	34.0	7.3	10.1	12.2	12.0	5.5
2010	200	29.1	5.8	8.5	11.4	11.9	3.7
2011	115	24.8	0.9	2.8	7.1	8.0	1.8
2012	99	33.3	0.0	2.1	8.3	8.2	1.1
2013	92	26.4	0.0	2.3	5.7	5.7	2.2
2014	90	25.8	1.1	3.4	3.4	4.5	1.2
2015	102	19.2	1.0	3.1	5.1	6.9	2.0
2016	65	29.2	1.6	3.2	9.4	6.5	1.6
2017	70	31.3	2.9	7.5	10.6	14.7	4.5
2018	99	27.3	0.0	0.0	6.1	5.1	0.0
2019	53	19.2	0.0	3.8	1.9	3.8	3.8

B) High-level resistance to non-nucleoside reverse transcriptase inhibitors.

Calendar year	Number of sequences	Nevirapine	Efavirenz	Etravirine	Rilpivirine
2000	63	27.9	17.9	3.8	15.0
2001	86	30.6	25.0	3.8	10.6
2002	148	40.1	30.0	2.5	16.1
2003	192	41.3	34.9	2.5	18.2
2004	178	52.6	45.6	6.8	21.8
2005	158	42.1	37.0	3.0	19.7
2006	162	53.8	45.0	4.8	19.6
2007	187	38.0	30.8	3.2	15.9
2008	232	39.5	34.5	5.0	15.5
2009	190	36.0	31.5	3.6	12.1
2010	200	26.2	21.5	3.8	10.0
2011	115	23.7	19.3	1.9	8.0
2012	99	32.3	28.0	2.2	7.6
2013	92	27.8	23.0	2.4	12.2
2014	90	29.5	26.4	0.0	2.3
2015	102	19.4	14.4	3.2	11.1
2016	65	22.2	16.7	0.0	8.1
2017	70	26.1	17.5	0.0	10.3
2018	99	9.1	4.3	0.0	4.2
2019	53	22.6	19.6	0.0	7.5

C) High-level resistance to protease inhibitors.

Calendar year	Number of sequences	Nelfinavir	Saquinavir	Indinavir	Atazanavir	Fosam-prenavir	Lopinavir	Tipranavir	Darunavir
2000	64	48.4	8.1	5.1	6.6	6.3	3.3	1.6	0.0
2001	85	47.6	21.6	18.3	17.7	13.8	11.1	2.5	0.0
2002	148	30.1	10.6	7.4	6.5	5.8	4.2	0.0	0.0
2003	190	17.0	9.3	9.9	9.6	7.6	8.1	1.6	0.0
2004	178	16.0	7.1	7.2	7.5	5.8	4.7	0.6	0.0
2005	158	17.1	4.2	6.8	4.0	3.4	4.0	0.7	0.0
2006	161	13.8	6.4	8.2	7.7	5.7	7.5	2.6	0.0
2007	187	9.2	4.4	4.4	6.5	3.3	2.7	1.1	0.0
2008	232	7.0	3.5	4.9	4.4	4.8	3.6	0.4	0.0
2009	190	7.5	3.7	4.3	4.3	4.3	2.7	1.1	0.0
2010	200	6.6	3.1	4.1	3.0	4.1	1.6	0.0	0.0
2011	113	2.7	0.9	0.9	0.9	0.9	0.9	0.0	0.0
2012	99	5.1	2.1	2.1	2.0	2.0	2.0	0.0	0.0
2013	87	3.4	0.0	1.2	1.1	2.3	1.2	0.0	0.0
2014	76	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2015	87	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2016	54	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2017	56	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2018	70	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2019	19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0