The effect of HIV on adult mortality: evidence from a large cohort of South African gold-miners with known dates of seroconversion and 10 years of follow-up

JR Glynn[1], P Sonnenberg[1,2], G Nelson[3], A Bester[4], S Shearer[4], J Murray[3,5]

1. Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, UK
2. Health Protection Agency, London, UK
3. School of Public Health, University of the Witwatersrand, South Africa
4. Gold Fields Limited, South Africa
5. National Institute for Occupational Health, National Health Laboratory Service, South Africa

Background

Dramatic changes in adult mortality patterns are occurring in Africa. Much of this is due to the HIV epidemic,[1] yet estimating the exact contribution of HIV is complex. One of the key factors influencing mortality trends is the direct impact of HIV on survival, yet current knowledge of survival with HIV following seroconversion in developing countries comes from only a few hundred individuals.[2,3] We present data on nearly 2000 South African gold miners with known dates of seroconversion and use this to estimate the proportion of adult male deaths in South Africa attributable to HIV over time.

Methods

Mortality rates were estimated in miners with and without HIV infection in a retrospective cohort study with 10 year follow-up. The study used data collected on four gold mines in Gauteng Province, South Africa. Routine data sources were used, and unique industry numbers allowed linking of medical records to routinely collected demographic and occupational information. Permission for the study was received from the ethics committees of the University of Witwatersrand and the London School of Hygiene & Tropical Medicine.

HIV testing was carried out with counselling and consent during random surveys in the early 1990s, in sexually transmitted disease clinics, and on surgical, medical and tuberculosis wards. The HIV database is kept confidential from the mine authorities. Since many individuals were tested more than once, a cohort of individuals with new seroconversions to HIV could be defined.

HIV positive individuals were included in the cohort if there was evidence of seroconversion and the interval from the last negative to the first positive test was < 3 years. Tests done on medical and TB wards were excluded when defining the cohort (to avoid over inclusion of those with fast progression) but were used to refine the seroconversion date where available. HIV negative individuals were included in the study

as a comparison group; they were included if they were negative in a survey with no subsequent evidence of HIV infection in either tests or clinical diagnoses.

Follow-up information was available from the mine personnel records, accident records and hospital records for those who died while employed (or soon after), and for dates of employment; from TEBA (The Employment Bureau of Africa) for assessing vital status during and after leaving the mine; and from South African death registration. For those whose vital status was unknown in the electronic records, enquiries were sent to regional TEBA offices. These offices sought information from local informants, and arranged home visits if necessary. Death certificates were requested where available. Full follow-up information was sought for all HIV positive miners, all HIV negative miners who left the mine within 2 years of their last HIV negative test, and a 10% random sample of HIV negative miners. HIV status was not recorded on the lists requesting information, and as large numbers of HIV negative miners were included, inadvertent disclosure was not an issue.

For the analysis, HIV negative subjects entered the cohort at the time of their HIV negative test in the survey. HIV positive subjects entered at the time of the first positive test. Time since seroconversion was calculated from the midpoint of the seroconversion interval.

Subjects were followed until October 2002 unless they died before this date. Treatment for opportunistic infections was provided, but antiretroviral therapy was only available on the mines from 2004. Subjects who were lost to follow-up were censored at the time when they were last known to be alive (usually the time when they left the mine). Analyses were repeated censoring the HIV negative miners at 2 years after their last negative test to minimise inclusion of unknown seroconverters.

Mortality rates and rate ratios were estimated by duration of HIV infection, calendar time and age. Analyses used Poisson regression, and when adjusting for possible confounding, age and calendar time were treated as time varying co-variates. Median survival was estimated in HIV positive individuals overall and by age.

The UNAIDS epidemic projection package model, EPP, was used to explore the influence of different estimates of median survival on the proportion of deaths in the South African adult population that are attributable to HIV over time. A spreadsheet version of the model was fitted to antenatal clinic data from South Africa. The year of introduction of HIV was taken as 1985. The model was fitted using a range of median survival times between 8 and 12 years. It was assumed that no treatment was available.

Results

[These results are preliminary and should not be quoted]

1950 HIV positive miners with a seroconversion interval of less than 3 years were compared with 6171 miners tested in 1991-3 with no later evidence of HIV infection. The

seroconversion interval for the HIV positive miners was < 1 year for 58% and < 2 years for 86%.

At the end of follow-up in October 2002, 2744 miners from the cohort were still employed on the mines. Among the HIV positive miners, information on vital status by October 2002 was available on 84%. In the 10% random sample of HIV negative miners follow-up to October 2002 was complete for 78%, and for all the HIV negative miners follow-up to 2 years after the last negative test was complete for 97%.

Mortality rates were stable over time in the HIV negative miners when censored at two years after the last negative test. In the 10% sample the mortality rates were stable and similar to those overall up to 7 years but increased thereafter. Among the HIV positives the mortality rates rose quickly with time since seroconversion. Among the HIV positive miners median survival was 11 years overall. Survival was shorter in those who were older at seroconversion.

The effect of different median survival times on the proportion of deaths due to HIV and on total mortality rates among adults in South Africa is shown in figures 1 and 2. As the median survival increases, the proportion of deaths due to HIV and the mortality rate decrease. The differences in the proportion of deaths due to HIV are particular marked in the earlier years of the epidemic, ranging from 62% to 27% in 2001, for example, but are predicted to persist after the epidemic stabilises (ranging from 66% to 55%). These results assume no antiretroviral therapy.

Discussion

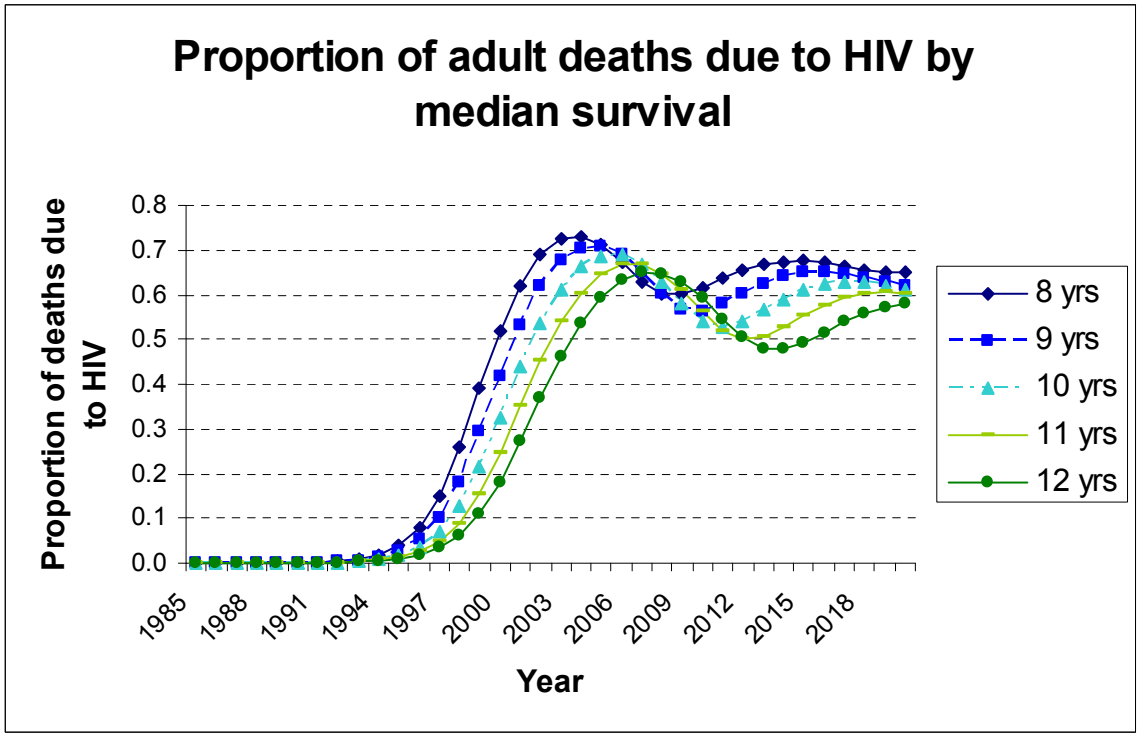
These are preliminary results; some further follow-up data are awaited. Nevertheless they represent much the largest cohort of individuals with known dates of seroconversion available in Africa and also one of the largest seroincident cohorts in the world of individuals with heterosexually acquired HIV.

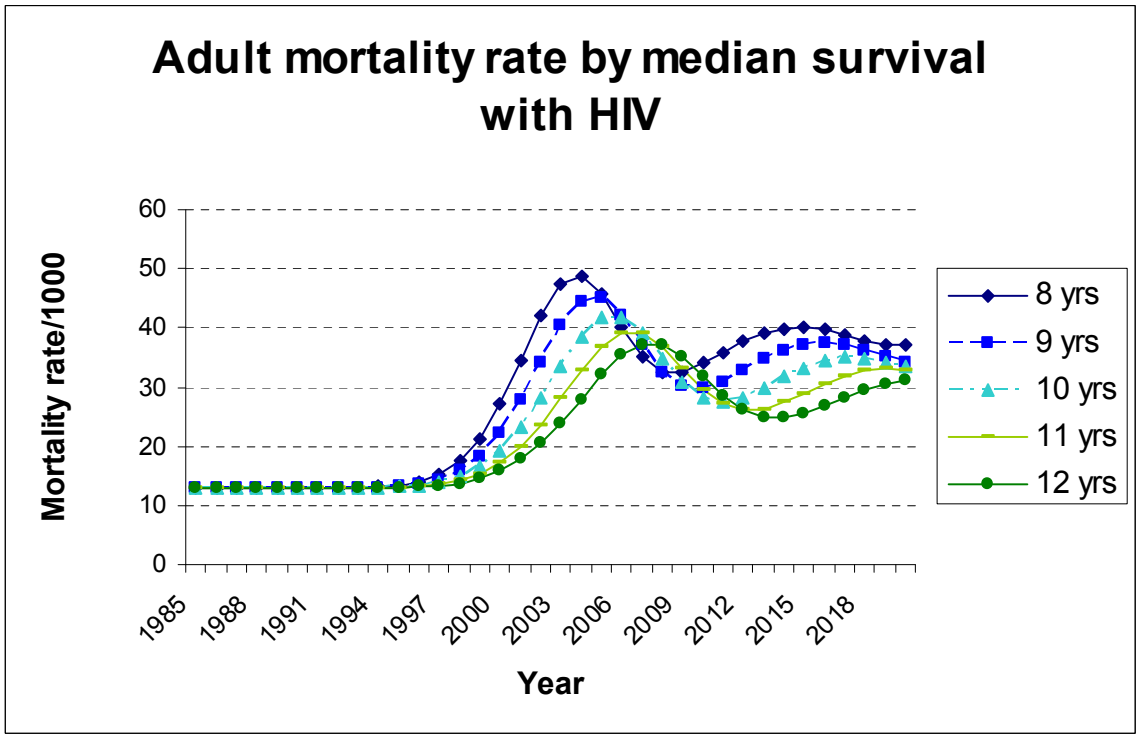
HIV infection increased mortality rates sharply to high levels. The mortality rates in the HIV positive men were slightly higher than those in the West before antiretrovirals,[4] but the median survival is slightly longer than that reported in Uganda.[2,5] Despite the high follow-up rates, the mortality rates may be slightly underestimated. Information may have been less likely to be available for those who died, and, in some cases individuals were reported dead but with no date of death. Individuals with no information after leaving the mine or no date of death were censored at the time of leaving the mine. The rates may also be lower than in a general population because of the healthy worker effect, although we continued follow-up after leaving the mines. Cause of death was only known reliably for those who died while still working on the mine: among HIV positive miners 22% of deaths on the mines were due to accidents or homicide/suicide, compared to 55% among HIV negative miners.

The implications of the varying estimates of median survival for interpreting what is happening to mortality rates in South Africa is apparent in the figures. The effects are particular large at the current time because the peak incidence of HIV as estimated by the model was probably about 1996. Nine years later we are therefore in a period of peak mortality, but both the height and timing of this peak depend on the exact duration of the median survival. The appropriate median survival to use depends on the average age of infection, which is not well known and may vary over time. Using the estimated median of 11 years, the model predicts that, assuming no antiretroviral treatment, the adult mortality rate in South Africa in 2005 will be 37/1000, and 65% of these deaths will be attributable to HIV infection.

References

1. Blacker J. The impact of AIDS on adult mortality: evidence from national and regional statistics. *AIDS* 2004:18 Suppl 2:S19-26.
2. Morgan D ,Whitworth JAG. The natural history of HIV-1 infection in Africa. *Nature* 2001:7:143-145.
3. Porter K ,Zaba B. The empirical evidence for the impact of HIV on adult mortality in the developing world: data from serological studies. *AIDS* 2004:18 Suppl 2:S9-S17.
4. Collaborative group on AIDS incubation and HIV survival including the CASCADE EU Concerted Action. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. *Lancet* 2000:355:1131-1137.
5. Morgan D, Muwonge R, Mahe C ,Whitworth J. Natural history of HIV infection in rural Uganda - results after 10 years. *XIII International AIDS Conference, Durban 9-14 July* 2000:Abstract TuOrC248.


Proportion of adult deaths due to HIV by median survival
Proportion of deaths due to HIV
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1985
1988
1991
1994
1997
2000
2003
2006
2009
2012
2015
2018
Year
8 yrs
9 yrs
10 yrs
11 yrs
12 yrs


Adult mortality rate by median survival with HIV
Mortality rate/1000
60
50
40
30
20
10
0
1985
1988
1991
1994
1997
2000
2003
2006
2009
2012
2015
2018
Year
8 yrs
9 yrs
10 yrs
11 yrs
12 yrs