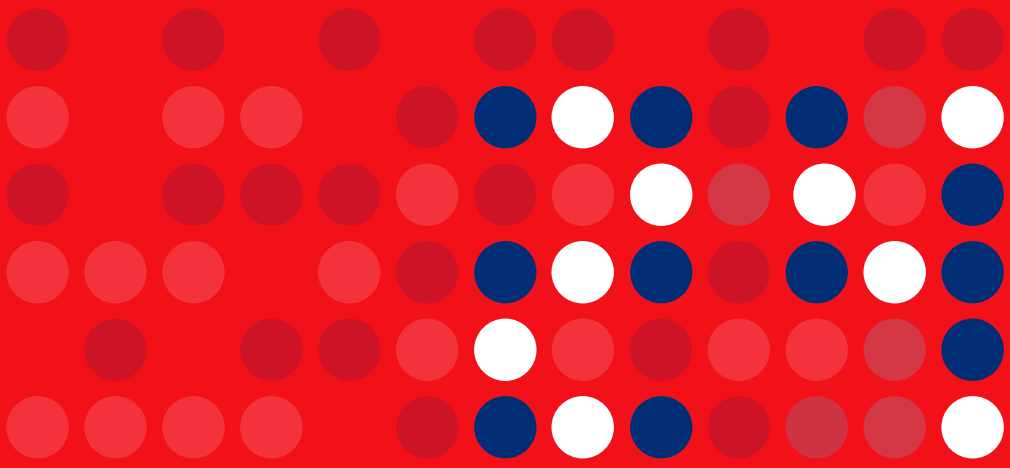
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2024

Chapter 4: Response to antiretroviral therapy



4. Response to antiretroviral therapy

Ferdinand Wit, Anders Boyd, Ard van Sighem, Kees Brinkman, Kees van Nieuwkoop, Anne Wensing, Marc van der Valk

Introduction

The primary goals of antiretroviral therapy (ART) are to prevent HIV disease progression, improve clinical outcomes, and prevent onward 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 including genotypic resistance testing) has been completed. The decision to initiate ART should always include consideration of a person's comorbid conditions and 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[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 onward 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 onward 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 good adherence to treatment.

The use of guideline-recommended ART regimen generally results in sustained suppression of HIV viral to undetectable levels. However, in the setting or repeated and/or prolonged episodes of loss of viral suppression while on ART, the used antiretroviral agents continue to exert selective pressures that may result in the selection of viral strains harbouring drug resistance-associated mutations. Over time, further accumulation of resistance-associated mutations in the HIV genome can occur, thereby increasing the risk of poor clinical outcomes[16-22].

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[23]. We also analyse the presence of transmitted and acquired HIV drug resistance.

Starting antiretroviral therapy

In total, 7,860 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 2014 and December 2023. 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. In *Table 4.1*, we have grouped people by calendar year of ART initiation: 5,299 started in 2014-2018, 682 in 2019, 509 in 2020, 452 in 2021, 470 in 2022, and 448 in 2023. 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 7,860 people known to have initiated ART since January 2014, 4,993 (63.5%) were men who have sex with men (MSM), 1,532 (19.5%) other men, 1,180 (15.0%) women, and 155 (2.0%) were transgender people. Overall, 4,479 (57.0%) originated from the Netherlands. The proportion of people born in the Netherlands has been steadily declining: from 60.8% in 2014-2018, to 51.2% in 2019, 51.5% in 2020, 49.3% in 2021, 47.4% in 2022, to 45.1% in 2023. There was a steady increase in the proportion of people born in eastern and central Europe (in recent years predominantly from Ukraine); from 5.8% in 2014-2018, to 14.7% in 2023. 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 42 days (interquartile range [IQR] 22-99) for those who entered care in 2014, to 25 (IQR 14-40) in 2018, to 19 (IQR 11-31) days in 2023. 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 (93.4% in 2023). People originating from sub-Saharan Africa, the Caribbean, north Africa and the middle East, and eastern Europe were overrepresented among those starting more than 1 month after HIV diagnosis. The delay between a positive HIV test result and initiating ART was mostly driven by a longer period between HIV diagnosis and being linked to care in an HIV treatment center.

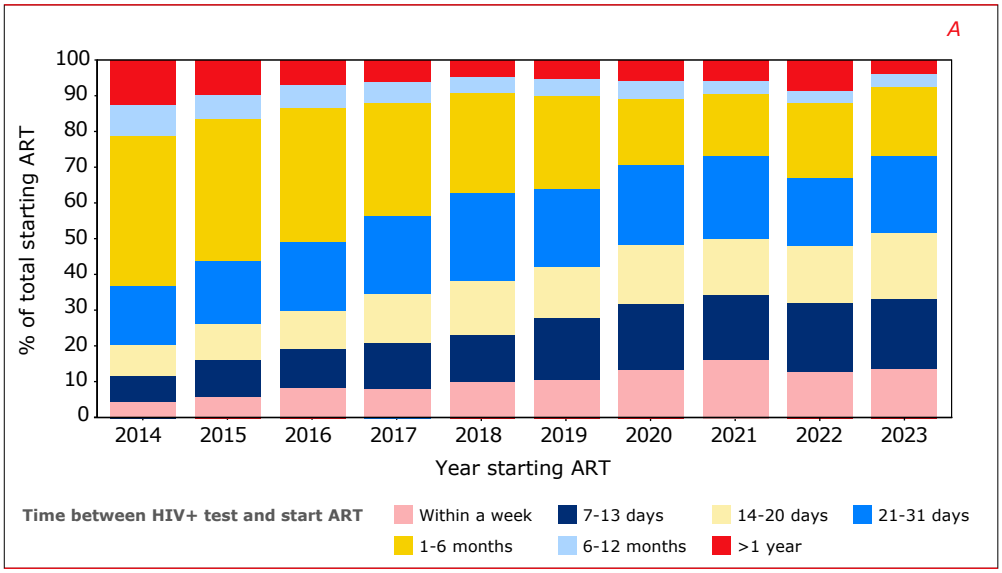
Table 4.1 Characteristics of people starting antiretroviral therapy in 2014–2023.

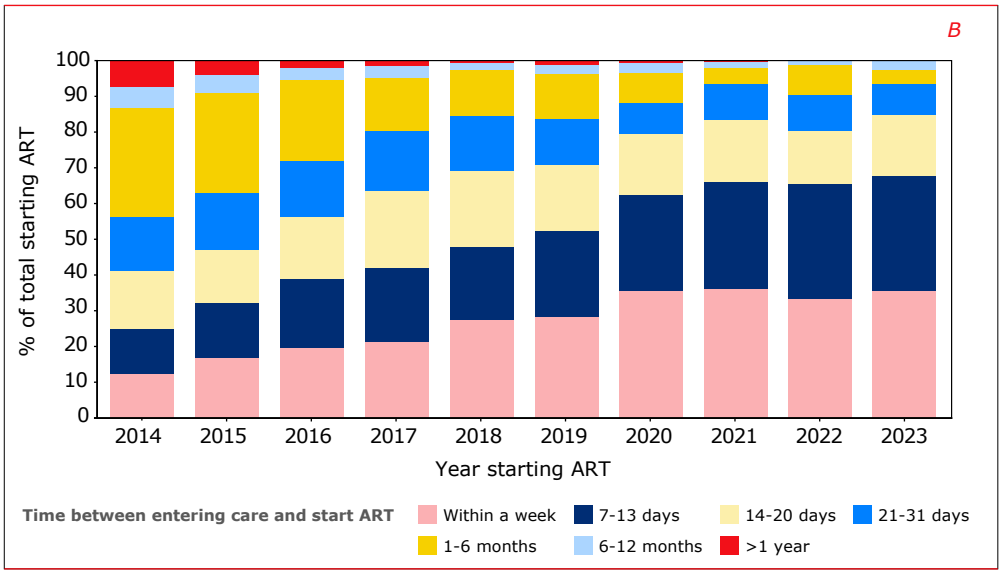
Year of ART initiation		**2014–2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2014–2023**
Number of individuals		5,299	682	509	452	470	448	7,860
DEMOGRAPHICS								
Age at ART initiation (years)	Median	39.4	39.3	39.2	40	39.6	38.8	39.4
	Q1–Q3	30.3–49.5	30–49.7	30.2–50.3	31.3–52.3	31.4–51.3	30.6–50.5	30.4–50
Male sex (at birth)	n	4582	557	417	377	375	367	6,675
	%	86.5	81.7	81.9	83.4	79.8	81.9	84.9
HIV acquisition group								
MSM	n	3,576	383	287	263	237	247	4,993
	%	67.5	56.2	56.4	58.2	50.4	55.1	63.5
Other men	n	930	159	110	100	123	110	1,532
	%	17.6	23.3	21.6	22.1	26.2	24.6	19.5
Women	n	717	123	92	73	95	80	1,180
	%	13.5	18	18.1	16.2	20.2	17.9	15
Transgender people	n	76	17	20	16	15	11	155
	%	1.4	2.5	3.9	3.5	3.2	2.5	2
Region of origin								
The Netherlands	N	3,220	349	262	223	223	202	4,479
	%	60.8	51.2	51.5	49.3	47.4	45.1	57
Western Europe/North America/	n	276	26	21	21	13	14	371
Australia	%	5.2	3.8	4.1	4.6	2.8	3.1	4.7
Eastern/central Europe	n	307	58	62	59	79	66	631
	%	5.8	8.5	12.2	13.1	16.8	14.7	8
Latin America and the Caribbean	n	654	118	70	72	50	73	1,037
	%	12.3	17.3	13.8	15.9	10.6	16.3	13.2
Sub-Saharan Africa	n	462	71	58	36	56	51	734
	%	8.7	10.4	11.4	8	11.9	11.4	9.3
Other	n	380	60	36	41	49	42	608
	%	7.2	8.8	7.1	9.1	10.4	9.4	7.7

Year of ART initiation		2014–2018	2019	2020	2021	2022	2023	2014–2023
CLINICAL								
Recent infection (within 12 months of diagnosis)	n	1,395	158	110	75	89	94	1,921
	%	26.3	23.2	21.6	16.6	18.9	21	24.4
Ever having tested HIV-negative	n	3,092	372	272	227	229	238	4,430
	%	58.4	54.5	53.4	50.2	48.7	53.1	56.4
CD4 count at start of ART	Median	403	368	325	301	360	360	385
	Q1–Q3	220–580	169–570	140–557	130–540	150–557	183–570	200–570
HIV RNA (log_{10} cp/ml) at start of ART	Median	4.7	4.8	4.9	5.2	4.8	5.1	4.8
	Q1–Q3	4.1–5.3	4.1–5.5	4.2–5.6	4.5–5.8	3.9–5.6	4.2–5.7	4.1–5.4
(Prior) AIDS at start of ART	n	686	102	105	88	78	76	1,135
	%	12.9	15	20.6	19.5	16.6	17	14.4
Hepatitis B status at start of ART								
HBV-negative (HBsAg-negative)	n	4,952	640	471	420	434	425	7,342
	%	93.5	93.8	92.5	92.9	92.3	94.9	93.4
HBV-positive (HBsAg-positive)	n	142	16	18	10	24	10	220
	%	2.7	2.3	3.5	2.2	5.1	2.2	2.8
Unknown	n	205	26	20	22	12	13	298
	%	3.9	3.8	3.9	4.9	2.6	2.9	3.8
Hepatitis C status at start of ART								
HCV-negative	n	5,055	644	479	420	442	415	7,455
	%	95.4	94.4	94.1	92.9	94.0	92.6	94.8
HCV RNA-positive	n	97	10	8	5	16	12	148
	%	1.8	1.5	1.6	1.1	3.4	2.7	1.9
HCV Ab seropositive	n	73	9	10	10	4	9	115
	%	1.4	1.3	2.0	2.2	0.9	2.0	1.5
Unknown	n	74	19	12	17	8	12	142
	%	1.4	2.8	2.4	3.8	1.7	2.7	1.8
ART started during pregnancy	n	99	18	10	9	8	6	150
	%	1.9	2.6	2	2	1.7	1.3	1.9

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 2014-2023 (A) and time between entry into HIV care and initiation of ART in 2014-2023 (B).





Legend: ART = antiretroviral therapy.

There was a slight decrease in the median CD4 count at the start of ART from 403 cells/mm^3 (IQR 220-580) in 2014-2018, to a low of 301 (130-540) in 2021 during COVID-19 lockdowns, followed by an increase to 360 (183-570) cells/mm^3 in 2023. The slightly higher CD4 counts in the period 2014-2018 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. In the period 2014-2018, at the start of ART, 12.9% of individuals had already been diagnosed with an AIDS-defining condition; this increased to 17.0% in 2023.

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, these 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 2013–2023.

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

Legend: *3TC = lamivudine; ABC = abacavir; BIC = bictegravir; DTG = dolutegravir; DRV = darunavir; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; RPV = rilpivirine.*
Source: *Medicines Evaluation Board http://english.cbg-meb.nl/ and European Medicines Agency http://www.ema.europa.eu/*

Initial ART regimen

In the period 2014-2023, 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, with the exception of the regimen 3TC/DTG. In the period 2014-2023, 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 much more common in recent years, but only in treatment-experienced individuals.

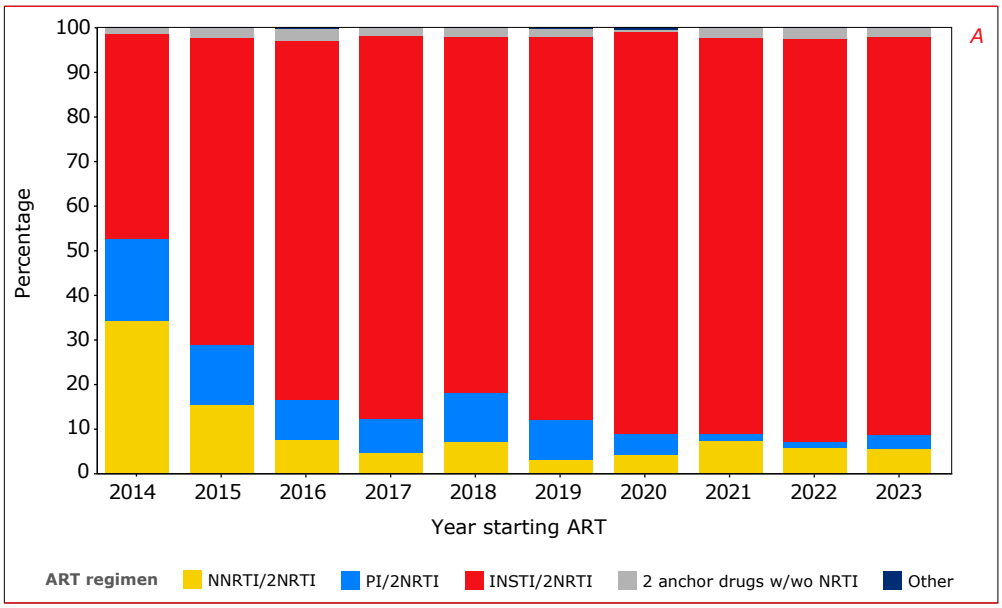
In recent years, in certain groups of newly diagnosed individuals, ART is initiated with a regimen containing 2 anchor-drugs plus 2 NRTI, with the intention to simplify this regimen as soon as possible. This includes individuals initiating ART during an acute HIV infection or individuals with low CD4 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. The starting regimens of the individuals who initiated therapy using this strategy have been set to their second simplified guideline-recommended regimen.

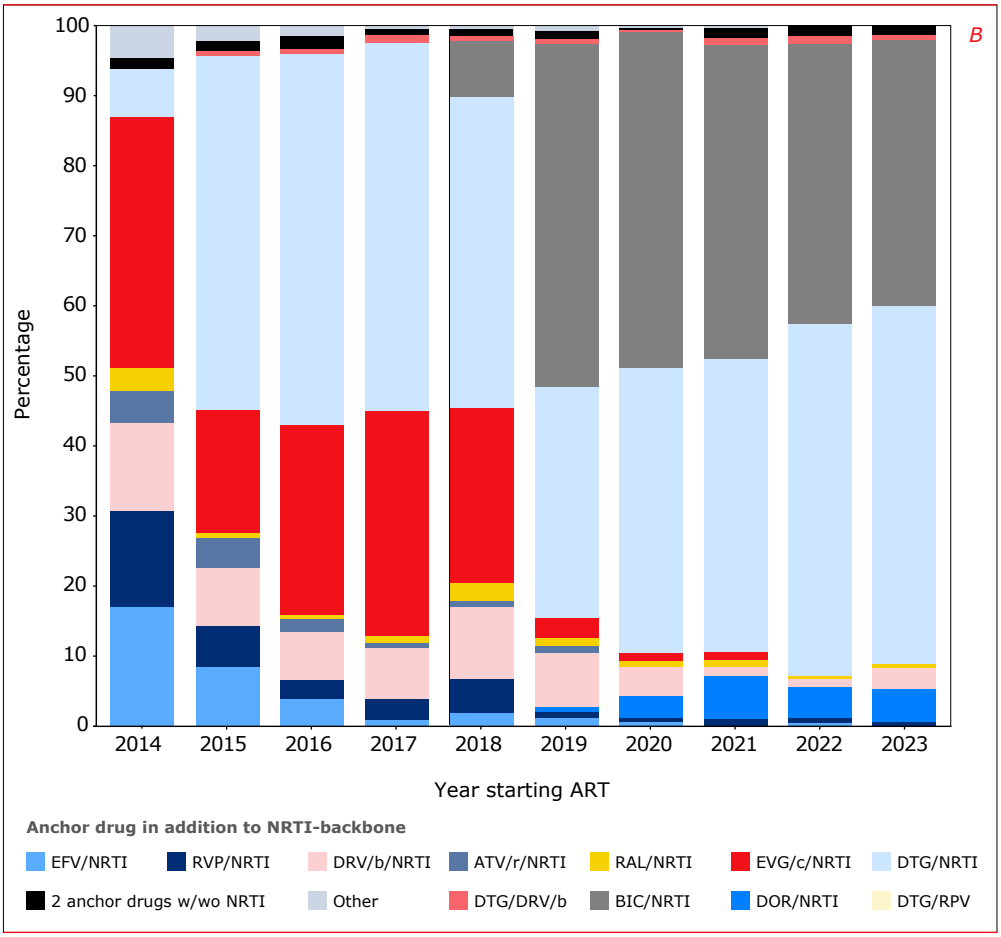
For the 7,860 ART-naïve people who initiated first-line ART between 2014 and 2023, *Figures 4.2A&B* show the trends over time in anchor-drug additions to the NRTI backbone used as part of the initial ART regimen. The use of INSTI in combination with a (mono- or dual-) NRTI backbone as initial therapy, increased from 46.0% in 2014 to 89.3% in 2023 (91.3% including other INSTI-containing dual anchor-drug regimen). The use of NNRTIs in combination with a NRTI backbone as the initial regimen decreased from 33.9% in 2014 to 5.4% in 2023. The use of PIs in combination with a NRTI backbone as the initial regimen also decreased from 18.6% in 2016 to 3.3% in 2022.

In the period 2014-2023, between 1% and 2.5% of individuals (2.0% in 2023) used 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.

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 2014-2023. 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 2014-2023.



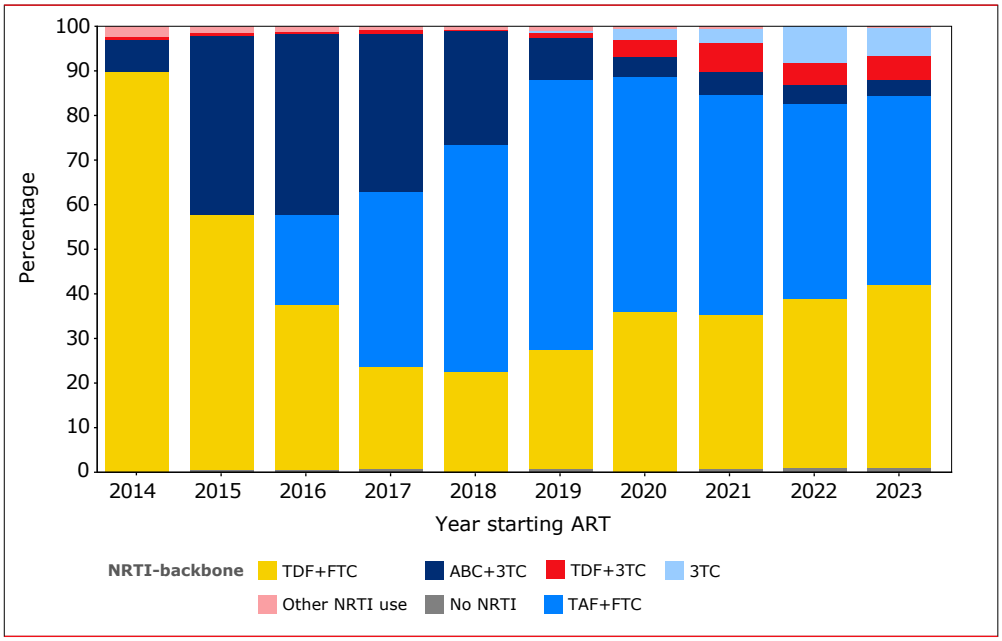


Legend: *ART = antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; ENTRY = entry inhibitor; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse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

Figure 4.3 provides an overview of the NRTI backbone components of the initial regimens used in 2014-2023. The combination of tenofovir disoproxil (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 61.0% in 2019, but has since slowly declined to 42.6% in 2023. At the same time, TDF use decreased from 90.9% in 2014 to a low of 22.1% in 2018, after which its use increased again to 46.7% in 2023. The use of abacavir steadily decreased from a high of 41.0% of all initial regimens in 2016 to 3.4% in 2023.

Figure 4.3: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the initial regimen in 2014–2023.*



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

The most common ART regimens initiated in 2014-2023 are presented in *Figure 4.4* and *Table 4.2*. In 2023, the most frequently used initial regimen was TDF/FTC/dolutegravir (39.5%). TAF/FTC/bictegravir was used in 37.7% of initial regimens. Additionally, 4.7% initiated a doravirine-containing, once-daily, fixed-dose combination with lamivudine (3TC) and tenofovir disoproxil (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*.

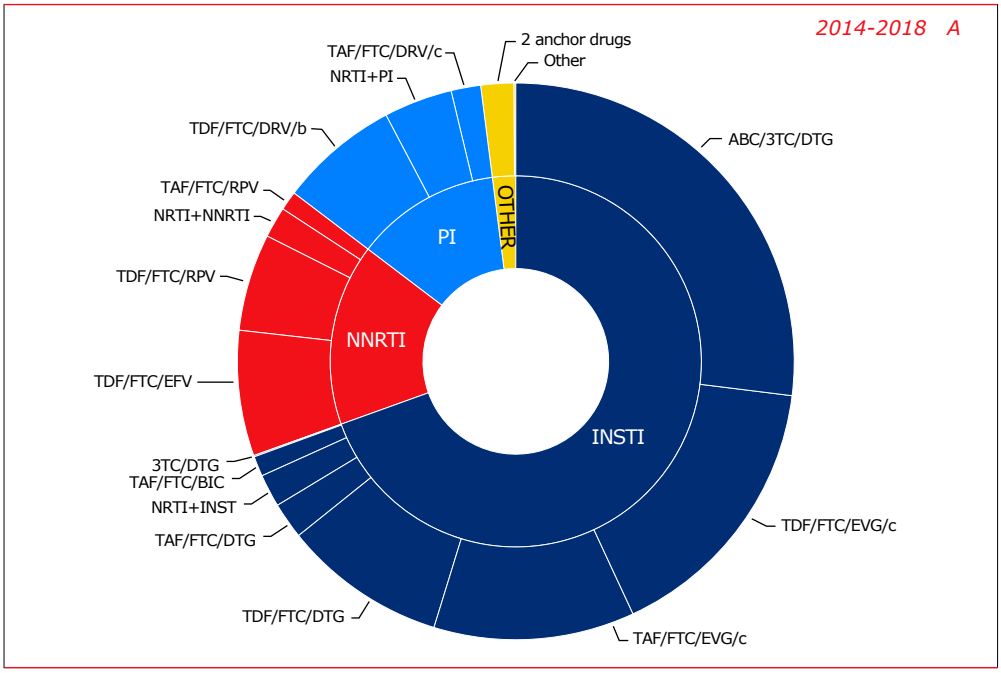
Table 4.2: Initial regimens in 2014–2023.

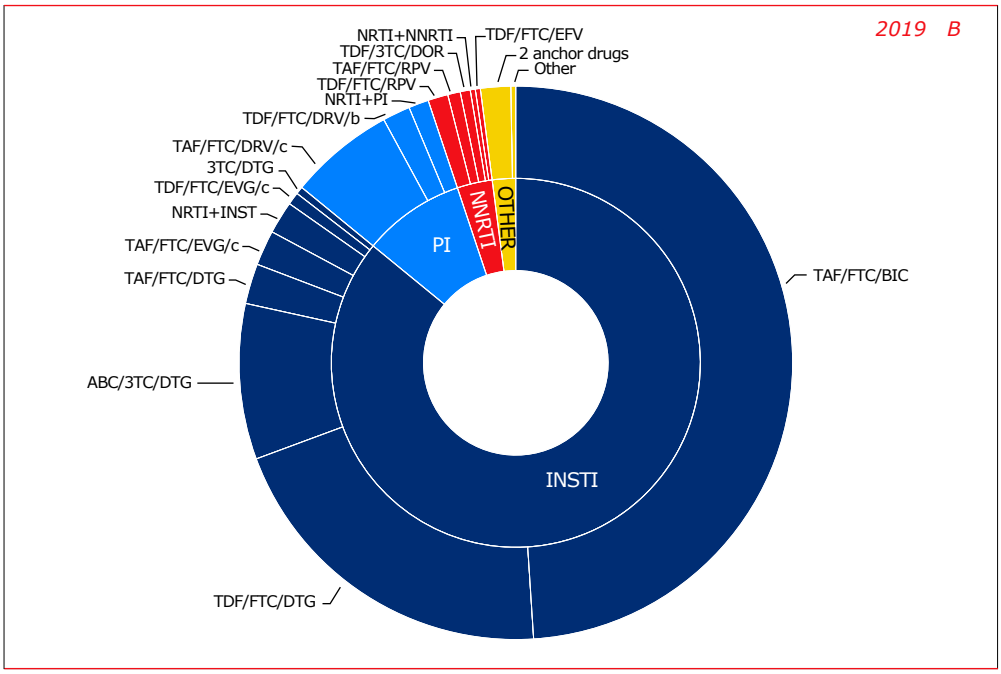
		2014–2018	2019	2020	2021	2022	2023	2014–2023
	n	5,299	682	509	452	470	448	7,860
INSTI + NRTI								
TAF/FTC/BIC	n	62	334	243	202	187	169	1,197
	%	1.2	49	47.7	44.7	39.8	37.7	15.2
DTG/3TC	n	4	3	12	14	37	28	98
	%	0.1	0.4	2.4	3.1	7.9	6.3	1.2
ABC/3TC/DTG	n	1429	62	23	23	20	15	1572
	%	27	9,1	4,5	5,1	4,3	3,3	20
TDF/FTC/DTG	n	503	139	162	141	169	177	1,291
	%	9,5	20,4	31.8	31.2	36	39.5	16.4
TAF/FTC/DTG	n	112	16	8	10	8	6	160
	%	2.1	2.3	1.6	2.2	1.7	1.3	2
TAF/FTC/EVG/c	n	618	14	6	2	.	.	640
	%	11.7	2.1	1.2	0.4	.	.	8.1
TDF/FTC/EVG/c	n	854	5	.	2	.	.	861
	%	16,1	0,7	.	0.4	.	.	11
TDF/FTC/RAL	n	64	6	3	4	1	.	78
	%	1,2	0,9	0.6	0.9	0.2	.	1
Other NRTI + INST	n	37	7	4	3	3	5	59
	%	0.7	1	0.8	0.7	0.6	1.1	0.8
NNRTI + NRTI								
TDF/FTC/EFV	n	386	8	2	2	3	.	401
	%	7,3	1,2	0.4	0.4	0.6	.	5.1
TDF/FTC/NVP	n	50	1	.	1	.	.	52
	%	0,9	0,1	.	0.2	.	.	0.7
TDF/FTC/RPV	n	299	2	.	2	.	1	304
	%	5,6	0,3	.	0.4	.	0.2	3.9
TDF/3TC/DOR	n	.	4	16	27	20	21	88
	%	.	0,6	3.1	6	4.3	4.7	1.1
ABC/3TC/NVP	n	7	.	.	.	.	.	7
	%	0.1	.	.	.	.	.	0.1
TAF/FTC/RPV	n	59	5	3	1	3	2	73
	%	1.1	0.7	0.6	0.2	0.6	0.4	0.9
Other NRTI + NNRTI	n	38	1	1	.	.	.	40
	%	0.7	0.1	0.2	.	.	.	0.5

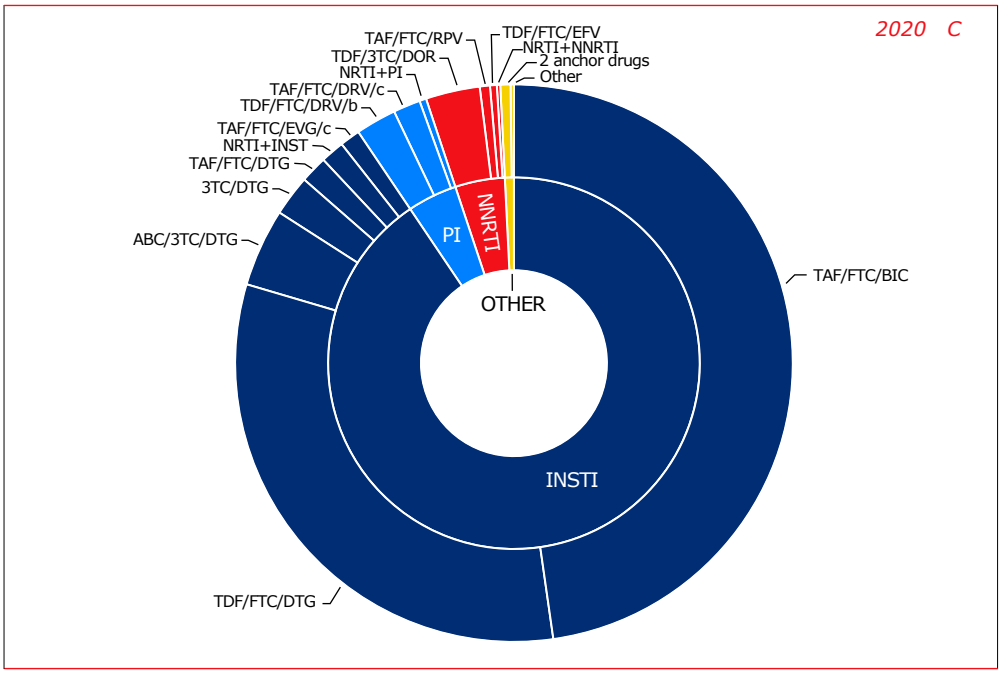
		2014–2018	2019	2020	2021	2022	2023	2014–2023
	n	5,299	682	509	452	470	448	7,860
PI + NRTI								
TDF/FTC/ATV/b	n	123	6	.	.	.	.	129
	%	2,3	0,9	.	.	.	.	1.6
TAF/FTC/DRV/c	n	91	42	8	5	5	12	163
	%	1.7	6.2	1.6	1.1	1.1	2.7	2.1
TDF/FTC/DRV/b	n	368	11	12	2	2	2	397
	%	6,9	1,6	2.4	0.4	0.4	0.4	5.1
TDF/FTC/LPV/r	n	10	.	.	.	.	.	10
	%	0,2	.	.	.	.	.	0.1
Other NRTI + PI	n	78	2	2	.	.	1	83
	%	1.5	0.3	0.4	.	.	0.2	1.1
2 anchor drugs								
DTG/DRV/b	n	25	3	1	4	5	3	41
	%	0.5	0.4	0.2	0.9	1.1	0.7	0.5
DTG/RPV	n	.	1	.	.	.	.	1
	%	.	0.1	.	.	.	.	0
2 anchor drugs w/wo NRTI	n	76	8	2	7	7	5	105
	%	1.4	1.2	0.4	1.5	1.5	1.1	1.3
Other ART	n	6	2	1	3	4	2	26
	%	0.1	0.3	0.1	0.3	0.5	0.3	0.5

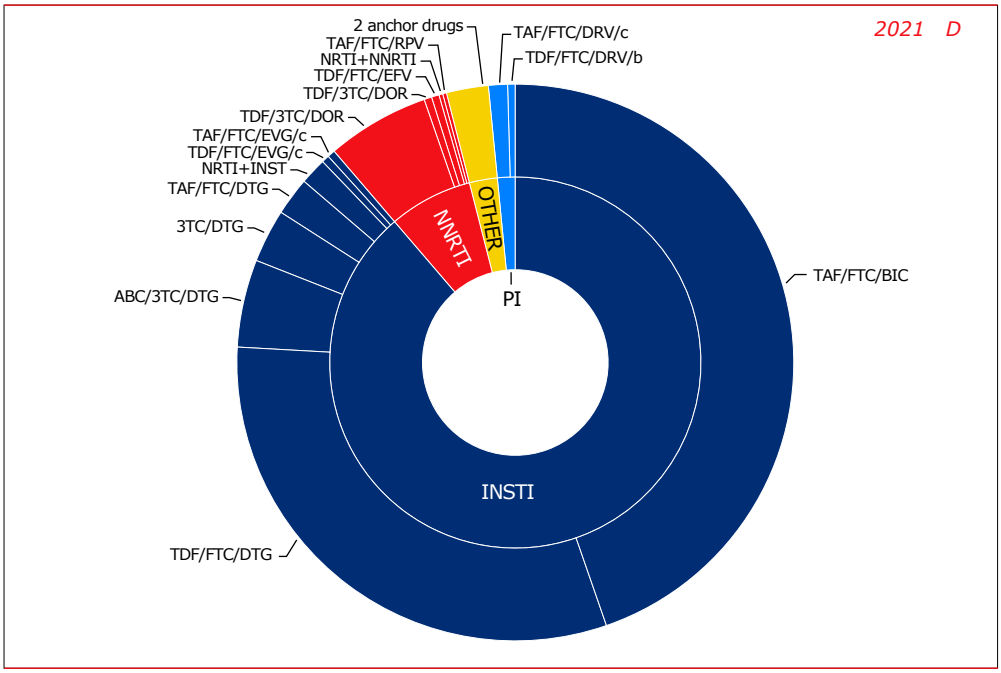
Legend: *ARVs = antiretroviral drugs; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CI = confidence interval; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG =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

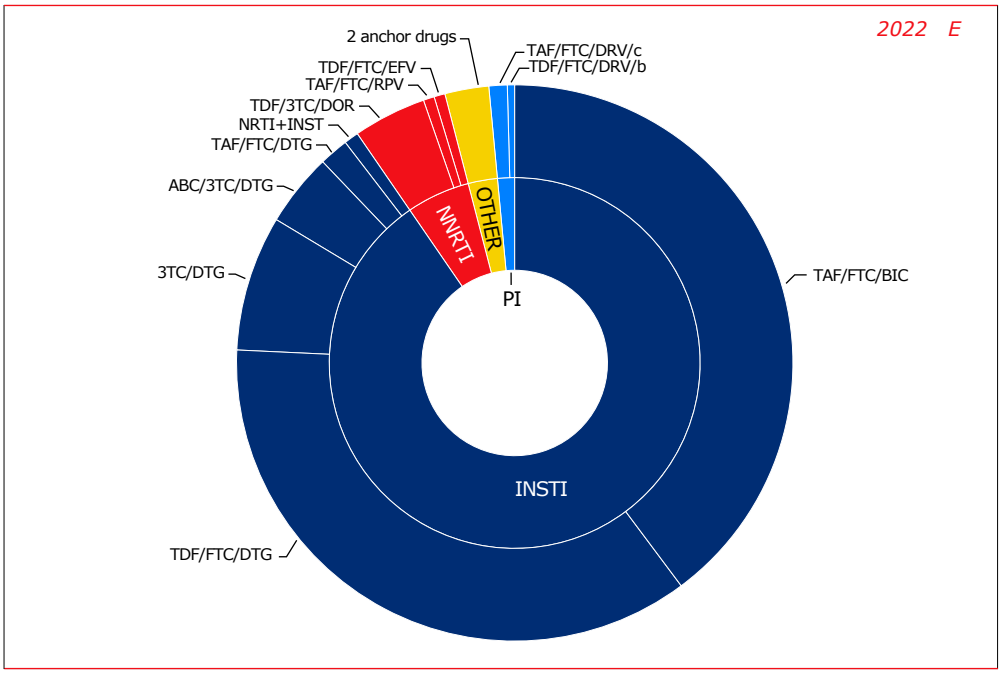
Figure 4.4: The initial antiretroviral therapy regimens given in 2014–2023.

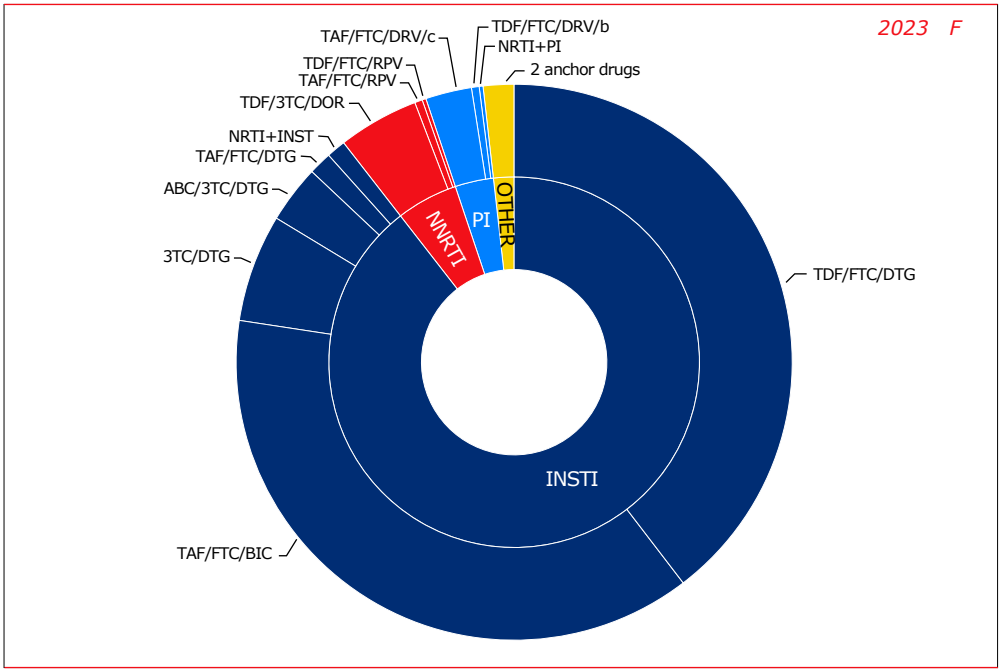





2020 C
TAF/FTC/RPV
TDF/3TC/DOR
NRTI+PI
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TAF/FTC/EVG/c
NRTI+INST
TAF/FTC/DTG
3TC/DTG
ABC/3TC/DTG
TDF/FTC/DTG
TDF/FTC/EFV
NRTI+NNRTI
2 anchor drugs
Other
TAF/FTC/BIC
PI
NNRTI
OTHER
INSTI


2021 D
2 anchor drugs
TAF/FTC/RPV
NRTI+NNRTI
TDF/FTC/EFV
TDF/3TC/DOR
TDF/3TC/DOR
TAF/FTC/EVG/c
TDF/FTC/EVG/c
NRTI+INST
TAF/FTC/DTG
3TC/DTG
ABC/3TC/DTG
TDF/FTC/DTG
TAF/FTC/DRV/c
TDF/FTC/DRV/b
TAF/FTC/BIC
PI
NNRTI
OTHER
INSTI





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 2023

A total of 25,939 people with HIV were in care and on ART between (part of the period) January 2014 and December 2023. The number of people who had initiated ART and were in active follow-up in the ATHENA cohort grew from 17,202 individuals in 2014 to 22,215 individuals in 2023. 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 are sufficiently resolved.

Table 4.3 shows the evolution over calendar time of the size, demographical, clinical and antiretroviral treatment 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 2023, 22,215 people on ART were in care (for part of or the entire) calendar year. Overall, 18,155 (81.7%) were men, and 13,931 (62.7%) were MSM. Their median age in 2023 was 52.8 (IQR 42.7-60.9) years. The majority (55.5%) originated from the Netherlands, followed by Latin America / the Caribbean (13.0%) and sub-Saharan Africa (11.8%). They had been diagnosed with HIV a median of 14.1 (IQR 8.4-20.4) years ago, and started their first-line ART regimen a median of 12 (IQR 7.5-17.9) years ago. Their last measured viral load was <50 copies/ml in 95.8% (97.9% <200 copies/ml), and 79.2% 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 2014–2023.

Calendar year		2014	2019	2020	2021	2022	2023
Total	n	17,202	20,899	21,292	21,570	21,970	22,215
	%	13.7	16.7	17	17.2	17.6	17.8
Age	Median	47.7	50.4	51	51.7	52.2	52.8
	Q1	39.8	41	41.4	41.9	42.2	42.7
	Q3	54.8	58.1	58.8	59.6	60.3	60.9
Male sex (at birth)	n	13969	17138	17473	17708	17959	18155
	%	81.2	82	82.1	82.1	81.7	81.7
HIV acquisition group							
MSM	n	10623	13200	13467	13627	13798	13931
	%	61.8	63.2	63.2	63.2	62.8	62.7
Other men	n	3206	3702	3746	3807	3877	3923
	%	18.6	17.7	17.6	17.6	17.6	17.7
Women	n	3230	3756	3814	3855	4002	4049
	%	18.8	18	17.9	17.9	18.2	18.2
Transgender people	n	143	241	265	281	293	312
	%	0.8	1.2	1.2	1.3	1.3	1.4
Region of origin							
The Netherlands	n	10423	12268	12398	12426	12398	12340
	%	60.6	58.7	58.2	57.6	56.4	55.5
Western Europe/North	n	1129	1319	1338	1343	1329	1343
America/Australia	%	6.6	6.3	6.3	6.2	6	6
Eastern/central Europe	n	480	829	912	995	1276	1381
	%	2.8	4	4.3	4.6	5.8	6.2
Latin America/Caribbean	n	1899	2566	2648	2747	2804	2884
	%	11	12.3	12.4	12.7	12.8	13
Sub-Saharan Africa	n	2271	2517	2549	2565	2597	2631
	%	13.2	12	12	11.9	11.8	11.8
Other	n	1000	1400	1447	1494	1566	1636
	%	5.8	6.7	6.8	6.9	7.1	7.4
CD4 at start ART							
No data	n	1246	1980	2144	2301	2620	2787
	%	7.2	9.5	10.1	10.7	11.9	12.5
<50	n	1821	2038	2065	2097	2106	2103
	%	10.6	9.8	9.7	9.7	9.6	9.5
50–199	n	3807	4082	4095	4111	4103	4083
	%	22.1	19.5	19.2	19.1	18.7	18.4
200–349	n	5424	5783	5822	5817	5798	5796
	%	31.5	27.7	27.3	27	26.4	26.1
350–499	n	2824	3569	3610	3616	3639	3666
	%	16.4	17.1	17	16.8	16.6	16.5
500+	n	2080	3447	3556	3628	3704	3780
	%	12.1	16.5	16.7	16.8	16.9	17

Calendar year		2014	2019	2020	2021	2022	2023
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	8.9	11.4	12.1	12.8	13.4	14.1
	Q1	4.6	6.3	6.8	7.4	7.9	8.4
	Q3	14.5	17.4	18.2	18.9	19.6	20.4
Years since start ART	Median	6.5	9.3	10	10.7	11.3	12
	Q1	2.9	5.1	5.7	6.4	7	7.5
	Q3	12.5	15.1	15.8	16.5	17.2	17.9
Current CD4 count							
missing	n	13	24	23	28	24	23
	%	0.1	0.1	0.1	0.1	0.1	0.1
<50	n	61	67	64	60	79	58
	%	0.4	0.3	0.3	0.3	0.4	0.3
50–199	n	495	462	438	407	412	403
	%	2.9	2.2	2.1	1.9	1.9	1.8
200–349	n	1549	1466	1414	1421	1441	1345
	%	9	7	6.6	6.6	6.6	6.1
350–499	n	3225	3009	3035	3092	2962	2796
	%	18.7	14.4	14.3	14.3	13.5	12.6
500–749	n	6566	7231	7132	7293	7327	7146
	%	38.2	34.6	33.5	33.8	33.4	32.2
750+	n	5293	8640	9186	9269	9725	10444
	%	30.8	41.3	43.1	43	44.3	47
Viral load <50 c/ml							
Missing	n	5	12	16	17	20	12
	%	0	0.1	0.1	0.1	0.1	0.1
≥50 c/ml	n	1918	1153	985	954	1014	913
	%	11.1	5.5	4.6	4.4	4.6	4.1
<50 c/ml	n	15279	19734	20291	20599	20936	21290
	%	88.8	94.4	95.3	95.5	95.3	95.8
Viral load <200 c/ml							
Missing	n	5	12	16	17	20	12
	%	0	0.1	0.1	0.1	0.1	0.1
≥200 c/ml	n	859	581	466	465	491	454
	%	5	2.8	2.2	2.2	2.2	2
<200 c/ml	n	16338	20306	20810	21088	21459	21749
	%	95	97.2	97.7	97.8	97.7	97.9

Calendar year		2014	2019	2020	2021	2022	2023
ART regimen							
ART temporarily interrupted	n	484	375	361	341	297	191
	%	2.8	1.8	1.7	1.6	1.4	0.9
INSTI + NRTI							
TAF/FTC/BIC	n	2	2060	2689	3152	3538	3821
	%	0	9.9	12.6	14.6	16.1	17.2
DTG/3TC	n	5	306	1064	1722	2341	2823
	%	0	1.5	5	8	10.7	12.7
ABC/3TC/DTG	n	325	3099	2573	2176	1880	1669
	%	1.9	14.8	12.1	10.1	8.6	7.5
TAF/FTC/DTG	n	4	601	544	522	489	473
	%	0	2.9	2.6	2.4	2.2	2.1
TDF/FTC/DTG	n	227	738	757	762	896	994
	%	1.3	3.5	3.6	3.5	4.1	4.5
TAF/FTC/EVG/b	n	12	2812	2507	2262	2012	1847
	%	0.1	13.5	11.8	10.5	9.2	8.3
TDF/FTC/EVG/b	n	770	657	583	532	456	406
	%	4.5	3.1	2.7	2.5	2.1	1.8
TDF/FTC/RAL	n	472	185	178	160	132	109
	%	2.7	0.9	0.8	0.7	0.6	0.5
Other INSTI + NRTI	n	161	265	253	238	245	244
	%	0.9	1.3	1.2	1.1	1.1	1.1
NNRTI + NRTI							
TDF/3TC/DOR	n	2	168	885	1398	1634	1794
	%	0	0.8	4.2	6.5	7.4	8.1
TDF/FTC/EFV	n	3623	1546	1378	1222	1051	965
	%	21.1	7.4	6.5	5.7	4.8	4.3
ABC/3TC/NVP	n	575	419	355	294	254	225
	%	3.3	2	1.7	1.4	1.2	1
TAF/FTC/NVP	n	3	734	712	719	709	694
	%	0	3.5	3.3	3.3	3.2	3.1
TDF/FTC/NVP	n	2405	1119	1031	917	790	726
	%	14	5.4	4.8	4.3	3.6	3.3
TAF/FTC/RPV	n	4	1088	955	988	950	932
	%	0	5.2	4.5	4.6	4.3	4.2
TDF/FTC/RPV	n	1787	686	601	436	369	336
	%	10.4	3.3	2.8	2	1.7	1.5
Other NNRTI + NRTI	n	789	323	314	315	274	245
	%	4.6	1.5	1.5	1.5	1.2	1.1

Calendar year		2014	2019	2020	2021	2022	2023
PI + NRTI							
TDF/FTC/ATV/b	n	1185	256	201	157	122	87
	%	6.9	1.2	0.9	0.7	0.6	0.4
TAF/FTC/DRV/b	n	1	1197	1244	1262	1261	1281
	%	0	5.7	5.8	5.9	5.7	5.8
TDF/FTC/DRV/b	n	1777	547	464	410	345	291
	%	10.3	2.6	2.2	1.9	1.6	1.3
TDF/FTC/LPV/b	n	216	28	20	16	12	9
	%	1.3	0.1	0.1	0.1	0.1	0
Other PI + NRTI	n	1006	404	316	241	192	177
	%	5.8	1.9	1.5	1.1	0.9	0.8
2 anchor drugs							
CAB/RPV injectables *	n	.	5	36	71	497	686
	%	.	0	0.2	0.3	2.3	3.1
DTG/DRV/b	n	25	340	346	355	367	372
	%	0.1	1.6	1.6	1.6	1.7	1.7
DTG/RPV	n	3	88	115	130	138	138
	%	0	0.4	0.5	0.6	0.6	0.6
2 anchor drugs w/wo NRTI	n	589	456	429	425	386	370
	%	3.4	2.2	2	2	1.8	1.7
Other ART	n	750	397	381	347	333	310
	%	4.4	1.9	1.8	1.6	1.5	1.4

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

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

Among the 22,215 individuals in HIV care and on ART in 2023, the vast majority (91.0%) received a regimen based on one or two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with either (*Figure 4.5A*) an integrase inhibitor (INSTI) (55.8%), a non-nucleoside reverse transcriptase inhibitor (NNRTI) (26.6%), or a protease inhibitor (PI) (8.6%).

The proportion of individuals who had (temporarily) interrupted ART at the end of the calendar year, decreased from 2.8% in 2014 to 0.7% in 2023. In a later section in this chapter more details are shown about then number, reasons, duration and outcome of these treatment interruptions.

The changes of time in the distribution of specific ART regimen among the population in care in 2023 is presented in *Figure 4.5B* and *4.7* and in *Table 4.3*. The most frequently used regimens (used by at least 5% of the population) were:

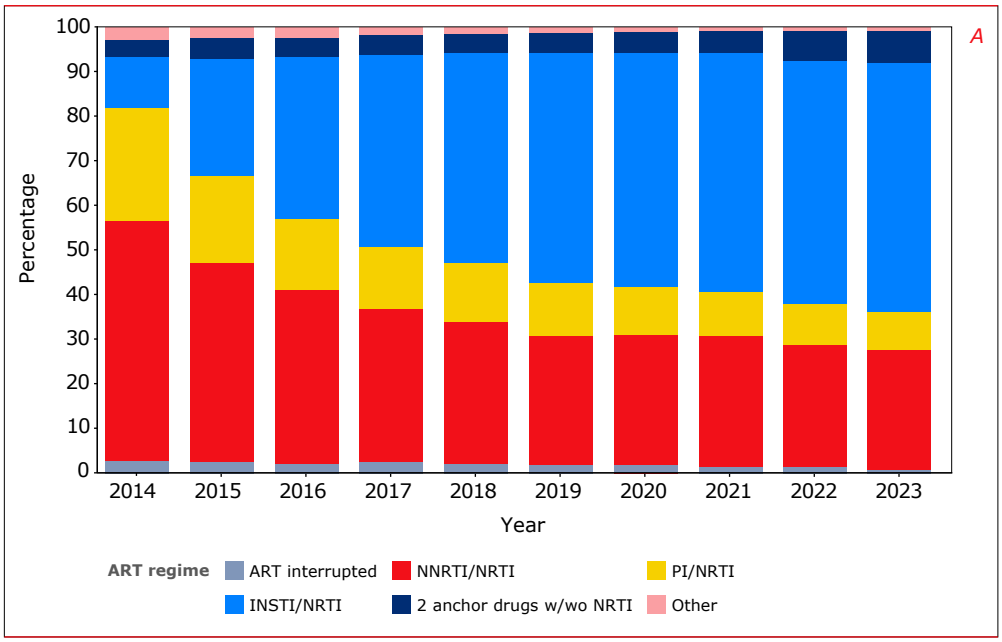
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/bictegravir (BIC) (17.2%);
- dolutegravir (DTG)/lamivudine (3TC) (12.7%);
- tenofovir alafenamide (TAF)/ emtricitabine (FTC)/elvitegravir (EVG)/cobicistat (8.3%);
- tenofovir disoproxil fumarate (TDF)/ lamivudine (3TC)/doravirine (DOR) (8.1%);
- abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) (7.5%); and
- tenofovir alafenamide (TAF)/emtricitabine (FTC)/darunavir (DRV)/cobicistat (5.8%)

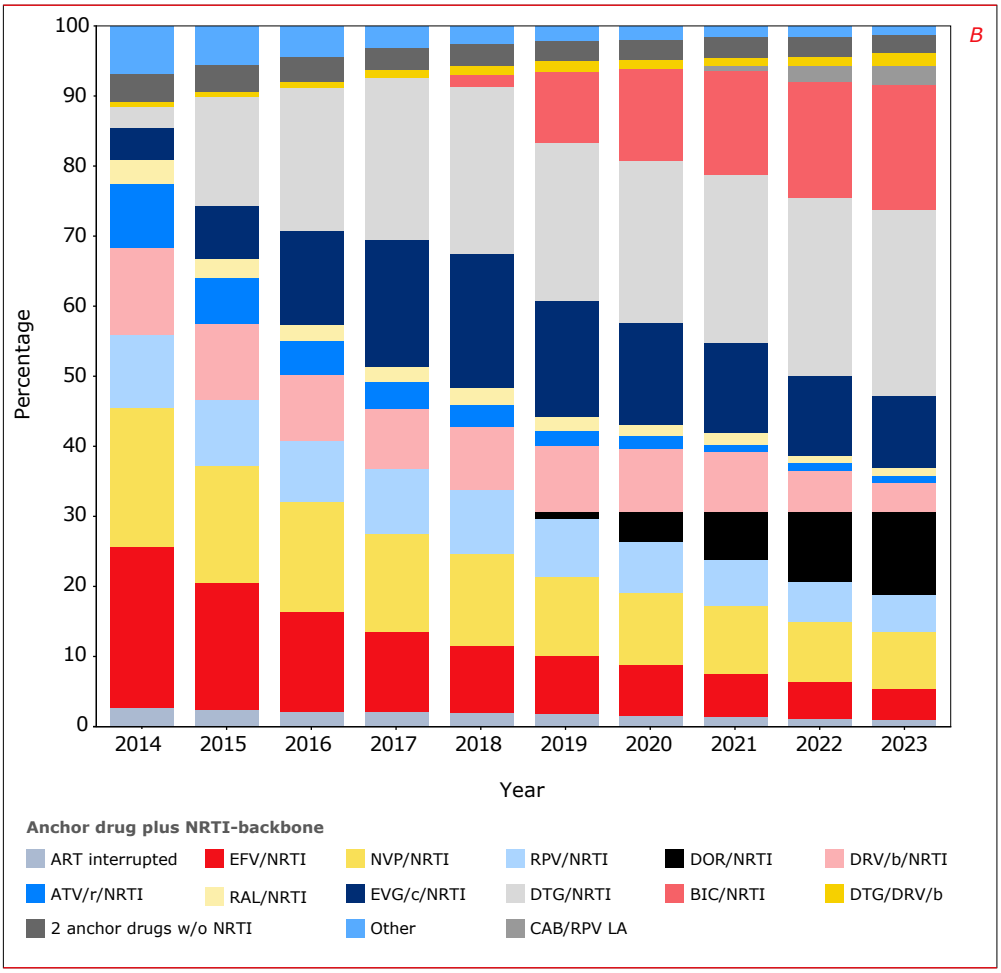
The use of ABC/3TC/DTG has decreased substantially following the DHHS guideline change from one of the "Recommended Initial Regimens for Most People With HIV" to a regimen recommended as part of "Other Initial Antiretroviral Regimens for Certain Clinical Scenarios" because of concerns over a potential increase in the risk of cardiovascular events by the use of abacavir. The use of this regimen decreased from 14.8% in 2014 to 7.5% in 2023, mainly driven by simplifications to 3TC/DTG. 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 2023, 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 7.4%. The most common of these regimens were a combination of cabotegravir/rilpivirine injectables (3.1%), dolutegravir/darunavir/cobicistat (1.7%), and dolutegravir/rilpivirine (0.6%).

Of those on ART with a plasma HIV RNA measurement in 2023, 95.8% had a viral load below 50 copies/ml, and 97.9% had a viral load below 200 copies/ml. In 2023, 79.2% had a CD4 count of 500 cells/mm^3 or higher.

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 2014-2023.

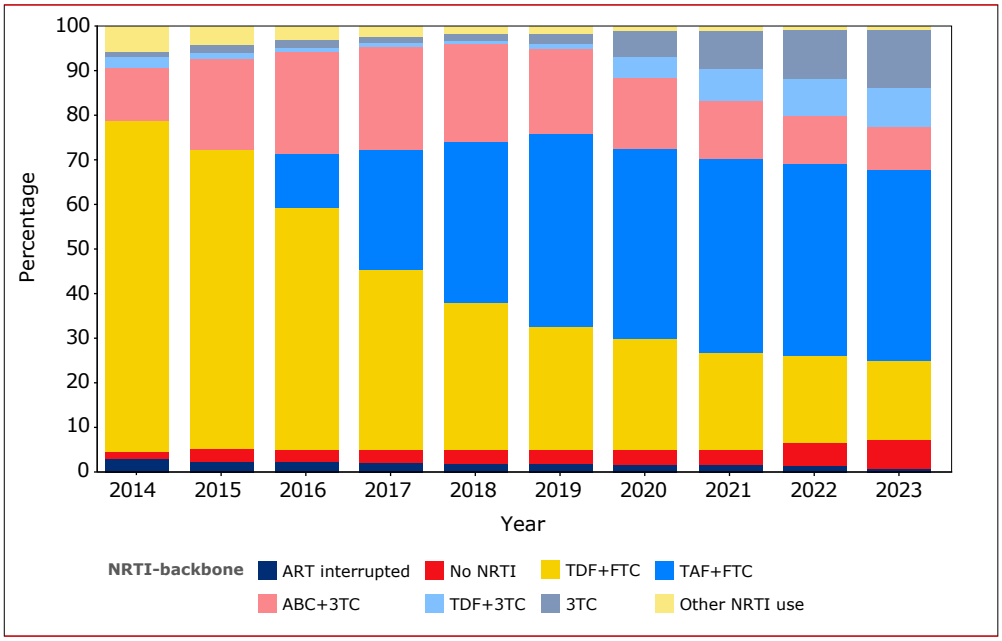




Legend: *ART = antiretroviral therapy; b = boosted (cobicistat or ritonavir); /c = cobicistat-boosted; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; ENTRY = entry inhibitor; INSTI = integrase inhibitor; NRTI = nucleoside analogue reverse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

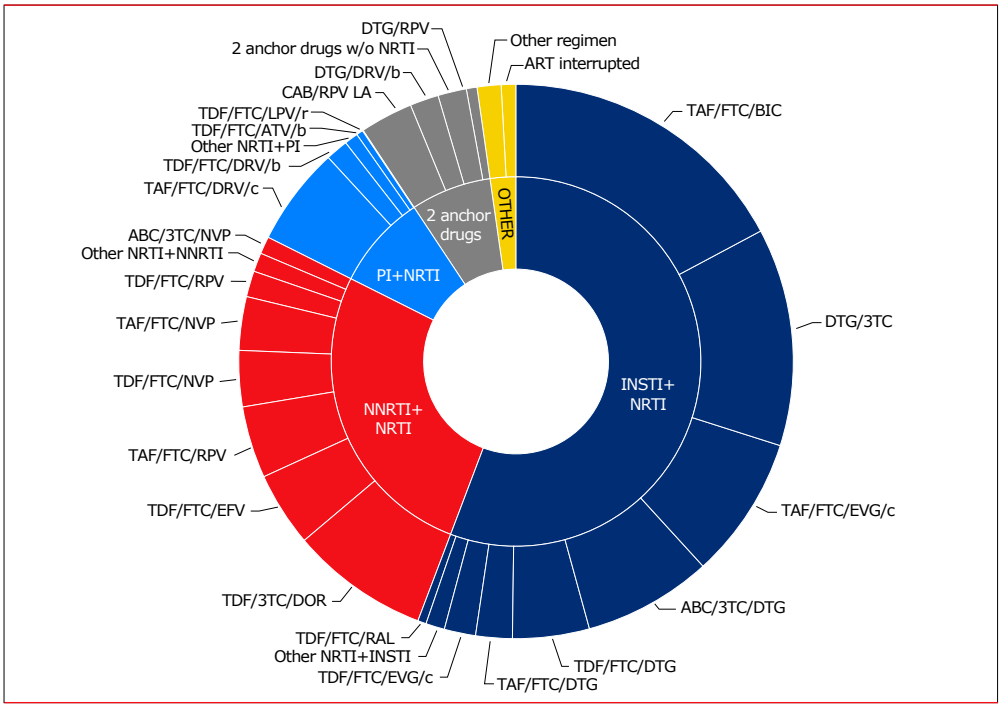
Figure 4.6 provides an overview of the NRTI backbone components of the current ART regimens used in 2014-2023. The combination of tenofovir disoproxil (TDF) or alafenamide (TAF) with emtricitabine (FTC) was the predominant backbone used, being part of 78.7% of the regimen used in 2014, and slowly declining to 69.9% in 2023. Following its introduction at the end of 2015, use of TAF in ART regimens rapidly increased with a maximum of 43.2% of all regimens used in 2019, and has since remained stable at that level. At the same time, TDF use decreased from 78.6% of all regimens used in 2014 to 29.9% in 2019, after which TDF use remained stable at that level until 2023. Abacavir was used in 13.6% of all regimen in 2014. Following the introduction of the fixed dose combination ABC/3TC/DTG its use increased to 23.7% in 2017, after which its use slowly decreased to 9.7% of all regimen used in 2023.

Figure 4.6: *Nucleoside analogue reverse transcriptase inhibitor backbone used as part of the current regimen in 2014–2023.*



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

Figure 4.7: antiretroviral therapy use in 2023.



Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ATV = atazanavir; ARVs = antiretroviral drugs; BIC = bictegravir; ART = antiretroviral therapy; 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 25,939 individuals who were on ART between (part of the period between) January 2014 and December 2023, 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

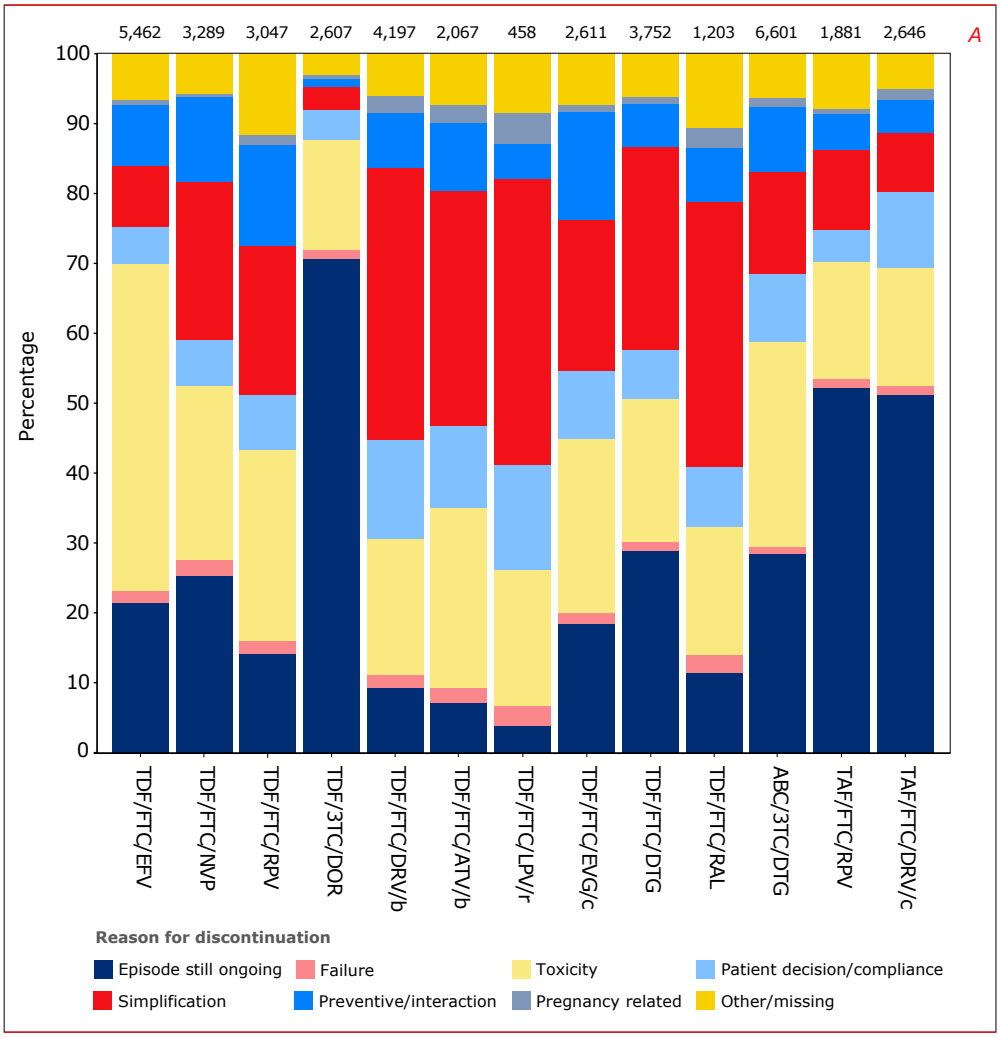
expensive) single tablet regimen (STR) into separately formulated (cheaper) generic components of the original STR, was also not considered a modification. A switch from one pharmacological booster to another was also ignored. We also ignored treatment interruptions that lasted less than 14 days. Whenever 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 particular regimen, the cumulative persons years of exposure to that particular 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*).

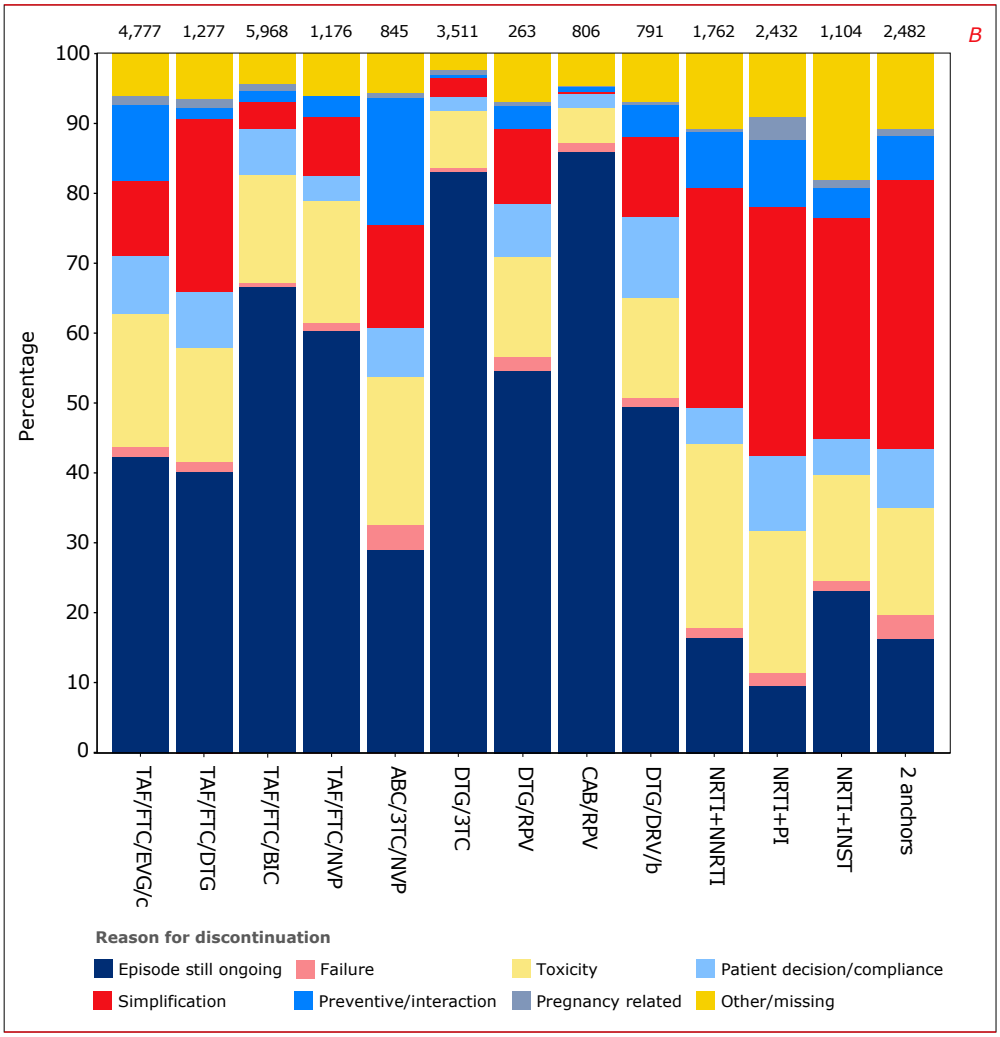
During the period 2014 to 2023, the cohort of 25,939 individuals on ART accrued a total of 187,467 person years of follow-up, during which a total of 69,621 ART regimen episodes were registered. At the end of the follow-up period in 2023 (but for some individuals follow-up ended earlier, i.e. because they died, moved out of the country, or otherwise became disengaged from HIV care), 34.3% of these regimen episodes were still in use, and 65.7% of the regimen episodes had ended in a regimen modification. The most common reasons for regimen modification were: toxicity (21.7%), treatment simplification (18.6%), patient decision/compliance (7.9%), and preventive modifications (7.2%). In only 1,218 (1.7%) 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, 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 2014 to 2023, the overall rate of regimen changes was 320.7 modifications per 1,000 person years of follow-up. This rate peaked in 2015 and 2016 at 331 and 340 modifications per 1,000 person years, after which the rate continuously decreased to 204 in 2022 and 141 in 2023 (*Figure 4.9*).

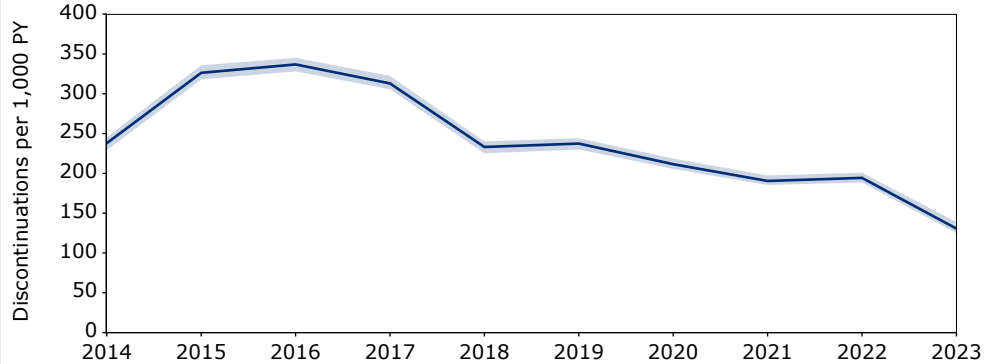
Figure 4.8A&B: Reasons for discontinuation / modification of antiretroviral therapy (ART) used in 2014-2023. The number at the top of each bar represent the total number of treatment episodes with that particular ART regimen.





Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ATV = atazanavir; ARVs = antiretroviral drugs; BIC = bictegravir; ART = antiretroviral therapy; 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 2014–2023.



Legend: Blue band represents the 95% confidence interval.

Table 4.4: *Exposure to various ARV regimen and reasons for discontinuation / modification in the period 2014–2023.*

	Person years exposure	Total ARV episodes	Reasons for discontinuation / modification			
			Episode still ongoing		Failure	
	PY	n	n	%	n	%
Total dataset	187467	69621	23877	34.3	1218	1.7
INSTI + NRTI						
TAF/FTC/BIC	13206	5968	3970	66.5	48	0.8
DTG/3TC	6855	3511	2910	82.9	32	0.9
ABC/3TC/DTG	21934	6601	1890	28.6	62	0.9
TAF/FTC/DTG	3409	1277	511	40	21	1.6
TDF/FTC/DTG	6288	3752	1091	29.1	41	1.1
TAF/FTC/EVG/c	17249	4777	2031	42.5	64	1.3
TDF/FTC/EVG/c	7128	2611	479	18.3	46	1.8
TDF/FTC/RAL	2384	1203	137	11.4	32	2.7
Other INSTI+NRTI	2023	1104	256	23.2	18	1.6
NNRTI + NRTI						
TDF/3TC/DOR	4906	2607	1841	70.6	36	1.4
TDF/FTC/EFV	19895	5462	1158	21.2	108	2
ABC/3TC/NVP	4073	845	245	29	32	3.8
TAF/FTC/NVP	4416	1176	710	60.4	15	1.3
TDF/FTC/NVP	14236	3289	833	25.3	80	2.4
TAF/FTC/RPV	6268	1881	983	52.3	25	1.3
TDF/FTC/RPV	9440	3047	426	14	62	2
Other NNRTI+NRTI	4227	1762	289	16.4	29	1.6
PI + NRTI						
TDF/FTC/ATV/b	4920	2067	145	7	50	2.4
TAF/FTC/DRV/c	6736	2646	1356	51.2	37	1.4
TDF/FTC/DRV/b	8903	4197	393	9.4	78	1.9
TDF/FTC/LPV/r	686	458	18	3.9	13	2.8
Other PI+NRTI	5064	2432	235	9.7	50	2.1
2 anchor drugs						
CAB/RPV injectables	977	806	692	85.9	12	1.5
DTG/DRV/b	2326	791	391	49.4	11	1.4
DTG/RPV	586	263	144	54.8	5	1.9
2 anchor drugs w/wo NRTI	4552	2482	408	16.4	89	3.6
Other ART	4778	2606	335	12.9	122	4.7

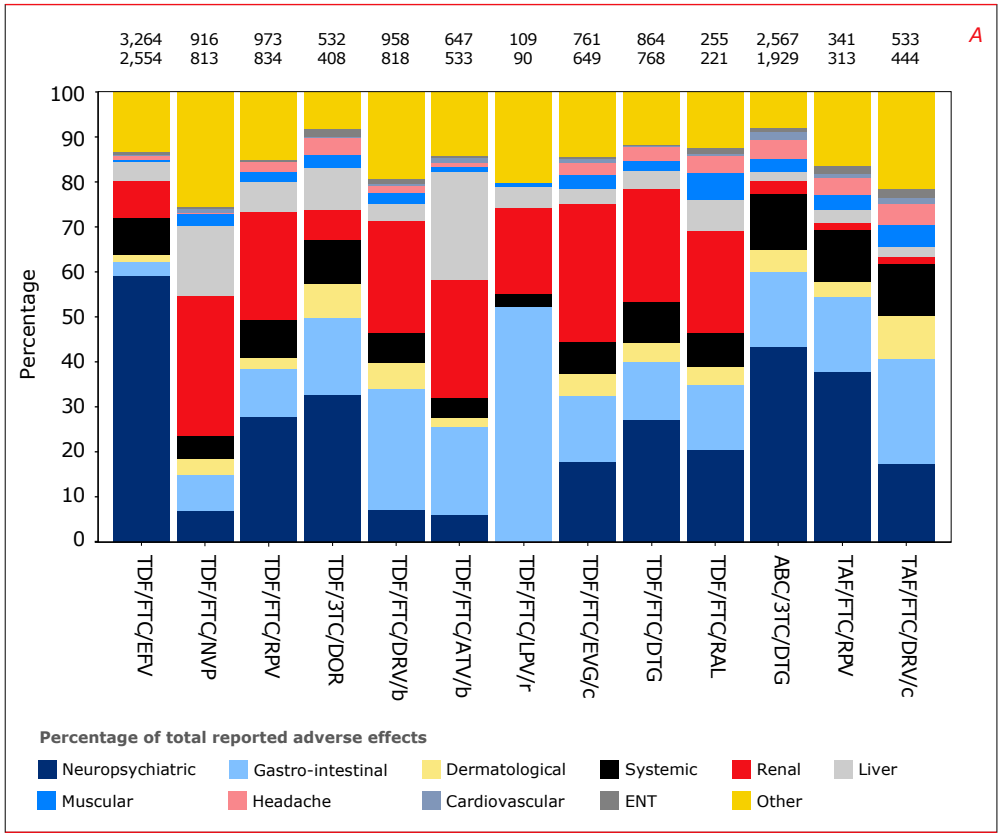
Legend: *3TC = lamivudine; b = boosted (cobicistat or ritonavir); /r = ritonavir-boosted; /c = cobicistat-boosted; ABC = abacavir; ATV = atazanavir; ARVs = antiretroviral drugs; BIC = bictegravir; ART = antiretroviral therapy; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG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

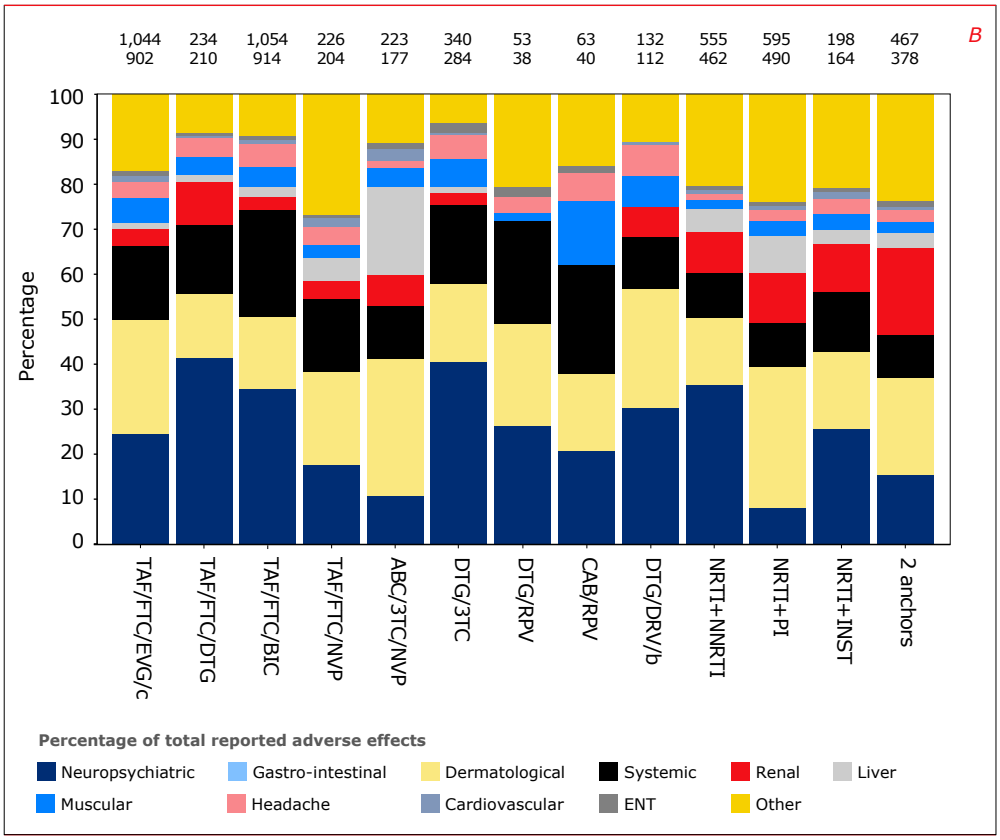
Reasons for discontinuation / modification

	Toxicity		Patient decision/ compliance		Simplification		Preventive/ interaction		Pregnancy related		Missing / Other reasons	
n	%	n	%	n	%	n	%	n	%	n	%
15140	21.7	5477	7.9	12963	18.6	5030	7.2	847	1.2	5069	7.3
914	15.3	394	6.6	231	3.9	88	1.5	53	0.9	270	4.5
284	8.1	71	2	93	2.6	17	0.5	21	0.6	83	2.4
1929	29.2	648	9.8	955	14.5	613	9.3	86	1.3	418	6.3
210	16.4	100	7.8	316	24.7	21	1.6	16	1.3	82	6.4
768	20.5	263	7	1091	29.1	229	6.1	37	1	232	6.2
902	18.9	399	8.4	514	10.8	511	10.7	69	1.4	287	6
649	24.9	254	9.7	568	21.8	398	15.2	25	1	192	7.4
221	18.4	102	8.5	456	37.9	92	7.6	36	3	127	10.6
164	14.9	60	5.4	345	31.3	50	4.5	11	1	200	18.1
408	15.7	116	4.4	84	3.2	29	1.1	14	0.5	79	3
2554	46.8	293	5.4	475	8.7	474	8.7	35	0.6	365	6.7
177	20.9	61	7.2	125	14.8	149	17.6	7	0.8	49	5.8
204	17.3	42	3.6	100	8.5	33	2.8	1	0.1	71	6
813	24.7	222	6.7	736	22.4	404	12.3	12	0.4	189	5.7
313	16.6	87	4.6	214	11.4	97	5.2	14	0.7	148	7.9
834	27.4	240	7.9	648	21.3	440	14.4	43	1.4	354	11.6
462	26.2	90	5.1	555	31.5	136	7.7	11	0.6	190	10.8
533	25.8	240	11.6	696	33.7	198	9.6	54	2.6	151	7.3
444	16.8	289	10.9	223	8.4	123	4.6	40	1.5	134	5.1
818	19.5	592	14.1	1633	38.9	329	7.8	99	2.4	255	6.1
90	19.7	67	14.6	188	41	23	5	20	4.4	39	8.5
490	20.1	262	10.8	865	35.6	225	9.3	85	3.5	220	9
40	5	15	1.9	2	0.2	8	1	.	.	37	4.6
112	14.2	93	11.8	89	11.3	36	4.6	4	0.5	55	7
38	14.4	20	7.6	28	10.6	8	3	2	0.8	18	6.8
378	15.2	211	8.5	946	38.1	156	6.3	27	1.1	267	10.8
391	15	246	9.4	787	30.2	143	5.5	25	1	557	21.4

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 nearly every year, 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 regimen. For the 15,140 toxicity-driven regimen modifications, 17,874 adverse effects were recorded. The predominant adverse effects were: neuropsychiatric (mainly insomnia, mood changes, dizziness, and depression) 31.6%; gastrointestinal (mainly diarrhoea and nausea) 14.7%; renal (renal insufficiency and increased serum creatinine) 12.3%; systemic (tiredness, apathy, and loss of appetite) 10.6%; liver (increased transaminases) 5.3%; 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 2014-2023. 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; ARVs = antiretroviral drugs; BIC = bictegravir; ART = antiretroviral therapy; 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 last 10 years, 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 2.4% in 2014 to 0.8% in 2023 (see *Figure 4.11* from the next section on *Virological response*).

During the period 2014 to 2023, the cohort of 25,939 individuals accrued a total of 187,467 person years of follow-up, in which a total of 69,621 ART regimen were used. In 2,905 individuals a total of 4,815 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 decided to interrupt their ART (71.5%), with their treating physicians becoming aware of the interruption only during the next clinic visit. A further 12.9% of interruptions had ART-associated toxicity as the recorded reason, and 3.2% of interruptions was pregnancy-related. 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 decided to interrupt ART, or thirdly if the interruption was decided on by their treating physician.
The median duration of the recorded treatment interruptions was 13.7 (IQR 5.0-37.1) weeks. During many of the longer treatment interruption the majority of these individuals were effectively temporarily disengaged from care. In 59.1% 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=2,109). In 1,101 of these 2,109 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 281 to 702, cells/mm^3). And in 1,282 episodes there was a CD4 count measured during (but at least 60 days after the start of) the treatment interruption (median 330, IQR 134 to 520 cells/mm^3). For 715 treatment interruptions of more than 90 days, a pre-interruption CD4 count was available and also a CD4 count had been measured during the interruption. During these 715 interruptions the median change in the CD4 count was -130 (IQR -30 to -260) 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 9.6, IQR 3.1-9.7 weeks), and women who interrupted ART after the pregnancy had ended (n=37, median duration of interruption 87, IQR 60-163 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 2014–2023.

	Duration of interruption (weeks)			Patients	Total episodes
	Median	Q1	Q3	n	n
Total dataset	12.6	4.7	31.6	2565	4224
INSTI + NRTI					
TAF/FTC/BIC	10.9	4.4	28.1	273	350
DTG/3TC	8.9	4.3	17.6	38	45
ABC/3TC/DTG	14.9	5.0	36.7	398	542
TAF/FTC/DTG	16.3	5.0	41.9	58	73
TDF/FTC/DTG	13.1	4.4	32.7	145	182
TAF/FTC/EVG/c	12.4	4.9	28.4	237	304
TDF/FTC/EVG/c	15.0	6.1	30.4	141	202
TDF/FTC/RAL	9.7	4.1	21.9	61	73
Other INSTI+NRTI	7.6	4.3	16.3	42	47
NNRTI + NRTI					
TDF/3TC/DOR	9.4	4.3	23.4	75	86
TDF/FTC/EFV	13.7	4.8	35.1	213	256
ABC/3TC/NVP	8.3	4.3	23.7	33	46
TAF/FTC/NVP	13.0	6.0	27.1	29	31
TDF/FTC/NVP	14.5	5.4	34.9	132	152
TAF/FTC/RPV	7.9	4.3	20.3	55	74
TDF/FTC/RPV	11.6	4.7	36.9	157	183
Other NNRTI+NRTI	13.4	5.4	26.1	64	74
PI + NRTI					
TDF/FTC/DRV/b	12.5	4.7	34.9	322	428
TDF/FTC/ATV/b	14.2	4.6	40.4	145	194
TDF/FTC/LPV/r	15.6	7.6	34.7	33	45
TAF/FTC/DRV/c	12.4	4.8	29.4	160	232
Other PI+NRTI	14.0	4.4	36.7	151	214
2 anchor drugs					
CAB/RPV injectables	7.7	2.9	20.6	9	9
DTG/DRV/b	11.4	5.6	29.3	55	63
DTG/RPV	17.9	4.1	24.1	9	14
2 anchor drugs w/wo NRTI	16.1	5.7	31.7	94	138
Other ART	8.7	4.4	26.9	134	167

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

							Reasons for interruption				Restarted same regimen
	Failure		Toxicity		Patient decision/ compliance		Pregnancy related		Other		
	n	%	n	%	n	%	n	%	n	%	%
	63	1.5	569	13.5	3101	73.4	43	1.0	448	10.6	63.6
	1	0.3	42	12.0	262	74.9	.	.	45	12.9	75.4
	.	.	11	24.4	28	62.2	1	2.2	5	11.1	66.7
	1	0.2	89	16.4	389	71.8	.	.	63	11.6	67.2
	1	1.4	8	11.0	57	78.1	.	.	7	9.6	68.5
	1	0.5	26	14.3	136	74.7	3	1.6	16	8.8	70.9
	6	2.0	49	16.1	221	72.7	.	.	28	9.2	66.4
	4	2.0	27	13.4	151	74.8	1	0.5	19	9.4	60.9
	4	5.5	11	15.1	46	63.0	3	4.1	9	12.3	46.6
	.	.	6	12.8	28	59.6	.	.	13	27.7	46.8
	3	3.5	14	16.3	62	72.1	.	.	7	8.1	62.8
	7	2.7	39	15.2	169	66.0	1	0.4	40	15.6	49.2
	3	6.5	8	17.4	30	65.2	.	.	5	10.9	67.4
	.	.	3	9.7	23	74.2	.	.	5	16.1	54.8
	3	2.0	16	10.5	123	80.9	2	1.3	8	5.3	52.6
	2	2.7	16	21.6	45	60.8	.	.	11	14.9	71.6
	5	2.7	25	13.7	131	71.6	.	.	22	12.0	54.6
	4	5.4	12	16.2	41	55.4	2	2.7	15	20.3	54.1
	4	0.9	41	9.6	347	81.1	5	1.2	31	7.2	60.5
	.	.	26	13.4	149	76.8	6	3.1	13	6.7	56.7
	1	2.2	5	11.1	36	80.0	2	4.4	1	2.2	53.3
	2	0.9	29	12.5	180	77.6	.	.	21	9.1	77.2
	.	.	26	12.1	154	72.0	16	7.5	18	8.4	64.5
	.	.	3	33.3	3	33.3	.	.	3	33.3	44.4
	.	.	3	4.8	53	84.1	.	.	7	11.1	76.2
	1	7.1	1	7.1	12	85.7	.	.	.	.	71.4
	5	3.6	10	7.2	108	78.3	.	.	15	10.9	76.1
	5	3.0	23	13.8	117	70.1	1	0.6	21	12.6	53.9

Virological response

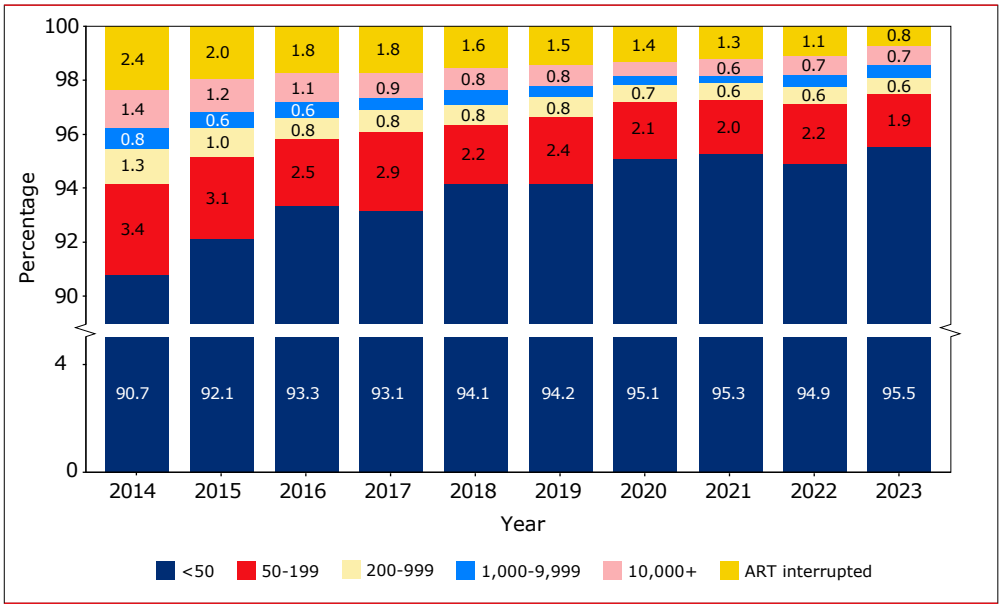
The study population for the analyses in this section consisted of all individuals on ART for more than 6 months who were in care during (part of) the period 2014-2023. For each calendar year between 2014 and 2023 we selected the last measured plasma HIV-RNA load measured in the 24 months prior to 31 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" between 20-50 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. 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 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 90.7% in 2014 (94.1% <200 copies/ml) to 95.5% (97.4% <200 copies/ml) in 2023. Likewise, all viral load categories higher than 50 copies/ml, decreased slowly over time (the number of analysed measurements and more precise percentages are shown in *Appendix Table 4.2*).

Quantifiable viral loads between 50-199 copies/ml are frequently observed in this population. 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 22,217 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 2014-2023. Of all individuals on ART, 74.8% had not 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 5.3% this proportion was between >10% and 20% of all viral load measurements. And in just 2.9% of all individuals there was evidence of sustained low-level viremia with more than 20% of all 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 2014–2023.



Box 4.3: Definitions of virological response and HIV drug resistance.

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.

HIV drug resistance

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

The 2022 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations [24].

Acquired HIV drug resistance
High-level resistance to at least one antiretroviral drug, detected at the time of an HIV viral load above 500 copies/ml, among people receiving ART for at least four months.

The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.6) was used to infer antiretroviral drug susceptibility and resistance scores [25,26].

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 2014-2023.
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 do not have data on adherence, and only a very limited number of ARV plasma concentrations are available. Nevertheless, the maximum viral load measured during episodes of loss of viral control is much higher (4.5 log10 copies/ml) in those individuals for whom we know ART had been discontinued compared to individuals who indicated to still use ART (3.0 log10 copies/ml) indicating that the distinction is meaningful.

A total of 25,911 individuals contributed 191,116 person years of follow-up during the period 2014-2023 (*Table 4.6*). In 4,307 individuals there were 6,896 episodes of loss of viral control: in 1,669 individuals there were 2,109 episodes of the loss of viral control during a treatment interruption, and in 3,220 individuals there were 4,787 episodes while the subject was continuing the use of ART.

The duration of loss of viral suppression during a treatment interruption is primarily determined by the duration of the treatment interruption: 78.2% of these episodes had a duration of less than 0.5 years, 7.6% lasted between 0.5 and <1.0 years, and 14.1% lasted more than 1 year. At the end of the follow-up period investigated, 90.4% of these episodes had resolved after restarting ART (with the same or a different ART regimen), while 7.2% of these episodes were still ongoing, and 2.4% of these episodes ended in death, with advanced HIV / AIDS-defining conditions as the predominant cause of death in 41.2% 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 5 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. In chapter 3 we explored which factors are associated with loss of virologic control using data from SHM and Statistics Netherlands.

The large majority (71.7%) of episodes of loss of viral suppression that occurred while ART had 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, 5.2% lasted between 0.5 and <1.0 years, and 5.7% lasted more than 1 year. 92.9% of episodes had been resolved at the end of the study period, in 71.6% of episodes without a modification of the used ART regimen, and 21.3% resolved after a regimen modification. 5.7% of episodes were still ongoing at the end of the follow-up period, and 1.2% of these episodes ended in death, again with death because of an advanced-HIV / AIDS-defining condition as the predominant (40.0%) 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.

In *Box 4.4* we show a summary of the findings of 3 recent studies that used the SHM dataset to investigate the virological response to three relatively new guideline-recommended treatment options (DTG/3TC; long-acting CAB/RPV and TDF/FTC/DOR) that are frequently used in treatment-experienced people with HIV in the Netherlands.

In the next section we report on the development of HIV drug resistance.

Table 4.6: Occurrence of loss of viral suppression during 2013–2024 in individuals on ART for more than 6 months.

	All		MSM + TG		Other men		Women	
Total cohort on ART								
N of subjects	25,911		16,346		4,902		4,663	
PY of follow-up	191,116		122,420		33,844		34,851	
N of episodes of failure	6,896		3,039		1,711		2,146	
Subjects with failure	4,307		2,107		1,028		1,172	
Loss of viral suppression because of ART interruption								
N of subjects	1,669		762		388		519	
N of episodes	2,109		946		493		670	
Duration of failure								
Single VL measurement	1181	56.0	522	55.2	293	59.4	366	54.6
<0.5 year	469	22.2	221	23.4	119	24.1	129	19.3
0.5 – <1 year	160	7.6	77	8.1	27	5.5	56	8.4
1 – <2 years	144	6.8	57	6.0	32	6.5	55	8.2
2+ years	155	7.3	69	7.3	22	4.5	64	9.6
Highest viral load	4.5		4.6		4.7		4.4	
$\log^{10}$ median, Q1–Q3	3.9–5.1		3.9–5.1		4.1–5.3		3.6–5.0	
Outcome								
Ongoing	151	7.2	73	7.7	37	7.5	41	6.1
Restarted, resolved	1907	90.4	851	90.0	440	89.2	616	91.9
Died while still off ART	51	2.4	22	2.3	16	3.2	13	1.9
Cause of death								
advanced HIV / AIDS	21	41.2	8	36.4	6	37.5	7	53.8
Non-AIDS malignancies	7	13.7	2	9.1	3	18.8	2	15.4
Cardiovascular disease	2	3.9	1	4.5	1	6.3	.	.
Non-AIDS infection	1	2.0	.	.	1	6.3	.	.
Liver disease	3	5.9	1	4.5	2	12.5	.	.
Lung disease	6	11.8	2	9.1	2	12.5	2	15.4
Non-natural death	1	2.0	.	.	.	.	1	7.7
Alcohol and substance use	1	2.0	1	4.5	.	.	.	.
Other causes	3	5.9	2	9.1	1	6.3	.	.
Unknown	6	11.8	5	22.7	.	.	1	7.7

	All		MSM + TG		Other men		Women	
Loss of viral suppression while on ART								
N of subjects	3,220		1,555		795		870	
N of episodes	4,787		2,093		1,218		1,476	
Duration								
Single VL measurement	3428	71.6	1565	74.8	857	70.4	1006	68.2
<0.5 year	839	17.5	348	16.6	209	17.2	282	19.1
0.5 - 1 year	248	5.2	86	4.1	72	5.9	90	6.1
1 - 2 years	158	3.3	57	2.7	48	3.9	53	3.6
2+ years	114	2.4	37	1.8	32	2.6	45	3.0
Highest viral load during episode	3.0		2.8		3.1		3.2	
median, Q1-Q3	2.5-4.0		2.5-3.6		2.6-4.2		2.6-4.2	
Outcome								
Resolved, no switch	3429	71.6	1548	74.0	874	71.8	1007	68.2
Ongoing, no switch	227	4.7	100	4.8	58	4.8	69	4.7
Resolved, switched	1021	21.3	408	19.5	258	21.2	355	24.1
Ongoing, switched	50	1.0	17	0.8	10	0.8	23	1.6
Died, no switch	34	0.7	12	0.6	8	0.7	14	0.9
Died, switched	26	0.5	8	0.4	10	0.8	8	0.5
Cause of death								
advanced HIV / AIDS	24	40.0	7	35.0	9	50.0	8	36.4
Non-AIDS malignancies	11	18.3	3	15.0	3	16.7	5	22.7
Cardiovascular disease	3	5.0	.	.	.	.	3	13.6
Non-AIDS infection	3	5.0	2	10.0	.	.	1	4.5
Liver disease	.	.	.	.	.	.	.	.
Lung disease	.	.	.	.	.	.	.	.
Non-natural death	2	3.3	2	10.0	.	.	.	.
Alcohol and substance use	1	1.7	.	.	1	5.6	.	.
Other causes	4	6.7	1	5.0	2	11.1	1	4.5
Unknown	12	20.0	5	25.0	3	16.7	4	18.2

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

Box 4.4: Summary of recent studies using SHM data.

Title: Dolutegravir/Lamivudine Is Noninferior to Continuing Dolutegravir- and Non-Dolutegravir-Based Triple-Drug Antiretroviral Therapy in Virologically Suppressed People With Human Immunodeficiency Virus: DUALING Prospective Nationwide Matched Cohort Study[27].

Background: Confirming the efficacy of dolutegravir/lamivudine in clinical practice solidifies recommendations on its use.

Methods: Prospective cohort study (DUALING) in 24 human immunodeficiency virus (HIV) treatment centers in the Netherlands. HIV RNA-suppressed cases were on triple-drug antiretroviral regimens without prior virological failure or resistance and started dolutegravir/lamivudine. Cases were 1:2 matched to controls on triple-drug antiretroviral regimens by the use of dolutegravir-based regimens, age, sex, transmission route, CD4+ T-cell nadir, and HIV RNA zenith. The primary endpoint was the treatment failure rate in cases versus controls at 1 year by intention-to-treat and on-treatment analyses with 5% noninferiority margin.

Results: The 2040 participants were 680 cases and 1380 controls. Treatment failure in the 390 dolutegravir-based cases versus controls occurred in 8.72% and 12.50% (difference: -3.78% [95% confidence interval (CI), -7.49% to .08%]) by intention-to-treat and 1.39% and 0.80% (difference: 0.59% [95% CI, -.80% to 1.98%]) by on-treatment analyses. The treatment failure risk in 290 non-dolutegravir-based cases was also noninferior to controls. Antiretroviral regimen modifications unrelated to virological failure explained the higher treatment failure rate by intention-to-treat. A shorter time on triple-drug antiretroviral therapy and being of non-Western origin was associated with treatment failure. Treatment failure, defined as 2 consecutive HIV RNA >50 copies/mL, occurred in 4 cases and 5 controls but without genotypic resistance detected. Viral blips occurred comparable in cases and controls but cases gained more weight, especially when tenofovir-based regimens were discontinued.

Conclusions: In routine care, dolutegravir/lamivudine was noninferior to continuing triple-drug antiretroviral regimens after 1 year, supporting the use of dolutegravir/lamivudine in clinical practice.

Title: Real-world effectiveness and tolerability of switching to doravirine-based antiretroviral therapy in people with HIV: a nationwide, matched, prospective cohort study[28].

Background: Currently, real-world data on doravirine are scarce. In a national prospective cohort, we assessed the effectiveness and tolerability of switching to doravirine-based antiretroviral therapy (ART) in people with HIV.

Methods: We did a nationwide, matched, prospective cohort study of people with HIV without previous virological failure and stable for at least 12 months on non-doravirine-containing triple or dual ART switching to doravirine before Sept 1, 2020 (exposed group). Participants in the exposed group were matched 1:2 to individuals continuing stable non-doravirine-containing ART, on age, sex, HIV acquisition category, time since ART initiation, calendar time, pre-ART CD4-count, pre-ART plasma viral load (PVL) and anchor drug class before switching. The primary outcome was protocol-defined virological failure (PDVF; PVL of ≥200 copies per mL) in the intention-to-treat (ITT) population at week 104, with participants modifying their regimen or becoming lost to follow-up considered as PDVF (non-inferiority margin +5%). In contrast, in the on-treatment population, those who modified their regimen or became lost to follow-up were censored from that moment onwards. Tolerability was a secondary outcome.

Findings: In total, 590 participants in the exposed group and 1180 participants in the unexposed group (of whom 55·3% used integrase strand transfer inhibitor-based regimens) were included. In the ITT analysis, PDVF occurred in 135 (22·9%) exposed participants and in 295 (25·0%) unexposed participants (risk difference -2·12%, upper limit of the one-sided 95% CI +1·40%). In the on-treatment analysis, 10 (2·2%) of 455 non-censored exposed participants and 26 (2·9%) of 885 non-censored unexposed participants had PDVF (risk difference -0·70%, upper limit of the one-sided 95% CI +0·73%). All exposed participants with a PVL of 200 copies or more per mL resuppressed without regimen modification: no confirmed virological failure (two consecutive PVLs of ≥200 copies per mL) was observed. 104 (17·6%) exposed participants and 211 (17·9%) unexposed participants modified their regimen. 73 (12.4%) exposed participants discontinued doravirine due to adverse events: abnormal dreams (1·7%) and insomnia (1·5%) were most common.

Interpretation: Switching to doravirine in well suppressed people with HIV without previous virological failure was non-inferior compared with continuing non-doravirine-containing regimens after 2 years in a real-world setting.

Title: Effectiveness of bi-monthly long-acting injectable cabotegravir and rilpivirine as maintenance treatment of HIV-1: results from the Dutch ATHENA national observational cohort.
Vita Jongen, Ferdinand Wit, Anders Boyd, Arne van Eeden, Annemarie Brouwer, Robert Soetekouw, Rachida El Moussaoui, Janneke Stalenhoef, Kim Sigaloff, Tatiana Mudrikova, Jet Gisolf, David Burger, Annemarie Wensing, Marc van der Valk.
Lancet HIV, 2024 *in press*.

Background: Real-world data demonstrating long-term effectiveness of long-acting injectable cabotegravir and rilpivirine (CAB/RPV) are scarce. We assessed the effectiveness of CAB/RPV in all individuals who switched to CAB/RPV in the Netherlands.

Methods: We used data from the ATHENA cohort, an ongoing observational nationwide HIV cohort. In primary analysis, we matched individuals who commenced CAB/RPV and had no history of virological failure (VF) (i.e., ≥1 plasma HIV RNA ≥1000 copies/mL, hereafter "exposed") 1:2 to individuals using oral antiretroviral therapy (ART) (hereafter "unexposed"). We assessed the effectiveness of CAB/RPV using restricted mean survival time (RMST) until loss of virologic control (≥1 plasma HIV RNA ≥200 copies per mL). In secondary analysis, we assessed loss of virologic control in individuals who commenced CAB/RPV with previous VF and/or an unsuppressed HIV-1 RNA at CAB/RPV initiation.

Findings: In primary analysis, 585 exposed and 1,170 unexposed individuals were included between February 2018-August 2023. Median follow-up was 1.3 year [IQR=0.9-1.7]. Fourteen exposed (2.4%) and 29 unexposed (2.5%) individuals experienced loss of virologic control, with no difference in RMST (difference= 0.026, 95%CI=-0.029-0.080). Seven exposed individuals re-suppressed without regimen change. Seven switched ART, of whom six had documented integrase inhibitor (INSTI) and/or non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistance. No unexposed individuals switched ART after loss of virologic control. In secondary Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation analysis, 105 individuals were included. During a median follow up of 1.4 years [IQR=0.8-1.8], nine (8.6%) experienced loss of virologic control; five had INSTI- and/or NNRTI-resistance.

Interpretation: Switching to CAB/RPV was not associated with a higher risk of loss of virologic control among individuals without previous VF compared to oral ART. However, INSTI and/or NNRTI mutations were selected in 43% of individuals with CAB/RPV failure, compared to none with oral ART. The high risk of loss of virologic control among individuals with previous VF and/or an unsuppressed HIV-1 RNA at CAB/RPV initiation warrants more careful monitoring.

HIV drug resistance

Preventing, monitoring and responding to HIV drug resistance is a key component of comprehensive and effective HIV care. When antiretroviral therapy does not result in complete suppression of viral replication, HIV drug resistance can be selected: mutations in the genetic structure of HIV can detrimentally affect the ability of a particular drug, or combination of drugs, to block replication of the virus. All current antiretroviral drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant HIV[29].

We assessed the occurrence of HIV drug resistance in the Netherlands among adults for whom genotypic resistance test results were available. The genotypic test results presented in this section relate to the HIV-1 reverse transcriptase and protease gene. HIV-1 sequences of the integrase gene were relatively rare, therefore results of testing for integrase inhibitor resistance are described separately.

We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2022 International Antiviral Society-USA (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 9.6) 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 4.3*.

As of December 2023, 9,523 HIV-1 sequences had been obtained from 9,195 ART-naïve people prior to initiation of ART in between 2003 and 2023. 9,508 reverse transcriptase sequences were available from 9,183 individuals, 8,945 protease sequences were available from 8,632 individuals, and 588 integrase sequences were available from 587 individuals.

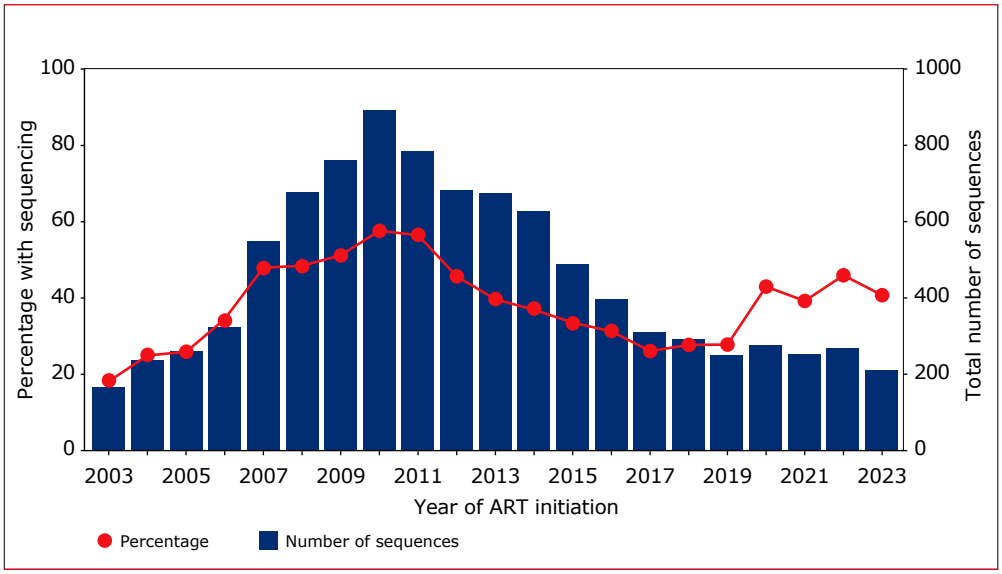
Screening for drug-resistant HIV before treatment initiation

Since 2003 Dutch treatment guidelines have included a recommendation to screen for HIV drug resistance in all people newly diagnosed with HIV at the time of entry into care. Transmitted HIV drug resistance occurs when people acquire an HIV strain that harbours drug-resistant mutations. Drug-resistant variants of HIV may remain dormant, awaiting more favourable replication conditions after treatment has started[30-32]. These dormant mutant variants may not be detected, which can make it difficult to distinguish between drug-susceptible and drug-resistant

strains[33]. Ideally, the presence of transmitted resistance should be identified as close as possible to the moment of infection in people who are antiretroviral (ARV)-naïve before initiating ART. Furthermore, individuals with insufficient coverage of pre-exposure prophylaxis (PrEP) for HIV could acquire HIV and if continuing to take PrEP, could develop resistance mutations associated with these antiretrovirals. Resistance mutations associated with specifically PrEP use are described in more detail in Chapter 2.

In total, 9,523 HIV-1 sequences were obtained between 2003 and 2023 from 9,195 ARV-naïve people before they initiated ART. The number of sequences and the percentage of ARV-naïve people with sequencing before ART initiation peaked in 2010 and have steadily declined since then (*Figure 4.12*). If someone had more than one sequence available before ART initiation, we selected the first available sequence (closest to the date of HIV-1 diagnosis) for our analysis to limit the effect of back mutation. Of those with pre-treatment drug-resistance data, the majority were MSM (65.7%), while 15.3% were women. Most people with an available pre-treatment sequence originated from the Netherlands (58.7%) or sub-Saharan Africa (11.2%). The main HIV-1 subtype was B (73.2%), followed by non-B subtypes (26.8%), including recombinant form CRF_02AG (6.7%), subtype C (5.1%), and CRF_01AE (3.7%).

Figure 4.12: *The annual number of sequences and the percentage of ARV-naïve people with sequencing before ART.*

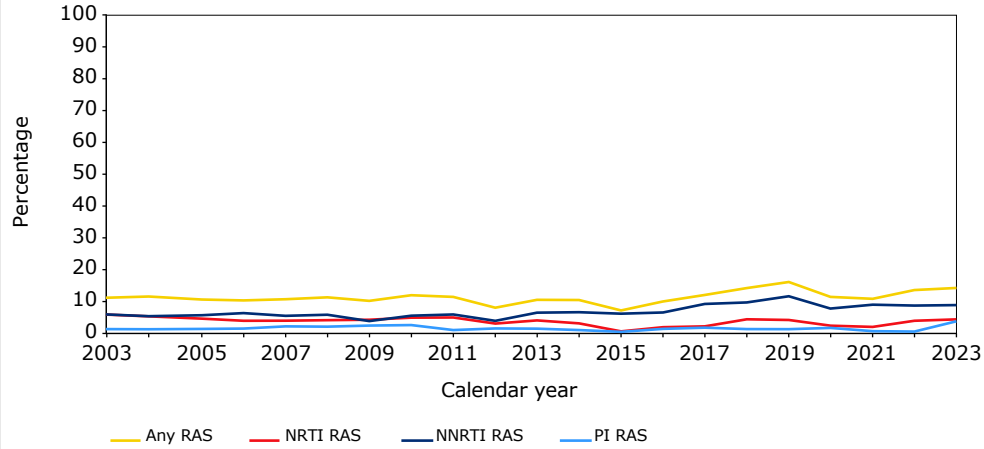


Legend: *ART = antiretroviral therapy.*

HIV drug resistance before treatment initiation

In total, at least one or more major resistance-associated mutation[24] was found in 1,030 (11.2%) of the ART-naïve people tested for resistance, including 370 (4.0%) with NRTI-associated resistance mutations, 590 (6.4%) with NNRTI-associated resistance mutations, and 162 (1.8%) with PI-associated resistance mutations. The prevalence of transmitted drug resistance was low and remained stable between 2003 and 2023 (*Figure 4.13*).

Figure 4.13: *The annual percentage of people with evidence of transmitted HIV drug resistance over time. Transmitted drug resistance was defined as the presence of at least one resistance-associated mutation detected before initiation of ART. The 2022 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations[24].*



Legend: *NRTI = nucleotide/nucleoside reverse transcription inhibitor. NNRTI = non-NRTI. PI = protease inhibitor. RAS = resistance associated substitution.*

In total, 301 (3.3%) individuals screened for drug resistance before ART initiation harboured high-level resistance[25,26] to at least one antiretroviral drug: 53 (0.6%) to at least one NRTI; 226 (2.5%) to at least one NNRTI; and 37 (0.4%) to at least one PI. On the basis of the available resistance data, 96.8% were fully susceptible to all antiretroviral drugs: 2.8% (260) harboured high-level resistance to one drug class; 0.3% (29) to two drug classes; and less than 0.1% (five) to three drug classes (i.e., NRTIs, NNRTIs and PIs).

It should be emphasised that this does not mean that entire drug classes are rendered unsuitable for use in antiretroviral combinations. Even for people with resistance to all three classes, it often remains possible to construct fully efficacious ART combinations.

Integrase inhibitor resistance before HIV treatment initiation

In total, 587 people had an integrase sequence available prior to ART initiation, of whom all but 13 were ARV-naïve. Only one major integrase resistance-associated mutation was detected in these individuals (Y143Y/C).

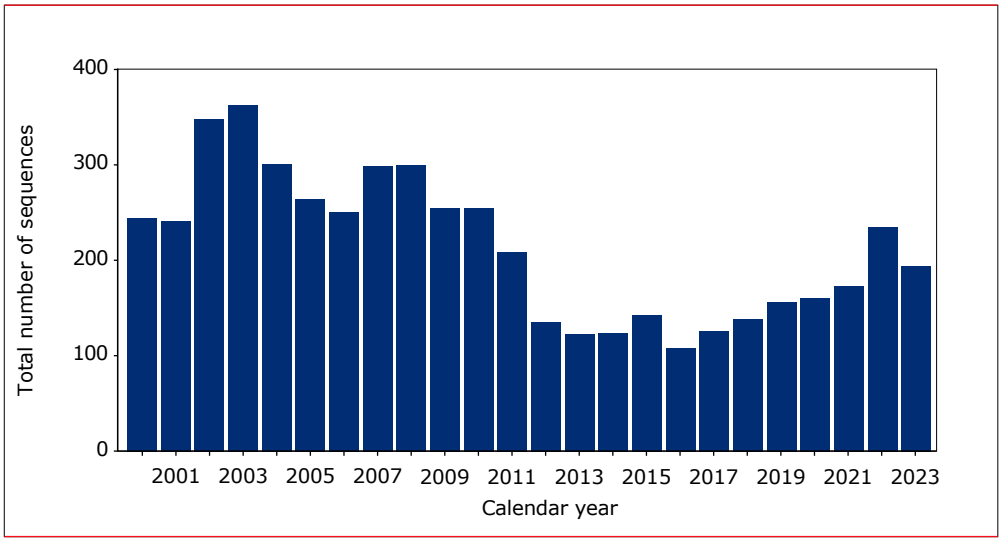
Acquired HIV drug resistance

The overall viral suppression rates of people receiving ART are very high and continue to improve in the Netherlands (see section *Virological response*). However, acquired-HIV drug resistance is still detectable in a subset of people receiving ART.

In this section, we describe the level of acquired drug resistance detected among the treated population with a viral load above 500 copies/ml, and resistance test results available after at least four months of ART in between 2000 and 2023. If ART had been interrupted more than two weeks before the test, the sequence was excluded from the analysis. As of December 2023, 5,147 HIV-1 sequences had been obtained from 3,071 people who received ART for at least four months in between 2000 and 2023. 3,732 sequences were from 2,312 people who had been ART-naïve before initiating ART. 5,050 reverse transcriptase sequences were available from 3,039 individuals, 4,790 protease sequences were available from 2,880 individuals, and 716 integrase sequences were available from 547 individuals.

The number of sequences in this group was consistently above 200 between 2000 and 2010, substantially declined in 2011, then slightly increased until 2023 (*Figure 4.14*). The median time between initial start of ART and resistance testing was 5.9 years (IQR 3.2-10.0). The main HIV-1 subtype was B (66.6%), followed by recombinant form CRF_02AG (11.3%), and subtype C (6.0%).

Figure 4.14: The annual number of HIV-1 sequences in people who received ART for at least four months.



Overall, sequences from people pre-treated with monotherapy or dual therapy were disproportionally represented: 1,415 (27.5%) sequences were obtained from 759 (24.7%) pre-treated people, and 3,732 (72.5%) sequences were obtained from 2,312 (75.5%) people who had started ART while not being pre-treated with NRTI mono- or dual-therapy. However, over time this difference became less distinct: in 2000, 72.8% of sequences were obtained from pre-treated people, compared with 36.1% in 2005, and less than 14% from 2010 onwards.

Of the 5,147 sequences obtained when the HIV RNA was above 500 copies/ml, 3,012 (58.5%) harboured high-level resistance to at least one antiretroviral drug. High-level NRTI resistance was detected in 3,040 (59.1%) sequences; of those, 2,584 (85.0%) harboured high-level resistance to emtricitabine or lamivudine. Notably, of the 1,872 individuals ever identified as harbouring the M184V or M184I mutation who were still in care in 2023, 1,196 (63.7%) were still on ART containing lamivudine or emtricitabine, of whom 944 (78.9%) had undetectable HIV-RNA at their last visit. In addition, 1,808 (35.8%) harboured high-level resistance to at least one NNRTI, and 1,041 (21.7%) to at least one PI.

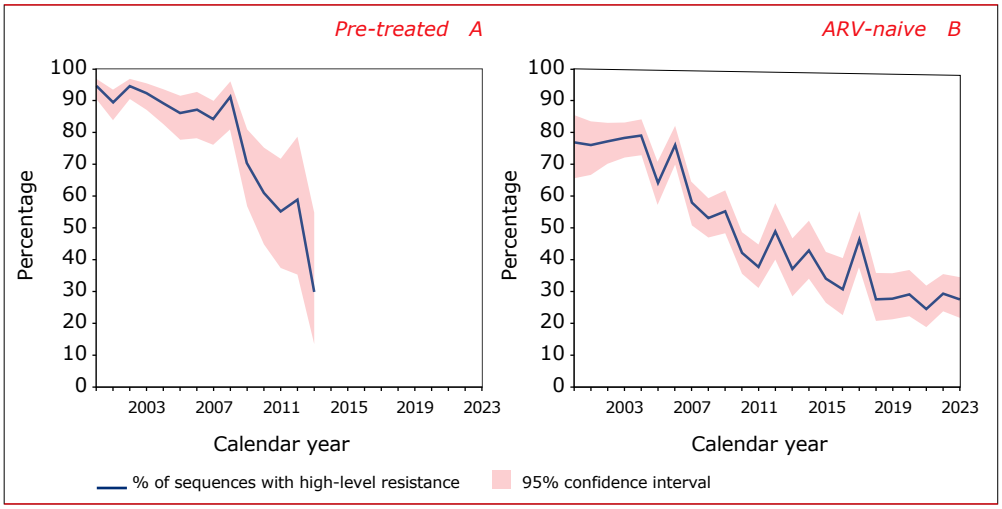
Previous antiretroviral drug exposure

The occurrence of acquired resistance was different for sequences obtained from people with mono NRTI therapy or dual NRTI therapy than for those from people who were ARV-naïve before initiating ART.

Among pre-treated people, the annual percentage of sequences harbouring high-level resistance to at least one drug was 94.9% (95% CI 90.5-97.3) in 2000, 61.1% (44.6-75.4) in 2010, and 29.4% (12.8-54.2) in 2013 (*Figure 4.15A*). The availability of new drugs both in existing and new drug classes largely explains the decline since 2008[34]. In recent years (2014-2023), both the number of pre-treated people, and the number of sequences from pre-treated people, were too low to provide meaningful percentages.

Among previously ARV-naïve people, high-level resistance to at least one drug was detected among 77.3% (95% CI 65.7-85.8) of sequences in 2000, 49.2% (40.3-58.1) in 2012, and 27.6% (21.6-34.6) in 2023 (*Figure 4.15B*). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naïve people has disappeared.

Figure 4.15: The annual percentage of sequences with evidence of high-level resistance to any antiretroviral drug, obtained at the time of virological failure when receiving antiretroviral therapy (ART), by prior antiretroviral (ARV) drug exposure, among A) people who were pre-treated with mono or dual nucleoside-analogue reverse transcriptase inhibitors, and B) previously antiretroviral drug-naïve people. The shaded area represents the 95% confidence interval.



Acquired HIV drug resistance among previously ARV-naïve people

In the remainder of our analysis, we focus solely on the 2,312 people who had not been pre-treated with NRTI mono- or dual-therapy before combination ART initiation. Overall, 2,046 (54.8%) of the 3,732 sequences from previously ARV-naïve people receiving ART harboured at least one major resistance mutation, which were associated with resistance to NRTI (1,585, or 42.5%), NNRTI (1,271, or 34.1%), or PI (380, or 10.2%).

In *Figure 4.16A.* the annual percentage of sequences harbouring high-level resistance is presented for each antiretroviral drug class. In 2000:

- 77.3% (95%CI 65.7-85.8) of sequences harboured high-level resistance to at least one NRTI;
- 27.7% (18.2-39.7) harboured high-level resistance to at least one NNRTI; and
- 49.2% (37.4-61.2) harboured high-level resistance to at least one PI.

The percentage of sequences with high-level resistance declined over time for these three drug classes, and in 2012:

- 49.2% (95%CI 40.3-58.1) of sequences harboured high-level resistance to at least one NRTI;
- 33.9% (25.9-42.9) harboured high-level resistance to at least one NNRTI; and
- 5.1% (2.3-10.9) harboured high-level resistance to at least one PI.

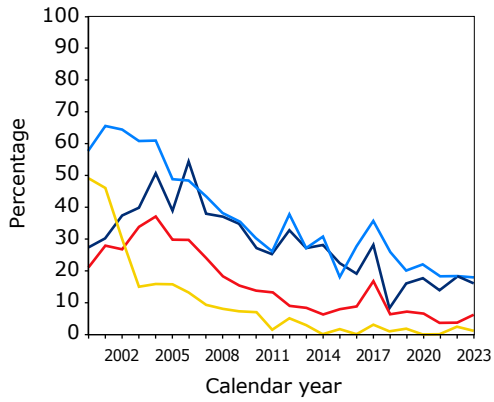
By 2023, these percentages were down to:

- 27.6% (95%CI 21.6-34.6) of sequences harbouring high-level resistance to at least one NRTI;
- 16.3% (11.5-22.6) harbouring high-level resistance to at least one NNRTI; and
- 1.3% (0.3-5.1) harbouring high-level resistance to at least one PI.

The percentage of sequences with at least one resistance mutation to all three drug classes (i.e., NRTI, NNRTI, and PI) also declined over time: from 9.1% (95% CI 4.1-18.8) in 2000 to 0% in 2014.

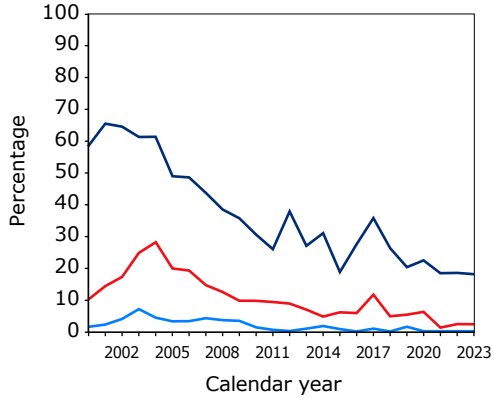
The annual percentage of sequences harbouring high-level resistance to individual antiretroviral drugs are presented in *Figure 4.16B-D*. The annual percentage of sequences harbouring major resistance mutations to specific drugs are outlined in *Appendix Table 4.3A-C*. *Figure 4.16E*, meanwhile, shows the annual percentage of sequences harbouring at least one high-level resistance mutation to all three drug classes. It should be pointed out that drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed, but instead remains viably archived in the viral reservoir.

Figure 4.16: *The annual percentage of sequences with evidence of high-level resistance by drug class and antiretroviral drug, obtained at the time of virological failure when receiving antiretroviral therapy (ART), among previously antiretroviral drug-naïve people. Results are shown by A) antiretroviral drug class: high-level resistance to at least one drug within class, B) antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors, C) antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors, D) antiretroviral drug: high-level resistance to protease inhibitors, and E) high-level resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.*



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

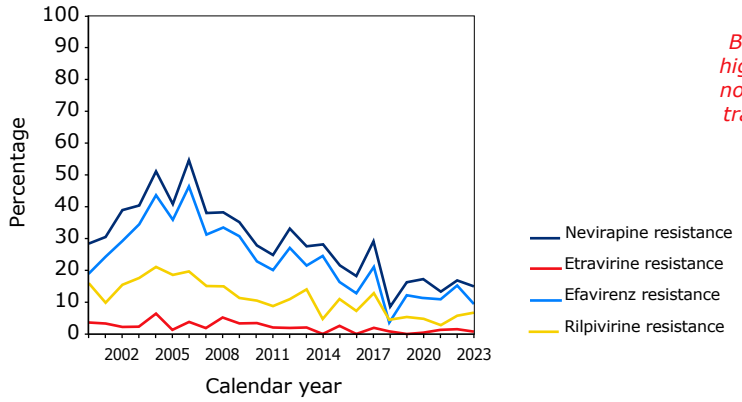
- Nucleoside reverse transcriptase inhibitor resistance (except emtricitabine/lamivudine)
- Emtricitabine/lamivudine resistance
- Non-nucleoside reverse transcriptase inhibitor resistance
- Protease inhibitor resistance



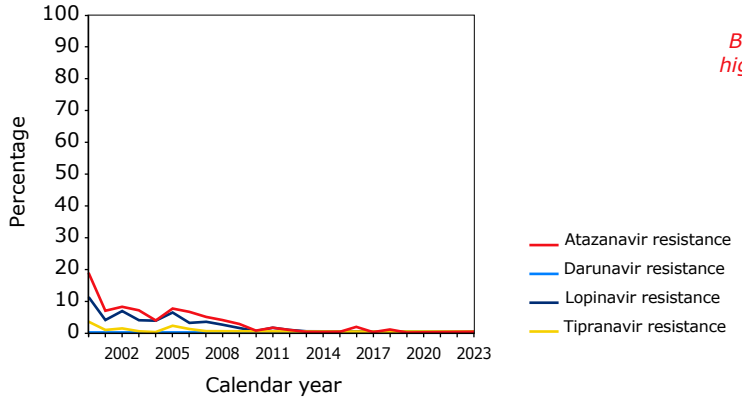
B
By antiretroviral drug: high-level resistance to nucleoside reverse transcriptase inhibitors

- Lamivudine/emtricitabine resistance
- Abacavir resistance
- Tenofovir resistance

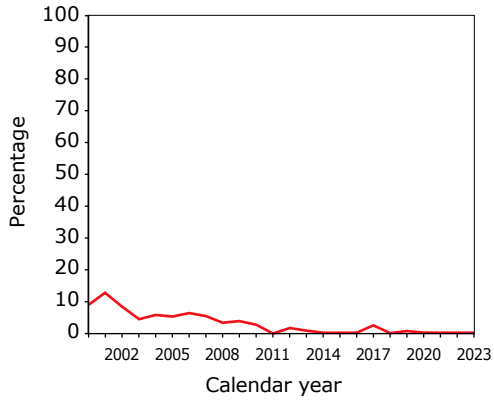
C
By antiretroviral drug: high-level resistance to non-nucleoside reverse transcriptase inhibitors



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



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



Legend: *NRTIs = nucleoside analogue reverse transcriptase inhibitors.*

Note: *The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 9.6) 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].*

Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on ART was relatively rare. The available 716 integrase sequences originated from 547 people who received ART for at least four months; 51 were pre-treated with monotherapy or dual NRTI therapy before initiating ART, and 496 were ARV-naïve before initiating ART. The median time between initial ART initiation and testing for integrase inhibitor resistance was 10.5 years (IQR 4.8-16.2). For each person, we used the most recent sequence in our analysis.

At least one acquired major mutation associated with integrase inhibitor resistance was detected in 58 of 547 individuals (observed in 77 of 716 sequences), which resulted in high-level resistance to at least one integrase inhibitor[24,25]. When assessing the last available integrase sequence of these 58 individuals, the following major INSTI resistance mutations were detected (numbers are given in parenthesis):

- N155H (19) and N155H/N (six);
- R263K (eight) and R263R/K (three);
- E92Q (six) and E92E/Q (three);
- Y143R (one) and Y143Y/C (one);
- T66I (three) and T66I/T (one);
- Q148H (one), Q148Q/H (one), Q148R (two); and
- S147G (one), S147S/G (one).

Minor mutations detected were at positions:

- T97 (any, nine; T97A, seven; T97T/A, two);
- T66 (any, five; T66T/A, three; T66T/K, one; T66K, one);
- L74 (any mutation, one; L74I/M, one);
- G140 (any, four; G140S, two; G140G/S, two); and
- E138 (any, two; E138K, two).

Seven of the 58 individuals who harboured major INSTI resistance mutations had ever received INSTI-monotherapy.

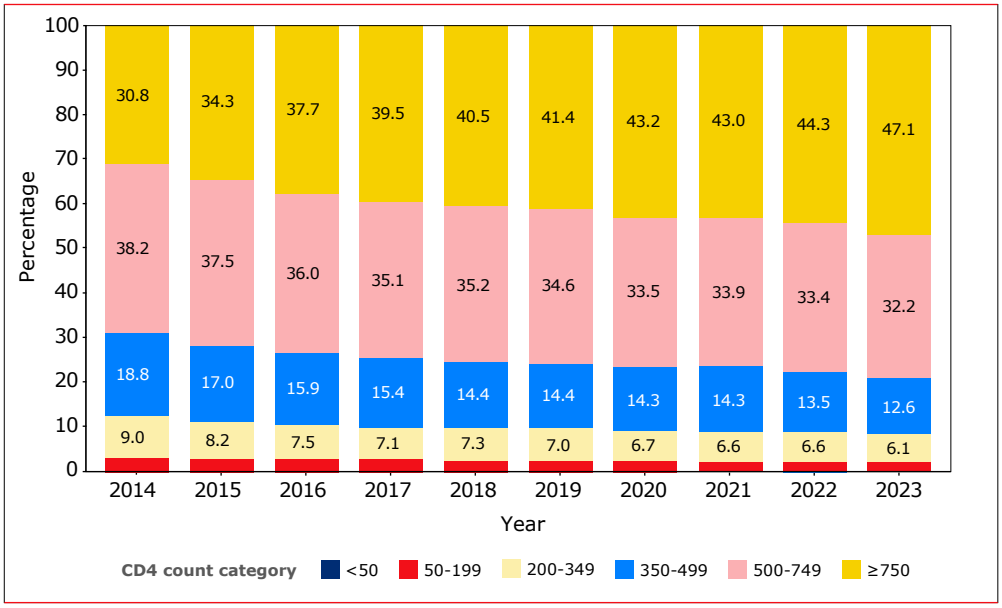
Immunological response

After initiation of ART, most people durably suppress 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[18,35]. 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[19]. Normal CD4 counts in men without HIV are on average approximately 830 cells/mm^3 and around 1000 cells/mm^3 in women, but this varies according to factors such as age, ethnicity, and smoking behaviour[36,37]. The clinical benefit of ART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)[38-42].

Immunological response by calendar year

Of all individuals who were on ART in the period 2014 to 2023, CD4 count data are shown in *figures 4.17*. The percentage of individuals on ART with a normalised CD4 count (i.e. with a CD4 count over 500 cells/mm^3) increased from 69.0% in 2014 to 79.3% in 2013. The percentage of individuals on ART with CD4 counts below 350 cells/mm^3 slowly continued to decrease from 12.2% in 2014 to 8.1% in 2023. 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 4.17: 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 (2014–2019)

The distribution of pre-ART CD4 counts in ART-naïve individuals initiating first-line ART has remained fairly constant in the period between 2014 and 2023 (*Figure 4.18*). In 2023, 25.2% of individuals initiating ART had a CD4 count below 200 cells/mm^3, and another 22.4% had a CD4 count between 200 and <350 cells/mm^3. This trend closely resembles the CD4 counts at HIV diagnosis (see Chapter 1).

We also assessed the immunological response in individuals who started ART between in 2014-2019 to allow for a potential follow-up of 5 years. The level of viral suppression and treatment interruptions after initiating ART were not taken into account in this analysis, but are generally very high. The changes in the CD4 count distribution following ART initiation are visualized in *Figure 4.19A*. Whereas at the initiation of ART 22.4% of individuals had a CD4 count below 200 cells/mm^3 and another 18.2% had a CD4 count between 200 and <350 cells/mm^3, these proportions had decreased after 5 years of ART to 7.2% with a CD4 count below 200 cells/mm^3 and 11.9% 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 4.19B* 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 10.3% of individuals who initiate ART with a CD4 below 50 remain below 200 after 5 years of ART, and only 3.6% 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 4.18: *The pre-ART CD4 count in ART-naïve individuals initiating first-line ART by calendar year (missing measurements/data were not taken into account).*

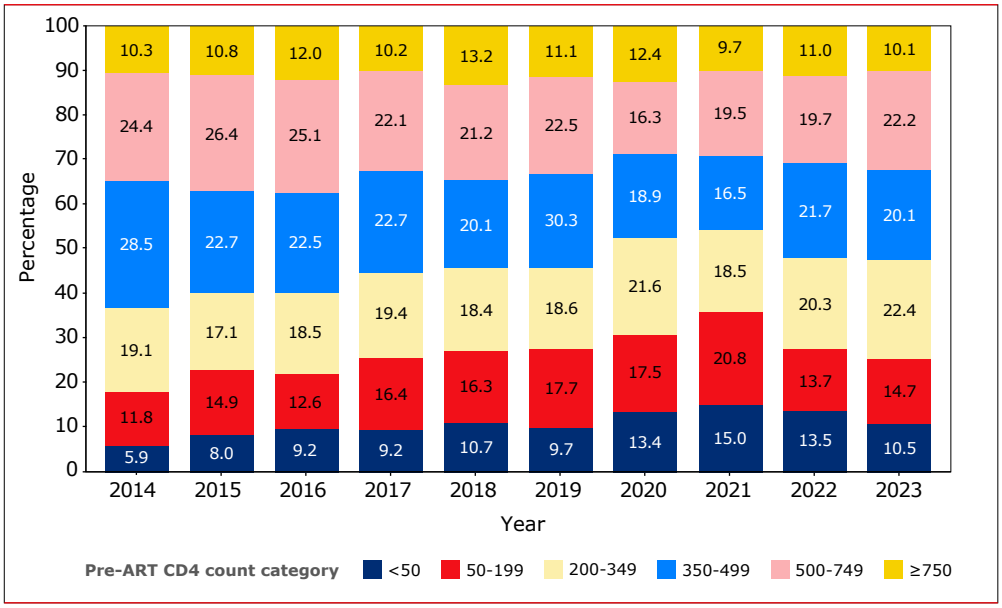
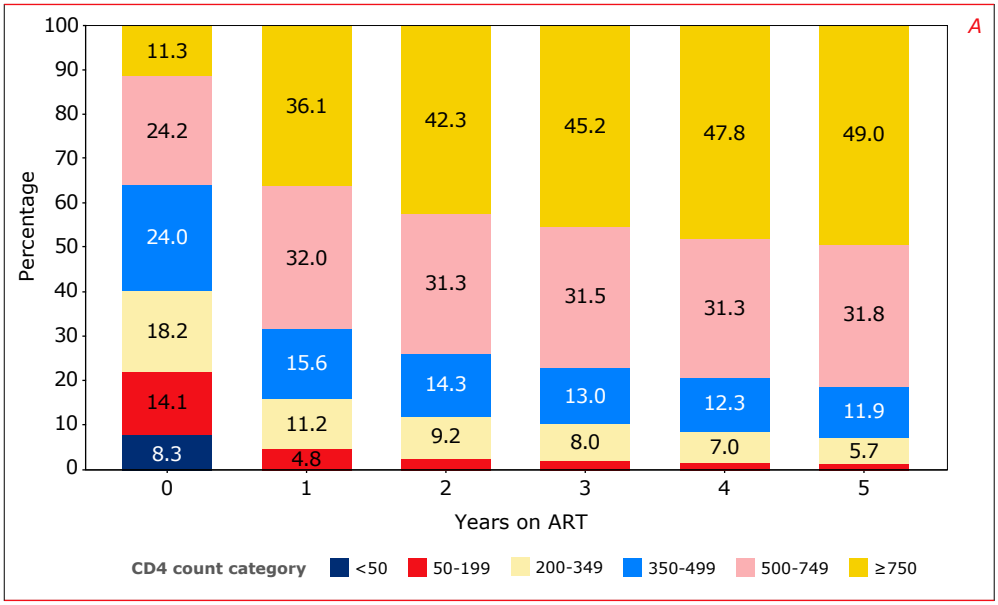
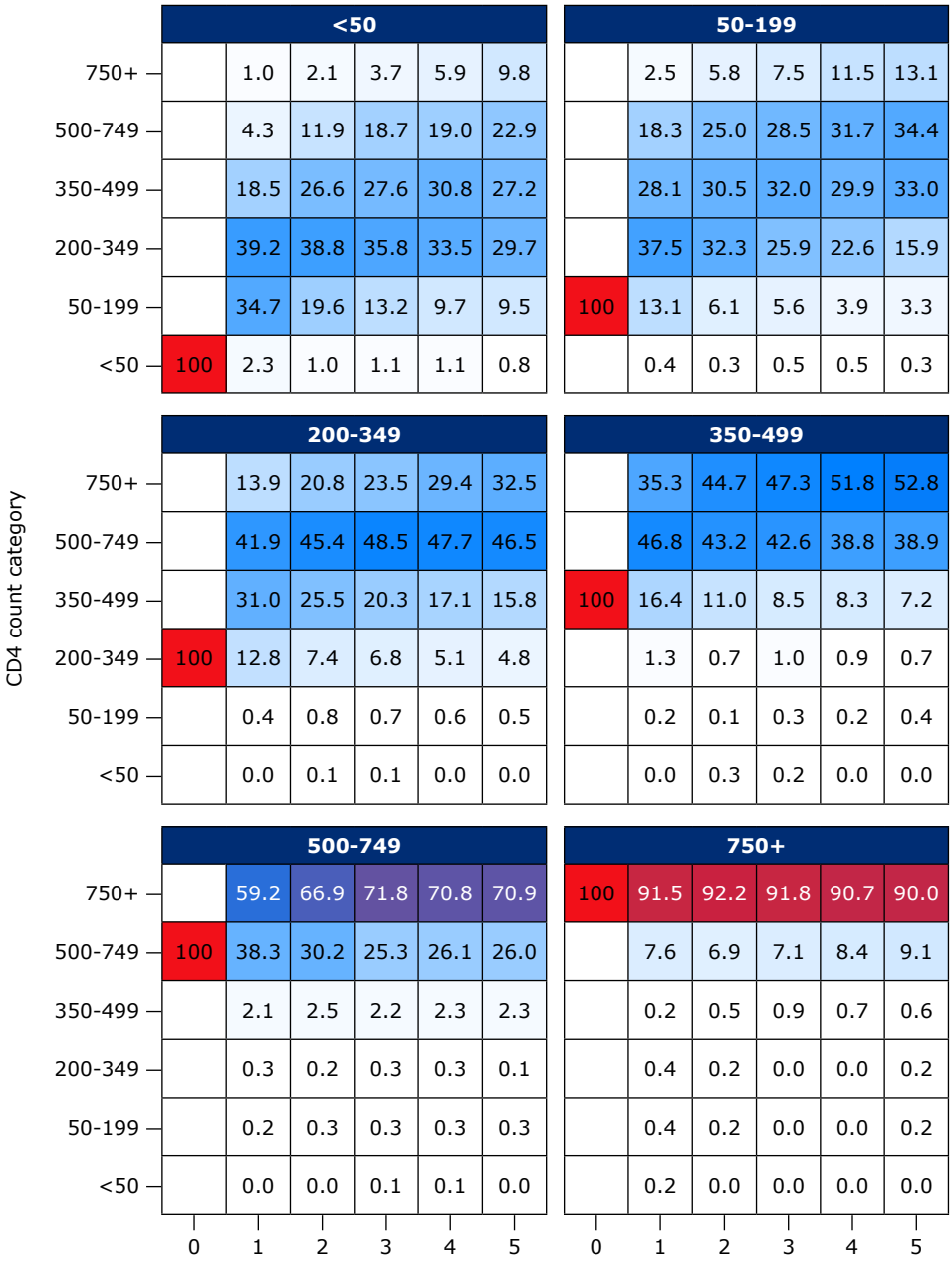


Figure 4.19A&B: Changes in CD4 count distribution over 5 years following the start of antiretroviral therapy (ART) in 2014-2019 (A) and stratified for the last measured CD4 count prior to start of ART (B).



B



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 2014 and 2023, 7,860 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 19 (IQR 11-31) days in 2023.
- Between 2014 and 2021 there was a slowly decreasing trend in the CD4 count at ART initiation. However, in 2022 and 2023 the CD4 count at the start of ART has risen slightly again. In 2023, 25.2% of individuals initiating ART had a CD4 count below 200 cells/mm^3, and another 22.4% 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 2023, 91.3% of initial regimens contained an integrase inhibitor. In 2023, the most frequently used initial regimen was TDF/FTC/dolutegravir (39.5%). TAF/FTC/bictegravir was used in 37.7% of initial regimens.

In care and receiving ART in 2023

- The number of people on ART and in active follow-up in the ATHENA cohort grew from 17,202 individuals in 2014 to 22,215 individuals in 2023.
- In 2023, the vast majority (91.0%) of individuals received a regimen based on one or two nucleoside analogue reverse transcriptase inhibitors (NRTIs), combined with an integrase inhibitor (55.8%), a non-nucleoside reverse transcriptase inhibitor (26.6%) or a protease inhibitor (8.6%).
- Long-acting injectables (cabotegravir/rilpivirine) were used by 3.1%.
- The population had been diagnosed with HIV a median of 14.1 (IQR 8.4-20.4) years ago, and started their first-line ART regimen a median of 12 (IQR 7.5-17.9) years ago.
- Their last measured viral load was <50 copies/ml in 95.8% (<200 copies/ml in 97.9%), and 79.2% 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 (21.7%), treatment simplification (18.6%), patient decision/compliance (7.9%), and preventive modifications (7.2%). In only 1,218 (1.7%) regimen the reported reason for modification was virological treatment failure. The rate with which ART regimens were modified slowly decreased over time.
- The proportion of the treated population that at any moment has temporarily interrupted ART continues to decrease, from 2.8% in 2014 to 0.7% in 2023, indicating the improved tolerability of modern ART regimen.

- In 2,905 individuals a total of 4,815 treatment interruptions (of 14 days or longer) were recorded. The median duration of the recorded treatment interruptions was 13.7 (IQR 5.0-37.1) weeks. Many long interruptions constitue temporary disengagement of care. During longer treatment interruptions the CD4 counts often drops significantly.

Virological and immunological response and drug resistance

The overall viral suppression rates of the population with HIV receiving ART is high and has continued to improve. Among the limited number of individuals who experienced virological failure, the annual percentage with acquired drug resistance remained low; this is in line with findings in other high-income settings[43,44].

Transmitted drug resistance was rare, and the overall prevalence was low and stable over time, in line with rates reported by other European countries[45].

Integrase inhibitor resistance data remain limited. Only one case of transmitted integrase inhibitor resistance was detected among the 587 people tested by the end of 2023. Detected rates of acquired integrase inhibitor resistance among available sequences remained low, with only a handful of cases with significant resistance to dolutegravir or bictegravir.

Virtually all individuals who initiated first-line ART who had high (500+ cells/mm^3) CD4 counts at the start of treatment, remained in the higher CD4 strata. Contrary, 10.3% of individuals who initiate ART with a CD4 below 50 cells/mm^3 remain below 200 cells/mm^3 after 5 years of ART, and 3.6% of individuals who initiate ART with a CD4 between 50 cells/mm^3 and <200 cells/mm^3 remain below 200 cells/mm^3 after 5 years of ART.

References

1. Cole SR, Hernán MA, Robins JM, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *American journal of epidemiology* 2003; **158**(7): 687-94.
2. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA* 2016; **316**(2): 171-81.
3. EACS. EACS Guidelines, version 12.0. October 2023. http://www.europeanaidsclinicalsociety.org/guid/index.html?b=annex&p=3.
4. Shilaih M, Marzel A, Yang WL, et al. Genotypic resistance tests sequences reveal the role of marginalized populations in HIV-1 transmission in Switzerland. *Scientific reports* 2016; **6**(May): 27580-.
5. DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. September 2024. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf.
6. WHO. World Health Organisation Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection; 2016.
7. Ryom L, Boesecke C, Bracchi M, et al. Highlights of the 2017 European AIDS Clinical Society (EACS) Guidelines for the treatment of adult HIV-positive persons version 9.0. *HIV medicine* 2018; **19**(5): 309-15.
8. NVHB. Richtlijn HIV - Nederlandse Vereniging van HIV Behandelaren (NVHB). 2024. https://richtlijnhiv.nvhb.nl/index.php/Inhoud.
9. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: Results from the phase 3 HPTN 052 randomised controlled trial. *The Lancet Infectious Diseases* 2014; **14**(4): 281-90.
10. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine* 2011; **365**(6): 493-505.
11. Prevention Access Campaign. Consensus Statement: Risk of sexual transmission of HIV from a person living with HIV who has an undetectable viral load - Messaging Primer & Consensus Statement. https://www.preventionaccess.org/consensus (accessed November 14, 2019.
12. Nederlandse Vereniging van HIVB. Het risico om hiv over te dragen is verwaarloosbaar klein indien de infectie goed behandeld wordt. 2017. http://nvhb.nl/2017/05/03/wetenschappelijk-onderzoek-toont-aan-dat-het-risico-om-hiv-over-te-dragen-verwaarloosbaar-klein-is-indien-de-infectie-goed-behandeld-wordt/.

13. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *The New England journal of medicine* 2000; **342**(13): 921-9.
14. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *Journal of Acquired Immune Deficiency Syndromes* 2002; **29**(3): 275-83.
15. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS* 2011; **25**(4): 473-7.
16. Raboud JM, Rae S, Woods R, et al. Consecutive rebounds in plasma viral load are associated with virological failure at 52 weeks among HIV-infected patients. *AIDS (London, England)* 2002; **16**(12): 1627-32.
17. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS (London, England)* 2004; **18**(7): 981-9.
18. Hughes RA, Sterne JAC, Walsh J, et al. Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. *HIV Medicine* 2011; **12**(10): 583-93.
19. van Lelyveld SF, Gras L, Kesselring A, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS* 2012; **26**(4): 465-74.
20. Zhang S, van Sighem A, Gras L, et al. Clinical significance of transient HIV type-1 viraemia and treatment interruptions during suppressive antiretroviral treatment. *Antiviral therapy* 2010; 15(4): 555-62.
21. Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to < 400 copies/ml. *AIDS* 2002; **16**(11): 1521-7.
22. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *Journal of Acquired Immune Deficiency Syndromes* 2004; **37**(1): 1147-54.
23. Boender TS, Smit C, Sighem Av, et al. AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. *BMJ open* 2018; **8**(9): e022516-e.
24. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. Special Contribution 2022 Update of the Drug Resistance Mutations in HIV-1. **30**.
25. University S. HIV Drug Resistance Database, version 9.6. https://hivdb.stanford.edu/page/release-notes/.
26. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis* 2006; **42**(11): 1608-18.

27. Vasylyev M, Wit F, Jordans CCE, et al. Dolutegravir/Lamivudine Is Noninferior to Continuing Dolutegravir- and Non-Dolutegravir-Based Triple-Drug Antiretroviral Therapy in Virologically Suppressed People With Human Immunodeficiency Virus: DUALING Prospective Nationwide Matched Cohort Study. *Open Forum Infect Dis* 2024; **11**(4): ofae160.
28. Oomen PGA, Wit F, Brinkman K, et al. Real-world effectiveness and tolerability of switching to doravirine-based antiretroviral therapy in people with HIV: a nationwide, matched, prospective cohort study. *Lancet HIV* 2024; **11**(9): e576-e85.
29. World Health O. HIV Drug Resistance Report 2017. Geneva: World Health Organization, 2017.
30. Little SJ, Frost SDW, Wong JK, et al. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. *Journal of virology* 2008; **82**(11): 5510-8.
31. Bezemer D, De Ronde A, Prins M, et al. Evolution of transmitted HIV-1 with drug-resistance mutations in the absence of therapy: Effects on CD4+ T-cell count and HIV-1 RNA load. *Antiviral Therapy* 2006; **11**(2): 173-8.
32. Barbour JD, Hecht FM, Wrin T, et al. Persistence of primary drug resistance among recently HIV-1 infected adults. *AIDS* 2004; **18**(12): 1683-9.
33. Boukli N, Boyd A, Collot M, Meynard J-L, Girard P-M, Morand-Joubert L. Utility of HIV-1 DNA genotype in determining antiretroviral resistance in patients with low or undetectable HIV RNA viral loads. *Journal of Antimicrobial Chemotherapy* 2018; **73**(11): 3129-36.
34. Lange JM, Ananworanich J. The discovery and development of antiretroviral agents. *Antiviral therapy* 2014; **19 Suppl 3**: 5-14.
35. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm3 or greater. *Journal of Acquired Immune Deficiency Syndromes* 2007; **45**(2): 183-92.
36. Tsegaye A, Messele T, Tilahun T, et al. Immunohematological reference ranges for adult Ethiopians. *Clin Diagn Lab Immunol* 1999; **6**(3): 410-4.
37. Gras L, May M, Ryder LP, et al. Determinants of Restoration of CD4 and CD8 Cell Counts and Their Ratio in HIV-1-Positive Individuals with Sustained Virological Suppression on Antiretroviral Therapy. *Journal of Acquired Immune Deficiency Syndromes* 2019; **80**(3): 292-300.
38. Effros RB, Fletcher CV, Gebo K, et al. Aging and Infectious Diseases: Workshop on HIV Infection and Aging: What Is Known and Future Research Directions. *Clinical Infectious Diseases* 2008; **47**(4): 542-53.
39. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* 2008; **22**(7): 841-8.

40. Baker JV, Peng G, Rapkin J, et al. Poor initial CD4+ recovery with antiretroviral therapy prolongs immune depletion and increases risk for AIDS and non-AIDS diseases. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2008; **48**(5): 541-6.
41. Antiretroviral Therapy Cohort C. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *The Lancet* 2008; **372**(9635): 293-9.
42. Lanoy E, May M, Mocroft A, et al. Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements. *AIDS* 2009; **23**(16): 2199-208.
43. Scherrer AU, von Wyl V, Yang W-L, et al. Emergence of acquired HIV-1 drug resistance almost stopped in Switzerland: A 15-year prospective cohort analysis. *Clinical Infectious Diseases* 2016; **62**(10): 1310-7.
44. Buchacz K, Baker R, Ward DJ, et al. Trends in decline of antiretroviral resistance among ARV-experienced patients in the HIV outpatient study: 1999-2008. *AIDS Research and Treatment* 2012; **2012**.
45. Hofstra LM, Sauvageot N, Albert J, et al. Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe. *Clinical Infectious Diseases* 2016; **62**(5): 655-63.

Appendix

Appendix Table 4.1: *Frequency of and reasons for discontinuation / modification of various ARV regimen in the period 2014–2023.*

				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	13206	5968	3970	48	3.6	914	69.2
DTG/3TC	6855	3511	2910	32	4.7	284	41.4
ABC/3TC/DTG	21934	6601	1890	62	2.8	1929	87.9
TAF/FTC/DTG	3409	1277	511	21	6.2	210	61.6
TDF/FTC/DTG	6288	3752	1091	41	6.5	768	122.1
TAF/FTC/EVG/c	17249	4777	2031	64	3.7	902	52.3
TDF/FTC/EVG/c	7128	2611	479	46	6.5	649	91.0
TDF/FTC/RAL	2384	1203	137	32	13.4	221	92.7
Other INSTI+NRTI	2023	1104	256	18	8.9	164	81.1
NNRTI + NRTI							
TDF/3TC/DOR	4906	2607	1841	36	7.3	408	83.2
TDF/FTC/EFV	19895	5462	1158	108	5.4	2554	128.4
ABC/3TC/NVP	4073	845	245	32	7.9	177	43.5
TAF/FTC/NVP	4416	1176	710	15	3.4	204	46.2
TDF/FTC/NVP	14236	3289	833	80	5.6	813	57.1
TAF/FTC/RPV	6268	1881	983	25	4.0	313	49.9
TDF/FTC/RPV	9440	3047	426	62	6.6	834	88.3
Other NNRTI+NRTI	4227	1762	289	29	6.9	462	109.3
PI + NRTI							
TDF/FTC/ATV/b	4920	2067	145	50	10.2	533	108.3
TAF/FTC/DRV/c	6736	2646	1356	37	5.5	444	65.9
TDF/FTC/DRV/b	8903	4197	393	78	8.8	818	91.9
TDF/FTC/LPV/r	686	458	18	13	18.9	90	131.1
Other PI+NRTI	5064	2432	235	50	9.9	490	96.8
2 anchor drugs							
CAB/RPV	977	806	692	12	12.3	40	40.9
DTG/DRV/b	2326	791	391	11	4.7	112	48.2
DTG/RPV	586	263	144	5	8.5	38	64.8
2 anchors w/wo NRTI	4552	2482	408	89	19.6	378	83.0

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

Stop reasons (n & rate per 1,000PY)									
Patient choice		Simplification		Prevention		Pregnancy		Other reasons	
(n)	(rate)	(n)	(rate)	(n)	(rate)	(n)	(rate)	(n)	(rate)
394	29.8	231	17.5	88	6.7	53	4.0	270	20.4
71	10.4	93	13.6	17	2.5	21	3.1	83	12.1
648	29.5	955	43.5	613	27.9	86	3.9	418	19.1
100	29.3	316	92.7	21	6.2	16	4.7	82	24.1
263	41.8	1091	173.5	229	36.4	37	5.9	232	36.9
399	23.1	514	29.8	511	29.6	69	4.0	287	16.6
254	35.6	568	79.7	398	55.8	25	3.5	192	26.9
102	42.8	456	191.3	92	38.6	36	15.1	127	53.3
60	29.7	345	170.6	50	24.7	11	5.4	200	98.9
116	23.6	84	17.1	29	5.9	14	2.9	79	16.1
293	14.7	475	23.9	474	23.8	35	1.8	365	18.3
61	15.0	125	30.7	149	36.6	7	1.7	49	12.0
42	9.5	100	22.6	33	7.5	1	0.2	71	16.1
222	15.6	736	51.7	404	28.4	12	0.8	189	13.3
87	13.9	214	34.1	97	15.5	14	2.2	148	23.6
240	25.4	648	68.6	440	46.6	43	4.6	354	37.5
90	21.3	555	131.3	136	32.2	11	2.6	190	44.9
240	48.8	696	141.5	198	40.2	54	11.0	151	30.7
289	42.9	223	33.1	123	18.3	40	5.9	134	19.9
592	66.5	1633	183.4	329	37.0	99	11.1	255	28.6
67	97.6	188	273.9	23	33.5	20	29.1	39	56.8
262	51.7	865	170.8	225	44.4	85	16.8	220	43.4
15	15.4	2	2.0	8	8.2	0	0.0	37	37.9
93	40.0	89	38.3	36	15.5	4	1.7	55	23.6
20	34.1	28	47.8	8	13.6	2	3.4	18	30.7
211	46.4	946	207.8	156	34.3	27	5.9	267	58.7

Appendix Table 4.2: Virological treatment response in 2014–2023 in people who started ART at least months earlier.

Calendar year	Total population N	Viral load categories (c/ml)											
			<50		50–199		200–999		1,000–9,999		10,000+		ART interrupted	
		N	%	N	%	N	%	N	%	N	%	N	%
2014	17,016	15,442	90.75	580	3.41	216	1.27	134	0.79	230	1.35	414	2.43
2015	17,916	16,497	92.08	552	3.08	187	1.04	106	0.59	214	1.19	360	2.01
2016	18,715	17,458	93.28	469	2.51	145	0.77	112	0.60	199	1.06	332	1.77
2017	19,405	18,075	93.15	568	2.93	156	0.80	82	0.42	183	0.94	341	1.76
2018	20,082	18,904	94.13	437	2.18	156	0.78	103	0.51	163	0.81	319	1.59
2019	20,686	19,476	94.15	501	2.42	161	0.78	89	0.43	157	0.76	302	1.46
2020	21,089	20,047	95.06	440	2.09	144	0.68	66	0.31	101	0.48	291	1.38
2021	21,306	20,297	95.26	418	1.96	137	0.64	59	0.28	128	0.60	267	1.25
2022	21,794	20,675	94.87	490	2.25	136	0.62	93	0.43	156	0.72	244	1.12
2023	22,119	21,132	95.54	421	1.90	141	0.64	96	0.43	160	0.72	169	0.76

Appendix Table 4.3A–C: Acquired drug resistance: annual percentage of available sequences with major resistance mutations after virological failure by antiretroviral drug, associated with people who received combination antiretroviral therapy and were previously antiretroviral drug-naïve. Results are shown by A) major resistance mutations to nucleoside reverse transcriptase inhibitors, B) major resistance mutations to non-nucleoside reverse transcriptase inhibitors, and C) major resistance mutations to protease inhibitors.

A

Treatment/mutation	Calendar year									
	2019		2020		2021		2022		2023	
	n	%	n	%	n	%	n	%	n	%
Emtricitabine/lamivudine		(N=133)		(N=115)		(N=125)		(N=180)		(N=150)
K65R. E or N	6	4.5	5	4.3	2	1.6	4	2.2	3	2
M184V or I	27	20.3	25	21.7	23	18.4	35	19.4	25	16.7
Abacavir		(N=130)		(N=112)		(N=121)		(N=174)		(N=145)
K65R. E or N	4	3.1	4	3.6	2	1.7	3	1.7	2	1.4
L74V	2	1.5	3	2.7	0	0	0	0	0	0
Y115F	2	1.5	3	2.7	0	0	0	0	0	0
M184V	20	15.4	18	16.1	13	10.7	23	13.2	18	12.4
Tenofovir		(N=129)		(N=110)		(N=123)		(N=176)		(N=147)
K65R. E or N	4	3.3	5	3.9	4	3.4	2	1.6	5	2.6
K70R	1	0.8	1	0.8	0	0	1	0.8	1	0.5

B

	Calendar year									
	2019		2020		2021		2022		2023	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Nevirapine		(N=134)		(N=110)		(N=124)		(N=175)		(N=146)
L100I	0	0	0	0	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	13	9.7	10	9.1	12	9.7	17	9.7	6	4.1
V106A or M	1	0.7	4	3.6	0	0	1	0.6	4	2.7
V108I	6	4.5	4	3.6	2	1.6	3	1.7	3	2.1
Y181C or I	7	5.2	8	7.3	5	4	6	3.4	8	5.5
Y188L. C or H	2	1.5	1	0.9	0	0	4	2.3	0	0
G190A	0	0	1	0.9	2	1.6	1	0.6	4	2.7
M230L	1	0.7	0	0	1	0.8	1	0.6	0	0
Etravirine		(N=125)		(N=107)		(N=122)		(N=175)		(N=142)
L100I	0	0	0	0	0	0	0	0	0	0
L101P	0	0	0	0	0	0	0	0	0	0
Y181C. I or V	0	0	0	0	2	1.6	3	1.7	1	0.7
Efavirenz		(N=128)		(N=106)		(N=122)		(N=175)		(N=141)
L100I	0	0	0	0	0	0	0	0	0	0
K101P	0	0	0	0	0	0	0	0	0	0
K103N or S	13	10.2	10	9.4	12	9.8	17	9.7	6	4.3
V106M	1	0.8	1	0.9	0	0	1	0.6	0	0
V108I	3	2.3	1	0.9	2	1.6	2	1.1	2	1.4
Y181C or I	1	0.8	2	1.9	2	1.6	4	2.3	2	1.4
Y188L	1	0.8	0	0	0	0	4	2.3	0	0
G190S or A	0	0	1	0.9	2	1.6	6	3.4	3	2.1
P225H	1	0.8	0	0	1	0.8	1	0.6	0	0
M230L	0	0	0	0	2	1.6	3	1.7	2	1.4
Rilpivirine		(N=129)		(N=107)		(N=122)		(N=177)		(N=143)
L100I	0	0	0	0	0	0	0	0	0	0
K101E or P	1	0.8	2	1.9	2	1.6	5	2.8	4	2.8
E138A. G. K. Q or R	7	5.4	11	10.3	6	4.9	13	7.3	12	8.4
V179L	0	0	0	0	0	0	0	0	0	0
Y181C. I or V	4	3.1	3	2.8	3	2.5	4	2.3	4	2.8
Y188L	1	0.8	0	0	0	0	4	2.3	0	0
H221Y	3	2.3	2	1.9	2	1.6	6	3.4	1	0.7
F227C	0	0	0	0	0	0	0	0	0	0
M230I or L	1	0.8	0	0	1	0.8	1	0.6	0	0

C

	Calendar year									
	2019		2020		2021		2022		2023	
Treatment/mutation	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Atazanavir		(N=105)		(N=82)		(N=98)		(N=119)		(N=128)
I50L	0	0	0	0	0	0	0	0	0	0
I84V	1	1	0	0	0	0	0	0	0	0
N88S	0	0	0	0	0	0	0	0	0	0
Darunavir		(N=104)		(N=82)		(N=98)		(N=119)		(N=128)
I47V	0	0	0	0	0	0	0	0	1	0.8
I50V	0	0	0	0	0	0	0	0	0	0
I54M or L	0	0	0	0	0	0	0	0	0	0
L76V	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	0	0	0	0	0	0
Lopinavir		(N=105)		(N=82)		(N=98)		(N=119)		(N=128)
V32I	0	0	0	0	0	0	0	0	0	0
I47V or A	0	0	0	0	0	0	0	0	1	0.8
I50V	0	0	0	0	0	0	0	0	0	0
I54V. L or M	1	1	0	0	0	0	0	0	0	0
L76V	1	1	0	0	0	0	0	0	0	0
V82A. F. T or S	0	0	0	0	0	0	0	0	0	0
I84V	1	1	0	0	0	0	0	0	0	0
Tipranavir		(N=104)		(N=82)		(N=98)		(N=119)		(N=127)
I47V	0	0	0	0	0	0	0	0	0	0
Q58E	0	0	1	1.2	1	1	0	0	1	0.8
T74P	0	0	0	0	0	0	0	0	0	0
V82L or T	0	0	0	0	0	0	0	0	0	0
N83D	0	0	0	0	0	0	0	0	0	0
I84V	0	0	0	0	0	0	0	0	0	0