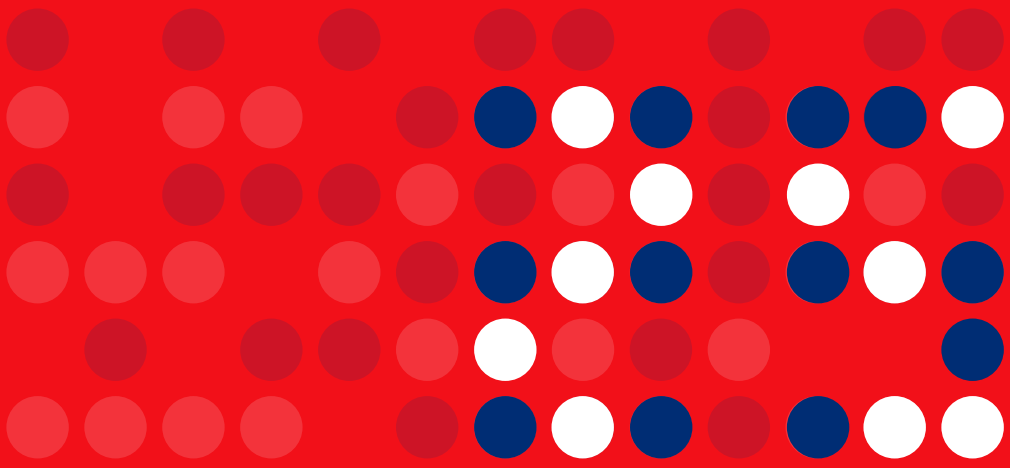
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2025

Chapter 4: Response to antiretroviral therapy



4. Response to antiretroviral therapy

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Introduction

The primary goals of antiretroviral therapy (ART) are to prevent HIV disease progression, improve clinical outcomes, and prevent HIV transmission[1,2]. Treatment guidelines across the globe recommend the initiation of ART as soon as possible in all people diagnosed with HIV, irrespective of CD4 count, HIV viral load or clinical disease stage. In people with very low CD4 counts or with active opportunistic infections, ART is often started as soon as possible, while in others ART is started after the initial evaluation (complete medical history, physical examination, and laboratory testing) has been completed. The decision to initiate ART should always include consideration of a person's comorbid conditions, possible drug resistance, as well as readiness to start and maintain ART[3-7]. In general, the guidelines of the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) follow the US Department of Health and Human Services guidelines[5,8].

Besides preventing clinical events, including but not limited to opportunistic infections and malignancies, the rapid start of ART is also more effective at preventing transmission of HIV than deferral of treatment[9,10]. People with HIV on ART with an undetectable viral load in their blood have no risk of sexual transmission of HIV, (i.e. undetectable equals untransmittable, or U = U[11-16]). Sustained suppression of HIV replication requires selection of appropriate treatment, and reliable access and good adherence to treatment.

In this chapter, we describe trends over time in the use of ART, and trends in the virological and immunological responses to ART during the last 10 calendar years, in adults registered by "stichting hiv monitoring" (SHM) and enrolled in the ATHENA cohort[17].

Starting antiretroviral therapy

In total, 7,069 ART-naïve people with HIV were aged 15 years or above at the time of diagnosis and initiated first-line ART in the Netherlands between January 2015 and December 2024. In *Table 4.1*, we have grouped people by calendar year of ART initiation: 4,605 started in 2015-2019, 517 in 2020, 467 in 2021, 490 in 2022, 518 in 2023, and 472 in 2024. SHM systematically collects the date of entry into the Netherlands for people born in other countries. For an increasing proportion of these people, it is known if they have been diagnosed with HIV and started ART before or after entering the Netherlands. People diagnosed with HIV in other countries who had already initiated ART prior to arriving in the Netherlands are not included in this analysis.

Of the 7,069 people known to have initiated ART since January 2015, 4,337 (61.4%) were men who have sex with men (MSM), 1,456 (20.6%) other men, 1,102 (15.6%) women, and 174 (2.5%) were transgender people. Overall, 3,790 (53.6%) originated from the Netherlands. The proportion of people born in the Netherlands has been steadily declining: from 57.2% in 2015-2019, to 45.3% in 2024. There was a steady increase in the proportion of people born in eastern and central Europe (in recent years predominantly from Ukraine); from 6.9% in 2015-2019, to 15.9% in 2024. The proportion of people from other world regions only fluctuated slightly.

Prompt initiation of ART following HIV diagnosis has increased over time, reflecting implementation and uptake of evolving HIV treatment guidelines (*Figure 4.1A*). Among people with an accurate date of HIV diagnosis in our database who started ART in the Netherlands, the median time between HIV diagnosis and ART initiation shifted from 35 days (interquartile range [IQR] 18-71) for those who entered care in 2015, to 24 days (IQR 13-41) in 2019, to 16 days (IQR 7-29) in 2024. Likewise, the time between entering care in an HIV treatment center and starting ART decreased over time (*Figure 4.1B*). The vast majority of newly diagnosed, ART-naïve people entering care in the Netherlands initiated ART within one month (93.8% in 2024), or even within one day (18.9% in 2024).

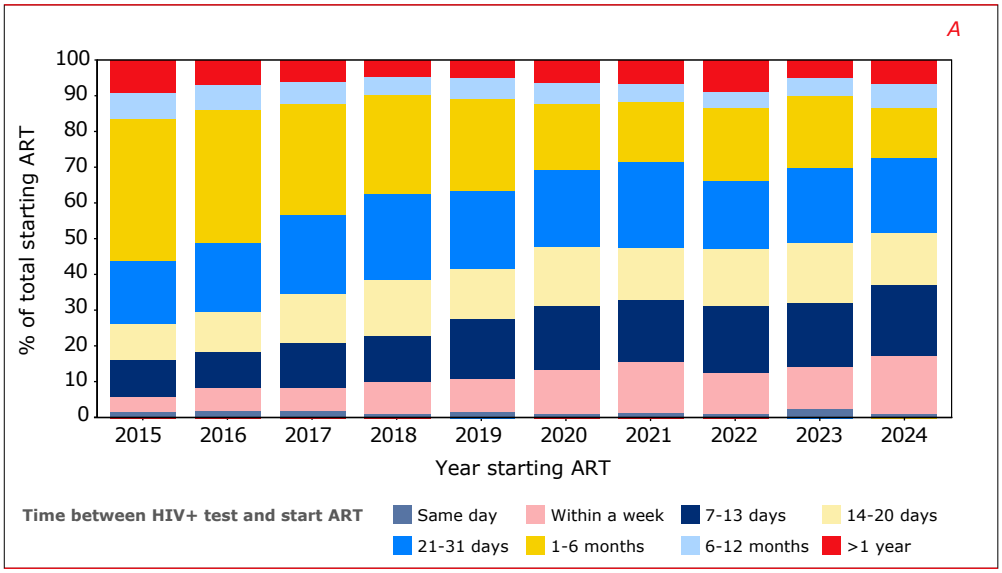
Table 4.1 Characteristics of people starting antiretroviral therapy in 2015–2024.

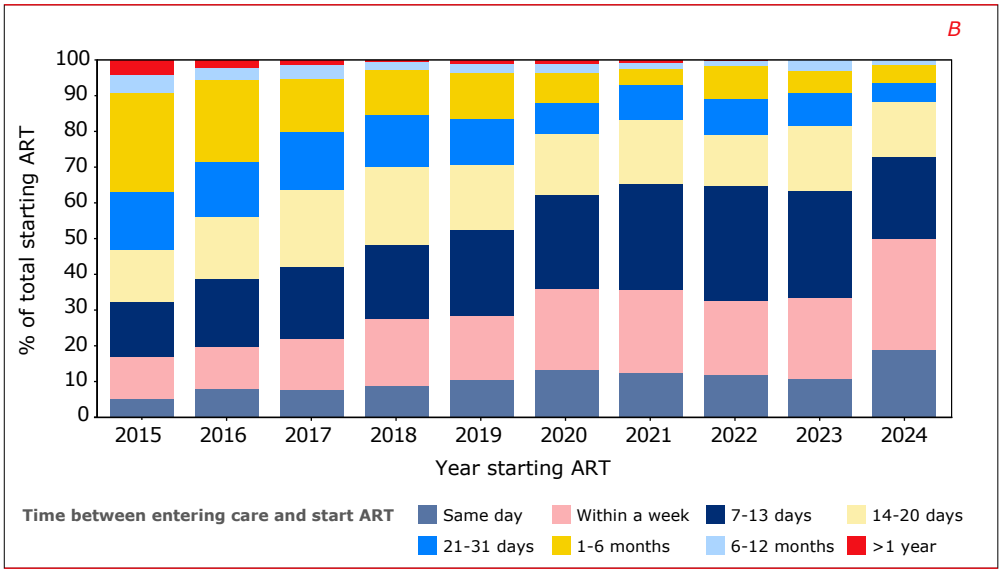
Year of ART initiation		2015–2019	2020	2021	2022	2023	2024	2015–2024
Number of individuals		4,605	517	467	490	518	472	7,069
DEMOGRAPHICS								
Age at ART initiation (years)	Median	39.2	39	39.7	39.6	39.1	37.7	39,1
	Q1	30	30.1	31.2	30.9	30.6	29	30,2
	Q3	49.8	50.2	52.2	50.9	50.2	49.9	50,1
Male sex (at birth)	n	3,938	423	392	390	422	394	5,959
	%	85.5	81.8	83.9	79.6	81.5	83.5	84,3
HIV acquisition group								
MSM	n	2,983	290	271	245	279	269	4,337
	%	64.8	56.1	58	50	53.9	57	61,4
Other men	n	877	111	105	129	131	103	1,456
	%	19	21.5	22.5	26.3	25.3	21.8	20,6
Women	n	664	94	73	100	95	76	1,102
	%	14.4	18.2	15.6	20.4	18.3	16.1	15,6
Transgender people	n	81	22	18	16	13	24	174
	%	1.8	4.3	3.9	3.3	2.5	5.1	2,5
Region of origin								
The Netherlands	n	2,636	259	225	229	227	214	3,790
	%	57.2	50.1	48.2	46.7	43.8	45.3	53,6
Western Europe/North America/	n	234	21	24	13	18	19	329
Australia	%	5.1	4.1	5.1	2.7	3.5	4	4,7
Eastern/central Europe	n	318	62	59	85	77	75	676
	%	6.9	12	12.6	17.3	14.9	15.9	9,6
Latin America and the Caribbean	n	619	75	76	50	81	61	962
	%	13.4	14.5	16.3	10.2	15.6	12.9	13,6
Sub-Saharan Africa	n	418	61	36	62	60	59	696
	%	9.1	11.8	7.7	12.7	11.6	12.5	9,8
Other	n	380	39	47	51	55	44	616
	%	8.3	7.5	10.1	10.4	10.6	9.3	8,7
CLINICAL								

Year of ART initiation		2015–2019	2020	2021	2022	2023	2024	2015–2024
Recent infection (within 12 months of diagnosis)	n	1,199	113	79	89	107	130	1,717
	%	26	21.9	16.9	18.2	20.7	27.5	24.3
Ever having tested HIV-negative	n	2,625	271	234	233	266	262	3,891
	%	57	52.4	50.1	47.6	51.4	55.5	55
CD4 count at start of ART	Median	395	320	303	351	351	410	380
	Q1	200	130	130	150	160	192	180
	Q3	580	555	543	544	563	610	580
HIV RNA (log_{10} cp/ml) at start of ART	Median	4.8	4.9	5.2	4.8	5.1	5	4.8
	Q1	4.1	4.2	4.5	3.9	4.1	4.1	4.2
	Q3	5.4	5.6	5.8	5.6	5.8	5.7	5.5
(Prior) AIDS at start of ART	n	639	108	90	79	92	62	1,070
	%	13.9	20.9	19.3	16.1	17.8	13.1	15.1
Hepatitis B status at start of ART								
HBV-negative (HBsAg-negative)	n	4,346	487	443	454	491	444	6,665
	%	94.4	94.2	94.9	92.7	94.8	94.1	94.3
HBV-positive (HBsAg-positive)	n	122	18	9	28	15	14	206
	%	2.6	3.5	1.9	5.7	2.9	3	2.9
Unknown	n	137	12	15	8	12	14	198
	%	3	2.3	3.2	1.6	2.3	3	2.8
Hepatitis C status at start of ART								
HCV-negative	n	4,410	487	438	462	490	450	6,737
	%	95.8	94.2	93.8	94.3	94.6	95.3	95.3
HCV RNA-positive	n	81	8	6	16	14	6	131
	%	1.8	1.5	1.3	3.3	2.7	1.3	1,9
HCV Ab seropositive	n	56	11	10	4	11	10	102
	%	1.2	2.1	2.1	0.8	2.1	2.1	1.4
Unknown	n	58	11	13	8	3	6	99
	%	1.3	2.1	2.8	1.6	0.6	1.3	1.4
ART started during pregnancy	n	98	10	9	8	13	3	141
	%	2.1	1.9	1.9	1.6	2.5	0.6	2

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

Figure 4.1A&B: Time between HIV diagnosis and initiation of antiretroviral therapy (ART) in 2015-2024 (A) and time between entry into HIV care and initiation of ART in 2015-2024 (B).





Legend: ART = antiretroviral therapy.

There was a slight decrease in the median CD4 count at the start of ART from 395 cells/mm^3 (IQR 200-580) in 2015-2019, to a low of 303 (130-543) in 2021 during COVID-19 lockdowns, followed by an increase to 410 (192-610) cells/mm^3 in 2024. The slightly higher CD4 counts in the period 2015-2019 are mainly caused by the substantial group people already in care but not on ART (because of their high CD4 counts), most of whom subsequently initiated ART in 2015 and 2016 following the 2015 guideline change recommending ART for all, irrespective of CD4 count.

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

Changes in the use of initial ART regimen

Data from clinical trials on contemporary antiretroviral drugs have shown good outcomes in terms of viral suppression, convenience, tolerability, and toxicity. Over the past years, several new antiretroviral drugs and new, once-daily, fixed-dose combination regimens have been approved in the Netherlands (*Box 4.1*). In this section, we evaluate the post-approval implementation of these new drugs/regimens in HIV treatment.

Box 4.1: Approval dates of new antiretroviral drugs/regimens for HIV treatment in the Netherlands in 2013–2024.

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

Legend: *3TC = lamivudine; ABC = abacavir; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.*

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

Initial ART regimen

In the period 2015-2024, all guideline-recommended first-line ART regimen consist of a nucleoside-analogue reverse transcriptase inhibitor (NRTI) backbone, plus one anchor-drug. The NRTI-backbone usually consists of two NRTI, except for the regimen 3TC/DTG. In the period 2015-2024, the recommended anchor-drugs are from the integrase inhibitor (INSTI), non-nucleoside RT inhibitor (NNRTI), or protease inhibitor (PI) class. The use of other ART regimen, i.e. dual-anchor class regimen with or without the addition of NRTI, have become more common in recent years, but only in treatment-experienced individuals.

In the studied period, in certain groups of newly diagnosed individuals, a 2-step 'induction-maintenance' approach has sometimes been used, where at the time of ART initiation it is the explicit intention to replace the first ART regimen as soon as possible with another regimen. For the purpose of our analyses here, when the

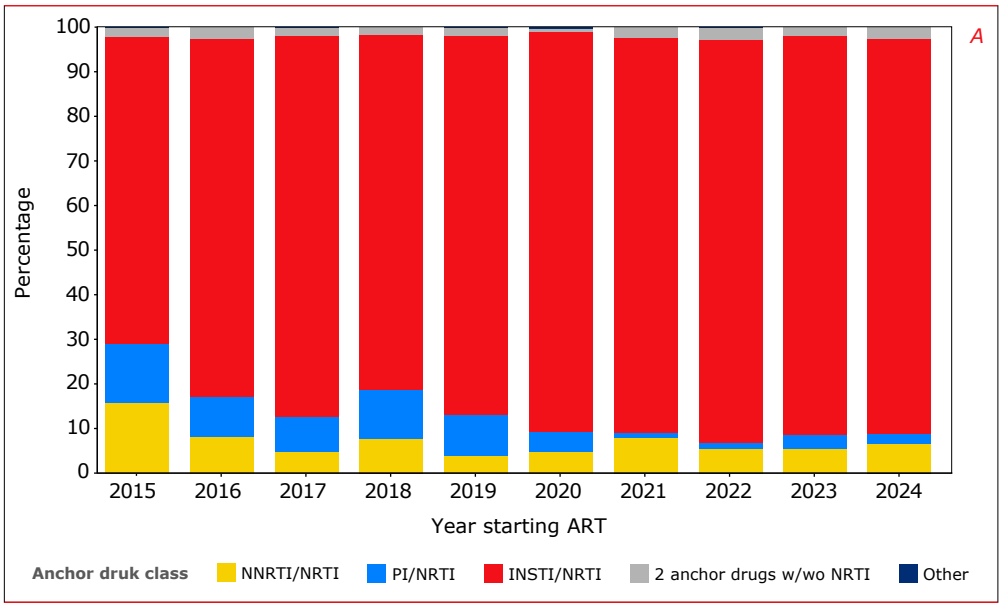
switch happened within 6 months and there was explicit mention of the 'induction-maintenance' approach in the electronic medical records, the starting regimens of the individuals who initiated therapy using this strategy have been set to their second simplified guideline-recommended regimen.
Common examples of this 'induction-maintenance' approach are ART initiation with a regimen containing 2 anchor-drugs plus 2 NRTI in individuals initiating ART during acute HIV infection (often as part of a study protocol) or individuals with low CD4 counts and opportunistic infections who quickly initiate ART before the results of HIV genotypic resistance testing (and HBV testing) have become available. In these individuals, ART is subsequently simplified to a guideline-recommended regimen as soon as the first undetectable viral load measurement and/or the results of the genotypic resistance testing have become available. This occurred 294 times. Another common similar strategy is that individuals are started on a dolutegravir-based regimen combined with 2 NRTI (n=258), which is than quickly 'simplified' to either 3TC/DTG or TDF/3TC/DOR, as soon as the first undetectable viral load measurement and/or the results of genotypic resistance testing have become available. Also in these cases, we considered their second simplified guideline-recommended regimen as their starting regimen, unless the reason for the switch was documented to be 'virological failure' or 'toxicity'.

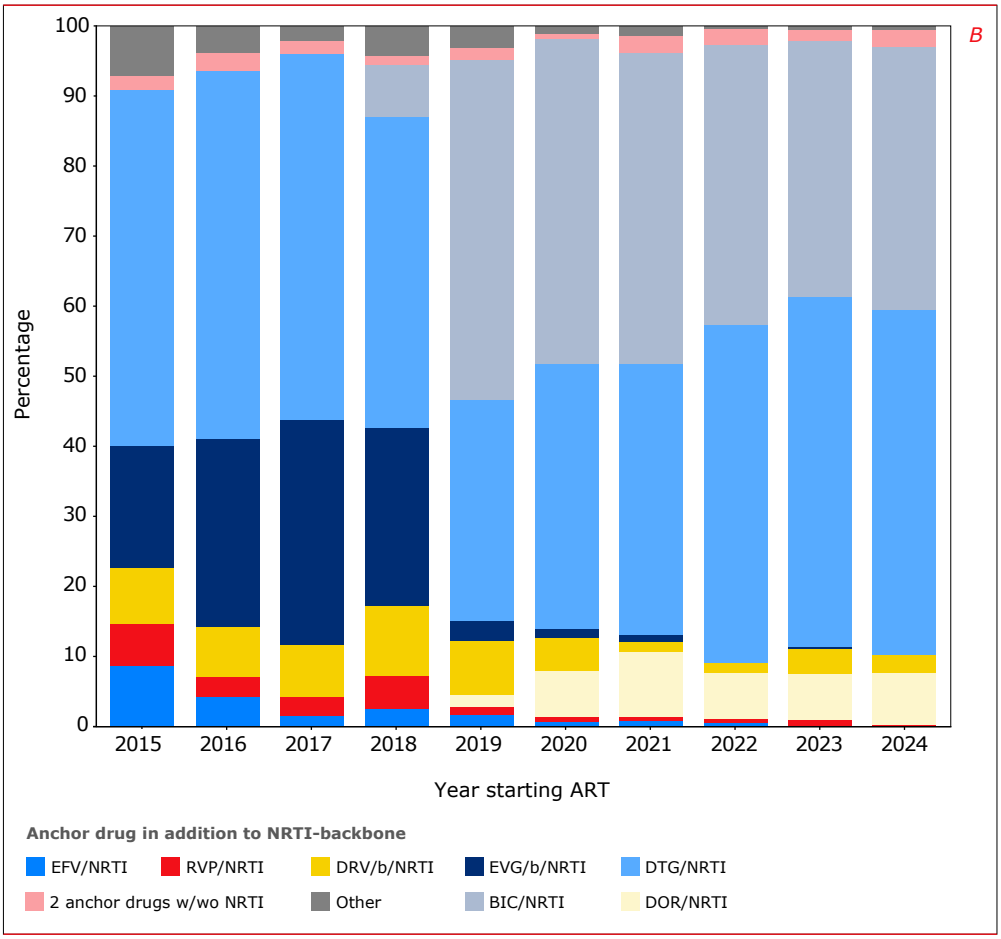
For the 7,069 ART-naïve people who initiated first-line ART between 2015 and 2024, *Figures 4.2A&B* show the trends over time in anchor-drug additions to the NRTI backbone used as part of the initial ART regimen. The use of INSTI in combination with a (mono- or dual-) NRTI backbone as initial therapy, increased from 68.9% in 2015 to 88.8% in 2024 (89.9% including other INSTI-containing dual anchor-drug regimens). The use of NNRTIs in combination with a NRTI backbone as the initial regimen decreased from 15.8% in 2015 to 6.4% in 2024. The use of PIs in combination with a NRTI backbone as the initial regimen also decreased from 13.2% in 2015 to 2.3% in 2024.

In the period 2015-2024, between 0.6% and 2.5% of individuals (2.5% in 2024) initiated ART with a dual anchor-drug regimen. As explained above, this excludes individuals in whom the abovementioned strategy was implemented of starting with a dual anchor-drug regimen quickly followed by a simplification to a standard guideline-recommended regimen when this was deemed to be safe.

Figure 4.2B shows all anchor-drug additions to the NRTI backbone that were used as part of the initial regimen in at least 5% of individuals during one or more calendar years between 2015-2024. The regimens that were used less frequently have therefore been included in the category 'other' in *Figure 4.2B*. Full details on the initial regimens are shown in Table 4.2.

Figure 4.2A&B: Anchor-class (A) and individual anchor-drug (B) plus nucleoside reverse transcriptase backbone used as part of the initial regimen in 2015-2024.

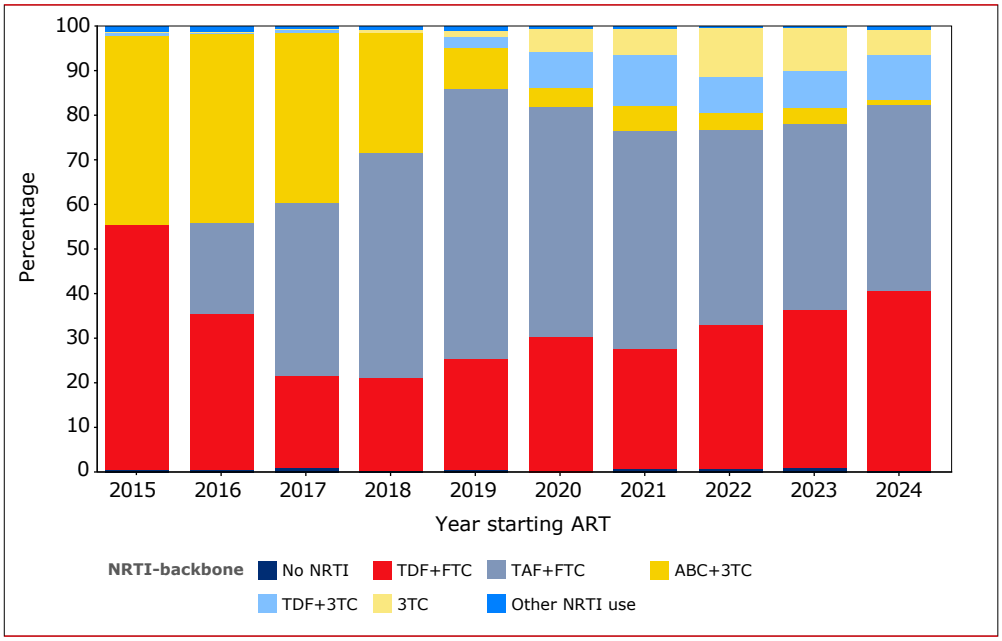




Legend: *ART = antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse transcriptase inhibitor;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

Figure 4.3 provides an overview of the NRTI backbone components of the initial regimens used in 2015-2024. The combination of tenofovir disoproxil fumarate (TDF) or alafenamide (TAF) with emtricitabine (FTC) was the predominant backbone prescribed. Following its introduction at the end of 2015, use of TAF in in initial ART regimens rapidly increased with a maximum of 60.3% in 2019, but has since slowly declined to 41.5% in 2024. At the same time, TDF use decreased from 54.9% in 2015 to a low of 20.7% in 2017, after which its use increased again to 40.5% in 2024. The use of abacavir steadily decreased from a high of 42.7% of all initial regimens in 2016 to 1.3% in 2024.

Figure 4.3: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2015–2024.*



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

The most common ART regimens initiated in 2015-2024 are presented in *Figure 4.4* and *Table 4.2*. In 2024, the most frequently used initial regimen was TDF/FTC/dolutegravir (38.3%). TAF/FTC/bictegravir was used in 37.5% of initial regimens. Additionally, 7.4% initiated a doravirine-containing, once-daily, fixed-dose combination with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF). *Table 4.2* provides more detail on the other initial regimens and other calendar years that are not further specified in *Figures 4.2A&B*, *4.3* and *4.4*.

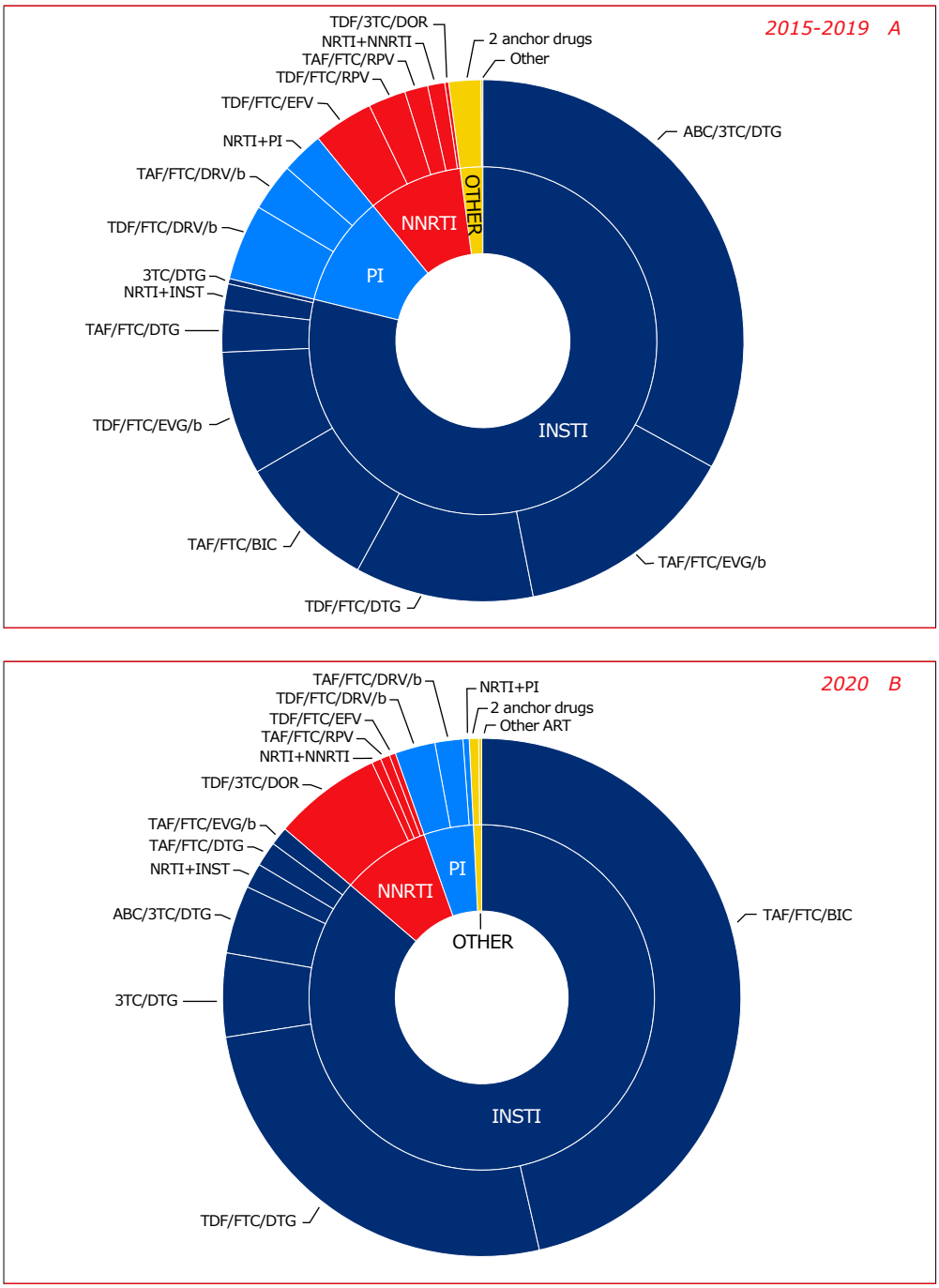
Table 4.2: Initial regimens in 2015–2024.

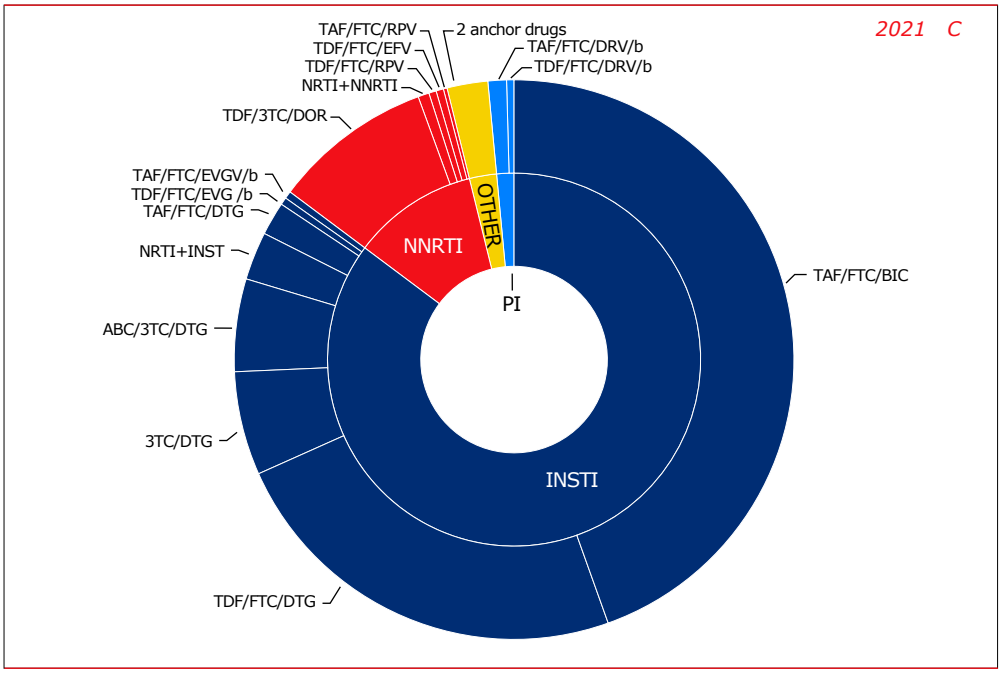
		2015–2019	2020	2021	2022	2023	2024	2015–2024
	n	4,605	517	467	490	518	472	7,069
INSTI + NRTI								
TAF/FTC/BIC	n	399	240	208	194	189	177	1,407
	%	8.7	46.4	44.5	39.6	36.5	37.5	19.9
TAF/FTC/DTG	n	120	8	9	10	9	6	162
	%	2.6	1.5	1.9	2	1.7	1.3	2.3
TDF/FTC/DTG	n	509	135	111	148	176	181	1,260
	%	11.1	26.1	23.8	30.2	34	38.3	17.8
ABC/3TC/DTG	n	1,520	22	25	19	19	6	1,611
	%	33	4.3	5.4	3.9	3.7	1.3	22.8
3TC/DTG	n	15	27	28	53	50	26	199
	%	0.3	5.2	6	10.8	9.7	5.5	2.8
TAF/FTC/EVG/c	n	640	6	2	.	1	.	649
	%	13.9	1.2	0.4	.	0.2	.	9.2
TDF/FTC/EVG/c	n	353	.	2	.	.	.	355
	%	7.7	.	0.4	.	.	.	5
TDF/FTC/RAL	n	34	3	4	1	1	.	43
	%	0.7	0.6	0.9	0.2	0.2	.	0.6
Other NRTI + INSTI	n	40	5	9	8	7	15	84
	%	0.9	1	1.9	1.6	1.4	3.2	1.2
NNRTI + NRTI								
TDF/3TC/DOR	n	11	35	43	31	36	35	191
	%	0.2	6.8	9.2	6.3	6.9	7.4	2.7
TDF/FTC/EFV	n	171	2	2	3	1	1	180
	%	3.7	0.4	0.4	0.6	0.2	0.2	2.5
TDF/FTC/NVP	n	19	.	1	.	.	.	20
	%	0.4	.	0.2	.	.	.	0.3
ABC/3TC/NVP	n	1	.	.	.	.	.	1
	%	0	.	.	.	.	.	0
TAF/FTC/RPV	n	66	3	1	3	2	1	76
	%	1.4	0.6	0.2	0.6	0.4	0.2	1.1
TDF/FTC/RPV	n	107	.	2	.	1	.	110
	%	2.3	.	0.4	.	0.2	.	1.6
Other NRTI + NNRTI	n	29	3	2	.	1	.	35
	%	0.6	0.6	0.4	.	0.2	.	0.5

PI + NRTI								
TDF/FTC/ATV/b	n	73	.	.	.	.	.	73
	%	1.6	.	.	.	.	.	1
TAF/FTC/DRV/c	n	136	9	5	5	13	9	177
	%	3	1.7	1.1	1	2.5	1.9	2.5
TDF/FTC/DRV/b	n	217	13	2	2	2	2	238
	%	4.7	2.5	0.4	0.4	0.4	0.4	3.4
TDF/FTC/LPV/r	n	6	.	.	.	.	.	6
	%	0.1	.	.	.	.	.	0.1
Other NRTI + PI	n	42	2	.	.	1	.	45
	%	0.9	0.4	.	.	0.2	.	0.6
2 anchor-drugs								
DTG/DRV/b	n	28	1	4	5	3	1	42
	%	0.6	0.2	0.9	1	0.6	0.2	0.6
DTG/RPV	n	1	.	.	.	.	1	2
	%	0	.	.	.	.	0.2	0
CAB/RPV	n	.	.	.	.	1	.	1
	%	.	.	.	.	0.2	.	0
2 anchor-drugs w/wo NRTI	n	62	2	7	7	4	9	91
	%	1.3	0.4	1.5	1.4	0.8	1.9	1.3
Other ART	n	6	1	.	1	1	2	11
	%	0.1	0.2	.	0.2	0.2	0.4	0.2

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

Figure 4.4: The initial antiretroviral therapy regimens given in 2015–2024.




2021 C
TAF/FTC/RPV
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TDF/FTC/EFV
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TDF/FTC/RPV
TDF/FTC/DRV/b
NRTI+NNRTI
TDF/3TC/DOR
TAF/FTC/EVGV/b
TDF/FTC/EVG /b
TAF/FTC/DTG
NRTI+INST
ABC/3TC/DTG
3TC/DTG
TDF/FTC/DTG
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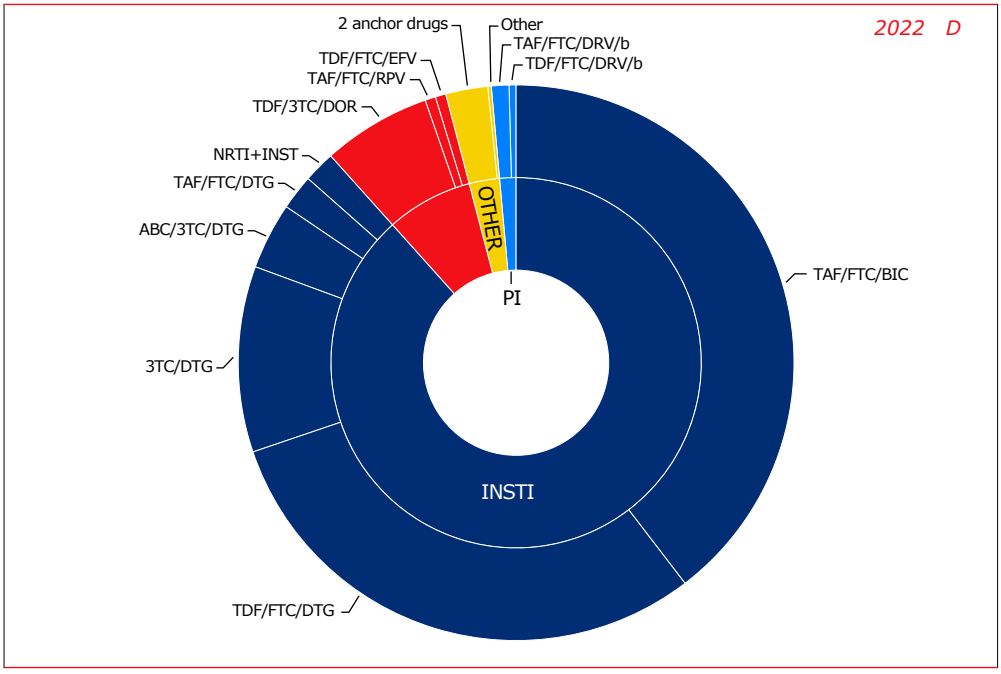
2022 D
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Other
TAF/FTC/DRV/b
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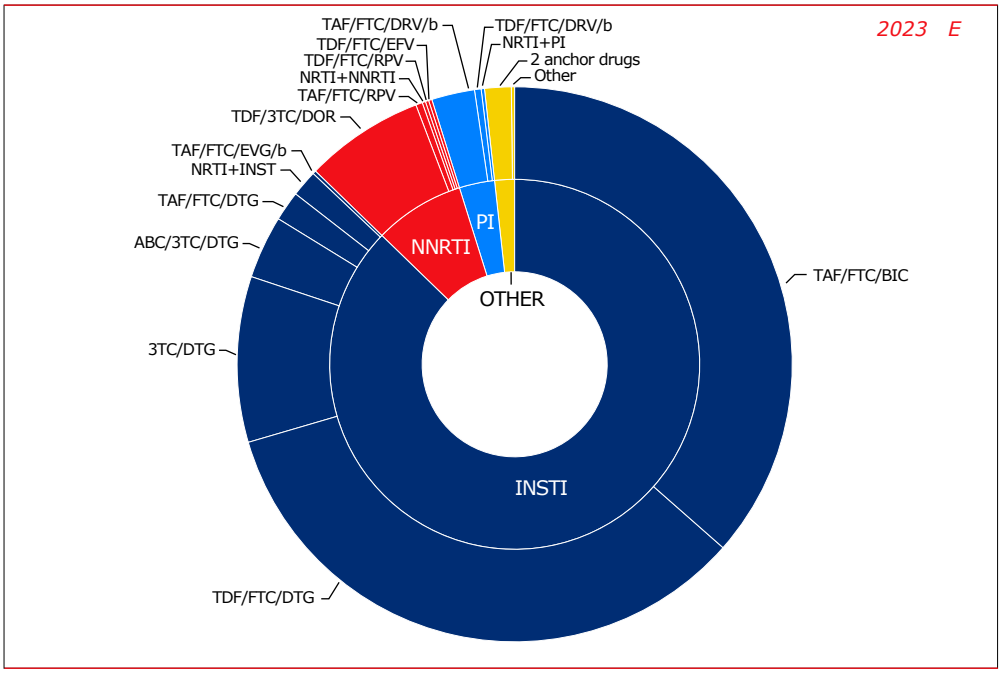
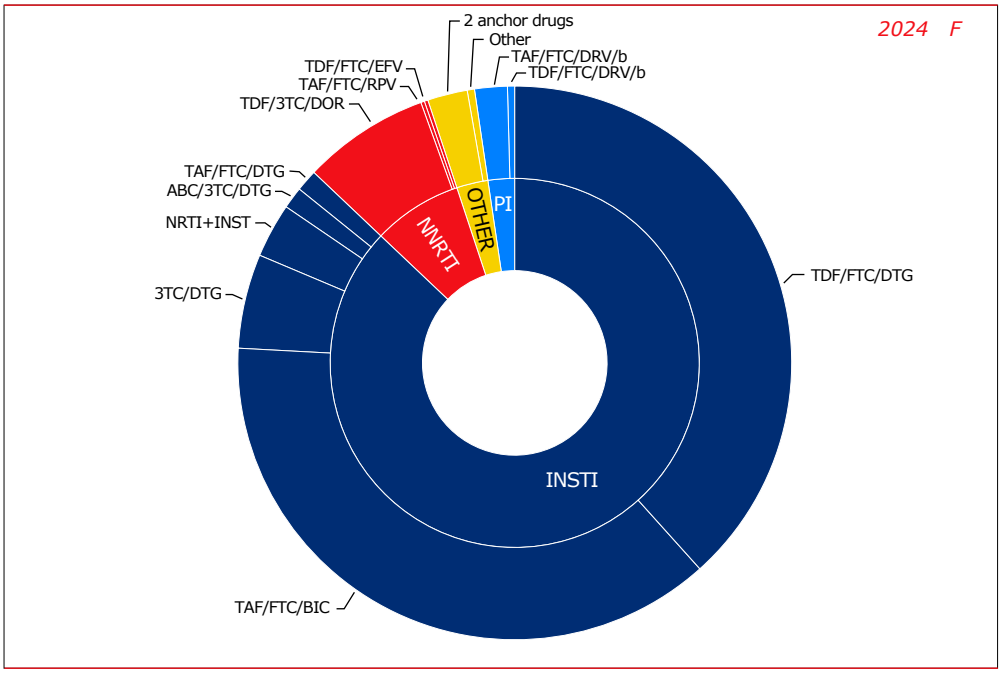
TDF/3TC/DOR
NRTI+INST
TAF/FTC/DTG
ABC/3TC/DTG
3TC/DTG
TDF/FTC/DTG
OTHER
PI
INSTI
TAF/FTC/BIC





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

In care and on ART in the Netherlands in 2024

A total of 26,519 people with HIV were in care and on ART between (part of the period) January 2015 and December 2024. The number of people who had initiated ART and were in active follow-up in the ATHENA cohort grew from 18,157 individuals in 2015 to 22,698 individuals in 2024. As ATHENA is an open cohort, over time new individuals enrol into the cohort as they enter HIV care in one of the Dutch HIV treatment centers, or they leave the cohort when they die, move abroad, withdraw consent, or otherwise become lost to follow-up. Contrary to our analyses in previous Monitoring Reports, in this section we have not excluded people who (temporarily) interrupted ART from the analyses. Most of these individuals had medical, psychiatric, and/or psycho-social issues that temporarily prevented them from continuing ART, and most of them re-started ART when those issues had been sufficiently resolved.

Table 4.3 shows the evolution over calendar time of the size, demographical, clinical and ART characteristics of the treated individuals who constitute the ATHENA cohort. For selected calendar years a cross section of the cohort is shown of all people in active follow-up in the cohort during that particular calendar year. For each included individual the status at the last clinic visit of that calendar year was used. In 2024, 22,698 people on ART were in care (for part of or the entire) calendar year. In 2024, 18,522 (81.6%) were men, and 14,191 (62.5%) were MSM. Their median age in 2024 was 53.2 (IQR 42.9-61.5) years. The majority (54.6%) originated from the Netherlands, followed by Latin America / the Caribbean (13.3%) and sub-Saharan Africa (12.0%). They had been diagnosed with HIV a median of 14.7 (IQR 8.9-21.0) years ago and started their first-line ART regimen a median of 12.6 (IQR 8.0-18.5) years ago. Their last measured viral load was <50 copies/ml in 95.6% (98.0% <200 copies/ml), and 80.3% had a last measured CD4 count of 500 cells/mm^3 or higher.

Table 4.3: Characteristics of people in care receiving antiretroviral therapy between 2015–2024.

Calendar year		2015	2020	2021	2022	2023	2024
Total population size	n	18,157	21,363	21,663	22,130	22,528	22,698
Age	Median	48.2	51.0	51.7	52.2	52.7	53.2
	Q1	39.9	41.4	41.9	42.2	42.5	42.9
	Q3	55.5	58.8	59.6	60.2	60.9	61.5
Male sex (at birth)	n	14,805	17,525	17,779	18,079	18,397	18,522
	%	81.5	82.0	82.1	81.7	81.7	81.6
HIV acquisition group							
MSM	n	11,304	13,497	13,670	13,865	14,075	14,191
	%	62.3	63.2	63.1	62.7	62.5	62.5
Other men	n	3,328	3,755	3,820	3,910	3,995	3,992
	%	18.3	17.6	17.6	17.7	17.7	17.6
Women	n	3,350	3,833	3,877	4,042	4,120	4,163
	%	18.5	17.9	17.9	18.3	18.3	18.3
Transgender people	n	175	278	296	313	338	352
	%	1.0	1.3	1.4	1.4	1.5	1.6
Region of origin							
The Netherlands	n	10,985	12,423	12,455	12,443	12,443	12,402
	%	60.5	58.2	57.5	56.2	55.2	54.6
Western Europe/North	n	1,196	1,343	1,354	1,347	1,367	1,355
America/Australia	%	6.6	6.3	6.3	6.1	6.1	6.0
Eastern/central Europe	n	550	919	1,002	1,301	1,425	1,500
	%	3.0	4.3	4.6	5.9	6.3	6.6
Latin America/Caribbean	n	2,014	2,664	2,769	2,837	2,957	3,018
	%	11.1	12.5	12.8	12.8	13.1	13.3
Sub-Saharan Africa	n	2,330	2,560	2,575	2,617	2,670	2,727
	%	12.8	12.0	11.9	11.8	11.9	12.0
Other	n	1,082	1,454	1,508	1,585	1,666	1,696
	%	6.0	6.8	7.0	7.2	7.4	7.5
CD4 at start ART							
No data	n	1,347	2,147	2,307	2,644	2,840	3,004
	%	7.4	10.1	10.6	11.9	12.6	13.2
<50	n	1,876	2,067	2,101	2,122	2,140	2,128
	%	10.3	9.7	9.7	9.6	9.5	9.4
50–199	n	3,883	4,111	4,134	4,136	4,139	4,105
	%	21.4	19.2	19.1	18.7	18.4	18.1
200–349	n	5,527	5,845	5,842	5,833	5,857	5,800
	%	30.4	27.4	27.0	26.4	26.0	25.6
350–499	n	3,045	3,624	3,634	3,666	3,712	3,719
	%	16.8	17.0	16.8	16.6	16.5	16.4
500+	n	2,479	3,569	3,645	3,729	3,840	3,942
	%	13.7	16.7	16.8	16.9	17.0	17.4

Calendar year		2015	2020	2021	2022	2023	2024
Viral load at start ART	Median	4.9	4.9	4.9	4.9	4.9	4.9
	Q1	4.3	4.3	4.3	4.3	4.3	4.3
	Q3	5.3	5.3	5.3	5.3	5.4	5.4
Years known HIV+	Median	9.3	12.1	12.8	13.4	14.1	14.7
	Q1	4.9	6.8	7.4	7.9	8.4	8.9
	Q3	15.0	18.2	18.9	19.6	20.3	21.0
Years since start ART	Median	7.0	10.0	10.7	11.3	12.0	12.6
	Q1	3.1	5.7	6.4	7.0	7.5	8.0
	Q3	12.9	15.8	16.5	17.2	17.9	18.5
Current CD4 count							
Missing	n	16	20	27	25	26	20
	%	0.1	0.1	0.1	0.1	0.1	0.1
<50	n	74	62	60	68	61	48
	%	0.4	0.3	0.3	0.3	0.3	0.2
50–199	n	466	442	414	424	416	380
	%	2.6	2.1	1.9	1.9	1.8	1.7
200–349	n	1,492	1,426	1,433	1,464	1,382	1,290
	%	8.2	6.7	6.6	6.6	6.1	5.7
350–499	n	3,080	3,050	3,108	2,984	2,850	2,748
	%	17.0	14.3	14.3	13.5	12.7	12.1
500–749	n	6,804	7,157	7,324	7,378	7,236	7,187
	%	37.5	33.5	33.8	33.3	32.1	31.7
750+	n	6,225	9,206	9,297	9,787	1,0557	1,1025
	%	34.3	43.1	42.9	44.2	46.9	48.6
Viral load <50 c/ml							
Missing	n	10	14	14	18	14	9
	%	0.1	0.1	0.1	0.1	0.1	0.0
≥50 c/ml	n	1,800	996	985	1,083	988	997
	%	9.9	4.7	4.5	4.9	4.4	4.4
<50 c/ml	n	16,347	20,353	20,664	21,029	21,526	21,692
	%	90.0	95.3	95.4	95.0	95.6	95.6
Viral load <200 c/ml							
Missing	n	10	14	14	18	14	9
	%	0.1	0.1	0.1	0.1	0.1	0.0
≥200 c/ml	n	740	475	490	535	498	456
	%	4.1	2.2	2.3	2.4	2.2	2.0
<200 c/ml	n	17,407	20,874	21,159	21,577	22,016	22,233
	%	95.9	97.7	97.7	97.5	97.7	98.0

Calendar year		2015	2020	2021	2022	2023	2024
ART regimen							
ART temporarily interrupted	n	459	390	377	341	293	181
	%	2.5	1.8	1.7	1.5	1.3	0.8
INSTI + NRTI							
TAF/FTC/BIC	n	2	2,688	3,159	3,563	3,927	4,235
	%	0.0	12.6	14.6	16.1	17.4	18.7
TAF/FTC/DTG	n	6	550	526	497	473	449
	%	0.0	2.6	2.4	2.2	2.1	2.0
TDF/FTC/DTG	n	665	764	768	914	981	1,089
	%	3.7	3.6	3.5	4.1	4.4	4.8
ABC/3TC/DTG	n	2,149	2,578	2,179	1,888	1,619	1,377
	%	11.8	12.1	10.1	8.5	7.2	6.1
3TC/DTG	n	20	1,067	1,728	2,365	3,041	3,481
	%	0.1	5.0	8.0	10.7	13.5	15.3
TAF/FTC/EVG/b	n	13	2,511	2,267	2,012	1,806	1,698
	%	0.1	11.8	10.5	9.1	8.0	7.5
TDF/FTC/EVG/b	n	1,337	580	532	459	401	362
	%	7.4	2.7	2.5	2.1	1.8	1.6
TDF/FTC/RAL	n	366	177	159	132	98	97
	%	2.0	0.8	0.7	0.6	0.4	0.4
Other INSTI + NRTI	n	158	257	244	249	243	225
	%	0.9	1.2	1.1	1.1	1.1	1.0
NNRTI + NRTI							
TDF/3TC/DOR	n	2	886	1,403	1,642	1,855	1,997
	%	0.0	4.1	6.5	7.4	8.2	8.8
TDF/FTC/EFV	n	3,001	1,378	1,223	1,054	945	876
	%	16.5	6.5	5.6	4.8	4.2	3.9
TAF/FTC/NVP	n	4	712	721	713	700	683
	%	0.0	3.3	3.3	3.2	3.1	3.0
TDF/FTC/NVP	n	2,220	1,031	915	791	703	641
	%	12.2	4.8	4.2	3.6	3.1	2.8
ABC/3TC/NVP	n	547	355	295	254	213	190
	%	3.0	1.7	1.4	1.1	0.9	0.8
TAF/FTC/RPV	n	7	956	990	951	918	876
	%	0.0	4.5	4.6	4.3	4.1	3.9
TDF/FTC/RPV	n	1,666	602	435	366	320	284
	%	9.2	2.8	2.0	1.7	1.4	1.3
Other NNRTI + NRTI	n	644	317	317	277	252	239
	%	3.5	1.5	1.5	1.3	1.1	1.1

Calendar year		2015	2020	2021	2022	2023	2024
PI + NRTI							
TDF/FTC/ATV/b	n	928	200	156	121	81	67
	%	5.1	0.9	0.7	0.5	0.4	0.3
TAF/FTC/DRV/b	n	2	1,250	1,269	1,271	1,283	1,288
	%	0.0	5.9	5.9	5.7	5.7	5.7
TDF/FTC/DRV/b	n	1,606	463	409	342	269	239
	%	8.8	2.2	1.9	1.5	1.2	1.1
TDF/FTC/LPV/b	n	130	21	17	11	6	5
	%	0.7	0.1	0.1	0.0	0.0	0.0
Other PI + NRTI	n	773	315	239	189	163	140
	%	4.3	1.5	1.1	0.9	0.7	0.6
2 anchor-drugs							
DTG/DRV/b	n	115	348	357	372	382	388
	%	0.6	1.6	1.6	1.7	1.7	1.7
DTG/RPV	n	6	114	130	139	147	152
	%	0.0	0.5	0.6	0.6	0.7	0.7
CAB/RPV injectables *	n	.	36	71	496	721	781
	%	.	0.2	0.3	2.2	3.2	3.4
2 anchor-drugs w/wo NRTI	n	593	430	427	389	375	361
	%	3.3	2.0	2.0	1.8	1.7	1.6
Other ART	n	738	387	350	332	313	297
	%	4.1	1.8	1.6	1.5	1.4	1.3

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

** Some individuals using this regimen were participating in a clinical trial.*

Among the 22,698 individuals in HIV care and on ART in 2024, the vast majority (87.8%) received a regimen based on one or two NRTIs, combined with either (*Figure 4.5A*) an integrase inhibitor (INSTI) (57.5%), a non-nucleoside reverse transcriptase inhibitor (NNRTI) (25.5%), or a protease inhibitor (PI) (7.9%).

The proportion of individuals who had (temporarily) interrupted ART at the end of the calendar year, decreased from 2.5% in 2015 to 0.7% in 2024. In a later section in this chapter more details are shown about the number, reasons, duration and outcome of these treatment interruptions.

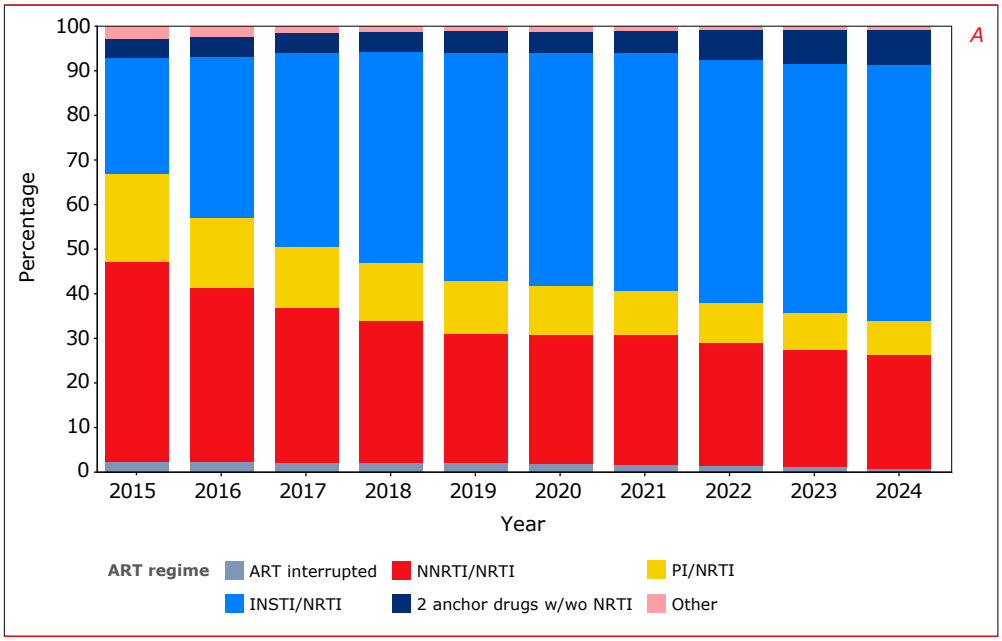
The changes over time in the distribution of specific ART regimens among the population in care in 2015-2024 is presented in *Figure 4.5B* and *4.7* and in *Table 4.3*. The most frequently used regimens in 2024 (used by at least 5% of the population) were:

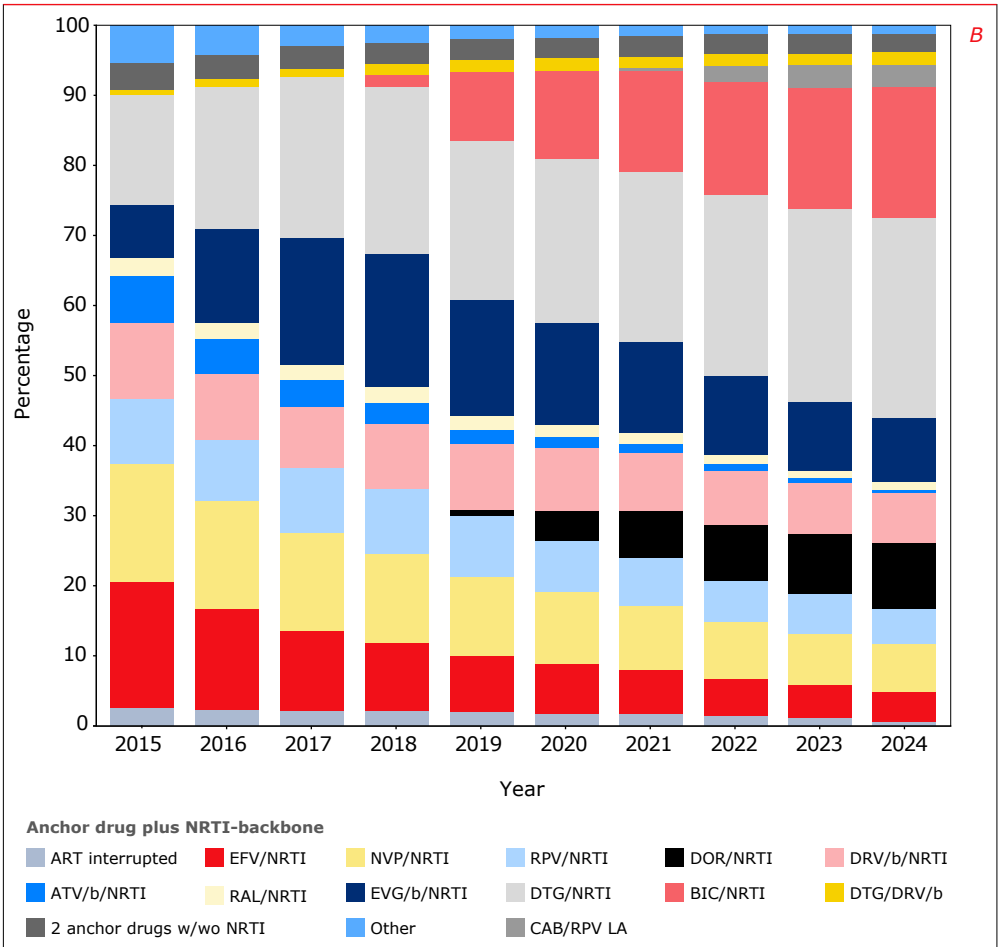
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/bictegravir (BIC) (18.7%);
- dolutegravir (DTG)/lamivudine (3TC) (15.3%);
- tenofovir disoproxil fumarate (TDF)/lamivudine (3TC)/doravirine (DOR) (8.8%);
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (7.5%);
- abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (6.1%); and
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (5.7%)

The use of ABC/3TC/DTG has decreased substantially following the DHHS guideline change from one of the "Recommended Initial Regimens for Most People With HIV" to a regimen recommended as part of "Other Initial Antiretroviral Regimens for Certain Clinical Scenarios" because of concerns over a potential increase in the risk of cardiovascular events by the use of ABC. In our cohort the use of ABC has also been shown to be independently associated with a higher risk of cardiovascular events (see Chapter 5, Morbidity and Mortality).

In 2024, the use of regimens consisting of 2 anchor-drugs (an NNRTI, PI, or INSTI) with or without one or two additional NRTI, continued to increase to 7.8%. The most common of these regimens were a combination of cabotegravir/rilpivirine injectables (3.4%), dolutegravir/darunavir/cobicistat (1.7%), and dolutegravir/rilpivirine (0.7%).

Figure 4.5A&B: Anchor-drug class (A) and individual anchor-drugs (B) plus nucleoside reverse transcriptase backbone used as part of the current regimen in 2015-2024.

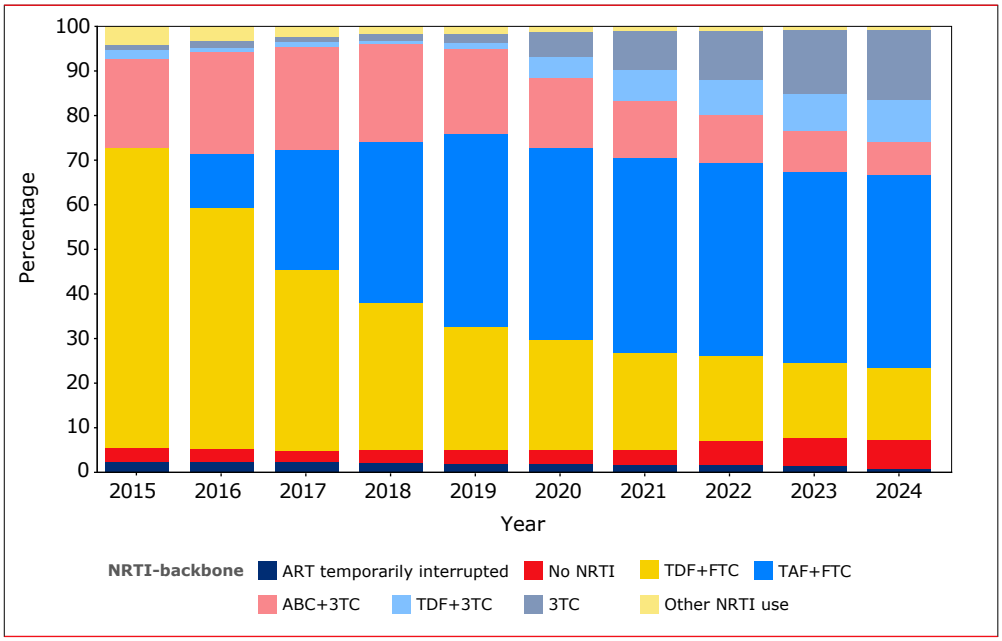




Legend: *ART = antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse transcriptase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

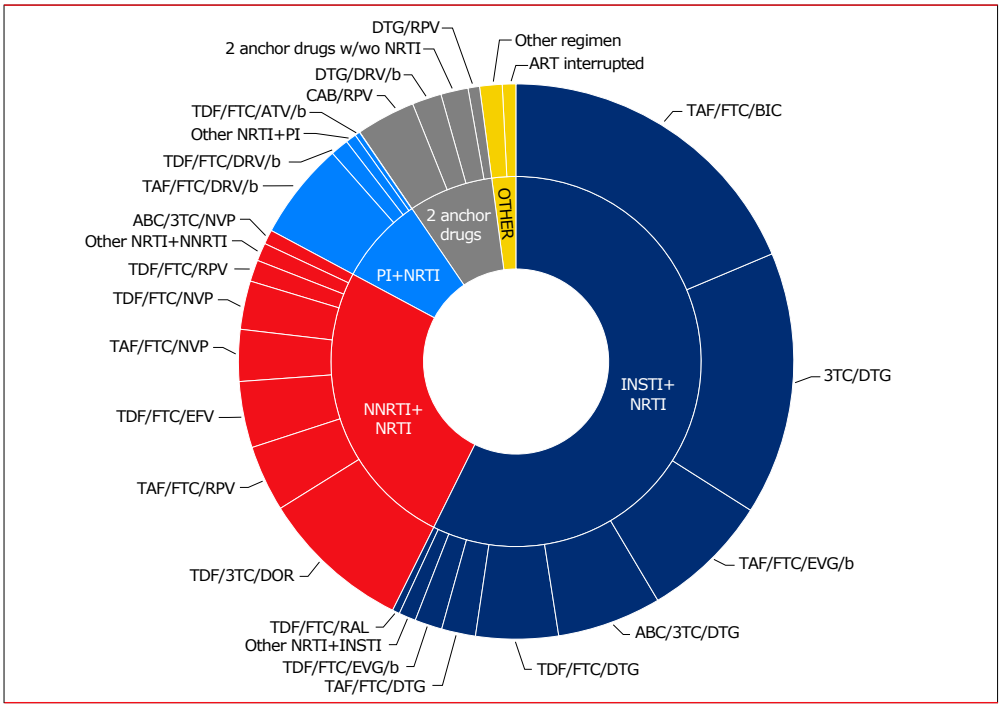
Figure 4.6 provides an overview of the NRTI backbone components of the current ART regimens used in 2015-2024. The combination of tenofovir disoproxil fumarate (TDF) or alafenamide (TAF) with emtricitabine (FTC) was the predominant backbone used, being part of 67.4% of the regimen used in 2015, and slowly declining to 59.2% in 2024. Following its introduction at the end of 2015, use of TAF in ART regimens rapidly increased to about 43% of all regimens used since 2019 and has since remained stable at that level. At the same time, TDF use decreased from 70.7% of all regimens used in 2015 to 29.8% in 2019, after which TDF use slowly continued to decrease to 25.9% in 2024. ABC was used in 21.0% of all regimens in 2015. Following the introduction of the fixed dose combination ABC/3TC/DTG its use increased to 23.6% in 2017, after which its use slowly decreased to 7.8% of all regimens used in 2024.

Figure 4.6: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the current regimen in 2015–2024.*



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

Figure 4.7: Antiretroviral therapy use in 2024.



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

Modifications and interruptions of ART use

For the 26,519 individuals who were on ART between January 2015 and December 2024, we assessed the frequency and reported reasons for modifications and (temporary) interruptions of ART. The unit of analysis for this section is therefore the treatment episodes, and a single individual can contribute multiple treatment episodes with multiple regimens to this analysis.

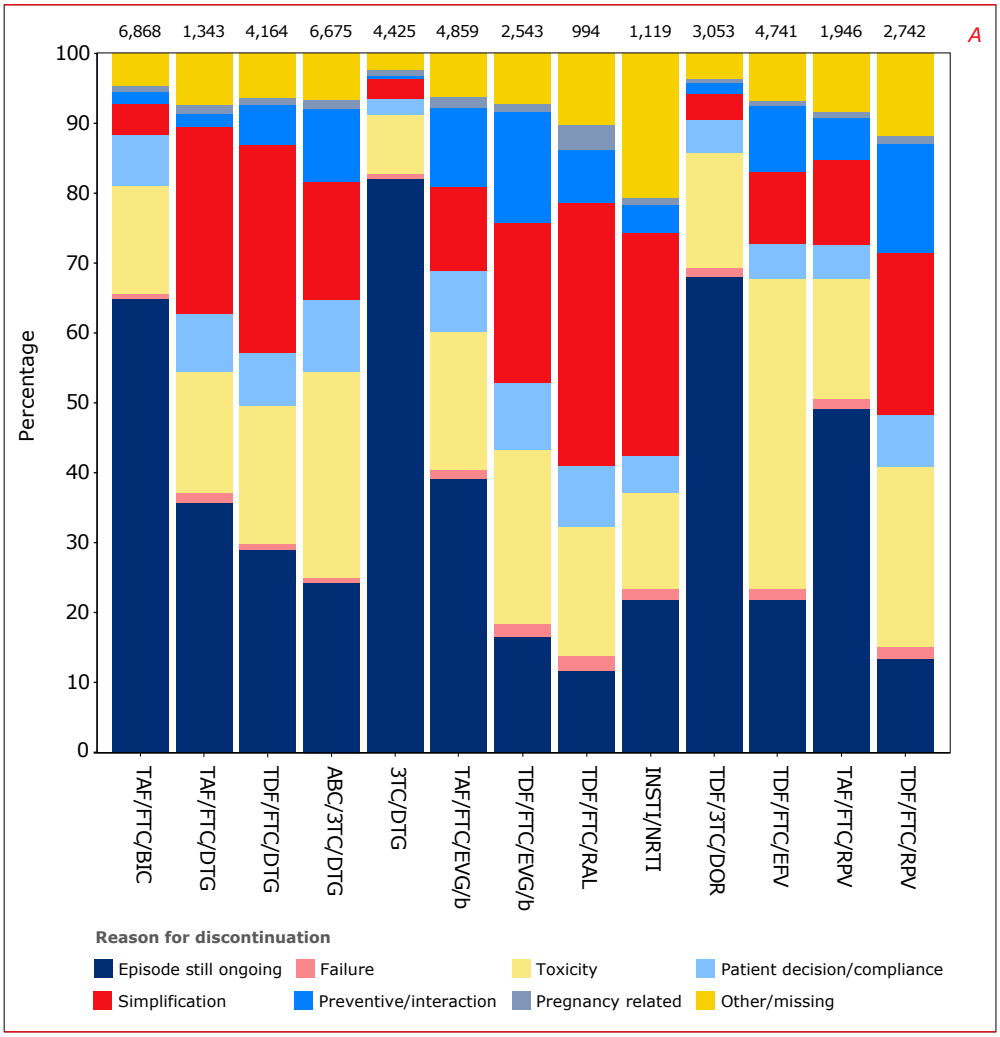
Modification of ART was defined as a change in, or discontinuation of, one or more of the drugs included in the regimen. Simplification to a fixed-drug combination formulation containing the same antiretroviral agents (in the same dose) was not considered a modification of the regimen. Likewise, the breakup of a (more

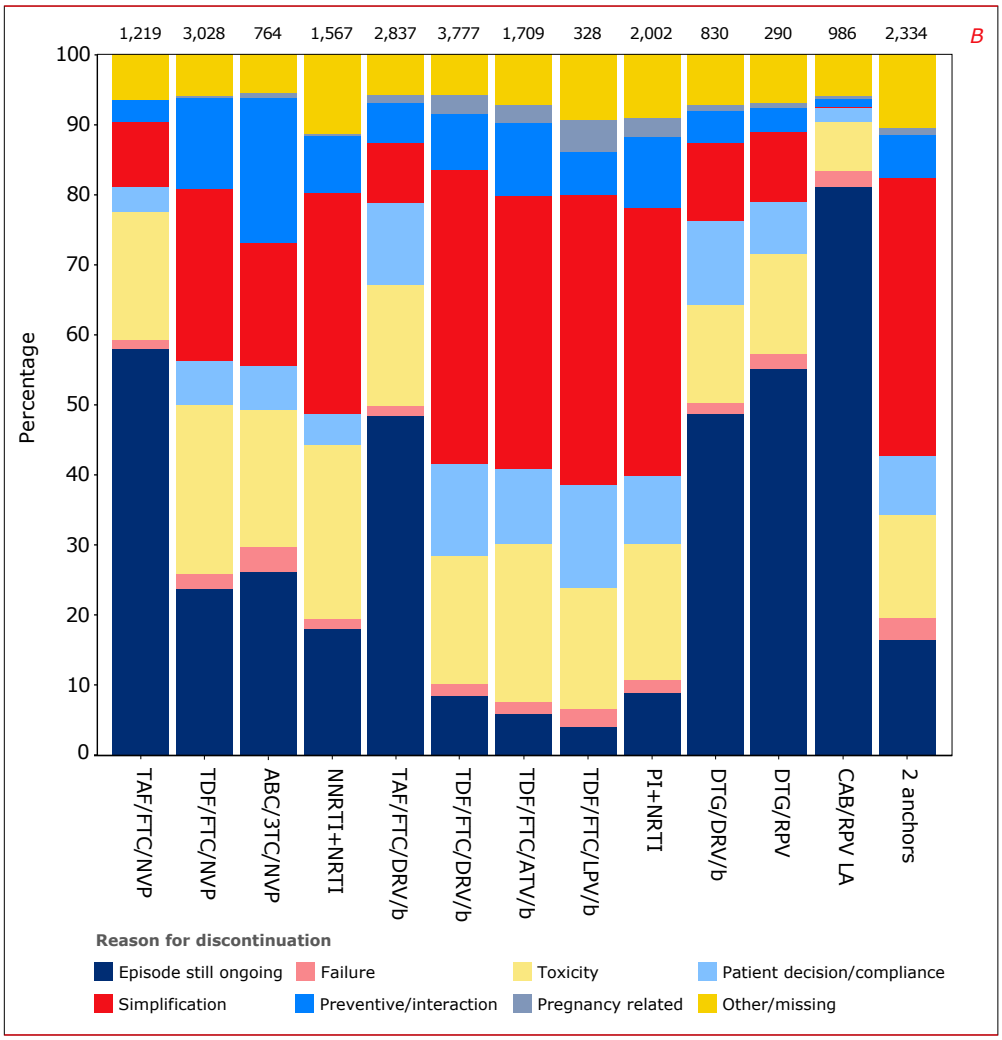
expensive) single tablet regimen (STR) into separately formulated (cheaper) generic components of the original STR, was also not considered a modification. A switch from one pharmacological booster to another was also ignored. We also ignored treatment interruptions that lasted less than 14 days. Whenever an individual became lost to follow-up (e.g. because they moved abroad) this was not considered to be a regimen discontinuation, instead regimens used at the end of available follow-up were categorized as "treatment episode still ongoing".
For each commonly used regimen we report the total number of treatment episodes with that regimen, the cumulative persons years of exposure to that regimen, the frequency of treatment modifications, and the distribution of the reasons for modification of that regimen. The denominator for these analyses is the total number of treatment episodes with any particular regimen (*Table 4.4*).

During the period 2015 to 2024, the cohort of 26,519 individuals on ART accrued a total of 193,960 person years of follow-up, during which a total of 76,730 ART regimen episodes were registered. At the end of the follow-up period in 2024 (but for some individuals follow-up ended earlier, i.e. because they died, moved out of the country, or otherwise became disengaged from HIV care), 32.1% of these regimen episodes were still in use, and 67.9% of the regimen episodes had ended in a regimen modification. The most common reasons for regimen modification were: toxicity (18.8%), treatment simplification (17.2%), patient decision/compliance (7.1%), and preventive modifications (6.7%). In only 1,128 (1.5%) regimens the reported reason for modification was virological treatment failure. Specific reasons for 'preventive modifications' consist of (CVD) risk optimization, prevention of long term renal, bone and metabolic toxicities, drug-drug interactions, (further) weight gain, etc.
Table 4.4 provides these statistics for all commonly used regimen and *Figure 4.8A&B* provides a visual presentation of the same data. However, it should be noted that the average duration of exposure varies greatly for different regimen, which biases cross-regimen comparisons and making them difficult to interpret. Treatment options that have been available for a shorter amount of time, are by virtue of that fact alone more likely to be still in use. *Appendix Table 4.1* provides the rates of the various reasons for treatment modifications for each particular regimen per 1,000 person years of cumulative exposure.

During the period 2015-2024, the overall rate of regimen changes was 236.3 modifications per 1,000 person years of follow-up. This rate peaked in 2016 at 340.3 modifications per 1,000 person years, after which the rate continuously decreased to 206.7 in 2022, 174.2 in 2023, and 125.0 in 2024 (*Figure 4.9*).

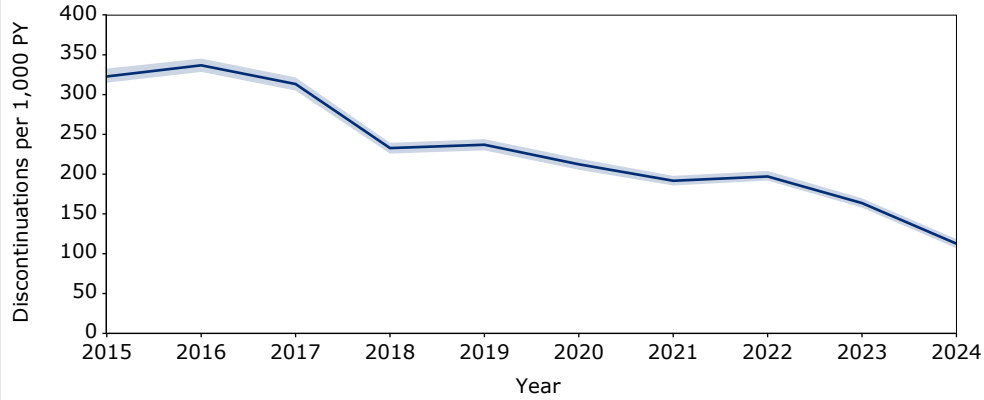
Figure 4.8A&B: Reasons for discontinuation / modification of antiretroviral therapy (ART) used in 2015-2024. The number at the top of each bar represent the total number of treatment episodes with that particular ART regimen.





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

Figure 4.9: Rate of regimen modifications in 2015–2024.



Legend: Blue band represents the 95% confidence interval.

Table 4.4: *Exposure to various ART regimen and reasons for discontinuation / modification in the period 2015–2024.*

	Person years exposure	Total ART episodes	Reasons for discontinuation / modification			
			Episode still ongoing		Failure	
	PY	n	n	%	n	%
Total dataset	193960	76730	24647	32.1	1128	1.5
INSTI + NRTI						
TAF/FTC/BIC	16776	6868	4441	64.7	56	0.8
TAF/FTC/DTG	3760	1343	477	35.5	21	1.6
TDF/FTC/DTG	7059	4164	1198	28.8	44	1.1
ABC/3TC/DTG	22786	6675	1602	24	66	1
DTG/3TC	9783	4425	3624	81.9	41	0.9
TAF/FTC/EVG/b	18727	4859	1889	38.9	71	1.5
TDF/FTC/EVG/b	7001	2543	422	16.6	43	1.7
TDF/FTC/RAL	1959	994	115	11.6	22	2.2
Other INSTI+NRTI	2070	1119	243	21.7	18	1.6
NNRTI + NRTI						
TDF/3TC/DOR	6619	3053	2074	67.9	39	1.3
TDF/FTC/EFV	16912	4741	1028	21.7	76	1.6
TAF/FTC/NVP	5027	1219	706	57.9	17	1.4
TDF/FTC/NVP	12403	3028	718	23.7	66	2.2
ABC/3TC/NVP	3618	764	199	26	28	3.7
TAF/FTC/RPV	7043	1946	955	49.1	27	1.4
TDF/FTC/RPV	8114	2742	365	13.3	51	1.9
Other NNRTI+NRTI	3676	1567	282	18	24	1.5
PI + NRTI						
TDF/FTC/ATV/b	3742	1709	101	5.9	33	1.9
TAF/FTC/DRV/b	7832	2837	1374	48.4	40	1.4
TDF/FTC/DRV/b	7388	3777	319	8.4	71	1.9
TDF/FTC/LPV/b	448	328	13	4	9	2.7
Other PI+NRTI	4131	2002	180	9	35	1.7
2 anchor-drugs						
DTG/DRV/b	2600	830	404	48.7	13	1.6
DTG/RPV	700	290	160	55.2	6	2.1
CAB/RPV injectables	1636	986	800	81.1	22	2.2
2 anchor-drugs w/wo NRTI	4293	2334	382	16.4	81	3.5
Other ART	4324	2346	317	13.5	107	4.6

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

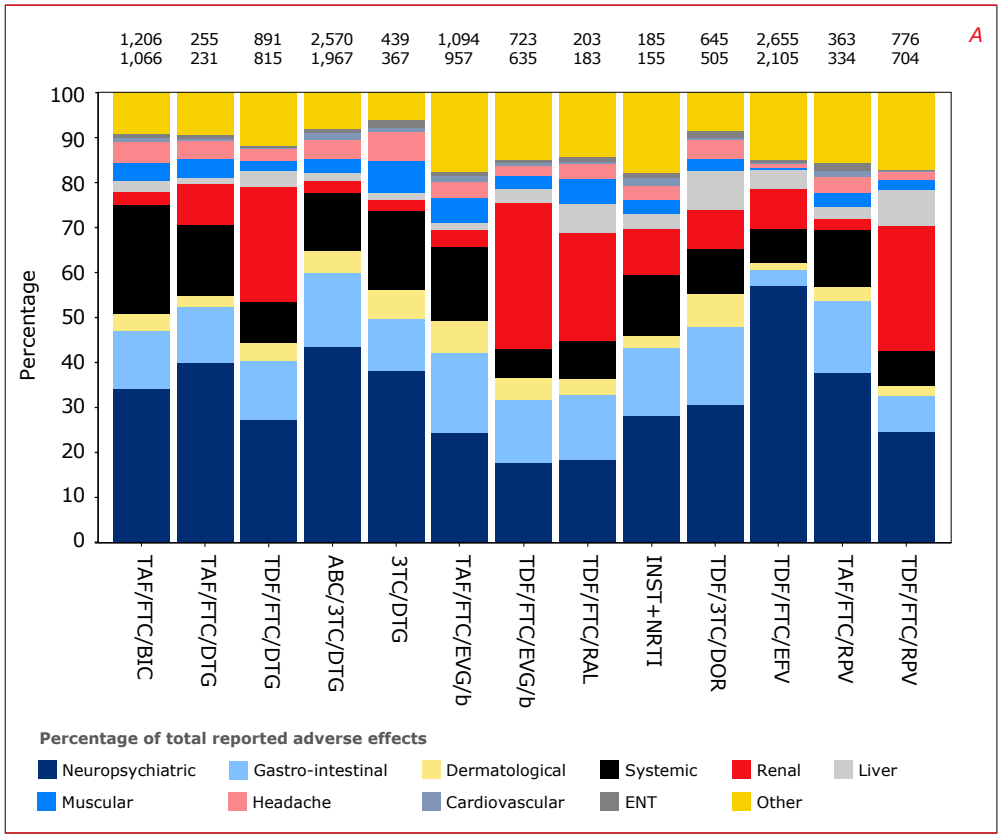
Reasons for discontinuation / modification

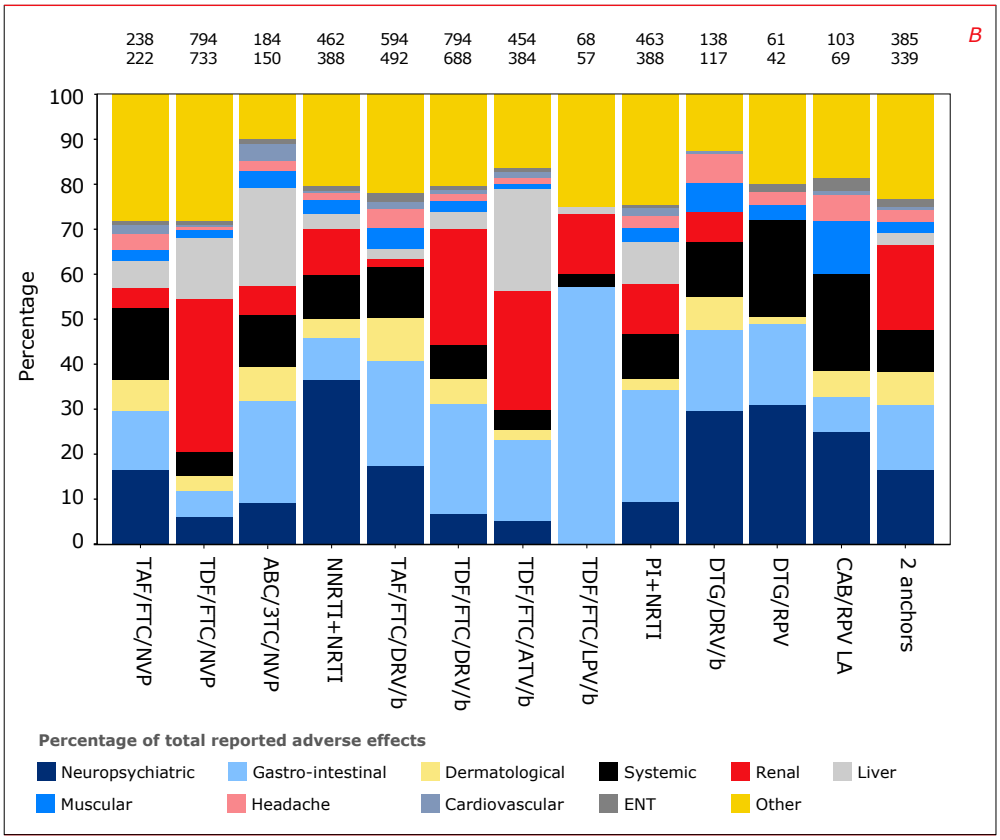
	Toxicity		Patient decision/ compliance		Simplification		Preventive/ interaction		Pregnancy related		Missing / Other reasons	
n	%	n	%	n	%	n	%	n	%	n	%
14428	18.8	5421	7.1	13218	17.2	5111	6.7	796	1	11981	15.6
1066	15.5	509	7.4	300	4.4	120	1.7	57	0.8	319	4.6
231	17.2	113	8.4	359	26.7	27	2	17	1.3	98	7.3
815	19.6	320	7.7	1238	29.7	246	5.9	38	0.9	265	6.4
1967	29.5	685	10.3	1133	17	685	10.3	90	1.3	447	6.7
367	8.3	106	2.4	127	2.9	21	0.5	27	0.6	112	2.5
957	19.7	433	8.9	579	11.9	552	11.4	70	1.4	308	6.3
635	25	242	9.5	583	22.9	405	15.9	25	1	188	7.4
183	18.4	88	8.9	373	37.5	77	7.7	34	3.4	102	10.3
155	13.9	59	5.3	356	31.8	46	4.1	11	1	231	20.6
505	16.5	149	4.9	112	3.7	44	1.4	16	0.5	114	3.7
2105	44.4	239	5	485	10.2	451	9.5	26	0.5	331	7
222	18.2	46	3.8	111	9.1	38	3.1	1	0.1	78	6.4
733	24.2	191	6.3	741	24.5	393	13	11	0.4	175	5.8
150	19.6	49	6.4	134	17.5	156	20.4	5	0.7	43	5.6
334	17.2	98	5	236	12.1	118	6.1	14	0.7	164	8.4
704	25.7	202	7.4	638	23.3	422	15.4	34	1.2	326	11.9
388	24.8	72	4.6	493	31.5	124	7.9	10	0.6	174	11.1
384	22.5	182	10.6	667	39	173	10.1	47	2.8	122	7.1
492	17.3	334	11.8	241	8.5	153	5.4	45	1.6	158	5.6
688	18.2	492	13	1590	42.1	303	8	96	2.5	218	5.8
57	17.4	48	14.6	135	41.2	21	6.4	15	4.6	30	9.1
388	19.4	194	9.7	769	38.4	200	10	59	2.9	177	8.8
117	14.1	100	12	92	11.1	38	4.6	5	0.6	61	7.3
42	14.5	21	7.2	29	10	10	3.4	2	0.7	20	6.9
69	7	20	2	2	0.2	12	1.2	2	0.2	59	6
339	14.5	195	8.4	926	39.7	144	6.2	25	1.1	242	10.4
334	14.2	225	9.6	759	32.4	131	5.6	13	0.6	460	19.6

The nature and severity of (presumed) ART-related toxicities leading to modification of the regimen have changed considerably over time. Because of the availability of a large number of potent and well-tolerated recommended and alternative regimens, with new treatment options becoming available regularly, as well as the very low risk of viral breakthrough following a switch, the threshold for modifying a regimen has become much lower over the years. *Figure 4.10A&B* provides a visual breakdown of the reported ART-related adverse events leading to the modification of the various regimen. As more than one adverse event can be reported for each toxicity-driven regimen modification, the total number of adverse events reported in *Figure 4.10A&B* is greater than the number of regimens.

For the 14,428 toxicity-driven regimen modifications, 16,743 adverse effects were recorded. The predominant adverse effects were: neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression) 31.2%; gastrointestinal (mainly diarrhoea and nausea) 13.7%; renal (renal insufficiency and increased serum creatinine) 12.3%; systemic (tiredness, apathy, loss of appetite, weight gain) 11.2%; liver (increased transaminases) 4.8%; and dermatological (rash due to medication, itching) 4.3%.

Figure 4.10A&B: *Adverse effects resulting in toxicity-related modifications of ART regimen used in the period 2015–2024. The bars represent the distribution of all reported adverse effects, by regimen. The numbers above the bars represent 1) the total number of adverse effects reported as reasons for regimen modification (top row), and 2) the total number of times that particular regimen was modified because of adverse effects (bottom row).*





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

Treatment interruptions

We have analysed treatment interruptions separately from regimen modifications. During the period 2015-2024, the proportion of individuals at any particular time that have interrupted their use of ART has continued to decrease. The proportion of individuals who had started ART at least 6 months ago, who at yearly cross-sectional evaluation of the virological response were observed to have (temporarily) interrupted ART, decreased from 2.1% in 2015 to 0.7% in 2024 (see *Figure 4.11* from the next section on *Virological response*).

During the period 2015-2024, the cohort of 26,519 individuals accrued a total of 193,960 person years of follow-up, in which a total of 76,730 ART regimens were used. In 2,536 individuals a total of 4,176 treatment interruptions (of 14 days or longer) were recorded (*Table 4.5*). However, it must be assumed that many more treatment interruptions have not been disclosed and hence have gone unrecorded in the medical dossier (see also the next paragraph on loss of viral suppression where we show evidence of frequent episodes of loss of viral suppression that resuppress to undetectable levels without a change in the used regimen).
In the majority of the treatment interruptions, it was the patients themselves who interrupted their ART (74.1%), with their treating physicians becoming aware of the interruption only during the next clinic visit. Unfortunately, we cannot with certainty determine from the available data if these treatment interruptions were caused by the circumstances of the patient (e.g. unintentionally running out of medicine while on vacation), or secondly if the patients themselves actively decided to interrupt ART, or thirdly if the interruption was decided on by their treating physician. A further 12.5% of interruptions had ART-associated toxicity as the recorded reason, and 0.8% of interruptions were pregnancy-related.
The median duration of the recorded treatment interruptions was 12.7 (IQR 4.7-31.7) weeks. During many of the longer treatment interruptions the majority of these individuals were effectively temporarily disengaged from care (i.e. they had no visits to the HIV outpatient clinic for more than 6 months). In 65.6% of the interruptions the same regimen as that was used at the start of the treatment interruption was restarted.

We evaluated the median change in CD4 count during treatment interruptions of more than 90 days duration (n=2,088). In 1,018 of these 2,088 treatment interruptions of at least 90 days duration a pre-interruption CD4 count had been measured within 180 days of the start of the interruption (median 478, IQR 280 to 720, cells/mm^3). And in 1,253 episodes there was a CD4 count measured during (and at least 60 days after the start of) the treatment interruption (median 320, IQR 133 to 521 cells/mm^3). For 646 treatment interruptions of more than 90 days, a pre-interruption CD4 count was available and also a CD4 count that had been measured during the interruption. During these 646 interruptions the median change in the CD4 count was -120 (IQR -20 to -440) cells/mm^3.

The treatment interruptions because of pregnancy-related reasons break down into: women who interrupted ART because of a "wish for pregnancy" (n=1), women who interrupted ART during pregnancy (n=5, median duration of interruption 9.4, IQR 3.1-9.7 weeks, in 4 of these 5 episodes one or more viral loads were measured during or shortly after the treatment interruption, in all 4 episodes viremia was detectable with a range from 42 to 1079 copies/ml), and women who interrupted ART after the pregnancy had ended (n=28, median duration of interruption 92, IQR 59-191 weeks). We do not know if these pregnancy-related treatment interruptions were initiated by the treating physicians or if the women themselves decided to interrupt ART.

Table 4.5: *Frequency, duration and reasons for treatment interruptions in the period 2015–2024.*

	Duration of interruption (weeks)			Patients	Total episodes
	Median	Q1	Q3	n	n
Total dataset	12.7	4.7	31.7	2536	4176
INSTI + NRTI					
TAF/FTC/BIC	11.3	4.4	30.4	339	450
TAF/FTC/DTG	16.3	5.0	44.1	65	83
TDF/FTC/DTG	12.8	4.4	32.6	177	234
ABC/3TC/DTG	15.1	5.1	36.7	417	580
DTG/3TC	9.7	4.3	21.6	59	67
TAF/FTC/EVG/b	12.3	4.9	30.1	257	337
TDF/FTC/EVG/b	15.6	6.9	33.7	127	188
TDF/FTC/RAL	10.0	4.3	31.7	53	62
Other INSTI+NRTI	7.9	4.3	17.6	40	46
NNRTI + NRTI					
TDF/3TC/DOR	10.0	4.4	26.0	99	119
TDF/FTC/EFV	13.1	4.7	32.7	165	198
TAF/FTC/NVP	12.9	6.0	25.3	28	31
TDF/FTC/NVP	13.9	5.3	45.0	105	126
ABC/3TC/NVP	8.0	4.9	20.7	28	37
TAF/FTC/RPV	7.9	4.3	19.0	63	85
TDF/FTC/RPV	11.6	4.7	36.9	126	145
Other NNRTI+NRTI	9.0	5.4	25.9	51	59
PI + NRTI					
TDF/FTC/ATV/b	15.2	5.2	40.7	106	136
TAF/FTC/DRV/b	12.6	4.7	30.7	189	283
TDF/FTC/DRV/b	13.1	5.0	37.2	270	348
TDF/FTC/LPV/b	21.6	8.6	34.7	22	29
Other PI+NRTI	13.3	4.4	35.7	110	154
2 anchor-drugs					
DTG/DRV/b	10.8	5.0	25.3	55	66
DTG/RPV	16.0	3.9	24.1	12	17
CAB/RPV injectables	7.1	4.3	10.7	13	13
2 anchor-drugs w/wo NRTI	16.9	5.7	31.7	84	121
Other ART	8.2	4.4	24.6	116	148

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

							Reasons for interruption				Restarted same regimen
	Failure		Toxicity		Patient decision/ compliance		Pregnancy related		Other		
	n	%	n	%	n	%	n	%	n	%	%
	56	1.3	520	12.5	3093	74.1	34	0.8	473	11.3	65.6
	2	0.4	48	10.7	344	76.4	.	.	56	12.4	79.6
	1	1.2	9	10.8	66	79.5	.	.	7	8.4	68.7
	1	0.4	29	12.4	178	76.1	4	1.7	22	9.4	76.1
	2	0.3	87	15.0	421	72.6	.	.	70	12.1	67.8
	.	.	14	20.9	42	62.7	1	1.5	10	14.9	62.7
	6	1.8	53	15.7	242	71.8	.	.	36	10.7	64.7
	4	2.1	19	10.1	146	77.7	1	0.5	18	9.6	61.2
	4	6.5	11	17.7	36	58.1	3	4.8	8	12.9	46.8
	.	.	6	13.0	27	58.7	.	.	13	28.3	47.8
	4	3.4	17	14.3	83	69.7	.	.	15	12.6	67.2
	5	2.5	21	10.6	138	69.7	1	0.5	33	16.7	51.0
	.	.	3	9.7	23	74.2	.	.	5	16.1	54.8
	2	1.6	9	7.1	103	81.7	2	1.6	10	7.9	51.6
	3	8.1	5	13.5	25	67.6	.	.	4	10.8	67.6
	2	2.4	17	20.0	52	61.2	.	.	14	16.5	70.6
	4	2.8	18	12.4	107	73.8	.	.	16	11.0	54.5
	3	5.1	9	15.3	33	55.9	2	3.4	12	20.3	55.9
	.	.	15	11.0	108	79.4	3	2.2	10	7.4	53.7
	2	0.7	34	12.0	218	77.0	.	.	29	10.2	77.4
	2	0.6	35	10.1	283	81.3	5	1.4	23	6.6	57.8
	1	3.4	2	6.9	24	82.8	1	3.4	1	3.4	58.6
	.	.	21	13.6	109	70.8	9	5.8	15	9.7	66.9
	.	.	3	4.5	57	86.4	.	.	6	9.1	84.8
	1	5.9	2	11.8	13	76.5	.	.	1	5.9	70.6
	.	.	4	30.8	4	30.8	.	.	5	38.5	46.2
	3	2.5	7	5.8	98	81.0	.	.	13	10.7	78.5
	4	2.7	22	14.9	105	70.9	1	0.7	16	10.8	56.1

Virological response

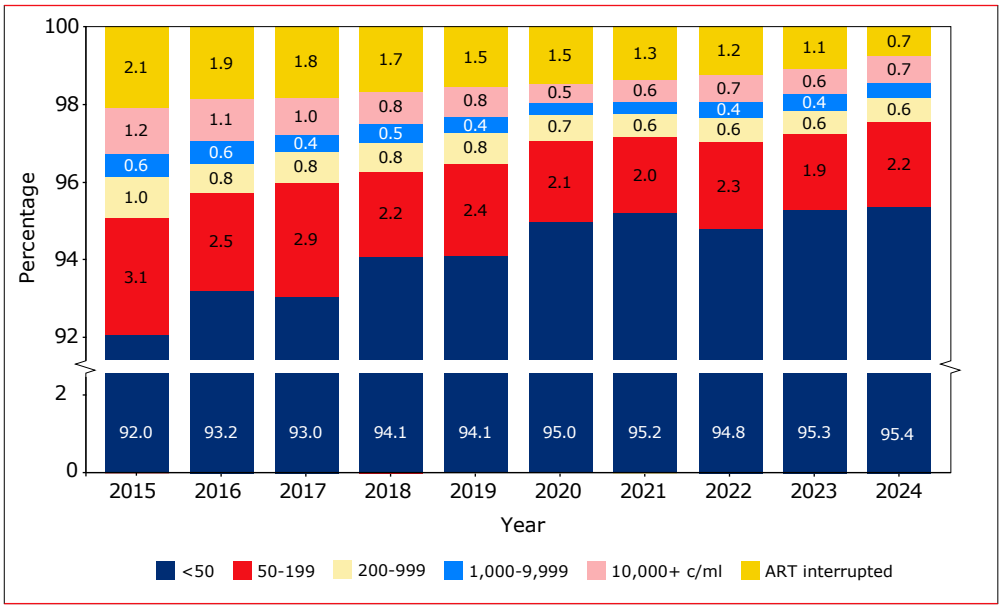
The study population for the analyses in this section consisted of all individuals on ART for more than 6 months who were in care during (part of) the period 2015-2024. For each calendar year between 2015 and 2024 we selected the last measured plasma HIV-RNA load measured in the 24 months prior to 31 December of that year. In the rare cases that no viral load had been measured in the investigated calendar nor in the year prior, that individual was excluded from the analysis of that calendar year.

Viral load measurements were classified into 6 categories: <50 copies/ml ("undetectable", this includes "residual viremia" below 50 copies/ml), 50-199 copies/ml ("low-level viremia", and isolated "blips"), 200-999 copies/ml, 1,000-9,999 copies/ml, and 10,000+ copies/ml (see Box 4.3). If at the moment of the last viral load measurement ART was (temporarily) interrupted this was categorized as a separate category.

Figure 4.11 shows the distribution of the yearly cross-sectional viral load evaluations. During the last 10 years of follow-up, the proportion of individuals on ART for more than 6 months who had a viral load <50 copies/ml increased from 92.0% in 2015 (95.1% <200 copies/ml) to 95.4% (97.5% <200 copies/ml) in 2024. Likewise, all viral load categories higher than 50 copies/ml, decreased slowly over time (the number of analysed viral load measurements and more precise percentages are shown in *Appendix Table 4.2*).

Quantifiable viral loads between 50-199 copies/ml are frequently observed. When a single isolated viral load measurement between 50-199 copies/ml occurs preceded by and followed by viral load measurements <50 copies/ml this is often referred to as a "blip". We investigated which proportion of the population on ART shows signs of sustained low-level viremia, i.e. individuals who had multiple consecutive viral load measurements between 50-199 copies/ml while on ART. We calculated what proportion of all viral load measurements within individuals classifies as low-level viremia, in all 23,211 individuals who had started ART more than 6 months earlier, who had not interrupted ART, and who had at least 5 viral load measurements available for analysis in the period 2015-2024. Of all individuals on ART, 75.4% did not have a single viral load measurement between 50-199 copies/ml. In 16.9% of individuals the proportion of viral load measurements between 50-199 copies/ml was between >0% and 10%. In a further 4.9% this proportion was between >10% and 20% of all viral load measurements. And in 2.8% of all individuals there was evidence of sustained low-level viremia with more than 20% of all their viral load measurements being between 50-199 copies/ml.

Figure 4.11: Yearly cross-sectional analysis of virological treatment response in people on ART for at least 6 months in 2015-2024.



Box 4.3: Definitions of virological response.

Virological response

Viral suppression
HIV viral load below 50 copies/ml in individuals on antiretroviral therapy (ART) for more than six months. This includes residual viremia between 20-50 copies/ml.

The last measured viral load measurement prior to 31 December of each calendar year was included in the analysis, irrespective of (temporary) treatment interruptions.

Viral 'blips'
A single quantifiable viral load measurement between 50-199 copies/ml, preceded by and followed by viral load measurements <50 copies/ml.

Low-level viremia
Two or more consecutive viral load measurements between 50-199 copies/ml.

Loss of viral suppression
Any viral load measurements of at least 200 copies/ml in individuals on ART for more than six months.

Loss of viral suppression

Loss of viral suppression was defined as a viral load measurement of at least 200 copies/ml in individuals on ART for more than six months. We assessed the frequency, magnitude, duration and outcome of all episodes of loss of viral suppression in all individuals on ART for more than 6 months and in care in the period 2015-2024.
Each individual could contribute more than one episode of loss of viral suppression to this analysis. We analysed episodes of loss of viral suppression that occurred during an ART interruption separately from those that occurred while ART had been used continuously. All analyses were stratified for MSM plus transgender people, other men, and women.
In those episodes that occurred while ART use was continued, we investigated whether or not the episode of loss of viral control resolved with or without a change in the ART regimen used. A major limitation is that we have very limited data on adherence. Nevertheless, the maximum viral load measured during

episodes of loss of viral control is much higher (4.5 log10 copies/ml) in those individuals who were known to have discontinued ART compared to individuals who indicated to still use ART (3.0 log10 copies/ml).

A total of 26,449 individuals contributed 199,650 person years of follow-up during the period 2015-2024 (*Table 4.6*). In 4,262 individuals there were 6,827 episodes of loss of viral suppression: in 1,652 individuals there were 2,119 episodes of the loss of viral suppression during a treatment interruption, and in 3,206 individuals there were 4,708 episodes while the subject was continuing the use of ART.

The duration of loss of viral suppression during treatment interruption was less than 0.5 years in 80.4% (n=1,704) of episodes, 6.7% (n=142) lasted between 0.5 and <1.0 years, and 12.9% (n=273) lasted more than 1 year. At the end of the follow-up period investigated, 89.6% (n=1,898) of these episodes had resolved after restarting ART (with the same or a different ART regimen), while 7.8% (n=165) of these episodes were still ongoing, and 2.6% (n=56) of these episodes ended in death, with advanced HIV / AIDS-defining conditions as the predominant cause of death in 39.3% (n=22) of cases, which is a much higher proportion compared to the distribution of the causes of death in the overall population in HIV care in the Netherlands (see Chapter 6 on Morbidity and mortality of this Monitoring Report). Compared to the group of MSM and transgender people, the other men, and even more so the women, are overrepresented among those with loss of viral suppression because of treatment interruption.

The large majority (72.3%) of 4,708 episodes of loss of viral suppression that occurred while ART was assessed to have been used continuously, consisted of a single viral load measurement above 200 copies/ml, 17.5% of these episodes consisted of 2 or more consecutive viral loads above 200 copies/ml but lasted <0.5 years, 4.8% lasted between 0.5 and <1.0 years, and 5.4% lasted more than 1 year. In total, 92.4% of episodes had been resolved at the end of the end of follow-up, in 72.1% of episodes without a modification of the used ART regimen, and 20.3% resolved after a regimen modification. 6.5% of episodes were still ongoing at the end of follow-up, and 1.2% (n=56) of these episodes ended in death, again with death because of an advanced-HIV / AIDS-defining condition as the predominant (33.9%, n=19) cause of death.
Compared to the group of MSM and transgender people, the other men, and even more so the women, are strongly overrepresented among those with loss of viral suppression. Women also more often modified their ART regimen before the episode of loss of viral control resolved.

Table 4.6: Occurrence of loss of viral suppression during 2015–2024 in individuals on ART for more than 6 months.

	All		MSM + TG		Other men		Women	
Total cohort on ART								
N of subjects	26,449		16,724		4,973		4,752	
PY of follow-up	199,650		128,175		35,102		36,372	
Subjects with failure	4,262		2,080		1,031		1,153	
N of episodes of failure	6,827		2,990		1,721		2,116	
Loss of viral suppression because of ART interruption								
N of subjects	1,652		758		392		502	
N of episodes	2,119		953		509		657	
Duration of failure, n/%								
Single VL measurement	1265	59.7	564	59.2	319	62.7	382	58.1
<0.5 year	439	20.7	202	21.2	119	23.4	118	18.0
0.5 – <1 year	142	6.7	68	7.1	22	4.3	52	7.9
1 – <2 years	129	6.1	57	6.0	29	5.7	43	6.5
2+ years	144	6.8	62	6.5	20	3.9	62	9.4
Highest viral load, log10 median	4.5		4.5		4.7		4.4	
Q1–Q3	3.8–5.2		3.9–5.2		4.0–5.3		3.6–5.0	
Outcome, n/%								
Ongoing	165	7.8	76	8.0	41	8.1	48	7.3
Restarted, resolved	1898	89.6	852	89.4	449	88.2	597	90.9
Died while still off ART	56	2.6	25	2.6	19	3.7	12	1.8
Cause of death, n / %								
Advanced HIV / AIDS	22	39.3	9	36.0	8	42.1	5	41.7
Non-AIDS malignancies	7	12.5	2	8.0	3	15.8	2	16.7
Cardiovascular disease	3	5.4	2	8.0	1	5.3	.	.
Non-AIDS infection	1	1.8	.	.	1	5.3	.	.
Liver disease	3	5.4	1	4.0	2	10.5	.	.
Lung disease	6	10.7	2	8.0	2	10.5	2	16.7
Non-natural death	1	1.8	1	4.0	.	.	.	.
Alcohol and substance use	3	5.4	2	8.0	.	.	1	8.3
Other causes	2	3.6	1	4.0	1	5.3	.	.
Unknown	6	10.7	4	16.0	.	.	2	16.7
Sudden death	2	3.6	1	4.0	1	5.3	.	.

	All		MSM + TG		Other men		Women	
Loss of viral suppression while on ART								
N of subjects	3,206		1,542		798		866	
N of episodes	4,708		2,037		1,212		1,459	
Duration, n/%								
Single VL measurement	3406	72.3	1514	74.3	871	71.9	1021	70.0
<0.5 year	822	17.5	345	16.9	215	17.7	262	18.0
0.5 – 1 year	225	4.8	88	4.3	52	4.3	85	5.8
1 – 2 years	138	2.9	51	2.5	42	3.5	45	3.1
2+ years	117	2.5	39	1.9	32	2.6	46	3.2
Highest viral load during episode,	3.0		2.8		3.0		3.2	
median, Q1-Q3	2.5-3.9		2.5-3.6		2.6-4.1		2.6-4.1	
Outcome, n/%								
Resolved, no switch	3395	72.1	1502	73.7	870	71.8	1023	70.1
Ongoing, no switch	257	5.5	124	6.1	77	6.4	56	3.8
Resolved, switched	955	20.3	377	18.5	237	19.6	341	23.4
Ongoing, switched	45	1.0	16	0.8	9	0.7	20	1.4
Died, no switch	31	0.7	9	0.4	9	0.7	13	0.9
Died, switched	25	0.5	9	0.4	10	0.8	6	0.4
Cause of death, n/%								
Advanced HIV / AIDS	19	33.9	6	33.3	7	36.8	6	31.6
Non-AIDS malignancies	11	19.6	2	11.1	4	21.1	5	26.3
Cardiovascular disease	2	3.6	.	.	.	.	2	10.5
Non-AIDS infection	3	5.4	2	11.1	.	.	1	5.3
Liver disease	.	.	.	.	.	.	.	.
Lung disease	.	.	.	.	.	.	.	.
Non-natural death	1	1.8	.	.	1	5.3	.	.
Alcohol and substance use	2	3.6	1	5.6	.	.	1	5.3
Other causes	2	3.6	1	5.6	1	5.3	.	.
Unknown	7	12.5	3	16.7	3	15.8	1	5.3

Legend: *MSM = men who have sex with men; TG = transgender people; PY = person years; ART = antiretroviral therapy; VL = viral load.*

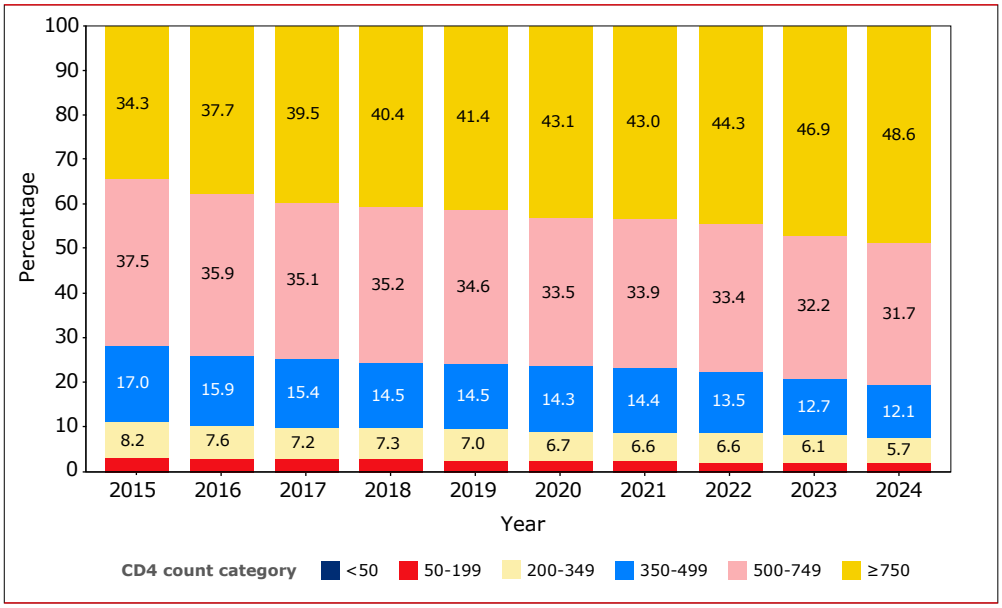
Immunological response

After initiation of ART, most people get durably suppressed plasma HIV RNA to levels below <50 copies/ml, and this is accompanied by recovery of the CD4 count. Failure to durably suppress HIV replication is associated with poorer recovery of the CD4 count[18,19]. In case of frequent and/or prolonged loss of viral suppression, HIV disease progression can develop with a significant decrease of the CD4 count and the occurrence of opportunistic diseases. However, even in the setting of prolonged viral suppression, a protracted and/or incomplete recovery of the CD4 count (i.e. a CD4 count persistently below 350 cells/mm^3) may still occur. This is a situation reported to be associated with an increased risk of progression to AIDS and development of non-AIDS-defining diseases[20]. Median CD4 counts in men without HIV are on average approximately 830 cells/mm^3 and around 1,000 cells/mm^3 in women, but this varies according to factors such as age, ethnicity, and smoking behaviour[21,22]. The level of recovery of the immune system is strongly correlated to the risk for adverse health outcomes, i.e. morbidity and mortality because of AIDS-defining and other clinical events (also see *Chapter 5*)[23-27].

Immunological response by calendar year

Of all individuals who were on ART in the period 2015-2024, CD4 count data are shown in *figures 4.12*. The percentage of individuals on ART with a normalised CD4 count (i.e. with a CD4 count over 500 cells/mm^3) increased from 72.8% in 2015 to 80.3% in 2024. The percentage of individuals on ART with CD4 counts below 350 cells/mm^3 slowly continued to decrease from 11.2% in 2015 to 7.5% in 2024. These favourable changes in the distribution of the CD4 count in the treated population is a consequence of 1) the current guidelines recommending ART initiation as soon as possible after HIV diagnosis and irrespective of the CD4 count, 2) a more pronounced immune recovery with longer ART use, 3) increasing virological suppression rates, and 4) attrition by the higher mortality rates in individuals with low CD4 counts.

Figure 4.12: Last available CD4 count of the population on ART by calendar year (missing measurements/data were not taken into account).



Immunological response after ART initiation (2015–2020)

The distribution of pre-ART CD4 counts in ART-naïve individuals initiating first-line ART has remained fairly constant in the period between 2015 and 2024 (*Figure 4.13*). In 2024, 24.6% of individuals initiating ART had a CD4 count below 200 cells/mm^3, and another 18.6% had a CD4 count between 200 and <350 cells/mm^3. This distribution closely resembles the CD4 counts at HIV diagnosis (see Chapter 1).

We also assessed the immunological response in individuals who started first-line ART between in 2015-2019 to allow for a potential duration of follow-up of 5 years. The level of viral suppression after initiating ART were not taken into account in this analysis, but are generally very high. Nor were temporary treatment interruptions taken into account. The changes in the CD4 count distribution following ART initiation are visualized in *Figure 4.14A*. Whereas at the initiation of ART 24.7% of individuals had a CD4 count below 200 cells/mm^3 and 18.0% had a CD4 count between 200 and <350 cells/mm^3, these proportions had decreased after 5 years of ART to 1.6% with a CD4 count below 200 cells/mm^3 and 6.1% between 200 and <350 cells/mm^3.

The speed and magnitude of the changes of the CD4 count after ART initiation strongly depend on the pre-ART CD4 count. The heatmap in *Figure 4.14B* shows the 5-year evolution of the CD4 count distribution stratified by the baseline CD4 count. The CD4 count distributions in all pre-ART CD4 count strata show favourable changes over time, but fail to converge even after 5 years of ART. Virtually all individuals who initiate ART while in the higher CD4 count strata remain in these higher strata, or increase their CD4 counts even further. The vast majority of individuals who initiate ART in the lower CD4 count strata have reached the higher CD4 count strata after 5 years of ART: only 10.5% of individuals who initiate ART with a CD4 below 50 remain below 200 after 5 years of ART, and only 3.0% of individuals who initiate ART with a CD4 between 50 and <200 remain below 200 after 5 years of ART. A limitation of this analysis is that attrition because of increased mortality in those who fail to increase their CD4 count is not taken into account.

Figure 4.13: *The pre-ART CD4 count in ART-naïve individuals initiating first-line ART by calendar year (missing measurements/data were not taken into account).*

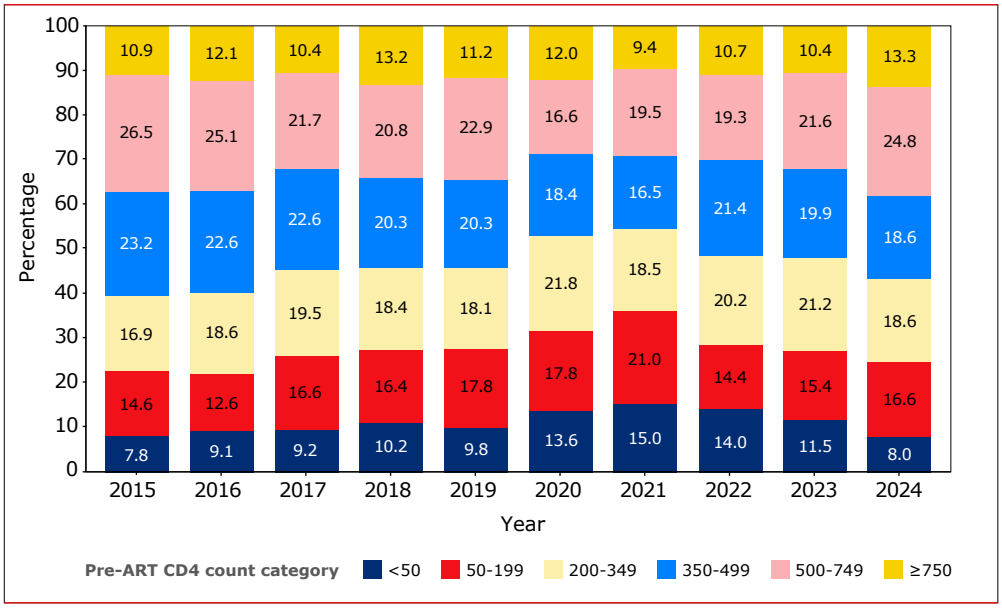
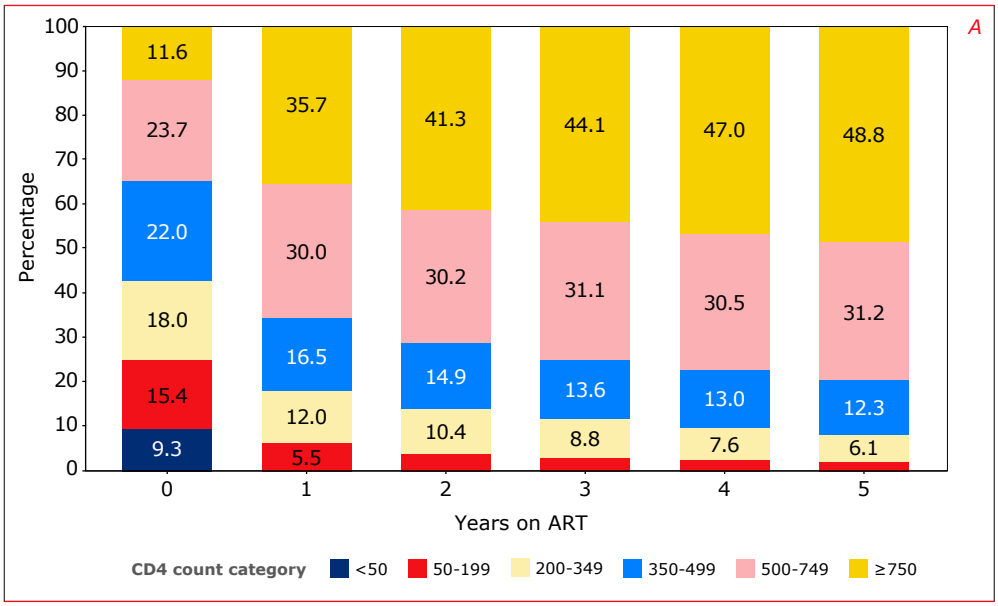


Figure 4.14A&B: *Changes in CD4 count distribution over 5 years following the start of antiretroviral therapy (ART) in 2015–2019 (A) and stratified for the last measured CD4 count prior to start of ART (B).*



B

CD4 count category

	<50					
750+		0.5	2.1	3.0	5.2	9.1
500-749		4.7	11.1	18.3	19.4	22.1
350-499		16.6	26.6	26.9	30.3	27.3
200-349		40.3	38.5	36.0	32.8	30.9
50-199		35.3	20.6	15.1	11.5	9.9
<50	100	2.6	1.1	0.8	0.8	0.6

	50-199					
750+		2.3	5.3	7.2	9.8	12.2
500-749		16.3	23.4	28.9	32.6	34.4
350-499		30.2	31.7	31.9	31.1	33.6
200-349		36.8	33.1	26.6	22.8	16.8
50-199	100	13.9	6.2	4.9	3.3	2.7
<50		0.5	0.3	0.5	0.3	0.3

	200-349					
750+		13.6	20.9	23.5	29.0	33.9
500-749		41.7	45.5	48.7	47.2	46.3
350-499		31.3	23.6	20.4	18.4	16.0
200-349	100	13.2	9.4	7.0	4.8	3.4
50-199		0.3	0.5	0.3	0.5	0.4
<50		0.0	0.0	0.1	0.0	0.0

	350-499					
750+		36.7	44.8	47.7	52.9	54.5
500-749		43.7	41.3	41.9	38.0	38.0
350-499	100	18.3	12.6	8.9	7.8	6.3
200-349		1.1	0.8	1.0	1.1	0.9
50-199		0.2	0.1	0.4	0.2	0.3
<50		0.0	0.4	0.1	0.0	0.0

	500-749					
750+		59.4	66.1	71.5	71.5	71.2
500-749	100	37.9	31.1	25.3	25.4	26.1
350-499		2.4	2.4	2.6	2.3	2.1
200-349		0.1	0.2	0.3	0.4	0.3
50-199		0.2	0.2	0.1	0.3	0.3
<50		0.0	0.0	0.1	0.1	0.0

	750+					
750+	100	91.9	92.6	91.0	92.6	90.8
500-749		7.1	6.6	8.2	6.6	8.1
350-499		0.2	0.4	0.6	0.6	0.8
200-349		0.2	0.2	0.2	0.2	0.2
50-199		0.4	0.2	0.0	0.0	0.0
<50		0.2	0.0	0.0	0.0	0.0

0 1 2 3 4 5 | 0 1 2 3 4 5

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

Summary and conclusions

Starting ART and the initial regimen

- Between 2015 and 2024, 7,069 newly diagnosed individuals aged 15 years and older entered into HIV care in the Netherlands and initiated first-line ART.
- Rapid initiation of ART following a diagnosis of HIV infection, irrespective of CD4 count, has generally resulted in a shorter median time to initiation of ART following diagnosis, which was 16 (IQR 7-29) days in 2024.
- Between 2015 and 2021 there was a slowly decreasing trend in the CD4 count at ART initiation. However, since 2022 the CD4 count at the start of ART has risen slightly again. In 2024, 24.6% of individuals initiating ART had a CD4 count below 200 cells/mm^3, and another 18.6% had a CD4 count between 200 and <350 cells/mm^3. Immunological recovery was much better when ART was started at a higher CD4 count.
- In 2024, 89.9% of initial regimens contained an integrase inhibitor. In 2024, the most frequently used initial regimens were TDF/FTC/dolutegravir (38.3%), TAF/FTC/bictegravir (37.5%), and TDF/3TC/doravirine (7.4%).

In care and receiving ART in 2024

- The number of people on ART and in active follow-up in the ATHENA cohort grew from 17,202 individuals in 2015 to 22,215 individuals in 2024.
- In 2024, the vast majority (87.8%) of individuals received a regimen based on one or two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with an integrase inhibitor (57.5%), a non-nucleoside reverse transcriptase inhibitor (25.5%) or a protease inhibitor (7.9%).
- Long-acting injectables (cabotegravir/rilpivirine) were used by 3.4%.
- The population had been diagnosed with HIV a median of 14.7 (IQR 8.9-21.0) years ago, and started their first-line ART regimen a median of 12.6 (IQR 8.0-18.5) years ago.
- Their last measured viral load was <50 copies/ml in 95.6% (<200 copies/ml in 98.0%), and 80.3% had a last measured CD4 count of 500 cells/mm^3 or higher.
- ART regimens were modified often, with the most common reasons for regimen modification being (mostly mild) toxicity (18.8%), treatment simplification (17.2%), patient decision/compliance (7.1%), and preventive modifications (6.7%). In only 1,128 (1.5%) regimen the reported reason for modification was virological treatment failure. The rate of ART regimen modifications continues to decrease over time from a peak of 340.3 modifications per 1,000 person years of follow-up in 2016 to 206.7 in 2022, 174.2 in 2023, and 125.0 in 2024.

- The proportion of the treated population that at any moment has temporarily interrupted ART continues to decrease, from 2.1% in 2015 to 0.7% in 2024, indicating the improved ease of use and tolerability of modern ART regimen.
- In 2,536 individuals a total of 4,176 treatment interruptions (of 14 days or longer) were recorded. The median duration of the recorded treatment interruptions was 12.7 (IQR 4.7-31.7) weeks. Many long interruptions constitute temporary disengagement from care. During longer treatment interruptions the CD4 counts often drops significantly, and is strongly associated with death due to advanced HIV/AIDS.

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Appendix

Appendix Table 4.1: *Frequency of and reasons for discontinuation / modification of various ART regimen in the period 2015–2024.*

				Stop reasons (n & rate per 1,000PY)			
					Failure		Toxicity
Calendar year	Exposure (PY)	Total episodes (N)	Ongoing episodes (n)	(n)	(rate)	(n)	(rate)
INSTI + NRTI							
TAF/FTC/BIC	16776	6868	4441	56	3.3	1066	63.5
TAF/FTC/DTG	3760	1343	477	21	5.6	231	61.4
TDF/FTC/DTG	7059	4164	1198	44	6.2	815	115.4
ABC/3TC/DTG	22786	6675	1602	66	2.9	1967	86.3
DTG/3TC	9783	4425	3624	41	4.2	367	37.5
TAF/FTC/EVG/b	18727	4859	1889	71	3.8	957	51.1
TDF/FTC/EVG/b	7001	2543	422	43	6.1	635	90.7
TDF/FTC/RAL	1959	994	115	22	11.2	183	93.4
Other INSTI+NRTI	2070	1119	243	18	8.7	155	74.9
NNRTI + NRTI							
TDF/3TC/DOR	6619	3053	2074	39	5.9	505	76.3
TDF/FTC/EFV	16912	4741	1028	76	4.5	2105	124.5
TAF/FTC/NVP	5027	1219	706	17	3.4	222	44.2
TDF/FTC/NVP	12403	3028	718	66	5.3	733	59.1
ABC/3TC/NVP	3618	764	199	28	7.7	150	41.5
TAF/FTC/RPV	7043	1946	955	27	3.8	334	47.4
TDF/FTC/RPV	8114	2742	365	51	6.3	704	86.8
Other NNRTI+NRTI	3676	1567	282	24	6.5	388	105.5
PI + NRTI							
TDF/FTC/ATV/b	3742	1709	101	33	8.8	384	102.6
TAF/FTC/DRV/b	7832	2837	1374	40	5.1	492	62.8
TDF/FTC/DRV/b	7388	3777	319	71	9.6	688	93.1
TDF/FTC/LPV/b	448	328	13	9	20.1	57	127.1
Other PI+NRTI	4131	2002	180	35	8.5	388	93.9
2 anchor-drugs							
DTG/DRV/b	2600	830	404	13	5.0	117	45.0
DTG/RPV	700	290	160	6	8.6	42	60.0
CAB/RPV LA	1636	986	800	22	13.4	69	42.2
2 anchors w/wo NRTI	4293	2334	382	81	18.9	339	79.0

Legend: *PY = person years of exposure; 3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LA = long acting; 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.*

Stop reasons (n & rate per 1,000PY)									
Patient choice		Simplification		Prevention		Pregnancy		Other reasons	
(n)	(rate)	(n)	(rate)	(n)	(rate)	(n)	(rate)	(n)	(rate)
509	30.3	300	17.9	120	7.2	57	3.4	319	19.0
113	30.1	359	95.5	27	7.2	17	4.5	98	26.1
320	45.3	1238	175.4	246	34.8	38	5.4	265	37.5
685	30.1	1133	49.7	685	30.1	90	3.9	447	19.6
106	10.8	127	13.0	21	2.1	27	2.8	112	11.4
433	23.1	579	30.9	552	29.5	70	3.7	308	16.4
242	34.6	583	83.3	405	57.8	25	3.6	188	26.9
88	44.9	373	190.4	77	39.3	34	17.4	102	52.1
59	28.5	356	171.9	46	22.2	11	5.3	231	111.6
149	22.5	112	16.9	44	6.6	16	2.4	114	17.2
239	14.1	485	28.7	451	26.7	26	1.5	331	19.6
46	9.2	111	22.1	38	7.6	1	0.2	78	15.5
191	15.4	741	59.7	393	31.7	11	0.9	175	14.1
49	13.5	134	37.0	156	43.1	5	1.4	43	11.9
98	13.9	236	33.5	118	16.8	14	2.0	164	23.3
202	24.9	638	78.6	422	52.0	34	4.2	326	40.2
72	19.6	493	134.1	124	33.7	10	2.7	174	47.3
182	48.6	667	178.3	173	46.2	47	12.6	122	32.6
334	42.6	241	30.8	153	19.5	45	5.7	158	20.2
492	66.6	1590	215.2	303	41.0	96	13.0	218	29.5
48	107.1	135	301.1	21	46.8	15	33.5	30	66.9
194	47.0	769	186.1	200	48.4	59	14.3	177	42.8
100	38.5	92	35.4	38	14.6	5	1.9	61	23.5
21	30.0	29	41.4	10	14.3	2	2.9	20	28.6
20	12.2	2	1.2	12	7.3	2	1.2	59	36.1
195	45.4	926	215.7	144	33.5	25	5.8	242	56.4

Appendix Table 4.2: *Virological treatment response in 2015–2024 in people who started ART at least months earlier.*

	Total population	Viral load categories (c/ml)											
			<50	50–199		200–999		1,000–9,999		10,000+		ART interrupted	
Calendar year	N	N	%	N	%	N	%	N	%	N	%	N	%
2015	17,935	16,504	92.02	550	3.07	188	1.05	107	0.60	212	1.18	374	2.09
2016	18,733	17,457	93.19	471	2.51	147	0.78	112	0.60	199	1.06	347	1.85
2017	19,425	18,074	93.05	571	2.94	155	0.80	81	0.42	187	0.96	357	1.84
2018	20,114	18,919	94.06	439	2.18	156	0.78	100	0.50	163	0.81	337	1.68
2019	20,728	19,499	94.07	499	2.41	162	0.78	89	0.43	160	0.77	319	1.54
2020	21,134	20,072	94.97	441	2.09	144	0.68	65	0.31	102	0.48	310	1.47
2021	21,358	20,329	95.18	418	1.96	135	0.63	59	0.28	130	0.61	287	1.34
2022	21,900	20,755	94.77	493	2.25	139	0.63	92	0.42	156	0.71	265	1.21
2023	22,353	21,301	95.29	435	1.95	136	0.61	91	0.41	145	0.65	245	1.10
2024	22,604	21,555	95.36	492	2.18	145	0.64	88	0.39	160	0.71	164	0.73