Influenza-Related Mortality Among Adults Aged 25–54 Years With AIDS in South Africa and the United States of America

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Background. Data are limited on human immunodeficiency virus (HIV)–associated influenza burden in sub-Saharan Africa and the impact of highly active antiretroviral therapy (HAART). We compared influenza-related mortality in adults with AIDS in South Africa and the United States in the pre-HAART era and evaluated mortality trends after HAART introduction in the United States.

Methods. Monthly all-cause and pneumonia and influenza (P&I) mortality rates were compiled for adults with AIDS aged 25–54 years in South Africa (1998–2005) and the United States (pre-HAART era, 1987–1994; HAART era, 1997–2005). We estimated influenza-related deaths as excess mortality above a model baseline during influenza epidemic periods. Influenza-related mortality rates in adults with AIDS were compared with rates for age peers in the general population and adults ≥65 years old.

Results. In the United States before HAART, influenza-related mortality rates in adults with AIDS were 150 (95% confidence interval [CI], 49–460) and 208 (95% CI, 74–583) times greater than in the general population for all-cause and P&I deaths, respectively, and 2.5 (95% CI, 0.9–7.2) and 4.1 (95% CI, 1.4–13) times higher than in elderly adults. After HAART introduction, influenza-related mortality in adults with AIDS dropped 3–6-fold but remained elevated compared with the general population (all-cause relative risk [RR], 44 [95% CI, 16–121]; P&I RR, 73 [95% CI, 47–113]). Influenza-related mortality in South African adults with AIDS in recent years was similar to that in the United States in the pre-HAART era.

Conclusions. Adults with AIDS experience substantially elevated influenza-associated mortality, which declines with widespread HAART introduction but does not disappear. These data support increased access to HAART and influenza vaccination for HIV-infected adults.

Influenza virus causes substantial global morbidity and mortality, with an average of approximately 23 600 deaths annually in the United States alone [1]. There are approximately 30 million persons infected with human immunodeficiency virus (HIV) worldwide, including 5 million in South Africa and 1.2 million in the United States [2, 3]. The burden of influenza in HIV-infected persons remains poorly studied, particularly in sub-Saharan Africa, where the HIV burden is greatest [4]. Furthermore, data are limited on the impact of widespread use of highly active antiretroviral therapy (HAART) on mitigating severe influenza outcomes [5]. There have been no population-based studies evaluating influenza-associated mortality in adults with AIDS from sub-Saharan Africa and none after the introduction of HAART in the United States.

During the pre-HAART era in the United States, adults with AIDS were reported to experience higher
influenza-related mortality rates compared with the general population and similar rates compared with those aged ≥65 years [6]. After the introduction of HAART in the mid-1990s [3], rates of influenza-related cardiopulmonary hospitalizations declined among US adults with AIDS but remained similar to those in other high-risk groups [5]. In South Africa, hospital-based studies have shown an elevated risk of influenza hospitalization and a potentially increased case-fatality rate in HIV-infected children [4, 7].

Influenza virus circulation in South Africa occurs mainly during the Southern Hemisphere winter [8]; excess death rates among persons aged ≥65 years are estimated to be 4–8 times greater in South Africa than in the United States. Although influenza vaccination is recommended for elderly and high-risk individuals in South Africa, in 2007 <3% of the population received influenza vaccination [9]. In contrast, approximately 33% of the US general population had received the annual influenza vaccine in the 2008–2009 season, and coverage in elderly adults has remained at approximately 65% since the mid-1990s [10].

In this study, we compared influenza-related mortality rates in young adults (aged 25–54 years) with AIDS in South Africa and the United States during the pre-HAART era. Furthermore, we evaluated trends in influenza-related mortality rates in young adults with AIDS after the widespread introduction of HAART in the United States and compared estimates with those from reference population groups.

METHODS

The mortality burden of influenza cannot be measured directly, because many influenza-related deaths are not coded as such in death certificates. Instead, indirect statistical regression methods are used to quantify the increase in mortality rates for broad disease categories occurring during influenza activity periods, termed “excess mortality” [11, 12]. We applied statistical regression models to monthly US and South Africa mortality statistics by age and cause of death, combined with country-specific estimates of the AIDS population sizes and deaths, as detailed below and in the supplementary material. We focused on the age group 25–54 years because this was the age group most affected by AIDS (Supplementary Table 1). For comparison purposes, we also considered a similar age group in the general population, as well as adults aged ≥65 years [13–16].

Mortality Data and Population Denominators

Monthly age-specific deaths from pneumonia and influenza (P&I) and all causes as well as population denominators by age group and HIV status were obtained for South Africa (1998–2005 [14–17]) and the United States (1987–2005 [13, 18] and see supplementary material).

Estimation of Deaths in Persons With AIDS

South Africa Estimates

In South Africa, it is estimated that 80%–90% of adult deaths were registered in 2000 [19]. A diagnosis of AIDS is rarely coded on the death certificate (<2% of deaths in 2002) [20], although the estimated percentage of deaths due to AIDS in persons aged 25–54 years increased from 28% to 72% during 1998–2005, reflecting the increasing burden of the AIDS epidemic [2]. To get around this coding issue, we compiled monthly deaths due to P&I (as the underlying or contributing cause) and total deaths in persons aged 25–54 years. To estimate the monthly number of deaths in young adults with AIDS we multiplied the total monthly numbers of all-cause and P&I deaths in young adults by the proportion of all deaths associated with AIDS in this age group and year, as estimated by the Actuarial Society of South Africa AIDS and Demographic model [17].

To estimate deaths in young adults with AIDS in the United States we included all deaths in persons aged 25–54 years with AIDS listed either as an underlying or contributing cause (an estimated approximately 90% of United States patients deceased with AIDS [22]). To estimate P&I deaths in young adults with AIDS, we included all deaths that had both AIDS and P&I listed anywhere on the death certificate.

Estimation of Influenza-Related Excess Mortality

To determine influenza-related excess mortality, we compared the mortality observed during influenza epidemic periods to a seasonal model baseline of “expected” mortality, separately for each population group and mortality outcome. First, we identified influenza epidemic periods by applying a linear seasonal regression model to influenza-specific deaths for all ages, which has been shown to accurately estimate the timing of influenza virus circulation in South Africa and the United States (Supplement and [8, 12]). Next, to obtain seasonal baselines for all-cause and P&I mortality, we fitted spline models to monthly mortality data for each outcome and population subgroup, after exclusion of influenza epidemic months (Supplement).


Nondemographic differences between countries and periods, such as access to healthcare and coding practices,
may affect influenza-related mortality estimates and bias comparisons. To adjust for baseline differences, we calculated the proportion of winter deaths attributable to influenza as the winter-season excess deaths divided by baseline expected deaths during influenza epidemic months [23, 24]. These proportions were compared between different population subgroups using logistic regression. To obtain an estimate of the relative risk (RR) of influenza-related mortality associated with AIDS, we compared seasonal excess mortality rates in young adults with AIDS in the United States and South Africa with rates in reference population groups (elderly adults, age peers), using negative binomial regression.

Ethics

Ethical approval for the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), South Africa. The United States census and national HIV surveillance system data do not contain personal identifiers, and their use in this report does not require human subjects oversight.

RESULTS

Overall Trends and Seasonality of Deaths Among Persons With AIDS

In South Africa between 1998 and 2005, there was a >8-fold increase in the estimated number of young adults aged 25–54 years living with AIDS and a >4-fold increase in annual deaths in young adults with AIDS (Table 1, Figure 1). In the United States, the annual number of deaths in young adults with AIDS increased 2-fold during the pre-HAART era, 1987–1994 and decreased >2-fold in the HAART era (Table 1; Figure 2).

Influenza seasons occurred between May and September in South Africa and November and March in the United States, averaging 4 months in duration. All-cause and P&I deaths among young adults with AIDS were particularly winter seasonal in South Africa, and seasonality increased over time (Figure 1). Mortality in young adults with AIDS in the United States was less seasonal, especially in the pre-HAART era (Figure 2).

Estimates of Influenza-Related Excess Mortality in Adults With AIDS, South Africa

Influenza-related seasonal excess mortality rates in young adults with AIDS were estimated at 574 and 127 per 100 000 for all-cause and P&I (Table 2). These excess mortality rates were 2.2-fold (95% confidence interval [CI], 1.0–5.1) and 3.8-fold (95% CI 2.2–6.6) greater than those in adults ≥65 years old for the same time period (Table 3). In contrast, the proportion of winter deaths attributable to influenza was lower in young adults with AIDS as compared with elderly adults (all-cause deaths, 5% vs 17%; P&I deaths, 7% vs 43%; P < .001; Table 2).

Table 1. Estimated Population Size and Number of Annual Deaths Among Adults Aged 25–54 Years With AIDS in South Africa and the United States

<table>
<thead>
<tr>
<th>Country and Year</th>
<th>Estimated Total Deaths</th>
<th>Estimated All-Cause Deaths</th>
<th>Estimated P&amp;I Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>63 923</td>
<td>37 912</td>
<td>3979</td>
</tr>
<tr>
<td>2005</td>
<td>583 371</td>
<td>205 042</td>
<td>32 485</td>
</tr>
<tr>
<td>United States (before HAART)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>26 249</td>
<td>12 996</td>
<td>1894</td>
</tr>
<tr>
<td>1994</td>
<td>167 462</td>
<td>41 925</td>
<td>6050</td>
</tr>
<tr>
<td>United States (after HAART)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>224 437</td>
<td>17 600</td>
<td>2573</td>
</tr>
<tr>
<td>2005</td>
<td>350 316</td>
<td>11 365</td>
<td>1591</td>
</tr>
</tbody>
</table>


Abbreviations: HAART, highly active antiretroviral therapy; P&I, pneumonia and influenza.

Trends in Influenza-Related Excess Mortality in Young Adults With AIDS Receiving HAART, United States

In the United States, in the pre-HAART era, young adults with AIDS experienced an average of 431 and 103 influenza-related excess all-cause and P&I deaths per 100 000 population, respectively (Table 2). Excess mortality rates declined by 3–6-fold with the widespread use of HAART (Table 3). In the pre-HAART era, influenza-related excess mortality rates in young adults with AIDS were similar to or greater than those in elderly adults, and 150–200 times greater than the experience in the general population aged 25–54 years. In the HAART era, influenza-related excess mortality rates in young adults with AIDS became similar to those experienced in elderly adults (RR not different from 1) but still remained substantially elevated when compared with those in their age peers (RR, approximately 40–70).

Similar to findings in South Africa, the influenza contribution to winter deaths in the pre-HAART era was lower in young adults with AIDS than in elderly adults (all-cause deaths, 2% vs 5%; P&I deaths, 5% vs 18%; P < .001; Table 2). Interestingly, although the absolute rate of influenza-related excess mortality declined from the pre- to the post-HAART era in young adults with AIDS, the percentage of winter deaths attributable to influenza increased during this period (from 2% to 5% of all-cause deaths and from 5% to 17% of...
P&I deaths; \( P < .001 \)). Influenza-related mortality rates in South African young adults with AIDS in recent years were similar to those in the United States in the pre-HAART era (RR not different from 1; Table 3).

**DISCUSSION**

This study evaluates influenza-related excess mortality both among adults with AIDS in South Africa and the United States in the pre-HAART era and in the United States during the HAART era. Our data suggest that in the absence of HAART, adults aged 25–54 years with AIDS experience a substantially elevated risk of influenza-associated death, 150–200-fold higher than that in the general population of the same age and 2–4-fold higher than that in adults aged ≥65 years. This is consistent with the overall dramatic increase in total risk of death in patients with AIDS. In the United States, influenza-related mortality rates in young adults with AIDS declined after the widespread introduction of HAART around 1995 but still remained approximately 40–70-fold higher than those of their age peers and similar to those of elderly adults [3]. The risk of influenza-related mortality in untreated young adults with AIDS was similar in South Africa and the United States. These findings suggest that AIDS remains a substantial risk factor for severe influenza-related disease in developed and developing world settings and support the ongoing importance of influenza prevention measures in persons with AIDS.

Studies from South Africa have reported an approximately 8-fold elevation of influenza-associated hospitalization rates and possible elevated case fatality ratios in HIV-infected children [4, 7]. A US study set in the pre-HAART era [6] found an average excess P&I mortality rate of 122 per 100 000 and a 100-fold mortality risk elevation in persons with AIDS aged ≥13 years relative to their age peers, which is the same order of magnitude as our estimates. Limitations of that study include the lack of adjustment for rapidly increasing background mortality in individuals with AIDS before HAART, which may have resulted in overestimation of excess mortality, and the inclusion of only 3 influenza seasons. Another US study in the pre-HAART era showed that HIV-infected women experienced excess rates of cardiopulmonary hospitalization 50–75 times greater than rates in their age peers [25]. Our study suggests even higher influenza-related excess mortality risks in persons with AIDS.

Our results suggest that the introduction of HAART in the mid-1990s in the United States substantially decreased...
influenza-related excess mortality in young adults with AIDS, coinciding with an overall mortality rate decline in this group. Similarly, a population-based study demonstrated that influenza-associated hospitalizations in adults with AIDS aged 15–50 years decreased after the introduction of HAART, although only 1 year of pre-HAART data was available for comparison [5]. Overall, our study was more robust than earlier population-based studies in the United States, because we compared 8 pre-HAART seasons with 7 post-HAART seasons and confirmed that the introduction of HAART has decreased the mortality burden of influenza among young adults with AIDS. Unfortunately, we were unable to evaluate the effect of HAART on influenza-related mortality in South Africa. Although a national treatment program for HIV-infected individuals was initiated in 2004 in this country, only an estimated 25% of those requiring treatment had started HAART by the end of our study period in 2005 [26].

Our study is subject to several limitations. We used different methods for estimating mortality rates among persons with AIDS in South Africa and the United States, given differences in coding of deaths. Whereas in the United States the majority of deaths in persons with AIDS receive an AIDS diagnosis on the death certificate (Supplement) [22], this is not the case in South Africa [20]. For this reason we estimated deaths in young South African adults with AIDS by multiplying total deaths in young adults by an estimated proportion of deaths due to AIDS in this age group, derived from a validated model [2, 17]. This method relies on the assumption that the proportion of deaths due to AIDS does not vary seasonally or by cause of death. Additional sensitivity analyses comparing our mortality estimates with those published by other sources and evaluating the impact of deaths with no specific code of death (Supplement), suggest that our estimates of the RR associated with AIDS are conservative.

Several internal and external consistency checks suggest the validity of our findings. Most importantly perhaps, we found similar levels of influenza-related excess mortality rates in untreated young adults with AIDS in South Africa and the United States. Furthermore, influenza-related mortality rate estimates were consistently 2–4 times greater in young adults with AIDS than in elderly adults in both countries. Our excess mortality approach to measure influenza burden produced estimates within 10% of those previously published for US elderly adults [8, 11]. The numbers of US AIDS deaths in our series was also within 10% of annual estimates of deaths among persons with AIDS from the Centers for Disease Control AIDS surveillance reports (Supplement and [22, 27]). Moreover, the increasingly strong winter seasonality of P&I and all-cause mortality in all South African young adults, at a
Table 2. Estimated Influenza-Related Seasonal Excess Mortality Rates in Different Population Groups and Time Periods in South Africa and the United States

<table>
<thead>
<tr>
<th>Mortality Rate</th>
<th>South Africa</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Persons With AIDS Aged 25–54 Years</td>
<td>General Population Aged ≥65 Years</td>
</tr>
<tr>
<td>Pre-HAART</td>
<td>Pre-HAART</td>
<td>Pre-HAART</td>
</tr>
<tr>
<td>Seasonal excess all-cause mortality, mean (95% CI), deaths per 100 000 population</td>
<td>574 (211–827)</td>
<td>264 (252–276)</td>
</tr>
<tr>
<td>Winter all-cause deaths attributable to influenza, mean (95% CI), %a</td>
<td>5 (3–7)</td>
<td>17 (12–22)</td>
</tr>
<tr>
<td>Seasonal excess P&amp;I mortality, mean (95% CI), deaths per 100 000 population</td>
<td>127 (65–189)</td>
<td>34 (33–35)</td>
</tr>
<tr>
<td>Winter P&amp;I deaths attributable to influenza, mean (95% CI), %a</td>
<td>7 (5–9)</td>
<td>43 (22–64)</td>
</tr>
</tbody>
</table>

Rates are based on excess all-cause and pneumonia and influenza mortality derived from a seasonal regression modeling approach. The pre-highly active antiretroviral therapy (HAART) period was 1987–1994 in the United States and 1998–2005 in South Africa; the HAART era in the United States was 1997–2005.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; P&I, pneumonia and influenza.

*a Excess mortality is expressed as the percentage increase over the baseline (excess deaths during influenza epidemic months divided by baseline expected deaths during influenza epidemic months).
Table 3. Relative Risk of Influenza-Related Excess Death Rates in Adults Aged 25–54 Years With AIDS, Compared With Reference Population Groups and Periods in South Africa and the United States

<table>
<thead>
<tr>
<th>Mortality Outcome</th>
<th>South African Adults Aged 25–54 Years With AIDS</th>
<th>US Adults Aged 25–54 Years With AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vs South African General Population Aged ≥65 Years</td>
<td>vs Pre-HAART vs General Population Aged 25–54 Years in Pre-HAART Era</td>
</tr>
<tr>
<td></td>
<td>vs US Adults Aged 25–54 Years With AIDS in Pre-HAART Era</td>
<td>vs General Population Aged ≥65 Years in Pre-HAART Era</td>
</tr>
<tr>
<td>Influenza-related excess all-cause death rate, RR (95% CI)</td>
<td>2.2 (1.0–5.1)</td>
<td>5.6 (1.3–24)</td>
</tr>
<tr>
<td></td>
<td>1.3 (0.3–5.3)</td>
<td>150 (49–460)</td>
</tr>
<tr>
<td>Influenza-related excess P&amp;I death rate, RR (95% CI)</td>
<td>3.8 (2.2–6.6)</td>
<td>2.6 (0.9–7.1)</td>
</tr>
<tr>
<td></td>
<td>1.2 (0.4–3.5)</td>
<td>208 (74–583)</td>
</tr>
</tbody>
</table>

All estimates given for South Africa are considered to predate the highly active antiretroviral therapy era in this country.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; P&I, pneumonia and influenza; RR, relative risk.

* Determined with negative binomial regression.

Notes

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Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit readers. Questions or messages regarding errors should be addressed to the authors.

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