

# Trends in Mortality of Insurance Applicants with HIV Infection

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**Objective.**—Provide a brief review of HIV history and determine the relative mortality of life insurance applicants who are HIV positive and how that has changed over time with advances in treatment.

**Method.**—By use of the Social Security Death Master File and multivariate analysis, mortality of those HIV positive relative to those HIV negative was determined for life insurance applicants from 1991 to 2009.

**Results.**—Relative mortality varied by type of testing (blood, urine or oral fluid) and by age, ranging from 320% at the oldest ages to over 1300% at the youngest ages for applicants with blood testing. Surprisingly, there was little change in relative risk among HIV-positive applicants over this period.

**Conclusion.**—Relative risk for life insurance applicants who are HIV positive remains high despite advances in therapy.

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## INTRODUCTION

In April 1980, the first known case of acquired immunodeficiency syndrome (AIDS) was reported to the Centers for Disease Control (CDC). While this was not the beginning of AIDS in the United States, it was the beginning of our awareness and would form the initial diagnostic criteria for this “new illness.” In June 1981, 5 cases of *Pneumocystis carinii* pneumonia were reported in previously healthy young men in Los Angeles; 2 had died and all were reported to be “homosexuals.”<sup>1</sup> Similar cases were

reported shortly thereafter from New York and San Francisco.<sup>2,3</sup>

While a formal case definition would not be adopted until 1982, the working case definition was the presence of unexplained immunodeficiency in an otherwise healthy patient presenting with Kaposi’s sarcoma and or life threatening opportunistic infection(s). Oral candidiasis, *Pneumocystis carinii* pneumonia and *Cryptococcus* were the most frequently identified opportunistic pathogens. By the end of 1981, 121 people were known to have died from the disease.<sup>4</sup>

Early laboratory testing for AIDS was tissue culture of patient blood to determine if the white cells would respond to bacterial antigens or lymphocyte mitogen blast stimulation.<sup>5</sup> In healthy blood, the number of white cells would increase while no stimulation occurred in blood from AIDS patients. Later tests included flow cytofluorographic phenotyping of white blood cells for the distribution of CD4/CD8 helper/suppressor lymphocytes. Prior to 1985, this was the most commonly requested test for the evaluation of patients. In 1983, Clinical Reference Laboratory (CRL) began testing insurance applicants for immunodeficiency; in 1983 and 1984, CRL processed more CD4/CD8 counts than the entire National Institute of Health. Beta-2-microglobulin, a marker of immune system activation, was also used as a surrogate to help identify applicants at risk of having AIDS.<sup>6</sup>

Before the viral etiology of AIDS was established, researchers in New York City suggested that substance abuse and exposure to amyl nitrite and inhaled sexual stimulants were associated with the increased prevalence of Kaposi's sarcoma.<sup>7-11</sup> These hypotheses illustrate many of the false trails that researchers would investigate before finally discrediting them as explanations for immunodeficiency in these patients. In the pre-molecular diagnostic world, isolation of putative agents was by tissue culture, with repeated attempts failing to identify an agent that caused immune cell destruction. In January 1983 this changed when Dr. Françoise Barré-Sinoussi, at the Pasteur Institute, isolated a retrovirus from an AIDS patient that killed T-cells.<sup>12</sup> The virus would be called various names (including LAV and HTLV-IIIb) before being renamed human immunodeficiency virus (HIV) in 1986. In 2008, the Nobel Prize in Medicine was awarded to Luc Montagnier and Françoise Barré-Sinoussi of the Pasteur Institute in Paris for the discovery of HIV.<sup>13</sup>

With the virus identified and a method to grow it in culture, commercial laboratory

testing for the presence of antibodies to HIV became available in March 1985. Widespread testing of insurance applicants began that year. Insurance applicant HIV prevalence in serum decreased sharply over the subsequent years from 0.4% to 0.046%, where it remains today.

In 1987, AZT (zidovudine), the first FDA approved antiretroviral drug, became available for the treatment of AIDS. At the time of AZT's introduction, the average life expectancy of a newly diagnosed patient was 12 to 18 months.<sup>14</sup> Within a year, it was apparent that AZT slowed progression but did not cure the infection. A greater concern was the appearance of resistance to AZT. Monotherapy selected pre-existing viral clones that were resistant to the drug. In 1992, the first FDA approved combination therapy, AZT and 3TC (lamivudine), became available but still only targeted the functioning of the virus' reverse polymerase enzyme.

In 1995, Saquinavir, a HIV specific protease inhibitor, was approved for treatment of AIDS patients. Its introduction heralded the beginning of highly active antiretrovirus therapy (HAART). With multiple drugs directed at multiple different HIV targets, the ability of the virus to evade treatment was greatly reduced. By 2001, the CDC reported a dramatic drop in the death rate for AIDS patients. Today more than 30 drugs have been approved by the FDA for the treatment of HIV and AIDS; they are from 5 different drug classes, each with a different mechanism to disrupt HIV replication.<sup>15-20</sup>

The 5 drug classes include nucleoside reverse transcriptase inhibitors (AZT-likes), non-nucleoside reverse transcriptase inhibitors (3TC-likes), protease inhibitors, entry/fusion inhibitors that block viral entry, and integrase inhibitors that reduce the integration of viral genome into the human host DNA. Many of these drugs are now marketed in convenient combinations that require the patient to take fewer pills per day; the greatest risk for disease progression is non-compliance with the treatment guidelines and emergence of drug resistant strains.

Before treatment is initiated, genetic testing of the patient's HIV is done to determine if any known pattern of drug resistance is present; at least 3 different drugs from 2 different classes are normally selected for initial therapy. The exact combinations vary, and as resistance occurs, the treatment is changed.<sup>21</sup> With the appropriate combination treatment, HIV virus can be reduced to non-detectable levels for most patients. HAART has changed the treatment landscape so that many HIV patients can be moved to a risk class of chronic illness that may be similar to any illness that shortens life expectancy by 10 to 20 years.

Published estimates for the effect of HAART on life expectancy vary. Some reports in the lay press indicate that treated HIV patients can enjoy a normal life expectancy, but published data does not support that conclusion.<sup>22-25</sup> This confusion occurs due to the failure to report all AIDS deaths correctly, in addition to the lack of a comprehensive count of the population positive for HIV. Several studies reported that early identification at, or close to, the time of infection and treatment prior to immune system suppression may affect short term mortality risk.<sup>24-29</sup> However, this does not equate to a return of a normal life expectancy.<sup>27-31</sup>

To help answer the question about how HAART has changed the mortality pattern of HIV patients, we conducted a study of life insurance applicants and compared mortality in those HIV positive vs. those HIV negative; sequential time periods were evaluated to determine if the mortality pattern had changed over time. Except where it is precluded by state insurance regulation or where the policy amount applied for is low, all individual life insurance applicants in the United States are tested for antibodies to HIV.

## METHODS

HIV results from approximately 14.1 million life insurance applicants age 20 to

79 tested between 1991 and 2009 were analyzed to determine their mortality pattern. Over 12,000 positive cases of HIV were identified through the testing of serum, urine or oral fluid. Deaths were determined from the Social Security Master Death file: 301,432 applicant deaths had occurred in this population through 2010 during 96 million person-years of exposure, with over 1800 deaths among HIV positives. Mean age of included applicants was 42 years and 56% were male. The years in which testing occurred were banded into 2-year groups, in order to decrease variability in the observed rates.

The data was analyzed using Cox regression, with HIV status, age, smoking and sex as covariates to determine hazard ratios. The Cox multivariate regression analysis of HIV test results was also stratified by age bands of 20-39, 40-59 and 60-79 years, with age, sex and smoking status as covariates.

All analyses were performed using IBM SPSS version 19.

## RESULTS

The distribution of the study population for all cases and HIV positives, age, prevalence of smoking and sex by the type of sample tested is presented in Table 1. The overall prevalence of HIV among insurance applicants varies from 0.045% in blood to 0.27% in oral fluid. The prevalence of tobacco smoking was substantially different by sample type, with 11.4%, 17.4% and 23.7%, respectively for blood, urine only, and oral fluid-tested applicants.

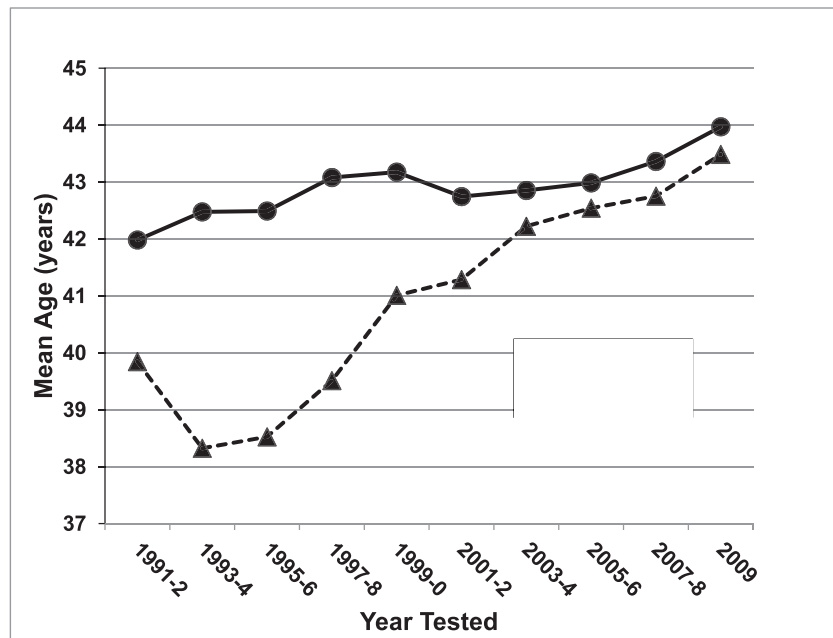
The mean age was determined by year tested for the population and split by HIV status; these data are presented in Figure 1 for blood tested applicants only. Blood testing has the longest experience, while oral fluid and urine HIV testing only started in 1997. Hazard ratios vary substantially by age, so it was important to determine if any age changes had occurred in the population testing positive compared to that testing

**Table 1.** Distribution of Cases by Type of Sample, Sex, HIV Positivity, Prevalence, Smoking Status and Mean Age

	Serum	Urine	Oral Fluid	Total
Total females	4,417,005	454,368	1,268,401	6,139,774
Total males	6,429,528	432,741	1,092,886	7,955,155
Total not specified	15,157	33	122	15,312
Total cases	10,861,690	887,142	2,361,409	14,110,241
HIV positive females	1260	393	2999	4652
HIV positive males	3621	583	3487	7691
HIV positive not specified	10	0	0	10
Total HIV positive cases	4891	976	6486	12,353
Prevalence rate, all cases (%)	0.0450	0.1100	0.2747	0.0875
Female HIV-neg. smoker (%)	8.4	13.8	19.3	11.0
Female HIV-pos. smoker (%)	19.8	19.6	34.6	29.4
Male HIV-neg. smoker (%)	13.4	21.1	28.8	15.9
Male HIV-pos. smoker (%)	27.0	29.2	44.7	35.2
Female HIV-neg. mean age (years)	42.0	42.7	38.7	41.4
Female HIV-pos. mean age (years)	41.3	49.2	38.2	40.0
Male HIV-neg. mean age (years)	43.8	41.2	38.8	43.0
Male HIV-pos. mean age (years)	41.4	46.2	39.6	41.0

negative. There were lower mean ages for applicants testing HIV positive using serum in the first half of the 1990s, with a roughly 4-year difference in the years 1993–1996. After 1996, mean ages for those who tested positive using serum rose to become only slightly lower than mean ages for those who tested negative.

Serum HIV prevalence for 3 age bands (20–39, 40–59 and 60–79) was evaluated to determine if any changes in prevalence had occurred over time within these applicant population subgroups. In Figure 2, after a large drop in HIV prevalence levels among all ages from the years 1991–1992, serum HIV results show a decreasing prevalence at



**Figure 1.** Mean applicant age by HIV status and year tested, serum only.

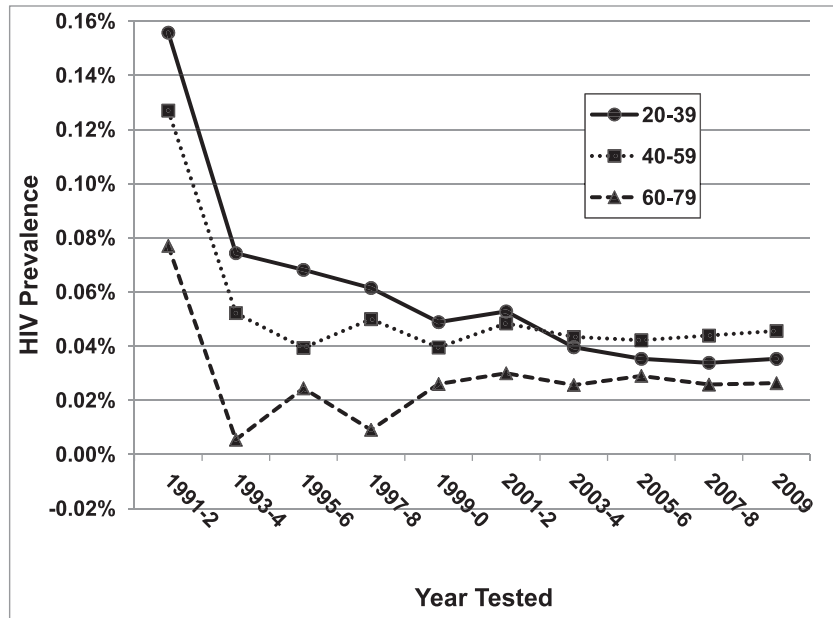


Figure 2. Serum HIV prevalence by age group and year tested.

younger ages with stability of prevalence among older age applicants. After the mid 1990s, the relatively lower prevalence rates among younger applicants may be related to an occurrence of fewer new cases among younger applicants along with possibly fewer deaths among the older age applicants. Urine and oral fluid show similar trends, with a gradual increase in the age of the HIV-positive population (data not shown).

Because HIV status varies by age, sex and smoking status, the relative mortality risk as a hazard ratio was calculated with Cox multivariate regression analysis using these factors as covariates. Hazard ratios for all durations of follow-up by age group and sample type are presented in Table 2. Although the analysis is done separately by age bands, age was included as a covariate to

adjust for the effect of age within these wide age ranges. Due to few deaths among females, the data was not analyzed separately by sex. While the relative mortality is similar for all 3 fluid types, there are substantial differences between the 3 age groups. The hazard ratio is highest for the youngest ages compared to the oldest age group; for all sample types, hazard ratios range from 1560% to 270% for ages 20–39 and 60–79, respectively.

To determine if any changes had occurred over time in the relative risk of death associated with positive HIV status at the time of insurance application, the data for serum samples was analyzed by year of testing for the first 5 years of follow-up. Cox hazard ratios (using the covariates of age, sex and smoking status) were calculated for the

Table 2. Hazard Ratios for HIV Positive Mortality by Sample Type and Age Group, All Durations

Age Group	Serum		Urine		Oral Fluid	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
20–39	14.8	13.1–16.8	13.7	9.6–19.6	15.6	14.2–17.2
40–59	6.5	5.8–7.3	7.5	5.6–10.0	6.1	5.6–6.6
60–79	3.2	2.5–4.0	2.7	2.3–3.3	3.3	2.6–4.2
All ages	7.4	6.8–8.0	3.9	3.4–4.5	7.7	7.2–8.2

**Table 3.** Five-Year Hazard Ratios for HIV Positive Mortality by Year Tested, Serum Only

Year Tested	Hazard Ratio	95% CI
1995–6	9.0	6.1–13.2
1997–8	9.9	6.8–14.2
1999–0	8.2	6.0–11.2
2001–2	10.9	8.3–14.3
2003–4	9.8	7.5–12.9

years 1995 through 2004 in 2-year increments. This analysis should identify if any change had occurred in the 5-year relative risk for death of HIV-positive applicants following widespread availability of HAART therapy.

The years 1995–1996 include applicants tested before the introduction of HAART, while the subsequent time periods reflect its increasing use. Years earlier than 1995 when HIV relative mortality was higher (data not shown) were not included in this particular analysis because it was likely there was more antiselection by applicants already diagnosed with AIDS but not admitting to such history. The year 2004 is the last year for which 5 complete years of mortality follow-up was available (because of delays in reporting events to the Death Master File). The resulting hazard ratios are presented in Table 3. Though the 95% confidence intervals are relatively broad, there is no obvious trend over time toward reduced mortality for those who tested positive for HIV at the time of application.

**DISCUSSION**

There is a 6-fold difference in the overall prevalence of HIV antibodies between blood and oral fluid samples (Table 1). This may be due to variation in the underlying prevalence of HIV in the different socioeconomic applicant groups from which the samples were collected, or may be attributable to self-selection by high risk applicants attempting to buy lower insurance policy amounts to avoid blood testing. Policy amounts allowed

are typically less than \$100,000 for oral fluid tested applicants, while serum testing normally starts at this amount. Two additional markers of risk behavior, cocaine and tobacco, are also more prevalent in the oral fluid-tested population (data not shown for cocaine). Taken together, these factors suggest socioeconomic differences between the oral fluid and blood tested populations.

When HIV prevalence is viewed by age group and year of testing, serum prevalence was initially more elevated but has remained relatively constant since 1995. Oral fluid results (not shown) have a similar pattern to serum with the HIV prevalence higher when the test was first introduced in previously untested applicants around 1997, reaching a zenith in 2001–2002 and then declining for all 3 age groups to about 0.19%. Similar changes in prevalence over time are observed in urine samples (not shown). The same trend is seen in all 3 sample types, an initial period of high prevalence (possibly attributable to antiselection by applicants diagnosed with HIV but not revealing such history) followed by a graded reduction in prevalence to the current sample type-specific HIV prevalence.

HIV relative mortality as shown in Table 2 varies by age. It remains above 500% until age 60 is reached and then drops below 350% for older ages. Since individual life insurance is not usually offered (nor is it financially practical for clients) above a risk of 400%, this means that a majority of HIV-positive applicants will likely still be declined coverage. In situations where coverage can be offered, the underwriter/medical director will have to review medical records to document level of HIV RNA, stability of CD4 counts, compliance with drug treatment, and the presence of dyslipidemia, diabetes, kidney disease, or cardiovascular disease.

In the HIV-positive population, non-compliance is more common than not and the emergence of drug resistance is a constant threat. Favorable information regarding

these factors would have some impact on reducing mortality further, perhaps to an “insurable range.” However, substantial excess mortality is likely to persist given the average level of relative risk that we report here.

We were also able to look at 5-year relative mortality based on year of testing (Table 3). The 1995–1996 period was before the widespread use of HAART, and serves as the benchmark for the other time intervals which occurred after the introduction of HAART. The hazard ratios are virtually identical for the HIV-positive population for all 5 time periods; the age, sex and smoking adjusted hazard ratios remained between 800% and 1100%. One would hope that with new treatment options, both the number under treatment and improvements in treatment would result in an improved outcome for this population with sufficient resources to purchase individual life insurance, but no improvement was seen. This is at odds with reported improvements in mortality,<sup>22,25–29</sup> and illustrates one of the important limitations of analysis of prevalence (shown here) instead of incidence data.

Incidence analysis allows the tracking of the natural history of the disease along with mortality estimates following infection; this has very important public health implications in providing guidance to clinicians about treatment options, and to government officials about planning for future HIV-related risks and costs. With prevalence data, this analysis can address only relative mortality risk, with no reference to when the infection was acquired.

However, a portion of the increased survival reported in the literature may come from length bias.<sup>32–33</sup> For HIV, there is a typical period of 10 or more years before the onset of AIDS. If you include that incubation period in the measurement of survival, the patient appears to live longer, as reported by the CASCADE Collaboration and others.<sup>22, 34–35</sup> This increase in survival is only relevant if we know when the infection occurred, and if

treatment was started before the immune system was irreparably harmed.<sup>36–37</sup> HAART treatment also comes with a long term risk of increases in kidney, heart and metabolic disorders (including diabetes) which may adversely impact mortality.<sup>30–31</sup> The most recent CDC analysis of HIV/AIDS mortality has also documented no change in the mortality pattern over the 2005–2007 time period.

An alternative explanation for the difference between our relative risk findings and those previously reported is that life insurance applicants may be unaware of their HIV status at the time of application, and are later in the disease process with more advanced disease at the time of detection. In other studies, time from infection and severity of disease at time of presentation are independent predictors of mortality risk.

## CONCLUSION

There has been continuing improvement in U.S. general population mortality and in insured-life mortality over the period covered by our studies, just as there has been improvement in mortality for those with HIV infection. When the trend in relative mortality risk is compared using 2-year bands of insurance applicants with and without HIV infection without selection based on time of infection or treatment, there appears to be little change. This means the absolute average risk of death in those with HIV declined but did not exceed the risk reduction in the HIV-negative insurance applicant population. Risk reduction for some HIV-positive applicants receiving and tolerating optimal treatment is likely greater, but many do not receive or cannot tolerate such therapy for a variety of reasons and their risk remains substantially higher. Studies of HIV-positive individuals of relatively recent onset receiving optimal therapy may not provide an accurate picture of mortality in a broad range of individuals with HIV infection of various durations relative to a population of healthy individuals (life insurance applicants).

Currently, HIV infection may remain largely uninsurable without extraordinarily high premium rates. The residual high risk represented by post-HAART 5-year mortality emphasizes the need for public health programs to increase early detection of infection, and the need for continuing improvements in the treatment of HIV patients.

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