# Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study

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## Summary

**Background** **Evidence on the effectiveness of highly active antiretroviral therapy (HAART) for HIV-infected individuals is limited. Most clinical trials examined surrogate endpoints over short periods of follow-up and there has been no placebo-controlled randomised trial of HAART. Estimation of treatment effects in observational studies is problematic, because of confounding by indication. We aimed to use novel methodology to overcome this problem in the Swiss HIV Cohort Study.**

**Methods** **Patients were included if they had been examined after January 1996, when HAART became available in Switzerland, were not on HAART, and were free of AIDS at baseline. Cox regression models were weighted to create a statistical population in which the probability of being treated at each time point was unrelated to prognostic factors.**

**Results** **Low CD4 counts and increasing HIV-1 viral load were associated with increased probability of starting HAART. Overall hazard ratios were 0·14 (95% CI 0·07–0·29) for HAART compared with no treatment, and 0·49 (0·31–0·79) compared with dual therapy. Compared with no treatment, HAART became more beneficial with increasing time since initiation but was less beneficial for patients whose presumed mode of transmission was via intravenous drug use (hazard ratio 0·27, 0·12–0·61) than for other patients (0·08, 0·03–0·19).**

**Interpretation** **Our results, which are appropriately controlled for confounding by indication, are consistent with reported declines in rates of AIDS and death in developed countries, and provide a context in which to consider adverse effects of HAART.**

## Introduction

Highly active antiretroviral therapy (HAART) is a combination of at least three drugs, typically including either a protease inhibitor or a non-nucleoside analogue reverse transcriptase inhibitor, and two nucleoside analogue reverse transcriptase inhibitors. Randomised trials have shown substantial reductions in disease progression in HIV-1-infected patients treated with HAART compared with those treated with dual therapy with two nucleoside analogue reverse transcriptase inhibitors,[1,2] although such evidence has several limitations. Most trials[3] have focused on increase in CD4 count and virological response after starting treatment, but these measures are imperfect surrogates for clinical progression to AIDS or death.[4,5] In many studies, follow-up was restricted to a year or less, but current treatments have to be taken for life. For ethical reasons, there has been no placebo-controlled randomised trial of HAART. The effectiveness of this treatment over several years is therefore unknown.

Such information is of obvious importance to patients and their carers and is necessary for a better understanding of the course of disease in patients treated with HAART, and to plan health services. Without trial evidence, this information must come from observational cohort studies. However, estimation of treatment effects in observational studies is not straightforward, because of time-dependent confounders (risk factors varying with time and predicting initiation of treatment) that are also affected by treatment.[6,7] For example, CD4 count is a time-dependent confounder for the effect of HAART, because patients with lower counts are more likely to be treated. CD4 count is also affected by HAART, and is thus intermediate on the causal pathway from such treatment to AIDS or death. In this situation, a type of confounding by indication,[8] standard approaches such as Cox regression will yield biased estimates of the effect of treatment.[6,9] We aimed to use novel methodology—marginal structural models[9]—to overcome this problem and estimate the effectiveness of HAART over several years.

## Methods

### Study design and participants

Participants in the Swiss HIV Cohort Study,[10,11] who were examined after January 1996, when HAART became available in Switzerland, were potentially eligible for analysis. Clinical AIDS diagnoses (Centers for Disease Control and Prevention [CDC] stage C) were made by the treating physicians on the basis of the 1993 CDC criteria.[12] The baseline month was that of the first follow up visit after January, 1996, during which all variables were available. Patients who died or refused further participation before 1996, who were on HAART or in clinical stage C at baseline, or whose treatment history before joining the cohort was uncertain were excluded. Data were organised by monthly intervals containing the earliest measurement of CD4 count, HIV-1 RNA, and

haemoglobin in that month. When no new measurement was made, the latest observation was carried forward. Additionally, each record contained indicator variables describing whether the patient was treated with monotherapy (one nucleoside analogue reverse transcriptase inhibitor), dual therapy (two such drugs), or HAART (at least two such drugs plus a protease inhibitor or non-nucleoside reverse transcriptase inhibitor or abacavir) during the month, and whether the patient had a CDC stage B event during the month. Until 1999, only the month, rather than the precise date, of starting therapy was recorded. We therefore assumed that patients started therapy at the end of the previous month: this assumption produced more conservative estimates of the effect of HAART than if precise dates were used (data not shown). Once a patient was on any therapy, we assumed he or she remained on it.

### Statistical analysis

We used weighted Cox proportional hazards models to estimate hazard ratios for progression to AIDS or death, controlling for time-dependent confounding. These models estimate the parameters of marginal structural models.[13] The weights are based on the inverse of each patient's probability of the treatment history they actually had, given their covariate history. The weighted analysis creates a statistical population in which the probability of being treated at each time is unrelated to the measured prognostic factors (the time-dependent confounders). Because these confounders are controlled by the weights rather than by inclusion as covariates in the Cox models, this approach avoids the problem that such confounders could also be intermediate on the causal pathway from HAART to the outcome of AIDS or death. Follow up ended when AIDS or death occurred, the patient was lost to follow up (defined as withdrawal from the study or a gap of more than 8 months since their last follow-up visit), or September, 2003, whichever came first. We estimated the effect of HAART on progression to AIDS or death in separate analyses in which the comparison groups were restricted to untreated individuals and individuals treated with dual therapy. For the first analysis, patients were excluded if they had been treated with monotherapy or dual therapy before January, 1996, and censored if they began monotherapy or dual therapy subsequently. For the second analysis, observation time started at Jan 1, 1996, or at the month after the patient was first treated with dual therapy, whichever was later.

We estimated the probability of treatment with HAART using a pooled logistic regression in which the outcome was treatment with HAART (of patients not already on such treatment). The covariates were CD4 count, concentration of HIV-1 RNA, haemoglobin, and CDC stage B events, together with lagged and baseline values of these variables, time since January 1996, baseline age, sex, and presumed transmission group. Lagged values were those 3 months previously (corresponding to the scheduled time between study visits): hence patients did not contribute follow-up time until 4 months after all variables had been first measured. We also modelled the effect of having experienced a CDC stage B event at any time before the present month on the probability of starting HAART. CD4 was modelled with cubic splines (with knots at the 5th, 25th, 50th, 75th, and 95th percentiles) calculated separately for each 2-year period, because the association of CD4 with starting HAART varied with calendar time. The use of cubic splines allowed for a non-linear

| | N (%) | Rate of clinical progression (per 100 person-years) | |
|---|---|---|---|
| | | On HAART | Not on HAART* |
| Total | 3245 | 2·5 | 3·5 |
| **Age at baseline (years)** | | | |
| 15–29 | 720 (22%) | 1·9 | 2·9 |
| 30–39 | 1699 (52%) | 2·8 | 3·5 |
| 40–49 | 575 (18%) | 2·1 | 4·1 |
| ⩾50 | 251 (8%) | 2·8 | 4·6 |
| **Sex** | | | |
| Male | 2144 (66%) | 2·5 | 3·8 |
| Female | 1101 (34%) | 2·5 | 3·2 |
| **Risk group** | | | |
| MSM | 926 (29%) | 1·5 | 3·3 |
| Heterosexual | 1098 (34%) | 1·7 | 2·6 |
| IDU | 1114 (34%) | 4·4 | 4·5 |
| Other | 107 (3%) | 3·2 | 4·0 |
| **Calendar year at baseline** | | | |
| 1996 | 1525 (47%) | 6·2 | 5·1 |
| 1997 | 528 (16%) | 3·6 | 4·2 |
| 1998 | 229 (7%) | 1·9 | 3·5 |
| 1999 | 227 (7%) | 2·4 | 4·1 |
| 2000 | 215 (7%) | 2·1 | 2·9 |
| 2001 | 221 (7%) | 2·1 | 2·9 |
| 2002 | 177 (5%) | 2·9 | 3·0 |
| 2003 | 123 (4%) | 2·6 | 1·7 |
| **CD4 count at baseline (cells per μL)** | | | |
| 0–49 | 77 (2%) | 7·2 | 37·7 |
| 50–99 | 92 (3%) | 4·5 | 28·5 |
| 100–199 | 349 (11%) | 3·7 | 8·3 |
| 200–349 | 772 (24%) | 1·9 | 4·4 |
| 350–499 | 791 (24%) | 2·5 | 2·8 |
| 500–749 | 762 (23%) | 1·3 | 1·9 |
| ⩾750 | 402 (12%) | 2·4 | 1·2 |
| **RNA at baseline (copies per mL)** | | | |
| <400 | 427 (13%) | 1·1 | 1·0 |
| 400–1000 | 238 (7%) | 2·9 | 0·9 |
| 1001–10 000 | 994 (31%) | 1·8 | 2·3 |
| 10 001–100 000 | 1182 (36%) | 3·0 | 5·0 |
| >100 000 | 404 (12%) | 3·9 | 13·5 |
| Not on monotherapy at baseline | 2132 (66%) | 2·2 | 3·6 |
| On monotherapy at baseline | 1113 (34%) | 2·7 | 3·3 |
| Not on dual therapy at baseline | 2205 (68%) | 2·3 | 3·7 |
| On dual therapy at baseline | 1040 (32%) | 2·6 | 3·1 |
| No CDC stage B event at or before baseline | 2306 (71%) | 2·0 | 2·7 |
| CDC stage B event at or before baseline | 939 (29%) | 3·1 | 6·0 |

*Patients' time on no treatment, monotherapy, or dual therapy. MSM=men who have sex with men. IDU=intravenous drug use.

*Table 1:* **Baseline characteristics, and crude rates of progression to AIDS or death during follow up**

association between CD4 and probability of starting HAART, without strong parametric assumptions about the shape of the nonlinear relation. HIV-1 RNA was grouped according to standard cut-off points (400, 1000, 10 000, 100 000 copies per mL), and the model also contained an interaction between detectable current RNA and detectable lagged RNA. Haemoglobin measurements were grouped into fifths, separately in men and women. Inverse probability weights were stabilised and modified to adjust for censoring.[9] We estimated the parameters of weighted Cox models using a pooled logistic model[14] in which the change in baseline hazard with time was modelled with cubic splines. We derived conservative 95% CIs using robust standard errors adjusted for within-patient clustering. Analyses were done using Stata version 8.2: a detailed account of the code used to derive the weights and fit the models has been published.[15] SAS programs can be found online.

See http://www.hsph.harvard.edu/causal

| | Patients not previously treated | | Patients on dual therapy | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | Wald p value | Hazard ratio (95% CI) | Wald p value |
| **Risk group** | | | | |
| MSM | 1 (reference) | <0·0001 | 1 (reference) | <0·0001 |
| Heterosexual | 1·15 (0·92–1·44) | | 0·84 (0·69–1·02) | |
| IDU | 0·75 (0·61–0·93) | | 0·66 (0·55–0·79) | |
| Other | 1·54 (1·00–2·39) | | 1·25 (0·89–1·76) | |
| **Current CD4 count (cells per μL)** | | | | |
| 0–49 | 1 (reference) | <0·0001 | 1 (reference) | <0·0001 |
| 50–99 | 0·94 (0·40–2·21) | | 1·05 (0·56–1·97 | |
| 100–199 | 0·47 (0·21–1·03) | | 0·79 (0·43–1·46) | |
| 200–349 | 0·16 (0·07–0·36) | | 0·67 (0·36–1·27) | |
| 350–499 | 0·05 (0·02–0·12) | | 0·40 (0·21–0·77) | |
| 500–749 | 0·03 (0·01–0·06) | | 0·30 (0·15–0·60) | |
| ⩾750 | 0·02 (0·01–0·07) | | 0·29 (0·13–0·64) | |
| **Lagged CD4 count (cells per μL)** | | | | |
| 0–49 | 1 (reference) | <0·0001 | 1 (reference) | 0·19 |
| 50–99 | 1·35 (0·47–3·89) | | 1·22 (0·64–2·32) | |
| 100–199 | 2·85 (1·09–7·41) | | 0·98 (0·52–1·83) | |
| 200–349 | 6·33 (2·38–16·83) | | 0·82 (0·43–1·58) | |
| 350–499 | 8·42 (3·14–22·61) | | 0·97 (0·50–1·91) | |
| 500–749 | 11·66 (4·24–32·12) | | 1·17 (0·58–2·37) | |
| ⩾750 | 7·90 (2·56–24·31) | | 0·95 (0·43–2·13) | |
| **Current RNA (copies per mL)** | | | | |
| <400 (undetectable) | 0·27 (0·13–0·57) | <0·0001 | 0·17 (0·11–0·24) | 0·0006 |
| 400–1000 | 0·15 (0·07–0·34) | | 0·31 (0·21–0·45) | |
| 1001–10,000 | 0·22 (0·15–0·33) | | 0·57 (0·41–0·79) | |
| 10 001–100 000 | 0·49 (0·37–0·63) | | 0·99 (0·73–1·35) | |
| >100 000 | 1 (reference) | | 1 (reference) | |
| **Lagged RNA (copies per mL)** | | | | |
| <400 (undetectable) | 1·30 (0·60–2·81) | 0·06 | 1·71 (1·18–2·47) | <0·0001 |
| 400–1000 | 1·54 (0·74–3·20) | | 1·23 (0·83–1·83) | |
| 1001–10 000 | 1·75 (1·20–2·56) | | 1·30 (0·93–1·81) | |
| 10 001–100 000 | 1·43 (1·08–1·89) | | 0·96 (0·70–1·32) | |
| >100 000 | 1 (reference) | | 1 (reference) | |
| CDC stage B event before current month | 1·27 (1·06–1·51) | 0·009 | 1·06 (0·92–1·21) | 0·46 |
| CDC stage B event during current month | 0·23 (0·06–0·95) | 0·04 | 0·29 (0·07–1·17) | 0·08 |
| Lagged CDC stage B event | 2·04 (1·04–4·00) | 0·04 | 0·78 (0·31–1·95) | 0·59 |

Hazard ratios and robust 95% CIs derived with pooled logistic regression model. MSM=men who have sex with men. IDU=intravenous drug use.

*Table 2:* **Association of prognostic factors with starting HAART**

**Role of the funding source**

The study sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

2161 patients contributed person-time to the comparison of HAART with no treatment, and 1276 to the comparison of HAART with dual therapy (192 patients contributed to both comparisons). 400 (12%) progressed to AIDS or death and 1705 (53%) were ever treated with HAART. Median follow-up was 54 months (IQR 20–84). Total observation time was 13 562 patient-years, of which 7145 (53%) were time on HAART. Overall progression rates per 100 person-years were lower for patients on HAART than for those who were not (crude rate ratio 0·70, 95% CI 0·58–0·86; table 1). Rates were substantially higher in patients with low baseline CD4 counts or high baseline HIV-1 RNA, especially when not on HAART. Rates increased with age, were raised in patients with presumed transmission via intravenous drug use, and declined with later year of enrolment. Patients who had had a CDC stage B event at or before baseline had a higher rate of progression to death or AIDS than those who had not.

Of 2161 patients included in analyses of HAART versus no treatment, 202 (9%) progressed to AIDS or death. There were 54 events in 2261 person-years on HAART, compared with 148 events in 4063 person-years not on HAART (crude rate ratio 0·79, 95% CI 0·61–1·03). Median follow-up was 27 months (IQR 8–60). For analyses of HAART versus dual therapy, 196 (15%) of 1276 patients progressed to AIDS or death. There were 126 events in 4871 person-years on HAART, compared with 70 events in 2187 person-years on dual therapy (crude rate ratio 0·80, 95% CI 0·60–1·08). Median follow-up was 80 months (IQR 53–85).

Table 2 shows hazard ratios and 95% CIs for the most important predictors of initiation of HAART. Patients with presumed transmission via intravenous drug use were less likely to start such treatment. Prognostic factors such as CD4 count were more strongly associated with starting HAART for patients not treated previously than for patients already on dual therapy. Low current CD4 count was strongly associated with starting HAART. For previously untreated patients, high lagged CD4 count was associated with a greater probability of starting HAART than low lagged CD4 count, indicating that the decision to start such treatment was based on both current CD4 and change in CD4 over the previous 3 months.[16] Higher current RNA, lagged RNA, and occurrence of CDC stage B events during the current and previous months were associated with starting HAART.

Table 3 shows hazard ratios for progression to AIDS or death, estimated with weighted Cox models. HAART reduced the rate of AIDS or death compared with no treatment (rate reduction 86%) or with dual therapy (51%). Hazard ratios from unweighted models including time-updated confounders were 0·64 (0·42–0·98) for the comparison with no treatment and 0·75 (0·51–1·11) for the comparison with dual therapy. Corresponding results from unweighted models including only confounders measured at baseline were 0·36 (0·23–0·56) and 0·69 (0·46–1·02). The figure compares hazard ratios estimated using standard methods (unweighted Cox models) and marginal structural models (weighted Cox models). As expected, estimates of the effect of HAART from weighted models were stronger than those from unweighted models, because the weighted models adjust for the measured confounding by indication without including the time-dependent covariates. The extent of confounding by indication seemed greater for the comparison with no therapy than for the comparison with dual therapy.

Compared with no treatment, HAART became more beneficial with increasing time since initiation. The hazard ratio for the comparison with no treatment 2 or more years after initiation was 0·04, indicating persistently low progression rates with HAART but increasing progression rates for patients who remained untreated. Compared with no treatment, HAART seemed less beneficial for patients with presumed transmission via intravenous drug use than for other patients (interaction p=0·01). Compared with both no treatment and dual therapy, the beneficial effect of HAART was greater in patients whose baseline CD4 count was less than 200 cells per μL. Compared with no treatment, HAART was less effective for women than for men, though the evidence for interaction was weak (p=0·13). There was little evidence that the effect of HAART varied with age.

| | HAART versus no treatment (2161 patients, 202 events) | | HAART versus dual therapy (1276 patients, 196 events) | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | p (interaction) | Hazard ratio (95% CI) | p (interaction) |
| Overall effect | 0·14 (0·07–0·29) | | 0·49 (0·31–0·79) | |
| 0–12 months | 0·45 (0·23–0·87) | | 0·65 (0·39–1·09) | |
| 13–24 months | 0·23 (0·11–0·49) | 0·0001 | 0·59 (0·29–1·23) | 0·053 |
| >24 months | 0·04 (0·01–0·09) | | 0·28 (0·15–0·53) | |
| Non-IDU | 0·08 (0·03–0·19) | 0·01 | 0·47 (0·26–0·84) | 0·74 |
| IDU | 0·27 (0·12–0·61) | | 0·53 (0·29–0·97) | |
| Baseline CD4 ⩾200 | 0·19 (0·09–0·41) | 0·005 | 0·61 (0·34–1·10) | 0·15 |
| Baseline CD4 <200 | 0·04 (0·01–0·12) | | 0·36 (0·20–0·66) | |
| 1996–97 | 0·20 (0·06–0·72) | | 0·56 (0·31–1·03) | |
| 1998–99 | 0·23 (0·10–0·51) | 0·66 | 0·35 (0·15–0·78) | 0·65 |
| 2001–02 | 0·12 (0·04–0·37) | | 0·62 (0·20–1·94) | |
| 2003–04 | 0·11 (0·03–0·36) | | 0·72 (0·24–2·15) | |
| Age <40 | 0·15 (0·07–0·34) | 0·66 | 0·58 (0·34–1·00) | 0·075 |
| Age ⩾40 | 0·12 (0·04–0·32) | | 0·29 (0·15–0·59) | |
| Men | 0·11 (0·05–0·24) | 0·13 | 0·49 (0·29–0·80) | 0·9 |
| Women | 0·26 (0·09–0·78) | | 0·51 (0·24–1·10) | |

IDU=intravenous drug use.

***Table 3:*** **Comparison of HAART versus no treatment or dual therapy for progression to AIDS or death**

## Discussion

Our results indicate that HAART reduced the rate of progression to AIDS or death by 86%, and that its effectiveness compared with no treatment increased with time since initiation. Because most HIV-1 infected patients starting HAART will not have been treated previously, estimates of its effectiveness compared with no treatment are required by patients and their clinicians, especially in view of possible adverse effects.[17] The widespread use of potent antiretroviral therapy since 1996 has substantially improved the outcomes of HIV-infected patients.[18–20] The very large benefits of HAART possible in developed countries provide a context for the debate about the relative cost-effectiveness of treatment compared with prevention in sub-Saharan Africa.[21]

The method used in this study required us to model the probability of starting HAART according to prognostic variables. An important strength of the Swiss HIV Cohort Study is that recorded values of prognostic markers are precisely those used by physicians to decide when to initiate therapy. We estimate that HAART is more beneficial than reported in a previous analysis using the same methods.[22] That analysis used data from studies[23,24] in which the prognostic factors recorded by the cohort were generally different from those used by treating physicians, which may result in residual confounding by indication.[22] The validity of the method depends on all prognostic factors that predict initiation of therapy being recorded, and their relation with starting HAART being correctly modelled. Potentially prognostic factors such as the presence or absence of comorbidities or the physical appearance of the patient could influence treatment decisions but are not recorded. In the context of treatment for HIV, we think it reasonable to assume that the most important prognostic variables that are determinants of treatment have been recorded.

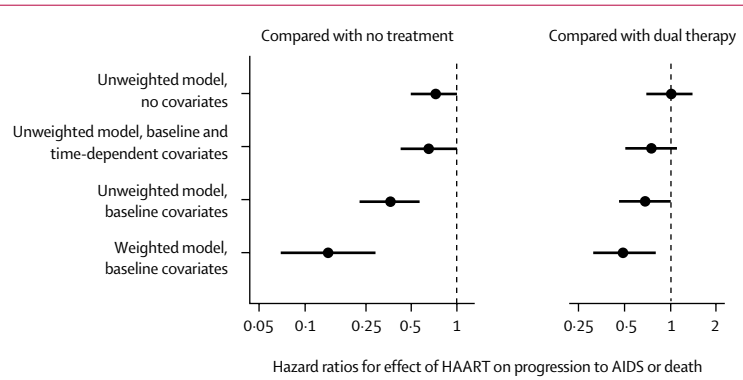


***Figure:*** **Estimated effect of HAART from unweighted (standard) and weighted Cox models**
Weighted model with baseline covariates estimates parameters of marginal structural model. Weights adjust for confounding due to measured time-dependent covariates.

Our results depend on the assumption that treated and untreated individuals with the same values of measured prognostic factors were similar. Prospective information about the reasons that patients remain untreated is not recorded in the database, so we cannot address this issue directly. Antiretroviral therapy is free in Switzerland, so patients will not remain untreated for economic reasons. Most patients are cared for in teaching hospitals, with physicians providing care under the supervision of senior colleagues, so patients are unlikely to remain untreated at low CD4 counts unless they explicitly refuse treatment. We cannot exclude the possibility that such patients have poor prognosis, but we know of no evidence that this is or is not the case.

We assumed that once on therapy a patient remains on therapy. Therefore our estimates are analogous to intention-to-treat estimates commonly reported in analyses of randomised controlled trials. The proportion of patients who ever interrupted HAART was small: for example in the comparison with no treatment, 87% of patients who started treatment did not interrupt it. Formally, our analysis estimated the effect of HAART therapy versus no such therapy in a hypothetical randomised clinical trial in which participants were randomly assigned to begin continuous HAART at different visits, all participants initially complied and began such treatment at their assigned visit, but 13% later interrupted or discontinued it. If many of the patients in the study that interrupted HAART did so because of toxic effects (rather than for non-medical reasons), it is this intention-to-treat effect, and not the effect of continuous HAART use, that would be the matter of public-health interest. Had we estimated the effect of continuous HAART, we would have been estimating the effect of forcing people to continue therapy, even in the presence of toxicity. We know that some reasons for interruption were unrelated to toxicity (for example, 8% of patients who interrupted therapy were participants in a trial of treatment interruption in patients with high CD4 counts), and our estimates may therefore be conservative compared with the effect of continuous treatment.

Marginal structural models can be used to estimate the effect of continuous treatment rather than the intention-to-treat estimate. To do so would require estimating the probability of receiving treatment for every person at all times and therefore we would need, in addition to our model for the probability of starting HAART, a model for the probability of discontinuing such treatment. The validity of the estimated effect of continuous HAART would then depend on the assumption that there are no unmeasured confounders of treatment discontinuation, and no mis-specification of this additional model: our analysis avoided these assumptions. Factors leading to treatment discontinuation are less well understood and less well measured than factors leading to treatment initiation: we therefore chose not to pursue this type of analysis.

Our results are consistent with the results of randomised controlled trials comparing HAART with dual therapy: for example the hazard ratio estimated in the AIDS Clinical Trials Group 320 trial was 0·50 (95% CI 0·33–0·76).[1] A meta-analysis estimated the odds ratio for AIDS or death comparing HAART with dual therapy as 0·6 (0·5–0·8).[3] However, trials of HAART versus dual therapy reported only short treatment periods, since continued follow-up was unethical. Our results suggest that the superiority of HAART over dual therapy increases with time since initiation.

We used a combined endpoint of AIDS or death from all causes, which has been widely used in clinical HIV/AIDS research. We would have liked to examine the two endpoints separately. In the era of HAART an increasing proportion of deaths is not associated with recent AIDS-defining events, and the current definition of AIDS is no longer a near-complete marker for overall progression. We could not do so for two reasons: the number of deaths during follow-up was small, and good information on causes of deaths is lacking in the Swiss and other cohort studies.[25]

Previous analyses of observational studies may have underestimated the effect of HAART, because time-dependent confounders affected by treatment were not correctly taken into account. For example, a 1997 report from the Swiss HIV Cohort study,[17] comparing HAART with no therapy, estimated the relative risks of progression to AIDS as 0·39 and to death as 0·35. A widely cited analysis from the HIV Outpatient Study (HOPS),[26] reported in 1998, estimated the hazard ratio for mortality and morbidity as 0·22 for patients with CD4 counts less than 100 cells per μL. The estimated relative hazard for HAART compared with no treatment in the Tuscany AIDS cohort[27] was 0·36, whereas a comparison of the results of three observational studies with those from randomised trials estimated the relative risk for HAART compared with dual therapy as 1·20 in one cohort.[28] We acknowledge that factors other than time-dependent confounding could have contributed to the differences in results. Several studies have analysed the risk of disease progression or death by calendar year or treatment period.[17,26,29] This method reduces confounding by indication under the assumption that HAART is the only variable responsible for changes in prognosis over time, but does not provide a direct estimate of treatment effectiveness. The introduction of HAART has been accompanied by a sharp decline in mortality and AIDS incidence in surveillance data, but these trends might be confounded by changes in the incidence of HIV infection and by reporting delays and under-reporting.[30,31]

The effect of HAART that we estimated did not vary greatly according to patient characteristics, except that it

may have been less beneficial in patients infected via intravenous drug use. There are several possible explanations for this finding. First, adherence to HAART is likely to be worse in this group:[32] physicians' concerns over poor adherence, with its consequences for development of drug resistance, may also explain the fact that these patients were less likely to start HAART (table 2). Independent of HIV infection, patients infected via intravenous drug use are known to be at increased risk of death from overdose and violent causes[33] and are more likely to be coinfected with hepatitis C virus.[34]

Compared with no treatment, HAART became more beneficial with increasing duration of therapy, which is expected considering declines in CD4 counts and increasing risk of opportunistic events without therapy. Surprisingly, there was little evidence for a change in the effectiveness of HAART over calendar time. The increasing experience of treating physicians and the availability of new drugs might have been counterbalanced by adverse factors such as increasing prevalence of strains that are resistant to common drugs or by evolutionary changes in virulence of HIV.[35,36] Clearly, it will be important to monitor trends in the effectiveness of HAART in coming years.

Although the method we used to adjust for confounding by indication has been used before, for example when assessing the effect of disease-modifying antirheumatic therapy with methotrexate for rheumatoid arthritis,[37] it is not widely used in clinical research. The reason may be that in many situations the factors determining treatment decisions are not well standardised or measured; HIV/AIDS is exceptional in this respect. Also, the method may not be widely known in the clinical research community. More applications are needed to clarify its place in clinical research.

#### Contributors

J A C Sterne, M A Hernán, and M Egger conceived the study and wrote the first draft of the report. All authors contributed to the final draft. J A C Sterne and M A Hernán did the analyses with assistance and advice from K Tilling, B Ledergerber, and J M Robins. R Weber and P Sendi contributed to data interpretation. B Ledergerber and M Rickenbach extracted the data for the Swiss HIV Cohort Study and prepared them for analysis.

#### The Swiss HIV Cohort Study

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#### Conflict of interest statement

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#### References

1 Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997; **337:** 725–33.

2 Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet* 1998; **351:** 543–49.

3 Jordan R, Gold L, Cummins C, Hyde C. Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy. *BMJ* 2002; **324:** 757.

4 Hughes MD, Daniels MJ, Fischl MA, Kim S, Schooley RT. CD4 cell count as a surrogate endpoint in HIV clinical trials: a meta-analysis of studies of the AIDS Clinical Trials Group. *AIDS* 1998; **12:** 1823–32.

5 HIV Surrogate Marker Collaborative Group. Human immunodeficiency virus type 1 RNA level and CD4 count as prognostic markers and surrogate end points: a meta-analysis. *AIDS Res Hum Retroviruses* 2000; 16: 1123–33.

6 Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000; **11:** 561–70.

7 Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004; **15:** 615–25.

8 Walker AM. Confounding by indication. *Epidemiology* 1996; **7:** 335–36.

9 Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the joint causal effect of nonrandomised treatments. *J Am Stat Assoc* 2001; **96:** 440–48.

10 Ledergerber B, von Overbeck J, Egger M, Luthy R. The Swiss HIV cohort study: rationale, organization and selected baseline characteristics. *Soz Praeventivmed* 1994; **39:** 387–94.

11 Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. *Lancet* 1999; **353:** 863–68.

12 Centers for Disease Control. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992; **41:** 1–20.

13 Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; **11:** 550–60.

14 D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med* 1990; **9:** 1501–15.

15 Fewell Z, Hernan MA, Wolfe F, Tilling K, Choi H, Sterne JAC. Controlling for time-dependent confounding using marginal structural models. *Stata J* 2004; **4:** 402–20.

16 Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. *BMJ* 1999; **319:** 245–49.

17 Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; **349:** 1993–2003.

18 Egger M, Hirschel B, Francioli P, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. *BMJ* 1997; **315:** 1194–99.

19 Hogg RS, Yip B, Kully C, et al. Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. *CMAJ* 1999; **160:** 659–65.

20 Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998; **352:** 1725–30.

21 Marseille E, Hofmann PB, Kahn JG. HIV prevention before HAART in sub-Saharan Africa. *Lancet* 2002; **359:** 1851–56.

22 Cole SR, Hernan MA, Robins JM, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *Am J Epidemiol* 2003; **158:** 687–94.

23 Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk F, Rinaldo CR. The multicenter AIDS cohort study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol* 1987; **126:** 310–18.

24 Barkan SE, Melnick SL, Preston-Martin S, et al. The women's interagency HIV study. *Epidemiology* 1998; **9:** 117–25.

25 Egger M, May M, Chêne G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002; **360:** 119–29.

26 Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; **338:** 853–908.

27 Pezzotti P, Napoli PA, Acciai S, et al. Increasing survival time after AIDS in Italy: the role of new combination antiretroviral therapies. Tuscany AIDS Study Group. *AIDS* 1999; **13:** 249–55.

28 Phillips AN, Grabar S, Tassie JM, Costagliola D, Lundgren JD, Egger M. Use of observational databases to evaluate the effectiveness of antiretroviral therapy for HIV infection: comparison of cohort studies with randomized trials. EuroSIDA, the French Hospital Database on HIV and the Swiss HIV Cohort Study Groups. *AIDS* 1999; **13:** 2075–82.

29 Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003; **362:** 22–29.

30 Gebhardt M, Rickenbach M, Egger M. Impact of antiretroviral combination therapies on AIDS surveillance reports in Switzerland. *AIDS* 1998; **12:** 1195–201.

31 Vittinghoff E, Scheer S, O'Malley P, Colfax G, Holmberg SD, Buchbinder SP. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. *J Infect Dis* 1999; **179:** 717–20.

32 Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0·200 to 0·350×$10^9$ cells/L. *Ann Intern Med* 2003; **139:** 810–16.

33 Selwyn PA, Hartel D, Wasserman W, Lost D. Impact of the AIDS epidemic on morbidity and mortality among intravenous drug users in a New York City methadone maintenance program. *Am J Public Health* 1989; **79:** 1358–62.

34 Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000; **356:** 1800–05.

35 Hirsch MS. HIV drug resistance: a chink in the armor. *N Engl J Med* 2002; **347:** 438–39.

36 Levin BR, Bull JJ, Stewart FM. Epidemiology, evolution, and future of the HIV/AIDS pandemic. *Emerg Infect Dis* 2001; **7**(suppl 3)**:** 505–11.

37 Choi HK, Hernán MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; **359:** 1173–77.