National review of deaths among HIV-infected adults

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ABSTRACT – This review describes patterns of mortality among adults infected with HIV in the UK and assesses the contributions of late diagnosis of HIV infection and non-HIV-related disease to such mortality. In total, 387 adults with HIV who died between 1 October 2004 and 30 September 2005 after receiving care at 90 clinical centres in the UK were reviewed. Causes of death and scenarios accounting for death were measured. Of the 387 deaths, 218 (56.3%) were readily attributable to infection with HIV. Only 123 (31.8%) deaths were considered not directly related to HIV. Late diagnosis of HIV accounted for 24.0% of all deaths and 35.2% of HIV-related deaths. Infection with HIV remains the main cause of mortality among infected patients in the era of highly active antiretroviral therapy. Late diagnosis of infection with HIV may be the largest potentially remediable factor for HIV-associated death.

KEY WORDS: HIV diagnosis, HIV infection, mortality

Introduction

Since highly active antiretroviral therapy (HAART) was introduced in 1996 and used widely in resource-rich countries, mortality among HIV-infected individuals in these countries has declined and the causes of death have altered.[1–3] The proportions of deaths directly due to HIV disease (including AIDS-defining events) have declined, while the proportions of deaths from cardiovascular disease, non-HIV-related cancer, and chronic liver disease have increased. This change is partly attributable to administration of HAART, which enables patients to live many years longer – even if they present relatively late on in the disease progression (as measured by the CD4 count in the blood). Nonetheless, diagnosis of HIV at a low CD4 count is associated with increased short-term mortality,[4] and many patients present late with advanced disease,[5] including opportunistic infections for which case-fatality rates remain high.[6] These patients represent missed opportunities for earlier diagnosis of HIV and inclusion into clinical treatment programmes following standard guidelines.[7]

In the UK, the causes of deaths among people infected with HIV and the surrounding circumstances, including timeliness of diagnosis, have not previously been reviewed on a national scale. In 2005, the British HIV Association (BHIVA) performed an audit of patterns of mortality.

Methods

Structured questionnaire forms were posted in late 2005 to the lead audit consultant at 176 clinical centres previously identified as providing care for adults infected with HIV in the UK. The forms sought information about the centre's arrangements for recording and reviewing deaths among patients infected with HIV and anonymised data on all patients infected with HIV aged ≥15 years who had died between 1 October 2004 and 30 September 2005 up to a maximum of 25 per centre. Information sought included immediate cause of death, other conditions that may have contributed to the death, the clinical scenario accounting for the death, the narrative circumstances of the death, the CD4 count and HIV viral load in the last six months of life, the timing of HIV diagnosis in relation to death, and whether or not an autopsy was performed.

Data were scanned and stored in a database and analysed in Excel by HC. Non-machine readable data (for example, narrative descriptions) were transcribed from digital images by HC. Data were reviewed and the immediate cause of death (that is, clinical pathology) and scenario (that is, circumstances) accounting for the death were coded by HC and SBL. In some cases, the data were reclassified to achieve consistency in attribution of cause of death to infection with HIV and to resolve discrepancies between tick-box and narrative answers. Deaths from opportunistic infections, Kaposi's sarcoma, lymphoma, and anal or cervical cancer were coded as related to HIV irrespective of the reporting clinician's opinion. Other malignancies and deaths due to chronic liver disease (including those related to hepatitis B virus (HBV) and hepatitis C virus (HCV)) or external causes were categorised as not related to HIV, as in other reports.[2,3,8,9] Ischaemic heart disease was classified as related or not related to HIV according to the reporting clinician's opinion. Deaths reported as being due to untreatable complications of HIV were reclassified as late diagnosis if they occurred within three months of diagnosis and were due to causes clearly preventable by the use of HAART.

Results

Responses were received from 133 clinical centres, 40 of which reported no deaths among adult patients infected with HIV within the previous year. Ninety centres took part in the review of case notes and submitted data on 397 patients; 10 of these patients were excluded as they had died outside the study period, which left 387 deaths for analysis.

Of the 387 patients, 287 (74.2%) were men (sex was not stated for nine (2.3%)); 220 (56.8%) were white, 128 (33.1%) black African, six (1.6%) black Caribbean, and 18 (4.7%) other (ethnicity was not stated for 15 (3.9%)); and 27 (7.0%) were younger than 30 years, 252 (65.1%) aged 30–50 years, and 104 (26.9%) older than 50 years (age at the time of death was not stated for four (1.0%)).

Table 1 shows immediate causes of death after reclassification in nine cases. Overall, 218 (56.3%) deaths were attributable to HIV disease (largely AIDS defining). A further 66 (17.1%) patients died of chronic liver disease, renal failure, and non-AIDS-defining malignancy. Cardiovascular disease was reported as the immediate cause of death in 25 (6.5%) cases; 17 of these deaths were considered by the reporting clinician not to be related to HIV. Finally, 46 (11.8%) patients died of other non-HIV-related causes and 32 (8.2%) were not classifiable.

Table 2 shows scenarios leading to death after reclassification in 47 cases (including five cases reported as untreatable complications and reclassified as late diagnosis of HIV). Overall, 123 (31.8%) deaths were considered not directly related to HIV. Ninety-three deaths were attributed to diagnosis of HIV too late for effective treatment, which represented 24.0% of all deaths or 35.2% after those not considered directly related to HIV were excluded.

Only four deaths following catastrophic events in patients being treated for HIV were clearly attributable to adverse effects of HIV-related treatment. Three cases were related to lactic acidosis presumed due to HAART; the other was related to fulminant liver failure in a patient who received isoniazid.

Discussion

In this national review, late diagnosis of HIV infection accounted for 24.0% of all deaths in HIV-infected people known to the HIV centres who responded to the questionnaire. This increased to 35.2% after deaths not directly related to HIV disease were excluded. In addition, any patients who died from HIV disease without ever being diagnosed and who thus remained unknown to HIV treatment services would have been omitted from the study.

Although data were based on subjective clinician reports, it is noteworthy that only 123 (31.8%) deaths were considered not

Table 1. Immediate cause of death.

Immediate cause of death	Number of patients (%)
Tuberculosis	16 (4.1)
Pneumocystis pneumonia	40 (10.3)
Bacterial sepsis anywhere	46 (11.9)
Other opportunistic infection	34 (8.8)
Lymphoma	28 (7.2)
Kaposi's sarcoma	7 (1.8)
Other malignancy	35 (9.0)
Cardiovascular disease	25 (6.5)
Chronic liver disease due to alcohol or viral hepatitis, or both	24 (6.2)
Renal failure	7 (1.8)
HIV dementia	2 (0.5)
Other disease probably related to HIV	25 (6.5)
Multiorgan endstage HIV disease, excluding above single categories	20 (5.2)
Other disease not related to HIV	28 (7.2)
Overdose of drugs of misuse	4 (1.0)
Accident or injury	6 (1.6)
Suicide or self-harm	8 (2.1)
Multiple causes stated	2 (0.5)
Not known or not stated	30 (7.8)

Table 2. Scenario accounting for death.

Scenario accounting for death	Number of patients (%)
Patient with multidrug-resistant HIV had run out of treatment options	11 (2.8)
Patient being successfully treated for HIV suffered a catastrophic event (for example, adverse reaction)	7 (1.8)
Patient was under care for HIV but had an untreatable HIV-related complication	61 (15.8)
Patient was under care for HIV but had chosen not to receive treatment	18 (4.7)
Patient was under care for HIV but treatment was ineffective due to poor adherence	26 (6.7)
Patient was under care for HIV but was unable to take treatment because of toxicity or intolerance	1 (0.3)
Patient was not treated or had treatment delayed because of ineligibility for care under the NHS	0
Patient was known to have HIV but was not under regular care and re-presented too late to treat effectively	13 (3.4)
Patient not diagnosed with HIV until too late for effective treatment	93 (24.0)
Patient died in the community without seeking care	1 (0.3)
Patient's death was not directly related to HIV	123 (31.8)
None of the above	8 (2.1)
Not known	25 (6.5)

directly related to HIV, including some deaths due to causes for which the role of HIV infection is uncertain. Patients coinfected with HCV and HIV have an accelerated and worse course than HIV-uninfected people,[10] and HCV chronic liver disease should probably be regarded as related to HIV. How many cases of non-AIDS-defining cancer (for example, lung adenocarcinoma) and coronary artery disease can be attributable to HIV is still uncertain, but HIV undoubtedly is a significant factor.[11–13] Infection with HIV thus may be a more significant contributory factor to mortality in the HAART era than other recent studies have suggested.[1,4]

Only 11 (2.8%) deaths were attributed to exhaustion of treatment options in patients with multidrug-resistant HIV. Even if some patients who chose not to receive treatment may have done so because of limited options and doubtful treatment efficacy due to drug resistance are taken into account, this suggests that death results rarely from failure of HAART with currently available regimens and is consistent with evidence that extensive treatment failure is increasingly rare.[14] Similarly, deaths attributed to adverse reactions to HAART were reassuringly rare.

In conclusion, late diagnosis of HIV is a potentially remediable circumstance that accounts for a high proportion of HIV-associated deaths. The recent policy guidelines of the World Health Organization and Centers for Disease Control and Prevention advocate that testing for HIV should be considered during all healthcare contacts.[15,16] More widespread testing will enable those with asymptomatic infection and non-specific but HIV-related symptoms to access programmes for the management of HIV earlier and to live longer.

Policy implications

Testing for HIV should be easily available on request and should move to an 'opt-out' basis in all healthcare settings. Clinicians should recommend HIV testing routinely for patients with a wide range of conditions that may indicate early disease to prevent later potentially untreatable serious complications.

Contributors

HC devised the study and data collection tools under the direction of the BHIVA Clinical Audit Sub-Committee, which was chaired by MJ. SBL and HC analysed the data and wrote the manuscript. All authors and selected members of the BHIVA Clinical Audit Sub-Committee commented on the final manuscript. HC is the guarantor.

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