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Cause of death among HIV patients in London in 2016

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Cause of death among HIV patients in London in 2016

Short title: Deaths among HIV patients in London: 2016

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ABSTRACT

Objectives: Since 2013, the London HIV Mortality Review Group has conducted annual reviews of deaths among people with HIV to reduce avoidable mortality.

Methods: All London HIV care Trusts reported data on 2016 patient deaths in 2017. Deaths were submitted using a modified Causes of Death in HIV reporting form and categorised by a specialist HIV pathologist and two HIV clinicians.

Results: There were 206 deaths reported; 77% were among men. Median age at death was 56 years. Cause was established for 82% of deaths, with non-AIDS malignancies and AIDS-defining illnesses being the most common causes reported. Risk factors in the year before death included: tobacco smoking (37%), excessive alcohol consumption (19%), non-injecting drug use (IDU) (10%), IDU (7%) and opioid substitution therapy (6%). Thirty-nine percent of patients had a history of depression, 33% chronic hypertension, 27% dyslipidaemia, 17% co-infection with HBV and/or HCV and 14% diabetes mellitus. At ~~the~~ time of death, 81% of patients were on antiretroviral therapy (ART), 61% had a CD4<350 cells/mm^3 and 24% a viral load ≥200 copies/ml. ~~Cause was established for 82% of deaths, with non-AIDS malignancies and AIDS-defining illnesses being the most common causes reported.~~ Thirty-six percent of deaths were unexpected; 61% of expected deaths were in hospital. Two thirds of expected deaths had a prior end-of-life care discussion documented.

Conclusions: In 2016, most deaths were due to non-AIDS conditions and the majority of patients were on ART and virally suppressed. However, several preventable deaths were identified~~,~~ and underlying risk factors were common. As London HIV patients are not representative of people with HIV in the UK, a national mortality review is warranted.

~~There are opportunities for improvement in HIV end-of-life care planning and in collaborative decision making with patients and other specialties.~~

INTRODUCTION

In 2016, there were 89,400 (95% credible interval (CI): 87,200-94,700) people living with HIV in England, of whom 38,700 (95% CI: 37,500-41,400) (43%) were resident in London.(1) London continues to account for the largest proportion of new HIV diagnoses in England (45%; 2,090/4,690 in 2016), particularly among men who have sex with men ~~(MSM)~~, and has the highest HIV prevalence (5.8 per 1,000 residents aged 15-59 in 2016).(2) The number of deaths ~~(from any cause)~~ among people with HIV in the region have remained relatively stable over the past decade, at about 200 per year.(3)

~~Survival of people living with HIV has improved significantly since effective anti-retroviral therapy (ART) was made widely available in the mid-1990s.~~With the widespread ~~introduction of~~use of antiretroviral treatment (ART), ~~and as people live longer with HIV,~~ cause of death among ~~HIV-infected individuals~~ people with HIV has shifted from primarily acquired immunodeficiency syndrome (AIDS)~~-related~~ to ~~non-AIDS related deaths~~other conditions~~, including cardiovascular disease, malignancies and liver disease~~.(4, 5) Nevertheless, ~~national studies and previous audits of death among people with HIV in the United Kingdom (UK) have shown that~~ late diagnosis of HIV continues to account for a high proportion of HIV-associated deaths~~.,~~(6, 7) ~~which is indicative of missed opportunities for intervention.~~

Since 2013, a collaborative multi-disciplinary review group, ~~made up of HIV and palliative care clinicians, pathologists, and public health professionals,~~ has conducted annual reviews of deaths among ~~adult~~ HIV patients in London to identify ~~such~~ missed opportunities for intervention ~~with an aim to ultimately reduce avoidable mortality and improve HIV patient care~~in the clinical care pathway. In this paper, we present the findings of the ~~2016~~-2017 ~~London~~ review, describing causes of death and exploring contributing factors.

METHODS

~~London HIV Mortality Review Group~~

The London HIV Mortality Review Group (LHMRG), ~~was formed~~ established in 2012, is made up of HIV and palliative care clinicians, pathologists and public health professionals. ~~to review deaths among people with HIV, who either died in London or accessed their routine HIV care in a London based service; the aim being, to reduce avoidable mortality and improve the quality of end-of-life care.~~ Deaths among people with HIV, who either died in London or accessed their routine HIV care in a London-based service are reviewed retrospectively on an annual basis. ~~to describe trends in causes of death and to identify scenarios worthy of further case investigation or demonstrating missed opportunities for intervention in the HIV patient~~

pathway. Data are presented annually at interactive meetings with clinicians for all London HIV care services.The group consists of HIV clinicians from London specialist HIV services, specialists in HIV pathology and palliative care, senior epidemiologists from Public Health England (PHE) and commissioners and public health specialists from NHS England.The evolution of the review process over time can be seen in Table 1. From 2015 onwards, Trusts have reported data directly to Public Health England. The Causes of Death in HIV (CoDe) form (8) was adopted in 2017 to standardise data collection, facilitate comparison with other studies and allow for a better understanding of the circumstances around each death (A full list of fields collected can be seen in Supplementary Table 1).

Reviewing deaths among HIV patients

Over the years, the death review process has evolved. The first review was carried out by the LHMRG in 2013-2014 (Table 1). Existing surveillance data on deaths among HIV patients occurring in 2010 and 2011 were validated by London NHS Trusts providing HIV care and trends were reviewed by the LHMRG. However, initial engagement from Trusts was low (n=8/17) and feedback highlighted existing data were difficult to validate due to the pseudo-anonymised nature. As such, from 2015 onwards, Trusts have reported data on deaths of HIV patients who either died at their centre or who attended their centre for care prior to death directly to PHE for this review process. NHS England, as the HIV services commissioner, is responsible for coordinating data collection and communication and PHE manages data collation, cleaning and analysis post submission.

The data items collected have also changed over time (Table 1). In the 2015 and 2016 reviews, Trusts provided a simplified pseudo-anonymised data set of deaths among HIV patients with basic diagnosis, care and death information. In 2017, the Causes of Death in HIV (CoDe) form was adopted to standardise collection, allow comparison with other studies and better understand the circumstances around each death. In addition to demographic and diagnosis data, this modified form collects information on risk factors in the year prior to death, co-morbidities and chronic conditions, autopsy results, end-of-life care and missed opportunities for earlier HIV diagnosis. Clinicians are also asked to make an assessment as to whether each death was likely to have been expected (e.g. those receiving planned end-of-life care or with a terminal condition) or unexpected (e.g. late presenters admitted at diagnosis and not responsive to treatment). A full list of fields collected can be seen in Supplementary Table 1.

Cause of death categorisation

As part of the annual review process, cause of death for each patient is categorised by at least two independent reviewers, as per the CoDe protocol. In 2017 (as in previous years), the 2016 deaths were reviewed independently by a specialist HIV pathologist and two HIV clinicians. Disagreements regarding categorisation were resolved through discussion.

Analyses

The descriptive analyses presented in thisThis paper focuses on deaths among adult HIV patients (≥15 years of age at death) occurring between 01/01/2016 and 31/12/2016 reported as part of the 2017 review. Once received from NHS Trusts providing HIV care, data were collated, de-duplicated and cleaned using Microsoft Excel (2007). Age at death was derived from year of birth and year of death. Deaths were reviewed independently by a specialist HIV pathologist and two HIV clinicians and Deaths were grouped into nine categories: AIDS,(9) non-AIDS infections, non-AIDS malignancies, cardiovascular disease (CVD) and stroke, liver disease (not related to alcohol), respiratory disease, accident/suicide, substance misuse (including alcoholic liver disease) and other (including diabetes mellitus, gastrointestinal haemorrhage, chronic kidney disease and non-specific diseases of body systems). Disagreements regarding cause of death categorisation were resolved through discussion. Late diagnosis was defined as having a CD4 count <350 cells/mm^3 at HIV diagnosis; patients were considered virally suppressed if they had a viral load <200 copies/ml. Data management and analyses were carried out in Stata v13 (College Station, Texas, USA).

RESULTS

Overview

All 17 London Trusts providing HIV care submitted data in 2017, reporting 207 206 deaths among HIV patients in 2016 after de-duplication. Information on the number of deaths by Trust can be seen in (Supplementary Table 2). Completeness was high across the vast majority of data fields for reported deaths, though few Trusts were able to provide information on late diagnosis and missed opportunities for earlier HIV diagnosis (Supplementary Table 1). After de-duplication, there were 206 deaths reported among adult HIV patients in 2016, the characteristics of which can be seen in Table 2. The majority of deaths were among men (77%; 159). MThe median age at death was 56 years [interquartile range (IQR): 47-62 years] and varied by cause (Table 2)], which was higher among men (57 years [IQR: 50-63]) than women (50 years [IQR: 45-56]).

Risk factors and co-morbidities

~~Risk factors reported in the year prior to death included: tobacco smoking (37%; 64/171), excessive alcohol consumption (19%; 33/174), injecting drug use (IDU) (7%; 13/175), non-IDU (10%; 17/174), and opioid substitution therapy (OST) (6%; 10/181). Men were more likely to have at least one risk factor in the year prior to death than women. Two in five men smoked tobacco and one in five consumed excessive amounts of alcohol in the year prior to death.~~

~~Co-morbidities were commonly reported, with over three quarters (81%; 157/194) of HIV patients who died diagnosed with at least one other condition. A third (33%; 64/196) of patients had hypertension, 27% (53/197) dyslipidaemia, 17% (34/196) chronic elevated liver transaminases (LT), 17% (34/198) coinfection with hepatitis B (HBV) and/or hepatitis C (HCV) and 14% (27/199) had diabetes mellitus. A higher proportion of women had hypertension compared to men.~~

~~Prevalence of mental health issues among HIV patients who died was high; over a third of both men and women had a history of depression (39%; 72/187) and 7% (12/179) had a history of psychosis. Prior CVD, including myocardial infarction, stroke or a condition requiring an invasive cardiovascular procedure, was reported among 16%(30/193) of patients. A history of liver decompensation was reported among 6% (12/193) of patients and 12% (21/179) had clinical evidence of liver failure in the four weeks prior to death. Only 10 patients had a liver histology available, with limited information on the stage of fibrosis.~~

Causes of death and contributing factors~~autopsy~~

Cause was ascertainable for 82% ~~(169/206)~~ of deaths ~~among HIV patients~~ (Table ~~2~~3). A quarter of deaths (22%~~; 37~~) were attributable to AIDS-defining illnesses. ~~Among t~~The 132 non-AIDS deaths ~~, most~~ were due to malignancies (30%~~; 40~~), ~~followed by: CVD and stroke~~ (17%~~; 23~~), infections (11%~~; 14~~), liver disease (9%~~; 12~~), respiratory disease (9%~~; 12~~), accident/suicide (8%~~; 10~~), substance misuse (5%~~; 6~~) and other causes (11%~~; 15~~). ~~While deaths due to substance misuse, respiratory disease and CVD/stroke were more common among men, non-AIDS infections and "other" causes were more common among women.~~

~~Median age of death varied by cause; the highest median age of death was among patients who died of non-AIDS malignancies (61 years [IQR: 52-67]) and the lowest among those who died of accident/suicide (48 years [IQR: 43-61]) (Table 3).~~ Almost half of patients (48%) had risk factors in the year prior to death, including: tobacco smoking, excessive alcohol consumption, injecting drug use (IDU), non-IDU and opioid substitution therapy (Table 2). Co-morbidities were reported in over three quarters (81%) of patients (Table 2); depression was the most common, experienced by over a third (39%) of patients. All patients who died of

substance misuse had risk factors in the year prior to death (excessive alcohol use: 80% (4/5); IDU: 75% (3/4); tobacco smoking: 60% (3/5)) and at least one co-morbidity (depression: 67% (4/6)). The prevalence of co-morbidities was also high among liver disease (HCV: 75% (9/12); chronic elevation of LT: 64% (7/11); clinical liver failure: 64% (7/11)) and accident/suicide deaths (depression: 75% (6/8)).

Over a third of deaths (36%; 64/178) were reported ~~by clinicians~~ as being unexpected (Table ~~2~~3). Of the 64 patients who died unexpectedly: 84% (54/64) were men, 69% (44/64) were aged 45-64 years old at death, 48% (31/64) died in hospital, 81% (43/53) were reported to be on ART at death and 79% (46/58) were reported to have an undetectable viral load at death ~~(<200 copies/ml)~~. Over half of deaths among patients who died of CVD and stroke (59%; 13/22) and substance misuse (60%; 3/5) were unexpected, as well as all accident/suicide ~~deaths~~ (100%; 10/10) deaths.

Overall, ~~There were~~ 26 autopsies were performed~~; the results of the autopsy revealed cause of death to be: AIDS (19%; 5), CVD and stroke (19%; 5), accident/suicide (12%; 3), respiratory disease (12%.3), substance misuse (7%; 2), non-AIDS infections (4%; 1) and other causes (12%; 3). There were~~; in four ~~reported autopsies~~ cases,~~where~~ cause of death ~~was~~ remained unknown ~~(15%; 4)~~.

~~Overall, T~~there were another ~~37~~ 33 deaths with an unknown cause. Common reasons ~~for an unknown cause of death~~ were: the HIV ~~care clinics reported they~~ service had no information on the death ~~(n=18), the~~(e.g. clinics were notified of the death by a patient's friends, family or other clinic ~~(n=5)~~ or the death~~s~~ occurred abroad~~) (n=5). A further six deaths occurred outside of healthcare settings with no information available to clinics, as either the patient withheld~~ , consent ~~for the clinic~~ to contact other healthcare providers was lacking or information was still pending. ~~their general practitioner (GP) (n=2) or the clinic was still awaiting the GP report at the time of submission (n=2). For three deaths, clinics reported awaiting information from the coronial autopsy.~~

Place of death and end-of-life care

Where reported, 58% (102/175) of HIV patients died in hospital, 18% ~~(32)~~ at home, 13% ~~(22)~~ in a hospice, 3% ~~(5)~~ in the community, 3% ~~(5)~~ in a nursing home and 5% ~~(9)~~ abroad. Death in hospital was slightly more common among expected deaths (60%; 63/104) compared to unexpected deaths (54%; 31/57). Two thirds of expected deaths (67%; 48/72) had a prior end-of-life care discussion; however,~~ though~~ information on end-of-life care was only available for 57% (118/206)~~ of patients~~.

Clinical care prior to death

Overall, 97% ~~(181/186)~~ of patients were reported to have ever been on ART. However only 81% ~~(134/165) of people~~ were ~~on~~ receiving ART at the time of death, of which 74% ~~(99/133)~~ had been on treatment for at least six months before ~~death~~they died. At death, 61%~~(113/185) of patients~~ had a CD4 count of <350 cells/mm^3 and 24% ~~(47/192)~~ a viral load of ≥200 copies/ml. ~~CD4 counts at death were highest among patients who died of CVD and stroke (CD4 ≥500 cells/mm^3: 43%; 9/21) and accident/suicide (CD4 ≥500 cells/mm^3: 57%; 4/7) (Table 3). Viral suppression was highest among patients who died of substance misuse (100%; 3/3), CVD and stroke (90%; 19/21) and non-AIDS malignancies (85%; 33/39) (Table 3).~~

~~Adverse effects~~

~~The deaths of six HIV patients were considered to be related to medical treatment; of these, three deaths were reported to be related to ART and three deaths were related to other treatments.~~

DISCUSSION

In 2016, over three quarters ~~(77%)~~ of deaths among adult HIV patients in London were due to non-AIDS conditions and the majority of patients were on ART and virally suppressed at death. However, a ~~significant~~ substantial number ~~of people with HIV~~ died from AIDS-related illnesses~~. While information on the late diagnosis and retention in care for these patients is unknown, it is widely recognised that AIDS-defining illnesses~~which are ~~largely~~ potentially preventable through earlier HIV diagnosis and/or support for ~~people~~ those not ~~actively~~ engaged in care and/or not adherent to treatment.(10, 11) Innovative strategies to further expand HIV testing outside of sexual health services should be complemented by strategies to reduce stigma and promote long-term integration into care in order to realise the benefits of wider testing and treatment on mortality among ~~HIV~~ people with HIV~~patients~~.(12) ~~As stigma has been found to have a strong negative impact care engagement, efforts to address stigma may be one way to improve patient outcomes and reduce deaths due to AIDS-defining illnesses.~~

To further reduce avoidable mortality from non-AIDS conditions, there is a need for optimal management of risk factors, co-morbidities and the complex psychological and socioeconomic needs of people living with HIV. The British HIV Association (BHIVA) recommends people attending HIV outpatient clinics should undergo regular screening ~~in order to detect~~for cardiovascular, renal, liver, bone and other co-morbidities.(13) In this review, 81% of HIV patients who died had at least one co-morbidity. This is much higher than reported diagnosed chronic conditions among HIV patients in care across England and Wales (73%).(14)~~(63.8%;~~

~~95% confidence interval: 58.8% – 68.8%).~~ Depression was the most common co-morbidity among people who died. Poor mental health is known to be particularly prevalent in the HIV population, with diagnosed depression at 33% versus 19% in the general population and diagnosed anxiety at 26% compared to 15% ~~(p<0.0001)~~.(14) ~~The high prevalence of poor mental health can be further complicated by high levels of unmet need; in a study of HIV patients accessing care in the UK, 20% reported needing support to deal with loneliness and isolation (75% of need unmet) and 33% reported needing support for stress management (55% unmet). Overall, the greatest area of unmet need reported by HIV patients in care was for social and welfare services, where in 62% of cases in need, services were either unavailable or not sought.~~

This review also demonstrates that in addition to co-morbidities, underlying risk factors~~, such as tobacco smoking and substance misuse~~ were common ~~among HIV patients who died~~. One in three people who died were known to be tobacco smokers compared to one in five HIV patients across England and Wales and in the general population.(14) Furthermore, levels of IDU were almost double (7%), compared to the HIV patient population (4%).(14) Risk factors in this review were not self-reported so may have been underestimated. Improved health promotion is crucial to increase uptake of risk reduction strategies~~, through peer support, community mobilisation and media campaigns~~. ~~Furthermore,~~ HIV patients should be screened annually for substance misuse and supported ~~by their HIV care team~~ to modify behaviours to improve their health ~~through provision of information, short behavioural interventions and clear referral pathways to appropriate specialist care services (e.g. drug and alcohol addiction teams and support services)~~.(13)

This is the first review ~~of~~ by the LHMRG to explore the end-of-life care among HIV patients. However, end-of-life data were poorly reported, with information available for only 57% of deaths ~~with available information~~. Where known, ~~only~~ two thirds of expected deaths had a palliative care discussion and, consistent with previous studies,(15, 16) ~~and~~ a high proportion of both expected and unexpected deaths ~~were~~ occurred in hospital. ~~This is consistent with the literature that suggests although, p~~Palliative care is effective in improving patient-reported outcomes,(17) although access among people with HIV ~~is poor~~may be limited.~~–~~(18) ~~and compared to death from other conditions, people with HIV are more likely to die hospital rather than at home. The goal of end-of-life care is to prevent and minimise suffering and optimise quality of life in patients with advanced disease. This review demonstrates that there are opportunities to improve end-of-life care planning and reporting and in collaborative decision making between HIV patients, the team providing their HIV care and other specialties, such as oncology and cardiology.~~ The 2018 BHIVA "Standards of care for people living with HIV"

~~now includes~~ recommend~~ation~~s ~~for palliative care;~~ HIV ~~care~~ teams ~~should~~ establish patients' palliative care preferences at an early stage and ~~should~~ offer advance care plans, ~~which should be~~that are reviewed regularly and be easily accessible to all care providers~~members of the care team~~.(13)

Causes of death reported in this review are consistent with LHMRG reviews among HIV patients carried out in London in previous years,(19, 20) and audits elsewhere in the United Kingdom (UK).(21) However, the ability to compare LHMRG findings across years and describe trends is limited by the changes in data collection over time. Comparisons by gender and cause of death should be interpreted with caution, given the small numbers. ~~Furthermore, t~~ .

This review was designed as a public health exercise to understand factors that may have contributed to death and not as an in-depth clinical case-note review. The extent to which co-morbidities were controlled and whether patients had the ability to change their life-style risk factors are unknown. Data on socio-economic factors, ethnicity and HIV acquisition were not collected. A minority of cases had information on late diagnosis; it is unclear if missing data were not reported because patients died over a year after diagnosis or if the information was unavailable to the reporting clinician. Misclassification of deaths as expected or unexpected may have occurred as this was based on clinician assessment only. Only 13% of patients had an autopsy; this rate is less than the general autopsy rate of 16% for deaths in England and Wales.(22) There are limitations for the replicability and generalisability of these findings to the population of HIV patients, as data are only available for those that died.

These ~~review~~ findings reflect the situation among ~~patients~~ individuals engaged in HIV care services; ~~deaths that Trusts were not aware of (e.g.~~ deaths in the community or among patients not ~~in~~ known to HIV care services ~~care) will not necessarily~~may not have been reported through this process. A large UK national cohort study of mortality among people diagnosed with HIV in the era of ~~effective~~ ART ~~in the UK~~ found 23% of people who died were never linked to HIV outpatient care services; AIDS was the most common cause of death (58%), driven by high rates of late diagnosis (76%).(7) As such, mortality among people with HIV in London and the contribution of AIDS-related illnesses may have ~~most likely~~ been underestimated ~~in the present review~~here.

~~Another limitation of this review is that data fields on late diagnosis and missed opportunities for earlier diagnosis among patients dying with a year of diagnosis were poorly reported. Only 46 patients had information reported as to whether they were diagnosed late; it is unclear whether data were missing for others because they died over a year after diagnosis or if the~~

information was unavailable to the clinician reporting the death. Finally, comparisons by gender and cause of death should be interpreted caution, given the small numbers.

Based on the feedback from this review, the design of the 2018 review of 2017 deaths among HIV patients in London has been updated to streamline the data collected and ultimately improve reporting. The CoDe reporting form has been further modified and the number of fields reduced to ease the burden for Trusts.

CONCLUSIONS

This review of mortality among adult HIV patients in London has identified a number of deaths that may have been avoided, through earlier diagnosis, and better management of co-morbidities (e.g. depression) and through support for risk reduction (e.g. smoking cessation support). As HIV patients in London are not representative of all people living with HIV in the UK, a national review of deaths is warranted.

Despite high uptake of free NHS care and treatment, HIV patients in London continue to die from AIDS-defining illnesses. For those with advanced disease, palliative care pathways should be strengthened, and end-of-life care planning integrated into clinical management.

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CONTRIBUTIONS

All authors contributed to interpretation of the data, commented on the manuscript and approved the final draft. SC carried out all data cleaning, collation and analysis, drafted the manuscript, incorporated author comments, and was responsible for the final draft to be published. SBL reviewed all deaths, creating short summaries of cause of death for each patient. RFM and FAP undertook the coding of deaths based on these summaries. IH created the mortality review reporting form; JF managed the review process on behalf of NHS England. IH and JF were responsible for all review communication with NHS Trusts. AKS was clinical lead for the review and led the development of the reporting form. RH provided expertise on

HIV end-of-life care, inputting into the development of the questions on end-of-life care and aided in interpretation of responses. VCD provided support for epidemiological analyses. SD led the development of previous reviews and contributed important intellectual content to the discussion and conclusions.

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Cause of death among HIV patients in London in 2016

Short title: Deaths among HIV patients in London: 2016

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ABSTRACT

Objectives: Since 2013, the London HIV Mortality Review Group has conducted annual reviews of deaths among people with HIV to reduce avoidable mortality.

Methods: All London HIV care Trusts reported data on 2016 patient deaths in 2017. Deaths were submitted using a modified Causes of Death in HIV reporting form and categorised by a specialist HIV pathologist and two HIV clinicians.

Results: There were 206 deaths reported; 77% were among men. Median age at death was 56 years. Cause was established for 82% of deaths, with non-AIDS malignancies and AIDS-defining illnesses being the most common causes reported. Risk factors in the year before death included: tobacco smoking (37%), excessive alcohol consumption (19%), non-injecting drug use (IDU) (10%), IDU (7%) and opioid substitution therapy (6%). Thirty-nine percent of patients had a history of depression, 33% chronic hypertension, 27% dyslipidaemia, 17% co-infection with HBV and/or HCV and 14% diabetes mellitus. At time of death, 81% of patients were on antiretroviral therapy (ART), 61% had a CD4<350 cells/mm^3 and 24% a viral load ≥200 copies/ml. Thirty-six percent of deaths were unexpected; 61% of expected deaths were in hospital. Two thirds of expected deaths had a prior end-of-life care discussion documented.

Conclusions: In 2016, most deaths were due to non-AIDS conditions and the majority of patients were on ART and virally suppressed. However, several preventable deaths were identified and underlying risk factors were common. As London HIV patients are not representative of people with HIV in the UK, a national mortality review is warranted.

INTRODUCTION

In 2016, there were 89,400 (95% credible interval (CI): 87,200-94,700) people living with HIV in England, of whom 38,700 (95% CI: 37,500-41,400) (43%) were resident in London.(1) London continues to account for the largest proportion of new HIV diagnoses in England (45%; 2,090/4,690 in 2016), particularly among men who have sex with men, and has the highest HIV prevalence (5.8 per 1,000 residents aged 15-59 in 2016).(2) The number of deaths among people with HIV in the region have remained relatively stable over the past decade, at about 200 per year.(3)

With the widespread use of antiretroviral treatment (ART), cause of death among people with HIV has shifted from primarily acquired immunodeficiency syndrome (AIDS) to other conditions.(4, 5) Nevertheless, late diagnosis of HIV continues to account for a high proportion of HIV-associated deaths.(6, 7)

Since 2013, a collaborative multi-disciplinary review group, has conducted annual reviews of deaths among HIV patients in London to identify missed opportunities for intervention in the clinical care pathway. In this paper, we present the findings of the 2017 review, describing causes of death and exploring contributing factors.

METHODS

The London HIV Mortality Review Group (LHMRG), established in 2012, is made up of HIV and palliative care clinicians, pathologists and public health professionals. Deaths among people with HIV, who either died in London or accessed their routine HIV care in a London-based service are reviewed retrospectively on an annual basis. The evolution of the review process over time can be seen in Table 1. From 2015 onwards, Trusts have reported data directly to Public Health England. The Causes of Death in HIV (CoDe) form (8) was adopted in 2017 to standardise data collection, facilitate comparison with other studies and allow for a better understanding of the circumstances around each death (Supplementary Table 1).

This paper focuses on deaths among adult HIV patients (≥15 years of age at death) occurring between 01/01/2016 and 31/12/2016 reported as part of the 2017 review. Age at death was derived from year of birth and year of death. Deaths were reviewed independently by a specialist HIV pathologist and two HIV clinicians and grouped into nine categories: AIDS,(9) non-AIDS infections, non-AIDS malignancies, cardiovascular disease (CVD), liver disease (not related to alcohol), respiratory disease, accident/suicide, substance misuse (including alcoholic liver disease) and other (including diabetes mellitus, gastrointestinal haemorrhage, chronic kidney disease and non-specific diseases of body systems). Disagreements regarding

cause of death categorisation were resolved through discussion. Late diagnosis was defined as a CD4 count <350 cells/mm^3 at HIV diagnosis; patients were considered virally suppressed if they had a viral load <200 copies/ml. Data management and analyses were carried out in Stata v13 (College Station, Texas, USA).

RESULTS

Overview

All 17 London Trusts providing HIV care submitted data, reporting 206 deaths among HIV patients in 2016 after de-duplication (Supplementary Table 2). The majority of deaths were among men (77%; 159). Median age at death was 56 years [interquartile range (IQR): 47-62 years] and varied by cause (Table 2).

Causes of death and contributing factors

Cause was ascertainable for 82% of deaths (Table 2). A quarter of deaths (22%) were attributable to AIDS-defining illnesses. The 132 non-AIDS deaths were due to malignancies (30%), followed by: CVD (17%), infections (11%), liver disease (9%), respiratory disease (9%), accident/suicide (8%), substance misuse (5%) and other causes (11%).

Almost half of patients (48%) had risk factors in the year prior to death, including: tobacco smoking, excessive alcohol consumption, injecting drug use (IDU), non-IDU and opioid substitution therapy (Table 2). Co-morbidities were reported in over three quarters (81%) of patients (Table 2); depression was the most common, experienced by over a third (39%) of patients. All patients who died of substance misuse had risk factors in the year prior to death (excessive alcohol use: 80% (4/5); IDU: 75% (3/4); tobacco smoking: 60% (3/5)) and at least one co-morbidity (depression: 67% (4/6)). The prevalence of co-morbidities was also high among liver disease (HCV: 75% (9/12); chronic elevation of LT: 64% (7/11); clinical liver failure: 64% (7/11)) and accident/suicide (depression: 75% (6/8)) deaths.

Over a third of deaths (36%; 64/178) were reported as being unexpected (Table 2). Of the 64 patients who died unexpectedly: 84% (54/64) were men, 69% (44/64) were aged 45-64 years old at death, 48% (31/64) died in hospital, 81% (43/53) were reported to be on ART at death and 79% (46/58) were reported to have an undetectable viral load at death. Over half of deaths among patients who died of CVD and stroke (59%; 13/22) and substance misuse (60%; 3/5) were unexpected, as well as all accident/suicide deaths (100%; 10/10).

Overall, 26 autopsies were performed; in four cases, cause of death remained unknown. There were another 33 deaths with an unknown cause. Common reasons were: the HIV service had

no information on the death (e.g. clinics were notified of the death by a patient's friends, family or other clinic or the deaths occurred abroad), consent to contact other healthcare providers was lacking or information was still pending.

Place of death and end-of-life care

Where reported, 58% (102/175) of HIV patients died in hospital, 18% at home, 13% in a hospice, 3% in the community, 3% in a nursing home and 5% abroad. Death in hospital was slightly more common among expected deaths (60%; 63/104) compared to unexpected deaths (54%; 31/57). Two thirds of expected deaths (67%; 48/72) had a prior end-of-life care discussion; however, information on end-of-life care was only available for 57% (118/206).

Clinical care prior to death

Overall, 97% of patients were reported to have ever been on ART. However only 81% were receiving ART at the time of death, of which 74% had been on treatment for at least six months before they died. At death, 61% had a CD4 count of <350 cells/mm^3 and 24% a viral load of ≥200 copies/ml.

DISCUSSION

In 2016, over three quarters of deaths among adult HIV patients in London were due to non-AIDS conditions and the majority of patients were on ART and virally suppressed at death. However, a substantial number died from AIDS-related illnesses, which are potentially preventable through earlier HIV diagnosis and/or support for those not engaged in care and/or not adherent to treatment.(10, 11) Innovative strategies to further expand HIV testing outside of sexual health services should be complemented by strategies to reduce stigma and promote long-term integration into care in order to realise the benefits of wider testing and treatment on mortality among people with HIV.(12)

To further reduce avoidable mortality from non-AIDS conditions, there is a need for optimal management of risk factors, co-morbidities and the complex psychological and socioeconomic needs of people living with HIV. The British HIV Association (BHIVA) recommends people attending HIV outpatient clinics should undergo regular screening for cardiovascular, renal, liver, bone and other co-morbidities.(13) In this review, 81% of HIV patients who died had at least one co-morbidity. This is much higher than reported diagnosed chronic conditions among HIV patients in care across England and Wales (73%).(14) Depression was the most common co-morbidity among people who died. Poor mental health is known to be particularly prevalent

in the HIV population, with diagnosed depression at 33% versus 19% in the general population and diagnosed anxiety at 26% compared to 15%.(14)

This review also demonstrates that in addition to co-morbidities, underlying risk factors were common. One in three people who died were known to be tobacco smokers compared to one in five HIV patients across England and Wales and in the general population.(14) Furthermore, levels of IDU were almost double (7%), compared to the HIV patient population (4%).(14) Risk factors in this review were not self-reported so may have been underestimated. Improved health promotion is crucial to increase uptake of risk reduction strategies. HIV patients should be screened annually for substance misuse and supported to modify behaviours to improve their health.(13)

This is the first review by the LHMRG to explore the end-of-life care among HIV patients. However, end-of-life data were poorly reported, with information available for only 57% of deaths. Where known, two thirds of expected deaths had a palliative care discussion and, consistent with previous studies,(15, 16) a high proportion of both expected and unexpected deaths occurred in hospital. Palliative care is effective in improving patient-reported outcomes,(17) although access among people with HIV may be limited.(18) The 2018 BHIVA "Standards of care for people living with HIV" recommends HIV teams establish patients' palliative care preferences at an early stage and offer advance care plans, that are reviewed regularly and be easily accessible to all care providers.(13)

Causes of death reported in this review are consistent with LHMRG reviews among HIV patients carried out in London in previous years,(19, 20) and audits elsewhere in the United Kingdom (UK).(21) However, the ability to compare LHMRG findings across years and describe trends is limited by the changes in data collection over time. Comparisons by gender and cause of death should be interpreted with caution, given the small numbers.

This review was designed as a public health exercise to understand factors that may have contributed to death and not as an in-depth clinical case-note review. The extent to which co-morbidities were controlled and whether patients had the ability to change their life-style risk factors are unknown. Data on socio-economic factors, ethnicity and HIV acquisition were not collected. A minority of cases had information on late diagnosis; it is unclear if missing data were not reported because patients died over a year after diagnosis or if the information was unavailable to the reporting clinician. Misclassification of deaths as expected or unexpected may have occurred as this was based on clinician assessment only. Only 13% of patients had an autopsy; this rate is less than the general autopsy rate of 16% for deaths in England and

Wales.(22) There are limitations for the replicability and generalisability of these findings to the population of HIV patients, as data are only available for those that died.

These findings reflect the situation among individuals engaged in HIV care services; deaths in the community or among patients not known to HIV care services may not have been reported through this process. A large UK national cohort study of mortality among people diagnosed with HIV in the era of ART found 23% of people who died were never linked to HIV outpatient care services; AIDS was the most common cause of death (58%), driven by high rates of late diagnosis (76%).(7) As such, mortality among people with HIV in London and the contribution of AIDS-related illnesses may have been underestimated here.

CONCLUSIONS

This review of mortality among adult HIV patients in London has identified a number of deaths that may have been avoided, through earlier diagnosis, better management of co-morbidities (e.g. depression) and through support for risk reduction (e.g. smoking cessation support). As HIV patients in London are not representative of all people living with HIV in the UK, a national review of deaths is warranted.

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CONTRIBUTIONS

All authors contributed to interpretation of the data, commented on the manuscript and approved the final draft. SC carried out all data cleaning, collation and analysis, drafted the manuscript, incorporated author comments, and was responsible for the final draft to be published. SBL reviewed all deaths, creating short summaries of cause of death for each patient. RFM and FAP undertook the coding of deaths based on these summaries. IH created the mortality review reporting form; JF managed the review process on behalf of NHS England. IH and JF were responsible for all review communication with NHS Trusts. AKS was clinical lead for the review and led the development of the reporting form. RH provided expertise on

HIV end-of-life care, inputting into the development of the questions on end-of-life care and aided in interpretation of responses. VCD provided support for epidemiological analyses. SD led the development of previous reviews and contributed important intellectual content to the discussion and conclusions.

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Table 1: Reviews of HIV mortality over time: London, 2013-2017

Review year	Year of deaths	Data source	Data provided	Trust response (N=17)	Deaths reported
2013-2014	2010-2011	PHE surveillance data	Gender, date of birth, ethnicity, infection route, country of birth, diagnosis date, diagnosis region, CD4 at diagnosis, date of death, causes of death, site of death, site of care, latest clinical information (CD4, ART, viral load)	8	Not applicable
2015	2014	Data submitted for review by Trust	Gender, diagnosis date, death year causes of death, place of death, latest clinical information (CD4, ART, viral load), ART adherence, expected/anticipated death	14	189
2016	2015	Data submitted for review by Trust	Gender, date of birth, diagnosis date, date of death, causes of death, place of death, latest clinical information (ART, CD4, viral load), ART adherence, expected/anticipated death	15	170
2017	2016	Data submitted for review by Trust	Modified Causes of Death in HIV (CoDe) form (Supplementary Table 1)	17	206

Table 2: Clinical and demographic profile of HIV patients who died by cause of death: London, 2016

		Cause of death																					
		All-cause mortality (N=206)		AIDS (N=37)		Non-AIDS infections (N=14)		Non-AIDS cancers (N=40)		CVD and stroke (N=23)		Liver disease (N=12)		Respiratory disease (N=12)		Accident and suicide (N=10)		Substance misuse (N=6)		Other causes (N=15)		Unknown (N=37)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gender	Men	159	100%	29	18%	10	6%	31	20%	19	12%	9	5%	11	7%	8	5%	6	4%	9	6%	27	17%
	Women	47	100%	8	17%	4	9%	9	19%	4	9%	3	6%	1	2%	2	4%	0	0%	6	13%	10	21%
Median age at death (years) [IQR]		56 [47-62]		53 [44-59]		51 [47-57]		61 [52-67]		57 [50-61]		50 [48-58]		60 [53-69]		48 [43-61]		59 [52-70]		57 [42-66]		51 [46-60]	
Risk factors in the year prior to death	Any	85	48%	14	44%	7	54%	12	34%	8	44%	6	55%	8	73%	4	50%	5	100%	5	38%	16	53%
	Tobacco smoking	64	37%	12	38%	7	54%	10	29%	6	33%	3	33%	5	50%	2	22%	3	60%	3	25%	13	45%
	Excessive alcohol	33	19%	4	12%	4	33%	2	6%	2	11%	2	25%	3	27%	3	38%	4	80%	3	23%	6	20%
	IDU	13	7%	1	3%	2	17%	1	3%	1	5%	1	10%	0	0%	0	0%	3	75%	1	8%	3	10%
	Non-IDU	17	10%	1	3%	0	0%	1	3%	0	0%	1	11%	1	9%	1	14%	3	60%	2	18%	7	23%
	OST	10	6%	0	0%	2	17%	0	0%	0	0%	4	36%	1	8%	0	0%	1	25%	1	8%	1	3%
Co-morbidities	Any	157	81%	18	55%	11	79%	28	72%	19	90%	12	100%	10	83%	8	100%	6	100%	13	87%	32	94%
	Hypertension*	64	33%	6	17%	4	31%	11	28%	11	48%	2	17%	6	50%	2	22%	1	25%	5	38%	16	46%
	Diabetes mellitus*	27	14%	2	6%	0	0%	4	10%	7	30%	1	8%	3	25%	0	0%	1	20%	2	14%	7	19%
	Dyslipidaemia*	53	27%	6	17%	2	14%	11	28%	10	45%	1	8%	1	8%	1	13%	2	50%	4	29%	15	42%
	Elevation of LT*	34	17%	1	3%	1	8%	5	13%	4	18%	7	64%	2	17%	3	30%	3	50%	1	8%	7	20%
	HBV and/or HCV*	34	17%	2	6%	6	43%	3	8%	3	13%	11	92%	1	8%	0	0%	2	40%	2	14%	4	11%
	CVD**	30	16%	2	6%	1	8%	6	16%	8	36%	1	9%	5	42%	1	13%	0	0%	1	7%	5	14%
	Depression**	72	39%	7	21%	7	54%	9	24%	4	40%	8	40%	3	25%	6	75%	4	67%	7	47%	17	52%
	Psychosis**	12	7%	2	6%	1	10%	1	3%	2	10%	0	0%	0	0%	1	17%	0	0%	1	7%	4	12%
	Liver decompensation**	12	6%	0	0%	2	14%	1	3%	2	9%	3	33%	0	0%	0	0%	2	40%	1	7%	1	3%
	Liver failure†	21	12%	2	6%	1	7%	2	5%	1	6%	7	64%	0	0%	1	11%	3	50%	3	20%	1	4%
Death unexpected		64	36%	7	19%	5	42%	5	13%	13	59%	2	17%	4	36%	10	100%	3	60%	4	29%	11	61%
Ever on ART		181	97%	35	97%	13	100%	35	100%	19	95%	12	100%	11	100%	7	78%	6	100%	12	100%	31	97%
ART at death		134	81%	24	75%	12	92%	30	88%	14	82%	7	58%	10	100%	4	50%	4	67%	9	82%	20	90%
CD4 at death (cells/mm^3)	<200	72	39%	24	69%	8	62%	15	39%	2	10%	4	40%	4	33%	1	14%	0	0%	6	46%	8	24%
	200-349	41	22%	7	20%	1	8%	9	24%	4	19%	4	40%	4	33%	0	0%	2	67%	3	23%	7	21%

	350-499	18	10%	0	0%	2	15%	5	13%	6	29%	0	0%	1	8%	2	29%	0	0%	1	8%	1	3%
	≥500	54	29%	4	11%	2	15%	9	24%	9	43%	2	20%	3	25%	4	57%	1	33%	3	23%	17	52%
Viral load at death (copies/ml)†	<200	145	76%	23	66%	10	71%	33	85%	19	90%	6	55%	10	83%	5	63%	3	100%	9	64%	27	77%
	≥200	47	24%	12	34%	4	29%	6	15%	2	10%	5	45%	2	17%	3	38%	0	0%	5	36%	8	23%

IDU=injecting drug use, OST=opioid substitution therapy, LT=liver transaminases, HBV=hepatitis B virus, HCV=hepatitis C virus, CVD=cardiovascular disease

Completeness: gender 100% (206), age at death 100% (206), any risk factor 85% (176), tobacco smoking 83% (171), excessive alcohol 84% (174), IDU 85% (175), non-IDU 84% (174), OST 88% (181), any co-morbidity 94% (194), hypertension 95% (196), diabetes mellitus 97% (199), dyslipidaemia 96% (197), elevation of liver transaminases 95% (196), HBV/HCV 98% (201), CVD 94% (193), depression 91% (187), psychosis 87% (179), liver decompensation 94% (193), liver failure 87% (179), death unexpected 86% (178), ever on ART 90% (186), ART at death 80% (165), CD4 at death 90% (185), viral load at death 93% (192)

Percentages based on where data were available and also may not add up to 100% due to rounding

**Chronic co-morbidities*

***History of co-morbidities*

†Clinical evidence for liver failure in the 4 weeks prior to death