Original Contribution


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Because the incidence of human immunodeficiency virus (HIV) infection is difficult to measure directly, prevalence trends often serve to track epidemiologic changes. Adult HIV prevalence in open population cohort studies, however, reflects changes in incidence, population factors (migration, deaths, and aging), and survey coverage. Data from an open cohort in rural Uganda enabled estimation of the contribution of these factors to prevalence trends from 1989 to 2007. New infections within this cohort represented on average 44% of new prevalent cases per year. Other factors affecting changes in prevalence included migration and death. Migrants and mobile people (those who leave and return to the study area) are in a higher-risk group and thus can affect prevalence trends. Incidence of HIV infection among mobile people was 2–4 times greater than among stable residents. The importance of mortality is shown by the rise in prevalence from 6.8% in 2005 to 7.4% in 2007, which was accompanied by a fall in mortality among HIV-infected participants (8.7% of HIV-infected in 2005, 5.2% in 2006, and 4.3% in 2007). Assessing HIV epidemic trends through prevalence requires consideration of population factors. Measuring HIV incidence directly remains the most accurate measure of trends with which to monitor the effect of intervention activities and should complement strategies such as national prevalence surveys.

Africa; cohort studies; HIV; prevalence; Uganda

In open population-based cohort studies, HIV prevalence reflects incidence, population factors (migration, deaths, and aging into inclusion criteria), and survey coverage (17–19). The longest-running annual HIV serosurvey in Africa is the open population-based cohort study in rural southwestern Uganda established in 1989 by the United Kingdom Medical Research Council and the Uganda Virus Research Institute (20). We used data from this cohort to estimate the contribution of population factors to adult HIV prevalence trends from 1990 to 2007.

MATERIALS AND METHODS

Setting

Since 1986, Uganda has been recovering from civil, political, and economic turmoil. The national prevalence of HIV infection reached a peak of 18% in 1992, subsequently declined through the 1990s, and reached a plateau of about 6% by the end of that decade (7, 21). Recent indications are that HIV prevalence is again rising (2). The present study site in Uganda was chosen as a typical rural African setting that HIV prevalence is again rising (2). The present study site in Uganda was chosen as a typical rural African setting and has been described previously (22, 23).

Annual survey

The annual HIV serosurvey of this cohort has previously been described elsewhere (24). In brief, all households are visited by the mapping, census, and survey teams (all accompanied by a village councilor). The annual census permits analysis of the contribution of population factors to calculations of HIV prevalence. A standardized questionnaire is used to enumerate household members and to record births, deaths, and in-migration and out-migration that have occurred since the previous census.

The annual household survey (initially conducted among the residents of 15 villages and increased to include 25 villages in 2000) currently has approximately 18,000 participants. This number varies each year because of migration, births, and deaths. Community members are interviewed at home by survey field workers and provide a blood sample for HIV testing. The focus of the present article is on the original 15 villages because there is an indication that the epidemiologic trends differ to some extent between the original villages and the additional villages (2). The original villages comprise approximately 11,000 participants, 7,000 of whom are adults (defined for survey purposes as persons aged 13 years or older).

Estimation of HIV prevalence and incidence

The methods used to estimate prevalence and incidence of HIV in adults in our study population have been described previously (1, 2). Each year, a survey round is conducted from November to October of the following year. Prevalence estimates are made by round and reported by year—for example, the results of round 1 (November 1989–October 1990) were reported as 1990. Prevalence in a given round is estimated from current residents with a confirmed HIV status; an individual who has moved away from the study area is not included in prevalence estimates in the given round. An individual who subsequently moves back into the area is again included in prevalence estimates, beginning in the round during which the person returned. The average percentage of residents for whom we had confirmed HIV status (positive or negative) in a given round was 75%. As has been described in detail previously (2), this includes persons for whom we were missing data in a given round but who tested HIV-positive in a previous round and were therefore counted as positive, as well as those who tested HIV-negative in a subsequent round and were therefore counted as negative in the round in question.

Incidence estimates are made by calendar year, with the date of seroconversion assigned in the middle of the interval between the last negative test and the first positive test, even if there is a gap of 1 round or more between the 2 tests. This method applies even if the person temporarily leaves the study area, as long as the person does eventually return. In portraying the impact of various factors on prevalence, however, an “incident” case was someone who was HIV-negative in one round and HIV-positive the next. If the person was HIV-negative when he or she left the area and HIV-positive when he or she returned several years later, then when considering the factors that influence prevalence, that person was classified as an HIV-negative out-migrant in the year of departure and an HIV-infected in-migrant in the year of return to the area. Similarly, the denominator of prevalence includes all people with a known HIV status. This number is larger than the person-years of observation used to estimate incidence because incidence estimates do not use imputed HIV status for missing results as prevalence estimates may. Details of prevalence and incidence estimation, including discussions of possible bias, have been reported previously (1).

HIV prevalence

The numerator for calculation of HIV prevalence is the number of residents with confirmed HIV infection, and the denominator is the number of residents with known HIV status. Factors contributing to changes in the numerator of prevalence from one year to the next are listed below. A plus sign indicates that the contribution adds to the numerator, whereas a minus sign means that it subtracts from the numerator:

- HIV-negative individuals who seroconvert (+);
- HIV-positive residents who are newly tested (+);
- HIV-positive in-migrants or returning mobile people (+);
- HIV-positive children aging into adulthood (+);
- HIV-positive out-migrants (−); and
- HIV-positive individuals who died (−).

Factors contributing to changes in the denominator of prevalence are:

- All of the above except persons who seroconvert;
- HIV-negative in-migrants or returning mobile people (+);
- HIV-negative children aging into adulthood (+);
- HIV-negative out-migrants (−);
- HIV-negative individuals who died (−); and
- HIV-negative individuals whose status became unknown (−).
HIV-positive residents who were newly tested include those who were tested for the first time, as well as those who were HIV-negative more than 1 year prior but were not tested in the previous year and whose HIV status in the previous year was therefore unknown. This category does not apply to HIV-negative residents because their HIV-negative status would have been back-imputed.

Mobile people are defined as those who leave the study area for more than 1 year and subsequently return; they are classified together with migrants. For example, when describing contributors to the numerator of HIV prevalence, an HIV-infected “in-migrant” could be a person completely new to the cohort or a person who had lived in the cohort, subsequently left the area, and then returned in the given year.

HIV incidence

The numerator for calculation of HIV incidence is the number of residents who have become infected with HIV in a year. The denominator is the number of person-years among HIV-uninfected individuals at risk in that year, so contributions are made by in-migrants, and contributions cease when someone dies, out-migrates, or seroconverts. Because incidence estimates vary greatly from year to year, incidence results are presented with a lowess smoothing algorithm applied. Incidence estimates are presented here to provide the background to understanding the contribution of population factors to prevalence. Detailed analyses of incidence in this cohort, including confidence intervals, have been published previously (1, 2).

Sensitivity analysis

Prevalence estimates take advantage of the longitudinal nature of the cohort data, with imputation of HIV test results from previous or subsequent rounds where possible when the individual is a resident but misses testing in the current round. We conducted a sensitivity analysis comparing these usual prevalence estimates with estimates in which we assumed that all residents with a missing HIV result even after our usual imputing were HIV-negative. We conducted this analysis to assess the maximum potential upward bias in the most recent years. This bias was most evident in recent years for which there were more missing HIV status results among people who might later be classified as uninfected.

Ethics

The study was approved by the Science and Ethics Committee of the Uganda Virus Research Institute and by the Uganda National Council of Science and Technology. Free voluntary HIV counseling and testing are available in the area. Since 2004, antiretroviral therapy has been available to all eligible members of the study population who know they are HIV-positive.

RESULTS

Overall incidence and prevalence

HIV prevalence in Uganda fell during the 1990s, from 8.5% in 1991 to 6.9% in 1999. Incidence per 1,000
person-years of observation fell from 6.2 in 1991 to 4.7 in 1999. Younger women had a higher incidence than did older women, whereas the reverse was true for men (Figure 1). However, among all subgroups, overall incidence fell. During the 2000s, prevalence rose slightly (Figure 2), although incidence showed an inconsistent pattern among subgroups (2) but generally continued to fall (Figure 1).

**Prevalence numerator**

Table 1 shows the annual changes in the number of HIV-positive participants. Incident cases represent less than 25% of new cases per year. In addition, some of the HIV-positive in-migrants were in fact mobile people who left the area while uninfected and returned infected more than 1 year later. This scenario represented a small proportion of the in-migrants, ranging from 1 individual (in 1994 and 2003) to a maximum of 8 individuals (in 2006). When these recently infected mobile people were included, new infections represented 14%–32% of new cases per year (Table 1). If net in-migration of HIV-infected people was considered rather than considering in-migrants and out-migrants separately, then new infections represented an average of 44% of new cases per year, with a range of 20%–94% (Table 1).

The declines in HIV prevalence in 1994 and 1996 were mainly due to a net outflow of migrants and more deaths of HIV-positive participants than in the years immediately preceding and following. In 1994, there were 28 HIV-positive in-migrants and 43 HIV-positive out-migrants, with a net outflow of 15 people. Similarly, in 1996, there was a net outflow of 7 people. This contrasts with all other years, in which there were more HIV-positive in-migrants than out-migrants. In 2005–2007, as prevalence rose, fewer HIV-positive people died than in earlier rounds. In these years, HIV-positive deaths averaged 24 per year, compared with 42 per year in 2002–2004. Antiretroviral therapy roll-out began in the area in 2004, and most people in need were receiving treatment by the end of 2005.

**Prevalence denominator**

Figure 3 shows the annual changes in contributions to the denominator of HIV prevalence, which were 7–8 times greater than changes in the numerator. Participants who turned 13 years old and were entered into the adult group made a sizeable contribution to the denominator (Figure 3). Deaths comprised a very small proportion of subtractions from the denominator. For example, if we account for migration by considering net out-migration in the subtractions to the denominator, then the relative contribution of deaths was 12% of subtractions in 2007. Net in-migration in 2007 was negative—that is, there were more out-migrants than in-migrants. Excluding migration, 13-year-old participants aging into inclusion criteria comprised 97% of additions to the denominator.

A large part of the subtractions from the denominator in a given year resulted from participants who previously tested HIV-negative and were never again tested or who missed at least 1 round of testing and then tested HIV-positive (labeled “not tested” in Figure 3). For example, in 2007, this group comprised 41% of subtractions. Accounting for all migration by using net out-migration, those who were never again tested accounted for 72% of subtractions in 2007; net out-migration was 64 people. Another source of subtractions from the denominator in many years was migration. Although in all but 2 years, there was a net in-migration of HIV-positive people, there was net out-migration among all people (denominator of prevalence) in more than half of the years (Table 1).

Part of the rise in HIV prevalence in 2005–2007 can be attributed to a reduced mortality rate among HIV-positive people (Figure 2), and another part can be attributed to a reduction in HIV-negative net in-migration (more out-migrants...
## Table 1. Changes (Number) in the Numerator and Denominator of Human Immunodeficiency Virus Prevalence, Uganda, 1990–2008

<table>
<thead>
<tr>
<th>Year</th>
<th>Subtractions</th>
<th>Numerator (Changes in Confirmed HIV-Infected Population)</th>
<th>Additions</th>
<th>New Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Died</td>
<td>Out-Migrated</td>
<td>Incident Cases</td>
<td>In-Migrated&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1990</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1991</td>
<td>18</td>
<td>0</td>
<td>22</td>
<td>52 (0)</td>
</tr>
<tr>
<td>1992</td>
<td>43</td>
<td>41</td>
<td>12</td>
<td>44 (0)</td>
</tr>
<tr>
<td>1993</td>
<td>41</td>
<td>35</td>
<td>15</td>
<td>51 (0)</td>
</tr>
<tr>
<td>1994</td>
<td>55</td>
<td>43</td>
<td>16</td>
<td>28 (1)</td>
</tr>
<tr>
<td>1995</td>
<td>42</td>
<td>28</td>
<td>11</td>
<td>38 (4)</td>
</tr>
<tr>
<td>1996</td>
<td>58</td>
<td>40</td>
<td>9</td>
<td>33 (4)</td>
</tr>
<tr>
<td>1997</td>
<td>25</td>
<td>27</td>
<td>15</td>
<td>45 (3)</td>
</tr>
<tr>
<td>1998</td>
<td>44</td>
<td>17</td>
<td>5</td>
<td>45 (5)</td>
</tr>
<tr>
<td>1999</td>
<td>30</td>
<td>20</td>
<td>15</td>
<td>41 (5)</td>
</tr>
<tr>
<td>2000</td>
<td>28</td>
<td>27</td>
<td>7</td>
<td>54 (7)</td>
</tr>
<tr>
<td>2001</td>
<td>44</td>
<td>28</td>
<td>15</td>
<td>34 (4)</td>
</tr>
<tr>
<td>2002</td>
<td>48</td>
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<td>2003</td>
<td>41</td>
<td>28</td>
<td>12</td>
<td>31 (1)</td>
</tr>
<tr>
<td>2004</td>
<td>34</td>
<td>29</td>
<td>12</td>
<td>42 (5)</td>
</tr>
<tr>
<td>2005</td>
<td>34</td>
<td>30</td>
<td>11</td>
<td>33 (4)</td>
</tr>
<tr>
<td>2006</td>
<td>20</td>
<td>24</td>
<td>6</td>
<td>35 (8)</td>
</tr>
<tr>
<td>2007</td>
<td>17</td>
<td>26</td>
<td>10</td>
<td>33 (7)</td>
</tr>
</tbody>
</table>

### Denominator (Changes in Those With Confirmed HIV Status)

<table>
<thead>
<tr>
<th>Year</th>
<th>Subtractions</th>
<th>Additions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Died</td>
<td>Out-Migrated</td>
</tr>
<tr>
<td>1990</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1991</td>
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</tr>
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<td>1998</td>
<td>70</td>
<td>345</td>
</tr>
<tr>
<td>1999</td>
<td>75</td>
<td>351</td>
</tr>
<tr>
<td>2000</td>
<td>59</td>
<td>358</td>
</tr>
<tr>
<td>2001</td>
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<td>323</td>
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<tr>
<td>2002</td>
<td>85</td>
<td>432</td>
</tr>
<tr>
<td>2003</td>
<td>79</td>
<td>353</td>
</tr>
<tr>
<td>2004</td>
<td>68</td>
<td>445</td>
</tr>
<tr>
<td>2005</td>
<td>78</td>
<td>463</td>
</tr>
<tr>
<td>2006</td>
<td>45</td>
<td>357</td>
</tr>
<tr>
<td>2007</td>
<td>49</td>
<td>367</td>
</tr>
</tbody>
</table>

Abbreviation: HIV, human immunodeficiency virus.

<sup>a</sup> Parentheses indicate those who out-migrated while HIV-negative and returned with HIV infection in the next round.

<sup>b</sup> Parentheses indicate those who were HIV-negative more than 1 round prior, were not tested during the previous round, and were HIV-positive in the current round.

<sup>c</sup> Number and percentage of new cases due to current round incidents or previously uninfected out-migrants who in-migrated in the current round with HIV infection (mobile people).

<sup>d</sup> Percentage of new cases due to incidents and migration, in which net in-migration (in-migration minus out-migration) determined migration contribution.

than in-migrants) and in HIV-negative people turning 13 years of age (Figure 3) in these years. The average number of HIV-positive deaths in 2002–2004 was 41 per year, and without these deaths, HIV prevalence would have been 7.7% rather than 6.9% in 2002, 7.4% rather than 6.7% in 2003, and 7.4% rather than 6.8% in 2004. By contrast, the average number of HIV-positive deaths in 2005–2007 was 24, and without these deaths, HIV prevalence would have been 7.5% rather than 6.9% in 2005, 7.4% rather than 7.1% in 2006, and 7.7% rather than 7.5% in 2007. In short, death of HIV-infected people reduced the prevalence by an average of 0.7% per year from 2002 to 2004, but only reduced it by an average of 0.3% per year from 2005 to 2007.

Migrants had a substantial impact on prevalence results through their uneven contribution to the numerator and denominator. Migrants, including mobile people, were more likely to be HIV-infected than were stable residents. Approximately 75% of new contributors to the numerator of prevalence were in-migrants (Figure 2), whereas only about 50% of new contributors to the denominator were in-migrants (Figure 3). This represents 33% of new contributors to the numerator among net in-migrants and 6% of losses to the denominator among migrants (Table 1); that is, there was more out-migration than in-migration in the denominator.

**Sensitivity analysis of prevalence estimates**

Figure 4 shows the results of the sensitivity analysis, comparing usual prevalence estimates in this cohort with an estimate in which we set all missing results (after imputing where possible) to HIV-negative. Although the estimates from the comparison are smaller than our usual estimates, the general shape of the trend from 1990 to 2007 is similar.

**DISCUSSION**

In an open population-based cohort study, we have shown that population factors such as migration, mortality, and aging have a greater impact on HIV prevalence estimates than do changes in incidence. This highlights the importance of those factors in addition to incident cases that contribute to HIV prevalence trends. Although the exact amount of migration, mortality, survey coverage, and incidence may vary from one open cohort study to another, the message of caution in relying on prevalence trends to monitor epidemiologic changes applies to any open population-based cohort study.

Figure 3. Contributions to the human immunodeficiency virus (HIV) prevalence denominator, Uganda, 1990–2007. “Not tested” refers to those people who tested HIV-negative in the previous round and were resident but not tested in the current round; the result for those who tested HIV-positive in the previous round is carried forward. (Similarly, the result for those who test HIV-negative in a subsequent round is imputed backward.) “Age 13 years” refers to those people who had turned 13 years of age since the previous round and thus were newly eligible for inclusion in the estimate of adult HIV prevalence. “Newly tested” refers to those people who resided in the catchment area in the previous round but were not tested for HIV; although they tested HIV-positive in the current round, it could not be assumed that they were also HIV-positive in the previous round, so they were excluded from the estimate of HIV prevalence in the previous round.

Figure 4. Sensitivity analysis of human immunodeficiency virus (HIV) prevalence, Uganda, 1990–2008.
In our cohort, seropositive in-migrants have represented a proportion of the recorded HIV-seropositive cases that varied over time between slightly less than 10% and slightly more than 20%. Seropositive in-migrants could therefore potentially make a substantial contribution to HIV prevalence and may be considered a group specifically suitable for targeting for prevention and treatment of HIV. Because the risk of HIV infection may be higher among mobile people (25–27), out-migration might tend to decrease HIV prevalence in the study population.

HIV prevalence in this cohort varied from 6.7% to 8.7%. With a prevalence of 8.7%, the denominator can be expected to be over 11 times larger than the numerator. One would therefore expect the magnitude of changes in the denominator of prevalence to be about 11 times the changes in the numerator. However, there was only about a 7-fold to 8-fold difference in the changes in number of people in the denominator compared with the numerator (Figures 2 and 3). This was because HIV-positive people, who made up the numerator of prevalence, were both more likely to die and more mobile than were HIV-negative people, who comprised the bulk of the denominator.

Unlike the situation with prevalence, we cannot assign a new incident case directly to an in-migrant; that is, we would not increase the numerator of incidence from one year to the next because of an HIV-infected in-migrant. Similarly, although out-migration or death among HIV-uninfected people affects the number of person-years at risk (denominator of incidence), we would not decrease the numerator because of an out-migration or death. This is because after the year of infection, the incident case would already have been removed from both the numerator and the denominator for estimating incidence some time before the death occurred. The fact that we cannot separate the contributing factors of incidence does not present a major problem. Whereas incidence provides direct measurement of epidemiologic trends, prevalence surveys need careful interpretation.

The proportion of adults with a confirmed HIV status in this cohort declined from about 80% during the mid-1990s survey years to about 70% by the mid-2000s (2). It is possible that part of this reduction was due to people tiring of the cohort study and being less willing to participate, which could have resulted in upwardly biased prevalence trends. Only the status of those confirmed HIV-positive individuals would be carried forward and imputed. Indeed, we see some evidence of this effect on trends by noting that the number of HIV-negative people who were lost from the denominator of prevalence estimates due to not being tested was about twice as high in 2002–2007 as it was during the mid-1990s (Figure 3).

Figure 4 demonstrates a methodological problem related to most recent prevalence estimates in cohorts in which information on the HIV status of nonattenders in a specific round is imputed. For example, people who were HIV-negative in 2007 but not subsequently tested would by definition have to be excluded from analysis in 2008 because their status became unknown. By contrast, people who were HIV-positive in 2007 had their result carried forward. This resulted in an upward bias for the prevalence estimate for the most recent survey round, in this case for 2008. For this reason, we did not include the 2008 prevalence estimate in the results presented in Figures 2 and 3. Although for the same reason there is likely to be an upward bias in the 2007 prevalence estimate, this bias would have been small, as most people in the cohort did not miss more than 1 year in a row of HIV testing and we have used serologic results from the 2008/2009 round to estimate 2007 prevalence.

Assessing and interpreting HIV epidemiologic trends through changes in HIV prevalence requires careful consideration of the population factors affecting prevalence. The roles of migration and mobility are likely to be less important in national surveys of prevalence than in small area surveys, such as that described in this article. However, aging into and out of inclusion criteria, death, and survey participation are likely to have similar impacts in national surveys. In assessing the effect of HIV interventions, HIV incidence remains the most accurate direct measure of HIV epidemiologic trends. Because the establishment and maintenance of population-based surveillance cohort studies is expensive and challenging, other approaches have been used widely, such as large-scale prevalence surveys, monitoring of HIV prevalence in well-defined subgroups, and constructing incidence estimates from prevalence. Although methods have been devised to estimate incidence from prevalence and some need to account only for a small amount of additional information, such as age-specific mortality or survival rates after infection (11), these estimates cannot be as reliable as direct incidence estimates. The solution lies in the combination of these approaches, as it allows interpretation of observed epidemiologic prevalence trends in subgroups in light of the prevalence and incidence trends obtained from 1 or 2 well-documented population-based surveillance cohort studies that may be affordable for national HIV-control programs.

In any survey of HIV and sexual behavior, selection biases may occur. For example, individuals with higher numbers of sexual partners might perceive themselves to be at higher risk of HIV and could be less likely to participate in the survey. Policy-makers should interpret with care epidemiologic changes suggested solely by monitoring prevalence. Although costly, monitoring HIV incidence through population-based cohort studies is important and should complement other monitoring strategies, such as national and antenatal clinic-based prevalence surveys.

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