

## COHORT PROFILE

# Cohort Profile: Antiretroviral Therapy Cohort Collaboration (ART-CC)

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The advent of effective combination antiretroviral therapy (ART) in 1996 resulted in fewer patients experiencing clinical events, so that some prognostic analyses of individual cohort studies of human immunodeficiency virus-infected individuals had low statistical power. Because of this, the Antiretroviral Therapy Cohort Collaboration (ART-CC) of HIV cohort studies in Europe and North America was established in 2000, with the aim of studying the prognosis for clinical events in acquired immune deficiency syndrome (AIDS) and the mortality of adult patients treated for HIV-1 infection. In 2002, the ART-CC collected data on more than 12,000 patients in 13 cohorts who had begun combination ART between 1995 and 2001. Subsequent updates took place in 2004, 2006, 2008, and 2010. The ART-CC data base now includes data on more than 70 000 patients participating in 19 cohorts who began treatment before the end of 2009. Data are collected on patient demographics (e.g. sex, age, assumed transmission group, race/ethnicity, geographical origin), HIV biomarkers (e.g. CD4 cell count, plasma viral load of HIV-1), ART regimen, dates and types of AIDS events, and dates and causes of death. In recent years, additional data on co-infections such as hepatitis C; risk factors such as smoking, alcohol and drug use; non-HIV biomarkers such as haemoglobin and liver enzymes; and adherence to ART have been collected

whenever available. The data remain the property of the contributing cohorts, whose representatives manage the ART-CC via the steering committee of the Collaboration. External collaboration is welcomed. Details of contacts are given on the ART-CC website ([www.art-cohort-collaboration.org](http://www.art-cohort-collaboration.org)).

**Keywords** HIV, AIDS, cohort study, antiretroviral therapy, prognosis

## Why was the cohort set up?

The Antiretroviral Therapy Cohort Collaboration (ART-CC) was established in 2000 to study the prognosis for adult patients treated for human immunodeficiency virus-1 (HIV-1) infection in Europe and North America. The widespread use since 1996 of combination antiretroviral therapy (ART) has substantially improved the prognosis for HIV-positive patients as compared with those treated with previously available drug regimens of nucleoside reverse transcriptase inhibitors (NRTIs), either in the form of monotherapy with zidovudine or as dual therapy with a second NRTI.<sup>1</sup>

The substantial reductions in the number of events and deaths related to acquired immune deficiency syndrome (AIDS) following the introduction of combination ART meant that modelling of prognosis among different patient groups and according to different prognostic factors often required larger numbers of patients than were available in individual cohorts at that time. Therefore, the important task of defining prognosis and prognostic factors in the era of combination ART required several cohorts to contribute data to a collaborative data base. The prognosis for patients starting treatment with combination ART, defined as a combination of at least three drugs belonging to two different classes of drugs, depends on their prior exposure to NRTI monotherapy or dual therapy, because the development of resistance to NRTI drugs as a result of incomplete viral suppression meant that 'treatment-naïve' patients who had not previously been treated when they began triple ART had a better prognosis. Because future patients would begin treatment with triple ART rather than with NRTIs, treating physicians and their patients needed to know the prognosis for treatment-naïve patients starting combination ART according to their demographic characteristics, disease stage, and treatment options. The ART-CC was able to address this key clinical question and thereby improve care for HIV-positive patients.

The co-ordinating centre of the ART-CC was established in the Department of Social Medicine (now the School of Social and Community Medicine) of the University of Bristol, UK. An annual international workshop for researchers working with observational cohorts of HIV-positive patients had been set up in 1997, under the sponsorship of the pharmaceutical company GlaxoSmithKline. At the fourth such

workshop, held in 2000 in Marbella, 16 cohorts, in Europe and North America, were approached, and 13 agreed to participate in the collaboration. The ART-CC Steering Committee consists of the Principal Investigator, a representative from each cohort, the co-ordinating team and representatives of patient groups. GlaxoSmithKline funded the first 6 months of the study, and it has since been funded by the UK Medical Research Council together with the fund providers for the contributing cohorts (see Appendix). The aim of the ART-CC, as specified in its detailed Principles of Collaboration, is 'to examine the prognosis of HIV-infected, antiretroviral drug-naïve patients starting combination ART, with a focus on questions that cannot be fully addressed in analyses of data from individual cohorts. In particular, analyses will focus on prognosis of major clinical events (particularly AIDS, AIDS-defining conditions, and all-cause and cause-specific mortality).'

## Which cohorts contribute to the collaboration?

The ART-CC is a collaboration of HIV cohort studies in Europe and North America. [Table 1](#) lists the cohorts that have contributed data to the ART-CC. Prospective cohort studies are eligible to participate if they have enrolled at least 100 HIV-1-positive patients aged 16 years or older who have not previously received antiretroviral treatment, who began ART with a combination of at least three antiretroviral drugs after 1996, and who have been followed for a median of at least 1 year after the initiation of ART. Patients are eligible only if they have had at least one measurement of their CD4 cell count and plasma viral load of HIV-1 RNA within 3 months before starting ART. All cohorts 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 for their patients.

## Who are the participants in the cohorts?

Each cohort in the ART-CC recruits patients in different ways, and the cohorts therefore differ in how

**Table 1** Description of cohorts in the Antiretroviral Therapy Cohort Collaborative

<b>Cohort</b>	<b>Cohort established</b>	<b>Joined ART-CC</b>	<b>Coverage and facilities</b>	<b>Representativeness</b>
<b>European</b>				
AIDS Therapy Evaluation Project (ATHENA), Netherlands	1998	2001	Provides 100% of national coverage. Facilities are entirely hospital-based.	Reported to be representative of the country.
ANRS CO3 Aquitaine, France	1998	2001	Provides 90% of provincial coverage. Facilities are entirely hospital-based.	Reported to be representative of the south-western part of France.
Köln/Bonn cohort, Germany	1997	2001	Two cities: Köln and Bonn. Facilities are entirely hospital-based.	Reported to be representative of the country.
Cohorte de la Red de Investigación en Sida (CoRIS), Spain	2004	2008	Provides 35% of national coverage. Facilities are entirely hospital-based except for one facility.	Reported to be representative of the country.
EuroSIDA Study Group	1994	2001	A multi-national cohort. Because this in many cases consists of university-based clinics in the capitals of the countries involved, EuroSIDA probably reflects the gold standard of management in participating countries.	Representative for the clinics included in the study.
ANRS CO4 French Hospital Database on HIV (FHDH)	1989	2001	Provides 57% of national coverage. Facilities are entirely hospital-based.	Reported to be largely representative of patients under care in the country. Includes French overseas territories
Frankfurt, Germany	1988	2001	One city: Frankfurt. Facilities are entirely hospital-based.	Reported to be largely representative of the country, but over-representative of women.
Italian Cohort of Antiretroviral-Naive Patients (ICONA), Italy	1997	2001	100% regional coverage. Facilities are entirely hospital-based.	Reported to be representative of all Italy.
Proyecto para la Informatización del Seguimiento Clínico-epidemiológico de la Infección por HIV y SIDA (PISCIS) Cohort, Spain	2000	2006	Provides 66% coverage of Catalonia and 80% coverage of of Balearic Islands. Facilities are entirely hospital-based.	Is not reported to be representative of the country, but aims to reach representativeness at regional level by 2013.
Royal Free Hospital Cohort, London, UK	1989	2001	One city hospital. Facilities are entirely hospital-based.	Is not reported to be representative of the country, but somewhat over-representative of men and people of white ethnicity.
Swiss HIV Cohort Study (SHCS), Switzerland	1988	2001	Provides 73% of national coverage. Facilities are entirely hospital-based. Patients are followed by hospital-based clinics and private physicians.	Is not reported to be representative of the country, but under-representative of those of sub-Saharan African ethnicity and of IDUs.

(continued)

Table 1 Continued

Cohort	Cohort established	Joined ART-CC	Coverage and facilities	Representativeness
<b>North American</b>				
South Alberta Clinic Cohort, Canada	1989	2001	Provides 50% of provincial coverage. Facilities are entirely community based.	Is not representative of the country, but representative of the province and over-representative of those of African/north American aboriginal ethnicity.
HAART Observational Medical Evaluation and Research (HOMER), British Columbia, Canada	1996	2001	Provides 99% of provincial coverage. Facilities are hospital and community-based.	Is representative of BC since it is a census of everyone on ART, but over-representative of those of Aboriginal ethnicity and IDUs compared with Canada overall.
HIV Atlanta Veterans Affairs Cohort Study (HAVACS), USA	1982	2008	Veterans in one city. Facilities are entirely hospital-based.	Is not reported to be representative of the country, but over-representative of men, older patients, those of black ethnicity and those who abuse alcohol.
University Alabama, Birmingham (UAB), USA	1992	2006	One city hospital. Facilities are entirely hospital-based.	Reported to be largely representative of the country, but over-representative of those of black ethnicity and under-representative of Latinos and Hispanics.
Veterans Aging Cohort Study (VACS), USA	1997	2008	Veterans database. Facilities are hospital and community-based.	Is not reported to be representative of the country, but over-representative of men and older patients.
Vanderbilt-Meharry Center for AIDS Research, Nashville, Tennessee, USA	1994	2008	Regional. Facilities are entirely community based.	Is representative of HIV demographic in USA with 35-40% African- American ethnicity.
University of Washington HIV Cohort, Seattle, USA	1995	2006	Facilities are hospital and community based.	Is representative of the Northwestern USA.

\*Cohorts that joined ART-CC and have since dropped out: ANRS CO 8 APROCO, France, Collaborations in HIV Outcomes Research-US (CHORUS) cohort, USA and VACH, Spain. IDU Injection drug use; ANRS Agence Nationale de la Recherches sur le SIDA et les hépatites virales. Abbreviations: AIDS, acquired immune deficiency syndrome; ATHENA, AIDS Therapy Evaluation Project Netherlands; HAART, highly active antiretroviral therapy; SIDA, síndrome de inmunodeficiencia adquirida; UAB, University of Alabama at Birmingham.

representative they are of their local HIV-positive and treated populations. Only a few cohorts, such as the Swiss HIV Cohort Study (SHCS), estimate the rate of response to requests for participation. For example, the ANRS CO4 French Hospital Database on HIV (FHDH), together with the ANRS C03 Aquitaine Cohort, are likely to be fairly representative of the French HIV-positive population in whom a diagnosis has been made and who are in care. However, the Veterans Aging Cohort Study (VACS) includes only veterans of the US armed forces and is therefore not representative of the HIV-positive population of the US. Table 1 provides details of the cohorts in the ART-CC, including the ways in which their patients are recruited and whether they consider their participants to be representative of HIV positive people in their region or country. A strength of the ART-CC is that most participating cohorts recruit patients who are in usual clinical care for HIV infection in a particular geographic setting, as opposed to subjects specifically recruited for the purpose of an epidemiological study, such as a randomised controlled trial. Figures 1 and 2 show maps indicating the sites of cohorts that contribute to the ART-CC.

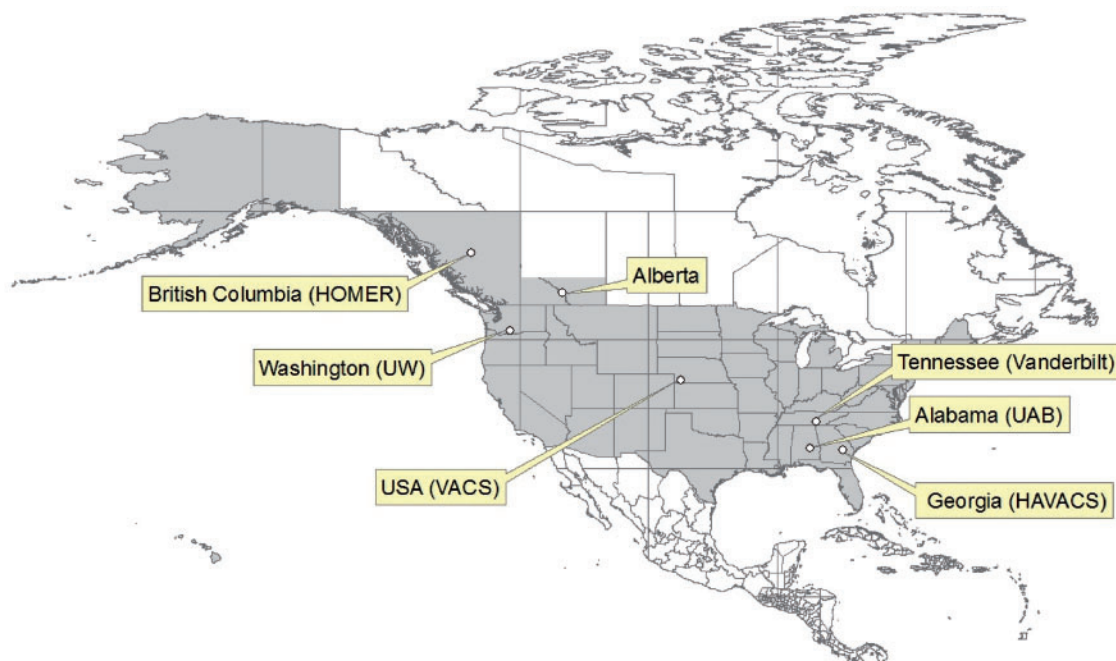
### How often has the database been updated?

The ART-CC database is updated approximately every 2 years. A protocol is written for the data extraction for each update; it specifies names and descriptions of variables collected, eligibility criteria, and coding

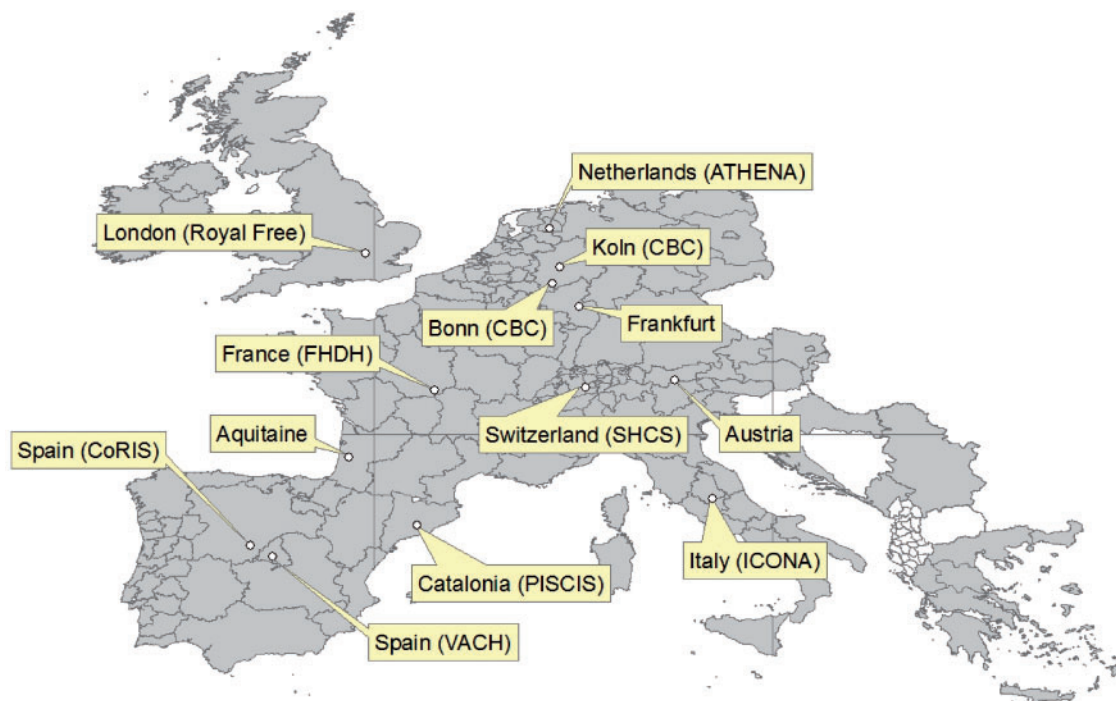
tables for opportunistic infections and antiretroviral drugs. The ART-CC data base has used the HIV Cohorts Data Exchange Protocol (HICDEP: [www.hicdep.org](http://www.hicdep.org)) since 2008. The first ART-CC database was compiled in 2001 and included 13 cohorts that contributed information on 12 574 patients. In 2004 the update collected longer follow-up data on existing patients as well as data on new patients who had started treatment in more recent years. Table 2 provides further information about updates in 2006, 2008, and 2010, including the number of cohorts and patients in each data set. The 2012 update is currently under way.

### What has been measured?

The variables collected at each update of the ART-CC data set have become more extensive over the years and are listed in Table 2. The first data set included only basic demographic, laboratory, and clinical variables at the beginning of a patients ART and at 6 months after the beginning of ART. In contrast, the most recent update collected comprehensive longitudinal data for laboratory values (including both prognostic markers in HIV infection such as CD4 cells and viral load, and non-HIV-specific biomarkers such as haemoglobin and creatinine), start and stop dates of antiretroviral drugs used during the observation period and the reasons for changes in a drug regimen, and data on causes of death. A panel of experts has retrospectively validated causes of death in ART-CC, using the CoDe system (<http://www.cphiv.dk/CoDe/tabid/55/Default.aspx>).<sup>2</sup>



**Figure 1** Map of North American cohorts in the Antiretroviral Therapy Cohort Collaboration



**Figure 2** Map of European cohorts in the Antiretroviral Therapy Cohort Collaboration. EuroSIDA covers 31 European countries plus Israel and Argentina; the Infección por HIV y SIDA (PISCIS) Cohort includes two regions: Catalonia and the Balearic Islands

Table 3 shows baseline characteristics of patients in each of the 19 ART-CC cohorts that supplied data for the 2010 update. The ANRS C04 FHDH cohort, which recruits patients from most regions of France, contributes the largest number of patients. The cohorts are heterogeneous in nature and outcomes.<sup>3</sup> Reported percentages of patients who have died vary from 1.4% in the Frankfurt cohort to 19% in the HOMER cohort, which recruited a large number of injection-drug users (IDUs). The proportion of female participants also varies greatly among cohorts, from 1.6% in HAVACS (a cohort of US military veterans) to 33% in FHDH (which has a large proportion of immigrants from sub-Saharan Africa).

### What is the extent of attrition?

Overall rates of loss to follow-up in the different ART-CC cohorts has ranged from 2%–18%, depending on opportunities for access to care outside the contributing centres, and cohorts' ability to track patient transfers and pursue patients who miss appointments. Thus, for example, losses to follow-up in the Royal Free cohort are partly due to patients' attending alternative clinics in London. In France, IDUs and immigrants, and patients with lower CD4 cell counts and higher viral loads, were more likely to be lost to follow-up. In contrast, patients in Switzerland with higher CD4 cell counts were more likely to be lost to follow up.

### What are the major findings to date?

#### Prognosis from the beginning of antiretroviral therapy and after accounting for response to therapy

Our first paper on the prognosis for HIV-1-infected patients from beginning of ART was published in 2002.<sup>4</sup> This and several other papers from the ART-CC have been cited in treatment guidelines.<sup>5–7</sup> We showed that the CD4 cell count at which individuals began ART strongly predicted disease progression. A higher viral load, older age, infection via injection-drug use, and a diagnosis of AIDS before the initiation of treatment were also predictors of poorer outcome. The probability of death within 3 years after the beginning of treatment ranged from 0.8%–43%, depending on these risk factors. The prognostic modelling methodology<sup>8</sup> has been used by several other collaborations,<sup>9,10</sup> and the ART-CC prognostic model has been validated with data from the CASCADE collaboration.<sup>11</sup> Further work examined the way in which prognosis depends on the initial response to ART.<sup>12</sup> Viral load and CD4 cell count at 6 months strongly predicted subsequent survival, whereas the values measured at the beginning of treatment no longer predicted survival after accounting for the 6 month measurements.

Analyses were updated in 2007 to include new patients who began ART up to 2003 and a longer

**Table 2** Measurements collected at each data update in the Antiretroviral Therapy Cohort Collaboration

Update	Cohorts N	Patients N	Data collected
2001	13	12 574	Demographic variables: age, sex, risk factors for transmission Laboratory variables: CD4 cell counts and viral loads at start of ART and at 6 months Clinical variables: ART start date, ART drug regimen at baseline, CDC disease stage at start of ART Outcome variables: AIDS events, last visit date, death, death date
2004	12	22 217	As above
2006	15	49 040	As above, plus: Demographic variables: Race/ethnicity, geographical origin based on country of birth, nationality Laboratory variables: CD4 cell count closest to event/death and last count during treatment, with dates. At least one 3-year measurement of each prognostic variable (CD4 cell count, HIV-1 RNA plasma viral load, haemoglobin), with dates and an indicator variable for being on/off treatment, and whether patient experienced virological failure (defined as a viral load of >500 during treatment) after 6 months and within 3 years of initiating treatment Clinical variables: Total number of ART drugs and classes to which patient was exposed at 3 years, whether patient has changed treatment from initial regimen, as ascertained when available Outcome variables: Causes of death, loss to follow-up indicator, and reason for loss to follow-up
2008 <sup>a</sup>	18	59 483	As above, plus: Demographic variables: current alcohol, injection-drug use and smoking Laboratory variables: longitudinal measurements of CD4 cells and viral load are now available, as well as other longitudinal laboratory measures (such as alanine aminotransferase, creatinine) and virology measures (such HCV/HBV status) Clinical variables: Detailed information about start/stop dates of drugs and reasons for drug changes.
2010	19	74 048	As above

<sup>a</sup>Data were collected according to the HICDEP (see <http://hicdep.org>) format from the 2008 update onwards. This enabled collection of longitudinal data.

Abbreviations: ANRS, Agence Nationale de Recherche SIDA; ART, antiretroviral therapy; CDC, US Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injection-drug user.

follow-up of existing patients in the ART-CC database.<sup>13</sup> Cumulative probabilities of AIDS and death at up to 5 years from the beginning of ART were provided in the paper that described the update<sup>13</sup> and as an interactive risk calculator on the ART-CC website ([www.bris.ac.uk/art-cc/research/calculator/](http://www.bris.ac.uk/art-cc/research/calculator/)). We investigated, in patients treated for at least 3 years, the prognostic importance, for AIDS and death, of the CD4 cell count and HIV-1 viral load measured at the beginning of ART and at 6 and 36 months later.<sup>14</sup> Although the most recent values of the CD4 cell count and viral load are the most important prognostic factors, changes in the CD4 cell count from 6 to 36 months after the beginning of ART, and the value of the viral load at 6 months, were also prognostic for AIDS.

We showed that the incidence of all AIDS-defining events decreased substantially after the beginning of ART, and that the decline was most pronounced for events with a viral aetiology.<sup>15</sup> We found that some patient groups, such as men who have sex with men, experience a greater benefit from ART than do other

groups,<sup>16</sup> and that AIDS-related events differed in their importance for subsequent prognosis.<sup>17</sup> In later updates data were collected on non-HIV biomarkers, for example, haemoglobin, liver enzymes and creatinine, and were incorporated into prognostic models.<sup>18</sup>

### Trends in mortality over time, life expectancy and cause-specific mortality

In 2006, after a decade of availability of combination ART, we reported on trends over time in the response to treatment for HIV and the prognosis for treated patients.<sup>19</sup> Standardised mortality rates in HIV-positive individuals were compared with those in country-matched background populations.<sup>20</sup> Estimates of life expectancy were shown to have increased by some 13 years for patients in whom ART was begun from 2003–2005 as compared with 1996–1999, with an accompanying decline in mortality of nearly 40% in the same period.<sup>21</sup> However, life expectancy in these patients remained well short of that of the general population, and patients treated later in the course of their infection had a shorter life expectancy.

**Table 3** Antiretroviral Therapy Cohort Collaborative data on numbers of patients, follow-up time, patient demographics, median CD4 cell count, and logarithm of viral load at start of antiretroviral therapy by cohort and overall: 2010 update

Cohort <sup>a</sup>	Number of patients (%)	Person-years of follow up	Median age (years)	Female (%)	AIDS at start of ART (%)	Risk transmission group					Median CD4+ cell count (cells/ml)	Median log Viral load (Log copies/ml)
						IDU (%)	MSM (%)	Hetero-sexual sex (%)	Blood products (%)	Other or unknown (%)		
ATHENA	6742 (9.1)	36 578	37	24	25	3	51	38	1.2	7	190	4.9
Alberta	706 (1.0)	3158	37	20	44	21	44	34	1.1	0.7	193	4.8
Aquitaine	1298 (1.8)	7029	36	25	12	15	43	34	2	6	273	4.8
HOMER	2839 (3.8)	13 931	39	18	16	30	16	5	0.4	49	180	5
Köln/Bonn	1078 (1.5)	4486	37	22	45	5	49	19	2.1	25	170	5
CoRIS	994 (1.3)	1828	37	26	26	18	33	45	0	4	181	5
EuroSIDA	1736 (2.3)	7725	36	24	20	15	46	33	0.5	6	211	5
FHDH	29 464 (40)	1 49 780	37	33	22	10	30	50	1.3	9	233	4.7
Frankfurt	146 (0.2)	258	38	23	19	10	49	31	0.7	9	186	5.2
HAVACS	386 (0.5)	1881	43	2	26	13	47	7	0	33	182	5
ICONA	3227 (4.4)	16 997	36	28	18	32	23	39	0.6	6	252	4.9
PISCIS	2970 (4.0)	11 841	36	23	22	29	30	37	0.7	4	210	5
Royal Free	1385 (1.9)	6156	36	27	26	2	53	43	0	2	194	5.1
SHCS	4538 (6.1)	25 403	36	31	21	20	34	42	0.8	3	204	4.9
UAB	502 (0.7)	1745	37	24	47	7	38	31	0	28	142	4.9
VACH	7038 (9.5)	39 037	35	23	20	34	27	34	0.5	5	210	5
VACS	7371 (10)	43 079	46	2	29	7	0	0	0	73	197	4.8
Vanderbilt	1005 (1.4)	3488	37	24	10	10	39	28	0	22	190	4.9
Washington	623 (0.8)	2730	37	16	28	25	49	24	0	1	180	5
All	74 048 (100)	3 77 129	38	26	23	17	30	37	0.9	16	215	4.9

<sup>a</sup>See Table 1 for full names of cohorts. Abbreviations: AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; IDU, injection drug use; MSM, men who have sex with men.



From 2006 onward, we collected and classified information about causes of death. Overall, almost 50% of deaths were caused by AIDS.<sup>2</sup> Because rates of death from AIDS declined with the duration of ART, rates of non-AIDS-related death exceeded those of death from AIDS after 4 years of ART. Lifestyle-related causes of death such as suicide, drug overdose, and liver diseases (mainly hepatitis) were the most frequent causes of non-AIDS-related deaths, with the most common non-AIDS-related cancer being lung cancer. Deaths from causes associated with ageing, such as cancers other than lung cancer and cardiovascular disease, will be of increasing importance in treated HIV-positive people over the next decade, and the ART-CC will have the capacity to explore these trends.

### **When to begin antiretroviral therapy**

The CD4 cell count below which ART should be begun remains a central issue in the care of HIV-positive individuals. In 2009 we attempted to address this question by combining data from observational cohort studies conducted before and after the era of combination ART,<sup>22</sup> and concluded that deferring treatment until the CD4 cell count was under 350 cells/ $\mu$ l was associated with increased rates of AIDS. International treatment guidelines were amended later in 2009 to account for our own and others' findings, mainly in cohort studies. However only a randomised controlled trial will definitively show whether deferring treatment on the basis of the CD4 cell count will increase the rates of AIDS. Results of the Strategic Timing of Antiretroviral therapy (START) trial<sup>23</sup> are awaited with interest in this regard.

### **Prognosis for patients infected through injection-drug use**

Patients infected with HIV-1 through injection-drug use have worse outcomes after treatment than do those infected sexually.<sup>24</sup> We found that mortality rates of IDUs were twice as high as those of non-IDUs, and that IDUs experienced higher rates than did non-users of infection drugs of almost all causes of death, particularly liver-related deaths and deaths from direct effects of substance abuse. The CD4 cell count predicted death more strongly for non-users of injection drugs than for IDUs, indicating that excess mortality in IDUs was related to factors other than HIV. Excess mortality in IDUs may also relate to suboptimal management of HIV disease in these individuals.

### **Estimated effects of different antiretroviral drugs on the basis of observational studies and clinical trials**

We found evidence that rates of AIDS and death varied according to the drugs included in the initial ART regimen,<sup>19</sup> and that between-regimen differences in rates of short-term virological failure (the outcome

most commonly used in clinical trials) do not necessarily translate to longer-term differences in rates of various clinical outcomes.<sup>25</sup> We compared the results of two randomized trials done by the AIDS Clinical Trial Group (ACTG 5095 and ACTG 5142) with those estimated in ART-CC cohorts, which follow patients in routine care.<sup>26</sup> Results for the ART-CC cohorts were comparable with those of the trials conducted in similar settings, and we concluded that the results of clinical trials appear to be generalisable to routine-care settings in resource-rich countries.

### **Other topics covered by the Antiretroviral Therapy Cohort Collaborative**

Collaborative analyses have compared mortality during the first year of ART in resource-limited and high income settings.<sup>9</sup> In the past, similar comparisons of the incidence of tuberculosis were reported.<sup>27,28</sup> Other questions addressed by the ART-CC include the way in which the effect of prognostic factors at the beginning of ART varies with the duration of treatment,<sup>29</sup> and the effect of baseline CD4 cell counts on the clinical significance of short-term immunologic responses to ART in individuals with virologic suppression.<sup>30</sup>

### **Current work**

We have recently examined the effect of sex,<sup>31</sup> race/ethnicity, and geographical origin<sup>32,33</sup> on the prognosis in HIV infection and investigated the heterogeneity in mortality rates among cohorts.<sup>3</sup> Ongoing analyses are addressing the durability of first-line ART and the cumulative incidence of and risk factors for different types of changes in regimen and of the interruption of ART. This work will be extended to use methods for causal inference<sup>34</sup> to examine the implications for subsequent mortality of different strategies for switching ART regimens after virological failure. As longer follow-up data become available, we will estimate the prognosis for patients treated for up to 10 years, investigate whether the prognosis in HIV-1 infection becomes stable after an initial response to ART, and investigate the effect of cumulative viral load on specific causes of death. We are also now investigating measures and effects of adherence to ART. The ART-CC is working increasingly closely with other collaborations of HIV cohort studies, in particular the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), which now merges the data for European cohorts participating in the ART-CC, as well as the HIV-Cohorts Analyzed Using Structural Approaches to Longitudinal Data (HIV-CAUSAL) Collaboration, and the International epidemiologic Databases to Evaluate AIDS (IeDEA) Southern Africa Collaboration. The ART-CC also works with the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), IeDEA West Africa, and the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) collaboration.

## What are the main strengths and weaknesses?

The generosity and collaborative spirit of researchers in the contributing cohort studies has been a key strength of ART-CC, which has brought together researchers with clinical, epidemiological and statistical expertise. The ART-CC data base includes large numbers of patients enrolled in diverse cohorts from two continents, so that the results for different cohorts are likely to be generalisable to patients in clinical care in this broad setting. All patients in the ART-CC were ART-naïve when they began treatment, and the results for the Collaboration are therefore relevant to new patients starting combination ART. However, prognostic models are fitted on historic data, and therefore provide trailing indicators of prognosis for new patients starting ART with improved drugs and co-formulations. The large data set of the ART-CC permits examination of prognoses for specific causes of death, but these data are incomplete. So far, it has been possible to classify only 85% of deaths, and there will have been some misclassification because of limitations of available data. There is likely to be some under-ascertainment of deaths, which may result in estimates of mortality rates and life expectancy being over-optimistic. Nevertheless, most of the cohorts in the ART-CC link to death registries, but at intervals that vary from monthly to tri-annually.<sup>3</sup> Because the data are mainly collected as part of routine clinical care, there are issues with the standardisation of definitions and completeness of data. Moreover, not all laboratory, demographic and lifestyle measures are available from all cohorts. Data on important life-style risk factors, such as smoking and substance abuse, which affect mortality and may be highly prevalent in some HIV-positive populations, have not yet been sufficiently widely available for inclusion in prognostic models. Data on adherence to ART are now being collected, but not data on patient physical and psychological symptoms or quality of life measures.

## Can I get the data gathered by the Antiretroviral Therapy Collaboration?

The data collected by the ART-CC remain the property of the contributing cohorts, and all analyses of these data must be approved by the ART-CC steering committee. Each cohort has a representative on the steering committee, which also includes patient representatives who provide guidance by asking research questions that are important and relevant to patients. Interested investigators should contact the co-ordinating centre and will be asked to fill in a concept sheet which gives brief details of the proposed study. All concept sheets are discussed by the steering committee, and projects must also be approved by contributing cohorts. We welcome

the addition of collaborating cohorts to the ART-CC; eight cohorts have joined since the Collaboration was established in 2000. More information, including details of collaborating centres, is available on the ART-CC website ([www.art-cohort-collaboration.org](http://www.art-cohort-collaboration.org)).

## Author Contributions

M.T.M. and S.M.I. wrote the first draft of the paper and compiled the tables. S.M.I. contributed the figures. All authors contributed to the study design and the writing of the manuscript, and approved the final version of the paper.

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### KEY MESSAGES

- Patients starting ART later in the course of their infection had worse prognosis, as did those infected via injection drug use.
- Life expectancy of HIV positive individuals increased by 13 years for those initiating ART in 2003–05 compared with 1996–99.
- Overall, almost 50% of deaths were from AIDS, but rates of non-AIDS death exceeded rates of AIDS death after four years of ART.
- Deferring treatment until CD4 count is less than 350 cells/ $\mu$ L was associated with increased rates of AIDS.

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