

# AUSTRALIAN HIV OBSERVATIONAL DATABASE ANNUAL REPORT

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## Long-Term Survival in HIV Positive Patients with up to 15 Years of Antiretroviral Therapy

**Background:** Life expectancy has increased for newly diagnosed HIV patients since the inception of combination antiretroviral treatment (cART), but there remains a need to better understand the characteristics of long-term survival in HIV-positive patients. We examined long-term survival in HIV-positive patients receiving cART in the Australian HIV Observational Database (AHOD), to describe changes in mortality compared to the general population and to develop longer-term survival models.

**Methods:** Data were examined from 2,675 HIV-positive participants in AHOD who started cART. Standardised mortality ratios (SMR) were calculated by age, sex and calendar year across prognostic characteristics using Australian Bureau of Statistics national data as reference. SMRs were examined by years of duration of cART by CD4 and similarly by viral load. Survival was analysed using Cox-proportional hazards and parametric survival models.

**Results:** The overall SMR for all-cause mortality was 3.5 (95% CI: 3.0–4.0). SMRs by CD4 count were 8.6 (95% CI: 7.2–10.2) for CD4<350 cells/ $\mu$ L; 2.1 (95% CI: 1.5–2.9) for CD4350–499 cells/ $\mu$ L; and 1.5 (95% CI: 1.1–2.0) for CD4 $\geq$ 500 cells/ $\mu$ L (Table 1). SMRs for patients with CD4 counts<350 cells/mL were much higher than for patients with higher CD4 counts across all durations of cART (Figure 1). SMRs for patients with viral loads >400 copies/ml were much higher across all durations of cART (Figure 2). Multivariate models demonstrated improved survival associated with increased recent CD4, reduced recent viral load, younger patients, absence of HBVsAg-positive ever, year of HIV diagnosis and incidence of ADI. Parametric models showed a fairly constant mortality risk by year of cART up to 15 years of treatment (Figure 3).

**Table 1: Mortality by patient characteristics**

	Deaths	Mortality rate(95% CI) <sup>2</sup>	SMR (95% CI)
<b>All mortality</b>	206	12.9 (11.3, 14.8)	3.5 (3.0, 4.0)
<b>Sex</b>			
Female	8	9.3 (4.6, 18.5)	6.0 (3.0, 11.9)
Male	198	13.1 (11.4, 15.1)	3.4 (3.0, 3.9)
<b>Age band</b>			
0-29	4	10.8 (4.0, 28.7)	12.4 (4.7, 33.0)
30-39	38	9.9 (7.2, 13.6)	8.6 (6.2, 11.8)
40-49	73	11.8 (9.4, 14.8)	5.9 (4.7, 7.4)
50-59	55	14.2 (10.9, 18.5)	3.2 (2.5, 4.2)
60-90	36	21.6 (15.6, 30.0)	1.4 (1.0, 2.0)
<b>Mode of HIV exposure</b>			
MSM	153	12.6 (10.7, 14.7)	3.3 (2.8, 3.9)
IDU	20	22.5 (14.5, 34.9)	11.3 (7.3, 17.5)
HET	12	8.8 (5.0, 15.5)	2.5 (1.4, 4.4)
OTHER	21	13.8 (9.0, 21.1)	3.3 (2.1, 5.0)
<b>ADI prior to cART</b>			
No	155	11.6 (9.9, 13.6)	3.2 (2.7, 3.7)
Yes	51	19.5 (14.8, 25.6)	4.7 (3.6, 6.2)
<b>HCV (ever)</b>			
No/ no tested	172	12.2 (10.5, 14.1)	3.1 (2.7, 3.7)
Yes	34	19.1 (13.6, 26.7)	7.2 (5.1, 10.0)
<b>HBVsAg (ever)</b>			
No/ not tested	183	12.1 (10.4, 13.9)	3.2 (2.8, 3.7)
Yes	23	30.0 (20.0, 45.2)	10.6 (7.0, 15.9)
<b>CD4 (cells/<math>\mu</math>L)<sup>1</sup></b>			
<350	131	32.0 (27.0, 38.0)	8.6 (7.2, 10.2)
350-499	32	7.7 (5.5, 11.0)	2.1 (1.5, 2.9)
$\geq$ 500	43	5.6 (4.1, 7.5)	1.5 (1.1, 2.0)
<b>Viral Load (copies/ml)<sup>1</sup></b>			
$\leq$ 400	99	8.4 (6.9, 10.2)	2.1 (1.7, 2.5)
>400	107	25.8 (21.3, 31.1)	9.0 (7.5, 10.9)
<b>Treatment prior to cART</b>			
No	81	9.7 (7.8, 12)	2.8 (2.2, 3.4)
Yes	125	16.5 (13.9, 19.7)	4.2 (3.5, 5.0)
<b>Year of cART commencement</b>			
$\leq$ 1995	17	16.1 (10.0, 25.9)	3.9 (2.4, 6.3)
1996-1999	159	13.6 (11.6, 15.9)	3.6 (3.0, 4.2)
2000-2003	24	11.7 (7.8, 17.5)	3.5 (2.4, 5.3)
$\geq$ 2004	6	5.3 (2.4, 11.8)	1.7 (0.8, 3.8)
<b>Regimen number<sup>1</sup></b>			
1st	12	5.7 (3.2, 10.0)	2.0 (1.1, 3.5)
2nd or 3rd	29	6.1 (4.3, 8.8)	1.7 (1.2, 2.5)
4th or more	165	18.1 (15.6, 21.1)	4.5 (3.9, 5.2)

<sup>1</sup>Time updated

<sup>2</sup>per 1000 patient years

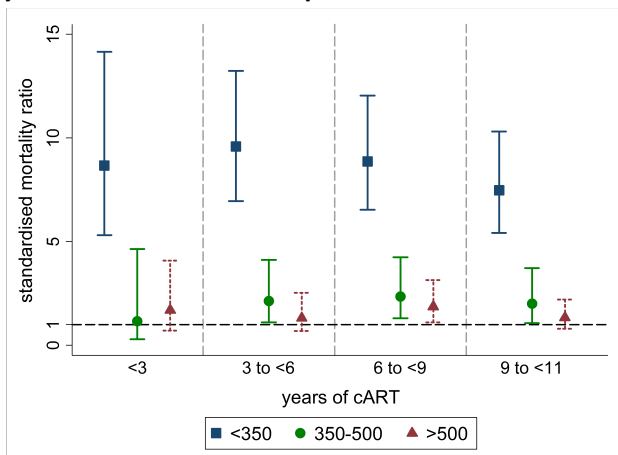
doi:10.1371/journal.pone.0048839.t002



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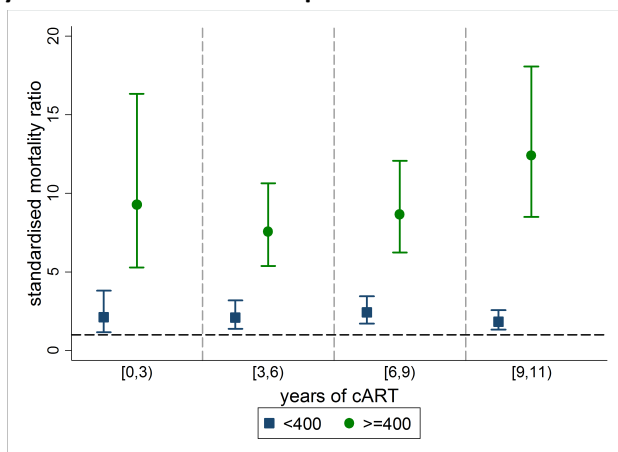


**Figure 1: SMRs and 95% confidence intervals by years of cART and time updated CD4 cell count.**



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**Figure 2: SMRs and 95% confidence intervals by years of cART and time updated HIV viral load**

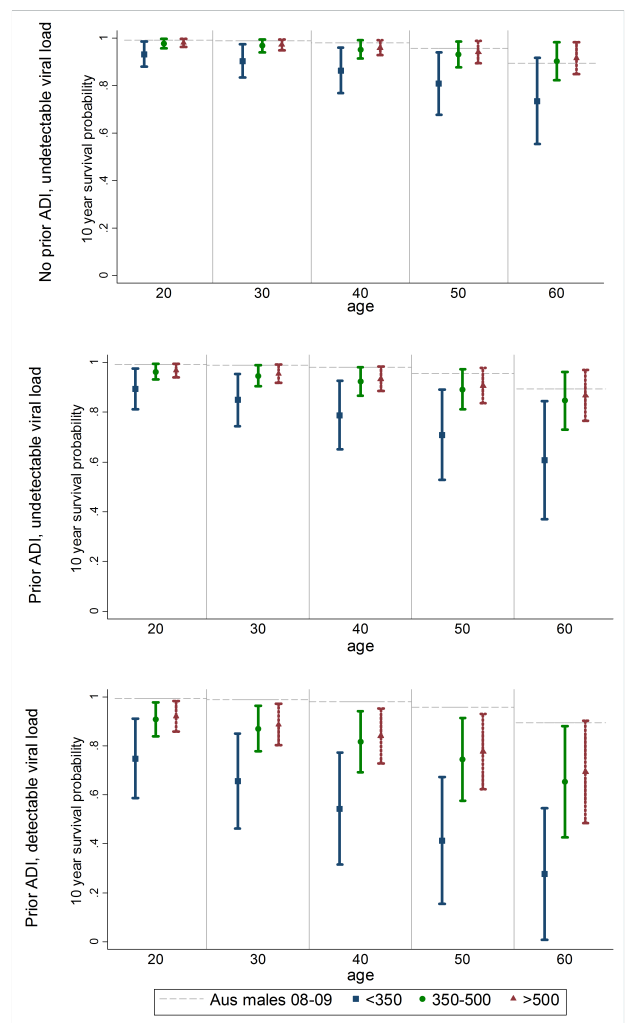


doi:10.1371/journal.pone.0048839.g002

**Conclusion:** Observed mortality remained fairly constant by duration of cART and was modelled accurately by accepted prognostic factors. These rates did not vary much by duration of treatment. Changes in mortality with age were similar to those in the Australian general population.

**Reference:** McManus H, O'Connor CC, Boyd M, Broom J, Russell D, et al. (2012) Long-Term Survival in HIV Positive Patients with up to 15 Years of Antiretroviral Therapy. PLoS ONE 7(11): e48839. doi:10.1371/journal.pone.0048839

**Figure 3: 10 year survival probabilities and 95% confidence intervals by age and time updated CD4 count**



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**Table 1: All AHOD demographics<sup>1</sup> (Total – 3 894)**

	Number	(%)		Number	(%)
<b>Sex</b>			<b>CD4 (cells/<math>\mu</math>l)<sup>1</sup></b>		
Male	3589	(92)	<200	415	(12)
Female	296	(8)	200-299	396	(11)
Transgender	9	(0)	300-499	1122	(32)
			500+	1618	(46)
<b>Age (years)<sup>1</sup></b>			Missing	343	
<30	405	(10)	Mean [SD]	504	[281]
30-39	1401	(36)			
40-49	1272	(33)	<b>HIV viral load (copies/ml)<sup>1</sup></b>		
50+	816	(21)	$\leq$ 400	2149	(60)
Mean [SD]	42	[10]	401-10 000	613	(17)
			>10 000	825	(23)
<b>Aboriginal/Torres Strait islander<sup>2</sup></b>			Missing	307	
Yes	42	(1)	Median [LQ – UQ] <sup>4</sup>	400	[400-789]
No	2396	(62)			
Not reported	1456	(37)	<b>Prior AIDS defining illness<sup>1</sup></b>		
			Yes	630	(16)
<b>Exposure category</b>			No	3264	(84)
Male homosexual contact	2855	(73)			
Male homosexual contact and IDU	133	(3)	<b>Hepatitis C ever</b>		
Injecting drug user (IDU)	94	(2)	Yes	407	(12)
Heterosexual contact	663	(17)	No	3054	(88)
Receipt of blood/blood products	23	(1)	No test reported	433	
Other	77	(2)			
Missing	49	(1)	<b>Hepatitis B ever</b>		
			Yes	173	(5)
<b>Estimated year of HIV infection<sup>3</sup></b>			No	3074	(95)
<1990	114	(3)	No test reported	647	
1990-1999	605	(16)			
2000-2013	427	(11)	<b>Total patients under active follow up in last 12 months (N=2339)<sup>5</sup></b>		
Missing	2748	(71)			
			<b>Recent CD4 (cells/<math>\mu</math>l)<sup>6</sup></b>		
<b>Patient care Setting</b>			< 200	81	(4)
General Practitioner	1371	(35)	200-299	125	(6)
Hospital Tertiary Centre	848	(22)	300-499	528	(24)
Sexual Health Clinic	1675	(43)	500+	1426	(66)
			Missing	177	
<b>Region of birth</b>			Mean [SD]	641	[295]
Australia and New Zealand	2095	(54)			
Asia and Oceania	227	(6)	<b>Recent HIV viral load</b>		
Britain and Ireland	137	(4)	$\leq$ 400	1944	(93)
Europe	99	(3)	401-10 000	64	(3)
Africa and Middle East	80	(2)	>10 000	85	(4)
North America	36	(1)	Missing	246	
South America	36	(1)	Median [LQ – UQ] <sup>4</sup>	400	[400-400]
Not reported	1184	(30)			

1. Age & prior AIDS defining illness at time of cohort enrolment. CD4 count & HIV viral load closest to and within 3 months of cohort enrolment date.

2. Data not available for 8 of 30 sites.

3. Year of HIV infection = mid date between date of first positive and last negative test (coded as not reported if either first positive or last negative date are missing).

4. LQ = Lower quartile UQ = Upper quartile.

5. Most recent visit is between March 31, 2012 and March 31, 2013.

6. Most recent CD4 count & HIV viral load between March 31, 2012 and March 31, 2013.

**Table 2: Follow up status by calendar year**

<b>Year</b>	<b>Entered study</b>	<b>Deaths</b>	<b>Lost to Follow up</b>
1999 <sup>1</sup>	818	6	37
2000	862	24	49
2001	248	29	66
2002	164	23	69
2003	196	22	59
2004	84	19	81
2005	98	26	66
2006	121	28	65
2007	98	26	83
2008	88	22	87
2009	308	17	88
2010	240	25	91
2011	202	20	125
2012	273	15	46
2013 <sup>2</sup>	94	4	0
<b>Total</b>	<b>3894</b>	<b>306</b>	<b>1012</b>

**Complete follow-up (percentage of patients)<sup>3</sup>: 74%**

**Loss to follow-up (per 100 person years): 3.89 (95% CI: 3.65-4.15 )**

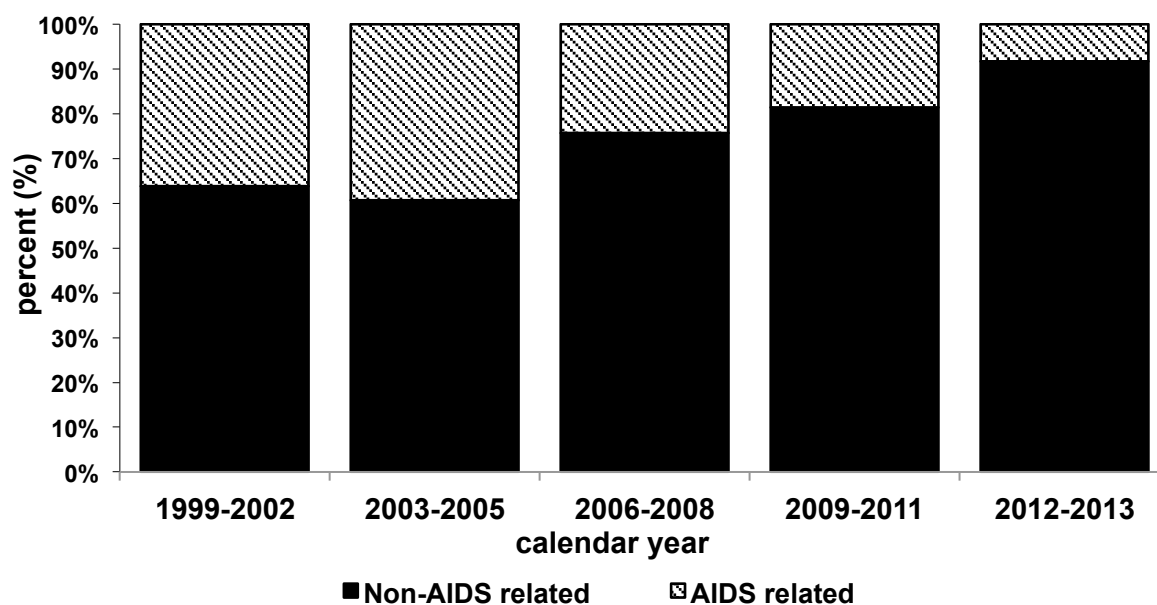
**Mortality (per 100 person years): 1.24 (95% CI: 1.10-1.38 )**

1. July 1 - December 31, 1999.

2. January 1 - March 31, 2013.

3. Patients who have died or any patients seen at clinic site within the last 12 months (March 31, 2012 - March 31, 2013) are considered to have complete follow-up.

**Figure 1: Proportion of AIDS and non-AIDS related deaths in AHOD since cohort inception by year grouping<sup>1</sup>**



<sup>1</sup>2012-2014 group includes all deaths reported from 1 January 2012 – 31 March 2013.

**Table 3: Total number of deaths in AHOD since cohort inception, by AIDS or non-AIDS related death classification and year grouping**

	1999-2002	2003-2005	2006-2008	2009-2011	2012-2013 <sup>1</sup>	All years
Non-AIDS related	51	40	53	35	11	190
AIDS related	29	26	17	8	1	81
Unknown	2	1	5	6	4	18
Missing Coding of Death	0	0	1	13	3	17
<b>Total deaths</b>	<b>82</b>	<b>67</b>	<b>76</b>	<b>62</b>	<b>19</b>	<b>306</b>

1. 1 January 2012 to 31 March 2013.

**Table 4: Summary of deaths reported in the last 5 year period<sup>1</sup>**

Coding of Death Classification <sup>2</sup>	Number
Cancer	16
AIDS (ongoing active disease)	14
Chronic viral hepatitis (progression of / complication to)	7
MI or other ischemic heart disease	6
Bacterial (with or without sepsis)	4
Suicide	4
Heart or vascular	4
Renal failure	3
Other Causes	16
Unknown (autopsy inconclusive, died overseas, etc)	9

1. 1 January 2008 to 31 December 2012.

2. Coding of Death classification (CoDE) – [<http://www.cphiv.dk/code/tabid/55/default.aspx>].

**Table 5: Trends in antiretroviral treatment<sup>1</sup>**

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Patients under active follow up <sup>1</sup>	<b>(n=1880)</b>	<b>(n=1984)</b>	<b>(n=1987)</b>	<b>(n=1985)</b>	<b>(n=2014)</b>	<b>(n=2019)</b>	<b>(n=1998)</b>	<b>(n=2099)</b>	<b>(n=2231)</b>	<b>(n=2171)</b>	<b>(n=2299)</b>
<b>Treatment</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
<i>Never treatment</i>	113 (6)	100 (5)	93 (5)	81 (4)	84 (4)	90 (4)	90 (5)	85 (4)	102 (5)	98 (5)	102 (4)
<i>Ever treatment</i>	<b>n=1767</b>	<b>n=1884</b>	<b>n=1894</b>	<b>n=1904</b>	<b>n=1930</b>	<b>n=1929</b>	<b>n=1908</b>	<b>n=2014</b>	<b>n=2129</b>	<b>n=2073</b>	<b>n=2197</b>
Currently <sup>2</sup>	1492 (79)	1572 (79)	1620 (82)	1635 (82)	1711 (85)	1719 (85)	1751 (88)	1881 (90)	2031 (91)	1994 (92)	2165 (94)
Previously, not currently	275 (15)	312 (16)	274 (14)	269 (14)	219 (11)	210 (10)	157 (8)	133 (6)	98 (4)	79 (4)	32 (1)
<b>Number of drugs ever<sup>3</sup></b>											
≤3	736 (42)	699 (37)	608 (32)	546 (29)	478 (25)	439 (23)	404 (21)	496 (25)	543 (26)	557 (27)	620 (28)
4-6	734 (42)	778 (41)	794 (42)	775 (41)	760 (39)	765 (40)	744 (39)	748 (37)	801 (38)	788 (38)	857 (39)
7-9	238 (13)	305 (16)	361 (19)	422 (22)	491 (25)	500 (26)	501 (26)	481 (24)	478 (22)	445 (21)	440 (20)
10+	59 (3)	102 (5)	131 (7)	161 (8)	201 (10)	225 (12)	259 (14)	289 (14)	307 (14)	283 (14)	281 (13)
<b>Number of drug classes ever<sup>3,4</sup></b>											
1	108 (7)	93 (5)	77 (4)	66 (4)	56 (3)	52 (3)	48 (3)	43 (2)	41 (2)	34 (2)	30 (1)
2	1014 (63)	1018 (59)	964 (55)	937 (53)	966 (53)	945 (52)	919 (51)	1010 (52)	1066 (52)	1077 (53)	1226 (56)
3	473 (29)	583 (34)	680 (39)	723 (41)	734 (41)	724 (40)	705 (39)	670 (35)	689 (33)	633 (31)	640 (29)
4	17 (1)	22 (1)	31 (2)	44 (2)	51 (3)	64 (4)	105 (6)	153 (8)	207 (10)	216 (11)	231 (11)
5	-	-	-	-	4 (0)	16 (1)	31 (2)	48 (2)	57 (3)	61 (3)	60 (3)

1. Treatment status for all patients under active follow during the calendar year. Table includes prospective data only (i.e. records prior to AHOD enrolment are excluded).

2. Currently on treatment is defined as receiving treatment at some point during the calendar year.

3. Denominator is the number of patients who have ever received treatment.

4. Broad class ARV groupings are: nucleos(t)ide reverse transcriptase inhibitors; non-nucleoside reverse transcriptase inhibitors; protease inhibitors; integrase inhibitors; entry inhibitors;

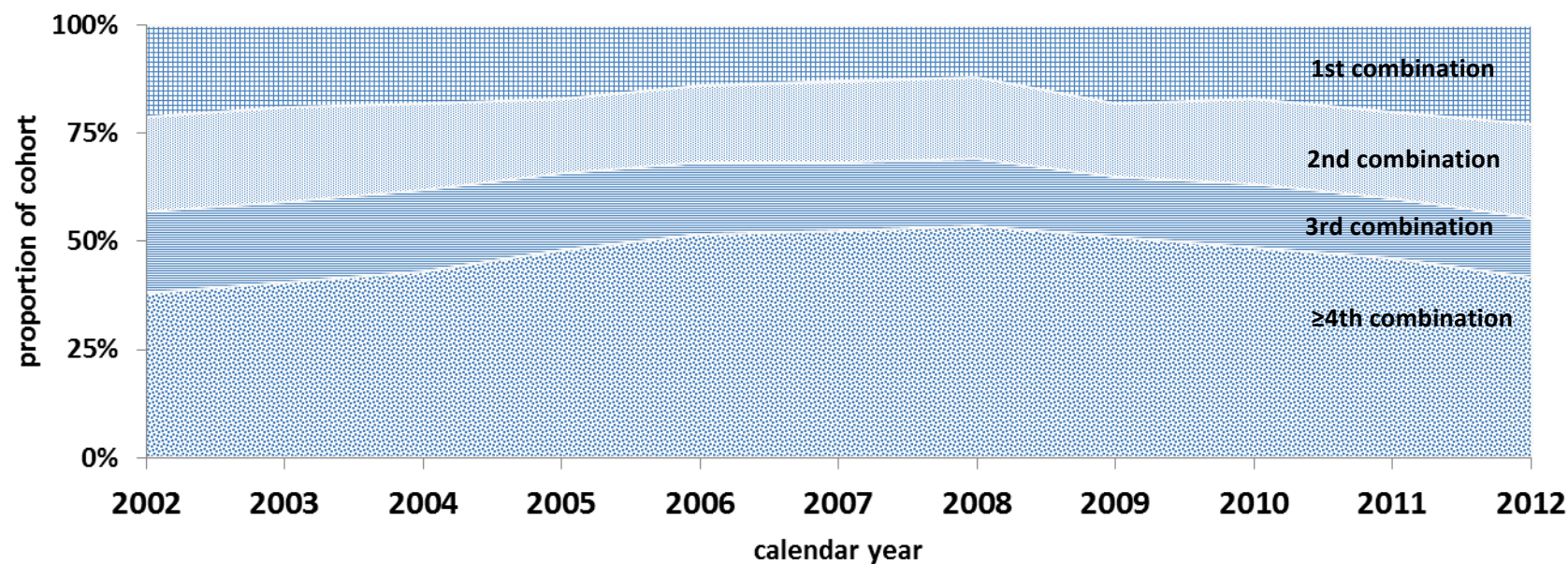
**Table 6: Trends in combination antiretroviral treatment<sup>1</sup>**

	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
<b>Combination<sup>2</sup></b>	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
1 <sup>st</sup> combination	336	(21)	321	(19)	319	(18)	301	(17)	258	(14)	230	(13)	222	(12)	337	(18)	344	(17)	392	(20)	497	(23)
2 <sup>nd</sup> combination	348	(22)	373	(22)	347	(20)	310	(17)	318	(18)	335	(19)	336	(19)	326	(17)	401	(20)	406	(20)	472	(22)
3 <sup>rd</sup> combination	309	(19)	328	(19)	332	(19)	313	(18)	299	(17)	287	(16)	279	(16)	274	(14)	302	(15)	281	(14)	296	(14)
≥4 <sup>th</sup> combination	618	(38)	703	(41)	767	(43)	853	(48)	936	(52)	955	(53)	963	(54)	977	(51)	995	(49)	920	(46)	901	(42)

1. Includes patients who commenced their first combination ART after January 1, 1996 for at least 14 days. The denominator includes all AHOD patients that received combination antiretroviral treatment in any calendar year (i.e. HIV positive), who commenced their first combination ART after January 1, 1996 for at least 14 days. Includes prospective and retrospective data.

2. Combinations include 3 or more antiretroviral drugs, does not include mono/dual therapy. Regimens with interruptions of less than 7 days were considered as continuous treatment.

**Figure 2: Trends in combination antiretroviral treatment (as above)**



**Table 7: Immunological and virological trends<sup>1</sup>**

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
<b>Viral load (copies/ml)</b>											
<b>Total N (with measure)</b>	2157	2137	2153	2201	2219	2271	2319	2237	2169	2138	2117
<b>Off Treatment<sup>2</sup></b>											
No. with a viral load count <sup>4</sup>	440	461	432	462	399	395	346	285	220	182	133
Median	20700	19000	22725	19053	14750	13700	12380	12900	9224	5573	4387
IQR	4075-65000	3900-64550	4738-69525	4340-64000	4070-50000	3320-40500	2706-38800	2550-37150	1421-36760	543-40500	125-27950
<b>On Treatment<sup>3</sup></b>											
No. with a viral load count <sup>4</sup>	1717	1676	1721	1739	1820	1876	1973	1952	1949	1956	1966
Median	275	104	50	50	50	49	49	49	49	40	32
IQR	50-1360	50-880	50-400	49-399	49-71	44-50	40-50	40-50	40-50	30-49	20-49
<b>CD4 count (cells/<math>\mu</math>l)</b>											
<b>Total N (with measure)</b>	2109	2143	2172	2216	2209	2277	2306	2268	2216	2194	2178
<b>Off Treatment<sup>2</sup></b>											
No. with a CD4 count <sup>5</sup>	444	468	450	478	405	401	351	293	230	186	138
Median	500	490	488	490	506	500	490	520	497.5	505	537
IQR	365-652	364-650	371-650	370-650	380-655	400-640	390-660	400-664	410-645	396-681	450-710
<b>On Treatment<sup>3</sup></b>											
No. with a CD4 count <sup>5</sup>	1665	1675	1722	1738	1804	1876	1955	1975	1986	2008	2040
Median	499	490	486	489	504	523	530	540	552	576	591
IQR	300-701	315-690	315-685	325-696	341-710	360-719	374-740	380-738	399-736	420-768	430-781

1. Includes retrospective and prospective data. Off treatment if never on a regimen of duration greater than 14 days for given calendar year. Viral load taken as median value during given calendar year. Undetectable assay level taken as  $\leq 50$  copies/ml. Data for 2000 and 2001 includes 2 sites with minimum assay sensitivity of 400 copies/ml. Data for 2002 includes 1 site with minimum assay sensitivity of 400 copies/ml.

2. Patients who have not received treatment during the calendar year.

3. Patients who have received any treatment during the calendar year.

4. Includes patients with a viral load measured during the relevant calendar year.

5. Includes patients with a CD4 count measured during the relevant calendar year.

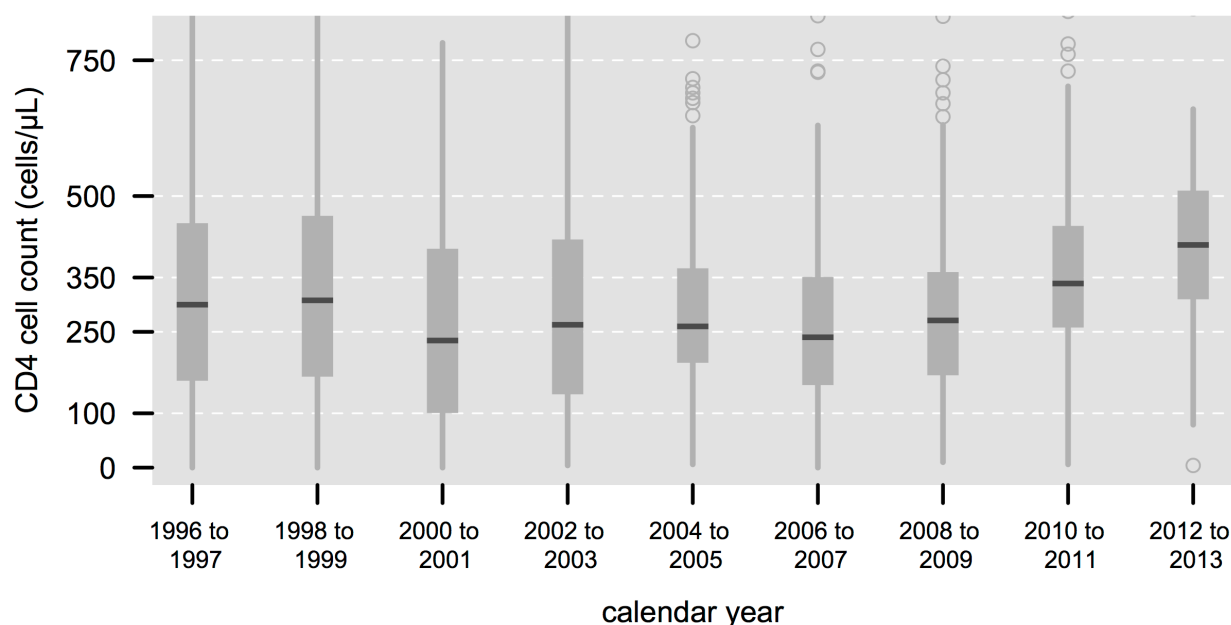


**Table 8: CD4 cell count at antiretroviral therapy initiation by calendar year<sup>1</sup>**

	1996 to 1997	1998 to 1999	2000 to 2001	2002 to 2003	2004 to 2005	2006 to 2007	2008 to 2009	2010 to 2011	2012 to 2013
<b>Number of participants initiating ART<sup>1</sup></b>									
Total N=	795	359	163	153	133	160	200	190	61
<b>CD4 cell count (copies/<math>\mu</math>l)<sup>2,3</sup></b>									
Mean	323	341	284	311	323	263	280	353	411
Median	300	308	234	263	260	240	271	339	410
IQR	160 - 460	173 - 470	87 - 403	135 - 420	196 - 364	151 - 350	182 - 373	247 - 445	310 - 540

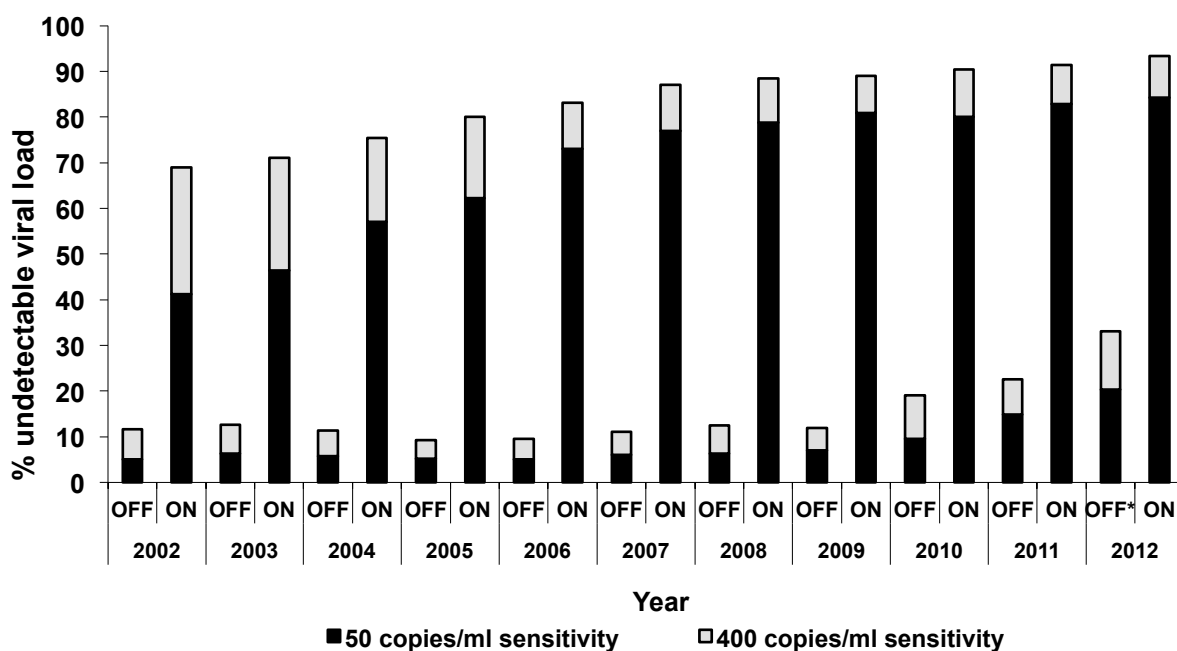
1. First ART defined as a combination of 3 or more antiretroviral agents and a duration of ART>14 days. Includes retrospective and prospective data. ATRAS sub study participants were excluded from analysis.
2. CD4 cell count selected from the observation closest to ART start date within a timeframe window of 12 months prior to ART start date and 1 month post ART start date.
3. A patient was excluded from the analysis if an undetectable viral load was recorded prior to initiating ART or was missing a viral load measurement prior to initiating ART.

**Figure 3: Empirical CD4 cell count distribution (boxplot) at antiretroviral therapy initiation by year of ART initiation<sup>1-3</sup> (median CD4 indicated by horizontal grey bar)**



1. First ART defined as a combination of 3 or more antiretroviral agents and a duration of ART>14 days. Includes retrospective and prospective data. ATRAS sub study participants excluded from analysis.
2. CD4 cell count selected from the observation closest to ART start date within a timeframe window of 12 months prior to ART start date and 7 days post ART start date.
3. A patient was excluded from the analysis if an undetectable viral load was recorded prior to initiating ART or was missing a viral load measurement prior to initiating ART.

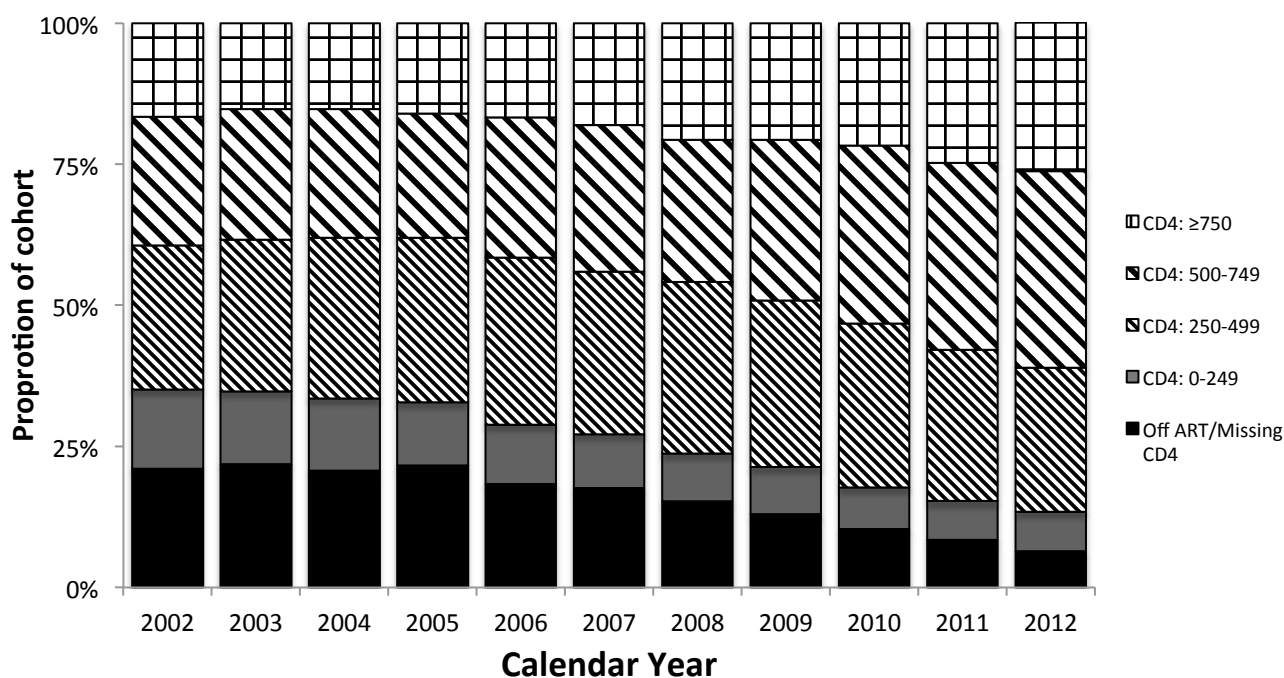
**Figure 4: Proportion of patients with an undetectable viral load, by treatment status (off /on treatment) and year according to assay sensitivity<sup>1</sup>**



1. Off treatment if never on a regimen of duration greater than 14 days for given calendar year. Viral load taken as median value during regimen of longest duration for given calendar year. Data for 2000 and 2001 includes 2 sites with minimum assay sensitivity of 400 copies/ml. Data for 2002 includes 1 site with minimum assay sensitivity of 400 copies/ml

\* In the "off-treatment" group (n=133), there are 34 patients where their viral load time series is strongly indicative of the patient receiving therapy, defined as 2 or more recent records where pVL <50 copies/ml. Data validation is ongoing with sites.

**Figure 5: CD4 cell counts (cells/ $\mu$ l) in patients receiving treatment by calendar year<sup>1-3</sup>**



1. Includes patients with a prospective CD4 measure during the relevant calendar year.

2. For patients on treatment, analysis based on the initial treatment intent, not on treatment administered (ITT), i.e. no adjustments are made for off-treatment following ART initiation.

3. Patients off treatment include those who have enrolled and have not initiated combination antiretroviral therapy.

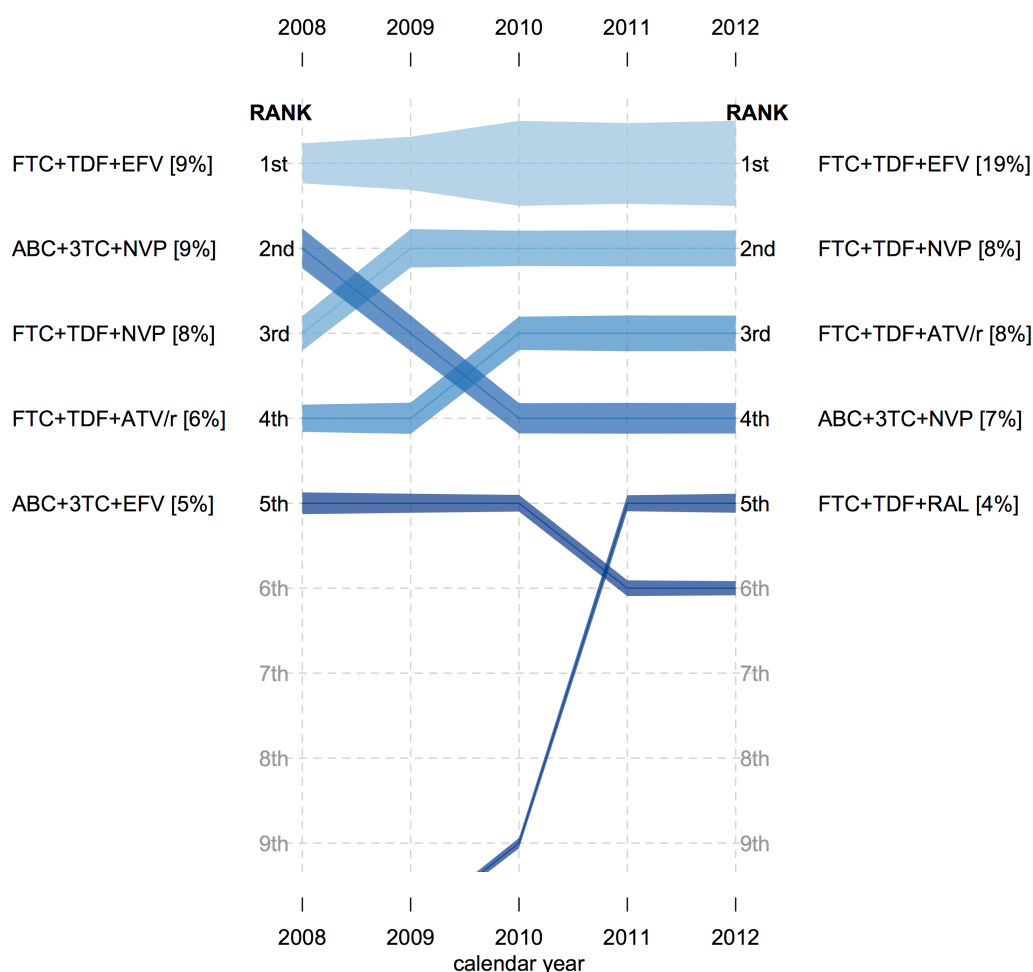
**Table 9: Top ten treatment combinations among the AHOD cohort<sup>1</sup>: January-December 2012**

In 2012, there were a total of 481 unique antiretroviral treatment (ART) combinations among the 2184 AHOD patients on combination ART. A total of 2439 combination regimens were recorded among these patients throughout 2012. The top ten most common ART combinations are described below.

ART combinations	Number of regimens recorded during 2012
emtricitabine+tenofovir+efavirenz	447
emtricitabine+tenofovir+nevirapine	192
emtricitabine+tenofovir+atazanavir+ritonavir	190
abacavir+lamivudine+nevirapine	163
emtricitabine+tenofovir+raltegravir	102
abacavir+lamivudine+efavirenz	76
abacavir+lamivudine+atazanavir+ritonavir	57
lamivudine+zidovudine+nevirapine	44
emtricitabine+tenofovir+ritonavir+darunavir	40
abacavir+lamivudine+ritonavir+darunavir	25

1. Includes retrospective and prospective data. Combinations include 3 or more antiretroviral drugs. Fixed dose combinations are separated into individual component antiretroviral drugs.

**Figure 6: Top five treatment combinations among the AHOD cohort<sup>1</sup> ranked by proportion<sup>2</sup> of total ART regimens recorded in years 2008-2012**



1. Includes retrospective and prospective data. Combinations include 3 or more antiretroviral drugs. Fixed dose combinations are separated into individual component antiretroviral drugs.

2. Proportion defined as frequency of ART line divided by total number of ART regimens recorded. For example, 2012 Rank 1 proportion calculated by  $481/2439=19\%$ . Thickness of line over time is proportional to calculated percentage.

**Table 10: Current use of individual antiretroviral treatments<sup>1</sup>**

	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<b>Nucleoside analogue reverse transcriptase inhibitors (RTI)</b>																						
Abacavir	568	(27)	535	(25)	549	(25)	523	(24)	461	(21)	370	(17)	355	(16)	258	(11)	245	(10)	222	(10)	195	(9)
Combivir <sup>2</sup>	384	(18)	357	(17)	406	(19)	408	(19)	364	(17)	275	(12)	221	(10)	190	(8)	175	(7)	140	(6)	112	(5)
Didanosine	453	(21)	415	(19)	369	(17)	291	(13)	214	(10)	146	(7)	108	(5)	73	(3)	61	(3)	42	(2)	36	(2)
Emtricitabine	1	(0)	1	(0)	2	(0)	40	(2)	97	(4)	69	(3)	97	(4)	127	(6)	154	(7)	183	(8)	191	(9)
Kivexa <sup>3</sup>	6	(0)	7	(0)	16	(1)	97	(4)	321	(15)	426	(19)	463	(20)	443	(20)	418	(18)	394	(18)	394	(18)
Lamivudine	993	(47)	953	(44)	980	(45)	977	(45)	891	(40)	579	(26)	496	(22)	371	(16)	344	(15)	303	(14)	282	(13)
Stavudine	641	(30)	450	(21)	303	(14)	203	(9)	140	(6)	91	(4)	73	(3)	58	(3)	46	(2)	29	(1)	29	(1)
Tenofovir	261	(12)	519	(24)	623	(28)	747	(34)	773	(35)	510	(23)	459	(20)	432	(19)	411	(18)	390	(17)	359	(16)
Trizivir <sup>4</sup>	147	(7)	159	(7)	147	(7)	141	(6)	123	(6)	89	(4)	71	(3)	55	(2)	46	(2)	34	(2)	27	(1)
Truvada <sup>5</sup>	5	(0)	8	(0)	9	(0)	18	(1)	369	(17)	545	(24)	705	(31)	887	(39)	931	(40)	747	(33)	771	(34)
Zalcitabine	28	(1)	19	(1)	13	(1)	11	(1)	9	(0)	7	(0)	7	(0)	6	(0)	6	(0)	6	(0)	6	(0)
Zidovudine	306	(14)	267	(12)	260	(12)	212	(10)	172	(8)	134	(6)	112	(5)	75	(3)	65	(3)	49	(2)	44	(2)
<b>Non-nucleoside analogue RTI</b>																						
Delavirdine	19	(1)	19	(1)	18	(1)	14	(1)	12	(1)	10	(0)	4	(0)	4	(0)	4	(0)	2	(0)	2	(0)
Efavirenz	399	(19)	429	(20)	470	(22)	461	(21)	489	(22)	521	(23)	534	(24)	548	(24)	505	(22)	306	(14)	295	(13)
Nevirapine	693	(33)	679	(32)	675	(31)	647	(30)	627	(28)	640	(29)	660	(29)	639	(28)	607	(26)	541	(24)	527	(23)
Etravirine									4	(0)	26	(1)	53	(2)	85	(4)	102	(4)	108	(5)	112	(5)
Rilpivirine														3	(0)	3	(0)	5	(0)	11	(0)	

1. All treatment records of ≥2 weeks of treatment in any calendar year were included in this analysis. The denominator includes all patients that could have been on antiretroviral therapy (i.e. HIV positive) in any calendar year. The proportion of patients on each drug in any calendar year does not add up to 100% across all ART drug groups in each calendar year as patients on more than one ARV during a calendar year period will be counted in all of the relevant ART groups. Includes retrospective and prospective data.

2. Comibivir – Lamivudine & Zidovudine.

3. Kivexa – abacavir & lamivudine.

4. Trizivir - abacavir & lamivudine & zidovudine.

5. Truvada – tenofovir & emtricitabine.

**Table 10 continued: Current use of individual antiretroviral treatments<sup>1</sup>**

	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<b>Protease Inhibitor</b>																						
Amprenavir	79	(4)	69	(3)	52	(2)	44	(2)	32	(1)	29	(1)	28	(1)	29	(1)	27	(1)	23	(1)	21	(1)
Atazanavir	4	(0)	139	(6)	265	(12)	388	(18)	442	(20)	477	(21)	527	(23)	538	(24)	551	(24)	511	(23)	492	(22)
Darunavir	0	(0)	0	(0)	8	(0)	14	(1)	41	(2)	74	(3)	119	(5)	161	(7)	195	(8)	221	(10)	238	(11)
Fosamprenavir	2	(0)	1	(0)	2	(0)	32	(1)	37	(2)	34	(2)	31	(1)	25	(1)	18	(1)	15	(1)	14	(1)
Indinavir	271	(13)	184	(9)	124	(6)	71	(3)	49	(2)	36	(2)	24	(1)	14	(1)	11	(0)	8	(0)	8	(0)
Kaletra <sup>6</sup>	328	(15)	394	(18)	415	(19)	410	(19)	386	(18)	365	(16)	336	(15)	313	(14)	307	(13)	248	(11)	210	(9)
Nelfinavir	193	(9)	138	(6)	105	(5)	71	(3)	48	(2)	36	(2)	12	(1)	11	(0)	9	(0)	7	(0)	7	(0)
Ritonavir	346	(16)	363	(17)	444	(20)	539	(25)	615	(28)	640	(29)	691	(30)	697	(31)	743	(32)	737	(33)	738	(33)
Saquinavir	127	(6)	111	(5)	97	(4)	79	(4)	64	(3)	55	(2)	46	(2)	30	(1)	23	(1)	20	(1)	16	(1)
<b>Entry Inhibitor</b>																						
Enfuvirtide	28	(1)	45	(2)	53	(2)	59	(2)	64	(3)	56	(2)	45	(2)	35	(1)	28	(1)	20	(1)	13	(1)
Maraviroc	-	-	-	-	-	-	8	(0)	7	(0)	6	(0)	14	(1)	21	(1)	28	(1)	31	(2)	24	(2)
<b>Integrase Inhibitors</b>																						
Raltegravir	-	-	-	-	-	-	-	-	12	(1)	67	(3)	179	(8)	310	(14)	439	(19)	469	(21)	507	(23)
Elvitegravir	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	19	(1)	19	(1)	19	(1)
Dolutegravir	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	(0)
<b>Class Combinations</b>																						
Atripla <sup>7</sup>	-	-	-	-	-	-	-	-	-	-	-	-	3	(0)	11	(0)	251	(11)	314	(14)	323	(14)
Eviplera <sup>8</sup>	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	29	(1)

1. All treatment records of ≥2 weeks of treatment in any calendar year were included in this analysis. The denominator includes all patients that could have been on antiretroviral treatment (i.e. HIV positive) in any calendar year. The proportion of patients on each drug in any calendar year does not add up to 100% across all ARV drug groups in each calendar year as patients on more than one ART during a calendar year period will be counted in all of the relevant ART groups. Includes retrospective and prospective data.

6. Kaletra – lopinavir & ritonavir.

7. Atripla – tenofovir & emtricitabine & efavirenz.

8. Eviplera - tenofovir & emtricitabine & rilipivirine.

## MONITORING DISPENSED ANTIRETROVIRALS VIA THE s100 PROGRAM

Data on the number of patients who were dispensed antiretroviral (ARV) drugs per state per financial year quarter, reported in the Public Hospital Dispensed National Patient Report from the Australian Government's Highly Specialised Drugs (HSD) (s100) program were analysed together with data on ART use from the AHOD sample to estimate total numbers of patients on ART by state and nationally, by year. At this time, all ARV drugs in Australia are publicly funded through the s100 program and should be recorded in the Public Hospital Dispensed National Patient Report. Since patients with HIV infection generally receive three or more ARV drugs in combination, and because the s100 program only collects data on individual ARV drugs, it is not possible to enumerate directly the number of patients receiving ART from the s100 data.

One of the commonly used ARV drugs for treatment of HIV infection is lamivudine. Yet, it is also used for the treatment of hepatitis B infection. As the PBS code is not included in the Public Hospital Dispensed National Patient Report, it is not possible to separate the number of patients who were dispensed lamivudine treatment for HIV from those receiving lamivudine for HBV. Therefore, we estimated the number of person years of lamivudine (100mg tablets) for HBV treatment from the Public Hospital Dispensed National Pack Number Report, which includes the PBS code, dosage and the total numbers of packs dispensed for each drug per financial quarter. To estimate the total number of patients dispensed lamivudine for HIV treatment, we deducted the total number of person years of lamivudine treatment for HBV each year from the total number of patient's dispensed lamivudine for HIV and HBV treatment. This method is based on the assumption that the majority of patients received a complete year of treatment during any calendar year period.

To estimate the number of patients receiving ART, we combined data on the proportion of patients receiving certain mutually exclusive ARVs in AHOD with data from the s100 program on the total number of people receiving the same ARVs. For example, lamivudine and emtricitabine are a common component of combination ART regimens in Australia, but should not be prescribed in combination. We calculated the proportion of all treated patients in AHOD who received lamivudine or emtricitabine as part of an ART regimen by year and state. We also estimated the total number of patients dispensed lamivudine or emtricitabine for HIV infection each year through the s100 program by calculating the average number of patients prescribed each drug from the corresponding four financial year quarters. An estimate of the total number of people receiving any ART was then obtained by dividing the total number of patients receiving lamivudine or emtricitabine through the s100 program by the proportion of treated patients in AHOD receiving the same ARV drugs. As a sensitivity analysis, we repeated this calculation for other commonly mutually exclusive drugs, including: 1) efavirenz and nevirapine; 2) Kaletra (lopinavir and ritonavir) and ritonavir; and 3) stavudine and zidovudine containing ARVs. In this report, we have only included results for the lamivudine and emtricitabine model.

Important Note: Prior to 2009, the HSD Report provided prescribed patient numbers by each antiretroviral agent. However after noting some inconsistencies with their methodology, they have since ceased providing these numbers. For years 2009-2010, instead we (The Kirby Institute) evaluated patient numbers by using a combination of total packs dispensed and an average "packs-per-patient" adjustment ratio. The packs-per-patient adjustment figure was calculated from 2008 data, where total packs dispensed and patient numbers were available. However, due to the relatively recent diversification of pack sizes, newer dosing schedules and the introduction of antiretroviral agents that were absent in 2008, we are uncertain as to how our packs-per-patient adjustment ratio has changed over time. Therefore we caution our estimates for 2011 & 2012 data for Table 11. We are working with the producers of the HSD Report to amend these issues and are currently revisiting our methodology for these figures.

**Table 11: Number of people dispensed antiretroviral treatment through the Highly Specialised Drugs (s100) program by year and antiretroviral agent**

Antiretroviral agent	Year of prescription <sup>1,2</sup>				
	2008	2009	2010	2011	2012
<b>Nucleoside analogue reverse transcriptase inhibitors</b>					
Abacavir	595	544	492	473	425
Didanosine	322	229	163	117	84
Emtricitabine	181	131	211	146	157
Lamivudine	1051	921	822	718	609
Stavudine	145	104	77	48	36
Zidovudine	190	156	128	98	70
Lamivudine & Zidovudine	980	846	719	602	461
Abacavir & Lamivudine	2367	2243	2220	2179	2041
Abacavir, Lamivudine & Zidovudine	276	240	163	133	103
Tenofovir	1419	1294	1586	1967	2039
Tenofovir & Emtricitabine	4097	5246	4772	4510	4404
<b>Non-nucleoside analogue reverse transcriptase inhibitors</b>					
Delavirdine	6	7	6	-	-
Efavirenz	2762	2996	2003	973	738
Nevirapine	2667	2791	2809	2728	2376
Etravirine	-	155	403	456	454
Rilpivirine	-	-	-	-	18
<b>Protease inhibitors</b>					
Atazanavir	2254	2609	2879	2906	2582
Darunavir	407	685	887	1058	1131
Fosamprenavir	233	219	181	148	111
Indinavir	76	52	31	21	18
Lopinavir & ritonavir	1775	1871	1734	1581	1341
Ritonavir	2413	2850	3181	3098	2652
Saquinavir	167	148	121	95	72
Tipranavir	31	27	20	15	11
<b>Entry inhibitors</b>					
Enfuvirtide	118	60	37	22	13
Maraviroc	-	-	55	118	122
<b>Integrase inhibitor</b>					
Raltegravir	287	821	1250	1848	2250
<b>Combination Class Agents</b>					
Tenofovir, Emtricitabine & Efavirenz	-	-	2013	2873	2786
Tenofovir, Emtricitabine & Rilpivirine	-	-	-	-	217
<b>Total patients<sup>3</sup></b>	<b>10,200</b>	<b>10,900</b>	<b>12,400</b>	<b>12,700</b>	<b>12,800</b>
<b>Total cost<sup>4</sup> (\$'000s)</b>	<b>136,625</b>	<b>156,810</b>	<b>181,508</b>	<b>200,165</b>	<b>210,005</b>

1. The number of people dispensed each antiretroviral drug during a calendar year was estimated by calculating the average of the total number of people dispensed each drug during the corresponding financial year quarters. Number of person years for July - December 2009 onwards estimated from the HSD Program Public Hospital Dispensed National Pack Number Report because of changes to S100 data collection methodology.

2. Dashes (-) indicate that data were not available.

3. Total patients calculated as (Lamivudine + Combivir (Lamivudine & Zidovudine)+Trizivir (Abacavir, Lamivudine & Zidovudine)+Kivexa (Abacavir & Lamivudine)+Emtricitabine + Truvada(Tenofovir & Emtricitabine) + Atripla(Tenofovir & Emtricitabine & Efavirenz) + Exiplera(Tenofovir & Emtricitabine & Rilpivirine) )/the proportion of patients in the Australian HIV Observational Database receiving any of the previously mentioned drugs in each year. Estimates of total patients are rounded to nearest 100 patients.

4. Public Hospital Expenditure.

**Source: Highly Specialised Drugs (S100) Program**







## **Publications:**

### **Long-term survival in HIV positive patients with up to 15 Years of antiretroviral therapy.**

Hamish McManus, Catherine C O'Connor, Mark A Boyd, Jennifer Broom, Darren Russell, et al. (2012). PLoS One 7: e48839.

### **Ageing and long-term CD4 cell count trends in HIV-positive patients with 5 years or more combination antiretroviral therapy experience.**

Stephen Wright, Kathy Petoumenos, Mark A Boyd, Andrew Carr, Sandra Downing, et al. (2013). HIV Med 14: 208-216.

### **High Rates of Sexually transmitted infections in HIV-positive patients in the Australian HIV Observational Database - a prospective cohort study.**

Brian P Mulhall, Stephen Wright, Debbie Allen, Katherine Brown, Bridget Dickson, et al. (2013). Sexual Health (*in press*).

### **Currently available medications in resource-rich settings may not be sufficient for lifelong HIV treatment.**

James Janssen, David Wilson, Andrew Carr, Kathy Petoumenos, Mark A Boyd. (2013). AIDS 27:1245-1251.

### **Rates and Factors Associated with Major Modifications to First-Line Combination Antiretroviral Therapy: Results from the Asia-Pacific Region.**

Stephen Wright, Mark Boyd, Evy Yuniastuti, Matthew Law, Thira Sirisanthana, et al. (2013). PLoS ONE 8(6): e64902.

### **The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report.**

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### **Adhoc Data Request Report No.8.**

Stephen Wright, Hamish McManus, Kathy Petoumenos and Matthew Law. (February 2012). <http://www.kirby.unsw.edu.au/publications/ahod-data-request-report-no-8-feb-2012>

### **Adhoc Data Request Report No.9.**

Stephen Wright, Hamish McManus, Kathy Petoumenos and Matthew Law. (July 2012). <http://www.kirby.unsw.edu.au/publications/ahod-data-request-report-no-9-jul-2012>

### **Adhoc Data Request Report No.10.**

Stephen Wright, Hamish McManus, Kathy Petoumenos and Matthew Law. (January 2013). <http://www.kirby.unsw.edu.au/publications/ahod-data-request-report-no10-jan-2013>

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*All data in this report are provisional  
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