Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study

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Abstract

Objectives: To examine trends in disease progression and survival among patients enrolled in the Swiss HIV cohort study during 1988-96 and to assess the influence of new antiretroviral combination therapies.
Design: Prospective multicentre study, with follow up visits planned at six monthly intervals.
Setting: Seven HIV units at university centres and cantonal hospitals in Switzerland.
Patients: 3785 men (mean age 35.0 years) and 1391 women (30.3 years) infected with HIV. 2023 participants had a history of intravenous drug misuse; 1764 were men who had sex with men; 1261 were infected heterosexually; and 164 had other or unknown modes of transmission. 601 participants had had an AIDS defining illness.
Results: During more than 15 000 years of follow up, there were 1456 first AIDS defining diagnoses and 1903 deaths. Compared with those enrolled during 1988-90, the risk of progression to a first AIDS diagnosis was reduced by 18% (relative risk 0.82 (95% confidence interval 0.73 to 0.93)) among participants enrolled in 1991-2, by 23% (0.77 (0.65 to 0.91)) among those enrolled in 1993-4, and by 73% (0.27 (0.18 to 0.39)) among those enrolled in 1995-6. Mortality was reduced by 19% (0.81 (0.73 to 0.90)), 26% (0.74 (0.63 to 0.87)), and 62% (0.38 (0.25 to 0.97)) respectively. Compared with no antiretroviral treatment, the risk of an initial AIDS diagnosis after CD4 lymphocyte counts fell to <200 cells $\times 10^6$/l was reduced by 16% (0.84 (0.73 to 0.97)) with monotherapy, 24% (0.76 (0.63 to 0.91)) with dual therapy, and 42% (0.58 (0.37 to 0.92)) with triple therapy. Mortality was reduced by 23% (0.77 (0.68 to 0.88)), 31% (0.69 (0.60 to 0.80)), and 65% (0.35 (0.20 to 0.60)) respectively.
Conclusions: The introduction of antiretroviral combination therapies outside the selected patient groups included in clinical trials has led to comparable reductions in disease progression and mortality.

Introduction

Antiretroviral treatment of HIV infection has undergone important changes recently. On the basis of trials showing that a combination of two nucleoside analogues was better than zidovudine alone,[1–4] dual drug therapy became the recommended initial treatment regimen in 1996.[5] More recently triple drug therapy including a protease inhibitor and two nucleoside analogues led to prolonged suppression of plasma HIV concentrations to undetectable levels,[6] which translated into substantial benefit in trials with clinical endpoints.[7 8] Regimens including at least two drugs that aim to reduce and maintain viral plasma concentrations below detectable levels are widely considered to represent the current standard of antiretroviral treatment.[9 10]

In 1997 a decline in the mortality of patients with AIDS and in the number of new cases of AIDS has been observed in routine data collected in several countries, including the United States,[11] France,[12] and Switzerland.[13] These trends have been attributed to the advances in antiretroviral treatment and to a decline in the number of new cases of HIV infection. Routine surveillance collects only limited information, however, and generally lacks follow up data. Reporting delays, changes in definitions of reportable events, and under-reporting can introduce bias that could entirely or partly explain such trends.[13 14]

The Swiss HIV cohort study, set up in 1988, is a large, prospective, community based study of people infected with HIV.[15] We examined the database to determine what changes had occurred in progression rates and survival and to what extent these trends correlate with the introduction of antiretroviral combination therapies.

Patients and methods

The Swiss HIV cohort study

The Swiss HIV cohort study continually enrols patients with HIV infection aged 17 years or over. The study design has been described in detail elsewhere.[15 16] Patients are followed in one of seven study centres (Basle, Berne, Geneva, Lausanne, Lugano, St Gall, and Zurich). Enrolment is independent of stage of disease or degree of immunosuppression, and information is collected according to standardised criteria on structured forms at enrolment and at follow up visits at six monthly intervals. The follow up questionnaire includes a detailed history of disease associated with HIV. The month for starting and discontinuing drugs are recorded, and laboratory tests are performed. Laboratories run regular quality controls to assure comparability of results. AIDS was defined according to category C clinical conditions of the 1993 revised classification system for HIV infection.[17]

Prospective data collection started in September 1988. The database analysed includes information recorded up to 6 February 1997, by which time 6918 participants had been enrolled. For the current analysis 1742 participants who could not be followed up after enrolment were excluded, leaving 5176 participants (74.8% of those enrolled). Age and sex distributions were similar for those included and

excluded, but those who were excluded had higher CD4 lymphocyte counts.

Statistical analysis

Participants were classified into four groups according to the date of enrolment—1988-90, 1991-2, 1993-4, and 1995-6. Baseline characteristics across groups were compared by analysis of variance and χ^2 tests for heterogeneity. Skewness in the distribution of CD4 cell count required a logarithmic transformation for statistical evaluation.

The proportion of participants who at some point during follow up were treated with antiretroviral monotherapy or with combination therapies was calculated for each group. The difference between the first and last CD4 cell count was calculated for each period. Results were expressed as mean changes (in cells $\times 10^6$/l) a year.

Disease progression and survival

Kaplan-Meier estimates of the cumulative probability of progression to a first AIDS diagnosis and death were calculated for the four enrolment periods. We chose the first CD4 cell count $<200\times10^6$/l or $<50\times10^6$/l as time zero in these analyses. For progression to AIDS we measured time from the date at time zero either to the date of the first AIDS defining event or to the date of the most recent follow up visit. For analyses of survival, time was calculated as the period between time zero and death, or, for those still alive, between time zero and 6 August 1996. This date takes into account up to six months' delay in reporting of deaths. A log rank χ^2 test was used to test for equality of rates across time periods. Patients who progressed to AIDS or died with a CD4 count $>200\times10^6$/l were excluded from these analyses.

Cox's proportional hazards regression models[18 19] were used for multivariate analysis of the risk of progression to a first diagnosis of AIDS or death in different enrolment periods. Time was measured from the date of enrolment. Models were adjusted for CD4 cell count, age, disease stage, and history of intravenous drug misuse. Interaction terms were introduced to examine whether period effects differed between age, sex, and transmission groups.

Separate Cox's models were calculated to examine the influence of antiretroviral treatments. The beneficial effects of treatments may be overestimated because patients who survive longer are more likely to get treated even if the treatment is ineffective.[20 21] To prevent such bias, we modelled treatments as time dependent covariates. Treatment variables took the value 0 before the start of treatment and switched to 1 as soon as treatment was started. Models used an "intention to continue treatment" approach.[20] Values were therefore not changed back to 0 when treatment was discontinued or changed. Because patients whose disease is rapidly progressing are more likely to get treated at any time, bias in the opposite direction may be introduced. To reduce the effect of such bias, additional analyses were performed, with time being measured from the date of the first CD4 cell count $<200\times10^6$ or of the first AIDS defining event. Models examining the effect of antiretroviral treatment were adjusted for CD4 cell count at enrolment, age, disease stage, history of intravenous drug misuse, use of prophylaxis against opportunistic infections, and year of enrolment.

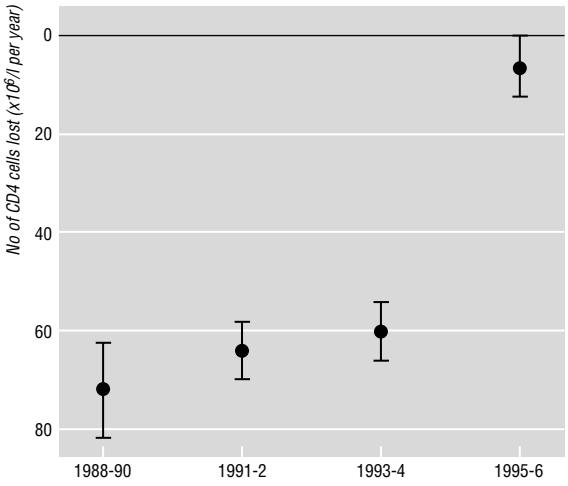

Fig 1 Mean number of CD4 cells lost per year in each time period

The validity of the proportional hazards assumption in Cox's models was assessed by examining plots of the cumulative incidence, on a logarithmic scale, stratified by categories of the variables of interest. We assumed proportionality if the curves appeared parallel. Results are presented as relative risks (hazard ratios), with 95% confidence intervals. Analyses were conducted with the SAS computer program (version 6.11, Cary, NC, USA).

Results

Of the 5176 participants included in the analysis, 2059 (39.8%) were enrolled during 1988-90, 1541 (29.8%) during 1991-2, 877 (16.9%) during 1993-4, and 699 (13.5%) during 1995-6. Over 15 000 person years of follow up were accumulated, with a mean follow up per participant of 2.9 years. There were 3691 category C clinical events, 1456 first AIDS defining events, and 1903 deaths.

Table 1 shows the participants' characteristics at baseline. Mean age at entry increased over time. The proportion of participants presumably infected

Table 1 Baseline characteristics of participants enrolled in different time periods. Values are numbers (percentages) of participants unless stated otherwise

	1988-90 (n=2059)	1991-2 (n=1541)	1993-4 (n=877)	1995-6 (n=699)	P value*
Mean (SD) age (years)	32.5 (8.5)	33.7 (8.9)	34.8 (9.5)	36.2 (9.3)	<0.001
Sex:					0.9
Male	1504 (73.0)	1120 (72.7)	648 (73.9)	513 (73.4)	
Female	555 (27.0)	421 (27.3)	229 (26.1)	186 (26.6)	
Transmission group:					<0.001
Men who have sex with men	673 (30.9)	503 (32.6)	330 (37.6)	258 (36.9)	
Intravenous drug users	948 (46.0)	621 (40.3)	271 (30.9)	183 (26.2)	
Heterosexual transmission	427 (20.7)	367 (23.8)	242 (27.6)	225 (32.2)	
Other/unknown	47 (2.4)	50 (3.2)	34 (3.9)	33 (4.7)	
Median (90% range) CD4 lymphocyte count ($\times10^6$/l)	340 (50-839)	310 (40-760)	265 (30-740)	210 (20-610)	<0.001
Clinical stage:					0.07
A	1239 (60.2)	942 (63.3)	506 (57.7)	392 (56.1)	
B	584 (28.4)	446 (28.9)	255 (29.1)	211 (30.2)	
C	236 (11.5)	153 (9.9)	116 (13.2)	96 (13.7)	

*By analysis of variance or χ^2 test.

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Table 2 Use of antiretroviral treatment for participants enrolled in different time periods. Values are numbers (percentages) of patients unless stated otherwise

	1988-90	1991-2	1993-4	1995-6	P value*
Mean (SD) follow up (years)†	3.8 (2.2)	3.1 (1.6)	2.1 (0.8)	0.9 (0.4)	
Antiretroviral treatment:					
None	791 (38.4)	568 (36.9)	307 (35.0)	170 (24.3)	<0.001
Monotherapy	1198 (58.2)	889 (57.7)	505 (57.6)	309 (44.2)	<0.001
Dual therapy	343 (16.7)	421 (27.3)	345 (39.4)	422 (60.4)	<0.001
Triple therapy	103 (5.0)	107 (6.9)	109 (12.4)	154 (22.0)	<0.001

Percentages exceed 100% because categories of antiretroviral treatments are non-exclusive.
The same patient may have received first monotherapy then dual or triple therapy at a later stage.
*Probability by χ^2 test.
†Censored at last follow up visit.

through intravenous drug misuse decreased from 46.0% in 1988-90 to 26.2% in 1995-6. The proportion of participants with presumed heterosexual transmission, however, increased from 20.7% to 32.2%. Median CD4 cell counts at enrolment declined from 340 cells $\times 10^6$/l to 210 cells $\times 10^6$/l.

Use of antiretroviral treatments

Table 2 shows use of antiretroviral monotherapy (in most cases zidovudine) and combination therapies (several nucleoside analogues and, more recently, protease inhibitors) during follow up. The proportion of participants using dual or triple therapies in 1995-6 was much greater than in earlier years. Only a minority of the patients enrolled before 1995 had received combination therapies.

Changes in CD4 cell counts

Figure 1 shows changes in CD4 cell count. The mean number of cells $\times 10^6$/l lost per year amounted to 72 during 1988-90, 64 during 1991-2, 60 in 1993-4, but only 6 in 1995-6. Among the 220 patients with a first CD4 cell count <50 cells $\times 10^6$/l in 1995-6, the last count was higher than this level in 93 (42%) patients. Such an increase was rare in previous periods, occurring in only 12 out of 136 (9%) patients in the same group in 1993-4.

Life table estimates of survival and progression to AIDS

Of the 4069 participants who joined the study with a CD4 cell count <200 cells $\times 10^6$/l or whose cell count declined to this level during follow up, 2544 (62.5%) had not developed AIDS, compared with 938 (37.2%) of the 2520 participants who joined with <50 cells $\times 10^6$/l or whose cell count declined to this level during follow up.

Figure 2 shows progression rates to a first AIDS diagnosis. Median survival without AIDS after the first CD4 cell count <200 cells $\times 10^6$/l was estimated at 22 months in 1988-90 and 30 months in 1993-4. A marked reduction in the probability of progression to AIDS was observed for 1995-6, with an estimated 82% still free of AIDS at 23 months. Disease progression after a CD4 cell count <50 cells $\times 10^6$/l was uniformly high during the first three periods, with an estimated median survival time without AIDS of about 10 months. This rate was again markedly reduced in 1995-6, with an estimated 59% free of AIDS at 18 months.

Median survival from <200 CD4 cells $\times 10^6$/l was 29 months in 1988-90, increasing to 38 months in 1993-4 (fig 3). For participants enrolled in 1995-6 median survival could not be determined, but it was estimated that 87% would be alive at 18 months. Median survival from <50 cells $\times 10^6$/l was estimated at about 18 months for the three earlier periods. The data for 1995-6 again show a reduction in mortality, with 65% of participants alive at 18 months.

Multivariate analyses

Table 3 shows the results from multivariate Cox regression models. Results reflect what was observed in the life table analysis (figs 2 and 3): some improvement during 1991-2 and 1993-4 and a more pronounced reduction in risk in the most recent period. Compared with 1988-90, the risk of AIDS was reduced by 73% in 1995-6 (relative risk 0.27 (95% confidence interval 0.18 to 0.39), $P<0.001$), and the risk of death by 62% (0.38 (0.25 to 0.59), $P<0.001$). There were no significant interactions between period of enrolment and age, sex, or transmission group.

Table 4 shows relative risk estimates for progression to AIDS and death from proportional hazards models according to use of antiretroviral monotherapy, dual therapy, and triple therapy. Patients who had never received such treatment served as the reference group. All estimates were adjusted for relevant baseline variables and also for use of prophylaxis against opportunistic infections. Estimates varied according to the time from which progression was measured. If progression was measured from the date of enrolment, a significant ($P=0.008$) increase in the risk of AIDS was observed among patients treated with

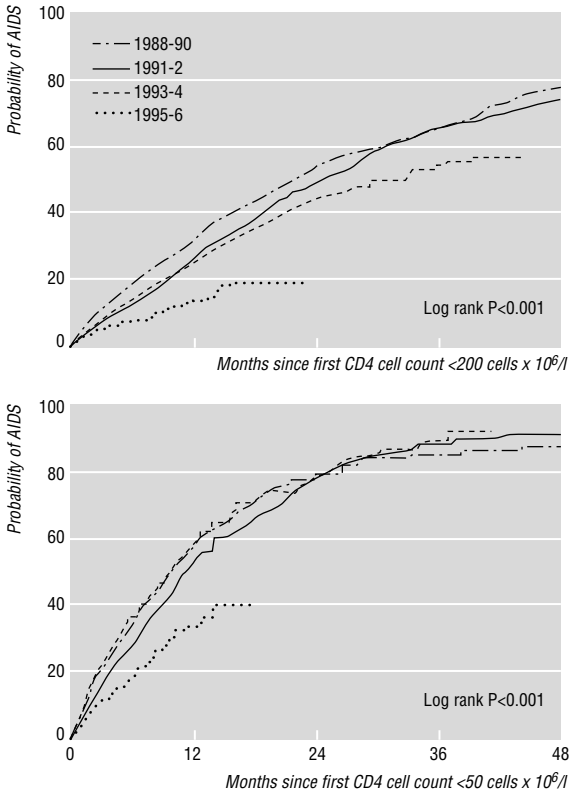

Fig 2 Kaplan-Meier life table estimates of progression to AIDS from first CD4 cell count <200 cells×10^6/l (top) and from first CD4 cell count <50 cells×10^6/l (bottom). Period relates to calendar year of CD4 cell count

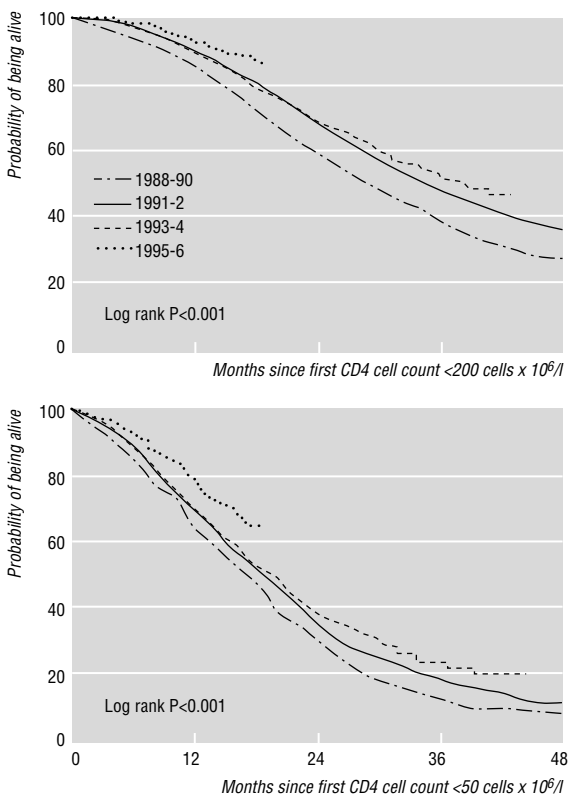

Fig 3 Kaplan-Meier life table estimates of progression to death from first CD4 cell count below 200 cells×10^6/l (top) and from first CD4 cell count <50 cells×10^6/l (bottom). Period relates to calendar year of CD4 cell count

antiretroviral monotherapy. Conversely, significant ($P < 0.05$) reductions in risk were seen if progression was measured from the first CD4 cell count $< 200 \times 10^6$/l, with combination therapies showing larger effects than monotherapy. Monotherapy did not seem to reduce mortality if progression was measured from the date of enrolment. If time was measured from the first CD4 cell count below 200×10^6/l or from the first AIDS defining illness, however, mortality reductions were seen for all treatments.

Discussion

The Swiss HIV cohort study is one of the largest cohorts of HIV infected individuals worldwide. It includes a large number of participants from each of the three predominant transmission groups as well as many women. No stringent inclusion and exclusion criteria exist, and the cohort includes a large proportion of all reported AIDS cases in Switzerland.[15] Participants in the study are thus likely to be representative of HIV infected patients in general practice. The analyses presented here suggest a marked reduction in progression rates during 1995-6. Both the risk of a first AIDS defining event and the risk of death were less than half of what was observed among patients enrolled in earlier years of the study. These reductions were similar for men and women and for different age and transmission groups.

The trends observed in CD4 cell counts among those enrolled in 1995-6 are in accordance with these findings. Although cell counts continued to decline in some patients, substantial increases were observed in others, and for the group of participants enrolled in 1995-6 as a whole, the steady loss of cells that characterised earlier periods was brought to a halt.

Table 3 Risk of progression to AIDS and to death in different enrolment periods

Progression to:	No of patients	No (%) of patients developing AIDS or dying	Relative risk (95% CI)*
AIDS:			
1988-90	1823	788 (43.2)	1.0 (reference)
1991-92	1388	482 (34.7)	0.82 (0.73 to 0.93)
1993-94	761	179 (23.5)	0.77 (0.65 to 0.91)
1995-96	603	36 (6.0)	0.27 (0.18 to 0.39)
Death:			
1988-90	2059	1071 (52.0)	1.0 (reference)
1991-92	1541	607 (39.4)	0.81 (0.73 to 0.90)
1993-94	877	204 (23.3)	0.74 (0.63 to 0.87)
1995-96	699	21 (3.0)	0.38 (0.25 to 0.59)

Time was measured from the date of enrolment.
*From proportional hazards regression models adjusted for CD4 cell count at enrolment, age, clinical stage, and history of intravenous drug misuse.

Evidence from clinical trials

The introduction of antiretroviral combination therapies is the most likely explanation for the marked improvements observed. This interpretation is supported by evidence from clinical trials comparing nucleoside analogue monotherapy with combination therapies. Compared with zidovudine alone, a combination of either didanosine or zalcitabine plus zidovudine reduced progression to AIDS or death by up to 35%,[1–3] and the combination of lamivudine and zidovudine led to reductions of around 60%.[4 22] In most trials beneficial effects were more pronounced among patients with little or no prior exposure to zidovudine.[1 2 4] More recently the addition of a potent protease inhibitor to two nucleoside analogues has been shown to lead to further important reductions in the risk of disease progression.[7–8]

Problems and potentials of observational studies

In the Swiss HIV cohort study the use of antiretroviral treatment was also associated with substantial benefit. Estimates of treatment effects from observational studies, may, however, be biased in various ways. For exam-

Table 4 Risk of progression to AIDS and to death, according to use of antiretroviral monotherapy and combination therapies

Progression to:	No of patients	Relative risk (95% CI)*		
		Monotherapy	Dual therapy	Triple therapy
AIDS				
Time measured from:				
Enrolment	4575	1.25 (1.06 to 1.48)	0.61 (0.52 to 0.72)	0.39 (0.21 to 0.71)
First CD4 cell count <200×10^6/l	2544	0.84 (0.73 to 0.97)	0.76 (0.63 to 0.91)	0.58 (0.37 to 0.92)
Death				
Time measured from:				
Enrolment	5176	1.09 (0.94 to 1.27)	0.72 (0.61 to 0.84)	0.35 (0.19 to 0.64)
First CD4 cell count <200×10^6/l	4069	0.77 (0.68 to 0.88)	0.69 (0.60 to 0.80)	0.35 (0.20 to 0.60)
First AIDS defining diagnosis	2610	0.85 (0.74 to 0.98)	0.67 (0.57 to 0.78)	0.37 (0.21 to 0.65)

Relative risks (hazard ratios) are derived from proportional hazards regression models with treatments modelled as time dependent covariates.
All models were adjusted for CD4 cell count at enrolment, age, clinical stage, history of intravenous drug misuse, use of prophylaxis against opportunistic infections, and year of enrolment.
*Reference group is "no therapy."

ple, rapidly progressing patients are likely to get treated sooner, and treatment may thus become a marker of a worse prognosis. Indeed, antiretroviral monotherapy was associated with faster progression when progression was measured from the time of enrolment. When the first CD4 cell count $<200\times10^6$/l or the first AIDS defining diagnosis was taken as the point of departure, the beneficial effect of monotherapy became evident. In this group of immunodeficient patients antiretroviral treatment was uniformly recommended throughout the study period, and selection bias was therefore unlikely. Other cohort studies have also shown a beneficial, although transient, effect of zidovudine monotherapy.[23 24] The effect of different treatment strategies will depend on the type of drug or drug combinations used and on previous exposure to antiretrovirals. We could not examine this in the present database, but such analyses will become possible as more person time accumulates.

Observational studies have an important role in the evaluation of treatment strategies in HIV infection.[25] The outcomes of interest—disease progression, survival, and long term toxicity—require trials with prolonged observation periods. Owing to the availability of new and potentially better drugs, however, results from such trials may be obsolete by the time they are completed. The use of surrogate end points, such as the course of CD4 cell counts and of plasma viral load, will mean that trials need not be so large or lengthy but can lead to erroneous conclusions.[26] For example, in the Concorde trial of zidovudine in individuals without symptoms, higher CD4 cell counts in the immediate compared to the deferred treatment group did not translate into a significant clinical benefit.[27] Viral load clearly is an important prognostic marker, but it does not seem to capture completely the effect of treatments on clinical outcomes.[28 29] Finally, observational data may in the future be better able to contribute to defining the optimum time to start treatment and when best to switch to another treatment strategy.

Conclusion

Our findings show that the introduction of antiretroviral combination therapies outside the selected patient groups included in clinical trials has so far led to comparable reductions in disease progression and mortality. The crucial question is whether these improvements will last. The emergence of resistant HIV variants remains a serious threat with combination therapies.[30] Suppression of viraemia to undetectable levels is feasible over prolonged periods of time if treatment regimens are adhered to,[6] and this will reduce the emergence of resistant strains. However, given the potential adverse effects and the complex and inflexible dosing schemes that need to be followed, strict adherence is hard to achieve for many patients.

The treatment strategies that have substantially improved prognosis of HIV infection in Switzerland over the past two years, and which hopefully will lead to sustained improvements in the future, are currently unavailable to most HIV infected people living in countries with poor resources. Initiatives are now needed to address this situation. It is equally if not more important that efforts to prevent new infections continue unabated, both in industrialised and in less developed countries.

Key messages

- The Swiss HIV cohort study is an ongoing prospective study that includes a large proportion of the patients infected with HIV in Switzerland
- Antiretroviral combination therapy with two nucleoside analogues was introduced in 1995, and triple therapy with protease inhibitors was introduced in 1996
- The risk of AIDS and death was substantially lower among patients enrolling in 1995 and 1996 than among those enrolled in earlier years
- Reductions in disease progression were similar among men and women and among patients from different transmission groups
- In Switzerland the introduction of antiretroviral combination therapies outside selected patient groups included in clinical trials has led to similar reductions in disease progression

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Helicobacter pylori infection and mortality from ischaemic heart disease: negative result from a large, prospective study

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Abstract

Objective—To determine whether there is an independent association between *Helicobacter pylori* infection of the stomach and ischaemic heart disease.
Design—Prospective study with measurement of IgG antibody titres specific to *H pylori* on stored serum samples from 648 men who died from ischaemic heart disease and 1296 age matched controls who did not (nested case-control design).
Subjects—21 520 professional men aged 35-64 who attended the British United Provident Association (BUPA) medical centre in London between 1975 and 1982 for routine medical examination.
Main outcome measure—Death from ischaemic heart disease.
Results—The odds of death from ischaemic heart disease in men with *H pylori* infection relative to that in men without infection was 1.06 (95% confidence interval 0.86 to1.31). In a separate group of 206 people attending the centre, plasma fibrinogen was virtually the same in those who were positive for *H pylori* (2.62 g/l) and those who were negative (2.64 g/l).
Conclusions—A study that by its size and design minimised both random error and socioeconomic bias found no relation between *H pylori* infection and ischaemic heart disease. The validity of the study was shown by its confirmation of the recognised association between *H pylori* infection and stomach cancer (odds ratio 4.0 (1.9 to 8.2); $P < 0.001$). Eradication of *H pylori* infection may greatly reduce the incidence of stomach cancer, one of the most common causes of death from cancer worldwide, but it cannot be expected to have any effect in preventing ischaemic heart disease.

Introduction

Mendall et al showed an association between *Helicobacter pylori* infection of the stomach and ischaemic heart disease in 1994-5,[1 2] and 18 studies have reported on the relationship over the subsequent two years.[3–20] The position remains uncertain, an assessment supported by a recent review.[21] Since the risk of acquiring *H pylori* infection in childhood increases with socioeconomic deprivation and overcrowding,[3 22] the association may be indirect; *H pylori* infection and ischaemic heart disease are both related to social class. Some studies have shown little or no excess risk,[4–9] but others reported a fourfold to fivefold increased risk without adjustment for measures of social class and other risk factors for ischaemic heart diseases[10–11] or a twofold to threefold increased risk after such adjustment.[1–3]

We report the results of an investigation using a prospective study of the determinants of major chronic disease.This study is well suited to determine whether there is an independent relationship between *H pylori* infection and ischaemic heart disease. With 648 deaths from ischaemic heart disease it is much the largest study to report on the association. The likelihood of an indirect association arising through social class differences is minimised by the homogeneity of the study population: the subjects were all professional men attending for a routine medical examination. Random error and systematic error are therefore likely to be small.

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