

# Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies

Matthias Egger, Margaret May, Geneviève Chêne, Andrew N Phillips, Bruno Ledergerber, François Dabis, Dominique Costagliola, Antonella D'Arminio Monforte, Frank de Wolf, Peter Reiss, Jens D Lundgren, Amy C Justice, Schlomo Staszewski, Catherine Leport, Robert S Hogg, Caroline A Sabin, M John Gill, Bernd Salzberger, Jonathan A C Sterne, and the ART Cohort Collaboration\*

## Summary

**Background** Insufficient data are available from single cohort studies to allow estimation of the prognosis of HIV-1 infected, treatment-naïve patients who start highly active antiretroviral therapy (HAART). The ART Cohort Collaboration, which includes 13 cohort studies from Europe and North America, was established to fill this knowledge gap.

**Methods** We analysed data on 12 574 adult patients starting HAART with a combination of at least three drugs. Data were analysed by intention-to-continue-treatment, ignoring treatment changes and interruptions. We considered progression to a combined endpoint of a new AIDS-defining disease or death, and to death alone. The prognostic model that generalised best was a Weibull model, stratified by baseline CD4 cell count and transmission group.

**Findings** During 24 310 person-years of follow up, 1094 patients developed AIDS or died and 344 patients died. Baseline CD4 cell count was strongly associated with the probability of progression to AIDS or death: compared with patients starting HAART with less than 50 CD4 cells/ $\mu$ L,

adjusted hazard ratios were 0.74 (95% CI 0.62–0.89) for 50–99 cells/ $\mu$ L, 0.52 (0.44–0.63) for 100–199 cells/ $\mu$ L, 0.24 (0.20–0.30) for 200–349 cells/ $\mu$ L, and 0.18 (0.14–0.22) for 350 or more CD4 cells/ $\mu$ L. Baseline HIV-1 viral load was associated with a higher probability of progression only if 100 000 copies/mL or above. Other independent predictors of poorer outcome were advanced age, infection through injection-drug use, and a previous diagnosis of AIDS. The probability of progression to AIDS or death at 3 years ranged from 3.4% (2.8–4.1) in patients in the lowest-risk stratum for each prognostic variable, to 50% (43–58) in patients in the highest-risk strata.

**Interpretation** The CD4 cell count at initiation was the dominant prognostic factor in patients starting HAART. Our findings have important implications for clinical management and should be taken into account in future treatment guidelines.

*Lancet* 2002; **360**: 119–29

## Introduction

The widespread use since 1996 of highly active antiretroviral therapy (HAART)—a combination of at least three drugs that typically includes either a protease inhibitor (PI) or a non-nucleoside-analogue reverse-transcriptase inhibitor (NNRTI) and two nucleoside-analogue reverse-transcriptase inhibitors (NRTIs)—has substantially improved the prognosis of HIV-1-infected patients.<sup>1–3</sup> However, accurate estimates of the probability of clinical progression in treatment-naïve men and women of different ages and exposure categories, according to different levels of immunodeficiency and viral replication, are not available at present. Information on prognosis is of obvious importance to patients and is also required to gain a better understanding of the treated history of HIV-1 infection, to develop treatment guidelines, to monitor and predict the progress of the HIV/AIDS epidemic, and to plan health services in the era of HAART. Such data are also important as a basis for comparisons with treatment outcomes in resource-poor settings, once HAART becomes more widely available in less developed countries.<sup>4</sup>

The analysis by Mellors and colleagues<sup>5</sup> of homosexual men enrolled in the Multicenter AIDS Cohort Study (MACS) who had frozen plasma samples on which HIV-1 RNA concentration (viral load) could be measured was influential in defining prognosis according to levels of viral load and CD4 cell count in the pre-HAART era. The Collaborative Group on AIDS Incubation and Survival provided precise estimates of the time from HIV-1 seroconversion to AIDS and death according to age at seroconversion and exposure category before the advent of HAART.<sup>6</sup> In these studies, a large proportion of patients developed AIDS during extended periods of follow-up. In the era of HAART, the relatively small number of patients who experience clinical progression on therapy, and the limited length of follow-up since

\*Members of the study groups who made this collaboration possible are listed at end of paper

**Department of Social and Preventive Medicine, University of Bern, CH-3012 Bern, Switzerland** (Prof M Egger MD); **Department of Social Medicine, University of Bristol, Bristol, UK** (M May MSc, J A C Sterne PhD); **INSERM U330, Université Victor Seglen, Bordeaux, France** (Prof G Chêne PhD, Prof F Dabis MD); **Department of Primary Care and Population Sciences, Royal Free and University College Medical School, London, UK** (Prof A N Phillips PhD, C A Sabin PhD); **Division of Infectious Diseases and Hospital Epidemiology, University of Zurich, Zurich, Switzerland** (B Ledergerber PhD); **INSERM EMI 0214, Centre Hospitalière Universitaire Pitié Salpêtrière, Paris, France** (D Costagliola PhD); **Institute of Infectious and Tropical Diseases, University of Milan, Milan, Italy** (Prof A D'Arminio Monforte MD); **HIV Monitoring Foundation and National AIDS Therapy Evaluation Centre, Academic Medical Centre of the University of Amsterdam, Amsterdam, Netherlands** (P Reiss MD); **HIV Monitoring Foundation, Amsterdam, Netherlands, and Department of Infectious Disease Epidemiology, Imperial College School of Medicine, London, UK** (F de Wolf MD); **Department of Infectious Diseases, Hvidovre University Hospital, Hvidovre, Denmark** (J D Lundgren MD); **VA Pittsburgh Healthcare System, Section of General Internal Medicine, Pittsburgh, PA, USA** (A C Justice PhD); **Zentrum der Inneren Medizin, J W Goethe Universität, Frankfurt, Germany** (S Staszewski MD); **Service des Maladies Infectieuses et Tropicales, Hôpital Bichat-Claude Bernard, Paris, France** (Prof C Leport MD); **Division of Epidemiology and Population Health, BC Centre for Excellence in HIV/AIDS, Vancouver, Canada** (R S Hogg PhD); **Division of Infectious Diseases, University of Calgary, Calgary, Canada** (MJ Gill MD); **Klinik I für Innere Medizin, Klinikum Universität Regensburg, Regensburg, Germany** (Prof B Salzberger MD)

**Correspondence to:** Prof Matthias Egger (e-mail: [egger@ispm.unibe.ch](mailto:egger@ispm.unibe.ch))

HAART became widely used, mean that the statistical power to define prognosis is limited even in large prospective studies. At present, no single cohort study can provide accurate estimates of progression to AIDS or death from initiation of HAART for treatment-naive patients at different levels of risk. Numerous analyses of trials and observational databases have focused on the increase in CD4 cell counts and virological response after commencing HAART, but these are imperfect surrogate endpoints for clinical progression.<sup>7,8</sup>

We report the results from the Antiretroviral Therapy (ART) Cohort Collaboration—an international collaboration between the investigators of 13 cohort studies from Europe and North America that was established to bring together a large body of data on clinical progression in treatment-naive patients starting HAART.

## Methods

### Eligibility of cohorts and patients

Prospective cohort studies were eligible if they had enrolled at least 100 patients with HIV-1 infection aged 16 years or older who had not previously received antiretroviral treatment (treatment-naive) and who had started antiretroviral therapy with a combination of at least three drugs, including NRTIs, PIs, and NNRTIs, with a median duration of follow-up of at least 1 year. One CD4 T-cell count (CD4 count) and one measurement of viral load 0–3 months before starting therapy were also required. Investigators from 16 cohort studies were approached; 13 agreed to collaborate.<sup>1,2,9–19</sup> All of the studies have been approved by local ethics committees or institutional review boards, use standardised methods of data collection, and schedule follow-up visits at least once every 6 months.

### Endpoints

We considered the probability of progression to a combined endpoint of an AIDS-defining disease or death and to death alone. In both definitions, we included deaths from all causes. We used the clinical part of the 1993 Centers for Disease Control and Prevention revision of the AIDS case definition (ie, people without an AIDS-defining disease but with a CD4 cell count below 200 cells/ $\mu$ L were not classified as having AIDS).<sup>20</sup> We examined progression to non-fatal AIDS events in sensitivity analyses.

### Data extraction and statistical analysis

Patients were selected and data extracted at the data centres of the participating cohort studies. Anonymised data on a predefined set of demographic, laboratory, and clinical variables were then pooled and analysed centrally. The EuroSIDA study may include patients who are also members of the other cohort studies. We therefore asked cohort data managers to provide the EuroSIDA study identification for patients also enrolled in EuroSIDA, which allowed exclusion of duplicate records. In all analyses, we used an “intent-to-continue-treatment” approach and thus ignored subsequent changes to treatment, including treatment interruptions and terminations. We measured time from the start of HAART to the date the endpoints occurred. In patients free of events, the same censoring strategy was used for all cohorts: for the combined endpoint, follow-up was censored on the date of the most recent follow-up visit, for mortality on the date the patient was last known to be alive. We modelled the instantaneous rate (hazard) of progression to AIDS or death according to baseline CD4 cell count, using kernel density smoothing of the Nelson-Aalen cumulative hazard function which was differentiated to give the estimated hazard function. We also derived bias-corrected bootstrap CIs for the estimated hazard functions by use of 2000 bootstrap replications.

### Development of prognostic models

A backwards stepwise selection procedure, based on Weibull proportional hazards models, was used to choose prognostic variables and their categorisation. A variable was omitted if the Wald p value was greater than 0.2. We then looked for evidence of interactions between the prognostic variables, and examined whether models allowing time-varying effects of the baseline measurements fitted better. Candidate interactions and time-varying effects were chosen for consideration in different prognostic models if the Wald p value for the likelihood ratio test was less than 0.05.

Candidate prognostic models were parametric survival models based on the Weibull, loglogistic, and lognormal distributions. The Weibull model assumes proportional hazards and the loglogistic model proportional odds for the covariate effects. The hazard function for these three survival distributions is either monotonically increasing or

	Reference	Country	Number of centres	Year of start of study	Interval between follow-up visits (months)	Number of patients included in analysis	Number of person-years of follow-up for progression to:	
							AIDS or death	Death
French Hospital Database on HIV (FHDH)	9	France	68	1989	6	4739	7601	7986
Italian Cohort of Antiretroviral-Naive Patients (ICONA)	10	Italy	65	1997	6	1641	2627	2763
Swiss HIV Cohort Study (SHCS)	1	Switzerland	7	1988	6	1268	2267	2431
AIDS Therapy Evaluation project Netherlands (ATHENA)	11	Netherlands	22	1998	3–4	919	2314	2457
EuroSIDA	12	20 in Europe	60	1994	6	840	1797	1981
Collaborations in HIV Outcomes Research US (CHORUS)	13	USA	4	1997	~2	601	1345	1435
Frankfurt HIV Cohort	14	Germany	1	1988	1–2	553	1310	1441
Antiprotease Cohort (APROCO)	15	France	47	1997	4	538	1068	1143
Aquitaine Cohort	16	France	5	1987	3–6	486	786	825
British Columbia Centre for Excellence in HIV/AIDS*	2	Canada	1	1992	1–2	422	495	846
Royal Free Hospital Cohort	17	UK	1	1993	~3	321	480	552
South Alberta Clinic	18	Canada	1	1989	2–3	154	271	300
Köln/Bonn Cohort	19	Germany	2	1995	3	92	133	150

\*Antiretroviral therapy is distributed centrally from a tertiary AIDS care hospital in Vancouver to pharmacies, clinics, and physicians located through British Columbia.

Table 1: Characteristics of cohort studies participating in the ART Cohort Collaboration

	Value	Number of events*	Number of deaths
<b>Age (years)</b>			
Median (IQR)	38 (34–45)	..	..
16–29	1130 (9%)	55	11
30–39	5820 (46%)	462	137
40–49	3703 (29%)	339	100
≥50	1921 (15%)	238	96
<b>Sex</b>			
Male	9890 (79%)	903	284
Female	2684 (21%)	191	60
<b>Risk factor for transmission</b>			
Male homosexual contact	5192 (41%)	428	127
Heterosexual contact	3859 (31%)	295	77
Injection-drug use	2400 (19%)	262	110
Other or unknown	1123 (9%)	109	30
<b>Clinical stage</b>			
CDC stage A/B	9925 (79%)	612	171
CDC stage C	2649 (21%)	482	173
<b>CD4 count (cells/μL)</b>			
Median (IQR)	250 (100–402)	..	..
<50	1917 (15%)	420	129
50–99	1219 (10%)	195	58
100–199	2088 (17%)	215	73
200–349	3217 (25%)	144	50
≥350	4133 (33%)	120	34
<b>Plasma viral load (copies/mL)</b>			
Median (IQR; log <sub>10</sub> )	4.87 (4.23–5.39)	..	..
<1000	998 (8%)	41	8
1000–9999	1333 (11%)	80	31
10 000–99 999	4702 (37%)	272	85
≥100 000	5541 (44%)	701	220

CDC=Centers for Disease Control and Prevention. \*New AIDS-defining diseases or death.

Table 2: Characteristics of the 12 574 treatment-naive study patients at the start of highly active antiretroviral therapy and number of patients with clinical progression

decreasing. We therefore additionally considered flexible parametric models, based on the same three distributions, which use cubic splines to model the baseline hazard allowing for the possibility that the hazard might decrease and then subsequently increase, for example as patients were adversely affected by toxic effects or drug resistance.<sup>21</sup> The amount of curvature in these models is determined by the number of knots used to fit the splines. We fitted models with one to five knots and compared models using Akaike's information criterion (AIC),<sup>22</sup> which penalises more complicated models. We found, for each survival distribution, that two knots gave the lowest AIC.

The selection of variables for inclusion in prognostic models was robust to choice of survival distribution; we therefore used the same variables in all models. However, the evidence for interaction between variables, and for the improvement in fit in stratified compared with unstratified models, depended on the choice of the survival distribution. For each choice of survival distribution, we therefore compared 64 different models, with and without interaction terms, with and without stratification, and with and without spline terms. For each survival distribution, we chose four candidate models—the two models with lowest AIC, with and without including spline terms for the hazard function—giving a total of 12 candidate models.

#### Validation of prognostic models

The final prognostic model was chosen by use of a leave-one-out cross-validation system, by fitting candidate models on pooled data from all but one of the cohorts and testing generalisability on the omitted cohort. Because the

smallest three cohorts did not have enough events to allow estimation of the models, we amalgamated them so that 11 datasets were used in the cross-validation procedure. This procedure was repeated 11 times, rotating the left-out cohort. The cross-validation process was applied to each of the 12 candidate models, together with all simpler models nested within them.

We used deviance differences to quantify the additional lack-of-fit when a model is fitted on one data set and predictions are made on another data set.<sup>23</sup> The deviance differences were summed across the 11 test cohorts: the best-generalising model was that with the lowest total deviance difference. The final prognostic model was re-estimated on the pooled data, ignoring the cohort structure, and used to estimate probabilities of progression to the endpoint at 1, 2, and 3 years after starting HAART. Bootstrapped replicates of the data were used to calculate 95% CIs for the probabilities.

We used Stata software (version 7.0) for analyses. Results are presented as Kaplan-Meier estimates of the probability of patients reaching an endpoint, hazard ratios with 95% CIs, and probabilities of progression to endpoints at 1, 2, and 3 years after starting HAART, with 95% CIs.

#### Role of the funding source

Our funders had no involvement in the design of the study; the collection, analysis and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

## Results

The characteristics of the 13 participating cohorts are shown in table 1. Ten cohorts were from European countries, including the multicentre EuroSIDA study, two from Canada, and one from the USA. The number of

	Hazard ratio (95% CI)	
	AIDS or death	Death
<b>Age (years)</b>		
17–29	1	1
30–39	1.08 (0.81–1.45)	1.35 (0.73–2.51)
40–49	1.12 (0.83–1.50)	1.41 (0.75–2.65)
≥50	1.51 (1.11–2.06)	3.09 (1.64–5.83)
<b>Sex</b>		
Male	1	1
Female	0.98 (0.82–1.17)	1.05 (0.77–1.42)
<b>Risk factor for transmission</b>		
Male homosexual contact	1	1
Injection-drug use	1.41 (1.19–1.66)	2.44 (1.86–3.20)
Heterosexual contact	0.90 (0.76–1.06)	0.84 (0.62–1.15)
Other	0.97 (0.78–1.21)	0.90 (0.60–1.34)
<b>Clinical stage</b>		
CDC stage A/B	1	1
CDC stage C	1.41 (1.23–1.62)	2.07 (1.62–2.63)
<b>Baseline CD4 count (cells/μL)</b>		
<50	1	1
50–99	0.74 (0.62–0.89)	0.72 (0.53–0.99)
100–199	0.52 (0.44–0.63)	0.66 (0.49–0.90)
200–349	0.24 (0.20–0.30)	0.36 (0.25–0.51)
≥350	0.18 (0.14–0.22)	0.22 (0.15–0.34)
<b>Plasma viral load (copies/mL)</b>		
≥100 000	1	1
10 000–100 000	0.73 (0.62–0.84)	0.79 (0.61–1.02)
1000–10 000	0.90 (0.71–1.14)	1.18 (0.80–1.74)
<1000	0.73 (0.52–1.01)	0.53 (0.26–1.09)

Adjusted for all variables listed in the table. CDC=Centers for Disease Control and Prevention.

Table 3: Hazard ratios of progression to AIDS or death, and to death alone, from Weibull models

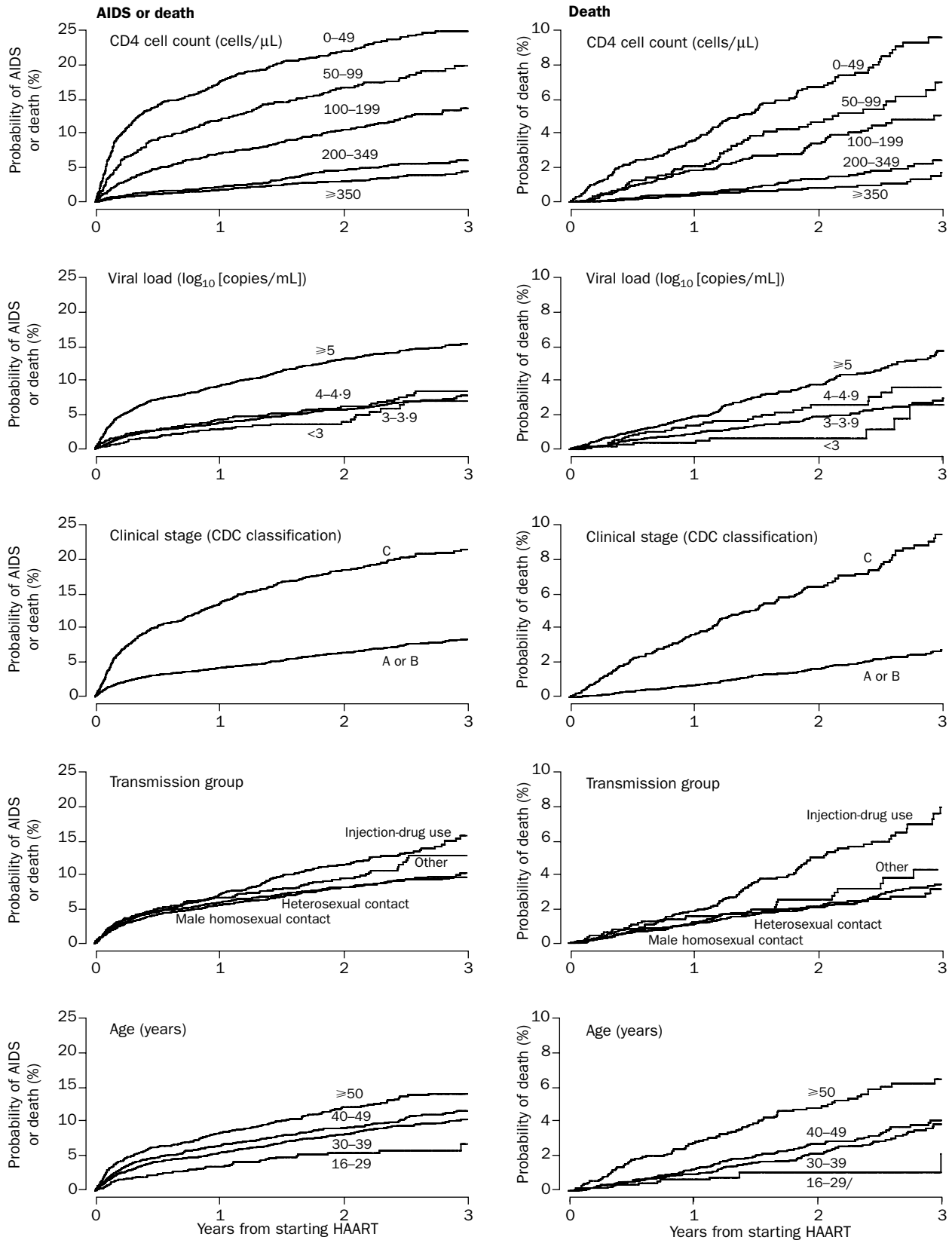


Figure 1: Kaplan-Meier curves of probability of survival free of a new AIDS event or death (left panels) or death (right panels) according to baseline CD4 cell count, viral load, clinical stage, transmission group, and age

study centres ranged from one to 68, the number of patients included in the present analysis from 92 to 4739.

12 574 patients met our inclusion criteria. The median calendar month of starting HAART was December, 1997

(IQR June, 1997, to July, 1998). The characteristics at the time of starting HAART are shown in table 2. The median age was 38 years, and most patients were men. Overall, sex between men was the most frequent risk



factor for HIV-1 transmission. This was true for all cohorts except for the ICONA study, which includes many patients with a history of injection-drug use (634, 39%), and the Swiss cohort for which heterosexual contact is the most important risk group (451, 36%). The median baseline CD4 cell count was 250 cells/ $\mu$ L and the median viral load 74 000 copies/mL. Most HIV-1 viral load determinations were done with the Amplicor Monitor PCR method (Roche Molecular Systems, Branchburg, NJ, USA) but the branched DNA assay (Chiron Diagnostics, Emeryville, CA, USA) and the NASBA-QT assay (Organon Teknika, Durham, NC, USA) were also used in some cohorts.

Treatment was started at lower CD4 cell counts in the ten European cohorts (median 245 cells/ $\mu$ L) than in the US cohort (310 cells/ $\mu$ L), with the two Canadian cohorts in an intermediate position (270 cells/ $\mu$ L,  $p=0.0001$  for difference between groups of cohorts). Most patients started on a three-drug regimen based on one PI and two NRTIs.

During 24 310 person-years of follow up, 870 patients developed at least one AIDS event, 344 patients died, and 1094 patients developed AIDS or died. 104 of the 224 patients who died with no new AIDS diagnosis had been diagnosed with AIDS before starting HAART. 727 patients developed one AIDS event, 118 patients developed two events, 19 developed three events, five developed four events, and one patient developed five events. Among the 1045 AIDS events, the ten most

frequent events were oesophageal candidiasis (126), Kaposi's sarcoma (113), tuberculosis (112), *Mycobacterium avium* disease (107), non-Hodgkin lymphoma (85), *Pneumocystis carinii* pneumonia (77), wasting syndrome (57), toxoplasmosis of the brain (55), HIV-related encephalopathy (54), and disseminated cytomegalovirus disease (53).

The protocol stipulated ten candidate prognostic variables: CD4 count, viral load, age, sex, transmission group, clinical stage, year of starting HAART, number of drugs in the regimen, inclusion of PIs in the regimen, and inclusion of NNRTIs. Five prognostic variables were included in the final model: CD4 count, viral load, age, transmission group, and clinical stage. The relative hazards of progression to AIDS or death and death from Weibull models are shown in table 3. The lower the baseline CD4 cell count, the higher the probability of progression. Patients with viral loads of at least 100 000 copies/mL, age at least 50 years, injection-drug use as the likely mode of transmission, or an AIDS diagnosis at baseline were also at increased risk of progression. Kaplan-Meier plots of the probability of progression to AIDS or death, and to death alone, for the five prognostic variables, are shown in figure 1. Because threshold effects were evident for age, viral load, and transmission group, they were dichotomised in subsequent prognostic models: age less than 50 years and 50 years or older, viral load less than 100 000 copies/mL (<5 log) and 100 000 copies/mL or

		CD4 cell count (cells/ $\mu$ L)									
		<50		50-99		100-199		200-349		$\geq 350$	
		Viral load $\geq 5^*$	Viral load <5*	Viral load $\geq 5^*$	Viral load <5*	Viral load $\geq 5^*$	Viral load <5*	Viral load $\geq 5^*$	Viral load <5*	Viral load $\geq 5^*$	Viral load <5*
<b>CDC stage A/B and no history of IDU</b>											
Age <50 years											
Year 1	12 (11-14)	9.5 (8.0-11)	9.2 (7.7-11)	7.0 (5.8-8.5)	6.2 (5.2-7.3)	4.7 (4.0-5.6)	2.6 (2.1-3.2)	2.0 (1.6-2.5)	2.0 (1.6-2.5)	1.5 (1.2-1.9)	
Year 2	17 (15-20)	13 (11-15)	13 (11-15)	10 (8.4-12)	9.5 (8.1-11)	7.3 (6.2-8.5)	4.5 (3.7-5.4)	3.3 (2.8-4.1)	3.3 (2.7-4.0)	2.5 (2.1-3.0)	
Year 3	20 (18-23)	16 (13-19)	16 (14-19)	12 (10-15)	12 (10-14)	9.3 (7.9-11)	6.1 (5.0-7.4)	4.7 (3.9-5.6)	4.4 (3.6-5.4)	3.4 (2.8-4.1)	
Age $\geq 50$ years											
Year 1	17 (14-20)	13 (11-16)	12 (10-15)	9.6 (7.7-12)	8.5 (7.0-10)	6.5 (5.3-7.9)	3.6 (2.8-4.5)	2.7 (2.2-3.4)	2.8 (2.2-3.5)	2.1 (1.6-2.7)	
Year 2	23 (19-27)	18 (15-21)	18 (15-21)	14 (11-17)	13 (10-15)	9.9 (8.2-12)	6.1 (5.0-7.6)	4.7 (3.8-5.8)	4.5 (3.6-5.7)	3.4 (2.8-4.3)	
Year 3	27 (23-32)	21 (18-25)	22 (18-26)	17 (14-20)	16 (14-19)	13 (10-15)	8.3 (6.7-10)	6.4 (5.1-7.9)	6.0 (4.8-7.6)	4.6 (3.7-5.8)	
<b>CDC stage A/B and history of IDU</b>											
Age <50 years											
Year 1	17 (14-20)	13 (11-16)	12 (10-15)	9.5 (7.7-12)	8.4 (7.0-10)	6.5 (5.3-7.9)	3.6 (2.8-4.5)	2.7 (2.2-3.4)	2.7 (2.1-3.5)	2.1 (1.6-2.6)	
Year 2	24 (21-28)	19 (16-23)	19 (16-22)	15 (12-18)	14 (12-16)	11 (8.8-13)	6.6 (5.4-8.1)	5.0 (4.1-6.1)	4.9 (3.9-6.1)	3.7 (3.0-4.6)	
Year 3	30 (26-35)	24 (20-28)	24 (20-28)	19 (15-23)	18 (15-22)	14 (12-17)	9.4 (7.6-11)	7.2 (5.8-8.8)	6.8 (5.4-8.6)	5.2 (4.2-6.5)	
Age $\geq 50$ years											
Year 1	22 (18-27)	17 (14-22)	17 (13-21)	13 (10-16)	11 (9.1-14)	8.8 (6.9-11)	4.9 (3.7-6.4)	3.7 (2.8-4.9)	3.8 (2.8-5.0)	2.9 (2.2-3.8)	
Year 2	32 (26-38)	25 (20-31)	25 (20-31)	20 (15-25)	18 (15-23)	14 (11-18)	9.0 (7.0-11)	6.9 (5.4-8.8)	6.7 (5.1-8.7)	5.1 (3.9-6.6)	
Year 3	39 (32-46)	31 (25-38)	33 (26-38)	25 (20-31)	24 (20-30)	19 (15-24)	13 (9.9-16)	9.8 (7.6-12)	9.3 (7.1-12)	7.1 (5.4-9.2)	
<b>CDC stage C and no history of IDU</b>											
Age <50 years											
Year 1	17 (15-19)	13 (11-15)	13 (11-15)	9.8 (8.1-12)	8.7 (7.2-10)	6.6 (5.5-8.1)	3.7 (2.9-4.7)	2.8 (2.2-3.5)	2.8 (2.2-3.6)	2.1 (1.7-2.7)	
Year 2	23 (21-26)	18 (16-21)	18 (15-21)	14 (12-17)	13 (11-16)	10 (8.4-12)	6.3 (5.1-7.8)	4.8 (3.9-5.9)	4.6 (3.7-5.9)	3.5 (2.8-4.4)	
Year 3	28 (25-31)	22 (19-25)	22 (19-26)	17 (14-21)	17 (14-20)	13 (11-15)	8.5 (6.9-11)	6.5 (5.2-8.1)	6.2 (4.9-7.9)	4.7 (3.7-6.0)	
Age $\geq 50$ years											
Year 1	23 (20-26)	18 (15-21)	17 (14-20)	13 (11-16)	12 (9.7-14)	9.1 (7.3-11)	5.1 (3.9-6.5)	3.8 (3.0-5.0)	3.9 (3.0-5.1)	3.0 (2.3-3.9)	
Year 2	31 (27-35)	24 (20-28)	24 (20-28)	19 (15-23)	18 (15-21)	14 (11-17)	8.6 (6.8-11)	6.6 (5.2-8.3)	6.4 (4.9-8.2)	4.9 (3.8-6.2)	
Year 3	36 (32-41)	29 (24-34)	29 (25-34)	23 (19-28)	22 (18-27)	17 (14-21)	12 (9.2-15)	8.9 (7.0-11)	8.5 (6.5-11)	6.5 (5.0-8.3)	
<b>CDC stage C and history of IDU</b>											
Age <50 years											
Year 1	23 (20-26)	18 (15-21)	17 (14-21)	13 (11-16)	12 (9.5-14)	9.0 (7.2-11)	5.0 (3.9-6.5)	3.8 (2.9-5.0)	3.9 (2.9-5.1)	2.9 (2.2-3.9)	
Year 2	33 (29-37)	26 (22-30)	26 (22-30)	20 (16-24)	19 (15-23)	15 (12-18)	9.2 (7.3-12)	7.0 (5.6-8.9)	6.8 (5.3-8.8)	5.2 (4.1-6.7)	
Year 3	40 (35-45)	32 (27-37)	32 (27-38)	25 (21-31)	25 (22-30)	19 (16-24)	13 (10-16)	10.0 (7.9-13)	9.5 (7.3-12)	7.3 (5.6-9.4)	
Age $\geq 50$ years											
Year 1	30 (25-36)	24 (19-29)	23 (18-28)	18 (14-23)	16 (12-20)	12 (9.5-16)	6.9 (5.1-9.2)	5.3 (3.9-7.1)	5.3 (3.9-7.2)	4.0 (3.0-5.5)	
Year 2	42 (36-49)	34 (28-41)	34 (27-41)	27 (21-33)	25 (20-31)	20 (15-25)	12 (9.6-16)	9.6 (7.3-13)	9.3 (7.0-12)	7.1 (5.3-9.5)	
Year 3	50 (43-58)	41 (34-49)	42 (34-50)	33 (27-41)	33 (26-40)	26 (20-32)	17 (13-23)	14 (10-18)	13 (9.6-17)	9.9 (7.4-13)	

IDU=injection-drug use. \*Log copies/mL.

Table 4: Probability of progressing to AIDS or death according to CD4 cell count, viral load, and sociodemographic factors

greater ( $\geq 5$  log), and injection-drug use versus other transmission routes. Sensitivity analyses of associations with AIDS alone (treating individuals who died without a previous AIDS event as censored) showed similar hazard ratios for CD4 cell count and viral load. The other associations were attenuated: the adjusted hazard ratio comparing age 50 years or older with less than 50 years was 1.23 (95% CI 0.88–1.73), the adjusted hazard ratio comparing injection-drug use with other transmission groups was 1.22 (1.01–1.47), and the adjusted hazard ratio comparing patients with and without an AIDS diagnosis at baseline was 1.29 (1.11–1.50).

The validation procedure showed that the model that generalised best was a Weibull model stratified on CD4 cell count and transmission group (injection-drug use *vs* others) with no interaction or spline terms. Stratification by CD4 and risk group means that the shape of the underlying hazard can differ according to the value of these two variables and that, in particular, hazard ratios can vary over time. Proportional hazards are assumed for the effects of all other variables. The validation results were very similar for both the combined endpoint and for death, and so the same model structure was used for both endpoints. Full details of the final prognostic models for the two endpoints are given in the appendix (<http://image.thelancet.com/extras/02art6009webappendix1.pdf>).

Tables 4 and 5 give probabilities of progression to the combined endpoint and death estimated from the

preferred Weibull model. The lowest estimated probability of progression to AIDS or death at 3 years was 3.4% in patients younger than 50 years, not infected through injection-drug use, and who started HAART with a CD4 cell count greater than 350 cells/ $\mu$ L and a viral load below 100 000 copies/mL. At the other end of the spectrum, the risk was estimated at 50% at 3 years in older patients infected through injection-drug use who started therapy with a CD4 cell count less than 50 cells/ $\mu$ L and a viral load equal or greater than 100 000 copies/mL (table 4). The corresponding estimates were 0.8% and 43% for death (table 5) and 2.6% to 36% for AIDS alone (table available from the authors). Estimates of disease progression probabilities for individual patients can be calculated with the model formulae and coefficients in the appendix. A risk calculator based on the prognostic models is available on the collaboration's website (<http://www.artcohortcollaboration.org>).

We modelled the incidence rate of progression to AIDS or death over time according to the baseline CD4 cell count (figure 2). Most of the reduction in the rate was achieved by 6 months. In patients with less than 50 cells/ $\mu$ L, and 50–99 cells/ $\mu$ L, the rate continued to decline up to 3 years, whereas in patients with 100–199 cells/ $\mu$ L, the rate stabilised after 12 months. In patients with baseline CD4 cell counts of 200 cells/ $\mu$ L or above, a decline was seen initially, followed by a slight increase in the rate after 12 months. Nevertheless, at

		CD4 cell count (cells/ $\mu$ L)									
		<50		50–99		100–199		200–349		$\geq 350$	
		Viral load $\geq 5^*$	Viral load <5*	Viral load $\geq 5^*$	Viral load <5*	Viral load $\geq 5^*$	Viral load <5*	Viral load $\geq 5^*$	Viral load <5*	Viral load $\geq 5^*$	Viral load <5*
<b>CDC stage A/B and no history of IDU</b>											
Age <50 years											
Year 1	1.6 (1.2–2.2)	1.4 (1.0–1.9)	1.0 (0.7–1.5)	0.9 (0.6–1.3)	1.0 (0.7–1.4)	0.8 (0.6–1.2)	0.4 (0.2–0.6)	0.3 (0.2–0.5)	0.3 (0.2–0.5)	0.2 (0.2–0.4)	
Year 2	2.9 (2.2–3.9)	2.5 (1.8–3.4)	2.1 (1.5–2.9)	1.8 (1.2–2.5)	2.0 (1.5–2.6)	1.6 (1.2–2.2)	1.0 (0.7–1.4)	0.8 (0.6–1.1)	0.6 (0.4–0.9)	0.5 (0.4–0.8)	
Year 3	4.1 (3.1–5.4)	3.4 (2.5–4.7)	3.2 (2.3–4.5)	2.7 (1.9–3.9)	2.9 (2.2–4.0)	2.5 (1.8–3.4)	1.8 (1.3–2.5)	1.5 (1.1–2.1)	1.0 (0.7–1.5)	0.8 (0.6–1.2)	
Age $\geq 50$ years											
Year 1	3.7 (2.6–5.1)	3.1 (2.1–4.4)	2.3 (1.5–3.4)	1.9 (1.2–2.9)	2.2 (1.5–3.1)	1.8 (1.2–2.7)	0.8 (0.5–1.3)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.6 (0.3–0.9)	
Year 2	6.4 (4.8–8.7)	5.4 (3.8–7.6)	4.7 (3.3–6.5)	3.9 (2.7–5.7)	4.3 (3.2–5.9)	3.6 (2.6–5.1)	2.2 (1.5–3.1)	1.8 (1.3–2.6)	1.4 (1.0–2.2)	1.2 (0.8–1.8)	
Year 3	8.9 (6.6–12)	7.5 (5.3–11)	7.1 (5.0–9.9)	5.9 (4.1–8.6)	6.5 (4.7–8.9)	5.5 (3.9–7.6)	3.9 (2.7–5.6)	3.3 (2.3–4.7)	2.2 (1.5–3.4)	1.9 (1.3–2.8)	
<b>CDC stage A/B and history of IDU</b>											
Age <50 years											
Year 1	3.4 (2.4–4.8)	2.9 (1.9–4.2)	2.1 (1.4–3.3)	1.8 (1.1–2.8)	2.0 (1.4–3.0)	1.7 (1.1–2.5)	0.7 (0.4–1.2)	0.6 (0.4–1.0)	0.6 (0.4–1.0)	0.5 (0.3–0.9)	
Year 2	7.3 (5.5–9.7)	6.1 (4.4–8.5)	5.3 (3.8–7.3)	4.4 (3.1–6.4)	4.9 (3.6–6.6)	4.1 (3.0–5.6)	2.5 (1.8–3.5)	2.1 (1.5–2.9)	1.6 (1.1–2.4)	1.4 (0.9–2.0)	
Year 3	11 (8.4–15)	9.5 (6.8–13)	8.9 (6.4–12)	7.5 (5.2–11)	8.2 (6.0–11)	6.9 (5.0–9.5)	5.0 (3.5–7.1)	4.2 (3.0–5.9)	2.9 (1.9–4.3)	2.4 (1.6–3.6)	
Age $\geq 50$ years											
Year 1	7.5 (5.0–11)	6.3 (4.0–9.8)	4.7 (2.9–7.5)	4.0 (2.4–6.5)	4.5 (2.9–6.9)	3.8 (2.4–5.9)	1.7 (1.0–2.9)	1.4 (0.8–2.4)	1.4 (0.8–2.4)	1.2 (0.7–2.0)	
Year 2	16 (11–22)	13 (9.0–19)	11 (7.9–17)	9.7 (6.4–14)	11 (7.4–15)	9.0 (6.2–13)	5.5 (3.6–8.2)	4.6 (3.1–6.9)	3.6 (2.3–5.7)	3.0 (1.9–4.7)	
Year 3	23 (17–32)	20 (14–29)	19 (13–27)	16 (11–24)	17 (12–25)	15 (10–21)	11 (7.3–16)	9.2 (6.1–14)	6.3 (3.9–10)	5.3 (3.3–8.3)	
<b>CDC stage C and no history of IDU</b>											
Age <50 years											
Year 1	3.4 (2.7–4.4)	2.9 (2.1–3.9)	2.1 (1.5–3.1)	1.8 (1.2–2.7)	2.0 (1.4–2.9)	1.7 (1.2–2.5)	0.7 (0.4–1.2)	0.6 (0.4–1.0)	0.6 (0.4–1.1)	0.5 (0.3–0.9)	
Year 2	6.0 (4.9–7.5)	5.1 (3.9–6.7)	4.4 (3.2–5.9)	3.7 (2.6–5.2)	4.1 (3.0–5.5)	3.4 (2.5–4.7)	2.0 (1.4–3.0)	1.7 (1.2–2.5)	1.3 (0.9–2.1)	1.1 (0.7–1.7)	
Year 3	8.4 (6.8–10)	7.1 (5.4–9.3)	6.6 (4.9–9.0)	5.6 (3.9–7.9)	6.1 (4.5–8.2)	5.1 (3.7–7.1)	3.7 (2.5–5.4)	3.1 (2.1–4.5)	2.1 (1.3–3.3)	1.8 (1.1–2.7)	
Age $\geq 50$ years											
Year 1	7.5 (5.8–9.8)	6.3 (4.6–8.7)	4.7 (3.2–6.9)	4.0 (2.6–6.0)	4.5 (3.1–6.5)	3.8 (2.5–5.6)	1.7 (1.0–2.8)	1.4 (0.8–2.3)	1.4 (0.8–2.4)	1.2 (0.7–2.0)	
Year 2	13 (10–16)	11 (8.2–15)	9.6 (7.0–13)	8.1 (5.7–11)	8.9 (6.5–12)	7.5 (5.3–10)	4.5 (3.1–6.7)	3.8 (2.6–5.7)	3.0 (1.9–4.7)	2.5 (1.6–3.9)	
Year 3	18 (14–22)	15 (11–20)	14 (10–19)	12 (8.5–17)	13 (9.6–18)	11 (7.9–15)	8.1 (5.5–12)	6.8 (4.6–10)	4.7 (2.9–7.4)	3.9 (2.5–6.2)	
<b>CDC stage C and history of IDU</b>											
Age <50 years											
Year 1	7.0 (5.2–9.5)	5.9 (4.1–8.4)	4.4 (2.9–6.7)	3.7 (2.4–5.8)	4.2 (2.8–6.2)	3.5 (2.3–5.3)	1.5 (0.9–2.6)	1.3 (0.8–2.2)	1.3 (0.7–2.3)	1.1 (0.6–1.9)	
Year 2	15 (12–18)	12 (9.3–17)	11 (7.9–15)	9.1 (6.4–13)	10 (7.3–14)	8.5 (6.0–12)	5.1 (3.5–7.6)	4.3 (2.9–6.4)	3.4 (2.2–5.3)	2.8 (1.8–4.4)	
Year 3	22 (18–28)	19 (14–25)	18 (13–24)	15 (11–21)	16 (12–22)	14 (10–19)	10 (6.9–15)	8.6 (5.8–13)	5.9 (3.7–9.3)	5.0 (3.2–7.8)	
Age $\geq 50$ years											
Year 1	15 (10–21)	13 (8.5–19)	9.6 (6.1–15)	8.1 (5.0–13)	9.1 (5.9–14)	7.7 (4.8–12)	3.4 (1.9–6.1)	2.9 (1.6–5.1)	2.9 (1.6–5.2)	2.4 (1.3–4.4)	
Year 2	30 (22–39)	26 (18–36)	23 (16–31)	19 (13–28)	21 (15–30)	18 (12–26)	11 (7.2–17)	9.4 (6.0–15)	7.5 (4.5–12)	6.3 (3.8–10)	
Year 3	43 (33–55)	38 (27–50)	36 (26–48)	31 (21–43)	33 (24–45)	29 (20–40)	21 (14–32)	18 (12–28)	13 (7.8–21)	11 (6.6–17)	

CDC=Centers for Disease Control and Prevention. IDU=injection-drug use. \*Log copies/mL.

Table 5: Probability of death according to CD4 cell count, viral load, and sociodemographic factors

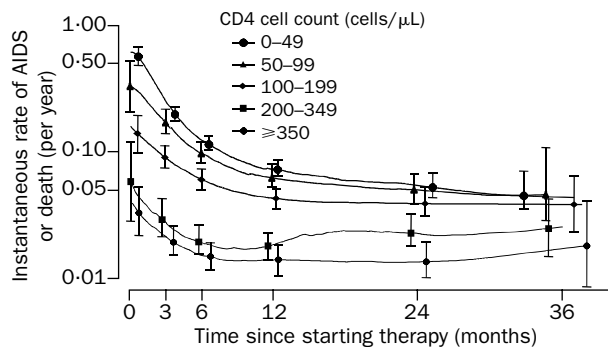


Figure 2: Incidence rates of progression to AIDS or death at baseline and different points during follow-up according to baseline CD4 cell count

Note logarithmic scale for incidence rates.

3 years, the rates were lower in patients who had started therapy with CD4 cell counts above 200 cells/ $\mu$ L than in patients who started therapy below this threshold.

Finally, to compare progression probabilities according to CD4 cell count and viral load in the pre-HAART and HAART eras, we replicated the analysis of the MACS study<sup>5</sup> that enrolled HIV-1-infected homosexual men in the mid-1980s and followed them up until 1995. The upper panel of figure 3 is adapted from MACS (pre-HAART era) and the lower panel shows our replication of that analysis in the collaborative database (HAART era). The latter analysis is based on 5152 drug-naïve homosexual men who started HAART between 1996 and 2000, 424 of whom developed AIDS.

## Discussion

The results of this collaborative study, involving 13 prospective studies and over 12 000 HIV-1-infected patients, showed that the prognosis of HIV-1 infection in patients starting HAART could be estimated with precision for groups of patients characterised by different

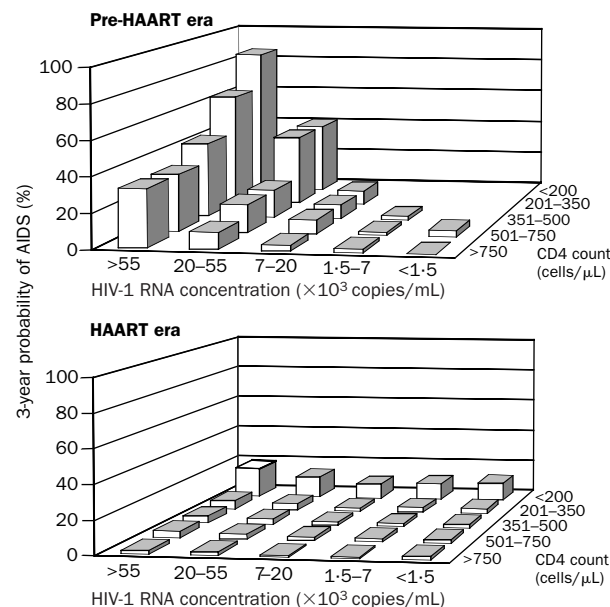


Figure 3: Prognosis according to CD4 cell count and viral load in the pre-HAART and HAART eras

Kaplan-Meier estimates of the probability of AIDS at 3 years are shown.

levels of CD4 count, plasma viral load, and other prognostic factors. Because all patients were treatment-naïve, our results are not confounded by previous antiretroviral therapy, and are relevant to most patients starting HAART at the present time. The prognostic model has strong discriminatory power, with estimated rates of progression to AIDS or death at 3 years ranging from 3.4% to 50%. The CD4 cell count at commencement of HAART was the most strongly prognostic factor: patients who started HAART with fewer than 200 cells/ $\mu$ L were at substantially higher risk of clinical progression than those with higher counts. Viral load at commencement was associated with subsequent clinical progression only if greater than or equal to 100 000 copies/mL. The other factors associated with clinical progression were age 50 years or greater, a prior diagnosis of AIDS, and infection through injection-drug use.

How applicable are our estimates to other HIV-1-infected patients? This is an important question because the accuracy of prognostic models tends to be lower when applied to data other than those used to develop them.<sup>24</sup> We addressed this issue by penalising model complexity, and by choosing models that generalised best to cohorts omitted from the estimation procedure. Our database included patients from many countries from Europe and North America, who were treated in different settings. The range of patients was broad: men and women, from teenagers to elderly people were included, and the major exposure categories were well represented. The severity of immunodeficiency at baseline ranged from not measurable to very severe, and viral load from undetectable to extremely high.

Generalisability can also be compromised if important independent predictors are omitted from the model.<sup>25</sup> We have included the prognostic factors that are measured as part of clinical care and are the most important of those so far identified, but we might not have considered all relevant variables. For example, in the EuroSIDA study and other cohorts, the latest haemoglobin value was found to be an independent prognostic marker for subsequent clinical progression.<sup>26</sup> Genetic factors, such as the *MDR1* 3435C/T polymorphism<sup>27</sup> or the *CCR5* $\Delta$ 32 mutation,<sup>28</sup> have been shown to affect response to antiretroviral treatment, but were not considered here. Another potential limitation of our analysis was that three different assays to quantify viral load were used in the participating cohorts. However, results were consistent across cohorts, in line with a comparative laboratory study<sup>29</sup> which concluded that all three assays are appropriate for application in multicentre studies and that there is no need for centralised analysis of routine EDTA-plasma samples.

The lack of cause-specific mortality information is clearly a limitation of our analysis. We used a combined endpoint of AIDS and death from all causes because most patients who died (224 of 344 deaths) were not recorded as developing a new AIDS event during follow up. An analysis of clinical progression relying on AIDS alone would have classified these patients as non-progressors, despite the fact that many of these deaths were probably HIV-1-related, and would thus underestimate the probability of both HIV-1-related and overall progression. By contrast with the pre-HAART era, when most deaths were associated with recent AIDS-defining events, the situation in the era of HAART is more complex. The current definition of AIDS is no longer a near-complete marker for overall progression, and possibly also an incomplete measure of HIV-1-related events. For example, the increased incidence of Hodgkin's disease in

people with AIDS is probably due to HIV-1-related immunosuppression.<sup>30</sup> Future analyses of clinical progression should distinguish between HIV-1-related, treatment-related, and other events; however, an endpoints committee will be needed to standardise definitions across cohorts.

The comparison of our results with those from MACS<sup>5</sup> (figure 3) illustrates the striking improvement of prognosis in the era of HAART. By contrast with the results of that study, ours show that at the time of starting HAART the CD4 cell count was a more important prognostic factor than viral load, but was strongly associated with progression only if it had fallen below 200 cells/ $\mu$ L. Indeed, differences were small in patients who started therapy with CD4 counts above this threshold. We stress that in addition to HAART the introduction of prophylactic treatments against opportunistic infections will have contributed to the observed improvement of prognosis.

In the pre-HAART era, the CD4 cell count was also prognostic at higher levels. For example, over 3 years, patients with 200–350 cells/ $\mu$ L were substantially more likely to progress to AIDS or death than patients with 351–500 cells/ $\mu$ L.<sup>5</sup> This is due to the fact that, in the absence of potent antiretroviral therapy, CD4 cells decline at a rate dictated by the viral load, whereas in most patients starting HAART, viraemia is reduced—often to undetectable levels—and the CD4 cell count increases.<sup>5,15,31</sup> In our study, viral load was associated with worse prognosis only if equal to or above 100 000 copies/mL. This finding accords with that of a recent collaborative analysis of three cohort studies which showed that patients with baseline viral loads of greater than 100 000 copies/mL had a slower rate of achieving viral suppression than those with less than this number.<sup>32</sup> A study from British Columbia, Canada,<sup>33</sup> also showed an increased risk of death in patients who started triple-drug therapy with viral loads above 100 000 copies/mL, although this difference did not reach conventional levels of statistical significance.

Age at seroconversion<sup>6</sup> and age at a given CD4 cell count<sup>34</sup> were shown to be important determinants of progression and survival before the widespread use of HAART. We found that age continues to be an independent prognostic factor in patients starting HAART, although its effect is evident after 50 years of age only and thus seems to be less important than in the pre-HAART era. Recent analyses of the EuroSIDA cohort<sup>35</sup> and MACS<sup>36</sup> showed that younger age favoured CD4 cell restoration on HAART, which is consistent with the effect of age on thymic function. The rate of clinical progression, and in particular mortality, was higher in patients infected through injection-drug use than in those infected by other routes. Independent of HIV-1 infection, these patients are known to be at increased risk of death from overdose and violent causes.<sup>37,38</sup> In HIV-1-infected patients, co-infection with hepatitis C virus and active injection-drug use are common additional risk factors for clinical progression.<sup>39</sup> In our study, survival curves separated after 6 months. Drug-induced liver toxicity in patients with pre-existing hepatic disease,<sup>40</sup> and a decline in adherence over time, might have contributed to this pattern. Our results confirm that previous AIDS-defining opportunistic diseases also increase the risk of clinical progression in patients starting potent therapy.<sup>41</sup> Finally, we found no difference in prognosis between men and women. Sex differences in treatment responses therefore do not seem to translate into differences in clinical progression.<sup>42</sup>

Although randomised clinical trials provide strong evidence that HAART is beneficial in patients with less than 200 CD4 cells/ $\mu$ L,<sup>43–45</sup> the optimum time to start antiretroviral therapy among symptom-free patients with CD4 cell counts above this threshold and low or intermediate viral load is a matter of debate. Immune restoration might be more complete if therapy is started early, the microarchitecture of lymphoid organs might be preserved, and the rare but serious complications that sometimes occur above 200 CD4 cells/ $\mu$ L—eg, lymphoma or tuberculosis—prevented.<sup>46,47</sup> These arguments in favour of early treatment need to be balanced against the risk of adverse effects including lipodystrophy and a possibly increased cardiovascular risk,<sup>48</sup> lacticacidosis and metabolic bone disease, difficulties in adherence, the loss of future treatment options due to emerging drug resistance,<sup>47</sup> and the possible loss of a chance to start therapy with newly developed drugs. This issue could be resolved in a large, pragmatic randomised trial comparing immediate with deferred HAART, but the feasibility of such a study is uncertain<sup>47</sup> and there is a danger that the results of such a study would be out of date by the time they were published.

In the absence of randomised trials, can data from observational studies inform this debate? We believe that observational data can make a contribution, but their limitations must be kept in mind. The decision to start HAART in routine practice is influenced by prognostic factors, which could bias crude comparisons between treated and untreated patients. Such “confounding by indication”<sup>49</sup> could occur, for example, if at the same CD4 cell count and viral load, patients starting HAART were more likely to have experienced a clinical event than those not given treatment.

At each level of CD4 count at the start of therapy, the incidence of clinical progression declined after starting HAART. The group of patients who started therapy at or above a CD4 cell count of 350 cells/ $\mu$ L had the lowest rates of progression at all times up to 3 years after starting therapy. Absolute differences were small, however. For example, the cumulative risk of progression to AIDS or death at 3 years was an estimated 3·4% in patients younger than 50 years and free of AIDS who started therapy at or above 350 cells/ $\mu$ L, and 4·7% in patients who started with 200–349 cells/ $\mu$ L. One might therefore conclude that, although starting HAART at higher CD4 cell counts is associated with improved prognosis, the difference compared with starting therapy at 200–349 cells/ $\mu$ L is small and might not justify exposing patients to the risk of HAART-related toxic effects and resistance. However, this comparison does not provide direct evidence about the optimum count at which therapy should be started. The appropriate comparison would be between patients starting therapy at or above 350 cells/ $\mu$ L and a comparable group of patients in whom therapy is delayed, and would record all events from the time at which patients were eligible for treatment at the higher threshold.

Our study can therefore not determine the optimum time for starting therapy. However, the difference in the risk of clinical progression between patients initiating HAART above 349 cells/ $\mu$ L and patients delaying HAART until the CD4 cell count has fallen below this threshold is unlikely to be more than a few percentage points. This observation, and the finding that viral load is prognostic only if very high, have important implications for clinical management and should be taken into account in future treatment guidelines.



The large number of patients and events analysed is an important strength of our study; however, in the current analysis, prognosis could be reliably estimated only up to 3 years. Differences not seen in the present analysis might emerge as more follow-up accumulates—eg, differences between earlier and later calendar years, and different types of initial regimens. Examination of whether and to what extent progression rates will converge in patients starting HAART at different levels of CD4 cell count is also important, as is whether a rebound of rates will occur in the future. The ART Cohort Collaboration will continue to monitor prognosis of HIV-1-infected patients who start HAART, and update analyses at regular intervals. The inclusion of patients from resource-poor settings, who are missing from the current analysis, is an important objective for future updates.

#### Contributors

M Egger conceived the ART Cohort Collaboration and coordinated the current analyses. M Egger, J Sterne, A Phillips, and B Ledergerber wrote the first draft of the study protocol. All authors contributed to the final version of the protocol. M May and J Sterne did statistical analyses and developed and validated prognostic models. P Royston advised on the development of prognostic models. M Egger, M May, and J Sterne wrote the first draft of the paper; all authors contributed to the final text. M May, B Beckthold, B Daurer, J Fusco, S Grabar, C Jungmans, V Lavignolle, F van Leth, E Pereira, P Pezzotti, A Phillips, C Sabin, and A Wohrmann were responsible for data management at the statistical centres of individual cohort studies. All investigators assisted in implementation, fieldwork, or data collection at study sites.

#### Conflict of interest statement

A Phillips has received travel grants, grants, consultancy fees, and honoraria from various pharmaceutical companies including Roche, DuPont, Bristol-Myers-Squibb (BMS), Boehringer-Ingelheim, and GlaxoSmithKline (GSK). M Egger has received travel grants, grants, or honoraria from BMS, Boehringer-Ingelheim, and GSK. B Salzberger has received honoraria for presentations at workshops from the following companies: BMS, Dupont Pharmaceuticals, Boehringer-Ingelheim, GSK, and Hoffmann-LaRoche. He has also served as a consultant for Abbott, BMS, GSK, Dupont Pharmaceuticals, and Merck, Sharp and Dohme (MSD), and has received travel grants from Dupont Pharmaceuticals, BMS, GSK, and MSD. B Ledergerber has received travel grants from Roche, Abbott, BMS, GSK, MSD, and Aventis. C Sabin has received honoraria, consultancies, and travel grants from a number of pharmaceutical companies including Roche, BMS, Boehringer Ingelheim, Gilead Sciences, and GSK. M May and J Sterne have received travel grants from GSK.

#### The Antiretroviral Therapy (ART) Cohort Collaboration

*Steering committee*—Dominique Costagliola, François Dabis, Antonella D'Arminio Monforte, Frank de Wolf, Matthias Egger, John Gill, Robert Hogg, Amy Justice, Bruno Ledergerber, Catherine Lepout, Jens Lundgren, Andrew Phillips, Bernd Salzberger, Shlomo Staszewski, Ian Weller.  
*French Hospital Database on HIV (FHDH)*—S Alfandari, F Bastides, E Billaud, A Boibieux, F Boué, F Bricaire, D Costagliola, L Cotte, L Cuzin, F Dabis, S Fournier, J Gasnault, C Gaud, J Gilquin, S Grabar, D Lacoste, JM Lang, H Laurichesse, C Lepout, M Mary-Krause, S Matheron, MC Meyohas, C Michelet, J Moreau, G Pialoux, I Poizot-Martin, C Pradier, C Rabaud, E Rouveix, P Saïag, D Salmon-Ceron, J Soubeyrand, H Tissot-Dupont (Scientific Committee); B Haury, S Courtial-Destembert, G Leblanc (Coordinating Centre, French Ministry of Health); S Abgrall, D Costagliola, S Grabar, L Lièvre, M Mary-Krause, V Potard (Statistical Data Analysis Centre, INSERM SC4).

*Italian Cohort of Antiretroviral-Naive Patients (ICONA)*—M Montroni, G Scalise, A Costantini, A Giacometti (Ancona); U Tirelli, G Nasti (Aviano); G Pastore, N Ladisa, ML Perulli (Bari); F Suter, C Arici (Bergamo); F Chioldo, FM Gritti, V Colangeli, C Fiorini, L Guerra (Bologna); G Carosi, GP Cadeo, F Castelli, C Minardi, D Vangi (Brescia); G Rizzardini, G Migliorino (Busto Arsizio); PE Manconi, P Piano (Cagliari); T Ferraro, A Scerbo (Catanzaro); E Pizzigallo, F Ricci (Chieti); D Santoro, L Pusterla (Como); G Carnevale, D Galloni (Cremona); P Viganò, M Mena (Cuggiono); F Ghinelli, L Sighinolfi (Ferrara); F Leoncini, F Mazzotta, M Pozzi, S Lo Caputo (Florence); G Angarano, B Grisorio, S Ferrara (Foggia); P Grima, P Tundo (Galatina); G Pagano, N Piersantelli, A Alessandrini, R Piscopo (Genova); M Toti, S Chigiotti (Grosseto); F Soccia, L Tacconi (Latina); A Orani, P Perini (Lecco); A Scasso, A Vincenti (Lucca); A Scalzini, G Fibbia (Mantova); M Moroni, A Lazzarin, A Cargnel, GM Vigevani, L Caggese, A d'Arminio Monforte, F Tordato, R Novati, A Galli,

S Merli, C Pastecchia, C Moiola (Milano); R Esposito, C Mussini (Modena); N Abrescia, A Chirrianni, C Izzo, M Piazza, M De Marco, V Montesarchio, E Manzillo, S Nappa (Napoli); A Colomba, V Abbadessa, T Prestileo, S Mancuso (Palermo); C Ferrari, P Pzzaferrì (Parma); G Filice, L Minoi, R Bruno, R Maserati (Pavia); S Pauluzzi, F Baldelli (Perugia); E Petrelli, A Cioppi (Pesaro); F Alberici, A Ruggieri (Piacenza); F Menichetti, C Martinelli (Pisa); C De Stefano, A La Gala (Potenza); T Zauli, G, Ballardini (Ravenna); G Magnani, MA Ursitti (Reggio Emilia); M Arlotti, P Ortolani (Rimini); L Ortona, F Dianzani, G Ippolito (Roma); A Antinori, G Antonucci, S D'Elia, P Narciso, N Petrosillo, V Vullo, A De Luca, L Del Forno, M Zaccarelli, P De Longis, M Ciardi, G D'Offizi, P Noto, M Lichtner, MR Capobianchi, E Girardi, P Pezzotti, G Rezza (Rome); MS Mura, M Mannazzu (Sassari); P Caramello, A Sinicco, ML Soranzo, L Gennero, M Sciandra, B Salassa (Torino); PA Grossi, C Basilio (Varese); A Poggio, G Bottari (Verbania); E Raise, S Pasquinucci (Venezia); F De Lalla, G Tositti (Vicenza); F Resta, A Chimienti (Taranto); A Cozzi Lepri (London).

*Swiss HIV Cohort Study (SHCS)*—M Battegay (Chairman of the Scientific Board), E Bernasconi, H Bucher, Ph Bürgisser, M Egger, P Erb, W Fierz, M Flepp (Chairman of the Clinical and Laboratory Committee), P Francioli (President), HJ Furrer, M Gorgievski, H Günthard, P Grob, B Hirschel, C Kind, Th Klimkait, B Ledergerber, U Lauper, M Opravil, F Paccard, G Pantaleo, L Perrin, J-C Piffaretti, M Rickenbach (Head of Data Center), C Rudin (Chairman of the Mother & Child Substudy), J Schupbach, A Telenti, P Vernazza, Th Wagels, R Weber.  
*AIDS Therapy Evaluation project Netherlands (ATHENA)*—Investigators: S N Blank, F W M N Wit, J M Prins, R P Koopmans, F J B Nellen, M H Godfried, J T M van der Meer, J K M Eeftinck Schattenkerk, T van der Poll, J C Bos, A Verbon, J M A Lange, M van der Valk, Th A Ruys, K Pogany, S H Lowe, O van Doorn, S Sankatsing, D Blanckenberg, P Reiss, P S van Dam, J H ten Veen, M E Hillebrand-Haverkort, H M Weigel, K Brinkman, P H J Frissen, P L Meenhorst, J W Mulder, A T A Malruhu, A van Eeden, S E Geerlings, S A Danner, R M Perenboom, M A van Agtmael, F A P Claessen (Amsterdam); H G Sprenger, W M A J Miesen (Groningen); S vd Geest, G Schreij, A J A M van der Ven (Maastricht); S de Marie, M E van der Ende, I C Gyssens, J L Nouwen (Rotterdam); B Bravenboer (Eindhoven); R W ten Kate (Haarlem); F P Kroon (Leiden); F F Schippers (Leiden); W Bronsveld (Alkmaar); M P Leemhuis (Leeuwarden); D P F van Houte, M Polé (Leeuwarden); C H H ten Napel (Enschede); J R Juttman (Tilburg); P P Koopmans, D S C Telgt (Nijmegen), C A M Schurink, I M Hoepelman, M M E Schneider, C A J J Jaspers, J C C Borleffs, M J M Bonten (Utrecht); F J F Jeurissen, R Vriesendorp, E L W Koger, R H Kauffmann (Den Haag); C Richter, R van Leusen, J van der Berg (Arnhem); W L Blok (Vlissingen). Virology Working Group: J Goudsmit (Leiden), N K T Back, S Jurriaans, F de Wolf, J M A Lange (Amsterdam); A D M E Osterhaus, H M G Niesters, M Schutten (Rotterdam); A C M Kroes, H C J Claas (Leiden); R Schuurman, C A B Boucher (Utrecht).

*The Multicentre Study Group on EuroSIDA (national coordinators in parentheses)*—Austria: (N Vetter), Vienna. Belgium: (N Clumeck), P Hermans, B Sommereijns, Brussels; R Colebunders, Antwerp. Czech Republic: (L Machala), H Rozsypal, Prague. Denmark: (J Nielsen), J Lundgren, T Benfield, O Kirk, J Gerstoft, T Katzenstein, B Røge, P Skinshøj, Rigshospitalet, Copenhagen; C Pedersen, Odense. Estonia: (K Zilmer), Tallinn. France: (C Katlama), M De Sa, J-P Viard, Paris; T Saint-Marc, P Vanhems, Lyon; C Pradier, Nice. Germany: (M Dietrich), C Manegold, J van Lunzen, H-J Stellbrink, Hamburg; V Miller, S Staszewski, Frankfurt; F-D Goebel, Munich; B Salzberger, Cologne; J Rockstroh, Bonn. Greece: (J Kosmidis), P Gargalianos, H Sambatakou, J Perdios, G Panos, I Karydis, A Filandras, Athens. Hungary: (D Banhegyi), Budapest. Ireland: (F Mulcahy), Dublin. Israel: (I Yust), D Turner, Tel Aviv; S Pollack, Z Ben-Ishai, Haifa; Z Bentwich, Rehovot; S Maayan, Jerusalem. Italy: (S Vella, A Chiesi), V Vullo, P Santopadre, P Narciso, A Antinori, P Franci, M Zaccarelli, Rome; C Arici, Bergamo; R Pristerà, Bolzano; F Mazzotta, A Gabbuti, Florence; R Esposito, A Bedini, Modena; A Chirrianni, E Montesarchio, Naples; A Lazzarin, R Finazzi, A D'Arminio Monforte, Milan. Latvia: (L Viksna), Riga. Lithuania: (S Chaplinskas), Vilnius. Luxembourg: (R Hemmer), T Staub, Luxembourg. Netherlands: (P Reiss), Amsterdam. Norway: (J Bruun), A Maeland, V Ormaasen, Oslo. Poland: (B Knysz), J Gasiorowski, Wrocław; A Horban, Warsaw; D Prokopowicz, A Wiercinska-Drupalo, Białystok; A Boron-Kaczmarek, M Pynka, Szczecin; M Beniowski, Chorzów; H Trocha, Gdansk. Portugal: (F Antunes), K Mansinho, R Proença, Lisbon. Romania: A Streinu-Cercel, D Duiculescu. Slovakia: (M Mikras), Bratislava. Spain: (J González-Lahoz), B Diaz, T Garcia-Benayas, L Martín-Carbonero, V Soriano, Madrid; B Clotet, A Jou, J Conejero, C Tural, Badalona; J M Gatell, J M Miró, Barcelona. Sweden: (A Blaxhult), A Karlsson, P Pehrson, Stockholm. Switzerland: (B Ledergerber), R Weber, Zürich; P Francioli, A Telenti, Lausanne; B Hirschel, V Soravia-Dunand, Geneva. UK: (S Barton), A M Johnson, D Mercey, A Phillips, C Loveday, M A Johnson, A Mocroft, A Pinching, J Parkin, J Weber, G Scullard, London; M Fisher, Brighton; R Brettle, Edinburgh Virology group; C Loveday, B Clotet (Central Coordinators) plus ad hoc

virologists from participating sites in the EuroSIDA Study Steering committee: F Antunes, A Blaxhult, N Clumeck, J Gatell, A Horban, A Johnson, C Katlama, B Ledergerber (Chair), C Loveday, A Phillips, P Reiss, S Vella. Coordinating centre staff: J Lundgren (Project Leader), I Gjørup, O Kirk, N Friis-Moeller, A Mocroft, A Cozzi-Lepri, D Mollerup, M Nielsen, A Hansen, D Kristensen, L Kolte, S Aabolt, L Hansen, J Kjør.

*Collaborations in HIV Outcomes Research US (CHORUS)*—S Raffanti, S Becker, A Scarsella, J Braun, A Justice, G Fusco, B Most, R Balu, L Gilbert, R Fleenor, T Ising, D Dieterich, J Fusco.

*Frankfurt HIV Cohort*—S Staszewski, E B Helm, A Carlebach, M Mösch, A Müller, A Haberl, S Korn, C Stephan, M Bickel, P Gute, L Locher, T Lutz, S Klauke (Clinical Group); H W Doerr, M Stürmer (Virology Group); C Sabin (Statistical Analysis); B Dauer (Scientific Advisor); B Jennings (Data Management).

*Antiprotease Cohort (APROCO)*—C Leprot, F Raffi (Principal Investigators); G Chêne, R Salamon (Methodologists); F Brun-Vezinet, H Fleury (Virologists); J-P Moatti, J Pierret (Social scientists); G Peytavin, R Garaffo (Pharmacologists), B Masquelier, B Spire.

*Aquitaine Cohort: Organisation and methodology:* G Chêne, C Marimoutou, F Dabis, R Salamon; *Clinical coordination:* D Lacoste, D Malvy, I Pellegrin, M Dupon, J F Moreau, P Morlat, J L Pellegrin, J M Ragnaud *Participating Hospital Departments (participating physicians):* Bordeaux University Hospital: J Beylot, P Morlat, N Bernard, D Lacoste, C Nouts, C Beylot, MS Doutre, C Conri, J Constans, P Couzigou, H Fleury, I Pellegrin, M Geniaux, A Simon, J Y Lacut, C Cazorla, M Dupon, B Leng, P Mercié, J L Pellegrin, M Le Bras, F Djossou, D Malvy, J P Pivetaud, J F Moreau, J L Taupin, J M Ragnaud, C De La Taille, H Dutronc, D Neau, C Series, A Taytard; Dax Hospital: M Loste, I Blanchard; Bayonne Hospital: F Bonnal, Y Blanchard, S Farbos, M C Gemain; Libourne Hospital: J Ceccaldi, X Jacquelin; Villeneuve-sur-Lot Hospital: E Buy, G Brossard. *Data management and analysis:* M-J Blaizeau, M Decoin, L Dequae-Merchadou, A M Formaggio, M Pontgahet, D Touchard, G Palmer.

*British Columbia Centre for Excellence in HIV*—C Alexander, P Braitstein, K Chan, H Cote, N Gataric, P R Harrigan, M Harris, K Heath, R Hogg, J Montaner, M O'Shaughnessy, E Wood, B Yip.

*Royal Free Hospital Cohort*—F Lampe, C Chaloner, H Gumley, D Ransom, C A Sabin, A Mocroft, M Lipman, A Phillips, M Youle, M Johnson.

*South Alberta Clinic*—J Gill, R Read.

*Köln/Bonn Cohort*—G Fatkenheuer, J Rockstroh, B Salzberger, K Voigt, J C Wasmuth, A Wöhrmann.

#### Acknowledgments

We thank all patients, doctors, data managers, and study nurses who were involved in the participating cohort studies. We also thank Patrick Royston for statistical help. The ART Cohort Collaboration is supported by the UK Medical Research Council (MRC) and GlaxoSmithKline. Sources of funding of individual cohorts include the Agence Nationale de Recherches sur le SIDA (ANRS), the Institut National de la Santé et de la Recherche Médicale (INSERM), the French, Italian and Swiss Ministries of Health, the Dutch Stichting HIV Monitoring, the European Commission, the British Columbia and Alberta Governments, the Michael Smith Foundation for Health Research, the Canadian Institutes of Health Research, and unrestricted grants from GlaxoSmithKline, Roche, and Boehringer-Ingelheim. The Department of Social Medicine of University of Bristol is the lead centre of the MRC Health Services Research Collaboration.

#### References

- 1 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.
- 2 Hogg RS, Yip B, Kully C, et al. Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. *Can Med Assoc J* 1999; **160**: 659–65.
- 3 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.
- 4 Farmer P, Leandre F, Mukherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet* 2001; **358**: 404–09.
- 5 Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; **126**: 946–54.
- 6 Concerted Action on Seroconversion to AIDS and Death in Europe. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. *Lancet* 2000; **355**: 1131–37.
- 7 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.
- 8 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.
- 9 Grabar S, Le Moing V, Goujard C, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. *Ann Intern Med* 2000; **133**: 401–10.
- 10 D'Arminio MA, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. *AIDS* 2000; **14**: 499–507.
- 11 Nieuwkerk PT, Sprangers MA, Burger DM, et al. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. *Arch Intern Med* 2001; **161**: 1962–68.
- 12 Lundgren JD, Phillips AN, Vella S, et al. Regional differences in use of antiretroviral agents and primary prophylaxis in 3122 European HIV-infected patients. *J Acquir Immune Defic Syndr* 1997; **16**: 153–60.
- 13 Becker SL, Raffanti SR, Hansen NI, et al. Zidovudine and stavudine sequencing in HIV treatment planning: findings from the CHORUS HIV cohort. *J Acquir Immune Defic Syndr* 2001; **26**: 72–81.
- 14 Brodt HR, Kamps BS, Gute P, et al. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. *AIDS* 1997; **11**: 1731–38.
- 15 Le Moing V, Thiebaut R, Chene G, et al. Predictors of long-term increase in CD4(+) cell counts in human immunodeficiency virus-infected patients receiving a protease inhibitor-containing antiretroviral regimen. *J Infect Dis* 2002; **185**: 471–80.
- 16 Binquet C, Chene G, Jacqmin-Gadda H, et al. Modeling changes in CD4-positive T-lymphocyte counts after the start of highly active antiretroviral therapy and the relation with risk of opportunistic infections: the Aquitaine cohort, 1996–1997. *Am J Epidemiol* 2001; **153**: 386–93.
- 17 Mocroft A, Barry S, Sabin CA, et al. The changing pattern of admissions to a London hospital of patients with HIV: 1988–1997. Royal Free Centre for HIV Medicine. *AIDS* 1999; **13**: 1255–61.
- 18 Mocroft A, Gill MJ, Davidson W, Phillips AN. Predictors of a viral response and subsequent virological treatment failure in patients with HIV starting a protease inhibitor. *AIDS* 1998; **12**: 2161–67.
- 19 Fatkenheuer G, Theisen A, Rockstroh J, et al. Virological treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients. *AIDS* 1997; **11**: F113–116.
- 20 Centers for Disease Control. Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep* 1992; **41**: 1–20.
- 21 Royston P. Flexible alternatives to the Cox model. *Stata J* 2001; **1**: 1–28.
- 22 Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Control AC* 1974; **19**: 716–23.
- 23 Spiegelhalter DJ, Best NG, Carlin BP, Van der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc B* 2002; **64**: 1–34.
- 24 Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med* 1999; **130**: 515–24.
- 25 Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15**: 361–87.
- 26 Lundgren JD, Mocroft A, Gatell JM, et al. A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study. *J Infect Dis* 2002; **185**: 178–87.
- 27 Fellay J, Marzolini C, Meaden ER, et al. Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. *Lancet* 2002; **359**: 30–36.
- 28 Valdez H, Purvis SF, Lederman MM, Fillingame M, Zimmerman PA. Association of the CCR5delta32 mutation with improved response to antiretroviral therapy. *JAMA* 1999; **282**: 734.
- 29 Schuurman R, Descamps D, Weverling GJ, et al. Multicenter comparison of three commercial methods for quantification of human immunodeficiency virus type 1 RNA in plasma. *J Clin Microbiol* 1996; **34**: 3016–22.
- 30 Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001; **285**: 1736–45.
- 31 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.
- 32 Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. *JAMA* 2001; **286**: 2560–67.
- 33 Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by



- baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 2001; **286**: 2568–77.
- 34 Phillips AN, Lee CA, Elford J, et al. More rapid progression to AIDS in older HIV-infected people: the role of CD4+ T-cell counts. *J Acquir Immune Defic Syndr* 1991; **4**: 970–75.
- 35 Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis* 2001; **183**: 1290–94.
- 36 Yamashita TE, Phair JP, Munoz A, et al. Immunologic and virologic response to highly active antiretroviral therapy in the Multicenter AIDS Cohort Study. *AIDS* 2001; **15**: 735–46.
- 37 Eskild A, Magnus P, Samuelsen SO, Sohlberg C, Kittelsen P. Differences in mortality rates and causes of death between HIV positive and HIV negative intravenous drug users. *Int J Epidemiol* 1993; **22**: 315–20.
- 38 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.
- 39 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.
- 40 Saves M, Vandentorren S, Daucourt V, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort, France, 1996–1998. *AIDS* 1999; **13**: F115–21.
- 41 Chaisson RE, Gallant JE, Keruly JC, Moore RD. Impact of opportunistic disease on survival in patients with HIV infection. *AIDS* 1998; **12**: 29–33.
- 42 Moore AL, Mocroft A, Madge S, et al. Gender differences in virologic response to treatment in an HIV-positive population: a cohort study. *J Acquir Immune Defic Syndr* 2001; **26**: 159–63.
- 43 Gulick RM, Mellor JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997; **337**: 734–39.
- 44 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.
- 45 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.
- 46 Lederman MM, Valdez H. Immune restoration with antiretroviral therapies: implications for clinical management. *JAMA* 2000; **284**: 223–28.
- 47 Harrington M, Carpenter CCJ. Hit HIV-1 hard, but only when necessary. *Lancet* 2000; **355**: 2147–52.
- 48 Egger M, Junghans C, Friis-Moller N, Lundgren JD. Highly active antiretroviral therapy and coronary heart disease: the need for perspective. *AIDS* 2001; **15** (suppl 5): S193–201.
- 49 Miettinen OS. The need for randomization in the study of intended effects. *Stat Med* 1983; **2**: 267–71.

## Clinical picture

### Unilateral anhidrosis of the leg

Joachim H Ficker

A 34-year-old friend of mine complained of an increased sensation of warmth in his left leg. The inside of his right sandal bore dark sweat stains, while that of the left sandal had no such stains (figure). I examined him and found complete anhidrosis of the left leg and tenderness of the left lower quadrant of the abdomen. Computed tomography of the abdomen showed a large left-sided retroperitoneal tumour extending from the pancreas to the aortic bifurcation in close contact with the spinal column. At surgery the tumour was completely removed and histology revealed a malignant extra-testicular germ cell tumour with no lymph node metastases. The patient was given adjuvant chemotherapy. 7 years later, the patient is well and the anhidrosis has completely disappeared. Unilateral anhidrosis of the leg may reflect compression of the sympathetic trunk by an otherwise asymptomatic large retroperitoneal tumour.



Department of Medicine I, University of Erlangen-Nuremberg, 91054 Erlangen, Germany (J H Ficker MD)