All-cause mortality in treated HIV-infected adults with CD4 $\geq 500$/mm$^3$ compared with the general population: evidence from a large European observational cohort collaboration

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord

Charlotte Lewden,1 Vincent Bouteloup,1 Stéphane De Wit,2 Caroline Sabin,3 Amanda Mocroft,3 Jan Christian Wasmuth,4 Ard van Sighem,5 Ole Kirk,6,7 Niels Obel,7 George Panos,8 Jade Ghosn,9 François Dabis,1 Murielle Mary-Krause,10 Catherine Leport,11 Santiago Perez-Hoyos,12 Paz Sobrino-Vegas,13 Christoph Stephan,14 Antonella Castagna,15 Andrea Antinori,16 Antonella d'Arminio Monforte,17 Carlo Torti,18 Cristina Mussini,19 Virginia Isern,20 Alexandra Calmy,21 Ramón Teira,22 Matthias Egger,23 Jesper Grarup24 and Geneviève Chène1

1INSERM, U897, ISPED, Université Bordeaux Segalen, Bordeaux, France, 2Department of Infectious Diseases, St Pierre University Hospital, Brussels, Belgium, 3Research Department of Infection and Population Health, UCL Medical School, London, UK, 4Department of Internal Medicine I, University of Bonn, Bonn, Germany, 5Stichting HIV Monitoring, Amsterdam, The Netherlands, 6Copenhagen HIV Programme, University of Copenhagen, Faculty of Health Sciences, Copenhagen, Denmark, 7Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, 8Department of Internal Medicine & Infectious Diseases, Patras University General Hospital & 1st IKA General Hospital, Patras, Achaila, Greece, 9Department of Internal Medicine and Infectious Diseases, APHP, Bicetre University Hospital, Kremlin Bicetre, France, 10INSERM, U943, Paris, France, UPMC Univ Paris 06, UMR S943, Paris, France, 11INSERM, UMR-S 738, UFR Médecine, site Bichat, Université Paris Diderot, Paris 7, Unité de Coordination du Risque Épidémique et Biologique, APHP, Paris, France, 12Methodological Support Unit on Biomedical Research (USMIB), Vall Hebrón Hospital Research Institute (VHIR), Barcelona, Spain, 13Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain, 14Internal Medicine & Infectious Diseases, HIVCENTER, Hospital of the Johann Wolfgang Goethe-University Medical Center, Frankfurt, Germany, 15Department of Infectious and Tropical Diseases, San Raffaele Scientific Institute, Milan, Italy, 16Clinical Department, National Institute for Infectious Diseases “Lazzaro Spallanzani”, IRCCS, Rome, Italy, 17Dipartimento di Medicina, Clinica di Malattie Infettive e Tropicali, Chirurgia e Odontoiatria, Polo Universitario-Azienda ospedaliera San Paolo, Milano, Italia, 18Infectious Diseases Department - HIV/AIDS Unit, Spedali Civili and University of Brescia, Brescia, Italy, 19Clinic of Infectious Diseases, Policlinico, Modena, Italy, 20Center for Epidemiological Studies on HIV/AIDS of Catalonia (CEEISCAT), Barcelona, Spain, 21Infectious Diseases Department, Geneva University Hospital, Switzerland, 22Servicio de Medicina Interna, Hospital de la Seguridad Social, Cantabria, Spain, 23University of Bern, Institute of Social and Preventive Medicine, Bern, Switzerland and 24Department of International Health, Immunology and Microbiology, CHIP, University of Copenhagen, Faculty of Health Sciences, Copenhagen, Denmark

*Corresponding author. INSERM U897, ISPED, Université Bordeaux Segalen, 146 rue Léo-Saignat 33 076 Bordeaux cedex, France. E-mail: charlotte.lewden@isped.u-bordeaux2.fr

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Background Using data from a large European collaborative study, we aimed to identify the circumstances in which treated HIV-infected individuals will experience similar mortality rates to those of the general population.

Methods Adults were eligible if they initiated combination anti-retroviral treatment (cART) between 1998 and 2008 and had one prior CD4 measurement within 6 months. Standardized mortality ratios (SMRs) and excess mortality rates compared with the general population were estimated using Poisson regression. Periods of follow-up were classified according to the current CD4 count.
Results  Of the 80,642 individuals, 70% were men, 16% were injecting drug users (IDUs), the median age was 37 years, median CD4 count 225/mm³ at cART initiation and median follow-up was 3.5 years. The overall mortality rate was 1.2/100 person-years (PY) (men: 1.3, women: 0.9), 4.2 times as high as that in the general population (SMR for men: 3.8, for women: 7.4). Among 35,316 individuals with a CD4 count ≥500/mm³, the mortality rate was 0.37/100 PY (SMR 1.5); mortality rates were similar to those of the general population in non-IDU men [SMR 0.9, 95% confidence interval (95% CI) 0.7–1.3] and, after 3 years, in women (SMR 1.1, 95% CI 0.7–1.7). Mortality rates in IDUs remained elevated, though a trend to decrease with longer durations with high CD4 count was seen. A prior AIDS diagnosis was associated with higher mortality.

Conclusions  Mortality patterns in most non-IDU HIV-infected individuals with high CD4 counts on cART are similar to those in the general population. The persistent role of a prior AIDS diagnosis underlines the importance of early diagnosis of HIV infection.

Keywords  HIV infection, CD4 lymphocyte count, mortality, anti-retroviral therapy, highly active

Introduction  Immune restoration occurs in most HIV-infected patients treated with combination anti-retroviral therapy (cART) and is associated with a dramatic decrease in AIDS-related mortality.¹⁻⁴ For the first time, it has become conceivable that treated HIV-infected individuals may experience mortality rates that are similar to those seen in HIV-negative individuals of the same age and gender.⁵,⁶ Indeed, among individuals in high-income countries with a known date of HIV seroconversion who were followed between 2004 and 2006, mortality in the first 5 years after seroconversion was similar to that in the general population.⁴ The absolute number of circulating CD4+ cells/mm³ (the 'CD4 count') is the most commonly used marker of HIV disease progression and of immune reconstitution after cART, with a lower CD4 count predicting the occurrence of both AIDS and non-AIDS-defining diseases.⁷⁻⁹ A trend towards improved survival among those with higher CD4 counts is apparent even among untreated patients with a CD4 count >350/mm³.¹⁰,¹¹ Currently, in most resource-rich countries, mortality in HIV-infected individuals receiving cART remains higher than in the general population¹²⁻¹⁶ even among individuals who experience a good initial response to cART.¹⁷ However, some subgroups do have a more favourable prognosis, including men who have sex with men (MSM) who initiated treatment for the first time, whereas AIDS-free⁶ and individuals who have maintained a high CD4 count while on cART for >6 years.⁵ Beyond the immune restoration measured in routine practice by the CD4 count, the reconstitution of the T-cell subsets may, however, remain incomplete despite several years of treatment.¹⁸ In a large European collaboration of HIV cohorts, we aimed to identify the optimal circumstances in which treated HIV-infected individuals will experience similar mortality rates to those of the general population. In particular, we wished to explore the impact on the mortality rate of attaining and maintaining over a long period, a CD4 count ≥500/mm³ in different subgroups.

Methods  Study population  The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE, http://www.cohere.org) was established in 2005 with the objective of conducting epidemiological research on the prognosis of HIV-infected people across Europe.¹⁹ The 33 participating observational cohorts have been approved by local ethics committees or institutional review boards according to local regulations. Each cohort submits information using a standardized data format to one of two coordinating centres at the Copenhagen HIV Project (CHIP), Copenhagen, Denmark or the Institut de Santé Publique d’Épidémiologie et de Développement (ISPED), University Bordeaux Segalen, France. Our analyses were based on data merged in November 2008. Patients were eligible if they met the following

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criteria: at least 18 years of age at cART initiation, cART initiation in 1998 onward, followed in an European country, known date of birth and gender, at least one CD4 measurement within 6 months prior to cART initiation and at least 1 day of follow-up.

Statistical analysis
We used three complementary estimates to express mortality.

(i) Mortality rates were expressed as number of deaths per 100 person-years (PY) with 95% confidence intervals (95% CIs) calculated using the exact Poisson method. These reflect mortality incidence over time.

(ii) Standardized mortality ratios (SMRs) were used to compare, in a multiplicative way, the mortality rates with those of the general population. The SMR is the ratio of the number of observed deaths to the number of expected deaths. Expected deaths were obtained by applying country-, calendar year-, gender- and age-specific mortality rates for the general population to the PY of follow-up of the HIV cohort. Mortality rates for the general population were extracted from the Human Mortality Database, www.mortality.org, or from the World Health Organisation statistical information system (WHOSIS, http://apps.who.int/whosis/data). SMRs were computed through Poisson models offsetting expected mortality rates, and adjusted for gender, age, HIV transmission group and history of AIDS at cART initiation. A random-effect for cohort studies was included to account for heterogeneity. An interaction term was included in the model to take into account an effect modification between HIV transmission category and age. SMRs were then estimated for the whole study population and separately by gender, age (18–39 years; 40–59 years; ≥60 years), HIV transmission group [injecting drug users (IDUs), MSM, heterosexual], clinical AIDS at cART initiation and the current CD4 count. To allocate PY and events to the current CD4 count, each year of age during follow-up was categorized according to the lowest CD4 measurement during the corresponding year. Where the CD4 count was missing for a particular age-year (1.3, 4.1 and 0.6% of overall PY, at the beginning, during and end of follow-up, respectively), a last-observation-carried-forward method or other simple methods were used to impute the missing values (these methods were judged to provide reliable estimates of SMRs in sensitivity analyses designed to assess the robustness of the method, data not shown).

Our specific interest was in assessing mortality rates and SMRs during periods where the CD4 count was ≥500/mm³. Within this subanalysis, we aimed to identify whether a longer time spent with a CD4 count ≥500/mm³ was associated with a higher likelihood of similar mortality rates to those reported in the general population. We thus estimated SMRs accounting for all years of age with CD4 counts ≥500/mm³ with the following time thresholds: ≥1 year spent with CD4 ≥500/mm³; ≥2 consecutive years spent with CD4 ≥500/mm³;..., ≥5 consecutive years spent with CD4 ≥500/mm³.

Mortality rates were considered as similar to the general population when the 95% CI for the SMR included the value 1 and when the point estimate was close to 1, i.e. <1.2.

(iii) Excess mortality rates quantified, in an additive way, the observed death beyond those expected. These were estimated by subtracting the expected number of deaths from the observed number, and dividing this by the total PY; 95% CIs were computed using the exact Poisson method assuming that the reference mortality rates were fixed. All statistical analyses were performed using Statistical Analysis System software (SAS, 9.1).

Results
In the COHERE database, 80 642 patients from 23 cohorts and 31 European countries were eligible for this analysis out of a total of 94 295 HIV-infected adults who initiated cART between 1998 and 2008 (Figure 1 and Supplementary Figure 1, available as Supplementary Data at IJE online). Patients excluded from the analysis (due to missing data on gender, CD4 measures within 6 months prior cART initiation or follow-up) did not differ from included patients in terms of their gender, age, transmission category, clinical stage, year of cART initiation or mortality rate (data not shown). Overall, 70% of eligible participants were men and the median age at cART initiation was 37 years (men 38 years, women 34 years) (Table 1). IDU was the HIV transmission category in 16%, of whom 1% were ≥60 years of age. Among men, 48% were MSM. Overall, 19% of individuals had AIDS at cART initiation, the median CD4 count was 225/mm³ (inter-quartile range: 107–357) and 44% had a CD4 count <200/mm³ (men 45%, women 40%). The median CD4 count at cART initiation was lower in individuals aged ≥60 years as compared with younger individuals. The median delay between HIV diagnosis and cART initiation was shorter in older individuals and was 0.3 and 1.2 years for patients starting cART with CD4 cell count <200/mm³ and ≥500/mm³, respectively. The median duration of follow-up was 3.5 years. Of the total duration of follow-up of 315 340 PY, 29% was spent with a CD4 count ≥500/mm³.
Mortality rates, SMRs and excess mortality
rates overall

Gender
Mortality rates were 1.15/100 PY overall, 1.29 in men and 0.86 in women (Table 1). Overall, mortality was higher than in the general population (SMR 4.2, 95% CI 3.5–5.2), both in men (SMR 3.8, 95% CI 3.1–4.7) and women (SMR 7.4, 95% CI 6.0–9.1). Conversely, excess mortality rates were slightly lower in women [0.74/100 PY (95% CI 0.60–0.92)] than in men [0.95/100 PY (95% CI 0.78–1.16)].

Age
As expected, mortality rates increased with age, whereas SMRs decreased with age from 8.5 at ages <40 years to 1.7 at ages ≥60 years. Conversely, the excess mortality rates increased with age from 0.73/100 PY at ages <40 years to 1.19/100 PY at ages ≥60 years (Table 1). The excess mortality represented 88, 75 and 41% of the observed mortality among individuals <40 years, 40–59 years and ≥60 years, respectively. Thus, whereas older HIV-infected individuals had mortality rates that were closer to those of a general population of the same age and gender when considered in relative terms, absolute excess mortality was higher in older individuals and this represented a smaller proportion of the observed mortality rates (Table 1 and Figure 2).

Mortality rates, SMRs and excess mortality
rates with CD4 counts ≥500/mm³

As the CD4 count increased, mortality rates dropped and were closer to those of the general population. Among 35 316 individuals with a CD4 count ≥500/mm³, the mortality rate was 0.37/100 PY (SMR 1.5, 95% CI 1.2–1.8) and excess mortality rate 0.12 (95% CI 0.10–0.15) (Table 2). Overall, mortality rates among the 24 479 HIV-infected men with a CD4
<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
<th>18-39 years</th>
<th>40-59 years</th>
<th>≥ 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>80,642</td>
<td>56,417</td>
<td>24,225</td>
<td>51,400</td>
<td>26,562</td>
<td>26,807</td>
</tr>
<tr>
<td>Women (%)</td>
<td>30.0</td>
<td>36.0</td>
<td>20.0</td>
<td>21.0</td>
<td>36.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Median age (years) (IQR)</td>
<td>37 (31–43)</td>
<td>38 (33–45)</td>
<td>34 (29–40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mode of HIV transmission (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug injection</td>
<td>16.0</td>
<td>17.0</td>
<td>12.0</td>
<td>13.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Homo or bisexual</td>
<td>33.0</td>
<td>48.0</td>
<td>32.0</td>
<td>36.0</td>
<td>30.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>42.0</td>
<td>27.0</td>
<td>79.0</td>
<td>41.0</td>
<td>53.0</td>
<td>53.0</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>9.0</td>
<td>9.0</td>
<td>8.0</td>
<td>10.0</td>
<td>16.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Median time between HIV diagnosis and cART initiation (years) (IQR)</td>
<td>1.0 (0.2–4.6)</td>
<td>1.1 (0.2–4.8)</td>
<td>0.9 (0.2–4.1)</td>
<td>1.1 (0.2–4.4)</td>
<td>1.0 (0.1–5.3)</td>
<td>0.3 (0.1–2.0)</td>
</tr>
<tr>
<td>Baseline AIDS (%)</td>
<td>19.0</td>
<td>21.0</td>
<td>16.0</td>
<td>24.0</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td><strong>Year of starting cART (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998–99</td>
<td>28.0</td>
<td>29.0</td>
<td>25.0</td>
<td>31.0</td>
<td>23.0</td>
<td>23.0</td>
</tr>
<tr>
<td>2000–02</td>
<td>32.0</td>
<td>32.0</td>
<td>33.0</td>
<td>33.0</td>
<td>32.0</td>
<td>31.0</td>
</tr>
<tr>
<td>2003–04</td>
<td>21.0</td>
<td>20.0</td>
<td>23.0</td>
<td>20.0</td>
<td>23.0</td>
<td>23.0</td>
</tr>
<tr>
<td>2005–08</td>
<td>19.0</td>
<td>19.0</td>
<td>19.0</td>
<td>17.0</td>
<td>22.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Median duration of follow-up (years) (IQR)</td>
<td>3.5 (1.5–6.1)</td>
<td>3.6 (1.6–6.2)</td>
<td>3.4 (1.5–5.9)</td>
<td>3.7 (1.7–6.3)</td>
<td>3.3 (1.4–5.7)</td>
<td>3.0 (1.3–5.4)</td>
</tr>
<tr>
<td>PY with CD4 ≥ 500/mm³ (% of total PY)</td>
<td>91,891 (29)</td>
<td>65,697 (29)</td>
<td>26,194 (28)</td>
<td>50,129 (30)</td>
<td>38,154 (28)</td>
<td>3,608 (25)</td>
</tr>
<tr>
<td>Mortality rates (per 100 PY) (95% CI)</td>
<td>1.15 (0.94–1.14)</td>
<td>1.29 (1.05–1.57)</td>
<td>0.86 (0.70–1.06)</td>
<td>0.83 (0.67–1.03)</td>
<td>1.38 (1.11–1.70)</td>
<td>2.91 (2.32–3.66)</td>
</tr>
<tr>
<td>SMR (95% CI)</td>
<td>4.2 (3.5–5.2)</td>
<td>3.8 (3.1–4.7)</td>
<td>7.4 (6.0–9.1)</td>
<td>8.5 (6.8–10.5)</td>
<td>4.2 (3.4–5.1)</td>
<td>1.7 (1.3–2.1)</td>
</tr>
<tr>
<td>Excess mortality rates (per 100 PY) (95% CI)</td>
<td>0.88 (0.72–1.07)</td>
<td>0.95 (0.78–1.16)</td>
<td>0.74 (0.60–0.92)</td>
<td>0.73 (0.59–0.91)</td>
<td>1.04 (0.84–1.29)</td>
<td>1.19 (0.95–1.50)</td>
</tr>
</tbody>
</table>

cART: combination antiretroviral therapy; CI: confidence interval; HIV: human immuno-deficiency virus; IQR: interquartile range; PY: person-years.
count $\geq 500/mm^3$ reached similar levels to those of the general male population after 3 years in this CD4 strata: SMR 1.0 (95% CI 0.8–1.4) (Figure 3a). Among the 10,837 HIV-infected women with a CD4 count $\geq 500/mm^3$, mortality rates did not reach similar levels to those of the general female population, even after 5 years spent above this threshold (Figure 3b). These results were similar in the sub-group of individuals with a high CD4 count at cART initiation.

Non-IDUs
Among non-IDUs, mortality rates were similar to those of the general population with a CD4 count $\geq 500/mm^3$: SMR 0.9 (95% CI 0.7–1.2) (Figure 3e and g). In women with a CD4 count $\geq 500/mm^3$, mortality rates were similar to those of the general population after 3 years in this CD4 strata, SMR 1.1 (95% CI 0.7–1.7) (Figure 3f).

IDUs
Among 12,503 IDUs, mortality was 13.1 times (95% CI 10.5–16.5) higher than in the general population, 11.7 times (95% CI 9.4–14.7) higher in men and 22.7 times (95% CI 18.0–28.7) higher in women; the excess mortality rate was 2.29/100 PY (95% CI 1.83–2.87). Even when the CD4 count was $\geq 500/mm^3$, mortality rates remained higher than those seen in the general population, SMR 5.7 (95% CI 4.2–7.8), with an excess mortality rate of 0.76 (95% CI 0.56–1.04). This was apparent even after 5 years spent above this threshold, though SMRs tended to decrease as individuals attained a CD4 count $\geq 500/mm^3$ for longer periods of time (Figure 3c and d).

Table 2 SMR and excess mortality rates in HIV-infected individuals with a CD4 count $\geq 500/mm^3$ after cART initiation, according to gender and age

<table>
<thead>
<tr>
<th></th>
<th>PY</th>
<th>Mortality rate/100 PY (95% CI)</th>
<th>SMR (95% CI)</th>
<th>Excess mortality rate/100 PY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global</strong></td>
<td>91,891</td>
<td>0.37 (0.30–0.46)</td>
<td>1.5 (1.2–1.8)</td>
<td>0.12 (0.10–0.15)</td>
</tr>
<tr>
<td><strong>Men (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–39</td>
<td>65,697</td>
<td>0.43 (0.35–0.53)</td>
<td>1.4 (1.1–1.7)</td>
<td>0.12 (0.10–0.15)</td>
</tr>
<tr>
<td>40–59</td>
<td>32,565</td>
<td>0.31 (0.24–0.40)</td>
<td>2.5 (1.9–3.2)</td>
<td>0.18 (0.14–0.24)</td>
</tr>
<tr>
<td>$\geq 60$</td>
<td>29,166</td>
<td>0.48 (0.38–0.62)</td>
<td>1.3 (1.0–1.7)</td>
<td>0.12 (0.09–0.15)</td>
</tr>
<tr>
<td><strong>Women (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–39</td>
<td>26,194</td>
<td>0.23 (0.17–0.32)</td>
<td>2.2 (1.6–3.0)</td>
<td>0.13 (0.09–0.17)</td>
</tr>
<tr>
<td>40–59</td>
<td>17,564</td>
<td>0.17 (0.12–0.24)</td>
<td>3.4 (2.5–4.8)</td>
<td>0.12 (0.09–0.17)</td>
</tr>
<tr>
<td>$\geq 60$</td>
<td>7,938</td>
<td>0.32 (0.23–0.45)</td>
<td>1.9 (1.3–2.6)</td>
<td>0.15 (0.10–0.21)</td>
</tr>
<tr>
<td></td>
<td>6,920</td>
<td>0.77 (0.50–1.21)</td>
<td>1.0 (0.6–1.5)</td>
<td>$-0.03$ ($-0.04$ to $0.02$)</td>
</tr>
</tbody>
</table>

cART: combination antiretroviral therapy; CI: confidence interval; HIV: human immuno-deficiency virus; PY: person-years.

Figure 2 SMRs and mortality rates according to age in HIV-infected individuals after initiation of cART and in the general population, the COHERE Collaboration 1998–2008 (logarithmic scale)
Age and baseline AIDS

The 1717 individuals aged ≥60 years who achieved a CD4 count ≥500/mm³ experienced mortality rates that were similar to the general population; this was true for both genders (Table 2). Nevertheless, in the group of older women who reached CD4 counts ≥500/mm³, the SMR was 1.7 (95% CI 0.7–4.0) among those who had AIDS at cART initiation (Figure 4h).
Among non-IDU men who had a CD4 count ≥500/mm³, mortality rates were similar to those in the general population at ages ≥40 years but were higher at ages <40 years. Nevertheless, among men aged 40–59 years who had high CD4 counts but who had AIDS at cART initiation, the SMR was 1.3 (95% CI 0.8–2.1) in heterosexuals and 1.2 (95% CI 0.8–2.0) in MSM (Figure 4f and j).

Among non-IDU women aged <60 years who had a CD4 count ≥500/mm³, mortality rates were higher than those of the general female population (Figure 4h). However, after 1 year with a CD4 count...
\( \geq 500 / \text{mm}^3 \), 40- to 59-year-old non-IDU women experienced similar mortality rates as those of the general population, SMR 1.1 (95% CI 0.7–1.7); in contrast, women aged 18–39 years never experienced similar mortality rates as those in the general population.

Overall, AIDS at cART initiation was associated with higher SMRs. This remained the case in all groups even when the current CD4 count was \( \geq 500 / \text{mm}^3 \) (Figure 4).

**Discussion**

This large cohort collaboration includes more than 80,000 patients from 31 countries. Given this large number of patients, as well as the inclusion of patients from 31 different European countries, and the fact that many of the participating cohorts are based within health-care delivery systems in these countries, the results presented may be considered to provide a fair representation of the wider situation of HIV-infected individuals in Europe over the first 10 years of widespread cART use. Between 1998 and 2008, the mortality rate in cART-treated European HIV-infected adults was 1.2/100 PY on average. Although IDUs continued to experience greater mortality than that seen in the general population, even when they had attained a CD4 count \( \geq 500 / \text{mm}^3 \) for more than 5 years, non-IDUs who attained a CD4 \( \geq 500 / \text{mm}^3 \) experienced mortality rates that were similar to those of the general population; this effect was seen immediately after reaching the threshold in men and after 3 years among women. AIDS at cART initiation was, however, associated with higher SMRs, regardless of the CD4 count attained.

The overall SMR among HIV-infected individuals on cART in our study is close to recent reports \(^5,21\) but lower than those from previous studies \(^5,14\) consistent with a decrease in mortality reported in the most recent years of the cART period. \(^4\)

**Gender**

Higher SMRs in women compared with men have already been reported. \(^12,17,21\) Non-IDU males aged \( \geq 40 \) years with CD4 counts \( \geq 500 / \text{mm}^3 \) reached similar mortality rates as men in the general population. Although the same was generally true of non-IDU women, SMRs did remain high in some specific subgroups, e.g. those aged 18–39 years. This may reflect differences between HIV-infected women and women of the general population that may lead to a higher mortality risk (e.g. lower socio-economic status, increased frequency of smoking) \(^22,23\) which are not captured within the COHERE study. Of note, mortality rates among women in the general population are much lower than those among similarly aged men. Conversely, the excess mortality rates were slightly higher in men than in women, representing the burden of mortality associated with HIV infection or associated conditions from a public health standpoint.

**Age**

The higher SMRs seen in younger individuals are partly explained by a higher proportion of IDUs in this age group. After excluding IDUs, the age trend remained, however, suggesting that other characteristics (e.g. smoking or socio-economic level) may also play a role. Older individuals had lower SMRs as compared with younger ones, due to higher mortality rates in the older general population, and higher excess mortality rates, as previously described. \(^13,17\)

From a public health perspective, these higher excess mortality rates should lead to further exploration of the causes of death in older HIV-infected individuals. In the French ‘Mortalité 2000-2005’ surveys, diversification of the causes of death was particularly marked in older individuals, with higher proportions of cancer- and cardiovascular-related deaths. \(^29\)

**IDUs**

Our results confirm that IDUs generally have a poor prognosis, though those who experience a good immunological response to cART for sufficiently extended periods of time have the best prognosis. Since adherence is a strong predictor of mortality, \(^26\) HIV-infected IDUs should therefore be reminded that the ability to adhere to ART over the long term is especially important for their health. In addition, these results emphasize the importance of sustained prevention of HIV infection in IDUs. In addition to high-risk behaviours, the role of co-infection with hepatitis C deserves further research. \(^27\)

**Baseline AIDS**

Occurrence of AIDS before cART initiation resulted in a poorer prognosis even in individuals who attained CD4 counts \( \geq 500 / \text{mm}^3 \). Our findings provide further arguments for early cART initiation in order to prevent the occurrence of AIDS-defining events that may still occur (albeit at low frequency) in high CD4 strata \(^40\) and which may have a long-term effect on subsequent prognosis. In fact, the median CD4 count at starting cART was 225/mm\(^3\) (lower in older individuals), highlighting the importance of widespread HIV testing in order to increase earlier HIV diagnosis.

**Current CD4 count**

We initially hypothesized that a longer time spent with CD4 counts \( \geq 500 / \text{mm}^3 \) might permit treated HIV-infected patients to attain mortality rates that were similar to those of the general population. When considering the overall sample of treated individuals, this was verified after 3 years in this CD4
strongly predictive of death, non-AIDS-related mor-
which have reported that CD4 measurement most
nadir. This is in accordance with other studies
non-IDUs aged <40 years), even with a high CD4
high CD4, other subgroups did not (e.g. IDUs,

In the subgroups where we see a higher risk of
death despite a CD4 count ≥500/mm³, we suggest
that any excess mortality may be driven by behaviour-
or socio-economic characteristics. If this is the case,
then a treatment target of a CD4 count ≥500/mm³
may not necessarily improve the prognosis of this
group, as suggested by a recent pooled analysis
among non-treated individuals in high-income set-
tings.11 When compared with our study of treated
individuals, these authors report a similar SMR
among MSM with a CD4 count ≥500/mm³ and a
higher SMR among heterosexuals.11

Strengths and generalizability

Only one previous study has analysed SMRs according
to updated CD4 in treated individuals from two
French cohorts.5 The current study provides further
evidence on this topic with greater potential for ex-
trapolation across Europe.

For the purpose of this analysis, which was to iden-
tify conditions associated with low mortality rates, we
selectively identified patients who succeeded in at-
taining a high CD4 count on cART. Our selection
means that these individuals had to survive long
enough for the count to reach this high level. Other
studies with similar aims to our own selected individ-
uals treated with cART for at least 24 weeks.17
Identification of the optimal conditions was useful
in order to define a target for complete success of
treatment in some subgroups and to advance research
as to how these favourable outcomes may be achieved
in other subgroups (e.g. younger individuals, women,
IDUs). Despite the selection of individuals with a
good response to treatment, however, the mortality
among some subgroups remained substantially
higher than in the general population of the same
age and gender.

Our results apply to the follow-up of HIV-infected
individuals over the first 10 years of cART. Further

Limitations

A description of the causes of death would help to
determine if the excess mortality in some subgroups
of HIV-infected individuals was related to AIDS con-
ditions, to comorbidities such as hepatitis C or B or to
emerging morbidities such as cardiovascular disease
or cancer. Nevertheless, such a description requires
standardized collection and determination of the
underlying cause of death.25,31 Such a valid determin-
ation of the causes of death was not available in our
study, though investigators of HIV cohorts should
make every possible effort to incorporate standardized
collection and validation of data on causes of death.
Increasing use of the Coding Causes of Death in HIV
(CoDe) protocol for describing the causes of death
among those with HIV is likely to result in improve-
ments in cause of death records in the future.31

We acknowledge that our results do not directly
apply to HIV-infected individuals living in low-
resource settings, due to differences in HIV care man-
agement, socio-economic conditions, characteristics
of patients and the spectrum of morbidities, with active
tuberculosis and invasive bacterial diseases being
more frequent in these settings than in high-income
countries.32

We chose to refer to all-cause mortality rates in the
general population, which include HIV-related deaths.
However, HIV-related mortality represents only a
small proportion of all-cause mortality in the general
population in Europe, allowing us to consider the
general population mortality rates as a reasonable
proxy for the mortality rates in a non-HIV-infected
population.

Although data available from the general population
did not allow us to take into account other risk for
mortality such as smoking, socio-economic level or
IDU, we considered the mortality rates in the general
population of the same age and gender as low mor-
tality rates that could be a rational target for therapy
to achieve for all subgroups of patients.
Clinical relevance
In conclusion, among treated HIV-infected individuals who attained a CD4 count \( \geq 500/\text{mm}^3 \), mortality rates were similar to those of the general population in non-IDU men and after 3 years in this CD4 strata in non-IDU women. Among IDUs, mortality rates remained higher than those in the general population, even after 5 years spent with a CD4 count \( \geq 500/\text{mm}^3 \), though SMRs tended to decrease with longer durations above this threshold. Further studies will be necessary to confirm this trend across several decades of cART. The persistent influence of a prior AIDS diagnosis even among those attaining a high CD4 count, underlines the importance of the current public health calls for earlier identification of HIV infection and entry into care. Our results emphasize the fact that factors other than quantitative immune restoration are necessary in order to reach low mortality rates in HIV-infected individuals.

Supplementary Data
Supplementary Data are available at IJE online.

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Steering Committee members from the contributing cohorts: Robert Zangerle (AHIVCOS), Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary-Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 IPOPILOT), Frank de Wolf (ATHENA), Peter Reiss (ATHENA), Maria Prins (CASCADE), Heiner Bucher (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fäkkenheuer (Cologne Bonn), Julia Del Amo (CORIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Antoni Noguera-Julian (NENEXP and CORISPE-cat), Andrea Antinori (ICC), Antonella d’Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), José Ramos (Madrid Cohort), Manuel Battegay (MoCHIV), Andri Rauch (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Stephane de Wit (St Pierre Cohort), Tessa Goetghebuer (St Pierre Paediatric Cohort), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH) and Myriam Garrido (VACH). European AIDS Treatment Group: David Haerry.

The Executive committee members: Ian Weller (Chair, University College London), Jordi Casabona (PISCIS), Dominique Costagliola (FHDH), Antonella d’Arminio-Monforte (ICONA), Manuel Battegay (MoCHIV), Maria Prins (CASCADE), Frank de Wolf (ATHENA), Jesper Grarup (Head of Copenhagen Regional Coordinating Centre) and Genevieve Chene (Head, Bordeaux Regional Co-ordinating Centre).

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edited the final version of the manuscript. V.B. and C.L. have full access to all the data in the study and had final responsibility for the decision to submit for publication.

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**KEY MESSAGES**

- The mortality rate in HIV-infected adults after cART initiation in Europe between 1998 and 2008 was 1.2/100 PY on average, consistent with a decrease in mortality reported in the most recent years of the cART period.
- In a large European collaborative study, non-IDUs infected by HIV and treated by cART who attained a CD4 count $\geq 500$/mm$^3$ experienced mortality rates that were similar to those of the general population, immediately after reaching the threshold in men and after 3 years among women.
- Mortality rates in treated IDUs remained elevated, though they tend to decrease with longer durations with high CD4 count. AIDS at cART initiation was associated with higher SMRs, regardless of the CD4 count attained.

**References**

Commentary: Can mortality rates among adult antiretroviral therapy patients in Europe reach levels similar to those experienced in the general population?

Andrew F Auld* and Tedd V Ellerbrock

United States Centers for Disease Control and Prevention (CDC), Division of Global HIV/AIDS (DGHA), Atlanta, GA, USA

*Corresponding author. United States Centers for Disease Control and Prevention (CDC), Division of Global HIV/AIDS (DGHA), 1600 Clifton Road, Atlanta, Georgia, 30333, USA. E-mail: ggv4@cdc.gov


Since 1996, widespread availability of combination antiretroviral therapy (ART) has significantly improved survival of HIV-infected persons in industrialized countries.1,2 This has prompted researchers in Europe3,4 and North America1,2,4 to investigate whether mortality among HIV-infected persons receiving ART might reach levels similar to those in the general population.

In this paper by Lewden et al.,2 more than 80,000 patients from 31 European countries are included in an analysis to estimate crude ART patient mortality rates for persons ≥18 years of age, who initiated ART...