Monitoring Report 2014

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

HIV Monitoring

Contributing to the quality of HIV care

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001. Based in Amsterdam, SHM was appointed by the Dutch Ministry of Health, Welfare and Sports (Ministerie van Volksgezondheid, Welzijn en Sport) as the national executive organisation for the registration and monitoring of HIV-infected patients in follow-up in Dutch HIV treatment centres.

Our mission:

To further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection.

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HIV Monitoring

Colophon

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Appendix

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Web Appendix Table 1.1: Characteristics of the 17,750 HIV-infected patients in follow-up as of June 2014. Co-infection with hepatitis B (HBV) was defined by the presence of the HBV surface antigen, whilst co-infection with hepatitis C (HCV) was defined as a positive HCV RNA measurement.

	MSM	Heterosexual		IDU		Blood or blood products		Other / unknown		Total	
	Men	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	N=10,753	N=2,273	N=3,035	N=252	N=96	N=146	N=91	N=847	N=257	N=14,271	N=3,479
Current age [years]											
0–12	0	0	0	0	0	0	0	57	60	57	60
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	6.7%	23.3%	0.4%	1.7%
13–17	0	0	3	0	0	1	2	37	32	38	37
	0.0%	0.0%	0.1%	0.0%	0.0%	0.8%	2.2%	4.4%	12.5%	0.3%	1.1%
18–24	201	17	54	1	0	5	2	47	37	271	93
	1.9%	0.7%	1.8%	0.4%	0.0%	3.4%	2.2%	5.5%	14.4%	1.9%	2.7%
25–34	1,356	239	609	16	3	16	13	102	30	1,729	655
	12.6%	10.5%	20.1%	6.3%	3.1%	11.0%	14.3%	12.0%	11.7%	12.1%	18.8%
35–44	2,639	553	1,097	35	12	31	31	177	37	3,435	1,177
	24.5%	24.3%	36.1%	13.9%	12.5%	21.2%	34.1%	20.9%	14.4%	24.1%	33.8%
45–54	3,871	829	843	122	48	48	22	235	38	5,105	951
	36.0%	36.5%	27.8%	48.4%	50.0%	32.9%	24.2%	27.7%	14.8%	35.8%	27.3%
55–64	1,994	428	308	74	30	26	14	123	17	2,645	369
	18.5%	18.8%	10.1%	29.4%	31.3%	17.8%	15.4%	14.5%	6.6%	18.5%	10.6%
≥65	692	207	121	4	3	19	7	69	6	991	137
	6.4%	9.1%	4.0%	1.6%	3.1%	13.0%	7.7%	8.1%	2.3%	6.9%	3.9%
Current age 50 years or older											
No	6201	1251	2263	103	29	80	60	551	218	8186	2570
	57.7%	55.0%	74.6%	40.9%	30.2%	54.8%	65.9%	65.1%	84.8%	57.4%	73.9%
Yes	4552	1022	772	149	67	66	31	296	39	6085	909
	42.3%	45.0%	25.4%	59.1%	69.8%	45.2%	34.1%	34.9%	15.2%	42.6%	26.1%
Current age 60 years or older											
No	9,240	1,913	2,794	223	86	117	79	728	248	12,221	3,207
	85.9%	84.2%	92.1%	88.5%	89.6%	80.1%	86.8%	86.0%	96.5%	85.6%	92.2%
Yes	1,513	360	241	29	10	29	12	119	9	2,050	272
	14.1%	15.8%	7.9%	11.5%	10.4%	19.9%	13.2%	14.0%	3.5%	14.4%	7.8%

	MSM	Heterosexual		IDU		Blood or blood products		Other / unknown		Total	
	Men	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	N=10,753	N=2,273	N=3,035	N=252	N=96	N=146	N=91	N=847	N=257	N=14,271	N=3,479
Region of origin											
Netherlands	7,901	1,024	832	153	50	95	19	385	109	9,558	1,010
	73.5%	45.1%	27.4%	60.7%	52.1%	65.1%	20.9%	45.5%	42.4%	67.0%	29.0%
Sub-Saharan Africa	130	659	1346	4	0	27	41	217	82	1037	1,469
	1.2%	29.0%	44.3%	1.6%	0.0%	18.5%	45.1%	25.6%	31.9%	7.3%	42.2%
Western Europe	702	73	74	25	29	5	2	40	24	845	129
	6.5%	3.2%	2.4%	9.9%	30.2%	3.4%	2.2%	4.7%	9.3%	5.9%	3.7%
South America	671	206	299	9	1	2	9	54	7	942	316
	6.2%	9.1%	9.9%	3.6%	1.0%	1.4%	9.9%	6.4%	2.7%	6.6%	9.1%
Caribbean	393	124	170	6	1	4	4	32	2	559	177
	3.7%	5.5%	5.6%	2.4%	1.0%	2.7%	4.4%	3.8%	0.8%	3.9%	5.1%
Other	917	184	311	55	15	12	16	114	30	1,282	372
	8.5%	8.1%	10.2%	21.8%	15.6%	8.2%	17.6%	13.5%	11.7%	9.0%	10.7%
Unknown	39	3	3	0	0	1	0	5	3	48	6
	0.4%	0.1%	0.1%	0.0%	0.0%	0.7%	0.0%	0.6%	1.2%	0.3%	0.2%
Years aware of HIV infection											
<1	472	87	74	1	2	3	2	36	3	599	81
	4.4%	3.8%	2.4%	0.4%	2.1%	2.1%	2.2%	4.3%	1.2%	4.2%	2.3%
1-2	1,361	261	260	4	2	20	4	71	20	1,717	286
	12.7%	11.5%	8.6%	1.6%	2.1%	1.7%	4.4%	8.4%	7.8%	12.0%	8.2%
3-4	1,442	260	311	6	1	7	7	83	30	1,798	349
	13.4%	11.4%	10.2%	2.4%	1.0%	4.8%	7.7%	9.8%	11.7%	12.6%	10.0%
5-10	3,181	682	878	25	9	15	22	232	58	4,135	967
	29.6%	30.0%	28.9%	9.9%	9.4%	10.3%	24.2%	27.4%	22.6%	29.0%	27.8%
>10	4,292	980	1,485	213	82	101	55	327	135	5,913	1,757
	39.9%	43.1%	48.9%	84.5%	85.4%	69.2%	60.4%	38.6%	52.5%	41.4%	50.5%
Unknown	5	3	27	3	0	0	1	98	11	109	39
	0.0%	0.1%	0.9%	1.2%	0.0%	0.0%	1.1%	11.6%	4.3%	0.8%	1.1%

	MSM	Heterosexual		IDU		Blood or blood products		Other / unknown		Total	
	Men	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	N=10,753	N=2,273	N=3,035	N=252	N=96	N=146	N=91	N=847	N=257	N=14,271	N=3,479
Current CD4 count [cells/mm³],	610	540	600	525	670	551	655	550	730	600	610
median / IQR	470-780	390-730	430-800	340-700	361-860	363-753	540-870	360-750	480-1030	450-770	440-820
Current CD8 count [cells/mm³],	920	880	803	822	850	815	860	830	830	910	810
median / IQR	670-1230	638-1210	600-1100	588-1150	620-1209	575-1121	630-1180	610-1140	530-1170	660-1220	600-1110
Current HIV RNA <500 copies/ml	9,231	1,965	2,548	222	89	131	77	658	206	12,207	2,920
	85.8%	86.4%	84.0%	88.1%	92.7%	89.7%	84.6%	77.7%	80.2%	85.5%	83.9%
Current HIV RNA <100 copies/ml	8,921	1,888	2,457	212	88	123	75	636	202	11,780	2,822
	83.0%	83.1%	81.0%	84.1%	91.7%	84.2%	82.4%	75.1%	78.7%	82.5%	81.1%
Ever AIDS	1,996	686	664	89	44	44	26	266	66	3,081	800
	18.6%	30.2%	21.9%	35.3%	45.8%	30.1%	28.6%	31.4%	25.7%	21.6%	23.0%
AIDS at diagnosis	1,036	472	377	21	12	23	13	192	31	1744	433
	9.6%	20.8%	12.4%	8.3%	12.5%	15.8%	14.3%	22.7%	12.1%	12.2%	12.4%
Current treatment											
cART	9,665	2,106	2,803	241	94	134	89	712	237	12,858	3,223
	89.9%	92.7%	92.4%	95.6%	97.9%	91.8%	97.8%	84.1%	92.2%	90.1%	92.6%
Non-cART	18	2	7	2	0	0	0	2	0	24	7
	0.2%	0.1%	0.2%	0.8%	0.0%	0.0%	0.0%	0.2%	0.4%	0.2%	0.2%
Not started	1,070	165	225	9	2	12	2	133	20	1,389	249
	10.0%	7.3%	7.4%	3.6%	2.1%	8.2%	2.2%	15.7%	7.8%	9.7%	7.2%
Co-infection											
HBV	657	169	144	26	1	9	2	45	14	906	161
	6.1%	7.4%	4.7%	10.3%	1.0%	6.2%	2.2%	5.3%	5.4%	6.3%	4.6%
HCV	838	68	75	197	75	36	5	57	33	1,196	188
	7.8%	3.0%	2.5%	78.2%	78.1%	24.7%	5.5%	6.7%	12.8%	8.4%	5.4%

Legend: *MSM=men who have sex with men; IDU=injecting drug use; IQR=inter-quartile range; cART=combination antiretroviral therapy; HBV=hepatitis B virus; HCV=hepatitis C virus.*

Web Appendix Table 1.2: Annual number of HIV-1 diagnoses amongst adults per transmission risk group, including men who have sex with men (MSM), patients infected via heterosexual contact, injecting drug use (IDU), contact with contaminated blood, or other or unknown modes of transmission. Note: data collection for 2012 and 2013 not yet been finalised at the time of writing.

	MSM	Heterosexual		IDU		Blood or blood products		Other/unknown		Total
Year of diagnosis	**Men**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	
≤1995	2,209	264	390	284	132	59	21	156	50	3,565
1996	385	91	82	32	11	4	4	36	4	649
1997	443	112	128	42	10	7	3	42	7	794
1998	332	107	113	22	6	6	5	30	8	629
1999	355	107	138	19	7	8	4	20	6	664
2000	378	158	190	18	3	3	4	34	4	792
2001	443	167	215	15	5	7	4	42	8	906
2002	463	165	250	15	3	14	7	59	4	980
2003	458	179	272	22	5	9	3	63	13	1,024
2004	578	198	264	9	4	4	3	70	10	1,140
2005	635	194	256	15	2	3	7	65	9	1,186
2006	664	162	194	10	5	4	7	53	4	1,103
2007	767	154	207	10	3	2	6	48	7	1,204
2008	844	177	175	6	1	4	2	54	6	1,269
2009	760	158	178	6	0	1	1	49	8	1,161
2010	760	172	160	4	1	6	3	38	7	1,151
2011	737	143	142	3	1	8	6	52	4	1,096
2012	675	138	138	6	1	4	3	33	9	1,007
*2012**	*695*	*142*	*142*	*6*	*1*	4	*3*	*34*	*9*	*1,036*
2013	654	105	106	1	2	11	1	39	6	925
*2013**	*726*	*117*	*117*	*1*	*2*	*12*	*1*	*43*	*7*	*1,026*
2014	113	26	22	0	0	2	1	8	0	172
Total	12,653	2,977	3,620	539	202	166	95	991	174	21,417

***Legend:** MSM=men who have sex with men; IDU=injecting drug use.*

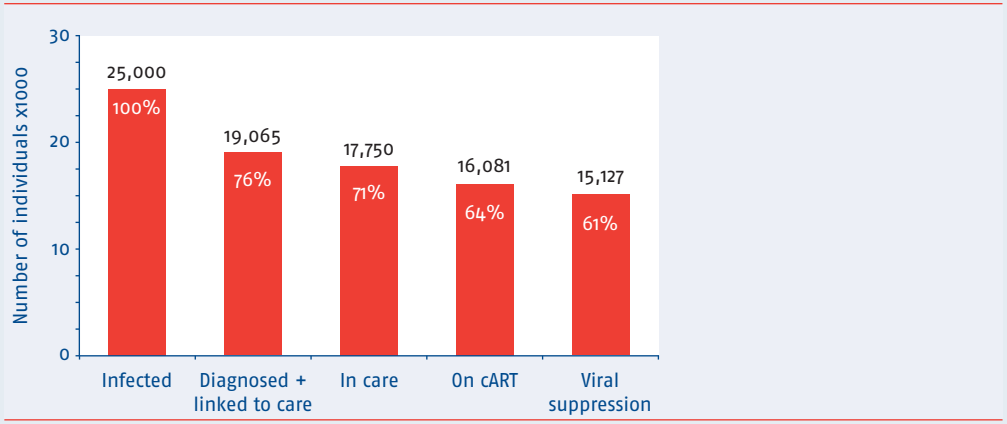
**Projected numbers*

Web Appendix Table 1.3: *Region of origin of the 21,417 adult HIV-1-infected patients with a recorded date of diagnosis. For men who have sex with men (MSM) and for heterosexual men and women, numbers are stratified according to year of HIV diagnosis.*

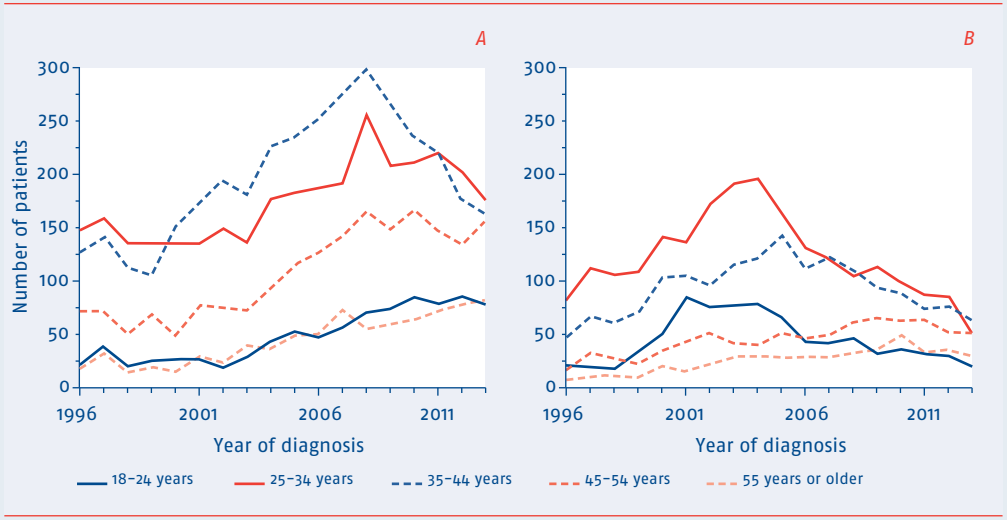
	MSM			Heterosexual men			Heterosexual women			IDU	Other
	<2011	≥2011	Total	<2011	≥2011	Total	<2011	≥2011	Total	Total	Total
The Netherlands	7,432	1,626	9,058	1,024	203	1227	772	121	893	444	624
	71.0%	74.6%	71.6%	39.9%	49.3%	41.2%	24.0%	29.7%	24.7%	59.9%	43.8%
Sub-Saharan Africa	146	27	173	856	87	943	1,543	155	1,698	8	349
	1.4%	1.2%	1.4%	33.4%	21.1%	31.7%	48.0%	38.0%	46.9%	1.1%	24.5%
Western Europe	862	116	978	95	11	106	89	11	100	141	116
	8.2%	5.3%	7.7%	3.7%	2.7%	3.6%	2.8%	2.7%	2.8%	19.0%	8.1%
Central Europe	179	66	245	67	17	84	43	14	57	26	51
	1.7%	3.0%	1.9%	2.6%	4.1%	2.8%	1.3%	3.4%	1.6%	3.5%	3.6%
Eastern Europe	55	16	71	10	2	12	20	8	28	27	23
	0.5%	0.7%	0.6%	0.4%	0.5%	0.4%	0.6%	2.0%	0.8%	3.6%	1.6%
South America	717	109	826	259	38	297	308	47	355	25	80
	6.8%	5.0%	6.5%	10.1%	9.2%	10.0%	9.6%	11.5%	9.8%	3.4%	5.6%
Caribbean	335	91	426	128	25	153	191	17	208	13	38
	3.2%	4.2%	3.4%	5.0%	6.1%	5.1%	5.9%	4.2%	5.7%	1.8%	2.7%
South and Southeast Asia	296	69	365	45	10	55	196	29	225	21	58
	2.8%	3.2%	2.9%	1.8%	2.4%	1.8%	6.1%	7.1%	6.2%	2.8%	4.1%
Other/unknown	452	59	511	81	19	100	50	6	56	36	87
	4.3%	2.7%	4.0%	3.2%	4.6%	3.4%	1.6%	1.5%	1.5%	4.9%	6.1%

Legend: *MSM=men who have sex with men; IDU=injecting drug use.*

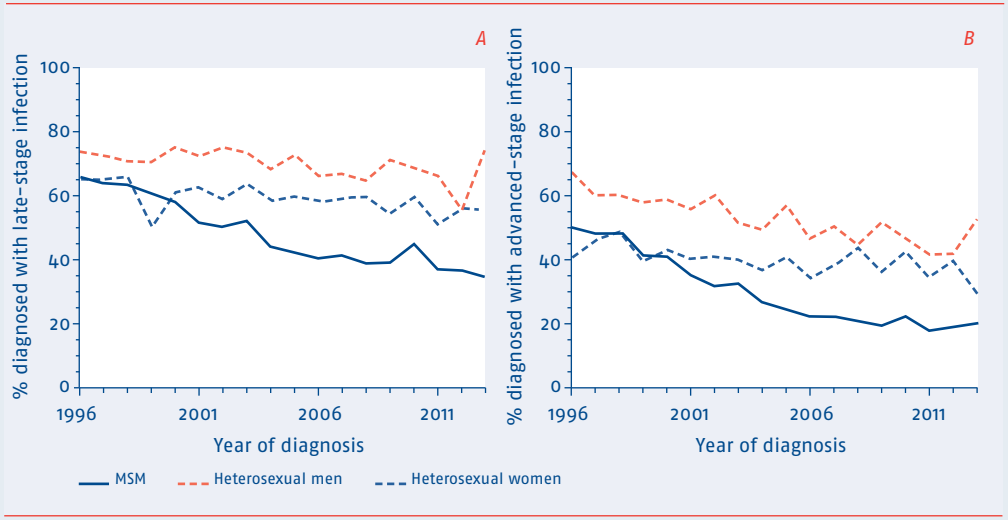
Web Appendix Figure 1.1: *Continuum of HIV care for the total estimated HIV-infected population in the Netherlands as of June 2014. According to UNAIDS, between 20,000 and 34,000 people were living with HIV in the Netherlands in 2013. In total, 19,065 patients were ever linked to care, registered by SHM, still alive, and not reported as having moved abroad (22,311 registered patients minus 2,271 patients who died minus 975 patients who moved abroad). Of these patients, 17,750 were still in care, whilst 16,081 had started combination antiretroviral treatment (cART). All together, 15,127 patients of those in care had a most recent RNA measurement below the limit of quantification or below 500 copies/ml.*



Web Appendix Figure 1.2: *Age distribution at the time of diagnosis amongst HIV-1-infected adult men who have sex with men (A) and heterosexual men and women (B). Note: data collection for 2012 and 2013 had not yet been finalised at the time of writing.*

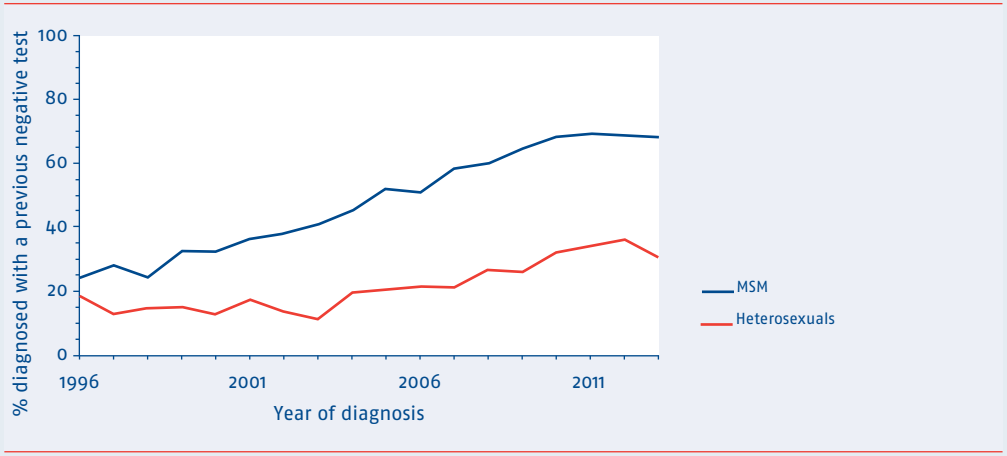


Web Appendix Figure 1.3: *Proportion of patients classified as presenting with (A) late or (B) advanced HIV infection at the time of HIV diagnosis. From 1996 onwards, 53% were diagnosed with late-stage HIV: men who have sex with men (MSM) 45%, heterosexual men 70%, heterosexual women 59%, injecting drug users (IDU) 67%. Overall, 35% were advanced presenters: MSM 26%, heterosexual men 52%, heterosexual women 39%, and IDU 49%. Late stage infection: CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Advanced stage infection: CD4 counts below 200 cells/mm³ or having AIDS.*



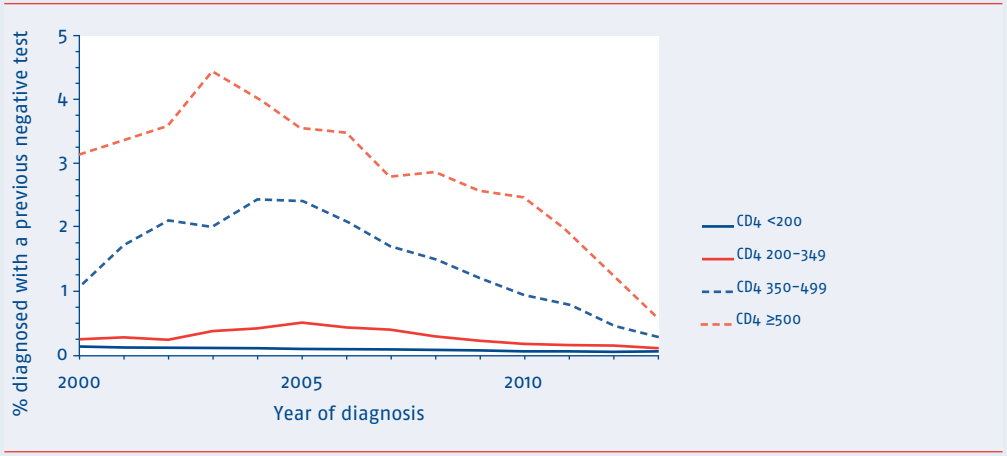
Legend: *MSM=men who have sex with men.*

Web Appendix Figure 1.4: *Proportion of patients diagnosed after a previously negative HIV test. All together, 68% of men who have sex with men (MSM) and 31% of heterosexuals (men 25%, women 37%) diagnosed in 2013 had a previously negative HIV test.*



Legend: *MSM=men who have sex with men.*

Web Appendix Figure 1.5: *Median time to start of combination antiretroviral treatment (cART) by year of diagnosis stratified by CD4 count at the time of diagnosis.*



Legend: *cART=combination antiretroviral treatment.*

Web Appendix Table 2.1: Baseline characteristics of 18,896 patients starting combination antiretroviral therapy (cART) between 1 January 1995 and 31 December 2013 by gender and region of origin.

Year of starting cART	1995–2001		2002–2007		2008–2012		2013	
	N	%	N	%	N	%	N	%
Total (N, %)	6,047	100.0	5,296	100.0	6,408	100.0	1,145	100.0
Male	4,900	81.0	3,850	72.7	5,411	84.4	997	87.0
Female	1,147	19.0	1,446	27.3	997	15.6	148	13.0
Region of origin in men								
Netherlands	3,255	66.4	2,264	58.8	3,680	68.0	704	70.7
W-Europe/N-America/Australia	572	11.7	332	8.6	370	6.8	51	5.2
Caribbean/S-America	433	8.8	453	11.8	557	10.3	99	9.8
Sub-Saharan Africa	344	7.0	491	12.8	351	6.5	40	4.0
Other	296	6.0	310	8.1	453	8.4	103	10.3
Region of origin in women								
Netherlands	383	33.4	296	20.5	256	25.7	59	39.9
W-Europe/N-America/Australia	109	9.5	47	3.3	33	3.3	4	2.7
Caribbean/S-America	146	12.7	216	14.9	155	15.5	13	8.8
Sub-Saharan Africa	422	36.8	750	51.9	416	41.7	54	36.5
Other	87	7.6	137	9.5	137	13.7	18	12.2

***Legend:** W-Europe=Western Europe; N-American=North America; S-America=South America.*

Web Appendix Table 2.2.: *Overview of the most frequently recorded adverse events leading to a toxicity-driven therapy stop from 2005 to 2011. Multiple adverse events in a patient during the same year are counted once. For every toxicity-driven therapy stop, up to three adverse events could be recorded; therefore, percentages do not add up to 100%.*

	2006		2007		2008		2009		2010		2011		2012		2013	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients with at least 1 toxicity-driven therapy stop	889		927		1,009		998		1,056		1,024		1,338		1,112	
Body composition and serum lipids																
Lipodystrophy, any	153	17.2	135	14.6	136	13.5	103	10.3	81	7.7	51	5.0	63	4.7	37	3.3
Lipoatrophy, peripheral fat loss	113	12.7	103	11.1	104	10.3	80	8.0	58	5.5	34	3.3	39	2.9	21	1.9
Lipohypertrophy – central fat accumulation	38	4.3	26	2.8	29	2.9	21	2.1	20	1.9	17	1.7	19	1.4	13	1.2
Lipodystrophy unspecified	4	0.4	6	0.6	3	0.3	3	0.3	4	0.4		0.0	5	0.4	3	0.3
Elevated cholesterol	18	2.0	17	1.8	20	2.0	11	1.1	13	1.2	15	1.5	16	1.2	20	1.8
Elevated triglycerides	12	1.3	9	1.0	17	1.7	17	1.7	16	1.5	23	2.2	9	0.7	11	1.0
Liver																
Icterus	13	1.5	8	0.9	6	0.6	8	0.8	25	2.4	24	2.3	31	2.3	35	3.1
Elevated gamma-glutamyl transpeptidase	9	1.0	13	1.4	12	1.2	26	2.6	22	2.1	24	2.3	24	1.8	10	0.9
Elevated aspartate aminotransferase	8	0.9	11	1.2	8	0.8	15	1.5	14	1.3	12	1.2	13	1.0	6	0.5
Elevated bilirubin	9	1.0	12	1.3	9	0.9	10	1.0	14	1.3	13	1.3	11	0.8	9	0.8
Elevated alanine aminotransferase	4	0.4	3	0.3	6	0.6	10	1.0	12	1.1	5	0.5	16	1.2	11	1.0
Lactate acidosis	7	0.8	5	0.5	3	0.3	1	0.1	2	0.2	1	0.1	1	0.1	1	0.1
Hepatic steatosis	4	0.4	1	0.1	2	0.2	4	0.4			8	0.8				
Elevated alkaline phosphatase	1	0.1			2	0.2	1	0.1	2	0.2	1	0.1	3	0.2	4	0.4
Liver cirrhosis			2	0.2	1	0.1			2	0.2	2	0.2	4	0.3	2	0.2
Renal																
Renal insufficiency	24	2.7	38	4.1	46	4.6	42	4.2	49	4.6	54	5.3	103	7.7	95	8.5
Elevated creatinine	16	1.8	19	2.0	21	2.1	23	2.3	22	2.1	32	3.1	42	3.1	38	3.4
Nephrolithiasis	5	0.6	4	0.4	2	0.2	2	0.2	5	0.5	10	1.0	5	0.4	8	0.7
Elevated proteinuria	1	0.1			1	0.1	1	0.1	4	0.4			9	0.7	4	0.4

	2006		2007		2008		2009		2010		2011		2012		2013	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Neurological / psychosocial																
Central nervous system toxicity *	81	9.1	98	10.6	112	11.1	141	14.1	169	16.0	171	16.7	247	18.5	216	19.4
Depression	22	2.5	22	2.4	39	3.9	45	4.5	46	4.4	64	6.3	93	7.0	65	5.8
Sleeplessness	24	2.7	19	2.0	23	2.3	29	2.9	41	3.9	62	6.1	66	4.9	65	5.8
Dizziness	26	2.9	36	3.9	28	2.8	46	4.6	41	3.9	32	3.1	47	3.5	39	3.5
Mood changes	9	1.0	20	2.2	25	2.5	30	3.0	45	4.3	38	3.7	64	4.8	52	4.7
Nightmares	17	1.9	16	1.7	26	2.6	23	2.3	33	3.1	28	2.7	56	4.2	54	4.9
Non-HIV-related neuropathy	35	3.9	31	3.3	21	2.1	14	1.4	13	1.2	14	1.4	12	0.9	8	0.7
Headache	9	1.0	14	1.5	7	0.7	9	0.9	27	2.6	24	2.3	16	1.2	24	2.2
Concentration disorders	4	0.4	8	0.9	9	0.9	10	1.0	8	0.8	11	1.1	16	1.2	9	0.8
Fear	5	0.6	3	0.3	4	0.4	9	0.9	10	0.9	4	0.4	7	0.5	7	0.6
Erection disorders	2	0.2	5	0.5	2	0.2	1	0.1	7	0.7	3	0.3	4	0.3	2	0.2
Paraesthesia (transient numbness or tingling)			3	0.3	7	0.7	5	0.5	2	0.2	3	0.3	2	0.1	1	0.1
Loss of libido	2	0.2	1	0.1	3	0.3	1	0.1	2	0.2	3	0.3	11	0.8		
Psychosis					1	0.1	4	0.4	2	0.2	7	0.7	2	0.1	1	0.1
Loss of memory	2	0.2	1	0.1	2	0.2			4	0.4	1	0.1	7	0.5	2	0.2
Confusion	1	0.1	1	0.1	1	0.1	3	0.3	2	0.2	1	0.1			1	0.1
Gastrointestinal																
Diarrhoea	76	8.5	83	9.0	101	10.0	99	9.9	104	9.8	96	9.4	80	6.0	60	5.4
Nausea	49	5.5	71	7.7	48	4.8	42	4.2	43	4.1	39	3.8	40	3.0	42	3.8
Vomiting	23	2.6	14	1.5	23	2.3	25	2.5	28	2.7	20	2.0	18	1.3	13	1.2
Abdominal pain	11	1.2	13	1.4	21	2.1	12	1.2	18	1.7	15	1.5	17	1.3	12	1.1
Flatulence	1	0.1	1	0.1	4	0.4	8	0.8	4	0.4	12	1.2	10	0.7	5	0.4
Loss of appetite	3	0.3	5	0.5	1	0.1	3	0.3	2	0.2	4	0.4	4	0.3	5	0.4
Weight loss	2	0.2	5	0.5	6	0.6	1	0.1	1	0.1	2	0.2	1	0.1	5	0.4
Change in taste	1	0.1	1	0.1	3	0.3	3	0.3	3	0.3	2	0.2	2	0.1	1	0.1
Constipation	3	0.3	1	0.1	1	0.1	1	0.1	3	0.3			2	0.1	1	0.1
Indigestion	1	0.1	1	0.1	1	0.1	2	0.2			3	0.3	1	0.1	2	0.2
Dermatological																
Rash	60	6.7	61	6.6	86	8.5	70	7.0	79	7.5	62	6.1	64	4.8	50	4.5
Itchiness	12	1.3	13	1.4	9	0.9	13	1.3	12	1.1	16	1.6	22	1.6	14	1.3

	2006		2007		2008		2009		2010		2011		2012		2013	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Systemic																
Fatigue	40	4.5	36	3.9	32	3.2	32	3.2	41	3.9	43	4.2	55	4.1	55	4.9
General discomfort	4	0.4	10	1.1	12	1.2	10	1.0	11	1.0	15	1.5	20	1.5	10	0.9
Fever	8	0.9	4	0.4	4	0.4	3	0.3	2	0.2	2	0.2	4	0.3	4	0.4
Night sweats	3	0.3	1	0.1	2	0.2	1	0.1	2	0.2	2	0.2	3	0.2	4	0.4
Haematological																
Anaemia	41	4.6	27	2.9	29	2.9	31	3.1	26	2.5	14	1.4	30	2.2	16	1.4
Leukopenia	15	1.7	9	1.0	5	0.5	7	0.7	4	0.4	5	0.5	6	0.4	6	0.5
Pancytopenia	5	0.6	2	0.2	5	0.5	2	0.2			2	0.2	6	0.4	2	0.2
Neutropenia	3	0.3					2	0.2	2	0.2	4	0.4	7	0.5	5	0.4
Thrombocytopenia	3	0.3			3	0.3	1	0.1	3	0.3	3	0.3	2	0.1	5	0.4
Neuromuscular																
Myalgia	5	0.6	4	0.4	7	0.7	10	1.0	7	0.7	4	0.4	6	0.4	9	0.8
Arthralgia	2	0.2	2	0.2	3	0.3	4	0.4	11	1.0	1	0.1	6	0.4	6	0.5
Myopathy	4	0.4	11	1.2	3	0.3	1	0.1	2	0.2			3	0.2		
Skeletal																
Osteoporosis	2	0.2			4	0.4	1	0.1	3	0.3	3	0.3	4	0.3	6	0.5
Osteopenia	1	0.1			3	0.3			3	0.3	2	0.2	4	0.3	2	0.2
Cardiovascular																
Hypertension	2	0.2	3	0.3	3	0.3	4	0.4	4	0.4	4	0.4	4	0.3	2	0.2
Myocardial infarction	1	0.1	1	0.1	3	0.3			2	0.2	1	0.1	2	0.1		
Arrhythmia	3	0.3					4	0.4	1	0.1	1	0.1	1	0.1		
Other																
Diabetes mellitus (both I and II)	3	0.3	3	0.3	1	0.1	6	0.6	6	0.6	6	0.6	4	0.3	4	0.4
Abacavir hypersensitivity	10	1.1	6	0.6	2	0.2	2	0.2	2	0.2			1	0.1	1	0.1
Cough			2	0.2	2	0.2	1	0.1	2	0.2	3	0.3	1	0.1	2	0.2
Pancreatitis	2	0.2	1	0.1	4	0.4	1	0.1			1	0.1	2	0.1	1	0.1

** CNS toxicity includes the following adverse events in the database: dizziness, sleeplessness, nightmares, mood changes, concentration disorders, and confusion.*

Web Appendix Table 3.1: *Number of patients with evidence of various levels of resistance to specific antiretroviral drugs, according to the Stanford algorithm for scoring mutations. Altogether, out of 17,750 patients still in follow-up as of June 2014, 2,094 (12%) patients with at least one major resistance-associated mutation from the March 2013 International Antiviral Society-USA (IAS-USA) list were included.*

	Susceptible		Potential low-level		Low-level		Intermediate		High-level	
	N	%	N	%	N	%	N	%	N	%
Protease inhibitors (PIs)[a]										
FPV	1,535	74	120	6	98	5	122	6	212	10
IDV	1,537	74	105	5	30	1	138	7	277	13
NFV	1,278	61	175	8	127	6	36	2	471	23
SQV	1,645	79	9	0	45	2	126	6	262	13
LPV	1,566	75	92	4	108	5	101	5	220	11
ATV	1,543	74	98	5	87	4	79	4	280	13
TPV	1,675	80	88	4	123	6	135	6	66	3
DRV	1,910	92	14	1	122	6	33	2	8	0
Any PI	1,248	60	178	9	148	7	33	2	480	23
Nucleoside RT inhibitors (NRTIs)										
ABC	547	26	143	7	528	25	315	15	561	27
AZT	1,106	53	37	2	190	9	182	9	579	28
d4T	983	47	44	2	201	10	289	14	577	28
ddI	522	25	526	25	202	10	267	13	577	28
TDF	1,077	51	145	7	230	11	247	12	395	19
Any NRTI	501	24	29	1	579	28	195	9	790	38
3TC/FTC	780	37	57	3	64	3	72	3	1.121	54
Non-nucleoside RT inhibitors (NNRTIs)										
EFV	960	46	131	6	35	2	212	10	756	36
NVP	960	46	58	3	48	2	65	3	963	46
ETR	1,127	54	327	16	161	8	399	19	80	4
RPV	1,127	54	59	3	346	17	360	17	202	10
Any NNRTI	783	37	32	2	237	11	77	4	965	46

Legend: *FPV=fosamprenavir; IDV=indinavir; NFV=nelfinavir; SQV=saquinavir; LPV=lopinavir; ATV=atazanavir; TPV=tipranavir; DRV=darunavir; ABC=abacavir; AZT=zidovudine; d4T=stavudine; ddI=didanosine; TDF=tenofovir; 3TC=lamivudine; FTC=emtricitabine; EFV=efavirenz; NVP=nevirapine; ETR=etravirine.*

[a] *protease not available for 7 patients.*

Web Appendix Table 3.2: *Number of patients with evidence of various levels of resistance to specific antiretroviral drugs, according to the Stanford algorithm for scoring mutations. Altogether, out of 17,750 patients still in follow-up as of June 2014, 7,305 (41%) with at least one genotypic sequence were included. Note that due to small differences in resistance-associated mutations between the Stanford algorithm and the International Antiviral Society-USA (IAS-USA) list, the number of patients with resistance may be different from those reported in Web Appendix Table 3.1.*

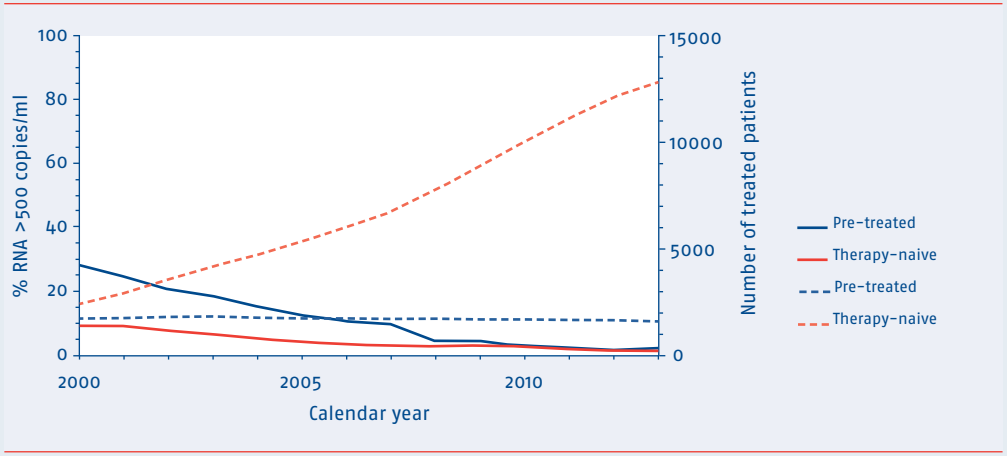
	Susceptible		Potential low-level		Low-level		Intermediate		High-level	
	N	%	N	%	N	%	N	%	N	%
Protease inhibitors (PIs)[a]										
FPV	6,672	92	165	2	98	1	122	2	212	3
IDV	6,694	92	128	2	32	0	138	2	277	4
NFV	5,905	81	647	9	205	3	41	1	471	6
SQV	6,823	94	9	0	49	1	126	2	262	4
LPV	6,746	93	93	1	109	1	101	1	220	3
ATV	6,716	92	103	1	91	1	79	1	280	4
TPV	6,833	94	109	1	126	2	135	2	66	1
DRV	7,092	98	14	0	122	2	33	0	8	0
Any PI	5,855	81	670	9	226	3	38	1	480	7
Nucleoside RT inhibitors (NRTIs)[b]										
ABC	5,611	77	281	4	528	7	316	4	561	8
AZT	6,168	85	42	1	325	4	183	3	579	8
d4T	6,031	83	62	1	336	5	291	4	577	8
ddI	5,529	76	715	10	204	3	272	4	577	8
TDF	6,276	86	149	2	230	3	247	3	395	5
Any NRTI	5,504	75	88	1	714	10	201	3	790	11
3TC/FTC	5,980	82	60	1	64	1	72	1	1,121	15
Non-nucleoside RT inhibitors (NNRTIs)[b]										
EFV	6,044	83	241	3	38	1	217	3	757	10
NVP	6,044	83	154	2	49	1	84	1	966	13
ETR	6,219	85	437	6	161	2	400	5	80	1
RPV	6,219	85	154	2	361	5	361	5	202	3
Any NNRTI	5,867	80	128	2	238	3	96	1	968	13

Legend: *FPV=fosamprenavir; IDV=indinavir; NFV=nelfinavir; SQV=saquinavir; LPV=lopinavir; ATV=atazanavir; TPV=tipranavir; DRV=darunavir; ABC=abacavir; AZT=zidovudine; d4T=stavudine; ddI=didanosine; TDF=tenofovir; 3TC=lamivudine; FTC=emtricitabine; EFV=efavirenz; NVP=nevirapine; ETR=etravirine.*

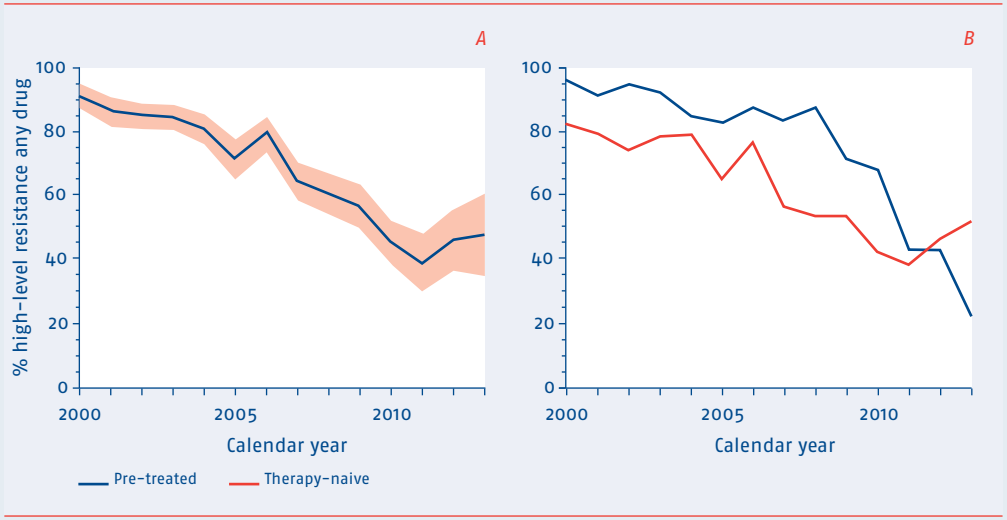
[a] *protease not available for 36 patients.*

[b] *RT not available for 8 patients.*

Web Appendix Figure 3.1: *Annual number of treated patients with a viral load measurement whilst on treatment (dashed lines) and the proportion of patients with virological failure (solid lines) (i.e., a viral load above 500 copies/ml whilst on treatment and measured at least four months after start of cART or four months after resuming treatment following a treatment interruption). Among approximately 1,700 pre-treated patients, the proportion with failure using a threshold of 500 copies/ml decreased from 28% in 2000 to 2% in 2013. Among previously therapy-naïve patients, failure was less common and decreased from 9% to 1% during the same period, whilst the number of therapy-naïve patients increased from approximately 2,375 to 12,800.*



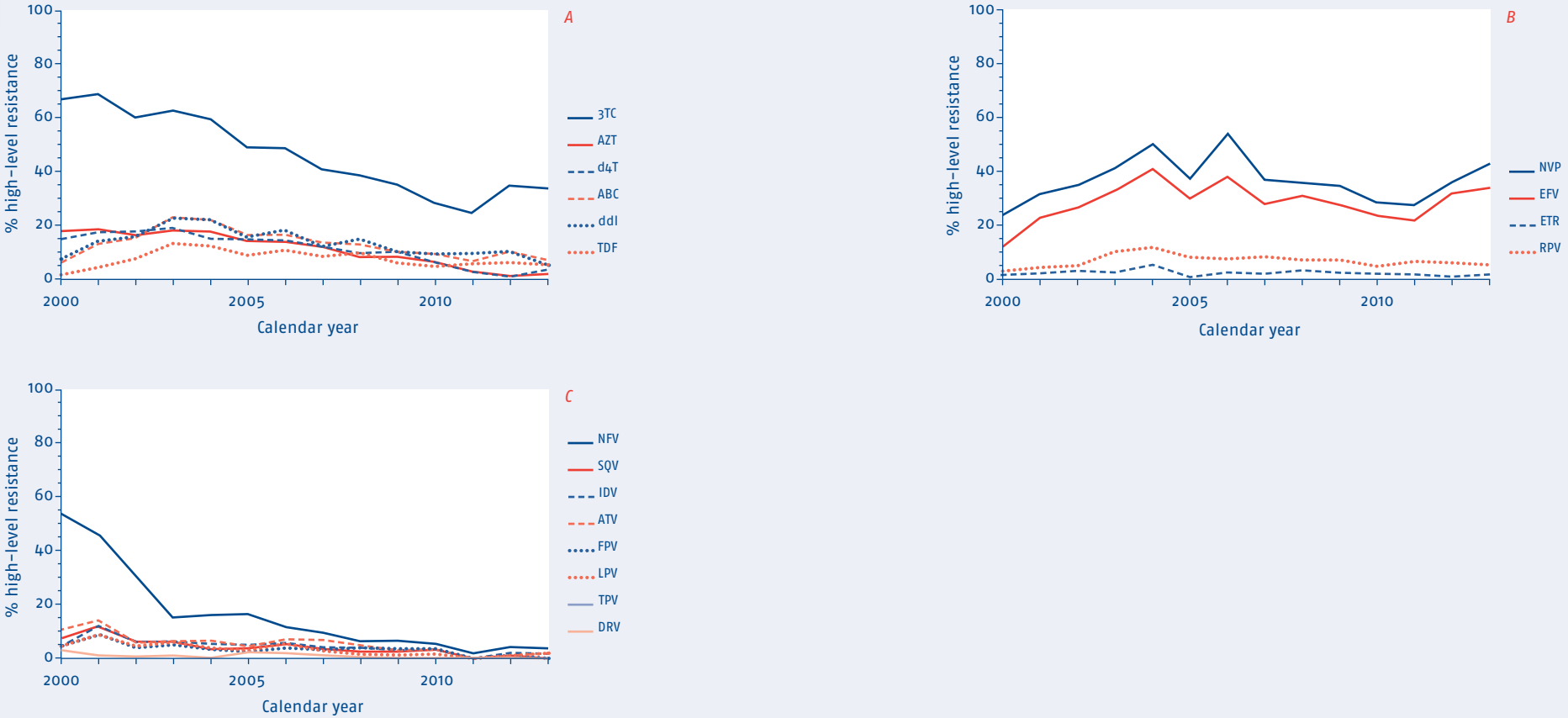
Web Appendix Figure 3.2: *(A) The proportion of sequences obtained at the time of virological failure with evidence of high-level resistance to any antiretroviral drug decreased from 91% in 2000 to 48% in 2013. The shaded area is the 95% confidence interval. (B) Resistance to any antiretroviral drug was found more often in patients pre-treated with monotherapy or dual therapy before commencing combination antiretroviral therapy (cART).*



Web Appendix Figure 3.3: *Annual proportion of available sequences from treated patients with evidence of high-level resistance, according to the Stanford mutation interpretation algorithm, in patients who received treatment regimens not considered combination antiretroviral treatment (cART). Resistance to individual drugs from the four original drug classes is shown, including (A) nucleoside reverse transcriptase inhibitors and lamivudine/emtricitabine, (B) non-nucleoside reverse transcriptase inhibitors, and (C) protease inhibitors.*

Legend: *3TC=lamivudine/emtricitabine; d4T=stavudine; ddI=didanosine; AZT=zidovudine; ABC=abacavir; TDF=tenofovir; NVP=nevirapine; EFV=efavirenz; ETR=etravirine; RPV=rilpivirine; NFV=nelfinavir; IDV=indinavir; FPV=fosamprenavir; TPV=tipranavir; SQV=saquinavir; ATV=atazanavir; LPV=lopinavir; DRV=darunavir.*

Web Appendix Figure 3.4: *Annual proportion of available sequences from treated patients with evidence of high-level resistance, according to the Stanford mutation interpretation algorithm, in previously therapy-naïve patients who started with combination antiretroviral treatment (cART) as their first treatment regimen. Resistance to individual drugs from the four original drug classes is shown, including (A) nucleoside reverse transcriptase inhibitors and lamivudine/emtricitabine, (B) non-nucleoside reverse transcriptase inhibitors, and (C) protease inhibitors.*



Legend: *3TC=lamivudine/emtricitabine; d4T=stavudine; ddI=didanosine; AZT=zidovudine; ABC=abacavir; TDF=tenofovir; NVP=nevirapine; EFV=efavirenz; ETR=etravirine; RPV=rilpivirine; NFV=nelfinavir; IDV=indinavir; FPV=fosamprenavir; TPV=tipranavir; SQV=saquinavir; ATV=atazanavir; LPV=lopinavir; DRV=darunavir.*

Web Appendix Table 4.1: Demographic and clinical characteristics at the start of cART of the 15,364 and 3,676 included men and women.

Patient characteristics		Total	Men		Women		P-value
			N	Percentage (%)	N	Percentage (%)	
Region of birth	The Netherlands	11,026	10,034	65	992	27	<0.0001
	Other or unknown	8,014	5,330	35	2,684	73	
HIV-1 transmission route	Homosexual	11,217	11,217	73	0	0	<0.0001
	Heterosexual	5,917	2,670	17	3,247	88	
	IDU or blood contact	857	599	4	258	7	
	Other or unknown	1,049	878	6	171	5	
Age at the start of cART	Under 35 years	6,666	4,626	30	2,040	55	<0.0001
	35 to 44 years	6,789	5,736	37	1,053	29	
	45 to 54 years	3,905	3,536	23	369	10	
	55-64 years	1,368	1,190	8	178	5	
	Over 65 years	312	276	2	36	1	
CD4 cell count**	Less than 200 cells/mm^3	6,963	5,568	36	1,395	38	<0.0001
	200-500 cells/mm^3	8,655	7,144	47	1,511	41	
	More than 500 cells/mm^3	1,800	1,411	9	389	11	
	Unknown	1,622	1,241	8	381	10	
HIV RNA load **	Less than 100 copies/ml	291	201	1	90	2	<0.0001
	100-1,000 copies/ml	667	457	3	210	6	
	More than 1,000 copies/ml	15,876	12,945	84	2,931	79	
	Unknown	2,206	1,761	11	445	12	
Body mass index**	Less than 18.5 kg/m^2	805	650	4	155	4	<0.0001
	Between 18.5 and 25 kg/m^2	8,837	7,553	49	1,284	35	
	More than 25 kg/m^2	3,582	2,685	17	897	24	
	Unknown	5,816	4,476	29	1,340	36	
Hepatitis B virus status***	Positive	1,039	903	6	136	4	<0.0001
	Negative	8,217	6,351	41	1,866	51	
	Unknown	9,784	8,110	53	1,674	46	
Hepatitis C virus status***	Positive	9,830	892	6	272	7	<0.0001
	Negative	1,164	8,332	54	1,489	41	
	Unknown	8,046	6,140	40	1,906	52	

*** Last known before the start of cART but within a year of this date.*

Web Appendix Table 4.2: Annual number of cases of death and first AIDS events amongst 21,928 HIV-1-infected patients in the Netherlands recorded up to June 2014. Note: data collection for 2012, 2013, and 2014 is not yet finalised.

		AIDS		Death	
Year	Total	≥6 weeks after diagnosis	≥4 weeks after start of cART	Total	After start of cART
≤1995	769	489	3	34	-
1996	364	290	94	48	31
1997	306	185	115	87	68
1998	242	133	110	84	72
1999	233	131	107	89	87
2000	247	113	88	84	79
2001	261	148	97	82	79
2002	296	147	108	118	81
2003	294	146	110	141	121
2004	281	173	112	145	130
2005	353	198	134	140	123
2006	283	166	116	120	104
2007	295	171	116	149	126
2008	269	165	126	149	134
2009	265	143	103	159	145
2010	285	149	124	129	122
2011	222	132	97	148	140
2012	246	146	126	154	148
2013	190	93	75	133	128
2014	25	13	11	39	37
Total	5,726	3,331	1,972	2,232	1,955

Legend: cART=combination antiretroviral therapy.

Web Appendix Table 4.3: The causes of death for patients after the start of cART during the periods 1996-2001, 2002-2006 and 2007-2013.

	1996-2001	2002-2006	2007-2013
Cause of death	**Total**	**Total**	**Total**
All AIDS-defining causes	**212**	**194**	**204**
Infection	67	69	96
Malignancy	66	55	67
Not specified	79	70	41
Non-AIDS defining malignancy	**35**	**91**	**162**
All cardiovascular diseases	**16**	**36**	**47**
Myocardial infarction	11	18	28
Stroke	3	10	13
Other ischemic heart disease	0	0	1
Other cardio vascular diseases	2	8	5
Non- AIDS defining infection	**19**	**46**	**43**
Liver failure, cirrhosis and hepatitis B or C infection at death	**21**	**33**	**43**
Lung related	**2**	**7**	**31**
Non-natural death	**26**	**32**	**34**
Accident or violent death	8	11	15
Suicide	10	17	16
Euthanasia	8	4	3
Substance abuse	**11**	**6**	**21**
Other causes	**11**	**49**	**97**
Unknown	**49**	**68**	**137**
Total	**418**	**562**	**819**

Web Appendix Table 4.4: Hazard ratios for time to death and AIDS from the start of cART.

Patient characteristics		Mortality		AIDS	
		Hazard ratio	95% CI	Hazard ratio	95% CI
Gender	Male	1		1	
	Female	0.71	0.61–0.82	0.91	0.81–1.03
Region of birth	The Netherlands	1			
	West Europe	0.82	0.70–1.00	0.81	0.67–0.96
	Sub-Saharan Africa	0.67	0.55–0.82	1.03	0.89–1.18
	Latin America and Caribbean	0.91	0.77–1.07	1.04	0.91–1.19
	Other or unknown	1.06	1.13–1.62	1.43	0.82–1.09
HIV-1 transmission route	Homosexual	0.91	0.79–1.04	0.80	0.72–0.90
	Heterosexual	1		1	
	IDU or blood contact	1.61	1.33–1.95	1.31	1.09–1.57
	Other or unknown	1.53	1.28–1.85	1.29	1.10–1.51
Age at the start of cART	Under 35 years	0.65	0.57–0.74	1.01	0.91–1.11
	35 to 44 years	1		1	
	45 to 54 years	1.68	1.49–1.88	1.17	1.05–1.51
	55–64 years	2.69	2.32–3.12	1.29	1.10–1.51
	Over 65 years	5.45	4.32–6.88	1.33	0.97–1.81
CD4 cell count*	Less than 200 cells/mm^3	2.13	1.71–2.65	2.34	1.93–2.84
	200–500 cells/mm^3	1.05	0.84–1.32	0.99	0.81–1.20
	More than 500 cells/mm^3	1		1	
	Unknown	1.07	0.80–1.43	1.45	1.14–1.84
HIV RNA load *	Less than 10,000 copies/ml	1		1	
	10,000–100,000 copies/ml	1.04	0.90–1.21	1.22	1.05–1.41
	More than 100,000 copies/ml	1.04	0.90–1.21	1.51	1.30–1.75
	Unknown	1.36	1.13–1.62	1.88	1.58–2.25
Body mass index*	Less than 18.5 kg/m^2	1.40	1.16–1.69	1.33	1.13–1.57
	Between 18.5 and 25 kg/m^2	1		1	
	More than 25 kg/m^2	0.75	0.65–0.87	0.71	0.62–0.81
	Unknown	1.20	1.08–1.34	1.20	1.09–1.31
Hepatitis B virus status**	Positive	1.38	1.17–1.62	1.13	0.99–1.32
	Negative	1		1	
	Unknown	1.29	1.08–1.56	1.04	0.87–1.24
Hepatitis C virus status**	Positive RNA	1.78	1.38–2.28	1.15	0.90–1.46
	Positive antibody	2.31	1.91–2.77	1.23	1.00–1.50
	Negative	1		1	1
	Unknown	2.52	2.20–2.88	1.19	1.03–1.38

** Last known before the start of cART but within a year of this date.*

***Legend:** 95% CI=95% confidence intervals; cART=combination antiretroviral therapy.*

Web Appendix Table 4.5.a: Incidence of diabetes mellitus from June 2000 onwards according to gender and age.

	Men				Women			
Age	**N**	**PY**	**Incidence/1000 PY**	**95% CI**	**N**	**PY**	**Incidence/1000 PY**	**95% CI**
18-35	22	20,738	1.1	0.7-1.6	27	10,732	2.5	1.7-3.7
35-45	116	43,480	2.7	2.2-3.2	69	11,741	5.9	4.6-7.4
45-55	195	36,904	5.3	4.6-6.1	37	5,709	6.5	4.6-8.9
55-65	133	15,104	8.8	7.4-10.4	11	1,759	6.3	3.1-11.2
65-75	51	3,321	15.4	11.4-20.2	6	483	12.4	4.6-27.1
≥75	3	414	7.2	1.5-21.2	1	71	14.1	0.4-78.7
Total	520	119,961	4.3	4.0-4.7	151	30,494	5.0	4.2-5.8

***Legend:** PY=person years of follow-up; CI=confidence interval.*

Web Appendix Table 4.5.b: Incidence of cardiovascular disease (myocardial infarction, stroke, coronary artery by-pass grafting, coronary angioplasty or stenting and carotid endarterectomy) from June 2000 onwards according to gender and age.

	Men				Women			
Age	**N**	**PY**	**Incidence/1000 PY**	**95% CI**	**N**	**PY**	**Incidence/1000 PY**	**95% CI**
18-35	14	22,794	0.6	0.3-1.0	9	13,325	0.7	0.3-1.3
35-45	109	44,060	2.5	2.0-3.0	26	12,018	2.2	1.4-3.2
45-55	236	37,510	6.3	5.5-7.1	17	5,971	2.8	1.7-4.6
55-65	203	15,238	13.3	11.6-15.3	13	1,848	7.0	3.7-12.0
65-75	74	3,343	22.1	17.4-27.8	6	509	11.8	4.3-25.6
≥75	12	359	33.4	17.3-58.4	2	89	22.6	2.7-81.6
Total	648	123,305	5.3	4.9-5.7	73	33,760	2.2	1.7-2.7

***Legend:** PY=person years of follow-up; CI=confidence interval.*

Web Appendix Table 4.5.c: Incidence of chronic kidney disease (an estimated glomerular filtration rate below 60 ml/min, estimated with the Cockcroft-Gault equation, and confirmed after 3 months or longer) from June 2007 onwards, according to gender and age.

	Men				Women			
Age	**N**	**PY**	**Incidence/1000 PY**	**95% CI**	**N**	**PY**	**Incidence/1000 PY**	**95% CI**
18-35	9	12,484	0.7	0.3-1.4	3	6,502	0.5	0.1-1.3
35-45	46	23,383	2.0	1.4-2.6	22	7,062	3.1	2.0-4.7
45-55	94	25,312	3.7	3.0-4.5	52	4,067	12.8	9.5-16.8
55-65	158	10,816	14.6	12.4-17.1	44	1,189	37.0	26.9-49.7
65-75	126	2,455	51.3	42.8-61.1	26	233	111.7	73.0-163.7
≥75	31	164	189.0	128.4-268.3	4	26	153.0	41.7-391.6
Total	464	74,614	6.2	5.7-6.8	151	19,079	7.9	6.7-9.3

***Legend:** PY=person years of follow-up; CI=confidence interval.*

Web Appendix Table 4.5.d: *Incidence of non-AIDS malignancy (including Castleman's disease, but excluding precancerous stages of anal and cervical cancer, basal-cell carcinoma, and squamous-cell carcinoma of the skin) from June 2000 onwards, according to gender and age.*

	Men				Women			
Age	**N**	**PY**	**Incidence/1000 PY**	**95% CI**	**N**	**PY**	**Incidence/1000 PY**	**95% CI**
18-35	33	26,124	1.3	0.9-1.8	13	14,750	0.9	0.5-1.5
35-45	166	48,771	3.4	2.9-4.0	33	12,941	2.6	1.8-3.6
45-55	259	40,316	6.4	5.7-7.3	36	6,164	5.8	4.1-8.1
55-65	204	16,553	12.3	10.7-14.1	18	1,890	9.5	5.6-15.1
65-75	87	3,607	24.1	19.3-29.7	5	550	9.1	3.0-21.2
≥75	10	423	23.6	11.3-43.5	1	88	11.3	0.3-63.0
Total	759	135,795	5.6	5.2-6.0	106	36,383	2.9	2.4-3.5

Legend: *PY=person years of follow-up; CI=confidence interval.*

Web Appendix Table 4.5.e: Incidence of non-AIDS disease (first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS malignancy) from June 2000 onwards, according to gender and age.

	Men				Women			
Age	**N**	**PY**	**Incidence/1000 PY**	**95% CI**	**N**	**PY**	**Incidence/1000 PY**	**95% CI**
18-35	60	20,615	2.9	2.2-3.7	43	10,697	4.0	2.9-5.4
35-45	356	42,618	8.4	7.5-9.3	121	11,530	10.5	8.7-12.5
45-55	602	35,037	17.2	15.8-18.6	79	5,499	14.4	11.4-17.9
55-65	425	13,525	31.4	28.5-34.6	33	1,662	19.9	13.7-27.9
65-75	144	2,639	54.6	46.0-64.2	14	423	33.1	18.1-55.5
≥75	20	287	69.7	42.6-107.7	3	60	50.3	10.4-146.9
Total	1607	114,721	14.0	13.3-14.7	293	29,871	9.8	8.7-11.0

Legend: PY=person years of follow-up; CI=confidence interval.

Web Appendix Table 4.6: Adjusted risk factors for non-AIDS morbidity.

	Non-AIDS defining disease			Cardiovascular disease			Non-AIDS malignancy			Diabetes mellitus			CKD		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Female gender	0.79	0.68-0.91	0.00	0.56	0.42-0.74	0.00	0.89	0.70-1.15	0.38	0.74	0.59-0.93	0.01	2.09	1.64-2.65	0.00
Region of birth															
The Netherlands	1.00			1.00			1.00			1.00			1.00		
Other	1.05	0.93-1.18	0.43	0.80	0.65-0.99	0.04	0.65	0.53-0.80	0.00	1.68	1.40-2.02	0.00	1.52	1.23-1.88	0.00
HIV-1 transmission route			*0.006*			*0.02*			*0.38*			*<0.001*			*0.002*
Homosexual contact	1.00			1.00			1.00			1.00			1.00		
Heterosexual contact	1.33	1.04-1.70	0.02	1.17	0.77-1.78	0.46	1.13	0.79-1.62	0.50	2.03	1.30-3.15	0.00	2.15	1.41-3.28	0.00
IDU	1.20	1.05-1.37	0.01	1.35	1.10-1.66	0.00	0.96	0.78-1.19	0.72	1.44	1.17-1.78	0.00	1.33	1.05-1.68	0.02
Blood contact	1.25	1.04-1.49	0.02	1.25	0.94-1.67	0.12	1.23	0.94-1.60	0.13	1.60	1.21-2.12	0.00	1.27	0.93-1.74	0.13
Age**			*<0.001*			*<0.001*			*<0.001*			*<0.001*			*<0.001*
Under 35 years	0.40	0.32-0.50	0.00	0.27	0.16-0.45	0.00	0.44	0.31-0.62	0.00	0.47	0.34-0.65	0.00	0.29	0.16-0.53	0.00
35-45 years	1.00			1.00			1.00			1.00			1.00		
45-55 years	1.73	1.54-1.96	0.00	2.17	1.75-2.69	0.00	1.73	1.43-2.09	0.00	1.50	1.23-1.83	0.00	2.20	1.64-2.96	0.00
55 to 65 years	2.93	2.56-3.36	0.00	4.29	3.41-5.40	0.00	3.09	2.51-3.81	0.00	2.13	1.68-2.69	0.00	7.87	5.88-10.53	0.00
65 to 75 years	4.96	4.09-6.01	0.00	7.03	5.23-9.46	0.00	5.95	4.53-7.80	0.00	3.39	2.46-4.66	0.00	30.01	21.92-41.09	0.00
Over 75 years	5.77	3.75-8.86	0.00	9.64	5.47-17.01	0.00	5.56	2.98-10.36	0.00	1.67	0.61-4.54	0.32	75.90	48.72-118.23	0.00
CD4 cell count*			*<0.001*			*0.009*			*<0. 001*			*<0.001*			*<0.001*
Less than 50 cells/mm^3	3.12	2.30-4.22	0.00	2.54	1.44-4.50	0.00	2.40	1.52-3.81	0.00	4.36	2.67-7.09	0.00	2.06	0.95-4.44	0.07
50 to 200 cells/mm^3	1.31	1.07-1.59	0.01	1.53	1.13-2.09	0.01	1.20	0.91-1.59	0.20	1.39	0.98-1.97	0.06	1.77	1.25-2.52	0.00
200 to 350 cells/mm^3	1.00			1.00			1.00			1.00			1.00		
350 to 500 cells/mm^3	0.82	0.71-0.95	0.01	0.89	0.70-1.14	0.37	0.79	0.64-0.98	0.03	0.88	0.67-1.14	0.33	0.91	0.69-1.19	0.49
500 to 750 cells/mm^3	0.70	0.60-0.81	0.00	0.82	0.64-1.04	0.10	0.57	0.46-0.71	0.00	0.85	0.66-1.11	0.23	0.83	0.63-1.09	0.17
More than 750 cells/mm^3	0.83	0.71-0.98	0.03	0.96	0.74-1.25	0.78	0.66	0.52-0.85	0.00	1.08	0.82-1.42	0.60	0.68	0.50-0.92	0.01
Per year longer with <200 CD4 cells/mm^3	0.99	0.96-1.02	0.35	0.97	0.93-1.02	0.24	1.02	0.97-1.06	0.47	0.98	0.93-1.03	0.49	0.96	0.91-1.00	0.06
Per year longer HIV RNA load>1000 copies/ml	1.01	0.96-1.05	0.81	1.00	0.93-1.08	0.92	1.02	0.96-1.09	0.43	0.98	0.91-1.06	0.61	0.94	0.86-1.02	0.11
Treatment status			*<0.001*			*0.02*			*0.03*			*0.004*			*0.29*
Not (yet) started on cART	1.21	1.03-1.43	0.02	0.88	0.64-1.20	0.40	1.30	1.03-1.65	0.03	1.29	0.99-1.67	0.06	0.91	0.63-1.32	0.62
Treatment experienced at start cART	1.28	1.13-1.46	0.00	1.28	1.04-1.56	0.02	1.15	0.95-1.40	0.15	1.19	0.95-1.50	0.13	1.20	0.95-1.52	0.13
Naïve at start cART	1.00			1.00				1.00		1.00			1.00		

	Non-AIDS defining disease			Cardiovascular disease			Non-AIDS malignancy			Diabetes mellitus			CKD		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Per year longer on cART	1.02	1.01–1.03	0.00				1.01	1.00–1.02	0.12	0.95	0.92–0.95	0.00	1.02	1.01–1.04	0.00
Per year longer on LOP/r				1.02	0.99–1.04	0.18									
Per year longer on IDV				1.03	1.01–1.05	0.01									
Recent use of ABC***				1.66	1.39–1.98	0.00									
Per year longer on AZT										1.07	1.04–1.11	0.00			
Per year longer on d4T										1.15	1.10–1.19	0.00			
Per year longer on ddI										1.05	1.01–1.10	0.01			
Body mass index**			*<0.001*			*0.20*			*<0.001*			*<0.001*			*<0.001*
Less than 18 kg/m² (underweight)	1.40	1.09–1.78	0.01	1.15	0.75–1.75	0.52	1.56	1.13–2.16	0.01	1.40	0.84–2.32	0.20	4.10	3.07–5.49	0.00
Between 18 and 25 kg/m² (normal)	1.00			1.00			1.00			1.00			1.00		
Between 25 and 30 kg/m² (overweight)	1.07	0.95–1.19	0.27	0.86	0.72–1.04	0.12	0.70	0.58–0.83	0.00	2.18	1.80–2.64	0.00	0.32	0.26–0.41	0.00
More than 30 kg/m² (severely overweight)	1.57	1.33–1.85	0.00	0.97	0.71–1.32	0.85	0.71	0.51–0.99	0.04	4.39	3.48–5.55	0.00	0.21	0.13–0.33	0.00
Prior AIDS event	1.37	1.23–1.52	0.00	1.28	1.08–1.51	0.00	1.35	1.15–1.57	0.00	1.28	1.07–1.52	0.01	1.13	0.94–1.35	0.18
Hepatitis B virus positive	1.22	1.03–1.44	0.02	1.01	0.76–1.36	0.93	1.65	1.31–2.07	0.00	0.96	0.71–1.31	0.80	1.27	0.93–1.72	0.13
Hepatitis C virus positive	1.07	0.87–1.33	0.51	0.98	0.69–1.40	0.93	1.15	0.85–1.57	0.36	0.95	0.64–1.41	0.80	1.78	1.27–2.50	0.00
Hypertension	1.64	1.45–1.86	0.00	1.80	1.50–2.17	0.00	1.29	1.06–1.56	0.01	1.92	1.59–2.32	0.00	1.94	1.61–2.34	0.00
Smoking status			*<0.001*			*<0.001*			*<0.001*			*0.02*			*0.37*
Never	1.00			1.00			1.00			1.00			1.00		
Current smoker	1.47	1.26–1.72	0.00	1.94	1.49–2.52	0.00	1.71	1.34–2.19	0.00	0.94	0.74–1.20	0.63	1.05	0.81–1.35	0.71
Past smoker	1.26	1.05–1.51	0.01	1.31	0.96–1.78	0.09	1.21	0.90–1.62	0.21	1.37	1.05–1.80	0.02	1.10	0.83–1.46	0.52
Unknown	1.18	1.01–1.39	0.04	1.20	0.91–1.60	0.20	1.36	1.04–1.76	0.02	1.04	0.82–1.31	0.76	0.90	0.69–1.17	0.41

** Time updated and lagged by 3 months.*

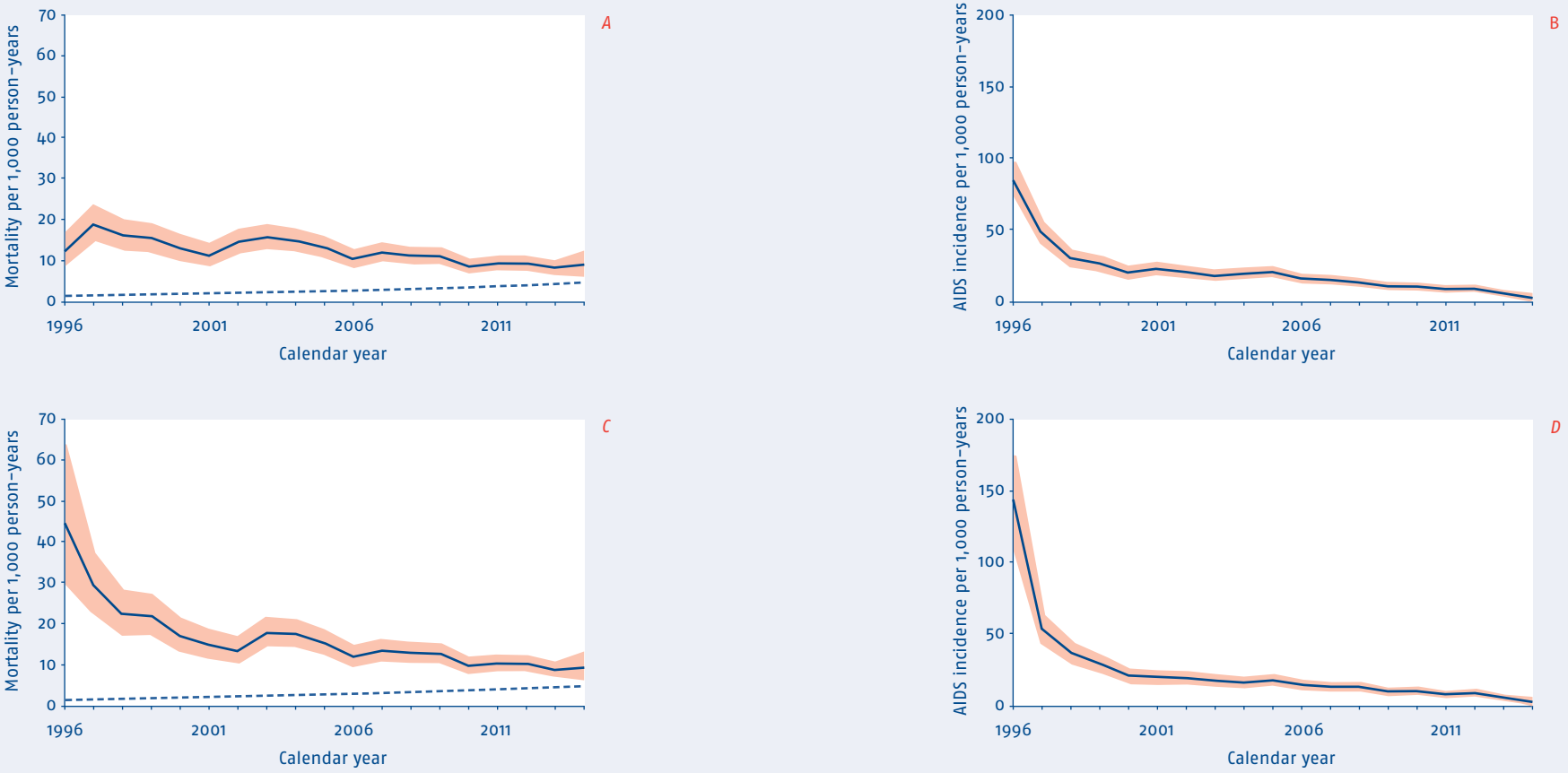
*** Time updated.*

**** Current use or recently used in the past 6 months.*

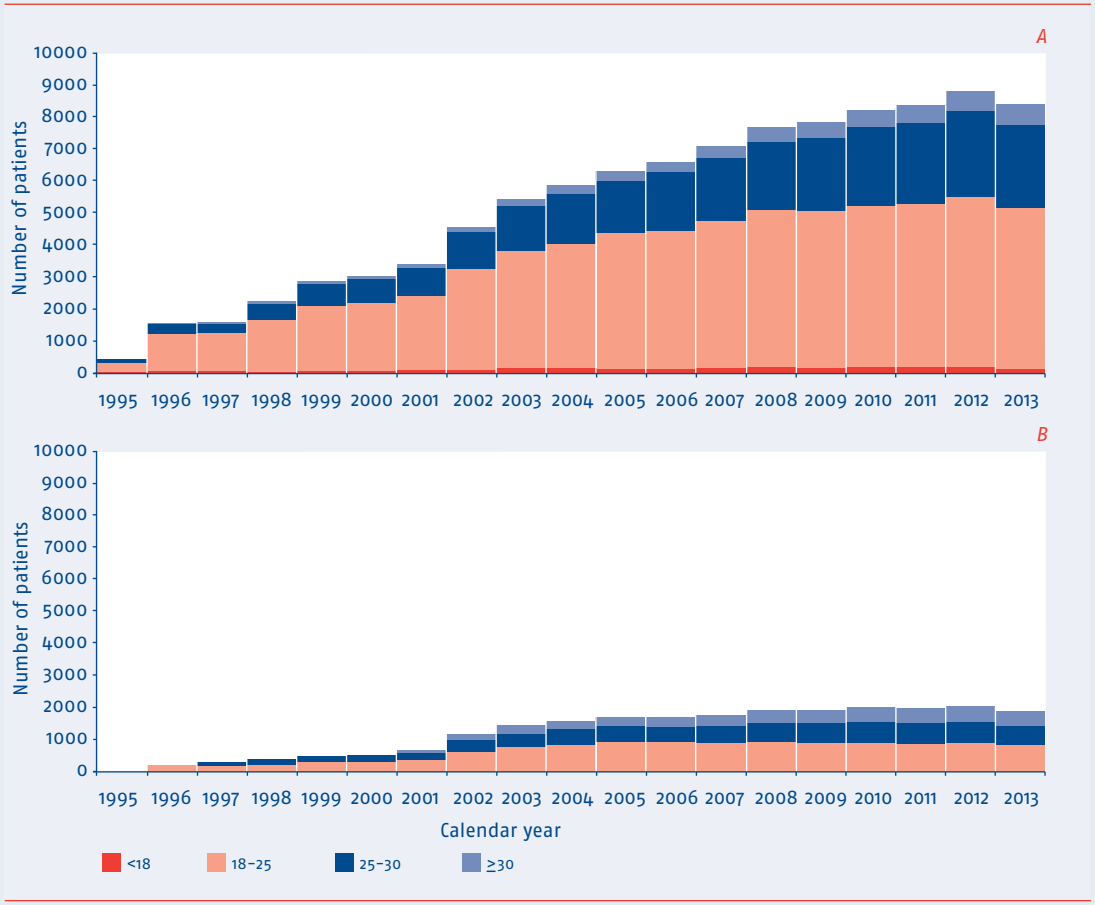
P-values in italic are overall p-values.

Legend: *IDU=injecting drug use; cART=combination antiretroviral therapy; CDC=Centers for Disease Control and Prevention; LOP/r=lopinavir/ritonavir; IDV=indinavir; ABC=abacavir; AZT=zidovudine; d4T=stavudine; ddI=didanosine.*

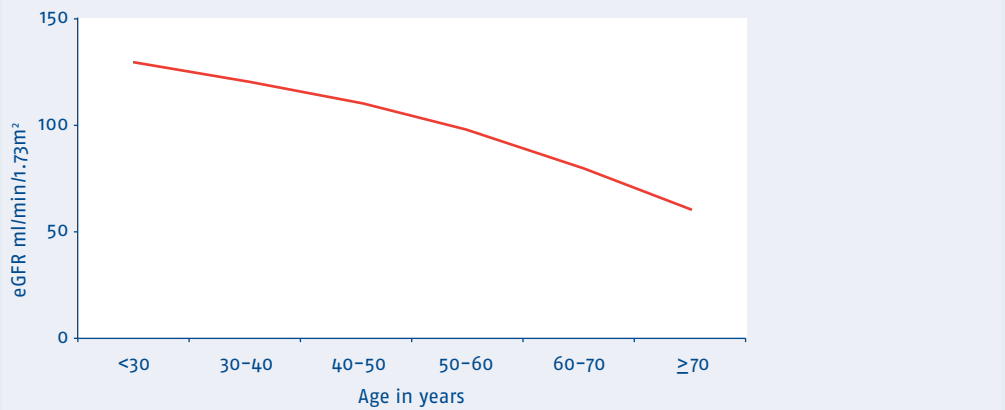
Web Appendix Figure 4.1: *Annual mortality (A, C) and incidence of AIDS (B, D) in 21,928 HIV-1-infected patients in the Netherlands after HIV diagnosis (upper plots) and in a subpopulation of 19,388 treated patients who started combination antiretroviral therapy (lower plots) from 1995 onwards. Solid lines represent the incidence, whilst the shaded areas are the 95% confidence intervals. The dotted line is the mortality rate for age- and sex-matched individuals from the general population in the Netherlands. A: 2,198 deaths, 189,489 person-years of follow-up; B: 2,842 AIDS cases after six weeks after diagnosis, 164,428 person years; C: 1,955 deaths, 146,824 person-years; D: 1,969 cases after 4 weeks after start of combination antiretroviral therapy, 135,284 person-years.*



Web Appendix Figure 4.2: *Absolute number of men (A) and women (B) within body mass index (BMI) categories at the end of each calendar year. For each patient the last available weight measurement in each year was selected.*

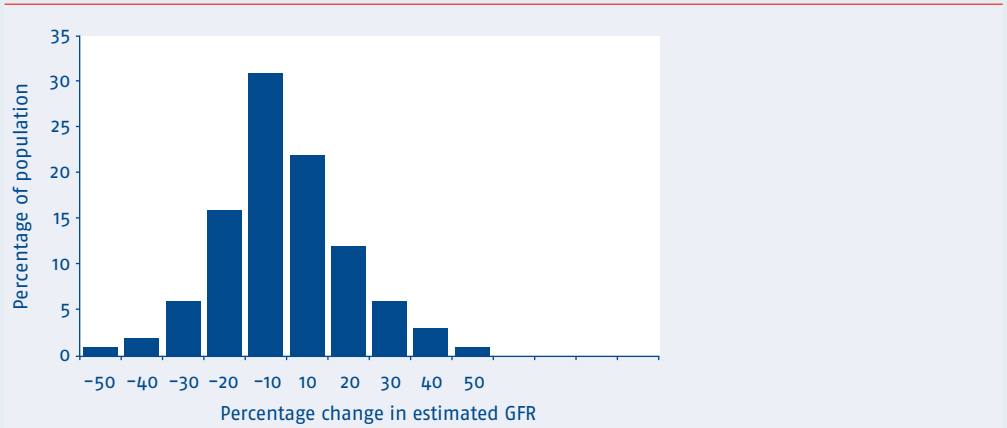


Web Appendix Figure 4.3: *Estimated glomerular filtration rate (eGFR) distribution by age.*



Legend: *eGFR=estimated glomerular filtration rate.*

Web Appendix Figure 4.4: *Distribution of percentage change in estimated glomerular filtration rate (eGFR) (Cockcroft-Gault) during first 2 years after the start of combination antiretroviral therapy (cART).*



Legend: *GFR=glomerular filtration rate.*

Web Appendix Table 6.1: Characteristics of 512 HIV-1 infected children in the Netherlands on combination antiretroviral therapy (cART).

Characteristic	Vertically infected children			Non-vertically infected children
Age at cART initiation	0-2 years	2-5 years	5-18 years	5-18 years
Time between HIV-1 diagnosis and cART initiation (months)*	1 (0.2-2)	10 (3-22)	17 (2-66)	3 (1-8)
CD4 count at start of cART initiation (cells/mm^3)*	1,290 (510-2125)	630 (350-1030)	310 (160-440)	280 (160-400)
CD4 z score at cART initiation*	-0.95 (-1.6 to -0.4)	-0.98 (-1.3 to -0.4)	-0.95 (-1.2 to -0.6)	-0.94 (-1.3 to -0.6)
HIV-1 RNA level at cART initiation (log cps/ml)*	4.0 (2.2-5.4)	3.6 (2.8-4.7)	3.4 (2.6-4.4)	2.9 (2.4-3.8)

** Median (IQR interquartile range)*

***Legend:** cART=combination antiretroviral therapy.*

Web Appendix Table 10.1: Annual number of HIV diagnoses in Curaçao stratified by sex and survival status as of June 2014.

	Alive, in clinical care		Alive, not in clinical care		Deceased		Total	
	Men	Women	Men	Women	Men	Women	Men	Women
Unknown	7	6	17	4	2	7	26	17
≤1995	33	12	11	10	35	10	79	32
1996	7	9	3	3	0	1	10	13
1997	7	7	2	6	7	3	16	16
1998	11	2	8	3	8	1	27	6
1999	10	6	5	2	6	2	21	10
2000	12	7	5	7	6	4	23	18
2001	7	6	3	7	5	4	15	17
2002	15	7	8	9	6	2	29	18
2003	17	10	8	6	11	2	36	18
2004	7	9	11	4	10	2	28	15
2005	18	3	6	8	5	4	29	15
2006	15	10	7	3	3	2	25	15
2007	14	7	8	3	5	1	27	11
2008	18	11	11	7	2	1	31	19
2009	20	13	10	5	0	2	30	20
2010	15	15	5	2	2	1	22	18
2011	25	17	5	4	0	0	30	21
2012	23	19	5	5	0	0	28	24
2013	41	19	-	-	0	0	41	19
2014	7	2	-	-	0	0	7	2
Total	329	197	138	98	113	49	580	344