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

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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 Europe[2,3] and North America[1,2,4] 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.*,[5] 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 during 1998–2008, had a known gender and date of birth, known baseline $CD4^+$ T-cell (CD4) count, and ⩾1 follow-up visit. The standardized mortality ratio (SMR) is used to compare mortality between ART patients and the general population. The SMR is the ratio of the observed number of deaths in the ART cohorts to the expected number of deaths if ART cohorts had experienced general population country-, calendar-year-, gender-, and age-specific mortality. SMRs were estimated using random effects Poisson models, adjusted for age, gender, HIV transmission group and history of AIDS at ART start.

The overall ART patient mortality rate of 1.2 per 100 person years (PY) is similar to that recently reported for 13 cohorts from nine countries in Europe and North America (0.95/100 PY for the period 2001–2009)[2] and 23 cohorts from 10 European countries, Australia and Canada (0.86/100 PY for the period 2004–2006),[1] supporting previous estimates that average annual risk of death for ART patients has declined since 1996–2001, when estimates of about 3/100 PY were reported.[1]

The authors were specifically interested in assessing whether ART patient mortality could reach levels similar to those experienced in the general population, if ART patients achieved and maintained CD4 counts ⩾500/mm^3. This article builds on previous work by Lewden *et al.* in 2007, which reported that ART patients in a French cohort, who maintained CD4 counts ⩾500/mm^3, had mortality rates similar to those of the general population 6 years after

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ART start.[3] In this analysis, only certain subgroups of patients who achieved CD4 counts ⩾500/mm^3 reached mortality rates similar to those observed in the general population.

First, among all male ART patients, who achieved and maintained a CD4 count ⩾500/mm^3 for ⩾3 years, mortality was similar to that of males in the general population [SMR 1.0, 95% confidence interval (CI) 0.8–1.4]. In contrast, mortality among all female ART patients, who achieved a CD4 count ⩾500/mm^3, was always higher than that of females in the general population, even after 5 years with a CD4 count ⩾500/mm^3. Higher SMRs among females compared with males has been documented in other studies.[6] Authors suggest that differences in the prevalence of low socio-economic status (SES)[7] and/or smoking[2,8,9] between HIV-infected and uninfected persons may be more pronounced for females than males and this might explain the higher SMRs for females. Adjustment of SMRs for SES indicators and smoking burden, variables not available to authors for this analysis, would be needed to further investigate SMR differences by sex.

Secondly, among the subgroup of non-injection drug users (non-IDUs) with a CD4 count ⩾500/mm^3, males immediately on achieving this CD4 threshold (SMR 0.9, 95% CI 0.7–1.2), and females after 3 years in this CD4 stratum (SMR 1.1, 95% CI 0.7–1.7), had similar mortality rates to those in the general population. In contrast, for male and female IDUs, SMRs remained high (5–10), even after 5 consecutive years of maintaining a CD4 count ⩾500/mm.[3] This finding supports observations from other studies that HIV-infection for IDUs still carries a relatively poor prognosis in industrialized countries.[1–3] Besides the mortality risk associated with substance abuse,[1] IDUs are more likely to have mental health illnesses, co-infections (especially with hepatitis C), delayed presentation to healthcare facilities and poor adherence.[10] Tailored adherence interventions for IDUs, and interventions to reduce substance abuse, may improve outcomes in this population.[10]

Finally, among those aged ⩾60 years with a CD4 count ⩾500/mm^3, both males (SMR 0.7, 95% CI 0.5–1.0) and females (SMR 1.0, 95% CI 0.6–1.5) had similar mortality to that in the general population. This finding, which has been documented in other studies,[6] is largely due to a reduction in the prevalence of IDUs in the elderly HIV-infected population, and increasing mortality in the older general population which, even in the context of rising *excess* mortality rates with age in the ART population, reduces observed SMRs.

The finding that mortality among certain subgroups remained greater than that of the general population, even if CD4 counts ⩾500/mm^3 were maintained, suggests that non-AIDS-related factors, such as socio-economic and behavioural factors, might be increasing mortality risk.[11] Several papers have reported that non-AIDS events in industrialized countries are now the most frequent underlying cause of death for HIV-infected patients.[4,12] In a French cohort, the proportion of deaths with AIDS-related causes declined from 47% in 2000 to 36% in 2005.[12] Non-AIDS-defining cancer, liver-related diseases and cardiovascular-related pathology were the predominant non-AIDS-related causes of death.[12] Thirty-eight percent of non-AIDS-related cancers affected the respiratory system and smoking, a risk factor found in ~50% of HIV-infected adults, likely plays a causative role. Smoking cessation programmes for HIV-infected adults and targeted cancer-screening programmes are interventions that could improve mortality among HIV-infected adults.[12] Along with

hepatitis C, alcohol was the most common underlying cause of liver-related mortality,[12] and programmes aimed at detection and treatment of alcohol abuse might improve mortality.[10] Further research to determine relative contributions of traditional cardiovascular risk factors, HIV and antiretrovirals to cardiovascular mortality might reveal additional interventions to reduce ART mortality in industrialized countries.[12]

However, authors also observed that, regardless of CD4 count attained during therapy, presence of AIDS at ART start increased SMRs. This suggests that, despite dramatic expansion of access to ART in industrialized countries since 1996, further expansion and earlier entry into HIV care and treatment are still needed to improve ART outcomes, a theme which is also relevant in resource-limited settings.

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