

AIDS diagnoses at higher CD4 counts in Australia following the introduction of highly active antiretroviral treatment

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Objectives: To assess whether AIDS cases in Australia have been diagnosed at higher CD4 counts since the widespread availability of highly active antiretroviral treatment (HAART) in mid-1996.

Methods: Data on the CD4 count at AIDS diagnosis for AIDS cases diagnosed between 1 January 1992 and 31 December 1997, and reported to the National AIDS Registry in Australia by 31 March 1998, were analysed. The median CD4 count at AIDS diagnosis, and the proportions of AIDS diagnoses with a CD4 count above 100 cells/ μ l, and above 200 cells/ μ l, were calculated by the year of diagnosis, both for all AIDS-defining illnesses, and for each illness separately. Analyses were also stratified by the time interval between HIV and AIDS diagnoses (less than or equal to, or more than, 3 months) because people diagnosed with HIV close to the diagnosis of AIDS would generally not have received any antiretroviral treatment before the diagnosis of AIDS, and so no trends in CD4 counts at the diagnosis of AIDS would be expected in this group.

Results: There was an increase in CD4 count at AIDS diagnosis in 1996 and 1997, although this increase was only apparent for AIDS-defining illnesses other than *Pneumocystis carinii* pneumonia (PCP), and was limited to AIDS cases diagnosed with HIV more than 3 months before AIDS. In cases of AIDS other than PCP, and diagnosed with HIV more than 3 months before AIDS, the median CD4 count increased from 50 cells/ μ l in 1995 to 80 cells/ μ l in 1996 and 134 cells/ μ l in 1997.

Conclusions: There has been an increase in the CD4 count at AIDS diagnosis for most AIDS-defining illnesses in Australia coincident with the widespread availability of HAART.

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Introduction

The introduction of highly active antiretroviral treatments (HAART) has been seen to slow down considerably the progression of HIV disease in Australia and other countries [1–3]. The incidence of AIDS has also decreased in Australia and other developed countries coincident with the widespread use of these treatments [4,5]. In Australia, the annual incidence of AIDS has decreased from a peak of 946 cases in 1994, to delay-

adjusted estimated 809 cases in 1995, 690 cases in 1996, and 432 cases in 1997 [4].

In Australia, there is limited information available on the uptake of HAART during the period 1996 to 1997. In the Sydney Men and Sexual Health Study, a cohort study of homosexually active men in Sydney, however, the proportion of HIV-infected respondents reporting that they were receiving three or more antiretroviral treatments increased from 12% in the first half

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of 1996, to 40% in the second half of 1996, and to 57 and 72% in the first and second halves of 1997, respectively [4]. The proportion reporting that they were receiving a protease inhibitor also increased from 11 and 45% in the first and second halves of 1996 to 52 and 68% in the first and second halves of 1997.

Before the widespread availability of HAART in Australia, the median CD4 count at AIDS diagnosis was gradually decreasing [6,7]. There have recently, however, been anecdotal reports in Australia of increased numbers of AIDS diagnoses being made at relatively high CD4 counts. Diagnoses of cytomegalovirus retinitis and *Mycobacterium avium* complex after HAART, at unusually high CD4 counts, have also been reported [8,9]. There are several reasons why AIDS diagnoses at increased CD4 counts might be expected in the era of HAART. First, the improved immune responses induced by HAART may only be for those immune responses that were present before treatment [10,11]. Therefore, for HIV-infected people with very low CD4 counts, HAART-induced increases in the CD4 count may leave gaps in the immune response. Second, it has been hypothesized that HAART may cause subclinical opportunistic infections to become clinically apparent with the sudden increase in cell-mediated immunity [9,12]. Third, the improved CD4 counts after HAART may lead to patients stopping effective prophylactic treatments.

In this paper we assess whether first AIDS diagnoses in Australia have been at increased CD4 counts since the widespread availability of HAART, based on surveillance data of AIDS diagnoses.

Methods

AIDS cases were notified to the Health Department of the state or territory of diagnosis and reported to the National AIDS Registry (NAR) [13] maintained by the National Centre in HIV Epidemiology and Clinical Research (Sydney). Each case in the Registry was identified by date of birth, sex and the first two letters of the family and given names. Other information collected included the date of AIDS diagnosis, date notification entered, the reported date of first HIV diagnosis, the CD4 cell count at the time of AIDS diagnosis, the date of CD4 cell count, initial AIDS-defining illness(es) and patient-reported mode of exposure to HIV.

The AIDS case definition established by the Centers for Disease Control and Prevention (CDC) in 1982 has been applied in Australia [14], including revisions in 1985, 1987 [15], and the revision in 1993, except for the criteria based solely on a CD4 count less than 200 cells/ μ l [16].

Because the CD4 count at AIDS diagnosis has only been systematically collected since late 1991, analyses were based on the AIDS cases diagnosed between 1 January 1992 and 31 December 1997 and reported to the NAR by 31 March 1998. This is a time period that covers the introduction of HAART in Australia, which became widely available in mid-1996.

The median CD4 count, and the proportion of AIDS diagnoses with a CD4 count of 100 cells/ μ l or more, or of 200 cells/ μ l or more, were calculated by the year of diagnosis, both for all AIDS-defining illnesses, and for each individual AIDS-defining illness separately. Also, as the *a priori* hypothesis was that HAART may be associated with AIDS diagnoses at higher CD4 counts, further analyses were performed separately according to whether the reported time between HIV and AIDS diagnoses was less than or equal to 3 months, or more than 3 months. Those people diagnosed with HIV close to AIDS would generally not have received any antiretroviral treatment before their AIDS diagnosis, and so no trends in CD4 counts at the diagnosis of AIDS would be expected in this group.

Statistical analysis

Trends over time in the proportion of AIDS diagnoses with a CD4 count of 100 cells/ μ l or more, or 200 cells/ μ l or more, were assessed using logistic regression techniques. Any increase in the median CD4 count at AIDS diagnosis was assessed using regression analyses applied to the ranked data.

To ensure that any apparent trends in CD4 counts were not caused by the as yet incomplete reporting of AIDS diagnosis to the NAR in 1996 and 1997, further statistical analyses were performed, which adjusted for the reporting delay between AIDS diagnosis and the date of notification of the case. In these analyses, the reporting delay was categorized as 0–3 months, 3–6 months, 6–12 months, 12–24 months and more than 24 months. Further statistical analyses were also performed adjusting for the time between the date of CD4 count and the date of AIDS diagnosis (categorized as more than one month before the diagnosis of AIDS, within one month of the diagnosis of AIDS and more than one month after the diagnosis of AIDS), age and state/territory of diagnosis.

Results

A total of 4310 adults and adolescents were diagnosed with AIDS in Australia between 1 January 1992 and 31 December 1997 and were reported to the NAR by 31 March 1998. CD4 cell counts at the diagnosis of AIDS were available for 3854 (89%) cases, and the date of HIV diagnosis was available for 3781 (98%) of these cases.

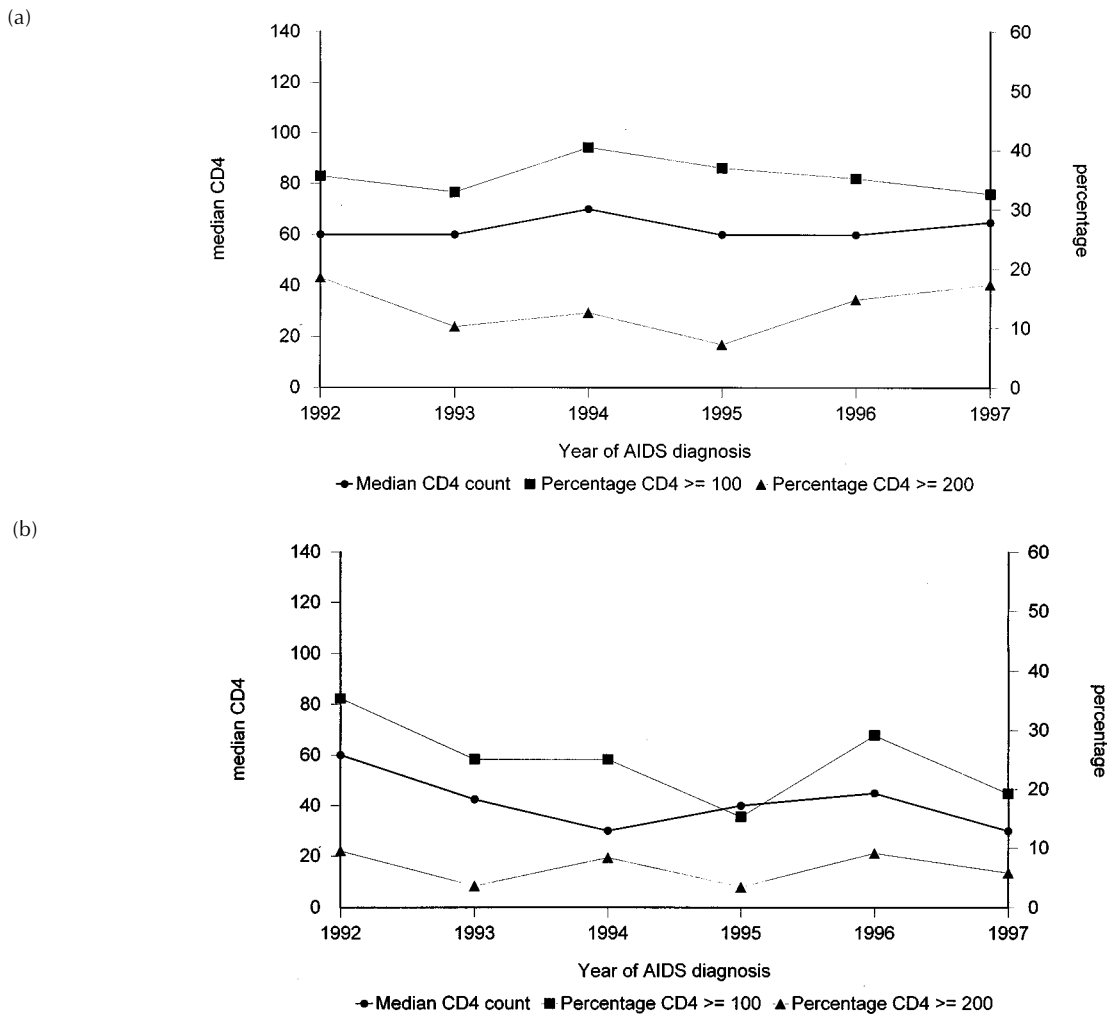


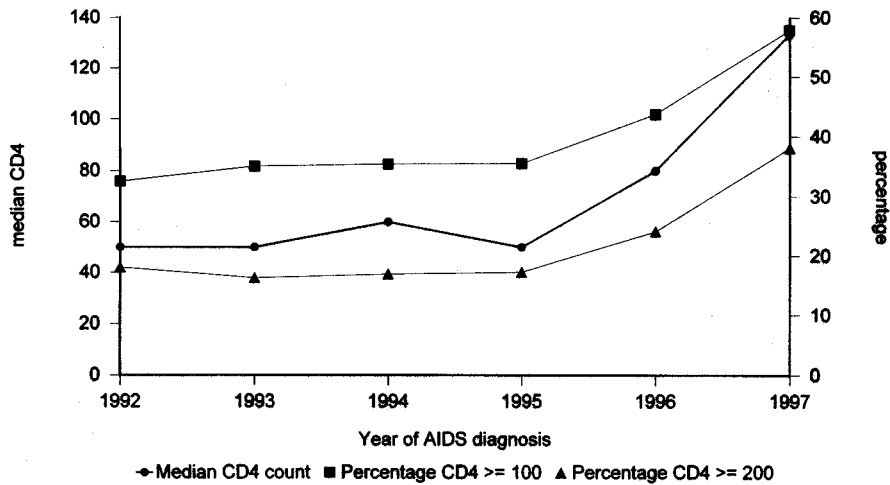
Fig. 1. CD4 count at AIDS diagnosis for cases of PCP diagnosed with HIV (a) more than 3 months before AIDS, and (b) less than or equal to 3 months before AIDS.

On the basis of all AIDS diagnoses, the median CD4 count and both the proportion of cases with a CD4 count above 100 cells/ μ l, or above 200 cells/ μ l, increased in 1996 and 1997, although as was expected these increases appeared to be limited to those AIDS cases for which HIV diagnosis was more than 3 months before the diagnosis of AIDS (data not shown). The trend of increasing CD4 cell counts at the diagnosis of AIDS was broadly apparent for all AIDS-defining illnesses, except for *Pneumocystis carinii* pneumonia (PCP). For PCP diagnoses there was no trend to increasing CD4 counts in 1996 and 1997, either in cases for which the time between HIV and AIDS diagnoses was less than 3 months, or in cases for which this time was greater than 3 months (Fig. 1(a and b)). Because the increasing trend in CD4 count was broadly true for all other AIDS-defining illnesses for which the time between HIV and AIDS diagnoses was 3 months or more, these cases are presented combined together (see Fig. 2(a)). As expected, however, no trend over time in

CD4 count was observed in AIDS cases with AIDS-defining illnesses other than PCP diagnosed with HIV within 3 months of AIDS diagnosis (see Fig. 2(b)).

Formal statistical analyses, based on the proportion of AIDS cases with either a CD4 count of 100 cells/ μ l or more, or of 200 cells/ μ l or more, are presented in Tables 1 and 2, respectively. These analyses confirm the impression given by the plots, with highly statistically significant increases in 1996 and 1997 in the proportion of AIDS cases other than PCP at increased CD4 counts, among those cases diagnosed with HIV at least 3 months before the diagnosis of AIDS. Among AIDS cases with AIDS-defining illnesses other than PCP, however, there was no increase in the proportion of diagnoses at high CD4 counts in those cases diagnosed with HIV within 3 months of AIDS. There was also no evidence of an increase in the proportion of PCP diagnoses at high CD4 counts, either in cases for which the interval between HIV and AIDS diagnosis was 3

(a)



(b)

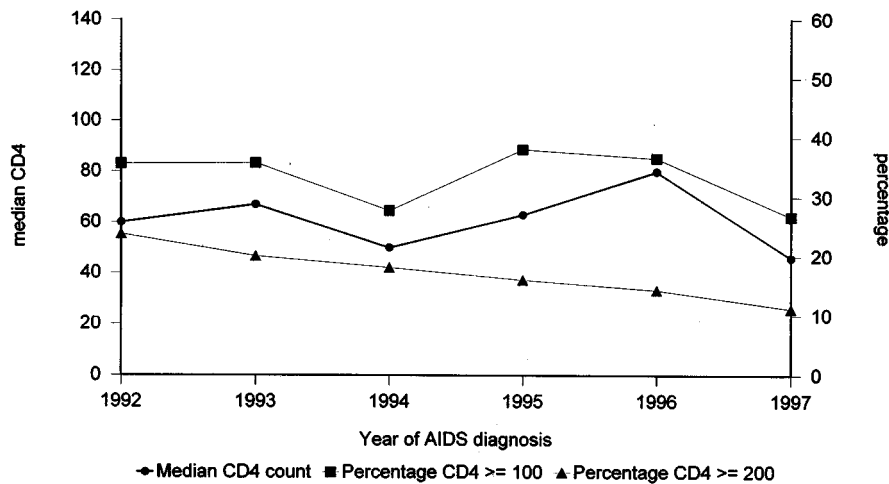


Fig. 2. CD4 count at AIDS diagnosis for AIDS-defining illness other than PCP diagnosed with HIV (a) more than 3 months before AIDS, and (b) less than or equal to 3 months before AIDS.

months or less, or in cases for which this time was greater than 3 months. Among PCP cases diagnosed with HIV within 3 months of AIDS, there was some suggestion of a decrease in the proportion of cases at high CD4 counts, although this was limited to statistically significant decreases in 1995 and 1997 for a CD4 count of 100 cells/ μ l or more.

Analyses treating the CD4 count as a continuous endpoint based on regression techniques applied to ranked data, and also all analyses adjusting for reporting delay, the time between the date of CD4 count and the date of AIDS, age and state/territory of diagnosis gave qualitatively identical results and are not presented.

Discussion

On the basis of surveillance data on AIDS diagnoses, in Australia we have seen an increase in the median CD4

count at AIDS diagnosis, and increases in both the proportions of AIDS cases diagnosed at 100 cells/ μ l or more, and 200 cells/ μ l or more, in 1996 and 1997. These increases, however, were restricted to AIDS cases diagnosed with HIV more than 3 months before the diagnosis of AIDS, and to AIDS-defining illnesses other than PCP. That these increases in CD4 counts at AIDS diagnosis were coincident with the widespread availability of HAART in Australia, and also because increases were not seen in AIDS cases in whom HIV was diagnosed close to AIDS (and who would generally not have received treatment before the diagnosis of AIDS) suggest that the use of HAART is associated with the increased CD4 counts at the diagnosis AIDS.

The fact that there were no increases in CD4 count at the diagnosis of PCP was unexpected, particularly as increased CD4 counts at AIDS diagnosis were seen for other similar AIDS-defining intracellular opportunistic infections, such as toxoplasmosis, *M. avium* complex, and cytomegalovirus (data not shown). It certainly

Table 1. Proportion of AIDS cases with CD4 counts of 100 cells/ μ l or more by year of AIDS diagnosis*

PCP	Time between HIV diagnosis and AIDS diagnosis 3 months or less					Time between HIV diagnosis and AIDS diagnosis more than 3 months				
	No. CD4 counts < 100 cells/ μ l	No. CD4 counts \geq 100 cells/ μ l	OR [†]	95% CI [†]	P	No. CD4 counts < 100 cells/ μ l	No. CD4 counts \geq 100 cells/ μ l	OR [†]	95% CI [†]	P
1992	55	30	1.0			87	48	1.0		
1993	42	14	0.61	0.29–1.29	0.199	92	45	0.88	0.54–1.46	0.638
1994	45	15	0.61	0.29–1.27	0.189	90	61	1.22	0.76–1.98	0.400
1995	50	9	0.33	0.14–0.76	0.009	70	41	1.06	0.63–1.79	0.822
1996	39	16	0.75	0.36–1.56	0.446	70	38	0.98	0.58–1.67	0.952
1997	42	10	0.44	0.19–0.99	0.048	31	15	0.88	0.43–1.78	0.717

Other AIDS-defining illness	Time between HIV diagnosis and AIDS diagnosis 3 months or less					Time between HIV diagnosis and AIDS diagnosis more than 3 months				
	No. CD4 counts < 100 cells/ μ l	No. CD4 counts \geq 100 cells/ μ l	OR [†]	95% CI [†]	P	No. CD4 counts < 100 cells/ μ l	No. CD4 counts \geq 100 cells/ μ l	OR [†]	95% CI [†]	P
1992	38	21	1.0			270	130	1.0		
1993	45	25	1.01	0.49–2.07	0.989	308	166	1.12	0.84–1.48	0.433
1994	60	23	0.69	0.34–1.42	0.318	345	189	1.14	0.86–1.50	0.356
1995	31	19	1.11	0.51–2.42	0.795	300	165	1.14	0.86–1.51	0.356
1996	40	23	1.04	0.50–2.18	0.916	201	156	1.61	1.20–2.17	0.002
1997	33	12	0.66	0.28–1.54	0.334	53	73	2.86	1.90–4.31	0.000

*Analyses presented are unadjusted. Analyses which adjusted for reporting delays, time between CD4 count and AIDS diagnosis, age and state/territory of diagnosis gave qualitatively identical results and are not presented. [†]OR, odds ratio; CI, confidence interval.

Table 2. Proportion of AIDS cases with CD4 counts of 200 cells/ μ l or more by year of AIDS diagnosis*

PCP	Time between HIV diagnosis and AIDS diagnosis 3 months or less					Time between HIV diagnosis and AIDS diagnosis more than 3 months				
	No. CD4 counts < 200 cells/ μ l	No. CD4 counts \geq 200 cells/ μ l	OR [†]	CI 95% [†]	P	No. CD4 counts < 200 cells/ μ l	No. CD4 counts \geq 200 cells/ μ l	OR [†]	CI 95% [†]	P
1992	77	8	1.0			110	25	1.0		
1993	54	2	0.41	0.08–2.06	0.281	123	14	0.54	0.26–1.12	0.097
1994	55	5	0.80	0.22–2.85	0.726	132	19	0.65	0.33–1.29	0.217
1995	57	2	0.39	0.08–1.95	0.252	103	8	0.35	0.14–0.84	0.020
1996	50	5	1.11	0.34–3.70	0.860	92	16	0.83	0.41–1.69	0.604
1997	49	3	0.68	0.17–2.76	0.592	38	8	0.92	0.37–2.33	0.863

Other AIDS-defining illness	Time between HIV diagnosis and AIDS diagnosis 3 months or less					Time between HIV diagnosis and AIDS diagnosis more than 3 months				
	No. CD4 counts < 200 cells/ μ l	No. CD4 counts \geq 200 cells/ μ l	OR [†]	CI 95% [†]	P	No. CD4 counts < 200 cells/ μ l	No. CD4 counts \geq 200 cells/ μ l	OR [†]	CI 95% [†]	P
1992	45	14	1.0			328	72	1.0		
1993	56	14	0.73	0.31–1.72	0.474	397	77	1.00	0.70–1.44	0.989
1994	68	15	0.65	0.28–1.50	0.313	444	90	0.98	0.69–1.40	0.911
1995	42	8	0.61	0.23–1.61	0.319	385	80	0.98	0.68–1.41	0.904
1996	54	9	0.54	0.21–1.35	0.187	271	86	1.52	1.05–2.18	0.025
1997	40	5	0.40	0.13–1.21	0.106	78	48	2.82	1.79–4.43	0.000

*Analyses presented are unadjusted. Analyses which adjusted for reporting delays, time between CD4 count and AIDS diagnosis, age and state/territory of diagnosis gave qualitatively identical results and are not presented. [†]OR, odds ratio; CI, confidence interval.

suggests, however, that the increased CD4 counts at AIDS diagnosis are not caused by HIV-infected people stopping prophylactic treatments as a result of improved CD4 counts after HAART. The most likely explanation is probably that those HIV-infected people who receive HAART before AIDS are also the people who

receive and comply with prophylactic treatments. Any tendency for people receiving HAART to be diagnosed with PCP at higher CD4 counts would thus be negated by these people also receiving effective prophylaxis. It is also interesting to note that in people diagnosed with PCP for whom the date of HIV

diagnosis was less than or equal to 3 months before their PCP diagnosis, there was some evidence of a continuing decrease in CD4 count in successive years, consistent with previous data on the CD4 count at PCP diagnosis before the introduction of HAART [7].

In our data, the pattern of increasing CD4 counts at the diagnosis of AIDS was as expected not seen in people diagnosed with HIV close to AIDS (within 3 months), a group of people who would generally not have received any antiretroviral treatment before the diagnosis of AIDS. The lack of any increasing CD4 count at the diagnosis of AIDS in people diagnosed with PCP was, however, not expected. Furthermore, for some AIDS-defining illnesses other than PCP, separate analyses of the CD4 count at diagnosis were based on small numbers of cases, and so although a broadly consistent pattern of increasing CD4 counts in 1996 and 1997 was seen in our data, these results are liable to some uncertainty. Our analyses should be regarded as exploratory, and the replication of our analyses on other surveillance and cohort data is required, both to replicate the lack of any trends in CD4 counts at the diagnosis of PCP, and also to identify whether CD4 counts at the diagnosis of AIDS are truly increasing for all AIDS-defining illnesses other than PCP.

The results reported here are based on surveillance data, so it is not possible to rule out entirely changes in surveillance mechanisms as a possible explanation for the observed increases in CD4 count at AIDS diagnosis. There have, however, been no known changes to surveillance mechanisms in Australia coinciding with the time period 1996 to 1997 that could explain these results. Furthermore, statistical analyses that adjusted for reporting delays and for the time between the date of the CD4 count and the date of the AIDS illness gave essentially identical results.

Although the incidence of AIDS in Australia has declined since the introduction of HAART, our results suggest that those AIDS cases now being diagnosed have increased CD4 counts. Incomplete immune restoration after HAART appears to be a more likely explanation for this increase in CD4 counts at the diagnosis of AIDS than the cessation of prophylactic treatments. A second possibility is that HAART has resulted in increased numbers of people with HIV living for much longer periods with higher CD4 counts than would otherwise have been the case. So, for example, there are now many more people living with HIV and with a CD4 count of between 100 and 500 cells/ μ l, and fewer with a CD4 count below 100 cells/ μ l. Therefore, although overall there are now far fewer AIDS diagnoses, a greater proportion of diagnoses are at higher CD4 counts as a result of the increased proportion of all people with HIV living with higher CD4 counts.

To assess reliably the extent to which the increasing trend in CD4 count at the diagnosis of AIDS is caused by the changing patterns of antiretroviral and prophylactic treatment is beyond the scope of these surveillance data. Previous treatment with zidovudine at the diagnosis of AIDS was sought on the NAR, but it was incompletely reported, particularly over the last couple of years, and there were no data regarding prophylactic treatments. Further research is needed based on cohort studies in which detailed data on antiretroviral and prophylactic treatments have been collected. Our results, however, suggest that patients with increased CD4 counts after HAART should be encouraged to continue prophylactic treatments, particularly those patients who previously had advanced HIV disease.

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