Estimating the population impact in Australia of improved antiretroviral treatment for HIV infection

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Objective: To estimate the reduction in AIDS incidence, if any, which has occurred in Australia following the availability of new combination antiretroviral treatments from 1995.

Design: Analyses were based on national surveillance data.

Methods: Back-projection analyses based on quarterly AIDS counts to the end of 1994 were used to estimate the numbers of AIDS diagnoses which would have occurred if new treatments had not reduced the rate of progression to AIDS. Estimates of the reduction in AIDS diagnoses between 1995 and 1998 were made by subtracting the observed delay-adjusted AIDS counts from the predicted AIDS incidence.

Results: AIDS incidence between 1995 and 1998 was estimated to have been reduced by 1093 cases (33%) following the availability of new antiretroviral treatments (95% confidence interval 831 (25%) to 1425 (43%) cases). The majority of this reduction in AIDS incidence was estimated to have occurred during 1997 (434 cases) and 1998 (427 cases).

Conclusions: AIDS incidence in Australia has declined since 1995 coincidental with introduction of new antiretroviral treatments. In particular, the more rapid decline in AIDS incidence since mid-1996 coincided with the availability and widespread uptake of combinations including protease inhibitors.

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Introduction

AIDS incidence in Australia has declined from a peak of 950 cases in 1994, to a reporting-delay-adjusted estimated 664 cases in 1996, 373 cases in 1997 and 351 cases in 1998. The decline in AIDS incidence was most rapid from the second half of 1996 onwards, even after proper allowance for the uncertainties in the delay-adjusted AIDS incidences. Similar decreases in AIDS incidence from 1996, following plateaux in 1994–1995, have also been seen in many European countries [1] and Canada [2].

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Because the observed decreases in AIDS incidence have been coincident with improved combination antiretroviral treatments, it is tempting to conclude that these observed decreases are entirely due to improved treatment. In Australia, however, AIDS incidence had been expected to plateau around 1994 to 1995, and then steadily decline, even if there were no improvements in treatment [3]. This plateau was expected as a result of the pattern of past HIV incidence, which has been consistently estimated to have peaked in the early 1980s, and then rapidly declined [3–5].

The objective of this paper was to assess the impact in Australia, at a population level, of improved antiretroviral treatment since 1995.

Methods

The analysis involved a comparison between observed AIDS diagnoses adjusted for reporting delays between 1995 and 1998 and estimates of the numbers of AIDS diagnoses which would have been predicted over this time period if new antiretroviral treatments had not reduced the rate of progression to AIDS.

In Australia, all AIDS diagnoses are reported to the National AIDS Registry maintained at the National Centre in HIV Epidemiology and Clinical Research, via state/territory health departments. The AIDS case definition established by the Centers for Disease Control and Prevention in 1982 has been applied in Australia [6], including revisions in 1985, 1987 [7] and the revision in 1993 except for the criteria based solely on a CD4 count less than 200×10^6 cells/l [8]. Analyses were based on quarterly AIDS counts to the end of 1998 and reported to the National AIDS Registry by the end of March 1999. The observed quarterly AIDS incidence counts during 1996 to 1998 were adjusted for reporting delay using methods described by Brookmeyer and Liao [9], with approximate 95% confidence limits given by the empirical procedure suggested by Bacchetti [10].

Back-projection methods

The number of AIDS diagnoses which would have occurred during 1995 to 1998 if the availability of new combination antiretroviral treatments had not reduced the rate of progression to AIDS were estimated using back-projection methods applied to quarterly AIDS counts to the end of 1994. The form of back-projection used in this paper was that suggested by Becker *et al.* [11].

The rate of progression from HIV infection to AIDS was modelled in two stages. First, a baseline progression rate distribution was modelled using a Weibull-with-levelling distribution [12] with a progression rate of 11% at 4 years, and a median time to AIDS of just under 10 years, consistent with Australian and overseas studies [13,14]. Second, the modifying effects of changes to the AIDS surveillance definition, and the availability of treatments, were superimposed on this baseline progression rate. The extended AIDS surveillance definition, adopted in Australia in January 1988, was assumed to result in a 10% increase in the progression rate [12]. The availability of antiretroviral treatments in Australia to the end of 1994, which started with zidovudine monotherapy from mid-1987, and was assumed to result in an overall 10% reduction in the progression rate [15–17].

Because back-projection estimates of HIV incidence are uncertain for the recent past due to the slow progression rate from HIV infection to AIDS, incidence was fixed at 450 cases per year between 1993–1998 based on data from other sources. First, there were around 200 diagnoses of newly acquired HIV infection in each year between 1993–1998 [18], putting a lower limit on HIV incidence in these years and also suggesting that HIV incidence was reasonably stable during this period. Second, there was between a five- and ten-fold decrease in HIV incidence between 1984–1994 among participants in the Sydney AIDS Prospective Study [19], suggesting that HIV incidence, estimated to have peaked at 3000 cases per year in the early 1980s [3–5], was between 300 and 600 per year in 1994. Third, HIV incidence during 1993 and 1994 at a level of 450 per year was also found to be broadly consistent with the back-projection analyses, which did not fix HIV incidence over this period. In any event, HIV incidence in recent years would result in few AIDS cases over the same time period.

Variability in the projected quarterly AIDS counts during 1995 to 1998 was assessed using an empirical procedure. Back-projections were performed based on quarterly AIDS diagnoses up to each quarter (Q) from 1988 Q4 to 1993 Q3, to give estimates of predicted AIDS incidence up to 16 quarters into the future for each analysis, over the time period 1989 Q1 to 1993 Q4. These quarterly estimates were then compared with observed AIDS incidence to give log relative errors in the predictions. The estimated variance of the log errors for projections of AIDS incidence was then simply the mean square of these log errors.

Sensitivity analyses

To allow for modelling uncertainties in the back-projection analyses as well as random variability, a series of sensitivity analyses were performed in addition to the preferred analysis described above. Six sensitivity

analyses were performed as follows: (1) faster and slower progression rate distributions were specified corresponding to median times to AIDS of 9.5 years and 10.5 years respectively; (2) upper and lower limits on the effectiveness of antiretroviral treatment to the end 1994 were respectively taken as a 20% reduction, and no reduction, in the rate of progression to AIDS; and (3) annual HIV incidence between 1993 and 1997 was fixed at levels of 600 and 300 new infections respectively.

Approximate upper and lower 95% confidence limits for projected AIDS incidence between 1995 Q1 and 1998 Q4 were calculated including both modelling uncertainties (by taking the upper and lower limits on predicted AIDS incidence given by the sensitivity analyses) and random variability (by adding or subtracting twice the square root of the mean square log relative error for each quarter).

Estimating the reduction in the number of AIDS diagnoses

Point estimates of the reduction in the number of AIDS diagnoses following the widespread availability of new combination antiretroviral treatments since 1995, and estimates of the increased number of AIDS-free person-years lived, were obtained by subtracting the observed delay-adjusted quarterly AIDS counts during 1995 to 1997 from the projected AIDS incidence given by the preferred back-projections. Variances were estimated by combining the mean square log errors of the observed delay-adjusted AIDS counts and the predicted AIDS counts using the Delta method [20].

Results

Back-projections were based on the 6004 AIDS diagnoses to the end of 1994 reported to the National AIDS Registry by the end of March 1999. All back-projection sensitivity analyses gave very similar fits to the observed AIDS incidence data during 1993 and 1994. Although, as expected, there was some divergence of projections during 1995 to 1998, reflecting modelling uncertainty, all analyses consistently projected a slow decline in AIDS incidence over this time period (data not shown).

In Fig. 1 the observed delay-adjusted AIDS incidences are compared with the preferred projections of AIDS incidence if new treatments had not reduced the rate of progression to AIDS over the period 1994 to 1998. Although the observed delay-adjusted AIDS incidence were generally lower than the projections between 1995 Q1 and 1996 Q3, the observed counts were still within the 95% confidence intervals for the projected counts. However, between 1996 Q4 and 1998 Q4, the

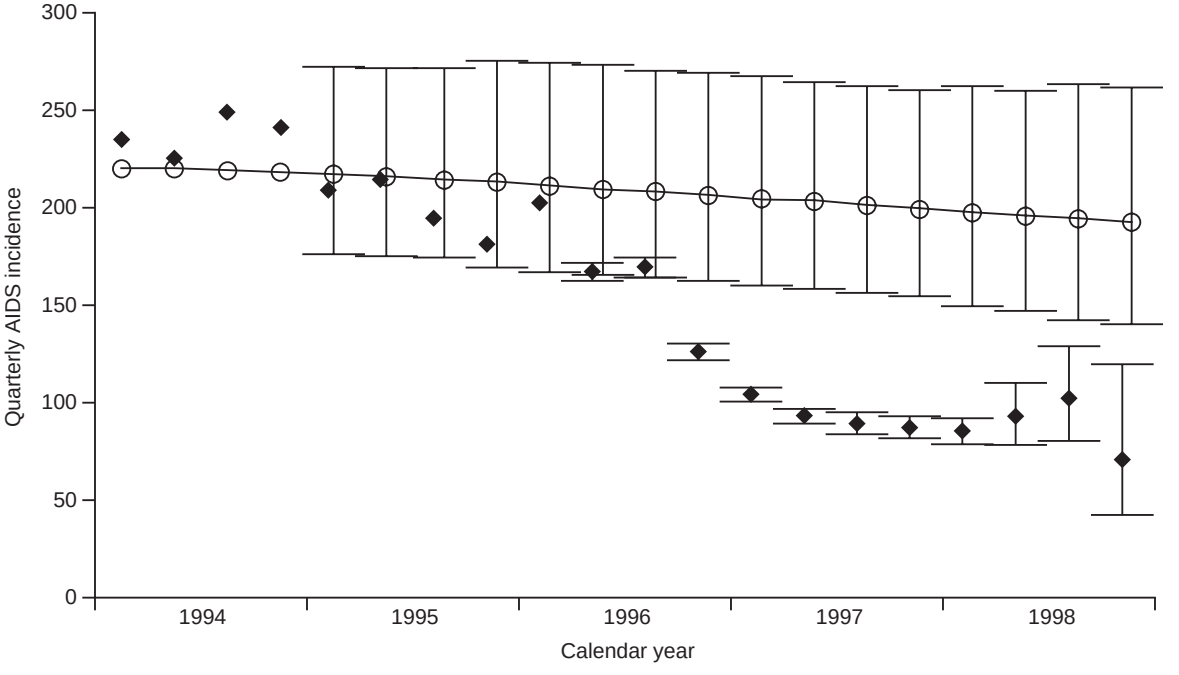

Fig. 1. Observed delay-adjusted AIDS incidence, and projected AIDS incidence, 1994–1998. Upper and lower bars on vertical lines identify 95% confidence limits; black diamonds identify delay-adjusted counts; open circles identify the best estimate of projected AIDS incidence assuming that new treatments had not further reduced the rate of progression to AIDS.

observed AIDS incidence were clearly lower than the projections of AIDS incidence.

Overall, between 1995 and 1998, AIDS incidence was estimated to have been 1093 (33%) diagnoses fewer than would have been projected if new antiretroviral treatments had not reduced the rate of progression to AIDS (95% confidence interval (CI) 831 to 1425 diagnoses (25 to 43%); see Table 1). The majority of the decrease in AIDS incidence was estimated to have occurred in 1997 (434 cases) and 1998 (427 cases). The overall increase in AIDS-free person-years lived was estimated to be 1462 years (95% CI 946 to 2148) years. The increase in AIDS-free person-years was again largest for AIDS diagnoses in 1997 and 1998 (a total of 857 person-years).

Discussion

These analyses show that there have been fewer AIDS diagnoses in Australia since 1995 than would have been expected if new combination antiretroviral treatments had not further reduced the rate of progression to AIDS, even though a slow decline in AIDS incidence had been predicted for 1995 to 1998. It was estimated that AIDS incidence has been reduced by 1093 cases (33%) between 1995 and 1998 [95% CI 831 (25%) to 1425 (43%) cases]. This study appears to be the first to show a national decline in AIDS incidence that is far more substantial than would have been expected without any improvement in treatments.

The majority of the reduction in AIDS incidence was estimated to have occurred since mid-1996 (see Fig. 1), coincident with the widespread availability of protease inhibitors in Australia. Data from the Sydney Men and Sexual Health Study, a cohort study of homosexually active men, indicate that among HIV positive participants the proportion of respondents reporting that they were receiving three or more antiretroviral treatments in combination increased from 12% in the first 6 months of 1996 to 40% in the second 6 months of that year, and to 57 and 72%, respectively, in the first and second 6-month periods of 1997 [18]. This study also found that the proportion reporting that they were receiving a protease inhibitor increased from 11 and 45% in the first and second 6-month periods of 1996 to 52 and 68%, respectively, in the corresponding 6-month periods of 1997.

Although the observed decline in AIDS incidence in Australia has been coincident with the availability of new combination antiretroviral treatments, and in particular the steep decline in AIDS incidence since mid-1996 is coincident with the widespread use of combination antiretroviral treatments including protease inhibitors, it is not possible to ascribe the observed reduction in AIDS incidence entirely to the use of treatments. There may have been as yet unknown factors other than new treatments which had some effect in reducing the rate of progression to AIDS in Australia over this period. Furthermore, these analyses are based on national AIDS surveillance data, and some of the observed decrease in AIDS incidence may reflect changes in patterns of either diagnosis or reporting. However, the availability of improved antiretroviral treatments, and particularly the use of protease inhibitors which coincided with the large decrease in AIDS incidence seen in Australia during the second half of 1996, appears to be the most likely explanation for at least a substantial proportion of the reduction in AIDS incidence.

Table 1. Observed and projected annual AIDS incidence, estimated reduction in number of AIDS diagnoses, and estimated increased number of AIDS-free person-years lived, in Australia 1995–1998.

Year	Observed annual AIDS incidence[a]	Projected AIDS incidence[b]	Reduction (%) in AIDS diagnoses (95% CI)[c]	Increased AIDS-free person-years[d] (95% CI)[c]
1995	798	860	62 (−33 to 179) 7% (−4 to 21%)[e]	206 (−124 to 615)
1996	664	834	170 (67 to 302) 20% (8 to 36%)[e]	399 (141 to 731)
1997	373	807	434 (325 to 562) 54% (40 to 70%)[e]	646 (481 to 842)
1998	351	778	427 (291 to 573) 55% (37 to 74%)[e]	211 (142 to 287)
Overall	2186	3279	1093 (831 to 1425) 33% (25 to 43%)[e]	1462 (946 to 2148)

[a]Adjusted for reporting delays; [b]best estimate of projected AIDS incidence assuming that new treatments had not further reduced the rate of progression to AIDS; [c]95% confidence interval; [d]AIDS-free person-years to end of 1998, by year of AIDS diagnosis; [e]percentage reductions in AIDS diagnoses.

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