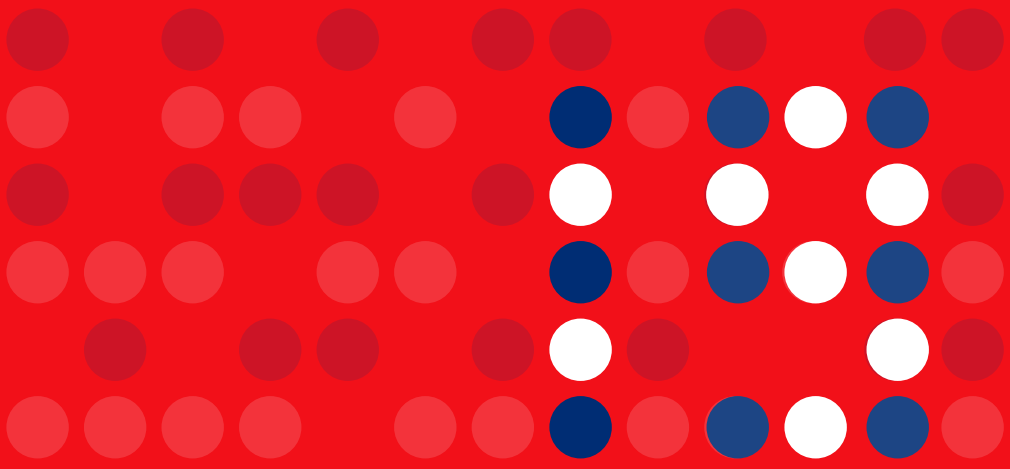
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2019

Chapter 2: Response to combination antiretroviral therapy (cART)



About Stichting HIV Monitoring

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001 and appointed by the Dutch minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-positive individuals in the Netherlands.

In collaboration with the HIV treatment centres in the Netherlands, SHM has developed a framework for systematically collecting HIV data for the long-term follow up of all registered individuals. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care.

SHM contributes to the knowledge of HIV by studying the course of the infection and the effect of its treatment. To this end, SHM follows the treatment of every HIV-positive man, woman and child in care in the Netherlands and registered in the national observational HIV cohort, ATHENA. Continuous collection of data is carried out at 24 HIV treatment centres and subcentres and 4 paediatric HIV centres in the Netherlands. Patient data are collected and entered into the database in a pseudonymised form for storage and analysis. In this way SHM is able to comprehensively map the HIV epidemic and HIV treatment outcomes in the Netherlands.

Our mission

To further the knowledge and understanding of all relevant aspects of HIV infection, including comorbidities and co-infections (such as viral hepatitis), in HIV-positive persons in care in the Netherlands.

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HIV Monitoring

Monitoring Report 2019

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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Guide to buttons

Content page

Next chapter

Preceding chapter

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2. Response to combination antiretroviral therapy (cART)

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Introduction

Since the introduction of combination antiretroviral therapy (cART) in 1996, there have been substantial advances in the use of antiretroviral drugs for the treatment and prevention of HIV infection. The primary goals of cART are to prevent HIV disease progression, improve clinical outcomes and limit transmission[1,2]. Treatment guidelines across the globe recommend cART for all people with HIV, regardless of CD4 count. The decision to initiate cART should always include consideration of a person's comorbid conditions and his or her willingness and readiness to initiate therapy. Thus, although cART may be deferred because of clinical and/or psychosocial factors on a case-by-case basis, therapy should be initiated as soon as possible[3,4,5,6,7]. In general, the guidelines of the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) 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 deferment 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; undetectable equals untransmittable, i.e., U=U[1,10,11,12,13,14]. Depending on the drugs employed, it may take as long as six months for the viral load to become undetectable. Moreover, sustained HIV suppression requires selection of appropriate treatment and adherence to treatment. HIV viral suppression should therefore be monitored and documented to assure 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 include elvitegravir as a boosted integrase inhibitor, darunavir as a boosted protease inhibitor 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)[9]. Additionally, tenofovir alafenamide (TAF) and tenofovir disoproxil

< Back to Chapter 1

fumarate (TDF) are two forms of tenofovir approved by the European Medicines Agency. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. On the other hand, TDF use should be avoided in people with reduced renal function and in people with osteoporosis or at risk for osteoporotic fractures[15,16]. Safety, ease of use, food effects, and potential for significant drug-drug interactions are among the factors to consider when choosing between these drugs. Finally, although still frequently used, efavirenz is no longer recommended as the preferred first-line cART regimen in the Netherlands, but remains an alternative[3,5,7].

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 and thereby increase the risk of poor clinical outcomes[17,18,19,20,21,22,23].

This chapter reports on the prescription of, and responses to, cART in HIV-1 positive adults in the Netherlands. 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.

Of the 26,173 registered adults (≥18 years at the time of diagnosis) with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   24,603 people were known to have initiated cART between January 1996 and December 2018.

2. **In care and on cART in the Netherlands in 2018**
   Out of 24,603 people who initiated cART between January 1996 and December 2018,
   ➔ 19,189 were in care and had a clinical visit in 2018;
   ➔ 3,812 of those were diagnosed with HIV before the year 2000, and 1,966 before 1996 (referred to as 'long-term HIV survivors').

3. **Changes in the use of initial cART regimen**
   Out of 24,603 people who initiated cART between January 1996 and December 2018,
   ➔ 6,729 initiated cART between January 2013 and December 2018;
   ➔ 5,508 people started 'common' and guideline-recommended initial regimens in 2013-2018: TDF/FTC/EFV (15.9%), TDF/FTC/RPV (10.9%), TDF/FTC/DRV/b (11.5%), TDF/FTC/EVG/c (16.4%), TDF/FTC/DTG (7.5%), ABC/3TC/DTG (23.4%), TAF/FTC/EVG/c (10.4%), TAF/FTC/RPV (0.8%), TAF/FTC/DTG (1.6%), TAF/FTC/DRV/c (1.0%), TAF/FTC/BIC (0.8%).

4. **Virological response**
   Out of 24,603 people who initiated cART between January 1996 and December 2018,
   ➔ 20,166 people were ART-naive, not pregnant at cART initiation, and had a viral load result after ≥3 months of cART initiation.

5. HIV drug resistance

Transmitted HIV drug resistance

As of January 2019, 7,401 HIV-1 sequences were obtained from 7,127 ART-naive people before initiating cART in 2003-2018.

➔ 25 people had pre-treatment integrase sequences available.

Acquired HIV drug resistance

As of January 2019, 3,802 HIV-1 sequences were obtained from 2,348 people who received cART for at least 4 months in 2000-2018.

➔ 2,518 sequences from 1,637 people who were ART-naive before initiating cART.

➔ 144 integrase sequences to assess resistance to INSTI class drugs were available from 122 people.

6. Immunological response

Out of the 24,603 people who initiated cART between January 1996 and December 2018

➔ 24,037 had CD4 cell count data available after initiating cART.

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

Starting combination antiretroviral therapy

In total, 24,603 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 2018 (*Box 2.1*). Of these, 2,592 (10.5%) had prior exposure to mono or dual nucleoside-analogue antiretroviral therapy (ART) at the start of cART and 22,011 (89.5%) were ART-naive. The proportion of pre-treated persons initiating cART has decreased over time to <1%. In *Table 2.1*, we grouped people according to calendar year of starting cART: 5,936 started between 1996 and the end of 2001, 5,326 between 2002 and the end of 2007, 6,612 between 2008 and the end of 2012, and 6,729 between 2013 and the end of 2018.

Table 2.1: Characteristics of people starting combination antiretroviral therapy in 1996–2018.

Year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	1996–2018
Total	n	5,936	5,326	6,612	6,729	**24,603**
DEMOGRAPHIC						
Age at cART initiation (years)	Median	37.6	38.6	40.3	39.2	**38.8**
	Q1	32.2	32.0	32.7	30.3	**31.8**
	Q3	44.6	45.7	48.0	48.9	**46.9**
Male (at birth)	n	4,827	3,896	5,615	5,824	**20,162**
	%	81.3	73.2	84.9	86.6	**82**
Transmission risk group						
Missing	n	2	4	5	13	**24**
	%	0.0	0.1	0.1	0.2	**0.1**
Men who have sex with men	n	3,469	2,546	4,377	4,644	**15,036**
	%	58.4	47.8	66.2	69.0	**61.1**
Heterosexual contact	n	1,656	2,220	1,791	1,628	**7,295**
	%	27.9	41.7	27.1	24.2	**29.7**
Injecting drug use	n	407	159	83	33	**682**
	%	6.9	3.0	1.3	0.5	**2.8**
Blood or blood products	n	107	67	47	65	**286**
	%	1.8	1.3	0.7	1.0	**1.2**
Vertical transmission	n	0	0	3	3	**6**
	%	0.0	0.0	0.1	0.0	**0.0**
Other/unknown	n	295	330	306	343	**1274**
	%	5.0	6.2	4.6	5.1	**5.2**
Region of origin						
Missing	n	29	20	18	34	101
	%	0.5	0.4	0.3	0.5	0.4
The Netherlands	n	3,566	2,567	3,963	3,966	14,062
	%	60.1	48.2	56.0	58.9	57.2
Western Europe/North America/Australia	n	679	412	474	405	1,970
	%	11.4	7.7	7.2	6.0	8.0
East/central Europe	n	87	135	252	411	885
	%	1.5	2.5	3.8	6.1	3.6
South America and the Caribbean	n	580	673	756	870	2879
	%	9.8	12.6	11.4	12.9	11.7
Sub-Saharan Africa	n	732	1,217	784	594	3,327
	%	12.3	22.9	11.9	8.8	13.5
Other*	n	263	302	365	449	1,379
	%	4.4	5.7	5.5	6.7	5.6

Year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	1996–2018
CLINICAL						
Recent infection	n	326	434	1,277	1,749	**3,786**
(within 12 months of diagnosis)	%	5.5	8.2	19.3	26.0	**15.4**
Ever tested HIV-negative	n	1,144	1,423	3,187	3,851	**9,605**
	%	19.3	26.7	48.2	57.2	**39.0**
CD4 cell count at start cART	Median	200	190	280	393	**260**
	Q1	80	90	170	230	**130**
	Q3	340	280	370	567	**400**
HIV RNA (log_{10}) at start cART	Median	4.8	5.0	4.9	4.8	**4.9**
	Q1	4.2	4.5	4.4	4.2	**4.3**
	Q3	5.3	5.4	5.4	5.3	**5.3**
(prior) AIDS at start cART	n	1,914	1,413	1,108	827	**5,262**
	%	32.2	26.5	16.8	12.3	**21.4**
ARV-naive at start cART	n	3,789	5,080	6,512	6,630	**22,011**
	%	63.8	95.4	98.5	98.5	**89.5**
Hepatitis B status at start of cART						
HBV-negative (HBsAg-negative)	n	5,295	4,859	6,101	5,985	**22,240**
	%	89.2	91.2	92.3	88.9	**90.4**
HBV-positive (HBsAg-positive)	n	369	315	315	175	**1,174**
	%	6.2	5.9	4.8	2.6	**4.8**
Unknown	n	272	152	196	569	**1,189**
	%	4.6	2.9	3.0	8.5	**4.8**
Hepatitis C status at start of cART						
HCV-negative	n	5,256	4,914	6,222	5,975	**22,367**
	%	88.5	92.3	94.1	88.8	**90.9**
HCV RNA-positive	n	81	131	135	96	**443**
	%	1.4	2.5	2.0	1.4	**1.8**
HCV Ab seropositive	n	146	64	44	26	**280**
	%	2.5	1.2	0.7	0.4	**1.1**
Unknown	n	453	217	211	632	**1,513**
	%	7.6	4.1	3.2	9.4	**6.2**
cART started during pregnancy	n	112	344	171	99	**726**
	%	1.9	6.5	2.6	1.5	**3.0**

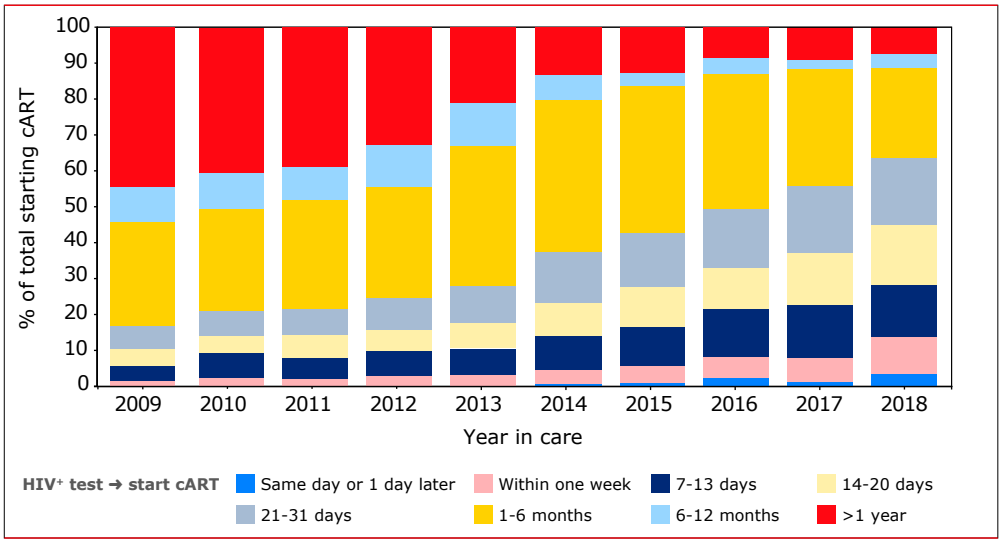
**The 48 people from other regions of origin who started in 2018 were from south-east Asia (n=22), North Africa and the Middle East (n=20), and Oceania and the Pacific (n=6).*

***Legend:** Ab=antibody; cART=combination antiretroviral therapy; ARV=antiretroviral; HBsAg=hepatitis b surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus.*

Of the 24,604 people who had initiated cART since January 1996, 20,162 (82.0%) were men, of whom 15,036 (74.6%) were men who have sex with men (MSM). Overall, 14,062 (57.2%) 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 over time. Since 1996, there was a slight but steady increase in people from eastern and central Europe, from 2-3% until 2009, to 4-5% in 2010-2014 and to 6-7.5% in 2015-2018. Simultaneously, the number of people from western Europe/North America/Australia slightly decreased from 11.5% in 1996-2001 to 5.6% in 2018, with a decrease in those from sub-Saharan Africa from 23.0% in 2002-2007 to 11.9% in 2008-2012 to 8.9% in 2013-2018.

Prompt initiation of cART following an HIV-positive diagnosis has increased over time, reflecting implementation and uptake of evolving HIV treatment guidelines (*Figure 2.1*). 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 134 days (interquartile range (IQR) 33-704) for those who entered care in 2011 to 105 days (IQR 30-505) in 2012, 65 days (IQR 27-279) in 2013, 42 days (IQR 21-107) in 2014, 36 days (IQR 18-51) in 2015, 30 days (IQR 14-55) in 2016, 27 days (IQR 14-48) in 2017, and 23 days (IQR 13-42) in 2018. The proportion of subjects initiating cART on the same day (or one day later) as their HIV-positive diagnosis increased from 0.5% in 2010, to 1.1% in 2015, 2.5% in 2016, 1.7% in 2017, and 3.5% in 2018. Likewise, the time between entering care and starting cART decreased over time (*Appendix Figure 2.1*).

Figure 2.1: Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) in persons starting cART in 2008-2018.*



**The time between entry into HIV care and initiation of cART therapy can be found in the Appendix.*
***Legend:** cART=combination antiretroviral therapy.*

Furthermore, the proportion of those with a known previous negative HIV test increased over the years, and an increasing proportion of those starting cART had evidence of recent infection (i.e., within 12 months of a last negative HIV test). At the same time, there has been an increase in the median CD4 cell count at the start of cART, followed by stabilisation: from 190 cells/mm^3 (IQR 90-280) in 2002-2007 to 280 cells/mm^3 (IQR 170-370) in 2008-2012 and to 393 cells/mm^3 (IQR 230-567) in 2013-2018 (p for trend <.0001). In 2018, the median CD4 cell count at the start of cART was 380 cells/mm^3 (IQR 163-606). Since 2016, both the number of people initiating cART per calendar year and the median CD4 cell count at cART initiation have decreased. This trend is likely due to the substantial group who were already in care but not on cART (because of their high CD4 cells counts) and subsequently initiated cART in 2015 and 2016 because of the 2015 guideline change recommending ART for all irrespective of CD4 count.

Chapter 1 provides more detailed information on trends in CD4 cell count at the start of cART over time and additional aspects of the continuum of HIV care.

In care and on cART in the Netherlands in 2018

Out of the 24,603 people who were known to have initiated cART between January 1996 and December 2018, 18,993 (77.2%) were alive, receiving cART, and had a visit for HIV care in the Netherlands in 2018. *Table 2.2* shows their treatment and clinical characteristics at their last clinic visit in 2018. Overall, 15,692 (82.6%) were men, and 12,310 (64.8%) were MSM. Their median age on 31 December 2018 was 50 (IQR 42-58) years. The majority (60.7%) originated from the Netherlands, followed by sub-Saharan Africa (11.6%) and South America and the Caribbean (11.5%).

Table 2.2: *Characteristics of people who had started combination antiretroviral therapy and were known to be in care in 2018.*

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	All
Total	n	3,676	3,761	5,509	6,047	**18,993**
	%	19.4	19.8	29.0	31.8	**100**
Sex						
Male	n	2,956	2,775	4,709	5,252	**15,692**
	%	80.4	73.8	85.5	86.9	**82.6**
Female	n	720	986	800	795	**3,301**
	%	19.6	26.2	14.5	13.2	**17.4**
Age on 31 December 2018	Median	57.2	52.6	49.3	42.9	**50.5**
	Q1	52.3	46.2	41.4	33.8	**41.7**
	Q3	63.3	59.0	56.4	52.5	**58.0**
Transmission risk group						
No data	n	1	3	4	11	**19**
	%	0.03	0.08	0.07	0.2	**0.1**
Men who have sex with men	n	2,277	1,977	3,807	4,249	**12,310**
	%	61.9	52.6	69.1	70.3	**64.8**
Heterosexual contact	n	1,065	1,484	1,418	1,419	**5,386**
	%	29.0	39.5	25.7	23.5	**28.4**
Injecting drug use	n	134	64	48	22	**268**
	%	3.7	1.7	0.9	0.4	**1.4**
Blood or blood products	n	72	45	34	56	**207**
	%	2.0	1.2	0.6	0.9	**1.1**
Vertical transmission	n	.	.	2	3	**5**
	%	.	.	0.04	0.05	**0.03**
Other/unknown	n	127	188	196	287	**798**
	%	3.5	5.0	3.6	4.8	**4.2**
Region of origin						
No data	n	10	12	15	31	**68**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	All
	%	0.3	0.3	0.3	0.5	**0.4**
The Netherlands	n	2,309	2,008	3,531	3,685	**11,533**
	%	62.8	53.4	64.1	61.0	**60.7**
Western Europe/North America/Australia	n	337	217	326	321	**1,201**
	%	9.2	5.8	5.9	5.3	**6.3**
East/central Europe	n	47	93	187	361	**688**
	%	1.3	2.5	3.4	6.0	**3.6**
Latin America and the Caribbean	n	366	474	580	760	**2,180**
	%	10.0	12.6	10.6	12.6	**11.5**
Sub-Saharan Africa	n	423	737	564	486	**2,210**
	%	11.5	19.6	10.3	8.0	**11.6**
Other	n	184	220	306	403	**1,113**
	%	5.0	5.9	5.6	6.7	**5.9**
cART regimen						
TDF/FTC/EFV	n	229	507	758	289	**1,783**
	%	6.2	13.5	13.8	4.8	**9.4**
TDF/FTC/NVP	n	423	356	465	88	**1,332**
	%	11.5	9.5	8.4	1.5	**7.0**
TDF/FTC/RPV	n	90	133	294	309	**826**
	%	2.5	3.5	5.3	5.1	**4.4**
TDF/FTC/DRV/b	n	114	154	285	204	**757**
	%	3.1	4.1	5.2	3.4	**4.0**
TDF/FTC/ATV/r	n	69	85	159	63	**376**
	%	1.9	2.3	2.9	1.0	**2.0**
TDF/FTC/LPV	n	7	18	9	3	**37**
	%	0.2	0.5	0.2	0.1	**0.2**
TDF/FTC/EVG/c	n	57	98	159	434	**748**
	%	1.6	2.6	2.9	7.2	**4.0**
TDF/FTC/DTG	n	70	91	141	337	**639**
	%	1.9	2.4	2.6	5.6	**3.4**
TDF/FTC/RAL	n	33	46	79	44	**202**
	%	0.9	1.2	1.4	0.7	**1.1**
ABC/3TC/DTG	n	335	512	789	1,633	**3,269**
	%	9.1	13.6	14.3	27.0	**17.2**
TAF/FTC/EVG/c	n	325	450	784	1,404	**2,963**
	%	8.8	12.0	14.2	23.2	**15.6**
TAF/FTC/RPV	n	101	163	346	324	**934**
	%	2.8	4.3	6.3	5.4	**4.9**
TAF/FTC/DTG	n	81	77	166	229	**553**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	All
	%	2.2	2.1	3.0	3.8	**2.9**
TAF/FTC/DRV/c	n	152	139	202	234	**727**
	%	4.1	3.7	3.7	3.9	**3.8**
TAF/FTC/BIC	n	41	32	57	99	**229**
	%	1.1	0.9	1.0	1.6	**1.2**
Other: 2NRTI+NNRTI	n	612	419	366	85	**1,482**
	%	16.7	11.1	6.6	1.4	**7.8**
Other: 2NRTI+PI	n	143	167	154	76	**540**
	%	3.9	4.4	2.8	1.3	**2.8**
Other: 2NRTI+INSTI	n	63	59	75	51	**248**
	%	1.7	1.6	1.4	0.8	**1.3**
Other: NNRTI+INSTI	n	16	5	10	.	**31**
	%	0.4	0.1	0.2	.	**0.2**
Other: PI+INSTI	n	146	67	67	45	**325**
	%	4.0	1.8	1.2	0.7	**1.7**
Other: NRTI+PI+INSTI (3ARVs)	n	59	24	10	5	**98**
	%	1.6	0.6	0.2	0.1	**0.5**
Other: NRTI+PI+INSTI (4ARVs)	n	121	34	38	30	**223**
	%	3.3	0.9	0.7	0.5	**1.2**
Other	n	389	125	96	61	**671**
	%	10.6	3.3	1.7	1.0	**3.5**
CD4:CD8 ratio						
No data	n	445	498	720	1,390	**3,053**
	%	12.1	13.2	13.1	23.0	**16.1**
<0.50	n	629	550	742	1,166	**3,087**
	%	17.1	14.6	13.5	19.3	**16.3**
≥0.50 <1.00	n	1,684	1,857	2,714	2,356	**8,611**
	%	45.8	49.4	49.3	39.0	**45.3**
≥1.00	n	918	856	1,333	1,135	**4,242**
	%	25.1	22.8	24.2	18.8	**22.3**
CD4 count (cells/mm^3)						
No data	n	6	12	36	633	**687**
	%	0.2	0.3	0.7	10.5	**3.6**
<50	n	4	11	8	26	**49**
	%	0.1	0.3	0.2	0.4	**0.3**
50–199	n	67	67	56	204	**394**
	%	1.8	1.8	1.0	3.4	**2.1**
200–349	n	246	229	283	473	**1,231**
	%	6.7	6.1	5.1	7.8	**6.5**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2018	All
350–499	n	547	646	821	772	**2,786**
	%	14.9	17.2	14.9	12.8	**14.7**
500–749	n	1,260	1,392	2,097	1,728	**6,477**
	%	34.3	37.0	38.1	28.6	**34.1**
≥750	n	1,546	1,404	2,208	2,211	**7,369**
	%	42.1	37.3	40.1	36.6	**38.8**
Viral load <50 copies/ml						
No data	n	35	99	168	274	**576**
	%	1.0	2.6	3.15	4.5	**3.0**
Yes	n	3,230	3,180	4,733	4,906	**16,049**
	%	87.9	84.6	85.9	81.1	**84.5**
No	n	411	482	608	867	**2,368**
	%	11.2	12.8	11.0	14.3	**12.5**
Viral load <200 copies/ml						
No data	n	35	99	168	274	**576**
	%	1.0	2.6	3.1	4.5	**3.0**
Yes	n	3,580	3,572	5,254	5,534	**17,940**
	%	97.4	95.0	95.4	91.5	**94.5**
No	n	61	90	87	239	**477**
	%	1.7	2.4	1.6	4.0	**2.5**

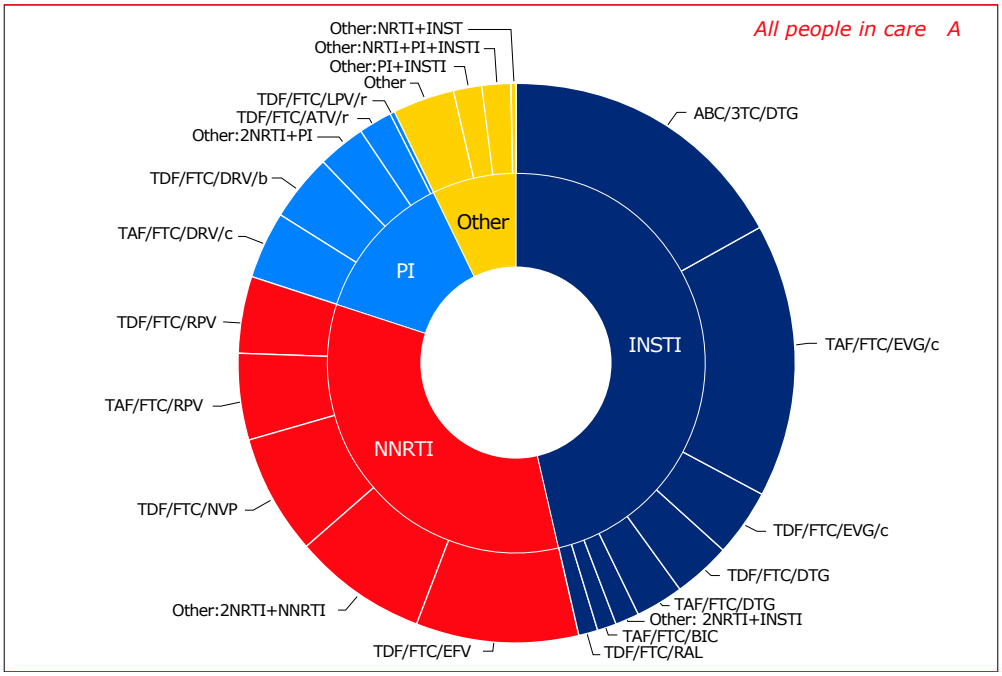
Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; ARVs=antiretroviral drugs; BIC=bictegravir; cART=combination antiretroviral therapy; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine;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

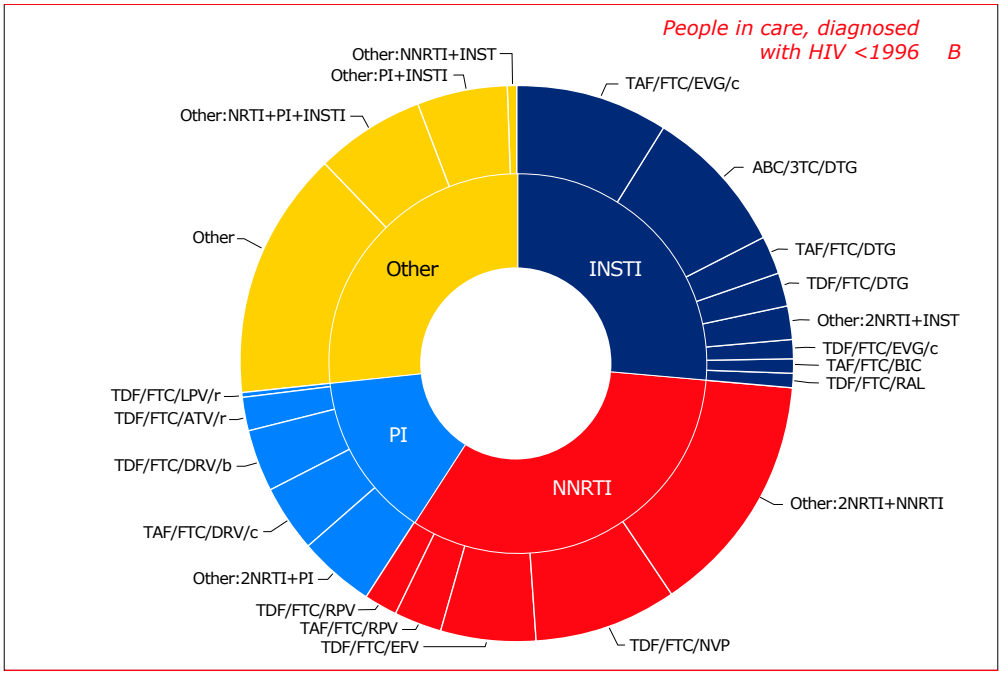
Among the 18,993 people in HIV care and on cART in 2018, the vast majority (92.8%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitor (NRTIs), combined with either an integrase inhibitor (INSTI) (46.6%), an NNRTI (33.4%), or a protease inhibitor (PI) (12.7%). The distribution of cART use among the population in care in 2018 is presented in *Figure 2.2A*. The most common regimens were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (17.2%), tenofovir alafenamide (TAF)/emtracitabine (FTC)/elvitegravir (EVG)/cobicistat (15.6%), and tenofovir disoproxil fumarate (TDF)/FTC combined with efavirenz (EFV) (9.4%) or nevirapine (NVP) (7.0%). Most people who initiated cART in 2018 did so with TAF/FTC/cobicistat-boosted EVG (25.0%) or ABC/3TC/DTG (23.4%). The proportion of the population in care in 2018 that uses TDF continues to decline (from 46.4% in 2017 to 35.3 in 2018); the proportion using TAF continues to increase (from 24.4%

of the population in care in 2017 to 33.2% in 2018). Zidovudine was still used by 206 individuals (1.1%, mostly in combination with lamivudine), didanosine by 2 (<0.1%), and stavudine by none. In total, 552 (2.9%) and 337 (1.8%) individuals used a cART regimen without any or with just a single NRTI. There were 526 individuals who used a 2-drug regimen (excluding pharmacological boosters): the most common 2-drug regimen were a combination of PI+INSTI (325, 61.8%), NRTI+INSTI (68, 12.9%), NRTI+PI (62, 11.8%), NNRTI+INSTI (31, 5.9%), and NNRTI+PI (19, 3.6%).

Of those with a plasma HIV RNA measurement in 2015-2018, 85.0% had a viral load <50 copies/ml, and 95.9% had a viral load <200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-2018, 72.8% had a CD4 cell count of 500 cells/mm^3 or higher, and 24.4% had a CD4:CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (cART) use in 2018 by A) all people in care and B) people in care who were diagnosed with HIV <1996.





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

See Appendix Table 2.1 for a more detailed overview of the regimen used by people who were diagnosed with HIV before <1996.

Long-term HIV survivors

Out of 19,189 people in HIV care in the Netherlands in 2018, 3,757 (19.6%) had been diagnosed before the year 2000; of those, 3,158 (84.1%) were 50 years of age or older by the end of 2018. Furthermore, 1,933 (10.1%) were diagnosed before 1996, and 1,749 (90.5%) of those were 50 years or older by the end of 2018.

The data presented below focus on the 1,933 people who were diagnosed before 1996 (i.e., before the introduction of cART in the Netherlands, and thus considered *long-term HIV survivors*). Their median age at HIV diagnosis was 31 years (IQR 27-36). The majority were men (82.5%), and the main HIV transmission risk group was MSM (66.6%), followed by heterosexual contact (20.2%), injecting drug use (7.1%), and contaminated blood or blood products (2.4%); the remaining 3.7%

acquired HIV through another or an unknown transmission route. Most long-term survivors (65.8%) originated from the Netherlands, followed by western Europe, North America and Australia (13.8%), South America and the Caribbean (10.2%), sub-Saharan Africa (5.4%), and other regions (3.6%). At the start of cART, the median HIV viral load was 4.6 (IQR 3.9-5.1) $\log_{10}$ copies/ml (available for 1,462 people), and the median CD4 cell count was 240 (IQR 120-362) cells/mm^3 (available for 1,697 people). In total, 1,243 (64.3%) had a prior AIDS-defining event (CDC category C clinical event). The majority (57.8%) had initiated cART in 1996 or 1997 (35.7% and 22.0%, respectively), and 46.3% had received nucleoside analogue antiretroviral drugs as monotherapy or dual therapy before initiating cART.

As of 31 December 2018, the median age of these long-term survivors was 58 years (IQR 54-64). The majority (73.4%) received a dual NRTI backbone in combination with an NNRTI (32.7%), integrase inhibitor (26.6%), or protease inhibitor (14.1%). The most common regimens were TAF/FTC/EVG/c (9.1%), TDF/FTC/NVP (8.4%), ABC/3TC/DTG (8.4%), TDF/FTC/EFV (5.4%), and TAF/FTC/DRV/c (3.9%). Importantly, 26.6% received a non-standard regimen. The cART regimens are presented in *Figure 2.2B* and *Appendix Table 2.1*.

Based on the last available CD4 and CD8 cell count measurements (in 2015-2018), 2.1% had a CD4 cell count <200 cells/mm^3, 6.8% between 200 and 349 cells/mm^3, 17.5% between 350 and 499 cells/mm^3, 32.4% between 500 and 749 cells/mm^3, and 41.1% had 750 cells/mm^3 or higher. Furthermore, 23.1% had a CD4:CD8 ratio of 1 or higher. Of all long-term survivors receiving cART with a viral load measurement in 2018, viral suppression was high and comparable to the overall population in care: 89.1% had a viral load <50 copies/ml, and 97.1% had a viral load <200 copies/ml.

Changes in the use of 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 combinations 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.

< Back to page 114

Box 2.2: Approval dates of new antiretroviral drugs/regimens for HIV treatment in the Netherlands in 2013–2018.

Medicine	Authorisation date
TDF/FTC/EVG/cobicistat (Stribild®)	May 24, 2013
Cobicistat (Tybost®)	September 19, 2013
DTG (Tivicay®)	January 16, 2014
ABC/3TC/DTG (Triumeq®)	September 1, 2014
DRV/cobicistat (Rezolsta®)	November 19, 2014
TAF/FTC/EVG/cobicistat (Genvoya®)	November 19, 2015
TAF/FTC (Descovy®)	April 21, 2016
TAF/FTC/RPV (Odefsey®)	June 21, 2016
TAF (Vemlidy®)	January 9, 2017
TAF/FTC/DRV/cobicistat (Symtuza®)	September 21, 2017
DTG/RPV (Juluca®)	May 21 , 2018
TAF/FTC/BIC (Biktarvy®)	June 25, 2018
Doravirine (Pifeltro®)	Nov 22, 2018
TDF/3TC/doravirine (Delstrigo®)	Nov 22, 2018

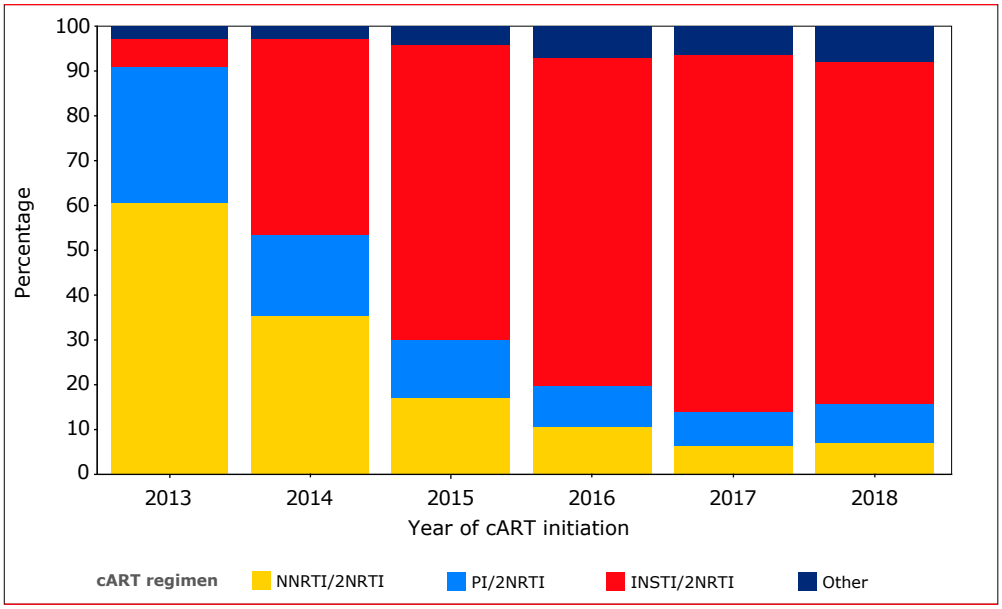
Legend: *3TC=lamivudine; ABC=abacavir; BIC = bictegravir; DTG=dolutegravir; DRV=darunavir; EVG=elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.*
Source: *Medicines Evaluation Board and European Medicines Agency.*

Initial cART regimen

Out of 24,603 people who were known to have initiated cART between January 1996 and December 2018, 6,729 (27.4%) started cART between January 2013 and December 2018. *Figure 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 has risen sharply from 6.2% in 2013, to 44.1% in 2014, 65.4% in 2015, 72.8% in 2016, 79.4% in 2017, and then slightly decreased to 76.3% in 2018. EVG/c was introduced in the Netherlands at the end of 2013 and was used in 34.3%, 17.4%, 26.0%, 31.3%, and 27.3% of the initial regimens in 2014, 2015, 2016, 2017, and 2018, respectively. Dolutegravir was introduced in the Netherlands in 2014 and was used in 6.8%, 47.3%, 46.1%, 47.3%, and 39.6% of the initial regimens in 2014, 2015, 2016, 2017, and 2018, respectively. With the introduction of (boosted) elvitegravir, dolutegravir and bictegravir, the use of NNRTIs in the initial regimen decreased from 60.6% in 2013 to 35.2% in 2014, 16.9% in 2015, 10.6% in 2016, 6.2% in 2017, but increased slightly to 7.2% in 2018. The use of protease inhibitors in the

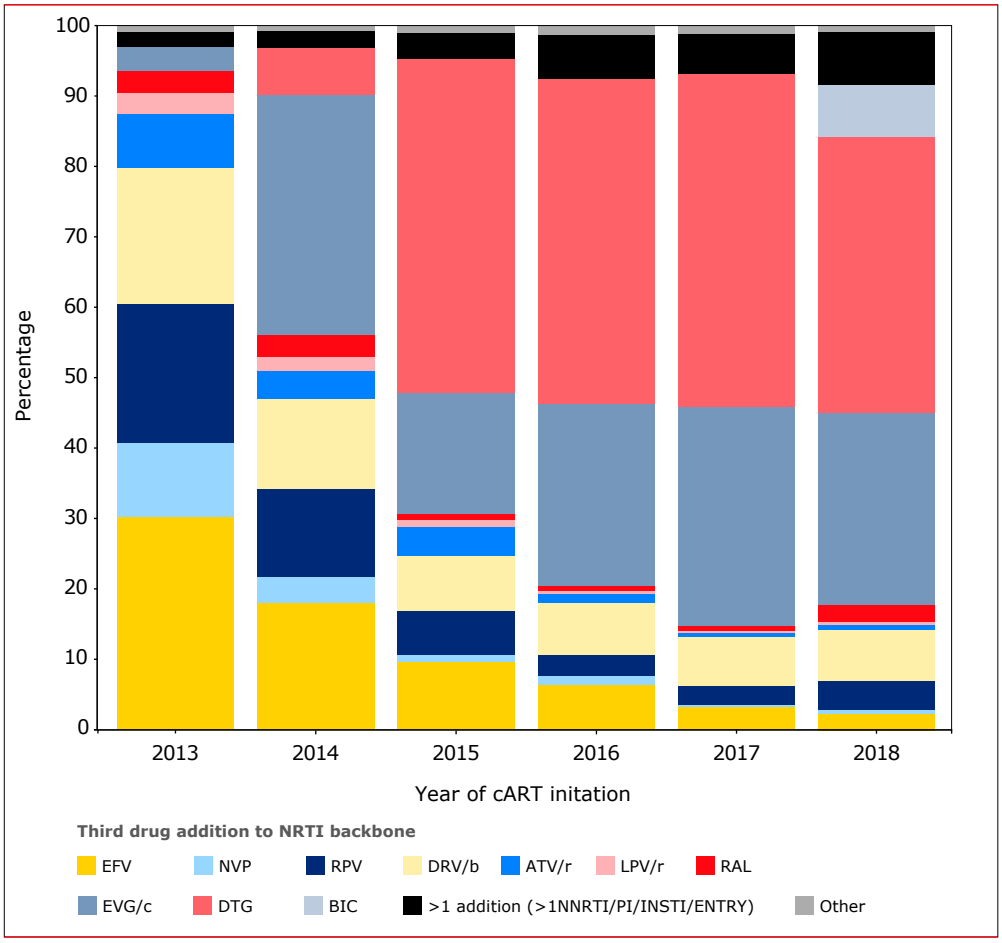
initial regimen decreased from 29.9% in 2013 to 7.7% in 2017 and increased slightly to 8.4% in 2018. In 2013-2018, 4.1% of people received more than one 'third-drug' addition to the NRTI backbone in their initial cART regimen, the majority of whom were people initiating cART during an acute HIV infection, with the regimen consisting of a PI (mainly boosted darunavir) plus an INSTI (mainly dolutegravir) with or without the addition of an NRTI.

Figure 2.3: Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2013-2018.



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

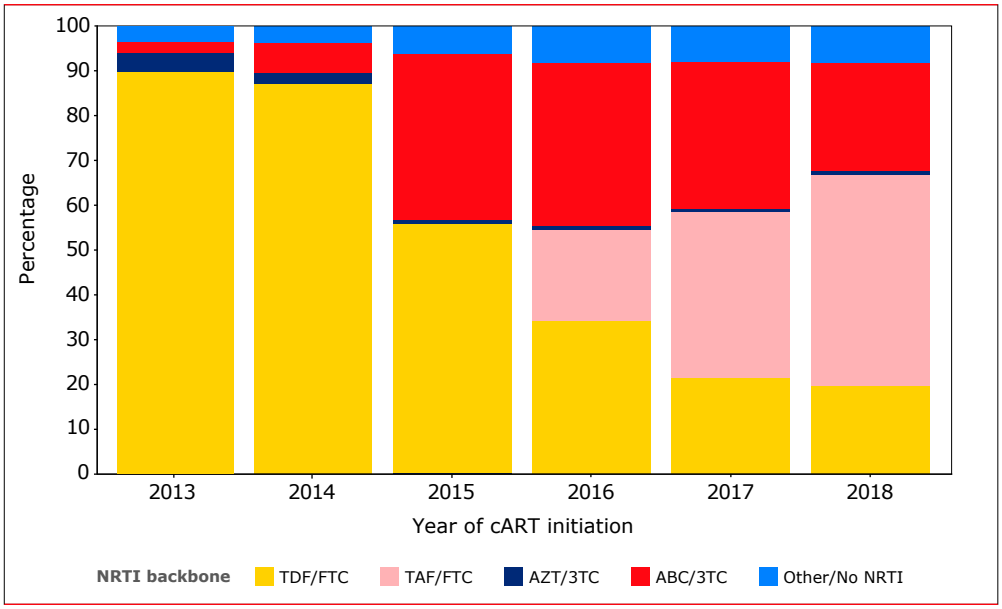
Figure 2.4: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2013-2018.



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

Figure 2.5 provides an overview of the NRTI backbone components of the initial cART regimens used between 2013 and 2018. The combination of tenofovir (TDF or TAF) and emtricitabine was the predominant backbone prescribed in initial cART regimens. Following its introduction at the end of 2015, TAF was prescribed in 19.3%, 37.1% and 47.3% of the initial regimens in 2016, 2017 and 2018, respectively. At the same time, TDF use decreased from 89.5% in 2013 to 19.7% in 2018. The use of abacavir in combination with lamivudine, which was already available as a fixed-dose combination in Kivexa, became more frequently used after it was introduced as a once-daily fixed-dose combination with dolutegravir in Triumeq by the end of 2014. Its use increased from <3% of all initial regimens in 2013, to about a third of all initial regimens in 2015-2017, but decreased to 23.8% in 2018. The combination of zidovudine and lamivudine, often used by migrants who had already initiated cART before migrating to the Netherlands, further decreased to <1% since 2015.

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2013-2018.*



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 2013 and 2018 are presented in *Figure 2.6* and *Table 2.3*. In 2018, most people (39.5%) initiating cART received a dolutegravir-based regimen combined with either abacavir and lamivudine as part of the once-daily fixed-dose combination (23.2%), or they were provided with emtricitabine and tenofovir separately (tenofovir 15.6%; TDF 10.4%/TAF 5.2%). Additionally, 27.3% initiated an EVG/c-containing once-daily fixed-dose combination with emtricitabine and tenofovir (TDF 2.2%/TAF 25.1%). Raltegravir use in an initial regimen decreased to <1% between 2015 and 2017, but increased to 2.3% in 2018. The combination of ritonavir or cobicistat-boosted darunavir with tenofovir and emtricitabine was used in 7.2% of initial cART regimens in 2018: 2.0% based on TDF and 4.9% on the new 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*.

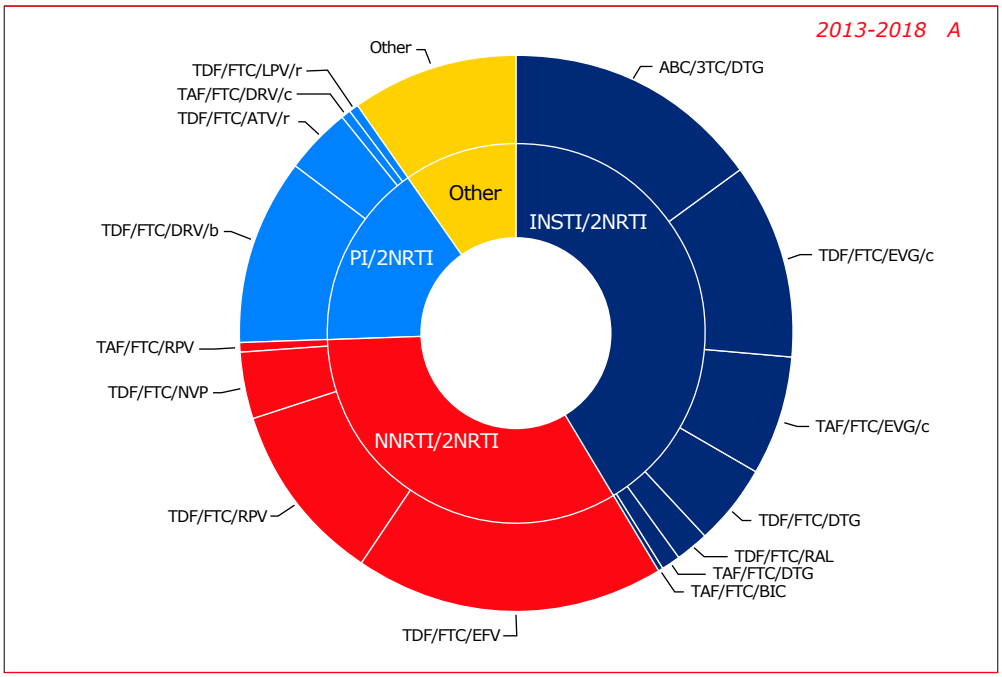
***Table 2.3:** Initial regimen in 2013–2018*

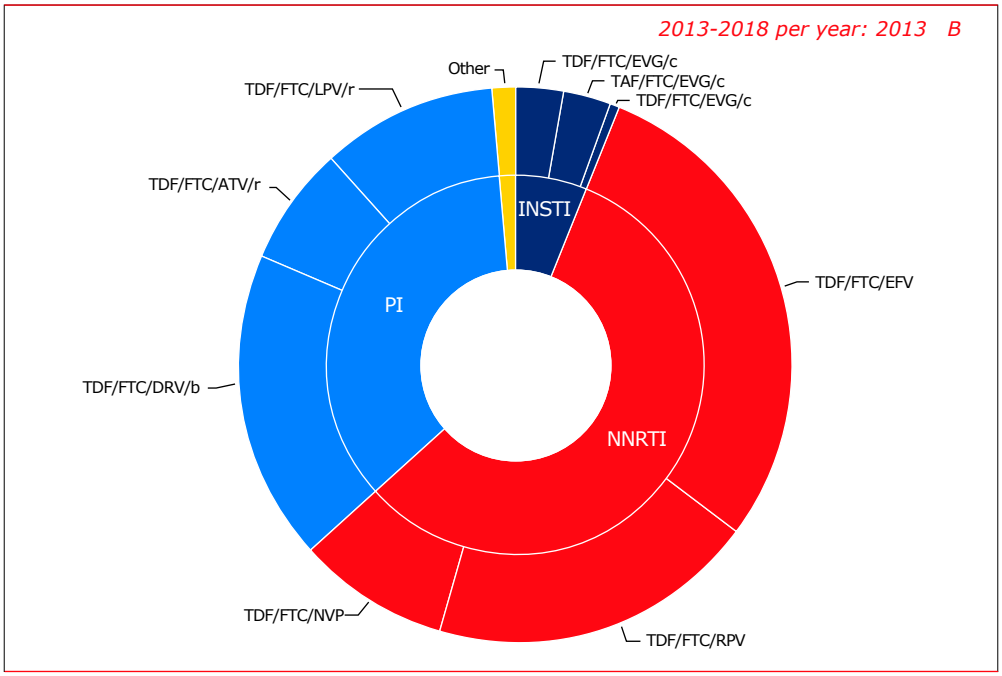
Regimen		2013	2014	2015	2016	2017	2018	2013–2018
Total	n	1,510	1,487	1,219	1,022	892	599	**6,729**
TDF/FTC/EFV	n	440	253	97	58	19	15	882
	%	29.1	17.0	8.0	5.7	2.1	2.5	13.1
TDF/FTC/NVP	n	132	35	7	8	2	2	186
	%	8.7	2.4	0.6	0.8	0.2	0.3	2.8
TDF/FTC/RPV	n	293	197	76	26	7	1	600
	%	19.4	13.3	6.2	2.5	0.8	0.2	8.9
TDF/FTC/DRV/b	n	275	159	91	62	34	12	633
	%	18.2	10.7	7.5	6.1	3.8	2.0	9.4
TDF/FTC/ATV/r	n	104	57	43	16	4	4	228
	%	6.9	3.8	3.5	1.6	0.5	0.7	3.4
TDF/FTC/LPV/r	n	19	5	8	1	.	.	33
	%	1.3	0.34	0.7	0.1	.	.	0.5
TDF/FTC/EVG/c	n	44	509	210	82	46	13	904
	%	2.9	34.2	17.2	8.0	5.2	2.2	13.4
TDF/FTC/DTG	n	.	39	139	101	77	62	418
	%	.	2.6	11.4	9.9	8.6	10.4	6.2
TDF/FTC/RAL	n	41	39	8	6	3	9	106
	%	2.7	2.6	0.7	0.6	0.3	1.5	1.6
ABC/3TC/DTG	n	.	62	435	361	290	140	1,288
	%	.	4.2	35.7	35.3	32.5	23.4	19.1

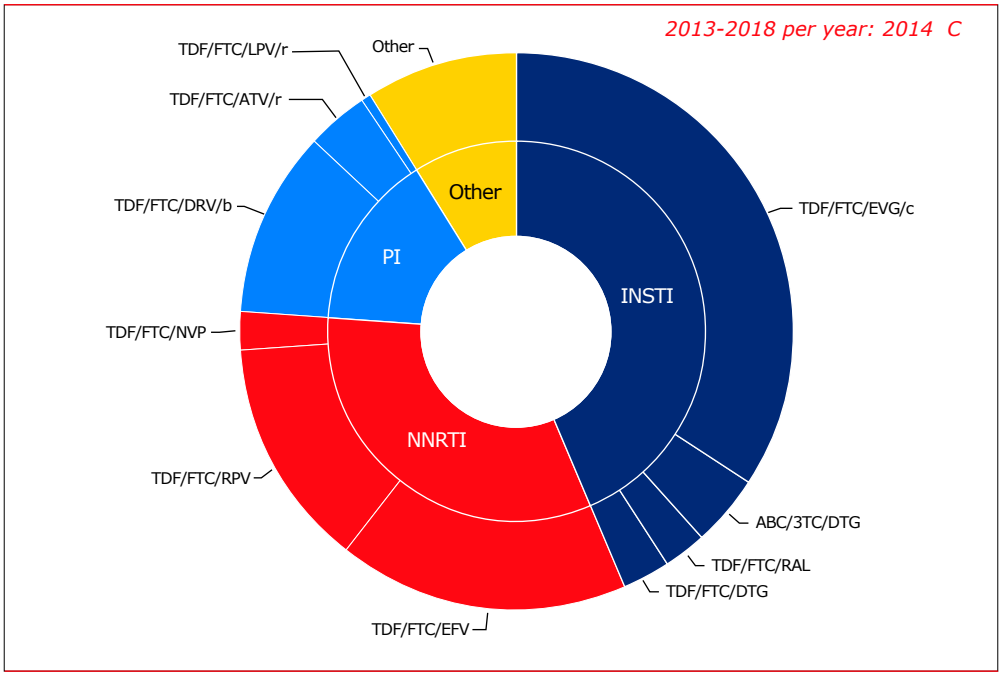
TAF/FTC/EVG/c	n	6	.	1	183	232	150	572
	%	0.4	.	0.1	17.9	26.0	25.0	8.5
TAF/FTC/RPV	n	.	.	.	4	16	24	44
	%	.	.	.	0.4	1.8	4.0	0.7
TAF/FTC/DTG	n	.	.	1	7	52	31	91
	%	.	.	0.1	0.7	5.8	5.2	1.4
TAF/FTC/DRV/c	n	.	.	.	2	26	29	57
	%	.	.	.	0.2	2.9	4.8	0.9
TAF/FTC/BIC	n	.	.	.	.	.	43	43
	%	.	.	.	.	.	7.2	0.6
Other: 2NRTI+NNRTI	n	53	40	26	13	12	1	145
	%	3.5	2.7	2.1	1.3	1.4	0.2	2.2
Other: 2NRTI+PI	n	56	46	19	13	5	5	144
	%	3.7	3.1	1.6	1.3	0.6	0.8	2.1
Other: 2NRTI+INSTI	n	9	7	2	3	8	9	38
	%	0.6	0.5	0.2	0.3	0.9	1.5	0.6
Other: PI+INSTI	n	.	.	5	7	6	3	21
	%	.	.	0.4	0.7	0.7	0.5	0.3
Other: NRTI+PI+INSTI (3ARVs)	n	1	3	2	.	1	1	8
	%	0.1	0.2	0.2	.	0.1	0.2	0.1
Other: NRTI+PI+INSTI (4ARVs)	n	10	20	41	58	49	43	221
	%	0.7	1.3	3.4	5.7	5.5	7.2	3.3

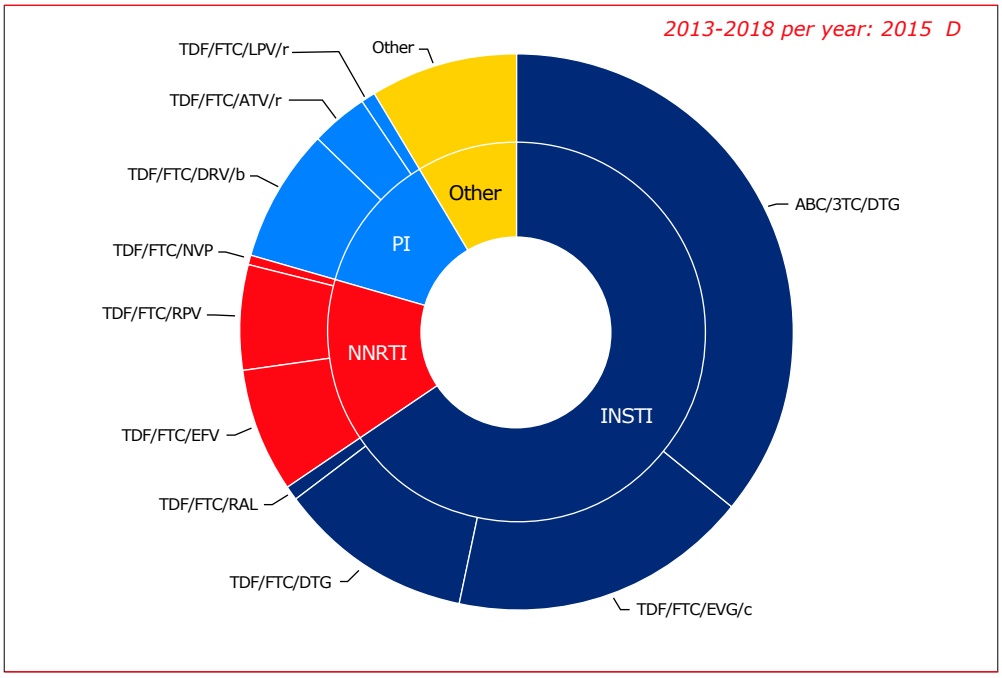
Legend: *ARVs=antiretroviral drugs; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV=lopinavir; INSTI=integrase inhibitor; NRTI=nucleoside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

Figure 2.6: Initial combination antiretroviral therapy regimen combinations in 2013-2018.

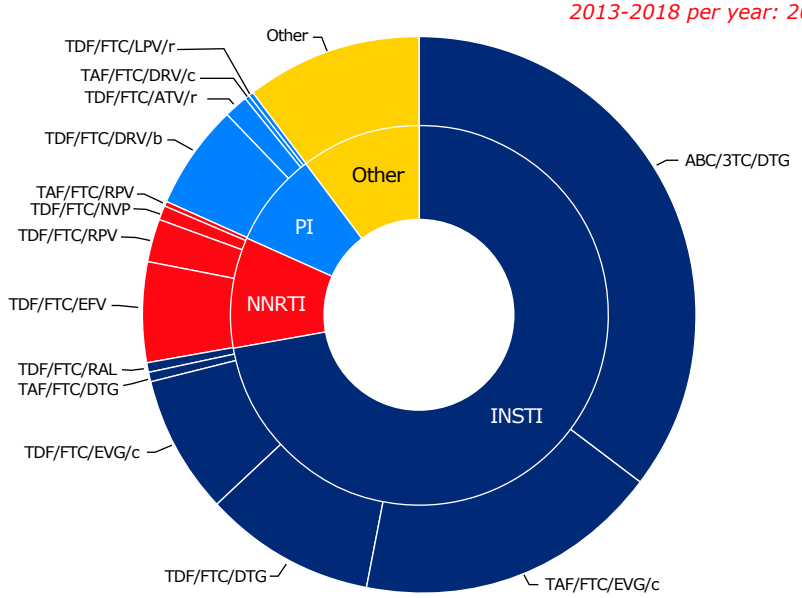




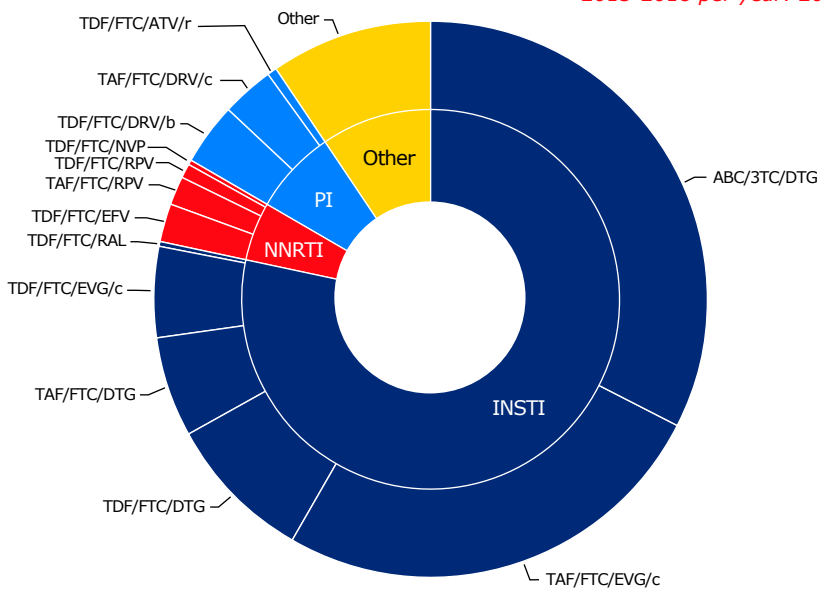

2013-2018 per year: 2014 C
TDF/FTC/LPV/r
Other
TDF/FTC/ATV/r
TDF/FTC/DRV/b
Other
PI
TDF/FTC/EVG/c
INSTI
TDF/FTC/NVP
NNRTI
TDF/FTC/RPV
ABC/3TC/DTG
TDF/FTC/RAL
TDF/FTC/DTG
TDF/FTC/EFV

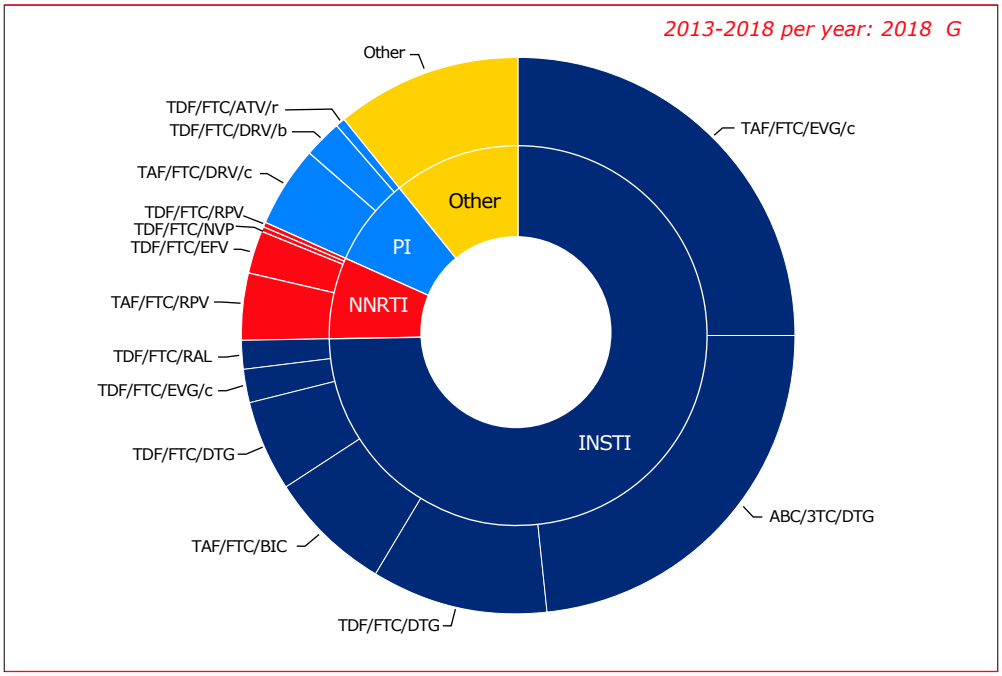

2013-2018 per year: 2015 D
TDF/FTC/LPV/r
Other
TDF/FTC/ATV/r
TDF/FTC/DRV/b
Other
PI
ABC/3TC/DTG
TDF/FTC/NVP
TDF/FTC/RPV
NNRTI
INSTI
TDF/FTC/EFV
TDF/FTC/RAL
TDF/FTC/DTG
TDF/FTC/EVG/c

2013-2018 per year: 2016 E



2013-2018 per year: 2017 F





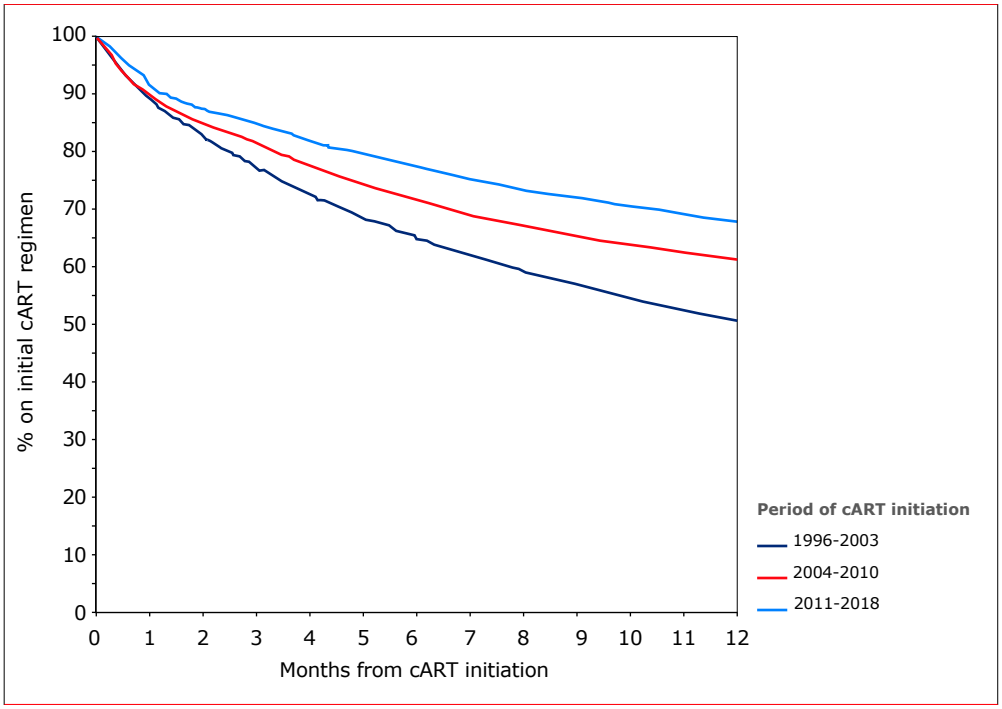
Legend: *3TC=lamivudine; ABC=abacavir; ATV=atazanavir; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; LPV=lopinavir; NNRTI=non-nucleoside 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

We assessed the time spent on the initial cART regimen among the 24,603 people who ever started cART between 1996 and 2018. Discontinuation of the initial cART regimen was defined as a change in, or discontinuation of, ≥1 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 TDF/FTC (Truvada) to the fixed drug combination EFV/TDF/FTC (Atripla) was not considered discontinuation of the initial regimen, but 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 1996-2018, 39.3% of persons discontinued their initial regimen within one year. The time on the initial regimen improved over the years: in 1996-2007, half discontinued their original regimen within a year, compared to approximately a third who discontinued their initial regimen in 2008-2018. The time spent on the initial regimen during the first year of cART stratified by 5-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).*



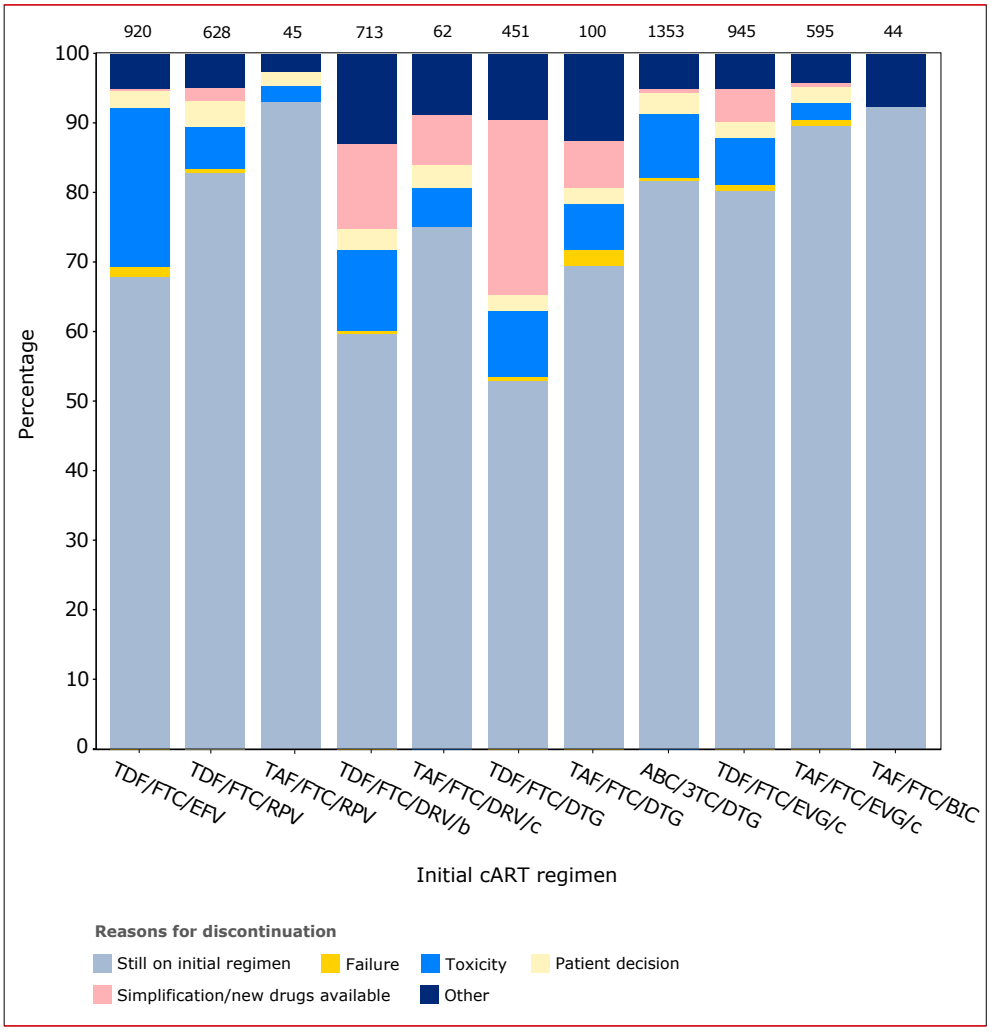
Legend: *cART=combination antiretroviral therapy*

Discontinuation of the initial cART regimen: 2013–2018

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among the 5,508 people who started 'common' and guideline-recommended initial regimens in 2013-2018. Common and guideline-recommended regimens considered in this analysis were: tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (TDF/FTC/EFV; 15.9%), rilpivirine (TDF/FTC/RPV; 10.9%), ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b; 11.5%), cobicistat-boosted elvitegravir (TDF/FTC/EVG/c; 16.4%), dolutegravir (TDF/FTC/DTG; 7.5%), or abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG; 23.4%), or tenofovir alafenamide/emtricitabine combined with cobicistat-boosted elvitegravir (TAF/FTC/EVG/c; 10.4%), rilpivirine (TAF/FTC/RPV; 0.8%), dolutegravir (TAF/FTC/DTG; 1.6%), cobicistat-boosted darunavir (TAF/FTC/DRV/c; 1.0%), bictegravir (TAF/FTC/BIC; 0.8%).

One year after cART initiation, 1,341 (24.4%) out of 5,508 who initiated one of these regimens had discontinued their initial regimen. The main reason for regimen discontinuation was toxicity (n=557; 41.5%), followed by simplification and/or availability of new drugs (n=254; 18.9%). 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*). Of all discontinuations, 6.3% discontinued their initial regimen for reasons of simplification and/or availability of new drugs in 2013, 14.2% in 2014, 27.6% in 2015, 24.5% in 2016, 19.6% in 2017 and 20.0% in 2018.

Figure 2.8: Reasons for discontinuation of the initial regimen during the first year of treatment 2013–2018, by regimen.

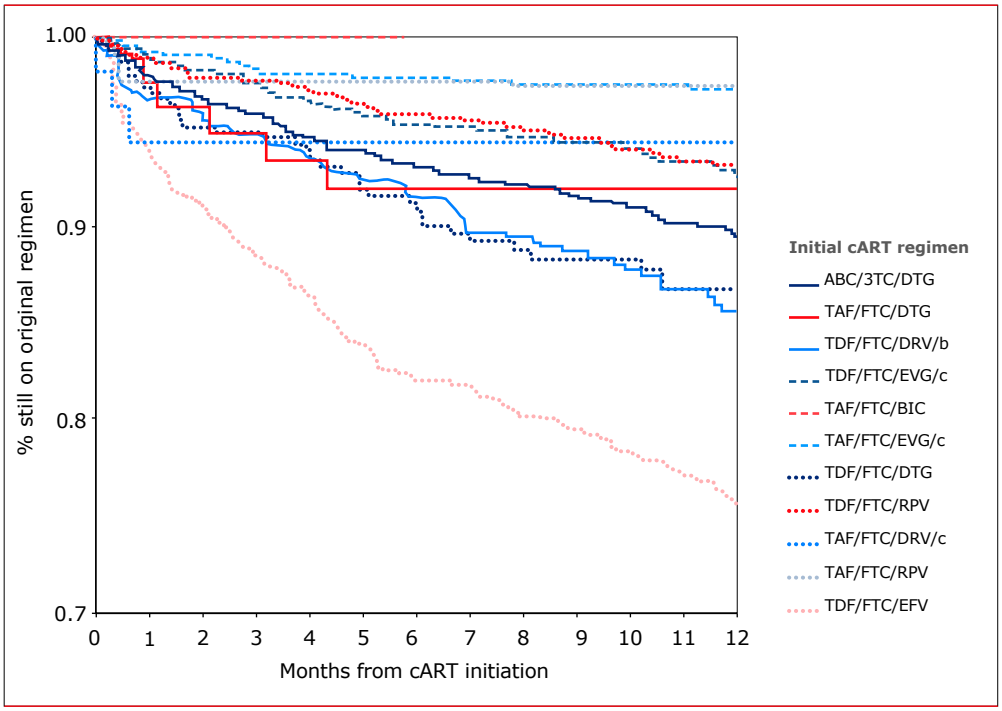


Legend: cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate. Numbers above the bars represent the total number of individuals using that particular regimen.

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 2013-2018, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).

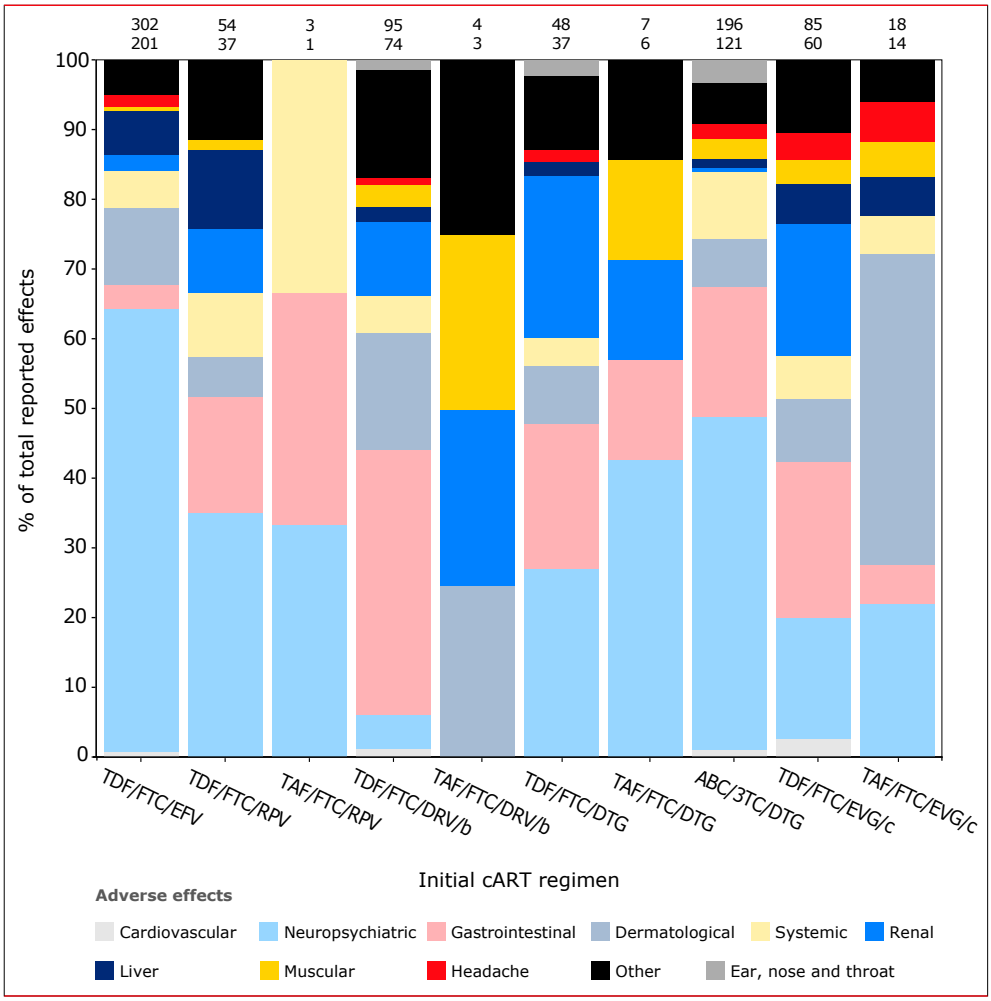


Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir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

Adverse effects

Among the 557 who discontinued their initial cART regimen due to toxicity within a year, 709 adverse effects were recorded. The predominant effects were: 42.7% neuropsychiatric (mainly insomnia, mood changes, dizziness and depression), 15.3% gastrointestinal (mainly diarrhoea and nausea), 10.7% dermatological (rash due to medication, itching), 6.7% systemic (tiredness, apathy, loss of appetite), and 6.3% 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 2013–2018. The bars represent the distribution of 709 reported effects among 557 people, by regimen. Numbers above the bars represent the number of adverse events reported as reasons for discontinuing that particular regimen (top row) occurring in a certain number of individuals on that particular regimen (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; 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 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 24,603 adults have started cART since January 1996. For the current analysis of virological outcomes, we will focus on the 21,304 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 also excluded people without an appropriate viral load test result after at least three months of cART initiation. Results in the following section on viral response to cART are therefore restricted to the remaining 20,166 people. 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 6 months after starting combination antiretroviral therapy (cART).

The viral load measurement closest to 6 months (±3 months) after cART initiation was included in the analysis, irrespective of the viral load level.

Viral suppression
Any viral load measurements <200 copies/ml, at least 3 months after cART initiation.

HIV drug resistance

Transmitted HIV drug resistance
At least one resistance-associated mutation detected among people who 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[24].

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 4 months.

The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.3) was used to infer antiretroviral drug susceptibility and resistance scores[25,26].

Initial virological success

Out of 20,633 with a viral load test result after at least 3 months of cART initiation, 18,209 (88.3%) had a viral load measurement 6 months (±3 months) after cART initiation. Of these people, 15,316 (84.1%) 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 61.4% in those starting cART between 1996 and 2003, to 87.9% in those starting between 2004 and 2010, 92.1% in those starting between 2011 and 2017, and 95.0% in those starting in 2018.

Initial virological success of common initial cART regimens (2013–2018)

We analysed the initial virological success among the 4,114 adults who started a common or guideline-recommended cART regimen in 2013-2018 that was used frequently enough to allow for a meaningful analysis (TDF/FTC/EFV; TDF/FTC/RPV; TDF/FTC/DRV/b; TDF/FTC/EVG/c; TAF/FTC/EVG/c; TDF/FTC/DTG; and ABC/3TC/DTG); described under 'Changes in use of initial antiretroviral therapy 2013-2018'), and had a viral load result after 6 months (±3 months) of cART initiation. In total, 94.2% (95% CI 93.5-94.9) of people achieved initial virological suppression, after a mean of 178 standard deviation (SD) 39 days. Overall, people receiving an integrase-inhibitor based regimen showed significantly higher rates of initial virological success: 94.5% (95% CI 94.5-96.1) of those on an integrase-inhibitor-based regimen had initial virological success, compared to 89.6% (95% CI 87.0-92.3) on a protease-inhibitor-based regimen and 93.9% (95% CI 92.5-95.4) on an NNRTI-based regimen. These differences are in line with results from randomised clinical trials.

We further evaluated the initial virological success rates stratified by viral load at cART initiation (</≥100,000 copies/ml), cART regimen, and regimen class through logistic regression analysis. Stratified analysis of initial virological success based on viral load at cART initiation showed similar differences between cART regimens as described above. The effect of cART regimen on the initial virological suppression rates was strongest in people with a viral load ≥100,000 copies/ml at cART initiation (*Table 2.4*).

Table 2.4: *Initial virological success rates (see definition in Box 2.3) by initial regimen, and initial viral load at cART start. Population characteristics, which may be associated with the initial prescribed regimen, were not taken into account in this analysis.*

	Total		By initial viral load at cART start					
					<100,000 copies/ml			
	n	%	n	%	Initial viral success	95% CI low	95% CI high	p-value
cART regimen								
TDF/FTC/EFV	616	15.0	341	12.9	97.9	96.4	99.5	Ref.
TDF/FTC/RPV	453	11.0	453	17.1	95.6	93.7	97.5	0.076
TDF/FTC/DRV/b	521	12.7	216	8.1	95.4	92.6	98.2	0.093
TDF/FTC/EVG/c	736	17.9	509	19.2	97.2	95.8	98.7	0.65
TDF/FTC/DTG	327	8.0	166	6.3	96.4	93.5	99.2	0.30
ABC/3TC/DTG	1037	25.2	700	26.4	97.6	96.4	98.7	0.70
TAF/FTC/EVG/c	424	10.3	268	10.1	97.4	95.5	99.3	0.65
cART regimen class								
NNRTI/2NRTI	1069	26.0	794	29.9	96.6	95.4	97.9	Ref.
PI/2NRTI	521	12.6	216	8.1	95.4	92.6	98.2	0.40
INSTI/2NRTI	2,524	61.4	1,643	61.9	97.3	96.5	98.1	0.32
All regimens	**4,114**	**100 .0**	**2,653**	**64.5**	**96.9**	**96.3**	**97.6**	

Legend: */b=boosted (cobicistat or ritonavir); /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; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

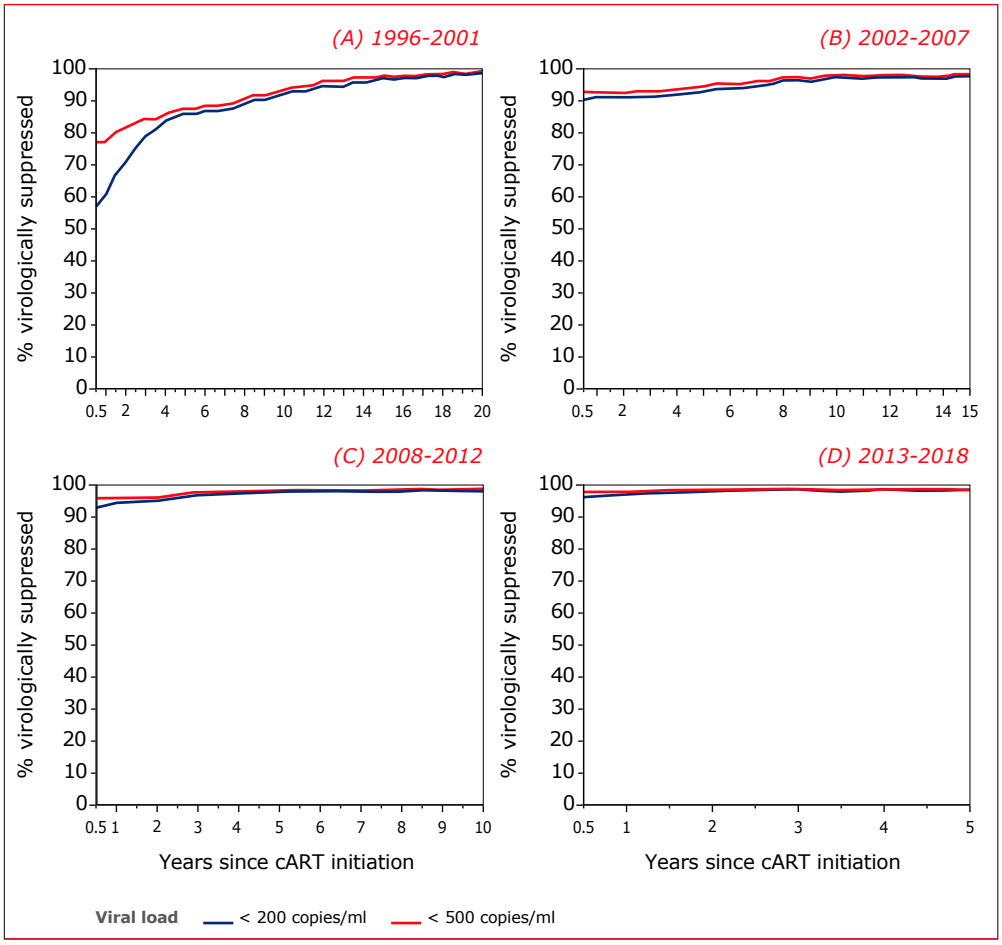
				By initial viral load at cART start			
						≥100,000 copies/ml	
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	cART regimen						
	TDF/FTC/EFV	275	18.8	86.2	82.1	90.3	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	305	20.9	85.6	81.6	89.5	0.83
	TDF/FTC/EVG/c	227	15.5	89.9	85.9	93.8	0.21
	TDF/FTC/DTG	161	11.0	88.8	83.9	93.7	0.48
	ABC/3TC/DTG	337	23.1	93.5	90.8	96.1	0.0031
	TAF/FTC/EVG/c	156	10.7	92.3	88.1	96.5	0.060
	cART regimen class						
	NNRTI/2NRTI	275	18.8	86.2	82.1	90.3	Ref.
	PI/2NRTI	305	20.9	85.6	81.6	89.5	0.83
	INSTI/2NRTI	881	60.3	91.5	89.6	93.3	0.010
	All regimens	**1,461**	**35.5**	**89.3**	**87.7**	**90.8**	

Viral suppression

We assessed long-term viral suppression rates (i.e., viral load <200 copies/ml) over time on cART during 6-month intervals among adults with a viral load test result after cART initiation. The viral load measurement after at least 3 months of cART and closest to each 6-month time point (±3 months) was included in the analysis, irrespective of the viral load of that time point.

Figure 2.11 shows viral suppression rates by calendar period of cART initiation: 1996-2001, 2002-2007, 2008-2012 and 2013-2018. In line with the initial virological success rates, the long-term viral suppression rates likewise improved over time. In people initiating cART in or after 2013, suppression rates ranged from 97.0% (95% CI 96.5-97.5) after 1 year of cART use to 98.2% (95% CI 97.7-98.7) after 4 years. The viral suppression rates over time during the full period (1996-2018) are shown in *Appendix Figure 2.2*.

Figure 2.11: Viral suppression since combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation.



Legend: cART=combination antiretroviral therapy.

Note: To some extent, the increasing trend in viral suppression over time 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. HIV drug resistance is caused by the selection of mutations in the genetic structure of HIV that affects the ability of a particular drug or combination of drugs to block replication of the virus due to unsuccessful viral suppression. All current antiretroviral drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant virus[27].

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 a separate section. It should be noted that SHM does not have drug resistance data from all HIV treatment centres and laboratories; therefore, presented figures might not be representative for the full population in HIV care.

We evaluated the presence of mutations in the HIV genome that are associated with drug resistance using the 2019 IAS-USA HIV drug resistance mutation list[24]. Furthermore, we assessed the association between these mutations and the susceptibility to antiretroviral drugs. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.3) 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[25,26]. 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

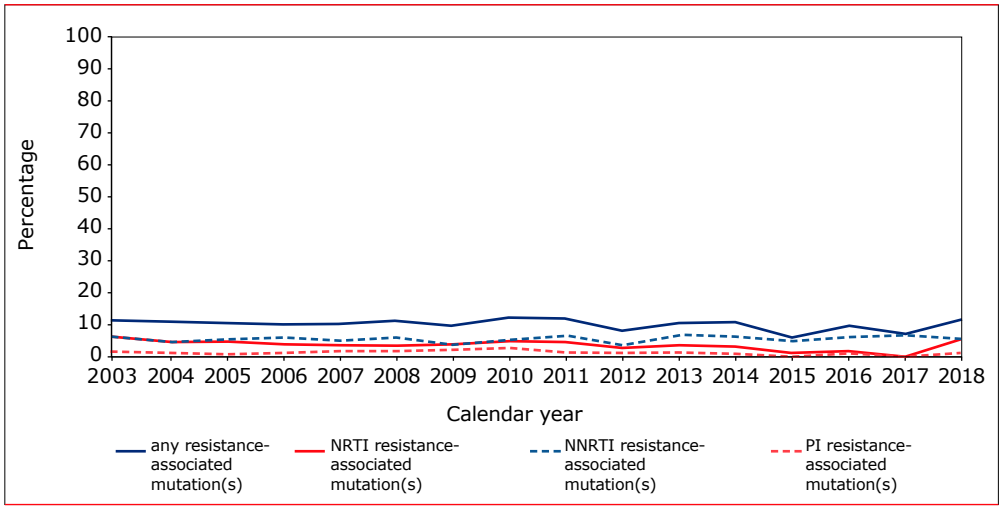
In the Netherlands, screening for HIV drug resistance at the time of entry into care has been incorporated in the treatment guidelines since 2003. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistance mutations. Drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[28,29,30]. These dormant mutant variants might not be detected, which could make it difficult to distinguish between drug-susceptible versus drug-resistant strains[31]. 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.

As of January 2019, 7,401 HIV-1 sequences had been obtained between 2003-2018 from 7,127 ARV-naive people before initiating cART. 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 further analysis to limit the effect of back mutation. Of those for whom pre-treatment drug-resistance data was available, the majority were MSM (68.6%) and, less often, women (14.5%). Most people with an available pre-treatment sequence originated from the Netherlands (60.8%) or sub-Saharan Africa (11.2%). The main HIV-1 subtype was B (76.5%), followed by non-B subtypes (23.5%), including recombinant form CRF_02AG (6.6%) and subtype C (4.8%).

Transmitted HIV drug resistance

In total, ≥1 major resistance mutation[24] was found in 768 (10.8%) of the people who were tested for resistance, including 296 (4.2%) with NRTI-associated resistance mutations, 412 (5.8%) with NNRTI-associated resistance mutations, and 130 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2018 (*Figure 2.12*).

Figure 2.12: *The annual proportion of people with evidence of transmitted HIV drug resistance over time.*



Legend: *Transmitted drug resistance was defined as the presence of at least one major drug resistance mutation detected before initiation of cART. The 2019 IAS–USA HIV drug resistance mutation list was used to score major drug resistance mutations[24]. NRTI=nucleotide/nucleoside reverse transcription inhibitor, NNRTI=non-NRTI, PI=protease inhibitor.*

In total, 189 (2.7%) screened for transmitted drug resistance harboured high-level resistance[25,26] to at least one antiretroviral drug; 32 (0.5%) to at least one NRTI, 139 (2.0%) to at least one NNRTI and 30 (0.4%) to at least one PI. On the basis of the available resistance data, >97% were fully susceptible to all antiretroviral drugs; 2.3% (n=162) harboured high-level resistance in one drug class, 0.3% (n=18) in two drug classes, and <0.1% (n=5) to three drug classes (i.e., NRTIs, NNRTIs and PIs). It should be emphasised that this does not mean that entire drug classes are rendered unsuitable for use in antiretroviral combinations. Even for people with resistance to all three classes, fully efficacious cART combinations can often still be constructed.

Integrase inhibitor resistance before HIV treatment initiation

Twenty-five people had an integrase sequence available prior to cART initiation; all of them were ARV-naive. No major or minor INSTI resistance 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 4 months of cART in 2000-2018. If cART had been interrupted >2 weeks before the test, the sequence was excluded from the analysis.

In total, 3,802 HIV-1 sequences were obtained from 2,348 people who received cART for at least 4 months. The number of sequences and people included in each subsequent analysis are outlined in *Box 2.1*. The median time between initial start of cART and resistance testing was 5.2 years (IQR 2.9-8.2). The main HIV-1 subtype was B (69.6%), followed by recombinant form CRF_02AG (10.0%) and subtype C (5.8%).

Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,284 (33.8%) sequences were obtained from 711 (30.3%) pre-treated people, and 2,518 (66.2%) sequences were obtained from 1,637 (69.7%) ARV-naive people. However, over time this difference has become less distinct. In 2000, 73.2% of sequences were obtained from pre-treated people, compared with 36.6% in 2005 and less than 15% since 2010.

Out of all 3,802 sequences obtained at the time of HIV RNA >500 copies/ml, 2,553 (67.2%) harboured high-level resistance[25] to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,195 (58.4%) sequences; of those, 1,829 (83.3% of 2,195) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,611 individuals ever identified as harbouring the M184V or M184I mutation and who were still in care in 2018, 1,100 (68.3%) were still on cART containing lamivudine and/or emtricitabine. In addition, 1,527 (40.6%) harboured high-level resistance to at least one NNRTI, and 998 (27.2%) to at least one PI.

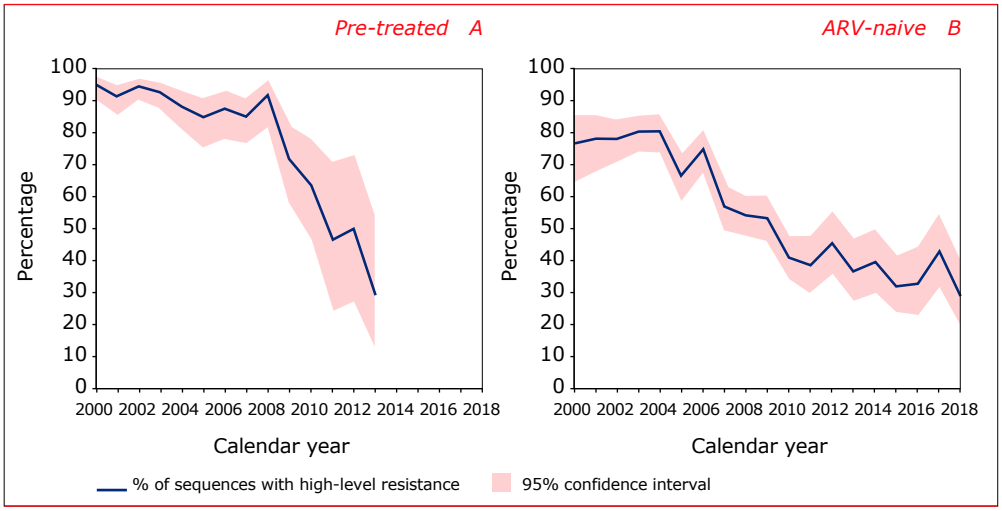
Differences in acquired HIV drug resistance between pre-treated and ARV-naive people

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 2.13A*). The availability of new drugs both in existing and new drug classes largely explains the decline since 2008[32]. In recent years (2014-2018), 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 76.6% (95% CI 64.7-85.4) of sequences in 2000, 74.7% (95% CI 67.4-80.8) in 2006, 45.5% (95% CI 36.0-55.3) in 2012, and 28.4% (95% CI 19.3-39.6) in 2018 (*Figure 2.13B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naive people has disappeared.

Figure 2.13: 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, 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 recent years (2014-2018) was too low to give meaningful proportions.*

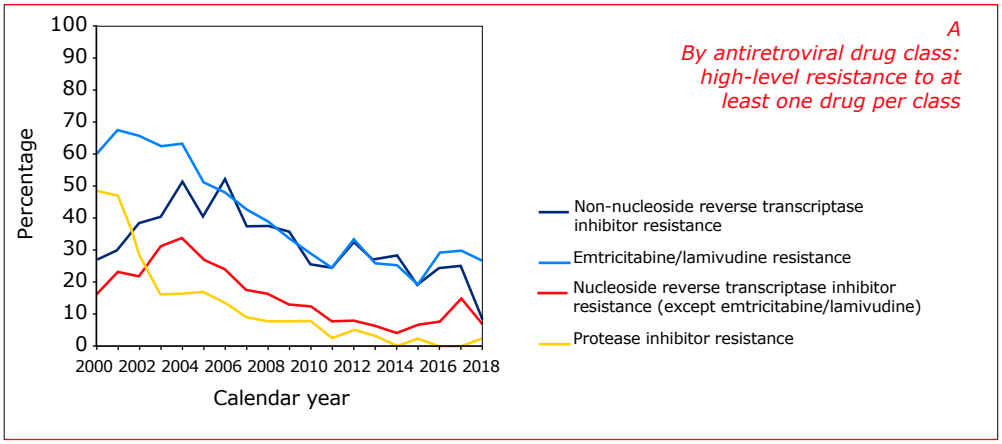
Acquired HIV drug resistance among previously ARV-naive people

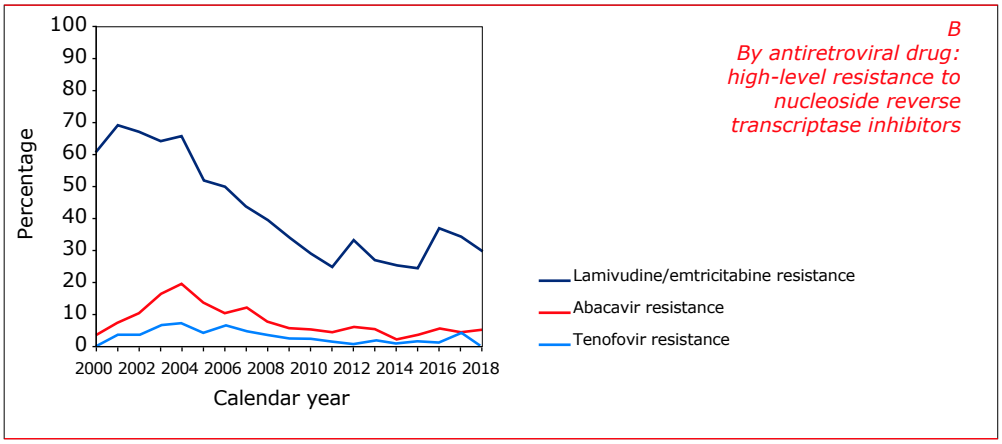
In the remainder of our analysis, we will focus solely on the 1,637 people who were ARV-naive before cART initiation. Overall, 1,543 (61.3%) out of all 2,518 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation, associated with resistance to NRTI (n=1,243; 49.4%), NNRTI (n=962; 38.2%) or PI (n=338; 13.4%).

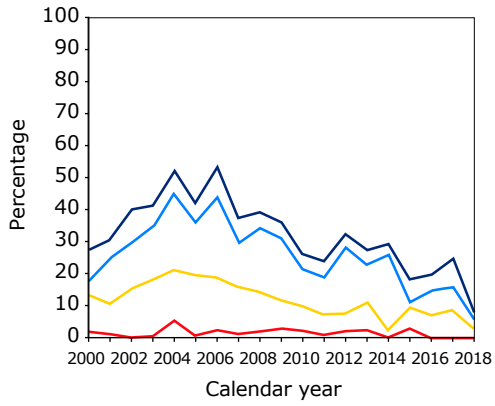
Figure 2.14A and *Table 2.5* present the annual proportion of sequences harbouring high-level resistance for each antiretroviral drug class. In 2000, 65.1% (95% CI 52.6-75.8), 27.0% (95% CI 17.5-39.2), and 48.4% (95% CI 36.5-60.5) of sequences harboured high-level resistance to at least one NRTI, NNRTI, 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 2018, 26.8% (95% CI 17.8-38.2), 8.5% (95% CI 3.8-17.6), and 2.6% (95% CI 0.3-16.5) 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 6.3% (95% CI 2.4-15.5) in 2000 to 0% as of 2014. The annual proportions of sequences harbouring high-level resistance for individual antiretroviral drugs are presented in *Figure 2.14B-D* and *Appendix Table 2.3*, and the annual proportion of sequences harbouring at least one high-level resistance mutation to all three drug classes is presented in *Figure 2.14E*.

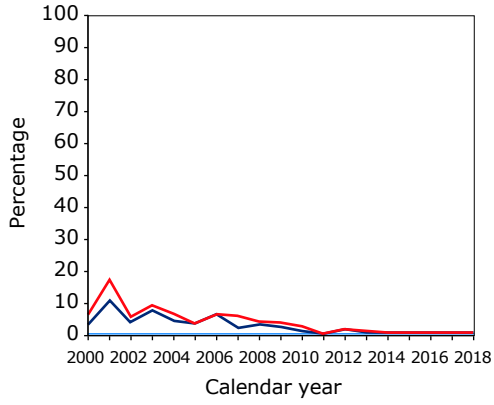
Figure 2.14: *The annual proportion of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving combination antiretroviral therapy (cART), among previously antiretroviral drug-naive people.*



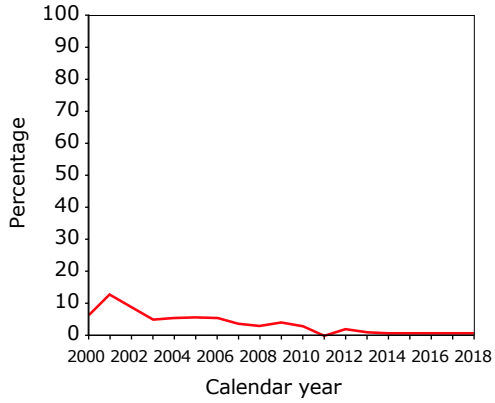




C
By antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors



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: *The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.3) 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*[37,38].

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.

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	65.1	52.6	75.8	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	72.6	64.8	79.2	38.4	30.8	46.5	29.5	22.6	37.3
2003	71.4	64.6	77.3	40.6	33.9	47.7	16.3	11.7	22.3
2004	70.1	62.9	76.3	51.4	44.1	58.7	16.4	11.6	22.6
2005	58.2	50.4	65.7	40.5	33.1	48.3	17.1	12.0	23.8
2006	55.6	47.8	63.0	52.5	44.8	60.0	13.7	9.2	19.9
2007	47.6	40.5	54.8	37.4	30.8	44.6	9.1	5.7	14.1
2008	43.3	37.0	49.8	37.7	31.6	44.1	7.8	5.0	12.0
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	27.2	19.8	36.1	24.6	17.5	33.3	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	26.4	18.3	36.4	28.6	20.2	38.7	0.0	0.0	0.0
2015	22.3	15.3	31.4	19.4	12.9	28.2	2.3	0.6	8.6
2016	29.2	19.5	41.4	24.6	15.7	36.5	0.0	0.0	0.0
2017	35.8	25.3	47.9	25.4	16.4	37.1	0.0	0.0	0.0
2018	26.8	17.8	38.2	8.5	3.8	17.6	2.6	0.4	16.5

See Appendix Table 2.3 for antiretroviral drug-specific results.

Acquired integrase-inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was relatively rare. The 144 integrase sequences that were available originated from 122 people who received cART for at least 4 months; 13 were pre-treated with monotherapy or dual therapy before initiating cART, and 109 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 9.0 years (IQR 2.9-13.9). 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 24 out of 122 people, which resulted in high-level resistance to at least one integrase inhibitor[24,25]. Among these 24 individuals, the following major INSTI resistance mutations were detected: N155H (n=10) and N155H/N (n=2); Y143R (n=3) and Y143Y/C (n=1); T66T/A (n=2), T66T/K (n=1), T66I (n=1); E92Q (n=3) and E92E/Q (n=1); Q148H (n=1, in combination with the G140S minor mutation); and R263K (n=1). Minor mutations detected were at position T66 (T66T/A, n=2), L74 (any mutation, n=6; L74I, n=5; L74M, n=1), T97 (any, n=2; T97A, n=2) and G140S (n=1).

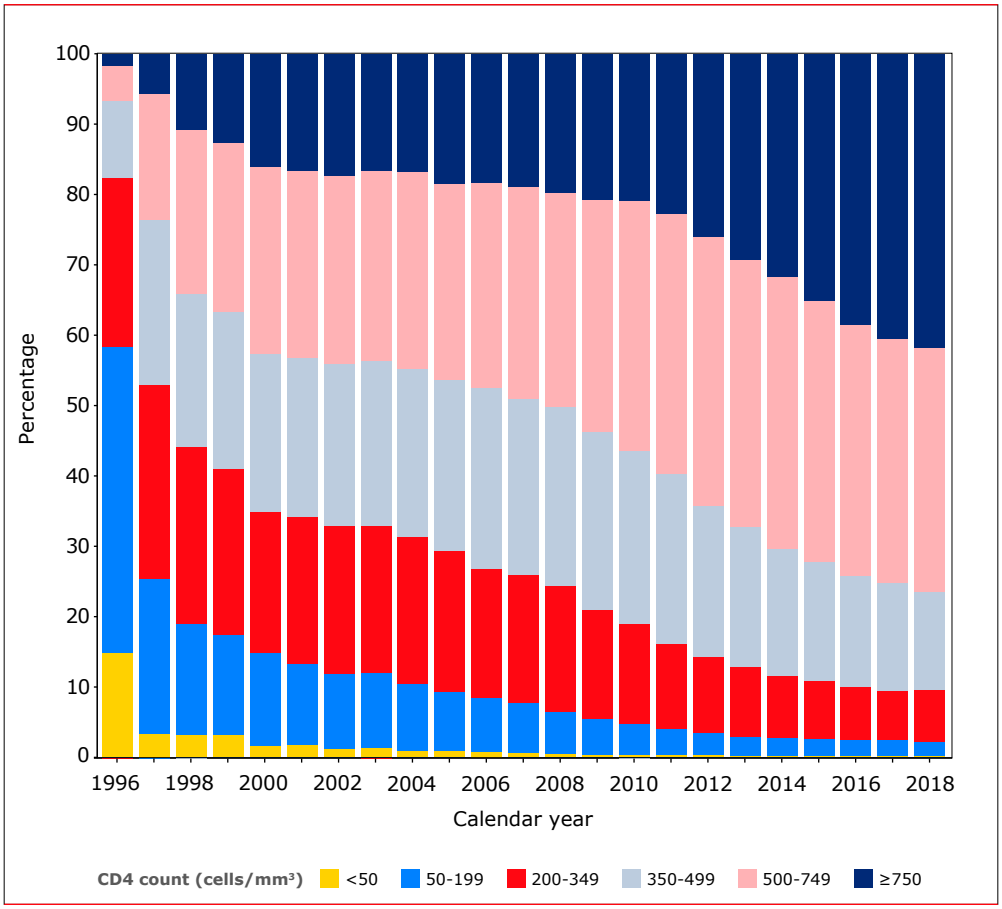
Immunological response

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[29,30,31,32,33]. 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[20]. 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[34]. 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[35,36,37,38,39,40]. The clinical benefit of cART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[41,42,43,44,45].

Immunological response – by calendar year

Out of the 24,603 people known to have initiated cART between January 1996 and December 2018, CD4 cell count data were available after cART initiation for 24,037 (97.7%). *Figures 2.15* and *2.16* 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 33.1% in 2002, 14.6% in 2012 and 9.7% in 2018 (*Figure 2.15*). Likewise, the absolute number of people with CD4 cell counts <350 cells/mm^3 at the end of each calendar year decreased from 2,124 in 2009, to 1,744 in 2013, and 1,371 in 2018; see *Appendix Figure 2.3*. The drop in absolute number of people with low CD4 cell counts at the end of each calendar year, which has been observed since 2007, reflects the trend of starting cART at higher CD4 cell counts, more pronounced immune recovery with longer cART use, but also attrition due to the higher mortality rates in those with low CD4 counts.

Figure 2.15: Last available CD4 cell count of the treated population by calendar year.

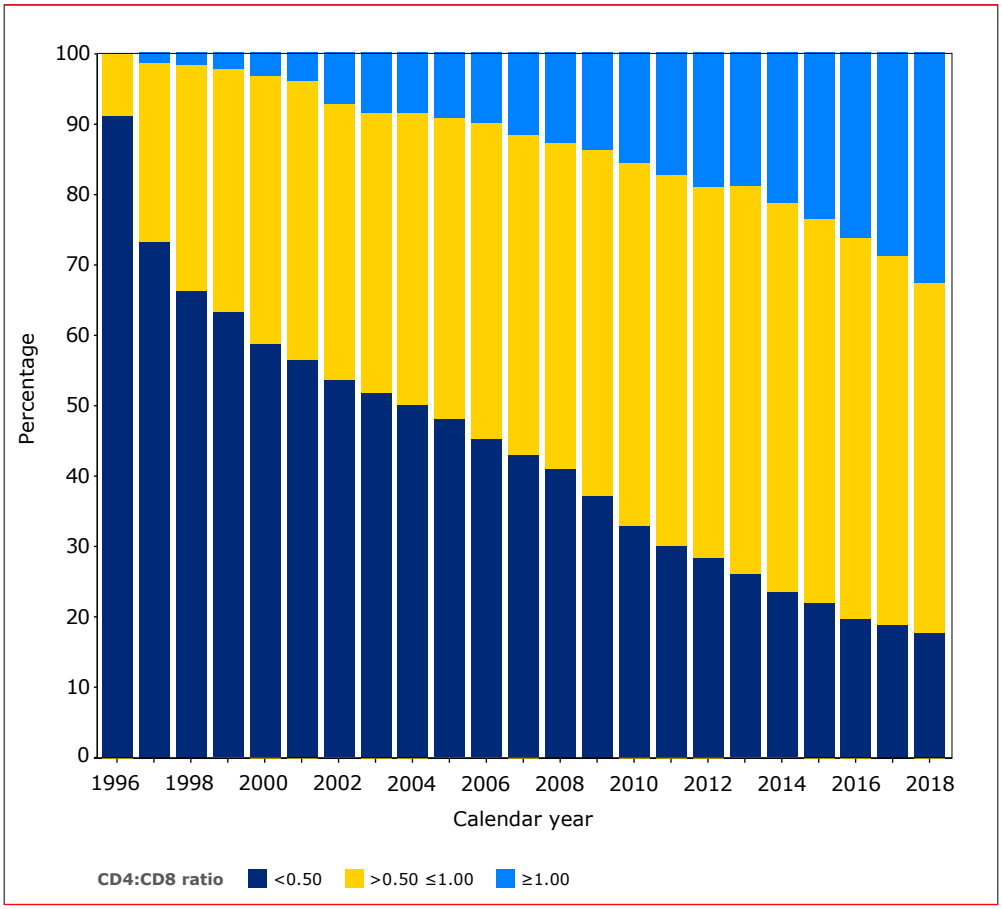


Legend: For each person, the last available CD4 cell count between January and December of each year, after starting cART, was selected (missing measurements/data not taken into account). Figures for 2018 may change slightly because data collection is not yet complete.

The percentage of those with a CD4:CD8 ratio of 1 or above increased from 2.4% in 1996-2001, to 9.1% in 2002-2007, to 15.6% in 2008-2012 and 25.0% in 2013-2018 (*Figure 2.16*). The absolute number of people in these CD4:CD8 categories per calendar year is plotted in *Appendix Figure 2.4*. Of all CD4:CD8 ratio measurements ≥1, 11.5% had a CD4 count of less than 500 cells/mm³, 33.1% had a CD4 count between 500-749 cells/mm³ and 55.5% had a CD4 count of ≥750 cells/mm³. When the CD4:CD8 ratio was ≥1, the median CD4 count was 780 cells/mm³ (IQR 610-990), and

remained fairly stable over time, with a median of 771 cells/mm^3 (IQR 596-1,010) in 1996-2001, 750 cells/mm^3 (IQR 570-961) in 2002-2007, median 730 cells/mm^3 (IQR 570-930) in 2008-2012 and median 810 cells/mm^3 (IQR 640-1,007) in 2013-2018.

Figure 2.16: Last available CD4:CD8 ratio in each calendar year after the start of combination antiretroviral therapy (cART).



Legend: For each person, the last available CD4 cell count between January and December of each year, after starting cART, was selected.

Immunological response – after cART initiation (2013–2018)

We assessed the immunological response in people who started cART in more recent years: 5,528 people started cART in 2013-2018, 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 5,528 people who started cART in 2013-2018 and had sufficient immunological data available, 7.8% had CD4 counts <50 cells/mm^3, 13.5% had between 50 and 199 cells/mm^3, 20.1% had between 200 and 349 cells/mm^3, 25.8% had between 350 and 499 cells/mm^3, and 32.8% had 500 or more CD4 cells/mm^3 at the time of cART initiation. The CD4 cell count at cART initiation has increased and stabilised in recent years (*Appendix Table 2.2*).

The CD4 cell count and CD4:CD8 ratio trajectories following cART initiation are plotted in *Figures 2.17* and *2.18* 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 recent study by the Antiretroviral Therapy Cohort Collaboration (ART-CC), including ATHENA data, that showed that the likelihood of normalisation of the CD4:CD8 ratio is strongly related to baseline CD4 cell count[46].

Figure 2.17: CD4 cell count over time after the start of combination antiretroviral therapy (cART) in 2013–2018.

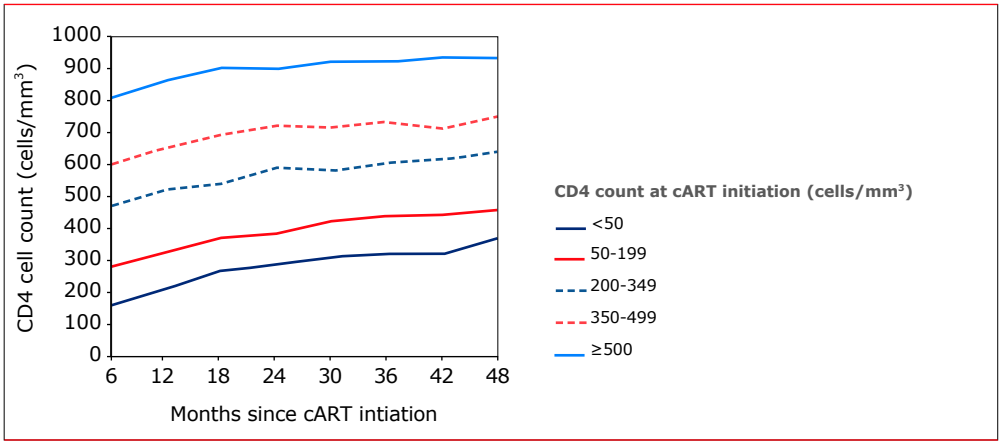
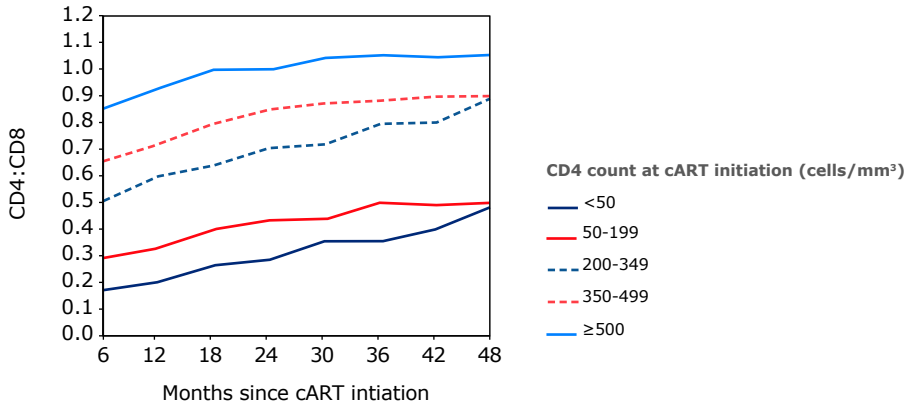


Figure 2.18: CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART) in 2013–2018.



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[47]. 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 & the initial regimen

- Rapid initiation of cART following a diagnosis of HIV infection, irrespective of CD4 cell count, continues to improve over time.
- The CD4 cell count at cART initiation has increased over time and peaked at a median of 420 cells/mm³ (IQR 220-600) in 2015, when new guidelines came out recommending rapid initiation of cART at any CD4 count. These changes in guidelines resulted in substantial numbers of individuals with preserved CD4 counts who, until that time, had postponed starting cART and who subsequently decided to initiate treatment. Since then, the median CD4 count at start of cART has decreased somewhat. Among HIV-positive individuals starting cART in 2018, the median CD4 cell count was 330 cells/mm³ (IQR 116-564). Immunological recovery was strongly related to the CD4 cell count at the start of cART.
- In 2018, the majority of individuals initiating cART did so within a month after diagnosis. Most persons who initiated cART in 2018 received TAF/FTC/EVG/c or ABC/3TC/DTG.

- Discontinuation of the initial regimen has become less common over time, with regimen switches occurring mainly because of 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 2018

- Integrase inhibitor-based cART has been further implemented on a large scale in the Netherlands. Integrase inhibitor-based cART was prescribed to 46% of those in care in 2018, compared with 39% in 2016[48].
- While 35% of the population on cART received TDF, newly-available fixed-dose combinations led to an increase in the prescription of ABC/3TC (23%) and TAF/FTC (33%) as the backbone.
- Of those receiving cART for at least 12 months and who had a plasma HIV RNA measurement in 2018, 98% had a viral load less than 200 copies/ml. Long-term survivors (i.e., individuals in care in 2018 who were diagnosed with HIV before 1996) had equally high levels of viral suppression.

Virological response and drug resistance

- The overall viral suppression rates of the HIV-positive population receiving cART is high and continues to improve. Among those who experience virological failure, the annual proportion of persons with acquired drug resistance continues to decline; this is in line with findings from other high-income settings[49,50].
- Transmitted drug resistance is rare, and the overall prevalence is low and stable over time, in line with reported rates from other European countries[51].
- Integrase inhibitor resistance data are limited. No transmitted integrase inhibitor resistance was detected among 25 people tested up to 2018. Detected rates of acquired integrase inhibitor resistance among available sequences were very low, with only a few sequences showing major resistance to dolutegravir.

Immunological response

- After starting cART, the percentage of people with CD4 cell counts <350 cells/mm^3 dropped from 53.1% in 1997 to 33.1% in 2002, 14.6% in 2012 and 9.7% in 2018.
- The percentage of people with a CD4:CD8 ratio of 1 or above increased from 2.4% in 1996-2001, to 9.1% in 2002-2007, to 15.6% in 2008-2012 and 25.0% in 2013-2018.

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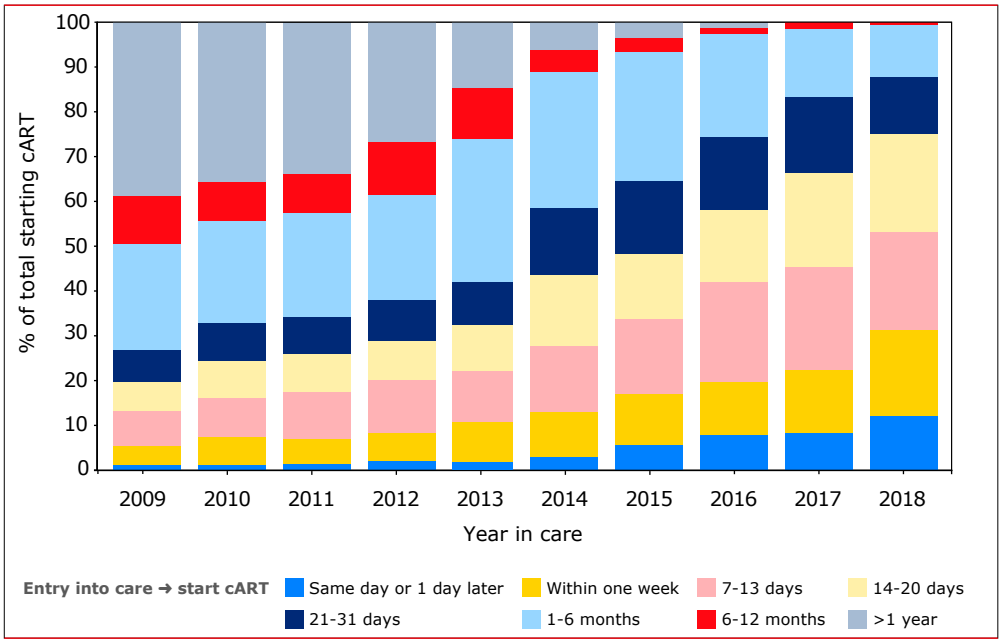
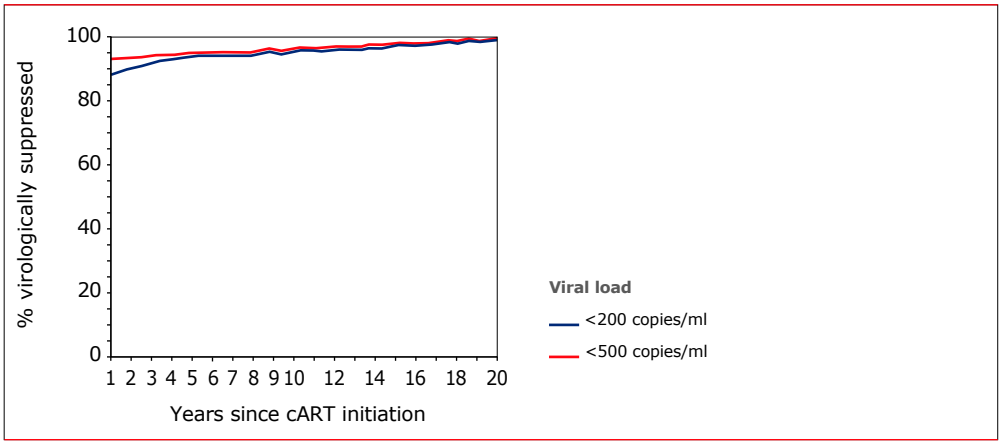
Appendix: supplementary figures and tables

Appendix Figure 2.1: Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) of people starting cART in 2009–2018.



Legend: cART=combination antiretroviral therapy.

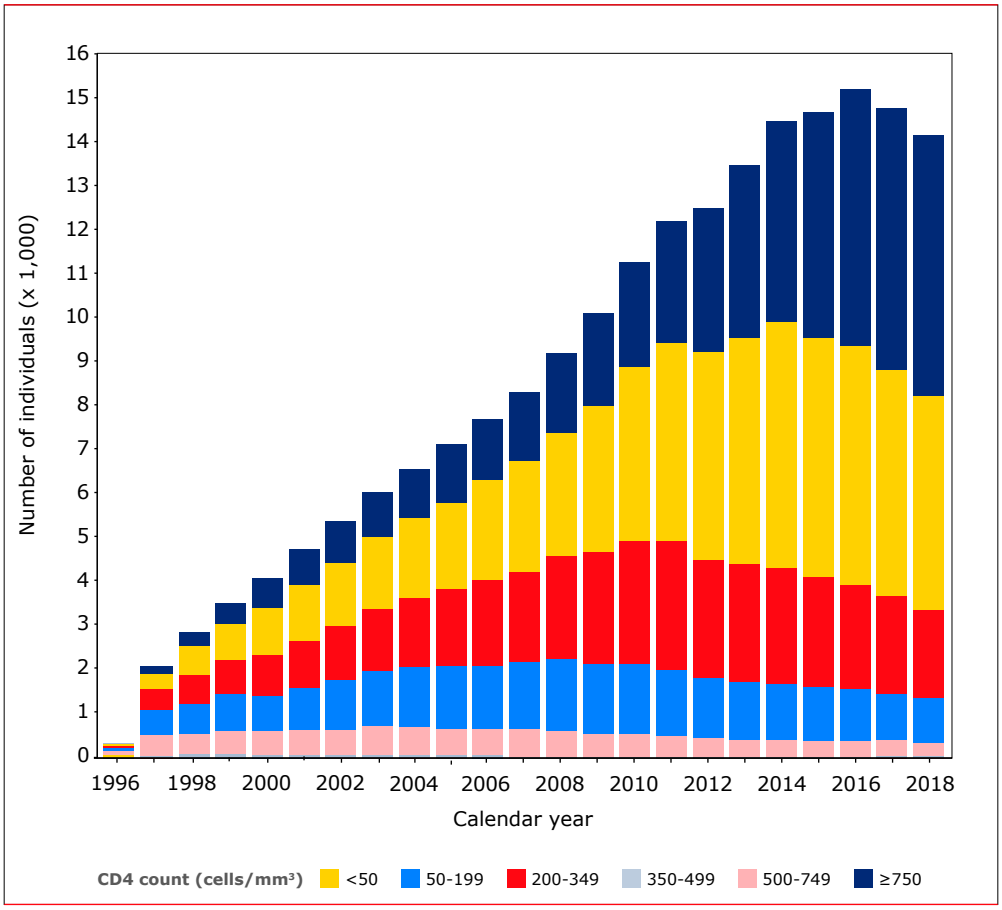
Appendix Figure 2.2: Viral suppression since initiation of combination antiretroviral therapy.



Legend: cART=combination antiretroviral therapy.

< Back to page 82

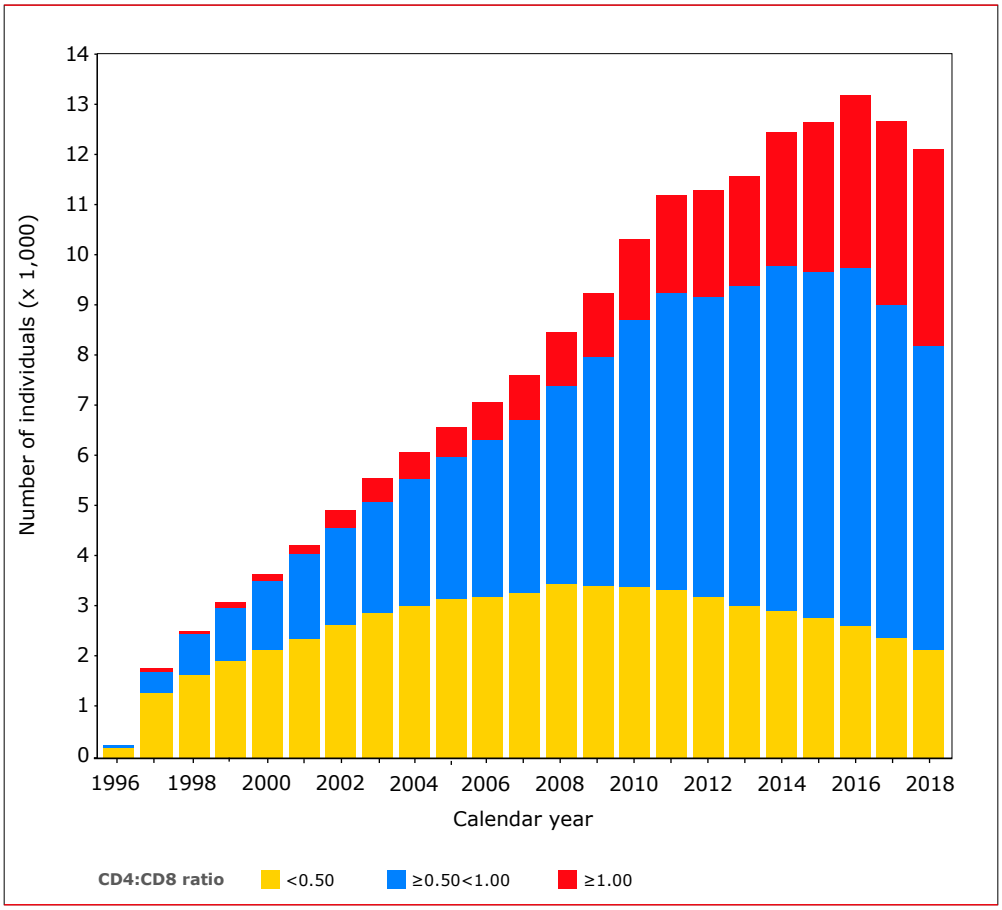
Appendix Figure 2.3: *Last available CD4 cell count (cells/mm³) in each calendar year after the start of combination antiretroviral therapy.*



Note: Numbers for 2018 may increase slightly because data collection is not yet complete.

< Back to page 121

Appendix Figure 2.4: Last available CD4:CD8 ratio in each calendar year after the start of combination antiretroviral therapy.



Note: Numbers for 2018 may increase slightly because data collection is not yet complete.

< Back to page 122

Appendix Table 2.1: *Combination antiretroviral therapy (cART) regimen used by long-term HIV survivors in 2018.*

cART regimen	n	%
TDF/FTC/EFV	104	5.4
TDF/FTC/NVP	162	8.4
TDF/FTC/RPV	40	2.1
TDF/FTC/DRV/b	69	3.6
TDF/FTC/ATV/r	41	2.1
TDF/FTC/LPV/r	5	0.3
TDF/FTC/EVG/c	21	1.1
TDF/FTC/DTG	38	2.0
TDF/FTC/RAL	16	0.8
ABC/3TC/DTG	162	8.4
TAF/FTC/EVG/c	174	9.1
TAF/FTC/RPV	53	2.8
TAF/FTC/DTG	47	2.5
TAF/FTC/DRV/c	74	3.9
TAF/FTC/BIC	18	0.9
Other: 2NRTI+NNRTI	270	14.1
Other: 2NRTI+PI	83	4.3
Other: 2NRTI+INST	35	1.8
Other: NNRTI+INST	7	0.4
Other: PI+INSTI	102	5.3
Other: NRTI+PI+INSTI(3ARVs)	42	2.2
Other: NRTI+PI+INSTI(4ARVs)	79	4.1
Other	277	14.4
Total	**1,919**	**100**

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

< Back to page 90

Appendix Table 2.2: CD4 cell count at combination antiretroviral therapy (cART) initiation by calendar year 2013–2018.

Year of cART initiation	2013	2014	2015	2016	2017	2018	Total (2013–2018)
CD4 cell count available at cART initiation	1,366	1,334	1,074	862	668	224	**5,528**
CD4 cell count, median cells/mm³ (IQR)	370 (250–510)	410 (270–567)	420 (220–600)	410 (230–579)	370 (181–550)	330 (116–564)	**390 (230–560)**
CD4 cell count (cells/mm³)							
<50	92	74	86	79	60	38	**429**
	(6.7)	(5.6)	(8.0)	(9.2)	(9.0)	(17.0)	
50–199	163	161	161	109	116	37	**747**
	(11.9)	(12.1)	(15.0)	(12.7)	(17.4)	(16.5)	
200–349	341	257	180	157	136	41	**1,112**
	(25.0)	(19.3)	(16.8)	(18.2)	(20.4)	(18.3)	
350–499	408	380	249	201	148	42	**1,428**
	(29.9)	(28.5)	(23.2)	(23.3)	(22.2)	(18.8)	
≥500	362	462	398	316	208	66	**1,812**
	(26.5)	(34.6)	(37.1)	(36.7)	(31.4)	(29.5)	

< Back to page 124

Appendix Table 2.3: *Acquired drug resistance: annual proportion of available sequences with evidence of high-level resistance after virological failure by antiretroviral drug from people who received combination antiretroviral therapy and were previously antiretroviral drug-naive.*

A) High-level resistance to nucleoside reverse transcriptase inhibitors.

Calendar year	Number of sequences	Emtricitabine/ lamivudine	Zidovudine	Stavudine	Abacavir	Didanosine	Tenofovir
2000	64	60.9	10.3	7.4	3.6	10.3	0.0
2001	86	69.0	17.1	17.8	7.5	16.7	3.8
2002	146	67.1	10.9	14.6	10.7	17.8	3.6
2003	192	64.2	18.5	24.4	16.4	23.5	6.8
2004	178	65.7	17.7	23.1	19.7	26.3	7.5
2005	158	51.9	13.7	17.9	13.8	18.3	4.6
2006	162	50.0	9.3	14.8	10.4	18.9	6.6
2007	188	43.8	8.9	12.8	12.3	13.1	4.9
2008	231	39.6	7.4	11.0	7.9	14.1	3.7
2009	190	34.0	6.7	9.6	5.8	10.2	2.7
2010	200	29.1	5.8	8.0	5.5	9.1	2.6
2011	114	25.0	0.9	2.8	4.6	8.1	1.8
2012	99	33.3	0.0	2.1	6.4	8.2	1.1
2013	93	27.2	0.0	2.3	5.6	5.6	2.2
2014	91	25.6	1.1	2.3	2.3	3.4	1.1
2015	109	24.5	0.9	2.9	3.8	6.5	1.9
2016	73	37.0	1.4	1.4	5.8	5.8	1.4
2017	70	34.3	2.9	7.5	4.7	13.4	4.4
2018	74	29.7	0.0	0.0	5.5	5.4	0.0

< Back to page 117

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

Calendar year	Number of sequences	Nevirapine	Efavirenz	Etravirine	Rilpivirine
2000	64	27.4	17.5	1.9	13.3
2001	86	30.6	25.0	1.3	10.6
2002	146	40.0	29.7	0.0	15.4
2003	192	41.3	34.9	0.6	18.2
2004	178	52.0	44.9	5.4	21.2
2005	158	41.8	35.9	0.7	19.6
2006	162	53.1	43.9	2.4	18.8
2007	188	37.3	29.6	1.3	15.8
2008	231	39.2	34.2	2.0	14.4
2009	190	36.0	31.1	2.9	11.6
2010	200	26.2	21.5	2.2	10.0
2011	114	23.9	18.7	1.0	7.3
2012	99	32.3	28.0	2.2	7.6
2013	93	27.5	22.7	2.4	11.1
2014	91	29.2	26.1	0.0	2.3
2015	109	18.1	10.9	3.0	9.5
2016	73	19.7	14.7	0.0	7.1
2017	70	24.6	15.9	0.0	8.8
2018	74	8.1	5.6	0.0	2.7

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	86	47.1	21.3	18.1	17.5	13.6	11.0	2.5	0.0
2002	146	29.9	10.1	6.7	5.8	5.1	4.2	0.0	0.0
2003	192	16.8	9.2	9.8	9.5	7.5	8.0	1.6	0.0
2004	178	15.4	6.5	6.6	6.9	5.2	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	162	13.0	5.7	7.5	7.0	5.1	6.8	2.5	0.0
2007	188	9.2	4.4	4.4	6.4	3.2	2.7	1.1	0.0
2008	231	6.6	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	114	2.6	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	93	3.2	0.0	1.1	1.1	2.2	1.1	0.0	0.0
2014	91	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2015	109	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2016	73	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2017	70	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2018	74	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0