Monitoring Report 2012

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Appendix

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 Minister of Health, Welfare and Sports (Ministerie van Volksgezondheid, Welzijn en Sport) as the national executive organization for the registration and monitoring of HIV-infected patients in follow-up in one of the 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.

www.hiv-monitoring.nl

HIV Monitoring

Colophon

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Appendix

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collaborative
HIV treatment
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List of tables and figures

The Web Appendix contains tables and figures supplementary to SHM's Monitoring Report 2012. The first number in the table or figure numbering below relates to the relevant chapter of the report.

Web Appendix Table 1.1: Characteristics of the 16,169 HIV-infected patients in follow-up as of June 2012.

	MSM	Heterosexual		IDU		Blood or blood products		Other / unknown		Total	
	Men	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	N=9542	N=2134	N=2839	N=264	N=98	N=121	N=83	N=835	N=253	N=12896	N=3273
Current age [years]											
0-12	0	0	0	0	0	1	1	66	62	67	63
	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	1.2%	7.9%	24.5%	0.5%	1.9%
13-17	0	0	1	0	0	1	0	28	33	29	34
	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	0.0%	3.4%	13.0%	0.2%	1.0%
18-24	197	21	66	0	0	2	1	43	22	263	89
	1.7%	1.0%	2.3%	0.0%	0.0%	1.7%	1.2%	5.1%	8.7%	2.0%	2.7%
25-34	1164	253	671	20	3	15	14	102	32	1554	720
	12.2%	11.9%	23.6%	7.6%	3.1%	12.4%	16.9%	12.2%	12.6%	12.1%	22.0%
35-44	2660	613	1072	45	12	23	26	190	43	3531	1153
	27.9%	28.7%	37.8%	17.0%	12.2%	19.0%	31.3%	22.8%	17.0%	27.4%	35.2%
45-54	3454	756	710	133	61	45	25	226	42	4614	838
	36.2%	35.4%	25.0%	50.4%	62.2%	37.2%	30.1%	27.1%	16.6%	35.8%	25.6%
55-64	1590	347	231	62	21	23	10	123	14	2145	276
	16.7%	16.3%	8.1%	23.5%	21.4%	19.0%	12.0%	14.7%	5.5%	16.6%	8.4%
≥65	477	144	88	4	1	11	6	57	5	693	100
	5.0%	6.7%	3.1%	1.5%	1.0%	9.1%	7.2%	6.8%	2.0%	5.4%	3.1%
Current age 50 years or older											
No	5939	1281	2230	130	43	71	56	564	215	7985	2544
	62.2%	60.0%	78.5%	49.2%	43.9%	58.7%	67.5%	67.5%	85.0%	61.9%	77.7%
Yes	3603	853	609	134	55	50	27	271	38	4911	729
	37.8%	40.0%	21.5%	50.8%	56.1%	41.3%	32.5%	32.5%	15.0%	38.1%	22.3%
Region of origin											
Netherlands	7039	923	757	164	51	77	18	394	110	8597	936
	73.8%	43.3%	26.7%	62.1%	52.0%	63.6%	21.7%	47.2%	43.5%	66.7%	28.6%
Sub-Saharan Africa	118	663	1296	5	0	25	37	212	81	1023	1414
	1.2%	31.1%	46.6%	1.9%	0.0%	20.7%	44.6%	25.4%	32.0%	7.9%	43.2%
Western Europe	639	67	69	27	30	5	2	41	31	779	132
	6.7%	3.1%	2.4%	10.2%	30.6%	4.1%	2.4%	4.9%	12.3%	6.0%	4.0%
Latin America	600	205	267	9	2	3	10	46	5	863	284
	6.3%	9.6%	9.4%	3.4%	2.0%	2.5%	12.0%	5.5%	2.0%	6.7%	8.7%
Caribbean	319	113	164	7	1	2	4	27	2	468	171
	3.3%	5.3%	5.8%	2.7%	1.0%	1.7%	4.8%	3.2%	0.8%	3.6%	5.2%
Other	789	159	285	52	14	9	12	111	21	1120	332
	8.3%	7.5%	10.0%	19.7%	14.2%	7.4%	14.5%	13.3%	8.3%	8.7%	10.1%
Unknown	38	4	1	0	0	0	0	4	3	46	4
	0.4%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	1.2%	0.4%	0.1%

	MSM	Heterosexual		IDU		Blood or blood products		Other / unknown		Total	
	Men	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	N=9542	N=2134	N=2839	N=264	N=98	N=121	N=83	N=835	N=253	N=12896	N=3273
Years aware of HIV infection											
<1	511	124	103	1	0	5	3	39	6	680	112
	5.4%	5.8%	3.6%	0.4%	0.0%	4.1%	3.6%	4.7%	2.4%	5.3%	3.4%
1–2	1421	271	314	7	1	4	4	80	35	1783	354
	14.9%	12.7%	11.1%	2.7%	1.0%	3.3%	4.8%	9.6%	13.8%	13.8%	10.8%
3–4	1450	270	322	9	4	4	4	86	30	1819	360
	15.2%	12.7%	11.3%	3.3%	4.1%	3.3%	4.8%	10.3%	11.9%	14.1%	11.0%
5–10	2537	700	967	41	12	20	25	250	61	3548	1065
	26.6%	32.8%	34.1%	15.5%	12.2%	16.5%	30.1%	29.9%	24.1%	27.5%	32.5%
>10	3596	759	1107	203	81	86	47	261	112	4905	1347
	37.7%	35.6%	39.0%	76.9%	82.7%	71.1%	56.6%	31.3%	44.3%	38.0%	41.2%
Unknown	27	10	26	3	0	2	0	119	9	161	35
	0.3%	0.5%	0.9%	1.1%	0.0%	1.7%	0.0%	14.3%	3.6%	1.2%	1.1%
Current CD4 count [cells/mm³],	560	509	550	466	579	530	627	480	560	550	557
median / IQR	430–730	360–680	410–730	275–660	350–770	330–670	390–737	320–670	400–830	410–719	407–740
Current CD8 count [cells/mm³],	900	850	800	800	920	810	750	830	735	890	800
median / IQR	660–1220	600–1200	578–1102	520–1100	610–1240	560–1058	520–927	590–1125	540–1071	650–1210	570–1106
Current HIV RNA <500 copies/ml	7738	1746	2278	228	85	103	77	541	149	10356	2589
	81.1%	81.8%	80.2%	86.4%	86.7%	85.1%	92.8%	64.8%	58.9%	80.3%	79.1%
Ever AIDS	1839	648	606	91	43	37	25	255	65	2870	739
	19.3%	30.4%	21.3%	34.5%	43.9%	30.6%	30.1%	30.5%	25.7%	22.3%	22.6%
AIDS at diagnosis	941	434	349	22	11	16	13	187	31	1600	404
	9.9%	20.3%	12.3%	8.3%	11.2%	13.2%	15.7%	22.4%	12.3%	12.4%	12.3%
Current treatment											
cART	8096	1874	2530	251	94	111	80	662	226	10994	2930
	84.8%	87.8%	89.1%	95.1%	95.9%	91.7%	96.4%	79.3%	89.3%	85.3%	89.5%
Non-cART	24	6	15	1	0	0	0	5	1	36	16
	0.3%	0.2%	0.5%	0.4%	0.0%	0.0%	0.0%	0.6%	0.4%	0.3%	0.5%
Not started	1422	254	294	12	4	10	3	168	26	1866	327
	14.9%	11.9%	10.4%	4.5%	4.1%	8.3%	3.6%	20.1%	10.3%	14.5%	10.0%
Coinfection											
HBV	661	164	136	31	4	9	3	43	13	908	156
	6.9%	7.7%	4.8%	11.7%	4.1%	7.4%	3.6%	5.1%	5.1%	7.0%	4.8%
HCV	855	103	126	242	89	42	9	89	48	1331	272
	9.0%	4.8%	4.4%	91.7%	90.8%	34.7%	10.8%	10.7%	19.0%	10.3%	8.3%

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

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, via injecting drug use (IDU), via contact with contaminated blood, or via other or unknown modes of transmission. Note: data collection for 2010 and 2011 is not yet finalised.

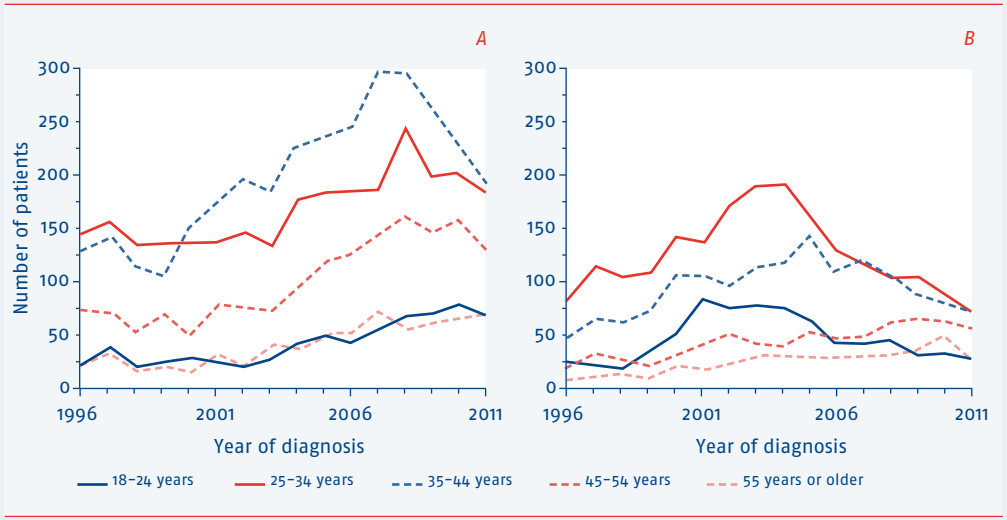
	MSM	Heterosexual		IDU		Blood or blood products		Other/unknown		Total
Year of diagnosis	Men	Men	Women	Men	Women	Men	Women	Men	Women	
≤1995	2189	260	385	282	124	55	22	157	52	3526
1996	383	91	82	32	13	4	4	37	4	650
1997	437	111	129	41	8	7	3	47	8	791
1998	329	106	112	22	4	5	5	29	11	623
1999	351	106	137	17	6	7	4	22	5	655
2000	374	158	188	17	3	3	4	34	7	788
2001	441	169	211	13	6	6	4	42	9	901
2002	460	165	250	15	2	10	7	60	5	974
2003	454	176	269	22	5	8	3	64	15	1016
2004	573	192	258	9	3	4	3	72	10	1124
2005	627	195	251	13	3	3	5	65	11	1173
2006	645	161	189	9	5	4	7	53	5	1078
2007	750	153	200	9	4	2	6	47	7	1178
2008	820	175	168	4	1	3	2	50	6	1229
2009	736	151	171	4	0	1	1	48	8	1120
2010	721	166	143	6	1	3	2	38	9	1089
2011	643	125	128	2	0	4	4	46	9	961
2012	146	40	37	2	0	1	0	9	2	237
Total	11079	2700	3308	519	188	130	86	920	183	19113

Web Appendix Table 1.3: *Region of origin of the 19,113 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.*

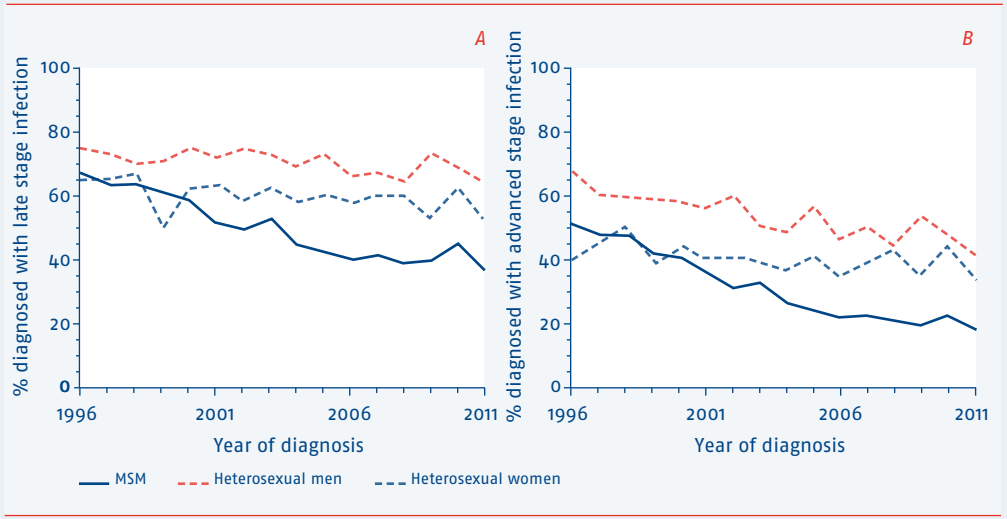
	MSM			Heterosexual men			Heterosexual women			IDU	Other
	<2010	≥2010	Total	<2010	≥2010	Total	<2010	≥2010	Total	Total	Total
The Netherlands	6851	1131	7982	923	173	1096	720	90	810	428	585
	71.6%	74.9%	72.0%	39.0%	52.3%	40.6%	24.0%	29.2%	24.5%	60.5%	44.4%
Sub-Saharan Africa	128	24	152	809	70	879	1449	121	1570	9	330
	1.3%	1.6%	1.4%	34.1%	21.1%	32.6%	48.3%	39.3%	47.5%	1.3%	25.0%
Western Europe	788	73	861	84	9	93	87	4	91	139	105
	8.2%	4.8%	7.8%	3.5%	2.7%	3.4%	2.9%	1.3%	2.8%	19.7%	8.0%
Central Europe	139	52	191	60	8	68	38	8	46	25	43
	1.5%	3.4%	1.7%	2.5%	2.4%	2.5%	1.3%	2.6%	1.4%	3.5%	3.3%
Eastern Europe	46	10	56	9	2	11	16	6	22	20	14
	0.5%	0.7%	0.5%	0.4%	0.6%	0.4%	0.5%	2.0%	0.7%	2.8%	1.1%
Latin America	642	73	715	240	32	272	287	28	315	24	76
	6.7%	4.8%	6.55	10.1%	9.7%	10.1%	9.6%	9.1%	9.5%	3.4%	5.8%
Caribbean	292	65	357	122	20	142	179	19	198	12	35
	3.1%	4.3%	3.2%	5.1%	6.0%	5.3%	6.0%	6.2%	6.0%	1.7%	2.7%
South and Southeast Asia	260	47	307	43	5	48	179	24	203	17	50
	2.7%	3.1%	2.8%	1.8%	1.5%	1.8%	6.0%	7.8%	6.1%	2.4%	3.8%
Other/unknown	423	35	458	79	12	91	45	8	53	33	81
	4.4%	2.3%	4.1%	3.3%	3.6%	3.4%	1.5%	2.6%	1.6%	4.7%	6.1%

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

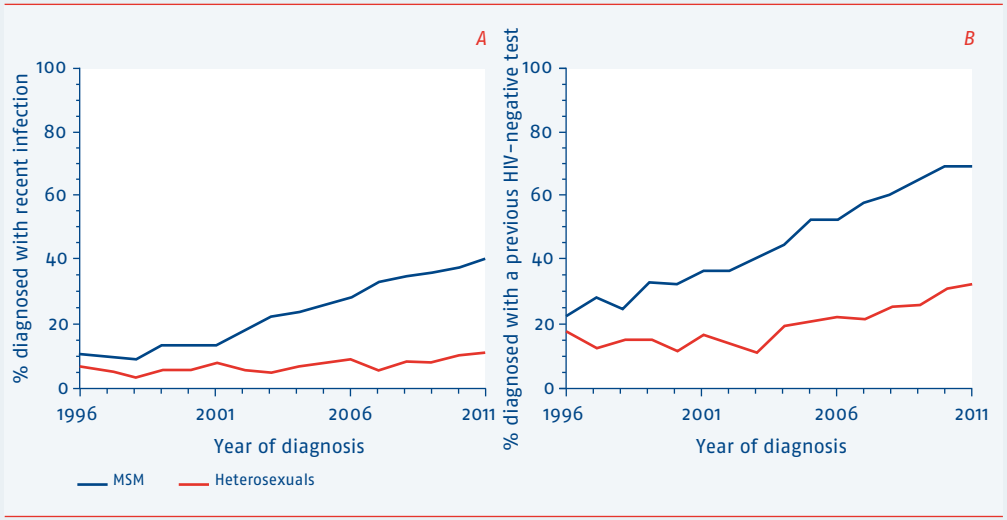
Web Appendix Figure 1.1: *Age distribution at the time of diagnosis amongst HIV-1-infected men who have sex with men (A) and heterosexual men and women (B). Note: data collection for 2010 and 2011 is not yet finalised.*



Web Appendix Figure 1.2: *Proportion of patients classified as having (A) late or (B) advanced HIV infection at the time of HIV diagnosis. Between 1996 and 2011, 55% were diagnosed with late stage HIV: men who have sex with men (MSM) 46%, heterosexual men 70%, heterosexual women 60%, injecting drug users (IDU) 66%. Overall, 36% were diagnosed with advanced stage infection: MSM 28%, heterosexual men 53%, heterosexual women 40%, and IDU 49%. Late stage infection: CD4 cell counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Advanced stage infection: CD4 counts below 200 cells/mm³ or having AIDS.*



Web Appendix Figure 1.3: *Proportion of patients diagnosed (A) with a recent HIV infection or (B) with a previous HIV-negative test. A diagnosed infection was considered to be recent if the time between the last negative HIV test and the first positive test was at most 1.5 years. The proportion diagnosed with a recent infection increased from 10% in 1996 to 40% in 2011 amongst men who have sex with men (MSM) and from 5% to 10% during the same period for heterosexual men and women. Median CD4 counts in those diagnosed with a recent infection were 500 (370-670) cells/mm³ in MSM and 450 (280-650) cells/mm³ in heterosexual men and women. Amongst those diagnosed with a non-recent infection, CD4 counts were 210 (76-400) cells/mm³ in 1996 and 360 (180-543) cells/mm³ in 2011 in MSM, whilst in heterosexuals CD4 counts increased from 200 (50-400) cells/mm³ to 280 (110-450) cells/mm³ during the same period. Altogether, 69% of MSM and 32% of heterosexuals (men 27%, women 36%) diagnosed in 2011 had a previous HIV-negative test.*



Web Appendix Table 2.1: *The characteristics of the 12,799 men and 3,350 women, who had a recorded date of HIV-1 diagnosis, but were not known to be HIV-2 positive as of 1 June 2012, had started combination antiretroviral therapy when they were at least 16 years old and had their last recorded contact with HIV-related care in the Netherlands.*

Patient characteristics		**Men** n = 12,799		**Women** n = 3,350		**P-value**
		Number	**Percentage***	**Number**	**Percentage***	
Region of birth	The Netherlands	8341	(65%)	877	(26%)	< 0.0001
	Other or unknown	4458	(35%)	2473	(74%)	
HIV-1 transmission route	Homosexual contact	9177	(72%)	0	(0%)	< 0.0001
	Heterosexual contact	2283	(18%)	2939	(88%)	
	IDU or blood contact	591	(5%)	250	(7%)	
	Other or unknown	748	(6%)	161	(5%)	
Age at the start of cART	Under 45 years	8749	(68%)	2878	(72%)	< 0.0001
	45 to 64 years	3849	(30%)	442	(13%)	
	Over 65 years	201	(2%)	30	(1%)	
Used ART before 2007?	No	4819	(38%)	978	(29%)	< 0.0001
	Yes	7980	(62%)	2372	(71%)	
HIV-1 diagnosis to cART	Less than one year	6487	(51%)	2026	(61%)	< 0.0001
	One to five years	3982	(31%)	793	(24%)	
	More than five years	2330	(18%)	531	(16%)	
CD4 cell count**	Less than 200 cells/mm^3	5026	(39%)	1293	(39%)	< 0.0001
	200 to 500 cells/ mm^3	5811	(45%)	1360	(41%)	
	More than 500 cells/ mm^3	865	(7%)	338	(10%)	
	Unknown	1097	(9%)	359	(11%)	
HIV RNA load **	Less than 1,000 particles/ml	587	5%	274	8%	< 0.0001
	More than 1,000 particles/ml	10420	81%	2581	77%	
	Unknown	1792	(14%)	495	(15%)	
Body mass index**	Less than 18.5 kg/m^2 (underweight)	561	(4%)	143	(4%)	< 0.0001
	Between 18.5 and 25 kg/m^2 (normal)	5912	(46%)	1102	(33%)	
	More than 25 kg/m^2 (overweight)	1995	(16%)	743	(22%)	
	Unknown	4331	(34%)	1362	(41%)	
Hepatitis B virus status***	Positive	653	(5%)	100	(3%)	< 0.0001
	Negative	5454	(43%)	1677	(50%)	
	Unknown	6692	(52%)	1573	(47%)	
Hepatitis C virus status***	Positive	696	(5%)	233	(7%)	< 0.0001
	Negative	6626	(52%)	1301	(39%)	
	Unknown	5477	(43%)	1816	(54%)	

** Percentages may not sum to 100 due to rounding; ** Last known before the start of combination antiretroviral therapy, but within a year of this date; *** At the start of cART.*

Legend: *cART = combination antiretroviral therapy, ART = antiretroviral therapy, IDU = intravenous drug use.*

Web Appendix Table 2.2: The number of men and women with HIV-1 infection who died without or after starting combination antiretroviral therapy and their death rate per 1,000 years of follow-up (in parenthesis) in the periods 1996 to 2001, 2002 to 2006 and 2007 to 2011.

cART	1996 – 2001			2002 – 2006			2007 – 2011		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
Before starting	–	–	–	62 (8.8)	17 (9.1)	79 (8.9)	48 (5.3)	11 (7.0)	59 (5.5)
After starting	363 (20.4)	51 (14.1)	414 (19.3)	473 (17.0)	82 (10.4)	555 (15.6)	447 (10.8)	78 (6.8)	525 (9.9)

Legend: cART = combination antiretroviral therapy.

Web Appendix Table 2.3: Hazard ratios for time to death from the start of cART for men and women.

Patient characteristics		Men		Women	
		Hazard ratio	95% CI	Hazard ratio	95% CI
Region of birth	The Netherlands	1		1	
	Other/unknown	0.758	0.667–0.861	0.786	0.591–1.044
HIV-1 transmission route	Homosexual contact	0.851	0.728–0.994	n/a	
	Heterosexual contact*	1		1	
	IDU or blood contact	1.235	0.978–1.560	2.434	1.641–3.611
	Other or unknown	1.427	1.146–1.777	2.882	1.847–4.497
Age at the start of cART	Under 45 years	1		1	
	45 to 64 years	2.031	1.816–2.271	1.780	1.277–2.480
	Over 65 years	5.467	4.190–7.133	3.474	1.381–8.740
HIV-1 diagnosis to cART	Less than one year	1		1	
	One to five years	1.454	1.269–1.667	1.224	0.853–1.756
	More than five years	2.075	1.811–2.377	1.792	1.269–2.530
CD4 cell count**	Less than 200 cells/ml	2.272	1.735–2.975	5.461	2.362–12.624
	200 to 500 cells/ml	1.053	0.798–1.389	2.837	1.214–6.632
	More than 500 cells/ml	1		1	
	Unknown	1.318	0.929–1.870	2.636	0.978–7.102
HIV RNA load **	Less than 1,000 particles/ml	1		1	
	More than 1,000 particles/ml	1.046	0.827–1.323	0.678	0.415–1.107
	Unknown	1.696	1.305–2.204	1.104	0.601–2.031
Body mass index**	Less than 18.5 kg/m^2 (underweight)	1.397	1.130–1.727	1.367	0.766–2.441
	Between 18.5 and 25 kg/m^2 (normal)	1		1	
	More than 25 kg/m^2 (overweight)	0.672	0.560–0.807	1.170	0.775–1.769
	Unknown	1.167	1.030–1.322	1.826	1.327–2.512
Hepatitis B virus status***	Positive	1.510	1.229–1.856	1.782	0.963–3.296
	Negative	1		1	
	Unknown	1.430	1.262–1.622	2.019	1.470–2.772
Hepatitis C virus status***	Positive	2.868	2.313–3.557	1.731	1.076–2.785
	Negative	1		1	
	Unknown	2.356	2.069–2.683	1.138	0.790–1.639

All types of sexual contact for women; ** Last known before the start of combination antiretroviral therapy, but within a year of this date; * At the start of cART.*

***Legend:** cART = combination antiretroviral therapy, IDU = intravenous drug use, CI = confidence interval*

Web Appendix Table 2.4: The causes of death for men and women after the start of cART in the periods 1996 to 2001, 2002 to 2006 and 2007 to 2011.

Cause of death	1996 – 2001			2002 – 2006			2007 – 2011		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
All AIDS-defining causes	183	27	210	160	32	192	112	22	134
Infection	52	13	65	54	14	68	37	9	46
Malignancy	60	6	66	64	6	70	42	6	48
Not specified	71	8	79	42	8	54	33	7	40
Non-AIDS defining malignancy	34	1	35	80	9	89	93	9	102
All cardiovascular diseases	21	0	21	51	0	51	42	5	47
Myocardial infarction	11	0	11	17	0	17	18	0	18
Stroke	2	0	2	10	0	10	7	3	10
Other ischemic heart disease	0	0	0	1	0	1	1	1	2
Other cardiovascular diseases	8	0	8	23	0	23	16	1	17
Non-AIDS defining infection	19	0	19	35	10	45	26	7	33
Liver failure, cirrhosis and hepatitis B or C virus infection at death	10	4	14	19	7	26	33	5	38
Lung-related	5	2	7	11	4	15	18	5	23
Non-natural death	24	2	26	27	4	31	19	1	20
Accident or other violent death	8	0	8	8	2	10	9	1	10
Suicide	9	1	10	15	2	17	9	0	9
Euthanasia	7	1	8	4	0	4	1	0	1
Substance abuse	10	1	11	6	0	6	15	4	19
Other causes	18	4	22	25	6	31	27	8	35
Unknown or unclassifiable causes	39	10	49	59	10	69	62	12	74
Total	363	51	414	473	82	555	447	78	525

Web Appendix Table 2.5: The number of men and women who became lost to follow-up without and after starting combination antiretroviral therapy (cART) and their rate of loss to follow-up (in parenthesis) per 1,000 years of follow-up in the periods 1996 to 2001, 2002 to 2006 and 2007 to 2011.

cART	Place of birth	1996 - 2001			2002 - 2006			2007 - 2011		
		Men	Women	Total	Men	Women	Total	Men	Women	Total
Before starting	Netherlands	-	-	-	33	5	38	75	3	78
					(7.3)	(9.2)	(7.5)	(12.0)	(5.6)	(11.5)
Before starting	Elsewhere	-	-	-	157	93	250	154	68	222
					(63.3)	(70.7)	(65.9)	(54.0)	(66.1)	(57.2)
After starting	Netherlands	18	1	19	62	7	69	125	19	144
		(1.5)	(0.7)	(1.4)	(3.4)	(3.1)	(2.6)	(4.6)	(6.0)	(4.7)
After starting	Elsewhere	33	7	40	262	201	463	331	160	491
		(6.0)	(3.2)	(5.2)	(26.9)	(35.9)	(30.2)	(23.4)	(19.2)	(21.9)

Web Appendix Table 2.6: The number and incidence (in parenthesis) per 1,000 years of patient follow-up of the first occurrence per patient of any and individual AIDS-defining events per time period for men, women and the total population.

Event	1996 – 2001			2002 – 2006			2007 – 2011		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
Any AIDS-defining event	628	131	759	569	164	733	555	149	704
	(42.3)	(44.8)	(42.7)	(23.1)	(23.3)	(23.5)	(15.0)	(14.5)	(14.9)
AIDS dementia complex / HIV encephalopathy	36	10	46	38	10	48	49	9	58
	(2.2)	(3.1)	(2.4)	(1.4)	(1.3)	(1.4)	(1.2)	(0.8)	(1.1)
Cryptococcosis	11	5	16	16	7	23	13	2	15
	(0.7)	(1.2)	(0.8)	(0.6)	(0.9)	(0.6)	(0.3)	(0.2)	(0.3)
Cryptosporidiosis	15	2	17	8	2	10	1	0	1
	(0.9)	(0.6)	(0.9)	(0.3)	(0.3)	(0.3)	(0.0)	(0.0)	(0.0)
Herpes simplex virus	36	7	43	38	12	50	29	18	47
	(2.2)	(2.2)	(2.2)	(1.4)	(1.5)	(1.4)	(0.7)	(1.6)	(0.9)
Disseminated or extrapulmonary histoplasmosis	8	0	8	5	2	7	4	1	5
	(0.5)	(0.0)	(0.4)	(0.2)	(0.3)	(0.2)	(0.1)	(0.1)	(0.1)
Kaposi's sarcoma	85	4	89	88	15	103	95	8	103
	(5.3)	(1.2)	(4.6)	(3.2)	(1.9)	(2.9)	(2.3)	(0.7)	(2.0)
Mycobacterium avium complex or kansasii clade, disseminated or extra pulmonary	57	12	69	25	7	32	32	7	39
	(3.5)	(3.8)	(3.6)	(0.9)	(0.9)	(0.9)	(0.8)	(0.6)	(0.7)
Other or unidentified mycobacterium	30	7	37	8	7	15	16	1	17
	(1.8)	(2.2)	(1.9)	(0.3)	(0.9)	(0.4)	(0.4)	(0.1)	(0.3)
Pneumocystis jiroveci (carinii) pneumonia	68	13	81	61	17	78	60	22	82
	(4.2)	(4.1)	(4.2)	(2.2)	(2.2)	(2.2)	(1.5)	(1.9)	(1.6)
Recurrent pneumonia	37	17	54	66	22	88	76	21	97
	(2.3)	(5.3)	(2.8)	(2.4)	(2.8)	(2.5)	(1.9)	(1.8)	(1.9)
Progressive multifocal leucoencephalopathy	21	4	25	22	0	22	25	2	27
	(1.3)	(1.2)	(1.3)	(0.8)	(0.0)	(0.6)	(0.6)	(0.2)	(0.5)
Cerebral toxoplasmosis	52	5	57	36	11	47	13	9	22
	(3.2)	(1.6)	(2.9)	(1.3)	(1.4)	(1.3)	(0.3)	(0.8)	(0.4)
HIV wasting syndrome	25	6	31	28	8	36	24	4	28
	(1.5)	(1.9)	(1.6)	(1.0)	(1.0)	(1.0)	(0.6)	(0.3)	(0.5)
Oesophageal or pulmonary candidiasis	143	32	175	128	44	172	115	36	151
	(8.9)	(10.1)	(9.1)	(4.7)	(5.7)	(4.9)	(2.8)	(3.2)	(2.9)
Cytomegalovirus infection	93	12	105	55	16	71	49	11	60
	(5.8)	(3.8)	(5.4)	(2.0)	(2.0)	(2.0)	(1.2)	(1.0)	(1.1)
Non-Hodgkin's lymphoma	57	4	61	65	9	74	71	6	77
	(3.5)	(1.2)	(3.1)	(2.6)	(1.1)	(2.1)	(1.7)	(0.5)	(1.5)
Tuberculosis	47	13	60	68	40	108	37	36	73
	(2.9)	(4.1)	(3.1)	(2.5)	(5.2)	(3.1)	(0.9)	(3.2)	(1.4)
Any other CDC-C-defining disease*	40	9	49	19	8	27	18	4	22
	(2.5)	(2.9)	(2.5)	(0.7)	(1.0)	(0.8)	(0.4)	(0.3)	(0.4)

** Including primary lymphoma of the central nervous system (23 cases), chronic intestinal microsporidiosis lasting more than one month (15 cases) and invasive cervical cancer (14 cases).*

Web Appendix Table 2.7: *P-values for the patient characteristics remaining in the final model of the multivariate analysis on factors associated with the incidence of AIDS, diabetes mellitus, invasive cardiac procedures, myocardial infarction, stroke, renal insufficiency, non-AIDS defining malignancies, liver disease and osteoporosis.*

Patient characteristics		AIDS	Diabetes mellitus	Cardiovascular diseases*	Renal insufficiency	Non-AIDS defining malignancies	Liver disease*	Osteoporosis
Region of birth	Men			0.0005		<0.0001		<0.0001
	Women					0.0106		
HIV-1 transmission route	Men	0.0015	<0.0001		0.0062			
	Women				0.0072			
Age***	Men		<0.0001	<0.0001	<0.0001	<0.0001		<0.0001
	Women				<0.0001	0.0039		<0.0001
Used ART before 2007?	Men			0.0002				
	Women							
HIV-1 diagnosis to cART	Men	0.0296						
	Women	<0.0001						
Time on cART	Men	<0.0001			0.0003			0.0157
	Women	0.0001				0.0267		<0.0001
CD4 cell count**	Men	<0.0001			0.0018	0.0001	<0.0001	
	Women							
HIV RNA load **	Men	<0.0001		0.0026	0.0004	0.0013	0.0151	0.0066
	Women							
Body mass index**	Men		0.0102			0.0014		<0.0001
	Women							
Hepatitis B virus status***	Men	<0.0001					<0.0001	
	Women							
Hepatitis C virus status***	Men	0.0111			0.0004		<0.0001	
	Women	0.0015			0.0413			

** Men and women combined; ** Last known before the start of combination antiretroviral therapy, but within a year of this date; *** At the start of cART.*

Legend: *ART = antiretroviral therapy*

Web Appendix Table 2.8: The number and incidence (in parenthesis) per 1,000 years of patient follow-up of the first occurrence per patient of diabetes mellitus, invasive cardiac procedures, myocardial infarction, stroke, renal insufficiency, non-AIDS defining malignancies, liver disease and osteoporosis per time period for men, women and the total population.

Event	2002 - 2006			2007 - 2011			P-value 2002-2006 versus 2007-2011	P-value 2002-2006 versus 2007-2011	P-value men versus women 2007-2011
	Men	Women	Total	Men	Women	Total	Men	Women	
Diabetes mellitus	128 (4.8)	35 (4.6)	163 (4.8)	170 (4.3)	53 (4.8)	223 (4.4)	0.0211	0.9680	0.0603
Cardiovascular diseases*	169 (6.3)	12 (1.5)	181 (5.2)	231 (5.8)	32 (2.8)	263 (5.1)	0.0043	0.1571	0.0226
Renal insufficiency	148 (5.5)	35 (4.6)	183 (5.3)	291 (7.3)	59 (5.3)	350 (6.9)	0.2156	0.6974	0.7202
Non-AIDS defining malignancies	210 (7.8)	27 (3.5)	237 (6.9)	348 (8.7)	49 (4.3)	397 (7.8)	0.4325	0.8507	0.0051
Liver disease**	135 (5.0)	41 (5.3)	176 (5.0)	231 (5.7)	32 (2.9)	263 (5.1)	0.3214	0.0040	< 0.0001
Osteoporosis	50 (1.8)	12 (1.5)	62 (1.8)	173 (4.2)	49 (4.3)	222 (4.2)	< 0.0001	0.0142	0.0448

** Includes myocardial infarction, stroke coronary artery by-pass grafting, coronary angioplasty/stenting and carotic endarterectomy; ** Includes cirrhosis, fibrosis (METAVIR scores F1, F2, F3 and F4) and hepatocellular carcinoma.*

Web Appendix Table 3.1: *Unadjusted and adjusted risk estimates for the hazard of virological failure obtained using Cox regression analysis. The 7625 included patients who are represented comprise a subgroup of the 16,149 patients shown in Table 3.1. Patients who were ART-naïve at the start of cART and tested with a HIV RNA assay with a lower detection limit of 50 copies/ml or less were included. Time to virological failure was defined as time from the start of cART to the first of 2 consecutive viral-load measurements above 200 copies/ml following at least six months of continuous antiretroviral therapy.*

	Unadjusted		Adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Female gender	1.78 (1.51, 2.10)	<0.0001		
Transmission risk group/region of origin				
MSM				
W-Europe/N-America	1.00		1.00	
Caribbean/S-America	1.12 (0.76, 1.65)	0.56	1.08 (0.73, 1.60)	0.70
Other	0.59 (0.32, 1.08)	0.09	0.57 (0.31, 1.04)	0.07
Sub-Saharan Africa	1.11 (0.41, 2.99)	0.83	1.14 (0.42, 3.07)	0.80
Heterosexual				
W-Europe/N-America	1.00		1.00	
Caribbean/S-America	2.81 (1.92, 4.11)	<0.0001	2.67 (1.75,2.84)	<0.0001
Other	1.44 (0.86, 2.42)	0.16	1.24 (0.74, 2.09)	0.42
Sub-Saharan Africa	2.91 (2.14, 3.96)	<0.0001	2.49 (1.81, 3.43)	<0.0001
Age at the start of cART				
16-29	1.71 (1.42, 2.06)	<0.0001	1.40 (1.15, 1.70)	0.0007
30-39	0.73 (0.59, 0.90)	0.003	0.87 (0.70, 1.07)	0.19
40-49	1.00		1.00	
50 or more	0.76 (0.58, 0.98)	0.03	1.02 (0.78, 1.33	0.90
CD4 cell count at the start of cART (cells/mm^3)				
<200	1.92 (1.61, 2.29)	<0.0001	1.38 (1.14,1.67)	0.0008
200-500	1.00		1.00	
≥500	1.58 (1.15, 2.19)	0.005	1.25 (0.89, 1.75	0.19
Year of starting cART				
1999-2002	2.69 (2.16, 3.35)	<0.0001	1.97 (1.56, 2.49)	<0.0001
2003-2005	2.07 (1.65, 2.60)	<0.0001	1.53 (1.21, 1.93)	0.0003
2006-2008	1.00		1.00	
2009-2011	0.71 (0.52, 0.98)	0.04	0.81 (0.59, 1.12)	0.20
HIV RNA at the start of cART (copies/ml)				
<10,000	1.03 (0.77, 1.38)	0.84	0.84 (0.62, 1.14)	0.27
10,000-100,000	1.00		1.00	
≥100,000	1.46 (1.22, 1.76)	<0.0001	1.50 (1.24, 1.82)	<0.0001

	Unadjusted		Adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value
AIDS at the start of cART	1.50 (1.27-1.78)	<0.0001		
HCV Positive	0.90 (0.66, 1.22)	0.49		
HBV Positive	1.33 (1.00, 1.76)	0.05		
Initial regimen				
NRTI + NNRTI	1.00		1.00	
NRTI + PI	2.74 (2.17, 3.46)	<0.0001	1.52 (1.19, 1.95)	0.001
NRTI + PI/r	1.62 (1.36, 1.93)	<0.0001	1.25 (1.04, 1.50)	0.02
3 NRTI	2.25 (1.60, 3.16)	<0.0001	1.65 (1.16, 2.23)	0.005
cART started during pregnancy	2.08 (1.60, 2.70)	<0.0001		

Web Appendix Table 3.2: Overview of the most frequently recorded adverse events leading to a toxicity-driven therapy stop 2004-2011. Multiple adverse events in a patient during the same year are counted once. For every toxicity-driven therapy stop up to 3 adverse events could be recorded. Therefore percentages do not add up to 100%.

	2004		2005		2006		2007		2008		2009		2010	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients with at least 1 toxicity-driven therapy stop	842		864		857		891		974		952		997	
Body composition and serum lipids														
Lypodystrophy - any	117	13.9	122	14.1	108	12.6	102	11.4	104	10.7	78	8.2	54	5.4
Lipoatrophy - peripheral fat loss	117	13.9	122	14.1	108	12.6	102	11.4	104	10.7	78	8.2	54	5.4
Lipohypertrophy - central fat accumulation	21	2.5	41	4.7	37	4.3	26	2.9	29	3.0	22	2.3	19	1.9
Lipodystrophy unspecified	5	0.6	5	0.6	4	0.5	2	0.2	3	0.3	3	0.3	3	0.3
Elevated triglycerides	24	2.9	21	2.4	12	1.4	10	1.1	17	1.7	16	1.7	16	1.6
Elevated cholesterol	15	1.8	14	1.6	18	2.1	16	1.8	19	2.0	11	1.2	11	1.1
Liver														
Elevated gamma-GT	13	1.5	13	1.5	8	0.9	13	1.5	10	1.0	26	2.7	22	2.2
Icterus	5	0.6	8	0.9	13	1.5	8	0.9	6	0.6	9	0.9	23	2.3
Elevated ASAT	10	1.2	3	0.3	9	1.1	11	1.2	8	0.8	14	1.5	14	1.4
Elevated bilirubin	3	0.4	6	0.7	9	1.1	11	1.2	9	0.9	10	1.1	14	1.4
Elevated ALAT	3	0.4	7	0.8	4	0.5	5	0.6	5	0.5	10	1.1	11	1.1
Lipodystrophy unspecified	5	0.6	5	0.6	4	0.5	2	0.2	3	0.3	3	0.3	3	0.3
Hepatic steatosis	1	0.1	4	0.5	4	0.5	2	0.2	1	0.1	3	0.3	1	0.1
Lactate acidosis	3	0.4	2	0.2	7	0.8	5	0.6	2	0.2	1	0.1	2	0.2
Renal														
Renal insufficiency	20	2.4	23	2.7	21	2.5	34	3.8	43	4.4	38	4.0	42	4.2
Elevated creatinine	9	1.1	5	0.6	17	2.0	20	2.2	20	2.1	24	2.5	25	2.5
Nephrolithiasis	4	0.5	9	1.0	4	0.5	3	0.3	2	0.2	2	0.2	4	0.4
Neurological / psychosocial														
Depression	12	1.4	23	2.7	22	2.6	21	2.4	37	3.8	42	4.4	43	4.3
Dizziness	27	3.2	21	2.4	26	3.0	36	4.0	28	2.9	44	4.6	40	4.0
Sleeplessness	18	2.1	11	1.3	22	2.6	18	2.0	23	2.4	29	3.0	38	3.8
Non-HIV related neuropathy	40	4.8	38	4.4	33	3.9	29	3.3	21	2.2	14	1.5	13	1.3
Mood changes	5	0.6	10	1.2	9	1.1	20	2.2	25	2.6	28	2.9	41	4.1
Nightmares	13	1.5	17	2.0	17	2.0	16	1.8	24	2.5	22	2.3	30	3.0
Headache	9	1.1	7	0.8	8	0.9	15	1.7	7	0.7	8	0.8	27	2.7
Concentration disorders	8	1.0	6	0.7	4	0.5	8	0.9	9	0.9	10	1.1	7	0.7
Fear	1	0.1	3	0.3	5	0.6	3	0.3	4	0.4	9	0.9	10	1.0
Paresthesia (transient numbness or tingling)	4	0.5	4	0.5	0	0.0	3	0.3	7	0.7	5	0.5	2	0.2
Erection disorders	2	0.2	3	0.3	2	0.2	5	0.6	2	0.2	1	0.1	7	0.7
Psychosis	4	0.5	2	0.2	0	0.0	0	0.0	1	0.1	4	0.4	2	0.2
Loss of libido	0	0.0	4	0.5	2	0.2	1	0.1	3	0.3	2	0.2	2	0.2
Confusion	1	0.1	3	0.3	1	0.1	1	0.1	1	0.1	3	0.3	2	0.2
Loss of memory	0	0.0	0	0.0	2	0.2	1	0.1	2	0.2	0	0.0	4	0.4

	2004		2005		2006		2007		2008		2009		2010	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gastrointestinal														
Diarrhoea	84	10.0	66	7.6	77	9.0	81	9.1	93	9.5	94	9.9	99	9.9
Nausea	51	6.1	40	4.6	48	5.6	69	7.7	44	4.5	38	4.0	41	4.1
Vomiting	26	3.1	23	2.7	21	2.5	15	1.7	23	2.4	24	2.5	27	2.7
Abdominal pain	12	1.4	13	1.5	10	1.2	11	1.2	20	2.1	10	1.1	17	1.7
Flatulence	1	0.1	2	0.2	1	0.1	2	0.2	4	0.4	8	0.8	4	0.4
Weight loss	3	0.4	4	0.5	2	0.2	3	0.3	3	0.3	2	0.2	0	0.0
Loss of appetite	2	0.2	1	0.1	3	0.4	5	0.6	0	0.0	3	0.3	2	0.2
Change in taste	2	0.2	3	0.3	1	0.1	1	0.1	3	0.3	3	0.3	3	0.3
Dermatological														
Rash	60	7.1	57	6.6	61	7.1	60	6.7	85	8.7	65	6.8	78	7.8
Itchiness	8	1.0	11	1.3	12	1.4	13	1.5	9	0.9	12	1.3	12	1.2
Systemic														
Fatigue	34	4.0	34	3.9	39	4.6	32	3.6	29	3.0	26	2.7	40	4.0
General discomfort	15	1.8	10	1.2	3	0.4	9	1.0	10	1.0	11	1.2	10	1.0
Fever	1	0.1	5	0.6	7	0.8	3	0.3	4	0.4	2	0.2	1	0.1
Night sweats	2	0.2	1	0.1	3	0.4	1	0.1	2	0.2	1	0.1	2	0.2
Haematological														
Anemia	43	5.1	34	3.9	36	4.2	20	2.2	27	2.8	21	2.2	17	1.7
Leucopenia	18	2.1	17	2.0	11	1.3	7	0.8	5	0.5	5	0.5	1	0.1
Pancytopenia	2	0.2	2	0.2	3	0.4	2	0.2	4	0.4	2	0.2	2	0.2
Trombocytopenia	5	0.6	3	0.3	3	0.4	0	0.0	3	0.3	1	0.1	1	0.1
Neuromuscular														
Myalgia	4	0.5	1	0.1	2	0.2	3	0.3	6	0.6	7	0.7	7	0.7
Myopathy	5	0.6	5	0.6	3	0.4	11	1.2	3	0.3	1	0.1	1	0.1
Arthralgia	0	0.0	0	0.0	2	0.2	2	0.2	3	0.3	4	0.4	11	1.1
Skeletal														
Osteoporosis	2	0.2	1	0.1	2	0.2	0	0.0	5	0.5	2	0.2	2	0.2
Cardiovascular														
Hypertension	3	0.4	2	0.2	2	0.2	3	0.3	3	0.3	4	0.4	3	0.3
Myocardial infarction	1	0.1	1	0.1	1	0.1	1	0.1	4	0.4	1	0.1	2	0.2
Elevated CPK	1	0.1	2	0.2	0	0.0	0	0.0	0	0.0	3	0.3	2	0.2
Cardiomyopathy	2	0.2	1	0.1	1	0.1	0	0.0	2	0.2	0	0.0	3	0.3
Other	2	0.2	3	0.3	1	0.1	1	0.1	3	0.3	3	0.3	3	0.3
Cough	1	0.1	2	0.2	0	0.0	2	0.2	2	0.2	1	0.1	2	0.2
Pancreatitis	7	0.8	2	0.2	1	0.1	1	0.1	4	0.4	1	0.1	0	0.0
Abacavir hypersensitivity	3	0.4	4	0.5	8	0.9	6	0.7	2	0.2	2	0.2	1	0.1
Diabetes mellitus (both I and II)	3	0.4	3	0.3	3	0.4	3	0.3	1	0.1	6	0.6	6	0.6

Web Appendix Table 4.1: *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 16,169 patients still in follow-up as of June 2012, 2304 (14%) patients with at least one resistance-associated mutation were included.*

	Susceptible		Potential low-level		Low-level		Intermediate		High-level	
	N	%	N	%	N	%	N	%	N	%
Protease inhibitors (PIs)[a]										
FPV	1746	76	131	6	94	4	116	5	212	9
IDV	1761	77	102	4	82	4	114	5	240	10
NFV	1418	62	195	8	171	7	49	2	466	20
SQV	1870	81	20	1	25	1	118	5	266	12
LPV	1772	77	161	7	81	4	139	6	146	6
ATV	1725	75	121	5	81	4	107	5	265	12
TPV	1965	85	47	2	137	6	125	5	25	1
DRV	2129	93	79	3	52	2	33	1	6	0
Any PI	1396	61	214	9	167	7	46	2	476	21
Nucleoside RT inhibitors (NRTIs)										
ABC	801	35	120	5	596	26	313	14	474	21
AZT	1236	54	28	1	262	11	202	9	576	25
d4T	1128	49	37	2	327	14	250	11	562	24
ddI	775	34	498	22	246	11	339	15	446	19
TDF	1415	61	75	3	251	11	354	15	209	9
Any NRTI	652	28	19	1	651	28	234	10	748	32
XTC	1028	45	52	2	69	3	48	2	1107	48
Non-nucleoside RT inhibitors (NNRTIs)										
EFV	1251	54	95	4	49	2	246	11	663	29
NVP	1177	51	118	5	63	3	29	1	917	40
ETR	1549	67	235	10	146	6	299	13	75	3
RPV	1549	67	189	8	141	6	301	13	124	5
Any NNRTI	1161	50	112	5	70	3	44	2	917	40

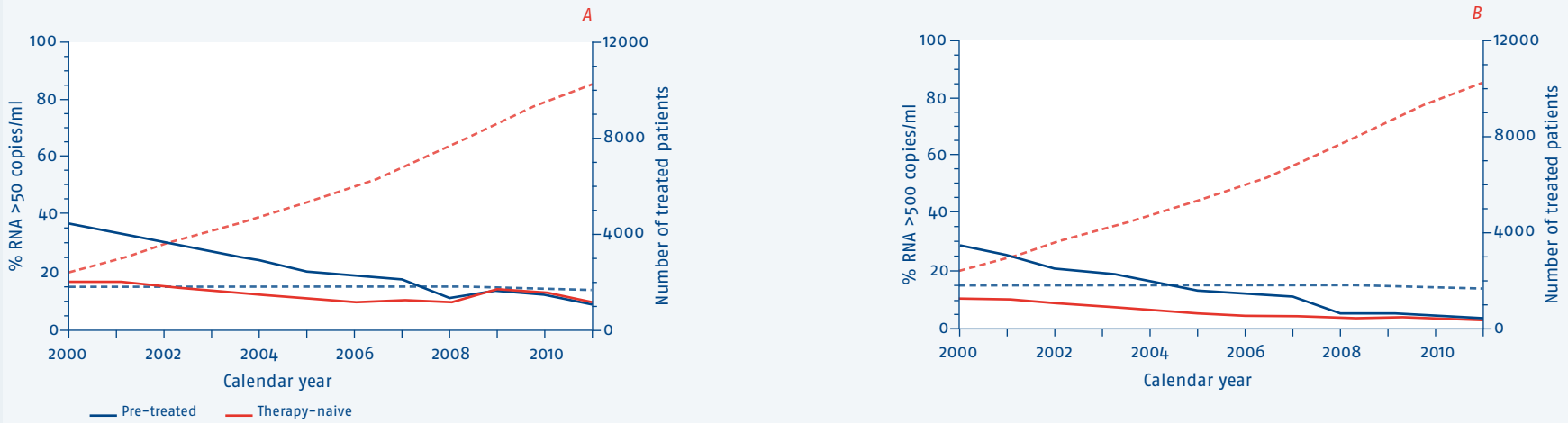
Legend: *FPV=fosamprenavir; IDV=indinavir; NFV=nelfinavir; SQV=saquinavir; LPV=lopinavir; ATV=atazanavir; TPV=tipranavir; DRV=darunavir; ABC=abacavir; AZT=zidovudine; d4T=stavudine; ddI=didanosine; TDF=tenofovir; XTC=lamivudine/emtricitabine; EFV=efavirenz; NVP=nevirapine; ETR=etravirine; [a]protease not available for 5 patients.*

Web Appendix Table 4.2: *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 16,169 patients still in follow-up as of June 2012, 6879 (43%) patients 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 4.1.*

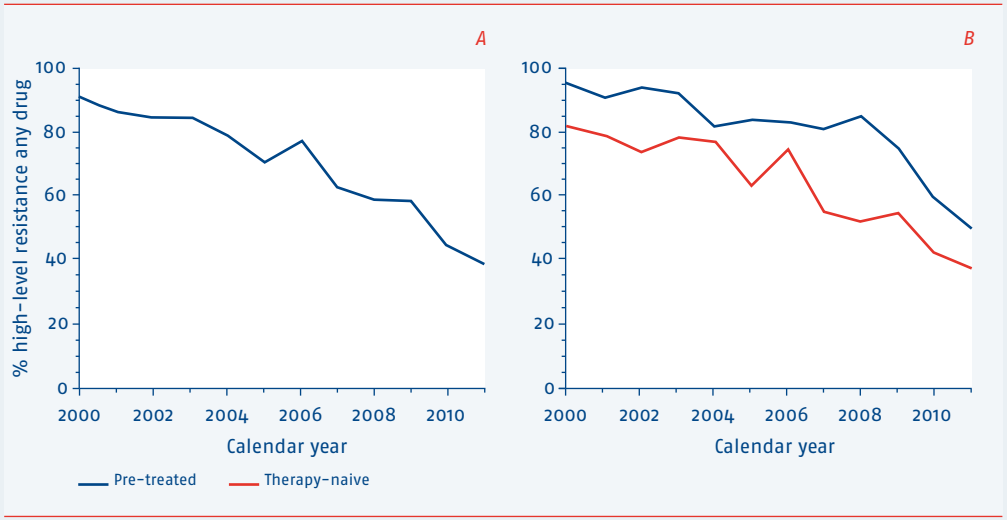
	Susceptible		Potential low-level		Low-level		Intermediate		High-level	
	N	%	N	%	N	%	N	%	N	%
Protease inhibitors (PIs)[a]										
FPV	6281	91	164	2	95	1	116	2	212	3
IDV	6330	92	102	1	82	1	114	2	240	3
NFV	5385	78	636	9	327	7	54	1	466	7
SQV	6438	94	21	0	25	0	118	2	266	4
LPV	6341	92	161	2	81	1	139	2	146	2
ATV	6291	92	124	2	81	1	107	2	265	4
TPV	6533	95	48	1	137	2	125	2	25	0
DRV	6698	98	79	1	52	1	33	0	6	0
Any PI	5351	78	667	10	323	5	51	1	476	7
Nucleoside RT inhibitors (NRTIs)[b]										
ABC	5363	78	123	2	596	9	314	5	474	7
AZT	5776	84	36	1	279	4	203	3	576	8
d4T	5662	82	50	1	345	5	251	4	562	8
ddI	5284	77	537	8	259	4	344	5	446	6
TDF	5978	87	78	1	251	4	354	5	209	3
Any NRTI	5150	75	59	1	674	10	239	3	748	11
XTC	5592	81	54	1	69	1	48	1	1107	16
Non-nucleoside RT inhibitors (NNRTIs)[b]										
EFV	5792	84	117	2	51	1	246	4	664	10
NVP	5716	83	138	2	63	1	33	0	920	13
ETR	6114	89	235	3	147	2	299	4	75	1
RPV	6114	89	189	3	142	2	301	4	124	2
Any NNRTI	5700	83	132	2	70	1	48	1	920	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; XTC=lamivudine/emtricitabine; EFV=efavirenz; NVP=nevirapine; ETR=etravirine; [a]protease not available for 11 patients; [b]RT not available for 9 patients.*

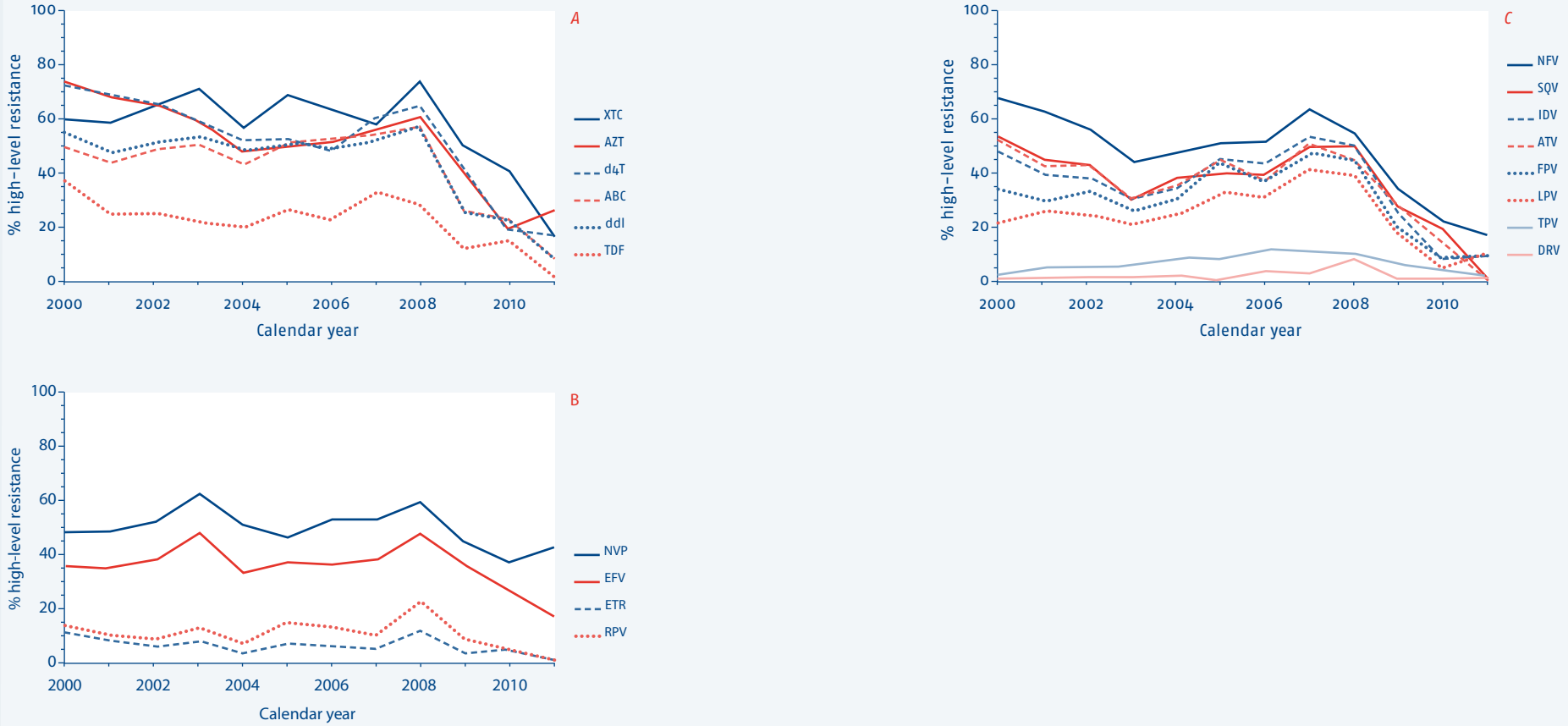
Web Appendix Figure 4.1: *Annual number of treated patients with a viral load measurement and the proportion of patients with virological failure, i.e., a viral load (A) above 50 copies/ml or (B) above 500 copies/ml whilst on treatment and measured at least 4 months after start of cART or 4 months after resuming treatment following a treatment interruption. Amongst approximately 1700 pre-treated patients, the proportion with failure with a threshold of 50 (500) copies/ml decreased from 36% (28%) in 2000 to 8% (3%) in 2011. Amongst previously therapy-naive patients, failure was less common and decreased from 16% (10%) to 9% (2%) during the same period, whilst the number of therapy-naive patients increased from approximately 2350 to 10,250. (Solid lines represent virologic failure and dashed lines represent number of treated patients.)*



Web Appendix Figure 4.2: *(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 39% in 2011. (B) Resistance to any antiretroviral drug was found more often in patients pre-treated with mono- or dual therapy before commencing combination antiretroviral therapy (cART) (95% in 2000 decreasing to 50% in 2011).*

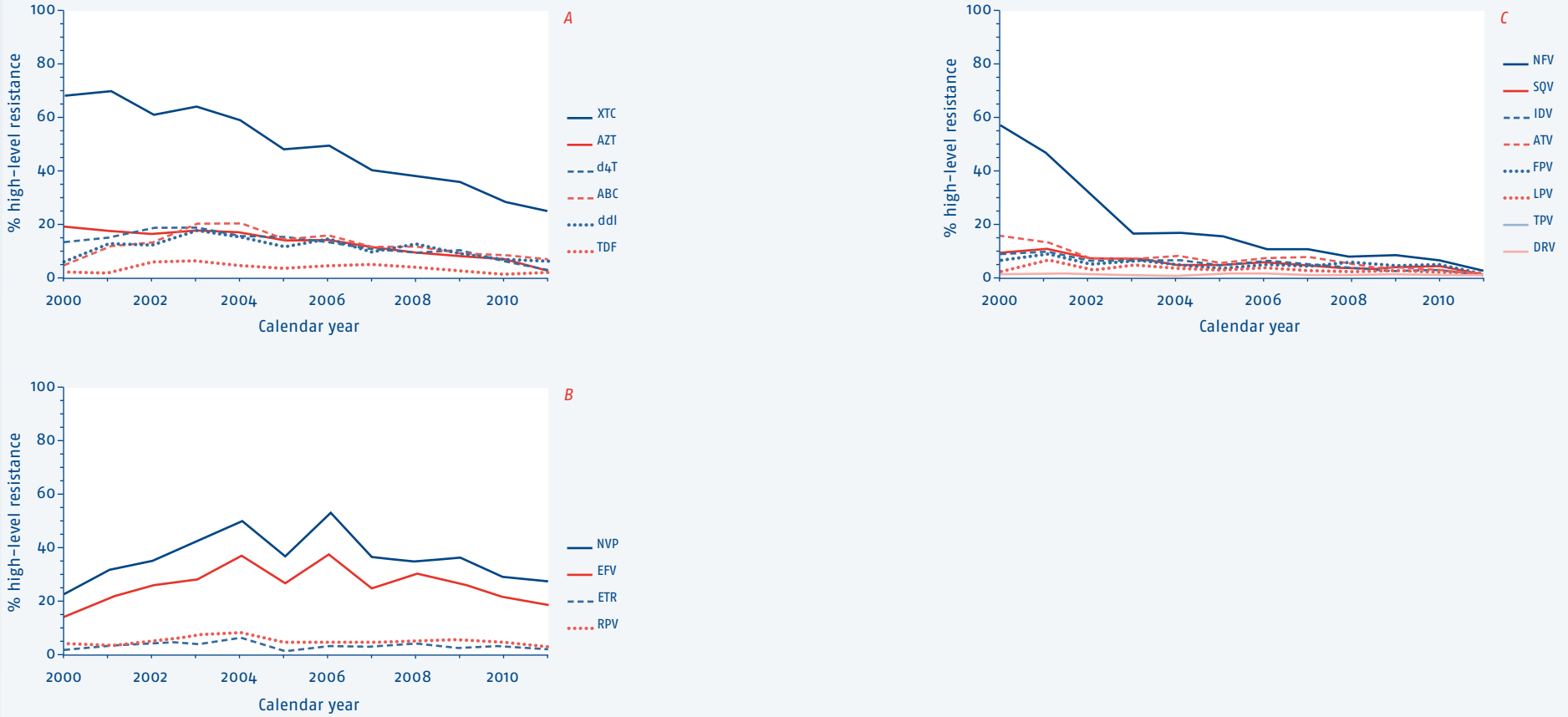


Appendix Figure 4.3: *Annual proportion of sequences from treated patients with evidence of high-level resistance, according to the Stanford mutation interpretation algorithm, in patients who received treatment regimens that were not considered combination antiretroviral treatment (cART). Resistance is shown to individual drugs from the four original drug classes including (A) nucleoside reverse transcriptase inhibitors and lamivudine/emtricitabine, (B) non-nucleoside reverse transcriptase inhibitors, and (C) protease inhibitors.*



Legend: *XTC=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.*

Appendix Figure 4.4: *Annual proportion of sequences from treated patients with evidence of high-level resistance, according to the Stanford mutation interpretation algorithm, in previously therapy-naive patients who started with combination antiretroviral treatment (cART) as their first treatment regimen. Resistance is shown to individual drugs from the four original drug classes including (A) nucleoside reverse transcriptase inhibitors and lamivudine/emtricitabine, (B) non-nucleoside reverse transcriptase inhibitors, and (C) protease inhibitors.*



Legend: *XTC=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 8.1: Annual number of HIV diagnoses in Curaçao stratified by sex and survival status as of June 2012.

	Alive, in clinical care		Alive, not in clinical care		Dead		Total	
	Men	Women	Men	Women	Men	Women	Men	Women
≤1995	35	17	9	7	35	10	79	34
1996	8	9	2	3	0	1	10	13
1997	8	12	1	1	7	3	16	16
1998	11	4	8	1	8	1	27	6
1999	14	5	2	2	5	2	21	9
2000	14	6	2	8	6	4	22	18
2001	7	7	3	5	5	4	15	16
2002	15	7	8	8	5	2	28	17
2003	17	14	7	3	11	2	35	19
2004	8	8	9	6	10	2	27	16
2005	25	8	1	4	3	4	29	16
2006	17	12	5	1	3	2	25	15
2007	16	4	6	6	5	1	27	11
2008	18	12	10	6	2	1	30	19
2009	21	15	7	2	0	2	28	19
2010	13	14	6	2	2	0	21	16
2011	26	21	0	0	0	0	26	21
2012	8	6	0	0	0	0	8	6
Total	281	181	86	65	107	41	474	287
Unknown	2	2	18	4	2	7	22	13