HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis

The Antiretroviral Therapy (ART) Cohort Collaboration*

Summary
Background  Highly active antiretroviral therapy (HAART) for the treatment of HIV infection was introduced a decade ago. We aimed to examine trends in the characteristics of patients starting HAART in Europe and North America, and their treatment response and short-term prognosis.

Methods  We analysed data from 22 217 treatment-naive HIV-1-infected adults who had started HAART and were followed up in one of 12 cohort studies. The probability of reaching 500 or less HIV-1 RNA copies per mL by 6 months, and the change in CD4 cell counts, were analysed for patients starting HAART in 1995–96, 1997, 1998, 1999, 2000, 2001, and 2002–03. The primary endpoints were the hazard ratios for AIDS and for death from all causes in the first year of HAART, which were estimated using Cox regression.

Results  The proportion of heterosexually infected patients increased from 20% in 1995–96 to 47% in 2002–03, and the proportion of women from 16% to 32%. The median CD4 cell count when starting HAART increased from 170 cells per μL in 1995–96 to 269 cells per μL in 1998 but then decreased to around 200 cells per μL. In 1995–96, 58% achieved HIV-1 RNA of 500 copies per mL or less by 6 months compared with 83% in 2002–03. Compared with 1998, adjusted hazard ratios for AIDS were 1.07 (95% CI 0.84–1.36) in 1995–96 and 1.35 (1.06–1.71) in 2002–03. Corresponding figures for death were 0.87 (0.56–1.36) and 0.96 (0.61–1.51).

Interpretation  Virological response after starting HAART improved over calendar years, but such improvement has not translated into a decrease in mortality.

Introduction  Accurate prognostic information on HIV-1 disease progression after starting highly active antiretroviral therapy (HAART) is important for patients, physicians, and health care providers. In 2002, the Antiretroviral Treatment (ART) Cohort Collaboration published estimates of the probability of disease progression up to 3 years after starting HAART, according to baseline age, transmission risk group, CD4 cell count, viral load, and clinical disease stage before HAART based on over 12 000 patients starting treatment between 1995 and 2000 in Europe, USA, and Canada. Prognosis might improve with time given greater physician experience with HAART, earlier diagnosis, appropriate management of associated toxicities, and the availability of more potent, and less toxic, drugs. The increasing availability of combined preparations has reduced the pill burden, which might facilitate patient adherence to regimens. Conversely, the emergence of drug-resistant strains of HIV circulating in the infected population and changes in the characteristics of the patients starting HAART could be associated with poorer outcomes.

We analysed the updated database of the ART Cohort Collaboration to examine whether patient characteristics at the time of starting HAART, response to therapy, and disease progression have changed over time, using data combined from 12 cohort studies that followed up antiretroviral-naive patients from when they started therapy.

Methods
Patients  The ART Cohort Collaboration is a collaboration of studies from Europe and North America, established with the aim of describing the prognosis of antiretroviral-naive patients starting HAART. The study design has been described in detail elsewhere. 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; and who had started antiretroviral therapy with a combination of at least three drugs, including nucleoside reverse transcriptase inhibitors, protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs), with a median duration of follow-up of at least 1 year. All cohorts provided data, which had been made anonymous, for a predefined set of demographic, laboratory, and clinical variables.

The database was updated in 2004 to include patients who had started HAART between 2000 and 2003. 12 cohorts contributed data: the French Hospital Database on HIV (FHDH) ANRS CO410 and the Aquitaine Cohort ANRS CO3 (France), the AIDS Therapy Evaluation project Netherlands (ATHENA), Italian Cohort of Antiretroviral-Naive Patients (ICONA), Swiss HIV Cohort Study (SHCS), Frankfurt HIV Cohort and Köln/Bonn Cohort (Germany), the EuroSIDA study (20 countries in Europe and Argentina), the Collaborations in HIV Outcomes Research US (CHORUS, USA), the Royal Free...
Hospital Cohort (UK), the British Columbia Centre for Excellence in HIV/AIDS, and the South Alberta Clinic (Canada).

Statistical analysis
Analyses were stratified by calendar year of starting HAART, with the earliest and latest years (1995–96 and 2002–03) grouped because fewer patients started treatment in these periods. Response to therapy 6 months after starting HAART was measured by the proportion of patients reaching an HIV-1 RNA viral load of 500 copies per mL or less, and by change in CD4 cell count in baseline in patients with available measurements. As pre-specified in the data collection protocol, the measurements of CD4 cell count and HIV-1 viral load nearest to 6 months and between 3 and 9 months after the start of treatment (median time of measurement 5.8 months, IQR 5.2–6.6 months) were used. Multi-variable logistic regression models were used to estimate the odds ratios of undetectable viral load at 6 months after starting therapy for each calendar year. In all analyses, the comparator year was 1998; before that time HAART was rapidly evolving, whereas from 1998 onwards both protease inhibitor-based and NNRTI-based HAART were available.

We examined clinical prognosis based on two endpoints: firstly AIDS events (including AIDS-related deaths), and secondly death from all causes. Kaplan-Meier estimates of the probability of these two endpoints up to 1 year after starting HAART were graphed by calendar year of starting. Cox proportional hazard models were used to estimate the crude and adjusted hazard ratio of these two endpoints for each calendar year. Models were adjusted for age, sex, transmission risk group, baseline CD4 cell count and viral load, and pre-HAART Centers for Disease Control and Prevention (CDC) disease stage, and were stratified by cohort. All patients were censored at 1 year after starting HAART in these analyses. In sensitivity analyses, we censored follow-up at 2 years after start of HAART, and estimated hazard ratios for the combined outcome of AIDS or death from all causes, because misclassification of deaths could lead to underestimation of the number of AIDS events. We also examined AIDS outcomes grouped as tuberculosis and non-tuberculosis AIDS.

We used Stata software version 9.0 for analyses. Results are presented as Kaplan-Meier estimates of the probability of patients reaching an endpoint, and odds ratios or hazard ratios with 95% CIs.

Role of the funding source
No funding source had any involvement in the study design, in the collection, analysis, and interpretation of data, writing of the report, or the decision to submit the paper for publication. 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
Data for 22,217 patients who were aged 16 years and over, were antiretroviral naive before starting HAART, and who started therapy between 1995 and 2003, were available for analyses. 19,560 (88%) patients had CD4 cell counts and 19,164 (86%) viral load measurements at 6 months. Table 1 shows patient characteristics at baseline by calendar year of starting HAART. The median age at

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Age (years)</th>
<th>Women (%)</th>
<th>CD4 cell count (cells per μL)</th>
<th>Log10 viral load</th>
<th>AIDS diagnosis</th>
<th>Transmission risk group</th>
<th>Initial HAART regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Men who have sex with men</td>
<td>Heterosexual drug user</td>
</tr>
<tr>
<td>1995-96</td>
<td>1232</td>
<td>36</td>
<td>170 (67-320)</td>
<td>5.0</td>
<td>386 (44-5.5)</td>
<td>(31%)</td>
<td>(20%)</td>
</tr>
<tr>
<td>1997</td>
<td>4785</td>
<td>35</td>
<td>267 (118-411)</td>
<td>4.9</td>
<td>959 (4.3-5.4)</td>
<td>(20%)</td>
<td>(25%)</td>
</tr>
<tr>
<td>1998</td>
<td>4583</td>
<td>36</td>
<td>269 (110-428)</td>
<td>4.8</td>
<td>970 (4.1-5.3)</td>
<td>(21%)</td>
<td>(25%)</td>
</tr>
<tr>
<td>1999</td>
<td>3699</td>
<td>36</td>
<td>250 (102-405)</td>
<td>4.8</td>
<td>825 (4.2-5.3)</td>
<td>(22%)</td>
<td>(30%)</td>
</tr>
<tr>
<td>2000</td>
<td>3203</td>
<td>37</td>
<td>209 (86-353)</td>
<td>4.9</td>
<td>679 (4.3-5.4)</td>
<td>(24%)</td>
<td>(30%)</td>
</tr>
<tr>
<td>2001</td>
<td>2783</td>
<td>37</td>
<td>198 (86-316)</td>
<td>5.0</td>
<td>689 (4.3-5.4)</td>
<td>(25%)</td>
<td>(30%)</td>
</tr>
<tr>
<td>2002-03</td>
<td>1932</td>
<td>37</td>
<td>202 (90-310)</td>
<td>4.9</td>
<td>477 (4.4-5.4)</td>
<td>(25%)</td>
<td>(34%)</td>
</tr>
<tr>
<td>Total</td>
<td>22,217</td>
<td>36</td>
<td>234 (99-380)</td>
<td>4.9</td>
<td>507 (4.3-5.4)</td>
<td>(23%)</td>
<td>(40%)</td>
</tr>
</tbody>
</table>

IQR=interquartile range. *Counting ritonavir-boosted protease inhibitors as one drug. Data are median (IQR) or n (%), unless otherwise specified.

Table 1: Patient characteristics at baseline by calendar year of starting HAART, ART-CC, 2004
starting HAART changed little over calendar time, but the proportion of female patients increased from 16% in 1995–96 to 32% in 2002–03. There were substantial changes in the proportions of patients in the major presumed transmission groups. 56% of patients starting HAART in 1995–96 were presumed to have been infected via male homosexual contact: this percentage decreased to 34% by 2002–03. By contrast, the proportion of patients infected via heterosexual contact increased from 20% in 1995–96 to 47% in 2002–03. The percentage of patients infected via injection drug use declined from 20% in 1997 to 9% in 2002–03. The remaining patients were infected through contact with contaminated blood (less than 1%) or the mode of transmission was not specified (around 9%).

The median CD4 cell count when starting HAART increased from 170 cells per μL in 1995–96 to 269 cells per μL in 1998 but then decreased to around 200 cells per μL. During 1995–98 most patients started a protease inhibitor-based HAART regimen whereas, from 1999 onwards, at least 40% started HAART with NNRTI-based regimens. The proportion of patients starting HAART with four or more drugs (counting ritonavir-boosted protease inhibitors as one drug) increased from 1% in 1995–96 to 11% in 2002–03.

Table 2 shows virological and immunological response to HAART by calendar year of starting HAART. In 1995–96, 58% of patients achieved an HIV-1 RNA of 500 copies per mL or less by 6 months; this increased to 73% in 1997 and 81% in 2002–03. Median post-HAART change in CD4 cell count at 6 months was slightly lower in 1995–96 compared with later years. Table 3 shows adjusted odds ratios for reaching HIV-1 RNA of 500 copies per mL or less at 6 months after starting HAART, by calendar year of starting HAART for all patients and separately for the three major transmission risk groups. Compared with 1998, the adjusted hazard ratios in 2002–03 were 1·18 (0·78–1·78) for men who have sex with men, 1·52 (1·07–2·16) for heterosexually infected patients, and 1·73 (0·84–3·55) for injecting drug users (webtable 1). However, CIs were wide and the test for interaction between transmission risk group and linear trend over time gave p=0·24. Adjusted mortality hazard ratios did not differ greatly with calendar year (table 4).

The figure shows Kaplan-Meier estimates of the cumulative proportion of AIDS (top) and death (bottom) for the first year after starting HAART, separately for time periods 1995–97, 1998–99, and 2000–03. The figure shows a lower proportion in 1998–99 than in either the earlier or later years. The estimated probability of death up to 1 year after starting HAART did not differ greatly by calendar period. Table 4 shows crude and adjusted hazard ratios from multivariable Cox models, for AIDS and for death from all causes, by calendar year. Compared with 1998, the adjusted hazard ratio for AIDS was 1·30 (95% CI 1·09–1·54) in 1997 and 1·35 (1·06–1·71) in 2002–03. There was some evidence that AIDS trends over time differed between transmission risk groups; compared with 1998, the adjusted hazard ratios in 2002–03 were 1·18 (0·78–1·78) for men who have sex with men, 1·52 (1·07–2·16) for heterosexually infected patients, and 1·73 (0·84–3·55) for injecting drug users (webtable 1). However, CIs were wide and the test for interaction between transmission risk group and linear trend over time gave p=0·24. Adjusted mortality hazard ratios did not differ greatly with calendar year (table 4).
In sensitivity analyses, the trend over calendar time in hazard ratios for the combined endpoint of AIDS or death was less marked than the trend for AIDS alone. For example, the adjusted hazard ratios comparing 2002–03 with 1998 were 1·26 (1·01–1·58) for AIDS or death but 1·35 (1·06–1·71) for AIDS (webtable 2). The estimated hazard ratios from models in which follow-up was censored at 2 years after start of treatment were much the same as the reported estimates based on 1 year of follow-up (webtable 3).

We investigated whether the increase in AIDS events in the most recent years was attributable to an increase in tuberculosis incidence. In the analysis with tuberculosis as outcome, follow-up time was censored at non-tuberculosis AIDS events, and vice versa. Table 5 shows the crude and adjusted hazard ratios separately for tuberculosis and non-tuberculosis AIDS for all patients. The analysis shows that the increase in AIDS in 2002–03 compared with 1998 is largely attributable to an increase in tuberculosis; the adjusted hazard ratio for tuberculosis was 2.94 (1·70–5·08) compared with 1·15 (0·88–1·50) for non-tuberculosis AIDS.

**Discussion**

The results of this collaborative study, which involved 12 prospective cohorts and over 20 000 patients with HIV-1 from Europe and North America, show that the virological response after starting HAART has improved steadily since 1996. However, there was no corresponding decrease in the rates of AIDS, or death, up to 1 year of follow-up. Conversely, there was some evidence for an increase in the rate of AIDS in the most recent period. These trends were accompanied by changes in the characteristics of patients starting HAART. In the early years when HAART was being introduced, most patients were men who have sex with men, but by 2002–03 most patients starting HAART had been infected through heterosexual transmission. Over the same time, the proportion of female patients doubled. The median CD4 cell count when starting HAART has declined in recent years.

The discrepancy between the clear improvement we recorded for virological response and the apparently worsening rates of clinical progression might be related to the change in the demographic characteristics of study participants, with an increasing number of patients from areas with a high incidence of tuberculosis. For example, in the Swiss HIV Cohort Study there was a steady increase in the number of patients from sub-Saharan Africa. These patients were younger, more likely to be female, and more likely to have been infected heterosexually than other study participants. Also, they had lower CD4 cell counts at the start of treatment.

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**Table 4:** Crude and adjusted hazard ratios for AIDS and death by year of starting HAART, ART-CC, 2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>Events</th>
<th>Crude hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)</th>
<th>Patients</th>
<th>Deaths</th>
<th>Crude hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995–96</td>
<td>1096</td>
<td>103 (9%)</td>
<td>1·55 (1·23–1·97)</td>
<td>1·07 (0·84–1·36)</td>
<td>1232</td>
<td>27 (2·2%)</td>
<td>1·20 (0·77–1·87)</td>
<td>0·87 (0·56–1·36)</td>
</tr>
<tr>
<td>1997</td>
<td>4460</td>
<td>287 (6%)</td>
<td>1·23 (1·03–1·46)</td>
<td>1·30 (1·09–1·54)</td>
<td>4785</td>
<td>98 (2·1%)</td>
<td>1·13 (0·85–1·52)</td>
<td>1·12 (0·84–1·51)</td>
</tr>
<tr>
<td>1998</td>
<td>4222</td>
<td>222 (5%)</td>
<td>1</td>
<td>1</td>
<td>4583</td>
<td>85 (1·9%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1999</td>
<td>3328</td>
<td>192 (6%)</td>
<td>1·08 (0·89–1·32)</td>
<td>1·07 (0·88–1·30)</td>
<td>3699</td>
<td>67 (1·8%)</td>
<td>1·00 (0·72–1·38)</td>
<td>0·93 (0·67–1·29)</td>
</tr>
<tr>
<td>2000</td>
<td>2873</td>
<td>204 (7%)</td>
<td>1·35 (1·11–1·63)</td>
<td>1·18 (0·97–1·43)</td>
<td>3203</td>
<td>63 (2·0%)</td>
<td>1·06 (0·76–1·47)</td>
<td>0·93 (0·67–1·29)</td>
</tr>
<tr>
<td>2001</td>
<td>2421</td>
<td>172 (7%)</td>
<td>1·35 (1·10–1·65)</td>
<td>1·23 (1·00–1·50)</td>
<td>2783</td>
<td>49 (1·8%)</td>
<td>1·02 (0·75–1·45)</td>
<td>0·87 (0·64–1·24)</td>
</tr>
<tr>
<td>2002–03</td>
<td>1656</td>
<td>105 (6%)</td>
<td>1·46 (1·15–1·85)</td>
<td>1·35 (1·06–1·71)</td>
<td>1932</td>
<td>25 (1·3%)</td>
<td>1·09 (0·69–1·71)</td>
<td>0·96 (0·61–1·51)</td>
</tr>
</tbody>
</table>

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**Figure:** Kaplan-Meier estimates of cumulative proportion of (A) AIDS and (B) death by calendar year of starting HAART, ART-CC, 2004
presentation, and the most frequent AIDS-defining event was tuberculosis.27 Similar trends have been seen in other European countries and in North America.24–27 In the USA, the rates of tuberculosis are increasing in foreign-born people, and outbreaks are increasingly common in other groups at high risk of HIV infection, including prisoners,26 homeless people,27 and gay, transvestite, and transsexual HIV-infected men.28 Immune reconstitution disease, an adverse consequence of restoration of pathogen-specific immune responses, might also be a problem, particularly in those infected with tuberculosis. This disease could have become more common in later years with the occurrence of more rapid reduction in viral replication and increase in CD4 cells due to the use of more potent antiretroviral drugs.29 The increasing number of heterosexual infected immigrants and refugees cannot fully explain the trends seen in our study. The same trends in the rate of AIDS were also present, although somewhat weaker, in men who have sex with men. Also, although the average CD4 cell count at baseline varied by transmission risk group, the same pattern of increase and decline with calendar periods was seen for each risk group, and for both sexes. We noted that the median time to the first AIDS event after starting HAART decreased over time.

In this collaborative study, AIDS diagnoses are not centrally reviewed or verified. The increase might thus be artifactual if ascertainment has become more complete in recent years. This might have been particularly true for tuberculosis, because of the growing awareness of physicians about co-infection.25,26,30 However, ascertainment bias is unlikely, because all cohorts use the same criteria for the prospective diagnosis of AIDS-defining events,32 and study clinics are based in special centres with extensive expertise in HIV medicine. Worse outcomes are also unlikely to be due to more drug-resistant strains of HIV in the population, as viral suppression at 6 months improved over calendar time, and the analysis was restricted to the first year of HAART. Indeed, improvements in viral suppression could conceivably translate into reduced rates of AIDS and death later on.

Unlike previous studies that have looked at changes in survival by calendar period,11,14 all patients in this study were followed-up from initiation of HAART and had not been previously exposed to antiretroviral therapy. Results are therefore not confounded by previous antiretroviral treatment. The database included patients from many countries in Europe and North America who started HAART in different settings since 1995. The spectrum of patients was broad: men and women, teenagers and elderly people were included, and the major exposure categories were well represented. The severity of immunodeficiency at baseline ranged from severe to non-existent, and viral replication from undetectable to extremely high. Our results should therefore be generalisable to other settings.

Limitations include the lack of data for ethnicity or country of origin. Information on immigrants is not obtained routinely in the studies participating in the ART Cohort Collaboration, and their contribution in the context of the trends seen could not be examined directly. However, we note that tuberculosis largely accounted for the reported increase in AIDS events. Also, we do not have adequate information on causes of death for all patients, which means that we are unable to discern whether the stability of mortality rates over time results from reductions in AIDS-related mortality being offset by an increase in competing non-HIV related causes of death.39 Finally, our results might be affected by selection bias because 12% and 14% of patients had missing CD4 cell counts and viral load measurements, respectively, at 6 months. The results are consistent with those from another multi-cohort analysis,38 which included studies not represented in the present collaboration.

The improvement in virological response was most pronounced in men who have sex with men, and less noticeable in heterosexual infected patients. In patients with a history of injecting drug use the picture was more complex, with an initial improvement followed by a worsening of virological response in later years. In earlier years, patients infected via injecting drug use might have been selected on the basis of their likely adherence to therapy, whereas such selection might have been less pronounced in more recent years. Clearly, the reasons why injecting drug users and heterosexual infected patients do not seem to achieve the same treatment response as do men who have sex with men need to be examined and strategies to improve outcomes developed and implemented.

The decline of CD4 cell count when starting HAART in recent years must also be of concern. Patients starting
treatment with CD4 count less than 200 cells per μL are at higher risk of disease progression and death in the long term compared with those with higher baseline CD4 cell counts. Early diagnosis and treatment is therefore of great importance to prevent clinical progression. A survey of new HIV diagnoses in the UK and Ireland showed that many opportunities for earlier diagnosis are missed.19 Our results indicate that such oversights could be common in many countries and settings, and that therefore an expansion of voluntary and cost-effective screening in health-care settings is likely to be beneficial.20 The ART Cohort Collaboration will continue to monitor the characteristics and prognosis of HIV-infected patients starting HAART and update analyses at regular intervals.

Contributors
M Egger conceived the ART Cohort Collaboration and wrote the original proposal with B Ledergerber, J Lundgren, J Sterne, and A Phillips. All M Egger wrote the first draft of the paper. C Sabin, A Phillips, A Justice, F Dabis, J Gill, J Lundgren, R Hogg, F de Wolf, G Fätkenheuer, S Staszewski, and A d’Arminio Monforte contributed to discussions on statistical analyses and to writing the paper.

Conflict of interest statement
We declare that we have no conflict of interest.

The Antiretroviral Therapy (ART) Cohort Collaboration


The members of the 12 study groups were as follows: French Hospital de Wolf: Matthaus Egger, John Gill, Robert Hogg, Amy Justice, Mari Kitahata, Bruno Ledergerber, Catherine Leport, Jens Lundgren, Margaret May, Andrew Phillips, Peter Reiss, Michael Saag, Caroline Sabin, Norbert Schmeiser, Schlorno Staszewski, Jonathan Sterne, Ian Weller.


Articles

A Phillips, C Sabin, C Smith (Epidemiology/Biostatistics); E Annoh, G Clewley, I Damm, B Gregory, J Jani, G Janossy, M Kahan, C Lovelady, M Thomas (Laboratory) South Alberta Clinic (1 site); J Gill, R Read, Köln/Bonn Cohort (2 sites): G Fätkenheuer, J Rockstroh, N Schmeisser, K Voigt, J C Wasmuth, A Wohrmann.

References


