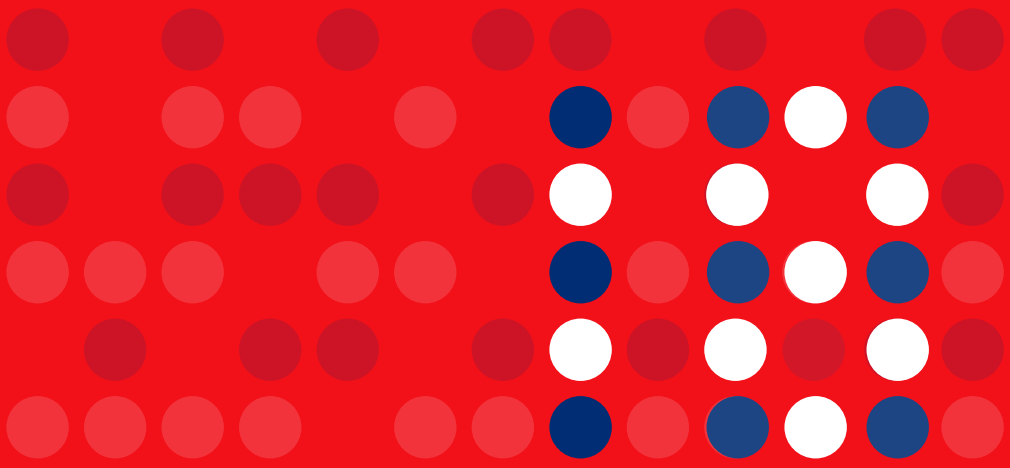
Human Immunodeficiency Virus (HIV)
infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2018

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.

SHM comprehensively maps the HIV epidemic and HIV treatment outcomes in the Netherlands, thereby contributing to the knowledge of HIV. 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.

In addition to national reports, healthcare professionals are provided with treatment centre-specific reports to enable them to monitor and optimise care provided in their centres. Moreover, upon request, SHM data are also made available for use in HIV-related research, both in the Netherlands and internationally. The outcome of SHM's research and international collaborations provides tangible input into policy guidelines and further improves HIV care 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.

HIV Monitoring

Monitoring Report 2018

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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To cite this report, please use: van Sighem A.I., Boender T.S., Wit F.W.N.M., Smit C., Matser A., Reiss P. Monitoring Report 2018. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring, 2018. Available online at www.hiv-monitoring.nl

ISBN/EAN: 978-94-90540-09-8
First edition: November 2018
Editing: Sally H. Ebeling, Boston, MA, USA

Art Direction & DTP: Studio Zest, Wormer, the Netherlands

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 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, AIDS, and tuberculosis, 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 a negligible to non-existent risk of sexual transmission of HIV; undetectable equals untransmittable, i.e. U=U [2,10,11,12,13,14]. Depending on the drugs employed, it may take as long as six months for the viral load to become undetectable. Sustained HIV suppression requires selection of appropriate treatment and continued adherence to treatment. HIV viral suppression should therefore be continuously monitored and documented to assure both personal health and public health benefits.

Most guidelines list an integrase inhibitor as the third agent of preferred first-line cART regimens, along with the options of darunavir as a boosted protease inhibitor or rilpivirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI) option (the latter only if viral load is <100,000 copies/ml), all in combination with a double nucleoside backbone (either tenofovir/emtricitabine or abacavir/lamivudine)[5]. Additionally, tenofovir alafenamide (TAF) and tenofovir disoproxil 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 functioning or risk thereof and in people with osteoporosis or at risk for osteoporotic fractures[15,16]. Safety, cost and access 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. Low-level viraemia above the reported threshold, however, may be associated with the development of drug resistance. High-level viraemia can lead to selection and accumulation of mutations in the HIV genome that are associated with drug resistance, which prevents successful viral suppression and thereby increases the risk of poor clinical outcomes[17,18,19,20,21,22,23].

This chapter reports on the prescription of cART and its outcome 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, the database maintained by SHM. We also analyse the presence of 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 23,893 registered adults (≥18 years at the time of diagnosis) with HIV-1 in the Netherlands

1. **Starting combination antiretroviral therapy**
   23,579 people were known to have initiated cART between January 1996 and December 2017.

2. **In care and on cART in the Netherlands in 2017**
   Out of 23,579 people known to have initiated cART between January 1996 and December 2017,
   ➔ 18,523 were in care and had a clinical visit in 2017;
   ➔ 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 23,579 people known to have initiated cART between January 1996 and December 2017,
   ➔ 5,767 initiated cART between January 2013 and December 2017;
   ➔ 4,630 initiated cART between January 2013 and December 2017 with a regimen composed of TDF/FTC in combination with EFV, RPV, DRV/b, EVG/c, or DTG; ABC/3TC/DTG; or TAF/FTC/EVG/c.

4. **Virological response**
   Out of 23,579 people known to have initiated cART between January 1996 and December 2017,
   ➔ 19,358 people were ARV-naive, not pregnant at cART initiation, and had a viral load result after ≥3 months of cART initiation.

   Initial virological success
   ➔ 15,645 individuals were ART-naive, not pregnant at cART initiation, and had a viral load result 6 months (±3 months) after cART initiation;
   ➔ 3,881 of those initiated tenofovir/FTC in combination with EFV, RPV, DRV/b, EVG/c, or DTG; ABC/3TC/DTG; or TAF/FTC/EVG/c in 2013-2017; and 3,456 of those also had viral load data available at the time of cART initiation.

5. **HIV drug resistance**

Transmitted HIV drug resistance

As of January 2018, 7,315 HIV-1 sequences were obtained from 6,981 ARV-naive people before initiating cART in 2003-2017.

➔19 people had pre-treatment integrase sequences available.

Acquired HIV drug resistance

As of January 2018, 4,242 HIV-1 sequences were obtained from 2,540 people who received cART for at least 4 months in 2000-2017.

➔ 2,816 sequences from 1,775 people who were ARV-naive before initiating cART.

➔ 107 integrase sequences were available from 89 people.

6. **Immunological response**

Out of the 23,578 people known to have initiated cART between January 1996 and December 2017

➔ 23,073 had CD4 cell count data available after initiating cART.

Legend: *ART=antiretroviral therapy (antiretroviral drug use that may prevent HIV from damaging the immune system by blocking the reproduction of HIV virus); 3TC=lamivudine; b=boosted (cobicistat or ritonavir); / c=cobicistat-boosted; cART=combination antiretroviral therapy (defined as a combination of three antiretroviral drugs from two different antiretroviral drugs classes); ABC=abacavir; ARVs=antiretroviral drugs; 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, 23,578 adults ever registered by SHM and followed in the ATHENA cohort were aged 18 years or older at the time of HIV-1 diagnosis and were known to have initiated cART (defined as a combination of at least 3 antiretroviral agents) between January 1996 and December 2017 (*Box 2.1*). Of these, 2,538 (10.8%) had prior exposure to mono or dual antiretroviral therapy (ART) at the start of cART and 21,041 (89.2%) 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: 5,928 started between 1996 and the end of 2001, 5,316 between 2002 and the end of 2007, 6,568 between 2008 and the end of 2012, and 5,767 between 2013 and the end of 2017. Those starting cART in 2018 were not included in the current analysis because their follow up is currently too short to allow meaningful reporting of their virological and immunological response to treatment.

Table 2.1 Characteristics of people starting combination antiretroviral therapy in 1996–2017.

Year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	1996–2017
Total	n	5,928	5,315	6,569	5,767	**23,579**
DEMOGRAPHIC						
Age at cART initiation (years)	Median	37.6	38.6	40.4	39.3	**38.9**
	Q1	32.2	32.0	32.8	30.6	**31.9**
	Q3	44.6	45.7	48.0	49.0	**46.9**
Male (at birth)	n	4,819	3,889	5,578	4,996	**19,282**
	%	81.3	73.2	84.9	86.6	**81.8**
Transmission risk group						
Missing	n	4	7	5	11	**27**
	%	0.1	0.1	0.1	0.2	**0.1**
Men who have sex with men	n	3,475	2,546	4,357	4,038	**14,416**
	%	58.6	47.9	66.3	70.0	**61.1**
Heterosexual contact	n	1,650	2,209	1,784	1,404	**7,047**
	%	27.8	41.6	27.2	24.4	**29.9**
Injecting drug use	n	405	159	83	25	**672**
	%	6.83	2.99	1.26	0.43	**2.85**
Blood or blood products	n	106	69	47	53	**275**
	%	1.79	1.3	0.72	0.92	**1.17**
Vertical transmission	n	0	0	3	1	**4**
	%	0	0	0.1	<0.1	**<0.1**
Other/unknown	n	288	325	290	235	**1,138**
	%	4.9	6.1	4.4	4.1	**4.8**
Region of origin						
Missing	n	28	20	19	27	**94**
	%	0.5	0.44	0.3	0.5	**0.4**
The Netherlands	n	3,556	2,562	3,963	3,505	**13,586**
	%	60.0	48.2	60.3	60.8	**57.6**
Western Europe/North America/Australia	n	681	409	459	343	**1,892**
	%	11.5	7.7	7.0	6.0	**8.0**
East/central Europe	n	88	136	246	320	**790**
	%	1.5	2.6	3.7	5.6	**3.4**
South America and the Caribbean	n	582	673	745	697	**2,697**
	%	9.8	12.7	11.3	12.1	**11.4**
Sub-Saharan Africa	n	730	1,215	776	505	**3,226**
	%	12.3	22.9	11.8	8.8	**13.7**
Other*	n	263	300	361	370	**1,294**
	%	4.4	5.6	5.5	6.4	**5.5**

Year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	1996–2017
CLINICAL						
Recent infection	n	326	433	1,270	1,531	**3,560**
(within 12months of diagnosis)	%	5.5	8.2	19.3	26.6	**15.1**
Ever tested HIV-negative	n	1,141	1,421	3,176	3,353	**9,091**
	%	19.3	26.7	48.4	58.1	**38.6**
CD4 cell count at start cART	Median	200	190	280	394	**260**
	Q1	80	89	170	240	**126**
	Q3	340	280	369	560	**398**
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**
AIDS at start cART	n	1,911	1,411	1,104	695	**5,121**
	%	32.2	26.6	16.8	12.1	**21,72**
ARV-naive at start cART	n	3,773	5,073	6,478	5,717	**21,041**
	%	63.7	95.5	98.6	99.1	**89.2**
cART started during pregnancy	n	122	356	170	52	**700**
	%	2.1	6.7	2.6	0.9	**3.0**
Hepatitis B status at start of cART						
HBV-	n	5,279	4,836	6,056	5,68	**21,339**
	%	89.1	91.0	92.2	89.6	**90.5**
HBV+	n	368	317	317	163	**1165**
	%	6.2	6.0	4.8	2.8	**4.9**
Unknown	n	281	162	196	436	**1,075**
	%	4.7	3.1	3.0	7.6	**4.6**
Hepatitis C status at start of cART						
HCV-	n	5,245	4,885	6,204	5,371	**21,705**
	%	88.5	91.9	94.4	93.1	**92.1**
HCV RNA+	n	79	135	141	87	**442**
	%	1.3	2.5	2.2	1.5	**1.9**
HCV Ab+	n	146	65	42	27	**280**
	%	2.5	1.2	0.6	0.5	**1.2**
Unknown	n	458	230	182	282	**1,152**
	%	7.7	4.3	2.8	4.9	**4.9**

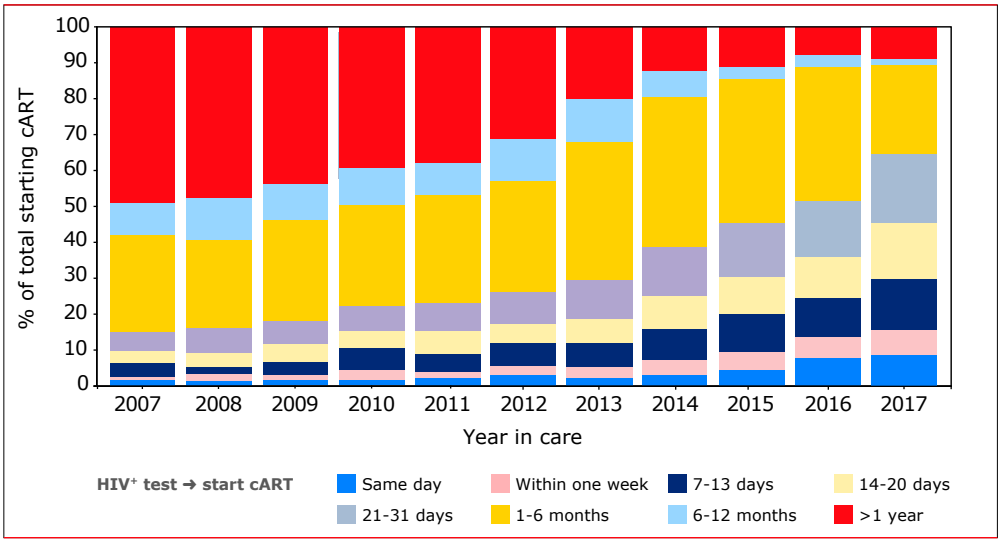
**The 63 people from other regions of origin who started in 2017 were from South-east Asia (n=29), North Africa and the Middle East (n=26), and Oceania and the Pacific (n=8).*

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

Of the 23,578 people who had initiated cART since January 1996, 19,282 were men (81.8%) of whom 14,416 (74.8%) were men who have sex with men (MSM). Overall, 13,586 (57.6%) 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. Over the past 20 years, 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% in 2015-2017. Simultaneously, the number of people from western Europe/North America/Australia slightly decreased from 11.5% in 1996-2001 to 4.9% in 2017, with a decrease in those from sub-Saharan Africa from 23.0% in 2002-2007 to 11.9% in 2008-2012 to 8.8% in 2013-2017.

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 133 days (interquartile range [IQR] 33-683) for those who entered care in 2011 to 98 days (IQR 30-491) in 2012, 65 days (IQR 41 21-106) in 2013, 41 days (IQR 21-106) in 2014, 35 days (IQR 17-76) in 2015, and 29 days (IQR 14-53) in 2016. In 2017, the time between an HIV-positive diagnosis and cART initiation further decreased to a median of 23 days (IQR 12-43). 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 2007–2017.*



**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 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 (IQR89-280) in 2002-2007 to 280 cells/mm^3 (IQR 170-369) in 2008-2012 and to 394 cells/mm^3 (IQR 240-560) in 2013-2017 (p for trend <.0001). In 2017, the median CD4 cell count at the start of cART was 380 cells/mm^3 (IQR 202-554). Since 2016, both the number of people initiating cART per calendar year and the median CD4 cell count at cART initiation have slightly decreased. This trend is likely due to the substantial group who were already in care but not on cART (with high CD4 cells counts) and subsequently initiated cART under recent guideline changes.

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 2017

Out of the 23,578 people who were known to have initiated cART between January 1996 and December 2017, 18,523 (78.6%) were alive, receiving cART, and had a visit for HIV care in the Netherlands in 2017. *Table 2.2* shows their treatment and clinical characteristics in the year 2017. Overall, 15,265 (82.4%) were men, and 11,996 (64.8%) were MSM. The median age on 31 December 2017 was 50 (IQR 41-57) years. The majority (61.0%) originated from the Netherlands, followed by sub-Saharan Africa (11.9%) and South America and the Caribbean (11.3%).

Table 2.2: *Characteristics of people who started combination antiretroviral therapy and known to be in care in 2017.*

Calendar year of cART initiation		1996-2001	2002-2007	2008-2012	2013-2017	All
Total	n	3,773	3,843	5,597	5,310	**18,523**
	%	20.4	20.8	30.2	28.7	**100**
Sex						
Male	n	3,040	2,836	4,776	4,613	**15,265**
	%	80.6	73.8	85.3	86.9	**82.4**
Female	n	733	1,007	821	697	**3,258**
	%	19.4	26.2	14.7	13.1	**17.6**
Age on 31 December 2017	Median	56.3	51.6	48.3	42.6	**49.9**
	Q1	51.3	45.2	40.5	33.3	**41.3**
	Q3	62.4	58.1	55.5	51.9	**57.4**
Transmission risk group						
No data	n	2	6	4	10	**22**
	%	0.1	0.2	0.1	0.2	**0.1**
Men who have sex with men	n	2,341	2,024	3,855	3,776	**11,996**
	%	62.1	52.7	68.9	71.1	**64.8**
Heterosexual contact	n	1,,093	1,505	1,458	1,259	**5,315**
	%	29.0	39.2	26.1	23.7	**28.7**
Injecting drug use	n	136	68	53	19	**276**
	%	3.6	1.8	1.0	0.4	**1.5**
Blood or blood products	n	71	49	36	45	**201**
	%	1.9	1.3	0.6	0.9	**1.1**
Vertical transmission	n	.	.	2	1	**3**
	%	.	.	0.04	0.02	**0.02**
Other/unknown	n	130	191	189	200	**710**
	%	3.5	5.0	3.4	3.8	**3.8**
Region of origin						
No data	n	11	12	16	26	**65**
	%	0.3	0.3	0.3	0.5	**0.4**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	All
The Netherlands	n	2,362	2,042	3,588	3,308	**11,300**
	%	62.6	53.1	64.1	62.3	**61.0**
Western Europe/North America/Australia	n	344	229	325	286	**1,184**
	%	9.1	6.0	5.8	5.4	**6.4**
East/central Europe	n	51	96	186	284	**617**
	%	1.4	2.5	3.3	5.4	**3.3**
South America and the Caribbean	n	380	488	595	633	**2,096**
	%	10.1	12.7	10.6	11.9	**11.3**
Sub-Saharan Africa	n	432	755	581	433	**2,201**
	%	11.5	19.7	10.4	8.2	**11.9**
Other	n	193	221	306	340	**1,060**
	%	5.1	5.8	5.5	6.4	**5.7**
cART regimen						
TDF/FTC/EFV	n	269	602	921	305	**2,097**
	%	7.1	15.7	16.5	5.7	**11.3**
TDF/FTC/NVP	n	500	398	524	110	**1,532**
	%	13.3	10.4	9.4	2.1	**8.3**
TDF/FTC/RPV	n	104	170	382	380	**1,036**
	%	2.8	4.4	6.8	7.2	**5.6**
TDF/FTC/DRV/b	n	165	219	416	293	**1,093**
	%	4.4	5.7	7.4	5.5	**5.9**
TDF/FTC/ATV/r	n	104	130	225	74	**533**
	%	2.8	3.4	4.0	1.4	**2.9**
TDF/FTC/LPV	n	7	24	10	3	**44**
	%	0.2	0.6	0.2	0.1	**0.2**
TDF/FTC/EVG/c	n	64	103	181	503	**851**
	%	1.7	2.7	3.2	9.5	**4.6**
TDF/FTC/DTG	n	69	99	151	292	**611**
	%	1.8	2.6	2.7	5.5	**3.3**
TDF/FTC/RAL	n	47	48	89	44	**228**
	%	1.3	1.3	1.6	0.8	**1.2**
ABC/3TC/DTG	n	342	511	810	1,476	**3,139**
	%	9.1	13.3	14.5	27.8	**17.0**
TAF/FTC/EVG/c	n	285	386	642	1,110	**2,423**
	%	7.6	10.0	11.5	20.9	**13.1**
TAF/FTC/RPV	n	72	108	246	190	**616**
	%	1.9	2.8	4.4	3.6	**3.3**
TAF/FTC/DTG	n	59	46	109	146	**360**
	%	1.6	1.2	2.0	2.8	**1.9**

Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	All
TAF/FTC/DRV/c	n	68	61	82	78	**289**
	%	1.8	1.6	1.5	1.5	**1.6**
Other: 2NRTI+NNRTI	n	619	422	357	72	**1,470**
	%	16.4	11.0	6.4	1.4	**7.9**
Other: 2NRTI+PI	n	175	190	174	75	**614**
	%	4.6	4.9	3.1	1.4	**3.3**
Other: 2NRTI+INSTI	n	58	52	61	41	**212**
	%	1.5	1.4	1.1	0.8	**1.1**
Other: NNRTI+INSTI	n	8	5	4	.	**17**
	%	0.2	0.1	0.1	.	**0.1**
Other: PI+INSTI	n	121	55	57	31	**264**
	%	3.2	1.4	1.0	0.6	**1.4**
Other: NRTI+PI+INSTI (3ARVs)	n	72	30	19	6	**127**
	%	1.9	0.8	0.3	0.1	**0.7**
Other: NRTI+PI+INSTI (4ARVs)	n	105	33	29	20	**187**
	%	2.8	0.9	0.5	0.4	**1.0**
Other	n	460	151	108	61	**780**
	%	12.2	3.9	1.9	1.2	**4.2**
CD4:CD8 ratio						
No data	n	444	496	706	759	**2,405**
	%	11.8	12.9	12.6	14.3	**13.0**
<0.50	n	661	585	772	1,114	**3,132**
	%	17.5	15.2	13.8	21.0	**16.9**
≥0.50 <1.00	n	1,725	1,911	2,785	2,320	**8,741**
	%	45.7	49.7	49.8	43.7	**47.2**
≥1.00	n	943	851	1,334	1,117	**4,245**
	%	25.0	22.1	23.8	21.0	**22.9**
CD4 count (cells/mm^3)						
No data	n	28	41	85	95	**249**
	%	0.7	1.1	1.5	1.8	**1.3**
<50	n	7	11	12	23	**53**
	%	0.2	0.3	0.2	0.4	**0.3**
50–199	n	76	69	54	174	**373**
	%	2.0	1.8	1.0	3.3	**2.0**
200–349	n	249	237	296	449	**1,231**
	%	6.6	6.2	5.3	8.5	**6.7**
350–499	n	574	665	856	741	**2,836**
	%	15.2	17.0	15.3	14.0	**15.3**
500–749	n	1,272	1,403	2,111	1,683	**6,469**

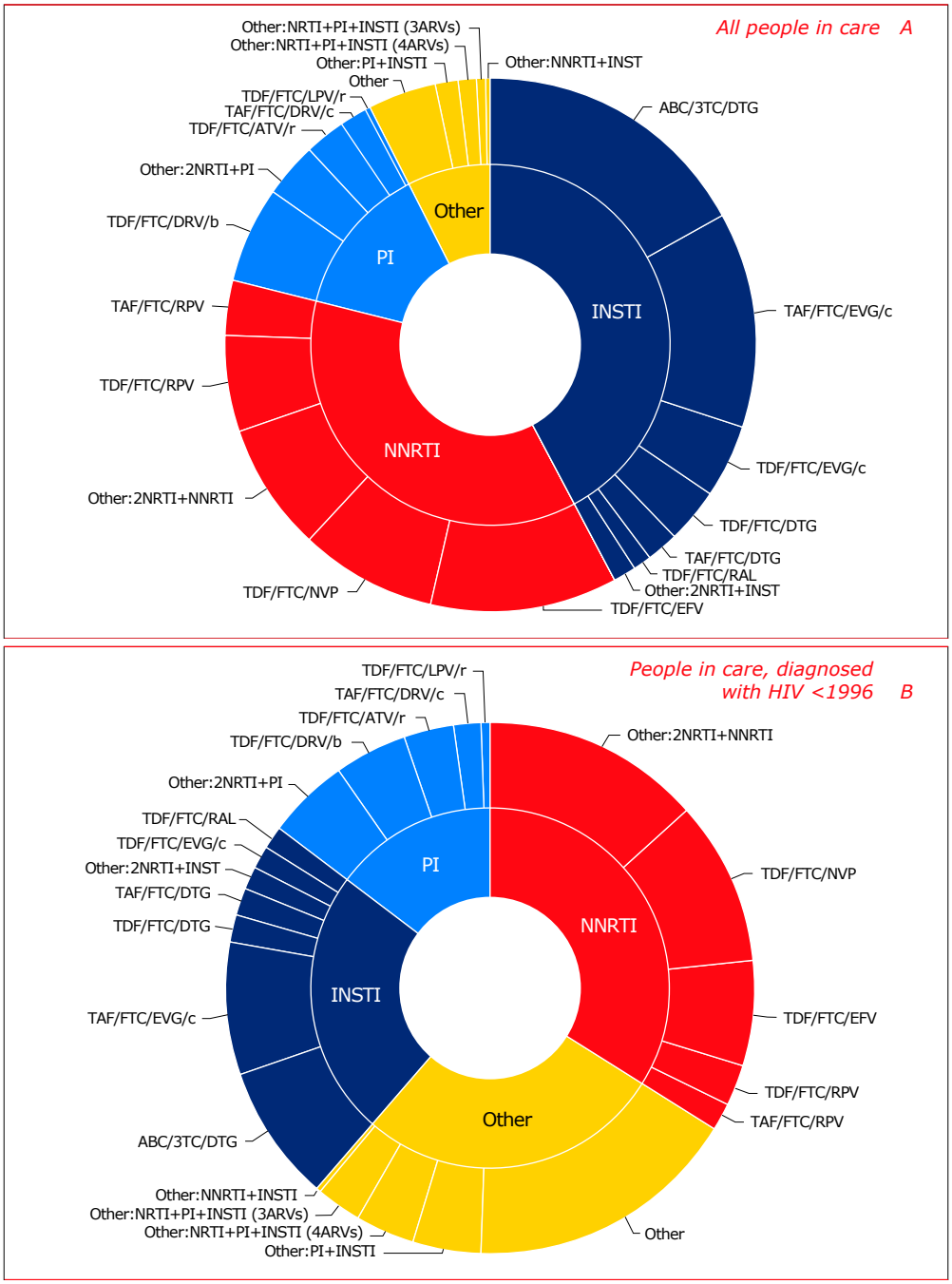
Calendar year of cART initiation		1996–2001	2002–2007	2008–2012	2013–2017	All
	%	33.7	36.5	37.7	31.7	**34.9**
≥750	n	1,567	1,417	2,183	2,145	**7,312**
	%	41.5	36.9	39	40.4	**39.5**
Viral load <50 copies/ml						
No data	n	38	100	161	226	**525**
	%	1.0	2.6	2.9	4.3	**2.8**
<50 copies/ml	n	3,217	3,173	4,721	4,161	**15,272**
	%	85.3	82.6	84.4	78.4	**82.5**
Viral load <200 copies/ml						
No data	n	38	100	161	226	**525**
	%	1.0	2.6	2.9	4.3	**2.8**
<200 copies/ml	n	3,661	3,650	5,344	4,841	**17,496**
	%	97.0	95.0	95.5	91.2	**94.5**

Legend: *3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; ARVs=antiretroviral drugs; 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 18,523 people in HIV care in 2017, the large majority (92.4%) received a regimen based on two nucleoside analogue reverse transcriptase inhibitor (NRTIs), combined with either an integrase inhibitor (INSTI) (42.2%), an NNRTI (36.4%), or a protease inhibitor (PI) (13.8%). The distribution of cART use among the population in care in 2017 is presented in *Figure 2.2A*. The most common regimens were abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (17.0%) and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) combined with efavirenz (EFV) (11.3%) or nevirapine (NVP) (8.3%). Most people who initiated cART in 2017 did so with ABC/3TC/DTG (35.1%) or tenofovir alafenamide (TAF)/FTC/cobicistat-boosted elvitegravir-cobicistat (EVG/c; 31.2%). TDF was used by a large proportion of the population in care (46.4%); however, this proportion has decreased with an increase in the use of TAF (24.4% of the population in care in 2017).

Of those with a plasma HIV RNA measurement in 2015-2017, 82.5% had a viral load <50 copies/ml, and 94.5% had a viral load <200 copies/ml. On the basis of the last available CD4 and CD8 cell count measurements in 2015-2017, 74.4% had a CD4 cell count of 500 cells/mm^3 or higher, and 2.9% had a CD4:CD8 ratio of 1 or higher.

Figure 2.2: Combination antiretroviral therapy (cART) use in 2017: A) all people in care, and B) people in care who were diagnosed with HIV before 1996.



Legend: 3TC=lamivudine; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; cART=combination antiretroviral therapy; ABC=abacavir; ATV=atazanavir; 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 18,580 people in HIV care in the Netherlands in 2017, 3,812 (20.6%) were diagnosed before the year 2000; of those, 3,071 (80.6%) were 50 years of age or older by the end of 2017. Furthermore, 1,966 (10.6%) were diagnosed before 1996, and 1,718 (87.4%) of those were 50 years or older by the end of 2017.

The data presented below focus on the 1,966 people who were diagnosed before 1996 (i.e., before the introduction of cART, and thus considered long-term HIV survivors). Their median age at cART initiation was 31 years (IQR 26-36). The majority were men (82.4%), and the main HIV transmission risk group was MSM (66.4%), followed by heterosexual contact (20.1%), injecting drug use (7.1%), and contaminated blood or blood products (2.3%); the remaining 4.1% acquired HIV through another or an unknown transmission route. Most long-term survivors (65.2%) originated from the Netherlands, followed by western Europe, North America and Australia (13.9%), South America and the Caribbean (10.1%), sub-Saharan Africa (5.5%), and other regions (4.1%). At the start of cART, the median HIV viral load was 4.6 [IQR 3.8-5.1] $\log_{10}$ copies/ml (available for 1,497 people), and the median CD4 cell count was 240 [IQR 120-364] cells/mm^3 (available for 1,743 people). The majority (57.8%) had initiated cART in 1996 or 1997 (36.1% and 21.7%, respectively), and 46.5% had received antiretroviral drugs as monotherapy or dual therapy before initiating cART.

As of 31 December 2017, the median age of the long-term survivors was 57 years (IQR 53-63). The majority (72.3%) received a dual NRTI backbone in combination with an NNRTI (33.9%), integrase inhibitor (23.8%), or protease inhibitor (14.6%). The most common regimens were TDF/FTC/NVP (10.1%), ABC/3TC/DTG (8.3%), TAF/FTC/EVG/c (8.1%), TDF/FTC/EFV (6.5%), and TDF/FTC/DRV/b (boosted darunavir) (4.5%). Importantly, 27.2% 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 2015-2017), 2.2% had a CD4 cell count <200 cells/mm^3, 6.5% between 200 and 349 cells/mm^3, 17.8% between 350 and 499 cells/mm^3, 32.2% between 500 and 749 cells/mm^3,

and 40.4% had 750 cells/mm^3 or higher. Furthermore, 22.9% had a CD4:CD8 ratio of 1 or higher. Of all long-term survivors receiving cART with a viral load measurement in 2017, viral suppression was high and comparable to the overall population in care: 86.1% had a viral load <50 copies/ml, and 96.9% 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 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 these new drugs in HIV treatment.

***Box 2.2:** Approval dates of new antiretroviral drugs for HIV treatment in the Netherlands in 2013–2017.*

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

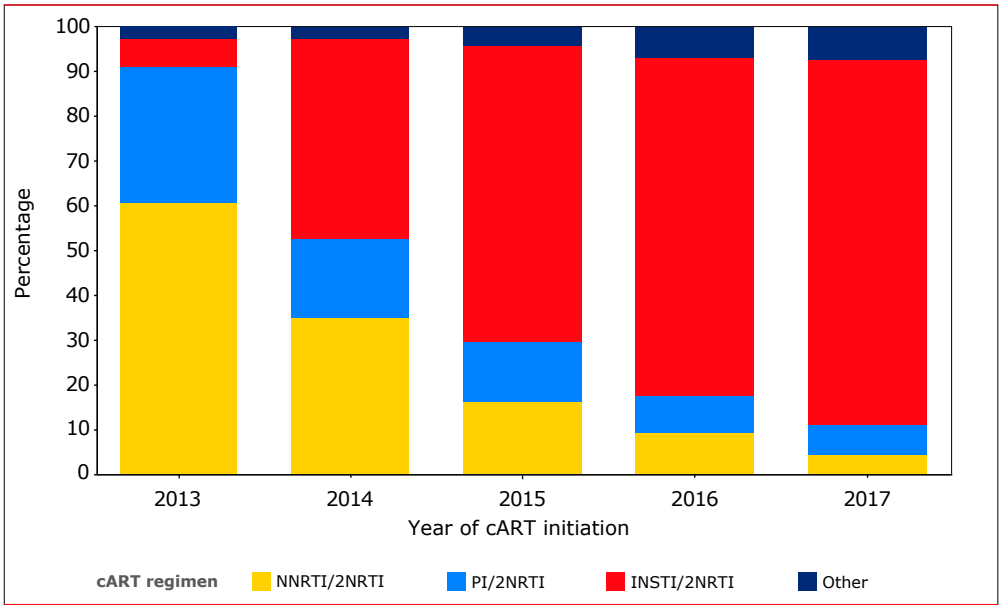
***Source:** Medicines Evaluation Board and European Medicines Agency.*
***Legend:** 3TC=lamivudine; ABC=abacavir; DTG=dolutegravir; DRV=darunavir; EVG=elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.*

Initial cART regimen

Out of 23,578 people who were known to have initiated cART between January 1996 and December 2017, 5,767 (24.5%) started cART between January 2013 and December 2017. *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 has risen sharply from 6.5% in 2013, to 44.4% in 2014, 65.8% in 2015, 75.3% in 2016, and 81.3% in 2017. EVG/c was introduced in the Netherlands at the end

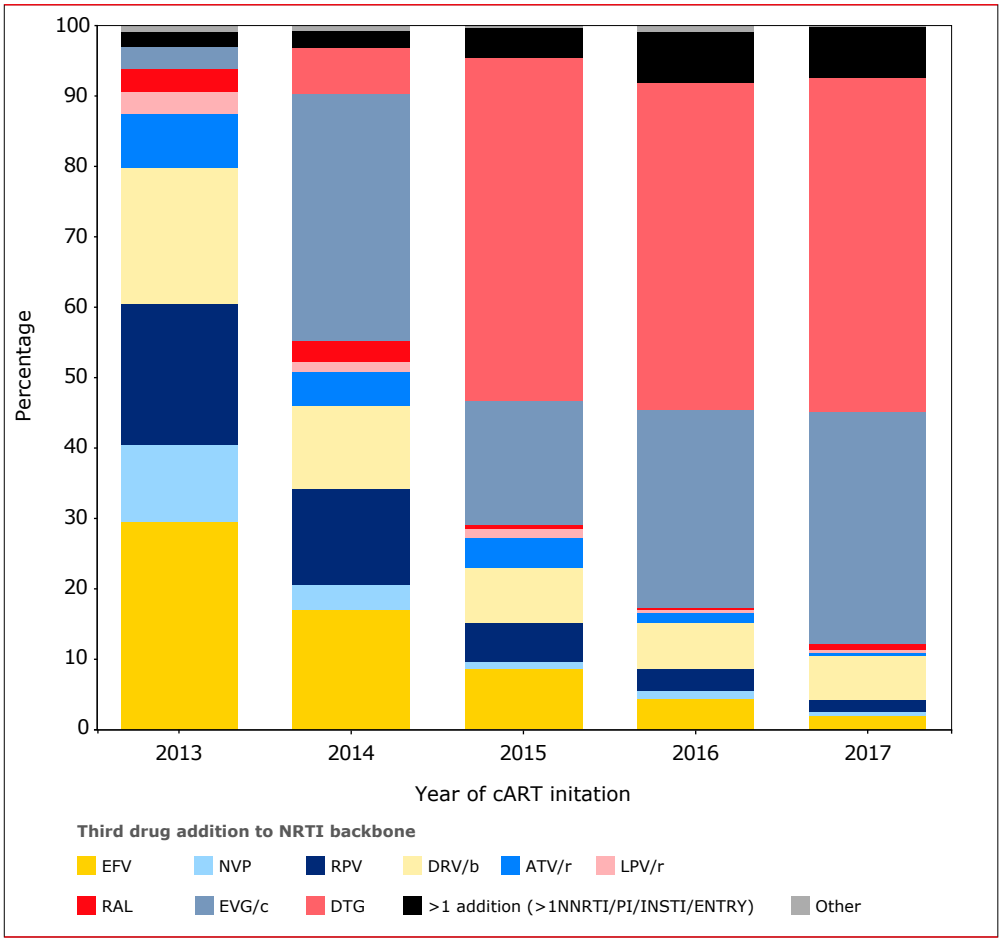
of 2013 and was used in 3.2%, 34.8%, 17.4%, 27.2%, and 33.0% of the initial regimens in 2013, 2014, 2015, 2016, and 2017, respectively. After its introduction in 2014, dolutegravir has become the predominant third-drug addition in the initial cART regimen and was used in up to 47% of initial regimens in 2015-2017. With the introduction of EVG/c and dolutegravir, the use of NNRTIs in the initial regimen decreased from ≥60% in 2013, to 35.0% in 2014, 16.4% in 2015, 9.4% in 2016, and 4.3% in 2017. The use of protease inhibitors in the initial regimen decreased from >30% in 2013 to 6.8% in 2017. In 2013-2017, 4% of people received more than one addition to the NRTI backbone in their initial cART regimen, the majority of whom were people initiating cART during an acute HIV infection.

Figure 2.3: *Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2013-2017.*



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

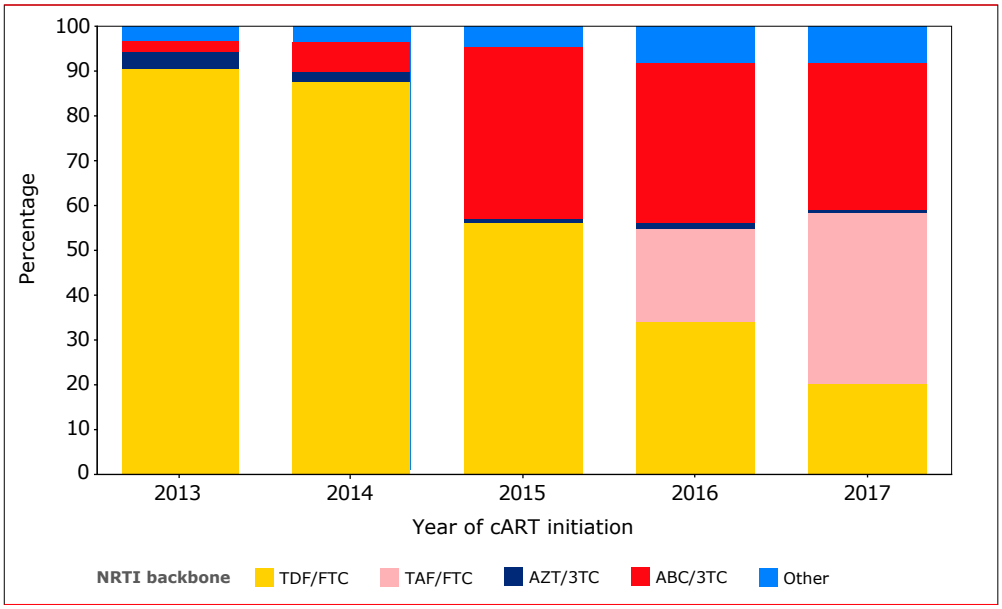
Figure 2.4: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2013-2017.



Legend: *cART=combination antiretroviral therapy; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ATV=atazanavir; 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 initial components of the NRTI backbone used between 2013 and 2017. 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 20.0% and 37.9% of the initial regimens in 2016 and 2017, respectively. At the same time, TDF use decreased from 87-90% in 2013-2014 to 20.3% in 2017. The use of abacavir in combination with lamivudine, which was introduced as a once-daily fixed-dose combination with dolutegravir by the end of 2014, increased from <3% of all initial regimens in 2013, to a third of all initial regimens in 2015-2017. The combination of zidovudine and lamivudine, often received by migrants, further decreased to <1% since 2015.

Figure 2.5: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2013-2017.*



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 full cART regimens initiated between 2013 and 2017 are presented in *Figure 2.6* and *Table 2.3*. In 2017, most people (46.9%) initiating cART received a dolutegravir-based regimen combined with either abacavir and lamivudine as part of the once-daily fixed-dose combination (32.3%), or they were provided with emtricitabine and tenofovir separately (14.7%; TDF 8.3%/TAF 6.4%). Additionally, a third initiated an EVG/c-containing once-daily fixed-dose combination with emtricitabine and tenofovir (TDF 4.9%/TAF 9.0%). Raltegravir use in an initial regimen (not recommended in starting regimens because it needs to be taken twice daily), has decreased further to ~1% since 2015. The combination of ritonavir or cobicistat-boosted darunavir with tenofovir and emtricitabine was used in 6.2% of initial cART regimens in 2017: 3.9% based on TDF and 1.8% in 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*.

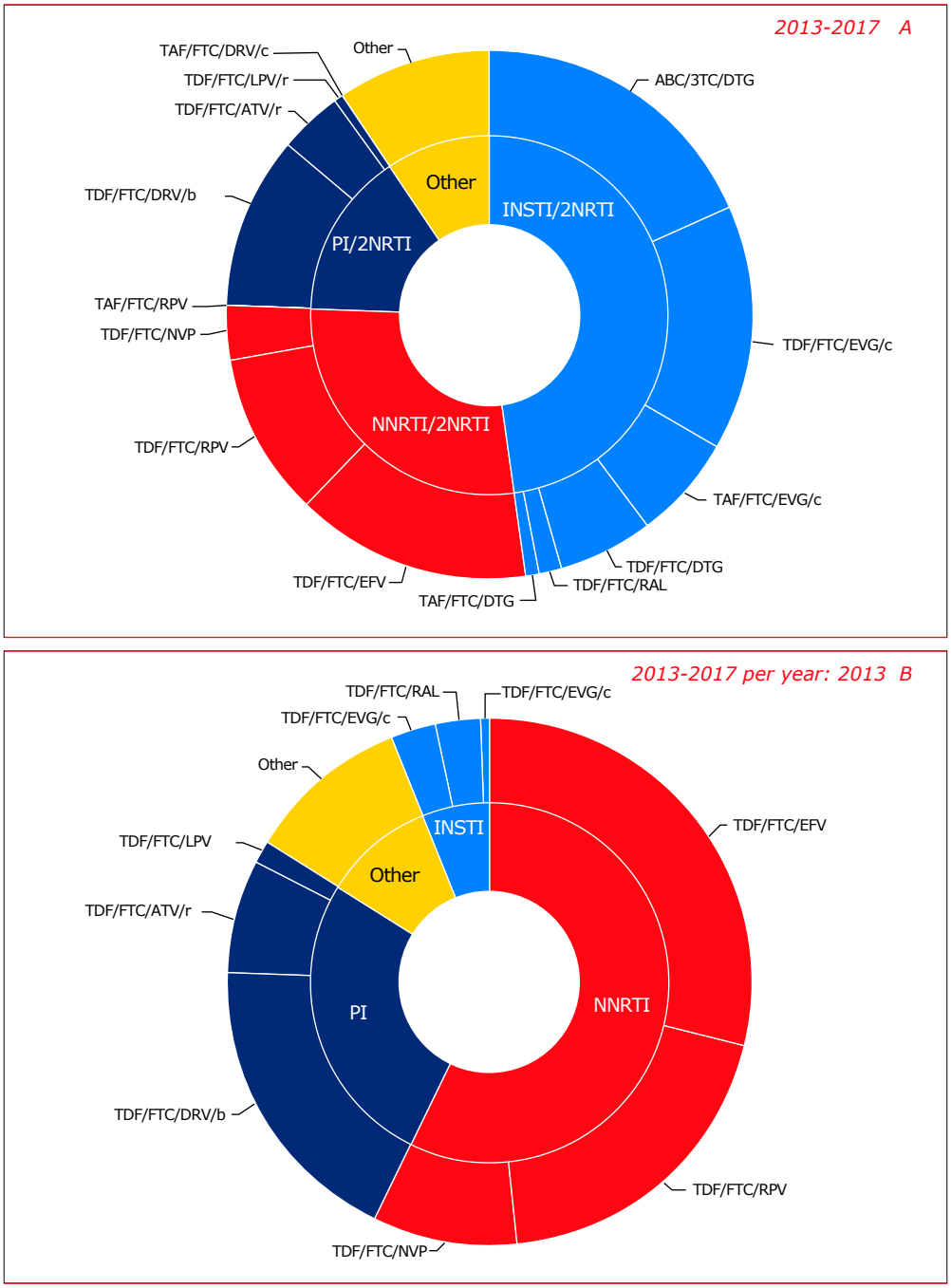
***Table 2.3:** Initial regimen in 2013–2017.*

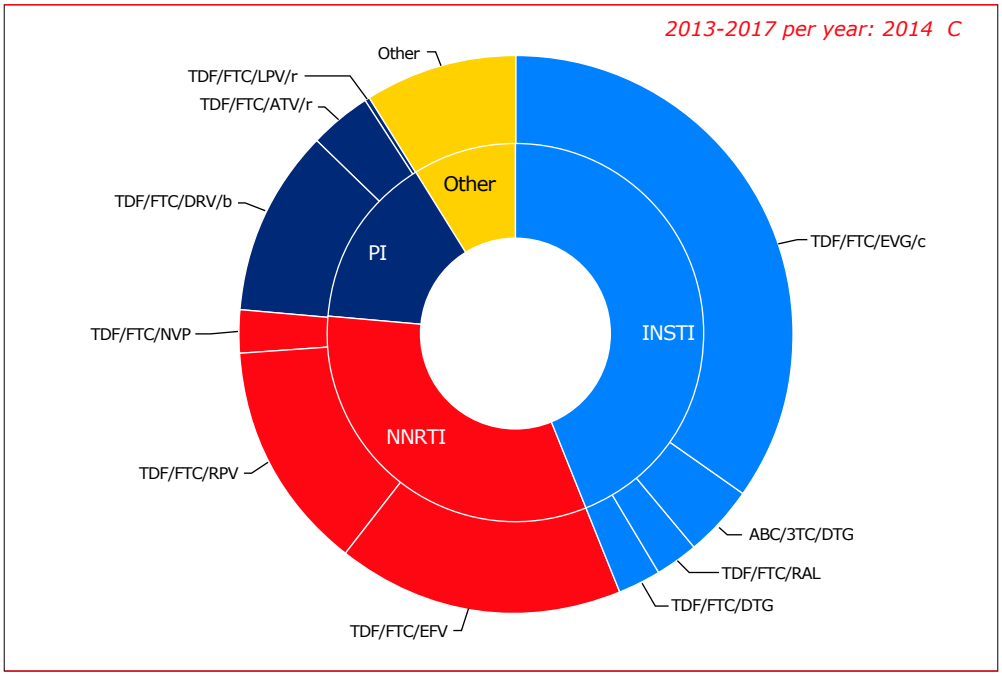
Regimen		2013	2014	2015	2016	2017	2013–2017
TDF/FTC/EFV	n	429	245	93	43	10	**820**
	%	28.9	16.8	7.9	4.5	1.5	**14.2**
TDF/FTC/NVP	n	131	35	7	9	2	**184**
	%	8.8	2.4	0.6	0.9	0.3	**3.2**
TDF/FTC/RPV	n	291	195	73	25	4	**588**
	%	19.6	13.4	6.2	2.6	0.6	**10.2**
TDF/FTC/DRV/b	n	273	157	90	56	26	**602**
	%	18.4	10.8	7.6	5.8	3.9	**10.4**
TDF/FTC/ATV/r	n	105	55	42	14	3	**219**
	%	7.1	3.8	3.6	1.5	0.4	**3.8**
TDF/FTC/LPV	n	18	5	8	1	.	**32**
	%	1.2	0.3	0.7	0.1	.	**0.6**
TDF/FTC/EVG/c	n	41	507	205	80	33	**866**
	%	2.7	34.8	17.4	8.3	4.9	**15.0**
TDF/FTC/DTG	n	.	36	137	96	56	**325**
	%	.	2.5	11.6	9.9	8.3	**5.6**
TDF/FTC/RAL	n	40	37	7	5	3	**92**
	%	2.7	2.5	0.6	0.5	0.4	**1.6**
ABC/3TC/DTG	n	.	61	425	355	218	**1,059**
	%	.	4.2	36.0	36.7	32.3	**18.4**
TAF/FTC/EVG/c	n	6	.	1	183	190	**380**
	%	0.4	.	0.1	18.9	28.2	**6.6**
TAF/FTC/RPV	n	.	.	.	3	7	**10**

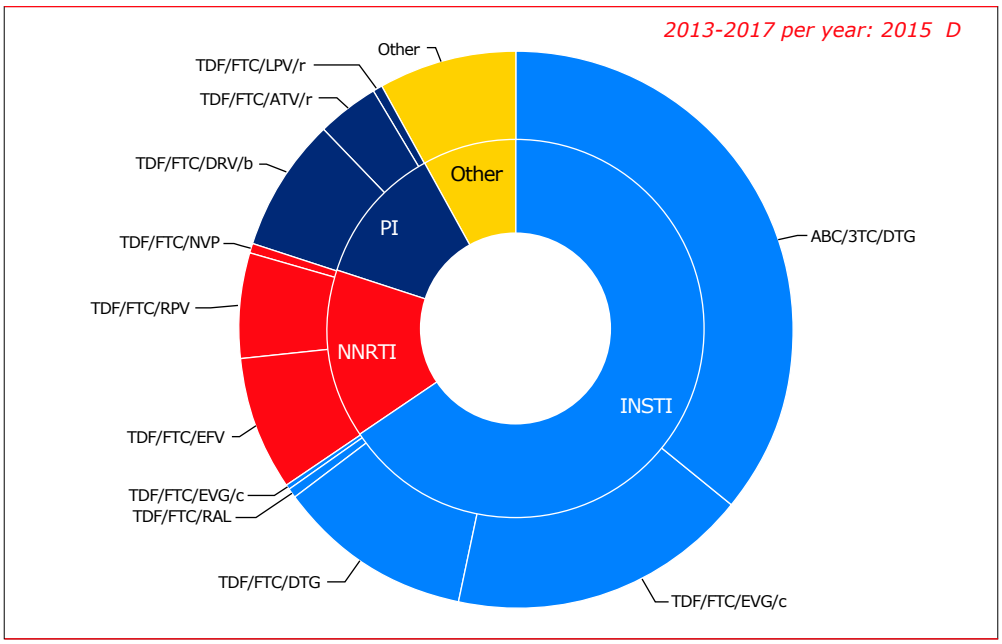
	%	.	.	.	0.3	1.0	**0.2**
TAF/FTC/DTG	n	.	.	.	6	43	**49**
	%	.	.	.	0.6	6.4	**0.9**
TAF/FTC/DRV/c	n	.	.	.	.	12	**12**
	%	.	.	.	.	1.8	**0.2**
Other:2NRTI+NNRTI	n	54	37	21	11	6	**129**
	%	3.6	2.5	1.8	1.1	0.9	**2.2**
Other:2NRTI+PI	n	55	45	19	11	5	**135**
	%	3.7	3.1	1.6	1.1	0.7	**2.3**
Other:2NRTI+INSTI	n	10	7	2	3	6	**28**
	%	0.7	0.5	0.2	0.3	0.9	**0.5**
Other: NRTI+PI+INSTI (3ARVs)	n	1	3	2	.	1	**7**
	%	0.1	0.2	0.2	.	0.2	**0.1**
Other: NRTI+PI+INSTI (4ARVs)	n	10	20	40	59	48	**177**
	%	0.7	1.4	3.4	6.1	7.1	**3.1**
Other	n	21	14	9	7	2	**53**
	%	1.4	1.0	0.78	0.7	0.3	**0.9**
Total	**n**	**1,485**	**1,459**	**1,181**	**967**	**675**	**5,767**
	%	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

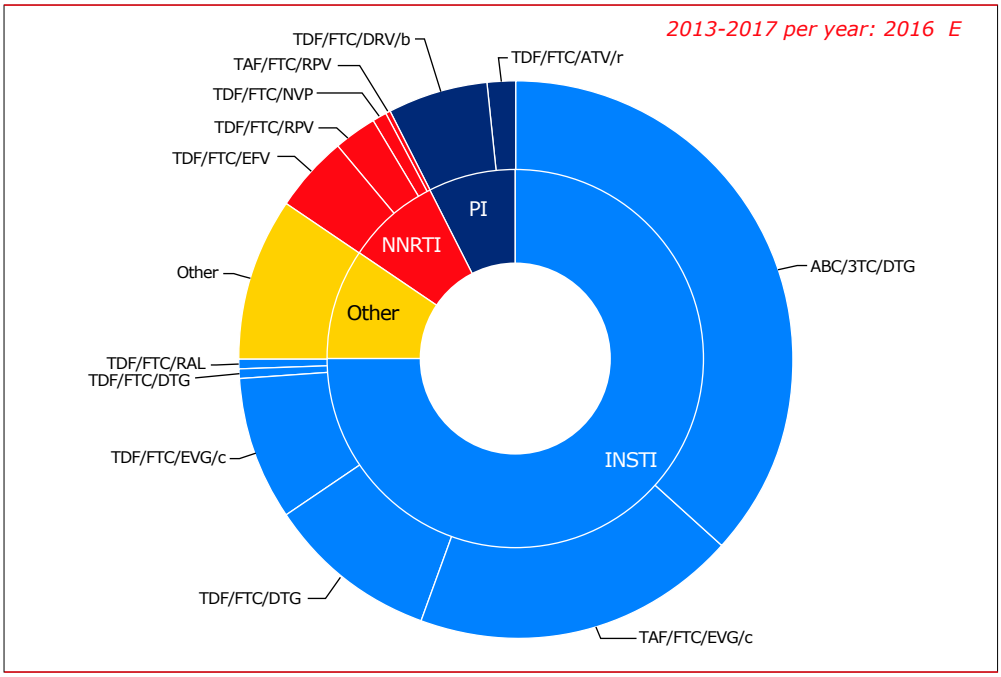
Legend: *ARVs=antiretroviral drugs; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV=lopinavir; INSTI=integrase inhibitor; NRTI=nucleoside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

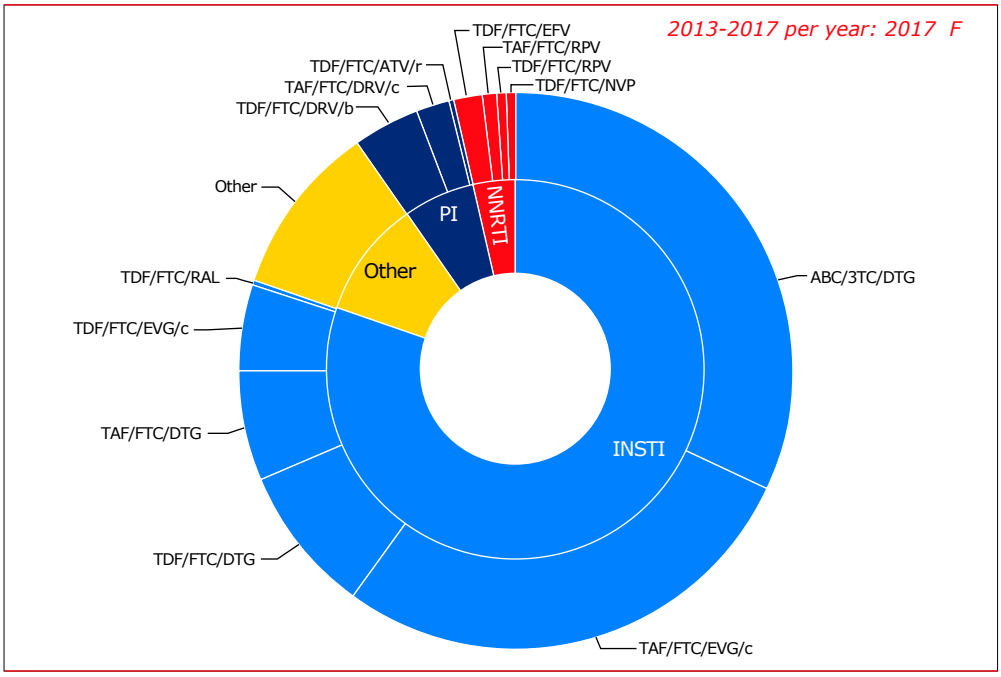
Figure 2.6: Initial combination antiretroviral therapy regimens in A) 2013–107 and B–F) per individual year.




2013-2017 per year: 2014 C
Other
TDF/FTC/LPV/r
TDF/FTC/ATV/r
TDF/FTC/DRV/b
TDF/FTC/NVP
TDF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/EVG/c
ABC/3TC/DTG
TDF/FTC/RAL
TDF/FTC/DTG
Other
PI
NNRTI
INSTI


2013-2017 per year: 2015 D
Other
TDF/FTC/LPV/r
TDF/FTC/ATV/r
TDF/FTC/DRV/b
TDF/FTC/NVP
TDF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/EVG/c
TDF/FTC/RAL
TDF/FTC/DTG
ABC/3TC/DTG
TDF/FTC/EVG/c
Other
PI
NNRTI
INSTI


2013-2017 per year: 2016 E
TDF/FTC/DRV/b
TAF/FTC/RPV
TDF/FTC/NVP
TDF/FTC/RPV
TDF/FTC/EFV
TDF/FTC/ATV/r
PI
NNRTI
Other
Other
ABC/3TC/DTG
TDF/FTC/RAL
TDF/FTC/DTG
TDF/FTC/EVG/c
INSTI
TDF/FTC/DTG
TAF/FTC/EVG/c


2013-2017 per year: 2017 F
TDF/FTC/EFV
TAF/FTC/RPV
TDF/FTC/ATV/r
TDF/FTC/RPV
TAF/FTC/DRV/c
TDF/FTC/NVP
TDF/FTC/DRV/b
Other
PI
NNRTI
Other
TDF/FTC/RAL
ABC/3TC/DTG
TDF/FTC/EVG/c
TAF/FTC/DTG
INSTI
TDF/FTC/DTG
TAF/FTC/EVG/c

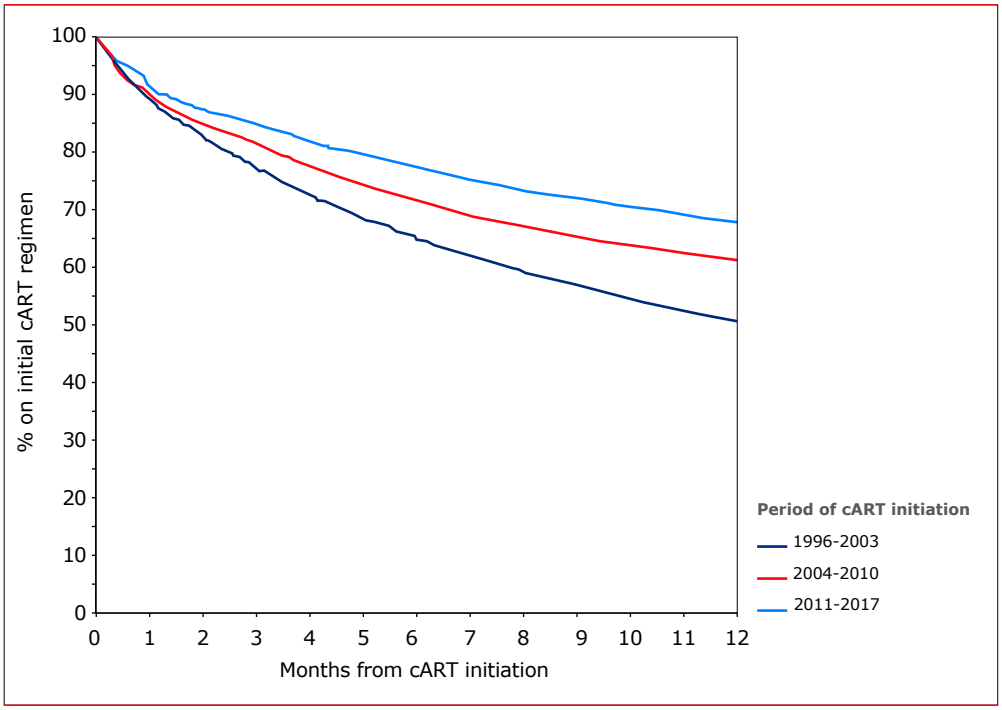
Legend: *3TC=lamivudine; ABC=abacavir; ATV=atazanavir; b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; LPV=lopinavir; NNRTI=non-nucleoside reverse transcriptase 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 23,578 people who ever started cART. 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. 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 1996-2017, 39.6% 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 2006-2017. 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

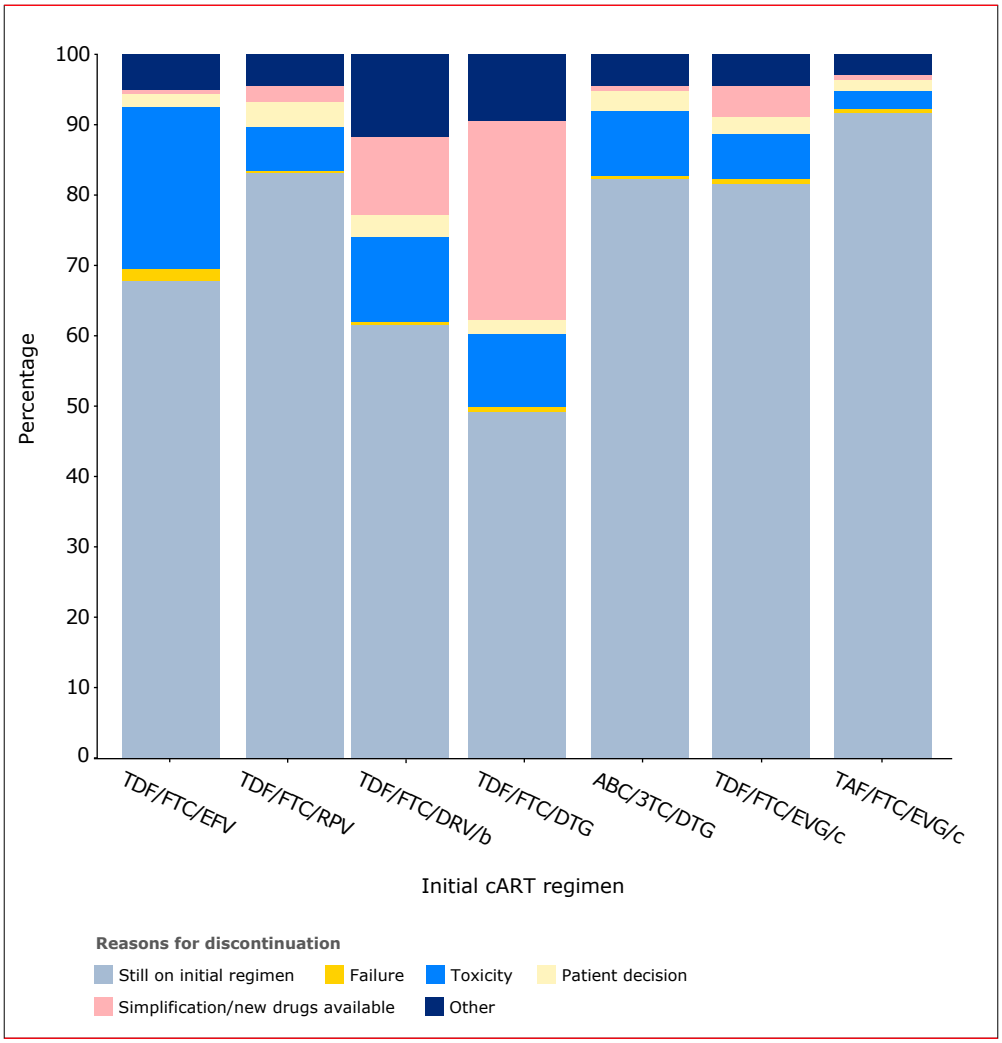
Discontinuation of the initial cART regimen: 2013-2017

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among 4,630 people who started common initial regimens in 2013-2017. Common regimens considered in this analysis were: tenofovir/emtricitabine combined with efavirenz (TDF/FTC/EFV; 17.8%), rilpivirine (TDF/FTC/RPV; 12.7%), ritonavir-boosted or cobicistat-boosted darunavir (TDF/FTC/DRV/b; 13.0%), cobicistat-boosted elvitegravir (TDF/FTC/EVG/c; 18.7% and TAF/FTC/EVG/c; 8.2%), dolutegravir (TDF/FTC/DTG; 7.0%), or abacavir-lamivudine combined with dolutegravir (ABC/3TC/DTG; 22.9%).

One year after cART initiation, 1,129 (24.4%) out of 4,630 who initiated one of these regimens had discontinued their initial regimen. The main reason for regimen discontinuation was toxicity (n=490; 43.4%), followed by simplification and/or availability of new drugs (n=215; 19.0%). The availability of new once-daily fixed-dose combinations contributed to an increase in initial regimen discontinuation due to simplification and/or availability of new drugs, especially for those receiving

TDF/FTC/DTG, and TDF/FTC/DRV/b (*Figure 2.8*). Of all discontinuations, 6.4% discontinued their initial regimen for reasons of simplification and/or availability of new drugs in 2013, 14.3% in 2014, 28.1% in 2015, 24.4% in 2016, and 22.7% in 2017.

Figure 2.8: *Reasons for discontinuation of the initial regimen during the first year of treatment 2013–2017, by regimen.*

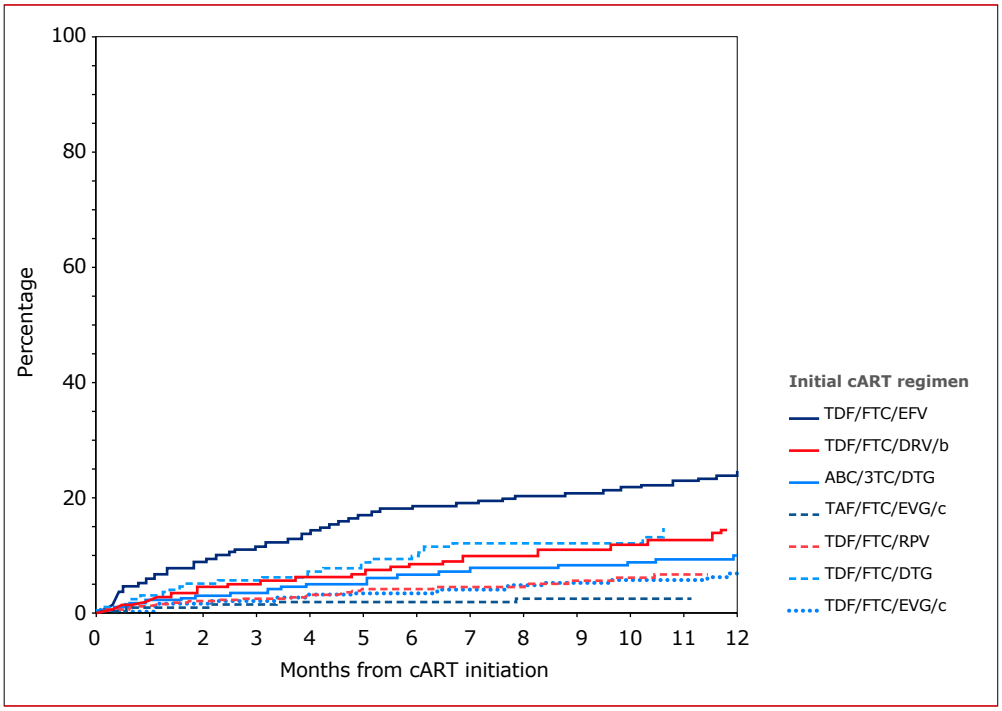


Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

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 2013-2017, by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank p<0.001).*

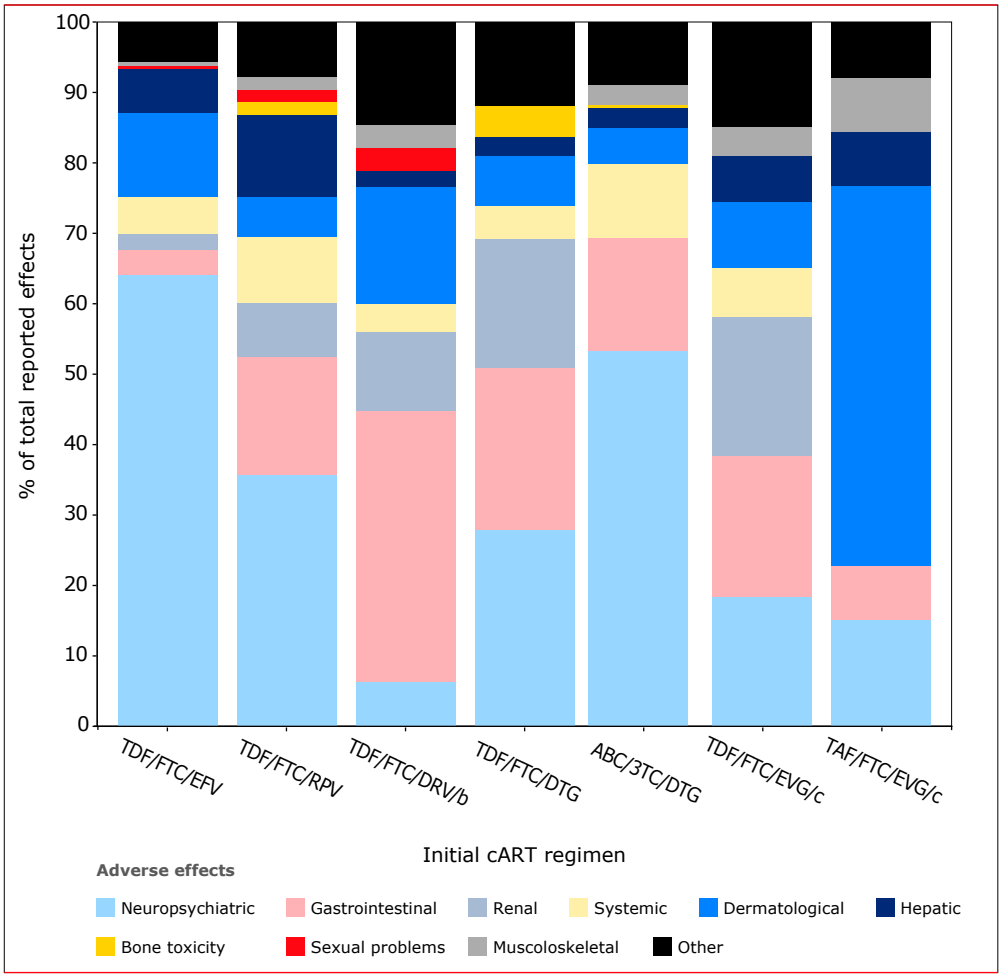


Legend: *cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.*

Adverse effects

Among the 490 who discontinued their initial cART regimen due to toxicity within a year, 709 adverse effects were recorded. The predominant effects were: 43.7% neuropsychiatric (mainly insomnia, mood changes, dizziness and depression), 14.7% gastrointestinal (mainly diarrhoea and nausea), 10.7% dermatological (rash due to medication, itching), 6.8% systemic (tiredness, apathy, loss of appetite), and 6.1% renal (renal insufficiency and increased serum creatinine). These adverse effects are stratified by cART regimen in *Figure 2.10*. Neuropsychiatric effects were associated with TDF/FTC/EFV, ABC/3TC/DTG (but less for TDF/FTC/DTG), and TDF/FTC/RPV. Hepatic effects were mainly reported by people discontinuing TDF/FTC/ATV/r (atazanavir plus ritonavir). Renal effects were only 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 2013–2017. The bars represent the distribution of 709 reported effects among 490 people, by regimen.



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.

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 23,579 adults have started cART since January 1996. For the current analysis of virological outcomes, we will focus on the 20,387 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 19,358 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 of that measurement.

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 2017 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutation[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].

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Initial virological success

Out of 19,358 with a viral load test result after at least 3 months of cART initiation, 15,645 (80.8%) had a viral load measurement 6 months (±3 months) after cART initiation. Of these people, 13,642 (87.2%) 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 73.1% (95% CI 71.4-74.7) in those starting cART between 1996 and 2003, to 88.1% (95% CI 87.3-88.9) in those starting between 2004 and 2010, 91.9% (95% CI 941.2-92.6) in those starting between 2011 and 2016, and 94.3% (95% CI 92.2-96.4) in those starting in 2017.

Initial virological success of common initial cART regimens (2013–2017)

We analysed the initial virological success among the 3,881 adults who started a common cART regimen in 2013-2017 (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 2013-2017'), and had a viral load result after 6 months (±3 months) of cART initiation. In total, 94.0% (95% CI 93.3-94.8) of people achieved initial virological suppression, after a mean of 179 (SD 39) days. Overall, people receiving an integrase-inhibitor based regimen showed significantly higher rates of initial virological success: 95.3% (95% CI 94.4-96.2) of those on an integrase-inhibitor-based regimen had initial virological success, compared to 90.1% (95% CI 87.5-92.6) on a protease-inhibitor-based regimen and 93.4% (95% CI 91.9-94.9) on a 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. Out of 3,881 individuals, viral load data were available for 3,456 at the time of cART initiation. 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	556	16.0	311	14.0	98.1	96.5	99.6	Ref.
TDF/FTC/RPV	358	10.4	358	16.1	95.3	93.0	97.5	0.015
TDF/FTC/DRV/b	497	14.3	211	9.5	95.7	93.0	98.5	0.105
TDF/FTC/EVG/c	696	20.0	484	21.7	97.7	96.4	99.1	0.718
TDF/FTC/DTG	248	7.2	131	5.9	98.5	96.4	99.1	0.409
ABC/3TC/DTG	821	23.8	557	25.0	97.1	95.7	98.5	0.633
TAF/FTC/EVG/c	280	8.0	178	8.0	98.3	96.4	100.0	0.424
cART regimen class								
NNRTI/2NRTI	914	26.5	669	30.0	96.6	95.2	97.9	Ref.
PI/2NRTI	497	14.4	211	9.5	95.7	93.0	98.5	0.259
INSTI/2NRTI	2,045	59.2	1,350	60.5	97.6	96.8	98.4	0.066
All regimens	**3,456**	**100.0**	**2,230**	**64.5**	**97.1**	**96.4**	**97.8**	

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

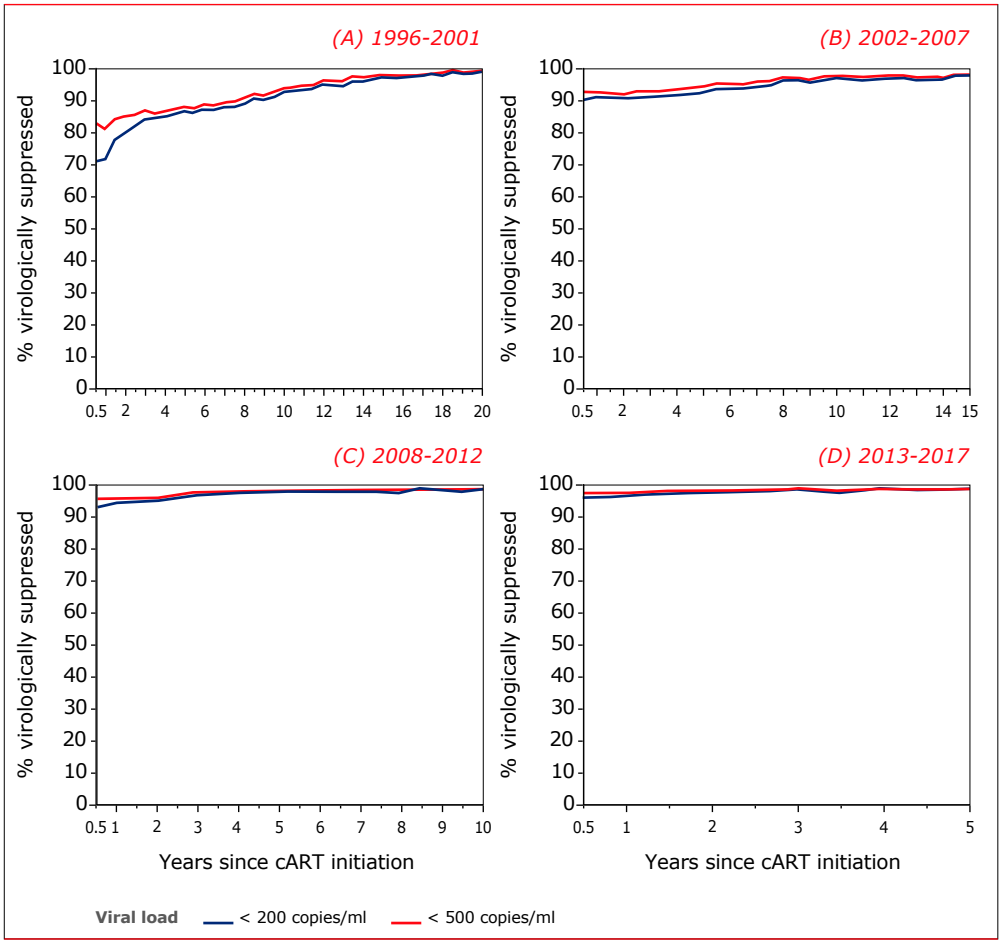
				By initial viral load at cART start			
				≥100,000 copies/ml			
		n	%	Initial viral success	95% CI low	95% CI high	p-value
	cART regimen						
	TDF/FTC/EFV	245	20.0	87.8	83.6	91.9	Ref.
	TDF/FTC/RPV	not recommended					
	TDF/FTC/DRV/b	286	23.3	85.7	81.6	89.7	0.026
	TDF/FTC/EVG/c	212	17.3	90.6	86.6	94.5	0.677
	TDF/FTC/DTG	117	9.5	88.0	82.1	93.9	0.491
	ABC/3TC/DTG	264	21.5	93.6	90.6	96.5	0.028
	TAF/FTC/EVG/c	102	8.3	91.2	85.7	96.7	0.588
	cART regimen class						
	NNRTI/2NRTI	245	20.0	87.8	83.6	91.9	Ref.
	PI/2NRTI	286	23.3	85.7	81.6	89.7	0.068
	INSTI/2NRTI	695	56.7	91.4	89.3	93.5	0.010
	All regimens	**1,226**	**35.5**	**89.3**	**87.6**	**91.0**	

Viral suppression

We assessed longitudinal 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, 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 2013-2017. 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 96.8% (95% CI 96.3-97.4) after 1 year of cART use to 98.9% (95% CI 98.3-99.5) after 4 years. The viral suppression rates over time during the full period (1996-2017) 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 with a viral load >500 copies/ml 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. Of note, 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. The 2017 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[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

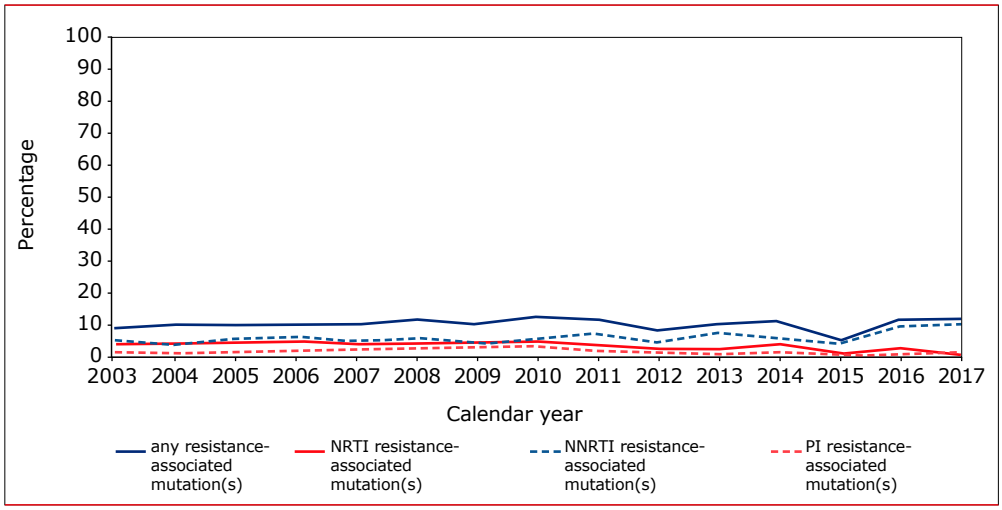
In the Netherlands, screening for HIV drug resistance at the time of entry into care has been incorporated in the treatment guidelines since 2003. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistance mutations. Although a drug-resistant virus strain may revert to a drug-susceptible virus, drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable replication conditions after treatment has started[28,29,30]. 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 2018, 7,315 HIV-1 sequences were obtained between 2003-2017 from 6,981 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 (66.2%) and, less often, women (14.2%). Most people with an available pre-treatment sequence originated from the Netherlands (57.7%) or sub-Saharan Africa (11.5%). The main HIV-1 subtype was B (75.8%), followed by non-B subtypes (24.2%), including recombinant form CRF_02AG (7.1%) and subtype C (5.2%).

Transmitted HIV drug resistance

In total, ≥1 resistance-associated major mutation[24] was found in 723 (10.4%) of the people who were tested for resistance, including 265 (3.8%) with NRTI-associated resistance mutations, 391 (5.6%) with NNRTI-associated resistance mutations, and 127 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2017 (*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 resistance-associated mutation detected before initiation of cART. The 2017 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[24].*

In total, 151 (2.2%) screened for transmitted drug resistance harboured high-level resistance[25,26] to at least one antiretroviral drug; 25 (0.4%) to at least one NRTI, 124 (1.8%) 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; 1.8% (n=127) harboured high-level resistance in one drug class, 0.3% (n=20) in two drug classes, and 0.1% (n=4) 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

Nineteen 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 4 months of cART in 2000-2017. If cART had been interrupted >2 weeks before the test, the sequence was excluded from the analysis. For analyses over time, we reported the results based on the last available sequence in cases where someone had more than one sequence available in any given calendar year.

In total, 4,242 HIV-1 sequences were obtained from 2,540 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 2.9-8.1]. The main HIV-1 subtype was B (70.3%), followed by recombinant form CRF_02AG (8.7%) and subtype C (6.8%).

Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,426 (33.6%) sequences were obtained from 765 (30.1%) pre-treated people, and 2,816 (66.4%) sequences were obtained from 1,775 (69.9%) ARV-naive people. However, over time this difference has become

less distinct. In 2000, 72.0% of sequences were obtained from pre-treated people, compared with 33.7% in 2005 and less than 15% since 2010.

Out of all 4,242 sequences obtained at the time of HIV RNA >500 copies/ml, 2,842 (67.0%) harboured high-level resistance[25,26] to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,421 (57.1%) sequences; of those, 2,065 (85.3% of 2,421) harboured high-level resistance to emtricitabine or lamivudine. In addition, 1,688 (39.8%) harboured high-level resistance to at least one NNRTI, and 1,120 (26.4%) to at least one PI.

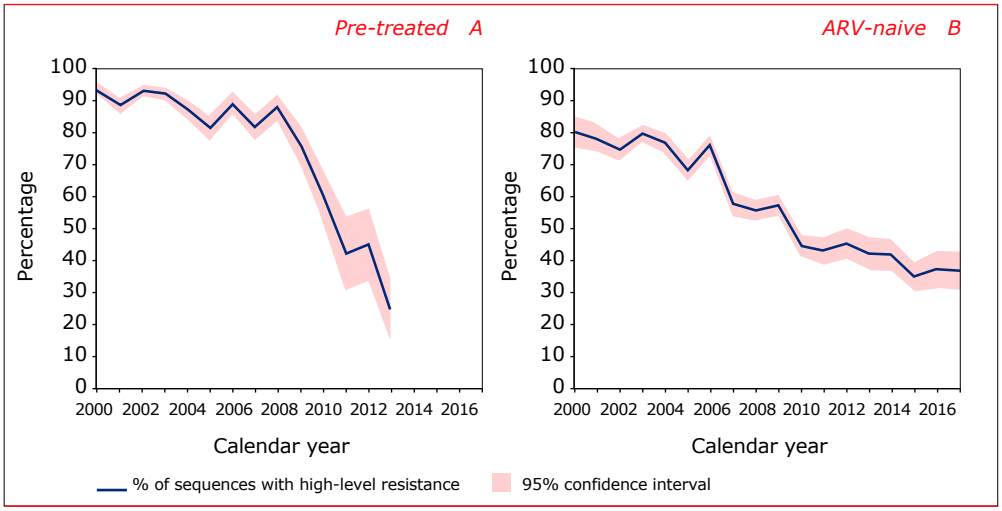
Previous antiretroviral drug exposure

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 93.8% (95% CI 91.9-95.7) in 2000, 87.3% (95% CI (84.2-90.4) in 2004, 60.0% (95% CI 51.6-68.4) in 2010, and 23.9% (95% CI 14.3-33.3) in 2013 (*Figure 2.13A*). The availability of new drugs both in existing and new drug classes largely explains the decline since 2008[31]. In recent years (2014-2017), 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 80.0% (95% CI 75.0-85.0) of sequences in 2000, 75.9% (95% CI 72.6-79.3) in 2006, 45.4% (95% CI 40.6-50.2) in 2012, and 36.6% (95% CI 30.9-42.4) in 2017 (*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 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 (2014-2017) was too low to give meaningful proportions.

Legend: ARV=antiretroviral therapy (antiretroviral drug use that may prevent HIV from damaging the immune system by blocking the reproduction of HIV virus).

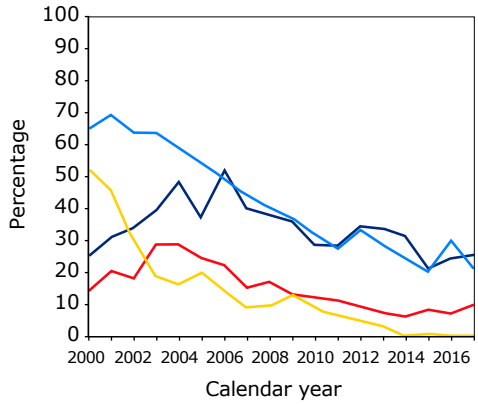
Acquired HIV drug resistance among previously ARV-naive people

In the remainder of our analysis, we will focus solely on the 1,775 people who were ARV-naive before cART initiation. Overall, 1,773 (63.0%) out of all 2,816 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation, associated with resistance to NRTI (n=1,427; 50.7%), NNRTI (n=1,106; 39.3%) or PI (n=428; 15.2%).

In *Figure 2.14A* and *Table 2.5*, the annual proportion of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000, 64.6% (95% CI 58.6-70.6), 24.6% (95% CI 19.2-30.0), and 52.3% (95% CI 46.1-58.6) 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, 36.4% (95% CI 33.1-39.6), 35.9% (95% CI 32.7-39.2), and 12.7% (95% CI 10.5-15.0) of sequences harboured high-level resistance to at least one NRTI, NNRTI, or PI, respectively. In 2017, 21.1% (95% CI 16.2-26.0), 25.4% (95% CI 20.2-30.6),

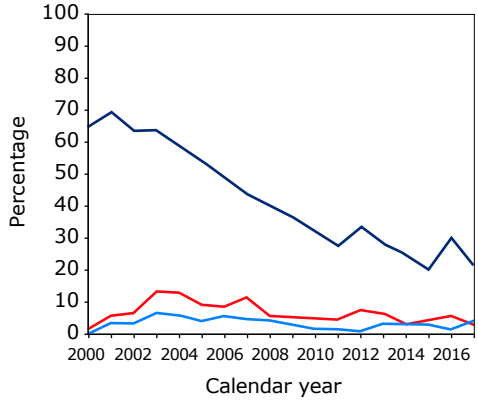
and 0.0% (95% CI 0.0-0.0) of sequences harboured high-level resistance to at least one NRTI, NNRTI or PI, respectively. The annual proportions of sequences harbouring high-level resistance for each antiretroviral drug are presented in *Figure 2.14B-D* and *Appendix Table 2.3*. Of note, drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed.

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



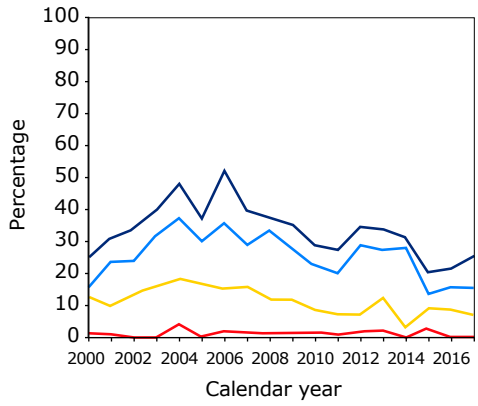
A
By antiretroviral drug class: high-level resistance to at least one drug per class

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

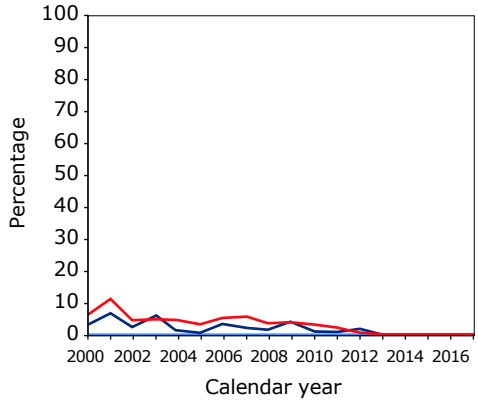


B
By antiretroviral drug: high-level resistance to at least one nucleoside reverse transcriptase inhibitor

- Lamivudine/emtricitabine resistance
- Abacavir resistance
- Tenofovir resistance



C
By antiretroviral drug: high-level resistance to at least one non-nucleoside reverse transcriptase inhibitor



D
By antiretroviral drug: high-level resistance to at least one protease inhibitor

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* [25,26].

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	NNRTI			NRTI			PI		
		95% CI			95% CI			95% CI	
Calendar year	%	low	high	%	low	high	%	low	high
2000	24.6	19.2	30.0	64.6	58.6	70.6	52.3	46.1	58.6
2001	30.7	25.7	35.6	69.3	64.4	74.3	45.5	40.1	50.8
2002	33.8	29.9	37.6	63.6	59.7	67.5	29.9	26.2	33.6
2003	39.3	36.0	42.7	63.5	60.2	66.8	18.5	15.8	21.2
2004	48.2	44.6	51.8	58.5	55.0	62.1	16.1	13.4	18.7
2005	36.9	33.3	40.6	54.0	50.2	57.7	19.9	16.9	22.9
2006	51.9	47.9	55.8	49.4	45.4	53.3	14.2	11.4	16.9
2007	39.8	36.2	43.3	44.0	40.4	47.6	8.9	6.8	11.0
2008	37.7	34.4	41.1	40.1	36.7	43.5	9.4	7.4	11.4
2009	35.9	32.7	39.2	36.4	33.1	39.6	12.7	10.5	15.0
2010	28.5	25.4	31.6	31.8	28.6	35.0	8.9	6.9	10.8
2011	28.1	24.3	32.0	27.4	23.6	31.3	6.7	4.5	8.8
2012	34.3	29.7	38.8	33.3	28.8	37.9	4.6	2.6	6.7
2013	33.7	28.8	38.6	28.4	23.8	33.1	3.2	1.4	5.0
2014	31.3	26.5	36.0	25.0	20.6	29.4	0.0	0.0	0.0
2015	21.1	17.2	25.0	20.2	16.3	24.0	0.9	0.0	1.8
2016	24.3	19.1	29.4	30.0	24.5	35.5	0.0	0.0	0.0
2017	25.4	20.2	30.6	21.1	16.2	26.0	0.0	0.0	0.0

See Appendix Table 2.3 for antiretroviral drug-specific results.

***Legend:** CI=confidence interval; NRTI=nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.*

Acquired integrase-inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was relatively rare. The 107 integrase sequences that were available originated from 89 people who received cART for at least 4 months; 14 were pre-treated with monotherapy or dual therapy before initiating cART, and 75 were ARV-naive before initiating cART. Most people had initiated cART years before; the median time between initial cART initiation and testing for integrase inhibitor resistance was 10.1 years [IQR 3.0-14.4]. 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 15 out of 89 people, which resulted in high-level resistance to at least one integrase inhibitor[24,25]. Among the 15, the following mutations were detected: N155H (n=6) and N155HN (n=1), associated with resistance to elvitegravir and raltegravir; Y143R (n=3) and Y143YC (n=1), associated with resistance to raltegravir; and T66TA (n=2) and T66TK (n=1), associated with resistance to elvitegravir. The remaining sequence harboured the Q148H mutation in combination with the G140S minor mutation, which is associated with resistance to all three currently available integrase inhibitors: dolutegravir (intermediate resistance), elvitegravir (high-level resistance) and raltegravir (high-level resistance). Minor mutations detected were at position L74 (any mutation, n=10; L74I, n=7; L74M, n=2; L74ILM, n=1), T97 (any, n=6; T97A, n=5; T97TA=1), G140S (n=1), and R263K (n=1).

Immunological response

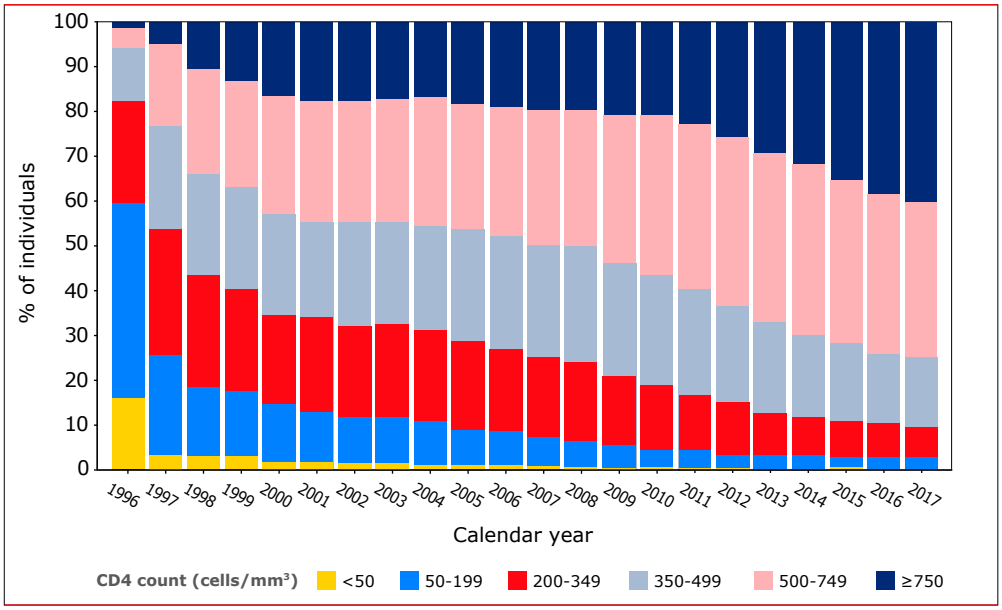
After initiation of cART, most people suppress HIV RNA to levels below the limit of detection, and this is accompanied by an increase in CD4 cell count. Failure to suppress viraemia is associated with poorer recovery of CD4 cell count[19,32]. However, incomplete recovery of CD4 cell count may also occur 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[33]. 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 23,579 people who were known to have initiated cART between January 1996 and December 2017, CD4 cell count data were available after cART initiation for 23,073. *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 33.11% in 2002, 14.6% in 2012 and 9.7% in 2017 (*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 2,112 in 2009, to 1,737 in 2013, and 1,296 in 2017; see *Appendix Figure 2.3*. The drop in absolute number of people with low CD4 cell

counts at the end of each calendar year may partly reflect the trend of starting cART at higher CD4 cell counts and longer cART use, which has been observed since 2007.

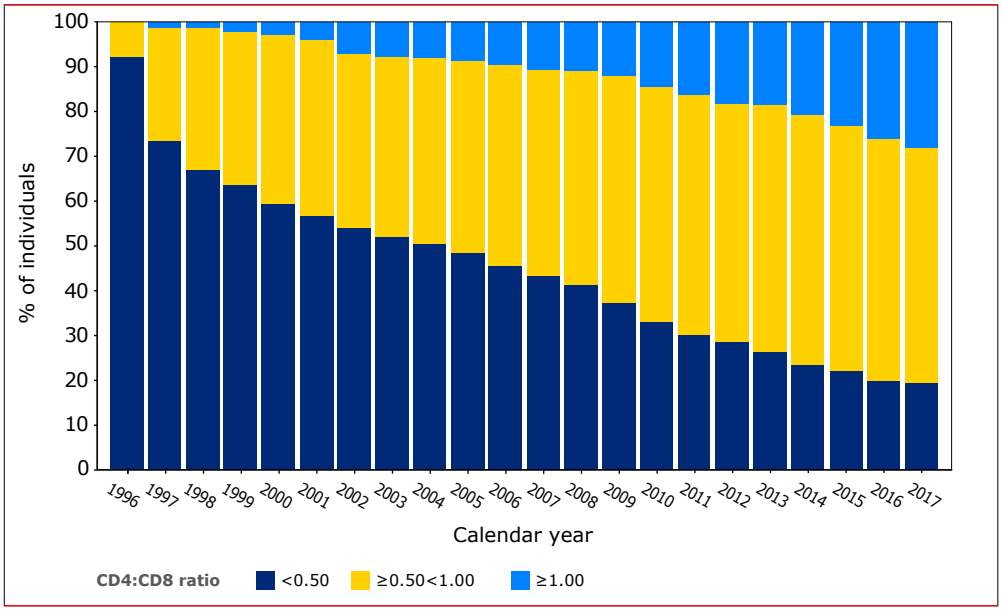
Figure 2.15: Last available CD4 cell count of the treated population by calendar year.



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 2017 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 2.5% in 1996-2001, to 9.0% in 2002-2007, to 14.9% in 2008-2012 and 23.5% in 2013-2017 (*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, 12.1% had a CD4 count of less than 500 cells/mm³, 33.6% had a CD4 count between 500-749 cells/mm³ and 54.3% had a CD4 count of ≥750 cells/mm³. When the CD4:CD8 ratio was ≥1, the median CD4 count was 778 cells/mm³ [IQR 600-980], and remained fairly stable over time, with a median of 771 cells/mm³ [IQR 596-1,010] in 1996-2001, 450 cells/mm³ [IQR 570-970] in 2002-2007, median 730 cells/mm³ [IQR 570-940] in 2008-2012 and median 800 cells/mm³ [IQR 630-1,000] in 2013-2017.

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

The immunological response to cART for both HIV-1 and HIV-2 infection has recently been well-studied in two international cohort collaboration studies, which include Dutch data from the ATHENA cohort. In the first study, the COHERE in EuroCoord collaboration evaluated the CD4 cell response to cART for HIV-1 infection and proposed reference curves that may be used as an additional tool for clinicians when evaluating responses to cART[46]. In the second study, the COHERE in EuroCoord and the ACHIeV2e Study Group aimed to assess CD4 cell recovery following first-line cART in people with HIV-2 compared to people with HIV-1[47]. A summary of both studies and the link to the web tool for the CD4 cell count reference curve can be found in *Box 2.4*.

Box 2.4: International collaborations.

Global trends in CD4 cell count at the start of cART[48]

In a large global cohort collaboration by International Epidemiology Databases to Evaluate AIDS (IeDEA) and COHERE, based on 951,855 people with HIV aged ≥16 years, the global trends in CD4 cell counts at cART initiation among adults from low-income, lower-middle-income, upper-middle-income, and high-income countries were investigated.

Overall, the modelled median CD4 cell count at the start of cART increased from 2002 to 2015 from 78 to 287 cells/mm^3 in low-income countries, from 99 to 234 cells/mm^3 in lower-middle-income countries, from 71 to 311 cells/mm^3 in upper-middle-income countries, and from 161 to 327 cells/mm^3 in high-income countries.

The study results show that median CD4 cell counts at the start of cART have increased in all country income groups over the last few years, and the proportion of people starting cART with severe immunodeficiency has decreased. However, the median CD4 cell count at cART start generally remained below 350 cells/mm^3 in 2015 and the decline in severe immunodeficiency appears to have plateaued in some countries. Substantial additional efforts and resources will be needed to achieve early diagnosis, rapid linkage to care, and prompt initiation of cART globally.

Box 2.4: International collaborations (continued).

Reference curves for CD4 T-cell count response to cART[46]

On behalf of COHERE in EuroCoord, Bouteloup *et al.* aimed to provide 'reference curves' for CD4 T-cell responses during the first 12 months of cART for people with virological suppression, according to their characteristics at cART initiation. Data from 27 cohorts across 35 European countries, including the ATHENA cohort in the Netherlands, were included in the analysis. A total of 28,992 people aged ≥18 years who initiated cART for the first time between 1 January 2005 and 1 January 2010 and who had at least one available measurement of CD4 count and a viral load ≤50 HIV-1 RNA copies/ml 6 months after cART initiation were included in the study.

The median CD4 T-cell count at treatment initiation was 249. The median observed CD4 counts at 6, 9 and 12 months were 382, 402 and 420 cells/mm^3, respectively. The two main factors explaining the variation of CD4 count after 6 months were AIDS stage and CD4 count at cART initiation. A CD4 count increase of ≥100 cells/ml was generally required for people to maintain a CD4 count at the same percentile as when they started, with slightly higher gains required for those who started with CD4 counts in the higher percentiles.

In conclusion, the study proposes reference curves for the CD4 count that may be used as an additional tool by the clinician when evaluating responses to cART.

A web tool is available at http://shiny.isped.u-bordeaux.fr/CD4refcurves

Box 2.4: International collaborations (continued).

CD4 cell count response to first-line cART: HIV-2 compared to HIV-1[47]

The COHERE collaboration in EuroCoord and the ACHIeV2e Study Group aimed to assess CD4 cell recovery following first-line cART in people with HIV-2 compared to HIV-1. ART-naive adults with HIV were included, if they started first-line cART (without NNRTIs or fusion inhibitors) between 1997 and 2011.

Overall, the study included 185 people with HIV-2 and 3,0321 people with HIV-1 with a median age of 46 years and 37 years, respectively. Median observed pretreatment CD4 cell counts/mm^3 were 203 (95% CI 100-290) in people with HIV-2 and 223 (100-353) in people with HIV-1. Mean observed CD4 cell count changes from start of cART to 12 months were +105 (95% CI 77-134) in people with HIV-2 and 202 (199-205) in people with HIV-1; an observed difference of 97 cells/mm^3 in one year. Overall, in adjusted analysis, the mean CD4 cell increase was 25 CD4 cells/mm^3/year lower in people with HIV-2 than into people with HIV-1.

In conclusion, a poorer CD4 cell increase during first-line cART was observed in people with HIV-2 infection than with HIV-1, even after adjustment for pretreatment viral load and other potential confounders. These results underscore the need to identify more potent therapeutic regimens or strategies against HIV-2.

Box 2.4: International collaborations (continued).

Effect of immediate initiation of cART in people with HIV aged ≥50 years[49]

Clinical guidelines recommend immediate initiation of cART for all people with HIV. However, those guidelines are based on trials of relatively young participants. On behalf of the HIV-CAUSAL Collaboration of HIV cohorts from Europe and the Americas, including the ATHENA cohort, Lodi *et al.* aimed to estimate the 5-year risk of all-cause mortality and non-AIDS mortality among ART-naive, AIDS-free people aged between 50 and 70 years.

The study included 9,596 people, with median age of 55 (IQR 52–60) years and CD4 count of 336 (182–513) cells/mm^3 at baseline. The 5-year risk of all-cause mortality was 0.40% (95% CI 0.10-0.71) lower for the general population with HIV, and 1.61% (0.79-2.67) lower for US veterans when comparing immediate initiation vs initiation at CD4 <350 cells/mm^3. The 5-year risk of non-AIDS mortality was 0.17% (95% CI 0.07-0.43) lower for the general population with HIV, and 1% (0.31-2.00) lower for US veterans when comparing immediate initiation vs initiation at CD4 <350 cells/mm^3.

In conclusion, immediate initiation of cART seems to be beneficial in reducing all-cause mortality in people who are AIDS-free and aged 50 years or older, despite their low baseline CD4 count. More effort should be made to diagnose HIV earlier, particularly in older people to ensure timely initiation of treatment and follow up for concomitant comorbidities, thereby maximising the benefit of early treatment for HIV.

2013–2017

We further assessed the immunological response in people who started cART in more recent years: 5,266 people started cART in 2013-2017, 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 5,266 people who started cART in 2013-2017, 7.4% had CD4 counts <50 cells/mm^3, 13.3% had between 50 and 199 cells/mm^3, 20.6% had between 200 and 349 cells/mm^3, 26.3% had between 350 and 499 cells/mm^3, and 32.4% 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 normalization of the CD4:CD8 ratio is strongly related to baseline CD4 cell count[50].

Figure 2.17: CD4 cell count over time after the start of combination antiretroviral therapy (cART) in 2013–2017.

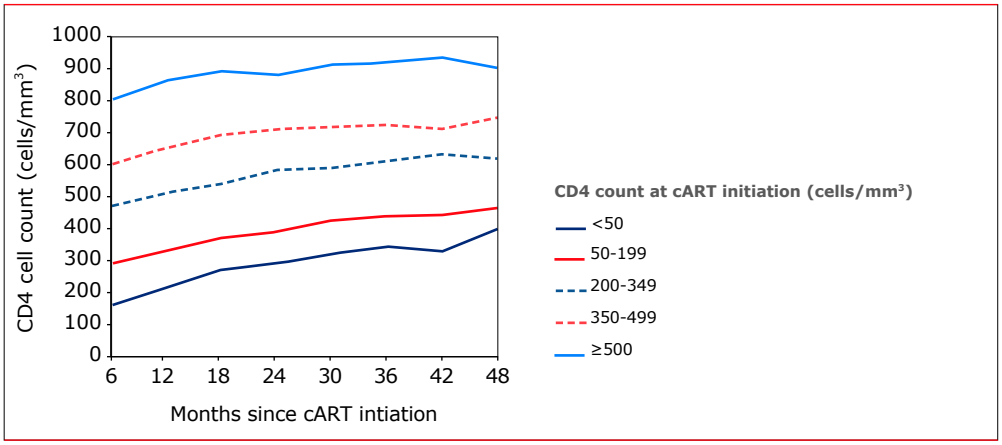
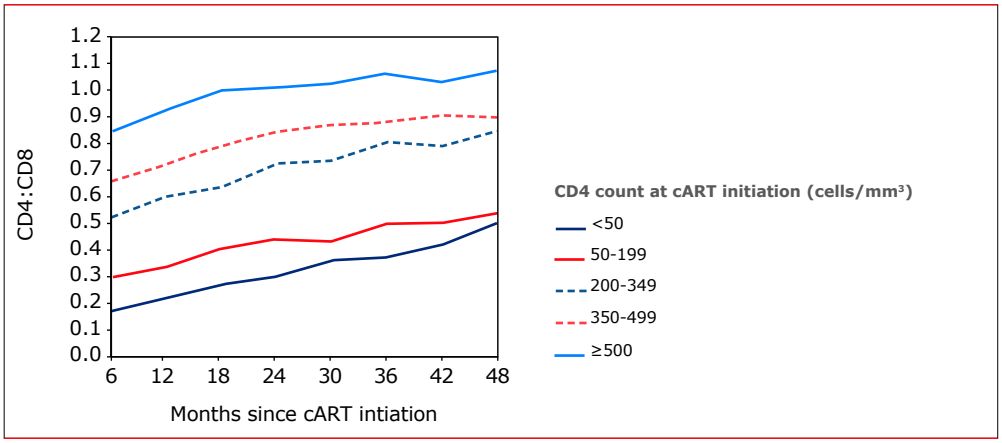


Figure 2.18: CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART) in 2013–2017.



Note: The presented immunological outcomes are based on available test results. For people with a low to moderate CD4 cell count (<350 cells/mm^3), CD4 cell count testing is recommended at least twice a year[51]. When a person has a CD4 cell count >350 cells/mm^3, 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. Among HIV-positive individuals starting cART in 2017, the median CD4 cell count was 380 cells/mm^3 [IQR 202-554]. Immunological recovery was strongly related to the CD4 cell count at the start of cART.
- In 2017, the majority of individuals initiating cART did so within a month after diagnosis. Most persons who initiated cART in 2017 received ABC/3TC/DTG or TAF/FTC/EVG/c.
- 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 2017

- Integrase inhibitor-based cART has been further implemented on a large scale in the Netherlands. Integrase inhibitor-based cART was prescribed to 45% of those in care in 2017, compared with 39% in 2016[52].
- While 43% of the population on cART received TDF, newly-available fixed-dose combinations led to an increase in the prescription of ABC/3TC and TAF/FTC as the backbone.
- Of those receiving cART for at least 12 months and who had a plasma HIV RNA measurement in 2017, 98% had a viral load less than 200 copies/ml. Long-term survivors (i.e., individuals in care in 2017 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[53,54].
- Transmitted drug resistance is rare, and the overall prevalence is low and stable over time, in line with reported rates from other European countries[55].
- Integrase inhibitor resistance data are limited. No transmitted integrase inhibitor resistance was detected amongst 19 people tested in 2017. Detected rates of acquired integrase inhibitor resistance among available sequences were very low, with virtually no resistance to dolutegravir.

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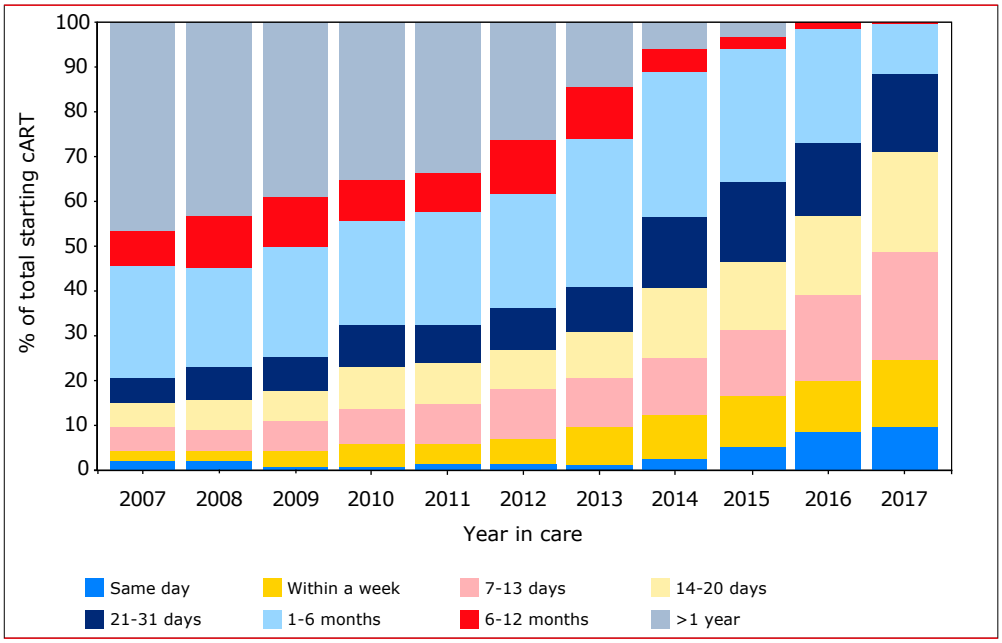
Appendix: supplementary figures and tables

Appendix Figure 2.1: *Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) of people starting cART in 2007–2017*.*



Legend: *cART=combination antiretroviral therapy.*

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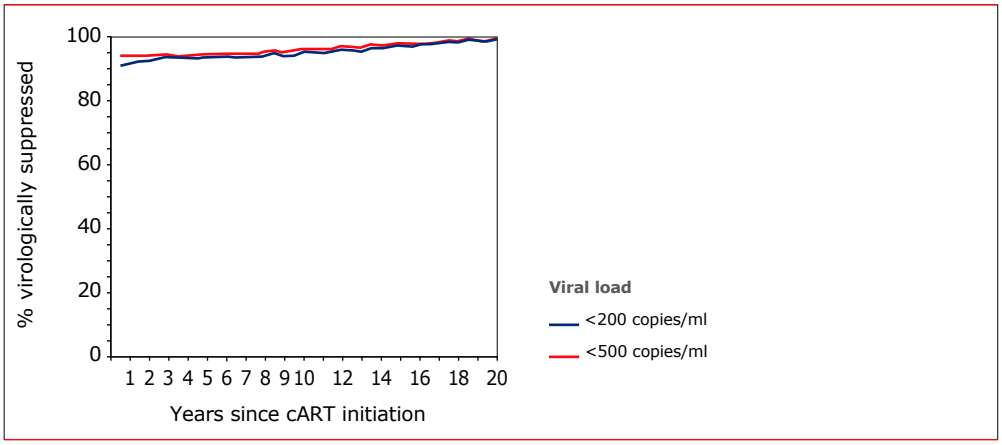
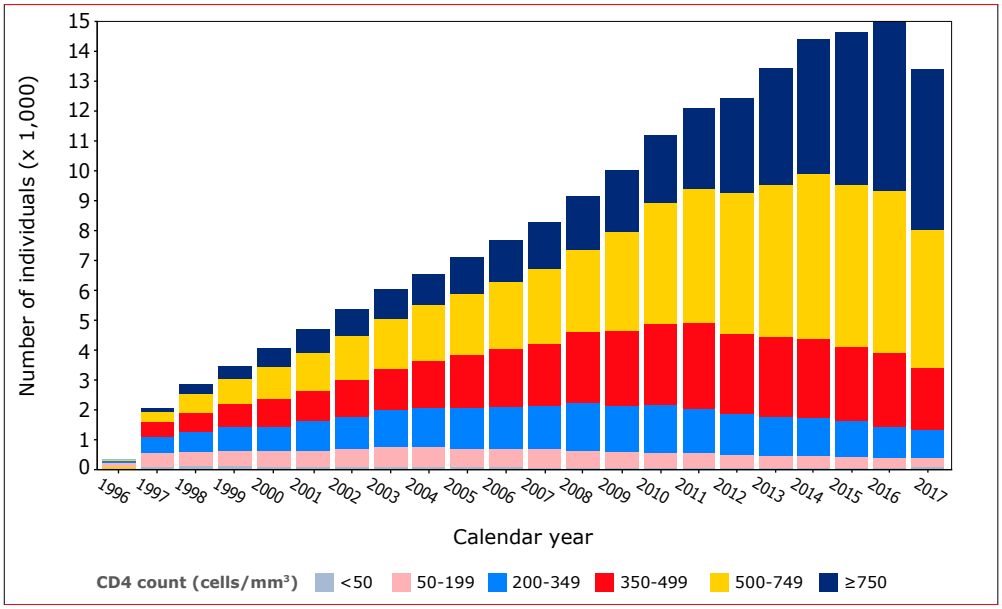
Appendix Figure 2.2: Viral suppression since initiation of combination antiretroviral therapy.



Legend: cART=combination antiretroviral therapy.

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 2017 may increase slightly because data collection is not yet complete.

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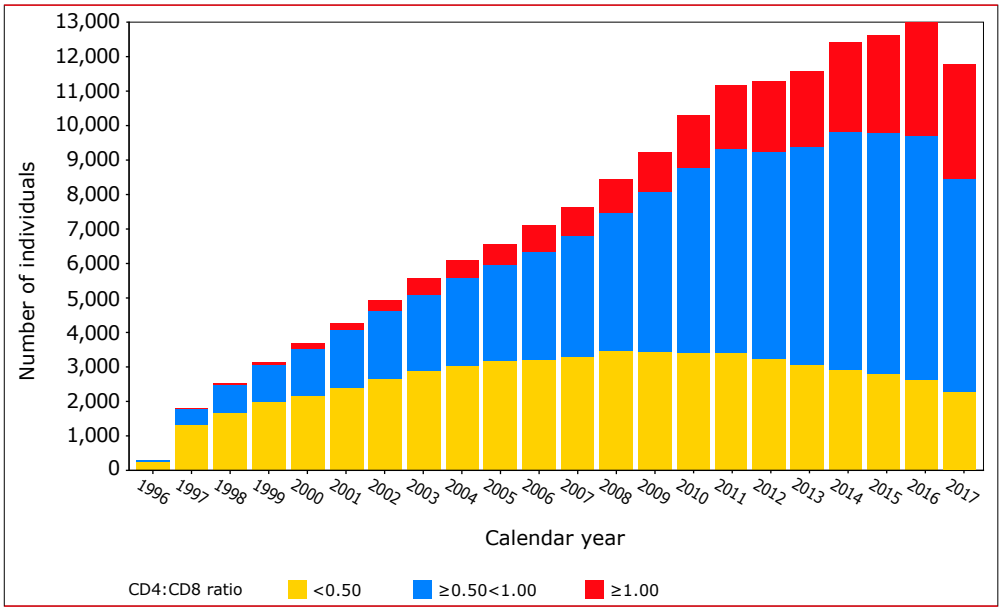
Appendix Figure 2.4: Last available CD4:CD8 ratio in each calendar year after the start of combination antiretroviral therapy.



Note: Numbers for 2017 may increase slightly because data collection is not yet complete.

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Appendix Table 2.1: Combination antiretroviral therapy (cART) regimen used by long-term HIV survivors in 2017.

cART regimen	n	%
TDF/FTC/EFV	127	6.5
TDF/FTC/NVP	198	10.1
TDF/FTC/RPV	46	2.3
TDF/FTC/DRV/b	89	4.5
TDF/FTC/ATV/r	60	3.1
TDF/FTC/LPV	6	0.3
TDF/FTC/EVG/c	27	1.4
TDF/FTC/DTG	36	1.8
TDF/FTC/RAL	23	1.2
ABC/3TC/DTG	163	8.3
TAF/FTC/EVG/c	159	8.1
TAF/FTC/RPV	35	1.8
TAF/FTC/DTG	33	1,7
TAF/FTC/DRV/c	35	1.8
Other: 2NRTI+NNRTI	264	13.4
Other: 2NRTI+PI	99	5.0
Other: 2NRTI+INSTI	27	1.4
Other: NNRTI+INSTI	5	0.3
Other: PI+INSTI	83	4.2
Other: NRTI+PI+INSTI (3ARVs)	52	2.6
Other: NRTI+PI+INSTI (4ARVs)	73	3.7
Other	326	16.6
Total	**1,966**	**100.0**

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

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Appendix Table 2.2: *CD4 cell count at combination antiretroviral therapy (cART) initiation by calendar year 2013–2017.*

Year of cART initiation	2013	2014	2015	2016	2017	Total (2013–2017)
CD4 cell count available at cART initiation	1,347	1,323	1,049	800	38	**4,900**
CD4 cell count, median cells/mm³ [IQR]	370 [250–508]	410 [270–570]	410 [210–600]	400 [230–570]	176 [347–520]	**390 [40–557]**
CD4 cell count (cells/mm³)						
<50	92	74	86	75	37	**364**
	(6.8)	(5.6)	(8.2)	(9.4)	(9.7)	
50–199	160	159	159	104	71	**653**
	(11.9)	(12.0)	(15.2)	(13.0)	(18.6)	
200–349	336	255	179	153	85	**1,008**
	(24.9)	(19.3)	(17.1)	(19.1)	(22.3)	
350–499	404	377	243	183	82	**1,289**
	(30.0)	(28.5)	(23.2)	(22.9)	(21.5)	
≥500	355	458	382	285	106	**1,586**
	(26.4)	(34.6)	(36.4)	(35.6)	(27.8)	

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

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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	65	64.6	9.2	6.2	1.5	4.6	0.0
2001	88	69.3	12.5	13.6	5.7	12.5	3.4
2002	154	63.6	7.8	11.0	6.5	11.7	3.2
2003	211	63.5	14.2	19.4	13.3	17.1	6.6
2004	193	58.5	13.0	16.6	13.0	18.1	5.7
2005	176	54.0	9.1	11.9	9.1	13.6	4.0
2006	162	49.4	6.8	10.5	8.6	14.2	5.6
2007	191	44.0	5.2	8.4	11.5	11.5	4.7
2008	212	40.1	7.5	11.3	5.7	12.3	4.2
2009	220	36.4	6.4	8.6	5.0	7.3	2.7
2010	214	31.8	5.6	6.5	4.7	7.9	1.4
2011	135	27.4	2.2	5.2	4.4	8.1	1.5
2012	108	33.3	0.0	1.9	7.4	9.3	0.9
2013	95	28.4	0.0	3.2	6.3	6.3	3.2
2014	96	25.0	1.0	4.2	3.1	5.2	3.1
2015	109	20.2	1.8	4.6	4.6	7.3	2.8
2016	70	30.0	1.4	1.4	5.7	5.7	1.4
2017	71	21.1	1.4	5.6	2.8	9.9	4.2

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

Calendar year	Number of sequences	Nevirapine	Efavirenz	Etravirine	Rilpivirine
2000	65	24.6	15.4	1.5	12.3
2001	88	30.7	23.9	1.1	10.2
2002	154	33.8	24.0	0.0	13.6
2003	211	39.3	31.8	0.0	16.1
2004	193	48.2	37.3	4.1	18.1
2005	176	36.9	29.5	0.6	17.0
2006	162	51.9	35.8	1.9	15.4
2007	191	39.3	28.8	1.6	15.7
2008	212	37.7	33.5	1.4	12.3
2009	220	35.5	27.7	1.8	11.8
2010	214	28.5	22.4	1.4	8.9
2011	135	27.4	20.0	0.7	7.4
2012	108	34.3	28.7	1.9	7.4
2013	95	33.7	27.4	2.1	12.6
2014	96	31.3	28.1	0.0	3.1
2015	109	20.2	13.8	2.8	9.2
2016	70	21.4	15.7	0.0	8.6
2017	71	25.4	15.5	0.0	7.0

C) High-level resistance to protease inhibitors.

Calendar year	Number of sequences	Nelfinavir	Saquinavir	Indinavir	Atazanavir	Fosamprenavir	Lopinavir	Tipranavir	Darunavir
2000	65	52.3	6.2	4.6	6.2	3.1	3.1	1.5	0.0
2001	88	45.5	14.8	8.0	11.4	6.8	6.8	1.1	0.0
2002	154	29.9	7.8	4.5	4.5	2.6	2.6	0.0	0.0
2003	211	18.5	7.6	6.6	5.2	4.7	6.2	1.4	0.0
2004	193	15.0	3.6	4.7	4.7	3.1	1.6	0.5	0.0
2005	176	19.9	2.8	1.1	3.4	2.3	0.6	0.6	0.0
2006	162	13.6	4.9	4.9	5.6	3.7	3.7	1.9	0.0
2007	191	8.9	4.2	3.7	5.8	3.1	2.1	1.0	0.0
2008	212	8.0	2.8	2.8	3.8	4.2	1.9	0.5	0.0
2009	220	11.8	4.1	5.5	4.1	5.5	4.1	0.5	0.0
2010	214	7.5	3.3	3.3	3.3	4.2	1.4	0.0	0.0
2011	135	6.7	2.2	2.2	2.2	1.5	0.7	0.0	0.0
2012	108	4.6	1.9	2.8	0.9	0.9	1.9	0.0	0.0
2013	95	3.2	0.0	0.0	0.0	1.1	0.0	0.0	0.0
2014	96	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2015	109	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2016	70	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2017	71	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0